The Recognition, Diagnosis, and Management of Coeliac Disease in New Zealand

A thesis submitted for the degree of Doctor of Philosophy
University of Otago

Kristin Kenrick, December 2018
Abstract

Background

Coeliac disease, an autoimmune-mediated sensitivity to gluten, is known to affect at least 1% of the population. It is widely acknowledged that it is underdiagnosed, and that management beyond the implementation of a gluten-free diet is inconsistent, despite there being several guidelines now available. This study investigated these issues as they relate to the New Zealand context, testing the hypothesis “that general practitioners in New Zealand have limited disease-specific knowledge about coeliac disease.”

Methods

Surveys of New Zealand general practitioners and gastroenterologists were undertaken, investigating their likely practices with respect to a range of variables associated with the recognition, diagnosis, and management of coeliac disease. Nine years of data from one of New Zealand’s major laboratories, relating to testing for coeliac disease were also audited.

Results

General practitioners in New Zealand have patchy knowledge about whom to test for coeliac disease, and how to diagnose and manage the condition. There is also a lack of consistency among gastroenterologists about aspects of its management. However, rates of testing for coeliac disease have steadily increased over time in the majority of regions examined, and its incidence is high in Otago-Southland. Furthermore, when people with very high coeliac antibody levels are biopsied, they almost always have evidence of coeliac disease.

Conclusions

General practitioners in New Zealand do have gaps in their knowledge about coeliac disease. Agreeing on a set of New Zealand-specific practice guidelines to promote consistent practice among clinicians, targeting gaps in knowledge, and reviewing policies around who should undergo biopsy to confirm the diagnosis, could all improve outcomes for patients with this condition.
Acknowledgements

There are many people without whom it would not have been possible for me to complete this work, and to whom I owe a great deal of thanks.

First and foremost, I owe a debt of gratitude to my supervisors Associate Professor Chrystal Jaye, Professor Andrew Day, and Associate Professor Michael Schultz. Between them they shepherded me through the travails that are PhD research, and I have greatly appreciated their guidance over the years. Especially thanks to Chrys, who accompanied me throughout the journey with calm wisdom and unwavering support.

Thank you to the many people who contributed to each of the three studies that comprise this work: the gastroenterologists and general practitioners who participated in the surveys; Helen van der Loo, Terry Taylor, and Roger Barton from Southern Community Laboratories in Dunedin, for help with setting up the laboratory study, and then with deciphering the data that emerged; Brent Glanville from HealthScope, Dr Richard Steele and SCL staff in Wellington, Simon Ross from the Ministry of Health, and Nicole Morris from the Southern District Health Board, for help with access to additional data related to the laboratory study; Dr Alesha Smith and Professor Murray Tilyard from bpacnz, for assistance with compiling the list of potential participants for the GP survey, and for the associated prize; and Andrew Thompson, the then Executive Officer of the New Zealand Society of Gastroenterology, for help distributing the gastroenterologist survey. Thanks also to Emeritus Professor Gil Barbezat, Dr Garry Nind, and Dr Jonathon Bishop, for feedback on the survey for gastroenterologists; to my colleagues and general practitioner friends who took the time to pilot test and provide feedback on the survey for GPs; to Janine Lucas for assistance with data entry; and to Dr Claire Cameron for biostatistics advice.

I would also like to acknowledge the financial support of Coeliac New Zealand, the University of Otago, and the Royal New Zealand College of General Practitioners, each of which provided me with a grant to pursue this work. In addition to this, the University of Otago granted me study leave at a crucial point in my journey, so particular thanks to my teaching colleagues in the Department of General Practice.
and Rural Health at the Dunedin School of Medicine who picked up the load to enable me to take this leave.

Thanks too to friends and colleagues who have provided moral support and encouragement along the way, especially my walking partner Dr Anne McGregor. I imagine that many of you now know more about coeliac disease than you ever thought possible!

But my greatest thanks go to my husband Greg Dawes, and our children Anna and Dante who have grown up alongside this project. Over the years all three have made sacrifices to enable me to pursue this dream. And now it is done. I could not have done it without you, and nor would I have wanted to.

*Ngā mihi nui ki a koutou.*
## Table of Contents

Abstract ................................................................................................................................. i  
Acknowledgements ............................................................................................................... iii  
List of Tables ........................................................................................................................ xiii  
List of Figures ....................................................................................................................... xviii  
List of Abbreviations ........................................................................................................... xxiii  

**Chapter 1: Introduction** .................................................................................................... 1  
1.1 A brief description of coeliac disease ........................................................................... 2  
1.2 Confirming the need for the present project ............................................................... 3  
1.3 Previous CD research with a primary care focus ....................................................... 5  
1.4 Investigating knowledge and practice about coeliac disease .................................... 7  
1.5 The research questions formally described ............................................................... 8  
1.6 Outline of the thesis ..................................................................................................... 10  
1.6.1 Conventions followed in this thesis ...................................................................... 11  

**Chapter 2: About Coeliac Disease** .................................................................................. 13  
2.1 Introduction ................................................................................................................... 13  
2.1.1 Search strategy ....................................................................................................... 13  
2.2 The History of Coeliac Disease .................................................................................. 14  
2.2.1 What is gluten? ....................................................................................................... 18  
2.2.2 The Coeliac enteropathy ......................................................................................... 20  
2.2.3 Coeliac antibodies ................................................................................................. 24  
2.3 Classifying and Defining Coeliac Disease ................................................................... 27  
2.4 Diagnostic criteria for CD ........................................................................................... 33  
2.4.1 ESPGHAN 2012 ..................................................................................................... 35  
2.5 Genetics and Pathogenesis of Coeliac Disease ......................................................... 39  
2.5.1 The genetics of CD ............................................................................................... 39
2.5.2 The role of the environment ................................................................. 41
2.5.3 Immune dysregulation and the pathophysiology of CD ......................... 45
2.6 The Prevalence of Coeliac Disease .................................................................. 49
  2.6.1 The dissenting voice .............................................................................. 52
  2.6.2 More recent studies ............................................................................. 54
  2.6.3 Coeliac disease prevalence in New Zealand ................................................. 55
  2.6.4 Prevalence based on other variables ........................................................ 58
2.7 The Incidence of Coeliac Disease .................................................................. 59
2.8 The Clinical Presentation of Coeliac Disease ................................................. 60
  2.8.1 Facilitating the recognition of CD .......................................................... 65
  2.8.2 Conditions associated with CD .............................................................. 68
  2.8.3 Dermatitis Herpetiformis and Gluten Ataxia .............................................. 70
2.9 Testing for Coeliac Disease .......................................................................... 71
  2.9.1 The gluten challenge ............................................................................ 73
  2.9.2 The role of HLA testing ....................................................................... 74
  2.9.3 Point-of-care testing ........................................................................... 75
2.10 The Management of Coeliac Disease ............................................................. 76
  2.10.1 The Gluten-Free Diet ......................................................................... 78
  2.10.2 New treatment possibilities ................................................................. 89
  2.10.3 Complications of CD ........................................................................ 91
  2.10.4 Monitoring after diagnosis .................................................................. 98
  2.10.5 Management additional to the GFD ...................................................... 103
2.11 The Patient's Perspective ............................................................................ 104
2.12 Conclusion .................................................................................................. 107

Chapter 3: Methods ........................................................................................... 109

3.1 Introduction .................................................................................................. 109
  3.1.1 Why surveys? ................................................................................... 110
3.2 Timeline .................................................................................................................. 113
3.3 Ethical Review Process ............................................................................................ 114
3.4 The Survey of Gastroenterologists ........................................................................ 114
  3.4.1 Introduction ........................................................................................................ 114
  3.4.2 Background ........................................................................................................ 115
  3.4.3 Development of the survey instrument ............................................................... 118
  3.4.4 Identifying the survey population ..................................................................... 122
  3.4.5 Implementing the survey ................................................................................. 123
  3.4.6 Data entry and analysis .................................................................................... 126
3.5 The Survey of General Practitioners ...................................................................... 126
  3.5.1 Development of the survey instrument ............................................................... 126
  3.5.2 Calculating the sample size ............................................................................... 130
  3.5.3 Selecting the study sample ............................................................................... 131
  3.5.4 Implementing the survey .................................................................................. 132
  3.5.5 Data entry ......................................................................................................... 134
  3.5.6 Data analysis ..................................................................................................... 135
3.6 The Laboratory Study .............................................................................................. 136
  3.6.1 Background ....................................................................................................... 137
  3.6.2 The study redefined .......................................................................................... 139
  3.6.3 Data retrieval ..................................................................................................... 141
  3.6.4 Data analysis ..................................................................................................... 143
3.7 Conclusion .............................................................................................................. 144

**Chapter 4: Results from the Survey of Gastroenterologists** .................................. 145
4.1 Introduction ............................................................................................................. 145
4.2 Response to the survey .......................................................................................... 145
  4.2.1 Identifying the survey population ..................................................................... 145
  4.2.2 Respondent numbers ....................................................................................... 146
4.2.3 Respondent demographics ................................................................. 147
4.3 Management of newly diagnosed Coeliac Disease ......................................... 151
  4.3.1 DEXA Scanning .................................................................................. 153
  4.3.2 Follow-up IgA-tTG antibody testing...................................................... 154
  4.3.3 Rebiopsy following diagnosis ............................................................... 154
  4.3.4 Analysis by demographics: Management of newly diagnosed CD .......... 156
  4.3.5 Responsibility for follow-up actions ................................................... 160
  4.3.6 The letter to Lucy's GP ....................................................................... 163
4.4 Long-term management of Coeliac Disease ..................................................... 164
  4.4.1 Including oats in the gluten-free diet ..................................................... 167
  4.4.2 Analysis by demographics: Long-term management of CD ................. 168
4.5 When the histology is normal ...................................................................... 170
  4.5.1 Analysis by demographics: When the histology is normal ...................... 175
4.6 A patient declining endoscopy .................................................................... 179
  4.6.1 The gluten challenge ......................................................................... 182
  4.6.2 Analysis by demographics: A patient declining endoscopy ................... 184
4.7 Key findings of the survey .......................................................................... 185
  4.7.1 Response to the survey and respondent characteristics ......................... 185
  4.7.2 Management of newly diagnosed CD .................................................. 185
  4.7.3 Long-term management of CD ............................................................. 186
  4.7.4 When the histology is normal .............................................................. 186
  4.7.5 A patient declining endoscopy ............................................................ 187

Chapter 5: Results from the Survey of General Practitioners ......................... 189
  5.1 Introduction ............................................................................................ 189
    5.1.1 Sample size .................................................................................... 189
    5.1.2 Modes of contact ............................................................................ 191
  5.2 Response to the survey ........................................................................... 192
Chapter 6: Results from the Laboratory Data Study

6.1 Introduction

6.1.1 Selection of data for analysis

6.2 Rates of testing

6.2.1 Otago-Southland

6.2.2 Nelson-Marlborough and South Canterbury

6.2.3 Hawkes Bay and Taupo

6.3 Who was tested?

6.3.1 Gender-specific data from Otago-Southland

6.3.2 Gender-specific data from Nelson-Marlborough and South Canterbury

6.3.3 Gender-specific data from Hawkes Bay and Taupo

6.3.4 Age-specific data from Otago-Southland

6.3.5 Age-specific data from other regions

6.3.6 Ethnicity Data

6.4 Who did the testing?

6.5 Which tests were done?

6.5.1 Coeliac antibody testing

6.5.2 HLA testing

6.6 What was found?

6.6.1 Positive IgA-tTG antibody results

6.6.2 Correlations between IgA-tTG and EMA results

6.6.3 Low and deficient IgA levels

6.6.4 Other findings

6.7 What happened next?

6.7.1 Repeat blood testing (serology and/or HLA testing)
Chapter 6: Key Findings of the Study

6.7.2 Duodenal biopsies

6.7.3 After positive biopsies

6.8 Incidence of Coeliac Disease

6.9 Key findings of the study

6.9.1 Rates of testing

6.9.2 Who was tested?

6.9.3 Who did the testing?

6.9.4 Which tests were done?

6.9.5 What was found?

6.9.6 What happened next?

6.9.7 Incidence of CD

Chapter 7: Discussion

7.1 Introduction

7.1.1 Overall strengths and limitations

7.1.2 Strengths and limitations of the survey of gastroenterologists

7.1.3 Strengths and limitations of the survey of GPs

7.1.4 Strengths and limitations of the laboratory data study

7.2 Recognising Coeliac Disease in New Zealand

7.2.1 GP survey data

7.2.2 Laboratory data

7.3 Diagnosing Coeliac Disease in New Zealand

7.3.1 Testing for CD: Survey data

7.3.2 Testing for CD: Laboratory data

7.3.3 Diagnosing CD: Survey data

7.3.4 Diagnosing CD: Laboratory data

7.3.5 The incidence of CD in three regions of New Zealand

7.3.6 When the diagnosis is uncertain: Gastroenterologist survey data
7.4 Managing Coeliac Disease in New Zealand .................................................. 343

7.4.1 Key variations in the management of CD ................................................. 344

7.4.2 Annual reviews ....................................................................................... 346

7.5 Why opinions and practices might differ .................................................. 347

Chapter 8: Conclusion ...................................................................................... 349

8.1 Recommendations to the New Zealand Society of Gastroenterologists ... 349

8.2 Recommendations to Coeliac New Zealand ................................................. 350

8.3 Recommendations for Future Research ..................................................... 351

8.4 Final comments .......................................................................................... 353

References ....................................................................................................... 355

Appendix A: Ethics Committee and Ngāi Tahu Committee Approvals .......... 383

Appendix B: Survey from Parakkal et al. .......................................................... 391

Appendix C: The RAND Appropriateness Method explained ....................... 399

Appendix D: The Survey for Gastroenterologists .......................................... 403

Appendix E: Invitation and reminder letters to gastroenterologists ............ 415

  Initial invitation ............................................................................................... 415

  First follow-up email .................................................................................. 416

  Second follow-up email ............................................................................. 416

  Letters to Auckland and female gastroenterologists ............................... 417

Appendix F: The survey of General Practitioners ......................................... 419

Appendix G: Emails and reminder letters to GPs .......................................... 428

  Initial email to GPs with both email and postal addresses available ....... 428

  Initial email to GPs with email address only ............................................. 429

  Reminder email to GPs with both email and postal addresses ............... 430

  Reminder email to GPs with email addresses only .................................. 431

  Reminder letter to GPs who received hard copy only .............................. 432

xii
List of Tables

Chapter 2
Table 2.1: Systems for describing intestinal mucosal changes seen in coeliac disease .......................................................... 23
Table 2.2: Coeliac antibody test characteristics .......................................................... 26
Table 2.3: CD Classifications used in the recent past .......................................................... 28
Table 2.4: CD Descriptors from the Oslo Definitions .......................................................... 31
Table 2.5: Global coeliac disease prevalence .......................................................... 51
Table 2.6: NICE data on CD prevalence associated with some pre-existing conditions .......................................................... 59
Table 2.7: Increasing incidence of CD evidenced in recent studies .......................................................... 60
Table 2.8: Symptoms and conditions associated with CD .......................................................... 62
Table 2.9: NICE Guidance on symptoms warranting testing for CD .......................................................... 67
Table 2.10: NICE Guidance on circumstances in which CD testing should be considered .......................................................... 67
Table 2.11: Gluten containing grains and products in which they are found ............ 78
Table 2.12: Comparative costs between gluten-containing and gluten-free products available in a New Zealand supermarket .......................................................... 87
Table 2.13: Novel treatment targets and proposed interventions .......................................................... 90

Chapter 3
Table 3.1: Content development for survey of gastroenterologists ......................... 119
Table 3.2: SCL Regional service provision .......................................................... 137

Chapter 4
Table 4.1: Demographic information of identified New Zealand Gastroenterologists (2013) .......................................................... 146
Table 4.2: Initial demographic information provided by survey participants .... 148
Table 4.3: Professional profiles of gastroenterology survey participants .............. 149
Table 4.4: Number of gastroenterologists seeing numbers of patients in differing contexts .......................................................... 150
Table 4.5: Factors influencing aspects of Lucy’s management in the year following CD diagnosis, with p-values .......................................................... 158
Table 4.6: Who should take responsibility for arranging follow-up tasks? ........160
Table 4.7: “Not necessary” responses compared with earlier “importance” responses ..........................................................................................................................................................161
Table 4.8: Discussions about joining CNZ, and testing relatives, among those who did not rate these tasks as important..........................................................................................................................................................................................................................................................163
Table 4.9: Factors influencing aspects of Lucy’s long-term management, with p-values ..........................................................................................................................................................................................................................................................................................................................169
Table 4.10: Factors influencing management actions when Joshua, an asymptomatic patient, has positive serology but normal histology, with p-values ..........................................................................................................................................................................................................................................................................................................................176
Table 4.11: Factors influencing management actions when Joshua is symptomatic and has positive serology but normal histology, with p-values ..........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................178
Table 4.12: Cross-tabulation of apparently contradictory question responses ....181

Chapter 5
Table 5.1: Mode of survey delivery and numbers of intended recipients for each ..........................................................................................................................................................................................................................................................................................................................191
Table 5.2: Modes of response to the survey of GPs from eligible respondents ....193
Table 5.3: GP survey recipient and respondent gender ..........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................194
Table 5.4: DHB regions of participants in the survey of GPs........................................195
Table 5.5: Participant professional profiles ..........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................196
Table 5.6: Likelihood of testing for CD in otherwise asymptomatic patients with the signs or symptoms listed; options most likely to lead to testing in bold ..........201
Table 5.7: Likelihood of testing for CD in otherwise asymptomatic patients with the conditions listed; conditions most likely to lead to testing in bold .................203
Table 5.8: Additional signs, symptoms, and conditions which lead to CD testing 205
Table 5.9: Collated score ranges for Questions 1 and 2 of the GP survey ..............208
Table 5.10: Comments relating to referral practice for patients with a positive coeliac test ..........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................213
Table 5.11: Likelihood that GPs will regard a range of test result options as confirming a patient has CD .................................................................220
Table 5.12: Factors influencing practices relating to diagnosing CD, with p-values ..........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................222
Table 5.13: Themes of comments about CD Annual Reviews ........................................226
Table 5.14: Management options that respondents would include in an annual review of CD patients ................................................................. 228
Table 5.15: Blood tests forming part of CD Annual Review ................................................. 229
Table 5.16: Characteristics of participants with coeliac patients compared with the overall respondent group in the survey of GPs ........................................ 232

Chapter 6
Table 6.1: Summary of SCL data included and excluded from analysis .................. 252
Table 6.2: Summary data relating to “testing events” (TE), total patients tested (TPT), and new patients tested (NPT), in Otago-Southland (OS), Nelson-Marlborough (NM), and South Canterbury (SC), by year ................................................................. 254
Table 6.3: Otago-Southland population rates of testing for CD, 2007 and 2015. 255
Table 6.4: Nelson-Marlborough and South Canterbury population rates of testing for CD, 2013 and 2015 .................................................................................................................. 257
Table 6.5: Hawkes Bay and Taupo population rates of testing for CD, first and last years of study period ................................................................................................. 258
Table 6.6: Female:Male ratios for CD testing, Otago-Southland 2007 – 2015 ...... 261
Table 6.7: Female:Male ratios for CD testing, Nelson-Marlborough and South Canterbury 2013 – 2015 .......................................................................................................................... 263
Table 6.8: Age range, mean (standard deviation; s.d.) and median age of patients tested for CD in Otago-Southland ........................................................................................................ 266
Table 6.9: Cumulative age ranges of patients tested for CD in other regions ....... 270
Table 6.10: Mean (standard deviation; s.d.) and median age of patients tested for CD in Nelson-Marlborough and South Canterbury, 2013 – 2015 .......................................................... 271
Table 6.11: Percentages of those tested for CD with prioritised ethnicity European (New Zealand or other) in Otago-Southland (OS), Hawkes Bay (HB), Taupo, Nelson-Marlborough (NM), and South Canterbury (SC) ................................................................................. 274
Table 6.12: Percentages of those tested for CD in each region with prioritised ethnicity New Zealand Māori ........................................................................................................ 274
Table 6.13: Origins of CD testing event requests in Otago-Southland, 2007 – 2015 .............................................................................................................................. 276
Table 6.15: Numbers of CD serology tests conducted by SCL per year, all regions
........................................................................................................................................280
Table 6.16: HLA test requests for Otago-Southland, Nelson-Marlborough, and South Canterbury........................................................................................................................................281
Table 6.17: Positive IgA-tTG results relative to all IgA-tTG tests performed in Otago-Southland, 2007–2015........................................................................................................................................285
Table 6.18: Positive IgA-tTG results relative to total IgA-tTG tests performed in Nelson-Marlborough and South Canterbury, 2013–2015 ........................................................................................................286
Table 6.19: Gender-specific analysis of new-patient tTG tests and positive new-patient tTG tests for Otago-Southland, 2007–2015 ........................................................................................................................................287
Table 6.20: Age-specific analysis of new-patient IgA-tTG tests and positive new-patient IgA-tTG tests for Otago-Southland, 2007–2015 ........................................................................................................................................288
Table 6.21: Correlation between EMA results and grouped positive IgA-tTG results ........................................................................................................................................290
Table 6.22: EMA positivity relative to low-high IgA-tTG values ........................................................................................................................................290
Table 6.23: Laboratory comments indicated by ****** ........................................................................................................................................292
Table 6.24: Repeat CD testing figures for Otago-Southland patients, 2007–2017 ........................................................................................................................................293
Table 6.25: Number of individual patients tested for CD more than once per year ........................................................................................................................................294
Table 6.26: Year-to-year tests for CD in Otago-Southland with year of first test identified ........................................................................................................................................295
Table 6.27: Summary data relating to Otago-Southland patients tested for CD in 2 or more years ........................................................................................................................................296
Table 6.28: Repeat tests per year as a proportion of patients tested per year by gender in Otago-Southland, 2007–2015 ........................................................................................................................................297
Table 6.29: Rates of duodenal biopsy for patients with raised IgA-tTG antibodies in Otago-Southland, 2007–2015 ........................................................................................................................................302
Table 6.30: Rates of duodenal biopsy for patients with raised IgA-tTG antibodies in Nelson-Marlborough, 2013–2015 ........................................................................................................................................304
Table 6.31: Rates of duodenal biopsy for patients with raised IgA-tTG antibodies in South Canterbury, 2013–2015 ........................................................................................................................................305
Table 6.32: Duodenal biopsy rate by gender, Otago-Southland ........................................................................................................................................305
Table 6.33: Duodenal biopsy rate per IgA-tTG grouping by age-group in Otago-Southland

Table 6.34: Overall duodenal biopsy rates by age-group for Nelson-Marlborough and South Canterbury

Table 6.35: Results for all CD-related duodenal biopsies, all regions combined

Table 6.36: Biopsy outcomes with respect to IgA-tTG levels, Otago-Southland, Nelson-Marlborough, and South Canterbury combined

Table 6.37: EMA results correlated with biopsy results, all regions

Table 6.38: Biopsy-proven CD incidence in Otago-Southland, 2007–2015


List of Figures

Chapter 2
Figure 2-1: The course of CD from Gee to the present day ........................................ 17
Figure 2-2: Constituents of wheat gluten ........................................................................ 19
Figure 2-3: Routes of passage across the epithelial barrier ........................................... 47
Figure 2-4: Inflammatory circuits in CD ........................................................................... 49
Figure 2-5: Contamination risks in the journey of gluten-free foods from field to plate ................................................................. 85

Chapter 3
Figure 3-1: Screen shot of opening page of online gastroenterology survey .......... 124
Figure 3-2: Delivering the questionnaire ........................................................................ 133

Chapter 4
Figure 4-1: Responses to the survey of New Zealand Gastroenterologists ............... 147
Figure 4-2: Sources of information about CD likely to be used by gastroenterologists .......................................................................................................................... 151
Figure 4-3: Importance of aspects of management in first 12 months of follow-up after CD diagnosis ................................................................................................................... 152
Figure 4-4: Preferred timing of follow-up IgA-tTG testing ............................................. 154
Figure 4-5: Importance of follow-up biopsy in the first 12 months after CD diagnosis ................................................................................................................................. 155
Figure 4-6: How often joining CNZ and testing first-degree relatives is discussed ........................................................................................................................................................................ 162
Figure 4-7: Likelihood these management issues will be commented on in letter to GP .............................................................................................................................................................. 164
Figure 4-8: Rating of importance of aspects of long-term management of CD ............ 165
Figure 4-9: Ratings of importance of an “Annual Review” of CD management .......... 165
Figure 4-10: Likelihood these long-term management issues will be commented on in letter to GP ................................................................................................................................. 166
Figure 4-11: The role of oats in the gluten-free diet ...................................................... 167
Figure 4-12: Rebiopsy practice when oats are included in the GFD .............................. 168
Figure 4-13: Rating of follow-up actions in context of an asymptomatic patient with normal biopsy result .................................................................................................................... 171
Figure 4-14: Advice to Joshua and his GP about likely diagnosis given normal biopsy
........................................................................................................................................172
Figure 4-15: Rating of follow-up actions in context of a symptomatic patient with normal biopsy result
........................................................................................................................................173
Figure 4-16: Comparison of likely or highly likely responses for undertaking particular actions in asymptomatic and symptomatic patients with a normal biopsy
........................................................................................................................................174
Figure 4-17: Comparison of advice most likely to be given to Joshua and his GP if he were asymptomatic or symptomatic ..................................................................................175
Figure 4-18: Likelihood of suggesting various actions to the GP of a patient declining biopsy
........................................................................................................................................179
Figure 4-19: Likelihood of advising GP to assume that the patient has CD, and to manage her accordingly ........................................................................................................180
Figure 4-20: Recommendations regarding quantity of bread (in slices per day) required for an adequate gluten challenge ..................................................................................183
Figure 4-21: Recommendations relating to the appropriate duration of a gluten challenge
........................................................................................................................................184

Chapter 5

Figure 5-1: Sample size information ..................................................................................190
Figure 5-2: Response rate calculations for the survey of GPs ........................................192
Figure 5-3: Ethnicity of GP survey respondents ..............................................................197
Figure 5-4: Predominant Socio-Economic Status of practice populations of GP survey respondents ..............................................................................................................198
Figure 5-5: Predominant ethnic make-up of practice populations of GP survey respondents ..........................................................................................................................198
Figure 5-6: Sources of information about CD utilised by GPs .......................................199
Figure 5-7: Comparative likelihood of testing for CD in the presence of specific signs and symptoms ..............................................................................................................202
Figure 5-8: Comparative likelihood of testing for CD in the presence of specific conditions ..........................................................................................................................204
Figure 5-9: Histogram showing frequency distribution of Question 1 cumulative scores
........................................................................................................................................206

xix
Figure 5-10: Histogram showing frequency distribution of Question 2 cumulative scores..........................................................207
Figure 5-11: Cumulative scores of likelihood of testing for CD in the presence of particular symptoms and conditions, among GP survey participants ..................209
Figure 5-12: Tests requested as part of initial testing for coeliac disease..............211
Figure 5-13: Frequency of referrals for gastroscopy when coeliac serology is positive. ..............................................................................................................................212
Figure 5-14: Advice about the timing of commencing a GFD with respect to having a biopsy ..................................................................................................................................215
Figure 5-15: Amount of gluten to reintroduce prior to testing for CD...............217
Figure 5-16: Required duration of gluten-containing diet prior to testing for CD ..................................................................................................................................218
Figure 5-17: Most popular sources of information regarding a gluten challenge .218
Figure 5-18: Collated responses of the likelihood that GPs will regard positive test results as confirming the diagnosis of CD .................................................................221
Figure 5-19: How necessary is an Annual Review of adult CD patients? ............224
Figure 5-20: Is an annual review something you try to do for your adult coeliac patients? ..................................................................................................................................227
Figure 5-21: Predominant SES of practice populations of all respondents compared with those with patients with CD .................................................................234
Figure 5-22: Predominant ethnic makeup of practice populations of all respondents compared with those with patients with CD .................................................................234
Figure 5-23: Person responsible for referring patients newly diagnosed with CD to a dietitian, and for applying for Special Authority numbers...........................................235
Figure 5-24: Patterns of referral for DEXA scanning among respondents with patients with CD ..................................................................................................................236
Figure 5-25: Likelihood of discussing the need for testing of first-degree relatives and of joining CNZ with adult patients newly diagnosed with CD ..................238
Figure 5-26: Frequency of review of adult patients specifically with respect to CD ..................................................................................................................................240
Figure 5-27: Frequency with which participants reinforce the importance of the GFD to their adult patients with CD ..............................................................................241
Figure 5-28: Coeliac serology retesting practices .............................................242
Figure 5-29: Frequency of testing adult patients with CD for associated conditions ................................................................. 243
Figure 5-30: Frequency of offering influenza and pneumococcal vaccinations to adult CD patients................................................................. 244

Chapter 6
Figure 6-1: Testing events and numbers of patients tested for CD by SCL in Otago-Southland, 2007 – 2015 ................................................................. 255
Figure 6-2: CD testing events for males and females in Otago-Southland, by year ................................................................................................. 259
Figure 6-3: Numbers of males and females tested for CD in Otago-Southland, by year ................................................................................................. 259
Figure 6-4: Numbers of males and females having first test for CD in Otago-Southland, by year ................................................................. 260
Figure 6-5: Comparison of new male and female patients testing in Otago-Southland, 2007 – 2015 ................................................................................................. 260
Figure 6-6: CD testing events for males and females in Nelson-Marlborough and South Canterbury, by year ................................................................. 262
Figure 6-7: Numbers of males and females tested for CD in Nelson-Marlborough and South Canterbury, by year ................................................................. 262
Figure 6-8: SCL CD testing events for males and females in Hawkes Bay, by year ................................................................................................. 264
Figure 6-9: SCL CD testing events for males and females in Taupo, by year ................................................................................................. 264
Figure 6-10: Numbers of males and females tested for CD by SCL in Hawkes Bay, by year ................................................................................................. 265
Figure 6-11: Numbers of males and females tested for CD by SCL in Taupo, by year ................................................................................................. 265
Figure 6-12: CD testing events in Otago-Southland grouped by age, per year ................................................................................................. 267
Figure 6-13: Number of first CD tests in Otago-Southland grouped by age, per year ................................................................................................. 268
Figure 6-14: Number of CD testing events in Otago-Southland per age-group, per year ................................................................................................. 269
Figure 6-15: Number of first CD tests in Otago-Southland per age-group, per year ................................................................................................. 269
Figure 6-16: Increases in numbers of testing events and first tests in Otago-Southland in each age-group, between 2007 and 2015..........................................................270
Figure 6-17: CD testing events per age-group in Nelson-Marlborough (NM) and South Canterbury (SC), 2013 – 2015..........................................................272
Figure 6-18: HLA requests in Otago-Southland each year, by requester ..................282
Figure 6-19: HLA requests for Nelson-Marlborough and South Canterbury each year, by requester ..........................................................283
Figure 6-20: Numbers of biopsy procedures performed per age-group in Otago-Southland on people with positive CD serology (or IgA deficiency), January 2007 – June 2016 ..................................................................................................................299
Figure 6-21: Changes over time of duodenal biopsy rates per IgA-tTG category, Otago-Southland 2007 – 2015..........................................................303
Figure 6-22: Annual total duodenal biopsy rates for Otago-Southland, 2007 – 2015 ..................................................................................................................304
Figure 6-23: Percentage of normal biopsies relative to low-high IgA-tTG levels.310
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACG</td>
<td>American College of Gastroenterology</td>
</tr>
<tr>
<td>AGA</td>
<td>Anti-gliadin antibodies</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen presenting cell</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>bpac(^{nz})</td>
<td>Best Practice Advocacy Centre of New Zealand</td>
</tr>
<tr>
<td>BSG</td>
<td>British Society of Gastroenterology</td>
</tr>
<tr>
<td>BSPGHAN</td>
<td>British Society for Paediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>CAP</td>
<td>Best Practice Advocacy Centre of New Zealand</td>
</tr>
<tr>
<td>CD</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>CDAT</td>
<td>Coeliac Disease Adherence Test</td>
</tr>
<tr>
<td>CDQ</td>
<td>Coeliac Disease Questionnaire</td>
</tr>
<tr>
<td>CDQL</td>
<td>Coeliac Disease Quality of Life questionnaire</td>
</tr>
<tr>
<td>CD-QOL</td>
<td>Coeliac Disease Quality of Life instrument</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CME</td>
<td>Continuing Medical Education</td>
</tr>
<tr>
<td>CNZ</td>
<td>Coeliac New Zealand</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual-energy Xray absorptiometry</td>
</tr>
<tr>
<td>DH</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>DHB</td>
<td>District Health Board</td>
</tr>
<tr>
<td>EATL</td>
<td>Enteropathy-associated T-cell lymphoma</td>
</tr>
<tr>
<td>EC</td>
<td>Epithelial cell</td>
</tr>
<tr>
<td>EMA</td>
<td>Endomysial antibodies</td>
</tr>
<tr>
<td>ESPGHAN</td>
<td>European Society for Paediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>FDA</td>
<td>Federal Drug Administration</td>
</tr>
<tr>
<td>FSANZ</td>
<td>Food Standards Australia New Zealand</td>
</tr>
<tr>
<td>GCED</td>
<td>Gluten Contamination Elimination Diet</td>
</tr>
<tr>
<td>GDG</td>
<td>Guidelines Development Group</td>
</tr>
<tr>
<td>GFD</td>
<td>gluten-free diet</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HB</td>
<td>Hawkes Bay</td>
</tr>
<tr>
<td>HMW</td>
<td>High molecular weight</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>IEC</td>
<td>Intestinal epithelial cell</td>
</tr>
<tr>
<td>IEL</td>
<td>Intraepithelial lymphocyte</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Interferon alpha</td>
</tr>
<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IL-15</td>
<td>Interleukin 15</td>
</tr>
<tr>
<td>IT</td>
<td>Information technology</td>
</tr>
<tr>
<td>LMW</td>
<td>Low molecular weight</td>
</tr>
<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NASPghAN</td>
<td>North American Society for Pediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>NG20</td>
<td>NICE Clinical Guideline 20</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NHI</td>
<td>National Health Index</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin's Lymphoma</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NK cells</td>
<td>Natural killer cells</td>
</tr>
<tr>
<td>NPT</td>
<td>New patients tested</td>
</tr>
<tr>
<td>NM</td>
<td>Nelson-Marlborough</td>
</tr>
<tr>
<td>NZMC</td>
<td>New Zealand Medical Council</td>
</tr>
<tr>
<td>NZSG</td>
<td>New Zealand Society of Gastroenterology</td>
</tr>
<tr>
<td>OS</td>
<td>Otago-Southland</td>
</tr>
<tr>
<td>PHARMAC</td>
<td>(New Zealand) Pharmaceutical Management Agency</td>
</tr>
<tr>
<td>POCT</td>
<td>Point-of-care testing</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RAM</td>
<td>RAND Appropriateness Method</td>
</tr>
<tr>
<td>RAS</td>
<td>RAND Appropriateness Scale</td>
</tr>
<tr>
<td>RCD</td>
<td>Refractory coeliac disease</td>
</tr>
<tr>
<td>RNZCGP</td>
<td>Royal New Zealand College of General Practitioners</td>
</tr>
<tr>
<td>SC</td>
<td>South Canterbury</td>
</tr>
<tr>
<td>SCL</td>
<td>Southern Community Laboratories</td>
</tr>
<tr>
<td>s.d.</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SIR</td>
<td>Standardised Incidence Ratios</td>
</tr>
<tr>
<td>SNZ</td>
<td>Statistics New Zealand</td>
</tr>
<tr>
<td>SSD</td>
<td>Super sensitive diet</td>
</tr>
<tr>
<td>T1DM</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>TE</td>
<td>Testing events</td>
</tr>
<tr>
<td>Acronym</td>
<td>Abbreviation/Definition</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>TPT</td>
<td>Total patients tested</td>
</tr>
<tr>
<td>tTG</td>
<td>Tissue transglutaminase-2</td>
</tr>
<tr>
<td>UCLA</td>
<td>University of California Los Angeles</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WGO</td>
<td>World Gastroenterology Organisation</td>
</tr>
</tbody>
</table>
In 1980, in the British Medical Journal, Swinson and Levi published a study on coeliac disease (CD) titled "Is Coeliac Disease Underdiagnosed?" They were reporting on work they had conducted investigating the prevalence of CD in their local district, having observed that their own hospital in Middlesex, England, was diagnosing many more patients than other hospitals in the region. One of the conclusions they reached was that CD was variably recognised by medical practitioners, which in turn led to variable rates of investigation and subsequent diagnosis. The extension of this, they suggested, was that perhaps CD was underdiagnosed. In the decades since their research was presented, their suggestion has been proven correct. The answer to the question posed in their title is a resounding “Yes”, as evidenced in numerous studies from around the world. (See for example Rubio-Tapia et al., Makharia et al., and Mustalahti et al.)

In 2004, aged in my mid-30s, I was diagnosed with CD. This came as a great surprise to me, although in retrospect it should not have done so. I had had symptoms for many years but had failed to identify them as such. But what surprised me more was that I was also a General Practitioner (GP), and had been for several of those years of symptoms. How had I not known what had been going on? And of more concern, if I had not been able to recognise CD in myself even though I was living with it, how many patients had I also failed to diagnose? As I began to discuss CD with colleagues it seemed that I was not alone in my ignorance. If that was the case, the implication was that there were people in our communities with CD who were receiving less than optimal care, perhaps not even realising that this was the cause of their illness. This would not have surprised those who had been studying CD, as it was by then a well-documented phenomenon.

This thesis, and the studies it describes, arose out of a desire to determine the scale of the phenomenon in New Zealand. There was no particular reason to expect the situation to be any different in this country, but I wanted to know to what extent was my failure to recognise CD simply a gap in my own knowledge? Or, as the literature from elsewhere suggests, was I but one of many doctors who have a CD-shaped blind spot? And if it transpired that such a blind spot does exist, what could and should be done about it?
1.1 A brief description of coeliac disease

Coeliac disease is an autoimmune condition that renders those who suffer from it unable to tolerate gluten, a group of proline- and glutamine-rich proteins found in wheat, barley, and rye. In genetically predisposed individuals, the small intestine is attacked by the immune system in a reaction triggered by ingested gluten. Detection of CD is generally achieved with blood tests that identify the presence of CD-specific antibodies, but confirmation of the diagnosis depends on the presence of certain histologic changes seen in biopsy samples taken from the duodenum of patients in whom the condition is suspected.\textsuperscript{5-11} It should be noted here that with the release of updated European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines in 2012,\textsuperscript{12} the requirement for biopsy confirmation in all circumstances has been called into question, at least for children. These guidelines are discussed in detail in Chapter Two of this thesis.

In the past CD was regarded as a relatively rare, purely gastroenterological disease, which predominantly affected children, especially those of Northern European or Celtic descent.\textsuperscript{13} These children became very unwell on the introduction of gluten into their diets, presenting with diarrhoea, malnutrition, and failure to thrive.\textsuperscript{14} In recent decades however, understanding of the condition has changed significantly.\textsuperscript{15}

Firstly, it is now known that CD can affect people at any age and stage of life, and does so in much greater numbers than previously believed.\textsuperscript{11} It is in fact one of the most common of the autoimmune conditions.\textsuperscript{16} The estimated prevalence of CD is widely accepted to be approximately 1\%, with evidence for this emerging in studies in New Zealand,\textsuperscript{17} Australia,\textsuperscript{18} the United States of America,\textsuperscript{2} and countries across Europe and Scandinavia.\textsuperscript{4} Coeliac disease has also been found to be a cause of morbidity in countries in both South and West Asia, such as India and Iran,\textsuperscript{19,20} and parts of North Africa and the Middle East.\textsuperscript{21} As already noted, there is also widespread evidence that the majority of people with the condition remain undiagnosed.

Secondly, it is recognised that, while the presence of gut damage remains one of the cornerstones of diagnosis (and biopsies of the small intestinal mucosa are generally still required to confirm this), the range of symptoms with which patients
can and do present is much greater than previously thought. These may include diarrhoea or constipation, vomiting, persistent fatigue, or neurological symptoms such as polyneuropathy.\textsuperscript{22} It is perhaps for this reason that it is so readily overlooked.\textsuperscript{23,24}

Thirdly, it is now clear that people with CD are at increased risk of developing other conditions such as anaemia, thyroid disease, osteoporosis and, on occasion, intestinal lymphoma.\textsuperscript{25} While this risk may be somewhat mitigated by the implementation of a gluten-free diet (GFD),\textsuperscript{26,27} which remains the only treatment available for CD, the implication is that it is not sufficient to assume that once on a GFD, the coeliac patient will be well. Management thus needs to be seen much more broadly than simply advising a GFD and then leaving patients to it.\textsuperscript{28-30}

To summarise: CD is common across ages and nations and is chameleon in its clinical manifestations and, as a consequence of this, is substantially underdiagnosed. Treatment revolves around removing the autoimmune trigger (gluten) from the patient’s diet, but should extend beyond this to managing the risk of potential complications. All of these issues are discussed in greater depth in Chapter Two.

1.2 Confirming the need for the present project

Following my diagnosis, I became involved with Coeliac New Zealand (CNZ), a not-for-profit organisation that supports people with CD. It quickly became apparent that this organisation was, and is, firmly of the view that GPs in New Zealand do not know enough about CD. The organisation made, and continues to make, statements such as the following:

Public recognition of coeliac disease and the potential reactions to gluten...have never been higher, yet awareness of the condition among medical professionals continues to be low. Coeliac disease remains one of the most underdiagnosed conditions in New Zealand and Australia. (CNZ Newsletter March 2015)

And again the following month:

With an estimated 65,000 kiwis having coeliac disease and 80% of those not even knowing, coeliac disease remains one of the most underdiagnosed conditions in New Zealand and Australia. Recognition of the condition among medical professionals also continues to be low. (CNZ Newsletter April 2015)
Though recent, these comments capture a sentiment that has prevailed over many years, fuelled by member experience and Australian research (among others) that continues to point to underdiagnosis.\textsuperscript{18}

Stories abound of members of CNZ experiencing years of ill-health and being given multiple alternative diagnoses before their CD was identified; of doctors (usually GPs) giving misinformation about when and how to test for the condition; and of there being little in the way of ongoing review or support once the diagnosis had been made. The substance of these anecdotes was borne out in a survey of CNZ members conducted in 2012 by University of Otago Masters of Dietetics student Kiri Sharp.\textsuperscript{31} In that survey, a sample group of over 900 CNZ members reported a mean length of time from the onset of symptoms to CD diagnosis of 11.6 years. A third of respondents reported consulting with two or more family doctors before the diagnosis was made. Alternative diagnoses they had attracted in the meantime included anaemia, stress, depression, and irritable bowel syndrome.

In New Zealand, gastroenterologists are the clinicians who perform small intestinal biopsies to confirm the diagnosis, and, together with paediatricians who look after coeliac children, have traditionally been regarded as the specialists with respect to CD. However, as the clinical face of CD has changed over the years, it has increasingly become the domain of primary care practitioners (in New Zealand and elsewhere) to identify those in whom the diagnosis should be considered.\textsuperscript{32} They need to recognise symptoms that could be explained by CD, and appropriately test patients to determine who needs to be referred for endoscopy. It is in the primary care setting that the vast majority of patients will first present their symptoms, and to which they will return when the diagnosis has been made.

Sharp’s evidence, which she has since published,\textsuperscript{33} signifies that patients’ symptoms have gone unrecognised as being indicative of CD, and raises questions about the quality and consistency of care that coeliac patients receive. In short, it suggests that New Zealand is indeed no different from elsewhere, and that CD in this country is both underdiagnosed and managed sub-optimally. Her research would also seem to vindicate CNZ’s concerns about GP knowledge. From this a number of questions arise about the nature of the limitations of that knowledge, and about the configuration of the CD blind spot in primary care. This thesis seeks to answer those questions.
1.3 Previous CD research with a primary care focus

Over the many decades in which the study of CD has been occurring, and among the many thousands of research papers published about the condition, only a tiny proportion of the work reported on has been conducted in the primary care setting. And while it may be tempting to attribute this to the fact that much of the research relating to CD has come from the United States of America (USA), where primary care and family medicine are comparatively less well developed than in other countries, this does not stand up to scrutiny. According to work published by Narotsky et al., the United Kingdom (UK) and Italy, where primary care is well established, were two of the top three sources of CD publications (the other being the USA) in the period 1995 to 2009. The more plausible explanation is that the great majority of research relating to CD has focused on questions relating to pathogenesis, diagnosis (including diagnostic criteria and prevalence), and principles of management, much of which has required histological data to test hypotheses. These data are of necessity usually generated in secondary and tertiary care settings.

The relatively few studies undertaken with a primary care focus have generally investigated rates of recognition of CD (analysing testing and referral data), and patterns of presentation among people with the condition. These emphases have been adopted as a means of quantifying levels of undiagnosed disease, and to evaluate the impact of case-finding strategies in particular. A more recent study by Spencer et al. investigated family physicians in the USA, using a survey to evaluate their likelihood of testing for CD among patients with iron deficiency anaemia.

In addition to these studies, information from the UK GP Research Database has been utilised to try and quantify healthcare costs of patients before and after the diagnosis of CD, and general practice data have sometimes been included in wider incidence studies, such as that conducted in Wales by Hurley et al. One study in Scotland has also looked at prescribing habits relating to gluten-free foods, finding that there was significant under-prescribing compared with local guidelines, although the authors did not draw any conclusions about why this might be.
Point-of-care testing (POCT) as a means for increasing the diagnosis of CD has also been evaluated with a primary care focus. In an early study of this technology, Korponay-Szabó and colleagues investigated the efficacy of POCT in the hands of district nurses in Hungary, while a more recent “proof of concept” study by Urwin et al. explored the role of community pharmacists in the UK in identifying people who may have CD. Both studies suggest that POCT used by healthcare professionals other than doctors may be a useful way of reaching and recognising undiagnosed CD patients, although a relatively recent review of the technology (for primary care users) warns that negative tests cannot be relied upon to rule out CD.

There have only been two studies that have explicitly examined what primary care doctors know about CD: one in North America, which involved internists and family doctors caring for adults, and one in Italy, involving family paediatricians. Other projects undertaken in this setting could, however, be regarded as reporting proxy measures of knowledge. One team of Italian researchers, led by Lanzarotto, were quite specific about this. They identified far fewer people with confirmed CD than expected based on assumed community prevalence data, and found that nearly a third of these people had not received appropriate dietary management. Based on these findings they called for increased awareness about CD symptomatology and management, to ameliorate “the under diagnosis of celiac disease in the primary care setting” that is “compounded by mismanagement”.

In Finland, where considerable effort over many years has gone into educating physicians about CD, Collin et al. investigated the impact of this effort. They found that in Tampere, the region in which there had been the greatest focus on physician education, the prevalence of diagnosed CD had risen to 0.7%, not far short of the 1.1% figure found in population-based screening studies. This, they said, was “achieved mainly by increasing alertness for celiac disease among health care staff.” They further asserted that “if celiac disease is to be detected extensively, this has to take place in primary health care.”

One further study, which sought to understand why the diagnosis of CD is so frequently missed in general practice, was undertaken by Kostopoulou and colleagues. The focus of their research was on the diagnostic reasoning process, and they included a scenario on CD in a larger project they were conducting on diagnosis in general. In this study, despite the presence of clinical cues, the majority
of family physicians participating did not think of CD as a possible explanation for the patient’s presentation. This made it impossible for the diagnosis to be reached.

1.4 Investigating knowledge and practice about coeliac disease

Despite the widespread recognition that CD is difficult to recognise and underdiagnosed, there has been very little research carried out to investigate what doctors (or any health professionals) actually know about, or how they practise, with respect to CD. Within the English language literature there have only been seven such studies published: two involving gastroenterologists;55,56 two involving paediatricians;51,57 two involving primary care physicians (as mentioned in the previous section);43,50 and a recent study in India,58 which attempted to quantify knowledge of CD among all physicians in that country. Unfortunately this project, which was based around an emailed questionnaire, was hampered by a very poor response rate, with only 10% of surveys returned.

The study by Kostopoulou et al.54 discussed in the preceding section could also be considered as having explored clinicians’ practice relating to CD, and one other study,59 which endeavoured to quantify how often haematologists consider CD as a cause for iron deficiency anaemia, could also broadly be described as assessing knowledge of CD. As with the Indian study, this too relied on an email survey, and was also limited by a poor response rate (of 8.5%).

Perhaps not surprisingly, all but one of these knowledge studies have demonstrated that there are wide variations in practice among the professionals studied, and/or deficits in practitioner knowledge about CD. It would seem also that all aspects of CD are affected, as the different studies have had a range of foci. So, for example, the gastroenterologist survey conducted by Silvester and Rashid focused on the management of CD in Canada,55 while Zipser et al.50 investigated awareness of CD by surveying primary care physicians in the USA about a number of variables associated with the condition, such as symptoms, complications and co-morbidities. The former found that gastroenterologists in Canada varied widely in their practice, and often diverged from the guidelines available at the time,55 while the latter showed that nearly two-thirds of respondents were unaware that CD could present in adulthood, and that few were aware of the association between CD and other conditions such as Type 1 Diabetes Mellitus (T1DM).50 Similarly, paediatricians in
Brazil surveyed by Vieira et al.\textsuperscript{57} were described as having “superficial information about CD” (p.799), with (for example) only 22\% of respondents acknowledging that CD could be asymptomatic, and the majority being unaware of an increased association between CD and several other conditions. The USA family physician study by Spencer et al.\textsuperscript{43} found a majority of their participants would start a GFD in patients with positive coeliac blood tests, before the diagnosis had been confirmed by histology.

The exception was a piece of work carried out among family paediatricians in the Puglia region of Italy by Fortunato et al.\textsuperscript{51} In this survey-based study, which had a 37\% response rate, participants were asked to rate their level of knowledge about CD as high, medium, low, or none. Their responses were linked to the number of CD patients they tended to see, about whom they had also been asked to provide information. The great majority reported their knowledge levels as medium or high with respect to making the diagnosis, although the authors did suggest that “they were probably missing the CD diagnosis in some children with atypical symptoms as the proportion of children typical symptoms [sic] was higher than what has been shown in screening studies.”\textsuperscript{51}(p.4 of 6)

Chapter Three of this thesis, which describes the methods employed for this project, will include details about how some of these existing studies informed the present work.

\textbf{1.5 The research questions formally described}

This project arose in the context described in the preceding sections. Its principal task was to describe what is happening in New Zealand with regards to the recognition, diagnosis, and management of CD, particularly as it affects adults. While not excluding consideration of CD in children, the emphasis was placed on CD in adult patients for the following reasons: they are the patients who report much longer delays to diagnosis;\textsuperscript{33} recognition that CD can develop and present in adulthood has only relatively recently become widely known;\textsuperscript{60} and the ongoing care of adult patients with CD is much more likely to reside with GPs than when it arises in childhood, when paediatricians maintain oversight of management for some time. (Although during the course of preparing this thesis this circumstance
has changed in New Zealand, with an increasing expectation emerging that GPs will also assume responsibility for the care of children with CD.

At the project’s heart is the question of knowledge, which gave rise to the hypothesis to be tested: **that GPs in New Zealand have limited disease-specific knowledge about CD.** If this hypothesis were to be correct, then this might be evidenced by the following:

a) CD is under recognised and/or
b) CD is underdiagnosed and/or
c) CD is sub-optimally managed.

A number of research questions were formulated to capture information about these issues.

The first major question pertained to GPs: *What do GPs in New Zealand know about coeliac disease?*

This was broken down into subsidiary questions:

- Whom do they test, and under what clinical circumstances will they test them?
- On what clinical information do they base decisions about diagnosis?
- How do they manage patients with the condition?
- From where (or whom) do they get their information about these issues?

A second major question related to the practice of gastroenterologists with respect to CD, specifically: *How do gastroenterologists in New Zealand manage the condition?*

This was important to understand because they are the secondary care providers most closely involved in looking after adult patients with CD, and their practice is most likely to influence that of GPs. In addition to this, the management of adult CD is not solely the domain or responsibility of GPs; and until relatively recently there has been a dearth of evidence-based guidelines about the management of CD, increasing the likelihood that such management may to some degree be based on opinion.
The third major question that emerged from consideration of the central hypothesis was: *Is CD in this country really as underdiagnosed as asserted by CNZ, and as it has been demonstrated to be in prevalence studies in other countries?* That is: *What is the prevalence of diagnosed CD in New Zealand today?*

To explore these questions three separate investigations were undertaken: a survey of New Zealand gastroenterologists; a survey of New Zealand GPs; and an interrogation of ten years of laboratory data relating to testing for CD. Together these studies were designed to provide the evidence necessary to test the project’s overarching hypothesis.

In the course of developing the study to answer the question relating to underdiagnosis, it emerged that the data were not readily available to enable an accurate calculation of a prevalence figure. The laboratory data that were accessible were limited to certain regions, and to the preceding decade, meaning that a number of assumptions would be required to generate such a figure. It would, however, be possible to calculate the incidence of CD in the regions from which the data arose, and to evaluate patterns of testing as a marker of practitioner knowledge, so this is what was done. These issues are discussed in more detail in Chapter Three.

### 1.6 Outline of the thesis

This thesis describes and brings together the three studies conducted to address the research questions outlined above. Following this introductory chapter, Chapter Two expands the definition of CD by drawing from the extensive literature that has been written about the many aspects of the condition: history, pathogenesis, prevalence, presentation, diagnosis, management, and complications. CD research that has been carried out in New Zealand is incorporated into the relevant sections of the chapter.

Chapter Three is a description of the methods employed in each of the three studies of this project. It provides background to why particular methods were chosen, and identifies some of the challenges that arose during implementation.

Chapters Four, Five, and Six separately present the results of the gastroenterologist, GP, and laboratory studies respectively. Presenting these results in individual chapters has been done to simplify the structure of this part of the
thesis, which otherwise risked becoming unwieldy. In addition to this, some very specific actions relating to each study, but that might be more strictly regarded as “methods”, have been included in the relevant results chapters. This has been done to assist the reader with following what was done at certain junctures.

The results chapters are followed by Chapter Seven, which discusses the important findings of each study. These are considered in the context of the recent literature, and are drawn together to provide a synthesis of what they collectively reveal about the recognition, diagnosis, and management of CD in New Zealand. The strengths and limitations of each study, and the project as a whole, are also considered.

The thesis concludes with Chapter Eight, in which the central hypothesis tested is considered in the light of the data generated by the three studies. The chapter concludes with recommendations for changes in practice that could improve the care of patients with CD, and gives some suggestions for future directions in research.

1.6.1 Conventions followed in this thesis

Throughout this work I have followed the University of Otago’s thesis guidelines with respect to formatting, and American Medical Association Manual of Style conventions relating to the use of voice, grammar, numerals, and punctuation such as quotation marks. I have used the first-person pronoun on occasions (such as this) to assist with clarity, particularly when discussing actions that I took during each phase of the research.

Throughout this thesis the word “gluten” is intended to mean the collective group of proteins found in wheat, barley, and rye, which are responsible for triggering the coeliac reaction. The word “coeliac” is spelled according to the British convention, except in direct quotations from works that utilise the North American spelling “celiac”.

11
Chapter 2: About Coeliac Disease

2.1 Introduction

Coeliac disease has a long and complex history about which much has been written. In recent decades it has also been the subject of a burgeoning research programme, driven in part by the search for a treatment that would remove (or at least ease) the requirement for people with the condition to adhere to a strictly gluten-free diet for life, and partly because CD has become an exemplar of autoimmune disease. It has a known trigger (gluten), the mechanism of injury induced by that trigger has been well characterised, in the majority of patients much of the harm caused is reversed on removal of the trigger, and many of the genetic prerequisites for developing the condition have been identified. It is also one of the most common autoimmune conditions, and its prevalence is increasing, and it is seen by many as a condition that has the potential to unlock at least some of the mysteries of autoimmune disease more generally. Ovid Medline searches on “coeliac disease” and “celiac disease” elicit many thousands of articles covering a vast array of research into the condition. Every year several hundred more titles are added. Similarly, a Google Scholar search (in April 2016) for only those articles with either “coeliac disease” or “celiac disease” included in the title generated a list with over 12,000 hits. At the time of searching, 183 of these articles had been added in 2016.

2.1.1 Search strategy

Given the huge amount that has been published on CD, material for this chapter was gathered in a range of ways, starting with review articles in the major medical journals. New reviews were added as these were published during the course of this project. Frequently cited references from these articles were followed-up and reviewed. In addition to this, key journals including Gut, Gastroenterology, The American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, The Journal of Pediatric Gastroenterology and Nutrition, and Alimentary Pharmacology and Therapeutics, were searched. Special editions relating to CD that featured in the journals Seminars in Immunopathology, and Best Practice and Research Clinical Gastroenterology, were also consulted, and searches were made for publications by known experts in the field. As guidelines documents became
available, these too were consulted.\textsuperscript{12,67-72} For any work retrieved, references cited were reviewed, and those that were of particular relevance to this project were also obtained. Ovid Medline searches on specific sub-topics were also conducted, but the primary focus of literature selected for this review largely remained on key authors and/or key journals. As this project spanned several years, these search processes were repeated every six to twelve months.

2.2 The History of Coeliac Disease

As with many conditions, CD has its origins in antiquity. This is not unexpected given that wheat, the principal source of gluten, has been a part of the human diet for millennia. Approximately 10,000 years ago, in the Neolithic period, humankind began the transition from living in small, nomadic, predominantly hunter-gatherer groups, to settling in larger agriculture-based communities.\textsuperscript{73} At about this point in time the cultivation of wheat began in the area known as the Fertile Crescent, a sweep of land in the region of Egypt and Mesopotamia and incorporating the Tigris and Euphrates rivers. This led to an increasing dietary dependence on wheat (and the related grains barley and rye), opening the way for CD (and other wheat-induced conditions) to develop. In fact, this represents what some have described as an “evolutionary paradox”,\textsuperscript{74}(p.1) given that CD (especially when it is untreated) renders those with the condition weak and ill, and sometimes infertile. Where this might have been expected to exert evolutionary pressure against the continuation of the condition, CD remains prevalent across the globe, including in countries in Europe and the Near East that have “long histories of wheat agriculture”.\textsuperscript{74}(p.1) It has been postulated by some, such as Abadie et al.\textsuperscript{75} and Lionetti et al.,\textsuperscript{76} that this is a consequence of advantageous immune reactions also conferred on those early communities by the components of the immune system responsible for CD.

The first written description of what is generally accepted to be CD comes from the noted physician Aretæus of Cappadocia, who lived and wrote in the second century CE (or possibly the first, the dates are contested).\textsuperscript{77} What remained of his work was translated into English by Francis Adams, and published in 1856 by the Sydenham Society of London.\textsuperscript{78} In Chapter VII, Book II of \textit{On the Causes and Symptoms of Chronic Disease}, Aretæus describes “the Coeliac Affection”. (Coeliac here has been translated by Adams from the Greek \textit{κοιλιακός}, which also means
abdominal or “of the bowels”). He wrote that this was a “very protracted and intractable illness” in which:

The stomach being the digestive organ, labours in digestion, when diarrhoea seizes the patient. Diarrhoea consists in the discharge of undigested food in a fluid state; and if this does not proceed from a slight cause of only one or two days’ duration; and if, in addition, the patient’s general system be debilitated by atrophy of the body, the Coeliac disease of a chronic nature is formed...\textsuperscript{78}(p.350)

He went on to describe the range of symptoms he had observed, namely that “the bowels rumble, evacuations are flatulent, thick, fluid or clayey”; that the patient may experience “heavy pain of the stomach now and then”; and that he or she was “emaciated and atrophied, pale, feeble, incapable of performing any of his accustomed works.” In addition to this, he noted that “[t]his illness is familiar to old persons, and to women rather than men”.\textsuperscript{(p.351)} The predominance of CD as an illness affecting women continues to this day, and there is evidence that it is a condition that ought not to be overlooked in the elderly, as its incidence among this group is increasing over time.\textsuperscript{79,80} And while some, such as Schuppan et al.,\textsuperscript{81} comment that Aretæus related the condition to diet (which is now known to be true), this needs to be considered in the context in which Aretæus was practising and writing. At that time one of the principal explanations for disease was that it was caused by a disruption of the balance that existed between “pneuma” and “the humors”. Dietary deficiencies were believed to be one of the leading factors in such disequilibrium occurring, thus in treating the majority of the sick there was “above all, an emphasis on dietary regimen.”\textsuperscript{77}(p.32)

That CD has an ancient history is supported by the discovery in 2008 of the remains of a young woman who lived in Cosa, Italy, in the first century CE.\textsuperscript{82} She was short and had fragile bones, and the enamel on her teeth was poorly formed. It is likely that she had suffered from severe malnutrition. She had lived in a region in which the economy was based on olives and wheat, and when her remains were recovered, it was hypothesised that she had had CD. It was postulated that the wealth of her family, as evidenced by the quality of her tomb and by the jewellery with which she had been buried, had ensured that she had a “good amount of wheat in her diet”.\textsuperscript{(p.502)} Hers are the only remains found at the site that showed evidence of malnutrition, and subsequent work on her DNA conducted by the team who
discovered her detected the presence of Human Leukocyte Antigen (HLA) DQ2.5, one of the genetic haplotypes associated with CD.83

Following Aretæus, it was not until 1888 that CD once again featured in the medical literature, when Dr Samuel Gee published in the *St Bartholomew’s Hospital Reports* the text of a lecture “On the Coeliac Affection” that he had given the previous year.84 It is generally accepted that he chose his title with Aretæus (and perhaps also his translator, Adams) in mind.85 In their respective histories of CD, both Dowd85 and Paveley84 note that Gee was the first person to signal that CD affected people of all ages, and that it was “especially apt to affect children between one and five years old.”84(p.1646) Gee’s very careful description of the condition, reproduced by both authors, is as follows:

There is a kind of chronic indigestion which is met with in persons of all ages...Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking,...the food having undergone putrefaction rather than concoction.84(p.1646),85(p.46)

In addition to this he noted that children with the condition were pale and weak, with muscle wasting,85 observations that are consistent with malnutrition. And although the cause of CD was still more than 50 years away from being identified, Gee’s clinical instinct was that treatment of the condition resided with dietary interventions. He experimented with putting his patients on a range of diets, including one child “who was fed upon a quart of the best Dutch mussels daily” and “throve wonderfully” until the season was over. Perhaps not surprisingly the child refused to go back to this diet the following season, and Gee commented in his paper that this was “an experiment I have not yet been able to repeat.”84(p.1647)

Following Gee’s description of CD, interest in the condition slowly and steadily increased, as discussed by Paveley and, among others, Auricchio and Troncone,60 Losowsky,86 and Tommasini et al.87 Each of these writers begins their narrative with Aretæus and moves on to Gee. From there they trace similar paths, summarised on the following page. (Figure 2-1)
1889
• R.A. Gibbons reports on the coeliac affection in children, describing four cases he had managed with diets in which “farinaceous foods” were to be limited, as recommended by Gee. He suggests that “a functional disturbance of the nervous supply” of the abdominal organs is cause of the disease.64 (p.1647)

1903
• W.B. Cheadle gives a lecture at St Mary’s Medical School in which he discusses a condition called “acholia”, so named because of the very pale stools which suggest an absence of bile. He speculates that “difficult dentition” might play a role in the aetiology of the condition.64 (p.1647)

1908
• C.A. Herter postulates that chronic inflammation of the intestine due to overgrowth of intestinal flora is to blame, and coins the name “Intestinal Infantilism” (after bacillus infantilis). He is the first to write of the condition in the US literature, and suggests that carbohydrates are less well tolerated than proteins and fats.60,86

1918
• G.F. Still gives a series of lectures in London about “coeliac disease or intestinal infantilism, name it what you will”, in which he draws attention to the “surprising inconsistence of the child’s size with its age”.64 (p.1647) He notes in particular that bread is poorly tolerated.64,66

1921
• J. Howland delivers an address to the American Pediatric Society on the “Prolonged Intolerance to Carbohydrates”5, including a case presentation of a child with similar symptoms to those earlier described by Herter. He recommends a diet which “rigourously excludes” carbohydrates, instead relying on proteins as the primary source of nutrition.68

1924
• S. Haas promulgates “the banana diet” on the back of heavy promotion of bananas by the United Fruit Company (UFC), which had included multiple endorsements from the medical profession about their nutritive value. For children with CD he advocates a diet restricted to a small range of protein sources, and several bananas a day. He becomes closely allied with the UFC.64,88

1940s
• W. Dicke makes the link between “Gee-Herter’s Disease” (CD) and wheat. He publishes his first report on the wheat-free diet in 1941, based on experiments he had conducted in the 1930s. The outbreak of war and ensuing grain shortages in Holland confirms his theory.60 In the US the war leads to a banana shortage, impacting celiac children following Haas’ diet.64,88

Early 1950s
• W. Dicke and J. van de Kamer develop a technique for measuring faecal fat content. They also identify gliadin as the component of wheat which is toxic in CD. In 1952 in the UK C. Anderson et al. confirm the link, replicating work by Dicke (not published in English until 1953), measuring changes in faecal fat content with diet.60,84,86,87 The GFD as treatment emerges.

Mid- to Late 1950s
• J.W. Paulley confirms characteristic histological changes of CD in samples taken from patients at laparotomy. In 1956 M. Shiner develops a “biopsy tube” for obtaining duodenal samples. In 1957 W.H. Crosby and H.W. Kugler develop the more flexible Crosby Capsule; J.M. French links adult ideopathic steatorrhoea to CD when he observes patients recovering on a wheat-free diet.60,84,86

1960s and beyond
• With the identification of antibodies to gliadin, endomysium, and tissue transglutaminase, and the recognition of specific genetic markers, CD is redefined as an inherited autoimmune disease. The ability to test for the presence of these antibodies, and the advent of flexible endoscopy revolutionises the diagnostic process. The search for alternative treatments continues ...

Figure 2-1: The course of CD from Gee to the present day
An additional player not mentioned by these writers but discussed by Emily Abel, is Luther Emmett Holt, a North American paediatrician of the late nineteenth and early twentieth centuries. While Gee might be considered the father of modern discussions of CD in Europe and the UK, it was Holt, as Professor of Diseases in Children at the Babies’ Hospital of the City of New York, and as one of the inaugurators of the Rockefeller Institute of Medical Research, who drove North American progress in trying to understand and better manage the condition. What Gee had referred to as the coeliac affection, Holt called “chronic intestinal indigestion”. His descriptions of children with the condition mirrored Gee’s, and while he did not undertake research into the disease himself, he encouraged Herter, Howland, and Haas to do so.\(^\text{88}^\text{(p.6)}\)

### 2.2.1 What is gluten?

One of the most crucial steps in unlocking the puzzle of CD was made by Willem Dicke, when he identified wheat as the trigger for the clinical signs he observed in his patients. Together with his colleagues Jan van de Kamer and others, he followed this by isolating gluten (and in particular the gliadin fraction) as the harmful constituent of wheat.\(^\text{90}\)

Gluten is the major storage protein in wheat, comprising approximately 80% of the total grain protein (which in turn constitutes between 8-15% of the grain, depending on its variety)\(^\text{73,91}\). Gluten itself has two principal components – the alcohol-soluble gliadin monomers, and the alcohol-insoluble glutenin polymers, both of which are sub-divided further. (Figure 2-2).
Figure 2-2: Constituents of wheat gluten

*Low- and high-molecular-weight, respectively*

The gliadins and LMW glutenins are all rich in the amino acids proline and glutamine, and it is this aspect of their make-up that renders them toxic to patients with CD. The α- and ω-gliadins contain the highest number of proline residues and are known to be the most immunogenic of the prolams (the collective name for alcohol-soluble, proline- and glutamine-rich peptides). The HMW glutenins contain less proline, and would also seem to be less harmful to CD patients. Proteins that are high in proline are relatively resistant to digestion (proteolysis) in the small intestine, resulting in moderately large peptide groups remaining in the lumen. As discussed in more detail in a later section of this chapter, in susceptible individuals, these peptide molecules are the progenitors of the CD pathogenic process.

Gluten is also the collective name given to the principal storage proteins found in rye and barley, which are also toxic to people with CD. In the past this group also included oats. The secalins in rye, and the hordeins in barley are analogous to the gliadins in wheat, and they too are rich in proline and glutamine. Both these grains are closely related to wheat, having evolved from a common ancestor in the grass family. Oats are more distantly related to wheat, and their potential toxicity in CD remains contested. The storage proteins in oats are the avenins, and while they have some similarities to the gluten proteins of the other grains already discussed, their differences outnumber these. Additionally, avenins form a much smaller portion of the total protein component in oats than do the analogous protein groups in wheat,
rye and barley. While it is recognised that a small percentage of people with CD (perhaps 5%) are truly sensitive to oats, it is generally accepted that the toxicity attributed to oats in the past was likely to have been due to wheat contamination.

### 2.2.2 The Coeliac enteropathy

As alluded to in Figure 2-1, in the mid-1950s J.W. Paulley confirmed that patients with idiopathic steatorrhoea (later to be recognised as adult CD) displayed a typical pattern of histological changes in their intestinal mucosa. These changes had been noted for some time in autopsy samples, but it was not clear whether they were genuine markers of CD, or if they were a post mortem artefact of autolysis. Using tissue obtained from steatorrhoea patients undergoing laparotomy, Paulley was able to demonstrate that the changes that had been previously observed were indeed present in patients with symptoms akin to those earlier described by Samuel Gee. He described finding evidence of “chronic inflammation of the jejunum”, and detailed his observations further:

> The steatorrhoea villi were approximately double the width of the controls. Other obvious differences are in the shape and cellularity of the villi, the presence of large numbers of inflammatory cells in the mucosa...

In one case he noted that

> [t]he inflammatory process had advanced to a stage of atrophy and fibrosis, and the villi were short and thick....and the delicate conifer-like appearance of the normal jejunal mucosa...was missing. (p.1321)

These appearances of mucosal inflammation quickly became acknowledged as typical in such patients, and by 1958, following the advent of instruments enabling per-oral biopsies to be taken from the jejunum, W.T. Cooke was describing “mucosal, mainly villous atrophy affecting the jejunum” as “the characteristic feature of adult coeliac disease.” (p.263)

The histological features of CD identified by Paulley, Cooke and others remain at the centre of descriptions of the condition today, albeit in more nuanced forms. Over time it has become appreciated that there is a spectrum of change that can be seen at the histological level, just as it has also been clearly established that there is a spectrum of symptoms with which patients present.

There are now three established classification systems for grading histological changes. The first to be developed was by Michael Marsh in the early 1990s.
Marsh was motivated by the desire to add rigour to the process of describing mucosal changes in the biopsies of CD patients and, as he has written more recently, by the hope that to do so might lead to renewed interest in the underlying pathogenic processes at work.\textsuperscript{103} He strongly advocated for a system that took account of the spectrum of observable histopathological changes, which he grouped according to the degree of mucosal damage detected. As he put it in his original paper, he “arbitrarily” labelled these groupings “infiltrative, hyperplastic, and destructive (flat)”.\textsuperscript{102}(p.338) The determinants of damage that were to be routinely noted under his proposed classifications were the numbers of intraepithelial lymphocytes (IELs), and the architecture of the crypts and villi present in biopsy specimens. Marsh suggested two additional labels: “pre-infiltrative” for those biopsy samples that were indistinguishable from normal but had come from patients with other gluten-sensitive conditions (usually dermatitis herpetiformis); and “hypoplastic” for the most severely damaged mucosa, arising in patients unresponsive to treatment with the GFD.\textsuperscript{102} This lesion is mostly irreversible and strongly associated with intestinal lymphoma.

The Marsh classification system was adopted by pathologists until modifications were proposed in 1999 by Oberhuber et al.,\textsuperscript{104} who sought to simplify the system while at the same time allowing for more discrimination of findings at the severe end of the spectrum. They also included numeric values for what constituted increased IELs, including in their discussion paper a description of how they had arrived at their suggested cut-off figure of 40 IELs per 100 epithelial cells (EC).\textsuperscript{104}(p.1186) Their recommendations were widely embraced and the “Marsh-Oberhuber” (or “Modified Marsh”) system became the classification system of choice.

In 2005, a third method of classification was proposed by Corazza and Villinacci, to “make the work of pathologists more uniform and to facilitate the relationship between pathologists and clinicians.”\textsuperscript{105}(p.574) In the intervening years between the release of Oberhuber’s paper and their own work, they reported that the accepted upper limit of normal for numbers of IELs per 100 ECs had been reduced, from 40 to 25, so they incorporated this change into their classification system. A review paper aimed at pathologists published the following year indicated that 30 IELs per 100 EC might be a preferable limit,\textsuperscript{106} but a subsequent
parallel serology and histopathology study by Walker et al.\textsuperscript{107} has confirmed that >25 IELs/100 ECs “is the likely cut off for abnormality”.\textsuperscript{(p.117)}

Corazza, Villinacci, and colleagues followed up the introduction of their revised classification with a study that compared the inter-rater reliability of their system and the Marsh-Oberhuber system.\textsuperscript{108} They had six pathologists use each system to evaluate 60 duodenal biopsy samples on two separate occasions. They found that where the Marsh-Oberhuber classifications afforded only a fair degree of comparability between users (mean kappa 0.35), their own system led to a moderate degree of concordance (mean kappa 0.55). Despite this, the Marsh-Oberhuber system remains in use, alongside that developed by Corazza.

The three classification systems are compared and contrasted on the following page. (Table 2.1)
Table 2.1: Systems for describing intestinal mucosal changes seen in coeliac disease

<table>
<thead>
<tr>
<th>Type 0: Pre-infiltrative</th>
<th>Marsh-Oberhuber</th>
<th>Corazza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mucosal architecture</td>
<td>Normal crypts</td>
<td>Normal</td>
</tr>
<tr>
<td>No increase in IELs</td>
<td>Normal villi</td>
<td></td>
</tr>
<tr>
<td>&lt;40 IEL/ 100 EC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 1: Infiltrative</th>
<th>Type 1</th>
<th>Non-atrophic: Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mucosal architecture</td>
<td>Normal crypts</td>
<td>Isolated increase in IELs</td>
</tr>
<tr>
<td>Marked IEL infiltration of epithelium</td>
<td>Normal villi</td>
<td>(&gt;25 IEL/ 100EC)</td>
</tr>
<tr>
<td></td>
<td>&gt;40 IEL/ 100 EC</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2: Hyperplastic</th>
<th>Type 2</th>
<th>Atrophic: Grade B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarged crypts</td>
<td>Hypertrophic crypts</td>
<td>&gt; 25 IEL/ 100 EC</td>
</tr>
<tr>
<td>Marked IEL infiltration</td>
<td>Normal villi</td>
<td>Villous Crypt ratio &lt; 3:1</td>
</tr>
<tr>
<td></td>
<td>&gt;40 IEL/ 100 EC</td>
<td>Detectable villi</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 3a</th>
<th>Type 3b</th>
<th>Type 3c</th>
<th>Atrophic: Grade B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 IEL/ 100 EC</td>
<td>Hypertrophic crypts</td>
<td>&gt; 25 IEL/ 100 EC</td>
<td>&gt; 25 IEL/ 100 EC</td>
</tr>
<tr>
<td></td>
<td>Mild villous atrophy</td>
<td>Villous Crypt ratio &lt; 3:1</td>
<td>No detectable villi</td>
</tr>
<tr>
<td></td>
<td>Marked villous atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 3: Destructive</th>
<th>Type 3a</th>
<th>Type 3b</th>
<th>Type 3c</th>
<th>Atrophic: Grade B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat mucosa</td>
<td>&gt; 40 IEL/ 100 EC</td>
<td>Hypertrophic crypts</td>
<td>&gt; 25 IEL/ 100 EC</td>
<td>&gt; 25 IEL/ 100 EC</td>
</tr>
<tr>
<td>Infiltration with IELs of varying morphology</td>
<td>Mild villous atrophy</td>
<td>Villous Crypt ratio &lt; 3:1</td>
<td>No detectable villi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked villous atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 4: Hypoplastic/Atrophic</th>
<th>Type 4</th>
<th>No longer required as emphasis on identifying aberrant IEL populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete absence of normal architecture consistent with end-stage T-cell mediated disease</td>
<td>(Extremely rare)</td>
<td>Normal IEL counts</td>
</tr>
<tr>
<td>Flat mucosa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A fourth system, which is a hybrid and modification of the classifications featured in Table 2.1, has been proposed more recently by Ensari. However, it does not seem to have been widely adopted, and the Marsh-Oberhuber system generally remains the most utilised.
Additional histopathological features of CD, which do not feature in any of the classification systems discussed, have also been identified. These include reduced numbers of goblet cells, thickening of the basement membrane, changes to the enterocytes themselves, and an increase in plasma cell density in the lamina propria.\textsuperscript{106,110,111}

It should also be noted that along with the typical histological features of CD, many patients will also display changes in the duodenum, visible at endoscopy. These include mucosal fold loss, and nodularity, scalloping, and fissuring of the mucosa. In severe cases the mucosa may have a mosaic appearance. These findings occur variably, therefore their presence cannot be relied upon to confirm the diagnosis without the need for biopsy, and nor can their absence be regarded as evidence that the patient does not have CD.\textsuperscript{112}

Recently Marsh, Johnson, and Rostami have reignited debate about these classification systems,\textsuperscript{113} in a rebuttal of Oberhuber’s revisions, which they describe as “untenable”.\textsuperscript{(p.99)} This has sparked a flurry of argument and counter-argument about the merits of each system,\textsuperscript{114-118} but it remains to be seen if this will lead to substantive change in practice. What should not be lost sight of is that CD cannot be diagnosed on biopsy alone, given that the histological features described, particularly those at the mild end of the spectrum, can also occur in a range of other conditions. These include drug-induced changes (especially due to non-steroidal anti-inflammatory drugs and proton pump inhibitors), infection (particularly with \textit{Helicobacter pylori}), other food protein allergies, other autoimmune disease, and inflammatory bowel disease (IBD).\textsuperscript{70,119-121} As Dickson has written:

In the interest of the patient, the diagnosis of coeliac disease is most soundly achieved through candid communication between the clinician and the pathologist. It necessitates incorporating details of the patient’s history and adjunct investigations, with the histopathological assessment of the small bowel mucosa.\textsuperscript{106(p.1014)}

\textbf{2.2.3 Coeliac antibodies}

The discovery in the late 1950s and 1960s that people with CD produced antibodies to gluten marked the beginning of a new era of understanding about the nature and aetiology of the condition, more clearly implicating the immune system in its genesis.\textsuperscript{86} Soon afterwards, the conception of CD as being immune-mediated
expanded, with the identification of auto-antibodies, first to reticulin and then to endomysium – both constituents of connective tissue, and both being gluten-dependent. Anti-jejunal antibodies were also identified, although they would appear not to have been pursued beyond recognising that they occur. Then, in a breakthrough discovery in 1997, Dieterich et al. identified tissue transglutaminase-2 (tTG) as the autoantigen being targeted in the smooth muscle endomysium of the small bowel. Alongside all of these discoveries, the capacity to test patients for the presence of these antibodies evolved, opening the way to earlier recognition of greater numbers of patients with CD than was possible when the only test available was the jejunal (or duodenal) biopsy. More recently antibodies to deamidated gliadin peptides (DGP) have also been recognised, and a test developed that enables these too to be measured.

Of the antibody tests that emerged over the years, those that have been utilised most extensively in clinical practice are tests for anti-gliadin antibodies (AGA), anti-endomysial antibodies (EMA), and anti-tTG antibodies. In the present day, DGP antibody testing is also gaining an increasing role. The following table presents key attributes of each of these tests, summarised from several reviews. (Table 2.2)
<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>An ELISA* test using gliadin extracts as its substrate. Can be automated. Both IgA and IgG tests available.</td>
<td><strong>IgA</strong>: Ranges between 52% and 91%. <strong>IgG</strong>: 76% to 88%&lt;sup&gt;122&lt;/sup&gt;</td>
<td><strong>IgA</strong>: 85% to 94%. <strong>IgG</strong>: 88% to 92%&lt;sup&gt;122&lt;/sup&gt;</td>
</tr>
<tr>
<td>EMA</td>
<td>Relies on indirect immunofluorescence, which needs interpretation by the test operator. Expensive. Uses either monkey oesophagus (MO) or human umbilical cord (HU) as its substrate; both difficult to source. Usually IgA-based, but IgG tests sometimes available.</td>
<td><strong>IgA</strong>: (Pooled) 93% (95% CI 92.1 – 93.8%); MO 98% in adults, HU 91.5% in adults&lt;sup&gt;128&lt;/sup&gt;</td>
<td><strong>IgA</strong>: (Pooled) 99.7% (95% CI 99.5 – 99.8%); MO 99.3% in adults, HU 100% in adults&lt;sup&gt;128&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-tTG antibodies</td>
<td>An ELISA test, using either guinea pig liver (gp) or human recombinant (rh) tTG extracts as substrate. Most now use rh, as sensitivity and specificity both higher. IgA and IgG tests available. Test kits produced by a number of different companies and are not standardised between them. Automated.</td>
<td><strong>IgA</strong>: (Pooled) 93% (95% CI 91.2 – 94.5%)&lt;sup&gt;129&lt;/sup&gt;  <strong>IgG</strong>: &gt;70% (Range 54.7 – 100%);&lt;sup&gt;127&lt;/sup&gt; 80 – 95% in IgA-deficient patients&lt;sup&gt;101&lt;/sup&gt;</td>
<td><strong>IgA</strong>: (Pooled) 96.5% (95% CI 95.2 – 97.5%)&lt;sup&gt;129&lt;/sup&gt;  <strong>IgG</strong>: &gt;90% (Range 80 – 100%);&lt;sup&gt;127&lt;/sup&gt; &gt;90% in IgA-deficient patients&lt;sup&gt;101&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-DGP antibodies</td>
<td>An ELISA test, using synthetic peptides. IgA and IgG tests available. May be detected earlier than anti-tTG antibodies in some patients. May be more accurate in children, especially those under two years old.</td>
<td><strong>IgA</strong>: (Pooled) 87.8% (95% CI 85.6 – 89.9%)&lt;sup&gt;129&lt;/sup&gt;  <strong>IgG</strong>: &gt;80%;&lt;sup&gt;124&lt;/sup&gt; (Range 80.1 – 98.6%)&lt;sup&gt;127&lt;/sup&gt;</td>
<td><strong>IgA</strong>: (Pooled) 94.1% (95% CI 92.5 – 95.5%)&lt;sup&gt;129&lt;/sup&gt;  <strong>IgG</strong>: &gt;95%;&lt;sup&gt;124&lt;/sup&gt; (Range 90.3 – 100%)&lt;sup&gt;127&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* ELISA – Enzyme linked immunosorbent assay
There is some evidence to indicate that the performance of these antibody tests in the “real world” is less impressive than “research world” studies would suggest, and that this varies between kits produced by different manufacturers. Not surprisingly, there is also evidence that the greater the degree of villous atrophy, the more sensitive will be the antibody tests.

