

**PARENTAL RESPONSES TO  
NEWBORN SCREENING FOR  
GENETIC SUSCEPTIBILITY TO  
TYPE 1 DIABETES**

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## **Abstract**

Advances in genomic medicine have led to considerable debate over the potential for inclusion of genetic tests for susceptibility to common complex disorders in newborn screening programmes. Empirical evidence concerning psychosocial reactions to genetic testing is a crucial component of both ethical debate and policy development, but while there has been much speculation concerning the possible psychosocial impact of screening newborns for genetic susceptibilities, there remains a paucity of data. In this thesis I aim to provide some of this missing empirical evidence, using type 1 diabetes as an example of a common disorder with multiple significant genetic contributors to its aetiology.

In the first section of the thesis (chapters 1 to 3) I provide background to the debate over newborn screening for genetic susceptibility to common disease. To achieve this I first examine what newborn screening currently involves, noting in particular its complexities, how target disorders are selected, and how this process has evolved over time, before reviewing the existing evidence base concerning parents' psychosocial reactions. I then describe recent advances in "genomic medicine", focusing particularly on type 1 diabetes to explain and explore how such complex disorders differ, in important ways, from those traditionally included in newborn screening panels.

In the second part of the thesis (chapters 4 to 7) I present the findings of my own empirical research. Firstly I describe a quantitative analysis of the psychological impact that newborn screening for genetic susceptibility to type 1 diabetes has upon mothers. To achieve this I report a prospective study involving administration of a range of psychological questionnaires to three mother-baby cohorts: 38 infants at increased genetic risk of type 1 diabetes, 73 at low risk and 76 who had not undergone testing. The results indicate that such screening is not associated with elevated levels of maternal anxiety, depressive symptoms, or heightened perceptions of infant vulnerability in the first postnatal year.

I then present qualitative data from 11 semi-structured interviews conducted with parents of children who had received increased risk results in a study involving newborn screening for genetic susceptibility to type 1 diabetes. These data illustrate that while parents generally report fairly minor levels of concern in response to increased risk results, their reactions are much more varied, complex and dynamic than those described in relation to existing newborn screening programmes.

In conclusion I argue that while it may be somewhat reassuring that parents do not suffer clinically significant levels of psychological harm in relation to newborn screening for genetic susceptibility to type 1 diabetes, the more subtle, complex and ongoing reactions described in the qualitative component are likely to be of considerable importance in terms of ethical analysis and policy development. Newborn screening for genetic susceptibility to complex disorders should not be considered for clinical application until psychosocial responses are better characterised and the implications of these reactions more completely understood.



## **Preface**

Some sections of this thesis have been published.

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## Glossary

AATD	Alpha 1 antitrypsin deficiency
CF	Cystic fibrosis
CNV	Copy number variation
CSM	Common sense model of self regulation of health and illness behaviour
DMD	Duchenne muscular dystrophy
EPDS	Edinburgh postnatal depression scale
FXS	Fragile X syndrome
GWAS	Genome wide association study
IPA	Interpretative phenomenological analysis
KEA	Key environmental aspects of type 1 diabetes in childhood
MCAD	Medium chain acyl dehydrogenase deficiency
NBS	Newborn screening
PKU	Phenylketonuria
PND	Postnatal depression
SNP	Single nucleotide polymorphism
STAI	State trait anxiety inventory
T1D	Type 1 diabetes
VBS	Vulnerable baby scale



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# Table of Contents

Abstract	3
Declaration	5
Preface	7
Glossary	9
Acknowledgements	11
<b>Chapter 1 Introduction</b>	<b>17</b>
1.1 Introduction	18
1.2 From genetics to genomics	18
1.3 Genomic medicine	18
1.4 Genomics and child health	19
1.5 Overview of the thesis	26
1.6 Summary	28
<b>Chapter 2 Scientific Background: NBS and Genomics</b>	<b>29</b>
2.1 Introduction	30
2.2 A brief overview of NBS	30
2.3 Genomic medicine	40
2.4 Combining NBS and genomic medicine	46
2.5 Chapter conclusion: a way forward	50
<b>Chapter 3 Psychosocial Aspects of NBS</b>	<b>51</b>
3.1 Introduction	52
3.2 Psychosocial Research and NBS	52
3.3 The profound importance of early experiences	52
3.4 Definition of NBS terms	57
3.5 Review of existing research related to psychosocial reactions to NBS	57
3.6 Conditions included in current, widely implemented NBS programmes	57
3.7 Conditions included in current less widely implemented NBS programmes	66
3.8 Conditions included in research related NBS programmes	67
3.9 Summary of existing research	72
3.10 Relevance of existing research to NBS for genetic susceptibility to T1D	75
3.11 Conclusion	78
<b>Chapter 4 Research Design</b>	<b>79</b>
4.1 Introduction	80
4.2 Influences upon research design	80

4.3	Methodology .....	83
4.4	Quantitative research .....	83
4.5	Qualitative research .....	94
4.6	Conclusions .....	98
<b>Chapter 5 Quantitative Study Methods and Results .....</b>		<b>99</b>
5.1	Introduction .....	100
5.2	Aims of phase 1 .....	100
5.3	Research design .....	100
5.4	KEA study .....	101
5.5	Psychological effects arm of the KEA study .....	103
5.6	Questionnaire Findings .....	107
5.7	Questionnaire scores .....	108
5.8	Summary .....	115
5.9	Limitations of the research .....	118
5.10	Conclusions .....	119
<b>Chapter 6 Preliminary Qualitative Analysis .....</b>		<b>121</b>
6.1	Introduction .....	122
6.2	Aims of phase 2 .....	122
6.3	Participants .....	122
6.4	Interview process .....	125
6.5	Parents' experiences of newborn genetic susceptibility testing .....	126
6.6	Summary .....	147
6.7	Conclusion .....	148
<b>Chapter 7 Detailed Qualitative Analysis .....</b>		<b>149</b>
7.1	Introduction .....	150
7.2	Analysis .....	150
7.3	Themes for analysis .....	151
7.4	Making sense of a child's risk status .....	151
7.5	Making use of the genetic information .....	160
7.6	The common sense model of self regulation of health and illness (CSM) .....	165
7.7	Summary and limitations .....	171
<b>Chapter 8 Conclusions .....</b>		<b>173</b>
8.1	Introduction .....	174
8.2	Summation .....	174
8.3	Key findings .....	174

8.4	Summary .....	177
8.5	New hypotheses.....	177
8.6	Implications for future research .....	179
8.7	Implications for the bioethical debate .....	184
8.8	Implications for clinical practice.....	194
8.9	Overall Summary .....	200

**References**

**Appendix A STAI (Y-1)**

**Appendix B EPDS**

**Appendix C VBS**

**Appendix D Qualitative interview schedule**

**Appendix E KEA Study participant information sheet**

**Appendix F Letter to parents of babies at increased genetic risk**

**Appendix G Letter to parents of babies at low genetic risk**

**Appendix H KEA Study phase 2 participant information sheet**

**Appendix I Information sheets for participants in the psychosocial effects study**

**Appendix J Information sheet for participants in qualitative interviews**



# Chapter 1 Introduction

## 1.1 Introduction

*"From an early age, I came to think of myself as others thought of me: chronically ill. Every skinned knee and runny nose was treated as if it were life-threatening." [1]*

As a result of DNA testing in the newborn period this character, from the 1997 film *Gattaca*, is aware of his genetic predisposition to heart disease and premature death. The film is a work of science fiction but, as Francis Collins wrote in 2003, "the genomic era is now a reality"[2]. In this first chapter I provide background to current discussions concerning the potential use of genetic susceptibility testing in the newborn period, describing two different contexts in which it could occur, namely newborn screening (NBS) and individual predictive genetic testing. I then briefly review the underlying justifications for existing NBS programmes and the ethical and psychosocial issues that have limited the extent of predictive genetic testing in childhood. I then describe how the general focus of my thesis will be on genetic susceptibility testing as part of NBS, and that in particular I will address the current lack of empirical evidence concerning the psychosocial effects of such testing.

## 1.2 From genetics to genomics

The Human Genome Project was completed in spring 2003, having accomplished its major goals of sequencing human DNA and identifying and mapping the 20-25,000 human genes[3]. This remarkable achievement not only represents an important milestone in the history of biology and medicine, but has also opened important new avenues for research into human disease and variation. Such research, facilitated by rapid improvements in infrastructure (such as the International HapMap Project [4]), analytical methods, and technology, has led to considerable advances in our understanding of the influence of genetic variation on human diversity and susceptibility to disease[2]. Both the dramatic expansion in capabilities and recognition of enormous potential health benefits, have contributed to a shift in scientific focus from a *genetics* paradigm, where the influence of individual genes on health outcomes is paramount, to a *genomics* paradigm, encompassing the complex influences of multiple individual genes and environmental exposures upon health outcomes [5].

## 1.3 Genomic medicine

These impressive advances have led to considerable speculation that genomics will play a central role in medicine and public health in the 21st century[6]. Some claim that the rewards of the human genome project will include "a new understanding of the genetic contribution to human disease and the development of rational strategies for minimising or preventing

disease phenotypes altogether”[7]. Similarly, it has been suggested that the traditional practice of medicine involving diagnosis and treatment of disease, will be replaced by a new pattern of maintaining health in an apparently symptom-free patient by prediction and prevention[8]. This concept of “personalised medicine” whereby genetic susceptibility tests provide patients with their individual risk of disease, and interventions on the basis of their genotype, has captured the imagination of scientists and the public[9, 10].

However, there is a lack of consensus regarding the likelihood of this type of development, and the expected timeframe if it does eventuate. Some commentators temper the optimism with notes of caution, suggesting that decades of epidemiological study and clinical evaluation of interventions will be required[11]. Others are sceptical that genomics will ever revolutionise the way in which common diseases are identified or prevented, with their doubts stemming from issues such as the low magnitude of risk for common diseases associated with most genetic variants discovered thus far, the absence of interventions that are specific to different genotypes, and the potential for genetic labeling that may cause personal and social harms[12, 13].

#### **1.4 Genomics and child health**

While we cannot be certain how useful genomics will prove to be in the clinical setting, we can say that many of the potential interventions based on personalised genomic risk information would have the greatest benefit if targeted to early childhood, a time of critical importance for primary prevention of adult-onset common conditions[14]. There would also be obvious advantages to using a pre-existing screening infrastructure if genetic susceptibility testing were to be implemented at a population level. Newborns are an attractive population for novel screening initiatives as total population screening is already widespread and successful, and the filter paper blood samples used in existing metabolic testing are also suitable for DNA analysis [15]. As of now, NBS for common complex diseases, such as asthma, is under consideration[16], and pilot screening for genetic susceptibility to type 1 diabetes (T1D)[17] is already under way in a research context. It has even been suggested that babies be screened at birth to provide a comprehensive map of individual genomic variation that could then be securely stored on an electronic patient record and used in the future to tailor preventative regimes to their needs[18-20]. This scenario is already technologically feasible, likely to become publicly affordable within the next 20 years [19] and is attractive to those who wish to “take maximum advantage of the application of the new genetic knowledge for the benefit of all patients”[20].

### **1.4.1 Newborn screening**

Before contemplating whether or not any of these suggestions are appropriate, and if so *how* they may be facilitated, it is necessary to understand something of the history and current practice of NBS. These aspects of NBS are reviewed extensively in chapter 2, but I will introduce some of the important concepts underlying this widespread population screening programme here, as well as highlighting some of the underlying ethical issues.

NBS programmes date back to the early 1960s, when the technology to conduct large-scale testing on dried blood spots for phenylketonuria (PKU) was developed. PKU remains the paradigm condition for NBS because features of the disease, and its relatively straightforward treatment, make it particularly suited to population screening[21]. Over the years other conditions have been added largely on the basis that they fulfill certain screening criteria, such as those developed by Wilson and Jungner in the 1960s[22].

#### **1.4.1.1. NBS criteria and aims**

The Wilson and Jungner criteria cover aspects of the disease, availability and effectiveness of treatment, the scientific validity of the test, and the organisational infrastructure associated with the screening programme[22], and are reproduced later, in table 2.1. Ensuring that conditions included in screening panels fulfill these criteria has helped to ensure that NBS achieves its fundamental aim of doing “more good than harm”[23]. However, over the last few years NBS criteria have begun to evolve, partly in response to difficulties in applying them, particularly comparatively, [24, 25] and partly so that contemporary values such as quality assurance, equity, and scientific evidence of effectiveness can be incorporated into policy decisions[26].

The changing nature of NBS criteria, combined with the advent of new technologies such as tandem mass spectrometry, appear to be leading to a shift in the underlying rationale for NBS. For example, although screening for most disorders included on recently expanded NBS panels utilising tandem mass spectrometry may still prevent mortality and morbidity, some of the benefits are less dramatic, less immediate or may not directly accrue to the child. In other words the notion of benefit in NBS seems to be becoming much broader, encompassing not only benefit to the child but also benefits to families and society[27].

Expansion of NBS panels has also highlighted the fact that, for a number of reasons, the evidence base of some current NBS applications is relatively weak. However, it is increasingly acknowledged that a less-than-rigorous approach to research on these large, expensive, and important public health programmes is no longer appropriate [28]. It has also

been argued that NBS, as a public health service, needs to be supported by a broad social consensus, informed by objective evidence but also inclusive of ethical concerns[29].

### **1.4.2 Predictive genetic testing in childhood**

Discussions regarding the potential clinical application of genetic susceptibility testing in childhood generally refer to the NBS context, and indeed this represents the main focus of my thesis. There are a number of reasons for this interest in NBS including: the relative ease of adding tests to NBS panels, the population based nature of current epidemiological studies investigating the pathophysiology of common multifactorial disorders and the fact that potential benefits of testing and interventions would be most widely distributed through NBS. However, it should not be forgotten that genomic testing could also be implemented in paediatric practice in a more individualistic paradigm, as currently exists for predictive genetic testing for single gene disorders. While this possibility is not the main focus of my research it remains an important consideration and indeed many of the ethical and psychosocial issues related to individual predictive testing in childhood may also be relevant to NBS. For this reason I will briefly review the arguments concerning ethical and psychosocial aspects of childhood predictive genetic testing, most of which refer to single gene disorders, before continuing with a description of the direction that my thesis will take.

The term “predictive genetic test” generally refers to a genetic test offered to a healthy person to assist in the determination of their risk of developing a given disease later in life. Most predictive genetic tests currently offered in clinical genetics practice are for single gene disorders such as Huntington’s disease (HD) or for conditions such as familial breast and bowel cancer in which single genes play a major role in determining disease risk[30]. Therefore, unlike population screening in which families may not know much about the disorder in question, predictive testing usually occurs in families that already have an understanding of the disease and awareness of their underlying risk status [31]. Although this type of testing has clearly been shown to provide benefits to individuals and other family members it is also accompanied by a range of ethical, legal, social and psychological issues[32]. These issues are more complex and pronounced when genetic testing is contemplated in the context of child health and international guidelines generally advise against such testing unless there is clear medical benefit to the child[28, 30-32], although more recently, it has been suggested that the concept of best interests in childhood should be widened to incorporate not only medical benefit, but also potential psychological or social benefits[33].

Both the international guidelines concerning predictive genetic testing in children, and the extensive body of literature arguing against such testing, outline three fundamental reasons for this generally prohibitive position. These are that:

1. Testing infringes upon the child's future autonomy
2. Testing breaches the child's confidentiality
3. Testing may cause psychosocial harm to the child[34].

Within these three categories the arguments used to oppose or support predictive genetic testing in children are based on either the consequences of parents knowing their child's genetic status or the direct consequences of the child becoming aware of their genetic status. Fairly recently, empirical evidence concerning psychosocial reactions to predictive genetic testing in childhood has started to emerge, and highlights the existence of significant psychosocial benefits as well as harms[35]. There is however, acknowledgement that many of the arguments documented above currently exist on the basis of possible effects rather than evidence based research detailing actual experience of harmful effects[31].

#### **1.4.2.1. Autonomy**

Many of the arguments against predictive genetic testing in childhood exist on the basis that such testing fails to respect the child's later autonomy to decide for themselves whether or not to undergo testing. Clearly in some instances disease onset is likely to occur before the child reaches this stage, in which case it has been suggested that "the rule of earliest onset" should apply. In other words genetic testing for disease predisposition in children should be permitted no earlier than the age of first possible onset of the disease[36]. Empirical support for protecting the right of individuals "not to know" their genetic status is most often derived from psychological research with adults who have a family history of HD, as the majority of these individuals choose not to be tested[37]. However, others have suggested that such arguments oversimplify the concept of autonomy and that in fact not testing children may also constrain autonomy as they lose the opportunity of growing up with genetic knowledge and adapting to it gradually over time[38]. It is further argued that such self knowledge may in fact promote more autonomous decision making about one's life[32].

#### **1.4.2.2. Confidentiality**

It has also been suggested that predictive genetic testing in childhood breaches the child's right to confidentiality, in that their parents or guardians are also aware of the test result[39]. This contrasts with the scenario in which an adult undergoes genetic testing, when every effort is made to ensure that they are the sole recipients of their test results[34].

However, counters to this argument suggest that it seems to ignore the practical reality that parents are necessarily privy to all sorts of sensitive information about their children[34].

#### **1.4.2.3. Psychosocial harm**

Perhaps the most extensive set of arguments against predictive genetic testing in childhood is based on the potential for psychosocial harm[34]. In terms of the psychosocial consequences of parents knowing their child's genetic test result it has been suggested that the child may be harmed through: altered family dynamics, or an altered parent child bond such that the parents expectations of the child change or a "vulnerable child syndrome" develops[40]. Direct consequences of children knowing their genetic status may include changes in how they view themselves, including feelings of unworthiness or loss of self-esteem, as well as anxiety and depression, and there are also concerns surrounding the possibility of stigmatisation or discrimination[31, 41]. Unfortunately there is a relative paucity of psychosocial data to support these arguments [42] or indeed the counter arguments that not testing may also cause harm for example if parents remain anxious, finding the uncertainty difficult to cope with[34]. Similarly the possible benefits such as that early testing may result in better psychosocial adjustment than later testing when lifestyle and life choices are already firmly established, are under researched[32]. Although these issues are by no means resolved, it has recently been suggested by those revising European guidelines concerning childhood genetic testing that the concept of best interests should be widened to incorporate not only medical benefit, but also potential psychological or social benefits[33].

#### **1.4.3 Similarities between NBS and predictive genetic testing**

Many of these arguments for and against predictive genetic testing are also relevant to tests in current NBS programmes. However, at present, because of the clear evidence of benefit related to the availability of medical intervention for the majority of conditions included in NBS panels, ethical and psychosocial issues may be considered, but are made explicit much less frequently. Depending upon the directions in which NBS expands, and particularly if it is to include testing for genetic susceptibility to complex disorders, these issues are likely to become more prominent. Similarly, further consideration will need to be given to the role of parents in decision making concerning genomic NBS.

#### **1.4.4 Parental autonomy**

Parents are generally allowed broad discretion when making health care decisions for, and on behalf of, their incompetent children[43],[38], with parental authority usually only overridden in cases of emergency, parental abandonment, child abuse, or when life-saving treatment is

being refused[44]. Respecting parental autonomy makes it likely that a child's best interest will be promoted (as parent have "insider" knowledge of these interests, as well as the motivation to make decisions that best promote them[45]), but also places value on the intimate family relationships that are likely to facilitate children's overall physical and emotional development [45]. These family relationships, and the social collaborations created around them, involve many subtleties, complexities and competing demands that are not easily articulated in ethical or legal terms but which are important, even fundamental to, human development[45].

However, despite the fact that parents generally have health care decision-making authority for their children, their choices regarding genetic testing, including NBS, may in fact be more constrained[43]. In the United States, NBS is mandated and although parents have the right to opt out, it is unclear to what extent this option is readily available in practice. In other countries, such as New Zealand and the UK, policies that both strongly recommend NBS but ultimately allow parental choice to predominate exist[46]. In providing NBS in this way health policy has been formulated to reach the best compromise between protecting the welfare of children, respecting the rights of parents and meeting societal obligations in relation to provision of healthcare and appropriate use of resources. In practice uptake rates for NBS in most developed countries are very high, with more than 99% of parents/infants participating[46].

In contrast, parents cannot generally obtain predictive genetic tests for their young children for late onset conditions, or for carrier status, because of the previously noted policy statements by numerous professional organisations that strongly discourage it [28, 30-32]. These apparently contrasting positions that exist for NBS and predictive genetic testing relate back to the underlying theme that the primary justification for genetic testing in children should be the presence of medical benefits that outweigh the risks[43]. However this dichotomous position is likely to be challenged if, as predicted, NBS continues to expand [47], and the concept of best interests in childhood predictive genetic testing is widened to incorporate not only medical benefit, but also potential psychological or social benefits[33]. As testing practices evolve, and the uniting ethical principles become increasingly evident, health policy approaches to NBS and predictive genetic testing may also begin to converge.

#### **1.4.5 Convergence of approaches to NBS and predictive genetic testing**

Earlier in this chapter I alluded to the recent expansion of NBS programmes and to speculation that the underlying rationale for NBS is evolving. If the conception of benefit from NBS becomes broader, encompassing not only medical and psychosocial benefit to the

child but also benefits to families and society, the underlying ethical principles discussed above will require more explicit consideration in policy making decisions. As this expansion of NBS has already commenced, reconsideration of the importance of psychosocial and ethical issues is relevant now and will become increasingly so if the nature of tests changes as significantly as has been predicted. Mandated testing and strongly recommended NBS may become less appropriate under evolving NBS paradigms.

In parallel to these developments there have recently been calls to allow greater parental discretion in decisions related to the predictive genetic testing of young children[38] as emerging empirical evidence points to psychosocial benefits associated with the certainty derived from a genetic test result[48]. At the same time as this gradual accumulation of evidence regarding the benefits of genetic testing for non medical purposes in children, there is also an increasing body of opinion that this type of testing fits within the realm of decisions over which parents should have authority[43]. Thus, although international guidelines still agree strongly that medical benefit is the main justification for testing[1-3], there is now a lack of consensus in the case of childhood-onset disorders for which preventive or therapeutic measures are not available[7]. In some countries the emerging empirical data, and increasing recognition that some parents are in favour of predictive genetic testing, even in the absence of medical benefits [9], has prompted re-examination of the indications for genetic testing in children [10]. The scope of predictive genetic testing in childhood therefore appears to be evolving as data concerning its overall utility, including psychosocial factors, gradually accumulates.

Thus, while this thesis aims to investigate psychosocial effects of NBS for genetic susceptibility to complex disorders, it is important to recognise that the distinctions between the two testing paradigms, united as they are by underlying ethical principles, are beginning to blur. It appears that within each context notions of benefit are evolving and that data concerning psychosocial effects is becoming increasingly important. While some such evidence has accumulated over the last few years it remains true that the two testing paradigms are also united by a relative paucity of empirical data concerning their psychosocial effects.

In contrast to this lack of psychosocial data the need for high quality basic scientific research in genomic medicine and population health has been widely acknowledged[2, 49], although some commentators have questioned the scientific basis, utility and ethics of conducting such studies[50]. A clear vision of how this scientific research should proceed has been developed [2], including population-based epidemiologic studies to quantify the impact of gene variants on the risk of disease, and to identify and quantify the impact of modifiable risk factors that

interact with gene variants. Epidemiologic studies will also be required in the process of clinical validation of new genetic tests, and ultimately in testing targeted interventions[51]. Such studies are likely to provide information concerning the potential medical benefits of genetic susceptibility testing, but the potential psychosocial risks and benefits of screening, may go unnoticed unless they are specifically investigated[15, 21]. Fortunately, these large population based studies provide an excellent opportunity to investigate the psychosocial consequences of providing information concerning a child's genetic risk of a specific disease in contexts similar to newborn population screening.

## **1.5 Overview of the thesis**

While the knowledge deficits concerning psychosocial reactions to newborn genetic susceptibility screening have been noted[15], this has not prevented much deliberation concerning the possible effects. It has been postulated that children with genetic predisposition to disease will mistakenly be perceived as “chronically ill” from birth in a similar way to the character from *Gattaca*, quoted in the opening paragraph of this thesis[52]. This concern is based on the theory that a parent's belief that their child is in some way vulnerable, or particularly susceptible to illness, can potentially have adverse long-term effects upon the child's development[53]. Conversely, others cite evidence from the literature concerning psychosocial effects of predictive genetic testing for single gene disorders that parents and children are not adversely affected by genetic information [54] and that genetic knowledge may be beneficial [38]. At present we simply do not know how parents will react to testing that reveals genetic susceptibility to common complex disorders in the newborn period.

In general this thesis is concerned with the urgent need to replace such speculative rhetoric concerning the psychosocial effects of newborn susceptibility screening with a scientific evidence base[5]. Without such evidence further theoretical advance in debates about which disorders should, or should not, be included in NBS panels is unlikely and it will not be possible to elucidate how such screening may actually operate in practice[55]. In particular, I will provide empirical data concerning the psychosocial implications of revealing disease susceptibility, rather than making a specific diagnosis, in the first months of life. To accomplish this I use T1D as a disease model for assessing the psychosocial effects of screening for genetic susceptibility to a common, complex disorder in a general population of newborns. I have chosen to provide empirical data in the NBS rather than predictive testing paradigm as this is the main focus of interest in the literature[18, 19, 34] and an opportunity arose for me to assess parents' reactions to genetic susceptibility test results given as part of a

longitudinal study investigating the natural history of T1D. The population basis of this research and the way in which genetic susceptibility test results were disseminated to parents more closely resemble a NBS rather than predictive testing paradigm.

My aim in this thesis is to investigate issues that are *specific* to testing in the newborn period, and that are *direct* effects of parental knowledge concerning their baby's genetic susceptibility to T1D. I acknowledge that there are many other concerns that may ultimately impact upon those who have been tested as newborns: a full understanding of the psychosocial effects of such testing would require an analysis of the ways in which genetic information and a genetic approach to disease affect people individually, within their families and communities, and in their social and working lives. For example, one of the most commonly expressed fears is that genetic information will be *used* in ways that could harm people such as to deny them access to health insurance, employment or education. [56] I will not contribute to the already considerable body of literature concerning the potential for misuse of genetic information [56-58] in this thesis.

In the first section of the thesis (chapters 1 to 3) I provide background to the debate over NBS for genetic susceptibility to common disease. To achieve this in chapter 2 I first examine what NBS currently involves, noting in particular its complexities, how target disorders are selected, and how this process has evolved over time. I then review recent advances in "genomic medicine", focusing on T1D to explain and explore how these complex disorders differ, in important ways, to those traditionally included in NBS panels.

Chapter 3 discusses the current evidence base concerning psychosocial consequences of NBS. In this chapter I discuss the empirical evidence that already exists concerning psychosocial effects of past and current NBS programmes and review background literature concerning the important role of postnatal experiences in shaping child development and influencing adult health. In particular, I review the literature pertaining to the "Vulnerable Child Syndrome" and describe how alterations in parents' perceptions of their child's health may affect parent-child interaction and ultimately impact on child development. I then highlight the critical gaps in our knowledge relating to the psychosocial effects of NBS for genetic susceptibility to T1D and note that as NBS policy needs to carefully weigh evidence of benefits and risks, particularly when they are likely to be more finely balanced, formal investigation of these potential effects is of considerable importance.

Based on chapters 2 and 3, chapter 4 describes how I developed an appropriate research method for investigating the potential psychosocial effects of screening newborns for genetic susceptibility to T1D. The discussion highlights the need for research that is reflexive to the

complexity of the issues, and explains why I chose to use a combination of quantitative and qualitative methodologies.

The results of my empirical work are contained in chapters 5-7. Chapter 5 is concerned with my attempt to quantify the degree of psychological impact that NBS for genetic susceptibility to T1D has upon mothers. To achieve this I report a prospective study involving administration of a range of psychological questionnaires to three mother-baby cohorts: 38 infants at increased genetic risk of T1D, 73 at low risk and 76 who had not undergone testing. The results of statistical analyses conducted to test for differences in questionnaire scores between the three groups are presented.

In chapters 6 and 7 I display qualitative data from interviews with parents of babies known to be genetically susceptible to T1D. The aim of chapter 6 is to present the subjective experiences of parents whose babies had undergone genetic susceptibility testing for T1D. In order to achieve this I present their descriptions with the minimal editing I felt necessary to make sense of their stories. In chapter 7 I analyse and interpret the descriptions that were conveyed to me by parents, through a process termed “Interpretative Phenomenological Analysis” (IPA)[59, 60]. This allows me to expand and elaborate on the nature of some of the psychosocial effects of newborn T1D screening, and also to enlarge upon the impact this may have on families.

In the final chapter I bring together past literature related to NBS and genomic medicine with my own empirical research findings, in order to draw conclusions about future research and clinical practice related to genetic susceptibility testing.

## **1.6 Summary**

In this introductory chapter I have discussed how genomic medicine and NBS may “collide”. While this synergy could bring about considerable benefits there are also potential risks. The psychosocial effects of genetic susceptibility testing in the newborn period are currently poorly described and researched. My thesis aims to address this gap in our knowledge by providing empirical evidence concerning parents’ reactions to NBS for genetic susceptibility to T1D.

## **Chapter 2      Scientific Background: NBS and Genomics**

## **2.1 Introduction**

In this chapter I provide background information to explain the context in which complex multifactorial disorders such as T1D are under consideration for inclusion in NBS panels. To accomplish this I first describe what NBS currently involves, noting in particular its complexities, how target disorders are selected, and how this process has evolved over time. I then review the recent advances in “genomic medicine”, focusing on T1D to explain and explore how these complex disorders differ, in important ways, to those traditionally included in NBS panels.

Finally, I assess how screening for genetic susceptibility to T1D fares under the scrutiny of current NBS criteria, and how this may change as both the criteria and knowledge about T1D evolve. In particular I note the importance of parents’ psychosocial reactions when assessing the potential harms and benefits of this type of screening, and the current paucity of relevant data in this field.

## **2.2 A brief overview of NBS**

### **2.2.1 History and development**

NBS programmes are public health initiatives that screen infants shortly after birth to identify conditions for which early intervention can prevent mortality or morbidity. Screening is accomplished through the collection of heel prick blood samples from babies between 2 and 5 days of age and their subsequent analysis at central laboratories. For positive results confirmatory tests are necessary but treatment can usually be instituted within 10-14 days of birth. NBS is one of, if not the, most efficient and effective of all screening programmes with most countries reporting coverage of between 95 and 100% of the population[61].

NBS began in the 1960’s when Dr. Robert Guthrie developed both a novel method of blood collection onto filter paper, and a simple test to detect the genetic metabolic disorder phenylketonuria (PKU)[62]. PKU is caused by a hereditary defect in the metabolism of phenylalanine, an amino acid found in many foods, and without dietary treatment infants develop serious cognitive impairment, usually beginning before the disorder has been clinically diagnosed. Screening at birth enables the introduction of a specialised diet early in life, thus preventing irreparable neurological damage.

However, NBS did not commence solely because of the existence of a laboratory technique. Rather development of the Guthrie test converged with new thinking about the intractable problem of “mental retardation”. The traditional educational, social and rehabilitative approaches were being reconsidered and medical prevention appeared increasingly attractive

to government agencies and legislators [63]. With such support, and with intensive lobbying from children's advocates, more and more US states introduced NBS, with many making it mandatory [64]. NBS also spread internationally and in many places tests for a small number of other disorders, such as congenital hypothyroidism, haemoglobinopathies and galactosaemia were added to what became NBS panels. NBS in New Zealand was established in the mid-late 1960s when Guthrie took sabbatical leave to Dunedin, with Professor Arthur Veale initiating the programme from the Otago School of Medicine.

Requirements for parental consent vary internationally in that NBS is still mandated in several US states (although parents can refuse on religious grounds in virtually all states), but is a matter of parental choice in other countries, albeit sometimes with a strong recommendation that it should occur[46]. Thus although many of the disorders included in NBS panels are single gene disorders this type of screening differs from other predictive genetic testing in several ways: parents do not actively choose to allow their child to undergo the testing, there is generally no family history of the disorders being tested for, and they do not undergo the extensive counseling that commonly occurs with other predictive genetic testing in childhood. NBS for this relatively small number of conditions continued over the next few decades and in general the programmes were remarkably successful, saving many children from significant morbidity or mortality. However, despite the inherent attractiveness of this preventative approach, NBS, even in its early forms, was not without problems. For example it gradually became clear that the inevitable false positive results were distressing for parents and that sometimes this anxiety did not dissipate even when the diagnosis was eventually refuted[65, 66]. It has also been noted that some families have difficulty accessing appropriate services for their children following a positive diagnosis. For example, although screening for haemoglobinopathies has been widespread in the US for many years recent reports have shown that many children detected through such programmes do not actually receive or comply with the necessary prophylactic antibiotics or vaccinations[67].

Thus with many years of experience of how NBS operates in practice, it has become increasingly clear that a successful NBS programme is much more than a good test and an effective treatment: it also requires, amongst other things, public and professional education and provision of a high-quality, accessible system for confirmation of diagnoses, counseling and initiation of treatment[27]. These aspects of the programme may be more challenging to implement than the test itself but are essential if benefits are to be maximised and harms minimised[26].

In the past 5 to 10 years there has been a much more rapid expansion in the number of conditions included on screening panels, due largely to the application of a technology called

tandem mass spectrometry[68]. Use of this tool allows simultaneous screening for dozens of different metabolic conditions through analysis of blood spots for characteristic changes in their biochemical profile[26]. Expanded screening using tandem mass spectrometry has been implemented in many parts of the world including several European countries (Austria, Belgium, Denmark, Germany, the Netherlands, Poland, Portugal, Spain, Switzerland, and the UK) as well as a few countries in the Middle East and North Africa (Israel, Qatar and Saudi Arabia), the US, Canada and Australia and New Zealand [69]. However, the number of conditions included in screening panels varies between 5 in the UK[70], and more than 20 in most Australian[71] and US states[72]. Up until 2006 New Zealand screened for 7 conditions, and since then for 28 [73, 74]. The processes underlying addition of disorders to NBS panels will be discussed in more detail below. However, before moving on to this discussion of screening criteria I will first discuss in more detail some of the conditions that are currently included in NBS panels. This will provide perspective on what NBS currently is, and will also highlight some of the complexities involved in NBS programmes. Details of other disorders not discussed in detail here (such as haemoglobinopathies, Congenital Adrenal Hyperplasia, Galactosaemia, Biotinidase deficiency, and a large number of metabolic conditions detectable by tandem mass spectrometry) can be found in published fact sheets [75].

## **2.2.2 Conditions and complexities of NBS**

### **2.2.2.1. PKU**

NBS for PKU has come to be considered the “epitome of the application of human biochemical genetics”, and a model for genetic medicine and public health[63]. PKU is a disorder of amino acid metabolism in which affected individuals cannot properly metabolise the amino acid phenylalanine, which accumulates and causes neurological damage. It is an autosomal recessive genetic disorder, meaning that the parents of an individual with the disorder each carry one copy of the mutated gene, but typically do not show signs and symptoms themselves. The incidence of PKU in the U.S., Britain, and most of Western Europe is approximately 1 in 11,000 to 1 in 15,000 births. Virtually all newborns are tested for the disorder in every American state, Canada, Australia, New Zealand, Japan, the nations of Western and most of Eastern Europe, and many other countries throughout the world [63]. Prior to the introduction of NBS PKU generally resulted in severe cognitive impairment with about 90 percent of those affected having IQs of less than 50. The untreated condition is also characterised by behavioural problems, hyperactivity and seizures. Neurological damage can be prevented, and symptoms mitigated if newborns are placed on a special diet from which most of the phenylalanine has been removed [75]. It was originally thought that the low

phenylalanine diet was only necessary during childhood but it has subsequently been shown that if the diet is not adhered to for life adults suffer increased rates of eczema, asthma, mental disorders, headache, hyperactivity and hypoactivity[76].

PKU is rightly held up as the poster child of NBS, and there is no doubt that overall NBS for PKU has been incredibly successful and has prevented much harm. Salient features of the disorder include that early symptoms and signs are typically absent or non-specific meaning that clinical diagnosis may be difficult or delayed. This means that without screening treatment may not commence before irreparable neurological damage occurs. With treatment, growth and development progress relatively normally [75].

However, screening for PKU has encountered some problems that were initially difficult to foresee. For example, in the early days of NBS, knowledge regarding phenylalanine metabolism was incomplete and some children with variants of hyperphenylalaninaemia, who were not at risk for cognitive impairment, were commenced on the diet. Unfortunately some of these children suffered neurological damage because of this unnecessary severe restriction of an essential amino acid and others died from the complications of malnutrition as a result of diet refusal[63, 77]. Subsequent improvements in knowledge have led to considerable clarification of treatment regimes but there remains some controversy regarding precisely what type of dietary restriction is required for children who exhibit “borderline” levels of phenylalanine. The fact remains that diagnosis of PKU (and other metabolic diseases) should not be considered in categorical terms but rather as a continuum of derangement of the normal metabolic pathway, from mild to severe[78].

Other issues have also arisen. For example, it was originally thought that the restricted diet could be discontinued in childhood but the survival of women with PKU to reproductive age led to unexpected problems with their children: it became apparent that although infants born to women with PKU do not themselves have the disease, high concentrations of phenylalanine in maternal blood easily cross the placenta and are teratogenic[79]. As a result, children of women with classical PKU who do not maintain good dietary control are at significant risk (over 90 percent) of neurological damage and microcephaly[63].

Finally, although in some respects it is true that dietary treatment of PKU is straightforward, at an individual level it can be very difficult[79]. Many people find the formula unpalatable and both the formula and special phenylalanine-free foods are burdensome to prepare and expensive[63]. Even generally high-functioning individuals with PKU often suffer from subtle cognitive deficits, that can make dietary calculations difficult, and despite the availability of specialised assistance compliance rates are often low[80].

### 2.2.2.2. Cystic fibrosis (CF)

CF is a disorder in which abnormalities in the cystic fibrosis transmembrane regulator (CFTR) protein result in highly viscous secretions, affecting many organ systems but primarily the gastrointestinal tract and lungs. Medical treatment includes a high calorie diet, replacement of digestive enzymes and aggressive use of physiotherapy, antibiotics and other medications for improving lung function [81].

CF is one of the most common life-threatening recessive disorders, with an estimated incidence of between 0.25 and 5 per 10,000 in most Caucasian populations. It is also found in most other populations but less frequently than in Caucasians [82]. The disorder is caused by mutations in both copies of the CFTR gene with more than a 1000 disease-causing mutations described [81].

The screening test varies in different countries and states but in general, elevated levels of immunoreactive trypsinogen (IRT) trigger confirmatory screening with a DNA mutation panel of the CFTR gene [83]. Infants with 1 or 2 detected mutations are referred for diagnostic sweat testing.

CF differs from paradigmatic NBS disorders such as PKU and there has been considerable variation between countries regarding whether or when to include it in NBS panels. These policy challenges have arisen largely because the weight of evidence that NBS for CF improves long-term outcome is not as clear as for other conditions such as PKU [84].

It has only been quite recently that consensus approval for including CF in NBS panels in the US has occurred [85], largely because of data from the Wisconsin CF Neonatal Screening Project, demonstrating nutritional benefits from early diagnosis [82]. It was widely expected that NBS would lead to respiratory benefits, and screening certainly provides *potential* for better pulmonary outcomes [82] but the Wisconsin study actually reported no difference in lung function at 7–8 years[86]. It is thought that this lack of benefit may relate to confounding factors such as imbalance of genotype and pancreatic status between groups, mild lung disease in both groups, and earlier acquisition of infectious agents in screened patients in one of the centres, but the fact remains that there is still a lack of evidence of some expected benefits. Despite this, other potential benefits have been noted such as the ability to inform parental reproductive decisions and streamlining of the diagnostic process for ill newborns,[87] and many believe there is now sufficient data to support routine NBS for CF[88].

However, not only have some of the expected benefits of NBS for CF not accrued but there have also been some negative effects. For example, it has been reported that very young, asymptomatic children with CF may be harmed through exposure to infectious agents through

person-to-person transmission in CF clinic. Although this is not an inherent risk of NBS, it is a potential cause of harm from early detection [85]. In addition, screening by DNA mutation analysis for CF also reveals infants who are unaffected genetic carriers, and at risk of having children with CF if their future partner is also a carrier. From the child's perspective the knowledge of being a carrier is not of direct and immediate benefit and could potentially be considered a violation of their "right-not-to know" [89]. Parents generally seem to regard carrier results as valuable information gained fortuitously[90] but concerns persist that parents may misunderstand its meaning, suffering unnecessary anxiety that their child will become ill [91].

Overall there is an evolving consensus that evidence collected over a number of years demonstrates that the benefits from NBS for CF exceed the risks[88]. However, the balance of benefits over risks is not as great as that for PKU and it has also been noted that this is contingent on how programmes are implemented[23]. CF screening programmes are inherently more complex than those for PKU, with both testing and treatment being less straightforward. The observation that complex screening programmes with less clear overall benefits require careful monitoring to ensure consistent quality and effectiveness [85] is clearly of relevance to potential future screening programmes, including genetic susceptibility screening.

### **2.2.2.3. Medium-Chain Acyl-Co A Dehydrogenase Deficiency (MCAD) and other disorders detected by tandem mass spectrometry**

The most common disorder currently screened for using tandem mass spectrometry is MCAD, with a birth prevalence of 1 in 10 – 20,000 in populations derived from Europe[92]. Most of the other conditions, while broadly similar to PKU and MCAD, in that they are autosomal recessive metabolic disorders, are much rarer with frequencies generally less than 1 per 100,000 births[93].

MCAD is a disorder of fatty acid metabolism caused by the lack of an enzyme required to metabolise fat to produce energy. Affected children may have life-threatening or neurologically damaging episodes of hypoketotic hypoglycaemia (a type of low blood sugar) during periods of catabolic stress (such as fasting or intercurrent illness). In between episodes children are healthy and may indeed never become sick[92]. It has been clearly shown that early diagnosis through screening, plus the adoption of management plans involving the avoidance of catabolic stress, have resulted in a much lower incidence of serious episodes or death[94]. In this respect MCAD shares some of the salient features I discussed in relation to

PKU, in that it is relatively common, difficult to diagnose clinically and has an effective intervention. It also shares another more problematic feature of testing for PKU in that benign or mild variants of the disorder may also be detected by screening. This issue appears to be more significant for MCAD in that the number of cases of benign hyperphenylalaninaemia detected is small, but screening for MCAD has detected almost twice as many cases as had been expected from clinical presentations[92]. It is thought that some forms of MCAD detected by screening may present in adulthood or be entirely asymptomatic [94] but these mild variants cannot presently be distinguished prospectively from those that are more severe. This means that some children may derive no benefit from early diagnosis or may even be harmed through unnecessary interventions. This observation that labeling a child as having a disorder, and applying an intervention that may be unnecessary, is an unwanted consequence of screening has implications for potential future screening programmes.

Some of the other disorders detected through tandem mass spectrometry raise similar issues. For example some disorders detected by screening such as short chain acyl-CoA dehydrogenase deficiency, may be entirely benign [95], some such as 3-MCC deficiency may be a reflection of benign maternal, rather than neonatal abnormality[92] and some may not have effective treatments[92]. The selection of disorders that should be included in panels, and or reported to parents, is therefore the subject of much debate, and has contributed to the evolution of screening criteria that will be discussed below.

#### **2.2.2.4. Implications of complexities in NBS**

This discussion has highlighted some of the complexities associated with even the most successful of NBS programmes. In particular, in relation to PKU screening, I have noted that unnecessary treatment of children not destined to develop disease can be harmful and that long term follow up is necessary to monitor for unexpected results such as maternal PKU syndrome. In relation to CF screening analysis of harms and benefits has been more complex than originally anticipated and the research that has been conducted has demonstrated that overall benefit is contingent on a well run programme. Expanded screening with tandem mass spectrometry has highlighted the genetic heterogeneity of metabolic conditions that may lead to “mis-labelling” and unnecessary treatment.

It is not my aim in this section to summarise all of the issues that have been raised in relation to early NBS or expanded screening with tandem mass spectrometry. Rather I wish to highlight the existence of such complexities and to note that they have important implications when considering further expansion of NBS, for instance to include genetic susceptibility screening. These implications include that harmful effects of NBS may be difficult to predict,

complex to study and may occur some time after the newborn period. In addition I wish to note that new technology has dramatically changed the pace of expansion of NBS. This rapid expansion has in turn helped to trigger debate over what conditions it is appropriate screen for. In the next section I will discuss some of the criteria that have traditionally been used to select disorders to be included in screening panels, and how these have been modified more recently to incorporate technological changes.

### **2.2.3 Aims and criteria for newborn screening**

It has long been recognised that public health initiatives such as the NBS programme should be guided by an underlying set of principles. These principles represent a channel through which important scientific, ethical, legal and other perspectives can be incorporated into decisions about which disorders to screen for. I begin the following discussion with a depiction of the Wilson and Jungner criteria that have guided NBS decisions for several decades and then move onto to discuss how these principles have themselves come under critical scrutiny and in some cases been modified. Finally I go on to discuss the underlying aims of NBS and the fact that even these may be subject to change in the moving landscape of NBS.

#### **2.2.3.1. NBS principles**

The classic principles by which to appraise disorders for screening are those written by Wilson and Jungner in the late 1960's[22]. Although they were designed for screening tests in general, they became the gold standard for NBS. These principles cover aspects of the disease, its treatment, the scientific validity of the test, and the organisational infrastructure associated with the screening programme, and are included here in table 2.1.

<b>Table 2.1 WHO Wilson–Jungner principles for appraising the validity of a screening programme [22]</b>
<b>Knowledge of the disease</b>
The condition must be an important health problem
There should be a recognisable latent or early symptomatic stage
The natural history of the condition, including development from latent to declared disease, should be adequately understood
<b>Knowledge of the test</b>
There should be a suitable test or examination

The test should be acceptable to the population
Case finding should be a continuing process and not a "once and for all" project
<b>Treatment for the disease</b>
There should be an accepted treatment for patients with recognised disease
Facilities for diagnosis and treatment should be available
There should be an agreed policy concerning whom to treat as patients
<b>Cost considerations</b>
Costs of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

### 2.2.3.2. The changing nature of NBS criteria

While these principles remain at the core of decisions about NBS, difficulties in applying them, particularly comparatively, have been noted[24]. These difficulties arise from issues with some of the principles such as: their inter-relatedness, their subjective nature, and difficulties in their quantification and comparison. For example, many of the principles are couched in qualitative terms: “the natural history of a condition should be *adequately* understood”, “there should be a *suitable* test or examination”, with no clear decision-point as to whether or not these requirements are met[96]. Thus there are difficulties when it comes to translating the principles into criteria, or conditions that must be fulfilled, before a candidate disorder can be accepted onto a screening panel. These difficulties have perhaps become more apparent as evidence-based medicine has achieved increasing acceptance, and more clarity is called for in the decision making process[26].

Recognition of these issues has led some centres to redevelop criteria in order to incorporate contemporary values such as quality assurance, equity, and scientific evidence of effectiveness[26]. For example the Human Genetics Society of Australasia (HGSA) has defined a set of criteria by which conditions can be recommended. These include:

- There is benefit for the baby from early diagnosis (benefit to the family may also benefit the baby)
- The benefit is reasonably balanced against financial and other costs
- There is a reliable test suitable for newborn screening
- There is a satisfactory system in operation to deal with diagnostic testing, counseling, treatment, and follow up of patients identified by the test.

The HGSA also makes multiple recommendations concerning the organisation of the programme, laboratory services, research and legal and ethical considerations [97].

Other countries have attempted to develop more proscriptive guidelines for selecting disorders to be included in NBS panels. The UK National Screening Committee (UK NSC) has developed 19 screening criteria and specifies 87 items of information under 35 general headings needed for their evaluation [96]. Similarly, the American College of Medical Genetics (ACMG), under contract to the federal Health Resources and Services Administration, also derived 19 criteria, based on the original Wilson and Jungner principles [98]. In an attempt to standardise application of these criteria the ACMG then developed a questionnaire allocating numerical scores to 84 candidate disorders, depending on the degree to which they met the criteria. Despite similarities in process between the 2 countries the final results were polarised with the UK NSC recommending screening for a total of 5 disorders and the ACMG 29 primary target conditions and an additional 25 secondary targets (defined as conditions that would be identified because they are part of the differential diagnosis of a condition in the core panel, are clinically significant and revealed with screening technology but lack an efficacious treatment, or represent incidental findings for which there is potential clinical significance)[96, 98].

These reports represents major efforts to provide objective means of assessing disorders for NBS but they have perhaps not yet achieved this aim, rather stimulating further debate and controversy[99]. For example concerns have been raised regarding limitations of the ACMG process, such as that respondents were biased toward individuals actively involved in NBS services and lay advocacy groups[21]. Similarly there are concerns that even if disorders fulfill specific criteria, if programs expand too rapidly, the infrastructure to deliver adequate services and monitor harms and benefits will not be in place[21, 100].

### **2.2.3.3. Aims of NBS**

The fundamental question of what the aims of NBS programmes should be has been relatively neglected in comparison to advances in relevant scientific knowledge and techniques[101]. However, it is helpful here to step back and consider these overall goals. As discussed in relation to PKU, the historical rationale for NBS was the prevention of devastating harm to affected infants by the provision of immediate treatment[29]. This rationale has been described as “an urgent response to avert a potential emergency of public health importance”[29]. The development of new technologies to conduct screening has caused some to question whether these traditional justifications for NBS are too narrow. Certainly, with the advent of tandem mass spectrometry the rationale seems to be evolving, as although screening for most disorders may still prevent mortality and morbidity, for some the benefits are less dramatic, less immediate or may not directly accrue to the child. In other words

whereas traditionally the only relevant benefit has been benefit directly to the infant of a timely and effective treatment for a serious condition [95] it now seems that the notion of benefit may have become broader, encompassing not only benefit to the child but also benefits to families and society[27].

These other benefits appear to fall into four categories: elimination of the “diagnostic odyssey”, provision of reproductive risk information to parents, enabling research with children affected by rare disorders, and the developmental, social and psychological benefits that may arise from early disease detection[26, 27]. There is as yet no consensus on whether a broadened conception of benefit is appropriate, and if it is how such benefits should be weighed and judged when making policy decisions[26, 102]. However, NBS already appears to operate not solely as a response to a “public health emergency”[29] but rather as a public health service with greater emphasis on more moderate and parent-centred benefits[29]. Expanded NBS, as a result of the application of tandem mass spectrometry, appears to have played a key role in creating a shift in how NBS is justified[29].

#### **2.2.3.4. Implications of evolving criteria and aims of NBS**

In section 2.2 I have described how NBS has evolved over the years. In particular I have noted that the rapid expansion that has occurred more recently is related both to technological advances and to changes in thinking about NBS criteria and aims. The fact that such a shift has occurred, or is occurring, clearly has important implications for the future of NBS. For example, the development of more detailed and proscriptive criteria, as by the UK NSC and the ACMG necessitates collection of more data concerning both the positive and negative effects of screening. In addition the changes to the underlying aims of NBS that appears to be occurring, such as a broadening of the conception of benefit, are likely to increase pressure to further expand NBS, for example to include screening for genetic susceptibilities to conditions such as T1D.

### **2.3 Genomic medicine**

In parallel with the evolutionary processes occurring in NBS, the field of genomic medicine has also been undergoing rapid development. To begin this section I briefly describe how medical genetics research has developed over the last few years and how this, in conjunction with technological advances, has lead to calls for genetic susceptibility tests to be included in NBS. I then describe a common multifactorial disorder, T1D, in more detail so that in the final section of this chapter I can discuss the significant differences between this type of testing and standard NBS tests.

### **2.3.1 Genomic research**

In the last decade the focus of research in medical genetics has shifted from single gene disorders to the role of genetic variation in multifactorial disorders[49]. While about 99.8 per cent of each individual's DNA sequence are identical across the population, the 0.2% that is variable, in conjunction with environmental effects, accounts for many of the differences between people. This genetic variation is made up of: single nucleotide polymorphisms (SNPs) or single-letter spelling differences between the DNA of different individuals; copy number variations (CNVs) or DNA regions that can carry anywhere from zero to more than a dozen copies of a gene; and epigenetic variation which involves "chemical tags" acting as switches that control how genes are read[103]. In addition, it is now thought that rare variants (with population frequencies of approximately 0.1-1.0%, compared to SNPs which by definition have frequencies >1%) may make a substantial contribution to the multifactorial inheritance of common chronic diseases[104].

SNPs have so far been the subject of the greatest level of research interest and it is clear that they play important roles in many of the non-Mendelian diseases, also called multifactorial, complex or common diseases that are the main cause of morbidity and mortality in developed countries. Examples include T1D, obesity, cardiovascular disease, Alzheimer's disease, age-related macular degeneration and asthma. SNPs also contribute to biological variation such as height and metabolism, and some are thought to have no effect[105].

This change in research focus has necessitated the use of alternative study types such as genome wide association studies (GWAS). GWAS involve rapidly scanning markers across the genomes of many people to find genetic variations associated with a particular disease. [106]. These studies have been successful in identifying genetic components for many common multifactorial diseases such as T1D, Crohn's disease and hypertension[107] and have lead to significant advances in our understanding of disease pathogenesis. However, they have still only explained a small part of the population attributable risk for these conditions and more recently it has become apparent that gene-gene and gene-environment interactions, as well as CNVs and epigenetic variation, account for much of the gap in our understanding. There is now considerable enthusiasm for large prospective longitudinal studies that aim to detect such associations[49] and for identification of rare variants through extensive resequencing of carefully selected candidate genes in relatively large numbers of cases[104].

### **2.3.2 Genomic technologies**

There have also been remarkable technological advances over the last few years such that the ability to incorporate genetic susceptibility tests into standard NBS programmes already

exists. More specifically, there are three areas in which advances pertinent to newborn genetic susceptibility screening have been made. Firstly, it has recently been demonstrated that using a new technology sufficient DNA can be obtained from less than 10% of a standard NBS specimen to support a programme of genome wide genetic testing[108]. Secondly, in the 1990s DNA microarray technologies became available, enabling simultaneous measurements of hundreds of thousands of DNA molecules. Microarray analysis can be used to determine an individual's DNA sequence at thousands or millions of specified locations in the genome, thereby creating a "genomic profile" or genotype. It is a fundamental part of research into the role of single or multiple genes, and DNA sequence variants, in disease processes, both in individuals and in populations[109]. Thirdly, the above processes have become highly automated compared with the labour intensive methods used previously, and as a result costs have fallen significantly while capacity has continued to rise. It should however be noted that if research into rare genetic variants proves their importance in multifactorial disease pathogenesis then DNA sequencing rather than genotyping at specific loci will become the mainline approach. The first example of a primary DNA assay in NBS has recently been incorporated into the Wisconsin programme in the form of a test for the rare immunodeficiency disorder, severe combined immune deficiency (SCID)[110].

