MAIN FINDINGS

> *The human genome consists of all the DNA of our species, the hereditary code of life. This newly revealed text was three billion letters long, and written in a strange and cryptographic four-letter code. Such is the amazing complexity of the information carried within each cell of the human body, that a live reading of that code at a rate of one letter per second would take thirty-one years, even if reading continued day and night.*
>
> Francis Collins, *The Language of God* (Simon & Schuster, 2007, p 1)

The completion of sequencing and mapping of the human genome by Francis Collins and others has enabled Dr Parry Guilford from the University of Otago Cancer Genetics Laboratory to make a significant difference in fighting gastric cancer in an extended Māori family or whānau with unusually high rates of this disease. Dr Guilford spent ten years working with the family. Systematic research led to the identification of mutations in the E-cadherin gene amongst family members who were highly susceptible to developing gastric cancer. One letter in a code of three billion letters was out of sequence. The particular gene is important in cell adhesion and structure and is thought to suppress cell invasion; in people with the mutation, the gene is switched off. Dr Guilford found that about 70 per cent of people with the mutation contract the disease. A relatively simple blood test was developed by the researchers and 133 people from the extended family were tested. Forty-seven were found to carry the mutation in the E-cadherin gene. Those identified with the gene were then screened by a chrome-endoscopy technique which uses coloured dyes to enhance the appearance of the cancers. So far, twenty people with very small tumours have been picked up through this screening programme. They have all had a gastrectomy and are doing well. The other members of the family who were screened were found not to have the mutation. Dr Guilford said:

> *… that's very significant because right across the family everyone was carrying this fear that they were going to get the disease. Now two-thirds of them are released from any concern at all, while the others have very good care and cancers are being found at a very early stage where their chances of a complete cure are extremely high.*

The research was funded by the Health Research Council of New Zealand and it shows how knowledge of the genetic make-up of a person can be very helpful in preventing the onset of disease and removing the fear of disease. Society, and particularly the health of the population, has much to gain from the proper use of genetic testing and the knowledge that has been derived from the discovery of the human genome.

Since the completion of the sequencing and mapping of the human genome in April 2003, the potential for genetic medicine to be used as a testing, diagnostic and treatment tool for multiple diseases is becoming a reality. However, because of the predictive nature of genetic diagnosis, there are fears that our future may be determined for us by scientists and medical clinicians. There is concern as to how the information that is obtained from genetic testing will be used by others. This Report analyses the current and future state of genetic medicine, the potential impacts it has on society both now and in the future, and the ethical and legal principles that must be in place to protect human vulnerability and the integrity of the individual.

This Report covers the use of genetic testing before birth, immediately after birth, on children and on whole communities. It explains new genetic tools such as whole genome screening for the benefit of clinicians who may be confronted by these technologies and the public who may wish to use the new technologies.

The primary purpose of this report is to be as accurate and accessible as possible regarding just what can and cannot be done with genetic testing technologies. The emphasis is on being as fair as possible in explaining and critiquing the issues that emerge from the use of genetic technologies. The researchers who worked on this report do not come solely from one discipline. This minimises the possibility of one particular mindset – whether it be scientific, ethical, cultural or legal – dominating the analyses and recommendations. We have all worked together and argued extensively about how to interpret our findings and present them in such a way that the public can understand what is at stake in formulating the best possible legal and regulatory frameworks for the use of genetic testing in our society.

EXTENDING THE REGULATORY FRAMEWORK FOR PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

In our first Report, we made recommendations on the use of preimplantation genetic diagnosis (PGD) in situations where there is potential for a child to be born with a serious impairment. In this Report, we look beyond that situation: first, to where PGD is used to select what have become known as 'saviour siblings'. Put simply, 'saviour sibling' refers to the selection of an embryo with cells that can be used once the child is born to help treat an already existing child in the family who is ill. At present, the guidelines in New Zealand regarding selection of an embryo for this purpose are narrow. A major limitation at present is that the child who is ill must have a *familial* genetic disorder. Children who are suffering from an illness which is not caused by a familial gene but is the result of spontaneous mutation (for example sporadic haemophilia which is not passed down through families but causes serious illness for the child) would not have access to this procedure. Such a limitation is unjustifiable. The underlying reason for the current limitation is that there will be

some benefit to the embryo if a familial gene which could cause harm to the embryo is not selected. However, this position is unconvincing in the light of arguments as to the potential benefits of modification of the current situation. The major benefit is that a wider range of sick children, with serious or life-threatening conditions, and their families would have access to the option of a saviour sibling, for the benefit of the sick sibling and the family as a whole.