As will be discussed in more depth in section 2.9 of this chapter, all current guidelines recommend that IgA-tTG antibodies should be the first-line test for CD, either singly, or in combination with EMA or anti-DGP antibodies. Tests for AGA have become largely obsolete due to their comparatively inferior sensitivity and specificity in detecting CD, including in young children in whom they were previously thought to be more reliable. Some do suggest that AGA assays may have a place in the detection of gluten ataxia, and non-coeliac gluten sensitivity.

2.3 Classifying and Defining Coeliac Disease

In 1993 Ferguson et al. published a “Leading article” in Gut, on the “Clinical and pathological spectrum of coeliac disease – active, silent, latent, and potential.” This was one of the first pieces to be written that formally classified CD into these subgroups, although the terms had been appearing sporadically in the literature before that time. The article focused largely on the histopathological subtleties, and the “several forms of coeliac disease” emerging as the CD diagnostic net widened to include people without the symptoms of classical CD (as previously described by Gee). They described “so called active coeliac disease”, which encompassed “malabsorption, and nutritional deficiencies” ranging “from profound to minimal”, and referred to “clinically silent coeliac disease” as disease that was being identified by testing people such as the families of existing CD patients. This they reported as being on the increase. Together, active and silent disease comprised what they called “fully expressed” gluten sensitive enteropathy. “Latent CD” was a term that they suggested should be limited to very specific situations, namely to describe patients who had “a normal jejunal biopsy while taking a normal diet” but who at some point had had or would have “a flat jejunal biopsy which recover[ed] on a gluten free diet”. They argued that even subtle abnormalities (such as high IEL counts) on biopsy samples taken while the patient...
was on a normal diet would require the diagnosis to “be revised from latent to low grade or mild gluten sensitive enteropathy”. An alternative label they suggested for this group was “potential coeliac disease”. (p.151)

In the years since this paper was published, the terms Ferguson et al. suggested have been variably applied, and the subject of much discussion. Other descriptors have also emerged including typical, atypical, symptomatic, asymptomatic, overt, and subclinical. It is these sub-classifications that exemplify some of the complexities of the disease in the twenty-first century. The following table compares the classifications used to describe CD in its various forms in review articles from some of the leading journals since the late 1990s. (Table 2.3)

Table 2.3: CD Classifications used in the recent past

<table>
<thead>
<tr>
<th>Author</th>
<th>CD Classifications utilised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maki &amp; Collin (Lancet, 1997)(^6)</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td>Silent</td>
</tr>
<tr>
<td></td>
<td>Latent</td>
</tr>
<tr>
<td>Fasano &amp; Catassi (Gastroenterology, 2001)(^1)</td>
<td>Classical (Typical)</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic (Silent)</td>
</tr>
<tr>
<td>Green &amp; Jabri (Lancet, 2003)(^4)</td>
<td>Classic</td>
</tr>
<tr>
<td></td>
<td>Silent</td>
</tr>
<tr>
<td>NIH Consensus Development Conference Statement on Celiac Disease (Gastroenterology, 2005)(^6)</td>
<td>Classical</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
</tr>
<tr>
<td></td>
<td>Silent</td>
</tr>
<tr>
<td></td>
<td>Latent</td>
</tr>
<tr>
<td>Green &amp; Cellier (NEJM, 2007)(^5)</td>
<td>Symptomatic/ active/ classic</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or silent</td>
</tr>
<tr>
<td></td>
<td>Latent</td>
</tr>
<tr>
<td>Hopper et al (BMJ, 2007)(^6)</td>
<td>Typical/ classic</td>
</tr>
<tr>
<td></td>
<td>Atypical or silent</td>
</tr>
<tr>
<td></td>
<td>Potential</td>
</tr>
<tr>
<td>Di Sabatino &amp; Corazza (Lancet, 2009)(^7)</td>
<td>Silent</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td></td>
<td>Major</td>
</tr>
<tr>
<td>Mooney et al (BMJ, 2014)(^8)</td>
<td>Classical</td>
</tr>
<tr>
<td></td>
<td>Non-classical</td>
</tr>
</tbody>
</table>
In separate efforts to tackle the issue of defining CD, two panels were convened in 2011. One (the Oslo group)\textsuperscript{22} took CD “and related terms” as its primary focus, while the other (Sapone et al.)\textsuperscript{134} took a broader view and considered the “spectrum of gluten-related disorders”, among which is CD. Both panels (which included several of the same CD experts) sought to bring order to the array of terms being used to describe CD and other gluten-induced clinical entities. Each group published the outcome of their work in 2012, in which year ESPGHAN also published its updated guidelines for the diagnosis of CD in children.\textsuperscript{12} The ESPGHAN document also included definitions of CD, which are discussed here. Their diagnostic guidelines are discussed more fully in the next section of the chapter.

The Oslo group was particularly concerned with the variability of definitions being used in research (especially with regards to CD) and the impact that this could have on how such research is conducted and reported.\textsuperscript{22} The panel was convened ahead of the International CD Symposium which was held in Oslo in June of 2011. Between them panel members conducted an extensive literature review, completed a web-based survey of proposed definitions, and participated in multiple discussions (both face-to-face in Oslo, and via phone conferences), before arriving at a consensus on a principal definition of CD, and on the definitions of the sub-classifications of CD that they believe should be routinely in use. They also formulated definitions for other gluten-related conditions that have emerged in recent decades, and identified a number of terms (including some listed in Table 2.3) that they believe should be removed from regular clinical parlance.

Sapone et al.\textsuperscript{134} were focused on setting CD within the broader context of gluten-related disease, and clarifying the nomenclature to be used when considering the range of conditions this comprises, in order to assist health care professionals grappling with the surge in “individuals embracing a gluten-free diet”.\textsuperscript{134}(p.1) The group met in London in February 2011, and developed a series of consensus statements, derived from the literature and from the outcomes of their discussions on the range of topics each member had been assigned to present.

The ESPGHAN group, which had begun its work in 2007, had a primary aim of updating the available guidelines “to achieve a high diagnostic accuracy and to reduce the burden for patients and their families.”\textsuperscript{12}(p.136) Defining CD was a necessary part of this task, but not their major objective.
The principal definitions of CD that each group advanced are the least controversial aspect of the work that they undertook, and are therefore reasonably similar. In referring to the condition, the Oslo group discouraged the continued use of historical terms such as sprue, coeliac sprue, non-tropical sprue, and idiopathic steatorrhoea.\textsuperscript{22} They also recommended against the use of the labels “gluten-sensitive enteropathy” and “gluten intolerance”.\textsuperscript{(p.45)} Instead they suggested that the condition always be referred to as “coeliac disease”, defined as “a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.”\textsuperscript{22}(p.43) Similarly, Sapone et al. defined CD as “an immune-mediated enteropathy triggered by the ingestion of gluten in susceptible individuals.”\textsuperscript{134}(p.4) Meanwhile, the ESPGHAN group, which gave the most comprehensive of the three descriptions, defined it as:

...an immune-mediated systemic disorder elicited by gluten and related prolamin in genetically susceptible individuals, characterised by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy.\textsuperscript{12}(p.140)

Where the groups differed more substantively however, is in their sub-classifications of CD.

The “Oslo Definitions” paper is devoted almost exclusively to CD,\textsuperscript{22} and focuses entirely on providing definitions for the range of sub-types of the condition that they identify. These are therefore more extensive than those given by Sapone et al.,\textsuperscript{134} and by the ESPGHAN group,\textsuperscript{12} which dedicates most of its publication to its practice guidelines. The Oslo definitions include terms that are recommended for future use, and terms that the authors “discourage the use of”.\textsuperscript{22} (Table 2.4)
Table 2.4: CD Descriptors from the Oslo Definitions

<table>
<thead>
<tr>
<th>Recommended descriptors of CD</th>
<th>Descriptors not to be used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical CD</strong>: presents with signs and symptoms of malabsorption</td>
<td><strong>Typical CD</strong>: not recommended because it has tended to refer to “classical” CD, but also implies that this is the most common form, which is not the case.</td>
</tr>
<tr>
<td><strong>Non-Classical CD</strong>: presents without signs and symptoms of malabsorption</td>
<td><strong>Atypical CD</strong>: implies that this is a less common form of presentation, contrary to what is now known.</td>
</tr>
<tr>
<td><strong>Symptomatic CD</strong>: identifiable symptoms of CD (either gastrointestinal or extraintestinal) attributable to gluten intake.</td>
<td><strong>Overt CD</strong></td>
</tr>
<tr>
<td><strong>Asymptomatic CD</strong>: no identifiable symptoms even on direct questioning and on removal of gluten from the diet.</td>
<td><strong>Silent CD</strong>: has been used to describe asymptomatic and subclinical CD, (and, by Green,⁶⁴ to describe atypical disease) which are not synonymous with each other, so risks confusion.</td>
</tr>
<tr>
<td><strong>Subclinical CD</strong>: CD which is “below the threshold of clinical detection without signs or symptoms sufficient to trigger CD testing in routine practice.” (p.46)</td>
<td><strong>Latent CD</strong>: has been used to describe several different variants of CD ranging from undiagnosed CD, to the definition intended by Ferguson et al.⁹⁹ described above, to include patients with CD diagnosed sometime after diagnosis with another autoimmune condition. Too imprecise to be meaningful.</td>
</tr>
<tr>
<td><strong>Potential CD</strong>: normal duodenal histology in the presence of elevated CD antibodies, indicating increased risk of developing CD.</td>
<td></td>
</tr>
</tbody>
</table>

Refractory CD is also defined, as “persistent or recurrent malabsorptive symptoms and signs with villous atrophy (VA) despite a strict GFD for more than 12 months”.²²(p.46) And there is a series of definitions relating to tests associated with CD, and for other gluten-related disorders.

Taking “Gluten Related Disorders” as their start point, Sapone and her team subdivided these on the basis of pathogenesis.¹³⁴ They classified CD as one of three autoimmune-mediated gluten-related diseases, along with Dermatitis Herpetiformis and Gluten Ataxia. Coeliac disease was further divided into “Symptomatic”, “Silent”, and “Potential” sub-types. (Note the continued use of
“silent”, in contrast to the Oslo recommendations.) These labels are enlarged upon in the text as follows:

The clinical spectrum of CD is wide...and includes symptomatic cases with either classical intestinal (for example, chronic diarrhoea, weight loss) or non-classical extraintestinal (for example, anemia, osteoporosis, neurological disturbances) features and silent forms that are occasionally discovered by use of serological testing.134(p.4)

“Potential CD” was said to be the diagnosis in patients who are auto-antibody positive but who are found to have normal intestinal mucosa on biopsy.(p.4) Sapone et al. also included detailed discussion about the other gluten-related conditions (wheat allergy and non-allergic, non-autoimmune gluten sensitivity), providing up-to-date information about the epidemiology, pathogenesis, clinical presentations, and diagnosis of each.

Following their detailed overarching definition of CD, the ESPGHAN also included nomenclature to differentiate sub-types of the condition.12 They described five sub-types, two of which are at odds with the Oslo group recommendations. Their classifications are as follows:

1) CD with gastrointestinal symptoms and signs;
2) CD with extra-intestinal symptoms and signs;
3) Silent CD: positive CD-specific antibodies, positive HLA, positive biopsy, but insufficient symptoms and signs to have aroused clinical suspicion;
4) Latent CD: compatible HLA and normal biopsy in someone with previous gluten-dependent enteropathy; may or may not have symptoms and/or positive antibodies;
5) Potential CD: positive CD-specific antibodies, compatible HLA, negative biopsy; may or may not have symptoms and may or may not go on to develop enteropathy in the future.12 (p.140)

Thus, despite the best efforts of several of the leading CD researchers and clinicians from around the world, consensus on descriptions pertaining to the varying clinical manifestations of the condition remains elusive. This point was highlighted in an editorial piece by Mäki,137 (another CD expert who was on neither consensus panel but who was in the ESPGHAN working group), and is further
evident in publications that have followed the release of each of the three
documents discussed.

In a Letter to the Editor of Gut published alongside the Oslo paper, Di Sabatino and Corazza queried the appropriateness of describing as “non-classical” the extra-intestinal manifestations of the disease that have been recognised since the 1960s. As a way of circumventing the issue of whether a symptom is truly classical or non-classical (or typical or atypical), they suggested a return to the terms “major” and “minor” disease, which they had previously proposed.7 Marsh similarly registered his unhappiness with the Oslo definitions, arguing against their exclusion of some terms (such as latent CD, and gluten sensitivity), while questioning their choice of others (such as chronic, instead of lifelong). Meanwhile Guandalini et al., having acknowledged that the panels just discussed had been convened to “put order in this chaos” of “a babel of nomenclatures” surrounding CD (p.9), suggested yet another variant on a principal definition, recommending the sub-classifications silent, potential and latent.

There is no immediately obvious solution to this issue, although Mäki has suggested that the way forward is to “focus on the patients and define who has a gluten-related treatable disorder”, (p.306) He goes on to divide these into three categories: coeliac gluten sensitivity, non-coeliac gluten sensitivity, and wheat allergy. But there the sub-classifications stop. Mäki’s concern would seem to be that getting caught up in debates about whether to label people as having silent, latent, or potential CD (for example) results in under-treatment. His view is that people in each of these categories should be treated by removing gluten from their diets, and he asks the question “[w]hy wait for end-stage disease?”(p.306), which is how he regards enteropathy. He is clearly advocating a more liberal interpretation of what constitutes treatable CD, which moves the discussion from a consideration of definitions and into the broader territory of diagnostic criteria.

2.4 Diagnostic criteria for CD

Alongside the clinical definitions of CD that have evolved over the years, specific diagnostic criteria have also been determined, bringing together its clinical and histopathological components. These have been promulgated by various professional bodies such as the ESPGHAN (who were the first), its North
American (NASPGHAN)\textsuperscript{143} and British (BSPGHAN)\textsuperscript{67} equivalents, the American College of Gastroenterology (ACG),\textsuperscript{69} the British Society of Gastroenterology (BSG),\textsuperscript{70,144} the United States’ National Institute of Health (NIH),\textsuperscript{62} and the World Gastroenterology Organisation (WGO).\textsuperscript{68,72} The UK National Institute for Health and Care Excellence (NICE) has also produced guidelines relating to the recognition and management of CD, which includes a brief direction about diagnosis,\textsuperscript{132} while the American Gastroenterological Association (AGA) has produced two “technical reviews” on its diagnosis and management.\textsuperscript{65,122}

The first acknowledged guidelines were issued by the European Society for Paediatric Gastroenterology (the group that became ESPGAN, and that is now known as ESPGHAN) following their 1969 annual meeting at Interlaken.\textsuperscript{141} These were “expert opinion” derived rather than strictly evidence-based, arising from consensus among the experts gathered for the meeting. In the paper released following the meeting,\textsuperscript{141} CD was defined as a “permanent gluten intolerance”, as evidenced by characteristic histological changes to the intestinal mucosa, obtained from biopsy of the duodenum or jejunum. To be certain of the diagnosis required three biopsies: the first to identify that changes were present; the second (one or two years later) to determine that these had resolved on a GFD; and the third to ascertain that they had recurred with the re-introduction of gluten. The second biopsy was deemed necessary to ensure that gluten was indeed the cause of enteropathy in the patient, while the third biopsy was regarded as necessary because “recurrence of disease...may even be silent.”(p.462) Thus the minimum criteria for reaching the diagnosis were “abnormal morphology of the small intestinal mucosa, its normalization on gluten withdrawal, and the reaction on reintroduction of gluten.”(p.462) The abnormal morphology to which they refered was characterised by “absent or almost absent villi”. As Lebwohl et al.\textsuperscript{145} have pointed out, these first diagnostic criteria made no reference to the presence (or otherwise) of CD-related antibodies in patients, which at the time was a newly emerging aspect of CD research.

By 1990, with the release of the first formal revision of the Interlaken recommendations,\textsuperscript{142} the number of biopsies required to confirm the diagnosis had been reduced to one, to be performed on patients in whom CD was suspected, and who continued to consume gluten. While the presence of CD-specific antibodies in
the serum of a patient increased the likelihood of that patient having CD, having histological evidence of enteropathy was considered an absolute requirement for the diagnosis. Findings that were consistent with CD enteropathy (which predated the first Marsh criteria summarised in Table 2.1 on page 23) were defined as “hyperplastic villous atrophy with hyperplasia of the crypts and abnormal surface epithelium”,¹⁴²(p.910) and an elevated IEL count. The second mandatory requirement was that patients showed demonstrable clinical improvement on the GFD “in a matter of weeks rather than many months”.(p.909) The need for a follow-up biopsy was reserved for those patients who had been asymptomatic at the time of diagnosis (for whom resolution of symptoms on a GFD could not be used as a marker of improvement, and therefore as a proxy confirmation of the diagnosis), and for those who did not show the expected improvement after several months. This strategy was endorsed in subsequent recommendations intended for adult practice,⁶²,⁶⁵,⁶⁸,¹²²,¹⁴⁴ and in the 2005 NASPGHAN paediatric guidelines,¹⁴³ an evidence-based extension of the 1990 ESPGAN recommendations. In each of these guidelines Marsh 3 histological changes were regarded as diagnostic of CD, and Marsh 2 as “compatible with” CD subject to correlation with symptoms and serological evidence of disease. Marsh 1 findings were deemed not specific for CD.

2.4.1 ESPGHAN 2012

The CD diagnostic environment has become somewhat more contentious since 2012, when the ESPGHAN released their revised guidelines.¹² As had been undertaken by the NASPGHAN, the European group moved to an evidence-based process and, following this, controversially recommended that in certain contexts a biopsy is no longer required for the diagnosis. The criteria they provided for invoking this option, or at least discussing it as a possibility with the parents and child concerned, are set out in a comprehensive algorithm that is summarised here. In a child or adolescent with suspected CD, the diagnosis can be made without a biopsy if all four of the following criteria are met:

1) the presence of symptoms and/or signs consistent with CD;
2) a tTG antibody level that is 10 times the upper limit of normal for the test which has been used;
3) a positive EMA titre, drawn on a separate occasion from the initial tTG sample;
4) positivity for either of the genetic markers HLA-DQ2 or DQ8.

This last requirement is the most flexibly applied, and in the text of the guidelines document the authors wrote that it “is advisable to check for HLA types in patients who are diagnosed without having a small intestinal biopsy to reinforce the diagnosis of CD.”12(p.138) (My emphasis.) Confirmation of the diagnosis comes with the resolution of symptoms and with a fall in antibody levels, the corollary of which is that if these things do not happen then the issue of biopsy should be revisited. The guidelines team acknowledged that their revised recommendations do require “a period of implementation and testing”(p.154), and “should be evaluated prospectively.”(p.136)

It is the lack of prospective data about the potential impact of observing the ESPGHAN’s recommended protocols that initially drew most comment, and which has led to a mixed response from guidelines groups since. At the time of completing this thesis (in late 2018), the updated BSPGHAN guidelines relating to CD in children in the UK (developed jointly with Coeliac UK).67 remain the only ones to promote the ESPGHAN processes. The NASPGHAN has yet to update its 2005 guideline document, although Ivor Hill, one of the key authors of that document has gone on record urging caution in omitting the biopsy.146 He is particularly concerned about the reliability of CD tests in North America, both in terms of a lack of standardisation between test kits produced by different companies, and in the variability of results across different laboratories. Hill has reiterated this view in a 2014 publication endorsed by the NASPGHAN,147 which makes it seem unlikely that that group will move to including a no-biopsy route to diagnosis in the foreseeable future. A more recent retrospective study by Elitsur and colleagues,148 in which records for children with CD from a number of North American clinical centres were reviewed with respect to how the diagnosis was reached, lends support to this position.

Hill’s concerns have also been echoed by some with expertise in antibody test performance,149,150 who argue that attempts to compensate for the lack of standardisation of assays by trying to “harmonise” results using multiples of the upper limit of normal (ULN) cut-offs is “the wrong approach”.149(p.733) The
contention of Egner et al.\textsuperscript{149} (based on audit data they have collected) is that the same patients, tested using different kits at different laboratories, would experience different outcomes using the ESPGHAN algorithm, due to the performance characteristics of the tests and laboratories. On the basis of this they have suggested that the guidelines as they currently stand are not generalisable, and should instead be interpreted (and applied) in the light of local test-performance characteristics. Their work has been corroborated more recently by Paul et al.,\textsuperscript{151} who suggested that standardising anti-\(t\text{-}TG\) assays (in this case in the UK) should be a priority if the ESPGHAN diagnostic criteria are to be successfully implemented.

None of the more recent guidelines applying to adult patients have endorsed the ESPGHAN algorithms either. Instead they maintain the \textit{status quo} that the gold standard for diagnosis is a duodenal biopsy demonstrating the changes typical of CD.\textsuperscript{69,70,132} This position has been defended by Kurien and colleagues on at least two different occasions.\textsuperscript{152,153} They base their defence on the following: that in the general population (as opposed to the often “CD-rich” research environment) the positive predictive value (PPV) of serology has been demonstrated to be not high enough to ensure that patients are not wrongly diagnosed with CD; that there are often other reasons that adult patients might require upper endoscopy anyway; that it provides an opportunity to assess the severity of the disease; and it “provides reassurance to the patient that the diagnosis is irrefutable, justifying the need for being gluten-free for life.”\textsuperscript{153}(p.146)

An additional concern with the ESPGHAN recommendations, which applies equally to diagnosing CD in children and adults, has been identified by Smarrazzo and colleagues.\textsuperscript{154} In one of the few prospective studies conducted to date, they investigated the diagnosis of CD across 13 Mediterranean countries and found that in countries with limited resources, not all tests required to fully adhere to the ESPGHAN protocol are available. All countries performed duodenal biopsies, and thus relied on these to confirm the presence of CD. These findings echo those of an earlier retrospective study by Tucci et al.,\textsuperscript{155} also conducted in several Mediterranean countries.

However, the reluctance of the adult guidelines groups to incorporate a no-biopsy option in their documents has also drawn criticism. Proponents of this option draw attention to the fact that biopsies also do not have a 100% PPV
(because of the patchy way in which mucosal lesions develop and because interpretation is dependent on specimens being correctly prepared), and cite increasing evidence that the diagnosis can be safely and reliably made without recourse to such an invasive procedure.\textsuperscript{156}

In fact, the ESPGHAN were not the first to propose a no-biopsy route to diagnosis. As early as 2003, Scoglio et al.\textsuperscript{157} asked the question “Is intestinal biopsy always needed for diagnosis of celiac disease?”, in a study in which they retrospectively examined correlations between antibody levels and biopsy results in a mixed population of adults and children. On the basis of their findings, they suggested that in select groups of patients, serial antibody testing with two different tests might obviate the need for biopsy to confirm the diagnosis. Barker et al.\textsuperscript{158} undertook similar work in a paediatric population, concluding that in children with antibody levels significantly higher than the ULN of the test kits they were using, the diagnosis of CD could accurately have been made without a biopsy. In 2008 Peter Hill,\textsuperscript{159} in a third study pre-empting the new ESPGHAN recommendations, calculated a tTG antibody level that would have a 100% PPV for CD, and which he believed could reliably be extended to “most second-generation transglutaminase antibody kits.”(p.572) He too concluded that a biopsy ought not to be mandatory to secure the diagnosis in patients with very high antibody levels. And in a study published at around the same time as the ESPGHAN Guidelines,\textsuperscript{160} Zanini et al. similarly concluded “that changes of the diagnostic paradigm involving serology alone for the diagnosis of CD is a potentially viable strategy”.(p.284)

Since the release of the revised ESPGHAN recommendations, research studies have steadily emerged that cautiously endorse the safety and utility of the suggested approach, in both children and adults. It should be noted that many of these are retrospective,\textsuperscript{161-164} and two have involved patients being screened for CD,\textsuperscript{165,166} which is outside the parameters the ESPGHAN suggest for being able to avoid biopsy. At least three prospective studies have also been completed, two in children,\textsuperscript{167,168} and one in adults.\textsuperscript{169} Together they involved close to 1200 patients from a wide range of countries, and concluded that the ESPGHAN recommendations can be safely applied, even when a number of different test-kits had been used.

In New Zealand one retrospective examination of paediatric CD diagnoses in Christchurch,\textsuperscript{170} although limited by incomplete data relating to all the ESPGHAN
criteria for avoiding biopsy, suggests that the ESPGHAN guidelines may well be appropriate to implement here, subject to prospective evaluation confirming acceptable levels of specificity and sensitivity. But a note of caution for Australia and New Zealand has been sounded by members of Coeliac Australia’s Medical Advisory Committee. They presented data at the 2013 Australian Gastroenterology Week, which demonstrated high inter-laboratory variability between laboratories in both countries that evaluated coeliac antibodies from the same patient (with biopsy-confirmed CD). They also found that not all laboratories used EMA testing, one of the tests required in the ESPGHAN algorithm, and that only a minority reported a tTG antibody result that was greater than or equal to ten times the ULN. Their conclusion was that these factors compromise the local application of the ESPGHAN guidelines, and work needs to be done before they could be reliably implemented in either country. (p.122)

2.5 Genetics and Pathogenesis of Coeliac Disease

With the discovery of gluten as its trigger, the recognition of the role of the immune system in its genesis, and the identification of hallmark mucosal changes present in the small intestines of patients with the condition, there have followed decades of intensive research aimed at piecing together the puzzle that is CD. Many of the underlying pathological and immunological mechanisms at the centre of the disease process have been elucidated, and much is now known about its genetic determinants. It is concisely described by Abadie and colleagues, as “a complex multigenic disorder that involves HLA and non-HLA genes, adaptive and innate immunity, and environmental factors.” (p.495)

The answer to the question of why some people develop CD while others do not remains elusive, but continual progress is being made towards solving this. Multiple research teams are also working on novel treatments targeting different steps in the pathogenic pathways that lead to disease manifestation.

2.5.1 The genetics of CD

It is well established that CD has a clearly genetic component to its development. This is evidenced by the facts that over 99% of patients with CD carry one of two genetic haplotypes; that up to 20% of first-degree relatives of coeliac patients will
also be affected; and that there is 75% to 80% concordance between monozygotic twins.\textsuperscript{174}

The most well-defined genetic elements of the condition are the HLA proteins encoded for in an area on the short arm of Chromosome 6 known as the Major Histocompatibility Complex (MHC). The MHC also contains genetic information for much of the immune system. There are three classes of HLA molecules, of which the class II variety are associated with CD. Class II molecules interact with peptides that have arisen outside cells, such as bacteria or those derived from food-protein, (as opposed to Class I molecules that respond to endogenous peptides, for example from tumour cells).\textsuperscript{175} Within HLA class II there are three groups: DQ, DR, and DP, encoded for by a diverse range of alleles. HLA-DQ has been identified as the principal HLA genetic player in CD, and accounts for an estimated 40% of the heritability of the condition.\textsuperscript{176}

Each HLA molecule has two α-chains and two β-chains, for which there are different genes. In HLA-DQ molecules, the α-chains are encoded for by the HLA-DQA1 gene, and the β-chains by the HLA-DQB1 gene. Together these chains form a protein complex (heterodimer) that acts as a receptor on the surface of antigen-presenting cells (APCs), binding antigens for presentation to T-lymphocytes.

When referring to HLA genes, the preferred way of expressing this is HLA-DQB1*02:01, where “02” indicates a specific allele group, and “01” a particular protein.\textsuperscript{174} Both the DQA1 and DQB1 genes can be comprised from a range of alleles, including ones known to be associated with increased CD risk. The DQ-A1 alleles associated with CD are 02:01, 03:01, 05:01, and 05:05, and the DQ-B1 alleles are 02:01, 02:02, and 03:02.\textsuperscript{175,174} Any of these alleles may be carried alongside each other (cis) on the Chromosome 6 inherited from one parent, or separately (trans) on the two chromosomes inherited from both parents, but CD only occurs when they are inherited in certain combinations.

The highest risk allele combinations for CD are HLA-DQB1*02 (either 02:01 or 02:02) with HLA-DQA1*05 (either 05:01 or 05:05). The HLA heterodimer that this encodes is referred to as HLA-DQ2.5, and it is present in approximately 90% of people with CD.\textsuperscript{177} A moderate degree of risk is conferred by HLA-DQB1*03:02 with HLA-DQA1*03:01, which together encode HLA-DQ8, while the low risk HLA-DQ2.2 arises from HLA-DQB1*02 and HLADQA1*02.\textsuperscript{177} The greatest risk of all occurs in
people who are homozygous for the genes associated with HLA-DQ2.5. These people have both a higher likelihood of developing CD, which they are more likely to develop at an early age, and of experiencing complications of the disease.\textsuperscript{174}

It is possible to test patients for the presence (or absence) of the risk-associated HLA alleles, although the results of these tests need to be thoughtfully interpreted, as it is well documented that they are present in substantially more of the population than is affected by CD. At least 30\%, and in some places perhaps more than 50\% of the population are either HLA-DQ2 (2.5 or 2.2) or HLA-DQ8 positive.\textsuperscript{18} This means that a positive test gives little useful information about whether an individual patient has CD, which has not always been appreciated by those requesting the test.\textsuperscript{177,178} On the other hand, given that more than 99\% of people with CD display one of these haplotypes, a negative test can exclude CD with almost 100\% certainty.

In recent years, genome-wide association studies and the development of the Immunochip platform, have identified additional non-HLA loci associated with CD (many with links to other autoimmune diseases as well). This work means that around 50\% of the heritability of CD can be explained, although the clinical application of this information remains limited.\textsuperscript{179} Work continues to expand this further.

\section*{2.5.2 The role of the environment}

Along with the necessary genetic make-up, and a gluten-containing diet, it is clear some other environmental trigger is also required in order for a person to develop CD. As already discussed, the role of gluten is well understood, as are some of the genetic components of the disease, while work continues to clarify others. As yet the environmental trigger, or triggers, has not been convincingly identified, but that it is required is evidenced by several factors. One of the most striking of these is that the prevalence of CD generally sits at around 1\% in genetically susceptible populations but, as already mentioned, the prevalence of the HLA aspect of that susceptibility is, in some populations, in excess of 50\%.\textsuperscript{18} And while it is known that HLA genotype accounts for only about 40\% of the genetic predisposition to CD,\textsuperscript{176} there is also evidence that clearly implicates environmental factors over and above gluten consumption in the aetiology of the condition.
One of these pieces of evidence is the variability in the prevalence of CD in otherwise similar populations. This has been most clearly demonstrated in a study by Mustalahti et al.,\textsuperscript{4} who found prevalence rates of CD among broadly similar groups of adults in Europe varied from 0.3% in Germany, to 2.4% in Finland. Similarly, Kondrashova et al.\textsuperscript{180} showed the prevalence of biopsy-proven CD was markedly different among children from Finland (1 in 107), and nearby Russian Karelia (1 in 486). The authors of this study suggested this difference cannot be accounted for by differences in genes, and was unlikely to be related to differing exposure to wheat. They drew attention to the vast socio-economic disparity between the two populations, and the attendant environmental differences that followed from this, and speculated on whether this was an example of the hygiene hypothesis at work.

Another event that points strongly to the role of environmental triggers in the initiation of CD (at least in children), is the Swedish CD epidemic that occurred between 1983 and 1995. Over that time period there was a four-fold increase in the annual incidence rate of young children (aged under two years) presenting with CD,\textsuperscript{181} mostly in its classical form. This was followed by an abrupt drop in presentations in 1995, which saw the incidence rate return to its pre-1983 levels. The risk of developing CD has remained elevated among the children born during this period, as was made apparent in a 2009 study by Myléus et al.\textsuperscript{182} In this study a cohort of just over 7500 children born in 1993, the year of peak CD incidence during the epidemic, were screened for CD when they were 12 years old. Among this group the prevalence of biopsy-confirmed CD was found to be 3%, substantially higher than expected based on earlier prevalence studies from Sweden, and elsewhere in Europe.\textsuperscript{182}

Ivarsson et al.\textsuperscript{181} have pointed out that this pattern of a marked increase followed by a rapid decrease in incidence is typical of infectious disease outbreaks, and had never previously been seen with a chronic disease associated with either autoimmunity or diet, as CD is.\textsuperscript{181}(p.168) It was clear from this event that there was something (or things) peculiar to the environment at the time that led to the spike in incidence.

To explore this further, and as part of their analysis of what had occurred, Ivarsson and her colleagues examined the environment in Sweden at the time.\textsuperscript{181}
They found that the onset of the epidemic coincided firstly with changes in advice to mothers about when to wean babies onto gluten-containing products (the recommendation became that this should be delayed until at least six months of age), and secondly with an increase in the total consumption of gluten (which nearly doubled due to a change in the composition of follow-on formulas). The sudden decline in CD presentations followed another change in advice, such that it was recommended that gluten be introduced into infants’ diets in smaller amounts, from the age of four months, and preferably while breastfeeding continued. Thus it became widely accepted that it was highly likely that breastfeeding patterns, the timing of the introduction of gluten into infants’ diets, and the amount of gluten introduced during weaning, played a role in the development of CD. And although subsequent studies produced conflicting results about the impact of these variables, recommendations that were developed erred on the side of caution, and the advice to parents was that small amounts of gluten should/could be introduced when a child was between four and six months of age, and while still being breastfed.

Recently these recommendations have been revised, following a systematic review and meta-analysis of available evidence, which included two recent prospective studies of babies at risk of developing CD. Between them these studies involved almost 1500 babies, and both found no discernible effect on the later incidence of CD from either the duration of breastfeeding, or its association with the introduction of gluten into infants’ diets. One of the two studies, conducted by Lionetti et al., also compared the effects of introducing gluten at six months of age, or delaying it until twelve months, and found no difference in CD incidence by the age of five years. They did find that the age of onset was delayed in the second group, which they suggested “might reduce the negative effects of the disease on vulnerable organs such as the brain.” The second study, by Vriezinga and colleagues, and part of the European “PreventCD” project, tested the impact of introducing small amounts of gluten between the ages of four and six months compared with placebo. Again, this study found no difference in the development of CD by the age of three years among their study groups. In the light of this recent work, the ESPGHAN’s latest position paper recommends the following:

1. Recommendations on BF [breastfeeding] should not be modified because of considerations regarding prevalence of CD.
(2) Introducing gluten while the infant is being breast-fed cannot be recommended as a means of reducing the risk of developing CD.

(3) Gluten can be introduced into the infant’s diet between the ages of 4 and 12 completed months.

(4) No recommendation can be made regarding the type of gluten to be used at introduction.

(5) Despite the limited evidence...ESPGHAN suggests that consumption of large amounts of gluten should be discouraged during the first months after gluten introduction.\(^{184}\)(p.512)

Largely since the Swedish epidemic, other factors that have also come under scrutiny as possible triggers for CD include the season of a child’s birth, mode of delivery, and occurrence of childhood infections. These studies suggest that: being born in the summer leads to a small increase in the risk of developing CD, mostly apparent in children under the age of two;\(^{188,189}\) that the evidence is conflicting on whether elective caesarean delivery is associated with an increased risk;\(^{190,191}\) and that it has been unclear what influence, if any, exposure to infection, with or without treatment with antibiotics, has on the subsequent emergence of CD.\(^{192}\)

Karl Mårild and colleagues have recently reviewed the research relating to perinatal influences on CD onset,\(^{193}\) including those mentioned above, as well as studies that have examined maternal health factors such as the use of antibiotics and iron supplements during pregnancy. They concluded that “[o]verall, the data on the perinatal environment and CD development are inconclusive”,(p.373) noting elsewhere in the article that “there is still only circumstantial evidence”(p.366) linking the two. Mårild has also been involved with a recently published large, prospective, cohort study investigating the relationship between childhood infections and CD.\(^{192}\) This study demonstrated a “modest but significantly increased risk for later CD according to infection frequency in the first 18 months of life”.(p.1483) This was particularly the case for respiratory tract infections, while gastrointestinal infections “yielded similar, but insignificant, increased relative risk estimates.”(p.1483) Antibiotic use (or not) did not affect this relationship. The authors urged caution in interpreting their results, pointing out that the association could also be non-causal.

The pathway that might link all these potential aetiological variables, and which is the subject of increasing investigative scrutiny, is their impact on the gut...
microbiome. The possibility of such a link has been explored in a review by Verdu et al.,\textsuperscript{194} in which they identify the key points in the trajectory of gut microbial colonisation: the prenatal environment, delivery mode (vaginal/caesarean), feeding type (breast/formula), treatment with antibiotics, and introduction of solid food.(p.498)

While all of the factors just described have been studied with respect to the onset of CD in childhood, there has also been research examining the role of antibiotic use in the onset of CD, irrespective of the age at which it presents.\textsuperscript{195} This was a large population study involving almost 6000 people of all ages with either biopsy-confirmed CD or intestinal inflammation, or CD antibody positivity and normal histology, who were then compared with almost 30,000 controls. The authors found a possible association with prior antibiotic use (in the preceding 12 months) and increased risk in all three subgroups, which led them to postulate intestinal dysbiosis as a plausible explanation for this finding. However, they did also point out that they could not rule out reverse causation, with antibiotic use being a consequence rather than a cause of subsequent CD.\textsuperscript{195}(p.7)

Verdu et al.\textsuperscript{194} refer to “the emerging role of the gut microbiota in the pathogenesis of coeliac disease”, but point out that while “[d]ysbiosis has been described in patients with coeliac disease...studies have failed to find a distinct coeliac microbiota signature”.(p.502) Much more work is needed to identify whether such a signature exists, and if so, how it is implicated in the initiation, and perhaps progression, of the disease. One hypothesis is that the microbiome changes immunological responses to oral antigens.\textsuperscript{196} The ultimate aim of present day research into the microbiome, and the extensive work directed at elucidating the complex web of environmental triggers of CD, is that therapeutic options for preventing CD, at least in people identified as being at high risk of the condition, may one day become a reality.

2.5.3 Immune dysregulation and the pathophysiology of CD

The culmination of the interplay between gluten and the factors just outlined is damage to the intestinal mucosa leading to the clinical entity that is CD. This damage is mediated through the immune system, in a process that activates both the adaptive and innate immune systems.\textsuperscript{75,197} Adaptive immunity is the arm of the
immune system deployed to mount a specific response to antigenic stimulus, utilising T-lymphocytes and B-lymphocytes that have adapted to respond to that stimulus. It must distinguish between harmful and beneficial stimuli, both of which are manifold in the gut. Innate immunity is a non-specific early response to perceived threat (usually infection) involving cells such as macrophages and Natural Killer (NK) cells.\(^{174}\)

As discussed earlier in this chapter (page 19), the high proline content in some of the constituents of gluten makes them more resistant to proteolysis in the small intestine, meaning the peptide groups that remain in the lumen can be moderately large.\(^ {176}\) A particular sequence of 33 amino acids derived from α-gliadin is one such peptide group.\(^ {198}\) For people without CD this is of little consequence, but in susceptible individuals this particular peptide chain contains a recurring amino acid motif that is an essential component of the CD pathogenic process.

In order for these peptides to exert their immunological effect they must come into contact with the cells that initiate the immune response. These cells are located in the lamina propria, which is generally not directly exposed to antigens. Because the epithelium of the gastrointestinal tract ordinarily forms a very efficient immunological barrier, how gluten peptides are able to cross into the lamina propria remains the subject of extensive investigation.\(^ {199}\) Four possible ways in which this can occur have now been identified: they may be transported directly through intestinal epithelial cells (IECs); they may pass between IECs due to loosening of the links between cells known as “tight junctions”; they may be picked up directly from the luminal space by APCs such as dendritic cells; or they may gain access through damaged areas of epithelium, where the barrier function has broken down. (Figure 2-3) Increased intestinal permeability due to loosening of tight junctions has received particular attention with the identification of zonulin, a protein known to trigger this process, and that has been found in the intestinal tissue of patients with CD.\(^ {200}\)
Figure 2-3: Routes of passage across the epithelial barrier. To initiate inflammation, gluten peptides need to move from the intestinal lumen to the lamina propria, crossing the epithelial cell barrier. Pathways include (1) transcellular passage, (2) paracellular passage, (3) direct sampling by dendritic cells, and (4) passage through an injured area.\(^{198}\) (Figure and caption used with permission from Springer.)

On gaining access to the lamina propria, gluten peptides are available to be acted upon by tTG. Found throughout the intestinal mucosa, tTG has a central role in the repair of damaged tissue. Under normal physiological circumstances it remains largely inert, but it becomes active in the presence of tissue damage and inflammation.\(^{201,202}\)

As well as its role in tissue repair, tTG also interacts strongly with gluten peptides, converting some of the neutral glutamine residues to negatively charged glutamate, in a process called deamidation.\(^{176}\) The deamidation of gliadin peptides by tTG is a crucial step in the adaptive immune response of coeliac patients, because the negatively charged gliadin peptides bind more tightly to the HLA heterodimers displayed on those patients’ APCs. These units then interact with gliadin-specific CD4+ T-helper cells that recognise these peptides as a threat, inducing an inflammatory reaction that includes the production of cytokines such as interferon-\(\gamma\) and interleukin-21.\(^{203}\) This inflammatory reaction contributes to the hallmark mucosal changes of CD, although it does not account for the degree of villous damage that occurs, or the chronicity of the inflammation.\(^{174,204}\)

As noted earlier in this chapter (page 25) tTG has also been identified as the autoantigen in CD pathogenesis,\(^{123}\) and the presence of IgA antibodies to tTG in the sera of people with CD is a key component of making the diagnosis. However, the
role of these antibodies in the pathogenesis of CD remains unclear.\textsuperscript{174,201} As pointed out by Setty et al.\textsuperscript{197}, CD has a higher prevalence among people with IgA deficiency than the IgA-normal population, which calls into question the significance of the IgA antibody response in the genesis of the condition.

The knowledge that people can have evidence of autoimmune activity (elevated anti-tTG antibodies) without histological evidence of disease (i.e. potential CD) has led researchers to examine what else is happening at the level of the intestinal mucosa that causes some people to manifest CD, when others do not.\textsuperscript{204-206} Innate immunity is crucial in this process, but what triggers and then drives this aspect of the immune response, which takes place within the intestinal epithelium,\textsuperscript{207} remains elusive.\textsuperscript{208}

The central players in the destructive processes that lead to the crypt hyperplasia and villous atrophy of CD would seem to be IELs.\textsuperscript{174} As discussed earlier (pages 21 to 23), the presence of increased numbers of IELs is one of the criteria on which the histological diagnosis is made. Under normal physiological (and immunological) conditions, IELs have a harm-minimisation role, responding to stress signals from IECs by producing anti-inflammatory proteins that promote healing and have "low cytolytic properties".\textsuperscript{204}(p.555) In CD, however, the stress response of IECs is characterised by the release of interleukin 15 (IL-15), a pro-inflammatory protein that induces a change in IELs to cytotoxic variants. CD8+ T cells and NK cells proliferate, and in a complex interplay between the range of receptors expressed on these cells, as well as on epithelial cells, and the cytokines that they produce, destruction of intestinal tissue takes place.\textsuperscript{174,206,209} The following image from Elliott summarises what is known about this process.\textsuperscript{198} (Figure 2-4) Questions still remain, however, about the event (or events) that set the process in motion and about how the adaptive and innate immune responses interact to effect damage.\textsuperscript{75,196,203}
Figure 2-4: Inflammatory circuits in CD. Multiple cell types are involved in the intestinal inflammation in CD. Anti-deamidated gliadin is taken up by an APC (macrophage or dendritic cell) and is presented to a T cells using a DQ2 or DQ8 antigen-presenting molecule. The activated T cells make IFN-γ and IL-17. The IFN-γ instructs epithelial cells to display HLA-E. The APC also makes IL-15 that causes IEL to proliferate and display NK receptors that recognize HLA and MICA on epithelial cells. The activated IEL then kills the targeted epithelial cells. B cells in the lamina propria also can present antigen to T cells that help the B cells mature into plasma cells that make anti-TTG or anti-deamidated gliadin antibodies.198(p.45)

(Figure and caption used with permission from Springer.)

2.6 The Prevalence of Coeliac Disease

It is now generally accepted that the worldwide prevalence of CD is approximately 1% of the general population, albeit with variations between different nations and peoples. This was captured in a 2014 article by Lionetti and Catassi,76 in which they collated data gathered from prevalence studies conducted in a range of countries from across the globe, and tabulated the mean prevalence estimate to be 1269/122858; that is, 1.0%.p.1059) This makes CD one of the most common lifelong conditions known to affect humankind.

As summarised by Catassi et al,210 there is also evidence that the prevalence of CD is increasing over time. Lohi and colleagues in Finland demonstrated an increase from 1.05% to 1.99% over a 20 year period,211 and Murray et al.212 and Rubio-Tapia et al.213 similarly identified increases in two different study populations in the USA.

It has not always been recognised that CD is common. For many years it was thought to be a rare condition that mostly affected children, and which was limited to people of European descent. This was largely due to the fact that up until the late
1950s, the diagnosis was made solely on clinical grounds, these being severe and persistent diarrhoea, associated with malnutrition. As already discussed, this changed with the advent of devices for obtaining jejunal biopsies, and the identification of characteristic changes in the intestinal mucosa. These were found to be present in patients (including adults) with a spectrum of symptoms, not just those who were desperately unwell.¹

In one of the earliest studies examining a possible genetic link in CD,²¹⁴ Carter et al. postulated that the prevalence of CD in Great Britain “appears to lie somewhere between 1 in 2000 and 1 in 6000.”(p.268) In their concluding remarks they refined the population risk to “about 1 in 3000”, and also noted that the risk among family members of patients was much higher than this.(p.272) Six years later MacDonald referred to this work,²¹⁵ writing that the “prevalence of celiac sprue in the United States is not known and is difficult to estimate...(but) 1 in 3000...is compatible with general clinical experience in North America”.²¹⁵(p.474) By 1969 this figure had been revised to 1 in 1850, in UK work cited by Swinson,¹ and by 1973 a study from the West of Ireland found a prevalence of 1 in 303, “[w]hen allowance is made for presentation of disease in adult life”.²¹⁶(p.703) Studies of CD prevalence, and insights into the wide range of peoples it affects, have steadily accumulated since then.

Since the mid-2000s several systematic reviews of CD prevalence studies have been published.²¹⁷⁻²²¹ Additional reviews include those by Barada,²¹ Catassi,¹³ Cummins,²²² Lionetti,²²³ and Yuan.²²⁴ Between them these papers cover hundreds of studies, and the investigations reviewed encompass vast swathes of the globe, including the USA, several countries from South America, a number of European and Mediterranean countries, North African and West Asian nations, India, Australia, and New Zealand.

The following table (Table 2.5) summarises the prevalence data presented by Lionetti and Catassi.⁷⁶(p.1059)
The CD prevalence rates that have been determined for the nations comprising this table range from zero in the Mossi people of Burkina Faso,\(^{225}\) (where it has also been ascertained that HLA-DQ2 and HLA-DQ8 are almost completely absent, and that very little wheat is consumed), to 5.6% among the children of a Saharawi community living near Algeria.\(^{226}\) This rate is strikingly higher than that found anywhere else and, while some have hypothesised evolutionary reasons for why this might be,\(^{76,227}\) a definitive cause has yet to be identified.

The Lionetti review also included more than one study from some countries, some of which found different prevalence rates. This is particularly apparent in studies from Iran, Italy, Sweden and Spain, and also Finland in which prevalence

### Table 2.5: Global coeliac disease prevalence

<table>
<thead>
<tr>
<th>Low prevalence (up to 0.4%)</th>
<th>Moderate prevalence (0.5% - 0.7%)</th>
<th>High prevalence (&gt;0.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>Brazil</td>
<td>Ireland</td>
</tr>
<tr>
<td>Germany</td>
<td>Egypt</td>
<td>Libya</td>
</tr>
<tr>
<td>Russian Karelia</td>
<td>Iran</td>
<td>Spain (children)</td>
</tr>
<tr>
<td>Indian Punjab</td>
<td>Netherlands</td>
<td>Italy</td>
</tr>
<tr>
<td>Spain (adults)</td>
<td>Sweden (adults)</td>
<td>USA (adults)</td>
</tr>
<tr>
<td>USA (children)</td>
<td>Argentina</td>
<td>Turkey (no biopsy)</td>
</tr>
<tr>
<td>Australia</td>
<td>Tunisia (no biopsy)</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td>Turkey</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>New Zealand</td>
</tr>
<tr>
<td></td>
<td>Sweden (children)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Algeria (no biopsy)</td>
<td></td>
</tr>
</tbody>
</table>
ranged from 1.0% in children to 2.4% in adults. The USA data that found a difference in prevalence between children and adults was subgroup data from one study.\textsuperscript{228}

Singh et al.,\textsuperscript{221} in their 2016 systematic review and meta-analysis of CD prevalence in Asia, noted that there have been no reports of CD from many Asian countries, including all those that form Central Asia and the majority of those in South East Asia, while there are only isolated case reports from South Korea, Bangladesh and Yemen. There are also limited data available relating to CD in Japan, and it seems likely that its prevalence is truly low there, due to comparatively low wheat consumption, and the fact that HLA-DQ2 is largely absent in the Japanese population.\textsuperscript{222} A recent study by Fukunaga and colleagues supports this supposition.\textsuperscript{229} In a population sample of just over 2000 asymptomatic people, they found a prevalence of just 0.05%.

At the time of completing this thesis, there have been no prevalence studies conducted in China, however it is known that CD is present there. From 2005 to 2008, Wang et al.\textsuperscript{230} investigated a group of children from four different cities in China who had chronic diarrhoea. They found that 11.9% of the cohort of 118 children had biopsy-confirmed CD. More recently Yuan and colleagues have carried out a systematic review of reports of CD, the frequency of the required HLA haplotypes, and gluten consumption in China.\textsuperscript{224} They conclude that "celiac disease is more common in China than commonly reported" (p.1 of 14), especially in Northwestern China where the population has both a higher frequency of HLA-DQ2, and wheat is a dietary staple. This was consistent among the dominant Han population, and the minority ethnic groups who also inhabit the region.\textsuperscript{224}(p.12 of 14) These researchers also predict that, with the expansion of “Western-style diets” across China, “a sharp rise in the prevalence of CD can be expected nationwide.”(p.13 of 14)

\textbf{2.6.1 The dissenting voice}

It should be noted that not all studies investigating the prevalence of CD are comparable. Some have reached their conclusions about disease prevalence based on screening blood tests alone, while others rely on biopsy confirmation of the diagnosis to determine this figure. And within the biopsy-determined studies, some authors have included in their calculations only those subjects found to have Marsh
3 changes, while others have taken a more liberal approach and included Marsh 2 changes. In addition to this, some studies have been truly random population studies, while others have been conducted using particular cohorts of subjects, such as blood donors or members of the armed forces. It has been argued that these two groups are not necessarily representative of the population as a whole, calling into question the appropriateness of extrapolating results to that population.

The variability in research methods and diagnostic criteria being utilised has been the source of at least one dissenting view about the conclusions that have been drawn about overall CD prevalence. In 2010 Biagi et al. conducted a systematic review of prevalence studies, which they published under the title “Are we not over-estimating the prevalence of coeliac disease in the general population?” They argued that the figure of 1% that is so commonly cited in the literature is an overestimation, and that the true prevalence is likely to be closer to 0.62% (or 6.2‰, as the authors express it). Their reasoning was largely based on the fact that many studies they looked at solely relied on a positive IgA-tTG antibody as proof of diagnosis, increasing the likelihood that at least some cases identified would be “false-positive” diagnoses. They also suggested that including patients who had already been diagnosed with CD in such studies led to an overestimation of prevalence, although it is difficult to know why this would be the case. Curiously, they also included some blood donor studies in the papers they analysed, and reported that they “could not find any significant difference between adults, children and blood donors”, a finding they describe as “very difficult to explain.” Indeed, studies involving blood donors should if anything lead to an underestimation of prevalence, given that people who are iron deficient, with or without anaemia, are often precluded from donating blood. Iron deficiency is well-recognised for its association with otherwise subclinical CD, particularly in Caucasian people.

In their table summarising worldwide CD prevalence cited in the first paragraph of this section, Lionetti and Catassi noted the diagnostic criteria on which each included study based its calculations, and which populations were involved. Studies involving blood donor populations were excluded.
2.6.2 More recent studies

There are some additional prevalence studies that are worthy of comment but which were not included in the Lionetti review. For the most part they had not been published at the time she was conducting her literature search.

In the USA, Mardini and colleagues analysed data from the National Health and Nutrition Examination Survey (NHANES), for racial differences in CD prevalence. They found an overall seroprevalence of 0.79% in the study’s 14,700 participants. Subgroup analysis revealed a seroprevalence of 1.08% among non-Hispanic whites, 0.23% in Mexicans, 0.22% among non-Hispanic blacks, and 0.38% in “other Hispanics”. Meanwhile, a study in Denmark involving almost 2300 participants has estimated the population CD prevalence to be 0.48%. The authors noted that this is “10 times higher than the registry-based prevalence”, which is Denmark’s record of diagnosed patients.

Elsewhere work is gradually emerging attempting to document the prevalence of CD in Asia. The first study from Malaysia, which involved 562 Kuala Lumpur university students, has found an overall seroprevalence of 1.25%. Subgroup analysis according to ethnicity showed this to be comprised of 0.8% among Malay, 1.7% among Chinese, and 1.3% among Indian participants. In this study, a CD diagnosis (for the purposes of determining prevalence) was made in those participants who had positive results in all three of AGA, IgA-tTG, and EMA antibodies. Samples from only those students who were positive for the first two of these were tested for EMA. Students who were only positive for IgA-tTG antibodies did not have the additional EMA titres done, and so were ruled out of consideration for having CD. This is somewhat surprising given that positive IgA-tTG antibodies alone has been all that was required for CD seroprevalence in many studies, and that the combination of this and EMA is regarded by many as being a reliable indicator of the condition. It is possible, therefore, that this study marginally underestimates the likely prevalence of CD in this cohort. The use of AGA tests is also questionable, as it is well known that they have poor sensitivity and specificity for CD, and their use is no longer recommended.

Recently another study from India involving over 23,000 adults has confirmed the variability of CD prevalence across the sub-continent. Ramakrishna and
colleagues recorded a prevalence of biopsy-confirmed disease of 0.85% in Northern India, 0.47% in North Eastern India, and 0.01% in the South. They also investigated HLA types and found that presence of the HLA-DQ2 and HLA-DQ8 genotypes did not vary significantly over the three regional groups tested. On the basis of this, and data they gathered on diet, they ascribe the difference in prevalence to wheat consumption, which was substantial in the North, and minimal in the South.\(^{(p.115)}\)

In contrast to the northern regions studied by Ramakrishna et al., the large majority (8/9) of participants from the south who underwent a biopsy were classified as having “Marsh 0” findings.\(^{(p.120)}\) Despite these people having elevated CD antibodies, many would regard this as a normal (and therefore negative) biopsy. Interestingly, in this study the authors chose to label all those who were antibody positive and biopsy negative as having “latent CD”, for which they also did prevalence estimations.

### 2.6.3 Coeliac disease prevalence in New Zealand

The first attempt to gain an indication of the likely prevalence of CD in New Zealand was carried out by Carrington in 1986,\(^{(235)}\) when she analysed membership records of the Coeliac Society (as CNZ was then known). While acknowledging that there were limitations to this method of predicting prevalence (namely that there were no data available about the proportion of newly diagnosed coeliac patients joining the society), she found that the membership rate of 9 per 100 000 population in New Zealand was one-third of that in England and Wales during the same time period. She postulated three possible reasons for this. Firstly it was possible that fewer patients with CD in New Zealand joined the society compared to similar societies in England and Wales; secondly she speculated on whether the actual prevalence of CD in this country might be lower, either due to differences in the toxicity of New Zealand wheat, or due to ethnic variation in the populations being compared (specifically she suggested that CD could be less common in New Zealand Māori due to a lower frequency of the necessary HLA gene); and thirdly she suggested that the diagnosis might be being missed more often in this country.\(^{(235)}\)

The following year Carrington and colleagues in Otago published the findings of a retrospective study looking at the prevalence of CD in the region.\(^{(236)}\) In addition
to this they sought to establish what proportion of people with CD joined the Coeliac Society. They reviewed the hospital records of children aged up to 12 years old who met at least one of the following inclusion criteria: they had been investigated for malabsorption or steatorrhea; they had had a small bowel biopsy; they had a recorded diagnosis of coeliac disease. They conducted a similar review for adults, and also obtained information from paediatricians looking after children with the condition, from dieticians who had worked with people on the GFD, as well as the names of people who had had gluten-free goods provided by community services. They collated all this data and then matched it with membership data from the Coeliac Society.

What Carrington and her colleagues found was an overall prevalence of CD in Otago of 9 per 100,000, which was low when compared to figures from overseas, and which they attributed to underdiagnosis. In addition to this, they found that only 35% of patients diagnosed with the condition in the period of their study were members of the Coeliac Society. They concluded their report with recommendations about the types of clinical situations in which the diagnosis should be considered, which went beyond the classical description of the condition as being one which affected children who presented with steatorrhea and failure to thrive.236

The most robust evidence available regarding the prevalence of CD in New Zealand is that from a study conducted by Bramwell Cook and colleagues in the late 1990s.17 Indeed it is the only prospective adult CD prevalence study ever undertaken in this country. Their investigation was carried out in the South Island city of Christchurch and continues to be widely cited in the literature as one of the early investigations into the actual prevalence of CD in a population outside Europe and Scandinavia. A random sample of 1064 adults (over the age of 18 years) was selected from the New Zealand Electoral Roll, and each was screened for CD with the EMA test. Those who returned a positive test then went on to have upper endoscopy with duodenal biopsy. Cook and his colleagues discovered that 1.2% of their sample had CD. Only one participant was already on the GFD, having already been diagnosed, and two others had previously had positive EMA tests but had not had the diagnosis confirmed by biopsy.
Almost thirty years after the publication of that research, the generalisability of the prevalence figure of 1.2% to the New Zealand population as a whole, needs to be considered with some caution. Cook’s study sample was overwhelmingly Caucasian, with 96% of the study participants identifying themselves as New Zealand European. Clearly the makeup of this group is not representative of the New Zealand population today. Data from the 2013 Census indicates that only 74% of the population identifies as European, either singly or as one of a number of ethnicities.237 The other major groupings in New Zealand are Māori and Pacific Islander, for both of whom the limited HLA data available indicates a low frequency of the CD-risk alleles;238 and Asian, a label that extends to an extremely diverse group of peoples in which HLA frequencies vary, and which is the fastest growing group in New Zealand.

In another more recent study, Tanpowpong et al. did find a CD prevalence of 1%.239 This work was from a study nested within the New Zealand Asthma and Allergy Cohort study, in which a cohort of 1105 children born in Wellington and Christchurch between 1997 and 2001 are being followed to monitor their health and development. In 2009 their caregivers were surveyed to determine rates of gluten-avoidance within the cohort, and to compare this with the prevalence of doctor-diagnosed CD. Responses for 916 children were able to be analysed. The ethnic make-up of the group reasonably reflects that of the New Zealand population, with 78% identifying as European, 13% as Māori, 4% as Pacific, and 5% as “other”.(p.13) The researchers found that 1% of their sample group (including one Māori child) were reported as having been diagnosed with CD, although only 44% of these children had had the diagnosis confirmed with biopsy. What is particularly interesting about these findings is how they contrast with the vast body of research suggesting that CD is underdiagnosed. In most prevalence studies, the figure of 1% has been determined by screening populations, and identifying people with CD who were previously unaware of the diagnosis. It is therefore somewhat surprising to have a study in which the number of children with diagnosed CD is apparently almost exactly what would be predicted.

There are several possible explanations for the contrast. Firstly, the reliance on biopsy to confirm the diagnosis in at least some of the prevalence studies that have been undertaken may have contributed to the lower rates of diagnosis seen in those
research populations. Secondly, perhaps there was something particular about the cohort Tanpowpong and colleagues were studying, which had led to an increased awareness of CD among the group. If this were the case, the 1% prevalence figure of diagnosed CD they found would not be representative of the state of affairs within the wider population. A third possibility is that the 1% figure in this study is unreliable as it relied on report by the parents of the children in the study, and was not verified against their medical records. However, it could also be that this finding indicates that perhaps the situation with regard to underdiagnosis, at least in New Zealand, is no longer as dire as previously documented.

2.6.4 Prevalence based on other variables

It should also be noted that the majority of the prevalence reviews discussed in the previous sections focus almost exclusively on the geographic (and therefore ethnic) distribution of CD. And while there is less information available regarding prevalence according to other variables such as sex, age, and risk factors associated with CD, the impact of these factors does need to be considered.

It is generally accepted that the prevalence of CD is greater in women than men, with the female-to-male ratio often given as 1.5–2:1, or 2–3:1. The higher of these two figures comes from a North American study by Green et al., in which 1138 people with CD were surveyed. Among this group women outnumbered men by 2.9:1. More recently Green and colleagues have hypothesised that women may have been over-represented in this study because of, among other things, their “more regular health care interaction”. Prevalence studies that have involved population screening, including Cook's New Zealand investigation, have tended to find a more equal distribution of disease between men and women, although this is not a universal finding.

With respect to age, some writers report that CD occurs with equal frequency among children and adults, while others note that there are peaks in prevalence in early childhood, and again in the fourth and fifth decades of life. These differences are likely to have arisen from the alternative ways in which prevalence has been determined, either through population-wide screening studies, or audits of groups of CD patients.
There are also a range of conditions that are known to be associated with an increased prevalence of CD. In 2015 NICE reviewed a substantial number of studies pertaining to these conditions, to inform their updated guideline on CD. The following table presents some of their conclusions, on those conditions most commonly considered in discussions about CD. (Table 2.6) Also calculated was a pooled prevalence of CD among first-degree relatives of CD patients of 8.2% (95% CI 4.6 to 14.3%). The Guidelines development group (GDG) note in their report that the quality of the evidence on which they drew was generally low.71(p.38)

**Table 2.6: NICE data on CD prevalence associated with some pre-existing conditions**71(p.38)

<table>
<thead>
<tr>
<th>Pre-existing Condition</th>
<th>CD Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thyroid disease</td>
<td>Pooled prevalence 2.4% (95% CI 1.5 to 3.8%)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>Pooled prevalence 6.0% (95% CI 4.0 to 8.9%)</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>Pooled prevalence 3.2% (95% CI 1.3 to 7.4%)</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>Pooled prevalence 5.5% (95% CI 4.1 to 7.4%)</td>
</tr>
</tbody>
</table>

**2.7 The Incidence of Coeliac Disease**

It is well established that the incidence of CD is well below what would be expected based on available prevalence data. This has led to one formulation of the “coeliac iceberg” image, in which the visible tip comprises those patients who have been identified, but a much larger submerged bulk of undiagnosed people sits below the diagnostic waterline.72,122,136 (Another configuration of the coeliac iceberg situates classical CD above the waterline and all other types below it,6,63 because these are the manifestations of CD that are much more likely to be overlooked.)

In recent years, several studies have been undertaken that have investigated the incidence of CD, and how it has changed over time.45,246-251 In all but one, CD incidence has increased in the time periods studied, as shown in the following table. (Table 2.7) The exception is in Finland, where Virta el al.251 have recently
documented a fall in the incidence of biopsy-confirmed CD from 33 per 100,000 person years in the 2005 to 2006 period, to 29 per 100,000 person years in 2013 to 2014.

Table 2.7: Increasing incidence of CD evidenced in recent studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Change in Incidence (measured in person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>2.72/100 000 to 6.65/100 000, between 1995 and 2010.249</td>
</tr>
<tr>
<td>Wales</td>
<td>3.08/100 000 to 6.89/100 000, between 1996 and 2005.45</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5.2/100 000 to 19.1/100 000, between 1990 and 2011.252</td>
</tr>
<tr>
<td>Scotland (children)</td>
<td>1.8/100 000 to 11.7/100 000, between 1990-94 and 2005-9.247</td>
</tr>
<tr>
<td>Olmsted County (North America)</td>
<td>11.3/100 000 to 17.3/100 000, between 2000-01 and 2008-10.248</td>
</tr>
<tr>
<td></td>
<td>The authors note a levelling off in incidence from 2004.</td>
</tr>
<tr>
<td>United States Military</td>
<td>1.3/100 000 to 6.5/100 000, between 1999 and 2008.246</td>
</tr>
</tbody>
</table>

That the incidence of CD has increased so markedly suggests that clinicians have greatly improved their efforts in looking for it, as evidenced in particular by the Welsh study by Hurley et al.,45 in which they also reported a 14-fold increase in the number of CD-related tests requested in the time period they examined.

2.8 The Clinical Presentation of Coeliac Disease

Through the late 1950s and early 1960s W.T. Cooke was one of the first clinicians to study a group of adults with CD, with the express purpose of characterising the condition among mature patients. He first published his work in 1963.253 In particular, Cooke and his colleagues wanted to “provide more factual evidence”(p.279) about what distinguished CD from other forms of idiopathic steatorrhoea. To that end, they collected data on a group of 50 patients, all of whom
had “flat” jejunal biopsies, carefully documenting their presenting symptoms, the results of a number of investigations, and their subsequent progress following diagnosis. They described a group of patients with “mild chronic ill health, recurrent glossitis, mild anaemia, and various degrees of intestinal upset”. (p.279) They drew attention to three additional symptoms: diarrhoea, which was present in all 50 subjects, and was the principal symptom in 80% of the group; metabolic bone disease, which affected 18% of the group; and neuropathy, which had a pronounced impact on 8% of their subjects. Lassitude and weight loss were also present in many of the study participants, but the researchers noted that it was difficult to determine whether these were a consequence of the diarrhoea patients experienced, or separate symptoms of the underlying disease process itself. Overall their conclusion was that for “the majority of patients, adult coeliac disease is a relatively mild disorder”, (p.289) already a contrast to the portrait of CD that had previously been painted by Gee, and discussed earlier in this chapter. The notion that patients with CD might present with differing constellations of symptoms and on a spectrum of severity had begun to emerge.

Now, several decades later, it is fair to say that CD has been extremely well characterised. In the vast body of literature written about the condition in the intervening years, a range of terms have been used to describe its clinical presentation. It has been referred to as a chameleon, as “the great imitator”, and as a disease with “many faces”. Its presenting symptoms are protean, myriad, heterogeneous, diverse, variable, and non-specific, to give just some of the epithets used to describe them. And such characterisations of CD are generally followed by the same message: CD is common but underdiagnosed, and clinicians need to be alert to its many modes of presentation in order to remedy this problem. As is written in the introduction to the 2004 NIH Consensus Development Conference Statement on CD, the “single most important step in diagnosing celiac disease is to first consider the disorder by recognizing its myriad clinical features.” (p.S2)

Patients with CD can and do experience a wide range of symptoms and/or problems with their health, as summarised in the following table. (Table 2.8)
Table 2.8: Symptoms and conditions associated with CD

<table>
<thead>
<tr>
<th>System</th>
<th>Symptom/ condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Fatigue; failure to thrive; delayed puberty; weight loss;</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Diarrhoea; steatorrhoea; nausea; vomiting; anorexia; dyspepsia; gastro-oesophageal reflux; malnutrition; micronutrient deficiencies; abdominal pain; bloating; constipation; deranged liver function tests (hepatitis; cholangitis)</td>
</tr>
<tr>
<td>Oral cavity\textsuperscript{256,257}</td>
<td>Dental enamel defects; Aphthous stomatitis; atrophic glossitis</td>
</tr>
<tr>
<td>Bone\textsuperscript{258}</td>
<td>Osteoporosis; low-trauma fractures; osteomalacia; arthritis;</td>
</tr>
<tr>
<td>Central Nervous System\textsuperscript{259}</td>
<td>Ataxia; peripheral neuropathy; migraine; seizures; depression;</td>
</tr>
<tr>
<td>Haematological\textsuperscript{260}</td>
<td>Anaemia; iron, folate, and/or vitamin B12 deficiency; hyposplenism; lymphoma; selective IgA deficiency;</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Amenorrhoea; recurrent miscarriage; infertility</td>
</tr>
<tr>
<td>Skin</td>
<td>Dermatitis herpetiformis; alopecia;</td>
</tr>
</tbody>
</table>

Where previously the symptoms of CD were thought to be limited to the gastrointestinal tract, and the consequences of damage to the gut such as malabsorption, it is now widely recognised that this is far from the complete picture. Indeed, at the other end of the spectrum, it is not uncommon for patients to be overweight at presentation\textsuperscript{261,262}

In many cases, the differing clinical manifestations of CD can be linked to the complex pathogenic processes now known to be at work. Some, such as diarrhoea and symptoms of malabsorption, can be directly attributed to the damage to the intestinal mucosa. Some, such as fatigue and (perhaps) arthralgia and myalgia, can be at least partly ascribed to inflammation being generated by the immune system\textsuperscript{263} And some, such as the association of CD with T1DM and autoimmune thyroid disease, can be connected via a genetically mediated predisposition to autoimmune disease\textsuperscript{264}

As presented earlier in this chapter (page 31) there are several different classifications of CD, each one signifying a different constellation of symptoms.
Using the Oslo definitions, Classical CD is characterised by diarrhoea and/or steatorrhoea, weight loss (or failure to thrive in children), and evidence of malabsorption and malnutrition, such as anaemia, or oedema due to hypoproteinaemia. Children with classical CD may also have abdominal distention and muscle wasting, and tend to present at a young age following the introduction of gluten into the diet.

Non-classical CD is CD in the absence of malabsorption. The example given is that of a patient with constipation and abdominal pain, and may also include many patients who would previously have been described as having atypical disease. Symptoms cited by the Oslo group that would have been encompassed by the older label include irritable bowel syndrome-type presentations, abnormal liver function, peripheral neuropathy, depression, gynaecological dysfunction, bone disease, and skin and oral cavity lesions. Symptoms given by other writers include dyspepsia, fatigue, joint and muscle pain, and osteoporosis. In children, atypical CD would have also included nausea and vomiting, short stature, pubertal delay and dental enamel defects, as well as abdominal pain and constipation. Most of these symptoms, in both adults and children, appropriately come under the non-classical umbrella, although it is less clear under which Oslo label someone with low-grade abdominal symptoms and iron deficiency without anaemia would fit, or for that matter someone with osteoporosis due to impaired Vitamin D and calcium absorption. What is clear is that in adults and children alike, the patterns of presentation have changed over time. This has been formally demonstrated in several studies, both in New Zealand and elsewhere. One of the earliest of these studies is work conducted by Logan et al., in which two Scottish cohorts of patients with CD were compared with respect to their presenting symptoms. The two groups each spanned five years, one from 1960 to 1964, and the other from 1975 to 1979. The most striking difference that these researchers found was that in the earlier cohort 63% had had malabsorption syndrome (diarrhoea, weight loss, and anaemia, hypoproteinaemia, or hypocalcaemia), compared with just 13% of the second group who were similarly affected. In addition to this, among the first cohort of patients there were no presentations involving minor blood test abnormalities with no other associated symptoms, but this accounted for 29% of patients in the second cohort. In that
group a total of 55% of patients had “no gastrointestinal symptoms to attract attention to the relevant system”.96(p.97)

Probably the most widely cited and most extensive study relating to clinical presentations of CD in adults is that by Rampertab et al.,269 in which the records of patients diagnosed in New York city between 1952 and 2004 were interrogated for information about their presenting symptoms. This study involved 590 people with biopsy-confirmed CD who were divided into six cohorts. The first group was of patients diagnosed before 1981, and included some who had been diagnosed as children as far back as 1952. All other patients were divided into quinquennial groups, according to when they had been diagnosed. Rampertab and his colleagues found that among the cohort diagnosed before 1981, 93% had presented with diarrhoea, whereas by 2004 this number had fallen to 37.2%. In the early groups no-one who had been diagnosed with CD had been asymptomatic at the time, but from the mid-1990s this changed, with up to 17% of patients being identified through screening.

Most recently, Dominguez Castro and colleagues have published the results of their retrospective analysis of CD presentations in Ireland between 1960 and 2015.273 They too have found that over that time period the numbers of people presenting with classical CD fell (from 85.2% prior to 1985 to 48.4% since 2011) as the numbers with non-classical disease increased (from 14.8% to 51.6%). In addition to this they noted that the adult median age at diagnosis steadily increased from 34 years prior to 1985, to 46 years since 2011. They did not present median age data for children, whom they classified as being under the age of 18 years.

A recent study from Finland,274 which examined paediatric diagnoses over a similar time frame to the Irish study, charted an increase in the median age at diagnosis from 4.3 years prior to 1980, to 9.0 years between 1980 and 1999, then gradually falling again to 7.6 years by 2013. Interestingly in this study the authors tentatively suggested that the dramatic changes in presentation (and degree of histological damage) seen between cohorts of children diagnosed before and after 1980 have largely plateaued since the beginning of this century.

In New Zealand studies of patterns of presentation of CD, the emphasis has mostly been on children. In 2005, Westerbeek and colleagues published the findings of a retrospective review they carried out on the records of children diagnosed at
Auckland’s Starship Children’s Hospital. Their review covered the period 1999 to 2002, and included 48 children with CD. The median age of presentation was 6.9 years and, for children over the age of five years, the predominant symptom was abdominal pain, as opposed to failure to thrive, which occurred more frequently in the under-5s. Almost 20% of their sample was detected by screening of at risk children, who either had T1DM, or Down syndrome, or a family history of CD. More recently, a similar review has been conducted in Christchurch by Kho et al. Their study covers the 11-year period from 2000 to 2010, during which time 263 children under the age of 16 years were diagnosed with CD. The median age at presentation in this cohort was 7.9 years, and the study confirmed the findings of Westerbeek et al. that older children presented more commonly with abdominal pain, and that pre-school children were more likely to present with diarrhoea and low weight. In the Christchurch group almost 15% were identified through screening for CD, and were asymptomatic.

In similar studies of children from overseas, Whyte et al. found that 36% of South Wales children with CD were identified from screening, while Telega et al. observed that over the 17-year period from 1986 to 2003, the numbers of symptomatic children being diagnosed at a Wisconsin clinic fell as the mean age of diagnosis increased. Those that were symptomatic were more likely to present with gastrointestinal symptoms if they were younger than three years old, while extraintestinal symptoms predominated in older children. Khatib et al. found that among a cohort of 165 New York children diagnosed with CD in the ten years to 2013, over 50% presented with abdominal pain, and almost 40% suffered from constipation. Diarrhoea was present in only 31.1% of subjects.

2.8.1 Facilitating the recognition of CD

As already noted, the image of an iceberg is often used to describe CD, with the visible tip representing diagnosed patients, and the submerged bulk signifying the much greater number of people with the condition who are yet to be identified. In addition to this, there is good evidence from a number of countries that people with CD face delays in diagnosis of many (often in excess of ten) years. Unsurprisingly this has a negative impact on quality of life, and contributes to years of unnecessary morbidity. Work by Vavricka et al. suggests that responsibility
for this delay sits with practitioners failing to consider the diagnosis in a timely manner, rather than with patients failing to seek medical help for their symptoms.

In order to assist practitioners confronted with the coeliac iceberg, and in an effort to mitigate diagnostic delay, several guidelines have now been developed. Probably the most readily accessible of these are those from NICE. The first iteration of CD-related recommendations they produced were made available in 2009, and focused on recognition and assessment. These were updated in 2015, to include advice on management. NICE Clinical Guideline 20 (NG20) is a comprehensive synthesis of the available evidence pertaining to the recognition, assessment and management of CD, and applies to both adults and children.

With respect to the recognition of CD, NG20 presents guidance on symptoms that should prompt clinicians to offer testing for the condition, and on clinical situations in which testing should be considered. (Tables 2.9 and 2.10) The distinction between the two tables is determined by the degree of confidence of the GDG about the relative benefits to patients in each situation. Thus, testing should be offered in circumstances when “for the vast majority of patients, [it] will do more good than harm, and be cost effective”, and should be considered when it “will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective.” (p.15)
Table 2.9: NICE Guidance on symptoms warranting testing for CD

<table>
<thead>
<tr>
<th>Offer serological testing for coeliac disease to first-degree relatives of people with coeliac disease; AND to people with any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent, unexplained abdominal or gastrointestinal symptoms</td>
</tr>
<tr>
<td>Faltering growth</td>
</tr>
<tr>
<td>Prolonged fatigue</td>
</tr>
<tr>
<td>Unexpected weight loss</td>
</tr>
<tr>
<td>Severe or persistent mouth ulcers</td>
</tr>
<tr>
<td>Unexplained iron, vitamin B12, or folate deficiency</td>
</tr>
<tr>
<td>Type 1 Diabetes (at diagnosis)</td>
</tr>
<tr>
<td>Autoimmune thyroid disease (at diagnosis)</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome in adults</td>
</tr>
</tbody>
</table>

Table 2.10: NICE Guidance on circumstances in which CD testing should be considered

<table>
<thead>
<tr>
<th>Consider serological testing in people with any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic bone disorder</td>
</tr>
<tr>
<td>Unexplained neurological symptoms, especially peripheral neuropathy and ataxia</td>
</tr>
<tr>
<td>Unexplained sub-fertility or recurrent miscarriage</td>
</tr>
<tr>
<td>Persistently raised liver enzymes</td>
</tr>
<tr>
<td>Dental enamel defects</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
<tr>
<td>Turner syndrome</td>
</tr>
</tbody>
</table>

It is clear that these tables do not present all of the symptoms, signs and associated conditions that could lead to a diagnosis of CD. However, these are the symptoms
(and signs) for which there is at least some evidence that patients experiencing them are more likely to have CD than patients without them. Both tables also contain fewer items than did the equivalent tables in the 2009 iteration of the guidelines.280

Of the other recent CD-related practice guidelines available,12,67,69,70,72 the ACG,69 the WGO,72 the ESPGHAN and BSPGHAN,12,67 all make explicit recommendations about whom should be tested. All four guidelines have similar lists to those from NICE, with additions covering more of the symptoms and conditions included in Table 2.9. The BSG70 does not make separate recommendations about patients warranting testing, instead referring users to the 2009 NICE guidelines.

2.8.2 Conditions associated with CD

As indicated in the NICE recommendations, there are several conditions that have been found to have an association with CD, although, as also noted by NICE, the evidence supporting some of these associations is weak.71(pp.38–43) Nonetheless, the presence of any of these conditions should prompt the clinician to consider testing for CD, and can be loosely organised into two groups:

1. conditions that have arisen as a consequence of undiagnosed (and therefore untreated) CD; and
2. conditions that are associated with an increased occurrence of CD among affected people, compared to the non-affected population.

The first of these groups is comprised of disorders such as osteoporosis and anaemia, in which malabsorption of crucial nutrients can account for their onset. Persistent fatigue could also reasonably be included in this grouping, arising either as a consequence of the ongoing inflammatory process central to CD, and/or from anaemia. The second grouping consists primarily of autoimmune diseases, and also includes Down syndrome and Turner syndrome. Previously it was thought that Williams syndrome should also belong to this group, however a more recent study by Stagi et al.281 has found that CD is no more likely to occur in people with this disorder than in the non-affected population.

Many of the autoimmune diseases are associated with an increased risk of CD, although as the NICE GDG pointed out, many of the studies pointing to this increased
risk are low quality.\textsuperscript{71} Associated autoimmune conditions include T1DM, autoimmune thyroid disease, Addison’s disease, Sjögren’s syndrome, rheumatoid arthritis, psoriasis, systemic sclerosis, alopecia areata, and vitiligo.

In a 2016 review of CD and autoimmunity, Diamanti el al.\textsuperscript{282} reported that the prevalence of other autoimmune conditions among patients with CD is 30\%, as compared to a prevalence of between 3\% and 9.4\% in the general (non-CD-affected) population. Of these the most commonly associated are T1DM and thyroid diseases. The authors also noted a higher prevalence of autoimmune conditions among close relatives of people with CD.