### **2.3.3 Genomic medicine**

The term genomic medicine can be defined as “the use of genomic information and technologies to determine disease risk, diagnosis and prognosis, and to guide the selection of preventative and therapeutic options”[109]. Genomic profiling refers to the simultaneous detection of multiple genetic variants that have been associated with greater risk or predisposition to particular diseases or conditions through GWAS or longitudinal studies[11]. Some commentators have claimed that the rewards of human genome research will include “a new understanding of the genetic contribution to human disease and the development of rational strategies for minimising or preventing disease phenotypes altogether”[7]. Others are more cautious, suggesting that decades of epidemiological study and clinical evaluation of interventions will be required [11]. Some are sceptical that genomics will ever revolutionise the way in which common disease is identified or prevented with their doubts stemming from issues such as incomplete penetrance of genotypes conferring susceptibility to common diseases, the limited ability to tailor treatments to genotypes and the low magnitude of risks conferred by individual variants for the population at large[12].

While we cannot be certain how useful genomics will be in the clinical setting a number of commercial companies already offer personalised genomics services via the internet that

provide individualised disease-risk estimates based on genome-wide SNP genotyping[111]. It is also clear that there would be obvious advantages to using a pre-existing screening infrastructure if susceptibility testing were to be implemented at a population level. This point has not gone unrecognised with several commentators already noting that it is plausible that newborn babies will routinely undergo genomic profiling at birth in the not-too-distant future [19, 95]. However, screening for genetic susceptibility is inherently different from standard NBS and the implications of such an expansion require careful consideration. In order to facilitate discussion of these differences I will now focus on T1D, as an example of the type of complex multifactorial disorder that could be included in NBS panels.

### **2.3.4 Type 1 diabetes**

Later in this thesis I use T1D as a disease model to provide empirical evidence concerning the psychosocial effects of genetic susceptibility testing in the newborn period. In the next section I present my rationale for using T1D in this way, briefly discuss what is currently known about the disorder's pathophysiology and describe how NBS for this disorder currently operates in a research context.

T1D is representative of the type of condition that may be screened for using genetic susceptibility tests in that it develops as a consequence of a combination of genetic predisposition, largely unknown environmental factors, and stochastic events [112], [113]. It is one of the most common chronic childhood diseases, with a rising incidence (3-4% per year in most developed countries), particularly in the 0-4 yr age group[114, 115]. At present, development of T1D necessitates life-long adherence to a difficult therapeutic regime of injected insulin that is only partially effective in preventing acute conditions (for example, ketoacidosis and severe hypoglycaemia) and secondary complications (including heart disease, blindness and renal failure [112], [116]. These facts, as well as the existence of a long period of latent autoimmunity preceding the onset of clinical diabetes, make the possibility of disease prevention an attractive and potentially achievable goal[117].

#### **2.3.4.1. Genetic factors**

The chief genetic determinants of susceptibility to T1D, contributing approximately 50 % of the genetic risk, lie within the class II region of the major histocompatibility complex on chromosome 6[118]. The risk of T1D in the general population is 1 in 300 whereas people homozygous for the high risk DR4 allele on chromosome 6 have a 10-15 fold increased risk, and people heterozygous for the DR3/DR4 alleles a 20-30 fold increased risk [119].

Understanding of the genetic determinants of T1D began as early as the 1970s when the association between T1D and the HLA system was first described[120]. However, subsequent

progress in identifying other genetic determinants was slow, until the advent of GWAS resulted in a rapid increase in new discoveries, with more than 40 disease susceptibility loci now identified[121]. Many of these discoveries have occurred during the production of this thesis such that genetic susceptibility screening for T1D would now look different to that used in the research I describe in chapters 4 to 7. However the additional genetic loci that have been discovered in recent years have had only modest impact on risk prediction: the HLA DRB1 locus remains by far the most important, and the general concepts involved in testing remain unchanged [120].

#### **2.3.4.2. Population screening for genetic susceptibility to T1D**

Population screening for genetic susceptibility to T1D does not currently form part of clinical practice but is the object of several longitudinal prospective studies, including the Key Environmental Aspects of T1D (KEA) study described later in this thesis. An indication of the importance attributed to this type of research is the recent initiation of a larger National Institute of Health supported prospective study (the TEDDY study) involving a consortium of 6 centres in the US, Scandinavia and Europe [122].

These prospective studies typically screen children at birth to detect those with high-risk HLA- genotypes. The high risk children are then followed up with 3-6 monthly blood tests, for autoantibodies that mark immune responses suggestive of early, pre-clinical T1D. In addition, the child's diet, illnesses, allergies and other life experiences are monitored. By comparing the life experiences and blood tests of the children who develop autoantibodies and diabetes with some of those children who do not get autoantibodies or diabetes, researchers hope to identify the triggers of T1D in children with higher risk genes. The ultimate aim is that this information can be used to try to prevent T1D, and some genetically susceptible children are already involved in prevention trials[17].

#### **2.3.4.3. Environmental factors**

A number of environmental exposures have already been proposed to contribute to T1D risk, and many of these are the subject of the above ongoing studies. These include exposures occurring during pregnancy, infancy, childhood, and beyond[17]. For example, exposure to rubella during pregnancy is known to result in diabetes in about 20% of children and enteroviruses have also been implicated in a similar manner[123]. Other potential early risk factors include blood group incompatibility and hyperbilirubinemia, pre-eclampsia, maternal age, and high birth weight for gestational age[17].

Potential environmental triggers in infancy include exposure to infectious agents such as enteroviruses, and certain dietary constituents such as cows milk[124], low levels of vitamin

D[125, 126] and N-nitroso compounds found in some preservatives[124]. Alternatively, the “hygiene hypothesis” proposes that reduced exposure to environmental stimuli, including microbes, underlies the rising incidence of childhood autoimmune diseases, including T1D[127, 128]. It is also interesting to note that psychosocial factors such as stress [129] may directly contribute to the development of T1D. Ultimately it is hoped that identification of such factors will lead to a better understanding of disease pathogenesis and will eventually result in new strategies to prevent, delay or reverse T1D [122].

#### **2.3.4.4. Interventions**

At this time, an effective intervention for preventing T1D remains elusive, but is the subject of considerable ongoing research. In the case of T1D primary prevention would mean trying to prevent disease development before autoimmune destruction of pancreatic islet cells had begun. For example, in the future it may be possible to modulate a genetically susceptible infant’s diet such that their risk of T1D is diminished[130]. To this end, in 1994 the American Academy of Pediatrics (AAP) strongly encouraged exclusive breastfeeding and avoidance of intact cow milk protein in the first postnatal year for infants with first-degree relatives who have T1D. They also recommended the development of a randomised prospective trial to evaluate this issue, and although subsequent data are not entirely supportive of the AAP’s stance, research interest in this area continues[131]. There is also considerable interest in preventative options related to the hygiene hypothesis, such as the possibility of using live, nonpathogenic microbes or microbial components to modulate or “re-educate” the immune system and thereby vaccinate against T1D[127].

Secondary prevention of T1D refers to modulation of the auto-immune response implicated in beta cell destruction that leads to an eventual decline in endogenous insulin production. For example, the Diabetes Prevention Trial (DPT-1) was based on the hypothesis that administering insulin to individuals at increased genetic risk of T1D, and with signs of autoimmunity but without overt diabetes would permit development of beta cell tolerance. Unfortunately this study was unsuccessful at preventing or delaying onset of T1D[132]. Similarly early studies suggested that the antioxidant nicotinamide prevented oxidative injury to beta cells but subsequent larger scale studies showed that nicotinamide had no effect on progression of T1D[133]. More recently, monoclonal antibodies, that target specific aspects of the dysregulated autoimmune process that occurs early in the T1D disease process have become a significant focus for prevention research[112].

Although the trials mentioned above, and other similar research have so far proved unsuccessful in delaying or preventing progression to clinical T1D they have enhanced

understanding of disease pathogenesis and have helped to establish a collaborative network that continues to work towards the goal of T1D prevention[133]. There is considerable optimism that the volume of research in this area will lead to preventative options within the next few years [112, 134]. T1D is one of the first of many diseases with complex genetic and environmental determinants to be studied in this manner, but the characterisation of at risk groups by genotype with the view to instituting preventative measures could equally apply to other common multifactorial conditions, such as asthma and obesity.

## **2.4 Combining NBS and genomic medicine**

In this final section of chapter 2 I will first discuss the major differences between tests for genetic susceptibility to diseases such as T1D and standard NBS tests. I will then consider how the aims of NBS and screening criteria relate to testing for conditions such as T1D. Finally I will point to ways in which debates concerning NBS can be advanced, and particularly to the need for more evidence concerning the psychosocial effects of such testing on parents and families.

### **2.4.1 Major differences between existing NBS tests and testing for genetic susceptibility to T1D**

#### **2.4.1.1. Clinical validity and clinical utility**

When assessing genetic tests it is usual to consider, among other things clinical validity and clinical utility [135]. Clinical validity refers to the ability of the test to detect or predict the associated disorder[136] and includes the test's sensitivity (the proportion of subjects with the disorder in question detected by the test) and specificity (the proportion of subjects without the disorder that have a negative test result)[92]. Clinical utility is relatively straightforward to define, referring to the balance of risks and benefits that would eventuate if the test were to be introduced into clinical practice[136], but its meaning appears to vary between different subgroups of people[137]. In its narrowest sense it refers only to health outcomes such as morbidity and mortality, whereas in its broadest sense it refers to any outcomes considered important by individuals and families[137]. Complete measurement of clinical utility would therefore requires a broad evaluation of the medical and social outcomes associated with testing, and with subsequent interventions for people with both positive and negative test results[135].

### ***PKU: clinical validity and utility***

Although the initial test used to detect PKU in NBS does not involve direct analysis of DNA it has come to be considered the "epitome of the application of human biochemical genetics," and a model for genetic medicine and public health prevention[63]. This is largely because current NBS protocols for PKU, which includes follow-up testing for confirmation after an initial elevated phenylalanine level, lead to highly sensitive and specific identification of children with the disorder: the sensitivity is close to 100% for tests performed after 24 hours, and the false positive rate is very low indeed, generally occurring in preterm infants, and with use of total parenteral nutrition[92]. In other words the clinical validity of testing is high. In terms of clinical utility NBS for PKU also fares well as current protocols permit early institution of a diet that can largely prevent neurological problems and has few significant unwanted effects.

However, it should not be forgotten that early screening initiatives did not have this level of accuracy, and some children with only moderate phenylalanine elevations were classified as affected and subsequently suffered adverse consequences from a phenylalanine restricted diet[63]. In addition, although the low phenylalanine diet is undoubtedly effective, it can be difficult for certain groups to adhere to, for example young children, adolescents and disadvantaged families and the need for tight dietary control of phenylalanine during pregnancy only became apparent after several years of screening[138]. These issues are mentioned again here to reinforce the point that measurement of clinical utility requires assessment of outcomes to be both broad and ongoing.

### ***T1D: clinical validity and utility***

Current knowledge about T1D suggests a complex disorder in which many genes interact with each other and with a range of environmental factors to cause disease. At present we know that some gene variants are associated with increased risks of T1D but testing for them is very different from testing for PKU, as the information provided contains a much greater component of uncertainty, or much lower clinical validity. Whereas a positive newborn screening test for PKU means that the biochemical disorder is already present and the disease will develop rapidly without treatment, a positive susceptibility test gives individual information about their personal risk of developing a disease sometime in the future. For example parents of babies found to be in the increased genetic risk group in the KEA study described later in this thesis were told that their child had "an increased risk of developing diabetes by the age of 20 years, with a 1 in 16 risk of developing diabetes compared with the general population risk of 1 in 300" [139]. This type of information, derived from population

genetic studies, leaves individuals with considerable uncertainty as to whether their child will develop the condition, and if so, when. As up to 15% of the whole population of newborn babies possess the particular at risk versions of the diabetes susceptibility genes under study here [140] many families would live with the label of "at risk for diabetes" for years despite the fact that more than 90% of children identified in this manner would never develop T1D[141].

Over time, construction of panels of tests including multiple gene variants contributing to the same phenotype, and clarification of the interactions with major non-genetic risk factors, may increase the clinical validity of testing for T1D risk genotypes [135] . However, increasing clinical validity of the test may mean that individual risk predictions vary over time and require regular updating. This was recently demonstrated in the case of direct to consumer testing for type 2 diabetes where as population level risk prediction improved, a third of participants switched between risk categories (for example between below and above average risk) [142]. Such changes would require careful explanation to families if confusion and concern were to be avoided.

Knowledge about clinical utility of genetic susceptibility tests is currently limited because there are very few observational studies and almost no clinical trials that demonstrate the risks and benefits associated with screening for individual gene variants[143]. It is however possible to say that current tests for T1D do not fare well in terms of assessment of clinical utility, largely because of the current lack of an effective intervention. For other complex conditions, where risk-reducing behaviours have been identified, there are question marks surrounding the potential for genetic risk profiles to motivate such behaviour changes. For example, feedback of increased genetic susceptibility to lung cancer appears not to add value to existing smoking cessation programs[144]. On balance, the limited volume of published research concerning susceptibility tests for common disorders in adults suggests that they have little impact on behaviour [144].

Having said that there are already some medical benefits of genetic susceptibility testing for T1D, in that childhood T1D diagnosed through a screening and follow up programme has a less severe onset and a milder clinical course in the first year following diagnosis[145]. While these medical benefits are important and encouraging, analyses limited to medical outcomes do not provide complete information about the implications of testing. Other factors including the acceptability of the recommended treatment to patients, and the psychosocial consequences of genetic testing should also be considered.

#### **2.4.1.2. T1D and NBS criteria**

It is well recognised that NBS for PKU clearly fulfils the original and modified criteria discussed earlier in this section. For example, applying the HGSA criteria, there is clear benefit for the baby from early diagnosis, the benefit is reasonably balanced against financial and other costs, there is a reliable test and a satisfactory system in operation to deal with diagnostic testing, counseling, treatment, and follow up of patients identified by the test. The same cannot be said for T1D because, despite the fact it is an important health problem, there is, as yet, minimal benefit to the child from NBS for T1D and even if an effective intervention is found serious questions remain concerning who is a patient, and the likely compliance of at risk individuals or their parents with recommended lifestyle modifications or medications[146-148]. There are also a range of risks that may accrue to all who are found to be genetically susceptible, and not just those who eventually develop diabetes. As yet these risks are poorly defined and researched but may be quite different from those associated with standard NBS being based on the probabilistic nature of the information and parental responses to this level of uncertainty. The test as it currently stands cannot be said to be reliable in that it has limited predictive power and the meaning of different results may change over time as research data accumulates. Finally, there is no satisfactory system in operation to deal with patients identified by a T1D susceptibility test as the infrastructure required to support this type of testing is likely to be different to that which already exists for standard NBS.

#### **2.4.1.3. Implications of differences between PKU and T1D**

In section 2.4 I have shown that screening for susceptibility to T1D differs markedly from standard NBS and does not fulfill standard means of assessing genetic tests or NBS criteria. This does not mean that we should automatically condemn such testing; indeed the allure of preventing T1D both from an individual patient perspective and to reduce a major and increasing burden on the health care system remains strong and the subject of much ongoing research. If successful this research may ultimately lead to T1D tests with much improved validity and utility such that they meet the NBS criteria of the day, and it is with these expectations that T1D testing has already been considered in the panel of conditions evaluated for expanded NBS by the ACMG[25]. While ongoing research into the pathogenesis and prevention of T1D seems entirely appropriate, the implications of the considerable differences between existing NBS tests and susceptibility tests require careful consideration.

Incorporating susceptibility testing into NBS would represent a paradigm shift in policy and

may also necessitate new ways of thinking about and assessing the harms and benefits of testing.

## **2.5 Chapter conclusion: a way forward**

In the first part of this chapter I have shown how NBS has evolved over the years from a simple heel prick test for PKU, into a complex public health system. On balance NBS has proved to be a remarkably successful programme but on closer analysis it has also involved many challenges and complexities that may provide useful lessons in years to come. The technological aspects of NBS programmes have undergone rapid development, but changes in the way the underlying aims of screening and screening criteria are considered may prove to be of even greater significance in terms of potential expansion of programmes.

In the second part of the chapter I have considered advances in genomic medicine, and discussed the example of T1D. Standard means of appraising genetic tests, such as assessments of their clinical validity and utility are useful in highlighting current shortfalls in genetic susceptibility tests. However, it is clear that the considerable amount of research currently underway may eventually produce tests that, while likely to remain different from current NBS tests, may be more suitable for population use. Similarly, testing for T1D does not fare well when considered against current NBS criteria, but this may also change as both testing capabilities and screening criteria continue to evolve.

The debate concerning the underlying aims and criteria for NBS is important and should continue. This discussion should engage a wide spectrum of experts, scholars, advocates and lay people but their analyses and debates must be based on good data rather than hypothetical risks and benefits. What stands out most from the literature I have reviewed in this chapter is the current lack of evidence regarding the wider aspects of the utility of genetic susceptibility testing, specifically the psychosocial implications of incorporating it into NBS. Whether it is attempts to apply NBS criteria to such testing, or to assess its validity and utility the arguments of both proponents and sceptics ultimately remain speculative because of a lack of information regarding how parents will respond to such information.

When a screening paradigm is predicted to change significantly, particularly when the benefits of screening are less well substantiated, I believe there should be greater efforts to formally investigate the potential psychosocial impacts[26]. This data is currently lacking for genetic susceptibility screening. In chapter 3 I will first review the literature pertaining to psychosocial reactions to existing NBS programmes. Analysis and reflection upon this existing literature will help to highlight more specifically where the deficits in our knowledge regarding psychosocial reactions to genomic NBS lie.

## **Chapter 3      Psychosocial Aspects of NBS**

### **3.1 Introduction**

In this chapter I first discuss the broad types of psychosocial research that have been undertaken in relation to NBS, and then review background literature concerning the important role of postnatal experiences in shaping child development and influencing adult health. In particular, I describe how alterations in parents' perceptions of their child's health may affect parent-child interaction and ultimately impact on child development. I then review in more detail the empirical evidence that already exists concerning psychosocial effects of past and current NBS programmes. Finally I highlight gaps in our knowledge relating to NBS for genetic susceptibility to T1D

### **3.2 Psychosocial Research and NBS**

The majority of research in the field of NBS is designed to determine whether testing produces tangible clinical benefits for the child. However, some researchers have also examined the unintended effects of screening that are often psychosocial in nature. The focus of research relating to psychosocial aspects of NBS has primarily been the effects of false positive results, and to a lesser degree true positive results, upon parents[149]. The most commonly measured variables have been knowledge, anxiety and other affects and attitudes, with the majority of early studies focusing on a single disorder[149, 150]. There is less information available regarding effects of NBS on parent-child interaction[31] although some studies have investigated effects on parental perceptions of child health, parent-child bonding and parental behaviour[151-154].

More recently, as screening practices have evolved, interest has grown in other areas. For example, in relation to CF, studies have reported on issues such as: the effects of carrier identification; effects upon parental reproductive decision making and comparisons between infants diagnosed through screening and those diagnosed symptomatically at a later stage. There has also been renewed and widened interest in the effects of false positive results since the advent of tandem mass spectrometry and expanded NBS. Before reviewing this research in some detail I will first discuss some important background literature that highlights why we should be particularly concerned about psychosocial effects, including those occurring as a consequence of NBS programmes, arising in infancy.

### **3.3 The profound importance of early experiences**

Experiences in early childhood are potentially more important than those that occur in adult life. This is because there is increasing evidence linking early childhood experiences to permanent effects on child development, and even to adult health status [155, 156]. The

evidence arises from both epidemiological (or “life-course”) research [155, 157] and from physiological studies in animal[158, 159] and human infants[155, 160]. For example, Essex et al showed that infants exposed to early maternal stress or depression had elevated cortisol levels when subsequently exposed to stressful experiences, suggesting an early sensitisation of the children’s pituitary-adrenal responses. This contrasted with children without a previous history of early stress exposure who did not show such marked responses when later exposed to stress [161]. While the full implications of such findings remain speculative, there are likely to be long-term consequences. For example, preschoolers with elevated cortisol levels have been found to be more likely to experience emotional and behavioral difficulties throughout the school transition period[162] and other psychosocial factors, such as “social isolation” in childhood, have been shown to be associated with significantly worse cardiovascular risk status in adult life[157].

Neurobiological systems such as these are almost certain to be highly complex, with multiple potential pathways between early care-giving, physiological responses, child development and adult ill-health, and more research will be required to elucidate the underlying mechanisms. However, it has been suggested that infancy, namely the first two years of life, represents a critical period for the initiation of these effects[155] with this hypothesis arising because the brain is known to undergo rapid developmental change during this time period, and is highly susceptible to environmental influences. Such plasticity of neurobiological functioning, including physiological stress response systems, may be advantageous, providing the opportunity for environmental factors to permanently “hardwire” systems to respond to idiosyncratic environments [163] but may also be implicated in adverse developmental outcomes and adult disease [155, 156].

### **3.3.1 The importance of the early mother-child relationship**

For most young infants the majority of their very early environmental influences are derived from their primary caregiver, most commonly their mother. The formation of a close and satisfying maternal-infant bond has been recognised as the most important psychological process of the postnatal period [164] and necessary for optimal psychosocial development of the child [165]. While the relationship between mother and infant usually begins to develop in the newborn period it is increasingly viewed as an ongoing developmental process with a multitude of factors that may affect it [165]. Different styles of attachment between mother and baby have been articulated[166], and many specific variables that impact upon mother-infant interaction and development of the attachment relationship have been described. These include: maternal characteristics, such as autonomy, flexibility, and nurturing skills, that tend

to be associated with secure infant attachment; infant characteristics; maternal perceptions of her baby; and maternal experiences of success or failure in managing the child [167-169]. In turn, substantial evidence has accumulated on the association between the nature of the early mother-child relationship and biopsychosocial functioning (including social-emotional competence, cognition, physical health and mental health)[170]. A positive relationship is associated with better short and long term developmental outcomes, such as good childhood peer relationships and lower rates of adult mental health problems[168] as well as impacts on physical health, such as lowered rates of failure to thrive in infancy and early childhood, fewer chronic and recurrent health problems, and better health and lifestyle practices in adulthood [171]. A secure attachment relationship is thought to be one of the factors involved in preventing elevations of the stress hormone cortisol thus giving the infant greater ability to regulate physiological stress responses and potentially leading to improved long-term health[155].

### **3.3.2 Vulnerable child syndrome**

As mentioned above a mother's perception of her baby is a crucial element of the evolving mother-child relationship[169]. If this perception somehow becomes distorted then there may be serious implications for the maturation of this relationship and ultimately for child development. One example of this phenomenon that may be particularly relevant to questions regarding the potential effects of NBS on parents and children is the "Vulnerable Child Syndrome" (VCS). It has been noted that some parents, particularly mothers, become anxious specifically about their child's health, and may modify their parenting style as a result. Although this sphere of research currently appears to be entirely separate from that detailing long term effects of early experience, VCS does encompass adverse developmental outcomes [172] and may play an important role in such processes.

The term VCS refers to a set of clinical features in which unfounded parental anxiety about the health of a child leads to disturbances of parent-child interaction and eventually to child behaviour problems [173] [53]. It was first described in 1964 by Green and Solnit who observed "long term deleterious effects on both the parents and the child" following life threatening illness in infancy from which the child had subsequently completely recovered [174]. The authors observed that parents, particularly mothers, continued to be anxious about their child's health, and feared the child may die. It appeared that the parents' perception of their child as being uniquely vulnerable led to difficulties in parent-child interaction. In particular, the parents overprotected the child, were unable to set age-appropriate limits and displayed excessive concerns about their child's health in medical settings. The children,

apparently responding to their parents' expectations of vulnerability, showed exaggerated separation anxiety, sleep disorders, discipline problems, under-achievement at school and hypochondria [173, 174].

More recent research has shown that heightened perceptions of child vulnerability are not confined to life threatening situations. Much less serious illnesses or experiences may also trigger similar parental anxieties and cause them to believe that their child is at increased risk of illness or death[53]. For instance, parents whose baby had a false positive newborn screening test for PKU continued at times to fear that their child would be developmentally delayed [175] and 40% of parents of children with innocent heart murmurs imposed physical and psychological restrictions on their children despite there being no evidence of organic cardiac disease. The authors of the latter report concluded that disability from "cardiac non-disease" in childhood was greater than that due to actual heart disease [176]. Similar findings have been reported in relation to minor self-limited conditions such as croup [177], diarrhoeal illness [178] and physiological jaundice [179]. Finally, a recent study has suggested that higher parental perception of child vulnerability is correlated with worse developmental outcome in premature infants at 1 year adjusted age with maternal anxiety at neonatal discharge predicting this later heightened perception of vulnerability[172]. It is also notable that although the VCS can develop in relation to illness in older children it is more likely to develop in infancy and may be triggered by more minor events. This may reflect the fact that the maternal-child relationship is still developing, and less stable, in the early postnatal period[180, 181].

While not all of the families who featured in the research detailed above displayed the florid behavioural problems described in Green and Solnit's original report, presenting symptoms remain surprisingly consistent. The clinical hallmarks that may alert paediatricians to the disorder are excessive parental concerns and a high frequency of health-care use, with further questioning often uncovering an antecedent event that instigated the parental anxiety[173]. Affected children may have: sleep disorders, such as frequent night-time waking; problems with school, including avoidance and underachievement; behavioural problems such as disobedience and irritability; and distorted perceptions of their own health[173, 174, 181]. Parents typically are overprotective, show exaggerated separation anxiety, are unable to set age appropriate limits, have excessive concerns about their child's health and overuse medical services for their child[173]. Some of these symptoms may initially be difficult to define precisely as reported disturbances in the child may be in fact be representative of parental issues. For example, parents may complain that their child does not sleep through the night but on further questioning it may become evident that the parent is repeatedly waking the

child to check on them[174, 181]. Other symptoms may also crossover or be inter-related: children affected by VCS may complain of abdominal pain or headaches perhaps (subconsciously) as a means of decreasing periods of separation from their parents, and parents may respond by utilising medical services[181]. The incidence and prevalence of VCS are not known as there is a lack of large scale empirical analyses, but small studies suggest it is in the region of 5-10 % of the population as a whole[53, 182]. The importance of the VCS persists beyond childhood: children who have been high users of medical services are known to have higher than expected rates of psychological distress and mental health problems as adults, and often continue a pattern of frequent health-care use[173].

The best management of VCS is prevention. For example the risks and benefits of all laboratory tests should be weighed carefully as false positive or confusing results may affect parent-child interaction[181]. Physicians also need to be aware of the settings in which VCS may arise, and be prepared to uncover the source of parental anxiety when it does occur, so that they can provide re-education and reassurance about the child's health. This may be as straightforward as teaching parents appropriate interpretation of signs and symptoms, and reinforcing the child's healthy status at routine visits. Parents may also require assistance with some aspects of parenting such as the setting of appropriate limits and boundaries[173, 181].

### **3.3.3 Summary of experiences in early infancy**

In this brief review I have shown that any experience occurring in infancy is potentially important as it may contribute to permanent neurobiological effects, including adverse developmental and adult health outcomes. In particular I have described how psychological research reveals the importance of the early relationship between mother (or primary caregiver) and child, and how factors that adversely affect this may also have profound and permanent implications for child development. Finally I have described one specific example of alteration in early mother-child interaction related to maternal concerns about the child's health, namely the VCS.

Concern has been expressed that NBS may cause parental anxiety and stress, have a negative impact on parent-child interaction and may therefore contribute to the development of the VCS[31, 85, 183, 184]. I will now review existing evidence regarding these concerns and other psychosocial aspects of NBS, and then point to gaps in our knowledge relating to NBS for genetic susceptibility to T1D.

### **3.4 Definition of NBS terms**

A *false positive* result is an initial screening result that falls outside the normal range but which does not indicate metabolic disease when the child is subsequently further investigated. Generally these results represent transient findings, variant or carrier status rather than laboratory mistakes [185]. The number of false positive results is influenced not only by the specificity, or accuracy, of the test but also by the prevalence of each disorder and the number of tests included in the panels. A report completed prior to widespread implementation of tandem mass spectrometry concluded that there were more than 50 false-positive results for every true-positive result identified through newborn screening in the United States[186]. Testing for multiple rare disorders by tandem mass spectrometry may produce a relatively larger number of false positive results even though each individual test specificity is high [100, 187].

A *true positive* result occurs when an initial screening result that falls outside the normal range is followed by confirmation of a disorder on subsequent diagnostic testing[188].

In NBS a further category of *ambiguous results* exists that is more difficult to precisely define and quantify. Some infants, who have initial positive screening results that are subsequently confirmed as being "true" on further evaluation, may in fact have disorders that will never become clinically apparent. This has also been termed "pseudo disease"[100] and although the concept is less familiar than true and false positive results it has been described in the context of NBS[189, 190], and may become more prevalent as more disorders with poorly described natural histories and incompletely understood phenotypic variability are included in testing panels.

### **3.5 Review of existing research related to psychosocial reactions to NBS**

### **3.6 Conditions included in current, widely implemented NBS programmes**

#### **3.6.1 PKU**

"Atrogenesis: the PKU anxiety syndrome"[175] published in 1968 is usually cited in discussions of the psychosocial effects of NBS and probably served to create initial interest in this field. In fact it is not actually a research study but reports the authors' clinical experience

with parents who had continuing anxiety following an initial false positive result as part of PKU screening[149]. The report includes details of how the paediatricians involved responded to the situation by warning parents of the possibility of false positives and by using an intensive follow-up programme to support parents and reassure them with objective evidence of their child's good health[175].

There are no other published studies that address parents' responses specifically to PKU testing, perhaps because of the high specificity and sensitivity of the test and obvious benefits of screening. However, another early study addressed the impact of initial false positives in a NBS programme for several metabolic disorders, including PKU[66]. In this study sixty parents of infants recalled for retesting after an equivocal NBS result were interviewed twice, once at the time of retesting and again after the retest result was given. (Those with true positive results were excluded). Parental anxiety and depression were assessed with the Multiple Affect Adjective Checklist, and the high levels reported at the time of retesting reduced significantly once the normal result was known. However 36% of the parents of these normal infants reported concern about the health of their baby because of the repeat testing, with about half expressing great concern[66].

### **3.6.2 Hypothyroidism**

There are several papers describing the psychosocial sequelae of false positive NBS tests specifically for hypothyroidism[65, 191-194], although most of these relate to a pilot screening programme undertaken in Sweden in the 1970's[65, 191-193]. None of the studies included a control group, but all reported adverse psychological effects of the false positive result: a Dutch qualitative study reported "great strain" on families, adverse effects on the parent-child relationship and persistent fears about the child's health despite the subsequent negative test[194]. The Swedish studies reported that 78/102 families initially exhibited strong emotional reactions including feelings of shock and sleep disturbance, 18 families had persistent insecurity regarding the baby's health 6 to 12 months later [192] and 19 families displayed anxiety at four years[65].

### **3.6.3 CF**

There is more existing evidence concerning the psychosocial effects of screening for CF than for any other disorder. This probably relates to the more equivocal balance of benefits and risks of early detection through NBS programmes, and the complexity of the testing process. Some of the data originates from one of the very few randomised controlled trials of NBS, the Wisconsin study, in which all babies in the state were screened for CF (unless parents

objected on religious grounds) but half were randomised to a delayed disclosure arm. (Parents were not informed of the positive NBS result until the child was 4 years old or became symptomatic, whichever occurred first)[195]. As there is significantly more data in this section I have divided it into subcategories, although some studies report on several of these aspects.

### **3.6.3.1. False positive results**

#### ***Parents' Initial Reactions***

It has consistently been shown that it is psychologically distressing for parents to receive an initial positive CF NBS result for their child [62-66]. For example, Beucher et al. reported that 96.5% of parents were anxious at the time of the diagnostic sweat test and Moran et al, in a study involving semi structured interviews several years following screening, reported that the two most frequently reported types of feelings about the initial high positive NBS result were: “worried/concerned/nervous/upset” and “devastated/distraught/hysterical”[196]. Similarly, in a mixed quantitative and qualitative study Tluczek et al found that the majority of parents reported being shocked and surprised by the positive screening result and very distressed with feelings of worry, stress, guilt and sadness [197]. These qualitative findings were supported by their quantitative findings that both mothers and fathers in the abnormal NBS group showed significantly higher depression scores on the Center for Epidemiologic Studies Depression Scale (CES-D) prior to the sweat test than did parents in the comparison group [197].

Similarly strong negative emotional responses to the news of the positive NBS test were found in the Wisconsin study although the delayed disclosure group expressed significant anger regarding the delayed results as well as anxiety about their child’s health. The qualitative component of this study involved only parents of 4 yr old children in the delayed disclosure group. 78% demonstrated “emotionally charged “ responses with anger regarding the delay, extreme anxiety about their child (e.g. “I pictured him not being grown up”, “thought he would die before 10 years old”) that also intruded on their daily activities (e.g. I” couldn’t work for the last 2 days, couldn’t sleep”...)[198].

#### ***Waiting for Diagnostic Testing***

As well as this data confirming the psychological distress caused by an initial positive result in NBS for CF there is also conclusive evidence that waiting for confirmation, or otherwise, of the initial result is a very difficult time for families despite the efforts of many centres to reduce delays to a minimum [154, 197]. In particular, one paper that combined qualitative and

quantitative methods reported interview data detailing how parents experienced 2 interrelated psychological processes while waiting for a sweat test: namely, emotional distress, including shock, worry, depressive symptoms, and guilt, and cognitive uncertainty[197]. To reduce their uncertainty, these parents searched for more information but although obtaining this information reduced their feelings of uncertainty it also frequently increased their emotional distress because of the severity of the disorder. Many parents dealt with these cognitive and emotional difficulties by trying to determine whether their child actually had CF. Strategies for doing this included demanding a sweat test as soon as possible and conducting their own assessments of their child's health, often misinterpreting normal newborn symptoms as signs of CF. Parents described several strategies directed toward managing their emotional distress, included talking with others, praying or alternatively making a conscious choice not to discuss the results or their distress with others[197]. Similarly Moran et al in their qualitative study identified waiting for a repeat IRT test results as the most emotionally difficult stage for parents [196].

### ***Persistent Parental Distress and CF Carrier Status***

The majority of initial positive results in CF NBS ultimately represent false positives[186]. (The ratio of false-positive screens to true-positive cases is reported to be between 5 and 25 to 1 in the US, depending upon screening methodology[85]. This means that none of the potential benefits of NBS can accrue to the child or their parents, but they may still suffer the associated psychosocial harms, making the handling of false positives of some importance. Many NBS protocols do not report the initial result (raised IRT level) unless it is accompanied by one or two CF causing mutations on DNA analysis of the same blood spot sample or if the IRT is greater than the 99.9<sup>th</sup> centiles[150]. This reduces but does not eliminate false positive results, and also introduces a different issue, the identification of CF carriers. In other words a false positive result as part of CF NBS differs from false positives for disorders such as PKU which most commonly occur for reasons unrelated to carrier status, such as preterm birth[92]. Identification of CF carrier status may have an impact upon persistence of parental distress, the concern being that once carrier status is divulged there may be confusion regarding the difference between being an asymptomatic carrier and being affected by the disorder, leading to distress as well as potential for stigmatisation and discrimination. Identification of carrier status also raises other ethical issues[150]. These include the fact that because identification of carriers is only of reproductive relevance rather than having any medical implications, testing is generally not recommended in minors. Rather there is a general consensus among the clinical genetics community that it is better to delay testing until the young person can

consent or decline for themselves[33]. This creates a dilemma for NBS programmes: early recommendations stated that carrier status detected through NBS should not be disclosed to parents[87] but this was subsequently considered likely to contravene parents' expectations regarding informed consent, and more recently such results generally are divulged[33] leading to diametrically opposed recommendations in two different clinical settings [199]. Other ethical concerns include that extended carrier status testing can affect family dynamics, including sometimes raising questions over paternity[200].

Whether or not parental anxiety persists despite negative diagnostic testing is clearly a question of some importance, as is the relevance of carrier status to these reactions. However, evidence regarding these issues is much more limited than that relating to acute anxiety[200], and somewhat conflicting.

A few studies have addressed the issue of persistence or otherwise of parental distress following a false positive CF NBS result. In Tluczek's mixed method study the high incidence of depressive symptoms they reported on the CES-D following the initial positive NBS had decreased by 6 months after the sweat test such that there was no difference between the false positive NBS group and the control group [197]. However, an earlier study by the same author showed that although most parents were relieved by negative sweat test results subsequent to the abnormal IRT test some continued to have lingering concerns that their child may have CF. Factors associated with continued parental concern in this study included lower educational status, having an infant with low Apgar scores and receiving results by telephone [201]. The authors postulated that infants with low Apgar scores were more likely to have experienced difficult births which may have contributed to the parents misconceptions and anxiety about their child's health[198].

Similarly, Moran et al interviewed parents whose child had undergone CF screening in Leeds, UK where positive IRT samples are sent for genotyping, and repeat IRT tests organised before the genetics results become available. Negative genotyping and a normal repeat IRT test are interpreted as meaning CF is unlikely and no further investigations are performed whereas all other infants with an initial positive IRT go on to have a diagnostic sweat test [196]. The authors reported that after receiving a negative repeat IRT test over 80% of parents reported relief and "weight lifted". Most parents considered they suffered few residual effects rather preferring to "get on with things", although the researchers noted that a minority of parents felt ongoing upset or sadness regarding the screening process and in some cases anger [196].

Other studies have specifically addressed the issue of identification of carrier status. While there is some evidence to suggest that parents recall carrier status well[202] it also appears

that others continue to have misconceptions and knowledge deficits relating to the implications of carrier status when assessed some years later [203], [202]. Several studies have reported that continued concerns about the CF carrier infant's health are not the norm [154, 204], [202] but as many as 15–29% of parents continue to worry about the physical health of their carrier child or believe their child might still develop CF [202, 205-207].

Parsons *et al.* also showed that 6 months after NBS there was no evidence that the mother–baby relationship had been affected by carrier identification or that carrier status was seen by parents as a problem in terms of spoiled identity [153, 200]. Similarly, adult population screening for CF carrier status has also been viewed positively by participants and those with positive results generally correctly recall their carrier status and demonstrate no difference in anxiety compared to non-carriers [208].

One study has examined potential psychosocial effects occurring many years after screening. Cavanagh *et al.* employed the Child Vulnerability Scale (CVS) in order to measure parental concern about their child's vulnerability to health problems 11-14 years after NBS [53]. Their overall analysis showed that false positive NBS results for CF (that were subsequently confirmed as carrier results) were not associated with parental perceptions of child vulnerability 11-14 years later [203]. The authors of this study also reported on parental lack of understanding of CF genetics, particularly in those who had not received genetic counseling, although they did note that parents seemed to have effectively absorbed information about the most important outcome of the NBS process, namely their child's test results [203].

Finally, a single study provides data concerning the relative impact of false positive results and carrier status on persistent parental concerns. In their recent study, Beucher *et al.* assessed parental anxiety with their own standardised questionnaire, in conjunction with the Perceived Stress Scale and the Vulnerable Child Scale at 3 months, 12 months and 24 months after an initial positive screen was eventually confirmed as a negative result. In total, 86% to 100% of families studied no longer worried about CF at these time points and all parents stated that they would have the test performed again for another child [154]. In addition their scores on the Perceived Stress Scale did not differ from that observed in the general population at any of the time points and their scores on the Vulnerable Child Scale were high, associated with a low parental perception of child vulnerability [154]. However, the study involved 2 subgroups, one cohort of parents whose babies had elevated IRT levels on screening and a single CF gene mutations (heterozygote's or CF carriers) and the other cohort of babies with elevated IRT levels but no mutation detected in the CF gene, presumed unlikely to be CF carriers. In the CF carrier group, 11% of parents still expressed anxiety at the 2 year

interview, 14% thought of CF when their child was ill, and all expressed a desire to repeat the test in the future. By contrast, no parent in the elevated IRT group expressed any anxiety [154]. This suggests that a false positive result for CF may not in itself lead to persistent anxiety but for a small proportion of parents learning about their child's carrier status does appear to have this effect. Other CF studies either do not distinguish between different classifications of false positive result or do not include those with simple elevated IRT results.

### **3.6.3.2. Reproductive Decision Making**

A distinguishing characteristic of single gene disorders, such as CF, is that there are potential implications for future pregnancies[207] and other family members[209]. This is a significantly greater issue for CF than for other disorders detected through NBS simply because the frequency of carrier status in the population is much higher. The ability for couples to engage in genetic counselling to obtain information about their own carrier status and to assist them in reproductive decision making is often considered to be one of the benefits of this type of NBS programme[150] and several studies have investigated these responses [207, 209-212]. This empirical work has shown that attitudes, rates of uptake of prenatal testing, terminations and birth rates are very variable. For example in a 1994 study of 37 families with a first born child with CF only 22% of participants who became pregnant made use of prenatal testing[212]. This contrasts with an Australian study published in 2000 that reported that the uptake of prenatal diagnosis was 66% in women who had a subsequent pregnancy and of these 69% terminated or would have terminated an affected fetus[211]. The variability in results from different studies may relate to many factors including: methodological issues such as the small sample sizes studied; variation in the availability of counselling services and prenatal testing services; as well as difference in attitudes to sensitive issues such as termination of pregnancy between different populations[149, 150].

### **3.6.3.3. Psychosocial Responses to True Positive NBS Results Compared to Later Clinical Diagnosis**

CF differs from many other disorders included in NBS in that onset of clinical symptoms sometimes occurs beyond the newborn period. This, coupled with an average 15 month delay between symptom onset and diagnosis[213], means that a NBS diagnosis may come years before a conventional clinical diagnosis would have done.

A confirmed diagnosis of CF will always be distressing but it is important to determine whether diagnosis through NBS is more or less distressing, or disrupts the mother-child bond more than later clinical diagnosis. A systematic review of the evidence relating to this issue has concluded that diagnosis through NBS does not create more parental distress than later

clinical diagnosis[214]. Similarly, data from the Wisconsin study showed that parents of children diagnosed with CF through NBS did not show significantly higher parenting stress scores than their healthy or clinically diagnosed CF comparison families, although they did have higher frequencies of scores above the clinical referral cut-off for Total Parenting Stress scores (45%) and Child Demandingness subscale scores (50%)[215].

Several studies have addressed the issue of potential disruption of the mother-child bond. One study, used the Parental Attitude Research Inventory to compare the strength of overprotective child-rearing attitudes of twenty-nine mothers whose children were screened for CF (thirteen had symptomatic children and sixteen asymptomatic children) with the attitudes of twenty-nine mothers whose children were diagnosed after the onset of symptoms. The results indicated that NBS had not increased, and in some cases had decreased, a mother's tendency to overprotect her child with CF. The authors also noted that delays in diagnosis when screening was not conducted usually caused mothers considerable personal distress[216].

One study did report a short term disruption in the mother child relationship following a diagnosis of CF, with four mothers acknowledging temporary rejection of their baby during the diagnostic process[210]. However, because in this study data from 2 cohorts (NBS and later clinical diagnosis) were combined it was not possible to identify from which group the adverse responses arose.

In contrast to the majority of quantitative studies, a recent qualitative report has described how parents undergo a "transformative process" when a diagnosis of CF through NBS is made in a child who parents had previously viewed as healthy. In particular the researcher noted that this unexpected diagnosis that came so early in the postpartum period, before the parents really knew the infant themselves, affected parents' sense of competence and confidence in caring for their child and their view of the child's identity. Many of the parents reported making frequent contacts with healthcare professionals to obtain reassurance about potential symptoms and that their caregiving techniques were adequate. The researcher states that "parents perceive the locus of control over their child to lie with professionals".

Interestingly parents in this study were generally supportive of CF NBS (as has been reported in several other studies[217, 218]) but the only 2 mothers who had the option of delaying testing of a subsequent sibling of the affected child did so, opting for testing between 4 and 8 months. The paper balances these reports of difficulties in adjusting to early asymptomatic diagnosis with reports from parents of later clinically diagnosed children who experienced "helplessness" and considerable distress as they suffered prolonged "diagnostic odysseys" [219]. Several other studies have also reported on the overall psychosocial benefits of early

diagnosis through NBS in terms of reduction of the distress experienced by families in relation to diagnostic delay, and improved confidence in the medical profession[23, 210, 216, 220, 221].

#### **3.6.3.4. Ambiguous results**

Finally, a small minority of parents are left with equivocal diagnostic test results following an initial positive CF NBS. One qualitative study analysed the experiences of five couples whose children had normal or equivocal sweat test results and were healthy despite positive NBS results and two CF gene mutations. The health implications (if any) for this group of infants are currently uncertain. Parents described the difficulties they encountered in living with this uncertainty and some of the ways they coped, including searching for information, monitoring their child's health and consciously setting favourable expectations about their child's future[222]. The initial affective response to test results was negative for all families but particularly so for one couple who felt that the news of an abnormal NBS result had exacerbated pre-existing postpartum depression. Parents generally described less intense distress as time passed and their children remained healthy, but they continued to worry about their child's future health[222].

#### **3.6.4 Expanded NBS for metabolic disorders**

The recognition that expanded NBS utilising tandem mass spectrometry leads to increased numbers of false positive results has led to renewed interest in their psychosocial implications, particularly whether they may be implicated in development of the VCS [185, 223-225]. A 2003 paper compared the impact of early identification by expanded NBS on child health and development and parenting stress with that of a later clinical diagnosis of biochemical genetic disorder. Children diagnosed through NBS appeared to be less developmentally delayed and their parents less stressed than those with similar disorders diagnosed clinically[225]. However, in the same study, stress levels at 6 months (measured using the Parenting Stress Index) were elevated in parents of children with false positive test results and twice as many children in the false positive group compared to children with normal results had been hospitalised (usually following an Emergency Department visit) in the first 6 months of life compared to a group of children who had normal NBS results [225]. Similar results were obtained in a more recent (2006) study specifically examining the impact of false positive expanded NBS results on parental stress, family relationships, and perceptions of a child's health during the child's first year. Compared with parents who received normal results, both mothers and fathers who had received a false-positive NBS result had higher scores on the short form of the Parenting Stress Index and its "difficult

child” and “parent-child dysfunctional interaction” subscales. High scores on this latter subscale may indicate that the parent-child bond is either threatened or was not established adequately[185]. Mothers of children with false positive results also worried more about their child’s future and were more likely to believe their child required “extra care”. This study, while confirming the finding of the previous report did have limitations in that there was a significant disparity in the children's ages between the two groups (6 months for the normal screen group and 13 months for the false positive group) that may have biased results[185]. In contrast to these two studies documenting increased parenting stress in relation to false positive results one further study found no difference in health care utilisation up to six months of age between children with false positive NBS results and children with normal results. However, this study also had limitations in that there were significant socio-demographic differences between the groups, particularly that the false positive group was older than the control group. In addition, all data concerning health care utilisation was collected via a telephone call to the child’s mother, and based upon her recall of events that may have occurred some months earlier[223].

Overall, there is evidence to suggest that children who have false positive results on expanded NBS are more likely than children with normal results to experience hospitalisation, and their parents are more likely to be overprotective and more focused on their child’s physical symptoms[173].

### **3.7 Conditions included in current less widely implemented NBS programmes**

#### **3.7.1 Duchenne Muscular Dystrophy**

In some areas, such as Wales (UK), NBS programmes have included tests aimed at early detection of Duchenne Muscular Dystrophy (DMD) for several years. DMD is a lethal genetic disease normally transmitted to boys by healthy women who carry the defective gene on one of their two X chromosomes. Affected boys are healthy at birth, show early signs of muscle weakness by age three to four years, become wheelchair-bound by eleven to twelve years and usually die in their late teens to early twenties[226]. There have been several pilot studies of NBS for DMD and a few ongoing programmes, including the one in Wales in which the psychosocial implications have been carefully evaluated. The authors of these reports used a combination of quantitative and qualitative methodologies to compare parents/infants who had true positive, false positive and normal screening results at 6 months and 4 years and parents/infants who were not screened but later diagnosed clinically at 4 years[226].

Quantitative measures included questionnaires such as a rejection/protection index and a baby/child adjective checklist that was developed by the authors[227]. Other quantitative measures employed were the widely used and well validated short form of the State Anxiety Scale[228] and the General Health Questionnaire (GHQ), a screening tool for general mental health wellbeing. Direct assessments by health visitors of mothers interactions with their baby (FIRST scores[229]) were also included[227]. The qualitative component of the study involved semi structured interviews that explored various topic areas (e.g. how parents responded to the news, whether they felt their relationship with their son had changed, their future expectations) in greater detail[226].

The majority of families with an affected child were in favour of NBS as they felt it gave them time to come to terms with the diagnosis before their son became aware and to plan both emotionally and practically. They also valued the opportunity to assess their reproductive options. A small number of families were ambivalent or opposed to screening, feeling some regret around the earlier diagnosis[227].

The researchers found no negative effect of DMD NBS on the early mother–baby relationship, including no evidence of either rejection or overprotection of infants[227]. However, their analysis of baby descriptors showed that mothers in the diagnosis through screening group were less likely to use certain positive descriptors and more likely to choose “cuddly”, although their qualitative data indicated that this group of mothers felt that their sons had become “more precious” after diagnosis through screening. It therefore appears that the adjective checklist is very sensitive and while it noted a subtle qualitative change in the mother-baby relationship it is difficult to say whether or not this was disadvantageous[226]. The group also found that anxiety levels were slightly above threshold at the first interview (6 months) for the diagnosis through screening group and at the 4year interview for the clinically diagnosed group. The anxiety levels of the diagnosis through screening group had returned to normal by 4 years and there was no evidence, from anxiety or wellbeing scores, that the small false positive group had suffered any disadvantage. There was also some evidence that parents had modified their reproductive plans. For example four fetuses carrying a mutation causing DMD were terminated[226].

## **3.8 Conditions included in research related NBS programmes**

### **3.8.1 Alpha 1 antitrypsin deficiency**

Several of the early reports relating to parents’ reactions to NBS come from a Swedish programme that tested for  $\alpha$ 1-antitrypsin deficiency (AATD) from 1972-74 [147, 230-237].

$\alpha$ 1-antitrypsin is a protein, normally produced in the liver and released into the blood stream that protects the lungs from damage. Deficiency of the protein increases the risk of chronic obstructive airways disease in adulthood and can cause liver disease in a minority of children and adults. The main purpose of the screening programme was to study the natural history of the condition and to provide an opportunity to protect “at-risk” children from concentrated air pollutants (mainly cigarette smoke) in the hope of preventing or delaying onset of lung disease in adulthood[230]. The AATD screening programme therefore differed in several ways from other NBS programmes of the time (and even now): a positive result reflected only an increased risk of disease; if disease occurs it is usually of adult onset (lung disease) with only a minority of children becoming ill; the action to be taken in response to a positive screen involved parental behaviour change (stopping smoking) rather than any treatment applied directly to the child[149] and there was considerable uncertainty about the nature and implications of AATD at the time[230].

The screening programme was discontinued after five years because of the psychological stress it caused some families whose child had tested positive[151], and subsequently a number of retrospective psychological evaluations of the parents were performed [147, 230-237]. Data regarding this programme should be treated with caution as information provision and counselling services in the 1970s may not be analogous to those employed today, and the retrospective nature of the studies may have lead to some bias in findings. However, the results do merit consideration as the tests clearly have some features, in common with the type of susceptibility tests that could be employed today. Most parents of children with a positive newborn screen reacted negatively to the initial news of their child’s test result, usually with fear and anxiety[233]. These reactions were typically strong and only a third of parents felt relief after their first appointment with the specialist [233]. At follow-up 5-7 years later about half the mothers and a third of the fathers were judged to have poor long-term emotional adjustment when assessed by a physician and a psychologist[234] although parents themselves did not report any negative long term consequences at interview[230]. Comparing interview data from parents of affected children with matched controls, identification of AATD was found to have negatively influenced the parents' view of the child's general health, but there was no reported increase in attendance at Paediatric services[152]. The children also showed more problematic behaviour (such as aggression or inhibition) when interacting with their mothers in the context of a structured test[151]. While most parents reported feeling glad that their child’s AATD had been identified early this did not translate into a reduction in risk related behaviour: one or both

parents smoked in more than half of the homes concerned, and fathers of affected children smoked twice as frequently as control fathers[230].

### **3.8.2 Hypercholesterolaemia**

There is one other report relating to a NBS programme aimed at detecting predisposition to disease. This qualitative study described parental responses to population-based NBS for familial hypercholesterolaemia [238](FH). FH is an autosomal dominant disorder that greatly increases the risk of cardiovascular disease. The screening process used in this study involved assays for apolipoprotein B (apo B) and apolipoprotein A-1 (apo A-1) using samples from the standard NBS bloodspot card. Infants with raised apoB or a reduced apoA-1/apoB ratio were recalled, retested and referred to a Vascular Risk Clinic for further management if considered appropriate[239].

The authors of the qualitative study interviewed some of the parents whose child had tested positive and had been referred to the specialty clinic. They found that some parents perceived the screening test to be a way of detecting raised cholesterol and viewed the condition as familiar, dietary in origin, easily controlled and not very threatening. Conversely, other parents perceived the test as a genetic test, and they considered the disorder to be uncontrollable and very worrying. The authors concluded that if providing parents with genetic risk information made them fatalistic, they may be less likely to adopt risk reducing behaviours such as dietary modifications, which would defeat the objectives of the screening programme[238].

### **3.8.3 Fragile X**

Fragile X Syndrome (FXS) is the most common inherited form of intellectual disability. It is an X-linked single gene disorder with a complex inheritance pattern. Affected males typically exhibit moderate to severe intellectual disability as well as social and behavioural difficulties including features of autistic spectrum disorder. Females with the full mutation are more mildly affected, with as many as 50% having borderline or normal intellectual function due to cellular mosaicism and X inactivation.

Without screening FXS is not usually diagnosed until the child is approximately 3 years old, as the clinical features are fairly non-specific[240]. While there is no specific treatment for FXS early intervention services are helpful and parents can consider their future reproductive options[183, 241]. Until recently a test suitable for use in NBS was not available but latterly more accurate tests have been developed [242] [243]and pilot studies of population NBS for FXS are underway[242].