We recommend that the current limitation on the use of PGD to select a saviour sibling, which requires there to be a familial genetic disease (which means a disease that runs through the family), is too narrow. It should be possible to use PGD to conceive a child who may provide cord blood for a sick sibling who is suffering from, or has suffered from, a condition which is serious or life threatening, but is not necessarily a familial disease.

The current guideline restricts creation of a saviour sibling to situations where there are no other possibilities for treatment or where tissue is unduly difficult to obtain. The problem is that while cord blood from a public registry may contain a reasonable match for the sick child, sibling cord blood may constitute the best chance for a successful outcome. The current guideline is too onerous and inflexible. The emphasis should be on the best possible clinical outcome for the sick child rather than, as currently, on exhausting all other clinical options.

We recommend that, while other treatment possibilities and sources of tissue should be explored, if the transfer of blood tissue from a saviour sibling confers a reasonable chance of a disease-free life for the recipient sibling, that choice should be available to the family.

At present, if a saviour sibling is conceived to help an affected child, the current guideline says that the planned treatment for the affected child will utilise only the cord blood of the donor child. This limitation exists because of concern for potential exploitation of the vulnerable donor child. This guideline is beyond the authority of the Human Assisted Reproductive Technology Act (HART Act) 2004 because the Act is limited to assisted reproductive procedures and the use of sibling bone marrow for transplant which occurs after birth is not within the scope of the Act. The guideline is not consistent with current law and practice in relation to naturally conceived children whose bone marrow may be used to help a sick sibling.

We recommend removal of the guideline which says the planned treatment for the affected will utilise only the cord blood of the future sibling.

There is concern in the research literature in this area that a child brought into the world to help treat the illness of another child may be vulnerable to exploitation as a potential donor of other tissue and organs. In this argument, the child is denied

an open future and is essentially commodified. We note that the law concerning donation by children is to be found in well-established common law rules, which generally prioritise the interests of that child over the interests of third parties.

We recommend that, if there is to be ongoing donation of blood tissue or bone marrow, then it is good medical practice to require the appointment of an appropriately qualified advocate for the donor child and an independent physician to ensure the donor child is not being exploited.

We recommend strongly that the Ministry of Health set up a register to record the births of all children born to supply blood tissue to a sick sibling so that empirical studies may be undertaken on the effects on children who have been donors for their siblings.

Some people are carriers of genes that will not harm them in any way but that can be passed on to a future generation possibly leading to a serious disorder. The question we consider is whether PGD should be used to select against embryos which are carriers of a genetic disorder. An embryo that carries, but will not develop, such a disorder for the resultant child creates a 25 per cent chance that there will be an affected grandchild in the future.

Selection against carrier embryos may be justified on grounds of reproductive liberty and the reproductive and psychological interests of the future child. It can also be based on the concept of intergenerational benefit, whereby future members of the family are no longer at risk of carrying affected embryos. Arguments against allowing negative selection of carrier embryos are that it involves the destruction of healthy embryos; is an exercise based on genetic essentialism; harms society by reducing genetic diversity; and potentially stigmatises healthy carriers. Selection against carrier embryos reduces the success of a PGD cycle by reducing the number of available embryos, and has resource implications.

On a literal interpretation of the HART Order 2005, where the threshold test is 'serious impairment', negative selection against carrier embryos of X-linked disorders is permitted. The purposes and principles of the HART Act 2004 are broad enough to permit carrier testing and negative selection both as a contingent procedure to PGD and as the primary purpose of testing in the case of X-linked disorders.