It is postulated that the increased prevalence of CD among people with other autoimmune diseases could be explained by the presence of shared genetic loci. There is increasing evidence available to support this premise.\textsuperscript{264,283} Most, but not all, of the genetic overlap between CD and these conditions occurs at the MHC, with many sharing the HLA-DQ2 and/or HLA-DQ8 haplotypes. Non-HLA genetic loci in common with CD have also been identified in some of the autoimmune diseases, which may also indicate that there is a gene (or genes) for autoimmunity in general.\textsuperscript{284}

Down syndrome and Turner syndrome are also known to have an associated increased risk of CD.\textsuperscript{285,286} It remains unclear what the precise mechanisms are for these associations, but it is suggested that chromosomal abnormalities at the heart of each condition provide the explanation. Chromosome 21 is the site of the genes that encode interferon-α (IFN-α) receptors, which facilitate the action of IFN-α, one of the cytokines that has been shown to play an important role in the genesis of the CD immune reaction.\textsuperscript{75} Both the expression of IFN-α receptors, and IFN-α activity are increased in people with trisomy 21 (i.e. Down syndrome).\textsuperscript{174}

Women with Turner syndrome have either partial or complete monosomy of the X chromosome. It is now known that genes implicated in autoimmunity are located on the X chromosome,\textsuperscript{287} thus it is theorised that it may be a deficiency of immunoregulatory genes, due to the absent or incomplete X chromosome, that increases the risk of developing CD in this syndrome.\textsuperscript{286}

Perhaps paradoxically, it is also thought that the location of autoimmunity-associated genes on the X chromosome may contribute to the observed increased prevalence of autoimmunity (including CD) among women when compared with
men. This points to the complex interplay between promoter and regulatory genes and gene dosage effects, and is one genetic avenue presently being explored in detail.287

2.8.3 Dermatitis Herpetiformis and Gluten Ataxia

Dermatitis herpetiformis (DH) is the dermatological manifestation of CD. It is characterised by an intensely itchy, papulovesicular rash that most commonly localises to the extensor surfaces of the elbows and knees, the proximal forearms, sacrum and buttocks.288 It is generally symmetrical, and can also affect the face, scalp, shoulders and neck. Diagnosis is confirmed by the presence of IgA deposits (seen under immunofluorescence) in the dermal papillae of samples taken from normal skin adjacent to a lesion.134 The vast majority of people with DH will have evidence of villous atrophy on duodenal biopsy,22 but, because of the ubiquity of this finding, it is not generally necessary for people with a confirmed diagnosis of DH also to undergo endoscopy.134 It has the same HLA associations as CD, and IgA-tTG antibodies and EMA will usually be positive on serological testing. As with CD, treatment is with a GFD, although in some cases patients may also require dapsone, particularly in the early period following diagnosis. Over time, continued adherence to the GFD will enable many of those people to stop this additional treatment.22 Much rarer than CD, a 2009 study from Finland found the prevalence of DH was eight times lower than that of CD in the same population.289 Curiously, in this study, and in a similar 2013 study conducted in the United Kingdom,250 the incidence of DH was found to have been steadily falling, in contrast to that of CD which continues to rise. It is not clear how these two observations are linked, but West et al.250 postulated that perhaps diagnosing and treating CD prevented the onset of DH.

Gluten ataxia (GA) is defined by the Oslo group as “idiopathic sporadic ataxia and positive serum antigliadin antibodies even in the absence of duodenal enteropathy.”22(p.48) It arises as a consequence of damage to the cerebellum, and in particular to the Purkinje cells, and is treated with a strict GFD. It affects men and women equally, and tends to come on gradually in the fifth decade. The primary symptom is gait ataxia, which affects all patients, with associated limb ataxia also affecting the majority.290
Although it is recognised as an autoimmune condition,\textsuperscript{134} GA's relationship with CD is much less clear than that of DH and, unlike DH, it is not regarded as an alternative manifestation of CD. Antigliadin antibodies, which are required for the diagnosis of GA, are no longer used to reach a diagnosis of CD because they lack disease specificity,\textsuperscript{22} while the more CD-specific IgA-tTG antibodies are only positive in just over a third of people with GA.\textsuperscript{134} It is recommended that tTG antibody-positive GA patients should undergo duodenal biopsy to confirm the diagnosis of CD. Nonetheless, a GFD has been shown to halt the progression of, if not improve ataxia in AGA-positive patients, strongly implicating a role for gluten in GA's aetiology.

In the past decade interest has grown in the role of transglutaminases other than tTG (the autoantigen for CD; also known as TG2) in autoimmune diseases in general, and DH and GA in particular.\textsuperscript{291} Transglutaminase-3 (TG3; also known as epidermal transglutaminase) is now recognised as the autoantigen for DH,\textsuperscript{292} while antibodies to transglutaminase-6 (TG6) have been identified in neural tissue in patients with GA.\textsuperscript{293} Work by Stamnaes et al.\textsuperscript{291} and Hadjivassilou et al.\textsuperscript{293} suggests that TG6 antibodies in GA are gluten-dependent, and it is hoped that the development of reliable methods of testing for the presence of these antibodies may lead to a robust diagnostic pathway for this condition.

### 2.9 Testing for Coeliac Disease

All current guidelines pertaining to CD recommend that tTG antibody testing should be the first step in investigating both adults and children with possible CD.\textsuperscript{12,67,69-72} As this is an IgA-based test, it is also generally recommended that IgA levels be measured concurrently, so that IgA-deficient patients are identified, and alternative IgG-based tests arranged.

There are two schools of thought about whether tTG antibody testing should be the sole initial test for CD, or whether a combination of tests is required. Currently the more popular view is that IgA-tTG antibody testing alone is the appropriate first-line approach. This is recommended in guidelines from the ESPGHAN,\textsuperscript{12} the ACG,\textsuperscript{69} and NICE,\textsuperscript{132} and promoted in a number of recent review papers.\textsuperscript{11,81,207,240} Under this approach, a second test for EMA and/or anti-DGP antibodies may be recommended if the first test is equivocal, and IgG-based anti-
DGP testing is advised when a patient is found to be deficient in IgA. The alternative view, promulgated by the BSG, is that initial testing should include both IgA-tTG and either EMA or DGP antibody testing concurrently. Kelly et al. indicate that either simultaneous or sequential testing is appropriate, while the WGO presents recommendations stratified according to resource availability, with the most cost-effective test being the IgA-tTG antibody assay. Thus in better resourced countries the WGO indicates that any of IgA-tTG, EMA, or DGP antibody tests, either singly or in combination, would be an appropriate first-line investigation, while in less well-off countries, IgA-tTG testing should be the priority.

In studies that have directly compared the performance of available antibody tests, tTG, EMA, and DGP antibody tests have all performed well. In their 2006 systematic review, Lewis and Scott found that overall EMA tests tended to have higher specificity, while the human-recombinant IgA-tTG test had higher sensitivity. This led them to recommend that IgA-tTG antibody testing should be preferred. In their subsequent meta-analysis of studies comparing tTG and DGP antibody tests, they concluded that although both tests performed well, tTG antibody assays were superior. They reiterated their recommendation that IgA-tTG antibody tests should be preferred over others. This position was endorsed by Volta et al. in their review of the two tests, while the conclusions of a systematic review by Giersiepen et al., focused on testing in children, also largely accorded with those of Lewis and Smith.

Recently the role of DGP antibody assays in testing for CD has been receiving more attention. There is some evidence to suggest that IgG-based DGP antibody tests are highly specific, and more sensitive than their tTG equivalents, rendering them the better option for testing IgA-deficient patients. There is also a suggestion that DGP antibody tests may be more reliable in young children, (although it has also been shown that young children can demonstrate positive CD antibodies that resolve without intervention).

It should be noted that a small subset of people with CD are seronegative; that is, antibody testing returns normal results, but they have villous atrophy on duodenal biopsy, and are HLA-DQ2 or DQ8 positive. Other causes of villous atrophy (such as drug-induced or infection) must be excluded before the diagnosis can be made. A 2016 retrospective study by Volta et al. involving 810 patients with
CD, found that 14 (1.7%) were negative for EMA and anti-tTG antibodies. Antibodies to DGP had not been tested in these patients, but a study by Hoerter et al.\textsuperscript{299} suggests that had they been done, perhaps two of those 14 would have returned a positive test. Clinicians need to maintain a high level of suspicion that CD might be present for these patients to be diagnosed.

2.9.1 The gluten challenge

A prerequisite for the accurate interpretation of coeliac serology results is that the person being tested is eating a gluten-containing diet at the time of testing. In this era of enormous popularity of the GFD, it cannot always be assumed that this will be the case. Clinicians requesting CD testing therefore need to determine that their patients are indeed consuming gluten, and if not, should recommend that they undertake a “gluten challenge” before having any tests performed.

Until relatively recently the accepted norm for a gluten challenge comprised consuming 10gm of gluten per day (often recommended as four slices of bread), for six, and sometimes eight, weeks.\textsuperscript{8,69,122} In his 2008 review of CD, Anderson\textsuperscript{300} suggested that between two and four slices of bread per day would be appropriate, and that the duration of the challenge could be adjusted according to what the patient could tolerate.

With the exception of the 2015 NICE guidelines,\textsuperscript{132} which say that prior to testing a patient should “eat some gluten in more than one meal every day for at least 6 weeks” (p.2), all recent (adult) guidelines have referred to a 2013 paper by Leffler et al.\textsuperscript{301} In their study, Leffler and colleagues determined that “[o]ver 75% of adults will meet diagnostic criteria for coeliac disease after a 2-week gluten challenge”,\textsuperscript{301}(p.996) and that 3gm of gluten (or approximately 1.5 slices of bread) per day is a sufficient dose. Thus they recommend that a modified gluten challenge should consist of an initial 2-week period in which the patient eats 3gm of gluten per day. Patients who are unable to continue beyond this should then undergo duodenal biopsy and serology testing, while patients who are tolerating the process should continue for as many more weeks as they are able, up to a total of eight weeks. Serology testing should be performed at the completion of the challenge, and if negative, be repeated two weeks later. (This is because they also found that
antibody titres continued to rise for some time after the challenge period had ended.\textsuperscript{301}

While the study by Leffler et al. involved only 20 patients, and investigated patients with documented CD whom it would be expected would respond to the re-introduction of dietary gluten, their recommendations have been picked up, or at least alluded to, by the ACG,\textsuperscript{69} BSG,\textsuperscript{70} and WGO,\textsuperscript{72} as the approach to take when investigating people who have already excluded gluten from their diets.

\subsection*{2.9.2 The role of HLA testing}

As discussed earlier in this chapter (section 2.5.1) it is well established that CD is associated with the HLA haplotypes DQ2.2 and DQ2.5 (together known as DQ2), and DQ8. More than 99\% of people with CD possess one or other.\textsuperscript{174} However, as also noted already, these HLA markers are present in at least 30\% of the population, and in some places more than 50\%,\textsuperscript{18} limiting their usefulness in testing for CD.

In the context of CD, there are circumstances under which testing HLA status can be helpful, and is recommended. In all of these situations the utility of the test lies in its ability to rule out CD, rather than helping to confirm the diagnosis.\textsuperscript{125} Thus the majority of guidelines discourage the use of HLA testing as part of the CD diagnostic process.\textsuperscript{69,70,72,132} The exceptions are the 2012 ESPGHAN,\textsuperscript{12} and 2013 joint BSPGHAN and Coeliac UK guidelines,\textsuperscript{67} both of which include HLA testing as one of the requirements for diagnosing CD in children without a biopsy. All available guidelines concur that HLA testing should be carried out on patients in whom the diagnosis of CD is being considered but who are already on a GFD, so that a gluten challenge (and further unnecessary investigation) can be avoided if testing is negative. Similarly all guidelines suggest that HLA testing can be used to try and rule-out CD in people who are at risk of the condition (e.g. Down syndrome, first-degree relatives, T1DM), to spare them the need for ongoing surveillance. Other circumstances where an HLA test maybe helpful are in patients with negative serology but evidence of enteropathy on biopsy, patients with equivocal histology, and patients who do not respond as expected to a GFD.\textsuperscript{177}

Somewhat in contrast to the guidelines groups, Anderson et al.\textsuperscript{18} have cautiously proposed a diagnostic pathway for adults that does include HLA testing. The primary focus of their study was to determine whether it is possible to more
accurately (and cost-effectively) establish CD prevalence rates within communities than the current reliance on CD serology, with or without biopsy confirmation, allows. They found that by adding HLA testing to the process, people with false positive serology could be excluded from prevalence estimates, but also did not have to undergo costly endoscopies to confirm this. The reasonable conclusion to draw from this is that HLA testing of people with positive CD antibodies could reduce the number of unnecessary endoscopies by identifying those in whom CD is not a possible diagnosis. There is however a potential risk in following such a pathway. As is clearly stated in all discussions relating to CD and HLA-DQ2/DQ8, a positive HLA test does not confirm the diagnosis of CD. Unfortunately this message has not always been heard, as identified in a recent report by Paul et al.,\textsuperscript{178} in which they discussed cases of children being wrongly diagnosed with CD on the basis of positive HLA tests. This is in spite of ESPGHAN’s very clear directions on the appropriate ways to diagnose CD in children, which perhaps does not bode well for adopting similar pathways for adults. It might be that this risk would be ameliorated by standardised laboratory reporting of HLA test results, together with an interpretation of their significance, as suggested by Tye-Din and colleagues,\textsuperscript{177} but this remains to be seen. (There is some evidence to indicate that laboratory reports that include recommendations on responses to a result do influence practitioner behaviour.\textsuperscript{36} Sinclair and Duncan observed a substantial increase in referrals to gastroenterologists when their laboratory added a recommendation to do so on all new-positive anti-tTG and EMA antibody test results.)

2.9.3 Point-of-care testing

Since the early- to mid-2000s when they were developed in Finland,\textsuperscript{302} rapid test kits have been available that utilise fingerprick blood samples to test for CD-associated antibodies. Initially proposed as a means for improving diagnosis rates and as a tool for monitoring dietary adherence,\textsuperscript{5} interest remains in their role in early identification of disease.\textsuperscript{9} This is particularly the case in countries with limited healthcare resources and access to regular CD antibody assays.\textsuperscript{303,304} In the hands of a range of healthcare professionals, POCT enables more extensive testing to take place in communities, particularly in rural areas, that might otherwise be overlooked.\textsuperscript{47} Although as Costa et al.\textsuperscript{303} point out in their study of POCT in three
Mediterranean countries, the sensitivity and specificity of the tests varied markedly between users, signifying that a level of expertise is required to ensure their reliability.

The general consensus regarding POC testing is that the data on their performance are not yet consistent enough to support their general introduction into routine clinical practice. All commentators specify that positive POC tests should be followed-up with laboratory serology testing and, if indicated, duodenal biopsy, so that patients do not commence a lifelong GFD without a confirmed CD diagnosis.

2.10 The Management of Coeliac Disease

Broadly speaking, the aims of the management of CD can be regarded as threefold: to promote mucosal healing; to resolve (or at least improve) patient symptoms and nutritional deficiencies; and to reduce the incidence of long-term complications and mortality. Achieving these outcomes will, it is hoped, improve the patient’s quality of life.

Probably the most extensive review of CD management to have been conducted is that by Haines et al. Published in 2008, it preceded all the recent guidelines that now include recommendations pertaining to long-term follow-up. It followed a 2007 review of the then available guidelines carried out by Silvester and Rashid, who had determined that those guidelines that did address the issue of long-term management were highly variable. This was in large part due to a lack of clear evidence on which to base their recommendations. Haines and colleagues delved into the evidence that did exist, including 361 references in their review. These mostly concerned the potential complications of CD, and whether these could be predicted and/or influenced by review of the patient and management interventions. The authors concluded that “a planned long-term strategy for follow-up is essential”, and proposed a plan in which patients would be reviewed immediately following diagnosis, then at six weeks, six months, and 12 months following diagnosis, and annually thereafter.

Achieving mucosal healing is central to CD management, however there is conflicting evidence about its impact on future health. Some studies suggest that persistent villous atrophy is associated with an increased risk of
lymphoproliferative malignancy, but others have shown that there is no increased risk of mortality among those who have not achieved complete mucosal recovery. There is also evidence both that symptoms can improve without complete healing having occurred, and that symptoms may persist despite complete healing, a conundrum that makes assessment of disease recovery and treatment adherence particularly challenging.

Since the identification more than 70 years ago of gluten as the primary environmental trigger of CD, the mainstay of treatment for the condition has been adherence to a lifelong GFD. If strictly followed, this has been shown to lead to healing of the gut in a majority of people with CD, although this may take several years to achieve. However, this too is contested, most notably by Lanzini et al. In a study published in 2009 of 429 people with biopsy-proven CD, they found that just 8% could be said to have completely healed their intestinal mucosa, although another 65% were reported as having achieved “remission” but with persistently increased IELs. It should be noted that the median time on a GFD among participants in this study was 16 months.

Predicting who will achieve mucosal healing and who will not, remains problematic. A large study by Lebwohl et al. examined follow-up biopsy data from over 7600 patients over many years, and found that older age, being male, and being less educated were all associated with an increased risk of persistent villous atrophy. They also found that rates of healing have increased over time, perhaps because people are being diagnosed earlier (and therefore with lesser degrees of villous atrophy, a view consistent with work by Galli et al.312), or perhaps because access to gluten-free foods is improving. They postulated that the link between lower educational levels and persistent intestinal damage was mediated by poorer adherence to the GFD.

As Haines et al. demonstrated, the management of CD ought not to be limited to prescribing a GFD and leaving it at that. In recent years a more comprehensive approach to management has come to the fore in guidelines documents, and more broadly in the literature. This is especially important with respect to reducing long-term complications, and/or risk of associated conditions. In addition to this, as the various steps in the pathogenic process of CD have been elucidated, the way has been opened for the development
of novel treatments that it is hoped will relieve patients of the burden of adhering to a diet that is both challenging, and expensive to maintain. The following sections discuss these issues in more detail.

2.10.1 The Gluten-Free Diet

As has already been discussed in this chapter, gluten is the collective name given to the proline- and glutamine-rich proteins found in wheat, barley and rye. Removing these proteins from the diet therefore necessarily demands excluding the vast majority of products containing each of these grains, as well as triticale, a hybrid of wheat and rye. The list of food products that this encompasses is extensive, given the ubiquity of wheat in particular. (Table 2.11) Wheat-derived exceptions to the GFD are wheat glucose syrup, wheat dextrose, and caramel colour (occasionally made from wheat), which are produced from its carbohydrate component, and are so highly processed that no gluten remains in the end-product.320

Table 2.11: Gluten containing grains and products in which they are found

<table>
<thead>
<tr>
<th>Grain</th>
<th>Products in which it may be found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat (including spelt, durum, einkorn, emmer, farro, kamut)</td>
<td>Breads and bread products, pizza bases, bagels, flour, pasta, breakfast cereals, bran, biscuits, cakes and other baked products, couscous, bulgur, semolina, pastry, processed meats such as sausages, tinned foods such as baked beans and spaghetti, flavourings, seasonings, sauces, thickeners, confectionary, medications, beer, soy sauce, communion wafers, wheat starch§</td>
</tr>
<tr>
<td>Barley</td>
<td>Breakfast cereals, breads, flour, soups, malt and malted products, beer</td>
</tr>
<tr>
<td>Rye</td>
<td>Bread, crackers, flour, whisky*, vodka*</td>
</tr>
</tbody>
</table>

§ The place of wheat starch in the GFD remains controversial. It is a highly processed derivative of wheat but does retain detectable levels of gluten. It has long been included in the GFD in Europe, and more recently in the USA, but is excluded in New Zealand and Australia.306,321

* Although whisky and vodka are derived from rye, the general advice from organisations such as Coeliac New Zealand is that they are safe to include in a GFD because the distillation process filters out gluten containing proteins. They do acknowledge that there is some debate about whether tiny amounts may remain. (www.coeliac.org.nz/eating-gluten-free/what-alcohol-is-gluten-free. Accessed 7th September 2017)
There are many food groups and products that in their natural states will always be gluten-free. These include eggs, unprocessed meats, fruits and vegetables, legumes, and pure grains such as rice, corn, millet, and quinoa. However, there are also many opportunities for those products to become contaminated with gluten, derived from any of the three grains in which it is found, and the range of products that may or may not contain gluten is vast. Being able to identify those items that are safe to eat as part of a GFD, and those that are not, poses a continuing challenge for patients with CD (and those with other gluten-related disorders).

It is widely acknowledged that it is almost impossible to achieve a zero-gluten diet, which raises a question about whether there is a safe level of gluten that even people with CD can consume without doing themselves harm. This issue was addressed in 2008 in a systematic review by Akobeng and Thomas, in which they examined 13 studies investigating the impact that a range of amounts of gluten had on patients with CD. They reached the conclusion that “a daily intake of <10mg is unlikely to cause significant histological abnormalities” (p.1044), but also noted that there was a range in the amount tolerated. A figure of less than 10mg errs on the side of caution as no study included in their review found evidence of intestinal damage at this level. It is also consistent with the findings from a double-blind, randomised, controlled trial conducted by Catassi et al. to determine a safe level of exposure. Akobeng and Thomas further noted that only three of the studies they included were at low risk of bias, and recommended that further, rigorously designed studies are needed.

In the highly regulated food industry, the definition of what constitutes gluten-free carries with it technical as well as practical implications. In its “Standard For Foods For Special Dietary Use For Persons Intolerant To Gluten”, the Codex Alimentarius Commission of the WHO defines gluten-free foods as those that do not contain any wheat, barley, or rye, and in which “the gluten level does not exceed 20mg/kg in total” (Section 2.1.1). In addition to this, food products that do contain ingredients derived from these grains, but which have been processed to remove

---

*Oats are also named in the Codex standard as being gluten-containing, with a footnote that they “can be tolerated by most but not all people who are intolerant of gluten. Therefore, the allowance of oats that are not contaminated with wheat, rye or barley in foods covered by this standard may be determined at the national level.” (p.2)
gluten, may also make the claim of being gluten-free, if the level of detectable gluten is also less than 20mg per kilogram. This value is commonly expressed as 20 parts per million (20 ppm) and, if present, would translate to 500gm of food containing the 10mg of gluten that is suggested as safe for people with CD. To put this figure in context, a single slice of bread contains 1-2gms of gluten, which is between 100 and 200 times the safe level for a person with CD.\textsuperscript{306}

Gibert et al.\textsuperscript{325} have investigated the population-level of risk of unintentional gluten intake for those with CD in four European countries, using a probabilistic modelling approach. They incorporated three variables into their model: average consumption of commercial gluten-free products; the concentration of detectable gluten in a range of gluten-free-labelled products; and the gluten threshold for intestinal damage. They concluded that across the four countries they studied (Italy, Germany, Spain and Norway) the level of risk of mucosal damage was 0.47\% if the threshold for harm was assumed to be 10mg of gluten. There was variability between countries, with Italy having the highest level of risk due to Italians' higher average consumption of gluten-free wheat substitutes such as pasta. Almost all (99.5\%) products they tested for gluten traces had less than 20ppm, and 94\% of products had less than 5ppm (the lowest quantifiable level for the test kits they were using).\textsuperscript{325}(p.114) It would be interesting to undertake a similar study in New Zealand and Australia.

While the Codex standard has been adopted by the Food and Drug Administration (FDA) in the United States, and the European Communities Commission of the European Union,\textsuperscript{306,321} New Zealand and Australia have taken the gluten-free labelling threshold a step further.\textsuperscript{326} Through the regulatory body Food Safety Australia and New Zealand (FSANZ) it has been determined that in these countries food may only be labelled as gluten-free if it contains “no detectable gluten; and no oats or oat products; and no cereals containing gluten that have been malted, or products of such cereals”.\textsuperscript{327}(p.5) As technology has advanced, the capacity to detect the presence of trace amounts of gluten in foodstuffs has increased such that the threshold for “no detectable gluten” is now at less than 3ppm.\textsuperscript{326} While this has advantages in terms of ensuring that gluten-free labelled products in New Zealand and Australia are very safe for people with CD, it also has
the potential to narrow the range of available products more than is necessary, given that the Codex standard allows a higher level of gluten.

In their recent review of gluten thresholds, Bruins Slot et al.\textsuperscript{326} concluded that the labelling requirements legislated for in New Zealand and Australia should in fact be adopted internationally, to protect “sensitive and recovering patients”. (p.225) They argue that evidence suggests that this group do suffer from adverse outcomes when they consume foods with higher levels of detectable gluten, but which still fall within Codex sanctioned limits. They too advocate for more studies like that conducted by Catassi et al.,\textsuperscript{323} to determine safe thresholds of gluten ingestion for patients with CD with varying sensitivity.\textsuperscript{326}

\textbf{2.10.1.1 Oats in the gluten-free diet}

As noted in the footnote on page 79, the position of oats with respect to their place in the GFD remains unclear, even in the Codex Alimentarius where it is left to the discretion of national regulatory bodies to decide.

Oats are another grain closely related to wheat. As discussed earlier in this chapter, they too contain proline- and glutamine-rich proteins, known as avenins, and for some time were also thought to be unsafe for people with CD. However, as more evidence has come to light about how the avenins differ from the analogous constituents of wheat, barley and rye,\textsuperscript{94} it is now widely accepted that in the majority of patients, adverse outcomes previously attributed to oats were likely to have been due to their contamination by these other grains. This contamination was demonstrated by Lundin et al.\textsuperscript{328} in a study published in 2003, in which they tested a range of commercially available oats for evidence of gluten contamination, and also carried out an oats challenge (using “pure” oats) on 19 adult volunteers with CD. One patient among the study group developed villous atrophy following consumption of these oats, leading the researchers to conclude that “most CD patients tolerate oats in their diet...[h]owever, the finding that even pure oats can induce villous atrophy...in one CD patient raises some concerns.”\textsuperscript{328}(p.1652) A more recent study by Kaukinen et al.\textsuperscript{329} investigated the effects of the inclusion of oats in the GFD over the long term (up to eight years), and found no evidence of adverse impact on symptoms or the intestinal mucosa.
There have been four systematic reviews published examining the safety of oats for people with CD. All have endorsed their safety, although with varying caveats. In 2006, Haboubi et al. were only prepared to recommend the inclusion of oats “if the patient is undergoing a lifelong regular review under specialist care.” (p.677) In 2007, Garsed and Scott concluded that uncontaminated oats were safe for the majority of people with CD, but recommended that they only be included in a GFD once patients were established on this, and that they should be excluded again if symptoms recurred. Pulido et al. made similar recommendations in 2009, also suggesting that only moderate amounts of the grain should be consumed. The most recent review was conducted by Pinto-Sánchez et al. and published in 2017. They have written that “the results of our systematic review evaluating oat safety in...CD are reassuring, and suggest that non-contaminated oats are tolerated by the great majority of patients.” (p.408) The common theme from all four reviews is that caution is needed when drawing conclusions due to the lack of good quality data.

In the years since Lundin’s study, formal recommendations regarding the place of oats in the GFD have gradually evolved such that they are now cautiously sanctioned in all the major guidelines although there is some variation between them. The BSG guidelines are the most liberal, simply indicating that gluten-free oats may be included in the GFD from diagnosis. The NICE guidelines take a similar approach, while the WGO states that pure oats are permissible “in certain quantities”, noting also that there are concerns about contamination from other grains. (p.763) The ACG is more conservative, advising that “oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction” (p.665), while the most cautious recommendations come from the BSPGHAN. This group has recommended that oats not be introduced into a GFD until patients (in this case children) are clinically well, and established on a GFD. They suggest waiting up to a year, and then monitoring patients closely for evidence of relapse.

In New Zealand and Australia, food products containing oats are not permitted to make the claim of being gluten-free. This means that there is still no formal recommendation from the coeliac support groups in either country that gluten-free oats may be included in the GFD.
2.10.1.2 Adherence to the GFD

In their recent review of the GFD, See and colleagues discussed the issue of adherence to the diet, including presenting a summary table of studies that have measured rates of adherence among people with CD. The rates of strict adherence vary considerably, from 40% to 96% among adults, with the writers pointing out that figures gathered via self-report (which applies to several of the studies they reviewed, including those with the highest measures) tend to be higher than those gathered by interview-based dietary assessments. It has been postulated that an important factor in this may be incomplete knowledge about potential sources of gluten, rather than a deliberate misrepresentation of behaviour.

The figures presented by See et al. are similar to the findings of Hall et al. in their 2009 systematic review of studies that investigated factors that might be associated with adherence to the GFD among adults with CD. This review included 38 studies and reported a very similar range (42% to 91%) for strict adherence, despite there being little overlap between the studies interrogated by each team. Hall and colleagues noted that these rates depended heavily on how "strict adherence" to the diet was defined and measured. While noting there was only limited evidence to support their conclusions, they did conclude that adherence was "most strongly associated with cognitive, emotional and socio-cultural influences, membership of an advocacy group and regular dietetic follow-up." They further indicated that there was a lack of robust evidence that clearly linked particular variables with non-adherence, and that high quality studies would be necessary to determine such links. (The "cognitive, emotional and socio-cultural influences" to which they refer include knowledge about the GFD, concerns and beliefs about the harmful effects of exposure to gluten, and the ability to follow the GFD outside the home. These variables were highlighted in a study by Leffler et al. included in the review.)

In work completed subsequent to the Hall review, two tools have been advanced to try and standardise the measurement of adherence to the GFD. The Celiac Disease Adherence Test (CDAT) developed by Leffler et al. is a 7-item instrument that enquires about symptoms (headaches and low energy), self-efficacy, and gluten avoidance habits, using a Likert-type scale to measure responses. The total score gives an indication of GFD adherence, which Leffler and
his colleagues showed correlated well with the “gold standard” assessment of adherence by an expert dietitian, and was more accurate than IgA-tTG antibody testing. Along similar lines, the tool developed by Biagi et al.\textsuperscript{338} utilises four yes/no questions focused on the strategies people with CD employ to avoid consuming gluten. The questions are asked sequentially, and an overall score from zero to four is given. The authors compared patients’ scores with their histological and serological response to the diet, and found a statistically significant correlation. These findings were confirmed in a subsequent validation study conducted by Biagi and his team,\textsuperscript{339} suggesting that the questionnaire is a reliable means of verifying GFD adherence.

There is some significance in the fact that both these tools focus on variables other than specific details about what the patient is actually eating, and yet would seem to reliably indicate when someone is at risk of non-adherence. The important implication of this is that those administering either questionnaire do not themselves need to be expert in the GFD to be able to identify patients who would benefit from additional support with maintaining the diet.

\textbf{2.10.1.3 Challenges to adherence to the GFD}

The following issues have been identified as presenting challenges to adherence to the GFD for people with CD:\textsuperscript{306,321}

- Complexity of the diet, including knowing what is and is not safe, and reading and interpreting food labels;
- The risk of gluten contamination of otherwise gluten-free products;
- Cost;
- The availability of gluten-free products, especially when travelling;
- Difference from others, leading to awkwardness in social and work settings.

Under the aegis of bodies such as FSANZ and the FDA, regulations relating to the labelling of gluten-free products have tightened considerably. Despite this, many people with CD report difficulties with interpreting the information presented on food labels,\textsuperscript{31,275} and there is evidence that shopping for gluten-free foods takes longer. In an opinion piece published in 2005,\textsuperscript{340} Pietzak discusses the issue of gluten-free labelling in the United States noting that checking labels for gluten content probably adds between 10 and 20 hours per month to shopping time.
While this figure may have dropped since the advent of more rigorous labelling, the extra time required for grocery shopping remains an issue for those with CD.\textsuperscript{341,342}

The gluten contamination of gluten-free foods, and avoiding this risk, also presents considerable challenges for people with CD. This contamination can occur at a number of junctures on the way from field to plate, some of which are under the control of the person needing to avoid gluten, and some of which are not. For example, Thompson et al.\textsuperscript{343} tested a range of inherently gluten-free products available in the USA and found that several of them (e.g. soy flour, white rice flour, and millet flour) were in fact contaminated by gluten. The following chart, adapted from See et al.,\textsuperscript{306} sets out the range of sites where gluten contamination can occur. (Figure 2-5)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Contamination Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field</td>
<td>Crop rotation between gluten-free and gluten-containing grains from season to season. Mixed crops grown in adjacent fields and/or harvested together and/or using the same equipment, and then packaged, stored and transported together.</td>
</tr>
<tr>
<td>Factory</td>
<td>Gluten-containing and gluten-free grains milled, processed and stored in common facilities. Gluten-containing and gluten-free products made on shared equipment.</td>
</tr>
<tr>
<td>Retail</td>
<td>Bulk-bin products stored adjacent to each other with common scoops for dispensing. In-house products (e.g. breads) made in a shared environment and using shared equipment.</td>
</tr>
<tr>
<td>Home</td>
<td>Shared kitchen space, bench tops, equipment (e.g. toasters), and utensils (e.g. bread knives, colanders). Common spreads (e.g. margarine), dips, and condiments.</td>
</tr>
<tr>
<td>Eating out</td>
<td>Inadvertent inclusion of gluten-containing ingredients (e.g. wheaten cornflour). Shared food preparation spaces, fryers, grills, and serving implements. Display of gluten-containing foods adjacent to and/or above gluten-free foods.</td>
</tr>
</tbody>
</table>

**Figure 2-5: Contamination risks in the journey of gluten-free foods from field to plate**

In addition to the settings listed in Figure 2-5, travel to countries where the first language of the person with CD is not the local language brings an extra dimension of complexity to adhering to a GFD. Coeliac support groups worldwide play an
important role in mitigating this particular challenge, by providing resources such as cards with translated questions about food safety (for example), for use when food shopping or eating out in a range of different countries.

The increased cost of gluten-free foods when compared with gluten-containing equivalents is well documented, although it is not clear the degree to which cost impacts on adherence. While it undoubtedly affects the capacity of some people to maintain a strictly GFD, cost would seem to have a less significant role in deviations from the diet than do discomfort in social settings, difficulties understanding what is required, or finding foods unappealing. However it is possible that available studies underestimate the impact of cost on adherence, as people who are less well off financially may be under-represented in studies that have examined the issue. Neither of the studies just cited provide information on the socio-economic status of participants.

One more recent study that has partially explored this issue found that inadequate adherence to the GFD (as measured using the CDAT) correlated most clearly with lower levels of education, and to the belief that the cost of gluten-free foods was a limiting factor. Curiously there was only a “marginally significant correlation” between lower median annual household income and an unsatisfactory CDAT score, (p.756) which suggests that it is perception of cost that contributes to poor adherence. People who had unsatisfactory CDAT scores were also more likely to believe that the GFD does not help their symptoms, and it seems plausible that these two factors might be related.

As discussed by Estévez et al. the concept of the “basic food basket” is sometimes used in less well-off countries to determine the cost of maintaining adequate nutrition for their populations. In a 2016 study, they published a report on a “gluten-free basic food basket” in Chile. Not surprisingly they found that gluten-free products were much less readily available than their gluten-containing equivalents (even though they were regarded as basic to a nutritional diet), and the overall cost of their basket was three times higher. By way of comparison, the following table gives examples of the differences in cost between some gluten-free items and their gluten-containing alternatives available at a Dunedin, New Zealand, supermarket in September 2017. The cheapest version of each item was costed. (Table 2.12)
Table 2.12: Comparative costs between gluten-containing and gluten-free products available in a New Zealand supermarket

<table>
<thead>
<tr>
<th>Item</th>
<th>Gluten-containing cost</th>
<th>Gluten-free cost</th>
<th>Factor of cost difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain flour</td>
<td>$6.00 per 5 kg (=12c/100gm)</td>
<td>$4.50 per 750gm (=60c/100gm)</td>
<td>5x</td>
</tr>
<tr>
<td>Cornflakes</td>
<td>$2.00 per 300gm (=67c/100gm)</td>
<td>$4.49 per 250gm (=180c/100gm)</td>
<td>2.7x</td>
</tr>
<tr>
<td>Weet-Bix</td>
<td>$5.50 per 1.2kg (=46c/100gm)</td>
<td>$6.99 per 375gm (=186c/100gm)</td>
<td>4x</td>
</tr>
<tr>
<td>Pasta Spirals</td>
<td>$1.80 per 500gm (=36c/100gm)</td>
<td>$5.99 per 500gm (=120c/100gm)</td>
<td>3.3x</td>
</tr>
<tr>
<td>White Bread</td>
<td>$1.09 per 600gm loaf (=18c/100gm)</td>
<td>$6.49 per 495gm loaf (=130c/100gm)</td>
<td>7x</td>
</tr>
<tr>
<td>Pizza bases</td>
<td>$3.99 per 480gm (=83c/100gm)</td>
<td>$5.49 per 370gm (=148c/100gm)</td>
<td>1.8x</td>
</tr>
<tr>
<td>Frozen Pizza</td>
<td>$5.50 per 640gm (=86c/100gm)</td>
<td>$15.99 per 700gm (=228c/100gm)</td>
<td>2.7x</td>
</tr>
</tbody>
</table>

In New Zealand it is possible to obtain a limited range of partially subsidised gluten-free products (flour, pasta, bread mix, and baking mix) on prescription. Patients with biopsy-confirmed CD (or DH) are eligible for a Special Authority number that entitles them to the subsidy. However, since 2011 the New Zealand Pharmaceutical Management Agency (PHARMAC), which oversees the provision of prescription items in this country, has withdrawn from actively managing the funding of gluten-free foods. According to its website this means that they are no longer considering the listing of new products, or making subsidy, or other changes to the existing listings. As a result we anticipate that the range of funded items will reduce over time. Management of Coeliac disease with a gluten free diet is necessary for good outcomes. A range of gluten free options are available through retail outlets. (www.pharmac.govt.nz/Schedule?osq=Gluten%20free%20baking%20mix&code=C4210012918 Accessed September 2017)
In the 2012 New Zealand Coeliac Health Survey,\textsuperscript{31} Sharp found that a little more than 50% of respondents had a Special Authority number, which suggests that their usefulness is declining.

In addition to the prescription subsidy, people who meet the financial threshold for government support with a Community Services Card can also apply for a Disability Allowance to help cover the costs of gluten-free foods. This is a means-tested allowance, and requires applicants to furnish receipts or other evidence of the extra expenses they incur because of their illness. Sharp's study did not report the number of people accessing this support.

\textbf{2.10.1.4 Nutritional adequacy of the GFD}

In 2017 Newberry and colleagues published a review of the history of the GFD,\textsuperscript{351} drawing particular attention to what they termed "the nutritional implications" of the diet. Over many years concerns have been expressed about the nutritional adequacy of the GFD,\textsuperscript{352-357} both in terms of what it may lack (fibre and adequate amounts of micronutrients) and what it may contain (saturated fats and sugars).

As summarised by Newberry et al.,\textsuperscript{351} across most studies it has been a consistent finding that pre-packaged gluten-free products (such as cereals and pastas), and/or the GFD \textit{in toto}, are deficient in micronutrients, particularly iron and folate. This is in part due to the natural composition of gluten-free grains, and in part because gluten-free products are not usually fortified.\textsuperscript{356}

The findings have perhaps been less consistent with respect to macronutrients (fat, protein, and carbohydrates), although the GFD does tend to be lower in fibre and protein, and higher in sugars than gluten-containing diets. A large 2015 Australian study conducted by Wu et al.\textsuperscript{358} compared the make-up of gluten-free products and gluten-containing equivalents with respect to these components. Somewhat surprisingly they found that the fat, sugar, and salt content of the gluten-free products were on a par with their gluten-containing counterparts, at least as reflected in the Health Star Ratings (an Australian government endorsed system for providing nutrition information to consumers) and nutrition information panels of the products they examined. This should be of some reassurance to people with CD, however, as Staudacher and Gibson point out in their commentary on the study,\textsuperscript{359} the GFD is, at its core, a diet of exclusion and the risk of nutritional deficiency lies in
the “insufficient inclusion of suitable alternatives.”(p.1540) This is particularly the case for fibre, the B vitamins, and folate, none of which Wu et al. were able to assess for comparability in the products they studied.358

A nutritionally adequate diet depends both on the breadth of food choices of the person consuming the diet and on the nutritional quality of the foods he or she chooses to eat, issues that are acknowledged to affect the wider population than just those on a GFD.355,356,358 But the additional challenges to this presented by the GFD highlight the importance of ensuring that all people diagnosed with CD have access to skilled dietitians. Furthermore, many newly diagnosed patients are deficient in some or a number of micronutrients as a consequence of the disease so it is essential that their diets are adequate to meet any additional requirements. This may or may not include the use of supplements, but dietitians expert in CD management are best placed to guide patients accordingly.360 All guidelines relating to CD recommend that patients should be referred to a specialist dietitian once the diagnosis has been confirmed.67,69,70,72,132

2.10.2 New treatment possibilities

Because of the issues just discussed relating to the challenges of maintaining the gluten-free lifestyle necessary for the management of CD, extensive work has been, and continues to be done to produce alternative treatment options. Several studies have now demonstrated a desire among patients with CD for alternatives to the GFD to be developed.361-364 Alternatives being explored include treatments that would obviate the need for a GFD, and those that would be used as an adjunct to the diet by reducing the impact of the ingestion of trace amounts of gluten. The challenge in developing any new treatment is that it must be safe, as well as effective. As noted by Kaukinen and colleagues,173 “one must consider the possible risks versus benefits of the various treatments for a disease that is generally benign and reversed by a gluten-free diet that causes no major recognized adverse events.”(p.42)

As the complex pathogenesis of CD has become increasingly disentangled, several different steps in the process have been identified as possible targets for intervention. These targets, along with the potential options for moderating them, have been summarised in a number of review papers published in recent
The following table distills the key points from these reviews. Many of the options suggested are in various stages of the development process, ranging from pre-clinical to Phase 2 trials, while future targets may include genetic risk loci that are implicated in the aetiology of CD (Table 2.13).

**Table 2.13: Novel treatment targets and proposed interventions**

<table>
<thead>
<tr>
<th>Gluten Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed interventions: Pre-luminal</strong></td>
</tr>
<tr>
<td>• Selective breeding of low-immunogenic varieties of grains.(^{199,369})</td>
</tr>
<tr>
<td>• Genetic modification of disease-activating grains.(^{199,370,372})</td>
</tr>
<tr>
<td>• Pre-treatment of grains during food production (e.g. with <em>Lactobacilli</em> in sourdough bread making).(^{199,369,372})</td>
</tr>
</tbody>
</table>

| **Proposed interventions: Intra-luminal** |
| • Gluten detoxification by oral proteases: break down proline- and glutamine-rich peptides so they do not accumulate in the small intestinal lumen.\(^{366,369,372}\) |
| • Gluten sequestration by oral polymeric resins: bind gluten peptides preventing proteolysis and absorption.\(^{173,366,369,372}\) |
| • Neutralisation of gluten antibodies (e.g. using cows’ milk derived IgG antibodies).\(^{367}\) |
| • Degradation of gluten by probiotics such as *Bifidobacterium* species.\(^{173,369}\) |

| Gluten uptake into small intestinal epithelium |
| **Proposed interventions:** |
| • Reducing intestinal permeability by targeting tight junction regulators (e.g. zonulin-antagonists).\(^{173,367,369}\) |
| • Blocking transcellular transportation of gluten peptides by targeting the sIgA-receptor pathway that has been identified.\(^{173,369}\) |
Table 2.13 (continued): Novel treatment targets and proposed interventions

<table>
<thead>
<tr>
<th>The CD Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed interventions: Gluten tolerisation</strong></td>
</tr>
<tr>
<td>• Down-regulate autoimmune response: <em>Necator americanus</em> (hookworm) infection.(^\text{172,173,199,370}) May be useful in the context of gluten contamination.(^\text{369})</td>
</tr>
<tr>
<td>• Induce mucosal tolerance: vaccination with peptide antigens (e.g. Nexvax2)(^\text{199,366,367})</td>
</tr>
</tbody>
</table>

| **Proposed interventions: Reducing inflammation** |
| • Suppression of inflammatory response by inducing lymphopaenia: glucocorticoids (e.g. budesonide, which is topically active so works locally; needs reformulation to be effective in small intestine).\(^\text{172,366,369}\) |
| • Inflammatory cytokine blockade: monoclonal antibodies (e.g. Infliximab)\(^\text{172,369,370}\) |

| **Proposed interventions: Modulating the immune response** |
| • Blocking lymphocyte recruitment to the mucosa: e.g. CCR9 (chemokine receptor 9) blockade.\(^\text{172,173,199,367,369}\) |
| • Other: CD-specific HLA blockade with gluten peptide analogues; tTG inhibition to reduce deamidation of gliadin peptides; IL-15 blockade with anti-IL-15 antibodies.\(^\text{172,173,199,366,367,369}\) |

2.10.3 Complications of CD

The potential complications of CD have been widely canvassed in the literature, being discussed in many CD review papers,\(^\text{5,7-9,11,81,207,240}\) and referenced in several guidelines documents.\(^\text{69,70,72,122}\) Several papers focused on CD complications have also been published, with some reporting studies on specific potential sequelae such as pancreatitis,\(^\text{373}\) cardiovascular risk,\(^\text{374}\) or malignancy,\(^\text{26,375}\) and others examining morbidity and mortality more generally.\(^\text{25,27,376-378}\) One of the most comprehensive reviews of the topic is the 2014 book chapter by Lewis and
Holmes,\textsuperscript{379} in which an extensive list of co-morbidities is presented and discussed in the light of available research. The systematic review of long-term management by Haines et al.\textsuperscript{28} also presents an exhaustive list of potential complications.

As noted by Tack et al.,\textsuperscript{227} because of the increasingly wide range of clinical presentations recognised as being indicative of CD, there is some variability in what is classed as a complication of CD (as opposed to an association). This is a view shared by Lewis and Holmes,\textsuperscript{379} who suggest that “because CD is so common, it follows that many diseases will occur in association...as complications...as associations or simply as occurring by chance.”\textsuperscript{(p.210)} However, all review articles cited in the previous paragraph list refractory CD, malignancy, and death as the potential complications that warrant particular attention from clinicians managing CD patients. Many also refer to hyposplenism (and/or infection) and osteoporosis, and some discuss an increased risk of other autoimmune diseases.

\textbf{2.10.3.1 Refractory CD}

For a small proportion of people with CD, adherence to a strict GFD does not achieve remission of the disease, leading to a state known as Refractory Coeliac Disease (RCD). This has been defined by the Oslo group as consisting of “persistent or recurrent malabsorptive symptoms and signs with villous atrophy...despite a strict GFD for more than 12 months”.\textsuperscript{(p.46)}

The exact number of CD patients affected by RCD is unclear, with some writers suggesting it affects up to 5\%\textsuperscript{,207} but others maintaining that it is very rare, with an incidence of much less than 1\%\textsuperscript{.380} As suggested by Di Sabatino and Corazza,\textsuperscript{7} who postulate that the 5\% figure is an overestimate, the difference may lie in the populations from which these figures have been determined – tertiary referral centres for patients with persistent symptoms, versus the coeliac cohort as a whole.\textsuperscript{380} A recent study by Eigner et al.\textsuperscript{381} found an overall RCD incidence of 2.6\% among a cohort of 1138 people, over a 25 year period. Within that period they noted that rates have been falling since a peak of 3.3\% between 2000 and 2004, to 0.5\% from 2010 to 2014.\textsuperscript{381}(p.366) In their 2017 review article,\textsuperscript{382} Shannahan and Lebwohl put the prevalence of RCD at around 10\% of people with non-responsive
CD, and 1% of CD patients overall. Studies are conflicting on whether men or women are affected in greater numbers, but it is agreed that RCD is never found in children, and highly unlikely in those under the age of 50.

Refractory CD can take one of two forms, determined by the immunophenotype of IELs. The more common, and prognostically better, RCD-1 is regarded as being virtually indistinguishable from untreated and uncomplicated CD, and the phenotype of the IEL population is essentially normal. This is in contrast to RCD-2, in which aberrant IELs show T-cell clonal expansion, and lack the usual immunological surface markers of normal cells. It is more likely to be associated with HLA-DQ2 homozygosity, and the clinical presentation with diarrhoea, weight loss and abdominal pain is generally more severe. The prognosis for RCD-2 is poor, with a 5-year survival rate of 44% to 58%. This is largely due to the much increased likelihood of developing enteropathy-associated T-cell lymphoma (EATL). Risk factors for 5-year mortality from RCD have been identified as age (mortality increases with increasing age at diagnosis), low serum albumin levels (risk of mortality is inversely proportional to serum albumin level at diagnosis), and the presence of abnormal IELs in duodenal biopsy samples.

Specifically associated with CD, EATL is a very rare but aggressive T-cell Non-Hodgkin’s Lymphoma (NHL) of the upper small intestine, with a 5-year survival rate of less than 20%. Progression to EATL among people with RCD-2 occurs within five years of diagnosis in up to 52% of patients, although in absolute terms this represents a tiny proportion of people with CD. In their study of 12,243 CD patients, Ilus et al. found an overall RCD prevalence of 0.3%, with RCD-2 diagnosed in 0.08% (10) of the study population. Among their whole study group, two people died from EATL.

Before the diagnosis of RCD can be confirmed, it is essential that other possible causes of ongoing symptoms and persistent villous atrophy are excluded. Chief among these is continued ingestion of gluten, either deliberately or unintentionally, thus the assessment of a patient presenting with possible RCD must include a

---

b This article actually states that “RCD develops in about 10% of patients with non-responsive RCD” which I have interpreted as a typographical error, with the intended meaning being 10% of patients with non-responsive CD.
thorough review of his or her diet. In addition to this it may be that these patients warrant a trial of an even more rigorous diet than would usually be advocated. Daum et al.\textsuperscript{384} refer to a diet that is “as gluten free as possible”, making specific recommendations about what it can include, while Sharkey et al.\textsuperscript{318} implement a “Supersensitive Diet” (SSD) in their incompletely-responding patients. A “Gluten Contamination Elimination Diet” (GCED) has also been trialled by Hollon and colleagues.\textsuperscript{389} In their study of a cohort of patients with ongoing symptoms and/or persistent villous atrophy, adherence to the very restrictive GCED led to recovery in the majority. Included in this group were six patients who initially met the criteria for a diagnosis of RCD, five of whom recovered on the GCED. All of these patients had been assessed by an experienced dietitian as being adherent to the GFD, lending support to the belief that even traces of gluten are problematic for some patients.

Other steps that should be taken prior to making the diagnosis of RCD is confirming that CD was correctly diagnosed in the first place, which includes ascertaining that the patient is either HLA-DQ2 or DQ8 positive; ruling out alternative additional diagnoses, such as pancreatic insufficiency, microscopic colitis, other food intolerances, and malignancy; and repeating duodenal biopsies to confirm the presence of ongoing villous atrophy.\textsuperscript{11,69,70,386,390} Additional investigations such as video-capsule endoscopy and radiological imaging may also be required.\textsuperscript{382}

Treatment of RCD remains limited, particularly in the setting of RCD-2. Aggressive nutritional support and corticosteroids are the current mainstays of management, with other immunosuppressant agents such as azathioprine having a role in those who are no longer steroid responsive.\textsuperscript{69,70} Steroids will generally effect symptomatic improvement in both groups, and may lead to histological improvement in RCD-1. Immunosuppressant medications also ameliorate symptoms, but they do not bring about histological improvement, and, in patients with RCD-2, can increase the already high risk of progression to EATL. In these patients the treatment of last resort is myeloablative chemotherapy and autologous stem cell transplant, although this has had only limited success. Treatments targeted at blocking IL-15 are currently under investigation and showing some promise.\textsuperscript{385,386,390,391}
2.10.3.2 Malignancy and mortality

According to a 2005 review by Catassi et al.,\textsuperscript{26} the association between CD and malignant disease such as lymphoma has been recognised for many decades – perhaps even as early as the 1930s. Early on it was thought that CD carried with it a substantial increased risk of NHL in particular, but in more recent years this has been found not to be the case.

A large 2014 study, conducted by Ilus and colleagues,\textsuperscript{392} examined the incidence of malignancies in over 32,000 adult CD patients. They confirmed that the incidence of NHL was higher in those with CD, as were other small intestinal malignancies, but the magnitude of that risk was only modest. They calculated the Standardised Incidence Ratio (SIR) for NHL to be 1.94 (95\% Confidence Interval: 1.69 – 2.29), finding almost twice as many cases of NHL than would have been expected based on incidence rates for the whole population. Small intestine cancer had an SIR of 4.29 (95\% CI: 2.82 – 6.24). By way of comparison, within their paper Ilus et al. also calculated SIRs for data derived from earlier pieces of research, all of which had found much higher levels of risk of NHL. For example, studies by Grainge et al.\textsuperscript{375} (in 2012) and Elfström et al.\textsuperscript{393} (in 2011) generated NHL SIRs of 12.0 (95\% CI: 6.6 – 20.1) and 4.3 (95\% CI: 3.4 – 5.4) respectively. Somewhat in contrast, a separate 2012 study of 28,882 CD patients by Elfström and colleagues\textsuperscript{394} led to a lower SIR for small intestine cancer of 2.2 (95\% CI: 1.2 – 4.1). The increased risk was greatest in the first year following diagnosis, but did persist over the long term.

Ilus and his team also found that other cancers (specifically breast, lung, renal, bladder and pancreatic) occurred less frequently in people with CD, thus the overall risk of any malignancy was not increased (SIR 0.94; 95\% CI: 0.89 – 0.98).\textsuperscript{392} These findings are consistent with the outcomes of an earlier (2012) meta-analysis of studies investigating all-cause mortality, any malignancy and lymphoid malignancy in CD,\textsuperscript{395} although in the Ilus study, the any-malignancy risk did increase after more than five years of follow-up to an SIR of 1.31 (95\% CI: 1.04 – 1.63).\textsuperscript{392} It is not immediately clear why this might be the case, and the authors offered no explanation for this finding. On inspection of their published results it seems likely to have been accounted for by an increased risk of colon cancer, which only emerged with longer follow-up.(p.1474)
The evidence for an increased risk of colon cancer among CD patients is conflicting. Ilus et al.\textsuperscript{392} found a small overall increased risk, Elfström et al.\textsuperscript{394} found an increased risk that went back to the population risk after 12 months, while Volta et al.\textsuperscript{396} found a reduced risk among a cohort of 1757 Italian patients (SIR 0.29; 95% CI: 0.07 – 0.45). It is not obvious why these studies differ in their findings, but Volta and colleagues postulate that it may be related to differences in diet and the genetic background of the populations studied.

Data on mortality are also conflicting, with the most recent study to examine the risk of all-cause mortality among people with CD\textsuperscript{378} finding no increased risk relative to the general population, and only a 0.15% excess risk of dying from NHL. This is in contrast to earlier studies such as those led by Ludvigsson,\textsuperscript{397} and Grainge,\textsuperscript{377} and the meta-analysis by Tio et al.\textsuperscript{395} that concluded that patients with CD do have an increased risk of all-cause mortality (Odds Ratio 1.24; 95% CI: 1.19 – 1.30). This risk decreases over time, and the conclusion in recent review articles is that the absolute risk of death for people with CD is low or modest.\textsuperscript{9,11}

Biagi and Corazza\textsuperscript{398} have speculated that apparently discrepant findings relating to mortality could be related to national variations in gluten consumption and CD management, as well as to differences in the study populations with respect to definitions and the severity of disease affecting included patients.

2.10.3.3 Hyposplenism and infection

Splenic hypofunction is a well-documented phenomenon among people with CD,\textsuperscript{379} although it is not clear how many CD patients are actually affected.\textsuperscript{399} The mechanism of its aetiology is postulated to be due to chronic folate deficiency, and perhaps secondary to lymphocyte losses in the atrophic and inflamed small intestine.\textsuperscript{379} Some evidence suggests that it is more common in CD patients with additional autoimmune conditions, in which group the prevalence may be as high as 59%, and RCD in which it may occur in up to 80% of patients.\textsuperscript{400} Among a study population of 36 patients with uncomplicated CD, Di Sabatino and his colleagues found a prevalence of hyposplenism of 19%.\textsuperscript{400} It does not appear to affect children with CD,\textsuperscript{399,401} which may be due to their much shorter period of pre-diagnosis exposure to gluten.\textsuperscript{379}
The principal reason for being aware of the possibility of hyposplenism is that it predisposes patients to more serious illness when they are infected with encapsulated bacteria such as *Streptococcus pneumoniae*. The spleen plays an important role in fighting infection and regulating immune responses, so impaired function has the potential to lead to significant morbidity and even death.\(^{401}\)

Work in 2008 by Ludvigsson et al.\(^{402}\) found a “modestly increased risk of sepsis” among a cohort of over 15,000 people with CD. This was largely accounted for by pneumococcal infection, and they postulated that hyposplenism was one mechanism likely to be at play. Similarly, Zingone et al.,\(^{403}\) in their study of community acquired pneumonia (CAP), also found that an increased incidence of pneumococcal infection contributed to the increased relative risk of CAP among CD patients who had not previously been vaccinated against *Strep. pneumoniae*. More recently, a large cohort study\(^{404}\) that investigated the link between CD and invasive pneumococcal disease found a 46% increased risk among people with CD, although the actual incidence of infection among their cohort of over 29,000 patients was just 0.15%. A recent systematic review and meta-analysis of similar studies,\(^ {405}\) and including this one, has confirmed the increased risk of pneumococcal infection.

There is mixed support in current guidelines documents for actively managing this risk, with only the BSG\(^ {70}\) and WGO\(^ {72}\) recommending that patients with CD should be offered pneumococcal vaccination. Two recent review articles, by Mooney\(^ {8}\) and Lebwohl\(^ {11}\) also include this recommendation. Separate pneumococcal vaccination is not an issue for children with CD as most childhood immunisation schedules include this already.

### 2.10.3.4 Osteoporosis

It is well established that CD impacts on bone health, and as discussed earlier in this chapter, “metabolic bone disorder” is one of the indications that should prompt consideration of testing someone for CD.\(^ {132}\) It is known that between 50% and 70% of newly diagnosed patients will have reduced bone mineral density (BMD)\(^ {25,258,263}\) and a recent systematic review and meta-analysis of studies relating to fracture risk in CD suggests that this is also increased.\(^ {406}\) Interestingly a recent small retrospective analysis of New Zealand patients who underwent bone density scanning in the year following diagnosis of CD found that while the average bone
density Z-score was slightly lower than expected, it still lay within the normal range for the great majority of patients. In untreated CD, the mechanism by which BMD is reduced is thought to be primarily due to calcium and vitamin D malabsorption, but it is also likely that circulating inflammatory cytokines interfere with bone formation, and it may be that autoimmune factors are playing a role. There is good evidence to show that BMD will recover, at least to some extent, following implementation of a GFD.

2.10.3.5 Other autoimmune diseases

As also discussed earlier in this chapter, the presence of a range of autoimmune diseases is associated with an increased risk of CD. There are mixed data on whether this association is bidirectional, and on whether implementing a GFD will reduce the risk of other autoimmune conditions developing.

The two conditions for which there is some evidence of increased risk of these developing in CD patients are T1DM and thyroid disease. Children and adolescents (up to the age of 20 years) with CD were found to be between two and three times more likely to develop T1DM than non-coeliac population controls. Patients with CD were also found to be between two and six times more likely to develop any type of thyroid disease. The highest risk was associated with hypothyroidism, and children were more at risk.

2.10.4 Monitoring after diagnosis

In view of the range of complications that can arise in the context of CD, and given the challenges patients face in adhering to treatment, it is now widely recommended that the care of patients with CD should include ongoing support and surveillance by a healthcare professional with expertise (or at least an interest) in managing the condition. That professional may be a primary care physician, a gastroenterologist, a paediatrician, a dietitian, or a nurse working in either the primary or secondary care sector. A survey of 126 UK patients conducted in the early 2000s by Bebb et al. found that their preferred follow-up option would be with a dietitian, with medical back-up if required. However, the study also found that almost 40% of respondents were not having regular follow-up of their CD, and subsequent studies from North America have indicated that among those who are being reviewed on a reasonably regular basis, the substance of their follow-
up has been variable,29,55 (Although it should be noted that both these studies were completed before the release of the ACG guidelines that include formal recommendations about long-term management,69 so consistency in practice may have improved since then.)

In the past few years updated CD guidelines documents have been produced by the ACG,69 BSG,70 NICE,71 and WGO.72 Having also developed separate paediatric guidelines,67 the BSG guidelines are specific to adults with CD, while the other three encompass CD in all age groups.

All guidelines include recommendations on monitoring after diagnosis, although there is variation between them with respect to some aspects of management. All acknowledge the importance of adherence to the GFD as being central to recovery and ongoing good health, and all recognise that how best to assess adherence is uncertain. All indicate that an expert dietitian should be consulted when the diagnosis is first made, and should also be involved when there is concern about adherence. It has been suggested by NICE that it could be a dietitian who conducts any routine reviews,132 while the WGO recommends clinically stable patients see a nutritionist every one or two years.72 All guidelines either recommend, or imply, that blood tests to assess micronutrient levels, and state of health more generally, should form part of the early assessment of newly diagnosed patients. The ACG gives the most extensive list of suggestions including a range of vitamin levels, and copper, zinc, and carotene.69 Tests in common between the guidelines are a full blood count, ferritin and iron studies, folate, vitamins B12 and D, calcium, and alkaline phosphatase.

The BSG is the only group to address the issue of testing for possible complicating associated conditions. They suggest annual thyroid function, liver function, and glucose testing in the body of their document,70(p.7) although this has not made it into their separately identified (and presumably more formal) recommendations. Other writers have suggested that, at least with respect to the possible endocrine complications of CD, a reasonable approach to take would be to screen patients for suggestive symptoms, and target testing to those in whom there is a suspicion, however faint, of concomitant disease.412
2.10.4.1 Repeat serology testing

Despite the fact that CD serology tests have proven so successful in facilitating the diagnosis of the condition, the same cannot be said for their use in monitoring. It is widely accepted that they lack the sensitivity to determine whether a CD patient has achieved mucosal healing, although a recent meta-analysis of studies investigating the correlation between serology and persistent villous atrophy found that IgA-tTG antibody and EMA tests have high specificity in this setting.\textsuperscript{413} Thus, while a negative serology test does not reliably indicate mucosal healing has occurred, a positive test is highly suggestive of ongoing damage, and indicates that the patient is probably continuing to ingest gluten, either knowingly or inadvertently. The utility of repeat testing therefore lies in predicting non-adherence.\textsuperscript{28} This is not universal however, as demonstrated by Newnham and colleagues.\textsuperscript{314} They found that among their cohort of 49 patients with positive tTG antibodies at diagnosis, 23 still had elevated levels after 12 months on a GFD, but of these, seven had normal histology on rebiopsy. This equates to 14.3\% of the initial cohort, but 30.4\% of those with persistent antibodies.

The available guidelines documents all indicate that there is a place for CD serology in the surveillance of the condition, but that it should be used in conjunction with other aspects of monitoring such as a reviewing symptoms and diet adherence.\textsuperscript{69,70,72,132} All recommend repeating serology tests in the first year following diagnosis, generally in association with a clinical review. Thereafter, the ACG advocates testing tTG or DGP antibodies on an annual basis,\textsuperscript{69} while the WGO recommends “periodic” evaluations.\textsuperscript{72} The BSG and NICE make no reference to the use of serology for monitoring purposes, although the BSG document includes the comment that “it is reasonable to assume that positive antibody titres correspond to some gluten intake”.\textsuperscript{70}(p.8)

There is evidence (albeit from a small study)\textsuperscript{414} to suggest that coeliac antibodies (tTG, DGP, and EMA) fall significantly during the first year of a GFD, and that strict compliance has more of an impact on overall levels than does partial compliance. This same study also found that after more than four years on the diet, antibody levels for strictly compliant patients had continued to fall, whereas levels in the partially compliant had tended to flatten or even increase slightly.\textsuperscript{414} The guidelines’ recommendations are generally consistent with this study.
2.10.4.2 Follow-up biopsy

The place of rebiopsy in the monitoring and management of CD remains unclear, as summarised in this statement in the BSG guideline document: “There is no conclusive evidence of the benefit of universal follow-up biopsy, and we were unable to reach a consensus.” The essence of the dilemma is whether rebiopsy should be routine for all CD patients, or whether it should only be offered on an “as indicated” basis. At the centre of the dilemma is whether clinical outcomes (and the patient’s best interests) are influenced by the practice, especially given that it is an expensive and invasive procedure to undertake.

On the one hand are groups such as the Cambridge Coeliac Clinic who include routine rebiopsy in their CD pathway. They found that this practice enables them to stratify their patients into different treatment pathways (e.g. early discharge to primary care versus increased dietetic intervention), and thus predict more accurately which patients need closer clinical supervision. Haines et al. similarly advocate for the inclusion of rebiopsy as part of follow-up, “no earlier than 1–2 years after commencement of the GFD.” On the other hand, a recent study from Finland found no difference in long-term clinical outcomes between those who underwent routine follow-up biopsy at around 12 months following diagnosis, and those who did not. The authors therefore concluded that “a more personalised follow-up” would be appropriate, for individuals selected on specific clinical grounds, and at least two years following diagnosis.

The guidelines groups have on the whole opted for a middle road. The ACG notes that it is “reasonable to do a follow-up biopsy in adults after 2 years of starting a GFD to assess for mucosal healing,” but they make a strong recommendation that rebiopsy should be undertaken in patients who fail to respond, or whose symptoms relapse despite a GFD. Similarly, the BSG recommends that follow-up biopsies “may be considered in patients with CD, and are potentially helpful in identifying patients at increased risk of lymphoma”, but they “should be undertaken in patients with CD whose condition does not respond to a GFD.” The WGO likewise states that “intestinal biopsies should be considered mandatory in patients with persistent symptoms despite evidence of a strict GFD”, while NICE advise referring for endoscopy patients who have persistent symptoms and/or high antibody titres that are not changing after 12 months of a GFD.
Recently Silvester et al.\textsuperscript{413} have identified an important issue with regards to persistent villous atrophy, commenting “that it is an important question whether persistent villous atrophy is related to lack of healing, or if there are interspersed periods of healing and re-injury.”\textsuperscript{(p.698)} It would seem prudent to bear these two possibilities in mind when discussing positive rebiopsy results with patients.

\textit{2.10.4.3 Bone density assessment}

As already discussed, reduced bone density is common among people with CD. However, if and when this should be formally assessed by DEXA scanning remains an open question. In their 2008 systematic review Haines et al.\textsuperscript{28} proposed that this should be done as part of the initial work-up of newly diagnosed patients, but that subsequent assessments should be based on overall risk of fracture. More recently the BSG has recommended that bone density should be assessed after a year of the GFD, in patients over 55 years of age, or who have other risk factors for osteoporosis.\textsuperscript{70} However, they do also recommend testing calcium, Vitamin D, alkaline phosphatase, and parathyroid hormone levels as part of the initial assessment of coeliac patients. The NICE guideline recommends that decisions about DEXA scanning should be made in accordance with their separate osteoporosis guidelines,\textsuperscript{132} while the WGO has suggested that in the first year of follow-up a DEXA scan “can be performed to provide a baseline measure”.\textsuperscript{72}(p.764) The ACG is agnostic on the issue, making no reference to DEXA scanning in any of their recommendations, but including it, with a question-mark alongside, in the monitoring algorithm presented in the document.\textsuperscript{69}(p.666)

\textit{2.10.4.4 Annual review}

All of the listed guidelines recommend that patients should be reviewed on an annual basis, or, in the case of the WGO, “every 1 – 2 years” once they are clinically stable.\textsuperscript{72} In fact, as noted in Silvester and Rashid’s 2007 review of management guidelines,\textsuperscript{307} this is not new. Without being specific about what they should consist of, the BSG nicely captures the role of such reviews as being “to ensure response to symptoms, prevention of consequences, and continued maintenance of motivation to remain gluten free.”\textsuperscript{70}(p.14). The ACG expresses a similar set of goals.\textsuperscript{69}

The NICE guideline recommends that an annual review should include measuring height and weight, and reviewing symptoms, dietary adherence, and the
need for specific blood tests. The BSG formally recommends “annual haematological and biochemical profiles” (p.9), but the ACG does not make any specific recommendations about what to include. The WGO recommends that patients should see a nutritionist every one or two years.

Paediatric guidelines from both the UK, and North America recommend that children should also be reviewed annually, for growth and development, symptoms, adherence, micronutrient status, and IgA-tTG antibody levels.

2.10.5 Management additional to the GFD

Alongside treating CD with a GFD, there are other management interventions that are variably recommended. Thus the BSG, NICE, and WGO each explicitly recommend that newly diagnosed patients should be encouraged to join, or be given information about local coeliac support groups. Paediatric guidelines make similar recommendations. And although the ACG does not formally recommend this, reference is made to the role of support groups in an algorithm for suggested management presented in the guideline. Earlier statements on CD from the American Gastroenterological Association Institute make explicit reference to the importance of these groups.

The testing of first-degree relatives of newly diagnosed CD patients is another issue that is addressed in some guidelines, although not at the level of formal recommendations. It is also noted within the earlier algorithm proposed by Haines et al. Within the body of their document the ACG notes that “newly diagnosed patients with CD should inform their first-degree family members of the potential increased risk for CD and the recommendation for testing.” The statement is made in the context of discussion about testing for CD, rather than management per se. Similarly, the WGO note that “first-degree relatives of index cases should be screened for CD” (p.759), when considering who should be tested for the condition. The BSG and NICE do not make any reference to newly diagnosed patients informing their families about increased risk, but both include having a CD-affected first-degree relative as an indication for testing for CD. A 2015 survey of patients with CD found that recommendations to have their first-degree relatives tested were not being routinely made by treating clinicians.
As already noted in the earlier discussion of the complications of CD, whether or not to offer people with CD specific vaccinations is also variably acknowledged. The BSG make a clear (level C) recommendation that newly diagnosed patients should be vaccinated against *Streptococcus pneumoniae*, but note that whether they should also be vaccinated against *Haemophilus influenzae, Neisseria meningitidis*, or the influenza viruses is “unclear”.\(^{(p.9)}\) The WGO recommends that vaccination against all three bacteria should be performed,\(^{(72)}\) while the ACG and NICE do not refer to the issue at all.

### 2.11 The Patient’s Perspective

While a diagnosis of CD may bring with it a sense of relief to patients who have struggled with unexplained symptoms for many years,\(^{(418)}\) it is also a condition that is challenging to manage. The complexities of the GFD already discussed, and the fact that this is still the only available treatment for people with CD, mean that for many the burden of the disease is high. This is exemplified in work by Shah et al.\(^{(342)}\) In this study, alongside people with a range of other chronic health conditions, including end-stage renal disease (ESRD), people with CD were surveyed about their health and perceived burden of treatment. Despite the fact that those with CD reported the highest health state of all groups, they also had some of the highest levels of treatment burden, equal only to that of the patients with ESRD. A recent study from North America has also suggested that partner-burden is relatively common among the life-partners of people with CD,\(^{(419)}\) with more than 35% of the study group reporting mild-to-moderate burden associated with their partner’s CD. (It should be noted that this was a small study involving 94 patient/partner pairs, corresponding to a response rate of only 22% from those who were invited to participate. Nonetheless it suggests that this is an issue that warrants further investigation, and attention by clinicians involved in the care of people with CD.)

A number of surveys of patients living with CD have been conducted over the years in an effort to assess their quality of life (QoL),\(^{e.g.275,345,347,348,420}\) and how that has been impacted by CD. The consistent finding is that while adhering to a GFD improves QoL from pre-diagnosis levels,\(^{278}\) it is onerous and, in particular, negatively affects dining out, travel, and social events. As found by Barratt et al.,\(^{420}\) for many people with CD it is the degree of difficulty adhering to the GFD that has
the greatest impact on them. Specifically because of the negative effects noted above, at least one study (by Lee et al.\textsuperscript{348}) has found that high numbers of people with CD (80\% of a study population of over 1700) deliberately compromised their GFD in social situations, despite also reporting a high degree of adherence overall. And in another pointer to the burden of the GFD, Whitaker et al.\textsuperscript{345} found that people who had been diagnosed with only minimal symptoms, or on the basis of screening, were more likely to regret having being diagnosed than their classically-symptomatic counterparts. This was despite the screening-detected individuals generally having similar or better QoL scores than the symptomatic participants in the study.

In addition to survey-based inquiries into the impact of living with CD, there have also been qualitative studies that have sought to capture the experiences of affected patients.\textsuperscript{e.g.341,421-423} These too demonstrate that the GFD is burdensome, providing personal insights into the issues people with CD face. Interview subjects’ comments include “I miss...being able to just eat anything...I hate having to think about it. I hate having to explain that I can’t eat it” from Taylor,\textsuperscript{341}(p.5); “It impacts what I eat, where I eat, when I eat, if I can eat...”, from Leffler et al.\textsuperscript{423}(p.641); and from Rose and Howard “I sometimes feel I have lost myself...”\textsuperscript{422}(p.36), and (from another participant) “[I]f I was ever told I could eat a normal diet again I would eat so much I would burst...I am probably healthier than I was but I don’t enjoy my life as much as I used to when I could go out and eat anything”.\textsuperscript{422}(p.37) From their analysis of written narratives by 130 adults with CD,\textsuperscript{422} Rose and Howard conclude that the “losses and changes entailed [in gluten-free living] impact on the personal and social identities of those living with coeliac disease, and on the behaviour of others towards them.”(p.30)

There are now a number of tools that have been developed to try and measure health-related quality of life (HRQoL) specific to CD. These include the Celiac Disease Questionnaire (CDQ),\textsuperscript{424} the CD Quality of Life instrument (CD-QOL),\textsuperscript{425} and the recently developed CD Quality of Life questionnaire (CDQL).\textsuperscript{426} However, while these tools may prove useful for research purposes, and in trials of potential new treatments in particular, it is not clear how they should best be deployed in the day-to-day clinical setting. They each take some time to complete, ranging in complexity from the CD-QOL that comprises 20 items with a 5-point Likert scale tick-box for
each, to the CDQL that includes over 40 items to be rated. Scoring and interpreting patient responses also takes time. The combined impact of these factors seems likely to inhibit their routine use with CD patients, and yet the burden of living with CD does need to be appreciated by treating clinicians. A review of the literature by Zingone et al. pertaining to psychological morbidity associated with CD concluded that CD leads to “considerable psychological impact”, at least some of which relates to “the patient's subjective perception of the disorder and of the GFD used to treat it.”

A possible way forward might be to develop a much briefer screening tool, somewhat like the depression screening questions advanced by Arroll and colleagues. They identified two questions that can be asked of patients verbally (rather than requiring them to complete a paper-based questionnaire), the answers to which can be used to determine whether or not a more formal evaluation of the patient’s mood is indicated. With respect to living with CD, several domains that affect HRQoL have been identified, but they almost all come back to the challenges associated with adhering to the GFD. Perhaps then there would be merit in exploring whether a single question to patients about how they are managing the challenges of a GFD (for example) could be used to identify those in whom it would be important to assess their HRQoL more extensively. Encouraging clinicians to include one such question during reviews of patients with CD is likely to be considerably more acceptable (to clinicians and patients alike) than implementing comprehensive HRQoL assessments as part of routine CD follow-up, although this too would need to be evaluated.

As already noted in the previous section, when patients were asked about what they want with regards to their CD care, their preference was for dietitian follow-up, but with medical review available. Barratt et al. also concluded that dietitians are “best placed to safeguard the Coeliac individual’s QOL in the long term, and with the greatest potential for benefit.” In New Zealand, where access to dietetic services is often limited, being able to identify those patients who would stand to gain the greatest benefit from ongoing dietitian input would be of value. The judicious use of a CD-specific HRQoL could help with this process.
2.12 Conclusion

This chapter has traversed the extensive history of CD from the earliest descriptions given by Aretæus of Cappadocia, to the identification of gluten as the principal trigger, the recognition of typical histological changes seen in the intestinal mucosa of affected patients, and the discovery of tTG as the target autoantigen in the small bowel. Clinical definitions of the condition, its complex pathogenesis, and its varying prevalence in different populations have been discussed, along with its myriad patterns of presentation, and recent guidelines relating to testing and management. Issues relating to the GFD have also been explored, together with future treatment possibilities that are under investigation, and a discussion about the impact that living with CD and having to adhere to a GFD have on patients.

With respect to the studies that comprise this project, the principal areas of interest are:

(1) The many and varied ways in which CD may present, which requires of practitioners an understanding that it is more than a disease of the gastrointestinal tract, and a level of knowledge that enables them to recognise CD as a potential explanation for a patient’s constellation of symptoms. (Section 2.8)

(2) Pre-requisites for making the diagnosis are that the person being investigated is consuming an adequate amount of gluten; that appropriate tests are requested; and that test results are correctly interpreted. (Section 2.9)

(3) Management of CD encompasses much more than advising the patient to go on a GFD. It should also include ongoing support, and surveillance for complications and associated conditions. (Section 2.10)
Chapter 3: Methods

3.1 Introduction

As outlined in Chapter One, the principal task of this project was to describe what is happening in New Zealand with regards to the recognition, diagnosis, and management of CD, with a particular emphasis on adult disease. The major hypothesis underpinning this task is that GPs in New Zealand have limited disease-specific knowledge about CD. If this hypothesis is indeed correct, then this might be evidenced by the following:

- CD is under recognised and/or
- CD is underdiagnosed and/or
- CD is sub-optimally managed.

As also discussed in the earlier chapter, the primary hypothesis gives rise to a number of research questions:

- What do GPs in New Zealand know about CD?
  
  This question is elaborated by the additional questions
  
  i.   Whom do they test, and under what clinical circumstances will they test them?
  ii.  On what clinical information do they base decisions about diagnosis?
  iii. How do they manage patients with the condition?
  iv.  From where (or whom) do they get their information about these issues?
  
  - How do gastroenterologists in New Zealand manage patients with CD?
    
  and
  
  - What is the prevalence of diagnosed CD in New Zealand today?

In order to adequately address these questions the project was broken down into three separate studies, all of which were observational studies with a descriptive emphasis. Observational studies are those in which the study describes the current state of affairs within a population with regards to a topic of interest. Limited analysis of associations between variables are sometimes undertaken, but
research questions are predominantly “what” questions and interest is centred on profiling particular characteristics of the study population. This is as opposed to experimental studies in which the project includes making an intervention and then assessing its impact on a group of interest within the study population.429

Two of the studies in this project were cross-sectional and utilised self-administered surveys. That is, they investigated the populations of interest at a specific point in time.429 The third interrogated laboratory data relating to CD that covered an extended period of time. These data had been processed by Southern Community Laboratories (SCL), one of the major laboratory service providers in New Zealand.

This chapter describes the methods employed in each of the three studies. Although the two survey studies had many aspects in common with each other, they also had a number of differences and are therefore discussed individually. Following on from this is a description of the laboratory data investigation.

3.1.1 Why surveys?

Self-administered surveys are a well-recognised way of gathering descriptive information from and about a population of interest.430 For this project, they were chosen as the most appropriate way in which to gather the necessary information from gastroenterologists and GPs because, as discussed by Boynton and Greenhalgh in their BMJ “Hands-on guide to questionnaire research” series,431,432 they “offer an objective means of collecting information about people’s knowledge, beliefs, attitudes and behaviour”.432 (p.1312) By gathering this information in a systematic fashion from a representative sample of a population, it should be possible to generalise results to that population as a whole.433

As well as using self-administered questionnaires, survey data can also be gathered via telephone or face-to-face interview in which a surveyor personally administers the survey questions to participants, or by asking participants to complete the survey with the investigator present to assist with any questions they might have. Neither of these options was going to be practical for the present studies, which were to involve large numbers of busy health professionals dispersed across New Zealand.
There are also alternative options for evaluating physician practices, none of which were deemed appropriate for this project. These are direct observation of consultations (either with someone sitting in, or by recording them and reviewing those recordings at a later date); having practitioners see standardised patients (either knowingly or unknowingly) and assessing their management against a pre-determined set of outcomes; or conducting reviews of sets of doctors’ medical records. Each of these is time-consuming and likely to be expensive. Each can also lack the objectivity afforded by utilising a well-designed survey, in which questions are standard for all participants and can cover a much broader range of topic-specific issues than any of these three modes allows. This was particularly important for this project, in which broad knowledge about CD was the primary area of interest. Moreover, the first two of these modes of evaluation focus quite explicitly on the individual and do not afford participants any anonymity, at least while the data are being collected. These forms of data-gathering could much more readily be construed by participants as being a “test” of them as individuals, which is counter to the aim of a research project such as the present one, which was to be able to describe practices at a population level. In a 2005 review on the use of vignettes in surveys of health professionals, Veloski et al. pointed out there is a risk that even when completing surveys, participants may be drawn into treating the exercise in the same way that they would take an exam. That is, they may give the answers they believe to be right according to textbooks or guidelines, rather than which represent their actual practice. It is not unreasonable to assume that these more individually-focused alternative forms of investigation of physician practice would be likely to magnify this effect, beyond what might occur with a survey.

3.1.1.1 Total Survey Error

An issue that does need to be borne in mind when conducting surveys is that of “total survey error”, a term used by Dillman (a leading expert on survey design and delivery) to encompass the ways in which surveys can fail to produce accurate data that can be confidently generalised to the population of interest. He has divided total survey error into four groups:
• coverage error, which arises when not all members of the target survey population have the same chance of being included in the sample population;
• sampling error, which arises because not every person in the population is sampled;
• non-response error, which arises when not everyone who was sampled responds; and
• measurement error, which arises when respondents’ answers are inaccurate or imprecise. (pp. 16-18)

The importance of addressing each of these potential sources of error is widely covered in the survey methods literature. The first two sources of error can be minimised by appropriate sample selection, and the latter two by maximising design features that reduce ambiguity and other potential sources of misinterpretation, and by implementing strategies to promote participation. Steps taken to ameliorate these sources of potential error in the two surveys that were part of the present project are described in the following discussion of methods.

3.1.1.2 Using incentives to increase survey response rates

There is extensive research investigating the use of incentives in survey-based research as a means for increasing response rates (and thus reducing non-response error), including studies that have looked specifically at the impact on surveys involving medical practitioners. The majority of these studies have found that using incentives has a positive impact on response rate, particularly when they are monetary and unconditional (i.e. included with the survey rather than dependent on a completed survey being returned).