There are many potential psychosocial issues associated with NBS for FXS [183]. These include issues such as: the potential impact upon parents of early diagnosis of an untreatable disorder and detection of relatively large numbers of females and to a lesser extent males with normal intellectual functioning who would not otherwise have been diagnosed[183]. I will not discuss these issues at length as the majority have not yet been subject to empirical investigation as population screening capability has only very recently become available. Despite these potential problems there is some preliminary evidence regarding the views of parents and medical practitioners on the acceptability of NBS for FXS. One survey of parents of children with FXS asked if they thought that receiving a diagnosis at birth would have affected the way in which they bonded with the child. 60% believed there would have been no effect, 9% felt bonding would be easier and 10% felt it would be more difficult. The 10% who considered it may be more difficult thought that new parents would worry about how they would manage a child with FXS. Overall, these parents were in favour of both NBS and carrier testing[244]. Other survey have shown that only 31% of Paediatricians and 20% of Genetic Counsellors (in 2005) supported NBS for FXS[245, 246].

### **3.8.4 T1D**

As discussed in chapter 2 population screening for genetic susceptibility to T1D does not currently form part of clinical practice but is the object of several longitudinal prospective studies. The empirical evidence concerning psychosocial effects of such screening presented in chapters 5-7, is the result of my evaluations of parents involved with one such study, the Key Environmental Aspects of T1D (KEA) study. At the outset of this research there was virtually no data concerning psychosocial effects of NBS for T1D but, more recently, other groups have reported their evaluations of parents involved in similar longitudinal research[122], and this accumulated data is reported here.

Yu et al measured parenting stress (using the Parenting Stress Index (PSI)) 5-7 weeks after birth (prior to risk notification) and 4-5 months after T1D risk notification in a sample of 23 mothers with infants at risk for T1D and 65 mothers whose infants were not at increased risk. Mothers of infants at increased risk reported greater stress than mothers of low risk infants but the difference was not statistically significant[247]. While these results are interesting, the appropriateness of the PSI in research with mothers of very young infants has been questioned, as when used at this time there are frequently high numbers of missing item responses that potentially invalidate results[149, 248].

More recently, Bennett Johnson et al measured anxiety 3.5 weeks, 4 months and 1 year after T1D risk notification using the short form of the State Trait Anxiety Inventory (STAI) in a

cohort of 435 infants found to be at increased genetic risk. The study did not include a control group but the authors reported that for the entire cohort anxiety levels at 3.5 weeks were similar to those previously reported in pregnant women and working women, dissipated further by 4-5 months and remained low at 1 year. However, Hispanic mothers, those with infants classified as extremely high risk (through a combination of genetic analysis and family history) and mothers who overestimated their child's risk experienced considerable anxiety, comparable with that of pregnant women undergoing amniocentesis. Mothers of infants at real or perceived extremely high risk also tended to remain more anxious across all three interviews[249].

Hood et al measured maternal depressive symptom with the Center for Epidemiologic Studies-Depression Scale (CES-D) 1 month and 3.5 months after notification of increased risk of T1D. This study also did not include a control group but the authors concluded that NBS for T1D risk does not lead to depressive symptoms in most mothers. However, they reported considerable variability in maternal responses with those from ethnic minority backgrounds and with limited education reporting more depressive symptoms. Evidence of postpartum depressive symptoms was also a powerful predictor of depressive symptoms in response to risk notification[250].

A recent report from a study of longer duration used a modified version of the Swedish version of the PSI to evaluate the psychological burden upon parents of their genetically susceptible child either developing pre-clinical signs of T1D (multiple permanently positive autoantibodies) or progressing to clinically apparent T1D. Questionnaires were administered a mean of 2.9 years (range 0.5 to 6.7 years) after parents had been notified of autoantibody positivity. Using the genetically susceptible cohort as a control group the authors found that autoantibody positivity did not alter stress levels but parents whose child had actually developed T1D showed higher stress scores and considered parenthood and child care more difficult. Stress levels in the autoantibody positive group were similar regardless of participation or non-participation in a prevention trial of intranasal insulin[251].

Unfortunately it is not possible to determine from this study report whether or not stress scores of parents in the genetically susceptible control group fell within the normal range. Finally, Simonen et al assessed parental anxiety and feelings in relation to the population based T1D prediction and prevention project in Finland. 2 weeks after notification of results they found no difference in anxiety (measured with the state subscale of the STAI) between parents of high risk and low risk babies. However, more than half of the mothers and one third of the fathers of high risk infants reported feeling worried and one quarter of the mothers reported depressive feelings, shock or helplessness[252].

In addition to these reports of psychological reactions to NBS for T1D one paper also reports on maternal efforts to prevent T1D in genetically susceptible children. The authors concluded that even in the absence of known prevention methods most mothers of at risk children report T1D prevention behaviours, most commonly monitoring behaviours and modifications of the child's diet or physical activity [253].

### **3.9 Summary of existing research**

The volume of research regarding psychosocial reactions to NBS has waxed and waned over the years. Following the initial description of “PKU anxiety syndrome” several reports documented parents' reactions to screening programmes in the 1970s, including those for hypothyroidism and AATD. This group of studies makes an important contribution to literature in the field as it represents a clear attempt to study a broad range of psychosocial effects, including parent-child interaction, over a relatively prolonged period. However, methodological issues such as lack of control groups and use of non-standardised assessment methods, as well as issues related to the historical nature of the programmes mean that the findings must be considered with reference to their original context, and may not be entirely relevant to modern programmes.

The next resurgence of interest in psychosocial issues was related to NBS for CF. Indeed, a relatively large volume of data exists pertaining to NBS for CF, most likely because the balance of benefits and risks has not been as great as initially anticipated and psychosocial harms have therefore become relatively more important. Many of these studies are of good quality in terms of methodological issues such as sample sizes, assessment tools and use of control groups, and they have investigated many different psychosocial aspects of this complex screening programme. This body of research also includes a small number of qualitative studies that have investigated some of the more subtle and complex aspects of CF screening programmes. Despite the larger volume, and generally improved quality of research, results of different studies have sometimes been conflicting. This most likely relates to issues such as sample sizes (that may be adequate to detect large differences, but not more subtle alterations in reactions), demographic differences, precise methodology employed and the differing nature of screening protocols themselves.

Finally interest in the psychosocial effects of false positive results has re-emerged in the last few years since the advent of tandem mass spectrometry and expanded NBS. These studies have largely concentrated on parenting stress, including aspects of parent-child interaction, and on the potential for increased utilisation of healthcare resources. While the data suggests that false positive results increase parenting stress, there have been conflicting results in terms

of increased healthcare utilisation, and again demographic differences between study groups may have contributed to these findings. Overall, these studies suggest that false positive expanded NBS results may create expectations of illness in an otherwise healthy child, in a similar manner to antecedent health problems, such as innocent heart murmurs or jaundice, implicated in the VCS[173].

Although it is possible to criticise the existing body of research, and its perceived importance has fluctuated somewhat over the years, it is apparent that there have been robust attempts to investigate psychosocial issues related to NBS. I have therefore summarised the findings of this somewhat diverse group of studies in Table 3.1 to highlight what is currently known. For each element of the NBS pathway I have summarised the evidence relating to short and long term parental emotional reactions and effects on parent-child interaction, including perceptions of child health.

**Box 3.1 Psychosocial reactions associated with past and current NBS programmes**

<b>Element of NBS pathway</b>	<b>Evidence</b>
<b>Immediate reaction to abnormal NBS result</b>	<p><b>Short term emotional reaction</b></p> <p>Consistent evidence of significant parental distress e.g. anxiety, depression [35, 60, 62-66, 101-103]</p> <p>Degree of distress may be less if parents well informed[254, 255]. Limited evidence that parents report willingness to tolerate this distress to achieve potential gains[256].</p>
	<p><b>Parent-child interaction</b></p> <p>Limited evidence of altered parent-child interaction[194]</p>
<b>Reaction while awaiting results of diagnostic tests</b>	<p><b>Short term emotional reaction</b></p> <p>Consistent evidence of significant parental distress e.g. worry, depression [196, 197, 219]</p> <p>State of uncertainty described as major source of distress[196, 197]</p> <p>Possible to reduce this through attention to protocols e.g. minimising waiting periods [154, 197]</p>
	<p><b>Parent-child interaction</b></p> <p>Evidence of altered parent – child interaction such as monitoring child’s health and “medicalisation” [196, 197, 219]</p>

<b>Reaction to true positive results</b>	<b>Short term emotional reaction</b> Consistent evidence that parental distress considerable but no more than that created by clinical diagnosis[214, 225, 227]
	<b>Parent-child interaction</b> Most quantitative studies suggest mother-child interaction not adversely affected[216, 227] but qualitative data suggests subtle difficulties[219, 227] Parents value ability to access information, support and services for their child[196, 205, 257, 258]
	<b>Reproductive decision making</b> Parental attitudes and uptake of prenatal services very variable[216, 227]
<b>Reaction to false positive results</b>	<b>Short term emotional reaction</b> As for “immediate reaction to abnormal NBS result” (as the eventual nature of the result is unknown initially)
	<b>Long term emotional reaction</b> Evidence conflicting. Some studies demonstrate absence of persistent anxiety [154, 227, 259] others report anxiety up to 4 yrs later[65, 192] Some evidence long term anxiety associated with carrier status [154] or unrelated medical issues of the child[201]
	<b>Parent-child interaction</b> Long term. Evidence conflicting: some studies show absence of parenting stress [154], others evidence of continued parenting stress and ongoing concerns about child’s health [185, 191, 192]. Conflicting evidence regarding healthcare utilisation from no increase[223] to increased hospitalisation rates[225] Very long term – no evidence of altered perception of child’s health at 11-14yrs[203]
<b>Reaction to carrier status (CF studies only)</b>	<b>Short term reaction</b> Anxiety, knowledge deficits and misconceptions about health status common[202, 203]

	<p><b>Parent-child interaction and long term emotional reaction</b></p> <p>Continued anxiety and concern about the carrier infant's health not the norm[153, 200, 204] [154] [202] but consistently occur in a significant minority [202, 205-207]</p>
<p><b>Reaction to susceptibility to later onset disorder (AATD, hypercholesterolaemia, T1D)</b></p>	<p><b>Short term emotional reaction</b></p> <p>Evidence of significant short term parental distress for AATD[233]. For T1D overall no distress on rating scales, but did occur in subgroups e.g. ethnic minority, very high risk[247, 249, 250, 252]. Some parental reports of distress[252]</p>
	<p><b>Long term emotional reaction</b></p> <p>Evidence of long term parental distress for AATD[234]</p> <p>For T1D long term reaction as for short term</p>
	<p><b>Parent-child interaction</b></p> <p>Evidence of impaired mother child interaction[151, 152, 260] and increased risk-related behaviour among parents (smoking) for AATD[230]. No analysis of mother-child interaction for T1D but behaviour change reported[253]</p>
<p><b>Reaction to ambiguous results (CF, small number of studies)</b></p>	<p><b>Short term emotional reaction</b></p> <p>Evidence of short term distress[222]</p>
	<p><b>Long term emotional reaction</b></p> <p>Long term distress less but continued worry[222, 261]. Difficulty in coping with uncertainty[222]</p>
	<p><b>Parent-child interaction</b></p> <p>Evidence of altered parent child interaction and parental monitoring of child health[222]</p>

### 3.10 Relevance of existing research to NBS for genetic susceptibility to T1D

I have reviewed the existing body of research related to psychosocial reactions to NBS in some detail because it is important and highly relevant in considering how parents may react to NBS for genetic susceptibility to T1D. As discussed in chapter 2, there are clear differences between tests currently included in NBS panels and those for T1D, but an exhaustive review of the current literature also reveals many areas of similarity. In particular, the following list

(adapted from chapter 2.4.1) articulates some of these important differences but then highlights specific aspects of the existing body of evidence that may assist in our understanding of parents' reactions to T1D susceptibility testing.

**1. NBS for genetic susceptibility to T1D is likely to involve a relatively large number of parents being informed of a “positive” result (as up to 15% of children possess increased risk alleles[140]), although most will remain healthy and not develop T1D.**

Existing NBS research tells us much about parents' reactions to “positive” results in apparently healthy children:

- There is clear evidence that when the initial NBS result is positive parents experience considerable distress regardless of whether the initial result eventually turns out to be false positive, true positive, ambiguous or reflect carrier status, and regardless of the particular disorder.
- There is evidence to suggest that this distress may persist for some time, particularly in relation to ambiguous results or carrier status.
- There is some evidence that being informed of a positive NBS result, even when this is later shown to represent a false positive or ambiguous result, or carrier status, causes altered parental perceptions of child health.
- Similarly there is some evidence that false positive or ambiguous NBS results contribute to parental monitoring of child health and increased healthcare utilisation.

**2. A “positive” result in NBS for genetic susceptibility to T1D reflects only a risk or probability of disease (clinical validity of the test is low).**

Some aspects of existing or past NBS programmes also involve parents being informed of increased risks, rather than actual disease. These include: the period of waiting for a sweat test in NBS for CF, ambiguous results in NBS for CF and screening programmes for AATD and hypercholesterolaemia. Studies related to these aspects of NBS programmes tell us that:

- There is increasing evidence that uncertainty appears to be difficult for parents to cope with and is likely to result in parents pursuing a range of strategies to attempt

to reduce uncertainty, including searching for information and monitoring their child's health.

**3. There is currently no way of reducing the risk of genetically susceptible children developing T1D (clinical utility is low).**

There are several current, past or research related NBS programmes that involve “untreatable” disorders including screening for DMD, FXS and AATD. Studies related to these NBS programmes tell us that:

- Parents of children with DMD and FXS are supportive of diagnosis through NBS even though there is a lack of specific treatment. Reasons for their support include: the ability to understand the cause of their child's problems, the ability to prepare emotionally and practically for the future, the immediate access to early intervention services and information, elimination of the frustrations associated with delayed diagnosis, and provision of information relevant to reproductive decisions[227, 244].
- Diagnosis of DMD through NBS does not significantly affect the mother-child relationship although in the AATD screening programme parent-child interaction was adversely affected and parent behaviour was opposite to that advised.

**3.10.1 Important knowledge deficits concerning NBS for genetic susceptibility to T1D**

Given the profound importance of early childhood experiences documented at the beginning of this chapter, and existing evidence concerning psychosocial reactions to NBS programmes, there is an urgent need to investigate parents' reactions to NBS for genetic susceptibility to multifactorial disorders such as T1D. In particular:

- There is limited evidence regarding short and longer term parental affective responses to NBS for genetic susceptibility to T1D.
- There is virtually no evidence regarding parental perceptions of child health following NBS for genetic susceptibility to T1D.
- There is very little evidence regarding parental monitoring of child health, or other parental behaviours, following positive NBS for genetic susceptibility to T1D.
- There is no evidence regarding the value or importance parents attach to T1D genetic risk information.

- The role of uncertainty in parental responses to NBS results has not been adequately explored and is of particular relevance to testing for genetic susceptibility to T1D.

### **3.11 Conclusion**

In the first part of this chapter I highlighted why experiences in early infancy are so important and introduced the concept of the VCS. I then reviewed the existing literature pertaining to NBS finding that there are clear examples of persistent parental distress and altered parental perceptions of child health in relation to certain aspects of existing NBS programmes. While there has been considerable speculation regarding the potential for NBS for genetic susceptibility for conditions such as T1D to contribute to important developmental disorders, such as VCS, there is currently very little evidence regarding this. As NBS policy needs to carefully weigh evidence of benefits and risks, particularly when they are likely to be more finely balanced, formal investigation of these potential effects is of considerable importance. In the next 4 chapters I describe how I conducted empirical research in order to begin to address these knowledge deficits.

## **Chapter 4      Research Design**

## **4.1 Introduction**

My overall aim in this thesis is to advance discussions concerning genetic susceptibility screening in the newborn period by replacing speculative rhetoric with empirical data concerning its psychosocial effects. At the end of the last chapter I articulated several important knowledge deficits concerning NBS for genetic susceptibility to T1D, and in this chapter I describe the research I designed to investigate these issues, beginning with a description of the factors that influenced my research design.

## **4.2 Influences upon research design**

The design of my research has been affected by many factors including those related to my personal background and to ideas formulated through literature review.

### **4.2.1 Reflexivity and researcher background**

Good research should be reflexive. This means that the researcher should regularly assess how they are conducting the research, and the role they are playing in the research process. These “background” elements of the research should be subjected to the same degree of critical scrutiny as the actual data.

*“Reflexive research acknowledges that the researcher is part and parcel of the setting, context and culture they are trying to understand and analyse. That is to say the researcher is the instrument of the research....Rigorous qualitative research is honest about the role of the researcher in the project.” [262]p41*

Although these arguments about researcher reflexivity are most commonly applied to qualitative research it has also been acknowledged that while quantitative researchers may strive to be neutral and objective, this aspiration may be difficult to attain fully [263]. I therefore acknowledge that in both phases of my research, my background and beliefs may be relevant in relation to both research design and process.

At the time I began the research reported in this thesis I was 33 years of age, married to a doctor and had one child age 2 years. I have subsequently had three more children, one now aged 5yrs who has Down syndrome, and identical twins, now aged 2yrs. I am a Paediatrician by training and have also completed a Masters Degree in Bioethics at Melbourne University (2000).

### **4.2.2 Literature review**

In addition to these features of my background, the literature I reviewed prior to and during the research process also contributed significantly to my research design. In particular, my

analysis of the history and development of NBS highlights its complexity and the frequent occurrence of unexpected findings. Although the history of genomic medicine is somewhat shorter it is also marked by significant complexity and uncertainty.

Upon this broad general background, the literature pertaining to psychosocial consequences of NBS is more constrained. The focus of this research has primarily been the effects of false positive results, and to a lesser degree true positive results upon parents and has predominantly been undertaken within a quantitative psychological paradigm. There is a paucity of qualitative research within the NBS field. However, I did note in chapter one that calls to broaden the conception of a child's best interests in relation to predictive genetic testing later in childhood have begun to emerge in the ethics and genetics literature. These calls have been supported by important qualitative data concerning psychosocial benefits of such testing even in the absence of medical benefits[48].

#### **4.2.3 Convergence of literature review and personal experience**

My biomedical background, interests developed during my Master's degree programme in Bioethics, and the quantitative nature of the existing literature concerning psychological effects of NBS reinforced my concern with applying a similar methodology to newborn genetic susceptibility screening. There appeared to me to be a clear gap in the existing evidence base in this regard. I was already aware of this gap as I completed my Master's degree programme and was subsequently appointed as a Paediatrician and Clinical Lecturer at Dunedin Public Hospital and Dunedin School of Medicine respectively. Shortly after my arrival in Dunedin I became aware of the KEA study (that was at an early development stage) and discussions with the Principal Investigators of this study culminated in the addition of the psychosocial arm reported here. In other words my academic interests and position within the Paediatric Department facilitated the very existence of the work reported in this thesis, while other aspects of my background and the existing quantitative literature shaped the nature and focus of my quantitative study.

However, my personal experience is much more than just my academic and professional background, and my role as a mother, particularly of a child with a disability, has also affected the way that I have designed and undertaken my research. My life is at least as complex and rich as the literature I mention above: I walk within a diverse range of communities, and have a keen awareness of varying perspectives and ways of acting. In addition my interest in Bioethics, and in particular , a social research module component of my Masters degree reinforced my belief that evidence is crucial to bioethical debate, but that there are many different ways of investigating and describing phenomena. While a thorough

review of sociological literature pertaining for example to parenting, disability, technology or risk is beyond the scope of this thesis I am aware of these discourses and recognise their importance. I believe that the ways in which people interpret and give meaning to events and things are equally as important as attempts to quantify specific aspects of their responses. This is particularly true for situations that are complex, uncertain and novel, hence my inclusion of a study employing qualitative methodology within my research.

#### **4.2.4 Ontology and epistemology**

These varied perspectives, including the belief that quantitative and qualitative methodologies should be combined, are reflected in the ontological and epistemological perspectives that have guided my research. The ontological position of “subtle realism” suggests that while a social reality may exist, it is somewhat tenuous and can only be accessed through people’s experiences and interpretations of it[264]. So while it is legitimate to study this underlying reality, good research should attempt to represent the multiple perspectives and interpretations of that reality rather than striving to attain a single “truth”[265]. This aim fits with the epistemological perspective of constructionism, which as Crotty describes is one in which, “truth or meaning come into existence in and out of our engagement with the realities of the world. There is no meaning without a mind. Meaning is not discovered but constructed” [266] The compatibility of subtle realism and constructionism is further articulated by Crotty, “accepting a world and things in a world existing independently of our consciousness of them does not imply that meaning exists independently of consciousness....The existence of a world without a mind is conceivable . Meaning without a mind is not.”[266]

#### **4.2.5 Ontology and epistemology in context**

The ontological perspective of subtle realism and epistemology of constructionism guided me throughout my research. I believe that a real world exists, a world where parents may choose genetic susceptibility tests for their babies to provide predictive information concerning their chances of developing various diseases. I also consider that certain elements of parents’ reactions to this genetic information (such as their anxiety state) can be measured and phase 1 of my research aims to provide this quantitative data. However, a gap may exist between such a quantifiable psychological state and the individual’s perception of it [59] and without exploring the nature of this gap, or the way in which individuals interpret the test result and construct their own meaning from it, the research would be incomplete. These meanings and interpretations are not amenable to quantification, hence the use of a different method, semi-structured interviewing, to capture data [262]. Phase 2 of my research therefore aims to gather

qualitative data to further explain some of the statistical findings of phase 1, and to provide more detail and depth of understanding about how parents experience their baby's genetic susceptibility testing. The next section documents and describes the methodologies employed.

### **4.3 Methodology**

Methodology refers to the “strategy or plan of action” used to carry out the research. [266] A qualitative-quantitative divide is often assumed because of the perception that the two methodologies are relevant to different fields, or because of a presumed philosophical incoherence between the underlying epistemological positions [264, 267]. However, more recently, there has been increasing recognition that the dichotomy between qualitative and quantitative approaches has been overstated, [268,264] and that whatever research we engage in it is possible for either qualitative, quantitative or both methods to serve our purpose [266]. It has been argued that the major distinction between these two approaches occurs at the level of methods, and not necessarily at the level of epistemology [266].

The ontological and epistemological positions I have adopted (subtle realism and constructionism) are indeed compatible with both quantitative and qualitative methodologies. In choosing my own research methods I simply chose to use the methodologies that best suited the research questions that I was asking, necessitating the use of both quantitative and qualitative methodologies. The overall aim of using different methods in this study is therefore to augment the integrity of the research and extend the breadth and depth of analysis. Some of the resulting data will quantifiably produce reliable facts about mothers' reactions to the genetic testing process, whereas other parts will examine subjective experiences of the same phenomenon and generate more in-depth understanding.

In the next sections I outline the development of my quantitative research instrument employed at three different time points in phase 1, and an interview schedule used during the semi-structured interviews of phase 2. Further details of the specific methods employed in each of these two phases will be given in chapters 5 and 6 where the results of the research are also presented.

### **4.4 Quantitative research: development of the phase 1 research instrument**

In chapter 3 I discussed the existing evidence base regarding parental reactions to NBS, much of which is quantitative. This type of data is currently lacking for NBS for genetic susceptibility to multifactorial disorders such as T1D, but is of considerable importance given the potential long term effects of altered parent-child interactions. In phase 1 of this research

my aim is therefore to provide quantitative data concerning parent's reactions to NBS for genetic susceptibility to T1D. The specific hypotheses generated for this phase of the study are:

1. That knowledge of a baby's genetic risk of T1D may affect maternal mental state, particularly symptoms of anxiety and depression.
2. That knowledge of a baby's genetic risk of T1D may affect maternal perceptions of her baby's health or vulnerability.
3. That maternal assessment of her baby's risk of T1D after being told the genetic test result may differ from the medical model.

In developing my research instrument I reviewed the existing literature concerning psychosocial aspects of genetic testing and NBS, and discussed the study with clinical and research psychologists. From this reading and discussion I developed a research instrument consisting of five separate, but related parts.

#### **4.4.1 Part 1: state component of the State Trait Anxiety Inventory (STAI)**

The STAI is the most widely used self-report measure of anxiety in adults. It clearly differentiates between the temporary condition of "state anxiety" (assessed with Form Y-1) and the more general and long-standing quality of "trait anxiety" (assessed with Form Y-2). The essential qualities evaluated by the STAI (Y-1) are feelings of apprehension, tension, nervousness, and worry and scores on the STAI (Y-1) are known to increase in response to physical danger and psychological stress. As these were precisely the type of responses I wished to evaluate in parents of newborns undergoing genetic susceptibility testing the state component (Form Y-1) was used in my study.

When using the STAI (Y-1) participants are given 20 brief statements and asked to rate the intensity of their feelings of anxiety "right now/at this moment" on a 4-point scale, from "not at all" to "very much so." Typical items include, "I feel upset," and, "I am relaxed." Higher scores indicate greater state anxiety. Mean scores on the STAI (Y-1) are known to vary with age and sex. To put this study in context, a previous study involving post partum women reported mean scores of 30.4 at 14 weeks and 31.2 at 30 weeks.[269] The scale has been shown to be a reliable and well validated measure of acute anxiety and in particular has good construct validity, discriminating adults with generalized anxiety disorder[270]. The standard instructions accompanying the form were used in this study and permission to use the

questionnaire was obtained from Mind Garden Inc. The STAI (Y-1) is reproduced in Appendix A.

#### **4.4.2 Part 2: Edinburgh Postnatal Depression Scale (EPDS)**

The Edinburgh Postnatal Depression Scale (EPDS) consists of ten short statements [271] with the mother underlining which of four possible responses is closest to how she has been feeling during the past week. An example of a typical item is: “I have looked forward with enjoyment to things” with possible responses: as much as I ever did; rather less than I used to; definitely less than I used to; hardly at all.

The scale was developed as a response to evidence demonstrating a failure to diagnose depression in the puerperium, and concerns that this may lead to long term negative impacts upon families [271]. The EPDS was devised because it was felt that established depression screening instruments were suboptimal when applied to postnatal women because normal postnatal symptoms, such as changes in appetite and sleep as well as loss of energy, could easily be misconstrued as depressive symptomatology[271]. The EPDS has been demonstrated to be acceptable to women in the postnatal period who may or may not regard themselves as unwell or in need of medical help and is quick and straightforward to complete [271].

The EPDS has been used widely in clinical practice and epidemiological and clinical studies [272] and is reproduced in Appendix B. Its reliability and validity in the postnatal period in hospital and community settings,[271, 273] and in cohorts of non-postnatal women with older children have been clearly demonstrated[274].

As my study involved women in the postpartum period this scale seemed the most appropriate measure of depression to use. When the EPDS is used as a postnatal depression screening tool a cut off score of >12 is usually employed, although other authors use lower cut-off scores to identify those with more minor depressive symptoms and a difference in score of 3 or more at different time points has been considered clinically significant even below the threshold of 12[275].

#### **4.4.3 Part 3: Vulnerable Baby Scale (VBS)**

In addition to consulting with psychologists regarding the design of my research instrument I also discussed the study with Paediatricians and Clinical Geneticists. From these discussions, and my review of the literature pertaining to NBS and treatment[52, 172, 276, 277], it became clear that an entirely standard approach to examining psychosocial aspects of newborn genetic susceptibility testing would not be sufficient. An additional section within my research

instrument was required to address the important issue of whether genetic knowledge of an infant's susceptibility to T1D may initiate a "vulnerable child" syndrome.

Much of the research that has been performed in the area of reaction to genetic testing has been undertaken with adults or competent young people. In these situations their reactions, as measured with standard scales such the STAI or EPDS are paramount. However, when testing occurs in the newborn period the situation is more complex and requires assessment not only of the parents' personal reaction to testing but also an assessment of how this may affect their perception of their child. As discussed in chapter 3 significant changes in the way parents perceive the health and well being of their child may contribute to permanent psycho-developmental issues for the child [53, 172, 278, 279]. It is therefore necessary to specifically look for any evidence of the first element of the vulnerable child syndrome, namely an altered perception of the child's vulnerability.

#### **4.4.4 Development of a new Vulnerable Baby Scale**

Several questionnaires assessing perceptions of child vulnerability exist in the literature but on careful assessment none proved appropriate for use with mothers of young infants in a current New Zealand setting. I therefore modified one of the existing questionnaires, again utilising the expertise of several clinicians and psychologists, to design a novel instrument, the Vulnerable Baby Scale (VBS)[280]. In developing new psychological measures such as this it is important to follow accepted methods and to ensure that the new scale exhibits appropriate psychometric properties. In the next section I therefore describe in some detail how I undertook a separate study to develop, pilot and validate this measure.

##### **4.4.4.1. Psychometric properties of an existing Vulnerable Child Scale**

The most frequently used and best validated existing scale was Forsyth's Child Vulnerability Scale.[53] The original scale included 12 specific statements of concern about a child's health and well-being, for example: "In general my child seems less healthy than other children" and "My child usually has a healthy appetite". Respondents were asked to specify whether each item was definitely true, mostly true, neither true nor false, mostly false or definitely false. Evidence for the reliability and validity of this measure have been reported[281]. Later, Forsyth revised the original 12-item questionnaire to an eight-item measure with a four-point response scale[53]. Internal consistency of the revised scale was good with Cronbach alpha for the scale of 0.7 and item-total Pearson correlation coefficients ranging from 0.5 to 0.7 with  $P < 0.0001$  for all items. Evidence for the scale's validity came from the fact that 50% of children with two variables presumed to be important in determining perceptions of vulnerability (prior parental fear that the child may die, and an existing medical condition)

were rated as perceived vulnerable using the scale, whereas only 1.5% of children without either of these variables were classified as perceived vulnerable. Further evidence for the validity of the measure was reported as the scale's ability to predict more frequent future use of health-care services and future childhood behaviour problems.[53] Both the original and revised scales have been reproduced by the authors in full and are not subject to any restrictions or licensing requirements[53].

#### **4.4.4.2. Methods: initial development of a new Vulnerable Baby Scale**

Forsyth's scales were developed in the US in the 1980s for use with parents of older children. My reasons for modifying the original scale were two-fold. Firstly, some of the questions did not apply to young babies, and secondly it seems likely that parents of young babies today are concerned about some different issues in comparison to parents in the 1980s. To illustrate the first point, the question "My child seems to have more accidents and injuries than other children" that appears in Forsyth's scale is irrelevant to a relatively immobile 3 month old baby compared with a boisterous toddler. Five questions were removed for similar reasons and were replaced by six new questions which were designed to encompass the four different aspects of perceptions of vulnerability described in the literature [276]. Some of these new questions also enabled me to address the second point mentioned above relating to contemporary parental concerns about their young baby, in particular concerns related to risk of Sudden Infant Death Syndrome (SIDS; cot death). The new questions that I devised for the VBS related to: the degree of protectiveness of the parent; determining how readily the parent will allow separation from their baby; the level of parental concern about their baby's health or risk of dying (for example of SIDS) and finally to frequency of utilisation of non-routine medical services such as urgent GP consultations or emergency department attendances.

#### **4.4.4.3. Methods: further development and psychometric properties of the new Vulnerable Baby Scale**

After this initial development phase, the questionnaire was tested with three groups of mother/babies. The aim of this phase was to make final decisions about the inclusion/exclusion of specific items in the questionnaire, and to provide initial data concerning the scales validity by determining its relationship to other variables expected to correlate with perceptions of vulnerability, such as true medical fragility in the child, and maternal anxiety and depression.

The three mother/baby cohorts involved in this analysis were: mothers of babies known to have had a significant medical problem in the neonatal period ("medically fragile babies"), mothers of healthy jaundiced babies and mothers of healthy control babies.

For the medically fragile group a group of local paediatricians agreed upon a list of conditions and diagnoses that they felt might result in a 3-month-old baby being truly medically vulnerable (rather than simply being perceived as vulnerable). These criteria were: prematurity (between 28 and 34 completed weeks gestation), respiratory distress requiring continuous positive airway pressure (CPAP) or ventilation >48 hours, significant congenital abnormality, significant surgical intervention, exchange transfusion, apnoeas requiring apnoea monitor on discharge and bronchiolitis requiring hospital admission for more than 1 week. The list was clearly not designed to be exhaustive but to cover the more common, significant medical conditions found in the 0–3-month age group.

Criteria for inclusion in the jaundiced group were: three or more elevated serum bilirubin measurements before 1 week of age and/or phototherapy treatment, plus no serious underlying diagnosis and no admission to the neonatal intensive care unit.

Babies satisfying conditions for either of these groups between August and October 2002 were identified from admission records on the Neonatal Intensive Care Unit at Dunedin Public Hospital, Dunedin, New Zealand (medically fragile group) or postnatal ward (jaundiced group). Control babies were healthy full-term babies born at Dunedin Public Hospital and also identified from records on the postnatal ward.

Mothers of babies fulfilling the criteria for one of the three groups, and discharged home by age 10 weeks, were invited to take part in the study. Mothers were asked to complete three questionnaires. First, the new Vulnerable Baby Scale described above. Second, maternal state anxiety was assessed with the State subscale of the State–Trait Anxiety Inventory (STAI), Form Y-1[270, 271]. Finally, maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale[271]. Questionnaires with reply paid envelopes were posted to participants' homes for completion when the baby was 12 weeks old ( $\pm 2$  weeks). Follow-up telephone calls were made 1 week after posting to remind non-responders.

Statistical analysis was undertaken using SPSS 11.5 for Windows. Item-total Pearson correlation coefficients and Cronbach alpha for the revised scale were calculated. Unpaired *t*-tests were used to test the hypothesis that there would be differences between the mean vulnerable baby scores for the control group and the medically fragile and jaundiced groups. Pearson correlation coefficients were calculated to assess the relationship between vulnerable baby score and demographic factors and between vulnerable baby score and maternal anxiety and depressive symptoms. The study was approved by the Otago Ethics Committee (Ref 02/03/019) and written informed consent was obtained from all participants.

#### 4.4.4.4. Results

Mothers of 23 babies who satisfied the criteria for the medically fragile group were approached and 17 (74%) of these agreed to take part in the study. Similarly, mothers of 23 jaundiced babies were approached and 19 (83%) agreed to participate. Forty-five mothers of healthy full-term babies were approached and 39 (87%) participated.

Demographic characteristics of the three groups and age of baby when the questionnaire was completed are shown in Table 4.1.

**Table 4.1: Demographic Characteristics of Participants in the Validation of the VBS Study**

	<b>Medically fragile babies</b>	<b>Jaundiced babies</b>	<b>Control babies</b>
<b>Number in group</b>	17	19	39
<b>Sex (n, (%) female)</b>	8 (42)	7 (37)	15 (39)
<b>Mother's age, years (mean, range)</b>	32.2 (18-39)	31.3 (16-42)	31.6 (24-37)
<b>Children in family (mean, range)</b>	2.0 (1-4)	2.5 (1-5)	2.1 (1-7)
<b>Baby's age questionnaire completed, weeks (mean, range)</b>	11.4 (9.5-15.0)	10.6 (9.6-14.1)	13.4 (11.2-17.3)

Diagnoses of the babies in the medically fragile group were: prematurity 28–34/40 (13), diaphragmatic hernia (1), exchange transfusion for rhesus haemolytic disease (1), apnoeas in a 35/40 gestation baby (discharged on an apnoea monitor) (1) and respiratory distress in a 36/40 gestation baby (1).

#### **Final item selection**

Item-total correlations for three questions were  $<0.2$  and these were therefore discarded from the scale[282]. (These questions were: “I need to keep baby indoors for health reasons”, “In general I think my baby has a healthy appetite”, and “Would you be prepared to leave your baby in the care of someone else, e.g. relative, friend, child-care centre?”). Item-total correlations for the remaining questions were between 0.3 and 0.7. The final version of the questionnaire therefore consists of 10 questions, all scored on a 1–5 rating scale with a possible score range of 10–50[280]. (Appendix C).

#### **Internal consistency of the revised Vulnerable Baby Scale**

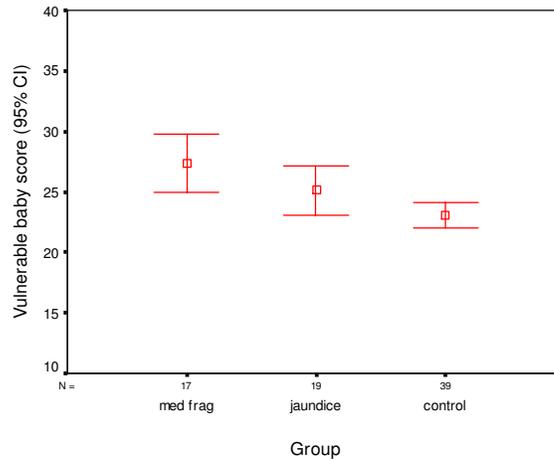
Cronbach alpha for the revised Vulnerable Baby Scale was 0.7.

#### **Validity of the revised Vulnerable Baby Scale**

Unpaired *t*-tests showed that mean vulnerable baby scores for the medically fragile group (mean 27.4, SD 4.6) were significantly higher ( $P=0.002$ ) than those for the healthy control group of babies (mean 23.1, SD 3.1). Scores for the jaundiced group (mean 25.1, SD 4.2)

were slightly higher than the control group but this result was not statistically significant (P=0.07). These results are displayed graphically in Figure 4.1.

**Figure 4.1: Vulnerable baby scores for the medically fragile, control and jaundiced groups (mean and 95% CI shown).**



There was a moderately strong relationship between maternal state anxiety and vulnerable baby score and a weaker relationship between maternal depressive symptoms and vulnerable baby score. Pearson correlation coefficients showed no relationship between vulnerable baby scores and maternal demographic factors or babies' age (Table 4.2).

**Table 4.2: Correlations Between Vulnerable Baby Score, Baby's Age and Maternal Demographic and Psychosocial Factors**

	<b>r</b>	<b>P value</b>
<b>Maternal age (years)</b>	-0.1	0.2
<b>Maternal parity</b>	-0.1	0.4
<b>Baby's age (postnatal weeks)</b>	-0.1	0.3
<b>Maternal state anxiety</b>	0.6	<0.001
<b>Maternal EPDS score</b>	0.3	0.003

r Pearson correlation coefficient  
 EPDS Edinburgh Postnatal Depression Scale

#### 4.4.4.5. Psychometric properties of the Vulnerable Baby Scale

##### Reliability

The final version of the Vulnerable Baby Scale has good internal consistency (or internal reliability) with Cronbach alpha for both my scale and Forsyth's original scale being 0.7.

Test–retest reliability for my scale was not assessed but for Forsyth's scale test–retest reliability yielded an aggregate correlation of  $r=0.84$ . [276] It is likely that the result would be similar for my scale as the content and format of questions are similar, but this requires verification in future studies.

### **Validity**

Validating a questionnaire such as this is difficult as a “perception of vulnerability” is not a physical reality, simply a useful artificial construct. However, it is possible to provide some information concerning the new scale's validity. First, the Vulnerable Baby Scale has *face validity*, in that it does ask about the sort of things likely to be relevant to perceptions of vulnerability. Second, other authors have suggested that it is possible to describe several distinct elements in the parental reaction to a child they perceive as being particularly vulnerable. For instance, the parent may tend to overprotect the child, experience separation anxiety, be overly concerned about the child's health and use medical services more frequently. [279, 283] The fact that my questionnaire has appropriate coverage of each of these elements lends *content validity* to the scale.

Finally, an accepted way of testing the *construct validity* of such a scale is to determine whether it has relationships with other variables that would be expected to correlate with perceptions of vulnerability. [283] Although it is accepted that perception of vulnerability is an artificial construct, some authors have attempted to construct a conceptual model of how the vulnerable child syndrome may develop. This must logically include factors related to the child, such as medical events and child temperament, as well as factors related to the parent, such as anxiety and previous life events. [276]

Considering the “child element” of the model first, it is likely that perception of vulnerability in a truly medically fragile baby and less well-founded perception of vulnerability in a relatively healthy baby are slightly different constructs, but it is also probable that the nature of parental concerns is similar between these groups. Therefore, the fact that in my study the mean vulnerable baby score of a group of mothers of medically fragile babies was significantly greater than mothers of healthy control babies lends validity to the questionnaire. Considering the “parent element” of the model next, perception of vulnerability has clearly been shown to correlate with maternal anxiety and to a lesser degree, depression in previous studies. [172] My findings that maternal state anxiety and depressive symptoms correlate with scores on our version of the Vulnerable Baby Scale support the questionnaire's validity.

#### **4.4.4.6. Jaundice and perceptions of vulnerability**

Previous research has suggested that neonatal jaundice and its treatment may increase early cessation of breast-feeding and development of the vulnerable child syndrome.[284] My study showed only a small (2.0 points) difference in mean scores between the jaundiced and control groups that was not statistically significant. It is possible that a larger sample size would confirm this difference although the clinical significance of such a small difference in score is unclear. The effect of neonatal jaundice and its treatment on parental perceptions of vulnerability may well be small, or even non-existent, as management of physiological jaundice has changed significantly since the original research was undertaken in 1989: 55% of babies in Kemper's study[284] received phototherapy (that necessitates separation of mother and baby), whereas only 21% (4) babies in our study had similar treatment.

#### **4.4.4.7. Future use of the Vulnerable Baby Scale**

Forsyth[53] suggested that although there is a spectrum of parental perceptions of vulnerability, the concept of normal and abnormal perceptions is important. He classified babies with scores greater than one standard deviation above the mean as “perceived vulnerable”. My study describes a mean score of 23.1 and standard deviation of 3.1 for a healthy control group. Therefore, a score of 27 or more in a baby known to be healthy is likely to reflect increased parental perceptions of vulnerability. Further confirmation of this cut-off point would require a larger study.

The Vulnerable Baby Scale described here represents a useful research tool for assessing important elements of maternal reaction to screening, and other procedures, in the newborn period. It seems to appropriately capture the concerns that genetic susceptibility screening may generate in some parents, and provides a useful adjunct to the standard psychological questionnaires measuring parental anxiety and depression.

#### **4.4.5 Part 4: subjective rating of level of concern about T1D genetic susceptibility test results**

The first three sections of my research instrument were designed to measure specific aspects of an individual's psychological reaction to the genetic testing process, namely symptoms of anxiety and depression and perceptions of infant vulnerability. Each of these measures has previously been tested and reliably demonstrated to perform its function [270, 271, 273, 280]. All three of the measures are self-report scales and as such rely upon the individual to answer a series of questions relating to how they are feeling. The sum of an individual's responses is taken to represent their anxiety state. The questionnaires do not, however, ask individuals to

specifically rate how they perceive their own anxiety or levels of concern. As the theoretical underpinnings of my research (described earlier in this chapter) suggest that obtaining multiple perspectives on the same phenomenon is beneficial to the quality of the research, I decided to add questions that performed this function. I reasoned that asking individuals to subjectively rate their own degree of concern about the genetic testing process might provide additional information concerning any “gap” between reactions measured on a rating scale and an individual's perception of it. This could then be further explored using the qualitative methods discussed later in this chapter. My research instrument therefore incorporated the following 2 questions concerning how much mothers *think* and *worry* about their child's genetic test result. As shown, responses were recorded on a five point scale.

1) How much do you think about your child's test result?

Not at all      **1**      **2**      **3**      **4**      **5**      All the time

2) Do you worry about the test result?

Not at all      **1**      **2**      **3**      **4**      **5**      Extremely concerned

#### **4.4.6 Part 5: maternal perception of infant's risk of developing T1D**

A further area of importance in the field of genetic testing is how well people understand the genetic information given to them. A considerable body of literature exists describing the difficulties involved in adequately communicating genetic risk to families [285-287]. This is likely to be more important in the context of susceptibility tests where the information generated is not only predictive but also probabilistic. It was therefore important to gain an insight into how mothers perceived their baby's risk of T1D following genetic testing, whilst avoiding any concern amongst participants that their recall was being tested. I settled on a simple scale in which mothers were asked to compare their baby's risk with “most people's” risk and resolved to also address this question in the qualitative phase of my study. This question was incorporated into the research instrument at both assessments following receipt of the genetic test result. It is reproduced below:

Now that you know the result of your baby's genetic test how would you define their risk of developing diabetes? (please circle the most appropriate response)

No risk at all	less risk than most people	same risk as most people	higher risk than most people	will definitely develop diabetes	uncertain
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In this section I have described, in five parts, the development of my quantitative research instrument. Further details of *how* and *when* this questionnaire was used to assess maternal psychological reactions to newborn genetic susceptibility screening are included at the beginning of chapter 5 where I also present the results of this phase of the study.

In the final part of this chapter I go on to describe aspects of the design of the second phase of my research, a series of semi-structured interviews with parents of children known to be at increased genetic risk of T1D.

#### **4.5 Phase 2: Qualitative research**

As described in the preceding sections, phase 1 of my research involves a quantitative assessment of maternal psychosocial reaction to newborn genetic susceptibility testing. While this is an important and well established way of measuring reaction to genetic test results there are two major drawbacks of using such a method in isolation. Firstly, this approach is unable to determine in any detail how mothers themselves describe and think about their reaction to the genetic testing process, and secondly the range of effects studied is narrow. Considering the first issue, it is unknown if maternal anxiety as measured on a rating scale corresponds with a mother's own perception of her level of concern in this setting. If it does not, it would be valuable to try to determine what might account for this gap between the quantitative measurement and subjective assessment by the participants themselves. Considering the second issue, there is currently a paucity of information concerning the *overall* impact of this type of genetic testing on the lives of parents and families, but this must surely be important if such testing is to be widely applied in clinical settings. I therefore wanted to obtain more contextual data including detailed accounts of parents' interpretations of the genetic susceptibility test results, and of how they then incorporate this information into their lives. These gaps in current knowledge about parental reaction to newborn genetic susceptibility screening are clearly suited to a qualitative research approach. Specific areas that have generally not been addressed in previous literature and that will be incorporated in phase 2 of my study include:

- parents' motivation for allowing their baby to participate in genetic susceptibility testing
- the immediate impact upon parents of an increased risk result
- parents' perceptions of the meaning, value and importance of T1D genetic risk information.
- the subsequent impact of an increased genetic risk result, including emotional reactions and any changes in parental behaviour towards their child
- parents' reflections upon the testing process.
- the impact of probabilistic results (as opposed to definitive diagnosis) upon parental responses.

In the next section I begin with a description of the particular theoretical framework, within the qualitative paradigm, that I employed, and then outline how I developed a schedule for the semi-structured interviews I undertook with parents of babies found to be at increased risk of T1D.

#### **4.5.1 Theoretical perspective**

A theoretical perspective or framework provides a context for the research process[266]. It fundamentally shapes the research focus and the choice of methods and techniques employed. Different theoretical frameworks direct attention toward different aspects of the phenomenon being studied. For instance, psychoanalytic theory points to the role of the irrational and unconscious in shaping behaviour[262] . Certain theoretical frameworks are better suited to some research problems than to others: Chapman and Smith, discussing the role of qualitative research in health psychology, pay particular attention to the emergence of qualitative studies concerning the “new genetics”. They note that a number of studies have been published using a particular qualitative theoretical framework, interpretative phenomenological analysis (IPA), to explore issues arising in this field [59]. This is the theoretical perspective that guided my own qualitative research.

##### **4.5.1.1. Interpretative phenomenological analysis**

IPA has its roots in phenomenology [288] and symbolic interactionism [289] but has been developed as a distinctive approach to conducting empirical research, particularly in health psychology, over the last 15 years. Phenomenology involves studying situations in the everyday world from the viewpoint of the experiencing person, and emphasises the individual's construction of a “life world”. The “life world” involves all of a person's

unquestioned, subjective experience of their biological world including taken for granted assumptions about everyday life. The aim of a phenomenologist is therefore to determine what an experience means for the person who has the experience and provide a comprehensive description of it[262]. Symbolic interactionists argue that experiences take on meaning as they become symbolically significant through shared interaction. They study the interactional sources and development of these shared symbol systems and explain actions with reference to them[262].

Although IPA was derived from these approaches it now has its own theoretical underpinnings, methodological procedures and an increasing body of research literature [59]. Health psychology assumes a chain of connection between the physical or mental state, cognition and verbal response. IPA is also concerned with this chain of connection, and in particular in exploring the gap that may exist between a particular situation or state and an individual's perception of it. Thus, while there are obviously some differences between quantitative work in psychology (for example the assessment of anxiety with a rating scale) and qualitative approaches, there is also considerable theoretical convergence which may lead to a useful symbiosis [59].

The aim of IPA is to explore, in detail, the participant's view of the topic being studied. Thus the approach is phenomenological in that it is concerned with individual accounts of an event rather than in developing an objective description of the event itself. At the same time IPA recognises that a researcher cannot directly or completely access the participant's personal world. Access depends upon the researcher, and their own conceptions are required in order to make sense of that other personal world through a process of interpretation. Hence the term interpretative phenomenological analysis to signal these two facets of the approach [60].

IPA has previously been suggested as a particularly useful approach for examining psychological aspects of the new genetics which may be novel and sensitive, and are often complex, dynamic and dilemmatic[59]. IPA was chosen for this study because as Smith has argued, it allows the researcher to investigate complexity and process through detailed analysis of in-depth interview data while also being committed to a concern with the cognitive entities underlying these accounts [290]. I felt that a qualitative study employing IPA would enrich my quantitative findings, and that the shared commitment to mind and cognitions underlying the two aspects of my research would permit valuable dialogue between the quantitative and qualitative findings[59]. While my quantitative measures may operate at one level, enabling construction of broad models such as of affective reactions, my qualitative research may operate in a different plane, exploring the content of particular individuals beliefs and responses and illuminating the processes operating within the models. This aspect

of my research has been significantly influenced by the background literature concerning psychosocial effects of NBS. My focus is therefore more upon detailed description of individual or individual family reactions and less upon the many possible social determinants and implications of these reactions. I believe this focus, although relatively narrow within a sociological research context, will provide important data, and may serve to highlight areas that would benefit from future study.

Within the theoretical framework of IPA the semi-structured interview is the specific method used most commonly [60]. In the following section I describe how I developed an interview schedule for phase 2 of my research. In chapter 6 I will describe in more detail *how* I conducted these interviews with eleven parents of babies at increased genetic risk of T1D, and will then report how I interpreted the findings in chapter 7.

#### **4.5.2 Interview guide**

In general researchers use semi-structured interviews to gain a detailed picture of a respondent's beliefs about or perceptions of a particular topic [291] (p9). This method gives the researcher and respondent much more flexibility than a questionnaire as the researcher is able to follow up interesting issues as they emerge and the respondent can give a fuller picture. This type of interviewing is especially suitable where an issue is personal, complex or controversial, terms that could all be applied to newborn genetic susceptibility screening.

In a semi-structured interview the researcher usually has an interview schedule but this *guides* the interview rather than dictates it. More specifically the ordering of questions is not of paramount importance, and the interviewer can probe any interesting issues that arise. This fits with the phenomenological position that I have adopted: while I was aware of particular issues regarding the genetic testing process that interested me before I undertook this research I also wanted to “enter, as far as possible, the psychological and social world of the respondent” [291].

Developing an interview schedule prior to commencing interviews is considered important as this enables the researcher to think explicitly about what they want to cover in the interview and to consider any sensitive areas or difficulties that may arise [291]. In constructing my interview schedule I first considered the broad range of themes I wanted to cover in the interview, basing this on my review of the literature pertaining to genetic testing in childhood, NBS and the vulnerable child syndrome, and the results of phase 1 of my study. More specifically I wanted to address in detail: how parents interpreted their child's risk of T1D, the type of psychological harms and benefits they experienced, and whether parents had changed

the way they acted towards their child. In order to do this I constructed the outline of the schedule to follow the chronological sequence of the genetic testing process as shown below.

#### **4.5.2.1. Interview schedule outline**

1. Introduction/background information
2. Joining the KEA study – parents’ motivation for allowing their baby to participate in genetic susceptibility testing
3. Before receiving the test result
4. The day of receiving the test result – the immediate impact of an increased genetic risk result
5. Evolving experience – the subsequent impact of the new knowledge on parents themselves and their perceptions of, and behaviour towards their child
6. The future

Within this framework I then developed questions related to each area concentrating on keeping these open rather than closed and neutral rather than value-laden. I also constructed some probes and prompts to use in situations where participants might have difficulty understanding the question or might give short or tangential replies. The interview schedule provided a structure to facilitate inclusion of the key elements of the testing process, while also allowing time for participants to expand upon other issues that were important to them. The interview schedule is included as appendix D. Further details regarding how these interviews were conducted and the data analysed will be presented in chapters 6 and 7.

## **4.6 Chapter conclusions**

In this chapter I have explained why I chose to conduct the empirical research that I describe further in the second part of this thesis. I began by describing factors that influenced the design of my research, recounted the ontological and epistemological positions that guided me and articulated my reasons for employing a combination of quantitative and qualitative methodologies. Finally, I described the development of my quantitative research instrument and the theoretical framework and interview schedule for my qualitative study.

In the next two chapters I will describe in more detail the specific methods employed in both phases of the research as well as presenting my findings. Chapter 5 is devoted to the quantitative phase whereas chapter 6 discusses qualitative method and analysis.

## **Chapter 5      Quantitative Study Methods and Results**

## **5.1 Introduction**

Chapter 5 begins the second part of my thesis. In part 1 (chapters 1-4) I set the scene around the current debate concerning genetic susceptibility testing in the newborn period and highlighted the need for research. In part 2 of the thesis (chapters 5-7) I reveal the findings of my own empirical research.

In chapter 4 I introduced the 2 phases of my empirical work and described the development of my quantitative research questionnaire and qualitative interview guide. In chapters 5 to 7 I describe the specific methods I used to investigate maternal psychosocial reaction to newborn genetic susceptibility testing for T1D. This chapter focuses on the first, quantitative phase of my study and chapters 6 and 7 on the subsequent qualitative phase. In this chapter I describe in detail the design of my prospective study of maternal psychological reaction to newborn genetic susceptibility testing and then reveal the findings of each section of the questionnaire in sequence. The chapter ends with a discussion of the limitations of my study and a summary of my findings.

## **5.2 Aims of phase 1: quantitative analysis of maternal psychosocial reaction to NBS for susceptibility to T1D**

The overall aim of this aspect of my research is to provide a similar level of empirical evidence about maternal psychological reaction to newborn screening for genetic susceptibility to T1D, to that which already exists in relation to other types of NBS. The more specific aims of this phase of my research are to:

- Determine whether maternal mental state is affected by knowledge of her baby's genetic risk of T1D, with particular reference to anxiety and depression
- Determine whether knowledge of her baby's genetic risk of T1D affects a mother's perception of her baby's "vulnerability"
- Examine mothers' own subjective assessments of their degree of concern about their baby's genetic test result
- Examine maternal perceptions of their baby's genetic risk of T1D

## **5.3 Research design**

Participants for this project were recruited during the Dunedin (New Zealand)-based KEA (Key Environmental Aspects of Type 1 Diabetes) longitudinal study investigating the natural history of T1D.