The postulated harms of carrier testing are not sufficient to displace the presumption of reproductive liberty in this context. The greatest potential for societal harm is that prospective parents may feel they have a 'real choice' aside from rejecting a carrier embryo. This can be dealt with by appropriate information from the clinicians involved on a case-by-case basis, rather than outright prohibition; for example, prospective parents would have to be informed that the number of available embryos

would be reduced and that everyone carries a certain number of recessive mutations. Some individuals, for example, are in high-risk ethnic groups with regard to being a carrier for certain conditions. Carriers of cystic fibrosis are found with greater frequency among people of European descent, while carriers of sickle-cell anaemia are found with greater frequency in people of African descent.

We recommend that it should be permissible to choose to select against 'carrier embryos' which carry serious disorders, such as X-linked disorders like haemophilia.

The future use of PGD will be influenced by technological advances. A recent development involving preimplantation genetic haplotyping (PGH) has the potential to increase the number of single-gene disorders that may be tested for and, in the case of X-linked disorders, to increase the number of embryos available for transfer by identifying unaffected male embryos. PGH was used in the United Kingdom in 2006 by parents who were both carriers of a cystic fibrosis mutation. The couple already had twins, one of whom had cystic fibrosis. With the help of PGH, the couple had a second set of twins who were free from cystic fibrosis.

THE ROLE OF PUBLIC CONSULTATION IN DECISION-MAKING

The Advisory Committee on Assisted Reproductive Technology (ACART) has a crucial role in regulating assisted reproductive technology in New Zealand. The HART Act 2004, which establishes and provides ACART with direction for its deliberations, allows for wide parameters within which the Committee can operate.

The deliberations of ACART and its engagement with the public are an integral part of its successful functioning. Given the vital role that the Committee plays in regulating assisted reproductive technology in New Zealand, particularly through the issuing of guidelines for use by the Ethics Committee on Assisted Reproductive Technology (ECART), it is important that ACART takes a considered approach with regard to its deliberations.

The HART Act 2004 requires that the Committee undergoes consultation and takes public submissions into account in the formation of guidelines. Given the flexibility of the HART Act 2004, there are strong democratic reasons in favour of involving the public in the development of ACART guidelines. It is therefore important for the Committee to establish its approach towards involvement of the public. This will assist the Committee in its functioning, and also give members of the public some insight into what they can reasonably expect from the consultation process.

The approach that ACART takes regarding the use of information arising from public consultation will depend on its overall method of deliberation. The example provided by the Environmental Research Management Authority (ERMA) shows a

thorough approach towards establishing the deliberative workings of a committee adjudicating over ethical matters. The breadth of issues that ACART must consider would favour the establishment of a less rigid and less formal approach than that of ERMA, while retaining the advantages of robustness.

The information provided through consultation can meaningfully contribute to ethical deliberation. It can provide real-world considerations that are likely to influence the effectiveness or consequences of ethical policy. It can help to reveal the range and nature of interests, and therefore the potential harms, benefits and wrongs that should be considered in reaching a decision. The reasoning of the Committee should be clear and reasonable.

We recommend that is important for ACART to demonstrate transparency of reasoning, especially in relation to the way in which a decision was reached by the Committee and why a particular decision was favoured over others that were also considered.

NEWBORN SCREENING: PRESENT AND FUTURE

Currently, in New Zealand, children at birth have their heel pricked to test for metabolic conditions which, if found early enough, can be treated. The present New Zealand newborn metabolic screening programme is a competent and successfully run programme with good detection and participation rates. The programme staff is committed to the success of newborn screening, is progressive in attitude towards the benefits of screening and fosters good links with other international programmes. The programme has avoided negative publicity, and has carefully managed access to the Guthrie cards in the interests of maintaining public confidence. New Zealand is well placed to have a flexible and responsive screening programme, given the small population; the single medical contact for each child (the lead maternity carer); a nationally consistent screening panel; centralised testing; and public funding.