The use of incentives in each of the two survey-based studies of this project was carefully considered. For the survey of gastroenterologist the initial decision was not to use incentives at all. Including money with the survey was ruled out both because the initial means of sending the survey was via email, but also because this has not been the norm in studies conducted in New Zealand and it did not seem an appropriate step to take. The evidence for the impact of including conditional incentives (i.e. a “reward” given on receipt of a completed survey) is weaker and so the study proceeded without this.436
The issue was revisited for the GP study, principally because surveys of GPs (as compared to other physicians) are particularly prone to poor response rates. It was therefore important to consider any strategy that might go some way towards ameliorating this. Once again including an unconditional monetary incentive with every survey was ruled out. Reasons included that it would be too expensive to do so, that there were practical limitations given that the survey was being sent to some people in electronic form only, that there was no guarantee that it would reach the intended recipient, and that New Zealand Post had restrictions around sending money through the mail. The same reservations about the propriety of including money that had arisen with regards to the gastroenterologist survey also remained. But on this occasion it was decided that it would be worth utilising a conditional incentive. This took the form of a prize-draw which participants could choose to enter. The prize was donated by bpacnz (The Best Practice Advocacy Centre New Zealand), which was acknowledged in the letter that went out with the survey, and comprised a $750.00 travel voucher to be used to attend a conference or educational event of the recipient’s choice.

3.2 Timeline

Of the two survey-based studies, the survey of gastroenterologists was developed and conducted first. The rationale for this was twofold. Firstly, because the survey population was relatively small it would be possible to evaluate different techniques relating to survey delivery, assessing their overall efficacy in the New Zealand context, while also being able to augment the process if response rates were proving to be unsatisfactory. Secondly, a possible survey instrument was already available, potentially reducing the amount of time required in getting the study underway. The survey was delivered in the latter part of 2013 and early 2014. The study involving GPs then followed, and the experience gained from the first study was able to be incorporated into its development. This survey was delivered in May 2015.

As will be discussed later in this chapter, the development of the laboratory study was an entirely different process and occurred in parallel with the two surveys. Initial laboratory data were obtained in early 2014. Additional data were gathered through the second half of 2015 and the first half of 2016.
3.3 Ethical Review Process

Each of the three studies that comprise this project was submitted separately for Ethical Approval from the University of Otago Human Ethics (Health) Committee. As part of the approval process, each study protocol was first peer reviewed by two academic members of staff from within the Department of General Practice and Rural Health, Dunedin School of Medicine. Any necessary amendments were made following each review, and then each protocol was endorsed by the Chairperson of the department’s Research Committee.

Proposals for each were also submitted to Te Komiti Rakahau ki Kāi Tahu, the Ngāi Tahu Research Consultation Committee. This is a committee of the Ngāi Tahu Rūnanga formed as part of a Memorandum of Understanding with the University of Otago. It reviews proposed research projects and makes recommendations to researchers to ensure that their research has an appropriate focus on Māori health.

Appendix A contains the Ethics Committee approvals and Ngāi Tahu Committee responses relating to each study. It also includes additional correspondence about issues on which the Ethics Committee sought clarification, and which were resolved to that committee’s satisfaction.

3.4 The Survey of Gastroenterologists

3.4.1 Introduction

Because the diagnosis of CD still depends on histological analysis of duodenal tissue obtained through endoscopy, gastroenterologists play an important role in assessing and managing patients with CD. As already discussed in the introduction to this work, CD was traditionally regarded as a primarily gastrointestinal disease. Although that view has been modified in recent decades with our increasing understanding of the underlying autoimmune-mediated mechanisms of the disease, gastroenterologists continue to be regarded as the CD specialists, especially with respect to adult patients. As such their practice relating to the diagnosis of CD and, perhaps more importantly its management, is likely to influence that of the GPs whose patients they see, and would be expected to contribute to the knowledge GPs have about the condition. As was also discussed in the introductory chapter, there is evidence that the practices of gastroenterologists with respect to the
management of CD are not always consistent with guidelines, or with each other.\textsuperscript{29,55} In situations in which GPs might be consulting with gastroenterologists for advice, or be receiving correspondence from them relating to their patients with CD, inconsistencies in practice between individuals raises the possibility that patient care will also be inconsistent. For these reasons it was appropriate to investigate the practices of New Zealand gastroenterologists relating to CD.

3.4.2 Background

There are two publications with which this study primarily interacts, particularly where methods are concerned. Both were introduced in Chapter One. The first was conducted by Silvester and Rashid,\textsuperscript{55} and published in 2010. They had already published a review of the then current practice guidelines relating to the long-term follow-up of people with CD,\textsuperscript{307} and they followed this with a study designed to examine the practices of Canadian gastroenterologists with respect to their management of their CD patients. The second was an article by Deepak Parakkal and colleagues,\textsuperscript{56} published in 2012. This paper reported on their investigation of the question “Do gastroenterologists adhere to diagnostic and treatment guidelines for celiac disease?”

The additional studies that also investigated physician knowledge about CD referred to in Chapter One were of less direct relevance to the present study because of their almost exclusive focus on the recognition, rather than the management of CD.\textsuperscript{50,57} The study of Italian paediatricians by Fortunato et al.\textsuperscript{51} had not yet been published when the present study was being conducted.

The study by Silvester and Rashid\textsuperscript{55} was a survey-based investigation in which all Canadian gastroenterologists were mailed a copy of a questionnaire. The principal aim of the study was “to investigate the practices of Canadian gastroenterologists who provide care to patients with celiac disease”.\textsuperscript{55} (p.500) The emphasis of the project was on how this practice may or may not coincide with available guidelines, particularly with regards to management over the long term. Participants were also asked for details about the make-up of their practices, their familiarity with CD practice guidelines, and about their actual practice in the care of patients with CD.
In their study, Parakkal and colleagues set out to test the hypothesis that there is significant variation between what guidelines suggest should be best practice relating to CD, and what is the actual practice of gastroenterologists. They used an international group of acknowledged CD experts to benchmark best practice as it applied to a set of vignette-type scenarios, against which they then compared the responses of their target group. Participants in their study were gastroenterologists from the USA attending the 2009 Digestive Diseases Week conference, who were invited to complete a self-administered survey during the course of the conference.

The tool Parakkal et al. used was a survey they had designed around four “controversial scenarios” relating to CD, and which included elements of both diagnosis and management. The scenarios they designed related to the following topics:

1) A patient already on a GFD, with a probable diagnosis of CD based on blood tests done five years previously. The test used had been anti-Gliadin antibodies, which are now known to be the least reliable of the available serology tests. The patient wants to know if he does in fact have CD.

2) An asymptomatic (at least with respect to the gastrointestinal tract) patient referred for investigation and management, on the basis of a positive family history (paternal uncle) and positive IgA anti-tTG antibodies, and found to have normal histology on biopsy. An alternative scenario in which the patient is symptomatic was also put for consideration.

3) A patient with dermatitis herpetiformis and a family history of CD but no GI symptoms herself, referred for investigation of possible CD.

4) A series of mini-vignettes relating to questions around when to screen for CD.

While a few questions were in the single-best answer format, most questions associated with each vignette asked participants in the study to rate the given options using a 1 – 9 “RAND Appropriateness Scale” (RAS). The authors then took these ratings and calculated various measures of agreement and disagreement between the study participants and the expert panel, who had also been asked to complete the same questionnaire.
Initially it seemed that there was a ready-made questionnaire that could be used in the present investigation, with only some minor adjustments required to take account of the local context. The actual questionnaire was available as an online supplement to the published article (Appendix B), and permission was granted by one of the authors to use it for a New Zealand-based study (Appendix B). However, on closer examination of the questionnaire it became apparent that it was going to need extensive revision before it could be used for this study.

Firstly, the vignettes themselves contained ambiguities that made the interpretation of the data associated with them problematic. In some cases it was not clear what the question was that was to be answered by participants. For example, from the first vignette:

*Five years ago, a 25 year old Caucasian male was diagnosed with probable celiac disease on the basis of positive IgG anti-Gliadin antibodies and started on a gluten free diet (GFD). He now wants to know if he really has celiac disease as the GFD is severely affecting his quality of life.*

1) Please rate the appropriateness of the following diagnostic tests as an initial step in the work up: ...

The problem with this question was with the word *initial*. Did this mean when the patient first presented five years ago, or did it mean the initial steps to take in the current presentation? It seemed most likely that the latter was intended, but an ambiguity was present nonetheless.

Secondly, inferring actual practice (or adherence to guidelines) from responses to questions relating to the appropriateness of suggested options carries with it the assumption that respondents do what they believe is most appropriate. While it is likely that this is the case, it does not allow for other circumstances that might also influence practice, such as resource availability and patient preference.

Thirdly, and perhaps most crucially, the use of an RAS in this context seemed questionable, and the methods employed by the authors of this study differed noticeably from the RAND Appropriateness Method (RAM) that they purported to be using. Appendix C gives a detailed description of the RAM, and how Parakkal et al. deviated from standard RAM practice. Ultimately these deviations led to the decision to move away from utilising an RAS when developing the survey instrument to be used in this study.
It is interesting to note that in a more recently published study, Valérie Pittet and colleagues conducted a RAM study among gastroenterologists, relating to the management of IBD, and consistent with the processes outlined in the RAM User’s manual. In their paper they cited Parrakal et al., not as another example of using the RAM, but as an example of a study in which “(c)linical vignettes have been used...to study variation in treatment decisions, processes of care, and physician adherence to guidelines”445(p.133) Where the present study also drew on Parakkal’s study was in the use of vignettes to try and elicit information about the practices of participants, and in the content of some of those vignettes.

3.4.3 Development of the survey instrument

In similar vein to Silvester and Rashid, the aim of the present study was to investigate the approach of New Zealand gastroenterologists to the diagnosis and management of CD in adult patients. It also included questions about what information they would be likely to communicate to GPs, and what they might expect of GPs involved in that management. A second aim was to compare New Zealand gastroenterologists’ practice with the available guidelines (discussed in Chapter Two) and with the practice of their international peers, as evidenced in the studies discussed here. Of particular interest were those areas of practice in which there was no clear consensus on what should constitute standard follow-up, and thus the degree of consistency of practice across New Zealand.

The final version of the questionnaire was developed over several months, with input from multiple sources. Topic areas to include were identified, along with questions related to each, and then patient vignettes relating to these topics were developed. (Table 3.1)
### Table 3.1: Content development for survey of gastroenterologists

<table>
<thead>
<tr>
<th>Topics to include</th>
<th>Questions</th>
<th>Scenario outline</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of newly diagnosed CD; and</td>
<td>How important are various aspects of follow-up?</td>
<td>35 year old woman with positive (Marsh 3) biopsy performed by you.</td>
<td>Elements of Parakkal 1(^{st}) scenario; some Silvester themes; available guidelines; Haines et al. for aspects of follow-up.</td>
</tr>
<tr>
<td>Long-term management of CD</td>
<td>Who should be responsible and for what?</td>
<td>Series of options related to management to rate in importance and likelihood of doing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>What will you advise GP?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>What is your advice about including Oats in the GF diet?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When the histology is normal</td>
<td>What will you do next?</td>
<td>Young man with positive serology on screening coming forward for biopsy, which turns out to be negative.</td>
<td>Modified Parakkal 2(^{nd}) scenario.</td>
</tr>
<tr>
<td></td>
<td>What will you call this?</td>
<td>Asymptomatic and symptomatic options included.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>What will you advise patient and GP?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A patient declining endoscopy</td>
<td>What to do with the patient refusing biopsy?</td>
<td>GP phones you for advice about a patient with positive serology refusing a biopsy.</td>
<td>Personal experience/anecdotes from GP colleagues. Aspects of Parakkal instrument.</td>
</tr>
<tr>
<td></td>
<td>What constitutes a gluten challenge?</td>
<td>Subsequently patient wants biopsy so what is a satisfactory gluten challenge?</td>
<td></td>
</tr>
</tbody>
</table>

Vignettes were chosen as the means to set the scene for each set of questions, because there is some evidence to suggest that in studies comparing vignette-based surveys with direct observation, “clinicians’ self-reported estimates of their behaviour were, overall, close to those generated by the direct measure”.\(^{447}\) (p.18 of 20) The systematic review paper in which this comment was made did urge caution because the number of studies suitable for making valid comparisons between direct and proxy measures was small (only four studies met their inclusion criteria.
for the review), and because this result concealed instances when over-reporting and under-reporting of likely practice cancelled each other out. But the authors also suggested that “careful and rigorous development of vignette cases” might overcome this problem.\textsuperscript{447} Jon Veloski and colleagues’ guide to writing vignette-based surveys was very helpful in this respect.\textsuperscript{434}

When it came to specific content, material that had been investigated in the Parakkal and Silvester studies was incorporated when this was thought to be germane to the project. This included one scenario that was very similar to one which featured in the Parakkal questionnaire, modified to suit the New Zealand context, and to minimise ambiguity. Areas of potential controversy relating to CD management that had been dispersed through the Parakkal instrument were grouped together into another scenario explicitly concerned with what advice the gastroenterologist would give to a GP if asked for it. The Systematic Review of CD management published by Haines et al.\textsuperscript{28} was also reviewed, and aspects of management discussed there, and not already in the instrument, were also considered for inclusion.

Initial versions of the survey also included a series of questions relating to testing for CD, based on the 2009 NICE Guidelines,\textsuperscript{280} however these were removed following pre-testing, which identified that the survey would take approximately 45 minutes to complete. Indications for testing patients for CD are clearly defined and relatively uncontroversial, so these questions were likely to have added the least value when it came to assessing consistency of practice among intended study participants.

Survey questions used a mix of formats, but were mostly closed-ended in order to avoid some of the difficulties posed by using open questions. As outlined by Dillman and colleagues, open questions have a higher tendency to deter potential respondents from either answering the question, or even completing the survey itself, as they “require more work to answer”.\textsuperscript{435} In addition to this, responses can be so brief as to be unhelpful, while those that are more expansive are time-consuming and sometimes difficult to enter and code for subsequent analysis. Therefore, for this survey, participants were asked either to select a single-best answer from a range of options (nominal responses), or to rate particular options on Likert-type scales (ordinal responses).\textsuperscript{433} Some scales were unipolar with
options ranging from “not at all important” to “very important” (that is, the zero-point is at one end of the scale), while others were bipolar with options going from “highly unlikely” through “neutral” (the zero-point in the middle of the scale) to “highly likely”. Dillman et al. suggest that the optimal number of options on a unipolar scale is four or five, and on a bipolar scale five or seven. (p.137) In the interests of maintaining a consistent approach throughout the survey, all scales in this questionnaire used five points.

The most notable potential drawback of using closed-ended questions in the context of this survey was that identified by Veloski et al. and Pham et al., namely that when used in conjunction with vignette-based surveys this format has been found to lead respondents to somewhat overestimate their practice. This is thought to be due to a cueing effect when participants are presented with a list of possible options they could or would take in a particular situation and are then asked to select those that apply to them (or similar instruction). To try and mitigate this, wherever possible questions were worded such that respondents were asked to rate how likely they would be to perform each of a range of actions, rather than simply to indicate which of those actions they would be likely to do.

When there was no clear range of options to list on a scale then open-ended free-text options were used. Participants were also given several opportunities through the survey to add comments if they wished. These were generally included to enable respondents either to extend a range of possible responses for single-best option questions (e.g. Other; please specify...), or to expand on a response to a question (e.g. Please comment on your response...).

**3.4.3.1 Pre-testing and pilot testing the instrument**

The survey instrument was pre-tested during a departmental research meeting in the Department of General Practice and Rural Health, which included both lay and medically trained staff. Feedback was sought and given on issues relating to formatting and presentation, and on the wording of the scenarios and related questions. Following this meeting additional individual feedback was provided by senior academics in the department.

A link to the survey was then sent to four of the five paediatric gastroenterologists in New Zealand, as experts in CD who would not also be
participating in the survey, but who could provide feedback on the content range and validity. The fifth was one of the study’s supervisors and so was already familiar with the instrument. Unfortunately only one of these people was able to give feedback but he provided valuable comments, including drawing attention to the fact that as it stood, it took at least 40 minutes to complete.

Following his feedback the questionnaire was modified to remove content (as discussed earlier). Demographic questions, which had been modelled largely on the Silvester instrument, were also modified to reduce the burden that answering these might pose. The modified survey was then sent to a retired local academic gastroenterologist, and to a personal acquaintance who is a gastroenterologist in Australia, neither of whom would be in the study sample. Both thought that the content was appropriate and reasonable, and the questions unambiguous. It was also a manageable length, down to around 25 minutes. Follow-up discussion with the retired gastroenterologist drew the further observation that patient choice complicates many of the issues raised in the questionnaire, and that this was not addressed. After some discussion about how this might be achieved it was concluded this would add a layer of complexity that risked creating ambiguity in how questions might be interpreted, so the issue was left.

3.4.4 Identifying the survey population

The population of gastroenterologists in New Zealand is relatively small thus selecting a sample from that population to participate in the survey would have resulted in low numbers of participants overall, even if a high response rate was assured. Glenn Israel, in his widely cited document “Determining Sample Size” has discussed the implications of sampling from small populations, the principal risk of which is to the level of precision able to be claimed for results. For this reason it was decided to invite the entire New Zealand gastroenterologist population to participate; that is, to conduct a census, as Israel recommends, rather than a probability-sample study. Silvester and Rashid adopted the same approach, when they sent their survey to all gastroenterologists in Canada.

It was, however, surprisingly difficult to identify all the gastroenterologists in New Zealand. To do this I first went to the New Zealand Medical Council (NZMC), but it transpired that they do not specifically collect this level of information, as
gastroenterologists are vocationally registered in the discipline of Internal Medicine and so are grouped with physicians in the other Internal Medicine specialities (such as Cardiology and Respiratory Medicine). I then sought assistance from the New Zealand Society of Gastroenterologists (NZSG). As this is the body that supports their ongoing professional development in the discipline, it was not unreasonable to assume that all gastroenterologists in New Zealand would belong to this organisation, and could therefore be reached through it.

After reviewing the study objectives and a final draft of the survey, the NZSG executive agreed to assist with the project, and gave permission for the survey to be sent out to its members. However, this would be done on my behalf by the secretary of the organisation, rather than by giving me access to their database. In addition to this they did not want the secretary to have to spend time selecting eligible participants from the broader membership of the organisation, so the survey was to be sent to the entire mailing list, which included nurses and dietitians, as well as medical professionals. The survey would be sent as a link embedded within an email, as this would be the most convenient way for it to be distributed.

Subsequent to this, and as the study progressed, I went to additional sources in an effort to more clearly identify the target population. Firstly, I went through the list of participants who had attended the 2013 NZSG Annual Scientific Meeting. These participants came from a diverse range of health professions, so I cross-checked names with the New Zealand Medical Register to determine who among them were vocationally registered in Internal Medicine. I also searched District Health Board (DHB) websites (some of which give lists of specialists), and the Southern Cross Endorsed Providers list for endoscopy, and followed links to private health clinics throughout New Zealand. The outcome of those endeavours is discussed in Chapter Four.

3.4.5 Implementing the survey

The questionnaire was developed to be web-based using SelectSurvey.NET software, and hosted at survey.otago.ac.nz. This was a software programme freely available to University of Otago staff at the time and had a range of tools for designing questions in a variety of formats. These included matrices for covering a wide range of topics in single questions, multiple choice type questions, and text
boxes for open questions. Radio-buttons were used where only one response was required (or desired), while tick-boxes were used when more than one answer was requested. Questions could also be made “compulsory”, which meant that respondents could not progress until an answer had been entered. (Appendix D is a printed version of the online questionnaire.) The survey was able to be configured so that, if they wished, respondents could save their answers and leave the survey, to return later to complete it. It was also configured so that respondents could only complete the survey once.

The survey was first sent in electronic format as a link to the website embedded in an email, distributed to members of the NZSG by the secretary of that organisation. This email was sent in mid-September 2013, and included information about the aim of the study, the names of those involved in the study, and a statement that the study had been approved by the University of Otago Human Ethics committee. Intended recipients were gastroenterologists, gastroenterology trainees, and surgeon endoscopists, which was also clearly stated in the email. (Appendix E). The first page of the survey contained additional information about how to complete it, assured participants that their responses would be anonymous, and gave them the opportunity to decline to participate. (Figure 3-1)

![Screen shot of opening page of online gastroenterology survey](image)

**Figure 3-1: Screen shot of opening page of online gastroenterology survey**

In line with best practice recommended by Dillman et al.,435 a follow-up reminder email was to be sent two weeks later, however, as the secretary of the
NZSG was away at that time, there was a delay of approximately two weeks before this occurred. (Appendix E) It seems unlikely that this delay would have had a substantial impact on the study.

In November 2013 the NZSG held its Annual Scientific Meeting in Wellington. In order to improve response rates to the survey, I took hardcopy versions of the questionnaire to that meeting and used a Coeliac NZ stand as a platform for distributing and then collecting them. During the course of the meeting announcements were made over the loud-speaker system inviting conference-goers to visit the stand to collect a copy of the survey, and during breaks in proceedings I approached individuals inviting them to participate. Following that meeting a third email was sent asking anyone who had taken a hard copy at the conference to return it, and once again inviting people who had still not completed the survey to do so. (Appendix E)

In early 2014, following some preliminary analysis on completed surveys, it became apparent that female gastroenterologists, and gastroenterologists practising in the greater Auckland area were under-represented among respondents. Therefore, at that stage a targeted mail-out was made to those two groups. Each person was sent an individually addressed letter explaining why he or she was being approached again, with a request to return the survey in a reply-paid envelope provided for the purpose. (Appendix E) As an extra prompt to participate, a pen was included with each survey.

In summary, the survey was delivered over a 7-month period in 2013 and 2014, utilising mixed modes, delivered sequentially. The decision to start with the online mode of delivery was a pragmatic one, because this was going to be the only way in which to access the target audience, at least in the initial stages of the project. As outlined above, the NZSG were prepared to facilitate the delivery of the survey, but in a limited way. Adopting a sequential approach to survey implementation has been shown to improve response rates from doctors when compared to those surveys which rely on online participation alone. In this study it was a means of addressing concerns about coverage, sampling, and non-response errors, which relying on a single mode of contact would have risked increasing.
3.4.6 Data entry and analysis

One of the advantages of online and web-based surveys is that participants enter their own data. While the survey is open to participants it can be configured such that only one person at any particular IP address can complete the survey, meaning that each person can only participate once. Their responses are stored on the platform that hosts the survey, in a form able to be exported for later analysis. Once the survey has closed the site can be reconfigured so that it is possible for one person to enter multiple survey responses. This means that responses that have been returned in hard copy are able to be entered into the same database. This was the process that was employed for this survey.

Once all the data had been entered, the dataset was exported from the website in Comma Separated Variables format. This was then converted into Excel spreadsheets. Data were then coded to facilitate analysis using Stata Corp statistical software (Version 13.1, Stata Corp, College Station, Texas, USA). The process of coding was also used to check that the data in the spreadsheet had been entered correctly.

Data generated were both ordinal and nominal. Analysis was primarily descriptive but, where appropriate, bivariate analysis of possible associations was undertaken using Pearson Chi-square or Fisher’s Exact tests. Thus frequencies of responses were measured, and associations between responses and the demographic profiles of respondents were examined. Patterns of responses between questions and scenarios were also investigated. Statistical significance was determined based on an alpha of 5%, (p≤0.05).

3.5 The Survey of General Practitioners

As discussed in both the introductory Chapter of this thesis, and in the introduction to this chapter, the primary research question of this project is “What do GPs in New Zealand know about CD?” This arm of the project was designed to be the principal resource with which to answer that question, once again by means of a survey.

3.5.1 Development of the survey instrument

This study is the first such study about CD to have been undertaken with primary care practitioners so there were no previously used instruments available which
could be used or modified. While aspects of the gastroenterologist survey could also be used in this second study, the focus of this enquiry was to be slightly different, and the range of topics to be covered broader, so many questions had to be developed de novo.

In the survey of gastroenterologists, the primary focus was on the likely practice of gastroenterologists in representative situations, for example when managing a patient newly diagnosed with CD. This meant the questionnaire could be developed around vignettes that exemplified such situations, and which would elicit responses from the group of participants about how they would each manage a similar patient. Among other things, their responses would identify variations in practice, as well as examples of when that practice was reasonably consistent.

The focus for the GP survey was to be GPs’ overall knowledge about CD, as might be evidenced by their practice in a wide range of clinical situations. Therefore, to use vignettes in this context risked having a questionnaire that would be either too specific to be able to draw conclusions about overall knowledge, or comprised of so many different vignettes as to render it too cumbersome (and therefore unappealing to potential respondents). For these reasons, the question stems that were developed were of a more general nature than those of the gastroenterology survey, and did not utilise vignettes. In addition to this, material relating to the recognition of CD and the steps necessary to reach the diagnosis did need to be included. As discussed in Chapter One, practices relating to these issues were at the heart of the concerns expressed about what GPs know about CD.

Content for the questions that constituted this survey was drawn principally from the 2009 NICE Guideline relating to CD (Clinical Guideline 86), which clearly sets out those situations in which patients should be tested for CD, those in which they could be tested, and how they should be tested and diagnosed. As a GP I was also aware of issues relating to CD that my colleagues sometimes found to be problematic, so questions addressing these issues were incorporated, along with examples of apparently erroneous practice that had been reported to me by CNZ. Management questions were modified from the gastroenterologists’ survey, and focused on areas of practice in which there remained a lack of clarity around what might be regarded as best practice. Review articles and Guidelines’
documents discussed in Chapter Two were also used to inform these questions.

The survey was divided into three sections with questions grouped accordingly. The first related to “Coeliac Disease in General”, the second to “Coeliac Disease in Your Practice”, and the third to “Demographic Information”. At the end of the first section respondents were invited either to continue with the next section if they had patients with CD, or to go straight to the demographics section if they did not.

As with the gastroenterologist survey, questions were mostly closed-ended, and utilised Likert-type scales with which participants were to rate their responses. Matrices were used when there was a wide-range of related variables to cover (e.g. presenting symptoms in a patient that might prompt testing for CD), and open-ended questions were also included when necessary. “I don't know” options were also included for some questions, and for the two principal matrices one or two “sleeper questions” (i.e. deliberately incorrect options) were included. This is a strategy recommended by Aday and Cornelius that can be helpful in evaluating responses to knowledge-related questions.429(p. 273)

In the second part of the survey relating to their experience with patients with CD, participants were asked to rate how often they would be likely to undertake a number of different actions. Once again, this was done to try and ameliorate the potential cueing effect of asking participants to tick a range of options. Response options were generally on a scale ranging from “almost never” to “almost always”. Because the focus was on knowledge, and to try and capture more nuanced information about motive, the “almost never” option was split into three:

- Almost never, I don’t think this is necessary.
- Almost never, I wasn’t aware that this was necessary.
- Almost never, I assume a gastroenterologist does this.

Respondents were also reminded in every question that they should be thinking about their adult patients with CD and, as recommended by Dillman and others,435 what was expected of them in each question (e.g. Please choose one option).
3.5.1.1 Pre-testing and pilot testing the instrument

When the development of the questionnaire was nearing completion it was presented to a group of first-year GP trainees for their input. They were asked to comment on the content and wording of questions, and on options for formatting the paper-based version that was to be mailed out to the study sample. They each completed the draft survey and then as a group we discussed it. In that discussion they identified some questions in which there was ambiguity about what was intended by the question, and this was subsequently able to be rectified. They were also strongly in favour of an A5 booklet format, rather than A4 pages stapled together, regarding the former as less intimidating. In the light of this feedback, and given that Dillman et al. also strongly recommend using booklets, this format was adopted.435

Once the booklet format had been finalised and necessary amendments made to individual questions, the questionnaire was then piloted with a group of GPs in Dunedin. They were asked about the appropriateness of the questions, whether there were any other questions that should be included, and how long the survey took to complete. All were positive about the content and presentation of the survey, and only a very few minor wording changes were suggested. They reported that the survey took approximately 20 minutes to complete, which they felt was not unreasonable.

3.5.1.2 Design features to improve response rates

Following pilot testing the final version of the questionnaire was sent for professional printing. It included a University of Otago Logo on the front cover, and a letter of introduction that outlined the purpose and context of the study, and why the recipient’s participation was requested. Each of these factors has been demonstrated to effect small increases in response rates to surveys.436

The letter of introduction formed the front cover of the booklet, rather than being separate from it, to minimise the number of pieces of paper that would confront recipients, and to make it more likely that the actual survey made it into a recipient’s hands (as opposed to being disposed of without a glance on reading a letter of request). The inside of the cover included the information that participants had been randomly selected and that the study had received ethical approval from
the University of Otago Human Ethics Committee, and gave an assurance of respondent anonymity. These factors are also regarded as important elements of survey design. The final version of the survey can be found in Appendix F.

3.5.2 Calculating the sample size

As already discussed, the aim of this study was to answer the question “What do GPs in New Zealand know about CD?” As there are well over 3500 GPs in New Zealand, this would require a probability-sample study as opposed to a census, as had been conducted with the gastroenterologists. A biostatistician was consulted for advice on how to proceed with this.

Because this study was to be descriptive rather than analytical, the issue of sample-size calculation was not clear-cut. There was no single question that could be said to test the major hypothesis of the project (that GPs have limited disease-specific knowledge about CD) and thus calculating a sample-size to ensure that the study was adequately powered to detect statistically significant differences between groups was meaningless. What was important was that the responses of participants could be reliably taken to be representative of the population from which the study sample had been drawn, and that the findings of the study derived from those responses would therefore be generalisable to the GP population as a whole.

Sample-size in this context is calculated to enable outcomes of interest to be measured with a specified confidence level (usually 95%) and with a desired degree of precision (often ±5%). These calculations also need to include an estimate of the proportion of the population displaying a given attribute with respect to the variable of interest (e.g. agree or disagree). This was problematic for a survey such as the present one, which was comprised of multiple variables, the majority of which were not dichotomous. However, based on the parameters given above and using an online sample-size calculator available from Creative Research Systems (www.surveysystem.com/sscal.htm), for a GP population of 3600, a minimum required sample-size of 350 completed surveys was derived.

In order to achieve this number of responses it was estimated that a sample population of 1200 would be required. This was because in recent years response rates to surveys from GPs in New Zealand have been relatively low (e.g. 26% in a
2013 study by Van Rij et al.\textsuperscript{452} investigating PSA testing practices among GPs, and 32% in a 2012 study by Reeder et al.\textsuperscript{453} investigating GP practices relating to Vitamin D). In fact, as budget was available to sample a much bigger proportion of the GP population, it was decided that given the descriptive nature of the study and the desire to focus on the representativeness of findings, it would be appropriate to expand the study sample to include approximately 50% of GPs in New Zealand.

3.5.3 Selecting the study sample

As outlined earlier in this chapter, one of the sources of error that can impact on survey studies is coverage error. This occurs when not all possible members of the intended study sample have the same chance of being selected to be a part of that sample. This was an issue that needed to be addressed with respect to the present study when it came to procuring a list from which to select potential participants.

One option was to purchase access to GP contact information from the Medidata Health Professional Database (available at medidata.co.nz). However, this database only held details for approximately 75% of GPs, which meant that at least 25% of the GP population would not be available for selection for the study. An alternative option was to approach bpac\textsuperscript{c}, a not-for-profit organisation responsible for delivering educational and professional development material to health professionals, especially GPs. They estimate that their database covers more than 95% of GPs in New Zealand\textsuperscript{c}, and they were willing to grant access to this database for the purposes of this study. Utilising this source of data meant that less than 5% of the GP population would not be eligible for selection for the study, substantially reducing potential coverage error.

In order to increase the representativeness of the study sample, particularly with respect to metropolitan versus regional and rural representation, a stratified random sampling technique was used.\textsuperscript{429,433} The sample frame (i.e. list from which the sample was to be drawn) was stratified according to DHB region of practice and, within each region, according to gender. A 50% sample was then randomly selected from each stratum. People for whom gender information was not available were also grouped, and 50% of that group were also randomly selected for inclusion.

\textsuperscript{c} Personal communication with the CEO of bpac\textsuperscript{nz}
Potential participants fell into one of three groups: those for whom only email addresses were available; those for whom only postal addresses were available; and those for whom email and postal addresses were both available. Including participants from all three of these groups further reduced the likelihood of coverage error, by not automatically excluding those without either postal or email addresses on record.

3.5.4 Implementing the survey

As with the gastroenterologist survey, this survey also employed mixed modes of delivery. As just outlined, it was developed as a paper-based booklet questionnaire, but on gaining access to email addresses for potential participants (including for people for whom there was no postal address on record) an online version was also developed using the SurveyMonkey™ platform. SurveyMonkey™ was chosen on this occasion because it had a wider range of design tools available when compared with SelectSurvey (used for the survey of gastroenterologists), and its mailing capacities were more straightforward to implement.

Adding an email option to the delivery process also opened up the possibility of pre-contact with participants. There is some evidence in the literature that contacting people shortly in advance of sending out a survey enhances response rates, but for a postal-only survey this is expensive to implement. However, with access to email addresses this became practical to do, at least for the majority of the study sample, and conferred the added advantage that it would not be necessary to send a hard copy of the questionnaire to those people who chose to respond to the initial online invitation.

The following chart outlines the steps taken in delivering the survey to each of the subgroups of the study sample. (Figure 3-2)
Initial contact was made via email, for all those in the sample whose email addresses were available. One email was sent to those for whom postal addresses were also available, telling them that they would shortly be receiving a survey about coeliac disease. If they preferred to do so they were also invited to follow the link to an online version of the survey that was embedded in the email. (Appendix G) A different email was sent to those for whom postal addresses were not available, introducing the project and inviting them to participate by following the embedded link. (Appendix G)

Emails were sent at lunchtime on a Thursday for the following reasons:

1. some might respond to it immediately in their lunchbreak;
2. it was close enough to the weekend for others to be able to put it aside until then, without forgetting it;
3. it was not Friday, which is often a very busy day in practice.

The following week a hardcopy version of the survey was sent to all those for whom postal addresses were available. Those who had already responded to the email were removed from the mailing list. Included with the survey was a prepaid addressed envelope in which the completed survey was to be returned. A web-address was also provided for those participants who might prefer to do the survey online but who may not have received the email invitation to do so.

Because there is evidence that repeated contact will increase response rates, reminder emails were sent approximately two weeks after the initial email had been sent. Once again these were sent on a Thursday. A reminder letter and second copy of the survey were sent to the postal-address-only group, and to those whose follow-up email had bounced, approximately two weeks after the first mail-out. In
this second mail-out the letter was separate to the booklet and was personally addressed to each recipient. (Appendix G) This had not been possible to do within the survey booklet but it seemed that perhaps this had had a negative impact on the response rate from this subgroup, which at the time of second contact was the lowest of the three groups. There is conflicting evidence about the effects of personalised letters on response rate, but there is a suggestion that it may have a positive impact, so it was decided that it would be worthwhile taking this additional step.

As mentioned earlier in this chapter, the survey also included an incentive, in the form of an invitation to enter a prize draw. To do so respondents had to give their name and a contact address. In the booklet version space for this was on the inside back cover so that it could be removed on receipt of the completed questionnaire, thus maintaining participant anonymity. In the online version this was the last screen to be completed. When response data were subsequently exported for analysis, columns of identifying information were removed.

Completing the survey was taken as consent to participate in the study.

3.5.5 Data entry

Data entry and analysis for this study closely resembled that described for the gastroenterologist study, except that it was on a larger scale.

Hardcopy responses were entered into the database that held the online responses, by a research assistant who was employed to undertake this work. (The research assistant was employed under a grant from the Royal New Zealand College of GPs.) Any answers that were unclear (either due to handwriting or to ambiguity) were discussed with me, and a separate “notes file” kept to record individual decisions that had been made about what to enter. When the research assistant was uncertain about what to enter but was unable to discuss this with me, she indicated this in the entered data by including a series of question marks. These were then followed-up as part of a subsequent data checking process. Each hard copy was numbered as it was entered into the database to facilitate this data checking, which was conducted once data entry was complete.

At the conclusion of the data entry phase a random sample of 25% of hardcopy surveys was selected and reviewed against the responses entered into the database.
An overall error rate of 0.26% emerged for this sample, calculated by dividing the number of errors identified (16) by the total number of data-points that had been entered (6080). Among the errors identified, 50% involved responses being omitted. All but one of these instances arose when more than one answer had been given to a question. The remaining errors were data that had been incorrectly entered. Each of these errors was unique – that is, no more than one error was identified for any single survey question. Considering all of this information together, along with the fact that hardcopy responses constituted just under half (46%) of the total analysable dataset, it was decided to accept this level of error as being unlikely to significantly impact on the outcomes of the survey.

Separate to the data checking outlined above, all comments from participants that had been entered by the research assistant were reviewed. Original surveys were consulted when the intent or coherence of comments was not immediately obvious, and in any instances that she had marked with question marks. Several amendments were made as a consequence of this process, generally because accurate interpretation of comments (particularly abbreviations) required a clinical background, which the research assistant did not have.

Once all the data had been entered, the dataset was exported from the SurveyMonkey™ website in Comma Separated Variables format. This was then converted into Excel spreadsheets, and data coded to facilitate analysis using Stata Corp statistical software (Version 13.1, Stata Corp, College Station, Texas, USA). Questions that had been left blank were assigned the numerical value of 99, which was well outside the range for all questions. Most questions had an inherent numerical value (such as those utilising a 1 to 5 Likert-type scale), but for those questions that included the possibility of combinations of answers, separate numbers were generated to indicate particular combinations. A codebook was created to keep track of these assigned variables.

3.5.6 Data analysis

As with the gastroenterologist survey, data generated were both ordinal and nominal, and analysis was primarily descriptive, concentrated on measuring frequencies of responses. In addition to this, a small number of bivariate analyses
were undertaken, using Pearson Chi-square or Fisher's Exact tests. Statistical significance was determined based on an alpha of 5%, \((p \leq 0.05)\).

Analyses were limited to investigating possible associations between question responses and the gender and rurality of participants, along with potential differences between those respondents who had patients with CD, and those who did not. These variables were selected because of the following:

- the potential role of gender in influencing responses was important to examine once it became clear that women were over-represented among participants, because of implications for the generalisability of conclusions drawn from the results;
- it seemed reasonable to expect that working in either a rural or urban location might affect practise (mediated through potentially differing access to resources); and
- caring for patients with CD might be expected to influence knowledge and practise with respect to the condition.

Chapter Five, the results chapter pertaining to this study, includes further description of how responses to the first two questions in the survey were collated and subsequently analysed. This has been done in order that the results these processes generated can be more readily interpreted in context.

3.6 The Laboratory Study

In the third component of the project, data relating to testing for CD were gathered from Southern Community Laboratories (SCL). They are the sole laboratory service provider for the lower half of the South Island of New Zealand, and have the largest network of diagnostic laboratories across the country. Having started out as a privately owned Dunedin-based service in the 1960s, SCL now provides medical laboratory services all over New Zealand, and is part of the HealthScope group of companies.\(^d\) Regions where SCL are the sole provider of laboratory services are Otago and Southland, (where this has been the situation since 2006), Taupo, Nelson and Marlborough, South Canterbury, Wellington, and the Wairarapa. They are also

\(^d\) Information obtained from SCL's website [www.sclabs.co.nz](http://www.sclabs.co.nz); accessed March 2016
the major provider in Hawkes Bay and Canterbury, although both these regions also have DHB owned laboratories providing services for their respective hospitals. The following table summarises information about the regions for which SCL provides services. (Table 3.2)

Table 3.2: SCL Regional service provision

<table>
<thead>
<tr>
<th>Region</th>
<th>% population served</th>
<th>Hospital/Community</th>
<th>Year service commenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otago</td>
<td>100</td>
<td>Both</td>
<td>Mid-2006</td>
</tr>
<tr>
<td>Southland</td>
<td>100</td>
<td>Both</td>
<td>Mid-2006</td>
</tr>
<tr>
<td>Canterbury</td>
<td>95 - 100*</td>
<td>Community only</td>
<td>Mid-2012</td>
</tr>
<tr>
<td>Hawkes Bay</td>
<td>100</td>
<td>Community only</td>
<td>2007</td>
</tr>
<tr>
<td>Taupo</td>
<td>100</td>
<td>Both</td>
<td>2008</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>100</td>
<td>Both</td>
<td>Mid-2012</td>
</tr>
<tr>
<td>Nelson/Marlborough</td>
<td>100</td>
<td>Both</td>
<td>Mid-2012</td>
</tr>
<tr>
<td>Wellington and Wairarapa</td>
<td>100</td>
<td>Both</td>
<td>End-2015</td>
</tr>
</tbody>
</table>

* All information provided by SCL’s Otago Southland Quality Co-ordinator. This indicated that SCL provide 100% of community laboratory services in Canterbury, however National Health Committee data from 2015 suggests that this figure is 95%.454

3.6.1 Background

Initially it was thought that it would be possible to calculate the New Zealand prevalence of diagnosed CD by cross-checking laboratory data with information from additional sources such as the New Zealand Ministry of Health (MoH), and CNZ. However, as more information about the actual data that would be able to be utilised became available, it became apparent that this would not be possible.

The first set of challenges arose with obtaining laboratory data that would encompass the whole population, and include all the necessary information (i.e. biopsy data as well as serology). In the past it was possible to access national data relating to blood tests performed in New Zealand, which was held in a laboratory
data warehouse. However, bulk data relating to coeliac serology tests are grouped with other autoimmune related tests, and so are not readily identifiable as a unique set. A recent report from the National Health Committee also indicates that data held in the warehouse over recent years is not robust, and that there is no longer a single reliable repository for publicly-funded tests. This further confirmed that it would not have been possible to gather a reliable national dataset of laboratory results. In addition to this, as the guidelines still state that the diagnosis of CD should be confirmed with a duodenal biopsy in order to reliably determine prevalence, data gathered would need to include histology. In 2016, histopathology data relating to individual conditions such as CD were not included in bulk datasets and, at the time of planning this project, the only way of extracting this information was going to be to do a manual search for individual results.

The fact of not having a set of laboratory data that covered the whole of New Zealand, and which included biopsy data, compounded a second set of challenges to being able to calculate the prevalence of diagnosed CD in New Zealand. These challenges resided with the possible alternative sources of the additional data that would be required to determine the prevalence of diagnosed disease in the community. (A complete set of national laboratory data would have enabled the calculation of annual incidence rates – the number of new diagnoses expressed as a proportion of the total population – but not prevalence, which is the total number of people in the community with the condition.)

Possible sources for additional data were CNZ membership lists, and the MoH, which has a list of CD patients with a Special Authority number for subsidised prescription gluten-free foods, referred to in Chapter Two (page 87). Unfortunately, neither of these lists is complete as not all people with CD join CNZ, and not all people with CD want, or are recommended to get a Special Authority number. In addition to this, people with DH are also entitled to a Special Authority number, and would appear on any MoH list and would therefore have had to be identified and removed. Furthermore, in recent years CNZ has begun accepting membership from

* Personal communication from SCL’s Chief Executive Officer.
people without biopsy-proven disease, who would also have had to be identified and removed from their list.

Calculating the prevalence of diagnosed CD would therefore have entailed the following steps:

- Identifying positive serology results and manually searching for a biopsy result for each identified patient.
- Matching those patients with a positive biopsy to those with Special Authority numbers. This would also have had to be done manually using patients’ National Health Index (NHI) numbers.
- OR matching patients with a positive biopsy to those on the CNZ membership list, also a manual process, using patients’ names.
- Calculating the proportion of patients with a positive biopsy who also had a Special Authority number. This would have needed to be done for several years’ data.
- Calculating the proportion of patients with a positive biopsy who were also members of CNZ.
- Applying these results to the datasets to calculate a predicted prevalence.

Such a labour-intensive process would at best have yielded a ballpark prevalence figure, had national laboratory data been available. However, the lack of national data introduced another layer of estimation. It was possible to obtain regional data (as will be discussed shortly) and it would theoretically have been possible to make national projections from regional data. But the assumptions inherent in that, chief among them that each region behaves similarly to the next, would have rendered a calculated figure so speculative as to be not much better than guesswork. For these reasons it was decided to modify the laboratory study to achieve more modest aims.

3.6.2 The study redefined

As discussed in Chapter Two, there have been a number of recent incidence studies related to CD, some of which utilised laboratory data to determine their figures.\textsuperscript{45,248,249} In addition to this there have been two pieces of research published that investigated patterns of testing for CD.\textsuperscript{37,455}
In the first of these, Evans et al.\textsuperscript{37} retrieved coeliac serology testing data from laboratory databases at Wycombe Hospital in England, for the period 1997 to 2006. The data they obtained related to all patients in their region who had been tested for CD, and their analysis included determining how many tests were requested each year and how this changed from year to year; what proportion of tests were positive and how this changed from year to year; the demographic characteristics of those who had been tested; the numbers of patients who went on to have a duodenal biopsy; and the correlation between serology and biopsy results.\textsuperscript{37}

The second study was conducted in Latvia.\textsuperscript{455} This study also looked at the numbers of coeliac serology tests being performed, this time at a national level and for the period 2004 to 2009. Unlike the English team they did not also look at biopsies, but they did calculate the proportions of positive results for the different types of tests performed, and they also compared the performances of different brands of tests.\textsuperscript{455}

Given that it would be possible to access testing data from SCL, which had the potential to provide information about several regions in New Zealand, the third arm of the project was reconfigured. The original research question relating to prevalence was modified to be one about incidence, and more thought was given to how available laboratory data could be used to corroborate information gathered in the survey arms of the project, and to the question “What information can laboratory data provide about the recognition and management of CD in New Zealand, particularly among GPs?” In addition to this, it would also be possible to situate this study within the recent international research context by analysing secondary issues relating to rates of positive serology tests, and correlations between positive serology and duodenal biopsies, such as had been done by both Evans and Leja and their teams. Thus the following questions were formulated to apply to the dataset provided by SCL:

- Which coeliac serology tests are doctors requesting and how many of each have been requested?
- How has this changed over time?
- Which doctors (i.e. GP, Gastroenterologist, Paediatrician, or other specialist) are requesting coeliac tests?
• How many tests are positive?
• How many positive serology tests are leading to patients having duodenal biopsies?
• How many of those biopsies are positive?
• How many patients are having more than one serology test, either with or without biopsy evidence of CD?
• What are the demographic characteristics of people tested for coeliac disease, and those with positive tests?
• Are there any regional differences in patterns of testing?

3.6.3 Data retrieval

Staff members from SCL involved in coeliac serology test analysis were consulted for background information about which tests are performed by the laboratory, how this has changed over time, and how test result information is stored. Using this information, a study protocol was developed and ethical approval sought and gained. (Appendix A) Because there would be a charge to retrieve the necessary information, funding was also obtained in the form of a University of Otago Research Grant, and from CNZ.

Once the necessary approval had been given, IT personnel from SCL wrote a programme that enabled them to extract the required data from SCL databases. The extracted data were then provided in a series of Excel spreadsheets. These data included identifying information, so all spreadsheets were immediately password protected and the columns containing patient names were hidden.

Data were initially provided for the years 2003 through to 2013 and, following a second extraction that took place in early 2016, for 2014 and 2015. Because SCL were not the sole laboratory provider for any region until 2006, it was decided to limit analysis to data covering the period from 2006 onwards. In addition to this, data from areas where a second laboratory provider is also present were excluded from analysis, to ensure that the datasets being interrogated were as complete as possible. For regions where SCL had become the sole laboratory services provider part way through a calendar year, analysis was limited to the full calendar years following this.
The serology results for each region included in the final set of data were all processed and analysed in SCL’s Dunedin laboratory. This continues to be the practice for these regions, and for centres outside Dunedin this necessitates sending samples by overnight courier. For the entire period of analysis, IgA-tTG antibodies were tested using Inova Diagnostics’ Quantalite kits, which are human red cell based, and which have an upper limit of normal of 20 units. Endomysial antibody tests were performed using Immuglo slides from Immco Diagnostics until the beginning of 2015, at which time the laboratory changed to slides from Inova Diagnostics. Both these brands of test kits use primate smooth muscle as the substrate for their slides.

Histopathology data were not included in the information provided because they could not be retrieved as a bulk set. This meant that individual searches were required to obtain biopsy results. In order to do this, serology results, which had been given as numerical values, were sorted in rank order. National Health Index numbers for all those patients with values above the normal threshold (20 Units) were then used to search the laboratory database to determine (a) whether the individual had had a biopsy, and (b) what the result of that biopsy was. Biopsy results were added to the existing spreadsheets and coded for subsequent analysis. Searches were also made on EMA results that were reported as equivocal when these were not associated with an elevated tTG level; on results that were registering as indecipherable on the spreadsheet (usually in the form of “*******”); and on rows in which all results columns were empty, despite a laboratory request code and patient details being present. Results identified by laboratory staff as being indicative of IgA deficiency were also checked. The required biopsy information was held in two separate databases, one in Dunedin and one in Wellington. Access to these databases was facilitated by HealthScope New Zealand, the company that owns SCL, and by SCL staff in Wellington.

Additional data relating to the ethnicity of patients was obtained from the New Zealand MoH, using the NHI information provided by the laboratory. Population data were taken from the 2007 and 2013 New Zealand Censuses.

The NHI is a repository of information relating to healthcare service use in New Zealand. Its purpose is defined by the MoH as being "to help with the planning, co-ordination and provision of health and disability support services across New
Zealand. The unique NHI numbers assigned to patients enable information to be collected and collated about a range of health-related activities, which (in coded form) is then used to inform health service policy and decision-making.

Ethnicity is one of the key variables about which information is gathered in association with NHI numbers. It is obtained by asking individuals to list up to three ethnic groups with which they identify. “Ethnic group” is defined by the ministry as “a group of people who have culture, language, history or traditions in common.” Once a person has identified his or her group (or groups), these are then recorded using codes that have been determined by Statistics New Zealand (SNZ), and which correspond to codes used for all government-mandated personal information records. In addition to this, a “prioritised ethnicity” is recorded, derived from an SNZ algorithm and applied when multiple ethnicities are given. Prioritised ethnicity data are central to MoH planning and service provision decisions. Of the 22 possible ethnic groups people can choose, the highest priority is given to Māori, and the lowest to New Zealand European. In practice this means that if a person gives her first ethnicity as NZ European, and her second ethnicity as Māori, Māori will be recorded as her prioritised ethnicity. In fact, any other ethnicity given along with NZ European will be regarded as the priority ethnicity. There are also codes for “don’t know”, “refused to answer”, and “response unidentifiable”, which are not prioritised.

3.6.4 Data analysis

The data provided by SCL were grouped and analysed to enable the questions set out on pages 140 and 141 to be answered. This was almost entirely descriptive work and, along with related calculations, was conducted within Excel (2016) spreadsheets. Limited analyses using Stata (version 13.1) were undertaken to determine if there were significant differences between years, between regions, and between male and female patients, with respect to rates of testing, positive IgA-tTG tests, and rates of biopsies undertaken. According to the comparisons being tested,

either two-sample proportions testing or Pearson Chi-square analyses were performed. This is indicated in the text at the relevant places. Statistical significance was determined based on an alpha of 5%, \( p \leq 0.05 \).

Prior to undertaking any analysis, extensive work was carried out cleaning and sorting the data. This included confirming whether patients were from the region to which their test results had been assigned, which was achieved by tracing the people who had requested the tests. Many of the doctors were known to me but, for those who were not, this involved consulting resources such as the NZMC register and the New Zealand Nursing Council register, and conducting Google searches.

**3.7 Conclusion**

In summary, three separate observational studies were undertaken to test the principal hypothesis that GPs in New Zealand have limited disease-specific knowledge about CD. Two of these studies utilised surveys, one of gastroenterologists and one of GPs, developed in accordance with best practice recommendations from experts such as Dillman et al.,\(^435\) and Aday and Cornelius.\(^429\) The third study drew on data from SCL to determine patterns of testing and CD incidence rates over time in regions in which they were the sole laboratory providers. The results of each study are discussed in the next three chapters, with one chapter devoted to each study. Chapter Seven will draw the threads of these chapters together with discussion of the results and reflection on their implications, both individually and collectively.
Chapter 4: Results from the Survey of Gastroenterologists

4.1 Introduction

The survey of New Zealand gastroenterologists was designed to capture information about their current practice with respect to CD. This chapter presents the results of that survey.

The survey took place in the latter part of 2013, and early 2014. As discussed in Chapter Three, it was initially conducted as an online survey that was followed by the distribution of paper copies at the Annual Scientific Meeting of the NZSG in late 2013. Subsequent to this a targeted mail-out to Auckland-based and female practitioners was also undertaken, as these two groups were, at that time, under-represented among respondents.

The chapter begins by providing details about the overall response to the survey and goes on to describe the characteristics of participants. Their responses are then presented under the following headings:

- Management of newly diagnosed CD.
- Long-term management of CD.
- When the histology is normal.
- A patient declining endoscopy.

These headings represent the principal areas of practice about which the three scenarios in the survey were designed to capture information. Responses are first described and then, when appropriate, analysis according to participant characteristics is reported. The chapter closes by drawing out the key findings.

4.2 Response to the survey

4.2.1 Identifying the survey population

As discussed in section 3.3.4 of Chapter Three, it proved challenging to determine the exact number of gastroenterologists in New Zealand and thus to identify the intended recipients for the survey. Following extensive searching, the total number of gastroenterologists identified as practising in New Zealand in 2013 was 81. This compared with the figure of 64 gastroenterologists registered on the Medidata
database, and 62 people who had recorded “gastroenterology” as one of their principal worksites in the New Zealand Medical Council (NZMC) Workforce Survey of 2012. (As noted in Chapter Three, gastroenterologists are vocationally registered with the NZMC in the discipline of Internal Medicine, so the Council does not have more detailed information about their numbers than that volunteered in the annual Workforce Survey.) Basic demographic information available for these 81 practitioners is summarised as follows. (Table 4.1)

Table 4.1: Demographic information of identified New Zealand Gastroenterologists (2013)

<table>
<thead>
<tr>
<th>Identified gastroenterologists</th>
<th>Male</th>
<th>Female</th>
<th>North Island</th>
<th>South Island</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>66</td>
<td>15</td>
<td>61</td>
<td>20</td>
</tr>
<tr>
<td>Greater Auckland DHBs</td>
<td>35</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>All other DHBs</td>
<td>26</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Canterbury DHB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There may still have been a small number of gastroenterologists who did not emerge through the searching process, but it seems highly unlikely that there would have been more than 85 gastroenterologists in practice in New Zealand at the time at which the survey was undertaken.

4.2.2 Respondent numbers

At the time of the survey there were 133 members of the NZSG, which was to be the principal point of contact with recipients. Due to the practical constraints discussed in Chapter Three, the request to participate initially went out to all 133 NZSG members, which included dietitians, nurses, and paediatric gastroenterologists, as well as the professional groups for whom the survey was intended. Following this, approximately 25 hardcopy versions were handed out or picked up from the CNZ

---


*Personal email communication from NZMC Senior Information Systems Analyst, 12/12/2013.
stand at the NZSG conference in November 2013, and then, after provisional analysis of responses in early 2014, another 31 copies were posted to Auckland-based and female practitioners.

Response to the survey is outlined below. (Figure 4-1)

Figure 4-1: Responses to the survey of New Zealand Gastroenterologists

The 45 gastroenterologists who completed the survey represented 55.6% of identified specialists practising in New Zealand at the time it was undertaken. Responses from gastroenterology trainees were excluded because the three respondents represented just 12.5% of that group. As the focus of the survey was on adult disease, the paediatric gastroenterologist’s answers were also excluded. It had not been intended that the paediatric specialists should participate. No surgeon endoscopists completed the survey, despite being invited to do so.

4.2.3 Respondent demographics

Demographic information was available for analysis from 42 of the 45 gastroenterologists who completed the survey. One person who participated online left the entire demographic section blank. Another, also online, commented that he or she was not happy with the level of personal detail being sought, writing “with my apologies, only Q37; 38; and 42 are definitely correct; the other questions may or may not be correct”. These questions corresponded to current position, years in
practice, and place of undergraduate training. A third online respondent evidently felt similarly, providing nonsense answers (e.g. “abc”) to several questions in this section of the survey. Because it was impossible to know which (if any) of these participants’ answers to the profile questions were reliable, they were excluded from presentation of demographic results. (Tables 4.2, 4.3 and 4.4)

Table 4.2: Initial demographic information provided by survey participants

<table>
<thead>
<tr>
<th>Total number of respondents</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Number of respondents</td>
<td>35 (77.8%)</td>
</tr>
<tr>
<td><strong>DHB region of practice</strong></td>
<td>North Island</td>
</tr>
<tr>
<td>Number of respondents</td>
<td>28 (62.2%)</td>
</tr>
<tr>
<td><strong>Undergraduate training</strong></td>
<td>Northern Hemisphere</td>
</tr>
<tr>
<td>Number of respondents</td>
<td>13 (28.9%)</td>
</tr>
<tr>
<td><strong>Postgraduate training</strong></td>
<td>NH</td>
</tr>
<tr>
<td>Number of respondents</td>
<td>15 (33.3%)</td>
</tr>
</tbody>
</table>

When considered as representatives of the New Zealand gastroenterologist community identified at the time the survey took place, the percentages of men and women who participated were 53.3% (35/66) and 46.7% (7/15) respectively, with three people undeclared.

Participants were asked to identify the DHB regions in which they worked but, in view of the very small numbers working in some regions and the expressed concerns about anonymity, this information was combined. Respondents represented 45.9% (28/61) of North Island, and 70% (14/20) of South Island practitioners, with three people undeclared. Information was also sought about where participants had undertaken their undergraduate and postgraduate training. Once again responses were grouped, this time into the Northern and Southern hemispheres. (Table 4.2) Of the 28 people who completed their medical degrees in the Southern hemisphere, 25 did so in New Zealand.
As a follow-on from the questions relating to participants’ clinical practice setting, a free text question asked for comments about “any factors about the setting (or settings) in which you work which may impact on your management of patients with possible coeliac disease.” Nineteen people responded to this invitation to comment, the majority being clinicians who worked in both the public and private settings. Of these, more than two-thirds (13/19) indicated that constrained resources in the public sector (or more readily available resources in the private sector) had impacted on their practice. This was apparent either in the timeframe to endoscopy, or in outpatient clinic capacity for the follow-up they offered. The
remaining six commenters reported no differences in management between the two settings, or thought that their coeliac patients could be “managed appropriately in all aspects” by DHB services.

There was a range of sub-specialty practice areas among respondents, with the biggest group (28.9%; 13/45) being those who identified IBD, either singly or in combination with other aspects of gastroenterology. Only one participant included CD as a sub-specialty area of their practice.

The survey also asked respondents to indicate how many adult coeliac patients they saw in a range of circumstances. (Table 4.4)

<table>
<thead>
<tr>
<th>Number of patients seen for each scenario</th>
<th>None</th>
<th>&lt; 10 per year</th>
<th>1 – 10 per month</th>
<th>11 – 20 per month</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>New referral; diagnosis not previously considered</td>
<td>1 (2.2%)</td>
<td>19 (42.2%)</td>
<td>22 (48.9%)</td>
<td>0</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>For biopsy to confirm the diagnosis</td>
<td>0</td>
<td>13 (28.9%)</td>
<td>27 (60.0%)</td>
<td>2 (4.4%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>For follow-up; recently diagnosed</td>
<td>0</td>
<td>20 (44.4%)</td>
<td>20 (44.4%)</td>
<td>1 (2.2%)</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>For follow-up; long-term diagnosed</td>
<td>8 (17.8%)</td>
<td>26 (57.8%)</td>
<td>6 (13.3%)</td>
<td>1 (2.2%)</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>For review; concern about recovery or complications</td>
<td>3 (6.7%)</td>
<td>31 (68.9%)</td>
<td>7 (15.6%)</td>
<td>0</td>
<td>4 (8.9%)</td>
</tr>
</tbody>
</table>

As indicated in this table, the CD-related work undertaken by the majority of gastroenterologists who completed the survey related to diagnosis, in particular carrying out duodenal biopsies, and follow-up of the newly diagnosed. With only 15.6% of respondents reporting seeing ten or more patients per year for long-term follow-up, it would seem that this aspect of CD management in adults was, on the whole, not being carried out in the secondary or tertiary care settings. This is unlikely to have changed in the years since the survey was conducted.
In addition to these demographic details, information was also sought about the sources from which participants got their information about CD, in a question that asked them to rate their likelihood of using Gastroenterology Conferences, Medical Journals, Practice Guidelines, Colleagues, and Coeliac New Zealand for this purpose. (Figure 4-2) Three people did not answer this question.

![Figure 4-2: Sources of information about CD likely to be used by gastroenterologists](image)

Among this group of practitioners, it is clear that conferences (at 84.4%) and medical journals (at 75.6%) were the means of updating clinical knowledge about CD that were most likely to be utilised. UpToDate was the only other source of information accessed, specified by one participant.

**4.3 Management of newly diagnosed Coeliac Disease**

The first scenario of the survey was developed to capture information about practices relating to newly diagnosed CD. Questions referred to the management of Lucy, a 35-year-old woman who had been referred for endoscopy with elevated IgA-tTG antibodies, and a long history of gut symptoms. Her biopsies had revealed that she had Marsh 3 histological changes consistent with a diagnosis of CD.

Respondents were unanimous that they were the person who would normally be responsible for referring this patient to a dietitian, and all but one person was likely or highly likely to comment on the importance of her seeing a dietitian in their
letter to Lucy’s GP. They were also almost unanimous in thinking that it would be important or very important for her to see a gastroenterologist following her endoscopy to discuss the diagnosis, with 95.6% (43 of 45 participants) responding accordingly. One person declared himself as neutral on the issue, and one that it would not be very important for such follow-up to take place. This person wrote that he would have discussed the diagnosis and its implications prior to endoscopy. Three people commented that a GP and/or a dietitian could also conduct this consultation.

A series of questions about Lucy’s management in the next year then followed. The first of these asked participants to rate the importance of various elements of her follow-up. (Figure 4-3)

![Figure 4-3: Importance of aspects of management in first 12 months of follow-up after CD diagnosis](image)

It can be seen from this chart that there was greatest agreement on the importance of monitoring abnormal blood tests, such as low iron, to ensure that they returned to normal. There was also widespread agreement that Lucy should be reviewed to confirm that any CD-related symptoms resolved, and a clear majority view that an application should be made for a Special Authority number, and that she should be advised to suggest to her first-degree relatives that they be tested for CD. Opinion was more divided on the issue of advising her to join CNZ, the importance of follow-up IgA-tTG antibody testing, DEXA scanning and, most notably, the need for follow-up biopsy.
Participants were also given the opportunity to provide comments on follow-up in the first 12 months following diagnosis, and in particular on whether there were any other things that they thought should be included in management. There were 17 responses to this. Most reinforced or expanded on the answers they had already given, with DEXA scanning drawing the greatest number of comments (five) relating to a single issue. These comments indicated practitioners would delay scanning either until menopause, an “older age”, or for at least a year after commencement of the GFD because “bone density rapidly returns to normal once on a GFD”. One person would only request DEXA scanning if there was some other indication to do so (such as a previous fracture). In addition to the comments about DEXA scanning, one person commented that follow-up biopsy should be delayed until at least two years after diagnosis, and one person suggested Vitamin D supplements should be given. Three participants noted they would include discussion about the importance of maintaining a strict GFD.

4.3.1 DEXA Scanning

As is apparent in Figure 4-3 (on the previous page), and in their comments just noted, respondents were divided on the importance of DEXA scanning for Lucy. Just over 55% believed including this in her management in the next year would be important or very important, while 44.4% were neutral, or regarded it as not important. The topic was further explored towards the end of the scenario with a more general question that asked participants “[w]hen do you think adults with newly diagnosed coeliac disease should be referred for DEXA scanning?” Of the 45 respondents, 26 (57.8%) thought that this should almost always happen, and 17 (37.8%) thought it should only occur in certain clinical situations. Two respondents (4.4%) thought that it should almost never happen.

Clinical situations that warranted DEXA scanning were given as older age, especially if the diagnosis had been preceded by a long period of symptoms; malnourishment or weight loss; a past history of fractures (particularly low impact fractures); other risk factors for bone disease; and the patient being a woman. One person also commented that implementing a GFD will lead to bone recovery in the first 12 months, so DEXA scanning should be delayed until after this time had
elapsed, as well as only being carried out in those patients with prolonged symptoms before diagnosis.

4.3.2 Follow-up IgA-tTG antibody testing

As also shown in Figure 4-3 on page 152, the majority of respondents believed that it was important or very important for Lucy to have follow-up IgA-tTG antibody testing, although at 60% of the participant group, this was a smaller majority than for other aspects of follow-up. This was also the aspect of follow-up that drew the second highest percentage of responses (17.8%) in the “not very” or “not at all important” categories.

Follow-up serology testing was teased out further with a question that asked when this should take place. A wide range of responses were given to this question, although the most favoured option was “Routinely at 6 months”. (Figure 4-4)

![Figure 4-4: Preferred timing of follow-up IgA-tTG testing](image)

“Other” comprised “Routinely at 6 months, and if symptoms don’t resolve”; “Routinely at 6 months, and then repeat test until normal”; and “Routinely at 3 and 12 months, and if symptoms recur”.

4.3.3 Rebiopsy following diagnosis

Respondents were most divided on the importance of Lucy having a follow-up biopsy at around 12 months after her diagnosis. (Figure 4-3, page 152) On this issue, 53% indicated that it would be not very, or not at all important; 11.1% declared themselves as neutral; and 35.6% believed it would be important or very important.
It is worth noting that these differences in attitudes occurred between respondents from within the same DHB regions, as well among those working in different regions.

A further question later in the survey also dealt with the topic of rebiopsy following diagnosis. In this question, in which respondents were asked to think more broadly than 35-year-old newly-diagnosed Lucy, reference was made to the fact that in some countries it is recommended that all patients should undergo a repeat biopsy approximately a year after diagnosis. Participants were asked to rate the importance of this practice. Their responses were then compared to their responses to the similar question about Lucy. (Figure 4-5)

![Figure 4-5: Importance of follow-up biopsy in the first 12 months after CD diagnosis](image)

When the two “not important” counts and the two “important” counts are collated for each scenario they are not too dissimilar. The “not important” tallies become 24/45 for Lucy, and 22/45 in the general case, while the “important” totals are 16/45 for both groups. On inspection of individual responses, the groups of respondents constituting the “important” group are identical, while there are a small number who have moved from “not important” to “neutral”, or vice versa. This gives rise to a pairwise correlation of $r=0.90$ between the two sets of responses, indicating a high degree of consistency between them.
This question also drew comments from just over 75% of respondents, in support of the answers they had given. Not surprisingly these comments ranged over a spectrum of views from “if symptoms have resolved outcome of biopsy is irrelevant” (rebiopsy not at all important) to “lifelong GFD is a considerable imposition and I think it is important to confirm a good response and the diagnosis as accurately as possible” (rebiopsy very important). This second writer went on to say that rebiopsy “also reinforces the concept that this is a ‘significant’ condition not just a lifestyle choice”.

Among those who favoured rebiopsy, the majority of those who commented made reference to issues such as being able to reassure the patient, confirm a histological response, and identify patients who were not responding as expected. Those who did not regard rebiopsy as important generally indicated that they relied on other indicators of recovery, especially the IgA-tTG antibody result. In between were those who reserved further biopsies for patients with ongoing symptoms, continued evidence of malnourishment, or IgA-tTG antibody levels that did not fall.

Four people commented on the resource implications of rebiopsy, suggesting that, in a resource-constrained environment, the expense and invasive nature of the procedure were not justified by the likely yield of useful information. One among these said he would do more such biopsies “in an ideal world”, while another acknowledged doing more biopsies “in private if patient symptomatic post diagnosis and treatment”. Another four respondents believed that 12 months was too early to be doing a further biopsy, saying that they wait at least 18 to 24 months before doing this.

4.3.4 Analysis by demographics: Management of newly diagnosed CD

Responses to questions of management in the first 12 months following diagnosis were analysed with respect to the demographic characteristics of participants, using Fisher’s Exact test. All demographic variables were included in this process, except areas of sub-specialty practice, which were too varied to meaningfully interpret. Responses were also analysed by participants' likely use of guidelines documents as a source of information about CD.

Initial analysis, without grouping Likert-scale responses, suggested that there were a small number of areas in which there were statistically significant
differences between groups of participants, and an additional few areas in which differences approached statistical significance. (Table 4.5) Analysis was then repeated with Likert-scale responses grouped together (important with very important, and not at all important with not very important and neutral). (Table 4.5) It is reasonable to postulate that these groupings would be more likely to represent clinically significant differences in practice, suggesting that any statistically significant differences between them might carry more importance.
Table 4.5: Factors influencing aspects of Lucy’s management in the year following CD diagnosis, with p-values

<table>
<thead>
<tr>
<th>Management action</th>
<th>Demographic variable</th>
<th>Ungrouped p-value</th>
<th>Grouped p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up biopsy (at 12 months)</td>
<td>Number of patients seen for long-term follow-up</td>
<td>0.001</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen when CD diagnosis not previously considered</td>
<td>0.03</td>
<td>0.181</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen for review due to concern about recovery or complications</td>
<td>0.054</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Number of tenths in gastroenterology practice</td>
<td>0.056</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Use of practice guidelines</td>
<td>0.129</td>
<td>0.005</td>
</tr>
<tr>
<td>Follow-up IgA-tTG antibody testing</td>
<td>Numbers of patients seen for long-term follow-up</td>
<td>0.057</td>
<td>0.027</td>
</tr>
<tr>
<td>Advise to join CNZ</td>
<td>Use of practice guidelines</td>
<td>0.008</td>
<td>0.63</td>
</tr>
<tr>
<td>Advise to have 1st degree relatives tested</td>
<td>Gender</td>
<td>0.037</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>Years in practice</td>
<td>0.042</td>
<td>0.239</td>
</tr>
<tr>
<td></td>
<td>Tenths in private practice</td>
<td>0.2</td>
<td>0.051</td>
</tr>
</tbody>
</table>

As presented on page 157, the importance of performing follow-up biopsies at around 12 months following diagnosis was the point on which there was least agreement among participants. There were no statistically significant differences in
participants’ attitudes to this issue according to their gender, (p=0.44), their years in clinical gastroenterology practice, (p=0.96), whether they worked in the private and/or public sectors, (p=0.72), whether they worked in the North or South Island, (p=0.96), whether they held an academic post or not, (p=0.56), or where they had undertaken their postgraduate training, (p=0.80).

Table 4.5 shows that their differences of opinion did reach statistical significance with respect to numbers of patients seen for (a) long-term follow-up, and (b) when the diagnosis had not previously been considered. They approached statistical significance according to how many tenths were worked in gastroenterology, and how many patients were seen for review because of concern about recovery and/or complications. However, as is also evident in this table, when the Likert-scale responses were grouped, these p-values changed, such that some of the variables identified were no longer associated with significant differences in responses, and one new significant association emerged. Thus, those people who placed lower importance on follow-up biopsy in the first 12 months of management were more likely to work in gastroenterology full-time (i.e. >8 tenths), see between one and ten patients per year because of concerns about their progress, and be variable in their use of practice guidelines. Almost all of those who rated follow-up biopsy as important (11/13) were likely to use practice guidelines as a source of information about CD.

When responses to the question about rebiopsy in general were grouped and analysed, p-values were identical to those found with respect to follow-up biopsy for Lucy across all variables, which further illustrates the consistency of participants’ answers between these two questions.

The remaining points on which statistically significant differences in opinions were detected were the importance of follow-up IgA-tTG antibody testing, and advising patients to have their first-degree relatives tested. Participants who saw no patients for long-term follow-up of their CD were less likely to think that follow-up antibody testing was important, while those who worked more than half-time in private practice all thought that it was important or very important to advise patients about having their first-degree relatives tested.
4.3.5 Responsibility for follow-up actions

Following the question on Lucy’s management in the next 12 months, respondents were asked about whom they felt should be responsible for arranging four of the follow-up tasks that had been included in that question. These were: applying for a Special Authority number for prescription gluten-free foods; referring her for a DEXA scan; advising her to join CNZ; and advising her that her first-degree relatives should be tested for CD. Options given were: I don’t think this is necessary; Me; One of my team; Her GP; Other. (Table 4.6)

Table 4.6: Who should take responsibility for arranging follow-up tasks? (Majority response in bold)

<table>
<thead>
<tr>
<th>Task</th>
<th>Not necessary</th>
<th>Me</th>
<th>One of my team</th>
<th>Her GP</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applying for SA number</td>
<td>5 (11.1%)</td>
<td>36 (80.0%)</td>
<td>2 (4.4%)</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Referring for DEXA scan</td>
<td>4 (8.9%)</td>
<td>30 (66.7%)</td>
<td>1 (2.2%)</td>
<td>8 (17.8%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Advising her to join CNZ</td>
<td>3 (6.7%)</td>
<td>29 (64.4%)</td>
<td>3 (6.7%)</td>
<td>5 (11.1%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Advising her about relatives</td>
<td>5 (11.1%)</td>
<td>36 (80.0%)</td>
<td>0</td>
<td>3 (6.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

It is very clear from this table that the majority of respondents believed that the responsibility for arranging these events rested with them. This is especially the case with regards to applying for a Special Authority number, and discussing the need for first-degree relatives also to be tested for CD. “Other” suggestions were that dietitians could apply for the Special Authority number, and that any (or all) of the three groups identified could be responsible for recommending CNZ. One respondent noted that he would discuss CNZ, but not recommend it, and another pointed out that as DEXA scanning was not funded, it was not always feasible for patients to obtain.

Responses from those participants who thought that the identified tasks were not necessary were then compared with their ratings of the importance of those same tasks in the earlier question. (Table 4.7)
At first glance it seems that at least one respondent had been inconsistent in his responses, rating the need for DEXA scanning as important but then deeming it not necessary. In fact, this participant had also written a comment relating to DEXA scanning in which he indicated that he thought that, given that bone mineral density recovers in the first year of a GFD, DEXA scanning should be delayed beyond 12 months after diagnosis. Viewed in the light of this comment, his response to the subsequent question, which referred explicitly to follow-up in the 12 months following diagnosis, is not at all incongruent. There were no comments from the three people who were neutral on the importance of advising Lucy that her close relatives should be tested for CD, who then indicated that they thought that this was not a necessary part of her follow-up in the next 12 months.

At the conclusion of the section based on the Lucy scenario, some of these issues of responsibility for follow-up were explored further, albeit from a slightly different angle. At this point in the survey, respondents were asked about how often they discuss joining CNZ with their newly diagnosed coeliac patients, and about how often they discussed the issue of testing those patients’ first-degree relatives. More than 75% of respondents indicated that they discussed these issues almost always or most of the time. (Figure 4-6)
Reviewing answers to these questions with reference to participants’ earlier responses to the questions about how important they believed these aspects of management to be, and who should be responsible for undertaking them, revealed generally good levels of consistency. This is especially true among those who believed the tasks are important, or very important. Of the 28 respondents who had indicated it would be important, or very important, to discuss joining CNZ with patients such as Lucy, 26 (92.9%) reported they mostly or almost always did this, and 25 (89.3%) had indicated it was their responsibility to do so. Only one of the 28 specified a GP should do this, and this person indicated he discussed the issue about half the time. The other two respondents answered that one of their team should be responsible, but then reported that they do this most of the time in one case, and almost always in the other.

When it came to discussing the testing of a newly diagnosed patient’s first-degree relatives, 90% (27/30) of those who had rated this as important or very important with respect to Lucy reported doing this with their patients most of the time, or almost always. Two specified they did this about half the time, and one, some of the time. Of the 30 respondents placing importance or high importance on this issue, all but one (96.7%) had indicated that it was their responsibility to have this discussion. The remaining person assigned responsibility for this to the patient’s GP, despite also reporting discussing this issue with his patients most of
the time. Among those who placed a lower level of importance on one or both of these aspects of management for Lucy, there was less consistency in their responses to how likely they would be to discuss these issues with their patients. (Table 4.8)

Table 4.8: Discussions about joining CNZ, and testing relatives, among those who did not rate these tasks as important

<table>
<thead>
<tr>
<th>Importance of CNZ</th>
<th>Discuss joining Coeliac New Zealand</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Almost never</td>
<td>Some of the time</td>
</tr>
<tr>
<td>Neutral importance</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Not important</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Importance of advising testing of relatives</th>
<th>Discuss testing 1st degree relatives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral importance</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Not important</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

A lack of consistency is particularly apparent among those who placed little or no importance on advising Lucy that her first-degree relatives should also be tested for CD, but then indicated they had this discussion with patients most of the time or almost always. One possible explanation for this is that these discussions are (at least in part) driven by patients asking questions, rather than solely by what the gastroenterologist may deem important.

4.3.6 The letter to Lucy’s GP

The final question concerning the management of newly diagnosed CD was framed in terms of what information participants would include in their letter returning Lucy to the care of her GP. Once again they were asked to rate a range of issues pertaining to her management, this time on how likely they would be to comment on them in their letter. Figure 4-7 presents the findings that emerged with respect
to her management in the next 12 months. (Note: one person did not provide answers for the final three variables given here.)

Figure 4-7: Likelihood these management issues will be commented on in letter to GP

When comparing participants’ responses to this question with their earlier evaluations of the importance of each of these events forming a part of Lucy’s management, there were very good correlations within most pairs of variables. Pairwise correlations ranged between \( r = 0.39 \) for the review of CD-related symptoms, to \( r = 0.85 \) for joining CNZ, with \( r \) values for the other four pairs all lying in the 0.7 to 0.8 range. The low correlation with respect to reviewing CD-related symptoms is largely accounted for by the answers of four individuals. Two of them reported that they were highly likely to include comment in their letters about the need to ensure CD-related symptoms were resolving, having rated themselves as neutral on the importance of this task, while the other two responded oppositely, rating the task as important, but their likelihood of including this in their letter as low.

4.4 Long-term management of Coeliac Disease

Scenario One also included questions relating to the long-term management of CD, continuing to focus on 35-year-old Lucy. Once more, participants were asked to rate a series of management actions according to their importance. (Figure 4-8)
They were also invited to comment on the actions identified, and to indicate if there were additional tasks that they thought should be included. Eleven people chose to do this. Among them, one commented that he would “seek ID [infectious diseases] advice with respect to Pneumococcal vaccination”, and two others noted that this vaccination was only indicated in the presence of hyposplenism. Two people suggested that DEXA scanning should be performed every few years, and four people advocated testing for absorption (e.g. blood count, iron studies, vitamin B12, folate) as well as associated conditions such as thyroid disease.

Two additional questions then explored the issue of whether Lucy should have an “Annual Review” of her coeliac management,(Figure 4-9), and, if so, who should be responsible for that.
From this chart it can be seen that 60% of participants (27/45) agreed that it would be important or very important for Lucy to have an annual review. Within this group, however, only a small number regarded this as very important. Nearly a third of respondents (14/45; 31.3%) gave a neutral response, and the remaining 8.9% (4/45) indicated their belief that an annual review was not important.

When it came to who should carry out such a review, 73.3% (33/45) indicated that this should be done by Lucy’s GP, while 15.6% (7/45) answered that a gastroenterologist would be the most appropriate person. No participants responded that a GP Practice Nurse should carry out this task, and only one person indicated that a dietitian should do so. One person wrote that anyone who could give appropriate advice and access any necessary services or professionals could carry out such a review, and one specified that it would depend on the patient’s clinical state: if she were well and compliant with the GFD then a GP could review her, but if she were symptomatic or had issues with complying with the diet then she would be at risk of complications, and as such should be reviewed by a gastroenterologist. One respondent who had responded that an annual review was not necessary wrote that “probably coeliac patients who are otherwise well need 2 yearly follow-up in gastro clinic”.

As already noted, participants were also asked to indicate how likely they would be to comment on specific areas of management in their letter returning Lucy to her GP. This included aspects of her long-term care. (Figure 4-10)
As with Lucy’s early management, there were generally good correlations between respondents’ assessments of the importance of these components of her long-term follow-up, and the likelihood that they would discuss these in their discharge letters. Pairwise correlations ranged from $r=0.58$ with respect to reinforcing the importance of the GFD, to $r=0.87$ relating to the need for periodic serology testing. But given that 73.3% of respondents indicated that they thought Lucy’s GP should be responsible for carrying out an annual review of her CD, it is worth noting that only just over half of these practitioners (19/33) answered that they would be likely or highly likely to refer to this in their discharge letter. The remainder were either neutral on the issue (8/33) or unlikely or highly unlikely to mention it (6/33). This gave rise to a pairwise correlation of $r=0.58$ for this aspect of care.

4.4.1 Including oats in the gluten-free diet

As discussed in Chapter Two, the issue of whether oats may be included in the GFD remains controversial. Therefore, in order to determine the attitudes of New Zealand practitioners to this topic, a question was included in the survey asking them what they “think about coeliac patients including non-cross-contaminated oats in their gluten-free diet?” Their answers were divided among the options given. (Figure 4-11)

![Figure 4-11: The role of oats in the gluten-free diet](image-url)
The two people who answered “other” to this question both commented. One said that he discussed the issue with patients but “would advise against, in an effort to simplify the situation and avoid mistakes”, while his colleague would “see how symptoms go”.

A follow-up question asked about the place of rebiopsy in the ongoing surveillance of patients who did include oats in their GFD. (Figure 4-12)

![Figure 4-12: Rebiopsy practice when oats are included in the GFD](image)

It is apparent that respondents were divided in their views on this, but with a small majority indicating they do not rebiopsy. One respondent did not select any of the available options, writing that “the oats are irrelevant”.