## 5.4 KEA study

This longitudinal study aimed to investigate the potential environmental triggers of disease onset in children genetically susceptible to T1D. In this section I provide details of the KEA study that are relevant to understanding the context of my assessment of maternal psychosocial reaction to newborn screening for genetic susceptibility to T1D.

### 5.4.1 Phase 1 of the KEA study

The initial phase of the KEA study involved identification of newborns at increased genetic risk of T1D using the following protocol.

#### 5.4.1.1. Recruitment

Pregnant women were enrolled into the KEA study at 28 weeks gestation via obstetricians or midwives at two large maternity centres in Dunedin, New Zealand, an urban centre of population 120,000. Informed consent was obtained from all participants and ethical approval was granted by the Otago Ethics Committee (Ref. 00/11/84). Written information (Appendix E) was provided for all prospective participants explaining that phase 1 of the study aimed to “screen children at birth and identify the 10% of children at increased genetic risk for developing diabetes.” Increased risk was defined as “a 1 in 16 chance of developing diabetes before age 20 years”. 86% of all parents approached gave consent for a cord blood sample to be taken for genetic analysis of T1D susceptibility alleles (Phase 1 of the KEA study). Only infants with severe congenital anomalies or who were stillborn were excluded.

#### 5.4.1.2. Molecular Analysis

Molecular analysis was undertaken by Dr Tony Merriman, Department of Biochemistry, University of Otago, Dunedin, New Zealand. Cord blood was obtained at delivery and genomic DNA prepared from 1-5 ml of blood using a guanidine hydrochloride based method. Allele-specific PCR was used to type HLA-DRB1 [292]. Samples were first genotyped for *HLA-DRB1 DR1-4, 6-12*. Individuals positive for *HLA-DRB1\*04* were sub-typed to identify those having the *\*0401 and \*0404* alleles. Infants were assigned to either an increased genetic risk group (*HLADR3/DR\*0401, DR3/DR\*0404, DR\*0401/\*0401, DR\*0401/DR\*0404, and DR\*0404/DR\*0404*) or a low genetic risk group (all other HLA DRB1 alleles).

#### 5.4.1.3. Communication of results

The dissemination of results to parents and the support offered to them over this period was intended to simulate how a population based NBS programme might operate:

### ***1) Parents of infants at increased genetic risk***

These parents were informed of their baby's results by letter. The letter (Appendix F) opened with both of the parents' first names and then reminded them of the collection of the cord blood sample as part of the KEA study. It went on to state that their baby had been found to be at "increased risk of developing diabetes by the age of 20 years, with a 1 in 16 risk of developing diabetes compared to the general population risk of 1 in 300"[293]. It was also stated that "not all genetically high risk babies go on to develop diabetes because development of diabetes also depends on other poorly understood factors, some of which are found in the environment." The parents were advised that they would be contacted by telephone a few days later and offered a face-to-face counselling meeting with a paediatrician. All parents accepted this offer. At this meeting the above risk statistics were re-iterated, there was general discussion about T1D in childhood and parents/children were invited to continue with phase 2 of the study.

### ***2) Parents of infants in the low genetic risk group***

These parents were also informed by letter. The letter (Appendix G) opened in the same way as that addressed to parents of babies at increased risk but went on to say that their baby was "not at high genetic risk of diabetes, but this did not imply or guarantee no risk". This was followed by a brief description of the presenting symptoms of T1D and advice to contact their General Practitioner (GP) if they had any concerns about their child's health in the future. A telephone contact was offered if parents wished to discuss the result further. These children were not invited to participate in phase 2 of the KEA study.

Parents of children in the "low genetic risk" group who were affected with T1D themselves ( $n = 2$  fathers, 1 mother) were sent a modified letter stating that "although the *HLA DRB1* gene test was negative their child remains at increased risk (approximately 1/50 quoted if the mother was affected and 1/15 if the father was affected) of diabetes because of their family history. This is because of sharing of other genes and unknown environmental factors[294-298]. These children were also not invited to participate in phase 2 of the KEA study.

## **5.4.2 Phase 2 of the KEA study**

This phase of the KEA study aimed to follow the estimated 10% of children at increased genetic risk for 5 years. During this period children would be tested every 3-6 months for the appearance of auto-antibodies that are early markers of diabetes, appearing before clinical symptoms of the disease. Potential environmental stresses or triggers would also be assessed, by collecting information on each child's environment, such as dietary habits, household

cleanliness and evidence of enteroviral infection. The information sheet provided to parents considering enrolling their child in Phase 2 of the KEA study is included as Appendix H.

Although the KEA study has now been discontinued, children at increased genetic risk continue to be followed with yearly autoantibody titres and will be offered entry into Trialnet[299], a network of 18 Clinical Centers working in cooperation with screening sites around the world that is dedicated to research into the prevention and early treatment of T1D, if positive results occur.

## **5.5 Psychological effects arm of the KEA study**

In this section I describe the design of my psychosocial arm of the KEA study and discuss how the results were analysed.

### **5.5.1 Recruitment**

Three mother-baby cohorts were recruited for the psychological effects arm of the KEA study. The increased genetic risk group was recruited from the pool of infants determined to be at increased genetic risk of T1D through the KEA study (8.2% of all of the infants tested). Of the 41 mothers approached in this way, 38 (93%) agreed to participate in the study evaluating maternal psychological reactions to newborn genetic screening for T1D. All of these mothers/babies were also participating in phase 2 of the KEA study.

In addition, 76 mothers of age-matched infants whose cord blood analysis revealed low genetic risk of T1D were recruited (97% participation rate). Three of these infants had a parent with T1D, putting them at increased risk, despite the absence of specific *HLA-DRB1* markers. Initially, these mothers and infants were included in the low-risk group but were excluded from the final analysis, because mothers were aware of their child's elevated risk status in relation to family history.

Seventy-six mothers of age-matched control infants who had not undergone any genetic testing were also recruited from the postnatal ward at Dunedin Public Hospital (92% participation rate). Informed consent (separate from that previously given for the main KEA study) was obtained from all participants and ethical approval was granted by the Otago Ethics Committee (Ref. 00/11/84). See Appendix I for information sheets for control and study participant mothers.

### **5.5.2 Study design**

The study used a longitudinal design with the questionnaire described in chapter 4 completed three times by each participant. Baseline assessment of maternal psychological reaction was at

9 weeks postpartum (baseline, questionnaire 1), notification of newborn genetic screening result for T1D susceptibility at 10 weeks (except for control babies who had not undergone genetic testing) and follow up assessment of maternal reaction at 16 weeks (questionnaire 2) and 54 weeks (questionnaire 3). Questionnaires were mailed to participants or handed directly to mothers of increased risk infants if they were attending a KEA study appointment at an appropriate time. Non-response prompted a follow-up phone call after 2 weeks.

#### **5.5.2.1. Covariates**

Possible influences upon maternal reaction to genetic risk information that I considered included maternal factors such as: age, parity, education status and time from notification of results to questionnaires. Paternal factors included education status and infant factors included gestation, birth weight, mode of delivery, NICU admission and family history of diabetes. Categorical variables were created for several of these covariates as follows: maternal age, using tertiles; parity class categorised as 1, 2 or  $\geq 3$ ; birth weight class categorized as low birth weight if  $< 2500\text{g}$ , otherwise normal weight; gestation classed as premature if  $< 37$  weeks, otherwise normal. Demographic data is reported in table 5.1 and data relating to timing of questionnaires in table 5.2.

#### **5.5.2.2. Statistical analysis**

Sample sizes were calculated using STATA v 8[300] and normative data available for each of the three questionnaires. The STAI required the largest sample size (33 mothers of increased genetic risk babies and 66 mothers of control and low risk babies) for 80% power at a 0.05 level of significance to detect a clinically significant difference in score (defined as  $> 5$  points on the STAI,  $> 2$  on the EPDS,  $> 2$  on the VBS scales).

As this study used a prospective design and involved several questionnaire assessments for each individual it was important to use an appropriate statistical method to adjust for these multiple measurements on the same individual, and to model time trends. Repeated measure data are usually correlated since sequential observations on the same individual tend to be closer in value than similar observations from different people.

Previously, statistical methods such as ANOVA (with the baseline measure as a covariate) or rANOVA have been used. However, problems with these methods include inflation of type 1 errors, difficulty analysing time trends and large effects from missing data. Various statistical methods exist for correcting for these errors but they tend to be conservative which may lead to difficulty detecting effects of interventions. These issues have led to the development of mixed effect regression models. This general term denotes models with fixed (e.g. the intervention) and random effects, covariance pattern models and combinations of these.

Alternative names for this type of method include: linear mixed model, random effects model; random regression model; multilevel model and hierarchical linear model. These models assume that individuals deviate randomly from the average response, and that there is random deviation at baseline and in response over time (slope).

The advantages of linear mixed models include: that they are able to use all available data on all subjects; can deal with unequally spaced measures over time; are unaffected by randomly missing data and can flexibly model time effects. Mixed models are used in conjunction with ways of actually specifying patterns of variance or correlation over time. For example variance may exhibit compound symmetry (equal variance at all time points and equal correlation between measures) or be autoregressive (correlation between measurements decreases over time). The best model for each particular application is chosen using indices of goodness of fit such as Akaike information criterion (AIC) or Schwarz Bayesian criterion (BIC). Using these methods allows more accurate assessment of intervention effects and standard error estimates; controls type 1 errors, improves accuracy and allows estimation of average time trends for groups as well as estimation of individual response depending on the baseline values. These models are becoming increasingly popular because of the development of reliable and efficient software for fitting them. Disadvantages include that as these methods are relatively new there is currently a fairly small body of published research in which they have been used and the models are complex, requiring the assistance of a statistician. Statistical advice and assistance with analysis for this study was obtained through Andrew Gray, Department of Preventative and Social Medicine, University of Otago.

In this study a linear mixed model was constructed for each sub-section of the questionnaire (STAI, EPDS, VBS and two subjective questions) initially including the possible covariates listed above, and modelling the covariances between the time periods using the most appropriate structure as determined using AIC and BIC (where autoregressive, Toeplitz, compound-symmetric, and unstructured covariance matrices were considered). The denominator degrees of freedom were calculated using Satterthwaite's approximation.

### **5.5.3 Study Participants**

Demographic characteristics of participants are shown in table 5.1.

**Table 5.1 Demographic characteristics of study participants**

	<b>Increased genetic risk N=38</b>	<b>Low genetic risk N=76</b>	<b>Control N=76</b>	<b>P value *</b>
<b>Maternal characteristics</b>				
Age at child's birth (years, mean, (95%CI))	31.1 (29.7,32.5)	31.3 (30.3,32.3)	30.6 (29.6,31.6)	0.61
Parity 1 (%)	60.5	40.8	43.4	0.2
2	21.1	40.8	34.2	
≥3	18.4	18.4	22.3	
Tertiary education (% none)	18.4	26.3	35.5	0.30
<b>Paternal characteristics</b>				
Tertiary education (% none)	21.1	19.7	32.9	0.38
<b>Child characteristics</b>				
Gestation (weeks, mean)	39.5(39.0, 40.0)	39.5(39.1, 39.8)	39.6(39.3, 40.0)	0.80
Birth weight (kg, mean)	3.6 (3.4, 3.7)	3.5 (3.4, 3.6)	3.5 (3.3, 3.6)	0.81
Sex (% female)	42.1	46.1	47.4	0.91
Type delivery† (% C/S)	23.7	32.9	22.4	0.32
NICU admission (%)	7.9	5.3	11.8	<0.0001
FH diabetes‡ (%)	39.5	43.4		0.30

\*P values for continuous outcomes are from one way ANOVAs and for categorical outcomes are for exact  $\chi^2$

†Classified as caesarean section (C/S) or vaginal delivery

### 5.5.3.1. Retention of study participants and timing of questionnaires

Participation rates at completion of the study were 100% for the increased genetic risk group, 96% for the low risk group and 86% for the control group. Questionnaires were administered during similar time periods for each group at each of the three assessments. This data is displayed in table 5.2.

**Table 5.2 Participation rates and timing of questionnaire assessments by group**

	<b>Increased genetic risk</b> Mean age, weeks (95%CI) Participation N (%)	<b>Low genetic risk</b> N=73 Mean age, weeks (95%CI) Participation N (%)	<b>Control</b> N=76 Mean age, weeks (95%CI) Participation N (%)	<b>P value for difference</b>
<b>Questionnaire 1</b>	10.2 (9.1,11.4) N = 36 (95 %)	8.6 (7.8,9.4) N = 73 (100%)	10.2( 9.4,11.1) N = 76 (100%)	0.01
<b>Questionnaire 2</b>	16.0 (14.4,17.6) N= 38 (100%)	15.8 (14.7,17.0) N = 71 (96%)	16.5 (15.3,17.6) N = 75 (99%)	0.7
<b>Questionnaire 3</b>	53.9 (52.6,55.1) N = 38 (100%)	53.8 (52.9,54.8) N = 71 (96%)	54.8 (53.9,55.7) N = 65 (86%)	0.3

## 5.6 Questionnaire Findings

In this section I first discuss results from the three previously validated measures included in my research questionnaire, namely the STAI, EPDS and VBS. I then go on to present results of the questions asking mothers to rate their own degree of concern in relation to the genetic susceptibility test, and their own perception of their child's risk of T1D.

## 5.7 Questionnaire scores

Questionnaire scores (SD and 95% CI) for the three groups at each time period are displayed in table 5.3.

**Table 5.3 Questionnaire scores by group and time**

	Increased genetic risk N=38 mean, (SD), (95%CI)	Low genetic risk N=73 mean, (SD), (95%CI)	Control N=76 mean, (SD), (95%CI)
STAI baseline	31.1 (8.1), (28.3, 33.8)	33.6 (9.6), (31.4, 35.8)	30.9 (7.8), (29.1, 32.7)
STAI 2	26.7 (5.8), (24.9, 28.7)	31.5 (8.3), (29.6, 33.5)	30.4 ((10.2), (28.1, 32.8)
STAI 3	29.6 (9.6), (26.4, 32.8)	30.1 (9.6), (27.8, 32.2)	30.0 ((9.6), (27.7, 32.4)
EPDS baseline	5.1 (2.5), (4.2, 5.9)	5.7 (3.8), (4.8, 6.6)	5.2 (3.5), (4.4, 6.0)
EPDS 2	3.4 (2.5), (2.6, 4.2)	4.7 (3.4), (3.9, 5.5)	4.6 (4.5), (3.6, 5.7)
EPDS 3	4.0 (3.8), (2.7, 5.2)	4.2 (3.2), (3.4, 4.9)	4.0 (3.8), (3.1, 4.9)
VBS baseline	25.4 (5.1), (23.7, 27.1)	25.9 (4.5), (24.9, 26.9)	25.1 (4.0), (24.2, 26.0)
VBS 2	24.5 (4.0), (23.2, 25.8)	24.0 (4.5), (22.9, 25.1)	23.5 (4.0), (22.6, 24.4)
VBS 3	22.0 (4.0), (20.7, 23.3)	22.8 (4.2), (21.8, 23.8)	21.5 (3.8), (20.6, 22.5)

### 5.7.1 Part 1: The State Trait Anxiety Inventory (STAI) State Subscale.

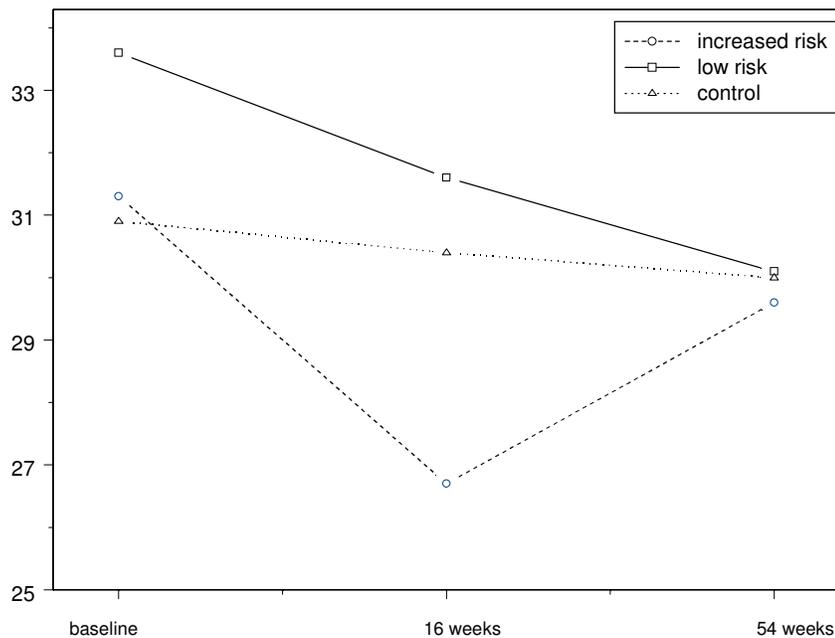
This measure demonstrated excellent internal consistency in this study (first assessment,  $\alpha=0.90$ ; second assessment,  $\alpha=0.92$ , third assessment  $\alpha=0.90$ ). The group mean scores for all three groups at all assessments were close to those reported in a cohort of post partum women where reported mean scores were 30.4 (SD 10.3) at 14 weeks and 31.2 (SD 9.9) at 30 weeks[269].

The mean scores in this study were also significantly lower than those for a group of adults given a positive T1D autoantibody result (a risk factor for T1D) or parents given a positive autoantibody result for their child where the mean scores were 44.7 (SD12.7) and 55.4 (14.4) respectively.

A linear mixed model was constructed to give more information about differences between the three groups and to model time trends, using a compound symmetry structure to account for correlation between questionnaire scores for individuals over time. Using this model there was no significant difference in scores between the three groups ( $P=0.6$ ).

Analysis of time trends indicated a clear time effect in that there was a gradual decrease in STAI score as baby's age increased,  $P=0.0009$ . The increased risk group actually displayed a larger initial decrease in STAI score followed by a small rebound. This group-time interaction (or the fact that the time trend appeared to be different for the increased risk group compared with the other two groups) was found to be weakly significant ( $P=0.04$ ), although post hoc tests were unable to identify a statistically significant difference between the groups at any specific time point. These results are displayed in figure 5.1

**Figure 5.1: STAI scores: time trends and mean scores at baseline, 16 and 54 weeks for increased risk, low risk and control groups**



### 5.7.2 Part 2: The Edinburgh Postnatal Depression Scale (EPDS)

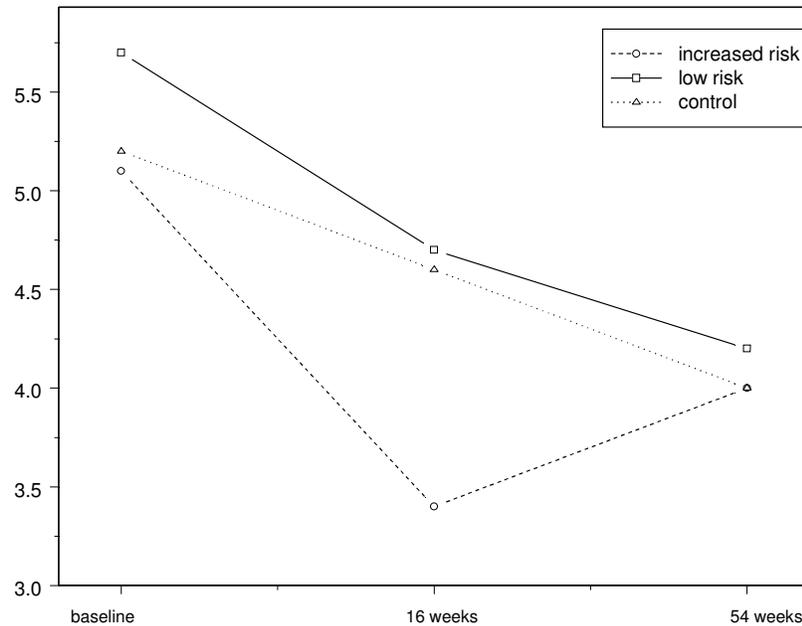
The measure demonstrated excellent internal consistency in this study (first assessment,  $\alpha=0.82$ ; second assessment,  $\alpha=0.87$ , third assessment  $\alpha=0.85$ ). The group mean scores for all three groups at all assessments were close to those reported in a cohort of post partum women

where reported mean scores were 4.7 (SD 4.0) at 14 weeks and 5.3 (SD 4.3) at 30 weeks[269].

When the EPDS is used as a postnatal depression screening tool a cut off score of >12 is usually employed, although some authors use lower cut-off scores (> 10) to identify those with more minor depressive symptoms, and a difference in score of 3 or more at different time points has been considered clinically significant even below the threshold of 12[275]. 8% of mothers in this study had scores greater than the clinical cut-off (12) at the first assessment, 7% at the second and 3% at the third. This is consistent with a previous study in New Zealand [275], although slightly lower than the average prevalence of 13% recorded in a meta analysis [301]. A follow-up phone call was made to any mother scoring > 12 on the EPDS to ensure that they were in contact with health professionals who could monitor and evaluate any depressive symptomatology.

A linear mixed model was again constructed, using a compound symmetry structure to account for correlation between questionnaire scores for individuals over time. Overall there was no significant difference in EPDS score between the three groups ( $P=0.61$ ). On analysing time trends a time effect was again observed ( $P<0.0001$ ) in that EPDS scores gradually decreased as baby's age increased. Again, the increased risk group appeared to have a larger initial drop in EPDS score and subsequent small rebound effect, although for this measure the group-time interaction was not statistically significant ( $P=0.30$ ). These results are shown in figure 5.2.

**Figure 5.2: EPDS scores: time trends and mean scores at baseline, 16 and 54 weeks for increased risk, low risk and control groups**

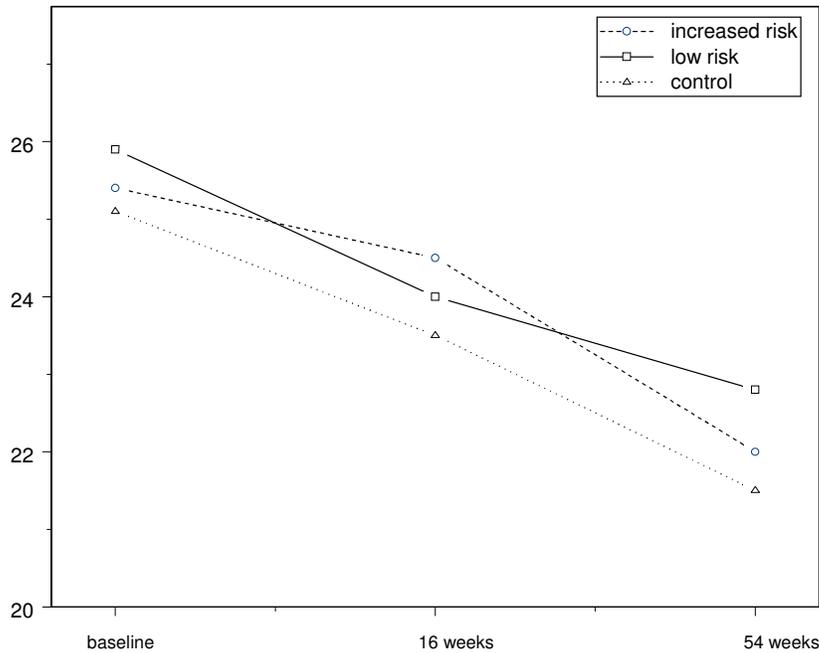


### 5.7.3 Part 3: Vulnerable Baby Scale Scores

This measure demonstrated good internal consistency in this study (first assessment,  $\alpha=0.72$ ; second assessment,  $\alpha=0.70$ , third assessment  $\alpha=0.73$ ). The group mean scores for all three groups at all assessments were close to those I reported in my validation and pilot study for the VBS (a mean score of 23.1 and standard deviation of 3.1 for mothers of a group of healthy 10 week old babies). In the same study I found that a score of 27 or more was indicative of increased parental perceptions of vulnerability[280] and none of the group mean scores from this study exceeded this value.

When constructing the linear mixed model for this data an autoregressive error covariance was used to account for correlation between questionnaire scores for individuals over time. Once again there was no significant difference in scores between the three groups ( $P=0.1$ ). A time effect (gradual decrease in VBS score as baby's age increased) was observed ( $P<0.0001$ ) with no significant difference in this time effect between the three groups ( $P=0.47$ ). These results are displayed in figure 5.3

**Figure 5.3 VBS scores: time trends and mean scores at baseline, 16 and 54 weeks for increased risk, low risk and control groups**



### 5.7.3.1. Covariates

The only covariate that was statistically significant was gestation category in the VBS model ( $P=0.0015$ ). (The effect of being in the gestational category "premature" (<37 weeks) was to raise VBS scores by 2.5 (95% CI 1.0, 4.0) over scores for mothers with babies in the full term category). Babies in the control group were more likely to be admitted to NICU (table 5.1) but this variable was not close to significance in any model ( $P>0.5$  in all cases). Including or omitting this variable from the models made no substantial difference to the parameter estimates.

## 5.7.4 Part 4: Subjective rating of level of concern about T1D genetic susceptibility test results

### 5.7.4.1. "How much do you think about your child's test result?"

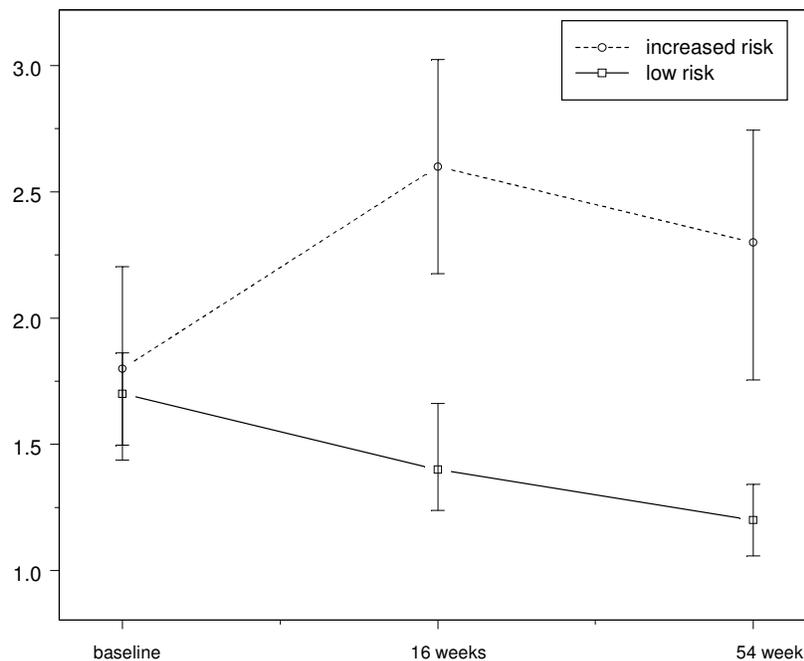
When the linear mixed model was developed for this data a clear group effect was observed ( $P<0.0001$ ) with the increased genetic risk group thinking about their child's test result more than the mother's of babies in the low risk group. There was also a group-time interaction ( $P<0.0001$ ) with the high risk group thinking about their child's test result more than the low

genetic risk group at both time periods after notification of results. These results are shown in table 5.4 and figure 5.4.

**Table 5.4 How much do you think about your child’s test result?**

<b>Timing</b>	<b>Increased genetic risk N=38 mean, (SD), (95% CI)</b>	<b>Low genetic risk N=73 mean, (SD), (95% CI)</b>
<b>Baseline</b>	1.8 (0.8), (1.6, 2.1)	1.7 (0.7), (1.5, 1.8)
<b>16 weeks</b>	2.6 ((0.9), (2.3, 2.9)	1.4 (0.7), (1.3, 1.6)
<b>54 weeks</b>	2.3 ((1.0), (1.9, 2.6)	1.2 (0.5), (1.1, 1.3)

**Figure 5.4: Subjective assessment of how much mothers think about their child’s genetic test result (mean scores +/- 95% CIs)**



**5.7.4.2. “How much do you worry about your child’s test result?”**

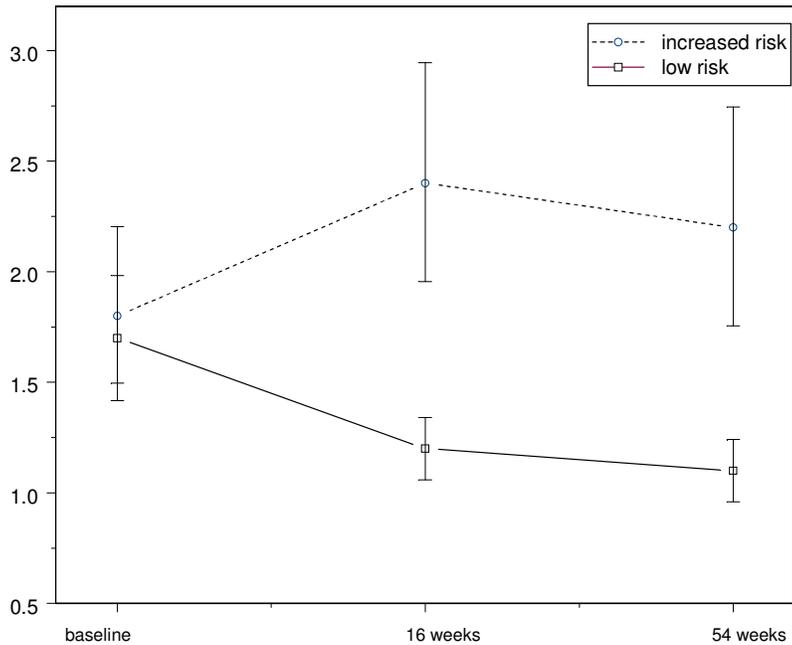
The linear mixed model for this data also clearly demonstrated a group effect ( $P < 0.0001$ ) with the increased genetic risk group worrying about their child’s test result more than the mother’s of babies in the low risk group. Again, there was a group-time interaction

( $P < 0.0001$ ) with the high risk group worrying about their child’s test result more at both time periods after notification of results. These results are shown in table 5.5 and figure 5.5.

**Table 5.5 How much do you worry about your child’s test result?**

<b>Timing</b>	<b>Increased genetic risk N=38 mean, (SD), (95% CI)</b>	<b>Low genetic risk N=73 mean, (SD), (95% CI)</b>
<b>Baseline</b>	1.8 (0.8), (1.6, 2.1)	1.7 (0.7), (1.5, 1.9)
<b>16 weeks</b>	2.4 (1.1), (2.1, 2.8)	1.2 (0.5), (1.1, 1.3)
<b>54 weeks</b>	2.2 (1.1), (1.9, 2.6)	1.1 (0.3), (1.0, 1.2)

**Figure 5.5: Subjective assessment of how much mothers worry about their child’s genetic test result (mean scores +/- 95% CIs)**



### 5.7.5 Part 5: Maternal perception of infant’s risk of developing T1D

At both 16 weeks and 1 year 92% of mothers of babies in the low risk group correctly defined their baby’s risk of developing T1D as the “same” or “less than most other people”. The remaining 8% were uncertain or incorrectly considered their baby to be at “no risk at all” of developing T1D. At 16 weeks 87% of mothers of babies at increased genetic risk of T1D

correctly defined their baby to be at “higher risk than most people” for developing T1D, and at 1 year this figure rose to 92%. The remaining mothers thought their baby would “definitely develop T1D”, was at the “same risk as most people” or were uncertain. These results are displayed in table 5.6.

**Table 5.6 Maternal perception of infant’s risk of developing T1D**

Maternal risk assessment	16 weeks		1 year	
	Increased risk group (N=38) (n, %)	Low risk group (N=71) (n, %)	Increased risk group (N=38) (n, %)	Low risk group (N=71) (n, %)
No risk at all	0	5 (7%)*	0	6 (8%)*
Less risk than most people	0	33 (47%)	0	31 (44%)
Same risk as most people	3 (8%)*	32 (45%)	2 (5%)*	34 (48%)
Higher risk than most people	33 (87%)	0	35 (92%)	0
Will definitely develop diabetes	1 (3%)†	0	0	0
Uncertain	1 (3%)	1 (1%)	1 (3%)	0

\*Underestimation of risk

†Overestimation of risk

## 5.8 Summary

In this sample I found that mothers who were informed that their baby was at increased genetic risk for T1D did not experience adverse psychological effects compared to control mothers when assessed on three different psychological rating scales (Figures 5.1- 5.3, table 5.3). At the final assessment, when babies were 1 year of age, scores on all three questionnaires were very similar for each of the three groups.

Measures of anxiety and depression are commonly used to assess the impact of genetic-risk assessment, screening, or testing in the adult population[302] and in the newborn period[149]. The measures I chose to use for assessment of maternal anxiety and depressive symptoms (STAI and EPDS) are well validated, including for women in the postnatal period [270, 271, 273, 274, 303]. I found the pattern of results to be very similar for both of these measures (Figures 5.2 and 5.3) with no difference between the groups at baseline or 1 year. Three recent reports documenting levels of maternal anxiety or depression in relation to genetic screening for T1D support these findings [249, 250, 252].

However, shortly after receiving the genetic risk information the increased genetic risk group in my study exhibited lower questionnaire scores than the other 2 groups (although only the STAI results reached a level of borderline statistical significance). This initial dip in anxiety levels exhibited by the increased genetic risk group is somewhat counter-intuitive, although could be explained by the reassurance of the face-to-face counselling visit and regular assessments involved in the KEA study, that were specific to this group.

An important additional component of my study, compared with the other two published reports, was to test the hypothesis that knowledge of an increased genetic risk of T1D may affect maternal perceptions of their child's vulnerability, and hence contribute to a "vulnerable child syndrome". This has not previously been empirically tested although "parental stress" has been measured in newborn screening research [185, 215, 247] using the Parenting Stress Index (PSI) [304] which includes questions concerning parental perceptions of their child. However the appropriateness of the PSI in research with mothers of very young infants has been questioned [149, 248], as when used at this time there are frequently high numbers of missing item responses that potentially invalidate results [185, 247].

Using the developmentally appropriate VBS I found that there was no discernable difference in VBS score between the three groups at any of the assessments (Figure 5.3). Mean scores at the second assessment were similar to the mean of a previously reported healthy control group of similar age [280] and, as expected, scores gradually decreased over time. These findings suggest that mothers cope well with the genetic information and do not appear to begin perceiving their child as ill on the basis of the genetic screening test, as has previously been proposed [52, 152].

Despite this reassuring data, when asked to rate their own degree of concern about their baby's genetic risk of T1D, mothers of babies at increased genetic risk reported significantly higher levels than mothers of babies with low genetic risk (Tables 5.4 and 5.5, figures 5.4 and 5.5). In many ways, this is not a surprising result: it seems unrealistic to think there will be no difference in psychological reaction between mothers of genetically susceptible or low risk

babies. In fact, a report on antenatal and neonatal screening in general noted that increased arousal is necessary to enable individuals to attend to information when making choices about treatment so increased anxiety at this time may assist individuals as they assimilate information and make decisions [149]. It is also clear that too high a level of anxiety will impair effective decision making, but at present what constitutes the “ideal” level of anxiety for effective information processing is unclear [149]. In the context of screening newborns for genetic susceptibility to T1D one of the aims of any programme must be to create some degree of heightened awareness of their child’s health risks among parents so that they participate in surveillance and/ or preventative measures. Although no preventative measure is currently available, early recognition of disease already leads to a milder initial clinical course [145], and parents play an important role in this process. While it would clearly be wrong to overburden parents and create problems akin to the vulnerable child syndrome, some degree of parental concern is necessary and may be justified.

Although it is becoming increasingly possible to accurately determine people’s risk of developing conditions such as T1D, considerable uncertainty remains over how this risk information will be evaluated [286]. People often have difficulty in processing statistical information and interpretation of results may depend upon a range of factors including personal and cultural preferences and ethical concerns [286]. The data from my study displayed in table 5.6 suggest that the majority of mothers evaluated their infant’s risk of developing T1D correctly. However, the risk categories I employed to test mothers’ risk perception were broad, so that within each category there would likely be a range of maternal understanding. In addition, despite these broad categories, some mothers in this study did under or over estimate their child’s risk: in the increased risk group 3 mothers thought their baby was at the same risk as most people for developing T1D (underestimating) and 1 mother overestimated thinking that her baby would definitely develop diabetes. In the low risk group an appropriate risk assessment was considered to be that the baby was at the same or less risk than most people of developing type 1 diabetes but several mothers (5 at 16 weeks, 6 at 1 year) considered their baby to be at no risk of T1D, despite having been informed by letter that their baby was “not at high genetic risk of diabetes, but this did not imply or guarantee no risk”. This “false-reassurance” could be harmful if parents ignored symptoms of T1D, considering it impossible for their child to develop the condition. As the numbers of mothers misinterpreting genetic risk information in this study were very small no assessment of the relationship between perceived risk and scores on psychological assessment measures was possible.

## 5.9 Limitations of the research

The limitations of this study include the relatively small size of the cohorts, although both participation and retention rates were excellent. In addition, the study design precluded me from detecting psychological distress occurring immediately after genetic risk notification, and it is also possible that despite the scores on the STAI and EPDS being similar at this study endpoint (1 year) they may continue to rise in the increased genetic risk group.

This study concentrated on maternal reaction to genetic risk information without including the views or responses of fathers. Fathers' reactions to genetic testing are likely to be important but in this study mothers were primary care-givers of their young infants making several aspects of the questionnaires employed most relevant to them. Future research should attempt to address the role of fathers' reactions to newborn genetic testing and in the next phase of my research I try to include this perspective.

My study population was predominantly of European origin (5.7% were Maori which is representative of this region of New Zealand) and hence analysis by ethnicity was not undertaken. I do not consider that New Zealanders differ markedly in their attitudes to genetics from other populations but my findings may not necessarily apply in other settings as it is well known that cultural differences can impact upon health beliefs which may in turn influence many aspects of the genetic testing process [305].

Efforts were made to simulate the type of informative process that would occur if NBS routinely included this type of test, in that participants were initially informed of their child's results by letter, followed by a counselling visit with a paediatrician. However, parents were then offered the opportunity to participate in a trial involving monitoring of auto-antibodies and aspects of the child's "environment" (but without an intervention arm). Autoantibodies were measured on a 3 monthly basis and no child had a positive test result during the course of this study. It is unlikely that low maternal scores on psychological questionnaires were related to reassurance from negative autoantibody results as these were not available to parents until several weeks after their 3 monthly visits, whereas psychological questionnaires coincided with the visits themselves. However, it is possible that contact with the research team and opportunity to ask questions alleviated anxiety, although it is also possible to conceive that bringing one's young baby for a blood test could have the opposite effect. Immunological follow-up would be necessary in any T1D risk screening programme which may differentiate genetic susceptibility screening for T1D from similar testing for other multifactorial disorders. Further research will be necessary to determine how parents cope if follow-up is less intensive and it may be that even if monitoring is unnecessary clinically it continues to be so at a psychological level.

## **5.10 Conclusions**

The psychological questionnaires employed in this study undoubtedly represent a useful way of assessing reactions to genetic risk information and allow me to state that neither clinically significant levels of anxiety and depression nor altered perceptions of infant vulnerability are likely to occur as a result of newborn genetic susceptibility testing for T1D. However, the responses to the subjective assessment questions suggest that mothers of children at increased genetic risk of T1D do experience some sort of psychosocial reaction to their child's testing. The implications of these more subtle, subjective effects remain unclear, but merit further investigation before conclusions regarding the risks and benefits of this type of screening can be drawn. In addition, more work is required to investigate parental interpretation of genetic susceptibility tests for T1D, and the ways in which parents may use this information. I will address these issues in more detail in the next 2 chapters of my thesis, detailing the results of phase 2, the qualitative component of my research.



## **Chapter 6      Preliminary Qualitative Analysis**

## **6.1 Introduction**

At the conclusion of the quantitative phase of my study (chapter 5) I stated that clinically significant levels of anxiety and depression are unlikely to occur as a result of newborn genetic susceptibility testing for T1D. This study is a useful way to begin analysis of parents' reactions to the testing process, but is perhaps not the most valuable way of furthering our understanding of their experiences. In setting out to measure only specific constructs such as anxiety or depression we fail to acknowledge the complexity of life for the parents and children involved in such testing. The impact that testing has for these parents, and the meaning they ascribe to the experience is broader than that. The qualitative phase of my study is designed to address these issues. In this chapter I describe how I conducted 10 semi-structured interviews with parents of babies at increased genetic risk of T1D, and then present the interview data.

## **6.2 Aims of phase 2**

The aims of these interviews were to:

- Present parents' accounts of their experiences of newborn genetic susceptibility testing (this chapter).
- Present my interpretation of the processes that may underlie and explain parents' reactions to the testing process (chapter 7).

## **6.3 Participants**

Ethical approval for this phase of my study was granted by the Otago Ethics Committee (Ref. 00/11/84). Participants were chosen from the pool of families who had received an increased genetic risk result in phase 1 of the KEA study. Starting with the youngest child in the cohort, I sent parents an information sheet concerning the interview (Appendix J). If parents did not want to take part in this interview they were asked to telephone and leave a message on an answer phone. Otherwise I telephoned them approximately one week after they had received the letter to discuss the study further and for them to make a final decision about participation. No parents telephoned to opt out of the study. However, when I telephoned parents to discuss the study further 5 parents declined to be interviewed, stating that they were too busy with their young child/children.

In qualitative research it is not usual to pre-empt the number of participants that will be required. Instead I stopped recruitment when a level of "saturation" occurred, in other words when emergence of new themes in the interviews became rare. This occurred after 10

interviews, 9 with mothers and 1 with both parents. In this phase of my study I attempted to include fathers, offering the option of either parent, or both together being interviewed. I was also flexible regarding the timing of interviews so that I could fit around work commitments of either parent. However, the vast majority of respondents were mothers with few fathers keen to be interviewed. In a further attempt to obtain some data concerning fathers' reactions I included a question to the mothers interviewed concerning how they thought their partner had reacted (see 6.5.3.2). However, I am aware that the lack of a paternal perspective on the genetic testing process leaves a gap in my research that could potentially be addressed in future studies.

Each of the ten interviews was labeled with a combination of the interview number, the child's pseudonym (using a name of the appropriate sex), the child's age at interview and whether the mother alone or both parents were interviewed; *1John 3yr2 M* thus refers to interview one, with the mother of "John", who was 3 yrs and 2 months old at the time of the interview. Details of the participants, including some background information parents discussed during the interviews is recorded in table 6.1.

This group of participants is in many ways fairly homogeneous. For example all of the participants recorded their ethnicity as New Zealand European, and although socio-economic status was not formally measured they all appeared to live as nuclear families in warm, comfortable houses, that were not overcrowded. All of the children that I met appeared clean, well nourished and content. All of the participants had access to transport, telephones and the children appeared to have an array of toys and other entertainment options. The majority lived within an urban environment although one family lived on a farm one hour's drive from Dunedin city.

**Table 6.1 Family Information from Interview Participants**

<b>Interview code</b>	<b>Parents occupations (M=mother, F=father)</b>	<b>Parents health status</b>	<b>Siblings ages</b>	<b>Children's health status</b>	<b>Family history of diabetes</b>
<b>1 John 3yr2 M</b>	M lab technician F builder	No concerns Family history malignant hyperthermia	Half sister, 8yr	John ear infections Sister nil	Nil
<b>2 Colin 2yr11 M</b>	M home-based childcarer F accountant	No concerns	3 sibs 9, 7, 5yrs	No concerns	Father's Aunt and Uncle type 2
<b>3 Neil 3yr3 M</b>	M research fellow F teacher	No concerns	Sister 5yr	No concerns	Father's father and brother type 1
<b>4 Anna 2yr9 M</b>	M housewife F printer	M recent carpal tunnel operation, postnatal depression	Brother 4yr	No concerns	Mother's cousin type 1 age 14yr
<b>5 Geoff 2yr11 M</b>	M nurse F farmer	F renal transplant 15yrs ago (childhood reflux)	2 sibs 7 and 5yrs	No concerns	Mother's father type 2
<b>6 Jen 2yr9 M</b>	M housewife F builder	No concerns	2 brothers 10 and 8yrs	No concerns	Mother's and father's grandmothers type 2
<b>7 Ben 3yr4 MF</b>	M housewife F butcher	No concerns	Sister 6 weeks	No concerns	No concerns
<b>8 Liam 2yr3 M</b>	M housewife F polytechnic lecturer	No concerns	Sister 4yrs	No concerns	Mother's uncle type 2
<b>9 Carl 2yr3 M</b>	M primary teacher F biometrician	No concerns	Brother 4yrs	No concerns	Father's grandfather type 2, father's grandfather's brother died early, type 1
<b>10 Meg 2yr8 M</b>	M store manager F garden maintenance	M no concerns F asthma	Nil	Grommets age 1yr	Aunty "from way back" type 2

## **6.4 Interview process**

I performed all interviews. Participants were asked to sign a consent form before the interview commenced. Each interview was tape-recorded and transcribed verbatim with all identifying information altered during this process.

### **6.4.1 Interview context**

Two interviews took place in the Department of Paediatrics, Dunedin Hospital, at the participants' request. These two interviews occurred in a quiet clinic room with no-one else present. In contrast, the remainder of the interviews occurred in participant homes, generally with at least one child present. This generally led to an informal, relaxed atmosphere although punctuated by the typical interruptions and demands of young children. Occasionally the tape recording was stopped for a short time while the mother attended to an issue related to her child/children. Time of day was very variable, being entirely dependant on the participants' preference.

### **6.4.2 Researcher perspective**

I felt that I developed a good rapport with each of the interviewees. They were all aware of my role as a Paediatrician, although I had never had clinical involvement with any of the families. They were also aware of my role in running the psychosocial effects arm of the KEA study, and my professional involvement with other the study investigators coordinating other arms of the protocol. This may have influenced the way in which participants responded to me, perhaps making it less likely that they would make strongly negative comments about the study.

However, participants were also aware that at the time of interview one of my children was the same age as their own child who had undergone genetic testing. This was very useful during the interview process as I felt that the interviewees shared aspects of their family life with me, mother to mother, that they might not otherwise have done. For example, several participants commented on their wish to provide healthy diets for their children but then discussed the real practical difficulties this may entail. Similarly participants described their dilemmas concerning how much to “wrap their child in cotton wool” or to let them experience life through semi-supervised risk taking.

### **6.4.3 Participant responses**

At each interview I had a copy of the interview schedule described in chapter 4 to refer to but the interviews generally flowed naturally, and it was easy to find seamless ways of moving

from one topic to the next. Often little or no prompting was necessary as responses to the questions in my interview schedule were given spontaneously by parents as they recounted their experiences in their own ways. The parents I interviewed were generally eager to talk about their children and the impact of the newborn genetic susceptibility testing.

The one interview that included a father was clearly different from the others. I found it more difficult to conduct, perhaps because the mother to mother relationship mentioned above was not evident, or possibly because the father was slightly antagonistic toward me because his wife had been very upset when she received the initial results letter. This father tended to dominate the interview, often giving his account of both his and his wife's reactions.

## **6.5 Parents' experiences of newborn genetic susceptibility testing**

"The main focus in qualitative research is the data itself, in all its richness, breadth, and depth. When all is said and done, the "quality" in a qualitative research project is based upon how well you have done at collecting quality data. So, it only seems natural that when it comes time to present "the fruits of your labor," you should make every effort to feature the data in your presentations....Present as much of the data you collected as is physically possible" [306]

This advice from Ronald Chenail about communicating qualitative data provides the foundation for my strategy in the rest of this chapter. I aim here to present parents' descriptions of what it was like to permit their newborn to undergo genetic susceptibility testing for T1D and to be given an increased risk result. I present their descriptions with only the minimal editing and organising I feel is necessary for the reader to make sense of their accounts. The experiences are presented in a "natural" way [306], in other words in a form that resembles the genetic testing process.

My focus here is the subjective experience of parents, not my interpretation of their experiences. In this chapter my interpretation is limited to the selection, categorisation and organisation of the parents' accounts, whereas in the following chapter (Chapter 7) I will present my own interpretation of these findings.

In presenting parents' accounts of their baby being tested for genetic susceptibility to T1D I will use the 5 categories or themes that arose during the initial phase of analysis. These categories reflect the chronological sequence of the genetic testing process and consist of:

- parents' motivation for allowing their baby to participate in genetic susceptibility testing
- the immediate impact of an increased risk result
- the meaning that parents' ascribe to the genetic information
- the subsequent impact of an increased genetic risk result
- parents' reflections upon the testing process.

### **6.5.1 Motivation for parents to allow their baby to participate in testing for genetic susceptibility to T1D**

Many parents described altruistic reasons for participating in the KEA study and allowing their child to undergo genetic susceptibility testing for T1D:

“Well it just didn’t seem like, well I think it was my midwife said this is what they were doing it wasn’t an invasive thing, it was just something that you could see that it was going to help...well I was really thinking about other people, the population in general I think.”(2Colin2yr11M)

“I do research so I sort of think I can support other people doing research and my husband is involved with a few studies with the kids in the psychology department.”(3Neil3yr3M)

“We thought it was a good idea, a good thing to do ... a good thing to do for other people.”(7Ben3yr4MF)

“Well I just thought if it was going to be an aid to research and the fact that it was possible to get blood from the cord, after his birth and I just sort of thought yeah, to help the study along.”(8Liam2yr3M)

“I just thought if it was, I don’t know, I guess it was something that I could do to help that maybe would benefit one of my children, grandchildren or anybody else along the way.”(Carl2yr3M)

Other parents were more interested in knowing their own child’s risk of developing diabetes, saying that this would allow them to prepare themselves:

“I kind of think the more you know about somebody the better you are prepared for things and John had genetic testing for malignant hyperthermia because it runs in my family so we were already familiar with genetic testing.”(1John3yr2M)

“Well as a nurse, it is the sort of thing that I would want to know, I mean in hindsight, I just wonder why I have done it, but I mean you can’t put your head in the sand basically... I mean the chances were quite remote of it being your child so you sort of think it is not going to be me and it was but that – I mean yeah, I think diabetes is the sort of thing that you would want to know quite early on about what was going on and that was the medical part of my brain decided that yes, I wanted to know.”(5Geoff2yr11M)

One mother reported that:

“It was probably because I couldn’t say no, I don’t say no to people.”(6Jen2yr9M)

### **6.5.2 Receiving the test results: immediate impact**

Some parents reported no real concern when they received the letter stating that their child was at increased genetic risk of T1D:

“It was very well put; it said that he had a higher risk than others of developing diabetes. It didn’t mean that he would have diabetes, he wasn’t necessarily going to get it but he had a higher risk than others and I read it quite a few times and I thought well it is not telling me that he has it, it is not telling me he is going to get it, it is just telling me that he is at greater risk than somebody else and probably sort of in the back of your mind you might have known or be prepared for that anyway... because it is there in the family and maybe my other three children have exactly the same risk that Colin has but I don’t know that, they haven’t been tested.”

“I wasn’t worried – it wasn’t as if you were going to tell me this is what he has got and he is going to die in X amount of years because of this. It wasn’t, it was nothing like that.”(2Colin2yr11M)

“I guess I was surprised but I can’t remember exactly, I managed to forget so much of it.”(8Liam2yr3M)

“I wasn’t really that worried about it initially I just thought well, that there was just nothing we could do about it.”(Carl2yr3M)

Other parents reported some sort of “mild” negative reaction:

“Yea, I was disappointed that John was going to be in this study because he has this potential but it didn’t particularly worry me because there is still a high chance of him not getting diabetes and not being fully aware of what the implications were I kind of thought oh right, that’s interesting, bugger.” (1John3yr2M)

“Oh I must admit I think I thought oh bother, and oh well, I wasn’t upset by it, I wasn’t upset by any of it because I know even though he is at risk there is still only a relatively small chance of him developing diabetes when you have got the genetic susceptibility and having had one family member who has got Type I, clearly there was something that increased the risk. So I thought at the time oh bother... but it didn’t

really worry me or upset me. It would have been nicer if he had been in the non at risk group.”(3Neil3yr3M)

“I was quite, I can’t really, I don’t think I fell to pieces, I don’t think I – it was just one of those things really. Something else to deal with, you know what I mean.”( 5Geoff2yr11M)

“We sort of were a little bit frightened I suppose that maybe that could happen but then you look at it realistically and she might not be one of those children in the group that does get it and all that sort of thing.”(10Meg2yr8M)

Other parents reported a more intense negative reaction:

“We were quite shocked for a start. I remember thinking we never thought we would have a child with a disability or anything like that but then after a little while we realised that it didn’t actually mean anything and in fact we were lucky to know and to watch out for anything like that.”(4Anna2yr9M)

“I thought it would have been better rather than reading it, they came and told me because then they could explain it. Jen thought, she read the letter and it said positive or whatever it was and she rung me up at work crying and I said well read the letter properly. She didn’t know it was just that he had the gene, that he hadn’t got diabetes... I was only working down the hill and I was in charge so I could leave when I wanted to so I went home and then I read the letter properly.”  
(7Ben3yr4MF)

Some parents were immediately concerned about their other children:

“We sort of thought then that it could mean all of our children could have that genetic disability as well, I mean quite likely Andrew has got it as well but we just don’t know with him but in fact it is telling us that any of our kids could get diabetes.”(4Anna2yr9M)

“I thought bugger and then I thought I wonder if the other kids would be positive too, maybe just one of the other two, my eldest, I don’t know why apart from the reason that he is a biggish kid and because he was 8 at that stage I thought if anything he might have had a leaning towards diabetes not that that has probably got any relevance because he is a biggish kid but in my mind it was.”(6Jen2yr9M)

### 6.5.3 The meaning of the genetic test result to parents

#### 6.5.3.1. Parents' interpretations of their child's risk

Many parents discussed how this test result meant that their child had a higher risk of developing T1D than other people, but was not certain to develop T1D. Some relayed this information in numerical terms, others in words:

“They were actually just saying that he had the right genes and was predisposed to it. It means that he is predisposed with a higher chance than I have of getting diabetes and I still go back to the fact that although he is predisposed he has only got a 5% chance. And I am not worried about it, it is more likely that he is in the 95% group.”  
(1John3yr2M)

“I can't remember any figures, I remember something about, all I really remember is that he had a higher risk of developing diabetes than somebody else by the age of 17 or something like that, that's all that went in.”(2Colin2yr11M)

“We know that he has the gene that everybody that develops childhood diabetes has got that gene but basically it is still only a 10% chance or even less that he will get diabetes so we don't really need to worry about it at all nor would anybody else.”(3Neil3yr3M)

“I don't like his odds; I mean it would be much better if he was in the one in three hundred chance as opposed to the one in sixteen. Someone is going to get it aren't they.”(5Geoff2yr11M)

“I would just say she is just in a higher risk of developing it, it doesn't mean she will get it, that's all you can really say, there is nothing else to go in to.”(6Jen2yr9M)

“Because they also said to us even though his chance is higher than those who don't get it, just because he has got that gene doesn't mean he is going to get it, it is just a chance so maybe even though he's got the gene and we cant change that, but at the moment he hasn't got it, there is nothing we can do to avoid him getting it, just get on.”  
(7Ben3yr4MF)

“Just that I had his blood tested from the cord sample and that it indicated that there was likelihood and I can't remember how much of a likelihood, of him developing childhood diabetes and that he is genetically more likely to develop diabetes.”(8Liam2yr3M)

“I would probably just say that he was tested at birth for the gene that was – I don’t know if it is a gene as such but for an indication of whether or not he was at greater risk of developing diabetes and his results came back showing that yes he was at an increased – I think it is one in sixteen risk of developing diabetes at any stage of his life.”  
(9Carl2yr3M)

“In my mind I think that she has got a higher possibility of having that susceptibility to have diabetes at an early age, before 21 isn’t it....”  
(10Meg2yr8M)

Some parents also discussed the concept of causation:

“And also for me personally, the way I considered it is if it’s genetically determined there is not a lot I can do about it so if it is going to happen it will happen...”(1John3yr2M)

“I think it is because you don’t feel as if it is just something that couldn’t possibly happen to you, it could be genetic, it could be life style, it could be anything, that there is no one particular group of people. Nothing I am doing wrong.”(2Colin2yr11M)

“... she has got a higher possibility of having that susceptibility to have diabetes at an early age...I sort of imagined that it was her environment and food which contributes to that... it is something that you can’t control, there is no point in – I mean you have got to do your best and do the things that you can do.”(10Meg2yr8M)

#### **6.5.3.2. Discussing their child’s results**

All of the parents interviewed discussed their child’s result with their partner. Several of the mothers reported a pragmatic attitude on the part of their husbands/partners:

“I think, he is very sort of unemotional anyway, it wasn’t something that was terrible, it was just a possibility...something that could happen and if you saw signs of something you could say test for this because it is a possibility.”(2Colin2yr11M)

“Oh he was quite matter of fact about the whole thing, I can’t remember what he said.”(5Geoff2yr11M)

“I think he felt that we would just cope with whatever would eventuate if he develops it.”(8Liam2yr3M)

“He just said well, he is very sensible about those kinds of things, that’s just the way it is and there is not much we can do about it, at least we are aware that it is something just to know about.”( 9Carl2yr3M)

Some mothers reported feeling that their partner had less understanding or was less involved in the genetic testing process and subsequent study:

“I still don’t know that he really understands what is going on and he is waiting for me to say we have had another letter from those people and everything is fine or go and see these people and go to the hospital with me and talk about it with me so I think until something happens like that, he is quite happy just to let me deal with it.”