New Zealand is following international trends in newborn screening but not in too hurried a fashion. Even before expansion, the New Zealand programme was screening for a respectable number of serious disorders (more than, for example, the United Kingdom). New Zealand has been able to use the implementation lag to absorb knowledge about and experience of these new technologies from overseas, and to put in place adequate support services, such as the employment of a clinical metabolic specialist, before launching tandem mass spectrometry (MSMS) screening.

There is little public awareness of the successful New Zealand newborn programme, beyond recognition that the 'heel prick test' is a routine procedure for newborns. The National Metabolic Screening Programme has been consulting on various aspects of the programme and the storage and use of the Guthrie cards. This consultation is a

positive move given the anecdotal evidence of growing anxiety surrounding the use of DNA samples and Guthrie cards. A small but growing number of parents who are requesting the return of the cards points to concern about potential uses of the DNA samples. This concern may have implications for the screening programme in the future.

We recommend that more public education and information regarding the programme, particularly in antenatal classes and on the internet, be made available to the general population.

Publications, whether scientific or popular, about newborn screening should be made more widely available to parents and members of the public who are seeking more information than is currently contained in educational pamphlets.

We recommend that audit, epidemiological and cost-effectiveness data should be gathered from the programme.

Given the constrained levels of financial support, and small number of key staff, this research would best be done in association with other researchers.

Screening expansion is an exciting move for many and the programme expects that an additional five to ten children with genetic disorders will be detected through the programme per annum. The MSMS screening is also to be used as a metabolic diagnostic tool. Given the expansion of newborn screening, and the versatility of the new technology and its potential for disease prevention, the purchase of MSMS was perhaps worthy of better governmental support, rather than the programme's reliance on a children's charity for financial support.

The newborn metabolic screening programme can be classed as a genetic service. At present, there is unofficial and ad hoc national co-ordination with respect to genetic services. There is apparently a review underway of the 2003 National Health Committee (NHC) report on co-ordination of genetic testing in New Zealand by the New Zealand District Health Boards, presumably with a view to implementation of at least some of the report; there is no other information available on this review at present. Newborn metabolic screening should be acknowledged in future genetic co-ordination initiatives; though, equally, the programme legitimately belongs within the mandate of screening services.

We recommend that when scientifically accurate, clinically useful, cost-effective, high-throughput screening processes are available, the pros and cons of inclusion of early onset, untreatable disorders, such as lysosomal or peroxisomal storage disorders, should be publicly discussed.

If screening of untreatable disorders is introduced, then there must be improved education so that parents are aware of the implications of screening.

In the future, it is likely that DNA screening for individual disorders will be introduced as adjunct tests to the metabolic screening programme. In view of the speed at which science is developing in genetics, it is impossible to say, with any certainty, what the longer-term future holds for newborn screening or even whether the screening time point might move to (non-invasive?) antenatal screening. Whole genome sequencing remains likely in the future, although how and when this information might be used, after the initial sequencing process, remains to be seen.

Expansion of newborn screening into DNA screening will require more characterisation of minority populations in New Zealand. It is likely that there will be differing allele frequencies for various disorders in these populations, compared with populations of Northern European descent (as for cystic fibrosis in the United States). It is also possible that a small number of genetic disorders, rarely found in Northern European populations, are more commonly found in minority populations here. If any were identified, there would be merit in evaluating them for screening.

We recommend that the current Wilson-Jungner criteria, which have been used as a foundation for newborn screening and which were originally formulated in 1968 for chronic adult disorders, need to be reformulated for newborn screening.

LEGAL ISSUES RELATING TO NEWBORN SCREENING

Parents should be informed about screening of newborns in terms of their rights under the Code of Rights and the uses to which newborn blood samples will be put. The analysis in this part of the Report is grounded in the rights-based Code of Rights, and takes into account the public health paradigm and how genetic risks are dealt with in families. It is important to distinguish public health screening from personal clinical services. Traditionally, public health law was prescriptive and compelled participation. This is in contrast with the present consumer-based approach which actively promotes informed choice and consent, and which seems more in keeping with the complexities and sensitivities surrounding genetic medicine.