### 4.4.2 Analysis by demographics: Long-term management of CD

Attitudes to the importance of various aspects of Lucy’s long-term management were also analysed with respect to the demographic characteristics of participants, using Fisher’s Exact test. Likert-scale responses were first analysed without grouping them, and then with them collated. It is apparent that when it came to Lucy’s long-term management there were few variables associated with statistically significant differences in responses. (Table 4.9)
Table 4.9: Factors influencing aspects of Lucy’s long-term management, with p-values

<table>
<thead>
<tr>
<th>Management action</th>
<th>Demographic variable</th>
<th>Ungrouped p-value</th>
<th>Grouped p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforce importance of GFD</td>
<td>Number of patients seen when CD diagnosis not previously considered</td>
<td>0.059</td>
<td>0.027</td>
</tr>
<tr>
<td>Periodic IgA-tTG antibody testing</td>
<td>Number of patients seen for review due to concern about recovery or complications</td>
<td>0.047</td>
<td>0.543</td>
</tr>
<tr>
<td>Periodic screening for associated conditions</td>
<td>Tenths in private practice</td>
<td>0.01</td>
<td>0.015</td>
</tr>
</tbody>
</table>

The importance of reinforcing adherence to the GFD reached statistical significance because all respondents who did not think this was important, or who were neutral on the issue, and for whom demographic information was available (6/8), saw more patients in whom the diagnosis of CD had not previously been considered. Participants who worked a higher number of tenths in private practice were more likely to rate the need for periodic screening for associated symptoms as important.

There were no statistically significant differences in opinion across all demographic parameters with respect to annual influenza vaccination, 5-yearly pneumococcal vaccination, or the importance of patients having an annual review of their CD.

Fisher’s Exact analyses for significance were also carried out on responses to the questions about whom should be responsible for carrying out annual reviews, whether non-cross-contaminated oats could be included in the GFD, and on the place of rebiopsy if oats were a part of the diet.

With respect to annual reviews, after excluding people who had indicated that they did not think this was necessary, only the number of patients seen per year for biopsy to confirm a CD diagnosis was determined to be a statistically significant variable, (p=0.046). This was because the one person who saw more than ten patients for biopsy per month, and who thought that annual reviews were
necessary, was the only person who thought that a dietitian should be responsible for them. Responses according to number of tenths worked in private practice approached statistical significance, \((p=0.062)\). As the number of tenths worked in private practice increased so too did the proportion of people who thought that responsibility for this should be with gastroenterologists. No-one who worked solely in the public sector thought that a gastroenterologist should carry out annual reviews, compared with 50\% (2/4) of those who worked in the private sector, and 18\% (5/28) of those who worked across both sites, although these differences did not reach statistical significance, \((p=0.086)\).

Opinions about the inclusion of oats in the GFD were generally not significantly associated with any demographic variable, apart from the view that they should “only be included if the patient had biopsy-proven recovery of the gut”. All three people who held this position worked in a South Island DHB and worked solely in the public setting, thus the \(p\)-values for these two variables were 0.046 and 0.034 respectively. With reference to if and when someone including oats in their GFD should be re-biopsied, only the number of patients seen for long-term follow-up influenced these responses to a statistically significant level, \((p=0.026)\). Participants who saw more patients for long-term follow-up were more likely to routinely rebiopsy following the introduction of oats, while those who saw fewer than ten long-term follow-up patients per year were more likely to not rebiopsy.

**4.5 When the histology is normal**

Case study B in the survey explored likely practice when the diagnosis of CD is uncertain. The “patient” in this second scenario was Joshua, a 20-year-old man who had been referred with significantly elevated IgA-tTG antibodies, detected when he was screened following his sister’s recent CD diagnosis. On questioning about symptoms, he reported he had never noticed any.

In response to the first question about their most likely course of action on receipt of the referral, 82.2\% (37/45) of participants indicated they would proceed to biopsy. Just 6.7\% (3/45) indicated they would repeat the tTG antibody test, and biopsy if it remained elevated, and only 4.4\% (2/45) answered that they would repeat the IgA-tTG, and test EMA and HLA-DQ2 or DQ8 status, and then biopsy if
these were all positive. No-one would recommend a GFD without biopsy if all of these tests were positive.

The question was then posed about what respondents would do if they biopsied Joshua and the result was reported as normal (Marsh 0). They were presented with a range of possible actions and asked to rate these according to how likely they would be to do each of them. (Figure 4-13)

![Figure 4-13: Rating of follow-up actions in context of an asymptomatic patient with normal biopsy result](image)

From this chart it can be seen that there are very high levels of agreement on some issues, such as not performing a capsule endoscopy, but divided opinion on others, for example requesting additional blood tests such as EMA and HLA-DQ2/DQ8. Respondents were also split on how likely they would be to recommend that nothing further happen in the meantime, but that Joshua be re-investigated at some point in the future, or if he became symptomatic.

In response to the opportunity to comment on whether there was anything else they would do in this situation, three participants stressed the importance of discussing the results and options with Joshua in some depth, and then deciding on
further management following that. One also indicated that he would do additional blood tests, specifically a full blood count, iron, vitamin B12 and folate levels.

The scenario then stated that it had been confirmed that Joshua’s biopsy result was indeed normal. Participants were now asked to indicate what they would advise Joshua and his GP about his likely diagnosis, if he was also found to be HLA-DQ2 or DQ8 positive, and if his IgA-tTG antibody levels remained elevated. (Figure 4-14)

![Graph showing advice to Joshua and his GP about likely diagnosis given normal biopsy](image)

**Figure 4-14: Advice to Joshua and his GP about likely diagnosis given normal biopsy**

The “Other” category was utilised by those who wished to comment, or vary their answer slightly from the options given. One would offer capsule endoscopy at this stage, three would offer a further biopsy, either now or in 12 months, and one would recommend a GFD, but wrote that it “doesn’t have to be completely gluten free”. One of those who would offer rebiopsy would also discuss a GFD trial, and another would monitor his micronutrients.

Joshua’s situation was then varied such that he was symptomatic, and the same series of questions were posed. (Figure 4-15)
Figure 4-15: Rating of follow-up actions in context of a symptomatic patient with normal biopsy result

Not surprisingly the presence of symptoms altered participants’ likely practice when it was compared to how they responded in the context of an asymptomatic patient. This can be seen most clearly when the numbers of people who were likely or very likely to undertake a particular action in the presence or absence of symptoms are directly compared. (Figure 4-16)
Figure 4-16: Comparison of likely or highly likely responses for undertaking particular actions in asymptomatic and symptomatic patients with a normal biopsy

Where 71.1% (32/45) of respondents would have reviewed the histology with a pathologist when Joshua was asymptomatic, 88.9% (40/45) would do so if he were symptomatic. There were also noticeable increases in the numbers who would be likely or highly likely to repeat the biopsy in the near future (from 6 to 17/45; 13.3% to 37.8%); those who would be likely or highly likely to arrange a capsule endoscopy (from 1 to 10/45; 2.2% to 22.2%); and those who would be likely or highly likely to start Joshua on a GFD (from 6 to 22/45; 13.3% to 48.9%). Conversely, when Joshua was reported as being asymptomatic, 44.4% (20/45) indicated they would have been likely or highly likely to have done nothing further apart from advising re-investigation at some point in the future, or if he became symptomatic. This compared with only 11.1% (5/45) doing nothing further if he had been symptomatic at the outset. With the exception of checking his HLA status and checking an EMA, all these differences reached statistical significance on Pearson Chi-square testing, with p-values ranging from 0.0004 for doing nothing further to 0.035 for reviewing the histology with a pathologist.
There was also a change in the advice that respondents would have given to Joshua and his GP, with an increase in those who would have recommended that Joshua start a GFD (from 9 to 15/45; 20% to 33.3%), and a decrease in the number who would adopt a watch and wait approach (from 28 to 18/45; 62.2% to 40%). (Figure 4-17)

![Comparison of advice most likely to be given to Joshua and his GP if he were asymptomatic or symptomatic](image)

As can be seen from this chart, the number of people answering “Other” also increased with the introduction of symptoms to the scenario. Among these, two would recommend a trial of a GFD to see if this made a difference, while two commented that it was likely that he did have CD but that biopsies may have missed this due to the patchy nature of the disease. Four thought that Joshua should undergo repeat biopsy, with two of these people saying this should occur after “high dose gluten”, and one commented that his symptoms needed to be reviewed to clarify their significance.

Of the changes shown in Figure 4-17, only the difference in numbers likely to advise that he may or may not have CD reached statistical significance, (p=0.035).

### 4.5.1 Analysis by demographics: When the histology is normal

As with the first scenario of the survey, responses to case B (Joshua) were analysed with respect to the demographic profiles of participants, and their likely use of guidelines as a source of information about CD, using Fisher's Exact test. Likert-
scale responses were analysed before and after being grouped. In this process a number of variables reached or approached statistical significance. Those that were significant on grouping responses are presented. (Tables 4.10 and 4.11)

Table 4.10: Factors influencing management actions when Joshua, an asymptomatic patient, has positive serology but normal histology, with p-values

<table>
<thead>
<tr>
<th>Management action</th>
<th>Demographic variable</th>
<th>Grouped p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat biopsy in near future</td>
<td>Years in gastroenterology practice</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen for review due to concern about recovery or complications</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Number of tenths worked in private practice</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen for long-term follow-up</td>
<td>0.042</td>
</tr>
<tr>
<td>Check HLA-DQ2 or DQ8</td>
<td>Number of recently diagnosed patients seen for follow-up</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen for biopsy to confirm diagnosis</td>
<td>0.039</td>
</tr>
<tr>
<td>Check EMA</td>
<td>Number of tenths worked in clinical gastroenterology</td>
<td>0.013</td>
</tr>
<tr>
<td>Advise to start a GFD; repeat serology to document a fall</td>
<td>Number of patients seen for review due to concern about recovery or complications</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Number of patients seen for long-term follow-up</td>
<td>0.047</td>
</tr>
<tr>
<td>Advise nothing further now; repeat investigations in future</td>
<td>Number of patients seen for review due to concern about recovery or complications</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Respondents’ likelihood of arranging capsule endoscopy was not significantly influenced by any demographic variable, and nor was the advice they would be likely to give Joshua’s GP about the possible diagnosis.
On examination of the statistically significant differences in the context of Joshua being asymptomatic, the following emerged:

(1) While 34 of 43 respondents were unlikely to arrange a repeat biopsy in the near future, there was a 50% likelihood that those who were likely to do this had worked in clinical gastroenterology practice between 21 and 30 years, and a 50% likelihood that those who had worked in gastroenterology for this number of years would be likely to rebiopsy.

(2) Two-thirds (4/6) of those who were likely to rebiopsy Joshua saw between one and ten patients per month for review because of concerns about their recovery, and they comprised just over half (4/7) of the people who saw this number of patients for this type of follow-up.

(3) The majority of those who were not likely to rebiopsy Joshua (28/34) worked fewer than four tenths in private practice, while those who were likely to rebiopsy worked a range of tenths privately.

(4) No-one who did not see any patients for long-term follow-up of CD indicated they would be likely to rebiopsy Joshua, while the one person who saw more than ten long-term follow-up patients per month was likely to rebiopsy him.

(5) Respondents who saw fewer recently diagnosed patients for follow-up were less likely to request HLA testing for Joshua, as were those who saw greater numbers of patients for biopsy to confirm a CD diagnosis. Those who saw fewer numbers of patients for biopsy were more likely to request HLA testing for Joshua.

(6) People who did more clinical tenths in gastroenterology were much more likely to request EMA testing for Joshua.

(7) Only six people were likely or highly likely to recommend that Joshua commence a GFD now, with repeat serology at a later date to document a fall in levels. These people were more likely to see between one and ten patients per month for long-term CD follow-up, and people who saw this many patients for this type of review were also much more likely to make this recommendation than people who saw fewer than ten such patients per year (50% versus 8%).
(8) Five of the six people who were likely to recommend that Joshua start a GFD saw between one and ten patients per month for review due to concern about their recovery, and the majority of those who would not have given this advice (33/35) saw fewer than ten such patients per year.

(9) The group of participants who would be unlikely to recommend doing nothing further for Joshua at this stage includes all those who see between one and ten patients per month for review due to concern about their recovery.

Analysis of responses to the amended scenario of Joshua being symptomatic revealed far fewer statistically significant differences. (Table 4.11)

Table 4.11 Factors influencing management actions when Joshua is symptomatic and has positive serology but normal histology, with p-values

<table>
<thead>
<tr>
<th>Management action</th>
<th>Demographic variable</th>
<th>Grouped p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat biopsy in near future</td>
<td>Number of recently diagnosed patients seen for follow-up</td>
<td>0.01</td>
</tr>
<tr>
<td>Arrange capsule endoscopy</td>
<td>Number of years in practice</td>
<td>0.052</td>
</tr>
<tr>
<td>Check HLA-DQ2 or DQ8</td>
<td>Number of patients seen for long-term follow-up</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Further investigation of these results identified that the majority of respondents who saw fewer than ten newly diagnosed patients per year for follow-up were unlikely to rebiopsy a symptomatic Joshua, while the majority of those who saw between one and ten such patients per month were likely to rebiopsy him. The majority of participants who had been in practice fewer than 30 years were unlikely to arrange capsule endoscopy, but just over half (4/7) of those who had been in practice more than 30 years indicated they were likely to do so. All participants who did not see any CD patients for long-term follow-up were likely to request HLA testing for him.
4.6 A patient declining endoscopy

The final part of the survey dealt with the increasingly common issue of patients with positive CD antibodies declining endoscopy, preferring to go straight to treatment with a GFD. In order to explore this question, participants were given the following scenario:

You are contacted by a local GP who has a patient whom she suspects has coeliac disease, based on symptoms and moderately positive IgA anti-tTG antibodies. The patient is unwilling to undergo endoscopy for biopsy, and has already commenced a gluten free diet. The GP asks you how you think she should proceed with this patient.

A range of possible courses of action were presented and participants were asked to rate how likely they would be to suggest each of these to the patient’s GP. (Figure 4-18)

A large majority of respondents (80%) indicated they would be likely or highly likely to recommend that the GP continue to encourage the patient to reconsider her decision, because the diagnosis of CD is unreliable without a biopsy. Within this
group, 66.7% (24 of 36 people) were highly likely to give this advice. They represented 53.3% of the respondent group. When it came to HLA testing, 75.6% were likely or highly likely to recommend this, to help determine whether CD was possible or not. Once again, among this group the majority (26 of 34 people) indicated they would be highly likely to do this, representing 57.8% of all participants.

Somewhat surprisingly, respondents were more divided over whether they would suggest to the GP that it could be assumed that the patient had CD. (Figure 4-19)

![Figure 4-19: Likelihood of advising GP to assume that the patient has CD, and to manage her accordingly](image)

On further inspection of these responses it was apparent that there was a degree of inconsistency when they were compared with responses to the essentially contradictory course of action informing the patient that the diagnosis of CD is unreliable without biopsy. (Table 4.12)
Table 4.12: Cross-tabulation of apparently contradictory question responses; (dark beige = consistent responses, blue = inconsistent responses)

| Inform the patient that diagnosing CD is unreliable without a biopsy | Assume the patient does have CD and manage her accordingly |
|---|---|---|---|---|---|---|
| | Highly unlikely | Unlikely | Neutral | Likely | Highly Likely | Total |
| Highly unlikely | 0 | 0 | 0 | 1 | 1 | 2 |
| Unlikely | 0 | 0 | 0 | 1 | 0 | 1 |
| Neutral | 0 | 0 | 2 | 2 | 2 | 6 |
| Likely | 2 | 2 | 3 | 3 | 2 | 12 |
| Highly likely | 11 | 4 | 4 | 1 | 4 | 24 |
| Total | 13 | 6 | 9 | 8 | 9 | 45 |

From this table it can be seen that all 19 respondents who had indicated they would be unlikely or highly unlikely to recommend that the GP assume the diagnosis of CD, had also indicated they would be likely or highly likely to advise her that the diagnosis was unreliable without biopsy. Similarly, the three people who had answered they would be likely or highly likely to suggest that the GP assume the patient does have CD, were all unlikely or highly unlikely to advise that the CD diagnosis is unreliable without a biopsy. Together these two groups of consistent responders constitute 48.9% of the total participant group. In contrast, ten participants (22.2% of respondents) indicated they would be likely or highly likely to suggest both possibilities to the GP. One participant acknowledged that “obviously some decisions are mutually exclusive, but depend on what patient decides after discussion”. Eleven people were neutral on one or other of the options and likely, or highly likely, to suggest the alternative to the GP.

There was an opportunity to comment following this set of questions, and, in addition to the comment above, seven other respondents did so. Here too their comments diverged, with one saying that he would
try to persuade the patient that biopsy is confirmatory for the diagnosis and helps to monitor the response to treatment. Persistently abnormal histology has implications re complications of coeliac disease.

while another wrote that “if the patient feels better on GFD and is happy with uncertainty of diagnosis, no need to investigate further as will not alter management.” One commented that he would prefer to see the patient himself to “counsel her accordingly”, and one person commented that it was the patient’s choice and that “it is difficult to suggest re-challenge and biopsy” if she felt better on the GFD. One participant noted that the patient would not be eligible for a Special Authority number without biopsy, while another would recommend monitoring of micronutrients. The final comment related to HLA testing, with a note that if this were negative CD could be excluded, but the patient could continue on a GFD if she wished.

4.6.1 The gluten challenge

As a follow-up question to the scenario outlined above, participants were asked what their advice would be regarding a gluten challenge, should the patient change her mind and decide to proceed with an endoscopy. In a free text question, they were asked how much gluten-containing food would constitute an adequate challenge.

Two people left the question blank, one person wrote “plenty” and one that the patient should “just eat a normal diet without gluten restriction”, but all other respondents referred to slices of bread per day, which had been given as an example alongside the question. (Figure 4-20)
It can be deduced from this figure that the majority of respondents thought that consuming somewhere between two and four slices of bread daily would constitute an adequate gluten challenge. One person added the rider that the bread should be “stodgy white bread”, and another that it should be “cheap”.

Participants were also asked to choose from a range of options for how long they would recommend the gluten-challenge should continue. There was a range of views on this, with the most popular option being “at least 4 weeks”, chosen by 46.7% (21/45). “Until she is symptomatic” was also given as an option, however no participants indicated that they would recommend this. (Figure 4-21)
The two “Other” responses were “at least 3 weeks” from one person, and “my preferred option is 4 weeks, but some will not tolerate this”, from the other.

4.6.2 Analysis by demographics: A patient declining endoscopy

On Fisher's Exact testing of grouped Likert-scale responses, there were no statistically significant influences on participants' likely advice to the GP in this scenario. With respect to the duration of a gluten challenge, statistical significance was reached for number of tenths worked in gastroenterology, (p=0.019), and for the hemisphere in which postgraduate study was undertaken, (p=0.048), while the influence of the setting in which participants worked approached statistical significance, (p=0.053). Thus those participants who indicated a gluten challenge should last at least four weeks were much more likely to work more than six tenths in gastroenterology, and were more likely to work in both the public and private settings, or in the private sector alone. People who worked in the public setting only were more likely to recommend a challenge of at least two weeks. The majority of those who thought that a gluten challenge should last at least six weeks had done their postgraduate training in the Southern Hemisphere, although this is of no particular clinical relevance.
4.7 Key findings of the survey

To conclude this chapter the key findings of the survey are summarised as follows.

4.7.1 Response to the survey and respondent characteristics

This survey gathered information from approximately 55% of gastroenterologists identified as practising in New Zealand at the time it was carried out, representing 53.3% of male and 46.7% of female gastroenterologists. The majority worked in both the public and private healthcare settings, had been practising in gastroenterology for up to 20 years, and worked six or more clinical tenths per week in the specialty. Most of their CD-related work related to diagnosis and immediate management, with 60% reporting they saw between one and ten patients per month for biopsy to confirm the diagnosis, and 44.4% seeing a similar number of recently diagnosed patients for follow-up. Only seven respondents (15.6% of the group) saw 10 or more patients per year for long-term follow-up, and only one participant declared a sub-speciality interest in CD. Conferences and medical journals were the sources of information most likely to be used to update knowledge with respect to CD, while 64.5% indicated they were likely or highly likely to utilise practice guidelines for this purpose.

4.7.2 Management of newly diagnosed CD

With respect to the management of newly diagnosed CD and follow-up in the first 12 months following diagnosis, the key findings are that there were high levels of agreement among respondents about the importance of monitoring abnormal blood test results to ensure that these return to normal, and widespread agreement that patients should be reviewed to confirm that CD-related symptoms resolve with treatment. There was much less accord with regards to follow-up CD serology testing, both in terms of its importance and the timing of when such testing should be undertaken. Opinion was also divided on the need for DEXA scanning to be performed, and in particular on the place of rebiopsy in the first 12 months following diagnosis. In general, reference to follow-up tasks that respondents rated as important was likely to be included in the discharge letter to go to the patient’s GP.
4.7.3 Long-term management of CD

There was less concordance among respondents when it came to considering long-term management of the condition, with the only aspect of care receiving a clear majority of support being the need to regularly reinforce the importance of adherence to the GFD. Just over 50% of respondents expressed themselves as neutral on the importance of annual influenza and 5-yearly pneumococcal vaccinations. With regards to implementing an “Annual Review” for CD patients, 60% rated this as important or very important, while 73.3% indicated that this should be carried out by a patient’s GP. However, just under 60% of those who thought the GP should be responsible for this were likely or highly likely to note this in their discharge letter.

On the inclusion of non-cross-contaminated oats in the GFD, attitudes varied towards if and when this should be recommended, and whether there should be any caveats attached. Opinion was also divided on the place of rebiopsy when oats are introduced, with a small majority (57.8%) of respondents simply advising patients to stop eating oats if symptoms re-emerge, compared with 26.7% who indicated they routinely rebiopsied if oats were included in the diet.

4.7.4 When the histology is normal

In the context of a patient with elevated IgA-tTG antibodies and a normal duodenal biopsy, there was a range of views on next steps in his assessment and management. The presence or absence of symptoms had a noticeable and statistically significant impact on this.

If the patient were asymptomatic there were high levels of agreement that it would be important to review the result with a pathologist, that arranging a capsule endoscopy would not be appropriate, and that recommending he starts a GFD at this juncture would also not be appropriate. However, opinions were clearly divided on the merits of checking his HLA status and EMA levels, and on how likely participants would be to recommend doing nothing further at this stage.

In the presence of a positive HLA test, ongoing elevated IgA-tTG antibodies, a confirmed normal biopsy, but no symptoms, just over 60% of respondents would have advised the patient’s GP that he may or may not have CD and to watch, wait, and reinvestigate in a year, or if symptoms emerged.
When symptoms were introduced into the scenario, opinions changed. A greater majority would have sought review of the histology, and higher numbers indicated that they would be likely or highly likely to request HLA and EMA testing. Most notably, almost 50% of respondents were likely or highly likely to recommend that the patient start a GFD (compared with 13.3% in the absence of symptoms), and just 11.1% would have been likely or highly likely to recommend doing nothing further. The proportion of participants advising a watch and wait approach also fell (to 40%).

4.7.5 A patient declining endoscopy

As with the other scenarios covered in this survey, responses were mixed with regards to how participants would advise a GP seeking their input on how to manage a patient with positive IgA-tTG antibodies, but already on a GFD. The large majority (80%) indicated they would be likely or highly likely to advise the GP to inform the patient that diagnosing CD without a biopsy is unreliable, and just over 75% would recommend testing her HLA status. Opinion was, however, divided on whether or not respondents would be likely to advise the GP that a diagnosis of CD could be assumed in this patient, with some inconsistent responses on this issue relative to other issues. There was also a diverse range of ideas on what constitutes an adequate gluten challenge, both in terms of its duration, and the amount of gluten required.
Chapter 5: Results from the Survey of General Practitioners

5.1 Introduction

The survey of GPs was designed to capture information about their practice relating to CD with respect to both its recognition and management, as a means of measuring their knowledge about the condition. It took place in the first half of 2015, and as discussed in Chapter Three, was delivered in both electronic and hard-copy formats. This chapter presents the results of that survey.

The chapter begins by providing details about the overall response to the survey and goes on to describe the characteristics of participants. Their responses are then presented under the following headings, which follow the structure of the survey itself:

- Coeliac Disease in General
  - Recognition
  - Diagnosis
  - Management
- Coeliac Disease in Your Practice
  - Newly diagnosed patients
  - Long-term management

Responses are first described and then, when appropriate, sections conclude with analysis according to participant characteristics. The chapter closes by drawing out the key findings.

5.1.1 Sample size

As outlined in Chapter Three (page 132), the sample for this survey was drawn from a database held by bpac®. A stratified random sampling technique was used, selecting 50% of males and 50% of females on the database for each DHB region. As some people in the database had not stated their gender, a 50% sample was selected from this group in each region also. This process generated a sample population of 2178.

Prior to sending out the survey to this group, preliminary data cleaning was undertaken, firstly to identify people within the population who might not be intended recipients, and secondly to try and ascertain the gender of the almost-300
people for whom this information was not held. It was important to check the eligibility of potential recipients because the services provided by bpac\textsuperscript{nz} are not exclusively for GPs, and for some of those on the list, the contact address given suggested that they might not work in general practice. In addition to this, the spreadsheet made available by bpac\textsuperscript{nz} included the number of years of medical practice of those listed. Several people on the list had been in practice for 45 years or more, so it seemed reasonable to assume that at least some of them would be retired. Through a process of checking the New Zealand Medical Register and conducting online searches, an initial group of 171 people were identified as not being eligible for the survey, leaving 2007 people who could be included. Common sense and online searching meant that the gender of the vast majority of potential participants was also able to be determined. (Figure 5-1)

\textbf{Figure 5-1: Sample size information}

If the sample group of 2007 had been entirely comprised of people working in general practice and eligible to participate, this would have represented approximately 46\% of the general practice workforce, as determined in the New Zealand Medical Council’s (NZMC) Workforce Survey of 2014.\textsuperscript{456} Due to the size of the sample however, it was not possible to check the eligibility of every intended participant. It is very likely that more people on the list were also ineligible, and indeed some of those people identified themselves once the survey was sent out. (See section 5.2)
Women constituted 47.9% of the study sample of 2007, and men 51.7%, which was equivalent to the proportions of women and men who were working in general practice at the time the survey was conducted.457

5.1.2 Modes of contact

As also discussed in Chapter Three, contact details for intended study participants took one or both of two forms: email addresses and postal addresses. In the course of the study period, participants for whom only email addresses were available were sent two emails; those for whom email and postal addresses were available were sent two emails and one hard copy of the survey; and those for whom only postal addresses were available were sent two hard copies. For the majority of the group, both forms of contact were available. (Table 5.1)

<table>
<thead>
<tr>
<th>Mode of survey delivery</th>
<th>Number of intended recipients</th>
<th>Assumed number who received survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email only</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Email first, to be followed by posted hard copy</td>
<td>1545</td>
<td>1525</td>
</tr>
<tr>
<td>Posted hard copy only</td>
<td>423</td>
<td>415</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2007</td>
<td>1978</td>
</tr>
</tbody>
</table>

This table also gives the numbers of people whom it is assumed actually received the survey. The difference between intended and actual recipients is accounted for by bounced or blocked emails, and postal surveys returned to sender and unable to be redirected.

During the process of sending follow-up emails and surveys, a further eight people were identified as being overseas or retired, thus reducing the eligible sample group to 1970. The proportions of women and men in this revised sample group remained essentially the same, with 48.1% of the group being women, and 51.6% men. There were six people in the sample for whom gender information was not available.
5.2 Response to the survey

Overall there were 736 responses to the survey, including seven people who declined to participate. One of these indicated that the lack of a “don’t know” option meant that he or she “could not complete this questionnaire without confabulating”, a point that will be discussed in Chapter Seven. Another person wrote a letter saying that in his 50 years of medical practice he had “not seen one patient with this condition”, although he had seen a few patients with DH, all of whom “had gluten allergy”. This too will be discussed further in Chapter Seven, along with a comment from a third respondent that he did not do surveys as “they are always used to pillory GPs”. In determining a response rate for the survey, all seven of these respondents were included in the group of eligible participants, but excluded from the number of people who completed the survey.

5.2.1 Response rate

The final response rate for the survey was derived as follows. (Figure 5-2)

![Response rate calculations for the survey of GPs](image)

From this figure it can be seen that there were 23 people who indicated that they were either retired, overseas, or not in clinical general practice, rendering them also ineligible for the survey. In the final calculation of response rate, these people were removed altogether. This gave an eligible sample group of 1947, and an overall response rate of usable responses of 35.5%. This should be regarded as a
conservative figure, as it is highly likely that additional surveys, other than the ones noted in Table 5.1 on page 190, did not reach their targets, due to a change in address (for example). It is also possible that there were more recipients who were ineligible, either through retirement, or not being in clinical general practice, but who did not respond to indicate this.

5.2.2 Mode of response

There were three modes of response utilised by the 706 eligible respondents to the survey. As noted in Chapter Three, a link to the survey was embedded in the emails that were sent out, and the booklet version included a web address that could also be accessed to enable hard copy recipients to complete the survey online if they so wished. (Table 5.2)

Table 5.2: Modes of response to the survey of GPs from eligible respondents

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Delivered</th>
<th>Eligible respondents</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email only</td>
<td>38</td>
<td>14</td>
<td>36.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Online: 14 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paper: 0</td>
<td></td>
</tr>
<tr>
<td>Email followed by hard copy</td>
<td>1502</td>
<td>561</td>
<td>37.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Online/web-based: 359 (64%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paper: 202 (36%)</td>
<td></td>
</tr>
<tr>
<td>Hard copy only</td>
<td>407</td>
<td>131</td>
<td>32.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Web-based: 15 (11.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paper: 116 (88.5%)</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>1947</td>
<td>706</td>
<td>35.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed paper: 318 (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed online/web-based: 374 (53%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incomplete: 14 (2.0%)</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

All the incomplete surveys excluded from final analysis had been commenced online.
5.2.3 Respondent characteristics

As is usual practice, the survey included a number of questions seeking information about participant demographics. Data generated by these questions are presented on the following pages. (Tables 5.3, 5.4, and 5.5, and Figures 5-3, 5-4, and 5-5) Details are given on the proportions of participants for each variable, and as proportions of overall response rates.

Table 5.3: GP survey recipient and respondent gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Not answered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of respondents</td>
<td>269</td>
<td>420</td>
<td>3</td>
</tr>
<tr>
<td>Proportion of respondents (% of N=692)</td>
<td>38.9%</td>
<td>60.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Response rate ( % of N = number of survey recipients)</td>
<td>26.9% (N=1000)</td>
<td>44.6% (N=941)</td>
<td>0.2% (N=1947*)</td>
</tr>
</tbody>
</table>

* Gender information was unavailable for six recipients of the survey

As can be seen in this table, women are over-represented in the respondent group.

When it came to identifying the DHB regions in which they worked, there were 29 people who indicated that they worked in more than one region. These people have been counted as respondents from the region to which they had been assigned when the survey was sent out. All but two of them did some of their work in this “DHB of origin”. (Table 5.4) Regional information was unavailable for two respondents only, one of whom did not have a designated DHB in the original sample, and one who did not complete this section of the survey and for whom the information could not be traced. It is apparent from Table 5.4 that although all DHB regions were represented in the respondent group, some regions drew higher response rates than others.
<table>
<thead>
<tr>
<th>DHB Region</th>
<th>Surveys delivered</th>
<th>Surveys returned</th>
<th>Response rate per region</th>
<th>% of respondent group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northland</td>
<td>76</td>
<td>26</td>
<td>34.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Auckland</td>
<td>260</td>
<td>118</td>
<td>45.4%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>152</td>
<td>37</td>
<td>24.3%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Waitemata</td>
<td>203</td>
<td>65</td>
<td>32.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Bay of Plenty</td>
<td>100</td>
<td>44</td>
<td>44.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Waikato</td>
<td>154</td>
<td>56</td>
<td>36.4%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Tairawhiti</td>
<td>18</td>
<td>3</td>
<td>16.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Lakes</td>
<td>50</td>
<td>10</td>
<td>20.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Taranaki</td>
<td>47</td>
<td>13</td>
<td>27.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Mid-Central</td>
<td>64</td>
<td>9</td>
<td>14.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Hawkes Bay</td>
<td>81</td>
<td>30</td>
<td>37.0%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Whanganui</td>
<td>25</td>
<td>7</td>
<td>28.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Wairarapa</td>
<td>18</td>
<td>6</td>
<td>33.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Capital and Coast</td>
<td>156</td>
<td>57</td>
<td>36.5%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Hutt Valley</td>
<td>60</td>
<td>16</td>
<td>26.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Nelson Marlborough</td>
<td>76</td>
<td>25</td>
<td>32.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>West Coast</td>
<td>10</td>
<td>6</td>
<td>60.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Canterbury</td>
<td>245</td>
<td>88</td>
<td>35.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>21</td>
<td>6</td>
<td>28.6%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Southern</td>
<td>153</td>
<td>68</td>
<td>44.4%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
<td>N/A</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
The vast majority of respondents (634 people, 91.6% of the study sample) held vocational registration with the Royal New Zealand College of General Practitioners (RNZCGP), and their professional profiles are summarised as follows. (Table 5.5)

**Table 5.5: Participant professional profiles**

<table>
<thead>
<tr>
<th>Total number of responses for analysis</th>
<th>692</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Position in general practice</strong></td>
<td></td>
</tr>
<tr>
<td>Practice owner</td>
<td>326 (47.1%)</td>
</tr>
<tr>
<td>Locum/associate/employee, one practice</td>
<td>279 (40.3%)</td>
</tr>
<tr>
<td>Locum, many practices</td>
<td>43 (6.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (4.1%)</td>
</tr>
<tr>
<td>Not answered</td>
<td>16 (2.3%)</td>
</tr>
</tbody>
</table>

| **Half-day sessions in general practice** |     |
| < 3                                      | 37 (5.4%) |
| 3 – 5                                    | 184 (26.6%) |
| 6 – 8                                    | 279 (40.3%) |
| > 8                                      | 174 (25.1%) |
| Not answered                             | 18 (2.6%) |

| **Years in clinical practice**          |     |
| 1 – 10                                  | 28 (4.1%) |
| 11 – 20                                 | 130 (18.8%) |
| 21 – 30                                 | 308 (44.5%) |
| > 30                                    | 225 (32.5%) |
| Not answered                            | 1 (0.1%) |

Respondents who selected “Other” for their work setting included GP registrars, people who held multiple positions (e.g. employed by a DHB and working as a locum in several practices), and those who had specialty roles (e.g. medical officer in prisons or aged-care facilities, or in occupational medicine).

Among respondents 540 (78.0%) reported that their place of work was situated in an urban area, while 137 (19.8%) were based rurally. This question was not answered by 15 people (2.2%). These figures are comparable to those reported by the RNZCGP for 2015, in which 76% of respondents identified themselves as urban-based, 17% as rural-based, and 6% as not clearly rural or urban.457
On further analysis of the demographic information provided by participants, it was apparent that male respondents were more likely to be practice owners, while female respondents were more likely to be working as long-term locums or associates. The men were also more likely than the women to be working more than five half-day sessions per week, and to have been working in general practice for more years. The numbers of male and female respondents working in rural practice were equivalent, but this represented a greater proportion of male participants. These differences all reached statistical significance on Pearson Chi-square testing. There was no significant difference between the genders with respect to vocational registration.

Participants were also asked about the ethnic group or groups with which they identified. This was a free text question, and responses were subsequently grouped according to SNZ's standardised codes, available from the MoH. The majority of respondents (531 people; 77% of the study sample) identified as either “New Zealand European” or “Other European”, while another 32 people wrote that they were “Kiwi” or “New Zealander”. Only 12 people identified as Māori. There were 43 participants who identified as Asian, 18 of them Indian and 15 Chinese. Four people were Pacific Islanders, while two people identified as Middle Eastern, one as Latin American, and one as South African-coloured. In addition, 66 people did not answer the question, either by leaving it blank, by giving an unrelated answer (e.g. secular), or by noting that they refused to answer this question. (Figure 5-3)

![Figure 5-3: Ethnicity of GP survey respondents](image_url)
By way of comparison, the 2015 RNZCGP Workforce Survey reported that 83% of GPs identified themselves as European.457

5.2.4 Patient/practice characteristics

The survey included questions about the populations and patients cared for by participants. Free text questions were used to gather information about the predominant socio-economic and ethnic groupings of respondents’ patients. Answers were coded post hoc and collated. (Figures 5-4 and 5-5)
It is apparent from these graphs that the majority of patients cared for by participants in the survey were in the lower and middle socio-economic groups, and of European ethnicity. Patients from these socio-economic groups comprised at least 58.7% of those seen by survey respondents, while just over 77% of participants cited “European” as a predominant group in the composition of their practice populations.

5.2.5 Sources of information about CD

The final question in the demographics section of the survey asked people to indicate the sources from which they had acquired their overall knowledge about CD. They were presented with a range of choices, along with the option of citing any other resources they utilised. (Figure 5-6) The question was not answered by 14 people.

“Other” sources included having CD oneself, or affecting a close family member or friend, which was cited by 40 participants (5.8% of the group); other internet sources such as UpToDate or BMJ Learning, listed by 22 respondents (3.2%); Health Pathways or other local guidelines, noted by 11 people (1.6%); and self-directed
learning, or other training or expertise (such as in Nutrition Medicine) which were cited by 32 people (4.6%).

The majority of respondents indicated that they utilised more than one of the options listed, with the range extending from only one option being utilised by 36 people (5.2%), through to all options being used by one person. Almost 68% of the respondent group indicated that they used between three and six of the resources given. The median number of sources used was 4, with a mean of 4.38 (standard deviation 1.97).

5.3 Coeliac Disease in General

The first section of the survey asked respondents to consider their approach to CD in general terms, focusing on issues such as whom they would be likely to test, how they would be likely to test them, and how likely they would be to implement a range of possible management options. This section was completed by 692 participants, although occasional questions were left unanswered. In these instances, the number of non-respondents to a question is included in the presentation of results.

5.3.1 Recognition of coeliac disease

The first two questions of the survey investigated the issue of testing for CD, asking respondents to rate how likely they would be to order coeliac testing for patients with any of the listed signs and symptoms (Question One), or conditions (Question Two), who were otherwise asymptomatic. (Tables 5.6 and 5.7)

Within the lists of symptoms and conditions included in the matrices of options for these questions were recurrent back pain (Question One), and asthma and Paget’s disease of the bone (Question Two). None of these appear as an indication for testing in any of the available guidelines relating to CD, and as such, it was not unreasonable to expect that clinicians with a reasonable degree of knowledge relating to CD would be unlikely to regard them as an indication for testing. They also served as “sleeper” questions, as suggested by Aday and Cornelius, and discussed in Chapter Three.
Table 5.6: Likelihood of testing for CD in otherwise asymptomatic patients with the signs or symptoms listed; options most likely to lead to testing in bold

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Highly Unlikely</th>
<th>Unlikely</th>
<th>Neutral</th>
<th>Likely</th>
<th>Highly Likely</th>
<th>No answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature reduced bone mineral density</td>
<td>78 (11.3%)</td>
<td>153 (22.1%)</td>
<td>140 (20.2%)</td>
<td>190 (27.5%)</td>
<td>124 (17.9%)</td>
<td>7 (1.0%)</td>
</tr>
<tr>
<td>Unexplained iron deficiency</td>
<td>19 (2.8%)</td>
<td>59 (8.5%)</td>
<td>67 (9.7%)</td>
<td>248 (35.8%)</td>
<td>297 (42.9%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Unexplained folate deficiency</td>
<td>30 (4.3%)</td>
<td>98 (14.2%)</td>
<td>126 (18.2%)</td>
<td>235 (34.0%)</td>
<td>197 (28.5%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Unexplained elevation of liver transaminases</td>
<td>83 (12.0%)</td>
<td>250 (36.1%)</td>
<td>230 (33.2%)</td>
<td>101 (14.6%)</td>
<td>24 (3.5%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>137 (19.8%)</td>
<td>265 (38.3%)</td>
<td>183 (26.5%)</td>
<td>67 (9.7%)</td>
<td>37 (5.4%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Recurrent aphthous stomatitis</td>
<td>77 (11.1%)</td>
<td>182 (26.3%)</td>
<td>188 (27.2%)</td>
<td>182 (26.3%)</td>
<td>57 (8.2%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Recurrent back pain</td>
<td>246 (35.6%)</td>
<td>300 (43.4%)</td>
<td>120 (17.3%)</td>
<td>20 (2.9%)</td>
<td>3 (0.43%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Unexplained neurological symptoms</td>
<td>193 (27.9%)</td>
<td>261 (37.7%)</td>
<td>146 (21.1%)</td>
<td>63 (9.1%)</td>
<td>25 (3.6%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>83 (12.0%)</td>
<td>183 (26.5%)</td>
<td>179 (25.9%)</td>
<td>169 (24.2%)</td>
<td>71 (10.3%)</td>
<td>7 (1.0%)</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>11 (1.6%)</td>
<td>14 (2.0%)</td>
<td>40 (5.8%)</td>
<td>309 (44.7%)</td>
<td>317 (45.8%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Persistent fatigue</td>
<td>24 (3.5%)</td>
<td>54 (7.8%)</td>
<td>138 (19.9%)</td>
<td>306 (44.2%)</td>
<td>167 (24.1%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Two or more of the above</td>
<td>9 (1.3%)</td>
<td>25 (3.6%)</td>
<td>101 (14.6%)</td>
<td>285 (41.2%)</td>
<td>269 (38.9%)</td>
<td>3 (0.4%)</td>
</tr>
</tbody>
</table>
As revealed in this table, several of the signs and symptoms listed elicited quite high numbers of “neutral” responses. This was most noticeable in the situation of a patient with an unexplained elevation of liver transaminases, with 230 people (33.3% of those who completed the survey) answering in this way. Over 25% of participants were also neutral about how likely they would be to test patients with unexplained infertility, recurrent aphthous stomatitis, or chronic constipation.

Apart from chronic diarrhoea, the presence of two or more of the symptoms and signs listed in Question One was more likely to lead to testing for CD than a presentation with any one of the possibilities given. Chronic diarrhoea was the single symptom most likely to prompt participants to test for CD, followed by unexplained iron deficiency, unexplained folate deficiency, and persistent fatigue. This information is displayed below, along with data relating to the symptoms and signs least likely to prompt CD testing. (Figure 5-7)

![Figure 5-7: Comparative likelihood of testing for CD in the presence of specific signs and symptoms](image-url)
Table 5.7: Likelihood of testing for CD in otherwise asymptomatic patients with the conditions listed; conditions most likely to lead to testing in bold

<table>
<thead>
<tr>
<th>Condition</th>
<th>Highly Likely</th>
<th>Unlikely</th>
<th>Neutral</th>
<th>Likely</th>
<th>Highly Likely</th>
<th>No answer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 Diabetes</strong></td>
<td>139 (20.1%)</td>
<td>188 (27.2%)</td>
<td>145 (21.0%)</td>
<td>128 (18.5%)</td>
<td>89 (12.9%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td><strong>Autoimmune thyroid disease</strong></td>
<td>110 (15.9%)</td>
<td>176 (25.4%)</td>
<td>133 (19.2%)</td>
<td>195 (28.2%)</td>
<td>73 (10.6%)</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td><strong>Dermatitis herpetiformis</strong></td>
<td>83 (12.0%)</td>
<td>138 (19.9%)</td>
<td>128 (18.5%)</td>
<td>122 (17.6%)</td>
<td>216 (31.2%)</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>224 (32.4%)</td>
<td>293 (42.3%)</td>
<td>150 (21.7%)</td>
<td>19 (2.8%)</td>
<td>4 (0.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td><strong>Down syndrome</strong></td>
<td>191 (27.6%)</td>
<td>230 (33.2%)</td>
<td>145 (21.0%)</td>
<td>75 (10.8%)</td>
<td>50 (7.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>Turner syndrome</strong></td>
<td>212 (30.6%)</td>
<td>237 (34.3%)</td>
<td>187 (27.0%)</td>
<td>38 (5.5%)</td>
<td>17 (2.5%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>Sjogren’s syndrome</strong></td>
<td>159 (23.0%)</td>
<td>212 (30.6%)</td>
<td>183 (26.5%)</td>
<td>100 (14.5%)</td>
<td>37 (5.4%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>Irritable bowel syndrome</strong></td>
<td>18 (2.6%)</td>
<td>25 (3.6%)</td>
<td>50 (7.2%)</td>
<td><strong>295 (42.6%)</strong></td>
<td><strong>304 (43.9%)</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Autoimmune liver disease</strong>*</td>
<td>63 (19.8%)</td>
<td>67 (21.1%)</td>
<td>84 (26.4%)</td>
<td>71 (22.3%)</td>
<td>30 (9.4%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td><strong>Paget’s bone disease</strong></td>
<td>180 (26.0%)</td>
<td>255 (36.9%)</td>
<td>209 (30.2%)</td>
<td>33 (4.8%)</td>
<td>13 (1.9%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td><strong>First-degree relative of coeliac patient</strong></td>
<td>12 (1.7%)</td>
<td>20 (2.9%)</td>
<td>61 (8.8%)</td>
<td><strong>248 (35.8%)</strong></td>
<td><strong>351 (50.7%)</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

* Due to an oversight that occurred in the transfer of the questionnaire from the booklet form to the online format, autoimmune liver disease appeared in the paper-based version of Question 2, but not in the electronic copy. This means that only the 318 people who completed the survey in its hardcopy form answered this part of the question. Percentages reported in Table 5.7 and Figure 5-8 refer to this subgroup of participants.
As is apparent in Table 5.7, when it came to testing for CD in the presence of particular conditions, only two among those listed were likely or highly likely to lead to testing. These were IBS, and having a first-degree relative with CD. And apart from DH, for all other conditions more respondents were unlikely or highly unlikely to test for CD than were likely or highly likely to do so. (Figure 5-8)

![Figure 5-8: Comparative likelihood of testing for CD in the presence of specific conditions](image)

Participants were also invited to comment on whether there were any other indications that would lead them to test someone for CD, and 332 people did so. This represents 48% of the total group. Of these, 316 (45.7% of the total group) gave reasons additional to those that had been included in the preceding questions. A wide range of examples were given, and these were grouped around common themes. (Table 5.8)
### Table 5.8: Additional signs, symptoms, and conditions which lead to CD testing

<table>
<thead>
<tr>
<th>Sign, symptom, or condition</th>
<th>Number of respondents (% of N = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss/ failure to gain weight</td>
<td>94 (13.6)</td>
</tr>
<tr>
<td>Abdominal pain and/or bloating</td>
<td>91 (13.2)</td>
</tr>
<tr>
<td>Patient request</td>
<td>61 (8.8)</td>
</tr>
<tr>
<td>Gluten or wheat intolerance</td>
<td>40 (5.8)</td>
</tr>
<tr>
<td>Bowel symptoms (not otherwise specified)</td>
<td>30 (4.3)</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>24 (3.5)</td>
</tr>
<tr>
<td>Second degree relative affected/ family history of CD</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td>Gastritis/ Gastro-oesophageal reflux/ dyspepsia</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Anxiety and /or depression</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td>Autism/ ADHD/ behavioural issues</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Other: eczema, nausea, “brain fog”, vasculitis, autoimmune disease in general, joint and/or soft tissue “issues”, rheumatoid arthritis, failure to respond to iron supplementation, amenorrhoea, headaches/migraine</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

#### 5.3.1.1 The incorrect options

From Table 5.6 and Figure 5-7 (on pages 200 and 201 respectively) it can be seen that the majority of participants (79%) indicated they would be unlikely or highly unlikely to test for CD in a patient with recurrent back pain. A further 17% of respondents were neutral on the issue, while only 23 people (3.3% of the group), said that they would be likely or highly likely to do so. In Table 5.7 and Figure 5-8 (on pages 202 and 203 respectively) it is also apparent that the majority of respondents would be unlikely or highly unlikely to regard either asthma or Paget’s disease as indications for testing for CD (74.7% and 62.9% respectively). Of these two, Paget’s disease, which is much less common than asthma in New Zealand, drew the higher number of neutral responses (30.2%, compared with 21.7%), suggesting
that participants were less certain about the relevance of CD testing in this situation. More participants (46 people, 6.6% of the total group) were also likely or highly likely to test for CD in the presence of Paget’s disease, than they were in the presence of asthma (23 people, 3.3% of the group).

On further inspection of responses from the people who were likely or highly likely to test for CD in the presence of one (or more) of these “sleeper” options, it seems probable that at least four individuals had inadvertently reversed the polarity of the scales, intending “1” to be “highly likely”, and “5” to be “highly unlikely”. Several more only used the “4” and “5” options across the whole matrix of options, to which the use of a “sleeper” is designed to draw attention.

5.3.1.2 Cumulative testing patterns

In order to provide an overview of their likely testing patterns, participants’ ratings of the likelihood that they would test for CD under each of the circumstances which comprised questions one and two were collated. The maximum possible scores were 60 for Question One, and 50 for Question Two, which would have arisen if participants had rated every option in the question (including the incorrect options) with a “5”. Total scores for the first (symptoms) ranged from 8/60 to 58/60, while those for the second (conditions) ranged from 10/50 to 47/50. The following histograms show the distributions of scores for each of these two questions. (Figures 5-9 and 5-10)
The person with the lowest score of 8/60 in the first question only gave answers for two of the symptoms listed (chronic diarrhoea and persistent fatigue), leaving all the other symptoms blank. Another respondent indicated that he was highly unlikely to test for CD with every symptom listed, giving him a total score of 12/60. (In a subsequent question this participant stated that he does not test for CD.) One person did not answer the question at all.

In the second question, three people indicated that they would be highly unlikely to test for CD in the presence of any of the conditions listed, giving them total scores of 10/50. This includes the participant noted above who scored similarly in Question One.

5.3.1.3 Optimal cumulative scores for testing

For each question an optimal score range was then calculated with optimal values, based on recommendations from the 2009 NICE Guidelines, assigned to each symptom, sign, or condition. Thus symptoms and conditions for which NICE indicated that testing for CD should be offered were given an optimal score of 5 (which equated to highly likely to test), and an acceptable score of 4 (likely to test).

---

1 Question 1: Unexplained iron deficiency, Unexplained folate deficiency, Chronic diarrhoea, Persistent fatigue, and Two or more symptoms; Question 2: Type 1 Diabetes, Autoimmune thyroid disease, Dermatitis Herpetiformis, Irritable bowel syndrome, and 1st degree relative of a coeliac patient.
Symptoms and conditions for which NICE recommended that testing should be **considered** were assigned an optimal score of 4 (likely to test), and an acceptable score of 3 (neutral). The optimal score for symptoms and conditions **not** associated with CD was 1 (highly unlikely to test), and an acceptable score was 2 (unlikely to test).

Once each symptom, sign and condition in the question matrices had been assigned a score, these values were collated and then grouped, using the rubrics set out in the following table. (Table 5.9)

**Table 5.9: Collated score ranges for Questions 1 and 2 of the GP survey**

<table>
<thead>
<tr>
<th>Rubric</th>
<th>Question 1 Collated Score range</th>
<th>Question 2 Collated Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly over testing</td>
<td>&gt; 51</td>
<td>&gt; 39</td>
</tr>
<tr>
<td>Likely to be appropriately testing</td>
<td>41 – 51</td>
<td>33 – 39</td>
</tr>
<tr>
<td>Possibly under-testing</td>
<td>36 – 40</td>
<td>28 – 32</td>
</tr>
<tr>
<td>Probably under-testing</td>
<td>30 – 35</td>
<td>23 – 27</td>
</tr>
<tr>
<td>Under-testing</td>
<td>&lt; 30</td>
<td>&lt; 23</td>
</tr>
</tbody>
</table>

Ratings for likelihood of testing for autoimmune liver disease were removed from calculations, because these scores were available for fewer than half of participants.

Participants' cumulative scores were then calculated and grouped according to the process just described. (Figure 5-11)

---

1 All other symptoms and conditions listed in questions 1 and 2, apart from Recurrent back pain, Asthma and Paget’s disease of bone, as already discussed.
The median and mean scores for Question One were both 38, which sits at the upper end of the “possibly under-testing” range. The standard deviation for the mean was 8.26, standard error 0.31, and 95% confidence interval 37.38 to 38.62. The median and mean scores for Question Two were 29 and 28.66 respectively, once again sitting in the “possibly under-testing” range, but this time at the lower end of that range. The standard deviation for the mean was 7.48, standard error 0.28, and 95% confidence interval 28.10 to 29.22. Pairwise correlation of the two scores generated $r=0.666$, indicating a moderate to strong positive correlation between them.

### 5.3.2 Analysis by demographics: Recognition of CD

Analysis of responses to the questions relating to the recognition of CD centred on the cumulative scores that had been calculated utilising participants’ individual item ratings. Using Pearson Chi-square or Fisher’s exact tests (when individual cell numbers were less than five), these were analysed with respect to participant gender and rurality. Responses were also analysed by whether or not participants had patients with CD.

Optimal scores for testing in the presence of particular signs and symptoms (derived from Question One) were associated with statistically significant
differences according to the gender of respondents, \((p<0.0001)\), and whether or not they had patients with CD, \((p=0.009)\), but not with respect to rurality, \((p=0.357)\). Optimal scores for testing in the presence of certain conditions (derived from Question Two), were also associated with statistically significant differences according to the gender of respondents, \((p=0.011)\), but not with rurality or whether or not they had patients with CD, \((p=0.902 \text{ and } p=0.088 \text{ respectively})\).

With respect to gender, for both sets of cumulative scores a greater proportion of female than male respondents were in each of the “possibly over-testing”, “likely to be appropriately testing”, and “possibly under-testing” ranges, while a greater proportion of male than female participants were in the “probably under-testing” and “under-testing” ranges. In addition to this, mean cumulative scores were also analysed by gender using a two-sample t-test. Female participants had a mean cumulative symptom score of 39.2 (CI 38.4 – 39.9) compared to their male counterparts whose mean score was 36.2 (CI 35.1 – 37.3), \((p<0.0001)\). Cumulative conditions scores were 29.6 (CI 28.9 – 30.3) and 27.3 (CI 26.4 – 28.2) respectively, \((p=0.0001)\).

Having patients with CD was more likely to be associated with cumulative symptoms scores in the “possibly over-testing” and “likely to be appropriately testing” ranges, and not having patients with CD was more likely to be associated with all three variants of under-testing. There was no significant difference in cumulative conditions scores between those with and without patients with CD.

Additional analyses were performed with responses separated into male and female groupings. There were no new significant associations identified in this process, and the effect of having CD patients on cumulative symptom scores was reduced. Thus, when cumulative scores for female respondents were analysed by whether or not they had CD patients, this generated \(p=0.055\). For male respondents this value was \(p=0.310\).

5.3.3 Diagnosing coeliac disease

Questions in the survey then moved on to explore issues pertaining to diagnosing CD, beginning by asking participants which test (or tests) they requested from among those listed, when they first tested someone for the condition. (Figure 5-12) The results shown include respondents who indicated they would request more
than one of the tests on the list. (Note: The “Coeliac antibodies” option came with
the descriptor “the lab will do what is appropriate”.)

![Figure 5-12: Tests requested as part of initial testing for coeliac disease](image)

Among the 21 people (3.0% of respondents) who requested HLA testing, only one
selected this test alone, although she also indicated that she tested for “antibodies
to all the other wheat proteins”. The remaining 20 people did HLA testing in
combination with one or more of the other options, most commonly “coeliac
antibodies”. Three respondents indicated in subsequent parts of the survey that
they did not know what the HLA-DQ2/DQ8 test is.

Just over 7% of respondents (50 people) included “Other” in the suite of tests
they requested. The majority of these (31 people; 62% of this subgroup) noted they
also did IgA testing, with some indicating that this was done routinely by their
particular laboratory provider, and some saying that they would request it if the
laboratory did not automatically do this. Another seven people indicated they
sometimes requested HLA testing, either as a follow-up test or to clarify an antibody
test result, while eight people included other tests such as a full blood count and
iron testing as part of their initial investigation of possible CD. One person
commented that she would like to do more HLA testing but that she was “actively
discouraged to do so by the lab”. Only three people indicated that they tested for
gliadin antibodies, with two of them specifying that they do this for children.
5.3.3.1 Referrals for endoscopy

Participants were next asked about how often they refer their adult patients for gastroscopy, when they return a positive coeliac test. (Figure 5-13) Two people did not answer this question.

Figure 5-13: Frequency of referrals for gastroscopy when coeliac serology is positive

An opportunity to comment on this question was provided, to which 323 participants (46.7%) responded, making this the issue that drew the greatest number of “additional comments” in the survey. Several major themes emerged from analysis of these comments. (Table 5.10)
Table 5.10: Comments relating to referral practice for patients with a positive coeliac test

<table>
<thead>
<tr>
<th>Major theme</th>
<th>Number of participants (% of comments)</th>
<th>% of total respondent group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy is the gold standard/ necessary for diagnosis/ necessary for Special Authority number</td>
<td>68 (21.1%)</td>
<td>9.8%</td>
</tr>
<tr>
<td>Depends on patient willingness to continue with or reintroduce gluten/ willingness to undergo endoscopy</td>
<td>56 (17.3%)</td>
<td>8.1%</td>
</tr>
<tr>
<td>Access to endoscopy is limited/ takes a long time/ difficult to get</td>
<td>56 (17.3%)</td>
<td>8.1%</td>
</tr>
<tr>
<td>Would refer to a gastroenterologist for review and decision on further investigation</td>
<td>29 (9.0%)</td>
<td>4.2%</td>
</tr>
<tr>
<td>Would depend on the presence of, or severity of symptoms</td>
<td>28 (8.7%)</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

As can be seen from this table, just over 20% of those who commented did so to indicate their understanding that biopsy is the gold standard or necessary for a CD diagnosis, and/or is necessary for patients to be eligible for subsidised prescription GF foods. This particular issue was cited by 12 people as a reason for almost always referring, but also by two people as a reason for seldom referring for endoscopy. In their words: “the only reason I can see for gastroscopy is so that they would be entitled to subsidised gluten free products”, and “main reason is histological diagnosis for SA number”. Another person, who referred about half the time, commented that “In the past referral was for a subsidy on gluten-free products. Today it is easier to do gluten-free without subsidy”.

Of note, among the comments were five from people pointing out that it was not gastroscopy that these patients needed, but endoscopy with duodenal or jejunal biopsy. Three of these people had indicated that they almost never referred for gastroscopy. On reflection, the use of the word “gastroscopy” in this question was imprecise, and may well have led to others answering similarly. However, additional comments were made by almost 60% of the people who indicated that
they almost never refer patients with a positive coeliac test (31 out of 53), and only three of them mentioned this issue. A further 16 people also made reference in their comments to endoscopy and/or duodenal biopsy.

Table 5.10 also shows that access to timely endoscopy was an issue for many, as was the issue of patients being unwilling to continue consuming gluten, or to resume eating it, in order for an endoscopy (and reliable biopsies) to be undertaken. These issues were often linked. Problematic access to endoscopy was identified by participants from 14 of the 20 DHB regions. When these data were analysed with respect to total numbers of respondents from each region, it emerged that there were four regions in which more than 20% of survey participants indicated that there were long delays in accessing this service. These figures need to be viewed with caution however, as three out of these four districts had very small numbers of respondents overall. It should also be noted that four people commented that they had excellent access to endoscopies in their particular areas, in contrast to others from the same regions who indicated that there were difficulties. None of these positive comments related to the four areas with the highest rates of dissatisfaction.

Another 15 respondents (not included in Table 5.10) used the opportunity for comment to note that they always refer patients, rather than “almost always” doing this, while 13 people commented about how rarely (if ever) they have found a positive result. One of these people, who almost always referred, wrote that it “is so uncommon to get a positive test that I get excited to see the endoscopy result.” Ten people indicated that they trialled a GFD first and only referred those patients who did not improve with this. An additional 35 comments traversed a range of individual opinions.

A question then followed concerning the advice that participants would give to patients who were being referred for biopsy, and when to start a GFD. (Figure 5-14) Three people left the question blank.
Of the 82 people who selected the “other” option, 69.5% did so to indicate that their practice was one of two combinations of the other two options, both involving patients being advised to be on a gluten-containing diet prior to the endoscopy. In the first of the combination responses, participants noted that they recommended that patients waited until they had had a gastroscopy before starting the GFD, but that for many patients this proved intolerable due to the length of time it generally took until this occurred. In these circumstances they would advise the patient that he or she must be on gluten for some weeks (the range varied among respondents) before the endoscopy was performed. The second combination was that respondents told patients that they could start the GFD immediately, but that they would need to reintroduce gluten prior to endoscopy. Another 13.4% commented that their practice depended on how long it would take for the endoscopy to occur, without indicating how that influenced their practice. The common theme among all of these responses was that there was almost always a lengthy delay between positive serology results and biopsies, unless the patient had the capacity to pay for the procedure, and that this posed challenges for their patients and for themselves in how best to proceed.

The remaining “other” responses included comments that patients should continue eating gluten until after biopsy results were known; that participants
relied on patients being guided by what a gastroenterologist tells them when they are seen prior to endoscopy; and that the respondent would seek advice before making any recommendation to the patient. A small number of respondents also indicated that they advised their patients to eat additional gluten-containing foods to ensure the biopsy is accurate.

A related question concerned the serology testing of patients who had already excluded gluten from their diets, an increasingly common occurrence in this day and age. Participants were asked to indicate what they would advise someone already on a GFD, whom they thought should be tested for CD. In this situation 52.9% of respondents (366 people) indicated that they would recommend that the patient reintroduce gluten into his or her diet, and if the patient did not wish to do this they would not go ahead with testing them for CD. This compared with 39.2% (271 people) who would test for CD, even if the patient declined to reintroduce gluten, and 7.5% (52 people) who would not make any recommendations about changing their diet, and would simply test them. Three people did not answer this question.

5.3.3.2 The gluten challenge

Participants were then asked about how much gluten-containing food they would suggest patients should re-introduce into their diets, prior to testing for CD. This was a free text question that drew a large range of responses, with 36 different identifiable options given. There was a prompt within the question that gave “slices of bread per day” as an example, and the vast majority of respondents gave their answer with reference to that. An “I don’t know, I would need to find out” alternative was also provided, and was utilised by 253 participants (36.6% of those who answered the question). Suggested quantities of gluten ranged from half a slice of bread per day recommended by one participant, through to six to eight slices per day recommended by another participant. Responses were grouped for ease of representation. (Figure 5-15) Thirteen people did not answer this question, including four of those who had previously indicated they would not recommend reintroducing gluten into the diet.
Just over 41% of those included in the “2 – 4 slices” range (115 people) specified that the amount should be 4 slices of bread per day (or equivalent), making this the most favoured option overall. “Other” suggestions included “enough to provide a reaction”, “until symptoms return”, “as much as tolerated”, and one person who answered “gluten 2.5 – 5 gm per day”. Across all the options suggested, 59 people (8.5% of respondents) qualified their answers by indicating that they would need to check to be certain, including some who wrote that they were guessing. Another four participants (not included in Figure 5-15) made a distinction between adults and children, recommending that adults consume 4 slices of bread per day, and children 2 slices of bread.

A follow-up question asked about how long these patients would need to be consuming gluten before testing them for CD. (Figure 5-16) There were two people who did not answer this question, while four people noted that they would need to check to be certain.
Answers from those who selected the “other” option ranged from five days (one person) to over six months (one person), with the majority of the remainder of this group settling on three weeks (eight people) or four to six weeks (six people).

Participants were then asked to choose the two most likely options they would utilise if they needed to check what constituted an adequate gluten challenge. (Figure 5-17)
Almost half of the group (317 people; 45.8%) selected only one option from the available list, with just over half of these indicating that they would “Go to an internet source such as BPAC or patient.co.uk”. Very few respondents relied solely on colleagues, dietitians, or Coeliac NZ for this information. Those who used more than one source of information chose myriad combinations of the available options, with the most popular being “Google” and “an internet source such as BPAC”, selected by 74 people (10.7% of the group). “Other” sources that would be consulted included HealthPathways, identified by 29 respondents, and local laboratories (or laboratory generated resources), chosen by 18 people. The question was not answered by 27 people, 26 of whom it seems likely did not feel the need to ask for advice on this issue.

5.3.3.3 Confirming the diagnosis of CD

The survey also explored the issue of what results participants would be likely to consider as confirmation that a patient has a diagnosis of CD. They were provided with six options and asked to rate them on a scale from “highly unlikely” to “highly likely”. Their responses are presented in the following table (Table 5.11). Answers that attracted the highest number of responses for each option are highlighted in bold.
Table 5.11: Likelihood that GPs will regard a range of test result options as confirming a patient has CD; most common response for each option in bold

<table>
<thead>
<tr>
<th>Test results</th>
<th>Highly Unlikely</th>
<th>Unlikely</th>
<th>Neutral</th>
<th>Likely</th>
<th>Highly Likely</th>
<th>No answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive HLA-DQ2/8 alone</td>
<td>86 (12.4%)</td>
<td>114 (16.5%)</td>
<td>294 (42.5%)</td>
<td>123 (17.8%)</td>
<td>27 (3.9%)</td>
<td>46 (6.7%)</td>
</tr>
<tr>
<td>Positive serology alone</td>
<td>29 (4.2%)</td>
<td>79 (11.4%)</td>
<td>161 (23.3%)</td>
<td>348 (50.3%)</td>
<td>57 (8.2%)</td>
<td>16 (2.3%)</td>
</tr>
<tr>
<td>Positive serology and positive HLA-DQ 2/8</td>
<td>22 (3.2%)</td>
<td>43 (6.2%)</td>
<td>140 (20.2%)</td>
<td>264 (38.2%)</td>
<td>182 (26.3%)</td>
<td>39 (5.6%)</td>
</tr>
<tr>
<td>Positive serology followed by positive biopsy</td>
<td>7 (1.0%)</td>
<td>1 (0.1%)</td>
<td>7 (1.0%)</td>
<td>18 (2.6%)</td>
<td>654 (94.5%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Positive serology followed by symptomatic improvement on a GFD</td>
<td>13 (1.9%)</td>
<td>43 (6.2%)</td>
<td>139 (20.1%)</td>
<td>323 (46.7%)</td>
<td>165 (23.8%)</td>
<td>7 (1.0%)</td>
</tr>
<tr>
<td>Positive serology which goes back to normal on a GFD</td>
<td>25 (3.6%)</td>
<td>48 (6.9%)</td>
<td>180 (26.0%)</td>
<td>265 (38.3%)</td>
<td>153 (22.1%)</td>
<td>19 (2.8%)</td>
</tr>
</tbody>
</table>

From this table it can be seen that a number of respondents did not give answers for every test result option listed. This is most noticeable for the finding of a positive HLA-DQ2/DQ8 test on its own, followed by positive serology combined with positive HLA-DQ2/DQ8. This may indicate either that these participants were unsure about how to interpret an HLA test result, or that they were so certain that the HLA test was not an appropriate tool for confirming the diagnosis of CD that the “highly unlikely” option did not express this definitively enough. The high number
of “neutral” responses for the HLA-alone option also suggests participant uncertainty about this test. In addition to this, two participants indicated that they were uncertain about the entire question and would have to look up the answers. They were not included among the “did not answer” group, having actually indicated a response to the question.

Participant responses were collated, likely with highly likely responses, and unlikely with highly unlikely responses. (Figure 5-18)

![Figure 5-18: Collated responses of the likelihood that GPs will regard positive test results as confirming the diagnosis of CD](image)

The responses of the eight people who indicated that they were unlikely or highly unlikely to accept “positive serology followed by a positive biopsy” as confirming CD were scrutinised more closely. They include three people whom it is likely had reversed the polarity of this scale, as they had done in earlier questions, and one other who probably reversed the polarity for this question alone.

5.3.4 Analysis by demographics: Diagnosing CD

Responses to key questions relating to diagnosing CD were analysed with respect to gender, rurality, and whether or not participants had patients with CD, using Pearson Chi-square tests, or Fisher’s Exact test when individual cell numbers were
less than five. Analyses were also performed with responses separated into male and female groupings. (Table 5.12)

Table 5.12: Factors influencing practices relating to diagnosing CD, with p-values

<table>
<thead>
<tr>
<th>Practice concerned with diagnosis</th>
<th>Demographic variable</th>
<th>p-value</th>
<th>p-value by gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing of people already on a GFD</td>
<td>Gender</td>
<td>0.535</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rural or Urban</td>
<td>0.717</td>
<td>M=0.893 F=0.859</td>
</tr>
<tr>
<td></td>
<td>CD patients or not</td>
<td>0.003</td>
<td>M=0.312 F=0.004</td>
</tr>
<tr>
<td>Frequency of endoscopy referrals when CD serology positive (Figure 5-13)</td>
<td>Gender</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rural or Urban</td>
<td>0.201</td>
<td>M=0.885 F=0.105</td>
</tr>
<tr>
<td></td>
<td>CD patients or not</td>
<td>0.001</td>
<td>M=0.041 F=0.019</td>
</tr>
<tr>
<td>Timing of commencing a GFD (Figure 5-14)</td>
<td>Gender</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rural or Urban</td>
<td>0.962</td>
<td>M=0.910 F=1.000</td>
</tr>
<tr>
<td></td>
<td>CD patients or not</td>
<td>0.022</td>
<td>M=0.006 F=0.442</td>
</tr>
</tbody>
</table>

The first of the actions analysed concerned the timing of serological testing among patients already on a GFD. As shown in Table 5.12, this was found to be influenced by whether or not participants looked after patients with CD. Thus those without any coeliac patients were more likely just to test for CD rather than making any recommendation to the patients being tested about reintroducing gluten into
their diets. This difference was influenced by gender, with separated analyses confirming the statistical significance in the responses from women, but not men.

When it came to analysing the frequency with which participants referred patients with raised coeliac antibodies for endoscopy, the gender of respondents was found to be significant. It was apparent that a greater proportion of the men than the women indicated they referred patients for endoscopy almost never or some of the time, while a greater proportion of the women than the men referred such patients most of the time or almost always. Those who currently had patients with CD in their care were much more likely to almost always refer for endoscopy than those who did not, and this was true for both men and women.

A possible association between the predominant SES of participants’ practice populations and their likelihood of referring for endoscopy was also investigated, but no such association was found. Specific comparisons were also made between low and high SES populations, again with no significant differences detected.

With regards to what advice participants gave to patients about when to start a GFD, women were more likely to recommend a combination of the response options provided (i.e. they selected “other” more frequently). Male respondents without CD patients were more likely to recommend starting the GFD immediately.

The other important issue explored in relation to diagnosing CD was the range of test result options that participants would be likely to accept as confirming the diagnosis. (Table 5.11; page 220) Pearson Chi-square analyses were performed, in which participants Likert-scale responses were grouped: likely with highly likely, unlikely with highly unlikely, and neutral. This was done to more closely reflect likely clinical outcomes. The only scenario that showed a significant difference was that of the likelihood of participants accepting a positive serology test alone as confirming the diagnosis. Having patients with CD influenced responses to this question, (p=0.029), with a much higher proportion of participants with patients with CD being likely or highly likely to do this. On separated analysis by gender, the difference remained for female participants, (p=0.009), but not for the males, (p=0.764). Women without patients with CD were more likely to be neutral in their response, and less likely to accept such a result as confirming CD.
5.3.5 Managing coeliac disease: annual reviews

The final part of the first section of the survey focused on the issue of annual reviews for patients with CD. Context was provided in the stem for the first question of the series, as follows:

Gastroenterologists in NZ and abroad are beginning to recommend that patients with coeliac disease have their management reviewed by a health professional on an annual basis. Assuming that children are reviewed in paediatric clinics, how necessary do you think this is for adult coeliac patients?

As well as being asked how necessary they believed an annual review to be, respondents were also asked about whom they thought should carry out such a review, whether this was in fact something they already did for their patients, and what they would include if this were to become a routine part of CD management. (Figure 5-19). Three people did not answer this question.

Figure 5-19: How necessary is an Annual Review of adult CD patients?

The 20 people who responded “Other” mostly did so to indicate what might be included in a review. Four people thought a review every two or three years would be sufficient, especially if the patient was well, while one person thought reviews should happen 3- to 6-monthly, especially when a patient was newly diagnosed.

When asked about who should usually perform an annual review, participants overwhelmingly thought this should be the GP, with 542 (78.3%) responding accordingly. Only 44 people (6.4% of the total group) thought an annual review
should usually be conducted by a gastroenterologist, while 32 (4.6%) thought a dietitian should do it. A tiny number (11; 1.6%) indicated that the role should be given to practice nurses. A further 50 respondents (7.2%) selected the “Other” option, of whom 30 thought that such a review could be carried out by either a GP or a Practice Nurse (or Nurse Practitioner), or a gastroenterologist, or a dietitian, or some combination of these. Some stipulated a GP could do this following an initial assessment by a gastroenterologist, and four people indicated that they either did not know, or did not have an opinion on whose responsibility this should be. Four people did not answer this question.

A free text opportunity to make additional comments about annual reviews, and who might do them, then followed. Almost one-third of participants (226 respondents) commented, of whom 180 (79.6%) had indicated that GPs should usually perform this task. Their comments fell into several thematic groups. (Table 5.13)
Table 5.13: Themes of comments about CD Annual Reviews

<table>
<thead>
<tr>
<th>Theme of Comments</th>
<th>Number of participants (% of comments)</th>
<th>% of total respondent group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggesting reviews could be carried out by different providers at different times and for different reasons</td>
<td>70 (31%)</td>
<td>10.1%</td>
</tr>
<tr>
<td>Requesting that guidelines or more education be provided</td>
<td>47 (21%)</td>
<td>6.8%</td>
</tr>
<tr>
<td>Affirming the value of an Annual Review and/or noting what it should include</td>
<td>33 (14.6%)</td>
<td>4.8%</td>
</tr>
<tr>
<td>General Comments about CD and related issues (such as the trend for gluten free diets)</td>
<td>27 (11.9%)</td>
<td>3.9%</td>
</tr>
<tr>
<td>Noting that there are resource implications (e.g. cost to patient, scarce specialist resources, lack of time)</td>
<td>19 (8.4%)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Questioning the value and/or the available evidence to justify an Annual Review</td>
<td>8 (3.5%)</td>
<td>1.2%</td>
</tr>
<tr>
<td>Other</td>
<td>22 (9.7%)</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Other comments mentioned issues such as patient choice; that who conducted a review might depend on patient symptoms; or merely endorsed the provider option that the respondent had selected in the preceding question.

When it came to whether an annual review was something participants in the survey already tried to do for their adult patients with coeliac disease, they responded as follows. (Figure 5-20). Eleven people did not answer this question, and another 101 (14.6% of participants) responded that they did not have any such patients.
Figure 5-20: Is an annual review something you try to do for your adult coeliac patients?

The “some of my adult coeliac patients” option included the additional question “Which ones and why?”, and was answered by 141 of the 169 people (83.4%) who had indicated that this was their practice. Among those who answered, 40 reported that these were the patients who were willing to come in for an annual review, the corollary being that they also had patients who declined the invitation to attend. Another 45 people wrote that they conducted such reviews on an opportunistic basis when patients were being seen for other things, which one person noted meant that those who never presented for anything did not get reviewed. (Seven people who had selected “Other” were also coded to this group, having indicated that they did in fact review their patients opportunistically). Other groups of patients identified include those who were unwell and/or not improving as expected, those who were getting prescriptions for gluten free foods, and those who were no longer being seen by a gastroenterologist. A small number of respondents (11 people) noted that they did not yet have a formal recall system in place for CD annual reviews, but would think about doing so in light of this survey.

The “Other” group included two people who had only recently diagnosed a patient with CD, and one who wrote that “I would rely on them requesting it and being willing to pay – which many aren’t”.

I don’t have any adult coeliac patients
No, I don’t do this for my adult coeliac patients
Yes, I do this for all my adult coeliac patients
Yes, I do this for some of my adult coeliac patients
Other

Percent of respondents
5.3.5.1 Content of annual reviews

In another free text question, participants were asked what they would include if they were to do an annual review of management with their CD patients. Of the 692 people who completed the survey, 32 (4.6%) did not answer this question. Twenty-five (3.6%) said that they did not know, were unsure, or would refer to any guidelines that were available. Another person wrote that he “wouldn’t do it”, while two others gave broad answers such as “all the usual stuff”, or “part of an annual health check”, which could not be otherwise classified. Two indicated that they would want to see good evidence both for the need for an annual review, and for what should be included in such a review, if indeed it were necessary, and one person’s comment was “I would need to discuss that with the person once they were diagnosed.” Answers from the remaining 630 people (91.0% of survey respondents) were able to be classified, and grouped thematically. (Table 5.14)

Table 5.14: Management options that respondents would include in an annual review of CD patients

<table>
<thead>
<tr>
<th>Component of Annual Review</th>
<th>Number who would include this (% of N = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>560 (80.9%)</td>
</tr>
<tr>
<td>Questioning about symptoms (including those related to associated conditions)</td>
<td>419 (60.5%)</td>
</tr>
<tr>
<td>Weight measurement</td>
<td>310 (44.8%)</td>
</tr>
<tr>
<td>Review of diet and any associated difficulties</td>
<td>245 (35.4%)</td>
</tr>
<tr>
<td>Consideration of need for DEXA scanning</td>
<td>147 (21.2%)</td>
</tr>
<tr>
<td>Clinical examination (other than weight)</td>
<td>124 (17.9%)</td>
</tr>
</tbody>
</table>

Responses varied greatly in the amount of detail included, with some merely writing “bloods” or “general check and routine bloods”, compared with others who gave an extensive list of the blood tests they would request, and the symptoms about which they would enquire.

Details of the blood tests that participants would request were further analysed. (Table 5.15)
Table 5.15: Blood tests forming part of CD Annual Review

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Number who would request (% of N = 580)</th>
<th>% of total respondent group (N = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin and/or iron studies</td>
<td>333 (57.4%)</td>
<td>48.1%</td>
</tr>
<tr>
<td>Full blood count</td>
<td>259 (44.7%)</td>
<td>37.4%</td>
</tr>
<tr>
<td>B12 and/or folate</td>
<td>257 (44.3%)</td>
<td>37.1%</td>
</tr>
<tr>
<td>Coeliac antibodies/serology</td>
<td>141 (24.3%)</td>
<td>20.4%</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>120 (20.7%)</td>
<td>17.3%</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>112 (19.3%)</td>
<td>16.2%</td>
</tr>
<tr>
<td>Glycated Haemoglobin (HbA1c)</td>
<td>93 (16.0%)</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

Small numbers of people (fewer than 15) also indicated that they would test other things such as zinc, magnesium, calcium, renal function, lipids, and “vitamin” levels not otherwise specified.

With respect to the questioning and examination of these patients, 40 people (6.3% of the 630 who positively answered the question) specifically mentioned that they would screen for other autoimmune diseases, 19 people (3.0%) indicated that they would check their skin, and 15 people (2.4%) that they would check for evidence of malignancy. Nine of these specified that they would be concerned about lymphoma. Of note, five people would include assessing the need for colonoscopy screening as part of their review.

5.3.6 Analysis by demographics: Managing CD

As for the sections of the survey related to the recognition and diagnosis of CD, responses relating to this part of the survey were analysed by gender, rurality, and having patients with CD. Once again Pearson Chi-square or Fisher's Exact tests were used.

Caring for patients with the condition did significantly influence opinions on the necessity of annual reviews, (p=0.002). More than half of those without CD
patients thought that an annual review was probably necessary, while those with CD patients expressed a wider range of views. On analysis separated by gender, significance remained for male respondents only, (p=0.01; female p=0.192). When it came to who should carry out such a review, none of the variables investigated showed a significant association with particular responses.

5.3.7 Part A: Additional comments

Part A of the survey concluded with an invitation for participants to note any additional comments they might wish to make about CD in general. Just over 26% of respondents (182 people) took advantage of this opportunity. Their comments ranged over a number of issues, and while many used the space to make a general comment about CD, there were some common themes.

Almost 35% of comments (63/182) related to some of the confusion surrounding the prevalence of diagnosed CD. Within this grouping were references to the issues of self-over-diagnosis (11 people), underdiagnosis (26 people), that it is more common than we think (8 people), and that it is a “fashionable” or “trendy” or “popular” or “vogue” or “fad” diagnosis at present. One person summed up this view, writing

significantly underdiagnosed in community but also self "overdiagnosed" creating an issue in community that it is a current trendy diagnosis – significant confusion regarding coeliac disease and so called gluten intolerance.

In similar vein, another person commented that the “current fad for 'gluten sensitivity' is making it a bit hard to diagnose as so many patients refuse to take gluten prior to testing”.

Another 18% of comments (33/182) were to do with the respondent’s level of knowledge about CD, as typified by the following:

“You’ve proved my ignorance”,
“ Probably need to know more!!”, and
“Would appreciate guidelines!”
5.4 Coeliac disease in your practice

Part B of the survey was intended for those participants who had adult coeliac patients in their practice, or under their care, and focused on the management of those patients. It was completed by 542 people, constituting 78.3% of the population who returned the survey. Results from Part B are reported in the following sections of this chapter as proportions of this subgroup.