When asked how she felt about this:

“I don’t actually mind because I do feel like I have a little bit more understanding than he does ... and so rather than have both of us confused, one of us can sort it out and that’s the main thing.”  
(1John3yr2M)

“I think he doesn’t think about it virtually at all much. And I guess that’s partly because I have been the one who has taken Neil in for all the blood tests and he hasn’t done that.”(3Neil3yr3M)

Parents reported discussing the study with a range of different people:

“I think I mentioned it in passing in antenatal group.”(1John3yr2M)

“another very good friend of mine’s daughter is in the study and “Sarah” – she is about 18 months now and I was really relieved when they came on board – well not relieved, that is an awful thing to say, but it was really nice, I didn’t realise how, not worked up, but it was really nice to have her there because “Phoebe” is a Pharmacist and it was really nice to have her to talk to and have her to – because she is such a good friend too, it makes it sort of – you know what I mean, what it’s like, you can air all your silly worries and concerns and I found it a lot easier since she has been part of it.” (5Geoff2yr1 1M)

“We were talking about it at work today.” (father) “And my nephew is doing it as well.” (mother) (7Ben3yr4MF)

However, some parents made a conscious decision not to tell others:

“I often wonder if maybe it is better to talk to the other people in the study group but then I actually don’t care about their children and while we intend to be in the 95% if there is a 5% then it has got to be some of those children as well. . .I’d feel happier if I was going to discuss it, to talk about it with the doctors because they know more about it and can correct any misconceptions I’ve got, I would rather have it from the horse’s mouth. I find that parents possibly have some strange ideas not even parents but people in general, they often have a little bit of information that they can create a whole story about.”(1John3yr2M)

“We didn’t tell anyone because we didn’t want people looking at her differently and thinking why is she eating that chocolate biscuit, if she was offered one . . .at one stage when she had her needle she had a plaster on her hand and I had run in to someone in town still with the cotton wool thing happening and forgot to whip it off and they asked me and I said it was routine and they never asked me again which was cool. . . I didn’t want any extra attention that wasn’t needed or them thinking oh my god, Jen’s a diabetic when she has only got a higher percentage rate of being a diabetic rather than if people don’t listen to that side of things, if you try and explain it, so it wasn’t worth –that’s why we just kept a lid on it. The boys, we haven’t said anything to the boys or anything, by the time she has had her blood test and come home but now, as she gets older I guess things will change because now, she hasn’t had one since she was 2 and she is completely fluent with speech and everything so from here on in, that’s when she will yabber about it so we will work that out when it comes.”(6Jen2yr9M)

Finally, as these were parents of young children we discussed the issue of if, when and how they would tell their children the genetic test results.

Some parents had not previously considered this:

“. . .hadn’t thought about it at all. Hadn’t even entered my head because we are not there yet.”(6Jen2yr9M)

“I haven’t actually, haven’t thought about it at all.”(10Meg2yr8M)

Most parents felt that their child either should know or would want to know:

“I think maybe when he is a teenager if he develops diabetes he should have an understanding there was the potential for this to happen and there is nothing that could be done about it, the outcome was going to be the same.”(1John3yr2M)

“I think there is going to come a time when he is going to want to know why he is doing this and the others aren’t.”(2Colin2yr11M)

One mother was less certain that her child should be told the test result:

“Not at this stage. I think that not unless it really did become a problem and then they should be informed for later on in the most tactful way possible.”(8Liam2yr3M)

Many parents felt that they would wait until their child was older before discussing the issue with them:

“I think probably you do it in stages, like you wouldn’t give him the full blown information by the time he is five because he is not going to understand what diabetes is ... as his level of understanding grows then feed him a little bit more information.”(2Colin2yr11M)

“Certainly not at age 3. .... I haven’t got children of that age, and even a 5 year old I don’t think really can understand that much. Lots of 10, 11, 12 year olds would understand.”(3Neil3yr3M)

“Yes, I guess I would. I probably wouldn’t tell her until she was quite a lot older though as she’s only 3. At the moment she doesn’t understand what it is. I’d tell her once she’s more responsible for her own health.”(4Anna2yr9M)

“About 10 or 11...I mean anything younger than that, and yet the younger they know it, it becomes part of them, it is not an issue... my niece, at 5, has been diagnosed with celiac disease and she is completely cool about the whole thing.”(5Geoff2yr11M)

“Probably when he is a little bit older so he can understand.”(7Ben2yr9M)

“I don’t know, possibly when she is a little bit older, because she will have to deal with any consequences herself, but I would wait until she is in her teenage years – at this stage she doesn’t really understand.”(10Meg2yr8M)

Some parents had also considered *how* they might tell their child:

“I guess you wouldn’t deal with it any different than if you were reading a story to another child if you were having a baby, it is just

giving the information that they need enough to comprehend what is going on.”(2Colin2yr11M)

“I would just tell her and I am a great one to just tell it like it is really so I think kids take that on board really easily.”(6Jen2yr9M)

### **6.5.3.3. Putting the genetic information in context**

Parents mentioned a range of factors that helped them to make sense of their child’s test result. Firstly some parents felt that their own personality played a role in helping them to come to terms with the information:

“I guess I think I am quite a pragmatic person. I don’t get stressed by too many things, really stressed, I mean I get stressed by some things but I guess I am a pragmatic person and if something happens then I deal with it but I don’t spend lots of time worrying about it before, there is nothing you can do about it anyway.”(3Neil3yr3M)

“It’s just the way I am as to I just put it on the back burner because if she has got it, we will deal with it.”(6Jen2yr9M)

“There is just plenty to worry about with your children so I am trying to minimise my worries as much as I can.... not overdoing it and relaxing as much as you can. Not being overly neurotic and worried about things” (8Liam2yr3M)

Secondly, some parents brought up the issue of our inability to “control our genes”:

“I don’t know, I think there has just got to be a balance, if you worry that much about something it is not going to help at the end of the day so yeah, sort of I guess it is something I think about but if I was worried sick about it, it wouldn’t make any difference as to whether or not he got it.”(9Carl2yr3M)

“I suppose it is something that you can’t control, there is no point in – I mean you have got to do your best and do the things that you can do, right? I suppose, at the end of the day you have got to live, there is no point in worrying your head off about things you can’t control. You are just going to stress yourself out, so we are not terribly bothered about it.”(10Meg2yr8M)

Thirdly, some parents stated that they considered T1D to be a manageable condition, with some of them having known friends or relatives with the condition:

“I don’t see this as something that can’t be managed. Like even if he did develop it, it is a manageable thing and if he did develop it, the chances are that it is not going to be for quite a number of years and there is quite a lot of research that will be going on in that time and you hear about it all the time. People are switched on to diabetes....I think if I hadn’t seen relations with diabetes and that they can function perfectly well and look very healthy and are very healthy then maybe I would worry about it a little bit more but I have seen them. I know what they have to do, I know they have to inject themselves and they have to do it at certain times, and they have to take things with them when they go out to make sure they are eating properly and there are things they can’t eat but it is just part of who they are and what they have to do. Nobody – none of their friends or their family look at it any different, they just adjust.”(2Colin2yr11M)

“If she did have diabetes, I mean that’s not the end of the world either, it is just treating it and making it easy for people to live so.”(10Meg2yr8M)

One mother, a nurse, was unsure whether her knowledge and experience of diabetes was a good or bad thing:

“I sometimes think having a slightly medical background, I don’t know whether that helps or you know when you have spent hours and hours dressing diabetics manky toes and especially through our general practice because a lot of them have had diabetes and it is all complications at the end and things like that but I don’t know whether that helps or makes it worse, you know a little knowledge can be a dangerous thing whereas if you didn’t know you think oh – you know what I mean but anyway, you have got to deal with it really don’t you.”(5Geoff2yr11M)

Fourthly, objective evidence of their child’s good health helped some parents:

“I was reassured by the way Anna herself just carried on. We couldn’t tell her about it, she doesn’t know to worry and she just carried on doing every normal thing and gave us absolutely no reason to worry so we decided it wasn’t a big deal that we were lucky to know for the future if she got sick what to start looking for straight away.”  
(4Anna2yr9M)

Finally parents described how they put their child's risk in perspective by comparing it to other risks their child faced that may be more imminent, more likely or more serious:

"Yesterday when I dropped him off at day care he cried for the first time since he was a little boy. If he is going to be funny when I drop him off at day care, he usually just holds my hand or wants another cuddle or something but yesterday he cried and I don't know if it was the antibiotics that upset him or that I was going to leave him there when he didn't know the guy. There was something else going on and that probably gave me more anxiety than anything, to do with the diabetes study."(1John3yr2)

"I think there is a lot worse things. Like I probably worry about him running down the path more than I worry about him developing diabetes."(Colin2yr11M)

"So probably there is other risks like the other day we found him standing at the back end of a horse in the paddock without a parent which is a real risk so I guess I think of it at least in terms of other things that can happen to him like out in the garden he can disappear off somewhere and things like that."(3Neil3yr3M)

"I am more worried about him not running down the tractor sheds and getting run over – do you know what I mean – those sort of risks are far more in my face knowing where he is and knowing he is not out playing with the bulls, do you know what I mean. There is real risk around here and puddles and ... keeping him safe, I mean if you worried about everything they could get you would be mental."(5Geoff2yr11M)

"I may have compared it if you hear there is a wee kiddy with cancer or that's got not much hope of getting through, that's when you say hell diabetes would be – they would love to have that, that would be a godsend to them, that would be the only thing you would think, the worse we have got to deal with if we have to is a bit of diabetes, that's where that lies."(6Jen2yr9M)

"I just get, children introduce such a level of chaos into your life so it is just keeping up with them, keeping them well fed, health wise, you worry about all those things, those nasties out there....the other worry would be other factors like just keeping up with all the bills."(8Liam2yr3M)

"I mean at the end of the day he has probably got just as great a risk of getting something else or being hit by a car, I mean there are so many things that can happen to them, if you worry about all of them, you

don't get to enjoy them do you.... at the moment I look more at development type things and is he meeting those milestones where he is meant to be and he is doing the best that he can... I probably get so far down the track thinking about it and I think well there is nothing you can do about it and I could also be worrying about whether or not they fall off the deck and could end up with a head injury which could have just as big an impact or a bigger impact on your life so it is not really something that I stress about.”(9Carl2yr3M)

“I probably worry more about her ripping her head open or making sure she can't get out the gate, things like that.”(10Meg2yr8M)

#### **6.5.3.4. Considering their child's future**

Parents were also asked to talk about their thoughts for their child's future, and whether the genetic knowledge affected this:

“No, I haven't got time to look at him and think are you going to develop diabetes today?”(2Colin2yr11M)

“No, most likely we wont have to worry about it, but if she does, I know a little girl who has got diabetes – two, one is a little 2 year old, and another is the relation of a friend who is 10 or something and they are all right, you can live with it, it is hard work but you can live with it and I am sort of thinking if it is something we have to face further down the track then that's fine.”(4Anna2yr9M)

“Not really, no, there is not much point. I did once – there is a – I think she might have come out with the Plunket nurse once, and it was a young nursing student in about her, I think it was her second year of nursing and she just developed Type I diabetes and I just thought about it then because she had obviously had quite a major life style change for her. For a young whippersnapper out in the big student world and I thought about her and I won't be able to – when he has left home I won't be able to nurture him and care for him and do all those sorts of things that a mother probably wants to do for their child when something like this happens.”(5Geoff2yr11M)

“Not at all, absolutely not, no.”(6Jen2yr9M)

“We thought about it at the start, like whether he will need insulin or whatever they do for it, whether we have to give it to him or however that goes, but not now really.”(7Ben3yr4MF)

“Well I just hope I mean it has been a conscious decision not to vaccinate him so hopefully if anything did happen he would be able to fight it off and get over it. No just hope that he will be all right.”  
(8Liam2yr3M)

“I sometimes think about how he would cope with it or how we would cope with it as a family if it did become something that he developed but I mean you can think about that so far and then I think well it might never happen and if it did well you would just have to deal with it at the time.”(9Carl2yr3M)

## **6.5.4 Receiving the test results: long term impact**

### **6.5.4.1. Emotional or psychological impact**

Most parents reported not thinking about their child’s genetic risk status very much:

“We don’t think about it.”(1John3yr2M)

“I guess I don’t think about it all the time, I don’t think about it that often.”(3Neil3yr3M)

“I haven’t thought about it.”(7Ben3yr4MF (Mother))

“I guess I have been so busy and flat out I haven’t really pondered on it too much and Liam has got a fairly strong disposition, he is quite a slight build, but that’s the way he is. I guess I am trying to look on it as the likelihood of being not high enough to be alarmed about, but hopefully I won’t have to deal with it.”(8Liam2yr3M)

“I think it just – I think it sort of does go to the back of your mind at a certain point.”(10Meg2yr8M)

Other parents commented that they thought about their child’s genetic risk status only intermittently, usually in relation to some sort of prompt:

“No, its just – it is not in your face all the time this study, you get things in the mail and you think that’s right, and then I do think when it comes around to his birthday oh we have got to go and do this again (meaning a blood test) and it is hard leading up to that because it is his birthday time and you think oh no.”(1John3yr2M)

“It doesn’t get thought about a lot, it doesn’t, it is when I get the letter that says Jen’s due for her blood test and maybe because she hasn’t shown any of the signs I have just thought maybe she isn’t the one in whatever it was that is going to definitely develop out of the 16 or whatever it was.”(6Jen2yr9M)

“Don’t even think about it, only when you see something on TV like children with diabetes, but it is always the other type, too much sugar and fat type.”(7Ben3yr4MF (Father))

Only one mother in this group had received a raised antibody result for her child in the subsequent monitoring phase of the KEA study:

“My feelings hadn’t changed until we got the blood tests back and the antibodies had gone up a bit. So until then it was pretty much unchanged, he was going to have these tests done and nothing really happened but then recently they have come back a bit higher and he has just had a repeat blood sample taken and then I just sort of thought oh that’s not so good and I mean we had seen Barry (paediatrician) after we had the first blood test taken but before they had the results and he told everyone they can go up and down rather than going up and up so again I wasn’t really concerned.”(3Neil3yr3M)

Some parents felt lucky or pleased to know their child’s genetic risk of T1D:

“And that’s where I thought we were very lucky because people who were born a year before John whose child is going to get diabetes, they’re not going to know whets going on, their child is going to be sick, it is going to be dreadful, if it happens to us then we will be forewarned.” (1John3yr2M)

“I feel lucky to know that I have got inside information in a way. I mean I sort of think that not that you are always looking for signs of it but if something were to happen then you think maybe that is a possibility but you don’t have to worry about doing anything else and you could say this could be what it is and just go straight to it, and if it is, fine, and if it is not....”(2Colin2yr11M)

“Apparently if it is going to happen, it is going to happen, regardless of any tests and if it does happen it was going to happen anyway and being tested in some ways gives you the chance to cope with it all, you can talk about it.”(3Neil3yr3M)

“In a way I felt lucky to be part of the study because I knew that Geoff would be looked after. I mean he was lucky because there are lots of

kids out there with the same gene who wouldn't have the same opportunities or who would know if he was starting to produce the antibodies blah de blah so I thought well you know if he has got to have it, which is kind of out of everyone's control, he was in the best care."

"Well I think the fact that he knows he is at risk is a real bonus, especially for something like diabetes ...I am so on to it, if they do something out of the norm I am aware of it and I think being aware is so helpful."

"I am quite lucky really and I have had three very normal, very healthy babies and my sister has had two and you just take it for granted don't you, sometimes it is quite a good wake up call that there are nasties out there lurking."(5Geoff2yr11M)

"In a way I am glad that we had it done now because we know the risks."(7Ben3yr4MF (Mother))

One mother reported that it took a while for her initial negative response to dissipate:

"It took about three or four weeks for us to settle down and not be so worried about the test results I suppose....my doctor said what did that mean to you and we ended up deciding it didn't really mean anything apart from taking part in the study."(4Anna2yr9M)

One mother reported worrying about her child developing T1D because she had seen a previous flat mate of hers develop complications of T1D:

"What things do concern me now that I am thinking back, I remember she (the flat mate) had to get her glasses changed very regularly and now thinking back towards John, that is the sort of thing that does scare me and I don't want him to get diabetes and I think it is not just the insulin but the eyesight going and the potential for gangrene, and a shortened life, all those things. So that's probably why I am thinking my son is going to be in the 95% group."(1John3yr2M)

#### **6.5.4.2. Impact on parents' behaviour towards their child**

Many parents felt that the information concerning their child's genetic risk of T1D had no effect on how they felt or behaved towards their child:

"No, I don't believe it affects how I feel about him. The malignant hyperthermia thing has more effect I think with the risk. He doesn't have a medic alert bracelet saying test me for diabetes. there is nothing special in the way we treat him."

“I don’t think I do anything differently, I think it is pretty much a none thing, it is just like I said before it isn’t an issue.”(1John3yr2M)

“I didn’t go to any efforts to give them anything different. I try to eat a healthier lifestyle, more healthy food for all of us, for everything’s sake, not just the diabetes. I try to find a healthy option for most things.”(4Anna2yr9M)

“No, ...I haven’t looked for the signs, no. I haven’t, I have probably forgotten what the signs would be, I know it is drinking an unacceptable amount, weight gain, ... haven’t even bothered to take Jen back to Plunket, she had a normal 2 year check, to me she is getting taller, she is happy, she is running riot, as far as I can see she is not listless or anything I mean that would probably be another one.”(6Jen2yr9M)

“No nothing. We didn’t change anything.”(7Ben3yr4M)

“No, I don’t do anything different but generally I try and keep to unprocessed foods and fresh fruit and vegetables and make the effort to actually put a decent meal on the table...just to keep them healthy and fortified as possible, I am just a really big believer in your diet affecting how you are and I know if I don’t eat right I start to feel like crap.”

“I don’t feel different about him...he is just as precious. I try and relax about him, I don’t think I am overly protective. It is not the safest house but I have done the best I have to make it as safe as possible, I just let him go for it.”(8Liam2yr3M)

“There’s no difference in how I think about him and James (older brother).”(9Carl2yr3M)

“No, it hasn’t changed what I think about her at all. I mean she is very precious anyway ... I suppose you couldn’t love a child any more really could you, she is pretty cool.”(10Meg2yr8M)

Other parents felt that they monitored their child more than they otherwise might have:

“No, I guess it is in your mind, I mean if they suddenly developed this huge thirst in the middle of the night I would think oh..”(2Colin3yr2M)

“I take her to the doctor if she has any sort of horrible cough or anything that lasts more than a couple of days.... and I also decided to apply it to Andy (older brother) as well. He could just as easily have the gene but we don’t know so in a way I watch him as much as I watch

her. I was sort of worried if she was drinking more than usual or anything and even now Andy drinks a lot of water, he is always coming in and saying I need a cold drink and in the start I thought is he all right but he is, he is perfectly well and healthy, he just likes to drink a lot.” (4Anna 2yr9M)

“I used to think, oh he’s drinking a lot today, but when I spoke to my friend, Phoebe, she would say, no he will be fine, she was quite relaxed, she doesn’t seem to panic and in a way we are probably quite good for each other because if one is having a ‘oh my god, he’s got it’ type moment, the other can say well don’t be so stupid. I mean you know how women talk and worry and it is quite nice to have that balance.”(5Geoff2yr11M)

“Possibly I worried more when he was ill...you know how when they are sick they smell differently, my husband says I am nuts but that ketoney sort of smell that they have is always associated with diabetes and I thought ooh he smells funny. There was that aspect when he was, yes I don’t know what it was, I looked more carefully at him and I worried more about his eating habits than I did with James (older brother) and I wondered if there was something that I could or could not do that might actually stop it from turning into anything.”(9Carl2yr3M)

Some parents did report either trying to or actually making changes to the way they treated their child because of the risk of T1D:

“I thought about the breast feeding, because I mean I know the story that longer breast feeding is meant to protect but then having said that I didn’t breast feed him for any longer or treat him any different than “Ella” in practice because I was working and the reality.... With the introduction of dairy foods, I am not sure I might have waited a wee bit longer than with her.”(3Neil3yr3M)

“I do try to watch what he eats but that doesn’t really work. Especially in the mornings he eats, and eats and eats, and sometimes he will have a vanilla wine or something when maybe I should give him something else and I know it is not diet related but in Winter too, I was giving him Vitadol C, just to give him that Vitamin D when he wasn’t seeing the sun.”

“My friend, Phoebe, she gave all her kids A2 milk and she reckoned it helped but I never went to a supermarket that had A2 milk, it was only at Countdown or something wasn’t it?”(5Geoff2yr11M)

“Yes, formula, we hit a wall at about three months when he had been sleeping through then all of a sudden he wasn’t and I had been feeding

him but I really just felt that I couldn't keep up with him and I wanted to give him a little bit of a top up with formula at night and I really thought twice about what formula to give him and whether or not I should be giving it to him. It was almost like a guilt thing, should I just be carrying on feeding this child and be putting up with getting up in the night. I really thought twice about that but I didn't when I did it with James. Especially when there was that whole thing about the milk types, I thought should I be giving him a soy milk instead of the basic formula and that but of course nobody had any answers so it was impossible to get any...I talked to the Plunket nurse before I did it, I gave her a frantic Saturday call because I had been up most of the night, oh should I put him on soy milk or normal milk or and she was very patient and listened to me and said it was my choice really and I don't know. In the end I put him on normal formula before bed and then slowly, I mean I fed him until he was 11 months anyway in the end but he slowly picked up having that little bit – it just became that it wasn't sensible to just keep breast feeding him if he wasn't satisfied as well.”

“He is a shocking eater, to get anything nutritious in to him in the day is a night mare and I am quite aware of that as well... he eats sometimes spaghetti but to actually get him to eat meat and regular vegetables and I often think is that going to have an influence later as to whether he actually does develop diabetes? The thing is there is absolutely nothing I can do to make him eat it, you can't jam it down their throat and things he used to eat he won't eat now, and that side of it, I think that dietary thing could have an influence later but at the moment I have no control over it. I can't negotiate with him, he is too little and if he shuts his mouth then you can't do anything about it.” (9Carl2yr3M)

“We have just been watching what she eats and that she doesn't eat too many carbohydrates and stuff like that and that she eats plenty of fruit and vegetables, yes just being proactive....we would do that in general but for a start we initially did it because of the diabetes but now I mean it is just healthy eating... when she started on solids and things like that we would stay with fruit and vegetables so basically she likes that food and will eat that food and that sort of thing which has proven really good ...we make sure she got plenty of exercise and was out as much as she could. She is an outdoors girl which is very good, she loves being outside.”(10Meg2yr8M)

### **6.5.5 Parents' reflections on the genetic testing process**

#### **6.5.5.1. Feelings about having participated in the genetic testing**

Most parents were glad that their child had been tested and so that they were aware of the risks of T1D:

“I think I probably feel relief because he’s going to be watched. It has no detrimental effect on him having a blood test.”(1John3yr2M)

“I’m glad because we will have some advance warning and that may be beneficial rather than suddenly having him at school suddenly collapsing.”(3Neil3yr3M)

“Fine, no problem ...it is great I would do it again.”(4Anna2yr9M)

“I am pleased he has had it, you can’t stick your head in the sand can you, sometimes I really would have liked to have and I think life would be so much easier if I didn’t know and then I think get real. You know what I mean – just because it is there you can’t pretend that it hasn’t happened.”(5Geoff2yr11M)

“No, I would probably do it again if we have another child and the study carries on.”(10Meg2yr8M)

One mother felt ambivalent about it:

“I sometimes think if I had never had done that I would never have known and it wouldn’t have been something that I had thought about but I don’t think it has really had that much of an impact for us that it would really have made much difference. I certainly probably still would have done the study knowing what I know now.”(9Carl2yr3M)

One mother wished they had not taken part:

“Don’t mind, but we wish we hadn’t done it in a way because all the blood tests now is not nice, you know screaming and that.”

Although her husband was more positive:

“Sometimes yes, but in a way I am glad that we had it done now because we know the risks.”(7Ben3yr4MF)

#### **6.5.5.2. Would parents undergo this type of testing with a future baby?**

Most parents would have a future baby tested:

“Yes I probably would, I would be interested to know if my other children were at the same risk”(2Colin2yr11M)

“Yes, definitely, but more for the study than to help us.”(4Anna2yr9M)

“Yes, I probably would, and I would kick myself for doing it but I think I would do it, you would be in a way foolish not to really.”  
(5Geoff2yr11M)

“Yes, I probably would but then because I wouldn’t want to say no and then there would be all these other people wanting me to do studies because they have heard she is an easy target.”(6Jen2yr9M)

“We would get her tested yes, but I wouldn’t want the study, just like go and get the bloods done.”(7Ben3yr4MF (Mother))

A couple of parents were unsure:

“Possibly, I don’t know.” (8Liam2yr3M)

“Probably, yes. No I wouldn’t really be too concerned either way I don’t think.”( 9Carl2yr3M)

One mother would not:

“I’d say the answers probably no.... I guess it’s because at the moment there’s nothing you can do. If that changed .. but at the moment none of the trials have shown there’s any intervention. So, although its good to have a bit of early warning, in a sense we’ve already got that with our kids, so if they started going to the toilet a lot or they had those early signs then were already aware what that could mean. And we go and get it checked out.”(3Neil3yr3M)

### **6.5.5.3. Parents views on genetic susceptibility testing in general**

When asked about genetic susceptibility testing in general parents discussed the benefits:

“I think it is a good idea. It is genetics and that. If they don’t do testing you would never find out about anything.”(7Ben3yr4MF)

“I still think also we are one step further down the track than maybe some parents who don’t know that their child has an increased risk so if we were to turn up at the hospital with him with symptoms that really did look like – I can’t help wondering if we would get action faster and maybe being able to put something in place quicker that would be of

benefit for him because there was a little tick on his hospital records.”  
(9Carl2yr3M)

They also discussed the possible risks:

“With diabetes, even if you are genetically susceptible, the risk is still relatively low. I don’t know that I would support screening everyone because a lot of people would just worry about it who don’t need to. So there is that worry, they might worry for years, whereas with something that is more certain then I would be more in favour of it.”  
(3Neil3yr3M)

“That’s a hard one, isn’t it, because I know some people, it would sort of slap them out.”(5Geoff2yr11M)

“I think it is good. I think it is – I mean probably people like us are not going to get terribly stressed about it but probably for other people who are more highly strung it probably wouldn’t be the best thing.”  
(10Meg2yr8M)

And emphasised that it should be a personal decision for individual parents to make regarding their children:

“I don’t know if I would say I think you should do this, I think it is personal – I would just say this is what Colin is doing and this is why. I don’t think I would tell them to go ahead and do it, it is just not that type of thing.”(2Colin2yr11M)

## 6.6 Summary

The qualitative data presented in this chapter provides important insights into how parents experience the process of newborn genetic susceptibility testing. I have relayed details of parents’ motivations for permitting their newborn to undergo such testing, including their desire to participate in research that may benefit others, as well as an interest in knowing their own child’s risk of developing T1D.

I have also detailed how parents’ accounts of the immediate impact of learning about their child’s genetic risk of T1D vary, with some reporting no real concern, others a “mild” negative reaction and some more intense negative emotions. Most of the parents interviewed describe how these initial emotional responses subside quickly. In general, parents report feeling glad that their child has been tested so that they are aware of the risks of T1D but some are either ambivalent about the process or wish they hadn’t taken part.

My interview data suggests that parents attribute considerable importance to the process of understanding the meaning of the genetic test result for their child. Most parents discuss the idea that while the genetic susceptibility test result increases their child's risk of developing T1D, it is by no means diagnostic. However, the terminology that parents use to describe this concept varies, with for instance some preferring to recount numerical odds and others using purely descriptive terms. I have relayed some interesting descriptions of *how* parents make sense of the genetic information, including by discussing it with relatives and friends, by comparing the risk of T1D with other risks that their child may face, and by reassuring themselves with objective evidence of their child's good health.

For most parents their child's genetic risk status remains "at the back of their mind" but intermittently comes to the fore, often in relation to a specific prompt such as a routine study visit or a television programme about diabetes. The majority of parents consider that knowing the test result has no effect on how they treat their child, whereas others feel they observe the child more closely for signs of T1D, particularly in the context of minor illnesses, such as coughs and colds. Some parents report attempts to reduce their child's risk of developing T1D through subtle lifestyle changes, such as extension of the duration of breast feeding. However, this concern with disease prevention is more often expressed in a wider context, with parents aiming for "a healthier lifestyle, more healthy food for all of us, for everything's sake, not just the diabetes." (4Anna2yr9M)

## **6.7 Conclusion**

In this chapter I have relayed the experiences of 11 parents whose baby was tested for genetic susceptibility to T1D. I have presented their descriptions at length with minimal analysis. In chapter 7 I present the next stage of analysis in which I analyse and interpret these experiences in more detail.

## **Chapter 7      Detailed Qualitative Analysis**

## 7.1 Introduction

In chapter 6, I presented lightly edited accounts of my interviews with parents in chronological sequence. This fulfils the first aim of Interpretative Phenomenological Analysis (IPA), that is to explore the participants' view of the world and to adopt as far as possible an insider's perspective of the phenomenon under study[290]. However, IPA also recognises that while one can attempt to get close to the participants' personal world, this cannot be done directly or completely. Access is both dependant upon, and complicated by, the researcher's own conceptions that are required to make sense of the participants' words through a process of interpretive activity. In this chapter I will therefore address the second aim of IPA by examining parents' reactions in more detail, developing my own theories concerning these reactions and discussing how these theories fit within the existing literature. In particular I will highlight how different elements of parents' reactions evolve over time and are interrelated, and how there are both similarities and differences in individual parents' reactions.

## 7.2 Analysis

As is usual in IPA I initially read and re-read each interview transcript until I became very familiar with the data. I highlighted key words or sentences and made notes in the margins, from which initial themes or categories emerged. I then developed narrative accounts for each of these themes, giving a brief description of the content of the theme and then recording all related transcript examples. This organised account of the data was presented in chapter 6. I subsequently undertook a further phase of analysis, again in keeping with the methodology of IPA. At this stage the initial themes were refined into "super ordinate themes" [59] through analysis of connections between the data from different interviews, and through my own interpretation or explanation of why the data was taking a particular form [263]. Each super ordinate theme is therefore connected to the underlying themes, which in turn are connected to the original annotations and extracts from the participants [59]. To assess reliability two of the transcripts were coded independently by an experienced qualitative researcher and no significant inconsistencies were found.

I will present the data from this phase of my analysis in two sections, representing the two super ordinate themes that emerged from this part of my study. I will use instances from the interview transcripts to illustrate this analysis but will keep quotations as brief as possible in view of the extensive presentation of interview data in chapter 6.

### **7.3 Themes for analysis**

The two broad themes that arose from my detailed reading and re-reading of the interview transcripts were:

- **Making sense of a child's risk status**
- and
- **Making use of the genetic information**

### **7.4 Making sense of a child's risk status**

When I asked parents to recollect their initial experiences of receiving their child's increased risk genetic susceptibility test for T1D, they all spoke first of affect or emotion, even if the reactions they described did not appear extreme. Only when they had discussed how these early feelings subsided did they go on to talk, often at length, about how they came to their own cognitive understanding of the genetic risk. In this section, I will therefore discuss firstly parents' emotional reaction to the testing process, and secondly their cognitive reaction.

#### **7.4.1 Parents emotional responses**

In the KEA study, parents were informed of their baby's results by letter, followed by a face-to-face meeting with a paediatrician a few days later. This process was described in more detail in chapter 4, with written information given to parents provided in appendices E to H. The qualitative interviews described here were conducted at least two years after this notification process, when children involved in the study were 2 to 3 years old. Despite the time lag between dissemination of test results and interview, all parents spontaneously recalled receiving the notification letter.

Parents' initial responses to receiving the letter notifying them of their child's increased risk of T1D occurred rapidly but generally involved no more than feeling slightly upset. For example:

“I wasn't really that worried about it.” (9Carl2yr3M)

“Oh, I must admit, I think I thought oh bother and oh well, I wasn't upset by it.” (3Neil3yr3M)

One parent explained this lack of distress by highlighting what she considered to be a clear distinction between the results of the genetic susceptibility test, and the thought of her child being given a definitive diagnosis:

“I wasn't worried—it wasn't as if you were going to tell me this is what he has got and he is going to die in X amount of years because of this. It wasn't, it was nothing like that.” (1John3yr2M)

However, although initial emotional distress experienced by parents was generally mild it did vary somewhat between individuals. The most negative response came from a mother who had experienced postnatal depression:

“I remember thinking we never thought we would have a child with a disability or anything like that ... we were a bit gutted.” (4Anna2yr9M).

This mother noted feeling “miserable” about the results for a few weeks, until she talked to her family doctor. She then reported deciding that:

“after a little while we realised that it didn't really mean anything straight away but we were actually fortunate to know.” (4Anna2yr9M).

Other parents reported that their initial feelings were very short-lived, meaning hours or days rather than weeks, and were superceded by a process of making sense of the genetic information. However, despite these descriptions of mild, transient reactions there was evidence from the interview data that parents' concerns sometimes recurred, with the probabilistic nature of the genetic test result being an important contributor to these fluctuations. While some parents felt able to put the notion of their child being ‘at risk’ to the back of their minds, for others worry became prominent again as a response to influences such as memories:

“What things do concern me now that I am thinking back, I remember she [a previous flatmate with T1D] had to get her glasses changed very regularly and ... that is the sort of thing that does scare me ... I think it is not just the insulin but the eyesight going and the potential for gangrene, and a shortened life, all those things.” (5Geoff2yr11M)

Other parents mentioned the time around measurement of children's autoantibodies as a difficult period:

“It doesn't get thought about a lot, it doesn't, it is when I get the letter that says Jen is due for her blood test.” (6Jen2yr9M).

This interview data is somewhat reassuring in that it suggests that parents' initial emotional reactions to a positive NBS test for susceptibility to T1D are milder than those described in relation to existing NBS programmes[149] or predictive genetic tests[302]. As one of the parents noted, this probably reflects the latitude that a probabilistic result permits: parents can hope that their child is one of the large group who will never develop the disorder. It therefore appears that although uncertainty is generally viewed negatively in medical or scientific contexts, in this situation it may play an important role in permitting hope and moderating parents' emotional reactions[307].

However, although uncertainty may have minimised parental worry it also seems to be implicated in the ongoing and dynamic nature of their concerns. Initial distress in relation to positive NBS or predictive genetic testing results tends to diminish rapidly[225, 302, 307], being replaced by the therapeutic opportunities associated with definitive early diagnosis[221, 258] and/or relief from uncertainty[48]. NBS for genetic susceptibility to common complex disorders contrasts sharply with such testing in that rather than this “benefit of certainty”[308], the tests highlight a specific and ongoing level of *uncertainty*. Parents given a definitive diagnosis for their child through NBS or predictive genetic testing can prepare for the future both emotionally and practically[33]. In contrast, parents whose child has a positive genetic susceptibility test face a dilemma between preparing themselves for a disease that may never eventuate, and choosing to ignore their child's genetic risk, potentially missing the opportunity for such planning. This ongoing tension appears to contribute to the dynamic nature of parents' emotional reactions to NBS for genetic susceptibility to T1D.

The interview data also suggest several other factors that may interact with parental uncertainty and lead to continued fluctuations in levels of worry. These include: contextual factors, such as routine disease surveillance visits and personal factors, such as memories, or underlying psychopathology, including postnatal depression. The supposition that PND may impact upon maternal reactions to newborn genetic susceptibility screening is supported by evidence from the literature that the most significant predictor of depression, distress or anxiety after predictive genetic testing is a pre-testing state of depression or anxiety[302]. While I acknowledge that it is not possible to extrapolate findings from one participant in a qualitative study to the general population the suggestion that some women with PND may experience more difficult reactions to news of their newborn's increased genetic risk of T1D requires further analysis. This may be of significant public health importance given that it is estimated that about 10% of women suffer from PND[301].

#### **7.4.1.1. Summary of emotional responses**

In this section, I have noted that the majority of parents experience a relatively mild emotional reaction to newborn genetic susceptibility screening for T1D. However, my data has also highlighted the primacy, dynamic nature and inter-individual variability of these parents' affective reactions. The interview data also suggest several factors that may interact with parental uncertainty to modulate levels of worry including: personal factors, such as memories, or underlying psychopathology such as postnatal depression; and contextual factors, such as routine disease surveillance visits. The complex interplay between these personal and contextual factors is likely to contribute to both the dynamic nature and individual variation in parental psychosocial reactions, and may at least partially explain why parents do not score highly on infrequently applied standard measures of anxiety or depression[249, 250], but report significant concern when rating their own level of worry about T1D[139]. Parents' emotional responses may also affect their behaviour, and this is discussed further in the section on parental behaviour change.

#### **7.4.2 Parents cognitive representations of their child's genetic risk**

In the next section, I will discuss in more detail the process by which parents come to a cognitive representation of their child's genetic risk of T1D. This discussion involves two main parts, namely parents' views regarding T1D itself and their perception of disease risk.

##### **7.4.2.1. T1D – Genes and Environment**

It is not surprising, given the nature of the testing that their child had undergone, that most parents specifically mentioned genes when talking about the aetiology of T1D. For instance, Anna's mother said:

“We know that she has the gene that everybody that develops childhood diabetes has got”. (4Anna2yr9M)

Parents' responses reflected an acceptance or feeling of resignation toward the genetic test result:

“he's got the gene and we can't change that” (7Ben 3yr4MF).

Genetic fatalism has been described previously in relation to genetic testing[238], and can be defined as “the view that we cannot avoid specific genetically predetermined outcomes, no matter what we do or what happens to us: our fate is in our genes” [309]. However, in my

research although some parents were resigned to the genetic test result, they were not fatalistic, also relating the potential for modification of the risk of T1D through environmental measures. For example Ben's father said:

“just because he has got that gene doesn't mean he is going to get it, it is just a chance” (7Ben3yr4MF)

and Carl's mother, who had also mentioned the immutable nature of genes, talked at length about her decision to introduce milk formula when Carl was 3 months old and how her knowledge of his genetic risk of T1D influenced the decision-making process. Thus, these parents report an element of “genetic pessimism” in that they understand the fixed nature of genes, but this view only represents part of the overall picture of their understanding. They also appear to retain a multifactorial disease model, (i.e. that such a disease is caused by the combined action of multiple genetic and environmental factors) often involving some theories about particular environmental factors that may be relevant, and potentially controllable. Some parents were able to articulate both concepts simultaneously, like Meg's mother:

“In my mind I think that she has got a higher possibility of having that susceptibility to have diabetes ... I sort of imagined that it was her environment and food which contributes to that.”

In other interviews the concepts of genes and potential environmental contributors were only evident at different time-points.

Previous research has shown that how people think about disease, particularly the perceived controllability of the disease, is an important determinant of what they do about it [310]. This notion has led to concern that offering genetic testing and information about late onset disorders may increase fatalistic illness representations and lead to a decline in protective health behaviours [238, 311]. However, data from this study suggests that parents are able to comprehend that while they have no control over the genetic risk as such, they may be able to influence the course and severity of any health consequences. Indeed, several parents commented that they considered T1D to be a manageable condition:

“I don't see this as something that can't be managed” (2Colin2yr11M)

“you can live with it, it is hard work but you can live with it”  
(4Anna2yr9M) “if she did have diabetes, I mean that's not the end of the world either, it is just treating it and making it easy for people to live” (Meg2yr8M)

#### **7.4.2.2. Perception of risk**

The uncertainty associated with the T1D susceptibility test results appeared to have a major impact upon parents' perceptions of their child's risk of developing T1D, as well as on their emotional reactions. Parents described a dynamic process of trying to make sense of the risk by locating it on a map of potential illnesses and situations they considered to be more serious or more likely. All but one of the parents in this study reported undertaking this process, but the range of conditions or experiences that they employed in the comparisons was fascinatingly diverse, and highly individualised, reflecting their varied lifestyles. Many of the examples featured concrete, highly visible risks, such as the presence of bulls on the farm, which would be evident to parents on a daily basis. As all but one of the parents engaged in this process in some way, I have presented their responses in tabular form (table 7.1). It is also interesting to note that parents mapped the genetic test result in comparison to conditions without obvious genetic aetiology, lending weight to the idea that genetic tests are not necessarily perceived as different or exceptional[312].

**Table 7.1 Parents' comparison of T1D risk with other conditions or situations**

<b>Interview</b>	<b>Perceived as more serious</b>	<b>Perceived as more likely</b>	<b>Perceived as both more likely and more serious</b>
1		Child being upset at daycare	Injury related to running down the path
2		Consequences of not "eating the things I want him to eat"	Injury related to running down path onto road
3			Drowning in puddles Disappearing off in garden Standing behind horse in paddock
4			Falling off climbing frame
5			Getting run over by a tractor Playing with the bulls
6	"Wee kiddies with cancer"		
7	No comparisons		
8	"Health wise, you worry about all those nasties out there"	Consequences of not keeping child well fed	Consequences of child accessing knives or cleaning products in the cupboard
9		Consequences of child "getting over the railing"	Being hit by a car
10		Consequences of child "getting out the gate"	Injury e.g. "ripping head open"

This type of process, in which comparison is made with a person in a similar situation who is doing less well, has been described previously, and termed downward social comparison [313]. These strategies may initiate positive effects such as increased self-esteem [313] but it has also been suggested that this type of coping mechanism may result in unrealistic optimism about health threats, and may make people less likely to comply with health-protective behaviour[314]. However, in this study parents do not appear to be unrealistic in their representations of the threat that T1D poses to their child, indeed the majority recall a broadly

correct level of risk. Rather parents seem to want to locate an unfamiliar type of risk in the context of their own family circumstances. In other words, I suggest that as an aid to their understanding, parents transfer the risk of T1D from the abstraction of medical terminology into the reality of their own lives. Even though, as part of this process, parents may be motivated to downplay their child's risk (by comparison with situations more likely or more serious) this does not apparently prevent parents from maintaining a certain degree of vigilance in relation to their child's health, and in some cases in engaging in potential risk reducing behaviour.

When articulating their child's risk of T1D parents used a range of different terms, including numerical estimates and descriptive accounts, but generally described a broadly similar degree of risk: they were aware of the increased risk, but also cognisant of the significant chance that the disease would not occur. This finding is consistent with evidence that people tend to extract the "gist" of numeric risk information, using relatively few verbal categories (such as "low" or "high" risk) to describe their understanding [315, 316], and also echoes my quantitative data.

However, although most parents seemed to extract the "gist" of the risk information appropriately, interpretation of this varied between parents, as well as intra-individually over time. For example, one mother said:

"basically it is still only a 10% chance or even less that he will get diabetes so we don't really need to worry." (3Neil3yr3M)

Whereas a different mother said:

'I don't like his odds; ... it would be much better if he was in the one in 300 chance as opposed to the one in 16. Someone is going to get it aren't they?' (5Geoff2yr11M).

In other words, it seems that very similar levels of numerical risk have been assigned different significance by different individuals. These differences in parents' perceptions of their child's risk may relate in part to their coping mechanisms, and the value they attach to the genetic knowledge. In three interviews in particular, parents reported feeling lucky to know about their child's risk of T1D, believing that their heightened awareness could eventually lead to benefits for their child. These parents described observing their children more closely for signs of T1D, particularly during periods of ill health, and I will present examples of this

“monitoring behaviour” later in this chapter. In contrast, in the other seven interviews parents focused more on a conscious process whereby they minimised the impact of the test result:

“It's just the way I am, as to I just put it on the back burner because if she has got it, we will deal with it.” (6Jen2yr9M);

“at the end of the day you have got to live, there is no point in worrying your head off about things.” (10Meg2yr8M).

This minimisation process appeared to be very deliberate and something these parents considered an inevitable part of parenting young children. Liam's mother articulates this nicely:

“There's plenty to worry about with your children so I am trying to minimise my worries as much as I can ... not being overly neurotic and worried about things.” (8Liam2yr3M)

and Colin's mother simply says:

“I haven't got time to look at him and think are you going to develop diabetes today?” (2Colin2yr11M)

My interview data therefore seems to suggest that parents in this study fall into one of two categories: those who tend to minimise their child's genetic risk, or put it to the back of their minds, and those who actively use the information to observe and monitor their child. This is interesting in that there is some evidence from the literature that individuals differ in the way that they cope with their own health-risk information[286]. Personal characteristics that have previously been reported as moderators of coping style include an individual's need for certainty, preference for information and sense of control over health outcomes [317]. Perhaps most pertinent to my data, Miller [318] has described the concept of “monitoring-blunting” coping styles with “monitors” tending to seek out high levels of information, and “blunters” more inclined to distract themselves from information and suppress or avoid cognitive and emotional threats[318]. It has also been suggested that monitors may be more vulnerable to stress and anxiety [286] and may be more demanding of medical services, wanting more tests and information, perhaps as a way of reducing their uncertainty and promoting feelings of reassurance[318]. While recognising that I did not formally assess coping style [319], and interviewed a small number of parents, my data does seem to suggest that personal coping style is related to the nature of parents' psychosocial reactions to newborn genetic susceptibility testing for T1D.

### **7.4.2.3. Summary**

My interview data reveal how the ongoing uncertainty related to their child's risk of T1D impacts upon parental cognitive reactions: while all of the parents adopted some type of comparison strategy to make sense of their own child's risk, subtle differences in this "mapping" process may have contributed to individual variation in risk perception. The dynamic nature of parents' risk perception may again be related to the difficulty that parents experience in determining the value of the genetic susceptibility test result for their child. Fluctuations in risk perception, and subsequent responses, could reflect their ongoing attempts to reach a position of compromise between planning for adversity and hoping for the best, in a situation of uncertainty. This psychological process appears to vary between individuals, with parents in this study falling into two broad categories: those who minimised the risk, or put it to the back of their minds, and those who actively used the information to observe and monitor their child.

## **7.5 Making use of the genetic information**

In the previous two sections, I have described in some detail parents' emotional and cognitive reactions to their child's genetic susceptibility test result. I will now discuss the second of my super-ordinate themes, how parents make use of the genetic information.

I reiterate here that there is currently no known intervention that can reduce a child's risk of developing T1D. Parents involved in the KEA study were informed of this fact, and indeed that the major aim of the study was to further elucidate the pathogenesis of T1D such that preventative measures may be developed at some point in the future. Other similar research is in progress, but with study endpoints several years away[17] it is likely that even if clinically useful preventative measures are feasible they will take many more years to develop and test. For this reason, no specific dietary or other lifestyle advice was given to parents as part of the KEA study although they may have been aware of various hypotheses about disease pathogenesis through general discussion or through inference in view of the type of data they were asked to collect, such as food diaries and cleanliness questionnaires.

Despite all of the above, some parents in this study did report making changes on the basis of their child's genetic test result. While acknowledging that these accounts are narratives of behaviour change, rather than direct evidence of behaviour change, I will now discuss them in three different categories. Firstly, changes in the way parents monitored their child's health; secondly, lifestyle changes that parents made that may have been partly related to their child's risk of T1D and finally, changes that were made specifically in an attempt to reduce the child's risk of T1D.

### 7.5.1 Health monitoring

In the previous section I noted that differences in coping style (such as “monitoring and blunting”) might contribute to variations in behaviour between individuals. In that section I also documented how three of the parents interviewed described a process of monitoring their children more closely than they might otherwise have done. I now present some descriptions of this process. Firstly, Carl’s mother reported how her knowledge of his genetic susceptibility to T1D caused her to be more concerned about him than she might otherwise have been when he was unwell. She said:

“possibly I worried more when he was ill ... you know when they are sick they smell differently...that ketone sort of smell...associated with diabetes and I thought ooh he smells funny” (9Carl2yr3M).

Similarly, Geoff’s mother discussed how she sometimes worried about behaviours that could represent symptoms of T1D. She said:

“I used to think, oh he’s drinking a lot today” and described having an “oh my God he’s got it moment.” (5Geoff2yr11M)

The three parents who described “monitoring behaviour” also frequently commented how objective evidence of their child’s good health reassured them. For instance, Anna’s mother said:

“I was reassured by the way Anna herself just carried on....doing every normal thing.” (4Anna2yr9M)

However sometimes she required the additional reassurance of her family doctor:

“I take her to the doctor if she has any sort of horrible cough or anything that lasts more than a couple of days ... and I also decided to apply it to Andy (older brother) as well. He could just as easily have the gene but we don’t know so in a way I watch him as much as I watch her.” (4Anna2yr9M)

The precise degree to which the T1D susceptibility test result contributed to this monitoring behaviour is unclear but these parents seem to be saying that it had at least some effect. In contrast, parents who tended to minimise the importance of the genetic test result did not appear to monitor their children's health in the same way:

'I haven't got time to look at him and think are you going to develop diabetes today?' (2Colin2yr11M)

### **7.5.2 Changes related to a “healthy lifestyle”**

The most common changes that parents reported making in relation to the T1D test result were attempts to provide their child with a “generally healthy lifestyle”. This practice was not necessarily wholly motivated by a desire to reduce their child’s risk of developing T1D, rather many parents felt that the T1D risk provided some incentive. Again, the degree to which the risk of T1D prompted this concern with a “healthy lifestyle” is difficult to determine precisely and seemed to vary from parent to parent, and over time. For example, in the context of diet one mother said:

“I am probably conscious of what the family are eating anyway but I don’t know if that is because of this (the T1D risk) or if it is because of just all the nutritional information out there or the childhood obesity that is going on, I can’t say that, whether that is something I would be doing anyway, I would like to think it is something I would be doing anyway.” (2Colin2yr11M)

Another mother commented that initially, when her daughter was very young, she had included lots of fruit and vegetables in her diet specifically because of the T1D test result but that this had evolved over time into a general concern with healthy eating. Other lifestyle strategies mentioned by parents included encouraging their children to play outdoors, be active, and not watch too much television. These behaviours were also only partly attributable to their child’s T1D risk.

This type of behavioural change clearly links with other domains of family life. In other words limiting the amount of TV one’s child watches may link with parents’ goals for child neurodevelopment, goals for child social interaction and goals around obesity prevention. Several parents in this study appeared keen to adopt what they considered to be potential T1D preventive behaviours when these were congruent with their existing views on how best to facilitate optimum health and development for their child. It is not possible to determine from my data how parents would respond if a prescribed lifestyle measure did not fit with their existing views of what may be good for their child, but it is likely that the level of incentive for behaviour change would be lower.

### **7.5.3 Specific behavioural changes**

I have so far discussed monitoring behaviour, and general lifestyle changes that may, in part, be related to T1D risk. However, three parents reported behaving differently or making

specific practical changes in their child's life at least largely, or possibly entirely, because of the risk of T1D. For two mothers this involved additional contact with health professionals. One mother telephoned a Plunket (Community Child Health) Nurse out of hours to discuss her wish to start supplementing breast-feeding with milk formula. She wanted to do this because she felt it would help make the child more settled at nighttime but was concerned that this strategy would impact on the child's risk of T1D. She recalled asking the nurse very specific questions about what type of formula e.g. soy milk or cow's milk would be best for her child in view of the genetic test result, and also that the nurse "was very patient and listened to me and said it was my choice." (9Carl2yr3M)

The other mother reported seeing her GP on several occasions when her child was very young, with concern about T1D being a significant motivator for the visits. For example, she relayed this account of part of one of her consultations with the doctor:

"I said to him, what about this drinking because he drinks a lot? And he said, you are worried about diabetes aren't you? And I said, yes, well I am not worried about it but I just want to know what you think about it, and he said, if any of your children were getting diabetes they would get very sick very quick so don't worry about it, so I was quite happy about that." (4Anna2yr9M)

I mentioned previously in the section on emotional reaction that individuals with a "monitoring" type coping style might be more demanding of medical services, wanting more tests and information, perhaps as a way of reducing their uncertainty and promoting feelings of reassurance [318]. The accounts I have included here, both come from parents who could be described as fitting into this coping style category, although Anna's mother also had an underlying diagnosis of PND. My data therefore provides supporting evidence for the theory that there is potential for increased use of medical services in relation to newborn genetic susceptibility testing, and that this may be more likely in those with particular coping styles or underlying psychopathology. The consultations mentioned above may have been difficult for the health practitioners involved, and occurred even in the context of a research study, supported by medical personnel and information resources.