We recommend that information about newborn screening should be given to parents by or during the third trimester, and again before samples are taken from the newborn. Parents should be informed about the entire screening pathway and what might occur before they take the first step in participating in the newborn screening programme. We recommend that clear, unambiguous information be given to parents, emphasising that the purpose of participation in the screening programme is in the interests of the newborn.

We recommend that parents or guardians be kept informed throughout the screening process, including being notified about the results.

The policy of 'no news is good news' may have to be reconsidered in the light of complex issues raised by technologies that reveal carrier status and the question of whether screening should be extended to include late-onset disorders.

Activities to monitor and evaluate the programme need to be more explicitly stated in information given to parents. Related to this is the importance of distinguishing between initiatives taken for the purposes of fulfilling the aims of the programme, such as picking up early metabolic conditions and monitoring the programme, and those that go beyond the aims of the programme, such as use for general research, paternity testing and police investigations.

We recommend that policies regarding retention and use of samples should clearly make that distinction and should be explicitly communicated to the public and in particular to parents.

The degree and scope of information that can be derived from dried blood spots with the use of new and emerging DNA technologies will potentially be very significant and have far-reaching implications. There is tremendous long-term value in retention, for example, for the purposes of quality management, programme expansion, research on testing, and treatment and epidemiological studies. Current and relevant scientific literature on the stability of metabolites, DNA extraction and testing technology and optimal storage conditions needs to be taken into account with regard to any policy development in this area.

We set out two options for reconciling the inter-relationships between the various provisions of the Code of Rights on consent, storage and quality assurance and the National Health Committee (NHC) screening guidance. The first option involves more actively communicating information about clause 7(9) and clause 7(10) of the Code of Rights.

Clause 7(9) provides the right to the return or disposal of blood samples taken in the course of a health-care procedure and clause 7(10) involves an exemption to the requirement to obtain informed consent for quality assurance (QA) activities such as professionally recognised QA programmes, external audits of services or external evaluations of services. **The second option involves explicitly prescribing, with legal authority, a minimum retention period to guarantee all samples are available for quality assurance-related activities.**

We recommend that policies and procedures setting out, for example, the taking and documenting of informed consent be publicly communicated and made more widely available to help increase parental and public awareness, understanding and confidence.

NEW POSSIBILITIES FOR NEWBORN GENETIC SCREENING: SCREENING FOR GENETIC SUSCEPTIBILITY TO COMMON DISEASE

Many challenges have been identified since the completion of the Human Genome Project, with one of the most significant, perhaps, being how genetic susceptibility testing (or genomic profiling) might be integrated into medical practices such as newborn screening.

The review of the psychosocial effects of newborn genetic susceptibility testing has highlighted the fact that there are several good reasons to be concerned about such testing. These include features inherent in the newborn period; characteristics of the tests themselves; and evidence from previous and current newborn screening programmes. There remains a relative paucity of empirical research in this area but evidence, including the results of research for this Report, is gradually accruing to suggest that families generally cope well with type 1 diabetes (T1D) genetic risk information concerning their children, if it is conveyed sensitively. At this stage, the research remains fairly limited both in focus and duration and the need for further research in this area has been highlighted.

Screening children for susceptibility to certain diseases which have a genetic base, for example T1D, has the potential to enable parents to ensure that the environment is appropriate for a child with the susceptibility. The major concern about widespread uses of such screening is that parents may overreact if they find out the child has a susceptibility to diabetes and overprotect the child.

In this Report, we have carried out our own research to see what the likely consequences would be. We studied three mother-baby cohorts: thirty-eight infants at increased genetic risk of T1D, seventy-three at low genetic risk and seventy-six who had not undergone testing. Our main focus was to see whether or not the parents who knew of the risk would have an urge to overprotect their child and to be overly zealous about surveillance. In fact, the outcome was surprising. The group of parents who knew their child had an increased risk of T1D were in fact lowest on the anxiety scale in terms of how they related to their child. This is only preliminary research but it does show that information about a child's risks does not necessarily lead to parents becoming over-anxious. There is potential for such information to empower parents to ensure that the environment is healthy for the particular child.