5.4.1 Participant characteristics

Characteristics of respondents with coeliac patients in their practices, and who went on to complete this second section of the survey, were compared with those of the total group of survey participants. (Table 5.16)

Not included in this table are the DHB regions in which people with coeliac patients worked. All DHBs were represented in this cohort and, as with the total participant group, the three DHB regions with the highest representation were Auckland (83 participants; 15.3% of the group), Canterbury (78 participants; 14.4%), and Southern (58 participants; 10.7%). Also not included is the ethnicity of respondents with CD patients. The ethnic make-up of this group closely resembled that of the whole group.
### Table 5.16: Characteristics of participants with coeliac patients compared with the overall respondent group in the survey of GPs

<table>
<thead>
<tr>
<th>Respondent characteristics</th>
<th>A: Respondents with characteristic (% of N=692)</th>
<th>B: Respondents with coeliac patients with characteristic (% of N=542)</th>
<th>B/A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>269 (38.9%)</td>
<td>205 (37.8%)</td>
<td>76.2%</td>
</tr>
<tr>
<td>Female</td>
<td>420 (60.7%)</td>
<td>336 (62.0%)</td>
<td>80%</td>
</tr>
<tr>
<td>FRNZCGP</td>
<td>634 (91.6%)</td>
<td>504 (93.0%)</td>
<td>79.5%</td>
</tr>
<tr>
<td>Own practice</td>
<td>326 (47.1%)</td>
<td>297 (54.8%)</td>
<td>91.1%</td>
</tr>
<tr>
<td>Long term locum/associate</td>
<td>279 (40.3%)</td>
<td>213 (39.3%)</td>
<td>76.3%</td>
</tr>
<tr>
<td>Work in many practices</td>
<td>43 (6.2%)</td>
<td>10 (1.9%)</td>
<td>23.3%</td>
</tr>
<tr>
<td>Other work situation</td>
<td>28 (4.0%)</td>
<td>13 (2.4%)</td>
<td>46.4%</td>
</tr>
<tr>
<td>Work &lt; 3 tenths</td>
<td>37 (5.3%)</td>
<td>11 (2.0%)</td>
<td>29.7%</td>
</tr>
<tr>
<td>Work 3 – 5 tenths</td>
<td>184 (26.6%)</td>
<td>138 (25.5%)</td>
<td>75%</td>
</tr>
<tr>
<td>Work 6 – 8 tenths</td>
<td>279 (40.3%)</td>
<td>243 (44.8%)</td>
<td>87.1%</td>
</tr>
<tr>
<td>Work &gt; 8 tenths</td>
<td>174 (25.1%)</td>
<td>139 (25.7%)</td>
<td>79.9%</td>
</tr>
<tr>
<td>1 – 10 years in practice</td>
<td>28 (4.0%)</td>
<td>17 (3.1%)</td>
<td>60.7%</td>
</tr>
<tr>
<td>11 – 20 years in practice</td>
<td>130 (18.8%)</td>
<td>102 (18.8%)</td>
<td>78.5%</td>
</tr>
<tr>
<td>21 – 30 years in practice</td>
<td>308 (44.5%)</td>
<td>259 (47.8%)</td>
<td>84.1%</td>
</tr>
<tr>
<td>&gt; 30 years in practice</td>
<td>225 (32.5%)</td>
<td>164 (30.1%)</td>
<td>72.9%</td>
</tr>
<tr>
<td>Rural</td>
<td>137 (19.8%)</td>
<td>109 (20.1%)</td>
<td>79.6%</td>
</tr>
<tr>
<td>Urban</td>
<td>540 (78.0%)</td>
<td>424 (78.2%)</td>
<td>78.5%</td>
</tr>
</tbody>
</table>
From this table it can be seen that the subgroup of participants with patients with CD in their care were slightly more likely to be female and vocationally registered in general practice, clearly more likely to own their own practice (and much less likely to work in several practices), and somewhat more likely to work more half-day sessions in general practice. They were reasonably similar with respect to years in clinical practice and rurality. Differences in the proportions of people who owned their own practice, worked fewer than three half-day sessions a week, and worked in many practices, reached statistical significance on Pearson Chi-square testing, (p= 0.01, p=0.003, and p<0.001 respectively).

Analysis of the characteristics of this subgroup of respondents was also conducted with respect to gender, with statistically significant results mirroring those from the whole sample population. Thus men with patients with CD were more likely to be practice owners and the women were more likely to work as a locum or associate in one practice; male respondents were more likely to work more than five half-day sessions per week and to have been in clinical practice for longer; and female participants were more likely to work fewer than five half-day sessions and to have been in clinical practice between 20 and 30 years. The women were also much less likely to have been in clinical practice for more than 30 years, and to work in urban settings.

5.4.2 Patient/practice characteristics

Patient and practice characteristics for participants in the survey who had patients with CD were also much the same as for the complete study group, as can be seen in the following figures, which present comparative data relating to the predominant SES of practice populations, (Figure 5-21), and the predominant ethnic makeup of these groups. (Figure 5-22)
Figure 5-21: Predominant SES of practice populations of all respondents compared with those with patients with CD

The differences between groups at each SES level were not statistically significant, but approached significance when SES levels were grouped middle through to high, and low with low to middle and mixed, (p=0.053).

Figure 5-22: Predominant ethnic makeup of practice populations of all respondents compared with those with patients with CD
There were no statistically significant differences between the groups with respect to any ethnic groupings within practices.

5.4.3 Newly diagnosed coeliac disease

The first set of questions in this section of the survey addressed issues relating to the early management of adults recently diagnosed with CD. The subject matter of questions paralleled questions from the survey of gastroenterologists included in the scenario which featured newly diagnosed Lucy, discussed in Chapter Four.

5.4.3.1 Referrals to dietitians and for Special Authority numbers

Participants were firstly asked about who usually refers newly diagnosed adult patients to a dietitian, and who usually applies for a Special Authority Number for prescription gluten-free foods. (Figure 5-23). Both questions were not answered by 3 people.

Figure 5-23: Person responsible for referring patients newly diagnosed with CD to a dietitian, and for applying for Special Authority numbers

Two respondents indicated that they did not refer patients to a dietitian at all, instead utilising practice staff who have CD themselves. With respect to applying for Special Authority numbers, 36 people (6.6% of the group) responded that “No-one does; they’re not necessary”. In subsequent comments a small number commented that, as GPs, they were not allowed or were unable to refer to dietitians.
5.4.3.2 Referrals for DEXA scanning

The questionnaire then asked how often participants referred their newly diagnosed adult patients for DEXA scanning. Respondents were fairly evenly split between those who almost never referred these patients for DEXA scanning (48.7%), and those who did (51%), with the majority of those who almost never referred indicating that they were unaware that this might be necessary. (Figure 5-24) Two people did not answer this question.

![Figure 5-24: Patterns of referral for DEXA scanning among respondents with patients with CD](image)

Among the 150 participants who referred patients for DEXA scanning “only in certain clinical situations” a variety of different reasons were given for doing so. Age was the most commonly identified variable that respondents took into consideration, being cited by 63 people (11.6% of the total subgroup), but the age that triggered such referrals varied greatly. One person would refer anyone over the age of 18 years old, while several indicated they would wait until a patient was in his or her fifties. Being a woman, and in particular a post-menopausal woman with CD was identified by 36 people (6.6%) as being an indication for requesting DEXA scanning, while the presence of risk factors for osteoporosis such as low body mass index, past fractures, family history, and cigarette smoking, also influenced similar numbers.
Cost and availability also featured as an issue, with 31 people (5.7% of the total group) indicating that the patient’s ability to pay, or the fact that if a gastroenterologist requests the test it will be free, influenced their practice. Two people noted that, in their DHB regions, as GPs they were unable to request DEXA scanning at all, and one person wrote that none of the options given applied because “it is not subsidised and most won’t pay. So – ‘almost never, aware it is a good idea but unfunded’.”

5.4.3.3 Prescribing gluten-free foods

Just over three quarters of respondents (421 people; 77.7%) indicated that they either currently provided prescriptions for subsidised gluten-free foods to their patients with CD, or had done so in the past. When then asked how they would determine the appropriate amount of food to include in each prescription, 408 participants (97% of those who prescribed) answered. Of these, 55.6% (227 people) relied on the patient to tell them how much of each product they needed. A further 12.5% (51 people) used information from dietitians and/or gastroenterologists, while 9.8% (40 people) left it to a pharmacist to work out. The remaining participants reported either that they did not know, or would guess how much to prescribe, or that it was many years since they had written such a prescription. Many of these commented that patients now generally did not seek prescriptions for subsidised gluten-free products because it was no longer worth their while to do so.

5.4.3.4 Testing first-degree relatives and joining Coeliac New Zealand

Participants were also asked about how often they discussed the issue of testing first-degree relatives with patients newly diagnosed with CD, and about how often they discussed joining CNZ with these patients. (Figure 5-25) These questions were not answered by four and seven people respectively. Three people commented that they were not aware of CNZ, while one person annotated her copy of the survey, changing the option from “Almost never; I wasn’t aware this might be necessary” to “Almost never; I wasn’t aware this might be a good idea”.
5.4.4 Analysis by demographics: Newly diagnosed CD

Analysis of responses in Part B of the survey again consisted of Pearson Chi-square or Fisher’s Exact testing, investigating possible associations with gender and rurality. The three “almost never” options were grouped for these analyses because all three would lead to the same clinical outcome.

The first question in this section of the survey investigated the issue of who, in the experience of the respondent, usually took responsibility for referring newly diagnosed patients to a dietitian. The majority of participants indicated it was either themselves or a gastroenterologist who did this. Gender and rurality both influenced this experience such that a higher proportion of male respondents reported it was usually they who had referred to dietitians, while a higher proportion of female respondents indicated that in their experience it was usually gastroenterologists who had done this, \(p=0.01\). In the rural setting, respondents themselves were more likely to refer to dietitians, as opposed to gastroenterologists.
doing this in the urban setting, (p=0.027). This was influenced by gender, with women in the rural setting being more likely to refer themselves, (p=0.007), but there being no significant difference in the experiences of the men, (p=0.831).

The frequency with which participants were likely to refer newly diagnosed patients for DEXA scanning was also influenced by gender, (p=0.031). Thus a higher proportion of male respondents indicated they almost never referred patients for DEXA scanning, while a higher proportion of the women were more likely to refer for scanning in “certain situations”.

When it came to whether or not participants would discuss the need for CD-testing of first-degree relatives of patients, gender was again influential, (p=0.02), with a greater proportion of female respondents indicating they almost always did this.

With respect to whether or not respondents recommended to their patients that they join CNZ, there was an association with rurality among men only, (p=0.001). Rural respondents were more likely to recommend CNZ almost always when compared with their urban counterparts, while urban respondents were more likely to almost never do this.

5.4.5 Long-term management

Questions then turned to the longer-term management of adult patients with CD, focusing on aspects of that management identified in the literature, and discussed in Chapter Two. These included the need to review patients with regards to their CD, the need to reinforce the importance of adherence to the GFD, if and when to retest serology, if and when to test for conditions associated with CD, and if and when to recommend influenza and/or pneumococcal vaccinations.

When it came to how often this group of respondents reviewed their adult patients with CD specifically with respect to their disease, the following practices emerged. (Figure 5-26) Six people did not answer this question.
Figure 5-26: Frequency of review of adult patients specifically with respect to CD

This chart shows that 61% (330 of the 542 participants in this survey who had adult patients with CD) reviewed those patients and their CD management either 6-monthly, annually, or opportunistically when they saw them for something else. Another 12.7% (69 people) did this occasionally, while 11.4% (62 people) indicated “Other”. In the majority of cases this option was utilised to enable participants to give a more nuanced response, which generally combined the options. Thus some indicated they reviewed their patients between 6- and 12-monthly, some asked them about their CD annually when they are being seen for something else, and some reviewed them “as often as required”. Within this group a small number also commented that they did not formally recall these patients, but would consider doing so if there was evidence to support such a process. The remaining 13.8% (75
people) almost never reviewed their patients specifically with respect to the condition.

The survey then asked participants about whether they ever reinforced the importance of adhering to the GFD. (Figure 5-27) Six people did not answer this question.

![Figure 5-27: Frequency with which participants reinforce the importance of the GFD to their adult patients with CD](image)

Among the 33 people who selected “Other” were two principal groups: one in which respondents indicated that they did this “occasionally”, “sometimes”, or “from time to time”; and the other in which they indicated that reinforcing the diet was not necessary because their patients tended to be so sensitive to gluten that they were highly motivated to remain gluten-free.

The issue of retesting coeliac serology as part of the long-term management of patients drew an enormous range of responses. Participants were asked when they retested coeliac serology in their adult coeliac patients, and were given a list of ten possible options from which to choose. They were given the instruction that they could choose as many answers as necessary, and many chose several. (Figure 5-28) Six people did not answer this question.
On further examination of responses, it was apparent that 355 participants (65.5% of the group) had selected only one option. Of these, 229 (64.5%) indicated that they almost never retested serology for one of the three reasons given: they did not think it was necessary, were not aware that it might be necessary, or assumed that a gastroenterologist did it.

Among the 181 respondents who selected more than one option for retesting serology, 63 different testing practice combinations were chosen. The most popular of these were:

(a) “if coeliac symptoms do not settle” along with “if coeliac symptoms recur” (25 people, 13.8% of the subgroup); and
(b) “if coeliac symptoms do not settle”, along with “if they recur” and “if the patient requests testing” (24 people, 13.3% of the subgroup).

The highest number of options selected by any participant was 6, and this was done by two people. The mean and median numbers of retesting practices were both 3, with the standard deviation from the mean of 0.95.

Figure 5.28: Coeliac serology retesting practices
As can be seen from Figure 5-28, a small number of people (8.7% of the group who answered the question) selected “Other”. In selecting this option, respondents were able to comment on their answers, which most of this group did to explain their practice further. Almost a quarter of this group indicated that they retested serology when they had concerns about a patient’s adherence to the diet, or if there were other changes (such as new iron deficiency) to suggest an increase in disease activity. A small number noted that they tested “opportunistically”, while a few tested on the advice of a gastroenterologist. Other comments included “there is no evidence to guide this”, “NB – our lab complains if we reorder it often”, and that “this varies with the individual client”.

The practices of respondents with respect to testing their adult coeliac patients for conditions associated with CD were less varied than those associated with serology retesting. (Figure 5-29) Nine people did not answer this question.

![Figure 5-29: Frequency of testing adult patients with CD for associated conditions](image-url)
The 13 people who selected “Other” included two who screened at diagnosis, two who screened from time to time and/or in the presence of symptoms, and two who would offer it annually but only if the patient came for review. One person commented that he “would need to know the degree of predictive association” because some associated conditions (such as Graves’ disease and Vitamin B12 deficiency) are “often tested, rarely seen”. Two people also commented that they would not necessarily test, but would examine their patients for signs of conditions associated with CD.

The last two questions pertaining to the long-term management of adult CD patients asked respondents about how often they recommended that these patients had an annual influenza vaccination, and/or a 5-yearly pneumococcal vaccination. (Figure 5-30) Nine people did not answer either question.

![Figure 5-30: Frequency of offering influenza and pneumococcal vaccinations to adult CD patients](image)
From this figure it can be seen that there was a great deal more uncertainty about the place of pneumococcal vaccination in CD management than there was about vaccinating against influenza.

A small number expanded their answers in comments that followed. One person who did not believe either vaccination was necessary wrote:

I am not aware of evidence that for people concordant with a gluten free diet there is any additional cost benefit from these imms (sic). I am not clear why there would be lowered immunity or increased susceptibility. If there is no evidence then stick with standard recommendations.

In contrast, three people indicated that they recommended the influenza vaccination to all their patients, irrespective of whether they had any underlying medical conditions, and another eight made reference to the cost of pneumococcal vaccination being a deterrent.

5.4.6 Analysis by demographics: Long-term management of CD

As with earlier parts of the survey, participant responses to questions in this final section were analysed with respect to their gender and rurality, using Chi-square or Fisher’s Exact tests. Once again, the three options of the “almost never” responses were grouped.

On the issue of how often respondents reviewed their patients with respect to their CD, the women were more likely to do this opportunistically, while the men were more likely to do this annually, (p=0.036). Neither gender nor rurality impacted on participants’ practice with respect to reinforcing the need for a GFD, but rurality did impact on frequency of testing for associated conditions, (p=0.027). Rural respondents were more likely to assess their patients with CD for the presence of associated conditions on an annual basis, while urban participants were more likely to do this from time to time. Additional analysis showed that gender did not affect this.

Neither gender nor rurality had any impact on practices relating to giving pneumococcal or influenza vaccinations. Responses relating to retesting coeliac serology were not subject to analysis because of the enormous range of answers provided.
5.4.7 Final comments from participants

At the conclusion of this section of the survey, participants were once again given the opportunity to offer any additional comments. Seventy-one people did this. Of the comments made, 19 referred to the preceding questions about influenza and pneumococcal vaccinations, while the remainder covered a range of issues, mostly revisiting areas that had been canvassed in the survey. Among the comments, were 25 from people who alluded to their knowledge about the condition either by expressing thanks for the prompt to update their learning about CD, or by acknowledging that they were “a bit rusty”, or by making a request for the answers and/or guidelines to be provided.

Three people sought to put CD (and, by extension, this survey) into context within the busy general practice setting and today's highly GFD-aware environment, with one of them summing this up as follows:

this is perhaps coeliac management for Doc who have OCD. Excellent management could be achieved with intense effort and resources but it is a small part of our practice and patients are motivated by symptoms to self manage. This survey brings into relief need perhaps to be a little more proactive but GF is really a call for all the crazies in your practice to express dietary choices they have gleaned from social media - coeliac disease is diagnosed by every quack web page from here to eternity - so we had better be clear about this or we will be overwhelmed by the misinformed worried well.

5.5 Key findings of the survey

To conclude this chapter the key findings of the survey are summarised as follows.

5.5.1 Response to the survey

This survey gathered information from 692 GPs from across New Zealand, who represented 35.5% of invited participants. Surveys were completed in both hardcopy and online formats, with the latter providing 53% of the final sample.

The rural/urban split of respondents was similar to that of the GP population in New Zealand at the time of the survey, but women were over-represented among participants. All DHBs were represented. Almost half of respondents owned their own practice, and 77% had been working in clinical practice for more than 20 years.
The practice populations served by participants were predominantly New Zealand European, and tended to be from the lower to middle socio-economic groups.

The first section of the survey investigated “Coeliac Disease in General”, and was completed by 692, while the second section was for people with adult patients with CD under their care. This part included more specific questions about their management of the condition, and was completed by 542 (78.3% of the total study sample). This subgroup of survey participants was generally similar to the overall sample group, but with statistically significant differences in the proportions who owned their own practice, worked fewer than three half-day sessions per week, and worked in many practices. While the proportion of women in this subgroup was higher than in the whole cohort, this did not reach statistical significance.

5.5.2 Part A: Recognition of CD

Participants’ capacity to recognise CD was investigated with questions about whom they would be likely to test for the condition, from an array of presenting symptoms, signs, and conditions. This revealed that there were some presentations that would lead the great majority to test (e.g. chronic diarrhoea, iron deficiency, IBS, and having a first-degree relative with CD), but many more that were not so likely to do so. Cumulative testing scores derived from responses to these questions suggest that, overall, respondents were likely to be under-testing for CD in both contexts investigated. There were significant associations between these findings and the gender of respondents.

5.5.3 Part A: Diagnosing CD

In this part of the survey participants were asked about how they tested for CD, and what test results they would be likely to accept as confirming the diagnosis. This section also included questions about what constitutes an adequate gluten challenge.

The majority indicated they would request “coeliac antibodies” from their laboratory provider, or specified which antibody tests they would do. A small number would include an HLA-DQ2/DQ8 test as part of their initial testing.

When a patient returned a positive coeliac antibody test, the majority would refer for endoscopy most of the time or almost always. Only a small proportion of respondents almost never referred for this investigation. Almost half of
respondents made additional comments in relation to this issue, and a common theme among their comments was that access to timely endoscopy is problematic both for their patients and themselves. This was reinforced in comments relating to the advice they give with respect to when patients awaiting endoscopy can start a GFD. While more than 80% indicated they tell patients to wait until they have had their biopsy before starting the diet, practical constraints on this recommendation were identified by several.

The issue of an adequate gluten challenge drew a wide range of suggestions, both in terms of how much gluten needed to be consumed, and for how long. Many respondents opted for the “Don’t Know” option, or indicated that they would need to check this out. Their preferred source of information was “an internet source such as BPAC”.

With respect to which tests could confirm the diagnosis of CD, positive serology followed by positive biopsy was almost unanimously accepted as doing so. However several other options were also likely or highly likely to be regarded as confirming the diagnosis by a majority of respondents. These ranged from “positive serology alone” at 58.5%, to “positive serology followed by symptomatic improvement on a GFD” at 70.5%. Gender, and whether or not participants had patients with CD, were significantly associated with some of the aspects of diagnosing CD investigated. The clinical import of these will be discussed in Chapter Seven.

5.5.4 Part A: Managing CD

In Part A of the survey, management questions related solely to the issue of annual reviews for patients with CD, and what these might comprise. Almost 70% of respondents thought that such a review was probably or definitely necessary, and 78.2% thought that GPs should be the clinicians carrying them out. More than 40% indicated that they reviewed some or all of their coeliac patients already. There was a wide range of suggestions about what an annual review might include, but the majority suggested that it should include blood tests of some sort (e.g. full blood count, ferritin and/or iron studies, vitamin B12 and folate). There was also a range of suggestions about what symptoms it would be important to check for, and what should be included in a physical examination.
5.5.5 Part B: Newly diagnosed CD

Among those participants with patients with CD who went on to answer the second part of the survey, there was a reasonably even split between those who referred their newly diagnosed patients to a dietitian themselves, and those whose experience was that gastroenterologists did this. They were also fairly evenly divided between those who almost never referred for DEXA scanning and those who did. The majority of those who almost never referred had indicated that they were not aware that this might be necessary. More than 50% mostly or almost always discussed with these patients the need for their first-degree relatives to be tested for CD, but much smaller numbers discussed joining CNZ as frequently. Almost 25% were not aware that involvement with CNZ might be necessary for these patients.

5.5.6 Part B: Long-term management

Issues canvassed in this final section of the survey related largely to the ongoing review and monitoring of patients with CD, and included questions on reinforcing the importance of the GFD, retesting serology, testing for associated conditions, and whether or not to give influenza and pneumococcal vaccinations.

Just over 60% of respondents indicated that they reviewed patients specifically with respect to their CD either 6-monthly, annually, or opportunistically when they came for other things. More than 50% made a point of regularly reinforcing the importance of adhering to the GFD.

There was a wide range of practices when it came to retesting coeliac serology, with no clearly favoured option among those given. There was somewhat more consistency with respect to testing for associated conditions, with more than 50% screening their patients from time to time or annually, and another 23% investigating them if they had suggestive symptoms. There was also a range of practices when it came to the frequency of recommending influenza vaccinations, but more than 60% of participants indicated they almost never recommended pneumococcal vaccination because “I wasn’t aware this might be necessary”.

249
Chapter 6: Results from the Laboratory Data Study

6.1 Introduction

As outlined in Chapter Three, the third component of the research undertaken for this work comprised the investigation and evaluation of data relating to testing for CD gathered from SCL, a major laboratory services provider in New Zealand. Additional information about the ethnicities of people being tested for CD was obtained from the New Zealand MoH.

This chapter begins by reporting inclusion and exclusion criteria for data used for analysis, and then presents results under the following headings:

- Rates of testing.
- Who was tested?
- Who did the testing?
- Which tests were done?
- What was found?
- What happened next?
- CD incidence.

Otago-Southland data, which constitute the biggest dataset, are presented first in each section, followed by the considerably smaller sets of more recent results from Nelson-Marlborough and South Canterbury. Trends apparent in results from Hawkes Bay and Taupo are also presented for comparison, but complete analysis of data from these regions has not been undertaken. The reasons for this are explained in the following section. The chapter concludes by summarising the key findings.

6.1.1 Selection of data for analysis

As outlined in Chapter Three, data were provided by SCL for the period from 1 January 2003, through to 31 December 2015. They came from all centres served by SCL, with the exception of Wellington and Wairarapa, which only came into their stable of laboratories in late 2015. This amounted to 149,129 lines of data, each connected to a CD-related testing event carried out by SCL, but not all of which were appropriate to include in all aspects of analysis. (Table 6.1)
Table 6.1: Summary of SCL data included and excluded from analysis

<table>
<thead>
<tr>
<th>Data included in all aspects of analysis</th>
<th>Data included in some aspects of analysis</th>
<th>Data excluded</th>
</tr>
</thead>
</table>

As discussed in Chapter Three, up until the middle of 2006, SCL was a co-provider of services in all the regions in which it had laboratories, and for some of these (e.g. Canterbury) they were a minor player only, processing around 20% of tests originating from community providers such as GPs. Data from 2003 to 2005 therefore incompletely represented what was happening with regards to testing for CD at the time in all regions, so they were excluded from analysis.

The most comprehensive set of results was from Otago-Southland, where SCL has been the sole provider of laboratory services since July 2006. Because 2006 data were incomplete, this material was largely excluded from analysis although some aspects have been utilised. In particular, 2006 information was included when determining which patients tested each year had previously been tested. Otago-Southland data from 2007 onwards have been extensively analysed and underpin the substantive part of the following sections.

Nelson-Marlborough and South Canterbury data were available from mid-2012, when both areas came under the SCL umbrella. Because the 2012 data from these regions were incomplete, only data pertaining to the three years from 1 January 2013 were included in analysis.

Both the Hawkes Bay and Canterbury regions have separate laboratories carrying out testing requested by community providers, and hospital-based practitioners. Data from the Hawkes Bay and Canterbury DHB laboratories (which includes biopsy data) were not available for this project, thus the datasets for these regions were incomplete. As the Canterbury data were also only available from mid-2012, they were completely excluded from analysis. However, the Hawkes Bay data
covered an extensive period of time and gave an indication of trends in community-provider practice in that region, so some analysis of this dataset was undertaken.

Taupo is unique among the centres for which data were obtained in that it is a smaller centre within a larger DHB region. It does have a hospital for which SCL is the laboratory provider, but the hospital itself offers only limited services, with the majority of specialist procedures being performed at the DHB’s larger Rotorua Hospital. This includes endoscopy services for the investigation of patients with positive CD serology tests, and many outpatients’ clinics. Laboratory services for Rotorua hospital are not provided by SCL, therefore data relating to biopsies were not available for analysis. It is also likely that there would have been patients tested for CD at the request of specialists at Rotorua hospital, and these data too were unavailable. In addition to those seen in Rotorua, some patients from Taupo are also seen at Waikato Hospital (Hamilton), which is the tertiary provider for the region. It is difficult to predict how many people would have been seen in either Rotorua or Hamilton although it seems probable that the numbers would have been small. Because Taupo data are therefore also incomplete, they have not been included in all aspects of analysis.

When these exclusion criteria were applied, 80,777 lines of data remained for inclusion in either complete or partial analysis. Of these, 65,263 were available for full analysis.

6.2 Rates of testing

Rates of testing were calculated by first determining how many tests had been requested in each region, and how many patients had had those tests. Where sufficient data were available, further calculations were then conducted to identify how many new patients had been tested each year. (Table 6.2) These data were then combined with New Zealand Census data. The information presented in Table 6.2 is referred to throughout the following sections.
Table 6.2: Summary data relating to “testing events” (TE), total patients tested (TPT), and new patients tested (NPT), in Otago-Southland (OS), Nelson-Marlborough (NM), and South Canterbury (SC), by year

<table>
<thead>
<tr>
<th>Year</th>
<th>OS TE</th>
<th>OS TPT</th>
<th>OS NPT</th>
<th>NM TE</th>
<th>NM TPT</th>
<th>SC TE</th>
<th>SC TPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>4362</td>
<td>4157</td>
<td>3955</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>4985</td>
<td>4738</td>
<td>4284</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>4790</td>
<td>4580</td>
<td>3940</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>5572</td>
<td>5302</td>
<td>4445</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>5566</td>
<td>5282</td>
<td>4213</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>6242</td>
<td>5935</td>
<td>4614</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>6838</td>
<td>6517</td>
<td>5128</td>
<td>2325</td>
<td>2267</td>
<td>1325</td>
<td>1264</td>
</tr>
<tr>
<td>2014</td>
<td>7309</td>
<td>6995</td>
<td>5299</td>
<td>2782</td>
<td>2692</td>
<td>1110</td>
<td>1066</td>
</tr>
<tr>
<td>2015</td>
<td>8001</td>
<td>7669</td>
<td>5631</td>
<td>3010</td>
<td>2901</td>
<td>1046</td>
<td>1018</td>
</tr>
<tr>
<td>Totals</td>
<td>53665</td>
<td>51175</td>
<td>41509</td>
<td>8117</td>
<td>7860</td>
<td>3481</td>
<td>3348</td>
</tr>
</tbody>
</table>

6.2.1 Otago-Southland

In the 10-year period from 1 January 2007 to 31 December 2015 there were 53,665 occasions on which some form of serological or genetic testing relating to CD was requested from SCL in Otago-Southland. These “testing events” steadily increased in number from 4362 in 2007, to 8001 in 2015. In that period, tests were carried out on 51,175 patients, with the annual number of patients tested increasing from 4157 to 7669. When year-to-year repeat testing was excluded, the total number of new patients tested by SCL in relation to CD from 2007 to 2015 was determined to be 41,509. Overall, in the 9-year period between 2007 and 2015, there was a 1.8-fold increase in the number of CD tests being carried out per annum, and a 1.4-fold increase in the number of new patients being tested. (Table 6.2; Figure 6-1)
The incomplete data from SCL for 2006 included 3035 CD-related tests performed on 2914 patients. When these patients were included in calculations to determine how many new patients were tested each year, it became apparent that by 2015 just over 25% of the patients being tested had had a previous test (or tests) performed by SCL at some point in the preceding decade. Given that the 2006 dataset is incomplete, this figure under-represents the true state of affairs, although this is likely to be by only a small margin.

According to New Zealand Census data, the population of the Otago-Southland DHB region was 286,224 in 2006, and by 2013 had reached 297,423. Assuming that the rate of population increase remained relatively steady at 0.56%, the estimated population in 2015 was 300,623. This information was used to calculate annual rates of testing for CD at the beginning and end of the time period under consideration. (Table 6.3)

Table 6.3: Otago-Southland population rates of testing for CD, 2007 and 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated Population</th>
<th>Testing events (% population)</th>
<th>Patients tested (% population)</th>
<th>New patients tested (% pop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>287,824</td>
<td>4362 (1.5)</td>
<td>4157 (1.4)</td>
<td>3955 (1.4)</td>
</tr>
<tr>
<td>2015</td>
<td>300,623</td>
<td>8001 (2.7)</td>
<td>7669 (2.5)</td>
<td>5631 (1.9)</td>
</tr>
</tbody>
</table>
As is demonstrated in Table 6.3, population rates of testing for CD increased between 2007 and 2015 across all three parameters evaluated. Each of these increases was statistically significant on two-sample proportions testing, \( p<0.0001 \). In addition to the figures shown, by the end of 2015, 13.8\% (41,509 individuals) of the Otago-Southland population had been tested for CD at least once since 2007.

### 6.2.2 Nelson-Marlborough and South Canterbury

The population for the Nelson-Marlborough DHB region was recorded as 136,995 in the 2013 Census. This was an increase of 5.3\% from the 2006 population, which gave an estimated annual increase of approximately 0.76\%. Extrapolating from the 2013 figure, and assuming a steady rate of population increase, the population of Nelson-Marlborough for 2015 was estimated to have been 138,975. In South Canterbury the 2013 census-derived DHB population was 55,626, an increase of 3.2\% on the 2006 population. Once again, assuming a steady rate of population increase annually, the 2015 population was estimated to have been 56,126.

Because data available for the Nelson-Marlborough and South Canterbury regions pertained to only three years, it was not possible to form an accurate picture of long-term trends in CD testing with respect to time. This was particularly the case for determining numbers of first tests for CD carried out each year, because there was no information available about patients’ testing histories. However, it was possible to make snapshot comparisons with Otago-Southland with respect to the 2015 rates of testing for CD. The data also showed that in the three years to 2015, testing rates increased in Nelson-Marlborough but fell in South Canterbury. (Table 6.4) Within each region, these changes in population testing rates were statistically significant on two-sample proportions testing, \( p<0.0001 \), however the differences between regions were not.
Table 6.4: Nelson-Marlborough and South Canterbury population rates of testing for CD, 2013 and 2015

<table>
<thead>
<tr>
<th>Region</th>
<th>Year</th>
<th>Estimated Population</th>
<th>Testing events (% population)</th>
<th>Patients tested (% population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson-Marlborough</td>
<td>2013</td>
<td>136,995</td>
<td>2325 (1.7)</td>
<td>2267 (1.7)</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>138,975</td>
<td>3010 (2.2)</td>
<td>2901 (2.1)</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>2013</td>
<td>55,626</td>
<td>1325 (2.4)</td>
<td>1264 (2.3)</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>56,126</td>
<td>1046 (1.9)</td>
<td>1018 (1.8)</td>
</tr>
</tbody>
</table>

When patients tested in 2015 who had also been tested in either 2013 or 2014 were removed from calculations, the Nelson-Marlborough population testing rate fell to 1.9% (2660/138,975). The testing rate in South Canterbury fell to 1.6% (893/56,126). These rates remained statistically significantly different from the 2013 rates, p=0.0001 for Nelson-Marlborough, and p<0.0001 for South Canterbury.

6.2.3 Hawkes Bay and Taupo

As for Otago-Southland, the 2007 Hawkes Bay population was interpolated from 2006 and 2013 DHB-region census data, which was also used to estimate the 2015 population. Because there were no DHB specific census data for Taupo (being a small centre within a larger DHB), these figures were derived from New Zealand Census District data. (Table 6.5)

Testing data (albeit incomplete) were available from Hawkes Bay and Taupo for a similar time period to that from Otago-Southland. As with Otago-Southland, rates of testing in Hawkes Bay increased, (p=0.014), although overall a smaller proportion of the population was tested each year. In contrast to this, rates of testing in Taupo fell, (p<0.0001), but testing rates in the mid-2000s were higher there than in either Otago-Southland or Hawkes Bay at the equivalent time. (Table 6.5) Once again, analysis was by two-sample proportions testing.
Table 6.5: Hawkes Bay and Taupo population rates of testing for CD, first and last years of study period

<table>
<thead>
<tr>
<th>Region</th>
<th>Year</th>
<th>Estimated Population</th>
<th>Testing events (% population)</th>
<th>All patients tested (% population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkes Bay</td>
<td>2007</td>
<td>148,740</td>
<td>892 (0.60)</td>
<td>858 (0.58)</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>152,694</td>
<td>1258 (0.82)</td>
<td>992 (0.65)</td>
</tr>
<tr>
<td>Taupo</td>
<td>2008</td>
<td>32,558</td>
<td>614 (1.9)</td>
<td>587 (1.8)</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>33,049</td>
<td>436 (1.3)</td>
<td>353 (1.1)</td>
</tr>
</tbody>
</table>

Over the 9-year period from 2007, 5.1% (7813 individuals) of the Hawkes Bay population were tested for CD at least once at an SCL laboratory. But, as previously noted, the population is also served by a DHB laboratory, so these figures underestimate the true figure of total CD testing in the region at the time.

In Taupo the number of new patients tested fell steadily from 2008 until 2013, when 276 people were tested for the first time by SCL, a rate of 0.84% (276/32,907). By the end of 2015 this had climbed back to 353, a rate of approximately 1.1%. Overall, in the time period for which data are available, 2853 people in Taupo had a first-test for CD performed at SCL, constituting approximately 8.6% of the population. This figure also underestimates total CD testing, because additional tests would have been requested by Rotorua and Hamilton-based specialists, and performed at other laboratories. It is not possible to predict how many people this was likely to have involved, although it is probable that the number was not great.

6.3 Who was tested?

When analysing the demographic characteristics of those patients who had undergone testing for CD, it was clearly apparent that women were tested more frequently than men. This difference held across all the regions for which data were available, the number of testing events per year, the number of patients tested per year, the number of first-test patients per year, and for the entire period of time under consideration. Graphs in the following sections present these data. Age and ethnicity data for the populations tested are also presented, in subsequent sections.
6.3.1 Gender-specific data from Otago-Southland

Otago-Southland data were analysed with respect to the gender of patients tested, as proportions of testing events, patients tested per year, and first-tests per year respectively. (Figures 6-2, 6-3 and 6-4) For the entire period for which data were available, only six patients were listed as “gender unknown” – one in each year from 2010 to 2015.

![Figure 6-2: CD testing events for males and females in Otago-Southland, by year](image)

![Figure 6-3: Numbers of males and females tested for CD in Otago-Southland, by year](image)
From each of these figures it is apparent that consistently more women than men were being tested for CD, in each category assessed, (p<0.0001), and in every year, (p<0.0001).

A direct comparison was made in the trends for new tests per year conducted on men and women. (Figure 6-5)
As illustrated in Figure 6-5, over this time period, the gap between the absolute numbers of men and women having a first test for CD widened. However, when these numbers were analysed with respect to the proportions of the total number of tests they represented, the gap in fact narrowed. Thus, in 2007, 33.4% (1324/3955) of new patients were men, rising to 35.5% (1882/5299) in 2014, although dropping back to 34.7% (1954/5631) in 2015. On two-sample proportions testing, the 2014 increase from 2007 was statistically significant, \( (p=0.045) \), but the 2015 increase was not, \( (p=0.223) \).

Ratios of women to men tested across the categories analysed were calculated, and found to have fluctuated with time. Some showed an overall increase, and some showed a decrease. (Table 6.6)

Table 6.6: Female:Male ratios for CD testing, Otago-Southland 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Total testing events</th>
<th>Patients tested</th>
<th>First tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1.99</td>
<td>1.98</td>
<td>1.99</td>
</tr>
<tr>
<td>2008</td>
<td>1.99</td>
<td>2.00</td>
<td>1.99</td>
</tr>
<tr>
<td>2009</td>
<td>2.02</td>
<td>2.02</td>
<td>2.03</td>
</tr>
<tr>
<td>2010</td>
<td>2.11</td>
<td>2.09</td>
<td>2.04</td>
</tr>
<tr>
<td>2011</td>
<td>2.10</td>
<td>2.08</td>
<td>2.01</td>
</tr>
<tr>
<td>2012</td>
<td>2.13</td>
<td>2.12</td>
<td>2.02</td>
</tr>
<tr>
<td>2013</td>
<td>2.07</td>
<td>2.06</td>
<td>1.97</td>
</tr>
<tr>
<td>2014</td>
<td>2.00</td>
<td>1.99</td>
<td>1.81</td>
</tr>
<tr>
<td>2015</td>
<td>2.07</td>
<td>2.07</td>
<td>1.88</td>
</tr>
<tr>
<td>All years</td>
<td>2.05</td>
<td>2.05</td>
<td>1.96</td>
</tr>
</tbody>
</table>

None of the differences between 2007 and 2015 reached statistical significance on two-sample proportions testing.
6.3.2 Gender-specific data from Nelson-Marlborough and South Canterbury

Despite the fact that testing data for Nelson-Marlborough and South Canterbury were only available for the three years from 2013 until 2015, they nonetheless gave an indication of testing trends emerging in those regions. (Figures 6-6 and 6-7) Numbers of first tests were not calculated because the time period was too short to make this meaningful.

![Graph showing CD testing events for males and females in Nelson-Marlborough and South Canterbury, by year](image)

*Figure 6-6: CD testing events for males and females in Nelson-Marlborough and South Canterbury, by year*

![Graph showing numbers of males and females tested for CD in Nelson-Marlborough and South Canterbury, by year](image)

*Figure 6-7: Numbers of males and females tested for CD in Nelson-Marlborough and South Canterbury, by year*
These figures both illustrate that, as in Otago-Southland, women being tested for CD consistently outnumbered men being similarly tested, albeit in smaller proportions in South Canterbury. Female to male testing ratios were calculated for both regions, which clearly demonstrated this difference. (Table 6.8)

Table 6.7: Female:Male ratios for CD testing, Nelson-Marlborough and South Canterbury 2013 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Total testing events</th>
<th>Patients tested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nelson-Marlborough</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>2.13</td>
<td>2.13</td>
</tr>
<tr>
<td>2014</td>
<td>2.16</td>
<td>2.13</td>
</tr>
<tr>
<td>2015</td>
<td>2.01</td>
<td>2.01</td>
</tr>
<tr>
<td></td>
<td>South Canterbury</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1.94</td>
<td>1.94</td>
</tr>
<tr>
<td>2014</td>
<td>1.82</td>
<td>1.82</td>
</tr>
<tr>
<td>2015</td>
<td>1.71</td>
<td>1.72</td>
</tr>
</tbody>
</table>

None of the differences in testing ratios between 2013 and 2015 reached statistical significance in either region.

6.3.3 Gender-specific data from Hawkes Bay and Taupo

Although the datasets for both Hawkes Bay and Taupo were incomplete, from the data that were available it was apparent that the patient groups who had been tested for CD in SCL laboratories were similar, but not identical to those from the Otago-Southland region. As in the south, many more women than men were tested, although the ratios between the two groups varied a little more in the northern areas. (Figures 6-8, 6-9, 6-10, and 6-11) It is unclear how these figures would change with the addition of data from DHB and other laboratory service providers in Hawkes Bay, Rotorua, and Hamilton.
Figure 6-8: SCL CD testing events for males and females in Hawkes Bay, by year

Figure 6-9: SCL CD testing events for males and females in Taupo, by year
Figure 6-10: Numbers of males and females tested for CD by SCL in Hawkes Bay, by year

Figure 6-11: Numbers of males and females tested for CD by SCL in Taupo, by year
6.3.4 Age-specific data from Otago-Southland

The age of patients tested for CD in Otago Southland between 2007 and 2015 ranged from 9 days old, to 98 years old. The mean age for adults was relatively stable at around 42 years of age, while that for children (those up to and including 16 years of age) was just over 8 years old. This has steadily increased since 2010. (Table 6.8)

Table 6.8: Age range, mean (standard deviation; s.d.) and median age of patients tested for CD in Otago-Southland*

<table>
<thead>
<tr>
<th>Year</th>
<th>Age range of those tested</th>
<th>All patients mean age (s.d.)</th>
<th>Adult mean age (s.d.)</th>
<th>Adult median age</th>
<th>Child median age</th>
<th>Child median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>7 months – 94 years</td>
<td>35.4 years (20.4)</td>
<td>42.4 years (16.8)</td>
<td>41 years</td>
<td>8.5 years (4.7)</td>
<td>8 years</td>
</tr>
<tr>
<td>2008</td>
<td>7 months – 92 years</td>
<td>35 years (20.3)</td>
<td>42.1 years (16.7)</td>
<td>41 years</td>
<td>8.4 years (4.8)</td>
<td>8 years</td>
</tr>
<tr>
<td>2009</td>
<td>2 months – 93 years</td>
<td>34.5 years (20.6)</td>
<td>42 years (16.9)</td>
<td>41 years</td>
<td>8.4 years (4.9)</td>
<td>8 years</td>
</tr>
<tr>
<td>2010</td>
<td>3 months – 91 years</td>
<td>34.8 years (20.4)</td>
<td>41.4 years (17.2)</td>
<td>40 years</td>
<td>8.3 years (4.7)</td>
<td>8 years</td>
</tr>
<tr>
<td>2011</td>
<td>2 months – 93 years</td>
<td>35.3 years (20.8)</td>
<td>42 years (17.6)</td>
<td>41 years</td>
<td>8.7 years (4.8)</td>
<td>9 years</td>
</tr>
<tr>
<td>2012</td>
<td>4 weeks – 98 years</td>
<td>34.9 years (20.7)</td>
<td>41.8 years (17.7)</td>
<td>40 years</td>
<td>8.9 years (4.7)</td>
<td>9 years</td>
</tr>
<tr>
<td>2013</td>
<td>9 days – 95 years</td>
<td>36 years (21)</td>
<td>42.5 years (17.9)</td>
<td>41 years</td>
<td>8.7 years (4.7)</td>
<td>9 years</td>
</tr>
<tr>
<td>2014</td>
<td>3 months – 92 years</td>
<td>36.1 years (21.2)</td>
<td>42.8 years (18.1)</td>
<td>42 years</td>
<td>8.9 years (4.7)</td>
<td>9 years</td>
</tr>
<tr>
<td>2015</td>
<td>3 months – 96 years</td>
<td>36 years (21.2)</td>
<td>42.5 years (18.3)</td>
<td>41 years</td>
<td>9.2 years (4.7)</td>
<td>9 years</td>
</tr>
</tbody>
</table>

* Mean and median calculations of age were performed using age in years at the time of testing, except for children up to the age of 2 years old. Calculations for children up to 2 years old used their age in months. This is why median ages are given in whole years.
As well as the 9-days old baby, ten other infants younger than four months of age were tested. At the other end of the spectrum, a number of the very elderly were also tested for CD. In every year for which data were available there were patients aged 90 years or older who were tested for CD for the first time, with numbers ranging from two to 13 per year.

The number of testing events each year and the number of first CD tests performed per year were analysed by age-group. The cohorts were grouped into those under 17 years of age (the age at which young people come under the care of adult-focused health services), and then in ten year age-bands above this. (Figures 6-12 and 6-13)

![CD testing events in Otago-Southland grouped by age, per year](image-url)
As shown in these graphs, from 2010 onwards, the age-group having the greatest number of tests for CD were the 17- to 26-year olds. They were followed by the under-17-year olds (a group which, it should be noted, covered a wider age range), who prior to 2010 were the most tested group. The third largest group to be tested was the 37- to 46-year olds. These comparisons held true for both the number of testing events, and the number of first tests carried out each year.

All age-groups had an increase in both the number of testing events carried out per year, and the number of first tests per year. This included the over-86-year olds, for whom testing events increased from 16 in 2007, to 33 in 2015, and first tests from 15 in 2007 to 28 in 2015. (Figures 6-14 and 6-15)
Between 2007 and 2015, the greatest increases in numbers of testing events, and in patients being tested for the first time, occurred in the 17 to 26 years old age-group. They were followed by the under-17-year olds, and then the 57- to 66-year olds. (Figure 6-16)
6.3.5 Age-specific data from other regions

The age ranges of patients tested in each of the other regions were similar to those of Otago-Southland, although there were fewer very young babies tested elsewhere. All regions tested the very elderly, including two 97-year olds. (Table 6.9)

Table 6.9: Cumulative age ranges of patients tested for CD in other regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Age Range</th>
<th>Time span</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson-Marlborough</td>
<td>4 months to 97 years</td>
<td>2013 to 2015</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>6 months to 97 years</td>
<td>2013 to 2015</td>
</tr>
<tr>
<td>Hawkes Bay</td>
<td>6 months to 94 years</td>
<td>2007 to 2015</td>
</tr>
<tr>
<td>Taupo</td>
<td>5 months to 90 years</td>
<td>2008 to 2015</td>
</tr>
</tbody>
</table>

Excluded from this table is a serology test from one of the regions, which was requested to be carried out on an umbilical cord blood sample. The laboratory did not process the request and indicated to the requester the reasons why this would not be appropriate.
Because data from Nelson-Marlborough and South Canterbury were complete, albeit for a shorter period of time, mean and median ages of patients tested for CD were also calculated for these regions. (Table 6.10)

Table 6.10: Mean (standard deviation; s.d.) and median age of patients tested for CD in Nelson-Marlborough and South Canterbury, 2013 – 2015*

<table>
<thead>
<tr>
<th>Year</th>
<th>Adult mean age (s.d.)</th>
<th>Adult median age</th>
<th>Child mean age (s.d.)</th>
<th>Child median age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nelson-Marlborough</td>
<td></td>
<td>South Canterbury</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>44.5 years (17.2)</td>
<td>44 years</td>
<td>9.0 years (4.7)</td>
<td>9 years</td>
</tr>
<tr>
<td>2014</td>
<td>46.0 years (17.3)</td>
<td>46 years</td>
<td>8.8 years (4.8)</td>
<td>9 years</td>
</tr>
<tr>
<td>2015</td>
<td>47.1 years (17.8)</td>
<td>48 years</td>
<td>9.5 years (4.6)</td>
<td>10 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Adult mean age (s.d.)</th>
<th>Adult median age</th>
<th>Child mean age (s.d.)</th>
<th>Child median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>44.9 years (18.2)</td>
<td>45.5 years</td>
<td>9.7 years (4.5)</td>
<td>10 years</td>
</tr>
<tr>
<td>2014</td>
<td>44.4 years (18.0)</td>
<td>46 years</td>
<td>9.6 years (4.7)</td>
<td>10 years</td>
</tr>
<tr>
<td>2015</td>
<td>44.2 years (17.9)</td>
<td>44 years</td>
<td>10.2 years (4.4)</td>
<td>11 years</td>
</tr>
</tbody>
</table>

* See note for Table 6.8 (page 272)

As with the Otago-Southland data, information from these two regions were further analysed with respect to the distribution of testing across age groups. (Figure 6-17)
Figure 6-17: CD testing events per age-group in Nelson-Marlborough (NM) and South Canterbury (SC), 2013 – 2015

As evident in this figure, children comprised the biggest group of those tested for CD in both regions in recent years. What is less apparent from the chart is that in Nelson-Marlborough the number of people over the age of 86 years being tested doubled from 13 in 2014 to 26 in 2015.

As already noted, the data from Hawkes Bay and Taupo were incomplete, missing those patients tested at the Hawkes Bay DHB laboratory, and Rotorua Hospital (and occasionally Waikato Hospital) respectively. This will have influenced age-related calculations, particularly with regards to children in Hawkes Bay who may have been seen by a paediatrician. However, cumulative means and medians were calculated for both regions, to give an indication of the age-profiles of those being tested for CD through SCL.

In the Hawkes Bay the mean age for adults being tested for CD by the SCL laboratory between 2007 and 2015 was 46.7 years (s.d. 17.4 years), and the median age was 47 years. For Taupo these figures were 45.6 years (s.d. 17.2 years) and 46 years respectively, for the time period 2008 to 2015. These figures are all slightly higher than the Otago-Southland values given earlier. With regards to children, the mean age of those tested through SCL was 9.9 years (s.d. 4.6 years) in Hawkes Bay, and 9.0 years (s.d. 4.5 years) in Taupo, and the median ages in these two regions
were 10-years and 9-years. The Hawkes Bay values are higher than those from Otago-Southland, while the Taupo values are equivalent.

On analysis of testing patterns across the age groups for these two regions, it was apparent that in Taupo the greatest number of tests carried out each year was consistently on children. Among adults being tested there was an even spread of testing across the ages from 17 years old through to 56 years old. Between them, these age-groups constituted on average 72% (range 70% to 76%) of adults tested every year between 2008 and 2015. In contrast to this, in Hawkes Bay the trend was that more tests were carried out on adults in the 37- to 56-years old age groups, although from 2012 more tests began to be conducted on children. In 2013 the children were the most tested, despite DHB data (which would include the bulk of paediatrician-derived test requests) not being included in this set.

6.3.6 Ethnicity Data

National Health Index number information was available for more than 99.5% of all patients tested for CD by SCL, in each of the regions being considered in this study. Using this information, ethnicity data were obtained from the New Zealand MoH. To be consistent with MoH and SNZ practice, discussed in Chapter Three, prioritised ethnicity was used for all analyses.

In every region for which data were available, the vast majority of patients had a prioritised ethnicity of European – either “New Zealand European”, “Other European”, or “European not further defined”. (Table 6.11)
Table 6.11: Percentages of those tested for CD with prioritised ethnicity European (New Zealand or other) in Otago-Southland (OS), Hawkes Bay (HB), Taupo, Nelson-Marlborough (NM), and South Canterbury (SC)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>90.3</td>
<td>90.2</td>
<td>90.2</td>
<td>89.6</td>
<td>89.5</td>
<td>88.2</td>
<td>88.0</td>
<td>87.4</td>
<td>87.2</td>
</tr>
<tr>
<td>HB</td>
<td>88.0</td>
<td>88.0</td>
<td>85.8</td>
<td>83.5</td>
<td>87.3</td>
<td>84.9</td>
<td>83.0</td>
<td>84.1</td>
<td>79.4</td>
</tr>
<tr>
<td>Taupo</td>
<td>85.6</td>
<td>82.4</td>
<td>84.6</td>
<td>83.6</td>
<td>82.2</td>
<td>82.4</td>
<td>80.2</td>
<td>81.3</td>
<td></td>
</tr>
<tr>
<td>NM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89.9</td>
<td>89.6</td>
<td>89.7</td>
</tr>
<tr>
<td>SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89.3</td>
<td>88.6</td>
<td>87.1</td>
</tr>
</tbody>
</table>

New Zealand Māori were the next largest group identified in each region, except South Canterbury. In that region, the numbers of people with either an unidentifiable response, or who did not give any ethnicity, exceeded those with a prioritised ethnicity of Māori. (Table 6.12)

Table 6.12: Percentages of those tested for CD in each region with prioritised ethnicity New Zealand Māori

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>4.3</td>
<td>4.1</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>5.1</td>
<td>4.9</td>
<td>5.0</td>
<td>5.7</td>
</tr>
<tr>
<td>HB</td>
<td>6.4</td>
<td>6.8</td>
<td>6.6</td>
<td>7.8</td>
<td>8.4</td>
<td>8.7</td>
<td>10.1</td>
<td>10.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Taupo</td>
<td>8.7</td>
<td>12.8</td>
<td>9.2</td>
<td>11.9</td>
<td>13.3</td>
<td>12.5</td>
<td>11.1</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>NM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3</td>
<td>5.5</td>
<td>4.8</td>
</tr>
<tr>
<td>SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.8</td>
<td>3.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

The collated group of “Not stated”, “Refused to Answer”, “Response Unidentifiable”, and “Don’t know” was the third largest grouping in all regions apart from South Canterbury, constituting between 2% and 3% of patients tested per year.

No other ethnic group in any region reached a level of 1% of the tested population in any year, apart from in Hawkes Bay in 2010 and 2015. In 2010 1.1% (9/796) of patients tested at SCL identified as Indian, while in 2015 this figure had
increased to 2.3% (23/992) of patients. These figures should be viewed with caution however, given that the dataset from this region does not include tests conducted at the DHB laboratory. It is not possible to predict the profiles of patients who were tested there, and how their inclusion would have impacted on the overall proportions of patient groups who were tested. People who identified as Indian, Chinese, or “other Asian” tended to be the next most tested groups, in the other regions albeit in small numbers. In no other region, did representation of any of these groups (or any other) among the tested populations exceed 1% in any year for which data were available.

6.4 Who did the testing?

Data relating to who requested blood tests for CD were available for all regions. However, for Hawkes Bay and Taupo, where additional laboratories provide some services in the region, this was incomplete. Because one of the variables of interest in this study was variation in practice between regions, which may be demonstrated in the origins of testing requests, analysis was limited to the regions from which data were complete. For both Taupo and Hawkes Bay, tests requested by practitioners other than GPs would be under-represented in the data available, rendering comparisons between groups within each region, and between each region, relatively meaningless.

Data from Otago-Southland, Nelson-Marlborough and South Canterbury are presented with respect to total CD-related testing events each year. (Tables 6.13 and 6.14) Those requesting the tests were categorised into the following groups: GP, Paediatrics, Gastroenterology, Other Specialty, Other Health Professional, and Unknown. Almost every other specialty discipline was represented in the “Other Specialty” group, with the biggest groups being Endocrinology and Rheumatology. “Other Health Professionals” included Nurses (both GP practice nurses and specialty clinic nurses), Nurse Practitioners, Dietitians, Midwives, and Naturopaths.

<table>
<thead>
<tr>
<th>Year</th>
<th>GP (% total requests)</th>
<th>Paediatrics; doctor or clinic (% total requests)</th>
<th>Gastroenterology; doctor or clinic (% total requests)</th>
<th>Other Specialty; doctor or clinic (% total requests)</th>
<th>Other health professional</th>
<th>Unknown requester</th>
<th>Total requests</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>3344 (76.7%)</td>
<td>175 (4.0%)</td>
<td>243 (5.6%)</td>
<td>390 (8.9%)</td>
<td>16</td>
<td>194</td>
<td>4362</td>
</tr>
<tr>
<td>2008</td>
<td>3700 (74.2%)</td>
<td>317 (6.4%)</td>
<td>371 (7.4%)</td>
<td>536 (10.8%)</td>
<td>16</td>
<td>45</td>
<td>4985</td>
</tr>
<tr>
<td>2009</td>
<td>3579 (74.7%)</td>
<td>359 (7.5%)</td>
<td>356 (7.4%)</td>
<td>470 (9.8%)</td>
<td>16</td>
<td>10</td>
<td>4790</td>
</tr>
<tr>
<td>2010</td>
<td>4214 (75.6%)</td>
<td>360 (6.5%)</td>
<td>348 (6.2%)</td>
<td>633 (11.4%)</td>
<td>14</td>
<td>3</td>
<td>5572</td>
</tr>
<tr>
<td>2011</td>
<td>4149 (74.5%)</td>
<td>383 (6.9%)</td>
<td>387 (7.0%)</td>
<td>627 (11.3%)</td>
<td>18</td>
<td>2</td>
<td>5566</td>
</tr>
<tr>
<td>2012</td>
<td>4803 (76.9%)</td>
<td>408 (6.5%)</td>
<td>377 (6.0%)</td>
<td>625 (10.0%)</td>
<td>25</td>
<td>4</td>
<td>6242</td>
</tr>
<tr>
<td>2013</td>
<td>5300 (77.5%)</td>
<td>479 (7.0%)</td>
<td>416 (6.1%)</td>
<td>609 (8.9%)</td>
<td>33</td>
<td>1</td>
<td>6838</td>
</tr>
<tr>
<td>2014</td>
<td>5660 (77.4%)</td>
<td>498 (6.8%)</td>
<td>418 (5.7%)</td>
<td>632 (8.6%)</td>
<td>95</td>
<td>6</td>
<td>7309</td>
</tr>
<tr>
<td>2015</td>
<td>6387 (79.8%)</td>
<td>453 (5.7%)</td>
<td>398 (5.0%)</td>
<td>725 (9.1%)</td>
<td>35</td>
<td>3</td>
<td>8001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>GP (% total requests)</th>
<th>Paediatrics; doctor or clinic (% total requests)</th>
<th>Gastroenterology; doctor or clinic (% total requests)</th>
<th>Other Specialty; doctor or clinic (% total requests)</th>
<th>Other health professional</th>
<th>Unknown requester</th>
<th>Total requests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Nelson-Marlborough</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1900 (81.7%)</td>
<td>68 (2.9%)</td>
<td>199 (8.6%)</td>
<td>150 (6.5%)</td>
<td>4</td>
<td>4</td>
<td>2325</td>
</tr>
<tr>
<td>2014</td>
<td>2266 (81.5%)</td>
<td>97 (3.5%)</td>
<td>235 (8.4%)</td>
<td>179 (6.4%)</td>
<td>5</td>
<td>0</td>
<td>2782</td>
</tr>
<tr>
<td>2015</td>
<td>2498 (83.0%)</td>
<td>86 (2.9%)</td>
<td>221 (7.3%)</td>
<td>200 (6.6%)</td>
<td>4</td>
<td>1</td>
<td>3010</td>
</tr>
<tr>
<td></td>
<td><strong>South Canterbury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1052 (79.4%)</td>
<td>69 (5.2%)</td>
<td>24 (1.8%)</td>
<td>160 (12.1%)</td>
<td>20</td>
<td>0</td>
<td>1325</td>
</tr>
<tr>
<td>2014</td>
<td>882 (79.5%)</td>
<td>59 (5.3%)</td>
<td>35 (3.2%)</td>
<td>109 (9.8%)</td>
<td>25</td>
<td>0</td>
<td>1110</td>
</tr>
<tr>
<td>2015</td>
<td>862 (82.4%)</td>
<td>40 (3.8%)</td>
<td>32 (3.1%)</td>
<td>95 (9.1%)</td>
<td>17</td>
<td>0</td>
<td>1046</td>
</tr>
</tbody>
</table>
During the time period under consideration, more than 1000 individual practitioners in Otago-Southland were responsible for the testing event requests analysed. In Nelson-Marlborough there were over 320 practitioners who requested CD testing, while in South Canterbury the number was approximately 165. (As some tests over the years originated in Emergency Departments and Outpatients’ Clinics, it was not possible to determine whether the same individual, or a number of individuals, were responsible for these requests. For the purposes of this analysis, each of these entities was counted once.)

In Otago-Southland the 2014 spike in the number of requests from “Other health professionals” (to 1.3% of total requests) was comprised almost entirely of requests from two Nurse Practitioners, both working in the primary care sector. The “Unknown” category in 2007 and 2008 (4.4% and 0.9% of requests respectively) was almost exclusively made-up of requests originating in Southland Hospital, but for which no further identifying details about the requesters were available. This issue had been resolved by 2008. Other “unknown” providers were people about whom it was not possible to find information, despite extensive searches of the New Zealand Medical Register, New Zealand Nursing Register, and the internet.

The “Other health professional” requests in South Canterbury came almost exclusively from two Nurse Practitioners, both working in rural primary care. The “Other Specialty” group in this region was largely comprised of general surgeons, who were also endoscopists.

6.5 Which tests were done?

The tests carried out by SCL in the time period being investigated fell into two groups: CD antibody testing, and HLA testing for CD-associated markers. In the course of analysing the available data, it became apparent that the tests performed in the first of these two groups had been determined as much by laboratory protocol, as by those requesting the tests. These protocols have changed over time, and have variously included IgA and IgG-AGA, IgA-EMA, IgA-tTG antibodies and, since 2015, IgA and IgG-DGP antibodies.
6.5.1 Coeliac antibody testing

In 2006 when “coeliac antibodies” were requested, these initially consisted of IgA- and IgG-AGA and IgA-EMA tests. In the early part of the year, AGA and EMA results that were either inconclusive or suggestive of CD had an IgA-tTG test added by laboratory staff, to assist with their interpretation. From March 2006, IgA-tTG tests began to become a routine addition to the CD testing panel, although this was not always consistently applied.

By 2007 SCL’s testing protocols had been consolidated, with the laboratory preferentially carrying out IgA-tTG tests for the investigation of CD, and actively discouraging the use of AGA tests. Results would often come with the message:

＞When screening for coeliac disease, TTG testing is more sensitive and specific than the anti-gliadin antibody (AGA) assay. Therefore routine AGA testing has been discontinued. However since the gliadin test may have value in other settings, it will still be available if specifically requested.＜

IgA-EMA tests were added to high-negative and most positive IgA-tTG results, and were sometimes also performed singly, if specifically requested.

From late 2015, DGP tests became part of SCL’s routine CD testing for some patients: children up to and including 6-years of age; patients with a high-normal IgA-tTG; patients with IgA deficiency. In these cases DGP testing was added by the laboratory. However, at the time of completing this study this was not yet a funded test so healthcare providers could not routinely request it. Its use was at the discretion of the laboratory, on application to the DHB for funding.

From 2007 total IgA levels were also measured alongside tTG levels, however from mid-2010 this changed. In that year SCL-Dunedin adopted a policy of only testing total IgA when the IgA-tTG level was not sufficiently high for the laboratory scientists to be confident that the patient had adequate IgA levels.

The total number of CD antibody tests performed by SCL from 2007 to 2015 were collated. (Table 6.15) Since all tests were processed in a single laboratory and according to the same protocols, data from all regions were combined for this table. Otago-Southland and Hawkes Bay contributed to all years, Taupo from 2008 onwards, and Nelson-Marlborough and South Canterbury from 2013.
<table>
<thead>
<tr>
<th>Year</th>
<th>Total IgA</th>
<th>tTG tests</th>
<th>EMA tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>5124</td>
<td>5155</td>
<td>438</td>
</tr>
<tr>
<td>2008</td>
<td>6412</td>
<td>6442</td>
<td>418</td>
</tr>
<tr>
<td>2009</td>
<td>6117</td>
<td>6141</td>
<td>357</td>
</tr>
<tr>
<td>2010</td>
<td>5527</td>
<td>6797</td>
<td>397</td>
</tr>
<tr>
<td>2011</td>
<td>2182</td>
<td>6774</td>
<td>359</td>
</tr>
<tr>
<td>2012</td>
<td>1069</td>
<td>7318</td>
<td>247</td>
</tr>
<tr>
<td>2013</td>
<td>1646</td>
<td>11687</td>
<td>432</td>
</tr>
<tr>
<td>2014</td>
<td>2043</td>
<td>12535</td>
<td>410</td>
</tr>
<tr>
<td>2015</td>
<td>1411</td>
<td>13526</td>
<td>467</td>
</tr>
</tbody>
</table>

The dataset provided for this time period did not include any AGA tests, because by 2007 the laboratory no longer regarded AGA as an appropriate test for CD. Results of DGP tests were also not included in the dataset provided.

6.5.2 HLA testing

The test that is performed only when requested (as opposed to in accordance with laboratory protocol) is that for HLA-DQ2/DQ8, often referred to as “the gene test”. Complete sets of data relating to requests for this test were available for Otago-Southland, Nelson-Marlborough, and South Canterbury, and are considered here. The proportion of total test requests that they comprised is also presented. (Table 6.16)
Table 6.16: HLA test requests for Otago-Southland, Nelson-Marlborough, and South Canterbury

<table>
<thead>
<tr>
<th>Year</th>
<th>Otago-Southland</th>
<th></th>
<th>Nelson-Marlborough</th>
<th></th>
<th>South Canterbury</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HLA tests</td>
<td>% of total tests</td>
<td>HLA tests</td>
<td>% of total tests</td>
<td>HLA tests</td>
<td>% of total tests</td>
</tr>
<tr>
<td>2007</td>
<td>104</td>
<td>2.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>139</td>
<td>2.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>140</td>
<td>2.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>203</td>
<td>3.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>214</td>
<td>3.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>275</td>
<td>4.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>312</td>
<td>4.6%</td>
<td>52</td>
<td>2.2%</td>
<td>20</td>
<td>1.5%</td>
</tr>
<tr>
<td>2014</td>
<td>217</td>
<td>3.0%</td>
<td>52</td>
<td>1.9%</td>
<td>34</td>
<td>3.1%</td>
</tr>
<tr>
<td>2015</td>
<td>311</td>
<td>3.9%</td>
<td>72</td>
<td>2.4%</td>
<td>22</td>
<td>2.1%</td>
</tr>
<tr>
<td>Totals</td>
<td>1915</td>
<td></td>
<td>176</td>
<td></td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

As is apparent in this table, with the exception of 2014, in Otago-Southland requests for HLA testing steadily increased over the years encompassed in this study, as did the percentage of total tests that they comprised. The three year time period of data relating to the other two regions is too short to determine any patterns in practice, although it does appear that HLA tests are requested less frequently there.

Included in the number of HLA tests requested in Otago-Southland were 41 duplicate tests – that is, tests conducted on patients who had already had an HLA test performed at an earlier date. The timeframe between repeat tests ranged from five days to seven years, with 17 of the 41 repeat tests having been requested by the same practitioner who had requested the first test. In the shorter time-period analysed for the other two regions there were no duplicate tests requested in Nelson-Marlborough, and only one in South Canterbury. It is reassuring to note that all repeat tests returned the same results as the original tests.
As noted earlier in this chapter, over the nine year period from 2007 more than 1000 individual practitioners requested CD testing of some sort in Otago-Southland. Over the same period, 287 of these practitioners requested HLA testing be carried out. In Nelson-Marlborough there were approximately 328 practitioners who requested CD testing from the beginning of 2013 until the end of 2015, while in South Canterbury the number was approximately 165 for the same period. HLA test requests were made by 62 practitioners in Nelson-Marlborough, and 31 practitioners in South Canterbury. Thus over 25% of Otago-Southland practitioners, and around 18% of Nelson-Marlborough and South Canterbury practitioners made a request for HLA testing on at least one occasion.

Analysis of who requested HLA tests, revealed that GPs were the major contributor of these requests. (Figures 6-18 and 6-19)

![Figure 6-18: HLA requests in Otago-Southland each year, by requester](image)

On further study of the data contributing to this graph, it became apparent that a relatively small number of practitioners were responsible for the majority of test requests. This was particularly the case for tests requested by practitioners in the “Other” category (specialists other than Paediatricians or Gastroenterologists), with marked increases from 2013 onwards. In 2013 a single practitioner accounted for 53.6% (15/28) of requests from this group. The same practitioner accounted for 89.8% (44/49) of requests in this category in 2014, and 91.9% (79/86) in 2015.
Over the entire period under consideration, 1259 HLA requests originated from GPs. Of these, 384 (30.5%) were generated by just three practitioners, while the top 10 requesters between them accounted for almost half (49.7%, 626/1259) of all requests.

![Figure 6-19: HLA requests for Nelson-Marlborough and South Canterbury each year, by requester](image)

In Nelson-Marlborough, over the three years from 2013, a single GP was responsible for 45% (54/120) of requests originating in primary care, which amounted to 30.7% of requests overall. The next highest GP requester ordered 9.2% (11/120) of tests, while the remaining 55 GP requests came from 38 practitioners. Of the total group of HLA test requesters, Paediatricians were the next most represented group, accounting for 16.5% (29/176) of requests. These came from eight individual doctors as well as an outpatients’ clinic and a children’s ward.

In South Canterbury, requests were more evenly distributed among practitioners. A Gastroenterologist made the highest number of requests (21.5%, 16/76), followed by one GP who ordered 11 tests (14.5% of the total number).

Patients who underwent HLA testing could be grouped into one of three categories of investigation. The largest of these categories was testing in conjunction with serology tests, presumably as part of the investigation for possible CD. The second group were patients for whom HLA tests were requested following a recommendation from laboratory scientists, made in the context of reporting on
serology results. There were two scenarios in which such a recommendation might have been made, to help the requester clarify a patient’s risk of CD: in the presence of ambiguous serology results (usually elevated tTG in conjunction with normal EMA); and when a patient had been found to be low or deficient in IgA. The third, and smallest, category was patients for whom HLA testing would seem, from the available data, to be the sole CD-related investigation that they had undergone. For these patients it is possible that additional CD testing may have occurred in another region (e.g. for patients recently moved into an area), or that their serology tests predated the time period of this study. This is particularly likely to have been the case for patients in the Nelson-Marlborough and South Canterbury regions, given that data for these areas were only available from the beginning of 2013.

It is difficult to calculate a precise figure for the number of tests requested secondary to a laboratory recommendation, but it is possible to estimate this from the data available. In Otago-Southland, the proportion of HLA tests likely to have arisen following a laboratory recommendation ranged from approximately 50% (in 2007) to 29% (in 2015). This would be consistent with there being particular practitioners who were routinely and frequently testing for HLA-DQ2/DQ8 in the later years of this study.

6.6 What was found?

Results of CD testing were grouped and analysed under the following headings: positive tTG results; correlations between tTG and EMA tests; results suggestive of IgA deficiency; and other findings. Data from all regions for which they were available were included in this component of the analysis.

---

k Results for HLA testing were only available for Otago-Southland. This was because the tests themselves were not carried out by SCL, which instead acted as a clearing house for test samples that were forwarded to the Canterbury Health Laboratory. As all requests initially went through SCL, these were included in the study dataset. Results of tests from Otago-Southland patients were sent back to SCL for release to requesters, and thus were also included in that dataset. Results for patients from the other regions were sent directly to the relevant health practitioners, so did not form part of the information available for the project.
6.6.1 Positive IgA-tTG antibody results

As discussed in Chapter Three, SCL used Quantalite tTG test kits throughout the period of this study. The ULN for these kits is 20 units, therefore any test above that level was regarded as positive. The numbers of positive tTG results returned in Otago-Southland, Nelson-Marlborough, and South Canterbury were tabulated, along with the percentages of all tTGs performed that these comprised. (Tables 6.17 and 6.18)

Table 6.17: Positive IgA-tTG results relative to all IgA-tTG tests performed in Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>All tTGs</th>
<th>Positive tTG</th>
<th>% of all tTGs</th>
<th>New patient tTGs</th>
<th>Positive tTG</th>
<th>% of new patient tTGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>4286</td>
<td>171</td>
<td>3.99</td>
<td>3954</td>
<td>137</td>
<td>3.46</td>
</tr>
<tr>
<td>2008</td>
<td>4911</td>
<td>223</td>
<td>4.54</td>
<td>4312</td>
<td>173</td>
<td>4.01</td>
</tr>
<tr>
<td>2009</td>
<td>4724</td>
<td>207</td>
<td>4.38</td>
<td>3974</td>
<td>155</td>
<td>3.90</td>
</tr>
<tr>
<td>2010</td>
<td>5462</td>
<td>236</td>
<td>4.32</td>
<td>4494</td>
<td>166</td>
<td>3.69</td>
</tr>
<tr>
<td>2011</td>
<td>5441</td>
<td>230</td>
<td>4.23</td>
<td>4273</td>
<td>154</td>
<td>3.60</td>
</tr>
<tr>
<td>2012</td>
<td>6043</td>
<td>213</td>
<td>3.52</td>
<td>4651</td>
<td>142</td>
<td>3.05</td>
</tr>
<tr>
<td>2013</td>
<td>6674</td>
<td>235</td>
<td>3.52</td>
<td>5182</td>
<td>157</td>
<td>3.03</td>
</tr>
<tr>
<td>2014</td>
<td>7184</td>
<td>263</td>
<td>3.66</td>
<td>5370</td>
<td>164</td>
<td>3.05</td>
</tr>
<tr>
<td>2015</td>
<td>7854</td>
<td>308</td>
<td>3.92</td>
<td>5706</td>
<td>171</td>
<td>3.00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>52,579</td>
<td>2086</td>
<td>3.97</td>
<td>41,916</td>
<td>1419</td>
<td>3.39</td>
</tr>
</tbody>
</table>

It is apparent from this table that early in the study period there was an increase in the number of positive IgA-tTG tests as a proportion of total tests being performed. However since 2008 these proportions have steadily fallen among patients having a first test for CD. The differences in proportions were statistically significant on two-sample proportions testing between 2008 and 2015, (p=0.002), but not between 2007 and 2015, (p=0.166).
For Nelson-Marlborough and South Canterbury the figures given for new patient tests are less reliable, as the data available to determine these figures encompassed a much shorter period of time. Thus it is possible that some of the people newly appearing in the SCL data each year had had earlier tests performed by another provider. Nonetheless, the impression given by the data presented is that proportions of new-patient positive tests were relatively stable in both regions. (Table 6.18)

Table 6.18: Positive IgA-tTG results relative to total IgA-tTG tests performed in Nelson-Marlborough and South Canterbury, 2013 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>All tTGs</th>
<th>Positive tTG</th>
<th>% of all tTGs</th>
<th>New patient tTGs</th>
<th>Positive tTG</th>
<th>% of new patient tTGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson-Marlborough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>2303</td>
<td>62</td>
<td>2.69</td>
<td>2261</td>
<td>54</td>
<td>2.39</td>
</tr>
<tr>
<td>2014</td>
<td>2747</td>
<td>90</td>
<td>3.28</td>
<td>2565</td>
<td>73</td>
<td>2.85</td>
</tr>
<tr>
<td>2015</td>
<td>2957</td>
<td>85</td>
<td>2.87</td>
<td>2643</td>
<td>64</td>
<td>2.42</td>
</tr>
<tr>
<td>TOTAL</td>
<td>8007</td>
<td>237</td>
<td>2.96</td>
<td>7469</td>
<td>191</td>
<td>2.56</td>
</tr>
<tr>
<td>South Canterbury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1308</td>
<td>45</td>
<td>3.44</td>
<td>1260</td>
<td>40</td>
<td>3.17</td>
</tr>
<tr>
<td>2014</td>
<td>1087</td>
<td>45</td>
<td>4.14</td>
<td>988</td>
<td>31</td>
<td>3.14</td>
</tr>
<tr>
<td>2015</td>
<td>1034</td>
<td>38</td>
<td>3.68</td>
<td>893</td>
<td>28</td>
<td>3.14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3429</td>
<td>128</td>
<td>3.73</td>
<td>3141</td>
<td>99</td>
<td>3.15</td>
</tr>
</tbody>
</table>

When the proportions of new-patient positive tests for all three regions were compared for the years 2013 through to 2015, there were no statistically significant differences detected between any two regions in any year.

6.6.1.1 Gender-specific analyses of Otago-Southland positive IgA-tTG test data

Gender analyses were also conducted on the Otago-Southland new-patient data. (Table 6.19)
Table 6.19: Gender-specific analysis of new-patient tTG tests and positive new-patient tTG tests for Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Male New tTG (% all tests)</th>
<th>Female New tTG (% all tests)</th>
<th>Male Positive tTG (% all positives)</th>
<th>Female Positive tTG (% all positives)</th>
<th>Positive Male new tests (% new)</th>
<th>Positive Female new tests (% new)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1323 (33.5%)</td>
<td>2631 (66.5%)</td>
<td>44 (32.1%)</td>
<td>93 (67.9%)</td>
<td>3.33</td>
<td>3.53</td>
</tr>
<tr>
<td>2008</td>
<td>1444 (33.5%)</td>
<td>2868 (66.5%)</td>
<td>61 (35.3%)</td>
<td>112 (64.7%)</td>
<td>4.22</td>
<td>3.91</td>
</tr>
<tr>
<td>2009</td>
<td>1316 (33.1%)</td>
<td>2658 (66.9%)</td>
<td>52 (33.6%)</td>
<td>103 (66.5%)</td>
<td>3.95</td>
<td>3.88</td>
</tr>
<tr>
<td>2010</td>
<td>1476 (32.8%)</td>
<td>3017 (67.1%)</td>
<td>59 (35.5%)</td>
<td>107 (64.5%)</td>
<td>4.00</td>
<td>3.55</td>
</tr>
<tr>
<td>2011</td>
<td>1416 (33.1%)</td>
<td>2856 (66.8%)</td>
<td>52 (33.8%)</td>
<td>102 (66.2%)</td>
<td>3.67</td>
<td>3.57</td>
</tr>
<tr>
<td>2012</td>
<td>1526 (32.8%)</td>
<td>3124 (67.2%)</td>
<td>38 (26.8%)</td>
<td>104 (73.2%)</td>
<td>2.49</td>
<td>3.33</td>
</tr>
<tr>
<td>2013</td>
<td>1739 (33.6%)</td>
<td>3442 (66.4%)</td>
<td>52 (33.1%)</td>
<td>105 (66.9%)</td>
<td>2.99</td>
<td>3.05</td>
</tr>
<tr>
<td>2014</td>
<td>1898 (35.3%)</td>
<td>3471 (64.6%)</td>
<td>49 (29.9%)</td>
<td>115 (70.1%)</td>
<td>2.58</td>
<td>3.31</td>
</tr>
<tr>
<td>2015</td>
<td>1972 (34.6%)</td>
<td>3733 (65.4%)</td>
<td>48 (28.1%)</td>
<td>123 (71.9%)</td>
<td>2.43</td>
<td>3.29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14,110 (33.7%)</td>
<td>27,800 (66.3%)</td>
<td>455 (32.1%)</td>
<td>964 (67.9%)</td>
<td>3.22</td>
<td>3.47</td>
</tr>
</tbody>
</table>

As demonstrated in this table, and consistent with earlier gender-specific data, women and men had IgA-tTG testing done in ratios of approximately 2:1 throughout the time period studied. Ratios within the numbers of patients having positive tests showed a little more variability, particularly in 2012, 2014 and 2015, although none of these annual differences between the genders reached statistical significance on Pearson Chi-square testing. On two-sample tests of proportions, no significant
differences were detected in the rates of positive tests between men and women as proportions of total tests per gender-group in any year, or overall.

6.6.1.2 Age-specific analyses of Otago-Southland positive IgA-tTG test data

Similar analyses to those pertaining to gender were carried out with respect to age and positive IgA-tTG tests. (Table 6.20) Patients up to and including the age of 16-years were counted as children.

Table 6.20: Age-specific analysis of new-patient IgA-tTG tests and positive new-patient IgA-tTG tests for Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Child New tTG (% all)</th>
<th>Adult New tTG (% all)</th>
<th>Child Positive tTG (% all pos)</th>
<th>Adult Positive tTG (% all pos)</th>
<th>% Child positive</th>
<th>% Adult positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>788 (19.9%)</td>
<td>3166 (80.1%)</td>
<td>33 (24.1%)</td>
<td>104 (75.9%)</td>
<td>4.19</td>
<td>3.28</td>
</tr>
<tr>
<td>2008</td>
<td>857 (19.9%)</td>
<td>3455 (80.1%)</td>
<td>42 (24.3%)</td>
<td>131 (75.7%)</td>
<td>4.90</td>
<td>3.79</td>
</tr>
<tr>
<td>2009</td>
<td>866 (21.8%)</td>
<td>3108 (78.2%)</td>
<td>44 (28.4%)</td>
<td>111 (71.6%)</td>
<td>5.08</td>
<td>3.57</td>
</tr>
<tr>
<td>2010</td>
<td>847 (18.9%)</td>
<td>3647 (81.2%)</td>
<td>36 (21.7%)</td>
<td>130 (78.3%)</td>
<td>4.25</td>
<td>3.56</td>
</tr>
<tr>
<td>2011</td>
<td>827 (19.4%)</td>
<td>3446 (80.7%)</td>
<td>40 (26.0%)</td>
<td>114 (74.0%)</td>
<td>4.84</td>
<td>3.31</td>
</tr>
<tr>
<td>2012</td>
<td>945 (20.3%)</td>
<td>3707 (79.7%)</td>
<td>29 (20.4%)</td>
<td>113 (79.6%)</td>
<td>3.07</td>
<td>3.05</td>
</tr>
<tr>
<td>2013</td>
<td>959 (18.5%)</td>
<td>4223 (81.5%)</td>
<td>37 (23.6%)</td>
<td>120 (76.4%)</td>
<td>3.86</td>
<td>2.84</td>
</tr>
<tr>
<td>2014</td>
<td>1036 (19.3%)</td>
<td>4334 (80.7%)</td>
<td>42 (25.6%)</td>
<td>122 (74.4%)</td>
<td>4.05</td>
<td>2.81</td>
</tr>
<tr>
<td>2015</td>
<td>1057 (18.5%)</td>
<td>4649 (81.5%)</td>
<td>38 (22.2%)</td>
<td>133 (77.8%)</td>
<td>3.60</td>
<td>2.86</td>
</tr>
<tr>
<td>TOTAL</td>
<td>8182 (19.5%)</td>
<td>33,374 (80.5%)</td>
<td>341 (24.0%)</td>
<td>1078 (76.0%)</td>
<td>4.17</td>
<td>3.20</td>
</tr>
</tbody>
</table>
The variables of primary interest in this table are the percentages of children and adults tested for IgA-tTG antibodies who returned positive results. With the exception of 2012, a greater proportion of children who were tested were found to have positive results, that is, an IgA-tTG level greater than 20 units.