In addition to these contacts with health practitioners there were also two other examples of specific practical changes in relation to the T1D test result. One of these involved Carl's mother whose phone call to the Plunket nurse is documented above. She eventually decided to introduce a small amount of cows milk formula at night but also made a conscious decision to continue breast feeding until 11 months (longer than she had anticipated) specifically because she perceived this to be beneficial in terms of his risk of T1D. This same mother also reported

significant concerns about her inability to achieve what she considered to be a healthy diet for her son, as he got older:

“He is a shocking eater, to get anything nutritious in to him in the day is a nightmare and I am quite aware of that as well... He eats sometimes spaghetti, but to actually get him to eat meat and regular vegetables ... and I often think is that going to have an influence later as to whether he actually does develop diabetes. The thing is there is absolutely nothing I can do to make him eat it, you can't jam it down their throat and things he used to eat he won't eat now, and that side of it, I think that dietary thing could have an influence later but at the moment I have no control over it. I can't negotiate with him, he is too little and if he shuts his mouth then you can't do anything about it.” (9Carl2yr3M)

This quote suggests that there may be considerable difficulty in applying interventions to young children, with potential for guilt and anxiety among parents who experience such difficulties. These issues may be particularly true for dietary interventions, as nutrition in early childhood involves not only food but a complex array of psychosocial and developmental issues [320]. There is existing evidence from predictive genetic testing for other conditions, such as the familial cardiac arrhythmia disorder, long QT syndrome, that parents' prolonged distress about their child's risk of sudden death is compounded by difficulties in complying with behavioural restrictions such as “avoiding mental stress, physical exhaustion by sports or work, and also avoiding loud noises” [321].

The final example of a specific change related to the risk of T1D involved a mother who gave her son Vitadol C (a readily available over the counter mixture of vitamins A, C and D) during the Winter months. This mother, a nurse, was aware of a hypothesis suggesting that high rates of T1D in New Zealand could be explained by a relative deficiency of vitamin D in children, as a consequence of the small amounts of vitamin D produced in the skin during the winter months and that it has been postulated that vitamin D supplementation in early childhood may offer protection against the development of T1D [322].

#### **7.5.4 Summary of behaviour changes**

In this section I have described the type of behaviour changes parents in this study made in relation to knowledge of their child's genetic risk of T1D. The most common type of change involved strategies aimed at “a generally healthy lifestyle”. Other than this most parents seemed to make a conscious decision to put the knowledge to the back of their minds and did not report making any behavioural changes in the context of this study in which none were advised. However, a subset of parents reported monitoring their children more closely,

particularly during illness, and some made additional contacts with health professionals. Two parents made specific practical changes, one involving duration of breastfeeding and the other vitamin supplementation.

These findings may be interpreted in contrasting ways. With the eventual aim of providing genetic risk information being to motivate risk reducing behaviour change [2] the fact that many parents are apparently amenable to lifestyle interventions, at least if these are congruent with their existing beliefs about health and development, is reassuring. Nevertheless, the data also highlights the fact that parents are likely to search for interventions that may help their child even when informed that none are advised. These parents may be highly susceptible to marketing of unproven interventions, and could inadvertently adopt harmful measures.

However, perhaps the most significant potential for harm is at a public health level, from the overuse of existing medical services in relation to this type of testing. My data suggests that this may occur in relation to particular parental coping styles and may also be more likely in women with PND. The latter is supported by previous research documenting significant positive relationships between maternal depression and paediatric health care use[323], and as discussed earlier in this chapter the prevalence of PND[301] could make this an issue of some public health importance.

So far in this chapter I have discussed parents' emotional and cognitive reactions to genetic risk information concerning their child, and their behavioural responses. I have considered each of these reactions in turn and in relative isolation. This is a useful strategy in terms of unpicking the fine detail relating to each of these components but it does not necessarily reflect the true complexity of the real life situation. Other authors have noted the relevance of theories about how individuals respond to health threats, and theories about why individuals perform certain health behaviours, to genetic testing research [324]. Therefore, in the final part of this chapter I draw on a theoretical model of health beliefs and behaviour to try to further advance our conceptualisation of the processes involved when parents are presented with genetic susceptibility test results concerning their child.

## **7.6 The common sense model of self regulation of health and illness (CSM)**

There are several theoretical models concerning health beliefs and behaviour, but the data I gathered during my interviews appears to fit most naturally with the CSM. This model is used widely to aid understanding of responses to illness[325] and it has recently been suggested that it is most consistent with the process of genetic counselling[324, 326]. I have therefore

used the CSM as a framework for examining some of the more complex features of parents' reactions to genetic susceptibility testing for T1D.

According to the CSM illness representations, defined as peoples' perceptions of and beliefs about an illness are important mediators between health threats and reactions to them[327, 328, 329]. The theory delineates five core domains of illness representations: *identity* (the 'label' and identifying symptoms), *cause* (e.g. infection, genetics), *consequences* (e.g. activity limitations, pain), *timeline* (e.g. acute, fluctuating, progressing), and *cure/control* (possibility of prevention or cure)[330, 331]. These representations are described as dynamic and changing and may originate from a variety of sources including personal experience, family and cultural values and media reports[326].

According to the CSM an individual's illness representation then guides their identification and use of procedures (or behaviours) for controlling the threat. In the context of the CSM this is articulated as the use of "if-then" contingency rules. For example "*if* obesity is caused by overeating and underactivity *then* diet and exercise will result in weight reduction." The success of these procedures is appraised and feeds back to influence both the representation of the threat and the coping procedures.

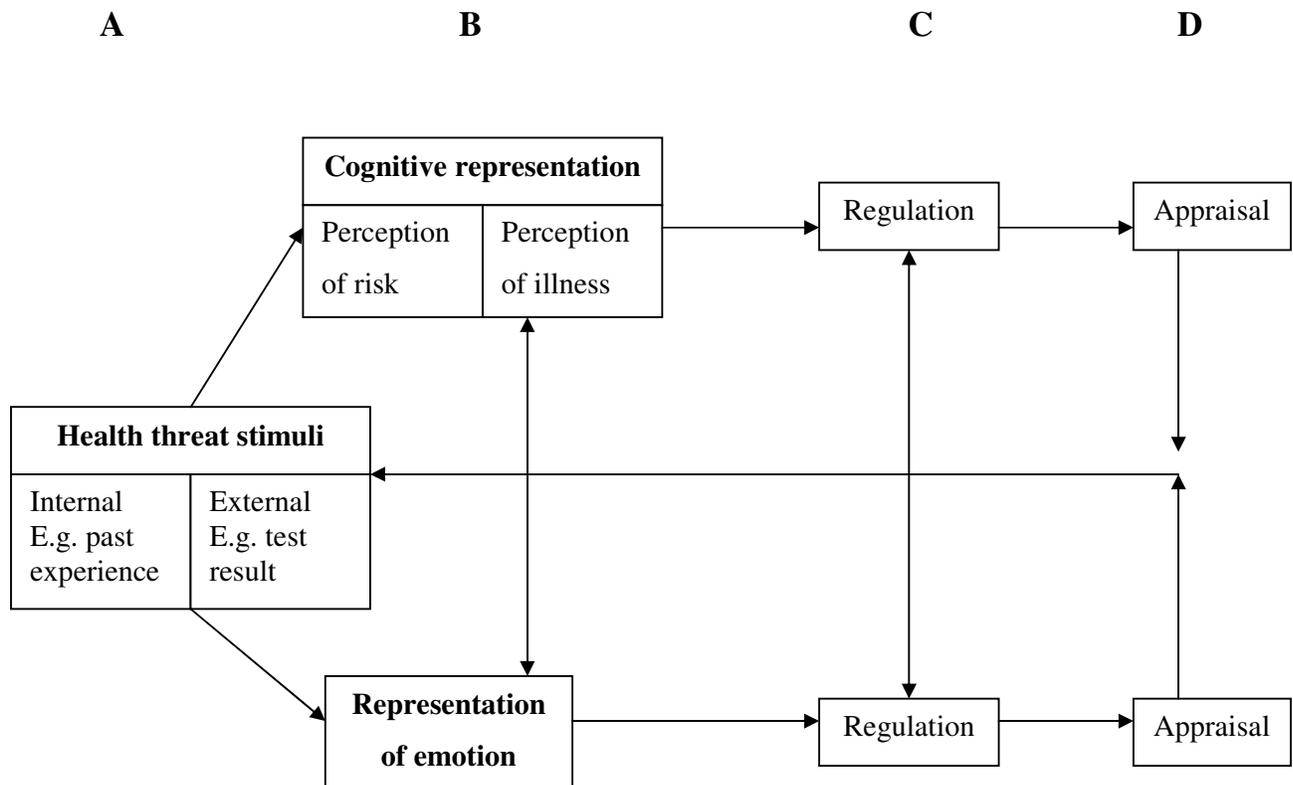
At the same time, both the health risk information itself and its cognitive representation activate an emotional response, most commonly fear-related responses such as worry and anxiety[325]. These cognitive and emotional processes operate in parallel and are partially independent in that they may activate either the same, or contrasting behaviours[332].

The process articulated in the CSM is clearly one of some complexity but at its core lies a simple, "common-sense" idea: how a person perceives and interprets health information, in combination with the emotional response this provokes, determines what action the person takes. This process is depicted in figure 7.1

The CSM is typically related to adults experiencing and reacting to illness themselves. It has rarely been utilised to discuss parental health-care decision-making in relation to their child[323], but because the parents in my study so clearly described both an affective and cognitive component of their reaction to the genetic risk information I have chosen to employ this model to illuminate further discussion. Similarly the model is usually applied in relation to existing symptoms or illness although it has recently been suggested that "risk" in general and genetic risk in particular could be included within this framework [325, 332]. In the next section I will begin by discussing how my interview data fits with existing knowledge of the CSM and will then highlight some areas where there is less certainty about how the CSM relates to newborn genetic susceptibility testing.

**Figure 7.1: The common sense model of the self-regulation of health and illness adapted to incorporate response to genetic risk information.**

(This diagram is an adaptation of a similar figure from Marteau, T and Weinman, J[325])



### 7.6.1 My interview data and the CSM

I have already discussed in some detail the different elements of parents' reactions to newborn genetic susceptibility testing for T1D. In this section, I will concentrate on how the CSM can help us to view the process more holistically, and in particular to note its complexity and dynamic nature. I will also allude to some issues that require further consideration.

#### 7.6.1.1. Section A: health threat stimuli

In the CSM health threat stimuli (A) are depicted as being both external and internal. This means it is not simply the T1D genetic test result that matters, but also many other personal and contextual factors such as parents' previous experiences. This combination of stimuli, that is clearly likely to vary between parents, then leads to the formation of both cognitive and emotional representations of the child's risk of T1D.

### 7.6.1.2. Section B: cognitive and emotional representations

Again, these representations (B) are likely to vary between individuals based on both personal and contextual factors. While it is possible to describe the emotional and cognitive reactions separately the processes by which parents formulate each representation appear to be closely entwined. For example, in my study, it appears that the initial emotional reaction plays a useful role in that it may act as a trigger that encourages parents to contemplate the cognitive aspects of their reaction. Both the CSM and my data suggest that while the cognitive and emotional processes appear to occur in parallel, the relative importance of each fluctuates over time, and each may affect the other [327, 330].

This continual activity of, and interaction between, the emotional and cognitive processes depicted in the CSM has been characterised as “the dance between affect and reason” [333]. However, despite this vivid depiction, the precise role of emotional processes in decision making and risk perception is much less well researched than that of cognitive processes [325, 334, 335]. In the existing literature affective reactions to genetic testing are most commonly researched and discussed in isolation from the other components of the response described in the CSM [302]. The aim of such studies appears to be to demonstrate a lack of clinically significant psychological distress in response to genetic testing, or to suggest ways that counselling may minimise participants distress [302]. These are clearly issues of some importance, but undue emphasis on such aspects of the emotional response may miss the point that some degree of negative affective reaction can play an important and ongoing role in peoples’ adaptive responses to predictive genetic information.

Although the potential importance of affective reactions has been relatively neglected in relation to predictive genetic testing there is some evidence from research into existing illnesses to suggest that emotion does play a useful role in illness representation and behaviour. For example, in adults, anxiety and worry have been shown to influence cognitive risk representations, by aiding the development of more extensive and detailed risk representations. Similarly anxiety or worry have also been shown to be strong motivational influences on behaviour [332].

The importance of affect is also being recognised increasingly by decision researchers who have suggested that affective reactions to stimuli are often the very first reactions, occurring automatically and subsequently guiding information processing and judgment. In other words affective reactions may serve as orienting mechanisms, helping people to navigate quickly and efficiently through a complex and uncertain world [334].

Conversely, other research has shown that mothers’ emotional reactions to their child’s symptoms may prompt and maintain additional paediatric health care use through a desire to

alleviate worry[323], and I have noted examples of this type of behaviour within my data. Thus there is evidence for both beneficial and detrimental effects of anxiety, or negative affect, in relation to illness behaviour. To further complicate matters I have discussed previously in this chapter that not only are affective reactions dynamic but there are also significant differences in the ways in which individual parents cope with their emotional reaction to their child's risk, based on both personal factors such as coping style and contextual factors, such as experience of the disease.

We are currently unaware of the precise nature or level of parental negative affect that may play a useful part in an adaptive response, and what may be harmful. The dynamic nature of the response and inter-individual variation make the issue one of some complexity, but given the centrality of emotional processes in response to genetic risk information I agree with others who suggest an urgent need for further theoretical and empirical research in this area[325].

The precise mapping of genetic risk perception within the CSM also requires further theoretical and empirical work[325, 332]. In my study parents clearly described threat representation in two distinct elements, firstly, their perception of genetic risk and secondly their perception of T1D itself. Perception of risk of T1D therefore appears to be a distinct domain that can influence, or be influenced by, the other five illness content domains described in the CSM (*identity, cause, consequences, timeline, and cure/control*). However, while these elements were separated in discussions they were also quite clearly connected, and it was a combination of the 2 that parents employed in processes where they compared their child's risk of T1D with other illnesses or situations. Hence, in my schematic representation of CSM, risk and illness perception are separated, but juxtaposed. (B) Evidence from my interviews, as well as other sources [336], suggests that risk perception is even more prone to inter and intra-individual variation than other aspects of illness representation. In particular, I highlighted the fact that on detailed analysis there was considerable variation between parents when it came to interpreting their child's genetic risk of T1D. I also noted that although nearly all of the parents in my study used comparison processes to contextualise their child's risk, the illnesses or situations they employed were diverse, presumably leading to subtle differences in risk perception. In other words interpretation of the risk of T1D varies between individuals based on personal factors such as "cognitive style" [337] and also with family and social context. Finally, my data shows that risk perception fluctuates over time for many parents. Risk information is not simply perceived and archived; rather it is actively processed by individuals and families[286].

In addition to the variation in parental perception of risk described above there are also ways in which actual risk may vary over time in the context of genetic susceptibility testing in childhood. For example, reported risk statistics may alter as scientific knowledge evolves; levels of risk may change as environmental exposure occurs during childhood and results from disease surveillance such as measurement of autoantibodies may alter a child's individual risk.

The dynamic nature of risk perception, inter-individual variation and variation in actual risk make this an issue of some complexity. It is also of considerable importance in the context of genetic susceptibility testing as there is clearly a relationship between risk perception and motivation for behaviour change[332]. The precise nature of this relationship requires further theoretical and empirical research.

### **7.6.1.3. Sections C and D: regulatory behaviours and their appraisal**

The emotional and cognitive elements of parents' reactions are only partially independent and may serve to motivate the same behaviours, such as contact with health professionals, or they may motivate contrasting behaviours. The outcomes of whatever process parents use to regulate, or cope with, these two aspects of their response then feedback to update their representation of their child's T1D risk (D). For example, for a parent who had decided that they would cope with the risk of T1D by not worrying about it they may be reassured by objective evidence of their child's good health. This process of regulation and appraisal, described as "if-then contingency rules" in the CSM, can, once again, be described as complex, dynamic and likely to vary between parents.

The "if-then" contingency rules articulated in the CSM are really mechanisms by which threat representation, behaviour and appraisal are linked. However, the nature of genetic susceptibility testing for conditions such as T1D means that even if a behavioural strategy exists that is known to be effective in reducing risk there may be no objective changes in health status when this is applied. There are no symptoms to treat, and no signs, such as weight loss to measure, simply an abstract reduction in risk. It may be difficult for parents to continue with a prescribed behaviour change in the absence of any objective motivation to do so. By applying the CSM to my data, I have articulated what may be a particularly important issue for future genetic susceptibility testing programmes. Future research, in situations where behaviour change is prescribed, should assess the veracity of this theory and what additional motivational techniques may be required.

#### **7.6.1.4. The context of genetic susceptibility testing**

In view of the fact that the children tested as part of this study were very young I have concentrated my discussion predominantly on parents' psychological reactions and behaviours. I have spent some time discussing how complex and dynamic these reactions can be, but it is also necessary to remember that the context in which they are occurring is also highly dynamic. In other words, childhood itself is a dynamic process. By this I mean that childhood is a period of very rapid physical and neurodevelopmental change and any parental reaction must be superimposed on yet another complex process. Just as the dynamic nature of risk perception may influence parental behaviour so too may the rapid changes that occur throughout childhood. Rapid changes in a child's physical and neurodevelopmental parameters could lead either to unnecessary concern that illness is imminent or false reassurance that the intervention is effective. For example, parents could be concerned by typical periods of rapid weight gain, or falsely reassured that acquisition of motor milestones reflects underlying good health.

### **7.7 Summary and limitations**

At present our understanding of parents' reactions to newborn genetic susceptibility testing, as well as the processes by which DNA risk information may motivate behaviour change are poorly described. By closely examining parents' reactions to testing for susceptibility to T1D, in conjunction with a model from health psychology, I have provided some of this much-needed data.

Using this approach, it is apparent that parents' responses to a positive NBS test for genetic susceptibility to T1D are quite different to those described in relation to positive results in most existing NBS programmes. They do however share certain features of parents reactions to the very small number of ambiguous results generated through CF screening programmes and the transient phase of waiting for sweat test results to confirm or rule out a diagnosis of CF. Both these differences, and similarities, appear to centre on the probabilistic nature, or *uncertainty* associated with the test result. In relation to NBS for genetic susceptibility to T1D, this uncertainty impacts significantly upon all aspects of parents' psychosocial reactions.

While parents generally reported fairly minor levels of concern in response to news of their child's increased risk, these concerns frequently recurred, being dynamic and variable. My interview data suggest that the intensity and duration of these reactions is affected by personal factors such as coping style and underlying psychopathology, as well as contextual factors such as study visits. Parents' perceptions of their child's risk also varied and fluctuated over

time, contributing to variation in behavioural responses such as monitoring of the child's health, or changes in health related behaviour.

Overall, parents' responses to positive results in NBS for genetic susceptibility to T1D are more complex, dynamic and variable than those described in relation to other NBS programmes, with individual factors being important determinants of reaction type and subsequent behaviour. When parents reactions are superimposed upon the highly dynamic context of childhood the process resembles a complex web, with potential for multiple and varied interactions between the different elements. This level of complexity both within individual parents' reactions and in terms of inter-individual variation has considerable implications for both future research and clinical practice.

The data I have presented in this chapter is rich in detail and provides a useful framework for conceptualising the issues at hand. However, the findings I have reported are based on an interpretative analysis of interviews with a small number of participants, who may differ from others undergoing similar testing. As is usual with IPA methodology the group of participants in this study was relatively homogenous and in particular they all share a similar cultural context. The study would need to be repeated within different cultural contexts before more general claims could be considered.

While I made every attempt to use an open questioning technique and to "look at each interview afresh, and in particular keep coding emergent from the interview text" [60] it is also possible that the findings reflect my interests rather than those of the participants, due both to the type of questioning and my interpretation of the data. There is therefore a need for my findings to be replicated, and extended by other researchers.

In addition my use of the CSM to further conceptualise parents' responses has both strengths and weaknesses. Strengths of the model include its ability to assist in articulation of the complexity of psychological responses to health threats, and to comment on reasons underlying differences in reactions between parents (for example that illness representations are dependant upon a wide variety of factors, including social context). Weaknesses include that the CSM does not significantly account for factors outside of a narrow health domain that may affect behaviours. For example, parents' responses may equally be affected by time constraints, financial issues and social acceptability. This may be particularly relevant when the health threat is a disease risk that, as I have described, is likely to be perceived in a highly dynamic, context dependant and individualised fashion.

## **Chapter 8    Conclusions**

## **8.1 Introduction**

In this final chapter I bring together literature related to NBS and genomic medicine with my own empirical research findings, in order to draw conclusions about future research and clinical practice related to genetic susceptibility testing. On examining what is known about the harms and benefits of such testing I conclude that it does not currently fit within a NBS paradigm but the potential for development of tests and interventions with greater utility should not be underestimated. I begin with a brief reminder of the major conclusions contained within the previous seven chapters.

## **8.2 Summation**

Ever since NBS began in the 1960s there has been debate regarding the addition of new disorders to screening panels. For many years these discussions occurred relatively infrequently, and involved consideration of the harms and benefits of adding a single new disorder, such as CF, to panels. More recently the pace of change in NBS has increased dramatically and, in particular, the adoption of tandem mass spectrometry by NBS programmes across the developed world means that many countries now screen for panels of 20 to 30 metabolic disorders. This technological change, as well as accompanying alterations in how the underlying aims of NBS are considered[47], have added to increasing speculation that genomic profiling will eventually become part of NBS[2, 19].

As these changes have been occurring there has also been a resurgence of interest in the psychosocial aspects of NBS, but although good data is beginning to emerge in relation to multiplex testing for metabolic disorders[225], debate concerning psychosocial effects of screening for genetic susceptibility to multifactorial conditions remains largely speculative. In this thesis I have argued that multifactorial disorders such as T1D differ in important ways from conditions currently included in NBS panels, and the lack of evidence concerning psychosocial effects is a significant barrier to advances in the debate around the inclusion of such tests in a NBS paradigm. The studies reported in this thesis represent my response to this gap in our knowledge: I have provided empirical evidence regarding maternal psychosocial responses to NBS for genetic susceptibility to complex disorders, using T1D as a paradigmatic example.

## **8.3 Key findings**

Here I describe the key findings of my empirical research, starting with my quantitative data and moving on to parents' qualitative accounts of their experiences of newborn genetic susceptibility screening for T1D.

### **8.3.1 Quantitative data**

#### **8.3.1.1. Standardised questionnaire data**

In the study reported in this thesis I found that mothers who were informed that their baby was at increased genetic risk for T1D did not experience adverse psychological effects compared to control mothers when assessed on three different psychological rating scales, measuring anxiety, depression and perception of child vulnerability up to 1 year after birth. My findings, relating to anxiety and depression, have recently been replicated in other similar studies [247, 249, 250, 252]. In addition, data from these reports also suggest that women in certain subgroups, such as those of ethnic minority status or with postnatal depression, may experience more difficult psychological responses to news of their infant's increased genetic risk of T1D [249, 250].

#### **8.3.1.2. Subjective assessments of concern about T1D susceptibility**

Despite this reassuring data, when asked to rate their own degree of concern about their baby's genetic risk of T1D, mothers of babies at increased risk reported significantly higher levels than mothers of babies with low genetic risk. In many ways, these are not surprising results as it seems unrealistic to think that there will be no difference in psychological reaction between mothers of genetically susceptible or low-risk infants. However, it currently remains unclear what degree of parental concern may be appropriate in such a situation.

#### **8.3.1.3. Maternal perception of infant's risk of developing T1D**

The majority of mothers in this study evaluated their infant's risk of developing T1D correctly (between 87 and 92% at 16 weeks and 1 year). However, the risk categories used to test mothers' risk perception were broad, so that within each category there would likely be a range of maternal understanding. Despite the broad categories, some mothers did underestimate or overestimate their child's risk: in the increased risk group, 3 mothers underestimated the risk, and 1 mother overestimated, thinking that her infant would definitely develop diabetes. In the low-risk group, several mothers were falsely reassured that their infant was at no risk of T1D.

### **8.3.2 Qualitative data**

By closely examining parents' reactions to testing for susceptibility to T1D, in conjunction with a theoretical model from health psychology, I have provided much-needed detail concerning the nature of parents' psychosocial responses.

### **8.3.2.1. Overall response**

Parents' reactions to a positive NBS test for genetic susceptibility to T1D are complex, dynamic and variable. When these reactions are superimposed on the highly dynamic context of childhood, they resemble a complex web, with potential for multiple and varied interactions between their affective, cognitive and behavioural components. In particular, parents' responses to a positive NBS test for genetic susceptibility to T1D appear to be quite different from those described in relation to positive results in most existing NBS programmes. These differences appear to be primarily related to the probabilistic nature, or uncertainty associated with a "positive" result, that impacts significantly upon all aspects of parents' psychosocial reactions.

### **8.3.2.2. Emotional response**

My qualitative data support my quantitative findings in that the majority of parents experienced a relatively mild emotional reaction to NBS for genetic susceptibility to T1D. However, their concerns frequently fluctuated and recurred over time. My interview data suggest that while the uncertainty associated with a positive result may have minimised parental distress, it may also be implicated in the ongoing and dynamic nature of their concerns, and in the considerable inter-individual variability. The intensity and duration of parents' affective reactions also appeared to be affected by personal factors, such as coping style and underlying psychopathology, as well as contextual factors such as routine disease surveillance visits.

### **8.3.2.3. Cognitive and behavioural response**

My interview data has highlighted the ability of parents to retain relatively complex ideas concerning the multifactorial aetiology of T1D. It has also demonstrated the dynamic nature and inter-individual variability of parents' perceptions of risk in relation to NBS for genetic susceptibility to T1D. Parents in this study appeared to fall into two categories: those who minimised their child's genetic risk, or put it to the back of their minds, and those who actively used the information to observe and monitor their child. "Monitors" responded to concern generated by increased risk perception by changing health-related behaviours, and being more demanding of medical services, perhaps as a way of reducing their uncertainty and promoting feelings of reassurance[318].

## **8.4 Summary of empirical findings**

The psychological questionnaires used in this study represent a useful way of assessing reactions to genetic-risk information and allow me to state that in a general population clinically significant psychological disturbance is unlikely to occur as a result of NBS for genetic susceptibility to T1D. However, while in some ways it is reassuring that parents do not generally appear unduly distressed by their child's positive result, the implications of the more subtle, complex and ongoing reactions described in my qualitative study are currently not fully understood.

## **8.5 New hypotheses**

While this analysis provides clear empirical data that begins to fill the knowledge gap that existed in terms of psychosocial reactions to NBS for genetic susceptibility, it also raises new questions. This is particularly true of the qualitative component of my research where the aim was to describe parental responses to NBS for genetic susceptibility to T1D and to develop new hypotheses rather than test pre-existing ones[262].

### **8.5.1 Hypothesis 1**

*Certain subgroups of parents may experience more significant distress following NBS for genetic susceptibility to T1D.*

While my data suggests that NBS for genetic susceptibility to T1D is unlikely to result in significant short-term psychological harm at a population level some subgroups may be adversely affected. These groups may include mothers with postnatal depression (PND)[250], and other researchers have suggested that mothers from certain ethnic minority groups may also be affected in this way[249]. This finding has important implications for culturally diverse population such as that in New Zealand. In some instances these subgroups may be numerically important, for example it is estimated that about 10% of women suffer from PND[301]. The implications of these potentially heightened degrees of distress for parents, parent-child interaction, child development and the public health system are currently unclear and merit further examination.

### **8.5.2 Hypothesis 2**

*Individual differences, such as coping style, are significant contributors to variation in parental response to NBS for genetic susceptibility to T1D and may lead to the balance of benefits and harms varying significantly between different parents/children.*

This hypothesis relates to the suggestions from my data that individual differences, such as coping style, affect parental response to the uncertainty associated with a positive result in NBS for genetic susceptibility to T1D. Without modification these differences may lead to significant variation in the balance of benefits and harms between different parents/children, representing a challenge for incorporating such testing in a clinical setting. Further research aimed at describing what we may consider to be the most appropriate type of parental reaction, and the extent to which responses are modifiable is required to address these issues.

### **8.5.3 Hypothesis 3**

*Subtle but ongoing alterations to the parent-child dynamic may have significant implications for children, families and public health.*

My qualitative data demonstrates that subtle parental responses, while remaining subclinical in the sense that they are not detected through standard rating scales, nevertheless involve elements of anxiety and distress. Given what we understand regarding the sensitivity and importance of early childhood experience it is likely that recurrent, albeit minor parental concerns about a child's health, particularly if accompanied by "monitoring" or other changes in health behaviour, will have some impact upon the parent-child relationship and individual child development, as well as the public health system. It remains possible that for some parents/children these effects may ultimately be harmful. This hypothesis should be addressed through further empirical analysis of parental reactions and of the impact upon the child as they get older.

### **8.5.4 Hypothesis 4**

*Parental responses that include psychological risk minimisation strategies may avoid the potential harms alluded to above, but they may also preclude expected benefits.*

For example, very minor degrees of concern generated by a positive result may be insufficient to assist parents with early disease recognition or to motivate any parental behaviour change that may ultimately be prescribed. This hypothesis may also be addressed with further empirical research concerning the behavioural implications of different parental reactions.

In the next section I take these key findings and hypotheses and consider the implications they have firstly for the future research agenda, secondly for the bioethical debate and finally for clinical practice.

## **8.6 Implications for future research**

### **8.6.1 General research requirements**

While there have been considerable recent advances regarding knowledge of gene – disease associations and understanding of disease pathogenesis, the debate concerning whether and when genomic discovery will yield tangible public health and clinical benefits at costs society can afford continues[5]. Deciding when to commit contestable research funds to investigation of the clinical implications of such gene-disease associations is not a straightforward process. However, I agree with others who suggest that a considerable research commitment should be made now in order to bridge the rapidly widening gap between scientific research and the “translational research” needed to assess the potential health benefits of genetic susceptibility testing[338]. If translational research, including analysis of psychosocial effects, lags too far behind basic scientific discoveries, harmful effects may occur if the powerful “push“ of scientific discovery and “pull” of the direct to consumer market lead to overly hasty introduction of such testing, without the mediating presence of a translational evidence base[5, 338].

Given the remarkable pace of genomic discoveries, and the need to institute psychosocial research protocols as soon as possible, some such research, including that which I have presented in this thesis, may not incorporate the full set of genetic markers that are envisioned for future use. It will instead feature tests for single or multiple disorders that are the subject of longitudinal studies, such as the KEA study, that display important characteristics of future tests. In this case I have noted that features of T1D, such as its prevalence, potential for prevention and seriousness of its complications both at an individual and population level, as well as features of the T1D genetic susceptibility test, such as the uncertainty associated with a positive result and the potential for those with a negative result to still develop the disease, make it a very useful example of such testing.

Ultimately it will be possible, indeed necessary, for translational research to encompass tests for multiple common disorders, but until then the results of the studies described in this thesis, and other future research can be extrapolated, in a cautious and considered manner, to help inform future clinical practice and public health policy in relation to NBS. In other words the rapid pace of basic scientific discoveries should not be used as an excuse to delay, or fail to utilise, translational research. Rather the two processes should proceed as far as possible in parallel with each informing the other. Such research is crucial not only to answer questions regarding the balance of benefits and risks but also in terms of defining the type of supportive

infrastructure that may be necessary if testing is to become part of clinical practice. In other words it is an ethical imperative.

In general terms research aimed at assessing the psychosocial and public health implications, and clinical utility of genetic susceptibility testing must be multifaceted. By this I mean that it will necessarily involve multidisciplinary teams, multi-modal measurement techniques and multiple different studies, as no single project can answer such complex questions[5].

Fortuitously, these general requirements can be met within the designs of some of the newer genomic studies that reflect an appreciation of the deepening complexity of genetic influences on common diseases. While GWAS have been the traditional means of evaluating associations between genes and disease and are likely to persist, future studies will likely involve even larger consortia and multilevel designs that aim to understand how environmental exposures and different types of genetic variation interact to cause disease[339]. Within such studies it will be necessary to evaluate many different potential components of disease pathways including biological factors, social and cultural contexts and environmental influences. They will therefore require multidisciplinary input (including for example basic scientists, epidemiologists, primary care clinicians, geneticists, paediatricians, social scientists, psychologists, ethicists and health service researchers) from the outset. While these new types of study will be costly and complex to oversee they may serve to facilitate a renewed appreciation of the importance of psychosocial reactions, both as potential contributors to disease pathogenesis and as factors that directly affect the utility and ethical acceptability of genetic susceptibility tests.

Collecting data relating to these widely differing aspect of people's lives will be challenging and already innovative techniques are under development, such as wearable biosensors to measure physiological responses, wireless skin patch sensors for stress and GPS based devices that will enable precise assessment of environmental exposures in natural settings [340]. Many of these innovative methods will provide valuable data for psychosocial research, although incorporation of valid psychological measures will also continue to be necessary. This complex research, that in part addresses ethical and psychosocial issues, must itself acknowledge important ethical principles and appropriately respect human rights, particularly when it involves children or those of ethnic minority status[341]. The general requirements I have articulated here highlight the need for a large scale, coordinated approach to the evaluation of genetic susceptibility tests, including psychosocial reactions. It is beyond the scope of this thesis to describe in detail all elements of this process but I will now provide more information on how I consider the investigation of the new hypotheses I have developed should proceed.

### **8.6.1.1. Hypothesis 1: Subgroup analysis**

The suggestion that some subgroups of women such as those with PND or of ethnic minority status experience more difficult reactions to news of their newborn's increased genetic risk of T1D requires further analysis. This will be particularly important in culturally diverse countries such as New Zealand, where for example the social and cultural contexts of the Maori or Asian populations may contribute to greater diversity of reactions. Quantitative studies with large cohorts, including parents of low risk control babies, will be required to enable detailed analysis of subgroups. These studies should carefully evaluate women for PND, and should employ well-validated psychometric measures such as the EPDS[271], the Center for Epidemiologic Studies–Depression Scale (CES-D)[342] and the STAI[270]. Study designs should be longitudinal, and other potential contributing factors, such as understanding of disease risk, including the relevance of cultural views on genetics and technology, and socio-demographic factors, should also be measured. Statistical analysis must employ techniques such as mixed effect regression models that account for analysis of repeated measures. Finally the implications of such responses upon the public health system should be assessed through, for example, analysis of numbers of consultations with child health providers and numbers of days absent from school and work.

### **8.6.1.2. Hypothesis 2: Further characterisation of parental response including factors underlying inter-individual variation**

My qualitative study has provided preliminary evidence concerning the complexity of parents' reactions. Many aspects of these reactions require further exploration but in particular the pivotal role of parents' emotional responses; factors underlying inter-individual variation in risk perception; and the effects of uncertainty should be further examined. This will require a combination of theoretical and empirical research[325].

Theoretical work will require consideration of psychological models, such as the CSM, and should include consideration of how recurrent but mild negative emotions impact upon cognitive and behavioural responses. In addition the precise mapping of uncertainty or probabilistic genetic test results within the CSM requires further analysis[325, 332].

In terms of empirical research my data suggests the need for longitudinal research designs with multiple measurement points to account for the dynamic nature of parents' responses. Quantitative elements of these studies will need to employ multimodal measurement approaches in order to fully understand the interactions between affective reaction, cognitive reaction (including risk perception) and behaviour. The active nature of these processes is unlikely to be entirely captured by traditional methods such as standard questionnaires and

rating scales, although analysis of parental coping style utilising measures such as the 32 item Miller Behavioural Style Scale[319, 343] would certainly be useful. Rather a combination of approaches will be required, that may also include physiological measures and measures of behaviour. It may also be necessary to develop new psychometrically sound measures to evaluate parents' attitudes and behaviours relating to genetic susceptibility tests[344].

Empirical research should also include qualitative studies, designed to further explore the role of parents affective responses; how parents interpret risk and how this may evolve over time; what factors underlie variation in emotional reaction and risk perception; and what strategies may assist parents to correctly interpret risk. Again these studies should attempt to include participants of different ethnicities, including those from Maori, Pacific and Asian populations.

### **8.6.1.3. Hypothesis 3: Implications of ongoing subtle parental responses**

Longer term studies of parent-child relationships in the context of NBS for genetic susceptibility to common disease are required. Such studies should include previously validated measures such as the Vulnerable Child Scale, that is useful in studies involving children beyond infancy[53], but there is also an urgent need to include children themselves in this research. Initially this could involve quantitative assessments of behaviour using measures such as the Child Behaviour Checklist, of which there are two versions, one for children ages 1.5–5 years and another for ages 6–18 years[345]. This measure includes assessments of levels of anxiety and depression, attention problems, social problems and somatic complaints. The State-Trait Anxiety Inventory for Children (STAIC)[346] may also be useful in this situation as it distinguishes between a general proneness to anxious behavior and more transient responses[346].

Qualitative studies involving children should also address some of the underlying ethical concerns regarding the impact of genetic test results upon young children. These include issues such as alteration of the child's sense of self, the impact (if any) upon their life plans or other aspects of autonomy, levels of worry and whether or not the child would have preferred not to know the test results. Many of these issues are affected by social and cultural context. For example in some cultures parenting is not focussed around the single mother-child pairing I have primarily considered in this thesis, and views regarding a child's autonomy may differ from those I have portrayed here[347]. These alternative viewpoints should be included in future research. Again, public health implications should also be included through, for example, case control studies involving prospective assessment of healthcare use and days absent from school.

#### **8.6.1.4. Hypothesis 4: Investigations of utility**

Much of the work within this thesis involves assessment of the potential negative psychosocial implications of NBS for genetic susceptibility to T1D. However, the qualitative data also raises questions about what action, if any, parents may take as a consequence of a positive result, and as such addresses the likelihood of potential benefits being achieved. Future research regarding maximising benefits of NBS for genetic susceptibility to common disorders should focus firstly on how information regarding testing can be conveyed to parents in a way that enables them to make choices appropriate to their own family circumstances. Subsequently, the best means of providing ongoing assistance regarding the implications of test results for children's health, and appropriate use of available health resources will be important[348].

The communication aspects of this research may involve assessment of various different systems and tools such as web and print-based resources, and numeric or descriptive modes of oral risk communication[55]. Careful analysis of demographic factors will also be important as the most appropriate methods of conveying information may vary with factors such as age, ethnicity, geographic location, and literacy level [338].

Psychological research should incorporate both quantitative and qualitative studies to elucidate how the “if-then” rules described in the CSM (in chapter 7) operate in relation to genetic risk and behaviour change[325]. These “if-then” rules are really mechanisms by which disease risk, behaviour and appraisal are linked. The nature of genetic susceptibility testing for conditions such as T1D means that even if a behavioural strategy exists that is known to be effective in reducing risk, there may be no objective changes in health status when this is applied. It may therefore prove difficult for parents to continue with a prescribed behaviour change in the absence of any significant motivation to do so. Future research, in situations where behaviour change is prescribed, should assess whether additional motivational techniques, such as the use of concrete, vivid images relating to the risk information may be required[325]. The opportunity genomics may offer for influencing behaviour change within families or other social groups also deserves attention, and the way that genomic risk information is shared within families, as well as the potential for family cooperation in making lifestyle changes, should be assessed[338].

Ultimately research that tests the balance between what can be described as “best practice” for communicating about genetic susceptibility to common disease against what can be effectively integrated into a variety of clinical settings will be required[5]. While this research is important it will also be necessary to reflect upon the underlying aims of NBS for genetic susceptibility to complex disorders, and the degree to which these aims should be pursued.

For example how much responsibility is it appropriate for health care providers to have for maximising parental motivation to adhere to prescribed lifestyle changes, and how appropriate may it be to intervene in parental noncompliance? These are not straightforward issues, rather they depend upon a complex array of factors including personal values concerning the relative importance of health, and the difficulty and compromises involved in implementing measures in the highly dynamic context of early childhood.

### **8.6.2 Crystal ball gazing**

As such translational research progresses, it will be necessary to continually anticipate the directions of genomic discovery, and adapt research programmes appropriately[338]. Recent advances, occurring during the course of the preparation of this thesis, suggest that the speed and extent of such developments should not be underestimated. For example it has become increasingly clear that testing is likely to move away from assessment of single-nucleotide polymorphisms to full-genome sequencing, and that biomarkers based on gene expression, as well as proteomic and epigenetic profiles are likely to be incorporated into disease- risk profiles. It is currently unclear whether such multiplex testing will mitigate or exacerbate the psychosocial issues I have described, and ultimately this will also require empirical analysis. Assuming that translational research can keep pace with these developments then all of the new knowledge pertaining to genomic testing, whether it be basic science or psychosocial data, will need to be synthesised, adapted to a specific context (such as a child's developmental stage) and any barriers to its use evaluated. In this way new knowledge can be used to inform clinical application of genetic susceptibility tests and primary prevention interventions[55].

## **8.7 Implications for the bioethical debate**

It is clear that NBS has recently undergone a period of unprecedented change. These dramatic changes related both to technological advances and to changes in thinking about what we may want from NBS, have important implications for the future of such programmes. As a discipline bioethics need to keep pace with these developments, ensuring that the potential application of new testing paradigms is actively considered as early as possible, and that arguments are appropriately supported by empirical data. In this section I focus on the implications of my empirical data for the ethical debate around NBS for genetic susceptibility to common complex disorders, as well as considering some of the other underlying ethical issues.

### **8.7.1 Balancing harms and benefits**

As discussed in chapter 1, ethical evaluation of genetic testing in children, including NBS, has traditionally been based on the balance of benefits and risks: genetic susceptibility testing in the newborn period is controversial largely because of the potential imbalance between benefits and risks for the child[18]. While the data I have presented in this thesis enables a more detailed analysis of NBS for genetic susceptibility to disorders such as T1D than was previously possible, gaps in our knowledge base remain, as evidenced by the series of new hypotheses and the research agenda I have developed. Here I am concerned with how my data fit into an analysis of harms and benefits.

#### **8.7.1.1. The ethical acceptability of NBS for genetic susceptibility to T1D**

Even in the absence of a full data set concerning the psychosocial implications of NBS for genetic susceptibility to T1D, we now know enough about the current balance of benefits and risks to reach a conclusion concerning its ethical acceptability, albeit in the knowledge that this may require revision once more empirical data accumulates. At present, relatively good predictions of T1D can be obtained by genotyping and measuring auto antibodies, but no preventative measure is available. Most (approximately 90%) of these genetically susceptible children will not develop T1D, and consequently would not benefit even if such a preventative measure was available. However, the minority that are destined to develop T1D do already benefit from early identification and being enrolled in longitudinal studies, showing improved health status at onset of T1D compared with children not involved in these studies[349]. This is presumably related to medical surveillance and the heightened awareness of parents.

These relatively modest benefits, accruing to a minority of children, must be balanced against the potentially harmful psychosocial effects investigated in this thesis that may accrue to any of the families with a child in the increased genetic risk group. Although my quantitative evidence suggests that families generally cope well with T1D genetic-risk information concerning their children, if it is conveyed sensitively, the data also suggests that some subgroups such as women with PND, may suffer significant emotional distress in relation to positive results. Similarly, while some families may perceive benefits to knowledge of their child's increase genetic risk, others may be adversely affected in subtle but ongoing ways. For example it appears that mothers with "monitoring" coping styles may become more concerned about their child's increased risk of T1D, and may respond to this by changing health-related behaviours and making additional contacts with medical services. Current data remains fairly limited both in focus and duration, with the longer-term impact of these more

subtle alterations in parental perception of their child's health status and the potential effects this may have on parenting practices still to be evaluated.

These parental reactions have important implications for individuals and families but significant potential for harm also exists at a public health level, from the overuse of existing medical services by parents of “at risk” children. My data suggests that this may occur in relation to particular parental coping styles, and may also be more likely in women with PND. The latter is supported by previous research documenting significant positive relationships between maternal depression and paediatric health care use[323] and is an issue of some importance given an estimated prevalence of PND of 12-13% [301]

The parental reactions to NBS for genetic susceptibility to T1D that I have described are very different from those described in relation to existing NBS programmes, and also appear to be subject to significant inter-individual variation. This suggests that the current infrastructure surrounding NBS is unlikely to address the needs of the large numbers of parents whose child will have an increased risk result. The absence of such an infrastructure makes it significantly more likely that the impact of the psychosocial reactions I have described is detrimental both for individuals and for the public health system. Consequently addition of such tests to NBS panels is currently ethically unadvisable. Clearly the balance of harms and benefits will shift dramatically if preventative measures are developed, and NBS provides the potential to maximise these benefits across the whole population. However, as with existing NBS programmes, these benefits can only eventuate through the full cooperation of parents, and are likely to be highly contingent on the provision of a suitable supportive infrastructure[36]. Conversely the balance of harms and benefits may shift significantly in the opposite direction if it is determined that children experience psychological difficulties as they themselves learn about their genetic susceptibilities to disease. Future research aimed at addressing the remaining gaps in or knowledge concerning parental reactions and direct impacts upon children, as well as at determining *how* such screening could be broadly facilitated in populations with varying underlying psychopathology and coping mechanisms is of considerable importance.

#### **8.7.1.2. Complexities in the analysis of harms and benefits**

Although balancing benefits and risks forms a critical component of the ethical evaluation of genetic testing and NBS programmes it must also be acknowledged that the interpretation of the benefits and risks themselves, and their subsequent balancing, are inherently value-based judgments[84]. As discussed in chapter 2 recent redevelopments of criteria for NBS reflect an acknowledgement of these difficulties[26, 350] but even with such guidelines the balancing

process is not straightforward and may in itself lead to controversies. This is particularly true for newer programmes that may be more complex to implement and where harms and benefits may be more finely balanced. The empirical data I have presented in this thesis highlight the complex nature of parental reactions to screening for genetic susceptibilities and lead to a number of specific areas of complexity associated with the analysis of harms and benefits.

### ***Incomplete knowledge of the effects of screening***

In traditional NBS paradigms it has proved difficult to accurately assess outcomes because of the rarity of some disorders and the impracticality of randomised controlled trials[351]. These particular problems do not apply to common complex disorders such as T1D but other barriers to the collection of complete data sets remain. The acceptability of tests for genetic susceptibility relies, at least in part, on a broader conception of benefit becoming accepted in the context of NBS, such that NBS is seen more as a “public health service” rather than a response to a “public health emergency”[29]. However, if conceptions of benefit are broader, and at the same time there are requirements for public health services to be evidence based[29], then empirical study of a wider range of both harms and benefits will also be necessary. While this seems appropriate, the nature of genetic susceptibility tests and the complexity of early childhood itself, mean that the implications of testing may be very wide reaching. For example they may include direct impacts upon children, parents, and families as well as indirect effects such as social stigma, and issues with education, employment, and insurance. The use of paradigmatic examples, such as T1D, and innovative research methods (mentioned earlier in this chapter) will be of critical importance but it may ultimately prove too difficult and too costly to fully investigate every possible effect for every genetic test. The current lack of empirical evidence is unacceptable, but some limitation on our knowledge of screening outcomes is likely to persist, and must be acknowledged in debates concerning the future of NBS.

### ***Disagreement as to what constitutes harm or a benefit***

As well as problems related to incomplete data concerning harms and benefits there may be more value based disagreements concerning what actually constitutes a harm or benefit. In relation to NBS for genetic susceptibility to disease it is not currently possible to define precisely what constitutes an “ideal” parental response, as the scientific knowledge base continues to evolve. Such a definition must depend in part upon the existence or absence of preventative measures that can be instituted by parents of babies with increased genetic risks. For example, if no preventative measure has been developed then it may be entirely

appropriate for a child's elevated risk to remain at the back of a parent's mind, to be considered only if specific symptoms develop. Conversely if a preventative measure has become available then the information would require more active and frequent consideration by parents such that they were motivated to adhere to any prescribed lifestyle changes or other measures. As psychosocial research data accumulates and scientific knowledge and clinical applications advance we need to develop a more nuanced account of how parents respond to increased risk results. Only when this account has been developed can we more clearly define which aspects of parents' reactions may be beneficial, which may be harmful and what infrastructure may be required to facilitate the most appropriate responses. It is entirely feasible that these more detailed accounts of parental responses can be achieved by utilising ongoing longitudinal studies and the research methods described earlier. It is also possible to envision how this may lead to the development of robust methods for supporting parents through the testing process. However, it may never be possible to articulate a universal ideal response model when such reactions are so variable, suggesting that any supportive infrastructure will need to include elements that can be adapted to individual needs and contexts, including those of a cultural nature.

### ***Disagreements about the significance and commensurability of benefits and risks***

Even if empirical analysis of all harms and benefits associated with NBS for genetic susceptibility to complex disorders were possible it may be difficult to reach a consensus concerning their relative significance and commensurability. This is true even for existing NBS programmes where, for example, there may be disagreement concerning the significance of increased height in children diagnosed with CF through NBS[84]. It has also proved difficult to accurately balance impacts that may be quite different in nature, for example those that are physical with those that are psychosocial[84]. These problems are likely to be exacerbated in the context of genetic susceptibility screening where parents' psychosocial reactions will be crucially important in achieving expected benefits but are highly complex, dynamic and vary markedly between individuals. These issues will likely be exacerbated further with multiplex testing, suggesting the need for high quality communication processes and "opt-in" designs in clinical practice, such that parents consciously choose the tests they consider to be appropriate for their child.

#### **8.7.1.3. Summary of harms and benefits**

The empirical data presented in this thesis informs the debate concerning the ethical acceptability of incorporating tests of genetic susceptibility into NBS programmes. However, it also highlights the complexity of the situation and need to reflect upon wider issues than

those typically considered in analysis of benefits and harms. Detailed analysis of harms and benefits is never likely to be complete, and is not a straightforward process, but until both benefits and harms are better characterised, a cautious approach to population screening for genetic susceptibility to T1D is warranted[21]. I will discuss below why this does not necessarily translate to complete prohibition of such testing.

### **8.7.2 Other ethical principles relevant to NBS**

While the analysis of harms and benefits associated with NBS is of considerable importance it does not necessarily capture all of the ethical issues at stake, particularly in a complex testing scenario such as that for genetic susceptibility to common disease. In fact, relying on benefits as the primary guiding moral principle may appear to minimise the value of other equally important ethical issues. Therefore, as discussed in the opening chapter of this thesis, there is a need to explicitly recognise the role of other ethical principles in decision making around NBS. These ethical issues were briefly reviewed in the context of NBS and predictive genetic testing for single gene disorders in chapter 1 and will be revisited here specifically in relation to genetic susceptibility testing. While the underlying issues are broadly similar, the complicated nature of parental reactions that I have described adds layers of complexity to arguments concerning the advisability of testing newborns for genetic susceptibility to common disorders.

### **8.7.3 Parental autonomy**

In chapter 1 I discussed the importance of respecting parental autonomy for a number of reasons, but particularly because this places value on intimate family relationships that are likely to facilitate children's overall physical and emotional development [45]. Despite this I have also noted that parental autonomy has traditionally been more constrained in relation to genetic testing of children. For example, in the current NBS paradigm, with its acknowledged medical benefits, policies that strongly recommend NBS while ultimately permitting parental choice predominate[46]. Conversely predictive genetic testing of young children is rarely performed in the absence of medical benefit because policy statements by numerous professional organisations strongly discourage it [28, 30-32], although latterly there have been calls to allow greater parental discretion [38].

The current absence of medical benefits in relation to genetic susceptibility tests makes them more closely aligned with predictive genetic testing for single gene disorders, where the balance of psychosocial benefits and risks is given significant weight. Even for single gene tests it is acknowledged that the range of psychosocial harms and benefits is wide and their

balancing may be influenced by individual characteristics[48]. This is more pertinent in relation to genetic susceptibility tests that involve not only a predictive element but also an ongoing level of uncertainty regarding whether the disease will develop at all. While my quantitative study revealed an absence of significant psychological harm, my qualitative data suggested considerable variation in parental response to NBS for genetic susceptibility to T1D: some parents may find such information useful in shaping their parenting practices, others may consider it of little relevance, and for some it may prove destructive, depending on their adaptive response to uncertainty. This degree of variation, and the fact that both beneficial and harmful effects have been reported in the context of such uncertainty[352], suggests that as genetic susceptibility tests edge closer to clinical application, parents will be best placed to determine whether such testing is appropriate for their own family. However, if parents are to make these decisions they will require explicit counselling about not only medical benefits and harms, but also the current evidence base concerning short term psychosocial responses as well as the potential longer term psychosocial implications that are as yet unknown. For example parents should be informed of the potential for children to suffer longer term anxiety over their health and to wish that they had not known of their disease risk.

Further empirical research concerning the responses of parents and children to the probabilistic nature of genetic susceptibility tests will assist with policy decisions concerning the degree to which parental autonomy should be respected or constrained in such situations. My own belief is that respect for parental autonomy should play a greater role in shaping genetic testing practices in child health settings, including in decisions related to the potential application of genetic susceptibility tests. However parental decisions should be based on evidence of both medical and psychosocial harms and benefits and I acknowledge that there may be considerable difficulties in conveying such information in a clinical context.

#### **8.7.4 Child welfare**

While the prospect of medical benefit is an important determinant of whether or not children undergo genetic testing there are additional considerations, including that:

- Testing may infringe upon the child's future autonomy
- Testing may cause psychosocial harm to the child[34]

#### **8.7.4.1. The child's future autonomy**

I have argued that parents are generally best placed to make healthcare decisions on behalf of their infants and young children. However, as children become older they should have increasing input into these decisions and eventually will themselves become autonomous individuals. Until then it is generally agreed that their future autonomy should be maximised, but how this should be achieved, in the context of genetic testing, is contentious. While it has been argued that predictive genetic testing in childhood may constrain a child's future "right not to know" it has also been argued that such self knowledge may in fact promote more autonomous decision making about one's life[32]. Certainly the paediatric oncology literature suggests that children cope better with concrete and frank information if it is available, as opposed to a policy of non-disclosure or suspended uncertainty[353].