Achieving a proper balance between the social good that may come from performing this type of research involving children, and the level of protection offered to child participants, is a significant challenge. Such research itself involves complex ethical and social issues.

We recommend that particular attention must be given to minimising risks to children and implementing procedures for obtaining the informed consent or assent of parents and child participants when screening newborns for genetic susceptibility for common diseases.

Empirical research concerning the potential psychosocial harms of newborn susceptibility testing is essential if we are to make rational decisions regarding the use of such tests. Analysis of harms and benefits is fundamental to the consideration of the introduction of new screening programmes.

Newborn screening for genetic susceptibility is currently only available in research settings because of the lack of detailed knowledge concerning harms and benefits; the lack of preventative measures; and the relative expense and complexity of testing. The research carried out here aims to provide more information on which to base decisions about future uses for these tests.

If the pathogenesis of T1D is eventually better understood, and a preventative measure developed, even if only partially effective, then the benefits of screening may well outweigh the risks. If this eventuates, screening for genetic susceptibility to T1D should be reassessed using the usual processes and screening criteria applied when considering the introduction of a new test on standard newborn screening panels.

GENETIC TESTING ON CHILDREN

Genetic testing raises new issues from those involved in other medical contexts, particularly for children. Most of the concerns relevant to minors are prompted by the familial and predictive aspects of genetic information. Genetic testing may have far greater personal implications for other family members than inquiries made in other medical contexts, and has the power to be more predictive of future health, which has implications for the minor's best interests and autonomy. Genetic information can also be difficult to understand and its implications are easily misunderstood, particularly in respect of its predictive power or lack thereof.

As genetic testing increasingly becomes part of regular practice, and is more widely available, it seems likely that parents will want to test their children. In our analysis, we looked at both children who are too young to give consent to the testing themselves and those who have sufficient understanding to give their own consent. With regard to very young children, there is a wide range of policy guidelines and some empirical research weighing up the risks and harms of testing, which all suggest that it is both ethically and legally responsible for parents to test children for conditions for which, if detected at an early stage, the environment can be adapted in order to give the child the best opportunity of coping with the disease. It is also generally accepted that, if

early testing would enable treatment or cure of the disease, then the testing should be undertaken – again to give the child the best possible chance of survival.

The main controversy arises in relation to diseases which have a late onset and diseases for which there is no effective cure, such as Huntington disease. In such cases, once a person has the genetic markers, the disease will inevitably arise at some stage, barring death from unrelated reasons. Child rights advocates argue that these decisions, because there is no immediate benefit to the young children, should be left to the children once they have sufficient understanding to make their own choices. The emphasis is on the children exercising their own autonomy rather than decisions being taken for them before they have had a chance to decide whether they wish to know about their future health status.

There are two strong objections to this point of view. One of them is that we allow parents to make lots of decisions for young children in terms of what they eat and how long they stay up at night and, above a minimum threshold, what sort of conditions they live in. All of these things have the potential to harm the future autonomy of the child and may not necessarily be in the best interests of the child but they are the price we pay in order to give parents a sufficient degree of freedom to bring up children as they see fit. On this line of reasoning, testing a child at a young age for a condition for which there is no treatment is just another parental choice, which may or may not harm the child in the future. The choice should be for the parents, because there is no overwhelming evidence that the child would be harmed by such early testing. The other objection is that within families knowledge about diseases at an early stage is inevitable to some degree because of family histories, even without genetic testing having been carried out. The testing simply confirms suspicions that are already present. If, for example, another member of the family has had Huntington disease, there is a reasonably strong chance that a future child in that family group could also have that disease. Whether or not the family's genetic understanding is sufficiently sophisticated is another matter; and, of course, the symptoms of Huntington disease may not have been identified as such.