In 2009, 2011, and 2014 there were statistically significant differences between children and adults with respect to the likelihood of having a positive IgA-tTG test, \( p=0.042, p=0.034, \) and \( p=0.037 \) respectively, on Pearson Chi-square testing. When all years were combined this was highly significant, \( p<0.0001 \). Two-sample tests of proportions comparing positive tests among children with those in adults also detected significant differences in 2009 and 2011, \( p=0.042 \) and \( p=0.034 \). Once again, when all years were combined the difference was highly significant, \( p<0.0001 \).

The mean age of children returning positive IgA-tTG results ranged from a minimum of 7.6 years (in 2010) to a maximum of 10.7 years (in 2012). Among adults this range was 39.8 years (in 2012) and 43.3 years (in 2013).

### 6.6.2 Correlations between IgA-tTG and EMA results

In the early years encompassed in this project, EMA tests were routinely included in the CD testing panel. In later years they were only performed on patients returning a positive or high-normal tTG result, the rationale being that the two tests together are a more reliable indicator of the presence of CD, over either test alone.

Analysis was undertaken to compare the results of the two tests, using combined data from the regions. Results of tTG tests were grouped according to whether they were very high (≥150 units), high (100 – 149 units), moderately high (60 – 99 units), or low-high (21 – 59 units). EMA results were reported as positive, weakly positive, negative, or indeterminate/equivocal. Positive EMA tests were correlated with positive tTG results. (Table 6.21)
Because there was such a marked difference in positivity between the two lower groups, the low-high group was analysed further, to more accurately identify the IgA-tTG level at which EMA positivity dropped off. (Table 6.22)

**Table 6.22: EMA positivity relative to low-high IgA-tTG values**

<table>
<thead>
<tr>
<th>tTG range</th>
<th>EMA done</th>
<th>EMA positive</th>
<th>EMA percentage positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 59</td>
<td>118</td>
<td>53</td>
<td>44.9%</td>
</tr>
<tr>
<td>40 – 49</td>
<td>238</td>
<td>58</td>
<td>24.4%</td>
</tr>
<tr>
<td>30 – 39</td>
<td>317</td>
<td>58</td>
<td>18.3%</td>
</tr>
<tr>
<td>21 – 29</td>
<td>530</td>
<td>24</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

The other reported EMA results (weak-positive, equivocal, and indeterminate) were more commonly associated with lower tTGs. There were 180 weak-positive EMA results in total, and these were much more prevalent in the low-high tTG group, increasing from 17 of the 304 (5.6%) moderately-high tTGs to 163 of the 1203 (13.5%) low-high results. There were 13 equivocal results, and 32 indeterminate results, one each associated with a high tTG, and the rest predominantly occurring with low-high tTGs.

At the other end of the spectrum, there were nine positive and 19 weak-positive EMA tests in patients with normal IgA-tTG antibody levels. The overall number of normal IgA-tTG tests over the time period in which these results occurred was close to 74,000, rendering these extremely rare events.
6.6.3 Low and deficient IgA levels

As discussed in Chapter Two, the primary tTG antibody and EMA tests for CD are both IgA-based, and therefore rely on the patient having enough IgA to produce antibodies in the presence of gluten, which the tests then measure.

In SCL laboratories, when a patient’s IgA levels are found to be deficient, or lower than the accepted normal range for his or her age, a comment is generally included in the reporting of the result. In the dataset available for this study the information came in various guises. In some cases “*******” appeared in either the tTG result column, or the IgA column, or both. In other cases, the tTG and IgA results columns were empty, but in many cases the information was obtained only by searching individual patient laboratory records, on the basis that the reported IgA level was low.

In Otago-Southland there were 348 tTG antibody tests done on 259 patients who were either IgA-deficient, or low in IgA. These results all came with a recommendation that the patients concerned should have an HLA test done to help exclude CD, or undergo duodenal biopsy to confirm the diagnosis. IgG-DGP testing was also offered on some occasions in the later years for which data were available. In the other regions, the numbers of patients similarly affected were: Nelson-Marlborough 25; South Canterbury 14; Hawkes Bay 28; and Taupo 11. However, given the variability in how the laboratory reported results for these patients, these figures could well underestimate the true numbers.

6.6.4 Other findings

Across the regions there were 252 results reported as “*******”, which required a search on each patient’s laboratory records to clarify what was meant by this. There was a range of reasons for this type of report, but the majority were an indication that the blood sample taken from the patient had haemolysed, rendering it unsuitable for tTG analysis. (Table 6.23)
Table 6.23: Laboratory comments indicated by ******

<table>
<thead>
<tr>
<th>Laboratory Comment</th>
<th>Number affected</th>
<th>Repeat tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample haemolysed</td>
<td>161</td>
<td>100</td>
</tr>
<tr>
<td>Insufficient sample/ incorrect tube</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Laboratory error (sample destroyed)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Already tested/ result reported elsewhere</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>Testing panel related comment</td>
<td>10</td>
<td>N/A</td>
</tr>
<tr>
<td>IgA related</td>
<td>31</td>
<td>N/A</td>
</tr>
</tbody>
</table>

In later years some of these samples were able to be tested for DGP, but many patients were re-bled so that the IgA-tTG could be repeated.

### 6.7 What happened next?

From the laboratory data available it was not possible to establish the management implemented (e.g. GFD started or not) for the patients who had been tested for CD. However, it could be determined that for substantial numbers of them, a first test of CD serology was not the last CD-related investigation they underwent. Many went on to have repeat serology testing, some had subsequent HLA testing, and some went on to have a duodenal biopsy. The following sections present material about these follow-up actions for patients from Otago-Southland, Nelson-Marlborough and South Canterbury.

### 6.7.1 Repeat blood testing (serology and/or HLA testing)

As indicated early in this chapter, in each year under consideration in this study many patients had more than one test for CD. In addition to this, several thousand patients were tested repeatedly over two or more years. Some of these were people with biopsy-proven CD, some were those with positive serology but for whom there was no evidence that they had ever undergone biopsy, some were those with ambiguous serology, and some were people with negative tests. Within these
groups were patients who also had multiple tests in one or more of the years in which they were tested.

Analysis was undertaken to establish the numbers of Otago-Southland patients who had more than one CD-related test in any one year, from the beginning of 2007 until the end of 2015. (Table 6.24) Year by year this amounted to 2304 patients, but when patients also having tests in more than one year were removed, the total was 2202 (5.3% of the 41,509 individual patients tested over the time period).

**Table 6.24: Repeat CD testing figures for Otago-Southland patients, 2007 – 2017**

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Number of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients having repeat tests within a year, year by year</strong></td>
<td>2304</td>
<td>4794</td>
</tr>
<tr>
<td><strong>Unique patients having repeat tests within a year</strong></td>
<td>2202</td>
<td></td>
</tr>
<tr>
<td><strong>Patients having repeat tests in more than one year</strong></td>
<td>95</td>
<td>433</td>
</tr>
<tr>
<td><strong>Patients tested in one year only, but on more than one occasion</strong></td>
<td>2107</td>
<td>4361</td>
</tr>
</tbody>
</table>

Included in these figures are 714 patients who had an HLA test performed, either singly or with repeat serology.

For both Nelson-Marlborough and South Canterbury, the time period for which data were available was too short to form an accurate picture of how many people were tested in multiple years. However, from the beginning of 2013 until the end of 2015 3.9% of patients tested in Nelson-Marlborough, and 3.1% of those tested in South Canterbury had had more than one test in a year.

In Otago-Southland the number of repeat tests per year being performed on patients ranged from two to seven. In Nelson-Marlborough this range was from two to four, while in South Canterbury the maximum number of times a single patient was tested in a year was three. (Table 6.25)
Table 6.25: Number of individual patients tested for CD more than once per year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2,044</td>
<td>236</td>
<td>129</td>
</tr>
<tr>
<td>3</td>
<td>138</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis of the numbers of patients in Otago-Southland who had year-to-year repeat tests was also performed. (Table 6.26) Available information from 2006 was included in this analysis because on examining the data from subsequent years, it was apparent that many patients had first been tested in 2006. However, the figures given for first tests in 2006 will be an underestimate of the true number, given that additional patients were tested by the region’s alternative laboratory provider still operating at the time.

The total values given along the bottom of the table represent the number of patients tested each year. The diagonal totals (in bold) are the numbers of patients having their first test in each year. The smaller values in each column are the numbers of patients in each year who had already been tested for CD, and the year in which they had that first test. So, for example, in 2010 there were 5302 patients tested for CD, of whom 4445 were being tested for the first time, while 170 had first been tested in 2006, 214 in 2007, 242 in 2008, and 231 in 2009. (Note: patients having more than one test that year were not excluded from these calculations).
For the time period 1 January 2006 to 31 December 2015, the “grand totals” for each of the groups identified were:

- Overall patients tested: 54,089
- New patients tested: 44,423
- Patients tested in each year also tested in more than one year: 9666

Among the 9666 patients tested in more than one year were people who were counted more than once, either because they had more than one test in one of the years they were tested, or because they had tests in multiple years. Further analysis revealed that the number of individuals who were tested in more than one year was 7295 (13.5% of the overall patient group). The majority of these had been tested in two or three different years, but two patients had been tested every year between 2006 and 2015. Only a small proportion had a positive test when they were first tested. (Table 6.27)
Table 6.27: Summary data relating to Otago-Southland patients tested for CD in 2 or more years

<table>
<thead>
<tr>
<th>Number of years tested</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients tested</td>
<td>5706</td>
<td>1138</td>
<td>275</td>
<td>93</td>
<td>43</td>
<td>15</td>
<td>20</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Positive first test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients having a single test in more than one year</td>
<td>6376</td>
<td>268</td>
</tr>
<tr>
<td>Number of patients having more than one test in one or more years</td>
<td>919</td>
<td>127</td>
</tr>
<tr>
<td>Number of patients tested in more than one year following a positive first test</td>
<td>395</td>
<td></td>
</tr>
<tr>
<td>Number of patients tested in 5 or more years</td>
<td>176</td>
<td>34</td>
</tr>
<tr>
<td>Number of patients tested annually for 4 or more consecutive years</td>
<td>126</td>
<td>32</td>
</tr>
</tbody>
</table>

Of the 126 patients who had annual testing for four or more years, 69 (54.8%) were children being tested by Paediatricians, with the majority of tests originating from the Paediatrics Diabetes Clinics. General practitioners were the next largest group to be regularly testing patients, being the principal annual test requesters for 47 patients (37% of the sample).

Among the 69 paediatric patients, nine had had positive serology when first tested, a further three developed positive serology during the period in which they were being monitored, and one who was IgA-deficient was found to be biopsy-positive and was subsequently monitored with IgG-DGP testing.

One adult patient had 17 tTG tests over a period of six years, following a first test that was positive. Serology in this patient was repeatedly positive, and the patient also underwent four duodenal biopsies. The first of these was normal, the
next two showed partial villous atrophy, and the fourth one was reported as normal. All but two of the serology tests requested for this patient were done so by GPs.

Another patient had 13 tests in the space of 11 months (over two calendar years). The initial test was requested by a GP, the second by a secondary care provider, and all subsequent ones apparently by a GP. All tests were negative, and it seems likely that CD serology had inadvertently been included on a monthly request card as it was always done in conjunction with other tests.

6.7.1.1 Repeat testing by gender

As with numbers of testing events and numbers of patients being tested for CD, women outnumbered men when it came to having repeat tests within a year, and from year to year.

On further scrutiny of figures pertaining to repeat testing within a year for Otago-Southland patients, it was apparent that this was a function of the overall numbers of male and female patients being tested per year, rather than women being more likely to have repeat tests. (Table 6.28)

Table 6.28: Repeat tests per year as a proportion of patients tested per year by gender in Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Males tested per year</th>
<th>Male repeat tests (% males tested)</th>
<th>Females tested per year</th>
<th>Female repeat tests (% females tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1395</td>
<td>122 (9%)</td>
<td>2762</td>
<td>265 (10%)</td>
</tr>
<tr>
<td>2008</td>
<td>1577</td>
<td>177 (11%)</td>
<td>3161</td>
<td>299 (9%)</td>
</tr>
<tr>
<td>2009</td>
<td>1515</td>
<td>141 (9%)</td>
<td>3065</td>
<td>262 (9%)</td>
</tr>
<tr>
<td>2010</td>
<td>1716</td>
<td>152 (9%)</td>
<td>3585</td>
<td>378 (11%)</td>
</tr>
<tr>
<td>2011</td>
<td>1712</td>
<td>161 (9%)</td>
<td>3569</td>
<td>385 (11%)</td>
</tr>
<tr>
<td>2012</td>
<td>1902</td>
<td>182 (10%)</td>
<td>4032</td>
<td>416 (10%)</td>
</tr>
<tr>
<td>2013</td>
<td>2131</td>
<td>192 (9%)</td>
<td>4385</td>
<td>425 (10%)</td>
</tr>
<tr>
<td>2014</td>
<td>2337</td>
<td>199 (9%)</td>
<td>4657</td>
<td>406 (9%)</td>
</tr>
<tr>
<td>2015</td>
<td>2498</td>
<td>205 (8%)</td>
<td>5170</td>
<td>427 (8%)</td>
</tr>
</tbody>
</table>
On Pearson Chi-square analysis comparing repeat testing with no repeat testing among men and women, there were no statistically significant differences detected. Differences between the groups approached significance in 2008, (p=0.057), and 2010, (p=0.056).

6.7.2 Duodenal biopsies

As discussed in Chapter Two, histological examination of duodenal biopsy samples, obtained during endoscopy, remains the recommended “gold standard” for diagnosing CD. Unfortunately, details relating to biopsies undertaken in the population comprising this study were not included in the dataset provided by the laboratory, however it was possible to obtain these by searching the laboratory records of each person who had had positive serology tests. As SCL processes all histology samples obtained from patients in Otago-Southland, Nelson-Marlborough, and South Canterbury, the relevant patient records for these regions were readily accessible. However, in Taupo and Hawkes Bay the endoscopies at which samples are obtained are performed (and therefore processed) at centres that do not use SCL as their laboratory service provider. Access to laboratory providers other than SCL was outside the scope of this study, and for this reason these regions have been excluded from further analysis.

Laboratory records were accessed for all patients with IgA-tTG levels higher than 20; for patients with any EMA result other than negative (thus including the few with normal IgA-tTG but positive or weakly positive EMA); and for patients with results suggestive of IgA deficiency. Any duodenal biopsy results were identified and retrieved for further analysis. While there may also have been a small number of patients with normal serology who underwent endoscopy, given the many thousands of normal results, it was not practical to search for these as well.

In total, from the beginning of 2007 until mid-June 2016, there were 1063 CD-related biopsy procedures performed on 979 Otago-Southland patients. This included 77 patients who had more than one endoscopy, two of whom who had three, one of whom who had four, and one of whom who had five procedures. It also included 11 patients who had had their serology test in 2006, and five patients who had their biopsies performed at another centre, four in Christchurch, and the other in South Canterbury.
Of the 979 patients biopsied, 685 were female and 294 were male. Children and young people under the age of 17-years underwent 269 biopsy procedures (25.4% of the total). The youngest child to have an endoscopy was 11-months old and the oldest adult was 85-years old. The numbers of endoscopies performed for duodenal biopsy decreased with increasing age. (Figure 6-20)

![Figure 6-20: Numbers of biopsy procedures performed per age-group in Otago-Southland on people with positive CD serology (or IgA deficiency), January 2007 – June 2016](image)

In Nelson-Marlborough there were 114 CD-related biopsy procedures performed on 109 patients, from the beginning of 2013 until mid-June 2016. Of these, 71 were female and 38 were male. The youngest child biopsied was 3-years old, and the oldest adult was 80-years old. Children and young people under the age of 17-years had 30 procedures, which constituted 26.5% of the total number.

Over the same time period 49 biopsy procedures were performed on 43 patients in South Canterbury. Males slightly outnumbered females in this group, with numbers of 23 and 20 respectively. The youngest child biopsied was 4-years old, and the oldest person was 68-years old. In this region 15 of the 49 procedures, or 30.6%, were carried out on children. (It is possible that some people in South Canterbury were seen in Christchurch so their data will be missing from this study.)
This is particularly likely to be the case for children, in whom there were only small numbers of biopsies performed, none of which were on the very young.)

6.7.2.1 Time to duodenal biopsy

In all three regions, the vast majority of biopsies were performed as a consequence of serology testing indicating that CD was possible, but 48 preceded that testing. In these cases, serology (which was found to be positive) had been performed following a biopsy that showed the hallmark histological features of CD. From laboratory data it was not possible to discern why these endoscopies had been undertaken. In Nelson-Marlborough and South Canterbury it is quite likely that earlier tests had been performed at the alternative laboratory provider before SCL took over services there, but in Otago-Southland it is more likely that they were performed for clinical reasons other than a suspicion of CD. It may also be that serology had been performed in another region, prior to the patient coming to Otago-Southland. For whatever reason, duodenal biopsies were taken at the time of endoscopy, suggesting the diagnosis of CD which was subsequently confirmed by serology.

There were also a number of patients in Otago-Southland for whom there was an extremely long time lapse between a first positive serology test and a duodenal biopsy result being recorded. The longest period was 5.5 years, but between 2007 and 2014 there were another 49 patients for whom this gap was more than a year. For several of these people the delay to biopsy was in excess of three years. From the data available, it is not possible to determine why this might have occurred, but it is highly likely that patient preference will have played a significant role in this. Many of these patients had multiple IgA-tTG tests in the intervening years.

With these groups of patients excluded, the median time to biopsy in Otago-Southland ranged from 10 weeks in 2007, to 14 weeks in 2012, and back to 12 weeks in 2015. The mean time to biopsy ranged from 12 (± 8) weeks in 2007, to 17 (±13) and (±12) weeks in 2010 and 2011 respectively, and back to 14 (± 9) weeks in 2015. In Nelson-Marlborough the median time to biopsy was approximately 10 weeks each year from 2013 to 2015, while the mean time was between 12 (±9) and 13 (±10) weeks. In South Canterbury the median time varied between 11 and 17
weeks, while the mean ranged between 16 (±10) and 19 (±13) weeks, with 2015 seeing the longest periods for both.

### 6.7.2.2 Duodenal biopsy rates

The rates at which patients with positive CD serology results went forward for duodenal biopsy varied over time, and according to how high their IgA-tTG result was. (Table 6.29) These results were grouped as very high (≥150 units), high (100–149 units), moderately high (60–99 units), and low-high (21–59 units).

Rates were determined by comparing the numbers of biopsies performed each year with the number of biopsies that were indicated. All positive results for patients that had not yet been followed by a biopsy were included in this “biopsy indicated” figure, which meant that the results from patients who had positive tests over a number of years before having a biopsy were all counted. Results from patients implied in laboratory reports as having CD without evidence of them ever having had a biopsy were also included in this figure, as the data available could not provide any certainty that this was the clinical situation. Completed biopsies were counted with respect to the year in which the serology test had been requested, rather than the year in which the biopsies were performed.

Repeat biopsies and positive results from tests performed after patients had had biopsies were also excluded from the calculation of these biopsy rates. Biopsies performed on IgA-deficient patients were considered separately, and the relevant findings are presented towards the end of this chapter.
Table 6.29: Rates of duodenal biopsy for patients with raised IgA-tTG antibodies in Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Very high tTG</th>
<th>High tTG</th>
<th>Moderately high tTG</th>
<th>Low-high tTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td>45</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>73.3%</td>
<td>57.9%</td>
<td>50%</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>61</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>68.9%</td>
<td>90.5%</td>
<td>77.8%</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td>43</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>65.1%</td>
<td>54.5%</td>
<td>50%</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>53</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>83%</td>
<td>80%</td>
<td>52.9%</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>48</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>81.3%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>47</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>80.9%</td>
<td>85.7%</td>
<td>66.7%</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td>55</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>72.7%</td>
<td>47.6%</td>
<td>76.9%</td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td>56</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>73.2%</td>
<td>52.9%</td>
<td>70.4%</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td>57</td>
<td>43</td>
<td>14</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td>75.4%</td>
<td>71.4%</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

On closer inspection of the figures in Table 6.29, it is apparent that there was no particular pattern to how biopsy rates fluctuated from year to year. (Figure 6-21)
When biopsy rates for 2015 were compared with those of 2007, it was evident that these had increased for all IgA-tTG result categories. Pearson Chi-square tests comparing biopsy with no biopsy for each of these categories in 2007 and 2015 showed that the differences were statistically significant for the low-high category, (p=0.01), and approached significance for the moderately high category, (p=0.053). Differences in the other two categories were not statistically significant. However, given the assumptions made about the data when calculating the biopsy rates, these values should be interpreted with caution.

The overall annual biopsy rate was also determined and can be seen to have increased from 48.2% in 2007, to 60.0% in 2015, (p=0.032). (Figure 6.22)
Biopsy rates were also calculated for Nelson-Marlborough and South Canterbury. (Tables 6.30 and 6.31)

Table 6.30: Rates of duodenal biopsy for patients with raised IgA-tTG antibodies in Nelson-Marlborough, 2013 - 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Very high tTG</th>
<th>High tTG</th>
<th>Moderately high tTG</th>
<th>Low high tTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td>15</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.2%</td>
<td></td>
<td>73.3%</td>
<td></td>
<td>85.7%</td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td>22</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.1%</td>
<td></td>
<td>68.2%</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td>18</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.1%</td>
<td></td>
<td>61.1%</td>
<td></td>
<td>85.7%</td>
</tr>
</tbody>
</table>

The overall biopsy rates for each year in Nelson-Marlborough were 68.9% (2013), 56.7% (2014), and 57.6% (2015), however the three year time-period is too short to derive any particular meaning from this.
Table 6.31: Rates of duodenal biopsy for patients with raised igA-tTG antibodies in South Canterbury, 2013 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Very high tTG</th>
<th></th>
<th></th>
<th>High tTG</th>
<th></th>
<th></th>
<th>Moderately high tTG</th>
<th></th>
<th></th>
<th>Low high tTG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
<td>Done</td>
<td>Indicated</td>
<td>Done</td>
</tr>
<tr>
<td>2013</td>
<td>Rate</td>
<td>71.4%</td>
<td>33.3%</td>
<td>42.9%</td>
<td>23.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Rate</td>
<td>60%</td>
<td>50%</td>
<td>66.7%</td>
<td>30.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Rate</td>
<td>42.9%</td>
<td>100%</td>
<td>40%</td>
<td>30.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall biopsy rates for South Canterbury were 36.6% (2013), 46.7% (2014), and 38.5% (2015). Once again the short time-period limits the usefulness of this information, however it is apparent that fewer biopsies per positive antibody test were performed in this region. This may in part be accounted for by patients travelling outside the region for further assessment.

6.7.2.3 Duodenal biopsy rates by gender and age

When the profiles of the patients who did and did not have biopsies were studied further, the following details emerged with respect to gender. (Table 6.32)

Table 6.32: Duodenal biopsy rate by gender, Otago-Southland

<table>
<thead>
<tr>
<th>tTG</th>
<th>Biopsy rate males</th>
<th>Biopsy rate females</th>
<th>p-value (Pearson Chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥150</td>
<td>73.4%</td>
<td>75.5%</td>
<td>0.640</td>
</tr>
<tr>
<td>100 – 149</td>
<td>78.0%</td>
<td>64.5%</td>
<td>0.089</td>
</tr>
<tr>
<td>60 – 99</td>
<td>60.0%</td>
<td>66.4%</td>
<td>0.406</td>
</tr>
<tr>
<td>21 – 59</td>
<td>30.6%</td>
<td>45.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>51.0%</td>
<td>59.5%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
In contrast to these overall figures for Otago-Southland, in Nelson-Marlborough the overall biopsy rates were 61.7% for males and 59.5% for females, (p=0.778), and those in South Canterbury were 55.3% and 30.5% respectively, (p=0.015). The only statistically significant differences between the regions were between the biopsy rates for South Canterbury women and those of Otago-Southland women and Nelson-Marlborough women, (p<0.0001 for both comparisons).

Biopsy rates per age-group were also calculated for each region, and can be seen to fluctuate between ages and also within ages between IgA-tTG levels. (Tables 6.33 and 6.34)

Table 6.33: Duodenal biopsy rate per IgA-tTG grouping by age-group in Otago-Southland

<table>
<thead>
<tr>
<th>IgA-tTG</th>
<th>≤16 years</th>
<th>17-26 years</th>
<th>27-36 years</th>
<th>37-46 years</th>
<th>47-56 years</th>
<th>57-66 years</th>
<th>67-76 years</th>
<th>≥77 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥150</td>
<td>77.6%</td>
<td>72.8%</td>
<td>69.0%</td>
<td>75.0%</td>
<td>72.7%</td>
<td>80.5%</td>
<td>57.1%</td>
<td>85.7%</td>
</tr>
<tr>
<td>100–149</td>
<td>64.3%</td>
<td>65.2%</td>
<td>75.0%</td>
<td>62.5%</td>
<td>66.7%</td>
<td>91.7%</td>
<td>60.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>60–99</td>
<td>68.8%</td>
<td>58.1%</td>
<td>75.9%</td>
<td>61.5%</td>
<td>58.3%</td>
<td>65.0%</td>
<td>85.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>21–59</td>
<td>30.1%</td>
<td>45.9%</td>
<td>53.3%</td>
<td>49.0%</td>
<td>38.4%</td>
<td>37.9%</td>
<td>34.0%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Overall</td>
<td>57.2%</td>
<td>57.2%</td>
<td>63.5%</td>
<td>58.0%</td>
<td>53.5%</td>
<td>60.3%</td>
<td>46.2%</td>
<td>34.1%</td>
</tr>
</tbody>
</table>

Table 6.34: Overall duodenal biopsy rates by age-group for Nelson-Marlborough and South Canterbury

<table>
<thead>
<tr>
<th></th>
<th>≤16 years</th>
<th>17-26 years</th>
<th>27-36 years</th>
<th>37-46 years</th>
<th>47-56 years</th>
<th>57-66 years</th>
<th>67-76 years</th>
<th>≥77 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM</td>
<td>69.0%</td>
<td>64.0%</td>
<td>60.9%</td>
<td>50.0%</td>
<td>51.9%</td>
<td>66.7%</td>
<td>80.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>51.9%</td>
<td>23.5%</td>
<td>25.0%</td>
<td>50.0%</td>
<td>54.5%</td>
<td>54.5%</td>
<td>22.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.7.2.4 Duodenal biopsy results

The results of every duodenal biopsy performed for CD in the three regions for which data were available were scrutinised for evidence of the presence or absence of the disease. Information gathered from this process was collated and summarised. (Table 6.35)

Table 6.35: Results for all CD-related duodenal biopsies, all regions combined

<table>
<thead>
<tr>
<th>Biopsy result</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent with CD</td>
<td>886</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>11</td>
</tr>
<tr>
<td>Normal</td>
<td>297</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1226</strong></td>
</tr>
</tbody>
</table>

A small number of samples were inconclusive. For some of these the pathologist was explicit about this, writing that “CD cannot be excluded”, the findings “could be” CD, or that the findings were “inconclusive”. However, in some reports this interpretation was omitted and only minimal changes were cited. Samples that were reported as duodenitis, cases in which mild but insignificant lamina propria inflammation was observed, two cases for which the full report was not accessible, and one case of adenocarcinoma, were all included in this table under the heading “Other”.

Biopsies were counted as positive if the pathologist indicated in his or her report that the result was consistent with CD (or other similar wording). In general results were not reported with overt reference to any of the recognised classifications discussed in Chapter Two of this work. All reports had a comment about villous architecture, variously described as normal, or as showing evidence of severe, complete, variable, moderate, or mild villous atrophy. Almost invariably there was a comment about the presence or absence of increased IELs, and of a chronic inflammatory infiltrate or plasma cells in the lamina propria. Only sometimes was there comment about crypt hyperplasia, and only three reports included a comment on the quality of the biopsy samples.
At the mild end of the spectrum of changes there did seem to be some variation in interpretation between pathologists. Several biopsies were reported as showing normal villous architecture, and mild or focal intraepithelial lymphocytosis. On many occasions this was then reported as being “consistent with coeliac disease”. Sometimes this was qualified with a “mild” or “early”, but often it was not. On a few occasions it was classified as duodenitis rather than CD. On one occasion the report was reclassified at a later date from “compatible with coeliac disease”, to “focal increased intraepithelial lymphocytes, otherwise normal”. In two other cases the reverse situation occurred, with biopsies that were initially reported as normal being reviewed and subsequently reported as showing normal villous architecture with increased intraepithelial lymphocytes and inflammation in the lamina propria, consistent with CD.

In Otago-Southland the youngest child to have a positive biopsy was 23-months old, and the oldest person was 85-years old. In Nelson-Marlborough these ages were 3-years and 74-years, and in South Canterbury 6-years and 64-years respectively.

Biopsy results from the three regions were then tabulated according to IgA-tTG results. (Table 6.36) Repeat biopsies were not included unless they clearly followed a recent tTG test.

Table 6.36: Biopsy outcomes with respect to IgA-tTG levels, Otago-Southland, Nelson-Marlborough, and South Canterbury combined

<table>
<thead>
<tr>
<th>IgA-tTG</th>
<th>Biopsy done</th>
<th>Biopsy CD positive</th>
<th>Positivity Rate</th>
<th>Biopsy normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥150</td>
<td>411</td>
<td>400</td>
<td>97.8%</td>
<td>6/411 (1.5%)</td>
</tr>
<tr>
<td>100 - 149</td>
<td>138</td>
<td>122</td>
<td>88.4%</td>
<td>15/138 (10.9%)</td>
</tr>
<tr>
<td>60 - 99</td>
<td>143</td>
<td>119</td>
<td>83.2%</td>
<td>18/143 (12.6%)</td>
</tr>
<tr>
<td>21 - 59</td>
<td>369</td>
<td>196</td>
<td>53.1%</td>
<td>152/369 (41.2%)</td>
</tr>
</tbody>
</table>

The biopsy reports associated with very high tTG levels (≥150) that were not clearly positive for CD were examined individually. This revealed the following:
• Two results were equivocal, with one report saying that it “could be” CD, and the other saying that CD was “not excluded” and that results should be correlated with serology;

• One result showed evidence of a mild increase in intraepithelial lymphocytes only, but this biopsy was on a patient with a previous clearly positive biopsy who may well have been on a GFD;

• One result showed “blunted villi only” but this patient went on to have a further biopsy five months later that showed marked villous atrophy;

• One sample was called “peptic duodenitis” with findings of “varying degrees of shortening and flattening of villi”, a mixed inflammatory infiltrate in the lamina propria, but no increase in intraepithelial lymphocytes.

• Two normal biopsies were from young children aged 3- and 5-years old. The younger of these was biopsied five months after the high IgA-tTG level had been identified (so may well have no longer been consuming gluten), while there was a gap of 10 weeks for the other child.

• Three adolescents, aged 13, 16, and 19, also returned normal biopsies. One of these was performed six weeks after the IgA-tTG test result, another was almost four months later, and the third was eight months following the positive serology, with no further serology testing done in the interim.

• The other normal biopsy was from a 40-year old and was carried out 10 weeks after serology testing.

The profiles of those with normal biopsies and high IgA-tTG levels (100 – 149) were also reviewed. The time between serology testing and biopsy ranged between four and 14 weeks for this group of patients. Of the group, six were children aged 10-years or younger. One of these children had had a negative EMA test in association with the high IgA-tTG, and was later also found to be HLA negative. Two of the children went on to have clearly positive biopsies some years after the original, in the presence of persistently raised serology. One of the adults in the group had a number of biopsies over the years, some of which showed evidence of
CD, and others which were reported as normal. This patient had consistently abnormal serology.

Further analysis of the low-high tTG group was carried out by separating the results into smaller bands. As the IgA-tTG level went down, the number of biopsies that were normal went up. Similarly, the number of normal biopsies accounted for by patients with lower tTG levels was also higher. (Figure 6-23) The blue line represents the percentage of biopsies that were carried out on patients at each tTG level that were found to be normal, while the orange line shows the percentage of the total number of normal biopsies accounted for by patients with these tTG levels.

![Figure 6-23: Percentage of normal biopsies relative to low-high IgA-tTG levels](image)

When considering biopsy positivity at these lower IgA-tTG levels the situation was not surprisingly reversed. Only 38.0% of patients with an IgA-tTG level between 21 and 29 units had a positive biopsy. This increased to 53.7% for those with levels between 30 and 39 units, 65.1% for those between 40 and 49 units, and 66.7% once the level was between 50 and 59 units.

In addition to the patients with raised IgA-tTG levels, there were also nine patients who underwent biopsy with levels within the normal range (i.e. less than 21 units) but an EMA that was either positive, weak-positive, equivocal, or indeterminate. Of these nine patients, four had positive biopsies and the remaining five were normal. Two of the people with positive biopsies had positive EMAs, one had a weak-positive EMA, and one was indeterminate.

All EMA results for patients who had undergone duodenal biopsy were correlated with the outcomes of those biopsies. (Table 6.37)
Among the study population who had had an EMA test performed, this table demonstrates that 93.3% (695/745) of positive EMA tests were associated with a positive biopsy, and that 68.6% (127/185) of negative EMA tests were associated with a negative biopsy. Conversely, 29.2% (54/185) of patients with a negative EMA were found to have biopsy evidence of CD, constituting 6.7% (54/809) of those people with CD. And of those patients who had a positive EMA, 6.4% (48/745) had normal biopsies. These patients comprised 25.3% (48/190) of all those whose biopsies showed no evidence of disease.

A third group on whom duodenal biopsies were performed were patients who had been identified as being low or deficient in IgA. Across the three regions for which biopsy data were available this amounted to approximately 300 people, of whom 90 had duodenal biopsies. Within this group, four patients had two biopsy procedures, and another person had five procedures. Among these IgA-deficient patients, 16 were found to have biopsy evidence of CD. One of these had a normal biopsy initially, and then a repeat biopsy two years later that was reported as being consistent with CD. This equated to a CD positivity rate of 17.8% in this group.

The patient who had five endoscopies for biopsy was initially found to have villous atrophy and intraepithelial lymphocytosis attributed to CD. Subsequent biopsies were conducted with refractory CD being under consideration, presumably because the patient was not recovering as expected (this is inferred from the laboratory reports examined). This patient was, however, found to be HLA-DQ2 and DQ8 negative, and was tested twice to confirm this. One of these tests was
undertaken at the National Tissue Typing Laboratory, regarded as the most reliable of HLA test providers in New Zealand. The patient’s most recent biopsy was reported as being consistent with autoimmune enteropathy, an alternative, but rare, differential diagnosis for CD.

6.7.3 After positive biopsies

Details about the management of the patients with biopsy-proven CD were not discernible from laboratory data, although it was possible to determine who among them had subsequent tTG testing. From the data available it was apparent that 438 of the 897 patients (48.4%) with positive or inconclusive biopsies had had further tTG testing, and 411 (45.8%) had not. The remaining 48 patients included those whose biopsies were too recent for follow-up tests to be included in the dataset provided, and IgA-deficient patients for whom IgA-tTG testing is clearly not helpful. As already outlined earlier in this chapter, 87 patients (9.6%) also had repeat biopsies as part of their ongoing management, of which the majority showed an improvement from their initial investigation.

6.8 Incidence of Coeliac Disease

From the data available for Otago-Southland it was possible to calculate incidence rates for CD over the nine years between 2007 and 2015. This gives some indication of how readily the condition was being identified. Incidence rates were tabulated on the basis of positive biopsies alone, and in the year in which the biopsy was performed (as opposed to when serology was first positive). Total population, and male and female population figures were interpolated from 2006 and 2013 national Census figures.
Table 6.38: Biopsy-proven CD incidence in Otago-Southland, 2007 – 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Positive biopsies</th>
<th>Total population</th>
<th>Incidence rate per 100,000</th>
<th>Male incidence rate</th>
<th>Female incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>45</td>
<td>287,824</td>
<td>15.6</td>
<td>8.5</td>
<td>22.5</td>
</tr>
<tr>
<td>2008</td>
<td>70</td>
<td>289,424</td>
<td>24.2</td>
<td>14.0</td>
<td>34.0</td>
</tr>
<tr>
<td>2009</td>
<td>76</td>
<td>291,024</td>
<td>26.1</td>
<td>16.8</td>
<td>35.1</td>
</tr>
<tr>
<td>2010</td>
<td>75</td>
<td>292,624</td>
<td>25.8</td>
<td>13.2</td>
<td>37.6</td>
</tr>
<tr>
<td>2011</td>
<td>90</td>
<td>294,224</td>
<td>30.6</td>
<td>23.6</td>
<td>37.4</td>
</tr>
<tr>
<td>2012</td>
<td>96</td>
<td>295,824</td>
<td>32.5</td>
<td>18.6</td>
<td>45.8</td>
</tr>
<tr>
<td>2013</td>
<td>72</td>
<td>297,423</td>
<td>24.2</td>
<td>14.4</td>
<td>33.6</td>
</tr>
<tr>
<td>2014</td>
<td>98</td>
<td>299,023</td>
<td>32.8</td>
<td>17.1</td>
<td>47.8</td>
</tr>
<tr>
<td>2015</td>
<td>93</td>
<td>300,623</td>
<td>30.9</td>
<td>15.0</td>
<td>46.3</td>
</tr>
</tbody>
</table>

It is apparent from these data that the annual incidence of biopsy-proven CD in Otago-Southland almost doubled between 2007 and 2015, with a pronounced increase in diagnoses among women.

Age-standardised incidence figures were also calculated. Census age-related data are presented in 5-year blocks, so these were combined into 15-year groupings for ease of presentation. (Table 6.39)

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence rate per 100,000 by age-band</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 15 years</td>
</tr>
<tr>
<td>2007</td>
<td>14.9</td>
</tr>
<tr>
<td>2008</td>
<td>35.2</td>
</tr>
<tr>
<td>2009</td>
<td>33.3</td>
</tr>
<tr>
<td>2010</td>
<td>35.1</td>
</tr>
<tr>
<td>2011</td>
<td>35.1</td>
</tr>
<tr>
<td>2012</td>
<td>27.6</td>
</tr>
<tr>
<td>2013</td>
<td>36.8</td>
</tr>
<tr>
<td>2014</td>
<td>31.2</td>
</tr>
<tr>
<td>2015</td>
<td>36.6</td>
</tr>
</tbody>
</table>

As displayed in this table, age-related diagnoses of CD have fluctuated over time, although the overall trend is that they have increased since 2007 across all ages (as grouped here). This is most noticeable in the 15- to 29-years old age-group. (The population has increased in each of these age-bands except for the 30- to 44-years old group, in which it fell by over 4000 between the 2006 and 2013 censuses.)

The overall population incidence rates and gender-specific rates were calculated for Nelson-Marlborough and South Canterbury for the three years for which data were available. (Table 6.39) The 2013 rates may underestimate the true situation because there may have been biopsies conducted that year as a consequence of testing that had been done in 2012 at an alternative laboratory provider. These tests would not have appeared in the SCL data provided and therefore in subsequent searching for biopsy results.

<table>
<thead>
<tr>
<th>Year</th>
<th>Positive biopsies</th>
<th>Total population</th>
<th>Incidence rate per 100,000</th>
<th>Male incidence rate</th>
<th>Female incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson-Marlborough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>24</td>
<td>136,995</td>
<td>17.5</td>
<td>15.0</td>
<td>19.9</td>
</tr>
<tr>
<td>2014</td>
<td>21</td>
<td>137,985</td>
<td>15.2</td>
<td>17.9</td>
<td>12.7</td>
</tr>
<tr>
<td>2015</td>
<td>32</td>
<td>138,975</td>
<td>23.0</td>
<td>11.8</td>
<td>33.6</td>
</tr>
<tr>
<td>South Canterbury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>7</td>
<td>55,626</td>
<td>12.6</td>
<td>3.7</td>
<td>21.2</td>
</tr>
<tr>
<td>2014</td>
<td>8</td>
<td>55,876</td>
<td>14.3</td>
<td>21.9</td>
<td>7.0</td>
</tr>
<tr>
<td>2015</td>
<td>6</td>
<td>56,126</td>
<td>10.7</td>
<td>18.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The three year period encompassed by these data is too short to determine any consistent trends in practice. It is evident that incidence rates have varied in both regions over that time, particularly with respect to gender. It is highly likely that the lower South Canterbury rates will also have been affected by that region’s lower biopsy rates of patients with positive IgA-tTG tests.

6.9 Key findings of the study

Enormous amounts of data were available for analysis for this component of the overall study. The important findings they revealed are summarised as follows.

6.9.1 Rates of testing

The numbers of tests performed and the number of people being tested for CD in Otago-Southland steadily increased over the period of time considered in this study: from 1.4% of the population in 2007 to 1.9% of the population in 2015, (p<0.0001). In Nelson-Marlborough rates also increased in the three years analysed, while they fell over that time-period in South Canterbury. By 2015, the proportions of the population tested in the year in all three regions were not significantly different.
6.9.2 Who was tested?

Throughout the period analysed, in all regions from which data were available, women consistently outnumbered men with respect to testing for CD. Over time the differences in proportions of men and women having a first test for CD in Otago-Southland narrowed slightly.

Patients being tested were grouped as children or adults, with children being all those under the age of 17-years old. In Otago-Southland, the mean and median ages for children being tested were both between 8- and 9-years old, with both increasing slightly over time. The adult mean age ranged between 41 and 42 years, and the median between 40 and 42 years. When the populations being tested were grouped according to age, it was apparent the younger cohorts (up to 17-years, and 17- to 26-years old) were tested more frequently. All cohorts showed an increase in testing over time. Mean and median ages for both children and adults were higher in Nelson-Marlborough and South Canterbury, and in Hawkes Bay and Taupo.

In all regions by far and away the majority of people tested were of New Zealand European or Other European ethnicity.

6.9.3 Who did the testing?

Over the years analysed in Otago-Southland between 74.2% and 79.8% of test requests arose in general practice. In Nelson-Marlborough more than 80% of tests were GP-initiated, while in South Canterbury the figure was around 80%. Gastroenterologists and paediatricians were the two next most frequent test requesters.

6.9.4 Which tests were done?

The tests performed as part of coeliac antibody testing were largely determined by laboratory protocol. In the period under investigation this almost always included IgA-tTG antibody testing, and sometimes included testing for EMA.

Testing for HLA-DQ2/DQ8 was done on the basis of practitioner requests. These showed a steady increase throughout the study period. In Otago-Southland and Nelson-Marlborough, a small number of practitioners accounted for the majority of test requests, while in South Canterbury they were more evenly spread across a number of providers.
6.9.5 What was found?

The proportion of positive IgA-\( \text{tTG} \) antibody tests among patients being newly tested for CD in Otago-Southland peaked in 2008 at 4.01%, and fell steadily from then to 3.00% in 2015. Proportions of positive tests in Nelson-Marlborough and South Canterbury in 2015 were not significantly different from this.

Among men and women the rates of positive tests varied from year to year, but were not significantly different between the two groups in any year. With respect to age, children had higher rates of positive tests than adults, and this difference reached statistical significance in some years, and for the time-period overall.

6.9.6 What happened next?

In Otago-Southland between 2006 and 2015, more than 2000 people had more than one test for CD in any one year. This included several patients who had multiple tests. More than 7000 people had CD tests in more than one year, the vast majority of whom had negative tests.

6.9.6.1 Duodenal biopsies

Rates of patients going on from a positive IgA-\( \text{tTG} \) test to duodenal biopsy fluctuated from year to year, and depending on the IgA-\( \text{tTG} \) level. The lowest rates of biopsy were among those with test results in the low-high range (i.e. between 21 and 59 units). Between 2007 and 2015 biopsy rates increased for all IgA-\( \text{tTG} \) result groupings. Biopsy rates in Nelson-Marlborough appeared to be comparable to those in Otago-Southland, but those in South Canterbury were lower than both the other regions.

In Otago-Southland women had higher rates of biopsy overall, as opposed to the other two regions where men tended to have higher rates. The lower rates of biopsy among women in South Canterbury were statistically significantly different from rates in the other two regions.

With respect to the outcomes of biopsies, 97.8% of patients who were biopsied with very high IgA-\( \text{tTG} \) antibody levels (i.e. \( \geq 150 \) units) returned a positive result. This level of positivity among biopsies fell to 88.4% for IgA-\( \text{tTGs} \) in the 100 to 149 unit range, 83.2% for those between 60 and 99 units, and 53.1% for results between
21 and 59 units. Among IgA-deficient patients who were biopsied, 17.8% were found to have biopsy evidence of CD.

Following positive biopsies, 48.4% of patients had further IgA-tTG testing, and 9.6% went on to have repeat biopsies.

6.9.7 Incidence of CD

The annual incidence of biopsy-proven CD in Otago-Southland increased from 15.9 per 100,000 in 2007, to 30.9 per 100,000 in 2015. Among women the increase was from 22.5 to 46.3 per 100,000, while for men it was from 8.5 to 15.0 per 100,000. Incidence rates fluctuated within different age-groups, but over the same period of time all age-groups saw an overall increase in diagnoses.

In Nelson-Marlborough the 2015 incidence was 23 per 100,000; 11.8 and 33.6 per 100,000 for men and women respectively. In South Canterbury the 2015 picture was somewhat different, with an overall CD incidence of 10.7 per 100,000; 18.2 per 100,000 among men, and 3.5 per 100,000 among women.
Chapter 7: Discussion

7.1 Introduction

As set out in Chapter One of this thesis, this project evolved out of a desire to determine what GPs in New Zealand know about CD. The central hypothesis was that GPs in this country have limited disease-specific knowledge about the condition, and that this might be apparent across the three domains of recognition, diagnosis, and management. The central investigation designed to test this hypothesis was the survey of GPs, the results of which were presented in Chapter Five. To offer some context in which to interpret the findings of the survey, New Zealand gastroenterologists were also surveyed, and an audit of laboratory data was conducted to provide some evidence with which GPs’ reported practices could be corroborated (or not).

This chapter first considers the strengths and limitations of the project as a whole, and of its constituent studies, and then discusses the findings that emerged from each of them. It explores how these relate to the recent literature discussed in Chapter Two, and some of the implications that ensue with respect to each of the major facets of care relating to CD: recognition, diagnosis, and management.

7.1.1 Overall strengths and limitations

This is the first time that primary care practitioners anywhere have been investigated in this way with respect to CD. It is also the first time data from three separate sources such as those described have been brought together to enable such a thorough exploration of the topic. As such, this work has much to contribute to ongoing discussions about CD, and the overall project benefits from the fact that data were drawn from several sources, enabling the central questions to be examined from different perspectives. Evidence gathered from each investigation has been able to be used to inform the interpretation of data from the other investigations, permitting more robust conclusions to be drawn. The extensive literature relating to CD has also been thoroughly reviewed, providing a comprehensive context in which to situate this project.

However, the scale of the work involved in managing three separate studies, and the vast body of background material, meant that the project as a whole has
been affected by the length of time it has taken to bring it to its conclusion. This is especially so with respect to the application of data gathered from the survey of gastroenterologists, which was conducted early on. It is reasonable to expect that some of the practices of gastroenterologists identified through this survey may have changed in the interim, particularly with the emergence of recent guidelines documents relating to CD. The breadth of territory covered in these studies has also meant that it has not been practical to thoroughly explore every interesting finding that emerged. That task will continue into the future.

7.1.2 Strengths and limitations of the survey of gastroenterologists

The strengths of the survey of gastroenterologists lie in the rigour of its development. Before implementation, the tool that was to be used was critically appraised and then reworked to address areas of ambiguity, and so that it more readily suited the New Zealand environment. It was pre-tested and pilot-tested, and amended following each of these events. In addition to this, exhaustive searches were undertaken to identify eligible participants, and multiple attempts were made to engage them, via a range of different approaches. These efforts generated a response rate of approximately 55%, which is a very reasonable representation of the New Zealand gastroenterologist population at the time.

Beyond gender and region of work, it was not possible to determine how gastroenterologist non-respondents might have differed from those who participated, but it seems unlikely that they would have included many more people with a specific interest in CD, or who saw large numbers of patients with CD for long-term management. Respondents diverged in their views on a number of issues canvassed in the survey, and there is no reason to believe that non-respondents would have been any more or less likely to agree on these matters. Given that there were few response outcomes that differed significantly according to any of the demographic variables investigated, it seems unlikely that differences (or similarities) in demography would be a source of non-response bias.

Surgeon endoscopists and gastroenterology trainees were also invited to take part in this survey, and their absence (in the case of the surgeons) or very low numbers (with respect to trainees, whose responses were subsequently excluded from analysis) means that results from this survey cannot be generalised to apply
to these groups, which is a limitation. While surgeons are unlikely to be involved in the management of CD, it is not inconceivable that they will occasionally make the diagnosis in patients referred to them for upper endoscopy. It is uncertain whether such patients would then be referred to a gastroenterologist or back to their GPs for follow-up. It is reasonable to conclude that, as with the gastroenterologists, there would be variations in practice within groups of surgeons and trainees. In all probability variations will also occur between the three groups of practitioners, adding to the mixed messages being communicated to patients and GPs, especially about how best to manage CD.

A further strength of the survey was in the high levels of consistency in responses to questions that explored the same issue from slightly different perspectives (e.g. the place of rebiopsy in Lucy’s follow-up and in general, presented in Figure 4-5, Chapter Four). This suggests that the survey instrument was reliably measuring what it was intended to measure.

Additional possible limitations of this study reside with the more general limitations of using surveys to measure practitioner behaviour. As has been pointed out in the literature, and discussed in Chapter Three, survey-based studies tend to lead to an over-estimation of participants’ practice. Every effort was made to mitigate this possibility by using vignettes to provide context, and by framing the closed-question scales in terms of how likely participants would be to undertake a particular action, rather than asking them to identify which actions they would take for any given scenario.

7.1.3 Strengths and limitations of the survey of GPs

As with the survey of gastroenterologists, the strengths of the survey of GPs also lie in the attention that was paid to its development, and to addressing each of the four potential sources of survey error identified by Dillman. This included using the most comprehensive database available from which to draw potential participants; adopting a stratified sampling technique to ensure equal representation across DHBs, rural and urban areas, and by gender; using an incentive and several other design techniques to encourage recipients of the survey to complete it; and pre-testing and pilot-testing both the content and format of the
hardcopy version to minimise the risk of participants misunderstanding questions and therefore giving inaccurate responses.

Another strength was in the response options for the Likert-type scales for several questions that separated out the “almost never” option into three variants. This allowed for a more nuanced interpretation of these responses, particularly with respect to participant knowledge, the key area of interest for the survey.

Utilising both online and hardcopy formats emerged as a strength, by providing different access points for participants. This enabled a broader range of people to be invited to participate and gave people the option of completing the survey in their preferred mode of response. The increasing appeal of completing surveys online was evidenced by early responses to the initial invitation to participate that also included a link to the survey itself, and by the fact that more than half of completed responses were online. Having an online option also reduced the costs of sending out hard copies, as people who had already responded online were able to be removed from the mailing list. It also meant that the timing of when the request to participate was received could be managed. Thus the online survey was sent at lunchtime on a Thursday: not on a Friday, when GPs are often busy in the lead-up to the weekend, but close enough to the weekend that potential participants might remember that it was awaiting their attention; and not at the end of the day when people are often trying to get their day’s work finished so that they can head home.

The principal disadvantage of having two versions of the survey was that it led to differences in what participants were completing. While one of these differences (namely the inclusion of altered liver function tests as an indication for testing for CD in the paper-based version but not in the online format) arose due to human error, and therefore could have been prevented, others arose because of inherent limitations in how questions could be formatted online. This was particularly the case when the Likert-scale options invited comment within them. (See, for example, Appendix F, Part A, question 16.) This could easily be accommodated in the hardcopy version, but necessitated the use of separate questions online. When it came to merging survey responses from the two formats, special care had to be taken to ensure that this was done accurately for these questions.
There were advantages and disadvantages with both formats. Paper-based versions allowed participants to annotate their answers with comments, many of which gave additional insight into responses. However, it also enabled respondents to skip questions, and/or to select more than the requested number of responses to individual questions. This made coding completed surveys challenging, and necessitated making judgement calls about what could and could not be included. In one case several questions were not answered and it appeared that the explanation for this was that the respondent had inadvertently turned over two pages together, completely overlooking that part of the survey.

On the other hand, the online version was configured such that respondents had to answer each question before moving to the next, and could only give one answer per question. This had both positive and negative consequences. It meant that those who completed the survey answered all questions, and that coding their responses was straightforward. But it also led to some people not finishing the survey – evidently giving up part way through. While it is not possible to know why those people did not finish, it is conceivable that this was in part due to not being able to leave out questions they did not feel able to answer, or where they would have liked to give a more nuanced response than was possible (e.g. by selecting two answers, and/or annotating their response).

A problem specific to this survey that emerged as it was underway was the lack of a “don’t know” option for several of the questions. As noted in Chapter Five, at least one person indicated that he would not participate because of this, and he is unlikely to have been the only person who felt this way. This absence was not identified as an issue in pilot-testing of the survey. On reflection it seems likely that this was because the group of people who participated in the pilot had a greater than average knowledge about CD (having heard several presentations about it at a range of local continuing medical education events) and could therefore complete the survey without having to resort to a “don’t know” response. This was completely unforeseen at the time pilot-testing was being undertaken.

7.1.3.1 Generalisability of results and non-response bias

The interpretation of results from the survey of GPs is limited by the response rate of 35.5%. While this level of response is better than other recent surveys of
GPs,\textsuperscript{452,453} and the large study sample group means that a substantial number (n=692) of completed surveys were available for analysis, it nonetheless raises issues about the generalisability of results.

There are multiple reasons why intended recipients in a study may not complete a survey, some of which may lead to bias, and some of which are less likely to do so. These include survey fatigue, being too busy, and not being interested in the topic.

A variable that is unlikely to contribute to bias is having a blanket policy not to complete surveys. Such a position may be held by practices, such that staff opening mail for intended recipients do not pass on any surveys received, or by individual practitioners. The respondent who wrote about surveys being used to “pillory GPs” quoted in Chapter Five exemplifies this, although this view is perhaps somewhat more negative than others. A Canadian study published in 2012 found that more than a third of physicians to whom they sent a survey had an office policy not to participate.\textsuperscript{458} That figure is not known for New Zealand.

More likely to lead to bias in survey results are those people who choose not to participate in surveys on a case-by-case basis. This decision may simply be a reflection of how busy the potential participant is at the time, but may also arise because he or she does not feel they have enough knowledge to take part. In a survey such as the present one, in which knowledge was being assessed, such decisions will have influenced the overall outcomes. Another reason for not participating may be perceived relevance of the study to the practitioner. The person who wrote saying that he had “not seen one patient with this condition” in 50 years of practice perhaps falls into this category. This is a somewhat surprising assertion and could indicate a failure to recognise CD in his patients. It seems plausible to conclude that his knowledge about CD was limited (corroborated by his comment that his patients with DH all “had gluten allergy”) but, because he chose not to participate, this was not captured by the study.

With respect to the generalisability of data gathered in the survey of GPs, one other fact warrants consideration. In this survey, women outnumbered men, both in terms of the overall proportion of participants (60.7% female and 38.9% male), and in terms of proportions of intended recipients who completed the survey (44.6% female and 26.9% male). On analysis of survey data it became apparent that
gender did have a statistically significant impact on several responses, which fact must be borne in mind when drawing conclusions about the outcomes that emerged.

7.1.4 Strengths and limitations of the laboratory data study

The great strength of the laboratory study was that an extensive set of “real world” data was available for investigation, as opposed to data that had been generated specifically for the purposes of research. For Otago-Southland, blood testing data were complete for a substantial period of time enabling an accurate picture to be drawn about the investigation of CD in that region. The availability of data from other regions, though limited, enabled cautious comparisons to be drawn.

For the purposes of this study as it was initially conceived, it was a limitation that data on testing for CD are not collected and collated at a national level. However had such a dataset existed it may well have been unmanageable in size. And while perhaps not a limitation, it was certainly a challenge to have to individually search for duodenal biopsy results. In addition to this, the lack of a central repository of information about patients who had undergone duodenal biopsy did mean that those with normal blood tests but positive histology have not been identified. A further limitation was lack of access to information from the alternative laboratory providers in Hawkes Bay and Taupo, meaning that data from those regions were incomplete thus limiting the conclusions that can be drawn from them.

7.2 Recognising Coeliac Disease in New Zealand

The principal vehicle for investigating the recognition of CD in New Zealand in this study was the survey of GPs. Specifically, the first series of questions asked respondents to indicate how likely they would be to test for CD given certain clinical situations. Evidence of testing rates from 2007 to 2015 that emerged from the laboratory study are also of relevance when considering whether or not recognition may have improved over time.

7.2.1 GP survey data

Results from questions One and Two in the GP survey paint a mixed picture. It is clear from the data they generated that there are some presentations that are well recognised as being indicators of potential CD. These include patients presenting
with chronic diarrhoea, or iron deficiency anaemia, or having IBS or a first-degree relative with CD. In each of these circumstances, and in the situation of a patient presenting with two or more of the symptoms that were cited in the question, a very clear majority of respondents indicated they would be likely or highly likely to test for CD. A clear, but slightly smaller majority were also likely or highly likely to test patients with persistent fatigue or unexplained folate deficiency.

Chronic diarrhoea has long been associated with CD and, as a signifier of malabsorption, comes within the Oslo definition of classical coeliac disease. It is not surprising therefore that it is a presentation that is highly likely to trigger GPs to test for CD. It is also not unreasonable to expect that non-respondents to the survey would be similarly likely to test affected patients.

The other symptoms or conditions that were most likely to lead to testing could be regarded as representing a broader understanding of the manifestations of CD. It is therefore encouraging to see such high numbers of respondents indicating a high likelihood of testing under these circumstances. This might suggest that knowledge of CD has expanded to encompass non-classical and potentially asymptomatic variants of the condition. However, it cannot be expected that non-responders to the survey would be as likely to test in these situations, if one of the principal reasons for non-participation could have been lack of knowledge about CD.

It is less encouraging that far fewer respondents indicated they would be likely to test in the presence of other symptoms and conditions also known to be associated with CD, and that for some of these, the majority indicated they would be unlikely to do so. These include abnormal liver function tests, unexplained neurological symptoms, T1DM, autoimmune thyroid disease, Down Syndrome, and Turner Syndrome. Some of these conditions also drew higher numbers of neutral responses, one interpretation of which is that participants were unsure of their relevance to CD. Vavricka et al. found that the delay to diagnosis that many patients with CD experience is largely attributable to their doctors failing to consider it as a possibility. These findings suggest that for patients with less clear-cut presentations this may well remain the case in New Zealand.

As discussed in Chapter Two, the NICE Guidelines (and others) relating to testing for CD make clear recommendations that testing should either be offered, or
at least considered, in any of the situations cited in the preceding paragraph. At the
time the survey was conducted the 2015 NICE guidelines had yet to be released. The
questionnaire itself was based on the 2009 version. On comparing these directly
with participant responses, it is reassuring to see that the majority of “should do
testing” scenarios that had been included in the first two questions of the survey did
in fact elicit high levels of likely or highly likely to test responses. This was especially
the case for symptoms and signs (Question One), but much less so for associated
conditions (Question Two). And although this study is not directly comparable with
that of Spencer et al. referred to in Chapter One, these data suggest that New
Zealand GPs are more likely to test for CD in patients with iron-deficiency anaemia
than their North American counterparts.

As discussed in Chapter Five, in an effort to gain a more global impression of
likely testing patterns, participants’ responses for each row of the question matrices
were collated, and their cumulative scores tabulated and grouped. (Figures 5-9 and
5-10) Appropriate score ranges for both questions were defined, and participants’
cumulative scores analysed to determine whether they sat above, below or within
these ranges. This process necessarily involved making somewhat arbitrary
decisions about values to assign to each symptom, sign, or condition, thus results
should be interpreted with caution. Nonetheless, the impression these scores give
is that despite there being some presentations that are highly likely to trigger
testing, in general respondents to the survey were likely to be under-testing for CD.
As reported in Chapter Five, the mean cumulative scores for each question were
both within the “possibly under-testing” range. With respect to presenting
symptoms, just under 34% of participants were in the “likely to be appropriately
testing” range, while only 26% scored similarly with respect to associated
conditions.

The gender of participants was significantly associated with overall testing
patterns, but rurality, and whether or not they had patients with CD was not. On the
whole, female participants were more likely to test for CD in a wider range of
settings than their male counterparts, and their mean cumulative scores for both
symptoms and conditions were significantly higher. Perhaps not surprisingly,
already having patients with CD also appeared to influence likelihood of testing,
although this was also found to be impacted upon by gender. Given that women
were over-represented in this survey, it is likely that the results may somewhat overstate the level of recognition of possible CD in the wider GP community.

7.2.2 Laboratory data

Data on rates of testing derived from the laboratory results reported in Chapter Six would tend to support the suggestion that the recognition of CD is indeed expanding, at least in some regions. Rates of new-patient testing for CD steadily (and significantly) increased in Otago-Southland between 2007 and 2015, and over the same period overall rates of testing at the SCL community laboratory also increased in the Hawkes Bay. Between 2013 and 2015 testing rates in Nelson-Marlborough also increased, although this time period is too short to enable any firm conclusions to be drawn about trends.

The Otago-Southland data are complete for the region for the period 2007 to 2015. The majority of requests originated in general practice, and there was an overall increase in this proportion over time, suggesting an increased awareness of the condition among GPs. However, additional factors may also have contributed. Firstly, there may have been an increase in CD prevalence in the region, leading to more patients presenting with symptoms suggestive of the condition triggering a test request (although this too requires the person requesting the test to have recognised such symptoms). An increase in prevalence would be consistent with studies from elsewhere in the world that have identified this.\textsuperscript{210,211,213} It is also likely that some of the increase in testing will have arisen due to patient request, as CNZ have worked to raise the profile of CD in the general population. In the survey of GPs, 8.8% of respondents cited “patient request” as a reason for testing for CD.

In contrast, rates of testing fell in Taupo between 2008 and 2015 (although these data were incomplete), and in South Canterbury between 2013 and 2015. It is not clear why this might be. In Taupo it is conceivable that a proportion of the fall is accounted for by increasing numbers of patients being tested in laboratories other than SCL, and it is not possible to know how many people this might have involved. In South Canterbury, as for Nelson-Marlborough, the time period under consideration was too short to draw any meaningful conclusions on this issue. One possible explanation is that more people had been tested in the period leading up
to 2013, meaning the pool of untested patients in the study period was smaller, and therefore fewer people required testing.

Of note, the data from all the regions included in the dataset provided by SCL clearly show that practitioners in this country are almost exclusively testing New Zealand (and other) European people for CD. The survey of GPs did not explore this issue, but these data suggest that looking for CD in people from other ethnic groupings is not something that GPs do often. This is despite the fact that it is now well recognised that CD affects people from a range of countries beyond those in the UK, Europe and Scandinavia.

Consistent with earlier research by Evans et al., the laboratory data also show that women were tested at twice the rate of men across all but one of the regions investigated. (In South Canterbury the ratio of testing was somewhat lower, but women still clearly outnumbered men among those being tested.) Evans et al. offered some thoughts about why this might be the case in their study, taking the position that CD “is equally prevalent in men and women” as their starting point. Their reasoning included that women are more likely than men to seek medical advice for gastrointestinal symptoms, and that pre-menopausal women have a higher incidence of iron deficiency and testing for CD may form part of the assessment of that. As discussed in Chapter Two, it is now more widely accepted that CD probably occurs more frequently in women, which, along with the reasons suggested by Evans et al., might explain their more frequent testing in this study. It may also be that GPs are less likely to associate CD with their male patients so are less likely to test them for it. However, if the testing of men is only done at a higher symptom threshold (that is, when CD is symptomatically more likely) than for women, one might have expected the proportion of positive tests for men to be higher than those for women. The data available in this study do not support that hypothesis.

The Evans study also noted that over the decade of their investigation the proportion of positive coeliac serology tests fell from 5.7% to 2.6%. They postulated that, coupled with their finding of increased rates of testing, this was likely to be due to testing being requested “at a lower symptom threshold”. Similarly in their study in Wales, Hurley et al. noted a fall in the rate of positive tests from 5.8% in 1996 to 1.1% in 2005, again in the context of a substantial
increase in the overall numbers of tests being requested. In the present study the proportion of positive tests also fell, but not to a significant extent. In the later years for which data were available, the proportion of positive new tests in Otago-Southland was stable at around 3.0%, while the number of tests requested in each year continued to increase. This might suggest that practitioners requesting tests in this region have a slightly higher symptom threshold for testing than their UK counterparts had, or perhaps that they are getting gradually more accurate in identifying possible CD.

7.3 Diagnosing Coeliac Disease in New Zealand

Having recognised that CD may be a possibility for a patient, the next step on the path to making the diagnosis is to appropriately test for it, and correctly interpret the results of tests undertaken. The survey of GPs explored both these issues, and the laboratory data provide some supporting evidence about the actual practice of clinicians in some regions in New Zealand. The survey of gastroenterologists also investigated the actions that practitioners would be likely to take, and the advice they would be likely to give to a GP when the diagnosis was uncertain.

7.3.1 Testing for CD: Survey data

As presented in Chapter Five, there is little uncertainty among GPs about how to test for CD, with the majority of respondents to the GP survey indicating they would request “coeliac antibodies” from their laboratory provider, or would specify that they wanted to test tTG and/or EMA antibodies. Few would request DGP antibodies, suggesting that this is a test that most are not yet familiar with, while reassuringly only three people indicated they would request the now obsolete gliadin antibodies. It is probable that non-respondents to the survey would be similarly familiar with the tests to request for CD, although the number who might still want to do gliadin antibody testing may be higher. Laboratory protocols are now such that this test is no longer available, and patients will generally be tested for CD with a predetermined panel of investigations.

Participants’ understanding of the role of HLA-DQ2/DQ8 testing in the diagnostic process is perhaps less clear, with a small number of respondents indicating they would include this in their initial work-up. As discussed in Chapter
Two, this approach has been suggested by some, and can be useful in certain settings when excluding CD would be helpful, but is not recommended in any of the current guidelines pertaining to adults. A small number of participants commented that they would request an HLA test as a follow-up test for clarification, but from the data available it is not possible to determine why those who indicated they would request an HLA test as part of their initial testing would do so.

Of more concern with respect to testing for CD was the finding that almost half of all respondents would test someone who was already on a GFD. The majority of these respondents indicated they would recommend that the person re-introduce gluten into their diet, but would test anyway even if the patient refused to do so. This implies a lack of clarity of thinking around the necessity of a person consuming an adequate amount of gluten for CD testing to be reliable. (Laboratory evidence that small numbers of children who would not yet be old enough to be consuming gluten had been tested for CD supports this suggestion). The survey did not explore the issue further by asking what value participants saw in testing patients who were not consuming gluten, and nor did it explore how participants would interpret test results in this setting.

Perhaps not surprisingly, the small number of respondents who would simply test without making any recommendation about restarting gluten were statistically more likely to have no coeliac patients under their care. Whether or not this is clinically significant is arguable. It is reasonable to assume that doctors with patients with a particular condition are likely to have increased knowledge about that condition, but which is cause and which is consequence is difficult to determine. However, it is at least conceivable that it is lack of knowledge (as evidenced in this instance by apparently not being aware that a patient should be consuming gluten for CD testing to be reliable) that has led to some of these respondents not having any patients with diagnosed CD. Assuming that this survey somewhat overestimates practices with respect to CD (as discussed earlier), this would at least make this a potentially clinically significant finding.

7.3.1.1 The gluten challenge

An issue related to testing patients who have already excluded gluten from their diets is that of what constitutes an adequate gluten challenge. This was canvassed
in both the GP and gastroenterologist surveys and drew a range of responses from both groups. The majority of gastroenterologist respondents would recommend that adults consume somewhere between two and four slices of wheat-bread daily for at least four weeks, while GP respondents were divided between those who did not know, and those who thought similarly to the gastroenterologists.

As discussed in Chapter Two, until relatively recently the suggested gluten challenge was four slices of bread daily for six weeks. In recent years this recommendation has been modified such that, with the exception of the 2015 NICE Guidelines, guidelines now advocate a less onerous regime of 1.5 slices of bread daily for at least two weeks, longer if the patient can tolerate it. Among the options suggested by the gastroenterologists and those GPs who were prepared to commit themselves to an answer on this, the vast majority fell within parameters that would be likely to enable CD to be detected (if the patient were able to complete the recommended challenge). The fact that there are variations in practice is therefore likely to be of little clinical significance. This is apart from the possibility that such apparent inconsistencies between practitioners may lead to patients’ loss of confidence in their doctors, when they talk among themselves and learn that their treatment was different from each other’s.

For those GPs who indicated that they did not know what constituted an adequate gluten challenge there are a range of resources available for them to consult, although it may take some searching to find them. In New Zealand, DHBs are increasingly moving to utilising HealthPathways, an online tool for guiding clinical practice and, in particular, referrals into the secondary care setting. Many now have a pathway for CD, and these include information about the gluten challenge, however these vary between regions. When accessed in late 2017, two DHBs advised two slices of bread daily, while the remainder advised four (either precisely or “about”), while the recommended duration ranged between four and six weeks.

1 See www.healthpathways.org.nz
7.3.2 Testing for CD: Laboratory data

Given that laboratory protocols determine which of the coeliac antibody tests will be performed in the investigation of CD, the most interesting data with respect to testing to emerge from the laboratory study pertains to testing for HLA-DQ2/DQ8. This is a test that is conducted on request, thus giving potential insight into practitioner knowledge.

From the Otago-Southland data it would seem that awareness about HLA testing is increasing. This is evidenced by the fact that early in the study period approximately half of all HLA tests were done following a laboratory recommendation to do so, but by the final year of the study this figure had fallen to less than one-third. But the data also show that throughout the study period only a relatively small proportion of the practitioners who tested for CD ever requested HLA testing, and that a very small number of individuals accounted for the majority of these test requests.

Collectively these data, along with data from Nelson-Marlborough and South Canterbury, suggest that knowledge about the place of HLA-DQ2/DQ8 in the wider context of testing for CD remains patchy. It is apparent that there are a small number of practitioners in each region (of whom not all are GPs, and none are gastroenterologists) who are requesting it more frequently than the guidelines indicate is appropriate. But it is not unreasonable to assume that at least some practitioners now recognise that it does have its place, for example when being able to exclude CD is important. The fact that the majority of people who have tested for CD have never requested an HLA-DQ2/DQ8 test may well reflect the fact that they are aware that its role is limited, but it may also be that some of them do not know that the test exists, or that as GPs they are allowed to request it.

One other finding of note that arose from these data is the thousands of people with negative IgA-tTG antibody tests who had multiple tests over the years. While HLA testing could have a role in limiting the number of patients having such repeat testing, these data suggest that there is a need for clearer recommendations to guide the practice of clinicians with patients experiencing persistent symptoms possibly attributable to CD, who repeatedly have negative serology tests. Given that the survey of GPs elicited that many respondents would test for CD in patients already
on a GFD, such recommendations should include a reminder that consuming adequate amounts of gluten is a pre-requisite for an accurate test.

7.3.3 Diagnosing CD: Survey data

Perhaps the most crucial step in correctly diagnosing CD lies in the interpretation of CD test results, and the actions that follow that. In the survey of GPs this was investigated from two angles: the frequency with which respondents referred people with positive serology for upper endoscopy, and the combinations of results they would be likely to accept as confirming that a patient does indeed have CD.

In line with current and previous guidelines, a clear majority of respondents indicated that when a patient returned a positive serology test they referred for gastroscopy almost always or most of the time. A clear majority of respondents also indicated they advised patients to continue to eat gluten until after they had had their gastroscopy. This stands in contrast to the findings of Spencer et al., who found that 80% of family medicine doctors in North America were likely to implement a GFD prior to patients with positive serology undergoing endoscopy. Given that these are longstanding expectations relating to the diagnosis of CD, it is to be hoped that in New Zealand people who did not participate in the survey behave similarly to those who did take part, although there is no certainty that this will be the case.

These issues also drew a large number of comments, many of which made it clear that access to timely endoscopy is often problematic, and that this had an impact on participants’ advice about continuing to eat gluten. Patient reluctance to undergo endoscopy also influenced referral practices. There was clearly also a degree of misapprehension about the correlation between symptoms and pathology, with a small group of participants noting that whether or not they referred for endoscopy would depend on the presence and/or severity of symptoms. Comments also illustrated some confusion among respondents regarding the reason for arranging duodenal biopsy. Two people indicated that the reason for confirming the diagnosis with a biopsy was in order for patients to be able to access subsidised gluten-free foods, and that now that these were much more readily available in supermarkets, there was no longer any need to do so. Although these last two factors appeared to influence the referral decisions of
relatively small numbers of participants, it is very likely that there will be others among those who did not complete the survey who think similarly.

In a related question, participants were asked to rate how likely they would be to accept a range of combinations of results as confirming the diagnosis of CD. This question is perhaps the best indicator of patchy knowledge about the condition. Thus, while almost all respondents would accept positive serology followed by positive duodenal biopsy as confirming the presence of CD (and those who did not had very likely reversed the polarity of question’s measurement scale), almost three-quarters would also be likely (or highly likely) to accept positive serology followed by an improvement in symptoms on a GFD as being sufficient to confirm the diagnosis. As presented in Table 5.11 and Figure 5-18 in Chapter Five, almost two-thirds were likely or highly likely to accept positive serology along with positive HLA-DQ2/DQ8, and a clear majority responded similarly with respect to positive serology that returned to normal on commencing a GFD. A majority indicated that they would be likely or highly likely to accept positive serology alone as confirmation that a patient had CD.

The question did not tease out these issues more carefully by, for example, putting numerical values on the positive serology. To do so would have rendered it unwieldy. It is entirely possible that the degree of positivity of serology does influence participants’ behaviour such that they might be more likely to rely on serology alone if it were very high. The laboratory data, which will be discussed in the next section, suggests that this may be a reasonable approach to take, but it also indicates that this is not in fact how many GPs appear to behave. Nor did this particular question allow scope to include patient preference, so it is also reasonable to accept that actual practice is more nuanced than implied by these results, and would depend on variables other than the options given. Nonetheless it is also not unreasonable to conclude that many respondents were unclear about the reliability of serology, symptoms, and response to a GFD as being indicative of the presence of CD, and that this uncertainty is likely to be more prevalent among those who chose not to participate in the study. The risk is that, along with there being many people in whom the diagnosis of CD has been overlooked, there are also likely to be people in our communities who have been wrongly diagnosed with CD, based on incomplete information.
Of some concern with respect to overall knowledge about CD was the finding that just over 20% of respondents would accept positive HLA-DQ2/DQ8 alone in making the diagnosis of CD. Although four of these responses were probably due to participants reversing the polarity of the measurement scale, this still leaves 20% who apparently believe that this is reasonable. There were also high numbers of neutral responses to this option. Taken together these findings would tend to support the premise discussed earlier in this chapter that GPs are uncertain (and in some cases misinformed) about the role of HLA testing and CD. This adds weight to the need for caution if HLA testing were to be incorporated into testing guidelines, as suggested by Anderson et al.\textsuperscript{18}

As with the recognition of CD, gender and whether or not participants had patients with CD influenced some of their likely behaviours with respect to diagnosing the condition. Thus the women who took part were more likely to refer people with positive CD serology for endoscopy, while the men were more likely only to refer some of the time or almost never. Given that women are over-represented in this study, it is reasonable to infer from these analyses that overall rates of referral for endoscopy are likely to be lower in the real world than among this study population. This would seem to have been borne out in the laboratory data, as will be discussed on the following page.

There was no evidence that either rurality, or the predominant SES of practice populations, influenced responses relating to referrals for endoscopy, although more detailed analysis of the second may paint a more nuanced picture of this issue.

With respect to results that would lead to respondents confirming a patient had CD, it was curious to find that those participants who indicated that they did have patients with CD under their care were significantly more likely to accept positive serology alone as confirmation of the diagnosis. This begs the question about how their coeliac patients had been diagnosed, a factor that was not explored in this survey. This group of respondents were also more likely to almost always refer for endoscopy, which seems a contradiction. However, referring for endoscopy is not the same as patients actually undergoing the procedure. A range of variables may disrupt this process, and the apparent discrepancy between these two questions may simply be a reflection of this.
The survey of gastroenterologists also explored the issue of diagnosis, within the context of a GP seeking advice about a patient with moderately raised IgA-\(\alpha\)-TG antibodies refusing endoscopy. As presented in Chapter Four, participants varied in their responses to this question. A clear majority were likely or highly likely to advise that a diagnosis of CD was unreliable without a biopsy, and a similar majority were also likely or highly likely to recommend HLA testing. But there were also those who would advise that the diagnosis of CD could be assumed to be correct, either on the basis of the serology testing alone, or if antibodies fell on the GFD. With this range of views being expressed by gastroenterologists advising GPs, it is not surprising that GPs hold a range of positions on how to appropriately reach a diagnosis of CD.

7.3.4 Diagnosing CD: Laboratory data

The SCL data presented in Chapter Six provide an insight into aspects of real world diagnosis of CD, augmenting the data gathered in the survey of GPs. What they confirm is that not all patients who return a positive IgA-\(\alpha\)-TG test go on to have a duodenal biopsy. They also seem to support the concern expressed by many survey participants about the challenges in accessing timely endoscopy for their patients, with the mean time between first blood test and biopsy being as high as 17 (±13) weeks in Otago-Southland in 2010, and 19 (±13) weeks in South Canterbury in 2015. But perhaps most importantly of all, these data have enabled correlations to be drawn between positive IgA-\(\alpha\)-TG antibody levels (tested with Quantalite kits) and biopsy results. In the current environment, in which the place of biopsy in confirming a CD diagnosis is hotly debated, these correlations may prove invaluable in formulating future recommendations to guide referral practices.

7.3.4.1 Biopsy rates following positive serology

In the regions for which data were available from SCL, overall rates of patients undergoing duodenal biopsy varied over time. In Otago-Southland rates in the early years of the study period were low (48.4% in 2007), especially when compared with similar studies from overseas.\textsuperscript{37,459} By 2015 Otago-Southland rates had increased to 60%, but in contrast South Canterbury levels were low at 38.5%.

Rates of biopsy fluctuated among patients with higher IgA-\(\alpha\)-TG levels, but were clearly lower among those with results in the low-high range. While proportions
were reasonably comparable in Otago-Southland and Nelson-Marlborough, they fluctuated more widely in South Canterbury. Notably, women in South Canterbury had significantly lower overall rates of biopsy than in the other two regions, as did people in the 17- to 36-years old age-groups. It is not possible to determine why this might be, although it is likely that there will have been a combination of factors at play. South Canterbury is a smaller and somewhat more rural region than the other two areas included in this part of the study, both of which are likely to influence health-related behaviours of patients. For example, it may be that people elected to go outside the region (to a larger centre such as Christchurch) to undergo endoscopy.

There are of course many reasons why duodenal biopsy may not follow a positive blood test. Chief among these is patient choice. This in turn may be influenced by a range of variables, among them: time to biopsy and not wanting to continue eating gluten in the interim; ready availability of gluten-free food options (so not feeling the need to have biopsy confirmation to gain access to a Special Authority number for subsidised foods); an aversion to the procedure itself; or an assumption that the blood test result is enough evidence of the presence of CD to accept that as the explanation for symptoms. This last attitude is the one most likely to be influenced by patients' doctors and, as already discussed, is a view that the data from the GP survey suggest is held by many GPs.

The waters around the issue of the need for biopsy to confirm the diagnosis of CD have been somewhat muddied by the promulgation of the 2012 ESPGHAN Guidelines for diagnosis in children.12 As discussed extensively in Chapter Two, these recommendations continue to be debated, and their application to adults is contested. And though these debates have for the most part been conducted within the academic literature, and in particular in journals aimed at gastroenterologists, clearly the uncertainty about the need for histological confirmation of the diagnosis is influencing GP practice.

7.3.4.2 Correlations between serology and histology

One of the most important findings to emerge from the laboratory data presented in Chapter Six was the 97.8% correlation between very high (≥150 units) IgA-tTG antibody levels and positive histology. This is similar to the findings of Zanini et
al., and Wakim-Fleming et al., and would tend to contradict the view expressed by Kurien et al. that the PPV of serology testing in “unenriched” populations is not high enough to confidently diagnose CD. That the correlation was not closer to 100% may be accounted for by the possibility that at least some among the 11 patients with very high antibody results and apparently normal (or inconclusive) biopsies had already commenced a GFD prior to their endoscopy. For some of these people a biopsy was not performed until several months after the positive blood test making this a very likely scenario. Correlations reached almost 90% for antibody levels in the 100 to 149 range also.