These latter arguments appear to be carrying increasing weight, with some policy statements evolving to allow greater parental discretion in testing choices. However, while such arguments have considerable merit in terms of single gene disorders where genetic testing can provide relief from an uncertainty that is frequently considered more burdensome than knowing either a positive or negative result[48], it remains unclear whether this can be extrapolated to genetic susceptibility testing for common complex disorders. Tests of genetic susceptibility in fact simultaneously reveal frank information *and* invoke a state of suspended uncertainty. For example, in the case of NBS for genetic susceptibility to T1D one would be introducing a new dimension of uncertainty regarding a condition for which there may be no family history, and that had not previously been actively considered by parent or child.

Whether this type of knowledge is autonomy enhancing or constraining is currently unclear and may depend upon underlying psychological factors, such as coping style, in a similar way to the likely balance of harms and benefits experienced by parents. Some young people may find such information useful, whereas others may find it burdensome, limiting or fatalistic[354]. My empirical research does not address these issues, but as children who are involved in various longitudinal studies get older it will increasingly be possible to test such hypotheses. My research also does not address the important issue of potential for external constraints upon autonomy from third parties, such as schools, employers or insurance agencies, if they have access to genetic susceptibility test results.

Finally it should be noted that my accounts of parental and child autonomy reflect the dominance of Western discourse within contemporary bioethics. Other cultures, including the Pacific and Maori populations in New Zealand, may have differing understandings of the concept of autonomy. For example, although Western notions of child development are predicated upon a gradual move towards individualisation and autonomy, Pacific beliefs may

prioritise interconnectedness within family and knowing one's place in relation to others[347].

#### **8.7.4.2. Direct psychosocial impact upon the child**

Concerns regarding psychosocial effects of genetic susceptibility testing directly upon children themselves centre around the development of a population of “worried – well” young people. The character from Gattaca quoted at the beginning of this thesis “*came to think of myself as others thought of me: chronically ill*” [1]. To my knowledge there is no empirical evidence concerning the impact of genetic susceptibility testing directly upon children, but the few investigations of direct effects of testing for single gene disorders in childhood suggest a wide range of both positive and negative psychosocial effects[48]. While the sort of reactions depicted in the above quotation are possible, it is also feasible to speculate that, just as parental reactions to such tests are milder than those described in relation to standard NBS or predictive genetic testing for single gene disorders, the same may hold true for effects upon the child. Knowing about a disease predisposition rather than the existence or inevitable progression to a disease state may be less likely to result in psychological disturbances such as effects upon self esteem or anxiety, but this and the impact of ongoing uncertainty clearly require empirical analysis[38].

Interestingly, a recent study of psychological adjustment of siblings of children with T1D (who have a cumulative incidence of T1D of approximately 6% by age 30 years, a similar level of risk to that derived from the tests described in this thesis [356]) demonstrated that there was no increased behavioural or emotional dysfunction relative to children in the general population and, according to their parents, these children were better adjusted than their peers[357]. While this data provides some insight into living with disease risk it is not possible to unpick the various factors that may have contributed to the study endpoints. For example it is unclear how this group of children viewed their own risk of T1D, how they compared themselves to their affected sibling or how they were affected in a practical sense by their sibling's illness.

#### **8.7.5 Resource allocation**

An additional consideration for any ethical analysis involving provision of healthcare is the issue of resource allocation. Technological capabilities for genetic susceptibility screening continue to advance and many of the associated costs continue to decrease. Adding such tests to existing NBS programmes may therefore result in only a modest cost increase. However, NBS, particularly if it involves a new testing paradigm, should be viewed as more than just a test. Adding any new disorder to a screening panel also involves additional expenditure in

areas such as parental education; follow up of all positive results, making definitive diagnoses, treatment of affected children and ongoing data collection and quality assurance processes. When the type of disorder proposed differs markedly from those already included in screening panels then the costs of any alteration in the underlying infrastructure must also be included in any cost-benefit analysis. For example screening for genetic susceptibility for T1D would include relatively expensive processes such as enhanced communication processes, ongoing surveillance for auto antibodies, as well as the need to attend to parental uncertainty and its various consequences over a number of years. For example, heightened parental concern regarding their child's health may lead to additional contacts with healthcare providers, and even to requests for additional investigations or treatments. Implications for other aspects of the health service, such as general practice, or Well-child Services (Plunket) must also be considered. Once a picture of the costs associated with NBS has been developed, the benefits can also be assessed and compared with the benefits that could be achieved if the resources were used elsewhere. Resource consumption without significant benefit must be considered a potential harm[358]. This type of decision-making process, aided by the existence of NBS criteria, currently exists although the considerable variation in conditions included in NBS panels suggests variation in approach. For example, as discussed in chapter 2, many countries have endorsed expanded NBS whereas Finland (where NBS currently consists of cord blood analysis for hypothyroidism only) [359] recently considered introduction of NBS for 5 conditions using tandem mass spectrometry, but following computer modelling of costs and benefits decided that the cost of establishing an entirely new system was prohibitive[360].

### **8.7.6 Summary of ethical analysis**

Analysis of harms and benefits continues to be of considerable importance in assessment of the ethical acceptability of genetic tests. The benefits of NBS for genetic susceptibility to T1D are currently minimal but the potential for this to change should not be underestimated. While my data in general suggests no major short term psychological harmful effects from NBS for genetic susceptibility to common disease, question marks remain over more subtle effects, significant harm for some people and longer term implications. In particular the direct effects upon children and long term parental views remain to be examined.

In addition to analysis of harms and benefits other ethical principles require active consideration in analysis of the potential for implementing genetic susceptibility testing in clinical practice. These principles include parental autonomy and the child's future autonomy, and empirical data concerning these issues would also considerably advance debate.

## **8.8 Implications for clinical practice**

In this final section I bring together my research findings, description of future research requirements and analysis of ethical issues to generate conclusions concerning the future of NBS for disorders such as T1D.

### **8.8.1 Current recommendations**

#### **8.8.1.1. NBS for T1D**

Population screening, including NBS, needs to concentrate on those disorders for which the balance of benefit over risk is clear. Currently, although some gaps in our knowledge of parents' psychosocial reactions to NBS for genetic susceptibility to T1D remain, enough is known to make recommendations regarding the use of such tests in NBS programmes, albeit in the knowledge that they may require revision once more empirical data accumulates. My data suggests that some families may be adversely affected by NBS for genetic susceptibility to T1D in subtle, but ongoing ways. When this is considered in conjunction with the current lack of preventative strategies for T1D, the lack of infrastructure to address the needs of large numbers of parents whose child will have a positive result and the lack of data concerning longer term psychosocial effects it is clear that such screening does not fulfil any existing NBS criteria. The addition of such tests to NBS panels is currently inadvisable.

#### **8.8.1.2. Other current options**

However, while I believe that current evidence concerning the balance of benefits and harms mean it is appropriate to adopt a precautionary approach to the use of genetic susceptibility within a NBS paradigm, this does not necessarily translate to complete prohibition of parental access to such testing. My analysis of other ethical principles suggests that parents should not be prevented from obtaining such tests for their children, if that is what they wish, following due consideration of all of the relevant issues.

Ideally such testing would take place in a paradigm closely aligned to that of current predictive genetic testing in childhood. However, while the prospect of offering testing in such a way initially appears to appropriately respect parental autonomy, achieving this in practice, particularly on a large scale, would currently be difficult and costly. Conveying probabilistic information raises special problems in terms of ensuring that parents appreciate the uncertain implications of a positive test for an individual child. In addition, conveying the wide range of potential positive and negative effects, both physical and psychosocial, would be challenging. Such discussions should include explicit reference to the potential for long term negative effects upon the child, such as anxiety or preoccupation with health, as well the

fact that some children may ultimately wish they had not known such test results, feeling that their autonomy had been constrained by the knowledge. The complexity of these issues would be clearly amplified in multiplex testing scenarios.

Such counselling may be particularly difficult to achieve when many parents feel pressure to accept medical tests when they are offered, in an attempt to “do everything” for their child.

How to counter such dogma with a more nuanced consideration of what is truly in the child’s best interests represents an important challenge for the future. In addition persuasive direct to consumer marketing of genetic susceptibility tests, particularly in poorly regulated settings such as the internet, may be difficult to counteract[361]. These acknowledged difficulties suggest that introduction of childhood genetic susceptibility tests into publicly funded health services is not advisable until robust educative resources are available.

If genetic susceptibility tests are not offered routinely, some parents may still wish to access them for their children outside standard clinical practice, for example through private providers. While I have argued that parents and children are generally best left to get on with their own lives without others imposing ideas of best interests, this right to freedom from external intervention cannot be absolute. Currently, I believe that if parents wish to discuss such testing, a dissuasive approach that alerts them to the limited benefits and potential for harm, while still ultimately respecting their choices is appropriate. This position mirrors that of the current approach to standard NBS that strongly recommends testing to parents but accepts that they are free to decline. Both of these positions assume that parents ought to listen to and be advised by health care providers, but also uphold the importance of parental rights and responsibilities within the family[45]. Further empirical work concerning how families make these individualised assessments of psychosocial benefits and risks, and deal with the long-term implications of their decisions would add considerably to debate in this area.

## **8.8.2 Future options for genetic susceptibility testing**

### **8.8.2.1. NBS**

I have already discussed that in future genetic susceptibility testing is likely to move from assessment of single or several SNPs to full genome sequencing, as well as measurement of biomarkers based on gene expression, and epigenetic profiles [362]. The predictive power of these panels of tests may prove to be superior to current genetic susceptibility tests. Similarly, if preventative measures are developed (and for T1D they have evolved considerably during the course of this thesis [363]), then NBS clearly provides the potential to maximise benefits across the whole population. However, as with existing NBS programmes, the potential for

harmful effects would also be increased and any benefits would likely be highly contingent on the provision of a suitable supportive infrastructure [36].

In terms of psychosocial reactions it will be necessary to remember that parents' responses to such genetic testing involve a complex interplay between affect, cognition and behaviour. Interventions designed to alter any single component will also likely impinge on others, as well as the process as a whole. For example it will not be sufficient (or even advisable) to simply attempt to minimise parental anxiety associated with such testing, rather to think creatively about how the complex interplay between affect and reason can be harnessed to assist parents to manage risk and engage in rational behaviour change[334].

This complex system is unlikely to fit into any typical genetic counseling or doctor patient models, but rather may require a more responsive and malleable system that can be tailored to individual requirements on an ongoing basis. It will be necessary to address not only the practical issue of disease surveillance but also the emotional threat of uncertainty about ones child's risk of disease. How to achieve an appropriate balance between unnecessary worry and behaviour motivation in the context of the dynamic nature of both the affective and cognitive processes and the considerable inter-individual variation represents a considerable challenge. Again, multiplex testing, which would provide a spectrum of different risks for multiple conditions would considerably amplify the complexity of parental reactions and add to the difficulties in communicating results and potential interventions.

#### **8.8.2.2. Childhood population screening**

Given that an entirely new infrastructure would be required to support NBS for genetic susceptibility to common disorders it may be preferable to delay such testing to later in childhood. The problems with such an approach include: the need for an additional blood test; that uptake rates may be much lower (although whether or not this is inappropriate is an open question) and that for some common complex disorders intervention would ideally occur as early as possible in the newborn period. Benefits include allowing more time for parental decision-making, separating the consent process from the assumed (or even absent) consent of current NBS and aligning testing more closely with current developmental surveillance and screening approaches in childhood (such as " Well Child Services"). Such a move would also avoid any potential adverse effects upon public confidence in NBS in general that may see uptake rates of standard NBS decline if tests for genetic susceptibility were added to existing panels. The resultant rise in mortality and morbidity would represent the ultimate harm; the technological imperative to expand and diversify NBS, if ill-considered, could subvert and defeat what is at present an undeniable public health good[148].

### **8.8.2.3. Individual testing paradigm**

I have already stated that I do not think that parents should currently be prohibited from obtaining genetic susceptibility tests for their child but that it is appropriate to try to dissuade them by giving them information concerning the potential risks and minimal benefits. If appropriate mechanisms for educating and supporting parents can be developed, genetic susceptibility testing would be well suited to a predictive genetic testing paradigm where parents are given time and flexibility around testing decisions. It is possible that parents who actively choose this type of testing may be better equipped to respond to the impact of a positive test. This issue is also empirically testable. Depending on how far the balance of benefits and risks related to genetic susceptibility testing shifts in a favourable direction then the dissuasive approach mentioned earlier may need to become more neutral or even persuasive.

### **8.8.2.4. Prenatal testing**

Discussions concerning childhood testing for susceptibility to common complex disorders may eventually become obsolete if the field of prenatal testing and diagnosis continues to evolve. Recent refinements in non invasive prenatal diagnosis mean that fetal DNA fragments circulating in maternal blood can now be accurately analysed for a limited range of chromosomal conditions[364]. In conjunction with rapid advancements in next generation sequencing technologies, a whole genome scan of a developing fetus, performed on a sample derived non-invasively from the mother, could become feasible in the relatively near term. The use of genetic susceptibility tests in a prenatal context clearly raises a host of additional complex ethical issues, discussion of which is beyond the scope of this thesis.

Although I have stated that NBS for genetic susceptibility to T1D is currently not appropriate I have described several different ways in which genetic susceptibility testing may eventually prove clinically useful. However, it also remains possible that such tests will never fit into any of these testing paradigms and some of the reasons for these possible limitations are discussed below.

## **8.8.3 Technical and scientific limits**

The greatest barriers to clinical use of genetic susceptibility tests may arise from the deepening complexity of the science itself, requiring a long-term, large, and consistent research commitment [365]. Even with this research funding and activity it may ultimately become apparent that while analysis of individual human genetic variation is useful for

learning about disease pathogenesis it may always be of limited predictive value. Obtaining knowledge of disease pathways is a very worthy goal of genomics research and may lead to development of new treatments with broad utility, often applicable to patients regardless of their genotype. However, although some risk prediction may be feasible and medically useful, there are likely to be fundamental limits on precise prediction. These limits relate to the complex architecture of common traits, including common variants with small effects, rare variants that cannot be fully described, complex epistatic interactions and the effects of many non-genetic factors that all contribute to the continuum of normal physiology and disease[366, 367].

Even if clinically useful tests are developed these are also likely to be complex. One example of this type of complexity is the potential for “subphenotyping” of complex behavioral disorders such as attention deficit hyperactivity disorder (ADHD): a recent study has demonstrated that children with ADHD carrying particular polymorphisms at 2 dopaminergic loci might form a cognitively distinct group with a differential prognosis. Even if these findings are replicated, precisely how such complex genetic information could eventually be incorporated into psychiatric diagnosis or treatment requires much consideration[368].

Similarly, it appears that in complex disorders such as obesity, genotypic variation contributes to large individual differences in responsiveness to treatment (such as dietary manipulations). The genes responsible for these differences have not been fully identified and are likely to be numerous considering the complexity of the biological systems involved[369], but this example nevertheless highlight the relevance of gene-environment interactions, not only for disease development but also in relation to preventative and treatment options.

Such scientific complexity is likely to lead to many difficult issues in a clinical setting: as others have said, “the translation of science into the clinic is inherently messy”[370]. For example, it may be difficult to know what to do with results of unknown significance, how to store data such that it can be reviewed as scientific evidence accumulates and how to continually update parents of these findings.

#### **8.8.4 Infrastructure requirements**

I have highlighted several times in this thesis that while NBS clearly provides the potential to maximise benefits across the whole population, these benefits are highly contingent on the provision of a suitable supportive infrastructure [36]. The practical challenges of developing such an infrastructure (that is totally different to that involved with current NBS ) is perhaps one of the most significant impediments to any proposal to expand NBS to include genetic susceptibility testing.

NBS follow-up is not currently well-positioned to support rapid expansion of the number of conditions included in screening panels and is ill-prepared to support families of children with common complex disorders that may or may not have effective interventions[348]. In addition we have not yet determined the nature of an “optimal” parental response to testing newborns for genetic susceptibility to common disorders, or indeed if this is even possible to define. These knowledge deficits mean that it is currently unclear how screening could best be implemented in a culturally sensitive way in populations with varying underlying psychopathology and coping mechanisms. Development of genetic services in particular may require careful deliberation and cooperation between providers and potential participants who do not share dominant Western beliefs[371].

It is however possible to articulate some general requirements, which largely relate to the uncertain implications of the genetic risk information and the dynamic nature of childhood[348]. These include: ongoing access to accurate comprehensible information concerning risk and management; ongoing access to support to enable parents to make use of genetic risk information obtained through NBS; surveillance of child health and development; and access to appropriate general and targeted interventions as they become available[348]. Achieving such infrastructure changes will be highly resource intensive and will require increased emphasis on psychosocial factors, including an increased role for both research and clinical psychologists. It remains possible that future research will demonstrate that parental reactions are so complex and varied that it is not feasible to provide an adequate support framework for widespread testing. This may be particularly true for multiplex testing where the provision of information detailing varying, and even fluctuating, risks for different disorders could ultimately lead to parental confusion and inaction despite the application of counselling resources.

### **8.8.5 Philosophical limits**

In addition to the practical limitations surrounding use of genetic susceptibility testing in childhood it is also worth considering what the philosophical limits may be. In other words what, if any, are the limits of what we want to know about our children? History tells us that this type of consideration should not be limited by consideration of what is technically possible, as scientific advances may occur much more rapidly than anticipated. The general presumption of modern science, including medical genetics, is that knowledge is a fundamental good, and that the more we know about ourselves the better our lives will be. This assumption is supported by many examples where medical knowledge and intervention

have dramatically improved the quality of people's lives. However, in reality the benefits of some types of knowledge may be much more ambiguous. Giving parents more choices around what they can know about their children's health does not necessarily improve their ability to conduct their parental duties, or their children's lives. In some ways parents may be more constrained by such choices as it may be difficult for them to decline offers to know whatever can be known about the health of their child. Similarly such knowledge could ultimately impose major constraints upon the lives of future adults, either through effects upon individual decision-making or through sanctions imposed by third parties. Such testing may also place an undue focus on health, that while obviously an important issue, should not necessarily dominate all other facets of life[95].

### **8.8.6 Management of uncertainty**

Uncertainty exists when details of situations are ambiguous, complex, unpredictable or probabilistic; when information is unavailable or inconsistent; and when people feel insecure in their own state of knowledge, or the state of knowledge in general[372]. In this thesis I have described in some detail the multiple complexities and uncertainties associated with genomic NBS, including scientific, psychosocial and philosophical issues. How these multiple uncertainties are communicated and managed represents one of the most significant challenges for the future of genomics. Some degree of uncertainty is typical of medical decision-making but when multiple, inter-connected and ongoing uncertainties exist it is much less clear how the situation should be managed. Further conceptual and empirical work concerning the meaning and experience of uncertainty, appraisal and emotional responses to uncertainty and its behavioural implications will be required and I have described some elements of such research. While this data will be relevant to the potential application of genomics in adult medicine, it is particularly important in the dynamic context of childhood.

## **8.9 Overall Summary**

It is becoming increasingly clear that complexity and uncertainty coexist at all stages of genomics from basic science to clinical application. If the potential benefits of genomics are to be realised this complexity and uncertainty must be better defined. The empirical work contained within this thesis goes some way towards achieving this aim, by better defining parents' psychosocial reactions to "genomic NBS", but also highlights the difficulties that are likely to be encountered in both future research and clinical settings. These difficulties should not be used as excuses to delay collection of good evidence regarding the use of genomic tests in early childhood: if we are to attain a future in which genomics leads to improvement in

human health the newborn period must be a research priority. A lack of rigorous translational research may result in missed opportunities or premature, inefficient or harmful adoption of new technologies. Rather, collection of robust empirical evidence should continue and expand, so that in conjunction with careful ethical analysis, it can inform best practice in applying genomic information in child health settings.

## References

1. Niccol, A., (writer and director) of *Gattaca, a science fiction film*, 1997.
2. Collins, F.S., et al., *A vision for the future of genomics research*. *Nature*, 2003. 422(6934): p. 835-47.
3. *Human Genome Project Information Website*. 2010 [cited 12/8/10]; Available from: [http://www.ornl.gov/sci/techresources/Human\\_Genome/home.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml).
4. Thorisson, G.A., et al., *The International HapMap Project Web site*. *Genome Res*, 2005. 15(11): p. 1592-3.
5. McBride, C.M., et al., *Putting science over supposition in the arena of personalized genomics*. *Nat Genet*, 2008. 40(8): p. 939-42.
6. Guttmacher, A.E. and F.S. Collins, *Welcome to the genomic era*. *N Engl J Med*, 2003. 349(10): p. 996-8.
7. Collins, F.S., *Shattuck lecture--medical and societal consequences of the Human Genome Project*. *N Engl J Med*, 1999. 341(1): p. 28-37.
8. Bell, J., *Predicting disease using genomics*. *Nature*, 2004. 429(6990): p. 453-6.
9. Khoury MJ, B.W., Thomson EJ., *Genetics and public health: a framework for the integration of human genetics into public health practices.*, in *Genetics and public health in the 21st century: using genetic information to improve health and prevent disease*, M. Khoury, W. Burke, and E. Thomson, Editors. 2000, Oxford University Press: New York. p. 3-24.
10. *Medical research: people's chief concerns*. *Public Agenda Website* 2007 [cited 7/5/07]; Available from: [http://www.publicagenda.org/issues/pcc\\_detail.cfm?issue\\_type=medical\\_research&list=9](http://www.publicagenda.org/issues/pcc_detail.cfm?issue_type=medical_research&list=9).
11. Haga, S.B., M.J. Khoury, and W. Burke, *Genomic profiling to promote a healthy lifestyle: not ready for prime time*. *Nat Genet*, 2003. 34(4): p. 347-50.
12. Holtzman, N.A. and T.M. Marteau, *Will genetics revolutionize medicine?* *N Engl J Med*, 2000. 343(2): p. 141-4.
13. Wilkie, A.O.M., *Genetic Prediction: What are the limits?* *Stud. Hist. Phil. Biol. and Biomed. Sci.*, 2001. 32(4): p. 619-633.
14. Tercyak, K.P. and V.L. Tyc, *Opportunities and challenges in the prevention and control of cancer and other chronic diseases: children's diet and nutrition and weight and physical activity*. *J Pediatr Psychol*, 2006. 31(8): p. 750-63.
15. Wilcken, B., *Ethical issues in newborn screening and the impact of new technologies*. *Eur J Pediatr*, 2003. 162 Suppl 1: p. S62-6.
16. Levy, H.L., *Lessons from the past--looking to the future. Newborn screening*. *Pediatr Ann*, 2003. 32(8): p. 505-8.
17. Anonymous, *The Environmental Determinants of Diabetes in the Young (TEDDY) Study*. *Ann N Y Acad Sci*, 2008. 1150: p. 1-13.
18. Almond, B., *Genetic profiling of newborns: ethical and social issues*. *Nat Rev Genet*, 2006. 7(1): p. 67.
19. Human Genetics Commission *Profiling the newborn: a prospective gene technology?* 2005 [cited 31/1/06]; Available from: [http://www.hgc.gov.uk/Client/news\\_item.asp?NewsId=38](http://www.hgc.gov.uk/Client/news_item.asp?NewsId=38).
20. Department of Health. *Our Inheritance, Our Future — Realising the potential of genetics in the NHS*. 2003 [cited 31/1/06]; Available from: <http://www.dh.gov.uk/assetRoot/04/01/92/39/04019239.pdf>.
21. Botkin, J.R., et al., *Newborn screening technology: proceed with caution*. *Pediatrics*, 2006. 117(5): p. 1793-9.
22. Wilson, J. and G. Jungner, *Principles and Practice of Screening for Disease*. *Public Health Papers*, ed. WHO. 1968, Geneva: WHO.

23. Farrell, M.H. and P.M. Farrell, *Newborn screening for cystic fibrosis: ensuring more good than harm*. J Pediatr, 2003. 143(6): p. 707-12.
24. Watson, M.S., *Current status of newborn screening: decision-making about the conditions to include in screening programs*. Ment Retard Dev Disabil Res Rev, 2006. 12(4): p. 230-5.
25. Watson, M.S., et al., *Newborn Screening: Toward a Uniform Screening Panel and System--Executive Summary*. Pediatrics, 2006. 117(5): p. S296-307.
26. Botkin, J.R., *Assessing the new criteria for newborn screening*. Health Matrix Clevel, 2009. 19(1): p. 163-86.
27. Alexander, D. and P.C. van Dyck, *A vision of the future of newborn screening*. Pediatrics, 2006. 117(5 Pt 2): p. S350-4.
28. Botkin, J.R., *Research for newborn screening: developing a national framework*. Pediatrics, 2005. 116(4): p. 862-71.
29. Grosse, S.D., et al., *From public health emergency to public health service: the implications of evolving criteria for newborn screening panels*. Pediatrics, 2006. 117(3): p. 923-9.
30. Tercyak, K.P., *Introduction to the Special Issue: Psychological Aspects of Genomics and Child Health*. J. Pediatr. Psychol., 2009. 34(6): p. 589-595.
31. Ross, L.F., *Predictive genetic testing for conditions that present in childhood*. Kennedy Inst Ethics J, 2002. 12(3): p. 225-44.
32. Savulescu, J., *Predictive genetic testing in children*. Med J Aust, 2001. 175(7): p. 379-81.
33. Borry, P., et al., *Genetic testing in asymptomatic minors: background considerations towards ESHG Recommendations*. Eur J Hum Genet, 2009. 17(6): p. 711-9.
34. Duncan, R.E., *Predictive genetic testing in young people: when is it appropriate?* J Paediatr Child Health, 2004. 40(11): p. 593-5.
35. Borry, P., et al., *Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers*. Clin Genet, 2006. 70(5): p. 374-81.
36. Kodish, E.D., *Testing children for cancer genes: The rule of earliest onset*. The Journal of Pediatrics, 1999. 135(3): p. 390.
37. Clarke, A. and F. Flinter, *The genetic testing of children: a clinical perspective*, in *The Troubled Helix: Social and Psychological Implications of the New Human Genetics*, T. Marteau and M. Richards, Editors. 1996, Cambridge University Press: Cambridge. p. 164-76.
38. Robertson, S. and J. Savulescu, *Is there a case in favour of predictive genetic testing in young children?* Bioethics, 2001. 15(1): p. 26-49.
39. Fryer, A., *Genetic testing of children*. Arch Dis Child, 1995. 73(2): p. 97-9.
40. Wertz, D.C., J.H. Fanos, and P.R. Reilly, *Genetic testing for children and adolescents. Who decides?* Jama, 1994. 272(11): p. 875-81.
41. Fanos, J.H., *Developmental tasks of childhood and adolescence: implications for genetic testing*. Am J Med Genet, 1997. 71(1): p. 22-8.
42. Michie, S. and T. Marteau, *Predictive genetic testing in children: the need for psychological research*, in *The genetic testing of children*, A. Clarke, Editor. 1998, BIOS Scientific Publishers Ltd: Oxford, UK. p. 331.
43. Wilfond, B. and L.F. Ross, *From genetics to genomics: ethics, policy, and parental decision-making*. J Pediatr Psychol, 2009. 34(6): p. 639-47.
44. Newson, A., *Should parental refusals of newborn screening be respected?* Camb Q Healthc Ethics, 2006. 15(2): p. 135-46.
45. Downie, R.S. and F. Randall, *Parenting and the best interests of minors*. Journal of Medicine & Philosophy, 1997. 22(3): p. 219.

46. Kerruish, N.J., D. Webster, and N. Dickson, *Information and consent for newborn screening: practices and attitudes of service providers*. J Med Ethics, 2008. 34(9): p. 648-52.
47. Bombard, Y., et al., *The expansion of newborn screening: is reproductive benefit an appropriate pursuit?* Nat Rev Genet, 2009. 10(10): p. 666-7.
48. Duncan, R.E., et al., "You're one of us now": young people describe their experiences of predictive genetic testing for Huntington disease (HD) and familial adenomatous polyposis (FAP). Am J Med Genet C Semin Med Genet, 2008. 148C(1): p. 47-55.
49. Robertson, S. and R. Poulton, *Longitudinal studies to detect gene × environment interactions in common disease - Bang for your buck? A commentary on Chaufan's "How much can a large population study on genes, environments, their interactions and common diseases contribute to the health of the American people?" (65:8, 1730-1741(2007))*. Social Science & Medicine, 2008. 67(4): p. 666.
50. Chaufan, C., *How much can a large population study on genes, environments, their interactions and common diseases contribute to the health of the American people?* Social Science & Medicine, 2007. 65(8): p. 1730.
51. CDC. *National Office of Public Health Genomics Website*. [cited 28/5/07]; Available from: <http://www.cdc.gov/genomics/hugenet/about/rationale.htm>.
52. Ross, L.F., *Minimizing risks: the ethics of predictive diabetes mellitus screening research in newborns*. Arch Pediatr Adolesc Med, 2003. 157(1): p. 89-95.
53. Forsyth, B.W., et al., *The child vulnerability scale: an instrument to measure parental perceptions of child vulnerability*. J Pediatr Psychol, 1996. 21(1): p. 89-101.
54. Michie, S., *Predictive testing in children: paternalism or empiricism?* in *The Troubled Helix: Social and Psychological Implications of the New Human Genetics.*, T. Marteau and M. Richards, Editors. 1996, Cambridge University Press: Cambridge. p. 177-86.
55. McBride, C.M. and A.E. Guttmacher, *Commentary: Trailblazing a Research Agenda at the Interface of Pediatrics and Genomic Discovery--a Commentary on the Psychological Aspects of Genomics and Child Health*. J. Pediatr. Psychol., 2009. 34(6): p. 662-664.
56. Clayton, E.W., *Ethical, legal, and social implications of genomic medicine*. N Engl J Med, 2003. 349(6): p. 562-9.
57. Burke, W., L.E. Pinsky, and N.A. Press, *Categorizing genetic tests to identify their ethical, legal, and social implications*. Am J Med Genet, 2001. 106(3): p. 233-40.
58. HumGen International website. [cited 2/5/11] available from <http://humgen.umontreal.ca/int/>
59. Chapman, E. and J. Smith, *Interpretative phenomenological analysis and the new genetics*. Journal of health psychology, 2002. 7(2): p. 125-130.
60. Smith, J., M. Jarman, and M. Osborn, *Doing Interpretative Phenomenological Analysis*, in *Qualitative Health psychology*, M. Murray and K. Chamberlain, Editors. 1999, SAGE Publications Ltd: London. p. 218-240.
61. Streetly, A., et al., *Survey of scope of neonatal screening in the United Kingdom*. Bmj, 1995. 311(7007): p. 726.
62. Guthrie, R. and A. Susi, *A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants*. Pediatrics, 1963. 32: p. 338-343.
63. Paul, D. *Final report of the task force on genetic testing. Appendix 5: the history of newborn phenylketonuria screening in the US*. 1997 [cited 1/12/09]; Available from: <http://biotech.law.lsu.edu/research/fed/tfgt/appendix5.htm>.
64. Baily, M.A. and T.H. Murray, *Chapter 1: Overview*, in *Ethics and newborn genetic screening: new technologies, new challenges*, M.A. Baily and T.H. Murray, Editors. 2009, The Johns Hopkins University Press: Baltimore, Maryland. p. 1-18.

65. Fyro, K. and G. Bodegard, *Four-year follow-up of psychological reactions to false positive screening tests for congenital hypothyroidism*. Acta Paediatr Scand, 1987. 76(1): p. 107-14.
66. Sorenson, J.R., et al., *Parental response to repeat testing of infants with 'false-positive' results in a newborn screening program*. Pediatrics, 1984. 73(2): p. 183-7.
67. Sox, C.M., et al., *Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease*. Jama, 2003. 290(8): p. 1057-61.
68. Wilcken, B., *Recent advances in newborn screening*. J Inherit Metab Dis, 2007. 30(2): p. 129-33.
69. The president's council on bioethics. *The changing moral focus of newborn screening. Appendix: Newborn screening: An international survey*. 2008 [cited 15/12/09]; Available from: [http://www.bioethics.gov/reports/newborn\\_screening/the%20changing%20moral%20focus%20of%20newborn%20screening%20-%20appendix%20-%20joseph%20raho.pdf](http://www.bioethics.gov/reports/newborn_screening/the%20changing%20moral%20focus%20of%20newborn%20screening%20-%20appendix%20-%20joseph%20raho.pdf).
70. *UK Newborn Screening Programme Centre Website*. [cited 1/12/09]; Available from: <http://newbornbloodspot.screening.nhs.uk/>.
71. *NSW newborn screening programme website*. [cited 1/12/09]; Available from: <http://www.chw.edu.au/prof/services/newborn/>.
72. *National newborn screening and genetics resource center*. [cited 1/12/09]; Available from: <http://genes-r-us.uthscsa.edu/>.
73. Matthews, G., *Newborn Screening*, in *Genes, society and the future*. 2006, Human genome research project: Dunedin, NZ. p. 197-249.
74. *National screening unit website*. [cited 15/12/09]; Available from: <http://www.nsu.govt.nz/Current-NSU-Programmes/914.asp>.
75. Kaye, C.I., et al., *Newborn screening fact sheets*. Pediatrics, 2006. 118(3): p. e934-63.
76. Koch, R., et al., *Phenylketonuria in adulthood: a collaborative study*. J Inherit Metab Dis, 2002. 25(5): p. 333-46.
77. Fost, N., *Ethical implications of screening asymptomatic individuals*. FASEB J., 1992. 6(10): p. 2813-2817.
78. Boneh, A., et al., *Three-year audit of the hyperphenylalaninaemia/phenylketonuria spectrum in Victoria*. J Paediatr Child Health, 2006. 42(9): p. 496-8.
79. Paul, D., *A double-edged sword*. Nature, 2000. 405(6786): p. 515.
80. Fisch, R.O., *Comments on diet and compliance in phenylketonuria*. Eur J Pediatr, 2000. 159 Suppl 2: p. S142-4.
81. Ratjen, F. and G. Doring, *Cystic fibrosis*. Lancet, 2003. 361(9358): p. 681-9.
82. Southern, K.W., et al., *Newborn screening for cystic fibrosis*. Cochrane Database Syst Rev, 2009(1): p. CD001402.
83. Comeau, A.M., et al., *Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections*. Pediatrics, 2004. 113(6): p. 1573-81.
84. Wilfond, B.S., R.B. Parad, and N. Fost, *Balancing benefits and risks for cystic fibrosis newborn screening: implications for policy decisions*. J Pediatr, 2005. 147(3 Suppl): p. S109-13.
85. Grosse, S.D., et al., *Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs*. MMWR Recomm Rep, 2004. 53(RR-13): p. 1-36.
86. Farrell, P.M., et al., *Bronchopulmonary Disease in Children with Cystic Fibrosis after Early or Delayed Diagnosis*. Am. J. Respir. Crit. Care Med., 2003. 168(9): p. 1100-1108.

87. Green, N., S. Dolan, and T. Murray, *Newborn Screening: Complexities in Universal Genetic Testing*. American Journal of Public Health, 2006. 96(11): p. 1955.
88. Farrell, P.M., et al., *Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough!* J Pediatr, 2005. 147(3 Suppl): p. S30-6.
89. Castellani, C., et al., *European best practice guidelines for cystic fibrosis neonatal screening*. J Cyst Fibros, 2009. 8(3): p. 153-73.
90. Kai, J., et al., *Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice*. Health Technol Assess, 2009. 13(57): p. 1-82, iii.
91. Miller, F.A., et al., *Understanding sickle cell carrier status identified through newborn screening: a qualitative study*. Eur J Hum Genet, 2009.
92. Wilcken, B. and V. Wiley, *Newborn screening*. Pathology, 2008. 40(2): p. 104-15.
93. Applegarth, D.A., J.R. Toone, and R.B. Lowry, *Incidence of inborn errors of metabolism in British Columbia, 1969-1996*. Pediatrics, 2000. 105(1): p. e10.
94. Wilcken, B., et al., *Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study*. Lancet, 2007. 369(9555): p. 37-42.
95. The presidents council on bioethics. *The changing moral focus of newborn screening*. [cited 2/5/11] Available at [http://bioethics.georgetown.edu/pcbe/reports/newborn\\_screening/](http://bioethics.georgetown.edu/pcbe/reports/newborn_screening/)
96. Pollitt, R.J., *Introducing new screens: why are we all doing different things?* J Inherit Metab Dis, 2007. 30(4): p. 423-9.
97. Human genetics Society of Australasia. *Newborn bloodspot screening policy*. 2004 [cited 16/1/09] Available at <http://www.hgsa.org.au/2009/12/newborn-blood-spot-screening/>
98. *Newborn screening: toward a uniform screening panel and system*. Genet Med, 2006. 8 Suppl 1: p. 1S-252S.
99. Moyer, V.A., et al., *Expanding newborn screening: process, policy, and priorities*. Hastings Cent Rep, 2008. 38(3): p. 32-9.
100. Tarini, B.A., D.A. Christakis, and H.G. Welch, *State newborn screening in the tandem mass spectrometry era: more tests, more false-positive results*. Pediatrics, 2006. 118(2): p. 448-56.
101. Chadwick, R., et al., *Genetic screening and ethics: European perspectives*. J Med Philos, 1998. 23(3): p. 255-73.
102. Bailey, D.B., Jr., et al., *Changing perspectives on the benefits of newborn screening*. Ment Retard Dev Disabil Res Rev, 2006. 12(4): p. 270-9.
103. National Institute of General Medical Sciences. *Human Genetic Variation Fact Sheet*. 2008 [cited 12/3/10]; Available from: [http://www.nigms.nih.gov/Publications/Factsheet\\_GeneticVariation.htm](http://www.nigms.nih.gov/Publications/Factsheet_GeneticVariation.htm).
104. Bodmer, W. and C. Bonilla, *Common and rare variants in multifactorial susceptibility to common diseases*. Nat Genet, 2008. 40(6): p. 695-701.
105. *Human Genome Project Information Website SNP Factsheet*. Cited 4/6/06. Available at [http://ornl.gov/sci/techresources/Human\\_Genome/faq/snps.shtml](http://ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml)
106. Health, N.I.o. *National Human Genome Research Institute website*. [cited 2/2/10]; Available from: <http://www.genome.gov/20019523>.
107. *Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls*. Nature, 2007. 447(7145): p. 661-78.
108. Hardin, J., et al., *Whole genome microarray analysis, from neonatal blood cards*. BMC Genet, 2009. 10: p. 38.
109. House of lords science and technology committee, *2nd Report of Session 2008-09; Genomic Medicine*. 2009, The Stationery Office Limited: London.

110. Mitchel L, Z., *Newborn SCID Screening Launches in Wisconsin*. Pediatric News, 2008. 42(5): p. 29.
111. Jakobsdottir, J., et al., *Interpretation of Genetic Association Studies: Markers with Replicated Highly Significant Odds Ratios May Be Poor Classifiers*. PLoS Genet, 2009. 5(2): p. e1000337.
112. Bluestone, J.A., K. Herold, and G. Eisenbarth, *Genetics, pathogenesis and clinical interventions in type 1 diabetes*. Nature. 464(7293): p. 1293-300.
113. Buzzetti, R., C.C. Quattrocchi, and L. Nistico, *Dissecting the genetics of type 1 diabetes: relevance for familial clustering and differences in incidence*. Diabetes Metab Rev, 1998. 14(2): p. 111-28.
114. EURODIAB ACE Study Group, *Variation and trends in incidence of childhood diabetes in Europe*. Lancet, 2000. 355(9207): p. 873-6.
115. Campbell-Stokes, P.L. and B.J. Taylor, *Prospective incidence study of diabetes mellitus in New Zealand children aged 0 to 14 years*. Diabetologia, 2005. 48(4): p. 643-8.
116. Devendra, D., E. Liu, and G.S. Eisenbarth, *Type 1 diabetes: recent developments*. Bmj, 2004. 328(7442): p. 750-4.
117. Vogt, R.F., Jr., et al., *Newborn screening and type 1 diabetes: historical perspective and current activities at the CDC Division of Laboratory Sciences*. Diabetes Technol Ther, 2003. 5(6): p. 1017-21.
118. Todd, J.A., *From genome to aetiology in a multifactorial disease, type 1 diabetes*. Bioessays, 1999. 21(2): p. 164-74.
119. She, J.X., *Susceptibility to type 1 diabetes: HLA-DQ and DR revisited*. Immunol Today, 1996. 17(7): p. 323-9.
120. Clayton, D.G., *Prediction and Interaction in Complex Disease Genetics: Experience in Type 1 Diabetes*. PLoS Genet, 2009. 5(7): p. e1000540.
121. Barrett, J.C., et al., *Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes*. Nat Genet, 2009.
122. Hagopian, W.A., et al., *TEDDY--The Environmental Determinants of Diabetes in the Young: an observational clinical trial*. Ann N Y Acad Sci, 2006. 1079: p. 320-6.
123. Dahlquist, G.G., et al., *Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. A population-based case-control study*. Diabetes, 1995. 44(4): p. 408-13.
124. Virtanen, S.M. and M. Knip, *Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age*. Am J Clin Nutr, 2003. 78(6): p. 1053-67.
125. Borkar, V.V., S. Verma, and A. Bhalla, *Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes*. Pediatr Diabetes, 2009.
126. Greer, R.M., et al., *Australian children and adolescents with type 1 diabetes have low vitamin D levels*. Med J Aust, 2007. 187(1): p. 59-60.
127. Petrovsky, N., *Immunomodulation with microbial vaccines to prevent type 1 diabetes mellitus*. Nat Rev Endocrinol. 6(3): p. 131.
128. Ponsonby, A.L. and A. Kemp, *Investigation of the hygiene hypothesis: current issues and future directions*. Allergy, 2008. 63(5): p. 506-8.
129. Hagglof, B., et al., *The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood*. Diabetologia, 1991. 34(8): p. 579-83.
130. Nucci, A., et al., *prevention of type 1 diabetes in children through nutrition intervention: the trial to reduce insulin dependent diabetes in the genetically at risk*. Journal of the American Dietetic Association, 2003. 103(Supplement 9): p. 79.
131. Caicedo, R.A., et al., *Neonatal Nutritional Interventions in the Prevention of Type 1 Diabetes*. Neoreviews, 2005. 6(5): p. e220-226.

132. Pozzilli, P., *The DPT-1 trial: a negative result with lessons for future type 1 diabetes prevention*. *Diabetes Metab Res Rev*, 2002. 18(4): p. 257-9.
133. Daaboul, J. and D. Schatz, *Overview of prevention and intervention trials for type 1 diabetes*. *Rev Endocr Metab Disord*, 2003. 4(4): p. 317-23.
134. Heath, V., *A crossroads for diabetes care?* *Nat Rev Endocrinol*, 2010. 6(3): p. 117.
135. Burke, W., *Clinical validity and clinical utility of genetic tests*. *Curr Protoc Hum Genet*, 2009. Chapter 9: p. Unit 9 15.
136. Haddow, J. and G. Palomaki, *ACCE a model process for evaluating data on emerging genetic tests*, in *Human Genome Epidemiology*, M. Khoury, J. Little, and W. Burke, Editors. 2004, Oxford University Press: New York. p. 217–233.
137. Grosse, S.D. and M.J. Khoury, *What is the clinical utility of genetic testing?* *Genet Med*, 2006. 8(7): p. 448-50.
138. Burke, W., et al., *Genetic test evaluation: information needs of clinicians, policy makers, and the public*. *Am J Epidemiol*, 2002. 156(4): p. 311-8.
139. Kerruish, N.J., et al., *Maternal psychological reaction to newborn genetic screening for type 1 diabetes*. *Pediatrics*, 2007. 120: p. E324 - E335.
140. Kupila, A., et al., *Feasibility of genetic and immunological prediction of type 1 diabetes in a population based cohort*. *Diabetologia*, 2001. 44: p. 290–297.
141. Ross, L.F., *Against newborn screening for type 1 diabetes*. *Arch Pediatr Adolesc Med*, 2007. 161(6): p. 616-7; author reply 617-8.
142. Mihaescu, R., et al., *Evaluation of risk prediction updates from commercial genome-wide scans*. *Genet Med*, 2009. 11(8): p. 588-94.
143. Hunter, D.J., M.J. Khoury, and J.M. Drazen, *Letting the Genome out of the Bottle -- Will We Get Our Wish?* *N Engl J Med*, 2008. 358(2): p. 105-107.
144. McBride, C.M., et al., *The behavioral response to personalized genetic information: will genetic risk profiles motivate individuals and families to choose more healthful behaviors?* *Annu Rev Public Health*. 31: p. 89-103.
145. Barker, J.M., et al., *Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up*. *Diabetes Care*, 2004. 27(6): p. 1399-404.
146. Marteau, T.M. and C. Lerman, *Genetic risk and behavioural change*. *Bmj*, 2001. 322(7293): p. 1056-9.
147. Thelin, T., et al., *Psychological consequences of neonatal screening for alpha 1 antitrypsin deficiency (ATD). Parental attitudes toward "ATD-check-ups" and parental recommendations regarding future screening*. *Acta Paediatr Scand*, 1985. 74(6): p. 841-7.
148. Kerruish, N.J. and S.P. Robertson, *Newborn screening: new developments, new dilemmas*. *J Med Ethics*, 2005. 31(7): p. 393-8.
149. Green, J., et al., *Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review*. *Health Technol Assess*, 2004. 8: p. 1-109.
150. Duff, A. and K. Brownlee, *Psychosocial aspects of newborn screening programs for cystic fibrosis*. *Children's health care*, 2008. 37: p. 21-37.
151. McNeil, T.F., et al., *Identifying children at high somatic risk: long-term effects on mother-child interaction*. *Acta Psychiatr Scand*, 1986. 74(6): p. 555-62.
152. McNeil, T.F., et al., *Identifying children at high somatic risk: possible effects on the parents' views of the child's health and parents' relationship to the pediatric health services*. *Acta Psychiatr Scand*, 1985. 72(6): p. 491-7.
153. Parsons, E.P., A.J. Clarke, and D.M. Bradley, *Implications of carrier identification in newborn screening for cystic fibrosis*. *Arch Dis Child Fetal Neonatal Ed*, 2003. 88(6): p. F467-71.
154. Beucher, J., et al., *Psychological effects of false-positive results in cystic fibrosis newborn screening: a two-year follow-up*. *J Pediatr*. 156(5): p. 771-6, 776 e1.

155. Luecken, L.J. and K.S. Lemery, *Early caregiving and physiological stress responses*. *Clinical Psychology Review*, 2004. 24(2): p. 171.
156. Webb, S.J., C.S. Monk, and C.A. Nelson, *Mechanisms of postnatal neurobiological development: implications for human development*. *Dev Neuropsychol*, 2001. 19(2): p. 147-71.
157. Caspi, A., et al., *Socially isolated children 20 years later: risk of cardiovascular disease*. *Arch Pediatr Adolesc Med*, 2006. 160(8): p. 805-11.
158. Liu, D., et al., *Maternal care, hippocampal synaptogenesis and cognitive development in rats*. *Nat Neurosci*, 2000. 3(8): p. 799-806.
159. Liu, D., et al., *Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress*. *Science*, 1997. 277(5332): p. 1659-62.
160. Teicher, M.H., et al., *Developmental neurobiology of childhood stress and trauma*. *Psychiatr Clin North Am*, 2002. 25(2): p. 397-426, vii-viii.
161. Essex, M.J., et al., *Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior*. *Biological Psychiatry*, 2002. 52(8): p. 776.
162. Smider, N.A., et al., *Salivary cortisol as a predictor of socioemotional adjustment during kindergarten: a prospective study*. *Child Dev*, 2002. 73(1): p. 75-92.
163. Welberg, L.A. and J.R. Seckl, *Prenatal stress, glucocorticoids and the programming of the brain*. *J Neuroendocrinol*, 2001. 13(2): p. 113-28.
164. Brockington, I., *Postpartum psychiatric disorders*. *Lancet*, 2004. 363(9405): p. 303-10.
165. Mertin, P.G., *Maternal-infant attachment: a developmental perspective*. *Aust N Z J Obstet Gynaecol*, 1986. 26(4): p. 280-3.
166. Tracy, R.L. and M.D. Ainsworth, *Maternal affectionate behavior and infant-mother attachment patterns*. *Child Dev*, 1981. 52(4): p. 1341-3.
167. Colin, V. *Infant attachment: what we know now*. 1991 [cited 1/4/10]; Available from: <http://aspe.hhs.gov/daltcp/Reports/inatrpt.pdf>.
168. De Wolff, M.S. and M.H. van Ijzendoorn, *Sensitivity and attachment: a meta-analysis on parental antecedents of infant attachment*. *Child Dev*, 1997. 68(4): p. 571-91.
169. Leavitt, L.A., *Research to practice: Emotional development and maternal/infant attachment*. *Journal of Pediatric Health Care*. 13(3, Part 2): p. S4.
170. Ranson, K.E. and L.J. Urichuk, *The effect of parent-child attachment relationships on child biopsychosocial outcomes: a review*. *Early Child Development and Care*, 2006. 178(2): p. 129-152.
171. Cooper, P.J., et al., *Improving quality of mother-infant relationship and infant attachment in socioeconomically deprived community in South Africa: randomised controlled trial*. *BMJ*, 2009. 338(apr14\_2): p. b974-.
172. Allen, E.C., et al., *Perception of child vulnerability among mothers of former premature infants*. *Pediatrics*, 2004. 113(2): p. 267-73.
173. Kokotos, F., *The vulnerable child syndrome*. *Pediatr Rev*, 2009. 30(5): p. 193-4.
174. Green, M. and A.J. Solnit, *Reactions To The Threatened Loss Of A Child: A Vulnerable Child Syndrome*. *Pediatric Management Of The Dying Child, Part Iii*. *Pediatrics*, 1964. 34: p. 58-66.
175. Rothenberg, M. and E. Sills, *Iatrogenesis: the PKU anxiety syndrome*. *Journal of the American Academy of Child Psychology*, 1968. 7: p. 689-92.
176. Bergman, A.B. and S.J. Stamm, *The morbidity of cardiac nondisease in schoolchildren*. *N Engl J Med*, 1967. 276(18): p. 1008-13.
177. Sigal, J.J., et al., *Later psychosocial sequelae of early childhood illness (severe croup)*. *Am J Psychiatry*, 1973. 130(7): p. 786-9.

178. Sigal, J. and P. Gagnon, *Effects of parents' and pediatricians' worry concerning severe gastroenteritis in early childhood on later disturbances in the child's behavior.* J Pediatr, 1975. 87(5): p. 809-14.
179. Leslie, L.K. and W.T. Boyce, *Consultation with the specialist. The vulnerable child.* Pediatr Rev, 1996. 17(9): p. 323-6.
180. Lipstein, E., *Helping "vulnerable" children - and their parents - lead normal lives.* Contemporary Pediatrics, 2006. 23: p. 26-37.
181. Duncan, A.F. and M.O. Caughy, *Parenting style and the vulnerable child syndrome.* J Child Adolesc Psychiatr Nurs, 2009. 22(4): p. 228-34.
182. Dogan, D.G., et al., *Perception of vulnerability among mothers of healthy infants in a middle-income country.* Child Care Health Dev, 2009. 35(6): p. 868-72.
183. Bailey, D.B., Jr., et al., *Ethical, legal, and social concerns about expanded newborn screening: fragile X syndrome as a prototype for emerging issues.* Pediatrics, 2008. 121(3): p. e693-704.
184. Ross, L.F., *Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy.* Am J Med Genet A, 2006. 140(8): p. 914-22.
185. Gurian, E.A., et al., *Expanded newborn screening for biochemical disorders: the effect of a false-positive result.* Pediatrics, 2006. 117(6): p. 1915-21.
186. Kwon, C. and P.M. Farrell, *The magnitude and challenge of false-positive newborn screening test results.* Arch Pediatr Adolesc Med, 2000. 154(7): p. 714-8.
187. Sweetman, L., *Newborn screening by tandem mass spectrometry: gaining experience.* Clin Chem, 2001. 47(11): p. 1937-8.
188. Derks, T.G., et al., *Neonatal screening for medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in The Netherlands: the importance of enzyme analysis to ascertain true MCAD deficiency.* J Inherit Metab Dis, 2008. 31(1): p. 88-96.
189. Ledley, F.D., et al., *Benign methylmalonic aciduria.* N Engl J Med, 1984. 311(16): p. 1015-1018.
190. Lam, W.K., et al., *Histidinaemia: a benign metabolic disorder.* Arch Dis Child, 1996. 74(4): p. 343-6.
191. Fyro, K., *Neonatal screening: life-stress scores in families given a false-positive result.* Acta Paediatr Scand, 1988. 77(2): p. 232-8.
192. Bodegard, G., K. Fyro, and A. Larsson, *Psychological reactions in 102 families with a newborn who has a falsely positive screening test for congenital hypothyroidism.* Acta Paediatr Scand Suppl, 1983. 304: p. 1-21.
193. Fyro, K. and G. Bodegard, *Difficulties in psychological adjustment to a new neonatal screening programme.* Acta Paediatr Scand, 1988. 77(2): p. 226-31.
194. Tymstra, T., *False positive results in screening tests: experiences of parents of children screened for congenital hypothyroidism.* Fam Pract, 1986. 3(2): p. 92-6.
195. Farrell, P.M., et al., *Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth.* Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics, 2001. 107(1): p. 1-13.
196. Moran, J., et al., *Newborn screening for CF in a regional paediatric centre: the psychosocial effects of false-positive IRT results on parents.* J Cyst Fibros, 2007. 6(3): p. 250-4.
197. Tluczek, A., et al., *Psychosocial risk associated with newborn screening for cystic fibrosis: parents' experience while awaiting the sweat-test appointment.* Pediatrics, 2005. 115(6): p. 1692-703.
198. Tluczek, A., et al., *Psychological impact of false-positive results when screening for cystic fibrosis.* Pediatr Pulmonol Suppl, 1991. 7: p. 29-37.
199. Borry, P., H. Nys, and K. Dierickx, *Carrier testing in minors: conflicting views.* Nat Rev Genet, 2007. 8(11): p. 828.