A recent poll published by the University of Michigan's CS Mott Children's Hospital claims that 54 per cent of the 1500 people who responded to the poll (out of a total of just over 2000 questioned) thought that genetic testing for disease risk was worthwhile even in the absence of treatment, while 30 per cent would want genetic testing for themselves or their children only if an effective treatment were available.

A recent 2007 meeting jointly sponsored by the Clinical Genetics Society and the British Medical Association concluded that, in the absence of childhood onset or the availability of medical interventions, predictive testing for adult-onset disorders should not be offered; nor should carrier testing, where the aim of the test is purely

to promote the child's reproductive choice. The results of the meeting showed that clinicians generally seemed more sympathetic to respecting a child's future autonomous choice and preferred to delay testing wherever possible. There were significant differences between European countries, with Southern and Eastern European countries being more likely to carry out carrier testing at the request of a parent than Northern or Western European countries.

The United Kingdom, possibly because of the *Gillick* case which recognised that children should be able to give their own consent once they understood the issues involved, tends to test minors two years earlier than Germany or France. The meeting agreed that imposing a strict age limit for genetic testing is generally inappropriate. The meeting concluded that, despite calls in 1994 for prospective and retrospective psychosocial research on genetic testing of children, evidence remains sketchy and more research is urgently needed. The 1994 guidance identified genetic testing of children undergoing adoption as a potential 'special case' for testing. It was generally felt that special cases for adoption were less justifiable than they had been in the 1990s.

Professional guidelines on genetic testing of minors take a generally prohibitive stance towards genetic testing of minors who cannot give their own informed consent for untreatable late-onset disorders. Medical benefits comprise the main justification for any genetic testing of children, although special circumstances, in which testing may result in greater psychosocial benefits than harms, are considered. There is some ambiguity regarding testing for untreatable early-onset conditions. There is less consensus regarding carrier testing of minors and fewer recommendations – those that exist take a more lenient view of such testing than testing for untreatable late-onset disorders.

Many of the professional guidelines, including those applicable to New Zealand practitioners (the HGSA Policy on *Predictive Testing in Children and Adolescents*), provide that minors can make their own decisions about genetic testing provided that they meet varying standards of competence, understanding and voluntariness.

There is a variety of evidence regarding the attitudes, awareness and practice of different groups of health professionals towards genetic testing of children, despite guidance against testing children for untreatable late-onset conditions. Geneticists appear more reluctant to test minors, particularly where there are no medical benefits, than are other physicians, parents and the general public. Geneticists, other health professionals, students, parents and the public give similar reasons regarding the appropriateness of genetic testing of minors for non-medical reasons, most of which accord with the issues considered in the professional guidelines. Reasons offered in favour of testing include parental desire to know; parental autonomy; opportunity

for planning; resolution of uncertainty for young people; relieving of anxiety; and reproductive decisions. Arguments given against testing include protecting the minor's autonomy; lack of medical benefit; possibility of harm; privacy concerns; and concerns over stigma. There appears to be more willingness to provide carrier testing of minors than predictive testing.

There is evidence that health professionals involved in genetics, paediatrics, neurology, haemoglobinopathies and other areas of medicine are approached about the possibility of genetic testing of minors, and that many health professionals and laboratories are acceding to requests, and performing genetic tests on minors. While most tests are undertaken for medical reasons, a significant number of tests have also been performed for non-medical reasons.

There is very little evidence available regarding attitudes towards, and the practice of, predictive or carrier testing of minors in New Zealand. At this time, requests for predictive or carrier testing of minors are very rare, and testing currently proceeds on a case-by-case basis.

While there is some professional guidance on genetic testing of minors from the HGSA, and laboratory protocols on predictive testing generally, these do not appear to be well publicised or formalised. The lack of a formal structure and process for genetic testing requests also means that GPs and other health professionals may be making inappropriate requests for testing that are not actioned by pathologists, resulting in a waste of time and resources, and increased stress for at-risk families and children.