These correlations are encouraging to find in an era in which the need for biopsy confirmation of CD is being debated, although a caveat applies. These data relate only to Quantalite IgA-tTG kits, as used by SCL during the period under investigation. If other laboratories use the same kits then it is highly likely that a similar study would reveal similar results, but comparable performance from other kits used in New Zealand cannot be assumed. It should also be noted that, as presented in Chapter Six, almost none of the pathology reports examined for this study explicitly referred to the Modified Marsh criteria (or any other recognised classification) when reaching the diagnosis of CD. All reports did include a comment on villous architecture and IELs, but at the mild end of the spectrum of histological changes there was some evidence of variability between pathologists on whether or not they would conclude that the changes were consistent with CD. In the absence of comments about crypt hyperplasia, patients with reportedly normal villous architecture and increased IELs would seem to have Type 1 Marsh-Oberhuber changes. Debate continues about whether this should be classified as CD. In the very high IgA-tTG group this amounted to 4.9% of positive biopsy results, although the presence of these very high antibody levels, particularly when they occurred in conjunction with a positive EMA, should be sufficient corroborating evidence to support the diagnosis.

The data that emerged with respect to the likelihood of having a positive biopsy in the presence of IgA-tTG levels in the low-high range are also important when considered alongside the rates of endoscopy among these patients. When compared with those who had higher antibody levels, their rates of endoscopy were considerably lower. From the data available it was not possible to determine what
happened to these people. Some may have been told they had CD and commenced on a GFD, while others may have been told the opposite. In either case there is a risk that that advice was incorrect with the associated negative impact on patient wellbeing.

Because there were no data available in this study from patients with negative serology who underwent duodenal biopsy, it is not possible to formally calculate PPVs at the differing IgA-tTG levels. However, from the data that were available, for a patient with an IgA-tTG of 29 units (Quantalite kit) told to commence a GFD there was an approximately 60% chance that this was unnecessary, while there was also an almost-40% chance that telling such a patient that CD was unlikely would result in a missed diagnosis. For tTG levels between 30 and 39 units these chances were fairly evenly split. In the light of these findings, especially in the context of scarce endoscopy resources, it would seem reasonable to recommend that GPs focus their energies with regards to referring patients for endoscopy on those patients with lower levels of IgA-tTG antibodies, for whom the diagnosis of CD is less certain.

7.3.5 The incidence of CD in three regions of New Zealand

As discussed in the early parts of this thesis, one of the initial intentions of this project was to try to ascertain the prevalence of CD across New Zealand. For reasons already outlined, this proved not to be possible. What was possible was to determine the annual incidence of CD in some of the regions in which laboratory services are provided by SCL, as presented in Chapter Six.

Between 2007 and 2015 the incidence of CD in Otago-Southland steadily increased. In fact, the incidence figures that emerged for this region are some of the highest in the world, at least among those that have been presented in the research literature.\textsuperscript{45,247-250,460} (Although the higher local figures will have been partly contributed to by the more liberal approach to diagnosis taken by pathologists discussed in the previous section.)

The peak Otago-Southland incidence of 32.8 per 100,000 in 2014 is second only to the 33 per 100,000 recorded in Finland in 2005, a rate that had fallen to 29 per 100,000 by 2013.\textsuperscript{251} Two things should be noted about this comparison however. Firstly, the Finns only diagnosed CD when there was villous atrophy and crypt hyperplasia present on duodenal biopsy, which would exclude several of the
patients diagnosed locally over the past decade. And secondly, the Finnish figures refer to the country as a whole, rather than a single region. It is apparent from the additional SCL data available from Nelson-Marlborough and South Canterbury, which both had lower incidence rates than Otago-Southland, that the picture is varied across this country. It is not clear why this might be.

It is possible that Otago-Southland has a higher prevalence of CD than other regions in New Zealand, although why that would be so is also unclear. Were this to be the case, it would be consistent with research from elsewhere (discussed in Chapter Two), which has demonstrated variations in CD prevalence even in adjacent locations. The alternative explanation for the higher Otago-Southland prevalence is that clinicians in the region look for it more frequently (which is consistent with testing rates data), suggesting a greater awareness of the need to consider the diagnosis for their patients. Otago-Southland is my home territory, and CD is a topic on which I have given many presentations over the years. Given that CME was the leading source for updating information about CD cited by participants in the survey of GPs, these laboratory data may well be evidence of the impact such education meetings can have. This would be consistent with the experience in Finland, in which their high rates of diagnosis of CD have been attributed to targeted education.

Nelson-Marlborough and South Canterbury incidence rates are both more comparable to international figures, with Nelson-Marlborough at the upper end and South Canterbury at the lower. As already noted, testing rates in South Canterbury were lower than other regions in this study, and the numbers of people with positive serology progressing to biopsy in the region were also lower, both factors that will have contributed to the calculated incidence rates. But, just as it might be that CD is more prevalent in Otago-Southland, it is equally possible that CD is less prevalent in South Canterbury, which might also have contributed to these findings.

As with the international studies, local incidence rates counted only those people with biopsy-proven disease. Given that every year many patients with positive serology did not undergo endoscopy, and that many of these had very high IgA-tTG antibody levels and positive EMA, the true incidence of CD will be higher than that stated.
There is much more that could be analysed and discussed with respect to the incidence data generated in this study but which is beyond the scope of the present work. This additional discussion will be undertaken in papers to be submitted subsequent to the completion of this thesis.

### 7.3.6 When the diagnosis is uncertain: Gastroenterologist survey data

The conundrum presented by a patient (Joshua) with elevated coeliac antibodies and normal histology was explored in the survey of gastroenterologists, and yielded a range of responses. Perhaps not surprisingly the presence or absence of symptoms significantly influenced likely behaviour. This is despite the fact that it is well documented that symptoms are not a reliable indicator of disease, and their absence does not necessarily mean the disease is also absent.\(^{22}\)

With respect to some aspects of Joshua’s management it seems hard to justify these differences in practice. For example, it is curious that respondents were divided on the place of testing for HLA-DQ2/DQ8, especially when he was asymptomatic, as a negative test in this situation would have been extremely helpful. Checking EMA also seems sensible, as a positive test might suggest that the IgA-tTG was a true positive, and that potential CD was therefore a likely diagnosis.\(^{461}\) This scenario was derived from the study by Parakkal et al.,\(^{56}\) who likewise found that their participants were divided on both these issues. This included their panel of experts, only a small majority of whom would have tested his HLA status or EMA in the absence of symptoms.

The situation with regards to implementing a GFD in the presence or absence of symptoms is probably more clear cut, although the research to support this has only emerged since this survey was undertaken. When Joshua was reported as being asymptomatic, a clear majority of respondents indicated that a GFD was not required. When he was reported to be symptomatic, one third of participants would advise starting a GFD, while 40% maintained their position that a watch and wait approach would be reasonable. Recent studies endorse the view that in patients with normal histology it would be reasonable to adopt a watch and wait approach,\(^{462,463}\) at least for those who remain asymptomatic.

As presented in Chapter Four, there were a number of participant demographic variables that significantly influenced their responses to aspects of this scenario,
particularly when Joshua was asymptomatic. However, given the small numbers of study participants overall, and the even smaller numbers in the various subgroups, it is not clear that this is important. Irrespective of the drivers of differences in practice, what has an impact on patients (and their GPs) is that those differences exist at all. While it may not matter a great deal if one “Joshua” has an EMA test and the next one does not, it will have a profound impact on one asymptomatic “Joshua” if he is commenced on a GFD when another is not. And it makes it challenging for GPs to make consistent management recommendations to their patients if they receive conflicting advice from the specialists they consult.

7.4 Managing Coeliac Disease in New Zealand

As set out in Chapter Two, the overarching aim of management for patients with CD is to improve their quality of life, ideally achieved through mucosal healing. In the majority of patients this should lead to symptom resolution, and a reduction in the incidence of long-term complications. It has become clear over time that, although the GFD remains central to effecting these outcomes, it is no longer sufficient to regard this as the sole focus of care. It is also clear that recommendations regarding the optimal management of CD have long been highly variable, and more recent guidelines do not yet agree on many aspects of care. It has been repeatedly pointed out in the literature that the management of CD is an area that needs further work to enable a consistent and evidence-based approach to be applied. It is in this context that the surveys of gastroenterologists and GPs explored likely practices relating to the management of CD in adult patients in New Zealand. And while there were aspects of management on which there were high levels of consensus, not surprisingly both surveys also found areas of considerable variability.

Among participants in the survey of gastroenterologists there was widespread agreement that in the first year after diagnosis it was important to ensure a patient’s symptoms were improving and abnormal blood test results were resolving. They were also consistently of the view that over the long term the importance of adhering to a GFD was reinforced on a regular basis. However, beyond these aspects of care, levels of accord among respondents fell, which is consistent with the 2010 findings of Silvester and Rashid. In practical terms what this means is that the way
in which a person with CD is managed in New Zealand is likely to vary according to whom they saw for the initial diagnosis, and the recommendations that that practitioner makes regarding their subsequent treatment. This will be heightened by the fact that among GPs who completed the GP survey, there was little consistency in likely practice across any of the management topics explored.

7.4.1 Key variations in the management of CD

A moderate majority of participants in the survey of gastroenterologists indicated that follow-up IgA-tTG testing within the first year following diagnosis was important or very important, but they varied on when this should take place. They were divided about whether this should take place routinely at six months or a year, or only if symptoms did not resolve. Almost 70% were likely to include a recommendation about this follow-up testing when discharging a patient back to his or her GP. They were somewhat more divided on the place of periodic IgA-tTG monitoring over the longer term, with almost 40% rating this as not important.

Participants in the GP survey were uncertain about the importance of follow-up serology testing, both in the short term and as part of longer term management. Over a quarter indicated that they were not aware that this might be necessary, and almost another fifth indicated that they did not think it was necessary. Only very small numbers would retest routinely, with testing most likely to be undertaken if a patient's symptoms recurred or did not settle, or at a patient's request. The laboratory data analysis demonstrated that just under half of patients with a positive (or inconclusive) biopsy had subsequent antibody testing.

As discussed in Chapter Two, currently available guidelines all make recommendations to repeat serology testing in the year following diagnosis. While it is agreed that antibody levels do not necessarily indicate what is happening at the level of the intestinal mucosa with respect to healing, it is also generally accepted that strict adherence to the GFD should at least lead to a fall in titres. Antibody levels that are not falling should therefore prompt a review with the patient to determine whether he or she is continuing to ingest gluten, either deliberately or unintentionally. This opportunity is lost when patients are not retested.
Variations in practice among gastroenterologists were also evident relating to the importance of rebiopsy in the first 12 months after diagnosis. Just over half of participant gastroenterologists did not regard this as important, but just over a third of their colleagues took the opposite view. Perhaps not surprisingly this was to some degree influenced by the number of tenths worked in private practice. An additional few participants reported that they thought that rebiopsy was important, but not until more time had elapsed. Collectively these responses suggest that some patients in New Zealand will have a follow-up biopsy more-or-less routinely, while many will not.

Participants who indicated that they were likely or highly likely to rebiopsy their patients routinely were significantly more likely to use guidelines as a source of information about CD. This is interesting given that, as identified by Silvester and Rashid,55 “practice guidelines do not offer any specific guidance regarding who should receive a repeat biopsy routinely”.(p.507) As discussed in Chapter Two, current guidelines do not explicitly recommend this approach, although they all endorse the practice in certain circumstances. Their collective reticence to make a strong recommendation on routine rebiopsy is in large part because the evidence that this intervention leads to an improvement in clinical outcomes for patients remains contested.

Referral for DEXA scanning was another issue on which gastroenterologists were divided. This too is an issue that has not been clearly resolved between the guidelines groups. Just over half of respondents indicated they thought it was important for a referral to be made for DEXA scanning for newly diagnosed patients, while others indicated that the decision would depend on the presence of additional risk factors, and a few that DEXA scanning is not important at all. Their differences in approach were reflected in the responses of participants in the GP survey. Thus nearly half of GP respondents almost never referred patients for DEXA scanning, with the majority of these people indicating that they were not aware that this might be necessary.

In addition to these aspects of follow-up care, participants in the GP survey also displayed mixed appreciation of the role of CNZ in supporting patients with CD. All the available guidelines direct that contact with a support group is an important component of coeliac management. Almost a quarter of GP respondents were not
aware that a recommendation to contact CNZ might be necessary, while close to 40% almost never recommended this to their coeliac patients. However, a clear majority of respondents to the survey of gastroenterologists indicated that they discussed this issue with newly diagnosed patients almost all or most of the time, so it seems likely that a substantial proportion of patients will receive this advice.

With respect to management over the longer term, issues such as the need for vaccination against influenza and pneumococcal infection drew high numbers of neutral responses from the gastroenterologists. Among GP respondents the majority indicated that they were not aware that pneumococcal vaccination might be necessary, but they would give the influenza vaccination at least some of the time. This may reflect a broader view of the importance of influenza prevention in general, rather than its specific relevance to CD. As discussed in Chapter Two, positions on these two aspects of long-term care are not yet consistent in the literature relating to CD, and that is clearly reflected in these findings.

### 7.4.2 Annual reviews

Guidelines documents pertaining to CD have long recommended that patients with the condition should be reviewed on an annual basis, specifically with respect to their CD.\textsuperscript{307} Despite this, research suggests that this is not the norm, at least as far as adults are concerned.\textsuperscript{29}

The surveys of gastroenterologists and GPs indicate that the experiences of patients in New Zealand are likely to be highly variable. A moderate majority of gastroenterologists regarded annual reviews as important or very important, and believed that GPs should be the practitioners to conduct them. However, fewer than two-thirds of those who thought this were likely to recommend the practice in their discharge letters. Almost 70% of GPs thought that such reviews were probably or definitely necessary, with a clear majority agreeing that GPs were the appropriate clinicians to perform them.

Among those GP respondents with patients with CD in their practices, there was a range of practices with respect to reviewing their disease management, with the biggest single group being the 30% who did so opportunistically when their patients presented with something else. A smaller group indicated they did this routinely. It seems unlikely that non-responders to this survey would be any more
likely than survey participants to regularly review these patients, and it seems much more plausible to assume that they would be less likely to do so.

The questions relating to annual reviews stirred many participants to comment, with some expressing concerns about the costs of implementing such a programme. The costs they foresaw were to their patients, who would have to pay for the consultation, and to themselves in terms of their time in an already stretched primary care sector. Many more also indicated that they would need additional information about what to include in such a review. Alongside this, there were many and varied ideas about what an annual review should encompass. It is clear that this is an area that would benefit from the dissemination of further information, although given the differences between guidelines documents, there is work still to be done on developing an agreed set of recommendations to suit the New Zealand environment.

7.5 Why opinions and practices might differ

Given the lack of consistency of recommendations across available CD guidelines, it is not surprising that for many aspects of care, opinions about their importance varied among gastroenterologists who participated in the survey, and likely practice differed widely among GPs. This is especially so for management and, as evidenced in research from elsewhere, this is not a problem that is unique to New Zealand.

With respect to the findings of the present survey of gastroenterologists, these may have been influenced by the fact that at the time it was conducted in late 2013 the WGO and ACG Guidelines were relatively new, and the BSG and NICE were yet to update their recommendations. Perhaps compounding this was the fact that just over a third of participants did not rate guidelines documents as one of their preferred sources of information about CD.

When a similar question was asked of GPs about sources of information they utilised relating to CD, only very small numbers indicated that they would refer to practice guidelines. This is also not surprising given that, with the exception of a summary of the NICE Guidelines published in the BMJ, all other CD-related guidelines (relating to the care of adults) have been published in the specialist gastroenterology literature. Instead GPs are more likely to rely on CME
meetings, bpac nz, and their patients with CD for their information. Unfortunately much of the bpac nz information on CD has not been updated for some years, with the most recent material (relating to dietary advice and prescription foods) dating back to 2011, and their last comprehensive review of CD dating to 2007. More than half of GP respondents also indicated that letters from gastroenterologists were an important source of their information, highlighting the degree of gastroenterologist influence on practice. And while not an important source of information for participants in this survey, it is likely that over time HealthPathways will become so. As already mentioned earlier in this chapter, these are not entirely consistent across DHBs, introducing another source of variation in practice.
Chapter 8: Conclusion

It has to be concluded from the studies that comprise this project that GPs in New Zealand, as in other countries, do indeed have limited disease-specific knowledge with respect to CD in adults. And although the deficits in knowledge are patchy rather than universal, it is likely that CD remains under-recognised, under-diagnosed, and sub-optimally managed.

The evidence gathered in these studies does suggest that, over time, knowledge about CD has improved. Rates of recognition (evidenced by testing) and diagnosis (evidenced by incidence) have clearly increased, at least in some of the regions from which laboratory data were available. In particular, Otago-Southland incidence rates compare very favourably with data from elsewhere in the world. The survey of GPs demonstrated that there are several clinical presentations that are highly likely to prompt testing for CD, but there are also situations in which it is probable that CD is still being missed. This may be because it is not tested for, or because positive IgA-tTG tests are not appropriately followed up. There are also likely to be people being wrongly diagnosed, as more weight than is warranted is given to results such as a positive HLA-DQ2/DQ8 test. But it is in the management of the condition that there is most room to improve. This is evidenced by the lack of consistency in the views of gastroenterologists about what follow-up care should include, which is reflected in the varied practices of GPs. Such differences in practice are entirely consistent with what is happening elsewhere, and with the fact that even the guidelines documents produced by experts diverge.

Standing at the centre of a project such as this are patients, in this case those with CD, be they already diagnosed or awaiting recognition. From the work presented here it is clear that there is work still to be done to improve the health outcomes of both groups of people. The following recommendations seek to begin that process.

8.1 Recommendations to the New Zealand Society of Gastroenterologists

One of the most important findings to emerge from the survey of gastroenterologists was that respondents to the survey held differing views and/or had differing practices relating to patients with CD, or possible CD. What was most
surprising about these differences was that they occurred not just between DHB regions, but also within them, among practitioners who presumably worked alongside each other. And while the majority of differences in practice did not reach statistical significance, they do represent variations in patient care. The clinical import of these variations will differ according to the nature of the practice that is in question, but what they will do is send mixed messages to GPs, who carry out the bulk of long-term management, and to their patients who simply want to know that they are receiving appropriate treatment. It is unlikely that variations in practice will have substantially lessened in the years since the survey was conducted.

- It would be of great value to patients and GPs alike if the NZSG sponsored an effort to develop an agreed set of CD practice guidelines appropriate for the New Zealand clinical environment. These should include policies relating to rebiopsy, DEXA scanning, and retesting serology, along with a template on which annual reviews of patients with CD could be based. Such guidelines could be promulgated among gastroenterologists, but also surgeon endoscopists, who were not represented in this survey, but who will on occasion diagnose patients with CD.

- Such guidelines should be made available to those developing CD-related HealthPathways to ensure that consistent messages are given everywhere in New Zealand.

### 8.2 Recommendations to Coeliac New Zealand

Over the past decade CNZ has put a great deal of effort into educating GPs about CD, with some evidence of success. This needs to continue, but could become more focused.

- From the survey of GPs it was apparent that they were much less likely to test for CD in the presence of some symptoms than others, and that testing in patients with conditions known to be associated with CD was less common than it could be. Targeting advice to address these evident gaps in knowledge may reap more benefits than a continued broad brush injunction to simply test more people.

- Respondents to the GP survey indicated a clear preference for CME meetings as a source of information about CD. Coeliac New Zealand should continue to
have a presence at major GP CME events, and to sponsor expert presentations, to increase the organisation’s visibility and be a ready source of reliable resources about the condition.

- GP survey respondents also indicated that their patients with CD are an important source of information about the condition, so perhaps this is a resource that CNZ could tap into more explicitly. For example, they could provide newly diagnosed people with guidelines about management to discuss with their GPs. Such a resource could also be made available to gastroenterologists to give to patients at the time of diagnosis.

8.3 Recommendations for Future Research

(A) One of the most important sets of findings to emerge from the laboratory study was the correlation data between IgA-tTG levels and biopsy results. If it were possible to safely exclude patients with very high IgA-tTG titres from the need for upper endoscopy, this would reduce demand for the service, and perhaps improve access for patients in whom the diagnosis is less clear cut. It would also mean that those patients for whom the diagnosis could be confirmed on the basis of serology alone would not be required to undergo an invasive procedure, and could begin treatment without delay.

- In an environment in which access to endoscopy resources is often limited, and in the context of ongoing debate about the place of duodenal biopsy in diagnosing CD, there is an urgent need to repeat this part of the laboratory study in other laboratories, especially those that do not use the Quantalite kits used by SCL. This would inform future decision-making about the requirement for duodenal biopsy to confirm the diagnosis. It would also enable analysis of the comparability of test-kits used throughout New Zealand.

- Repeating analyses of testing and biopsy data in regions other than Otago-Southland would enable incidence rates to be calculated for other parts of New Zealand. This would permit comparisons to be made between regions, and could lead to further investigations of differences and similarities where these exist.
(B) Guidelines documents have long recommended that patients with CD be reviewed annually, but it is clear from both the surveys in this project that there is some way to go before such reviews become routine in New Zealand. Among the obstacles to this happening are issues relating to cost, and a lack of clarity about what they should involve.

- It would be of benefit to patients and GPs alike if a tool were to be developed that could enable GPs to triage their patients with CD so that those for whom the benefit might be greatest could be prioritised for regular review. Such a tool might take the form of an online questionnaire that patients completed (via patient portals such as ManageMyHealth), with questions about symptoms and dietary adherence, for example. It might also include a panel of blood tests. Any such instrument would need to be developed in accordance with evidence-based practice, and with the input of people with CD.

(C) Several attempts have been made to find reliable ways of measuring CD-related QoL. To date none of these tools are particularly workable for use in the busy primary care setting.

- It would be of benefit to patients, GPs, and researchers evaluating the impact of new treatments for CD (for example), if a less cumbersome instrument to measure QoL could be developed. This might take the form of a screening tool, responses to which would indicate whether a patient needed a more in-depth exploration of how they were managing.

(D) The study by Anderson et al.\textsuperscript{18} suggested that the addition of HLA-DQ2/DQ8 testing for patients with positive coeliac serology could be used to more accurately ration scarce endoscopy resources by excluding those with false-positive antibody tests.

- A cost-benefit study in the New Zealand context of adding HLA testing for patients with positive coeliac serology would enable a recommendation to be made about whether or not such a practice would be of value in this country.
8.4 Final comments

No doctor ever sets out to treat his or her patients with anything less than the best possible care. Sometimes that care does not reach the standards that we might set for ourselves, and sometimes it does not meet the expectations of our patients and their supporters. Blind spots in knowledge about a condition will often be a contributing factor when these situations arise.

As documented in Chapter One of this thesis, CNZ has long held concerns about care relating to CD in this country, particularly with respect to delays in diagnosis. The results contained in this project suggest that there remains some justification for their concern, but that over time the situation has improved. If the lessons learned in the course of this project can be applied, and the recommendations derived from these three studies implemented, there is every reason to believe that such improvements will continue, and that the care of patients with coeliac disease in New Zealand could become the best possible.
References


424. Häuser W, Gold J, Stallmach A, Caspary WF, Stein J. Development and validation of the Celiac Disease Questionnaire (CDQ), a disease-specific


453. Reeder AI, Jopson JA, Gray AR. "Prescribing sunshine": a national, cross-sectional survey of 1,089 New Zealand general practitioners regarding their sun exposure and vitamin D perceptions, and advice provided to patients. BMC Fam Pract. 2012;13:85.

454. National Health Committee. 2015; An Overview of Laboratory Services in New Zealand.


Appendix A: Ethics Committee and Ngāi Tahu Committee Approvals

Assoc. Prof. C. Jaye
Department of General Practice & Rural Health
Dunedin School of Medicine

25 June 2013

Dear Assoc. Prof. Jaye,

I am writing to let you know that, at its recent meeting, the Ethics Committee considered your proposal entitled "An investigation of New Zealand gastroenterologists’ approach to adult coeliac disease".

As a result of that consideration, the current status of your proposal is: Approved.

For your future reference, the Ethics Committee’s reference code for this project is: H13/027.

The comments and views expressed by the Ethics Committee concerning your proposal are as follows:

While approving the application, the Committee would be grateful if you would respond to the following:

The Committee would like you to clarify how participants will receive their results given that this is an anonymous survey. Would you also comment on how follow-up is to be conducted?

Please provide the Committee with copies of the updated documents, if changes have been necessary.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.
NGĀI TAHU RESEARCH CONSULTATION COMMITTEE

Te Komiti Rakahau ki Kai Tahu

Tuesday, 23 April 2013.

Associate Professor Chrystal Jaye,
Dunedin School of Medicine - General Practice and Rural Health,
DUNEDIN.

Tēnā Koe Associate Professor Chrystal Jaye,

An investigation of New Zealand gastroenterologists approach to adult coeliac disease.

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 23 April 2013 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum it states "Ngāi Tahu acknowledges that the consultation process outlined in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

As this study involves human participants, the Committee strongly encourage that ethnicity data be collected as part of the research project. That is the question on self-identified ethnicity and descent, these questions are contained in the 2006 census.


The Committee suggests dissemination of the research findings to Māori health organisations regarding this study.

We wish you every success in your research and The Committee also requests a copy of the research findings.
Assoc. Prof. C Jaye  
Department of General Practice & Rural Health  
Dunedin School of Medicine

24 March 2014

Dear Assoc. Prof. Jaye,

I am writing to let you know that, at its recent meeting, the Ethics Committee considered your proposal entitled “An investigation of New Zealand General Practitioner’s approach to adult coeliac disease”.

As a result of that consideration, the current status of your proposal is:- Conditional Approval

For your future reference, the Ethics Committee’s reference code for this project is:- H14/044.

The comments and views expressed by the Ethics Committee concerning your proposal are as follows:-

Please address the following comments before proceeding with the research:

The Committee expressed concern with the assumed response rate of 30%, as noted in Section 2.1, and asks for further comment on this.

Before approval of the research to proceed can be granted, a response must be received addressing the issues raised above. The Committee expects that these comments will be addressed before recruitment of participants begins. Please note that the Committee is always willing to enter into dialogue with applicants over the points made. There may be information that has not been made available to the Committee, or aspects of the research may not have been fully understood. Please provide the Committee with copies of the updated documents, if changes have been necessary.
“The Committee expressed concern with the assumed response rate of 30%, as noted in Section 2.1, and as to whether this is scientifically valid and asks for further comment on this.”

Response:

It is well recognised that General Practitioners are difficult to engage with survey-based research. A review on the issue conducted by Creavin et al.\(^1\) in 2011 found that response rates reported in the literature ranged between 31% and 71%, while a study in the Australian Family Physician\(^2\) also published in 2011 reported that “GP response rates to surveys are lower than those from the general population”.

There are a number of resources available that outline evidence-based steps which researchers can take to enhance the likely response rate to mailed surveys.\(^3,4\) These include enclosing postage-paid return envelopes with the survey, having a prize draw associated with participation, and sending out reminders at regular intervals following the initial mail out. Dr Kenrick is aware of this literature and will be implementing many of these recommendations in an effort to maximise the response rate to the proposed survey.

Section 2.1 of the protocol in fact said “assuming the response rate could be as low as 30%”, in order to account for the high number of surveys we propose to send out. This is one of the steps Dr Kenrick will be taking to ensure that enough responses are gathered to be able to make meaningful internal comparisons between participants.

We acknowledge that if the response rate is indeed as low as 30%, then the generalisability of the study’s findings to the wider General Practice community will be limited. Discussion of this issue and its possible implications would be included in any reporting of the study.

References:

(1) Creavin ST, Creavin AL, Mallen CD. Do GPs respond to postal questionnaire surveys? A comprehensive review of primary care literature. *Fam Pract* 2011; 28: 461-467


Assoc. Prof. C. Jaye  
Department of General Practice & Rural Health  
Dunedin School of Medicine

14 April 2014

Dear Assoc. Prof. Jaye,

I am again writing to you concerning your proposal entitled “An investigation of New Zealand General Practitioner’s approach to adult coeliac disease”, Ethics Committee reference number H14/044.

Thank you for your e-mail of 8th April 2014 addressing the issues raised by the Committee.

The Committee appreciates the further comment and clarification given in respect of the assumed response rate and acknowledges that the possible implications that may arise with a low response rate will be included in any reporting of the study.

On the basis of this response, I am pleased to confirm that the proposal now has full ethical approval to proceed.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

[Signature]

Mr Gay Witte  
Manager, Academic Committees  
Tel: 475 6256  
Email: gay.witte@otago.ac.nz

c.c. Assoc. Prof. C. Jaye, Head of Department, Department of General Practice & Rural Health
Tuesday, 18 March 2014.

Associate Professor Chrystal Jaye,
Dunedin School of Medicine - General Practice and Rural Health,
DUNEDIN.

Tinā Koe Associate Professor Chrystal Jaye,

An investigation of New Zealand General Practitioners approach to adult coeliac disease

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 18 March 2014 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum it states "Ngāi Tahu acknowledges that the consultation process outline in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu-appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee bases consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

As this study involves human participants, the Committee strongly encourage that ethnicity data be collected as part of the research project. That is the questions on self-identified ethnicity and descent, these questions are contained in the latest census.

The Committee suggests dissemination of the research findings to relevant Māori health organisations.

We wish you every success in your research and the Committee also requests a copy of the research findings.

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 18 March 2014 to 7 September 2015.
Assoc. Prof. C Jaye  
Department of General Practice & Rural Health  
Dunedin School of Medicine

26 September 2013

Dear Assoc. Prof. Jaye,

I am again writing to you concerning your proposal entitled “Patterns of testing for Coeliac Disease in the past decade”, Ethics Committee reference number H13/061.

Thank you for your e-mail of 25 September 2013 with the attached Maori Consultation letter dated 18 September 2013 as per the Committee’s Conditional Approval request.

On the basis of this response, I am pleased to confirm that the proposal now has full ethical approval to proceed.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

Mr Gary Wite  
Manager, Academic Committees  
Tel: 479 8256  
Email: gary.wite@otago.ac.nz

c.c. Assoc. Prof. C Jaye  Head of Department  Department of General Practice & Rural Health
Wednesday, 18 September 2013.

Associate Professor Chrysal Jaye,
Dunedin School of Medicine - General Practice and Rural Health,
DUNEDIN.

Tia Koe Associate Professor Chrysal Jaye,

Patterns of testing for Coeliac Disease in New Zealand in the past decade.

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 17 September 2013 to discuss your research proposition.

By way of introduction, this response from The Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. It states that the consultation process outlined in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago. As such, this response is not “approval” or “mandate” for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon, adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (m that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

The Committee notes this research is an audit.

The Committee recommends recording ethnicity where available.

The Committee suggests including in the research team a researcher with expertise in analysing and interpreting data by ethnicity.

The Committee suggests dissemination of the research findings to Māori health organisations regarding this study.

We wish you every success in your research and The Committee also requests a copy of the research findings.

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 17 September 2013 to 8 March 2015.

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Otago Incorporated
Kāti Haupipoi Rūnanga ki Tuckeraki
Te Rūnanga o Mowaki
Appendix B: Survey from Parakkal et al.¹

Celiac Questionnaire for Gastroenterologists

AGE ________

GENDER ________

YEARS IN PRACTICE ________

SPECIALITY __________________________________________

CLINICAL HOURS PER WEEK ________

RESEARCH HOURS PER WEEK ________

MEMBERSHIP IN CELIAC SOCIETIES? (if yes, indicate which one)
___________________________________________

NUMBER OF CELIAC DISEASE PATIENTS SEEN PER MONTH ________

PRACTICE SETTING (Please circle)

PRIVATE

SOLO       GI GROUP       MULTISPECIALTY GROUP

HEALTH MAINTENANCE ORGANIZATION

UNIVERSITY BASED

VETERAN’S AFFAIRS HOSPITAL

OTHERS

GEOGRAPHIC LOCATION OF PRACTICE  (Please circle)

MIDWEST (USA)

NORTHEAST (USA)

SOUTH (USA)

WEST (USA)

INTERNATIONAL (PLEASE NAME COUNTRY OF PRACTICE)__________________________
Please rate the appropriateness of the tests/interventions on a RAND appropriateness scale of 1-9 in the following clinical vignettes.

<table>
<thead>
<tr>
<th>RAND Appropriateness Scale (RAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
</tbody>
</table>

1 = extremely inappropriate

5 = equivocal (neither clearly appropriate nor clearly inappropriate)

9 = extremely appropriate

**Vignette #1**

Five years ago, a 25 yr old Caucasian male was diagnosed with probable celiac disease on the basis of positive IgG anti-Gliadin antibodies and started on a gluten free diet (GFD). He now wants to know if he really has celiac disease as the GFD is severely affecting his quality of life.

1) Please rate the appropriateness of the following diagnostic tests as an initial step in the work up:

   a) Ig A anti-TTG antibodies
      Rating of Appropriateness (Circle One)
      1 2 3 4 5 6 7 8 9

   b) Ig A anti-Endomysial antibodies
      1 2 3 4 5 6 7 8 9

   c) Serum Ig A levels
      1 2 3 4 5 6 7 8 9

   d) IgA and IgG anti-Gliadin antibodies
      1 2 3 4 5 6 7 8 9

   e) EGD with Duodenal biopsy at presentation
      1 2 3 4 5 6 7 8 9

   f) None of the above
      1 2 3 4 5 6 7 8 9

2) Please rate the appropriateness of testing for the absence of HLA DQ2/8 heterodimer status to rule out celiac disease in this patient:

   Rating of appropriateness: (Circle One)
   1 2 3 4 5 6 7 8 9

392
3) Please rate the appropriateness of a gluten challenge to diagnose celiac disease in the above scenario:

Rating of appropriateness: (Circle One) 1 2 3 4 5 6 7 8 9

4) If you were to proceed with a gluten challenge, what is the minimum quantity of gluten intake you would ask the patients to consume per day? (Circle One)
   a) 5 grams/day
   b) 10 grams/day
   c) 20 grams/day

5) What is the duration of gluten intake you would allow before you would perform investigations to confirm celiac disease in the above scenario? (Circle One)
   a) 2 weeks
   b) 4 weeks
   c) 8 weeks
   d) 12 weeks
   e) As soon as symptoms develop

6) What would be a safe amount of non cross-contaminated oats that can be consumed in a day by a patient with celiac disease while on a GFD? (Circle One)
   a) Avoid consuming any oats
   b) No more than 2 ounces per day
   c) No more than 5 ounces per day

Vignette#2
A 20 yr old went to his primary care physician because his paternal uncle was recently diagnosed with celiac disease. He has no gastrointestinal symptoms, but was tested and found to have elevated Ig A anti-TTG antibodies. He was referred to your office for an EGD and duodenal biopsy to confirm celiac disease.

 RAND Appropriateness Scale (RAS)

 1 2 3 4 5 6 7 8 9

1 = extremely inappropriate
5 = equivocal (neither clearly appropriate nor clearly inappropriate)
9 = extremely appropriate
1) If, in the above scenario, the biopsy results were to be normal (Marsh type 0), indicate the appropriateness of the next set of investigations on a RAS scale of 1-9:

<table>
<thead>
<tr>
<th>Rating of appropriateness (Circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Review biopsy with an experienced pathologist</td>
</tr>
<tr>
<td>b) Repeat biopsy</td>
</tr>
<tr>
<td>c) Genetic testing for HLA DQ2/8 status</td>
</tr>
<tr>
<td>d) IgA anti-endomysial antibody</td>
</tr>
<tr>
<td>e) M2A capsule study</td>
</tr>
<tr>
<td>f) Small bowel radiograph</td>
</tr>
<tr>
<td>g) Start on GFD and repeat serology later to document fall in titer</td>
</tr>
</tbody>
</table>

2) In the above vignette if the patient were to report significant gastrointestinal symptoms along with positive celiac serology but normal biopsy (Marsh type 0), indicate the appropriateness of the next set of investigations on a RAS scale of 1-9:

<table>
<thead>
<tr>
<th>Rating of appropriateness (Circle One)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Review biopsy with an experienced pathologist</td>
</tr>
<tr>
<td>b) Repeat biopsy</td>
</tr>
<tr>
<td>c) Genetic testing for HLA DQ2/8 status</td>
</tr>
<tr>
<td>d) IgA anti-endomysial antibody</td>
</tr>
<tr>
<td>e) Start on GFD and repeat serology later to document fall in titer</td>
</tr>
</tbody>
</table>

3) Evaluate the role of gluten free diet in this scenario of positive serology and normal histology in a symptomatic patient on a RAS scale of 1-9:

<table>
<thead>
<tr>
<th>Rating of appropriateness (Circle One)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) GFD only if repeat biopsy is positive</td>
</tr>
<tr>
<td>b) GFD only if Positive for HLA DQ 2 OR 8</td>
</tr>
<tr>
<td>c) GFD if either repeat biopsy or HLA DQ2 OR 8 is positive</td>
</tr>
<tr>
<td>d) No role for GFD if biopsy and genetic testing is negative</td>
</tr>
</tbody>
</table>
e) Start on GFD and repeat serology later to document fall in titer

4) In the above scenario, is there a role for the development of non-invasive tests to diagnose or rule out celiac disease before proceeding for small intestinal biopsy?

Indicate by circling yes or no

YES  NO

Vignette #3

A 28 yr old Caucasian female is referred to your office with a diagnosis of dermatitis herpetiformis (DH) for evaluation of coexistent celiac disease. She currently has no gastrointestinal symptoms but she has a family history of celiac disease.

<table>
<thead>
<tr>
<th>RAND</th>
<th>Appropriateness Scale (RAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

1 = extremely inappropriate
5 = equivocal (neither clearly appropriate nor clearly inappropriate)
9 = extremely appropriate

1) Please rate the appropriateness of the following investigations on a RAS SCALE OF 1-9:

Rating of appropriateness (Circle One)

a) Ig A anti-TTG antibodies 1 2 3 4 5 6 7 8 9
b) Ig A anti-Endomysial antibodies 1 2 3 4 5 6 7 8 9
c) Serum Ig A levels 1 2 3 4 5 6 7 8 9
d) IgA and IgG anti-Gliadin antibodies 1 2 3 4 5 6 7 8 9

2) If, in the above scenario, she has antibodies that are diagnostic of celiac disease, rate the appropriateness of the possible next step in investigation on a RAS scale of 1-9:

Rating of appropriateness (Circle One)

a) Duodenal biopsy, which if positive will start GFD and if negative do nothing 1 2 3 4 5 6 7 8 9
b) Start GFD and no role for duodenal biopsy 1 2 3 4 5 6 7 8 9

c) Duodenal biopsy to confirm celiac disease but start GFD regardless of result 1 2 3 4 5 6 7 8 9

3) If you decide to start her on a GFD, rate the appropriateness of the reason on a RAS scale of 1-9:

Rating of appropriateness
(Circle One)

a) It would improve the rash of DH 1 2 3 4 5 6 7 8 9

b) It would improve intestinal mucosal morphology 1 2 3 4 5 6 7 8 9

c) It would improve both the rash and the mucosal morphology 1 2 3 4 5 6 7 8 9

Vignette#4
The following are a series of mini vignettes on conditions or manifestations where one might consider testing for celiac disease.

1) Please rate the appropriateness for screening for celiac disease in asymptomatic patients with the following conditions:

Rating of appropriateness
(Circle One)

a) Type 1 Diabetes Mellitus 1 2 3 4 5 6 7 8 9

b) Autoimmune thyroiditis 1 2 3 4 5 6 7 8 9

c) Down syndrome 1 2 3 4 5 6 7 8 9

d) Turner syndrome 1 2 3 4 5 6 7 8 9

e) Selective Ig A deficiency 1 2 3 4 5 6 7 8 9

f) First degree relative of celiac patient 1 2 3 4 5 6 7 8 9
## RAND Appropriateness Scale (RAS)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
</table>

1 = extremely inappropriate
5 = equivocal (neither clearly appropriate nor clearly inappropriate)
9 = extremely appropriate

2) In the following diseases rate the appropriateness of repeated serology testing if initial serology is negative for celiac disease:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rating of appropriateness (Circle One)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Type 1 Diabetes Mellitus</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>b) Down syndrome</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>c) First degree relatives of celiac patients</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>d) Selective IgA deficiency</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
</tbody>
</table>

3) Please rate the appropriateness for screening for celiac disease in asymptomatic patients with the following manifestations:

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Rating of appropriateness (Circle One)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Premature osteoporosis</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>b) Delayed puberty</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>c) Iron deficiency anemia</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>d) Unexplained elevation of liver transaminases</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>e) Primary biliary cirrhosis</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>f) Autoimmune hepatitis</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>g) Unexplained infertility</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>h) Recurrent migraine</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>i) Sjogren’s syndrome</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
</tbody>
</table>
Thank You for Participating In This Survey

Please include your e mail ID in the space below if you wish to be informed of the results when the study is completed. This information will be kept confidential during the analysis, presentation and publication of these data.

Please drop this questionnaire in one of the drop boxes or return it to one of the Research associates.

Reference

Appendix C: The RAND Appropriateness Method explained

The RAND Appropriateness Method (RAM) was developed in the 1980s by a team at University of California, Los Angeles (UCLA) and the RAND Corporation, as a tool to assess health systems for the appropriateness of care being provided.1 The particular area of interest was that of the underuse and overuse of surgical procedures, and the consequent variability in health care being provided to different patients and populations. It has subsequently come to be used to develop guidance for appropriate treatment across a range of disciplines. An appropriate treatment is defined by RAND as being one for which “the expected health benefit ... exceeds the expected negative consequences ... by a sufficiently wide margin that the procedure is worth doing, exclusive of cost”.1 (p.1)

The RAM is grounded in the belief that expert opinion must be considered alongside the best available evidence when making decisions about the appropriateness of a treatment because “(a)lthough robust scientific evidence about the benefits of many procedures is lacking, physicians must nonetheless make decisions every day about when to apply them”(p.1). Thus central to the RAM is the role of the expert panel which participates in a modified Delphi process, to evaluate a specific treatment option (or options) for appropriateness in a range of related clinical scenarios. But the authors of the RAM User’s Manual are careful to explain that while the process will identify when experts have a consensus view on the appropriateness or otherwise of an intervention, this is not a tool to forge that consensus.

For the procedure in question, generally the process follows the following steps:

- An extensive literature review is undertaken to gather and synthesise the available evidence relating to its use.
- A list of indications for its possible use, often in the form of clinical scenarios, is developed. This may run to hundreds of individual items.
- A list of definitions of potentially ambiguous terms is also developed, to try and minimise variation in how the scenarios may be interpreted by panel members.
A panel of experts is selected. This may be by reviewing the literature for key researchers in the area, or consulting with relevant specialist societies. The panel may have up to 15 members although 9 is the number recommended by RAND.

The panel is asked to evaluate its appropriateness for use in each of the scenarios. They do this using a 9-point scale, where 1 means that expected harms greatly outweigh expected benefits, and 9 that expected benefits greatly outweigh expected harms. A score of 5 can either mean that the expected benefit/harm ratio is equal, or that the evaluator is unable to make that judgement. At this stage in the process each panellist conducts his or her evaluations individually, and independently of other participants.

Panellists’ responses are collated and the panel is then convened for a facilitated discussion. Each panellist is given a copy of the collated responses together with his or her own responses, and areas of disagreement are discussed. There is also an opportunity to modify the lists of indications and definitions. The discussion is designed to determine whether disagreement is due to true differences in opinion and clinical practice, or to misunderstanding and fatigue.

Following discussion each panellist is asked to re-rate the list of indications. This second round of ratings may be done within the context of the meeting, or in the few days immediately following.

Results are collated and then, according to the median scores of panellists and the level of disagreement among them, each indication is categorised as being appropriate (7-9), uncertain (4-6), or inappropriate (1-3).

Following on from this process the results are then used to evaluate patient care retrospectively, or to guide future practice.

The RAM is not without its critics, with concerns expressed by some about the potential for bias to occur at a number of points (e.g. in panel selection, in facilitator selection, in the literature review process); about the cost of the process; about potential ambiguity in the word “appropriateness”; and about the fact that there is
no room in the method for the patient’s perspective to be considered. Some of these concerns are addressed by more recent groups employing the method, and a systematic review published in 2012 found that the RAM does have acceptable reliability and validity for assessing overuse and underuse of surgical procedures.

The study by Parakkal et al., at least as it is reported in their published article, bears little resemblance to the RAM as outlined above. While they did develop a set of scenarios and asked participants to evaluate the appropriateness of various interventions, their process seems otherwise unrelated to that developed by RAND/UCLA. They did not obviously provide their participants with the evidence to inform their decision making, and instead of an expert panel, they had two groups completing the task: one a group of 22 experts, the other a group of 169 conference-goers. While this is a useful way to compare the practice of the two groups, it is not equivalent to the RAM. In addition to this, all participants only rated the scenarios once and there was no discussion or opportunity to identify areas of ambiguity or misunderstanding, which calls into question the validity of the RAND Appropriateness Scales (RAS) which they then developed.

References

Appendix D: The Survey for Gastroenterologists

Current Approaches to Adult Coeliac Disease

If you are a gastroenterologist (consultant or registrar) or a surgeon endoscopist, I would be very grateful if you would complete the attached survey, which should take you no more than 20 minutes to do.

This survey forms part of my PhD project in which I am investigating adult Coeliac Disease in New Zealand. I am working with gastroenterologists Michael Schultz and Andrew Day, and Dr Chrystal Jaye, from the Department of General Practice and Rural Health in the Dunedin School of Medicine. We are particularly interested in developing strategies to improve the care of patients with CD, by identifying gaps in current approaches to the diagnosis and management of the condition. This part of the project seeks to understand the role of specialists in the care of patients with CD, and their expectations of GPs who are also involved in this care.

The survey presents three scenarios with questions which ask you to rate your likely responses. There is also scope for you to provide comments should you wish to do so. We are looking for information about your current practice, rather than the “right” answers.

For this project to produce meaningful results we need as many people as possible to take part, so I would really appreciate your participation. Please note there are questions on both sides of each page.

Thank you for taking part. Please drop your completed survey to the Coeliac NZ booth.

Kristin Kenrick
GP and PhD Candidate
Dunedin School of Medicine

This study has been approved by the University of Otago Human Ethics Committee (ref. H13/027). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated, and you will be informed of the outcome.
Case Study A

Lucy is a 35 year old woman who is referred to you for endoscopy. She has elevated IgA anti-TTG antibodies and has a long history of IBS-type symptoms. Her histology result is reported as showing Marsh 3 changes, consistent with a diagnosis of coeliac disease. She should be referred to a dietician for advice on the gluten free diet.

(1) In your experience, who would normally refer this patient to the dietician? (Please choose one)

- I would
- One of my team would
- Her GP would, on receipt of the histology report

(2) Following her endoscopy, how important is it that she sees you (or a gastroenterologist colleague) to discuss the diagnosis? (Please choose one)

- Not important at all
- Not very important
- Neutral
- Important
- Very important

(3) If you don’t think it is important for Lucy to come back to see you (or a gastroenterologist colleague), who should see her to discuss her diagnosis?

____________________________________________________________________________________
_________________________________________________________________

(4) When considering Lucy’s management for the NEXT 12 MONTHS, how important are each of the following? Please rate each option on the 1 - 5 scale of importance, where:

1 = not important at all  3 = neutral  5 = very important

<table>
<thead>
<tr>
<th>Rating of importance (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An application is made for a Special Authority number for prescription gluten free foods</td>
</tr>
<tr>
<td>She is referred for a DEXA scan</td>
</tr>
<tr>
<td>She has follow-up TTG testing</td>
</tr>
<tr>
<td>She is reviewed to ensure any CD symptoms have resolved</td>
</tr>
<tr>
<td>She is monitored to ensure abnormal blood tests (e.g. low iron) return to normal</td>
</tr>
<tr>
<td>She has a follow-up biopsy at around 12 months</td>
</tr>
<tr>
<td>She is advised to join Coeliac NZ</td>
</tr>
<tr>
<td>She is advised that her 1st degree relatives should be tested for CD</td>
</tr>
</tbody>
</table>
(5) Please comment on any of the above, or if there is anything else you consider would be an important part of Lucy’s management in the **NEXT 12 MONTHS**.

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

(6) Who should be responsible for arranging the following aspects of her management, in the **NEXT 12 MONTHS**? (Please tick one column for each aspect)

<table>
<thead>
<tr>
<th>Aspect</th>
<th>I don’t think this is necessary</th>
<th>Me</th>
<th>One of my team</th>
<th>Her GP</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applying for a Special Authority number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referring her for a DEXA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advising her to join Coeliac NZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advising her that her 1st degree relatives should be tested</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(7) If you answered “Other” to any of the above, please comment.

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

(8) When should follow-up TTG testing take place? (Choose as many options as you think appropriate)

- I don’t think this is necessary
- Routinely at 3 months
- Routinely at 6 months
- Routinely at 12 months
- Only if her symptoms don’t resolve
- Other; please comment
(9) When considering Lucy’s **LONG TERM** management, how important are each of the following?

Please rate each option on the 1 - 5 scale of importance, where:

1 = not important at all  
3 = neutral  
5 = very important

<table>
<thead>
<tr>
<th>Rating of importance (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Regular reinforcement of the importance of the gluten free diet
Periodic TTG testing
Periodic screening for associated conditions (e.g. thyroid disease)
Annual influenza vaccination
5-yearly Pneumococcal vaccination

(10) Please comment on any of the above, or if there is anything else you think it would be important to include in Lucy’s **LONG TERM** management.

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

(11) How important is it that Lucy has an “Annual Review” of her coeliac management? (Please choose one)

- [ ] Not important at all
- [ ] Not very important
- [ ] Neutral
- [ ] Important
- [ ] Very important

(12) Who should do this? (Please choose one)

- [ ] I don’t think this is necessary
- [ ] GP
- [ ] Practice Nurse
- [ ] Dietician
- [ ] Gastroenterologist
- [ ] Other; please comment

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
Following your confirmation that Lucy does have coeliac disease, you will at some stage send her back to the care of her GP.

(13) In your letter to her GP, how likely are you to comment on each of the following issues which relate to Lucy’s management for the NEXT 12 MONTHS?

Please rate each option on the 1 - 5 scale of likelihood, where:

1 = highly unlikely  
3 = neutral  
5 = highly likely

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- She should see a dietician
- She is eligible for a Special Authority number
- She should have a DEXA scan
- She should have follow-up TTG testing
- She should be reviewed to ensure any CD symptoms have resolved
- Her 1st degree relatives should be tested for CD
- She should be encouraged to join Coeliac NZ

(14) How likely are you to comment on each of the following issues which relate to her LONG TERM management?

Please rate each option on the 1 - 5 scale of likelihood, where:

1 = highly unlikely  
3 = neutral  
5 = highly likely

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- The importance of the gluten free diet should be regularly reinforced
- She should have periodic TTG testing
- She should have periodic screening for associated conditions (e.g. thyroid disease)
- She should have an annual influenza vaccination
- She should have a 5-yearly Pneumococcal vaccination
- She should have an annual review of her coeliac disease management

(15) Please comment if there is anything else you would include in your letter.

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
Recently diagnosed coeliac disease

Thinking more broadly than just Lucy in Case Study A,

(16) In some countries it is recommended that all coeliac patients should be re-biopsied at approximately 12 months following their diagnosis. How important do you think this is?

- Not important at all
- Not very important
- Neutral
- Important
- Very important

(17) Please comment on your response.

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

(18) In general, when do you think adults with newly diagnosed coeliac disease should be referred for DEXA scanning? (Please choose one)

- Almost never
- Only in certain clinical situations
- Almost always

(19) If you think that DEXA scans should only be done in certain clinical situations, what are those situations?

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

(20) How often do you discuss joining Coeliac NZ with your newly diagnosed coeliac patients? (Please choose one)

- Almost never
- Some of the time
- About half the time
- Most of the time
- Almost always

(21) How often do you discuss the issue of testing first degree relatives with your newly diagnosed coeliac patients? (Please choose one)

- Almost never
- Some of the time
- About half the time
- Most of the time
- Almost always
Case Study B

Joshua is a 20 year old man referred to you with significantly elevated IgA anti-TTG antibodies. He was tested because his sister has recently been diagnosed with coeliac disease. When you question him about symptoms, he tells you he has never noticed any.

(1) Which of the following would be your most likely course of action? (Please choose one)

- Proceed to biopsy
- Repeat his TTG, and biopsy if the level remains elevated
- Repeat his TTG, test endomysial antibodies and HLA DQ2/8 status, and biopsy if positive
- Repeat his TTG, test endomysial antibodies and HLA DQ2/8 status, and recommend a gluten free diet if positive
- Other; please comment__________________________
  _____________________________________________________________________
  _____________________________________________________________________
  _____________________________________________________________________
  _____________________________________________________________________
  _____________________________________________________________________

(2) If you were to biopsy this patient and the results were reported as normal (Marsh 0), how likely would you be to do the following?

Please rate each option on the 1 - 5 scale of likelihood, where:

1 = highly unlikely
3 = neutral
5 = highly likely

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  2  3  4  5</td>
</tr>
<tr>
<td>Review the biopsy result with a pathologist</td>
</tr>
<tr>
<td>Repeat the biopsy in the near future</td>
</tr>
<tr>
<td>Arrange for him to have a capsule endoscopy</td>
</tr>
<tr>
<td>Check his HLA DQ2/8 status</td>
</tr>
<tr>
<td>Check for endomysial antibodies</td>
</tr>
<tr>
<td>Start him on a gluten free diet and repeat his serology tests at a later date, to document a fall in levels</td>
</tr>
<tr>
<td>Do nothing further, but advise repeat investigations at some future time, or if he becomes symptomatic</td>
</tr>
</tbody>
</table>

(3) Please comment if there is anything else you would do in this situation
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

409
(4) If Joshua’s biopsy result is confirmed to be Marsh 0, but he is HLA DQ2/8 positive and his TTG antibodies remain elevated, which of the following would you most likely to advise him (and/or his GP)? (Please circle one)

- He has latent coeliac disease and should be treated with a gluten free diet
- He has latent coeliac disease so does not need treatment unless he becomes symptomatic
- He may or may not have coeliac disease. Take a watch and wait approach and reinvestigate in a year, or if he becomes symptomatic.
- Other; please comment

(5) If Joshua were instead SYMPTOMATIC and had NORMAL histology, how likely would you be to do each of the following?

Please rate each option on the 1 - 5 scale of likelihood, where:

1 = highly unlikely  
3 = neutral  
5 = highly likely

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Review the biopsy result with a pathologist</td>
</tr>
<tr>
<td>Repeat the biopsy in the near future</td>
</tr>
<tr>
<td>Arrange for him to have a capsule endoscopy</td>
</tr>
<tr>
<td>Check his HLA DQ2/8 status</td>
</tr>
<tr>
<td>Check for endomysial antibodies</td>
</tr>
<tr>
<td>Start him on a gluten free diet and repeat his serology tests at a later date, to document a fall in levels</td>
</tr>
<tr>
<td>Do nothing further, but advise repeat investigations at some future time</td>
</tr>
</tbody>
</table>

(6) Please comment if there is anything else you would do in this situation.

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
(7) In this situation with a SYMPTOMATIC patient who has elevated TTG antibodies, is HLA DQ2/8 positive, and has a biopsy result confirmed as Marsh O, which of the following would you be most likely to advise the patient (and/or his GP)? (Please choose one)

- He has latent coeliac disease and should be treated with a gluten free diet
- He has latent coeliac disease so does not need treatment
- He may or may not have coeliac disease. Take a watch and wait approach and reinvestigate in a year
- Other; please specify __________________________________________________________

Case Study C

You are contacted by a local GP who has a patient whom she suspects has coeliac disease, based on symptoms and moderately positive IgA anti-TTG antibodies. The patient is unwilling to undergo endoscopy for biopsy, and has already commenced a gluten free diet. The GP asks you how you think she should proceed with this patient.

(1) How likely would you be to suggest each of the following?

Please rate each option on the 1 - 5 scale of likelihood, where:

1 = highly unlikely 3 = neutral 5 = highly likely

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

Repeat the TTG to see if it has fallen on the gluten free diet. This supports the diagnosis of coeliac disease. 1 2 3 4 5
Test HLA DQ2/8 status to see whether coeliac disease is possible or not. 1 2 3 4 5
Inform the patient that diagnosing coeliac disease is unreliable without a biopsy; she should reconsider her decision. 1 2 3 4 5
Assume that the patient does have coeliac disease, and manage her accordingly. 1 2 3 4 5

(2) Please comment if there is anything else you would suggest to this GP.
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
Several months later the patient is finding it a challenge to stick to the gluten free diet and would now like to have a biopsy to find out if she really does have coeliac disease. She realises she will have to re-introduce gluten into her diet.

(3) How much gluten-containing food would you recommend that she needs to consume for an adequate gluten challenge? (e.g. slices of bread per day).
____________________________________________________________________________________

(4) How long would you recommend she should continue eating gluten-containing food before she can be biopsied? (Please choose one)
   ☐ Until she is symptomatic
   ☐ For at least two weeks
   ☐ For at least four weeks
   ☐ For at least six weeks
   ☐ Other; please specify: ________________________________________________________________
                                                                                           ________________________________________________________________

The patient does have coeliac disease, and wants to include oats in her diet.

(5) What do you think about coeliac patients including non-cross-contaminated oats in their gluten free diet? (Please choose one)
   ☐ They should avoid consuming any oats
   ☐ Oats may be included in the GFD as soon as it is commenced
   ☐ Oats should only be included once the patient is asymptomatic
   ☐ Oats should only be included once the patient is asymptomatic and their serology has returned to normal
   ☐ Oats should only be included if the patient has biopsy-proven recovery of the gut
   ☐ Other; please specify: ________________________________________________________________
                                                                                           ________________________________________________________________

(6) If patients choose to include oats in their gluten free diet, what is your practice with regards to re-biopsy? (Please choose one)
   ☐ I don’t re-biopsy. If they become symptomatic I advise them to stop eating oats
   ☐ I routinely re-biopsy, irrespective of symptoms
   ☐ I re-biopsy if symptoms recur
   ☐ Other; please specify: ________________________________________________________________
                                                                                           ________________________________________________________________

(7) Do you have any other comments you wish to make, with respect to the management (and/or diagnosis) of coeliac disease?
                                                                                           ________________________________________________________________

Page 10 of 11
Demographic questions

Thank you very much for completing this survey. In order to help us to interpret the information you have provided, we need some additional, descriptive information about you. Please could you also complete the following:

(1) What is your current position?

- Consultant Gastroenterologist
- Consultant Surgeon
- Gastroenterology Registrar

(2) How many years have you been practising in the area of gastroenterology?

- 1 – 10
- 11 – 20
- 21 – 30
- >30
- I am a surgeon who does endoscopies

(3) How many clinical tenths do you work in gastroenterology?

- < 3
- 3 - 5
- 6 - 8
- >8
- I am a surgeon who does endoscopies

(4) Do you hold an academic post?  
- Yes
- No

(5) What is your gender?  
- Male
- Female

(6) In which country (or countries) did you undertake your UNDERGRADUATE training?

____________________________________________________________________________________
____________________________________________________________________________________

(7) In which country (or countries) did you undertake your POSTGRADUATE training?

____________________________________________________________________________________
____________________________________________________________________________________

(8) What are your areas of sub-speciality?  

____________________________________________________________________________________
____________________________________________________________________________________

(9) In which DHB region (or regions) do you work?  

____________________________________________________________________________________
____________________________________________________________________________________

(10) In which practice setting (or settings) do you work?

- Public Hospital only
- Private Practice only
- Mix of Public and Private
- Other; please specify: ______________________________________

(11) How many tenths do you work in private practice?

- None
- 1 – 3
- 4 – 6
- 7 – 10
(12) Please comment on any factors about the setting (or settings) in which you work which may impact on your management of patients with possible coeliac disease. (E.g. patient expectations, resource availability, capacity for follow-up etc.)

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

(13) For each of the following clinical scenarios, how many ADULT Coeliac patients do you see? (Please tick the appropriate column for each scenario)

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>None</th>
<th>&lt; 10 per year</th>
<th>1 – 10 per month</th>
<th>11 – 20 per month</th>
<th>&gt; 20 per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>New referral; diagnosis not previously considered</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For biopsy to confirm diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For follow-up; recently diagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For follow-up; long-term diagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For review; concern about recovery or possible complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other – please specify:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(14) From which of the following sources are you most likely to get your information about Coeliac Disease? Please rate each option on the 1-5 scale of likelihood, where:

1 = highly unlikely, I never use this source    3 = neutral, I may or may not use this source
5 = highly likely, I often use this source

<table>
<thead>
<tr>
<th>Source</th>
<th>Rating of likelihood (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterology Conferences</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Colleagues</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Practice Guidelines</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Medical Journals</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Coeliac NZ</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

Other – please specify: ____________________________________________________________
Appendix E: Invitation and reminder letters to gastroenterologists

Initial invitation

Dear colleague,

My name is Kristin Kenrick, and I am a GP and PhD candidate investigating adult Coeliac Disease in New Zealand. I am working with Michael Schultz and Andrew Day, whom you know through the Society, and Chrystal Jaye from the Department of General Practice and Rural Health in the Dunedin School of Medicine.

My PhD research aims to develop strategies to improve the care of patients with CD, by identifying gaps in current approaches to the diagnosis and management of the condition. The first part of the project seeks to understand the role of specialists in the care of adults with coeliac disease, and their expectations of GPs who are also involved in this care. For this project to produce meaningful results we need as many people as possible to take part.

If you are a gastroenterologist (consultant or registrar) or a surgeon endoscopist, we would be very grateful if you would follow this link Coeliac Disease Survey and complete an anonymous on-line survey. It presents three scenarios, with questions which ask you to rate your likely responses. We are looking for information about your current practice. We are not looking for “right” answers. This survey will take about 25 minutes to complete, but you can do this in more than one sitting if you choose, as you can save your answers and return to it later.

The survey will be open for at least 4 weeks, and I will send a reminder email after 2 weeks.

If you would prefer to complete a paper-based version of the survey please email me (kristin.kenrick@otago.ac.nz) and I will send a form to you.

This study has been approved by the University of Otago Human Ethics Committee (ref. H13/027). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

With thanks in anticipation of your support,

Kristin Kenrick.
First follow-up email

Dear Colleagues,

Thank you very much to those of you who have already completed the Coeliac Disease survey, which was sent out 2 weeks ago.

If you are a gastroenterologist (consultant or registrar) or a surgeon endoscopist, and have not already done so, I would be very grateful if you would follow this link Coeliac Disease Survey and complete the anonymous on-line survey.

This survey will take about 25 minutes to complete, but you can do this in more than one sitting if you choose, as you can save your answers and return to it later.

If you would prefer to complete a paper-based version of the survey please email me (kristin.kenrick@otago.ac.nz) and I will send a form to you.

With thanks again in anticipation of your support,

Kristin Kenrick,
GP and PhD Candidate.

Second follow-up email

Dear Gastroenterology Colleagues,

Thank you very much to those of you who have completed the Coeliac Disease Survey, either on-line earlier in the year, or in hard-copy at the ASM last week.

If you still have a hard-copy of the survey which you completed, but didn't get a chance to give back to me, I would be very grateful if you would please send it back to me. The address is:

Dr K. Kenrick, Department of General Practice and Rural Health, University of Otago, P.O. Box 56, Dunedin 9054

Alternatively if you have not yet done the survey and would like to do so on-line, please click on the following link: Coeliac Survey

Many thanks again for your support with this project,

Kristin Kenrick.
Dear Doctor ...

Enclosed with this letter is a copy of the Coeliac Disease Survey which I first sent out in electronic form last year, and then gave out in hardcopy at the NZ Gastroenterology Society Annual Scientific Meeting in Wellington. You may have already seen it and, if you have already completed it, thank you for your help with this project, and please disregard this letter.

If you have not completed this survey I would be very grateful if you would be able to do so now. At present gastroenterologists from the Auckland region are significantly under-represented in the responses I have received, which is why I am writing to you. Improving on this will add considerable weight to the findings of the project.

This survey forms part of a PhD project in which I am investigating adult Coeliac Disease in New Zealand. I am working with gastroenterologists Associate Professor Michael Schultz and Professor Andrew Day, and Associate Professor Chrystal Jaye, from the Department of General Practice and Rural Health in the Dunedin School of Medicine. We are particularly interested in developing strategies to improve the care of patients with CD, by identifying gaps in current approaches to the diagnosis and management of the condition. This part of the project seeks to understand the role of specialists in the care of patients with CD, and their expectations of GPs who are also involved in this care. We are looking for information about your current practice, rather than the “right” answers. The survey should take you no more than 20 minutes to complete.

Please note there are questions on both sides of each page.

I would really appreciate your help with this project. Please return your completed survey in the postage-paid envelope provided.

Many thanks and best wishes,

Kristin Kenrick
GP and PhD Candidate
Dunedin School of Medicine

This study has been approved by the University of Otago Human Ethics Committee (ref. H13/027). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated, and you will be informed of the outcome.
Dear Doctor …

Enclosed with this letter is a copy of the Coeliac Disease Survey which I first sent out in electronic form last year, and then gave out in hardcopy at the NZ Gastroenterology Society Annual Scientific Meeting in Wellington. You may have already seen it and, if you have already completed it, thank you for your help with this project, and please disregard this letter.

If you have not completed this survey I would be very grateful if you would be able to do so now. At present the response rate from women gastroenterologists is substantially lower than that from your male colleagues, which is why I am writing to you. Improving on this will add weight to the findings of the project.

This survey forms part of a PhD project in which I am investigating adult Coeliac Disease in New Zealand. I am working with gastroenterologists Associate Professor Michael Schultz and Professor Andrew Day, and Associate Professor Chrystal Jaye, from the Department of General Practice and Rural Health in the Dunedin School of Medicine. We are particularly interested in developing strategies to improve the care of patients with CD, by identifying gaps in current approaches to the diagnosis and management of the condition. This part of the project seeks to understand the role of specialists in the care of patients with CD, and their expectations of GPs who are also involved in this care. We are looking for information about your current practice, rather than the “right” answers. The survey should take you no more than 20 minutes to complete.

Please note there are questions on both sides of each page.

I would really appreciate your help with this project. Please return your completed survey in the postage-paid envelope provided.

Many thanks and best wishes,

Kristin Kenrick
GP and PhD Candidate
Dunedin School of Medicine

This study has been approved by the University of Otago Human Ethics Committee (ref. H13/027). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated, and you will be informed of the outcome.
Appendix F: The survey of General Practitioners

A SURVEY OF NEW ZEALAND GENERAL PRACTITIONERS’ APPROACH TO ADULT COELIAC DISEASE

Dear Colleague,

I am a GP working on a PhD in which I am investigating the recognition and management of adult Coeliac Disease, a condition with increasing prevalence in our communities. I want to be able to develop a set of New Zealand-specific guidelines which will enable us all to better deliver consistent and evidence-based care to our coeliac patients.

To assist me with this project I really need information from GPs about their current practice relating to Coeliac Disease, so I would be very grateful if you would complete the following survey. It should take you no more than 20 minutes to do.

Participants who complete the survey will be eligible to enter a draw for a $750.00 travel voucher to attend a conference or educational event of their choice, donated by bpha

I have recently completed a survey of gastroenterologists, and your participation in this survey will complement the information I have gathered from them.

Please return your completed survey by 29th May 2015, or participate online at: www.surveymonkey.com/r/GP-Coeliac-Survey

With thanks in anticipation of your participation.

Kristin Kenrick
GP and PhD Candidate
Dunedin School of Medicine

This survey has been sent to a randomly selected sample of GPs across New Zealand.

No information which could identify you will be used at any time in the analysis or publication of this research.

This study has been approved by the University of Otago Human Ethics (Health) Committee (ref.H14/044). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph. 03 479 8256). Any issues you raise will be treated in confidence and investigated, and you will be informed of the outcome.
**PART A: COELIAC DISEASE IN GENERAL**

(1) How likely would you be to order coeliac testing for patients with any of the following signs and symptoms, but who are **otherwise asymptomatic**? Please rate each option on the 1 - 5 scale of likelihood, where:

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
<th>1 = highly unlikely</th>
<th>3 = neutral</th>
<th>5 = highly likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature reduced bone mineral density</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained iron deficiency</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained folate deficiency</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained elevation of liver transaminases</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent aphthous stomatitis</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent back pain</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained neurological symptoms</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent fatigue</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of two or more of the above</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(2) How likely would you be to order coeliac testing for patients with any of the following **conditions**, but who are **otherwise asymptomatic**? Please rate each option on the 1 - 5 scale of likelihood, where:

<table>
<thead>
<tr>
<th>Rating of likelihood (circle one)</th>
<th>1 = highly unlikely</th>
<th>3 = neutral</th>
<th>5 = highly likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paget’s disease of the bone</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree relative of coeliac patient</td>
<td>1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(3) Are there any other indications which would lead you to test someone for coeliac disease? If so, please comment:
(9) Many patients today are starting themselves on a gluten-free diet without having been tested for coeliac disease. If you thought that a patient in this situation should be tested for coeliac disease, what would you advise them about including gluten in their diet prior to testing? (Please choose one option)

- Nothing, I would simply test them
- I would recommend that they reintroduce some gluten into their diet but would test them even if they did not wish to do this
- I would recommend that they reintroduce some gluten into their diet and would not test them if they did not wish to do this

(10) If you did recommend re-introducing gluten, how much gluten-containing food would you suggest that a patient needs to consume for an adequate gluten challenge? (e.g. slices of bread per day) ____________

__________________________

OR: I don’t know; I would need to find out

(11) How long would you advise that they need to do this for, before being tested for coeliac disease? (Please choose one option)

- I don’t know; I would need to find out
- Until they are symptomatic
- For at least two weeks
- For at least four weeks
- For at least six weeks
- Other; please specify: ____________________________

(12) If you would need to find out the answer to Questions 10 or 11, how would you do that? (Please choose the two most likely options)

- Contact a local gastroenterologist
- Contact a dietician
- Ask a colleague
- Google it
- Contact Coeliac NZ
- Go to an internet source such as BPAC or patient.co.uk
- Other; please specify: ____________________________

__________________________

__________________________

(13) Gastroenterologists in NZ and abroad are beginning to recommend that patients with coeliac disease have their management reviewed by a health professional on an annual basis. Assuming that children are reviewed in paediatric clinics, how necessary do you think this is for adult coeliac patients? (Please choose one option)

- Totally unnecessary
- Probably unnecessary
- Neutral
- Probably necessary
- Definitely necessary
- Other; please comment: ____________________________

__________________________
(14) Who do you think should **usually** perform such a review? (Please choose one option)

- I don’t think it is necessary
- General Practitioner
- Practice Nurse
- Gastroenterologist
- Dietician
- Other; please specify: ____________________________

(15) Do you have any additional comments to make about this issue?

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

(16) Is an annual review something you try to do for your adult coeliac patients already? (Please choose one option)

- I don’t have any adult patients with coeliac disease
- No, I don’t do this for my adult coeliac patients
- Yes, I do this for **all** my adult coeliac patients
- Yes, I do this but only for **some** of my adult coeliac patients
  Which ones and why? ____________________________
  ____________________________
  ____________________________
- Other; please comment: ____________________________

(17) If you were to do an annual review of their management with your coeliac patients, what would you include in that review? ____________

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

(18) Do you have any additional comments you wish to make about coeliac disease in general? ____________

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

Thank you for your responses so far. You are now halfway through the survey.

If you **DO NOT** have any coeliac patients in your practice, please go to the last 3 pages of this booklet, which ask for demographic information about you.

If you would like to enter the prize draw please make sure you also complete your details on the last page of the booklet.

If you **DO** have coeliac patients in your practice, please continue with the following questions.
PART B: COELIAC DISEASE IN YOUR PRACTICE

(1) In your experience, who usually refers newly diagnosed adult coeliac patients to a dietician? (Please choose one option)
   ○ I don’t know
   ○ I do
   ○ My practice nurse does
   ○ A gastroenterologist (or member of their team) does

(2) In your experience, who usually applies for a Special Authority number for subsidised prescription gluten-free foods for newly diagnosed adult coeliac patients? (Please choose one option)
   ○ I don’t know
   ○ I do
   ○ My practice nurse does
   ○ A gastroenterologist (or member of their team) does
   ○ No-one does; they’re not necessary

(3) How often do you refer your newly diagnosed adult coeliac patients for DEXA scanning? (Please choose one option)
   ○ Almost never, I don’t think this is necessary
   ○ Almost never, I wasn’t aware this might be necessary
   ○ Almost never, I assume a gastroenterologist does this
   ○ Almost always
   ○ Only in certain clinical situations. Please list: __________

(4) If the diagnosis of coeliac disease has been made without the patient having a biopsy, how does your management of these issues change?
   __________________________________________
   __________________________________________

(5) Do you, or have you ever provided prescriptions for subsidised gluten-free foods for your coeliac patients?
   ○ Yes ○ No

   If yes, please comment on how you would determine the appropriate amount of food to include for each prescription.
   __________________________________________
   __________________________________________
   __________________________________________

(6) How often do you discuss the issue of testing first-degree relatives with your newly diagnosed adult coeliac patients? (Please choose one option)
   ○ Almost never, I don’t think this is necessary
   ○ Almost never, I wasn’t aware this might be necessary
   ○ Almost never, I assume a gastroenterologist does this
   ○ Some of the time
   ○ About half the time
   ○ Most of the time
   ○ Almost always
(7) How often do you discuss joining Coeliac NZ with your newly diagnosed adult coeliac patients? (Please choose one option)

- Almost never, I don’t think this is necessary
- Almost never, I wasn’t aware this might be necessary
- Almost never, I assume a gastroenterologist does this
- Some of the time
- About half the time
- Most of the time
- Almost always

(8) How often do you review your adult coeliac patients specifically with respect to their coeliac disease? (Please choose one option)

- Almost never, I don’t think this is necessary
- Almost never, I wasn’t aware this might be necessary
- Almost never, I assume a gastroenterologist does this
- Occasionally
- 6 monthly
- Annually
- I’ll ask them about it if I have time when they see me for something else
- Other; please comment: __________________________

(9) Do you ever reinforce the importance of adhering to the gluten-free diet with your adult coeliac patients? (Please choose one option)

- No, I don’t think this is necessary
- No, I wasn’t aware this might be necessary
- Yes, but only if they have symptoms which suggest they might not be adhering to the diet
- Yes, I make a point of doing this on a regular basis
- Other; please comment: __________________________

(10) When do you re-test coeliac serology in your adult coeliac patients? (Please choose as many answers as necessary)

- Almost never, I don’t think this is necessary
- Almost never, I wasn’t aware this might be necessary
- Almost never, I assume a gastroenterologist arranges this
- Routinely, 3 months after they’ve started the gluten free diet
- Routinely, 6 months after they’ve started the gluten free diet
- Routinely, annually
- If their coeliac symptoms do not settle
- If their coeliac symptoms recur
- If they request it
- Other; please comment: __________________________
(11) How often do you test your adult coeliac patients for conditions associated with coeliac disease? (e.g. thyroid disease) (Please choose one option)

○ Almost never, I don’t think this is necessary
○ Almost never, I wasn’t aware this might be necessary
○ Almost never, I assume a gastroenterologist arranges this
○ Only if they have symptoms suggestive of that condition
○ I screen them from time to time
○ I screen them annually
○ Other; please comment: ____________________________

(12) How often do you recommend that your adult coeliac patients have an annual ‘flu’ vaccination? (Please choose one option)

○ Almost never, I don’t think this is necessary
○ Almost never, I wasn’t aware this might be necessary
○ Almost never, I assume a gastroenterologist does this
○ Some of the time
○ About half the time
○ Most of the time
○ Almost always

(13) How often do you recommend that your adult coeliac patients have a 5-yearly pneumococcal vaccination? (Please choose one option)

○ Almost never, I don’t: think this is necessary
○ Almost never, I wasn’t aware this might be necessary
○ Almost never, I assume a gastroenterologist does this
○ Some of the time
○ About half the time
○ Most of the time
○ Almost always

(14) Do you have any additional comments that you wish to make?

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________
PART C: DEMOGRAPHIC INFORMATION

(1) Which of the following applies to you? (Please choose one option)
   ○ I own my own practice
   ○ I work as a long term locum/associate/ salaried employee in one practice
   ○ I locum in many practices
   ○ Other; please specify: ____________________________

(2) How many half-day sessions do you work in general practice in a typical week?
   ○ < 3  ○ 3 - 5  ○ 6 - 8  ○ >8

(3) What is your gender?  ○ Male  ○ Female

(4) With which ethnic group or groups do you identify?
    ________________________________________________

(5) Are you vocationally registered in General Practice?
   ○ Yes  ○ No

(6) How many years have you been in clinical practice?
   ○ 1 – 10  ○ 11 – 20  ○ 21 – 30  ○ >30

(7) Is your practice/the practice in which you work:
   ○ Rural  ○ Urban

(8) What is the predominant socio-economic status of the practice population you care for? ____________________________

(9) What are the predominant ethnic groups in the practice population you care for? ____________________________

(10) In which DHB region, or regions, do you practise?
    ○ Northland  ○ Auckland  ○ Counties/Manakau  ○ Waitemata
    ○ Bay of Plenty  ○ Waikato  ○ Tairawhiti
    ○ Lakes  ○ Taranaki  ○ Mid-Central  ○ Hawkes Bay  ○ Whanganui  ○ Wairarapa  ○ Capital and Coast
    ○ Hutt Valley  ○ Nelson Marlborough  ○ West Coast  ○ Canterbury  ○ South Canterbury  ○ Southern
(11) From which of the following sources have you gained your knowledge about coeliac disease? Please tick as many options as apply.

○ CME meetings/conferences  ○ Medical Journals
○ Colleagues/ Peer group discussions  ○ Coeliac NZ
○ Advice from a gastroenterologist  ○ BPAC NZ
○ Practice Guidelines (e.g. NICE)  ○ Medical School
○ Patients with coeliac disease
○ Letters from gastroenterologists about patients with CD
○ Other: ____________________________

__________________________________

Thank you very much for taking the time to complete this survey. I really appreciate your participation.

If you would like to enter the draw for the $750.00 travel voucher, please complete your contact details below. These will be separated from your responses to this survey to ensure that your anonymity is retained.

Name: __________________________________________

__________________________________

Preferred contact address: ________________________

__________________________________
Appendix G: Emails and reminder letters to GPs

Initial email to GPs with both email and postal addresses available

NZ GPs' Approach to Adult Coeliac Disease

Dear Dr …

I am a GP and am currently conducting some research on adult coeliac disease, a condition with increasing prevalence in our community.

Next week I will be posting you a survey relating to this topic and I would be very grateful if you would take the time to complete it. If you complete the survey you will be eligible to enter a draw for a $750.00 travel voucher (to attend a conference or educational event of your choice) donated by BPAC NZ.

If you would prefer to do the survey on-line you can do so by following the link at the end of this email.

With thanks in anticipation of your participation,

Kristin Kenrick,
GP and PhD Candidate
Dunedin School of Medicine.

Begin Survey
Dear Dr …

I am a GP and am currently conducting some research on adult coeliac disease, a condition with increasing prevalence in our community. I want to be able to develop a set of New Zealand-specific guidelines which will enable us all to better deliver consistent and evidence-based care to our coeliac patients.

To assist me with this project I really need information from GPs about their current practice relating to Coeliac Disease, so I would be very grateful if you would complete a survey by following the link at the end of this email.

If you complete the survey you will be eligible to enter a draw for a $750.00 travel voucher (to attend a conference or educational event of your choice) donated by BPAC NZ.

If you would prefer to do the survey in hardcopy format, please email me and I will send you a copy.

With thanks in anticipation of your participation,

Kristin Kenrick,
GP and PhD Candidate
Dunedin School of Medicine.

Please do not forward this email as its survey link is unique to you.

Opt out of receiving surveys from this sender
Dear Dr …

By now you should have received a hard copy of my Coeliac Disease survey. If you have not already done so, I would be very grateful if you would complete this and return it in the reply-paid envelope which was enclosed with it. The more responses I receive, the more reliable my findings will be.

If you would prefer to do the survey online, please click on the link below, and put the hardcopy in your recycling bin.

Participants who complete the survey are eligible to enter the draw to win a $750.00 travel voucher donated by BPAC NZ.

With thanks in anticipation of your participation,

Kristin Kenrick,
GP and PhD Candidate,
Dunedin School of Medicine.
Dear Dr …

Recently I emailed you about my Coeliac Disease survey. If you have not already done so, I would be very grateful if you would complete this by following the link below. The more responses I receive, the more reliable my findings will be.

Participants who complete the survey are eligible to enter the draw to win a $750.00 travel voucher donated by BPAC NZ.

With thanks in anticipation of your participation,

Kristin Kenrick,
GP and PhD Candidate,
Dunedin School of Medicine.

Begin Survey
Reminder letter to GPs who received hard copy only

Dear Dr …

Recently I sent you a survey entitled *New Zealand General Practitioners’ Approach to Adult Coeliac Disease*.

As I write this I have not yet received a response from you, so I would be very grateful if you would be able to take some time to complete the enclosed copy. Alternatively, if you prefer to participate online, you can go to: [www.surveymonkey.com/r/GP-Coeliac-Survey](http://www.surveymonkey.com/r/GP-Coeliac-Survey)

I would really appreciate your contribution to this research project because, to ensure that my results are meaningful, I need information from as many GPs as possible about their current practice relating to coeliac disease. If you have already completed the survey in the meantime, thank you very much.

**If you complete this survey you will be eligible to enter the draw for a $750.00 travel voucher to attend a conference or educational event of your choice, donated by bpacNZ.**

I have extended the timeframe to complete the survey until 5th June 2015.

Many thanks and best wishes,

Kristin Kenrick,
GP and PhD Candidate
Dunedin School of Medicine.