200. Parsons, E.P. and D.M. Bradley, *Psychosocial issues in newborn screening for cystic fibrosis*. Paediatr Respir Rev, 2003. 4(4): p. 285-92.
201. Tluczek, A., et al., *Parents' knowledge of neonatal screening and response to false-positive cystic fibrosis testing*. J Dev Behav Pediatr, 1992. 13(3): p. 181-6.
202. Lewis, S., et al., *Parental attitudes to the identification of their infants as carriers of cystic fibrosis by newborn screening*. J Paediatr Child Health, 2006. 42(9): p. 533-7.
203. Cavanagh, L., et al., *Long-term evaluation of genetic counseling following false-positive newborn screen for cystic fibrosis*. J Genet Couns. 19(2): p. 199-210.
204. Hayeems, R., J. Bytautas, and F. Miller, *A Systematic Review of the Effects of Disclosing Carrier Results Generated Through Newborn Screening*. Journal of Genetic Counseling, 2008. 17(6): p. 538.
205. Save babies through screening website. Available at <http://www.savebabies.org/>. [cited 26/5/03].
206. Ciske, D.J., et al., *Genetic counseling and neonatal screening for cystic fibrosis: an assessment of the communication process*. Pediatrics, 2001. 107(4): p. 699-705.
207. Mischler, E.H., et al., *Cystic fibrosis newborn screening: impact on reproductive behavior and implications for genetic counseling*. Pediatrics, 1998. 102(1 Pt 1): p. 44-52.
208. Ioannou, L., et al., *Population-Based Genetic Screening for Cystic Fibrosis: Attitudes and Outcomes*. Public Health Genomics, 2010, 13 (7-8) 449-56.
209. Denayer, L., et al., *Reproductive decision making of aunts and uncles of a child with cystic fibrosis: genetic risk perception and attitudes toward carrier identification and prenatal diagnosis*. Am J Med Genet, 1992. 44(1): p. 104-11.
210. al-Jader, L.N., et al., *Attitudes of parents of cystic fibrosis children towards neonatal screening and antenatal diagnosis*. Clin Genet, 1990. 38(6): p. 460-5.
211. Dudding, T., et al., *Reproductive decisions after neonatal screening identifies cystic fibrosis*. Arch Dis Child Fetal Neonatal Ed, 2000. 82(2): p. F124-7.
212. Jedlicka-Kohler, I., M. Gotz, and I. Eichler, *Utilization of prenatal diagnosis for cystic fibrosis over the past seven years*. Pediatrics, 1994. 94(1): p. 13-6.
213. Accurso, F.J., M.K. Sontag, and J.S. Wagener, *Complications associated with symptomatic diagnosis in infants with cystic fibrosis*. J Pediatr, 2005. 147(3 Suppl): p. S37-41.
214. Pollitt, R.J., et al., *Neonatal screening for inborn errors of metabolism: cost, yield and outcome*. Health Technol Assess, 1997. 1(7): p. i-iv, 1-202.
215. Baroni, M.A., Y.E. Anderson, and E. Mischler, *Cystic fibrosis newborn screening: impact of early screening results on parenting stress*. Pediatr Nurs, 1997. 23(2): p. 143-51.
216. Boland, C. and N.L. Thompson, *Effects of newborn screening of cystic fibrosis on reported maternal behaviour*. Arch Dis Child, 1990. 65(11): p. 1240-4.
217. Campbell, E. and L.F. Ross, *Professional and personal attitudes about access and confidentiality in the genetic testing of children: a pilot study*. Genet Test, 2003. 7(2): p. 123-30.
218. Quinlivan, J.A. and C. Suriadi, *Attitudes of new mothers towards genetics and newborn screening*. J Psychosom Obstet Gynaecol, 2006. 27(1): p. 67-72.
219. Grob, R., *Is my sick child healthy? Is my healthy child sick? changing parental experiences of cystic fibrosis in the age of expanded newborn screening*. Soc Sci Med, 2008. 67(7): p. 1056-64.
220. Helton, J.L., et al., *Parental attitudes toward newborn screening for cystic fibrosis*. Pediatr Pulmonol Suppl, 1991. 7: p. 23-8.
221. Merelle, M.E., et al., *Early versus late diagnosis: psychological impact on parents of children with cystic fibrosis*. Pediatrics, 2003. 111(2): p. 346-50.

222. Tluczek, A., A. Chevalier McKechnie, and P.A. Lynam, *When the cystic fibrosis label does not fit: a modified uncertainty theory*. Qual Health Res. 20(2): p. 209-23.
223. Lipstein, E.A., et al., *Impact of false-positive newborn metabolic screening results on early health care utilization*. Genet Med, 2009. 11(10): p. 716-21.
224. Hewlett, J. and S.E. Waisbren, *A review of the psychosocial effects of false-positive results on parents and current communication practices in newborn screening*. J Inherit Metab Dis, 2006. 29(5): p. 677-82.
225. Waisbren, S.E., et al., *Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress*. JAMA, 2003. 290(19): p. 2564-2572.
226. Parsons, E. and D. Bradley, *Complementary methodologies in the evaluation of newborn screening for duchenne muscular dystrophy*, in *The genetic testing of children*, A. Clarke, Editor. 1998, BIOS Scientific Publishers Ltd: Oxford. p. 211-222.
227. Parsons, E.P., et al., *Newborn screening for Duchenne muscular dystrophy: a psychosocial study*. Arch Dis Child Fetal Neonatal Ed, 2002. 86(2): p. F91-5.
228. Marteau, T.M. and H. Bekker, *The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI)*. Br J Clin Psychol, 1992. 31 (Pt 3): p. 301-6.
229. Salariya, E.M. and J.I. Cater, *Mother-child relationship--FIRST score*. J Adv Nurs, 1984. 9(6): p. 589-95.
230. McNeil, T.F., T. Sveger, and T. Thelin, *Psychosocial effects of screening for somatic risk: the Swedish alpha 1 antitrypsin experience*. Thorax, 1988. 43(7): p. 505-7.
231. Sveger, T. and T. Thelin, *Four-year-old children with alpha 1-antitrypsin deficiency. Clinical follow-up and parental attitudes towards neonatal screening*. Acta Paediatr Scand, 1981. 70(2): p. 171-7.
232. Sveger, T., T. Thelin, and T. McNeil, *A risk group's visits to medical services: five years' usage of well-baby and medical clinics by a group of children with alpha 1-antitrypsin deficiency*. Acta Paediatr Scand, 1985. 74(5): p. 782-6.
233. Thelin, T., et al., *Psychological consequences of neonatal screening for alpha 1-antitrypsin deficiency. Parental reactions to the first news of their infants' deficiency*. Acta Paediatr Scand, 1985. 74(5): p. 787-93.
234. Thelin, T., et al., *Identifying children at high somatic risk: parents' long-term emotional adjustment to their children's alpha 1 antitrypsin deficiency*. Acta Psychiatr Scand, 1985. 72(4): p. 323-30.
235. Thelin, T., et al., *Identifying children at high somatic risk: possible long-term effects on the parents' attitudes toward themselves as parents and toward having more children*. Acta Psychiatr Scand, 1985. 72(1): p. 74-80.
236. Thelin, T., et al., *Identifying children at high somatic risk: possible long-term effects on the parents' views of their own health and current life situation*. Acta Psychiatr Scand, 1985. 71(6): p. 644-53.
237. Thelin, T., T.F. McNeil, and T. Sveger, *Identifying children at high somatic risk (alpha 1 antitrypsin deficiency): possible long-term effects on parents' reproduction, marital status and social class level*. Acta Psychiatr Scand, 1985. 71(6): p. 636-43.
238. Senior, V., T.M. Marteau, and T.J. Peters, *Will genetic testing for predisposition for disease result in fatalism? A qualitative study of parents responses to neonatal screening for familial hypercholesterolaemia*. Soc Sci Med, 1999. 48(12): p. 1857-60.
239. Beeso, J., et al., *Screening for hypercholesterolaemia in 10,000 neonates in a multi-ethnic population*. Eur J Pediatr, 1999. 158(10): p. 833-7.
240. Bailey, D.B., Jr., et al., *No Change in the Age of Diagnosis for Fragile X Syndrome: Findings From a National Parent Survey*. Pediatrics, 2009. 124(2): p. 527-533.
241. Hayes, E.W. and R. Matalon, *Fragile X Syndrome*. Pediatrics, 2009. 124(2): p. 790-792.

242. Saul, R.A., et al., *Fragile X syndrome detection in newborns-pilot study*. Genet Med, 2008. 10(10): p. 714-9.
243. Hantash, F.M., et al., *Qualitative assessment of FMR1 (CGG)<sub>n</sub> triplet repeat status in normal, intermediate, premutation, full mutation, and mosaic carriers in both sexes: Implications for fragile X syndrome carrier and newborn screening*. Genet Med.
244. Skinner, D., K.L. Sparkman, and D.B. Bailey, Jr., *Screening for Fragile X Syndrome: parent attitudes and perspectives*. Genet Med, 2003. 5(5): p. 378-84.
245. Acharya, K., P.D. Ackerman, and L.F. Ross, *Pediatricians' attitudes toward expanding newborn screening*. Pediatrics, 2005. 116(4): p. e476-84.
246. Hiraki, S., et al., *Attitudes of genetic counselors towards expanding newborn screening and offering predictive genetic testing to children*. Am J Med Genet A, 2006. 140(21): p. 2312-9.
247. Yu, M.S., et al., *Impact on maternal parenting stress of receipt of genetic information regarding risk of diabetes in newborn infants*. Am J Med Genet, 1999. 86(3): p. 219-26.
248. Thomas, K.A., M.T. Renaud, and D. Depaul, *Use of the parenting stress index in mothers of preterm infants*. Adv Neonatal Care, 2004. 4(1): p. 33-41.
249. Bennett Johnson, S., et al., *Maternal anxiety associated with newborn genetic screening for type 1 diabetes*. Diabetes Care, 2004. 27(2): p. 392-7.
250. Hood, K.K., et al., *Depressive symptoms in mothers of infants identified as genetically at risk for type 1 diabetes*. Diabetes Care, 2005. 28(8): p. 1898-903.
251. Goldstein, E., et al., *From genetic risk awareness to overt type 1 diabetes: parental stress in a placebo-controlled prevention trial*. Diabetes Care, 2009. 32(12): p. 2181-3.
252. Simonen, P., et al., *Parental Reactions to Information About Increased Genetic Risk of Type 1 Diabetes Mellitus in Infants*. Arch Pediatr Adolesc Med, 2006. 160(11): p. 1131-1136.
253. Baughcum, A.E., et al., *Maternal Efforts to Prevent Type 1 Diabetes in At-Risk Children*. Diabetes Care, 2005. 28(4): p. 916-921.
254. Ghosh, A.K. and K. Ghosh, *Communication of false-positive tests--can it be improved?* The American Journal of Medicine, 2003. 114(9): p. 768.
255. Parsons, E., D. Bradley, and A. Clarke, *Disclosure of Duchenne muscular dystrophy after newborn screening*. Arch Dis Child, 1996. 74(6): p. 550-3.
256. Prosser, L.A., et al., *Parental tolerance of false-positive newborn screening results*. Arch Pediatr Adolesc Med, 2008. 162(9): p. 870-6.
257. Plass, A.M.C., et al., *Neonatal Screening for Treatable and Untreatable Disorders: Prospective Parents' Opinions*. Pediatrics. 125(1): p. e99-106.
258. Campbell, E. and L.F. Ross, *Parental attitudes regarding newborn screening of PKU and DMD*. Am J Med Genet A, 2003. 120(2): p. 209-14.
259. Parsons, E.P., D.M. Bradley, and A.J. Clarke, *Newborn screening for Duchenne muscular dystrophy*. Arch Dis Child, 2003. 88(1): p. 91-2.
260. McNeil, T.F., et al., *Identifying children at high somatic risk: possible long-term effects on parental conceptualizations of the children's personality and behavior*. Acta Psychiatr Scand, 1985. 72(6): p. 498-504.
261. Perobelli, S., et al., *Inconclusive Cystic Fibrosis neonatal screening results: long-term psychosocial effects on parents*. Acta Paediatr, 2009.
262. Rice, P.L. and D. Ezzy, *Qualitative research methods: a health focus*, ed. R. Singh. 1999: Oxford University Press. 295.
263. Ritchie, J. and J. Lewis, eds. *Qualitative research practice: a guide for social science students and researchers*. 2003, Sage: London.
264. Hammersley, M., *What's wrong with ethnography?* 1992, London: Routledge. 230.

265. Mays, N. and C. Pope, *Qualitative research in health care: Assessing quality in qualitative research*. BMJ, 2000. 320(7226): p. 50-52.
266. Crotty, M., *The foundations of social research: meaning and perspective in the research process*. 1998, Crows Nest, NSW: Allen and Unwin.
267. Smith, J., *The nature of social and educational enquiry: empiricism and interpretation*. 1989, Norwood, NJ: Ablex.
268. Pope, C. and N. Mays, *Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research*. Bmj, 1995. 311(6996): p. 42-5.
269. Stuart, S., et al., *Postpartum anxiety and depression: onset and comorbidity in a community sample*. J Nerv Ment Dis, 1998. 186(7): p. 420-4.
270. Spielberger, C., et al., *STAI Manual for the State Trait Anxiety Inventory*. 1970, Palo Alto, California: Consulting Psychologists Press.
271. Cox, J.L., J.M. Holden, and R. Sagovsky, *Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale*. Br J Psychiatry, 1987. 150: p. 782-6.
272. Pallant, J., R. Miller, and A. Tennant, *Evaluation of the Edinburgh Post Natal Depression Scale using Rasch analysis*. BMC Psychiatry, 2006. 6(1): p. 28.
273. Boyce, P., J. Stubbs, and A. Todd, *The Edinburgh Postnatal Depression Scale: validation for an Australian sample*. Aust N Z J Psychiatry, 1993. 27(3): p. 472-6.
274. Cox, J.L., et al., *Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women*. J Affect Disord, 1996. 39(3): p. 185-9.
275. Webster, M.L., et al., *Postnatal depression in a community cohort*. Aust N Z J Psychiatry, 1994. 28(1): p. 42-9.
276. Thomasgard, M. and W.P. Metz, *The vulnerable child syndrome revisited*. J Dev Behav Pediatr, 1995. 16(1): p. 47-53.
277. Sveger, T. and T. Thelin, *A future for neonatal alpha1-antitrypsin screening?* Acta Paediatr, 2000. 89(6): p. 628-31.
278. Green, M. and A.J. Solnit, *Reactions to the threatened loss of a child: A vulnerable child syndrome*. Pediatrics, 1964. 34: p. 58-66.
279. Leslie, L.K. and W.T. Boyce, *The Vulnerable Child*. Pediatrics in Review, 1996. 17(9): p. 323-326.
280. Kerruish, N.J., et al., *Vulnerable Baby Scale: development and piloting of a questionnaire to measure maternal perceptions of their baby's vulnerability*. J Paediatr Child Health, 2005. 41(8): p. 419-23.
281. Forsyth, B.W.C. and P.F. Canny, *Perceptions of Vulnerability 3 1/2 Year After Problems of Feeding and Crying Behaviour in Early Infancy*. Pediatrics, 1991. 88(4): p. 757-763.
282. Kline, P., *A handbook of test construction*. 1986, London: Methuen.
283. Bland, J.M. and D.G. Altman, *Statistics Notes: Validating scales and indexes*. Bmj, 2002. 324(7337): p. 606-7.
284. Kemper, K., B. Forsyth, and P. McCarthy, *Jaundice, Terminating Breast-Feeding, and the Vulnerable Child*. Pediatrics, 1989. 84(5): p. 773-778.
285. Parsons, E. and P. Atkinson, *Lay construction of genetic risk*. Sociology of health and illness, 1992. 14(4): p. 437-455.
286. Eiser, J.R., *Communication and interpretation of risk*. Br Med Bull, 1998. 54(4): p. 779-90.
287. Bates, B., et al., *What does "A gene for heart disease" mean? A focus group study of public understandings of genetic risk factors*. American Journal of Medical Genetics Part A, 2003. 119A(2): p. 156-161.
288. Giorgi, A., *Phenomenological psychology*, in *Rethinking methods in psychology*, J. Smith, R. Harre, and L. van Langenhove, Editors. 1995, Sage: London. p. 24-42.

289. Denzin, N., *Symbolic interactionism*, in *Rethinking methods in psychology*, J. Smith, R. Harre, and L. van Langenhove, Editors. 1995, Sage: London. p. 43-58.
290. Smith, J., *Beyond the divide: using interpretative phenomenological analysis in health psychology*. *Psychology and Health*, 1996. 11: p. 261-271.
291. Smith, J. and, *Semi-structured interviewing and qualitative analysis*, in *Rethinking methods in psychology*, J. Smith, Editor. 1995, Sage: London. p. 9-26.
292. Savelkoul, P.H., D.P. de Bruyn-Geraets, and E.M. van den Berg-Loonen, *High resolution HLA-DRB1 SSP typing for cadaveric donor transplantation*. *Tissue Antigens*, 1995. 45(1): p. 41-8.
293. Redondo, M.J., P.R. Fain, and G.S. Eisenbarth, *Genetics of type 1A diabetes*. *Recent Prog Horm Res*, 2001. 56: p. 69-89.
294. Bleich, D., et al., *Decreased risk of type 1 diabetes in offspring of mothers who acquire diabetes during adrenarchy*. *Diabetes*, 1993. 42(10): p. 1433-9.
295. Dahlquist, G., et al., *The Swedish childhood diabetes study--results from a nine year case register and a one year case-referent study indicating that type 1 (insulin-dependent) diabetes mellitus is associated with both type 2 (non-insulin-dependent) diabetes mellitus and autoimmune disorders*. *Diabetologia*, 1989. 32(1): p. 2-6.
296. Tillil, H. and J. Kobberling, *Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients*. *Diabetes*, 1987. 36(1): p. 93-9.
297. Tuomilehto, J., et al., *Epidemiology of childhood diabetes mellitus in Finland--background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. The Childhood Diabetes in Finland (DiMe) Study Group*. *Diabetologia*, 1992. 35(1): p. 70-6.
298. Warram, J.H., et al., *Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers*. *N Engl J Med*, 1984. 311(3): p. 149-52.
299. Trialnet website. [cited 5/4/06]; Available from: <http://www.diabetestrialnet.org/>.
300. Stata Corporation, *Intercooled Stata Version 8 for Windows*, C. station, Editor. 2003, Stata corporation: TX 77840.
301. O'Hara, M. and A. Swain, *Rates and risk of postpartum depression: A meta-analysis*. *Int Rev Psychiatry*, 1996. 8: p. 37-54.
302. Broadstock, M., S. Michie, and T. Marteau, *Psychological consequences of predictive genetic testing: a systematic review*. *Eur J Hum Genet*, 2000. 8(10): p. 731-8.
303. Eberhard-Gran, M., et al., *Review of validation studies of the Edinburgh Postnatal Depression Scale*. *Acta Psychiatr Scand*, 2001. 104(4): p. 243-9.
304. Abidin, R., ed. *Parenting Stress Index: Professional Manual*. 3rd ed. 1995, Psychological Assessment Resources: Odessa, FL.
305. Catz, D.S., et al., *Attitudes about genetics in underserved, culturally diverse populations*. *Community Genet*, 2005. 8(3): p. 161-72.
306. Chenail, R. and, *Presenting qualitative data. The Qualitative Report*, 1995. Volume 2, (Number 3).
307. Whitmarsh, I., et al., *A place for genetic uncertainty: parents valuing an unknown in the meaning of disease*. *Soc Sci Med*, 2007. 65(6): p. 1082-93.
308. Anonymous, *Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors*. *American Journal of Human Genetics*, 1995. 57(5): p. 1233-41.
309. Resnik, D. and D. Vorhaus, *Genetic modification and genetic determinism*. *Philosophy, Ethics, and Humanities in Medicine*, 2006. 1(1): p. 9.
310. Skinner, E., *A guide to constructs of control*. *Journal of Personality and Social Psychology*, 1996. 71: p. 549-570.

311. Evers-Kiebooms, G., et al., *The psychological complexity of predictive testing for late onset neurogenetic diseases and hereditary cancers: implications for multidisciplinary counselling and for genetic education*. Soc Sci Med, 2000. 51(6): p. 831-41.
312. Saukko, P.M., et al., *Are genetic tests exceptional? Lessons from a qualitative study on thrombophilia*. Social Science & Medicine, 2006. 63(7): p. 1947.
313. Hodges, L. and B. Dibb, *Social comparison within self-help groups: views of parents of children with Duchenne muscular dystrophy*. J Health Psychol. 15(4): p. 483-92.
314. Senior, V., et al., *Making sense of risk: an interpretative phenomenological analysis of vulnerability to heart disease*. Journal of health psychology, 2002. 7(2): p. 157-168.
315. Cameron, L.D., et al., *Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests*. Health Psychol, 2009. 28(3): p. 307-16.
316. Shiloh, S. and M. Sagi, *Effect of framing on the perception of genetic recurrence risks*. Am J Med Genet, 1989. 33(1): p. 130-5.
317. Wenzel, L., C. Lerman, and K. Glanz, *Stress, coping and health behaviour.*, in *Health behaviour and health education: Theory, research, and practice.*, K. Glanz, F. Lewis, and B. Rimer, Editors. 2002, Jossey-Bass: San Francisco, CA. p. 210-239.
318. Miller, S.M., *Monitoring versus blunting styles of coping with cancer influence the information patients want and need about their disease. Implications for cancer screening and management*. Cancer, 1995. 76(2): p. 167-77.
319. Miller, S.M., *Monitoring and blunting: validation of a questionnaire to assess styles of information seeking under threat*. J Pers Soc Psychol, 1987. 52(2): p. 345-53.
320. Samour, P., K. King, and C. Lang, *Handbook of Pediatric Nutrition*. 1999, Gaithersburg, Md: Aspen.
321. Hendriks, K.S., et al., *Can parents adjust to the idea that their child is at risk for a sudden death? Psychological impact of risk for long QT syndrome*. Am J Med Genet A, 2005. 138(2): p. 107-12.
322. Zipitis, C.S. and A.K. Akobeng, *Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis*. Arch Dis Child, 2008. 93(6): p. 512-7.
323. Moran, T.E. and M.W. O'Hara, *Maternal psychosocial predictors of pediatric health care use: Use of the common sense model of health and illness behaviors to extend beyond the usual suspects*. Clin Eff Nurs, 2006. 9(Supplement 2): p. e171-e180.
324. Gooding, H.C., et al., *Genetic susceptibility testing from a stress and coping perspective*. Soc Sci Med, 2006. 62(8): p. 1880-90.
325. Marteau, T.M. and J. Weinman, *Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research*. Soc Sci Med, 2006. 62(6): p. 1360-8.
326. Shiloh, S., *Illness representations, self-regulation, and genetic counseling: a theoretical review*. J Genet Couns, 2006. 15(5): p. 325-37.
327. Leventhal, H., et al., *Illness Representations: Theoretical Foundations*, in *Perceptions of Health and Illness*, K. Petrie and J. Weinman, Editors. 1997, Harwood Academic Publishers: Amsterdam. p. 19-46.
328. Leventhal, H., D. Nerenz, and D. Steele, *Illness representations and coping with health threats*, in *Handbook of Psychology and Health*, A. Baum, S. Taylor, and J. Singer, Editors. 1984, Erlbaum: Hillsdale, New Jersey. p. 227-231.
329. Leventhal, H., K. Kelly, and E.A. Leventhal, *Population risk, actual risk, perceived risk, and cancer control: a discussion*. J Natl Cancer Inst Monogr, 1999(25): p. 81-5.
330. Leventhal, H., E. Levanthal, and L. Cameron, *Representations, procedures, and affect in illness self-regulation: a perceptual-cognitive approach*, in *Handbook of health psychology*, A. Baum, T. Revenson, and J. Singer, Editors. 2001, Erlbaum: New York. p. 19-48.

331. Langston, A.L., et al., *Protocol for stage 2 of the GaP study (genetic testing acceptability for Paget's disease of bone): a questionnaire study to investigate whether relatives of people with Paget's disease would accept genetic testing and preventive treatment if they were available*. BMC Health Serv Res, 2008. 8: p. 116.
332. Cameron, L., *Conceptualising and assessing risk perceptions: a self regulatory perspective.*, in *Workshop on Conceptualising (and Measuring) Perceived Risk*. 2003: National Cancer Institute.
333. Finucane, M.L., C.A. Peters, and P. Slovic, *Judgement and decision making: The dance of affect and reason.*, in *Emerging perspectives on Judgement and Decision Research*, S. Schneider and J. Shanteau, Editors. 2003, Cambridge University Press: Cambridge, UK. p. 327-364.
334. Slovic, P., et al., *Risk as analysis and risk as feelings: some thoughts about affect, reason, risk, and rationality*. Risk Anal, 2004. 24(2): p. 311-22.
335. Slovic, P., et al., *Affect, risk, and decision making*. Health Psychol, 2005. 24(4 Suppl): p. S35-40.
336. Renner, B., B. Schuz, and F.F. Sniehotta, *Preventive health behavior and adaptive accuracy of risk perceptions*. Risk Anal, 2008. 28(3): p. 741-8.
337. Janis, I. and L. Mann, *Decision making: a psychological analysis of conflict, choice and commitment*. 1977, New York: Free Press.
338. McBride, C.M., et al., *Future health applications of genomics: priorities for communication, behavioral, and social sciences research*. Am J Prev Med. 38(5): p. 556-65.
339. Thomas, D., *Methods for investigating gene-environment interactions in candidate pathway and genome-wide association studies*. Annu Rev Public Health. 31: p. 21-36.
340. Pezzoli, K., et al., *The NIEHS Environmental Health Sciences Data Resource Portal: placing advanced technologies in service to vulnerable communities*. Environ Health Perspect, 2007. 115(4): p. 564-71.
341. Kerruish, N., *New possibilities for newborn genetic screening: screening for genetic susceptibility to common disease*, in *Genes, society and the future: volume 1/Human genome research project*. 2007, Human genome research project: Dunedin, NZ. p. 295-328.
342. Radloff, L.S., *The CES-D scale: A self report depression scale for research in the general population*. Applied Psychological Measurement, 1977. 1: p. 385-401.
343. Tercyak, K.P., et al., *Effects of coping style and BRCA1 and BRCA2 test results on anxiety among women participating in genetic counseling and testing for breast and ovarian cancer risk*. Health Psychol, 2001. 20(3): p. 217-22.
344. Peshkin, B.N., et al., *Brief assessment of parents' attitudes toward testing minor children for hereditary breast/ovarian cancer genes: development and validation of the Pediatric BRCA1/2 Testing Attitudes Scale (P-TAS)*. J Pediatr Psychol, 2009. 34(6): p. 627-38.
345. Achenbach, T.M., *Integrative Guide to the 1991 CBCL/4-18, YSR, and TRF Profiles*. 1991, Burlington, VT: University of Vermont, Department of Psychology.
346. Spielberger, C.D., et al., *STAIC preliminary manual for the State-Trait Anxiety Inventory for Children*. 1973, Palo Alto, CA: Consulting Psychologists Press.
347. Abel, S., et al., *Infant care practices in New Zealand: a cross-cultural qualitative study*. Soc Sci Med, 2001. 53(9): p. 1135-48.
348. Bailey, D.B., Jr., et al., *Supporting Family Adaptation to Presymptomatic and "Untreatable" Conditions in an Era of Expanded Newborn Screening*. J. Pediatr. Psychol., 2009. 34(6): p. 648-661.
349. Barker, J., et al., *Clinical characteristics of type 1 diabetic children identified by a genetic screening and intensive follow-up program*. Diabetes, 2003. 52(suppl 1): p. A188.

350. Elliman, D.A., C. Dezateux, and H.E. Bedford, *Newborn and childhood screening programmes: criteria, evidence, and current policy*. Arch Dis Child, 2002. 87(1): p. 6-9.
351. Wilcken, B., *Expanded newborn screening: reducing harm, assessing benefit*. J Inherit Metab Dis, 2010, 33 (suppl 2) s205-10.
352. Lipinski, S.E., et al., *Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling*. Am J Med Genet C Semin Med Genet, 2006. 142C(4): p. 232-40.
353. Beale, E.A., W.F. Baile, and J. Aaron, *Silence Is Not Golden: Communicating With Children Dying From Cancer*. Journal of Clinical Oncology, 2005. 23(15): p. 3629-3631.
354. Schulman, A. *The future of newborn screening: Clouds on the horizon*. The Presidents council on bioethics 2009 [cited 1/1/09]; Available from: [http://www.bioethics.gov/background/newborn\\_screening\\_schulman.html](http://www.bioethics.gov/background/newborn_screening_schulman.html).
356. Harjutsalo, V., T. Podar, and J. Tuomilehto, *Cumulative Incidence of Type 1 Diabetes in 10,168 Siblings of Finnish Young-Onset Type 1 Diabetic Patients*. Diabetes, 2005. 54(2): p. 563-569.
357. Sleeman, F., et al., *Psychological adjustment of well siblings of children with Type 1 diabetes*. Diabetic Medicine. 27(9): p. 1084.
358. Moyer, V., et al., *What is the role for evidence-based decision making in expanded newborn screening*, in *Ethics and newborn screening: New technologies, new challenges*, M. Baily and T. Murray, Editors. 2009, Johns Hopkins University Press: Baltimore, Maryland. p. 195-211.
359. McCabe, L.L. and E.R. McCabe, *Expanded newborn screening: implications for genomic medicine*. Annu Rev Med, 2008. 59: p. 163-75.
360. Autti-Rämö, I., et al., *Expanding screening for rare metabolic disease in the newborn: An analysis of costs, effect and ethical consequences for decision-making in Finland*. Acta Paediatrica, 2005. 94(8): p. 1126.
361. *My gene profile, disease susceptibility genetic test website*. [cited 10/12/10]; Available from: <http://www.mychildtalentprofile.com/genetictest/upsell-adult.html>.
362. Ozdemir, V., et al., *Risk assessment and communication tools for genotype associations with multifactorial phenotypes: the concept of "edge effect" and cultivating an ethical bridge between omics innovations and society*. Omics, 2009. 13(1): p. 43-61.
363. Raskin, P. and A. Mohan, *Emerging treatments for the prevention of type 1 diabetes*. Expert Opin Emerg Drugs. 15(2): p. 225-36.
364. Chiu, R.W., et al., *Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study*. Bmj. 342: p. c7401.
365. Carlson, R.J., *The disruptive nature of personalized medicine technologies: implications for the health care system*. Public Health Genomics, 2009. 12(3): p. 180-4.
366. Lander, E.S., *Initial impact of the sequencing of the human genome*. Nature. 470(7333): p. 187.
367. Buchanan, A.V., K.M. Weiss, and S.M. Fullerton, *Dissecting complex disease: the quest for the Philosopher's Stone?* Int. J. Epidemiol., 2006. 35(3): p. 562-571.
368. Mill, J., et al., *Prediction of heterogeneity in intelligence and adult prognosis by genetic polymorphisms in the dopamine system among children with attention-deficit/hyperactivity disorder: evidence from 2 birth cohorts*. Arch Gen Psychiatry, 2006. 63(4): p. 462-9.
369. Bouchard, C., *Gene-Environment Interactions in the Etiology of Obesity: Defining the Fundamentals*. Obesity, 2008. 16(Supplement 3s): p. S5.
370. Evans, J.P., et al., *Deflating the Genomic Bubble*. Science. 331(6019): p. 861-862.

371. Port, R.V., et al., *Cultural enhancement of a clinical service to meet the needs of indigenous people; genetic service development in response to issues for New Zealand Maori*. Clin Genet, 2008. 73(2): p. 132-8.
372. Brasher, D., *Communication and uncertainty management*. Journal of communication, 2001: p. 477-497.



## Appendix A

### State Trait Anxiety Inventory (State Subscale, Form Y-1)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number beneath the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to best describe your present feelings best.

	<b>Not at all</b>	<b>Somewhat</b>	<b>Moderately</b>	<b>Very Much</b>
			<b>So</b>	<b>So</b>
1) I felt calm	1	2	3	4
2) I felt secure	1	2	3	4
3) I felt tense	1	2	3	4
4) I felt strained	1	2	3	4
5) I felt at ease	1	2	3	4
6) I felt upset	1	2	3	4
7) I was worrying over possible misfortunes	1	2	3	4
8) I felt satisfied	1	2	3	4
9) I felt frightened	1	2	3	4
10) I felt comfortable	1	2	3	4
11) I felt self confident	1	2	3	4
12) I felt nervous	1	2	3	4
13) I was jittery	1	2	3	4
14) I felt indecisive	1	2	3	4

	<b>Not at all</b>	<b>Somewhat</b>	<b>Moderately So</b>	<b>Very Much So</b>
<b>15)</b> I was relaxed	1	2	3	4
<b>16)</b> I felt content	1	2	3	4
<b>17)</b> I was worried	1	2	3	4
<b>18)</b> I felt confused	1	2	3	4
<b>19)</b> I felt steady	1	2	3	4
<b>20)</b> I felt pleasant	1	2	3	4

## Appendix B

### Edinburgh Postnatal Depression Scale

As you have recently had a baby, we would like to know how you are feeling. Please CIRCLE the answer which comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

1) I have been able to laugh and see the funny side of things.

- |                            |   |
|----------------------------|---|
| As much as I always could  | 1 |
| Not quite so much now      | 2 |
| Definitely not so much now | 3 |
| Not at all                 | 4 |

2) I have looked forward with enjoyment to things.

- |                                |   |
|--------------------------------|---|
| As much as I ever did          | 1 |
| Rather less than I used to     | 2 |
| Definitely less than I used to | 3 |
| Hardly at all                  | 4 |

3) I have blamed myself unnecessarily when things went wrong.

- |                       |   |
|-----------------------|---|
| Yes, most of the time | 1 |
| Yes, some of the time | 2 |
| Not very often        | 3 |
| No, never             | 4 |

4) I have been anxious or worried for no good reason.

- |                 |   |
|-----------------|---|
| No, not at all  | 1 |
| Hardly ever     | 2 |
| Yes, sometimes  | 3 |
| Yes, very often | 4 |

5) I have felt scared or panicky for not very good reason.

- |                  |   |
|------------------|---|
| Yes, quite a lot | 1 |
| Yes, sometimes   | 2 |
| No, not much     | 3 |
| No, not at all   | 4 |

- 6) Things have been getting on top of me.
- |  |   |
|--|---|
| Yes, most of the time I haven't been able to cope at all | 1 |
| Yes, sometimes I haven't been coping as well as usual    | 2 |
| No, most of the time I have coped quite well             | 3 |
| No, I have been coping as well as ever                   | 4 |

- 7) I have been so unhappy that I have had difficulty sleeping.

- |                       |   |
|-----------------------|---|
| Yes, most of the time | 1 |
| Yes, sometimes        | 2 |
| Not very often        | 3 |
| No, not at all        | 4 |

- 8) I have felt sad or miserable.

- |                       |   |
|-----------------------|---|
| Yes, most of the time | 1 |
| Yes, quite often      | 2 |
| Not very often        | 3 |
| No, not at all        | 4 |

- 9) I have been so unhappy that I have been crying.

- |                       |   |
|-----------------------|---|
| Yes, most of the time | 1 |
| Yes, quite often      | 2 |
| Only occasionally     | 3 |
| No, never             | 4 |

- 10) The thought of harming myself has occurred to me.

- |                  |   |
|------------------|---|
| Yes, quite often | 1 |
| Sometimes        | 2 |
| Hardly ever      | 3 |
| Never            | 4 |

## Appendix C

### Vulnerable Baby (Pepi (M)) Scale

The following statements and questions relate to aspects of your baby's health and development. For each item please circle the number that best indicates your response.

- 1) I generally check on baby while he/she is asleep at night:  
Not at all    **1**    **2**    **3**    **4**    **5**    Frequently  
1-2 times    (at least every  
each night    30 mins)
  
- 2) If baby was awake and playing I would leave them unattended and out of earshot for\*:  
Not at all    **1**    **2**    **3**    **4**    **5**    More than an  
About 15    hour  
Minutes
  
- 3) If a friend came to visit and they had a cold I would\*:  
Not allow    **1**    **2**    **3**    **4**    **5**    Ask them in  
them in    allow them in    and not restrict  
the house    but not to    contact with  
hold baby    baby
  
- 4) My baby seems to get stomach (puku (M)) pains or other pains\*:  
All the time **1**    **2**    **3**    **4**    **5**    Not at all
  
- 5) I am concerned that my baby isn't as healthy as he/she should be\*:  
Always    **1**    **2**    **3**    **4**    **5**    Not concerned
  
- 6) In general when I compare my baby's health to that of other children (tamariki (M))  
the same age I think he/she is\*:  
Less healthy    **1**    **2**    **3**    **4**    **5**    More healthy
  
- 7) I find myself worrying that my baby may become seriously ill\*:  
All the    **1**    **2**    **3**    **4**    **5**    Not at all  
Time
  
- 8) I worry about cot death (SIDS)\*:  
All the    **1**    **2**    **3**    **4**    **5**    Not at all  
time

9) If you left baby with someone else would you make contact with them while you were away?\*

Yes, definitely 1 2 3 4 5 No, not at all

10) In the last 2 weeks I've contacted a health professional (eg. Midwife, GP, after hours or emergency doctors, Plunket, Maori Health Provider)) about baby:

Not at all 1 2 3 4 5 Daily, or more

About once

a week

(This should not include routine visits that your midwife makes to see baby or that you make to your GP or Plunket for well child checks/immunization etc)

\* Reverse scored questions

(M) Maori words included in the questionnaire to try to increase the acceptability of the questionnaire to Maori participants in a New Zealand setting.

## **Appendix D**

### **Semi-structured interview schedule**

**1. Can you tell me a little about your family?**

Prompts/probes: children's' ages and health, parents' employment and health, history of diabetes

**2. Can you tell me about your decision to join the KEA study?**

Prompts/probes: reason(s) for deciding to have child tested

**3. Can you tell me about the day you received the genetic test result?**

Prompts/probes: emotional/psychological, practical, anything help/make it hard?

**4. What about later on? (reaction to test results)**

Prompts/probes: emotional/psychological, practical, anything help/make it hard?

**5. What does your child's test result mean to you**

Prompts/probes: what would you say if you were telling someone about it?

**6. Has the test result had any effect on your family life?**

Prompts/probes: practical e.g. monitoring, diet, emotional/psychological

**7. How do you feel about your child having had the test?**

Prompts/probes: future baby tested? advice for other parents? child's future? telling the child their test result?

# Appendix E KEA Study Participant Information Sheet

Paediatrics and Child Health

## DETAILED INFORMATION: PHASE 1

### ENVIRONMENTAL FACTORS INFLUENCING ONSET OF CHILDHOOD DIABETES



#### Aims

**This study has 2 phases.**

##### **Phase 1 aims to:**

- Screen all children at birth and identify the 10% of children at increased genetic risk for developing diabetes, (where increased risk means a 1 in 16 chance of developing diabetes before age 20 years).

##### **Phase 2 will aim to:**

- Follow the 10% of children identified above for 5 years, regularly monitoring for the appearance of antibodies. This will involve a very small amount of blood taken from a heel prick every 3 months.
- Identify any environmental stresses, by collecting information on each child's environment, that may be associated with antibody appearance, and therefore childhood diabetes. This involves completing the environment questionnaire every 3 months.

*If environmental stresses that can be altered or eliminated are found for childhood diabetes, then prevention efforts can be started.*

## What is involved

Children at increased genetic risk for developing diabetes during childhood will be identified at birth. This requires a sample of blood, taken from the umbilical cord or after birth (not from baby) once baby has been born. We will also record birth details like weight and length.

Prior to baby's birth, we will also ask you some questions about your home environment (as an indicator of the living surroundings your baby will experience in the first years of life) and education.

If your baby is found to have genes with increased risk for diabetes, you will be contacted to discuss this information, and invited to take part in Phase 2 of the study.

If your baby is found not to be at increased genetic risk for diabetes, you will be sent a letter explaining this, and there is no further involvement required for most babies. Some parents may be asked to comment on whether this testing procedure has affected them.

## Confidentiality

No-one outside the small group of researchers doing the study will know any of your details. All of your information stays strictly private. When the results are published in a medical journal for other doctors and scientists to see, no information about individual people is used.

The blood sample will be labelled with a code (no names) known only to the researchers, and will be sent to Dr Merriman's laboratory at the Department of Biochemistry, University of Otago.

## Your rights

Taking part in this study is voluntary (your choice). We respect your cultural beliefs. You also have legal rights over the blood samples you give for research. The researchers are not allowed to sell it, export it, or use it for any commercial purposes without your permission.

## Implications of genetic testing

It is important that people who consent to participate in this study are aware of the broader implications of genetic testing. For example, genetic information can be used to predict the risk of diabetes development. You can imagine that insurance companies would be interested in such information. At the present point in time, insurance companies do not specifically ask for this information. However, if they were aware of it, insurance premiums may be adjusted upwards, as may occur if you have a family member with diabetes. We will not release any genetic information to any insurance company or other outside parties without your consent.

The researchers will not claim any right, ownership or property in your individual genetic information or that of your kinship group, hapu or iwi, without having first sought and obtained your informed consent to the transfer of any such right, ownership or property.

## Are you keen to be involved?

**If you do not wish to be involved, or would like further information, please phone Shirley (Research Nurse) on 474 7791, if she is not available please leave a message. Otherwise, one of the researchers will phone you in 1-2 weeks.**

If you choose not to take part, this will not affect any current or future care of you or your child.

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a

Health and Disability Advocates, telephone: (03) 479 0265 or freephone 0800 37 77 66.

**This study has received ethical approval from the Otago Ethics Committee.**

## Research Team

Please feel free to contact one of the researchers if you have any questions about this study.

**Shirley Jones / Debra McNamara** 474 7791

Research Nurses

**Dr Priscilla Campbell-Stokes** 474 0999

Research Fellow

**Dr Tony Merriman** 479 5798

Research Fellow

**Dr Nikki Kerruish** 474 7791

Paediatrician

**Prof Barry Taylor** 474 0999 Ext 8222

Professor of Paediatrics



## **Appendix F Letter to Parents of Babies at Increased Genetic Risk**

10 November 2011

«Initial» «Surname»

«Address\_1»

«Address\_2»

«Address\_3»

Dear «MotherName» & «FatherName»

### **Research Study - Environmental Factors Influencing Onset of Childhood Diabetes.**

As you will be aware, we have been identifying from cord blood taken at birth, the 10% of children at increased genetic risk for developing diabetes.

The genetic testing on «Babies\_Name» suggests he is at an increased risk of developing diabetes by the age of 20 years. He has a 1 in 16 risk of developing diabetes compared to the general population risk of 1 in 300. Ten percent of babies will have a similar result as «Babies\_Name» and only 6 percent of these babies will eventually go on to develop diabetes. Not all high risk babies go onto develop diabetes because development of diabetes also depends on other poorly understood factors, some of which are found in the environment.

We would like to talk to you about the implications of this result and our research nurse, Shirley or Debra will phone you in the next few days to make arrangements to meet with us. We would also like to discuss with you the possibility of you participating in Phase 2 of this study, which is looking for the environmental triggers of diabetes in the first few years of life. However if you have any immediate queries please feel free to contact one of us during office hours on 474 7791, or after hours you could phone Professor Barry Taylor on 021 616 229.

Yours sincerely

Prof. Barry Taylor

Dr Priscilla Campbell-Stokes

Dr Nikki Kerruish

Dr Tony Merriman

Shirley Jones / Debra McNamara

## Appendix G Phase 2 Brochure

Paediatrics and Child Health

### DETAILED INFORMATION: PHASE 2

#### ENVIRONMENTAL FACTORS INFLUENCING ONSET OF CHILDHOOD DIABETES



**We would like to invite you to participate in Phase 2 of the Study**

#### Phase 2 aims to:

- Follow the 10% of children at increased genetic risk for 5 years, by regularly monitoring for the appearance of antibodies. These antibodies are early markers of diabetes development, and appear before symptoms of diabetes. (We currently have funding for a year as a pilot study, but are seeking to have this extended to 5 years.)
- Identify any environmental stresses, by collecting information on each child's environment, that may be associated with antibody appearance, and therefore childhood diabetes. Because most children at increased genetic risk still do not develop diabetes, it is accepted that those who do develop antibodies and diabetes, have been exposed to an environmental stress which the other children haven't been exposed to.

*If it is found that the children who develop antibodies, and therefore diabetes, are exposed to an environmental stress that can be altered or eliminated, then prevention efforts can be started.*

#### What is involved

There are 2 aspects to this study. One is 'measuring' the environment your child lives in, and the other is measuring antibodies in your child's blood.

- 'Measuring' the environment:

Nutrition - You will be asked to complete a diary recording the milk diet of your child and his/her mother (if breast feeding), daily until the age of six months, and then weekly after that.

Infections - You would also record any symptoms of illness, visits to the doctor, and possible exposures to illness, in the diary. We may need to access your doctor's records to verify visits for immunisation and illness.

Living environment - A questionnaire about your home environment, similar to the one done before baby was born, will be repeated at 3 monthly intervals until your child is 3 years old.

- Measuring antibodies:

At 3 monthly intervals a 1 ml blood sample by heel prick will be taken to test for antibodies. Local anaesthetic ('fairy cream') will be provided to numb baby's skin prior to the blood test. Results of antibody testing will be made available to you if you wish. Using these blood samples, we would also look for evidence of exposure to certain viruses.

## Confidentiality

No-one outside the small group of researchers doing the study will know any of your details. All of your information stays strictly private. When the results are published in a medical journal for other doctors and scientists to see, no information about individual people is used.

It is important that people who consent to participate in this study are aware of the broader implications of genetic and antibody testing. For example, genetic and antibody information can be used to predict the risk of diabetes development. You can imagine that insurance companies would be interested in such information. At the present point in time, insurance companies do not specifically ask about for this information. However, if they were aware it, insurance premiums may be adjusted upwards, as may occur now if you have a family member with diabetes. We will not release any genetic or antibody results to any insurance company or other outside parties without your consent.

## Compensation

If a serious problem occurs from your child having a blood sample(s), you may be entitled to ACC cover (now called Accident Rehabilitation and Compensation Insurance, ARCIC). This isn't automatic and ACC makes the final decision. There is no longer any lump sum compensation.

If you have any questions about ACC, you should contact your nearest branch office for further information. These are listed in the blue section at the front of the phone book.

If you or your child suffers psychologically, there is no compensation available, but psychological support will be available, at no cost to you or your family.

## Taking Part

If you choose not to take part, this will not affect any current or future care of you or your child. Remember your participation in this study is entirely voluntary (your choice).

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocates, telephone: (03) 479 0265 or freephone 0800 37 77 66.

*This study has received ethical approval from the Otago Ethics Committee.*

## Research Team

Please feel free to contact one of the researchers if you have any questions about this study.

**Shirley Jones** 474 7791

Research Nurse

**Dr Priscilla Campbell-Stokes** 474 7791

Research Fellow

**Dr Tony Merriman** 479 5798

Research Fellow

**Dr Nikki Kerruish** 474 0999

Paediatrician

**Prof Barry Taylor** 474 0999 Ext 8222

Professor of Paediatrics



## Appendix H Letter to Parents of Babies at Low Genetic Risk

10 November 2011

«Initial» «Surname»

«Address\_1»

«Address\_2»

«Address\_3»

Dear «MotherName» & «FatherName»

### **Research Study - Environmental Factors Influencing Onset of Childhood Diabetes.**

As you will be aware, we have been identifying from cord blood taken at birth, the 10% of children at increased genetic risk for developing diabetes.

We are happy to advise you that <Baby's name> was **not at high risk** for developing diabetes during childhood using currently known markers. This makes Madison ineligible for participating in Phase 2 of this study. This however does not imply or guarantee no risk.

Diabetes commonly presents with symptoms of:

- Increased thirst
- Passing urine more frequently
- Weight loss

If you have any concerns regarding these symptoms in Madison please consult your General Practitioner, and we would also like to hear about this. If you have any queries regarding this result please do not hesitate to phone Shirley or Debra on 474 7791.

We thank you for your participation in this study and your contribution to the advancement of research into childhood diabetes.

Yours sincerely

Prof. Barry Taylor

Dr. Priscilla Campbell-Stokes

Dr. Tony Merriman

Dr. Nikki Kerruish

Shirley Jones / Debra McNamara

# Appendix I Information Sheets for Participants in the Psychosocial Effects Study

## Participant Information Sheet (Controls)

### A Study to Look at Mothers' Psychological Reactions to Having Their Baby Tested for Type 1 Diabetes

#### (Part of the KEA (Key Environmental Aspects of Type 1 Diabetes) Study)

Thank you for agreeing to help us with our study. This sheet tells you more about our research and who we are.

#### Background Information

Childhood diabetes is increasing around the world, including in New Zealand. Tests are now available (at this stage only for research purposes) to identify children at increased genetic risk of developing diabetes and to predict the development of diabetes before symptoms occur by measuring antibodies in the blood.

We are recruiting a group of parents whose children will be tested at birth for the genetic tendency to develop diabetes. We will then monitor the progress of some of these babies over a period of 5 years looking for the development of antibodies that suggest that they are developing diabetes. We will try to determine whether factors in the child's environment, such as their diet or virus infections may contribute to the development of diabetes.

*As part of the study we also want to assess whether the genetic testing process causes undue anxiety for the families involved. This is where we would appreciate your help. In order to see whether it is the testing process itself that causes stress we need to compare the stress levels of Mothers whose babies have been tested with those of Mothers not involved in the main study.*

### **What does this involve for you?**

We will ask you to fill in a questionnaire about your feelings similar to one that we are giving to Mothers in the main study. Our research nurse, Shirley, will give the questionnaire to you when baby is approximately 6 weeks, 3 months, and 1 year old. It will take you about 20 minutes to complete.

If you do not wish to take part in the study you may withdraw at any time.

### **Confidentiality**

No material that could identify you will be used in reports of this study.

Part of the questionnaire will ask about your feelings. Your responses will not be passed on (for example to your G.P) without your consent.

### **Results**

It is expected that the results of our study will be published in an international journal. A summary of the findings may be obtained by participants from the researchers at the end of the study.

### **Your Rights**

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate, telephone: (03) 479 0265 or freephone 0800 37 77 66.

### **Ethical Approval**

This study has received ethical approval from the Otago Ethics Committee.

### **Researchers**

Prof. Barry Taylor	Professor of Paediatrics	474 0999
Dr Priscilla Campbell-Stokes	Research Fellow	474 7791
Dr Tony Merriman	Research Fellow	479 5798
Dr Nikki Kerruish	Paediatric Registrar	474 0999
Shirley Jones	Research Nurse	474 7791

## **Participant Information Sheet (KEA study participants)**

### **A Study to Look at Mothers' Psychological Reactions to Having Their Baby Tested for Type 1 Diabetes**

#### **(Part of the KEA (Key Environmental Aspects of Type 1 Diabetes) Study)**

Thank you for agreeing to help us with our study. This sheet tells you more about this part of our research.

#### **Background Information**

As part of the KEA study we also want to assess whether the genetic testing process causes undue anxiety for the families involved. As your baby has undergone the blood test we would appreciate your help with this part of the study. In order to see whether it is the testing process itself that causes stress we would like to compare your levels of anxiety to those of Mothers who have not taken part in the main study.

#### **What does this involve for you?**

We would like you to complete a questionnaire about how you are feeling generally and about your baby. Our research nurse, Shirley, will give the questionnaire to you when baby is approximately 6 weeks, 3 months, and 1 year old. It will take you about 20 minutes to complete.

If you do not wish to take part in this aspect of the study you may withdraw at any time.

#### **Confidentiality**

No material that could identify you will be used in reports of this study. Part of the questionnaire will ask about your feelings. Your responses will not be passed on (for example to your G.P) without your consent.

## **Results**

It is expected that the results of our study will be published in an international journal. A summary of the findings may be obtained by participants from the researchers at the end of the study.

## **Your Rights**

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate, telephone: (03) 479 0265 or freephone 0800 37 77 66.

## **Ethical Approval**

This part of the study has also received ethical approval from the Otago Ethics Committee.

## **Researchers**

Prof. Barry Taylor	Professor of Paediatrics	474 0999
Dr Priscilla Campbell-Stokes	Research Fellow	474 7791
Dr Tony Merriman	Research Fellow	479 5798
Dr Nikki Kerruish	Paediatric Registrar	474 0999
Shirley Jones	Research Nurse	474 7791
Debra McNamara	Research Nurse	4747791

## Appendix J

Dear <first names of parents>,

We would like to invite you to participate in the following:

### **An interview study of parents' experiences of having their baby tested for genetic susceptibility to diabetes**

Thank you for taking part in the KEA study about the causes of childhood diabetes. As you know, part of this study has been looking at parents' reactions to finding out that their baby has an increased genetic risk of diabetes. So far you have been asked to fill in questionnaires about your feelings, and the way you think about your child. We appreciate the time you have spent doing this.

We also think it is important to hear what you think about the study, and the genetic test in your own words. We would therefore like to invite one of you to take part in an interview to discuss your experience of being in the study and your reaction to the genetic test result. As with all aspects of the KEA study, taking part is entirely voluntary (your choice). If you do agree to take part you can withdraw at any time without having to give a reason. This will in no way affect your child's continuing health care. If you don't want to take part please phone 474 7644 and leave a message on the answer machine. Otherwise, we'll phone you in the next few weeks to arrange a suitable time for the interview.

#### **More information about the interview**

The interview will involve an open-questioning technique where the precise nature of the questions is not decided before-hand but depends on the way the interview develops, and what you want to discuss. General areas to be covered include: why you joined the

study; how you feel about the genetic test result; how you interpret your child's risk of diabetes and what you think about this type of genetic testing in general.

- The interview will be carried out in a place of your choosing, such as your own home. If you prefer it can take place in the Department of Paediatrics.
- Mum or Dad can take part in the interview.
- The interviewer will be Dr Nikki Kerruish. No-one else will be present.
- It is expected that the interview will take approximately one hour, but you can stop at any time.
- The interview will be recorded on tape and then transcribed (typed out word for word). Quotes from the transcripts may be used in a report but they will be used in a way that means they cannot be linked to specific participants. No material which could personally identify you will be used in any reports on this study.
- Tapes will be destroyed at the end of the project. Written data will only be accessible to the researchers and in accordance with University of Otago policy it will be stored securely in the Department of Paediatrics for 5 years and then destroyed.

If you have any questions or concerns about your right as a participant in this study you can contact a Health and Disability Services Consumer Advocate. The telephone number is (03) 479 0265.

If you have any questions or concerns about our project, either now or in the future, please feel free to contact one of the researchers:

**Shirley Jones**

Research Nurse

Tel:474 7644

**Dr Nikki Kerruish**

Paediatrician

474 7836

**Prof Barry Taylor**

Professor of Paediatrics

474 0999 Ext 8222

The project has been approved by the Otago Ethics Committee.