It is vital that GPs and other health professionals know more about genetic testing and genetics services in New Zealand, so that they can better facilitate informed consent; recognise and acknowledge any limitations in their expertise, particularly as they will influence their patients when discussing testing possibilities; know when to refer patients for genetic testing; and can offer some degree of genetic counselling, if required.

Empirical evidence as to the benefits and harms of genetic testing is very limited. However, the most recent and extensive evidence points towards testing having the potential to be more beneficial than harmful for competent minors who request it. For some of the purported benefits and harms there is no evidence, or only inadequate evidence. Other purported harms do not sufficiently justify a decision against genetic testing of competent minors upon request because they relate equally to other health-care contexts; relate to adults also; or can be mitigated or resolved via alternative methods, rather than blanket prohibition. Many of the potential harms would not be an issue if correct procedures were adhered to, particularly around clear protocols and timeframes for counselling and testing and clear rules and procedures regarding method, timing and persons to whom disclosure of results will be made.

The same limited body of evidence exists against which to judge the effects of genetic testing of minors who cannot give their own consent. However, different conclusions have been reached because of the different consequences of testing each group. When testing a child who cannot give consent is not clinically indicated, there is reason to suspect that psychological or social harms may arise from such testing: whether from early knowledge that one will inherit an untreatable disorder because one has had no say in whether to be tested; because parents may treat the child differently; or because of an inability to prevent parental dissemination of one's genetic information.

We recommend that genetic testing of children who lack capacity to consent to genetic testing for non-medical reasons should be treated with caution. Many adults choose not to discover their own genetic risk status and the threat to the child's autonomy and right to confidentiality are the reasons for this caution. Also, where there is a lack of evidence about what the test results may signify for the child's health, this uncertainty is best dealt with by waiting until the child is able to make personal choices.

Predictive genetic testing for an early-onset condition for which no beneficial medical interventions exist raises fewer concerns. The same potential benefits exist but not the same harms, because the danger to the minor's future autonomy and potential to exercise the right to not know the information is not as salient: the child may never reach an age to decide whether to have predictive testing for the disorder (having already developed it, or having passed the likely age of onset, unaffected). Thus, the putative benefits of such testing (relieving anxiety, preparing for onset, etc.) may be weighted more heavily in this context regardless of whether or not the disorder is treatable. However, given that there are no clinical benefits to such testing, and that there may be some harms (changed parental expectations and treatment of child, etc.), parental requests for such testing should still be treated cautiously.

Health professionals generally cannot inform a minor about a heritable condition in the family without the permission of the person from whom the health information was gleaned (particularly without an explicit request for the information). And yet guardians are under no legal duty to inform children of heritable conditions for which they may be at risk. Guardians can be advised by a health professional about an appropriate age and the manner in which to inform children but families will make these decisions for themselves. The available evidence suggests that parents tend to be in favour of informing their children of their genetic risks, and of informing them themselves, rather than via a health professional. It is, however, obviously a delicate and often difficult task, and the ages at which parents consider disclosure appropriate vary.

As with disclosing familial genetic risk, there currently exists no legal duty to warn minors of their genetic test results, and minors might be refused access to their test results if the information were considered prejudicial to their interests, or their physical or mental health. Deciding whether to disclose a minor's genetic test result requires a careful, case-by-case approach. Parents do not appear to be legally obliged to inform their children of their own genetic test results. Genetic counselling will be necessary if minors are to be told that they carry a genetic mutation, and may be necessary regardless of the test result. The concerns raised by disclosure of the information, coupled with those raised by refusing to disclose the information, support our argument that carrier or predictive genetic testing that is not clinically indicated should generally be restricted to those who competently request it, and generally not be permitted on the basis of parental consent alone.

A register should be established to facilitate disclosure to persons who have reached the age of sixteen or eighteen years (or earlier if they are competent and personally seek access to the information) of the fact that they underwent genetic testing as children. Initially, the minors may be informed either that they underwent predictive or carrier testing as children, or that some information is available about genetic risk status should they wish to access it.

Such a register is the appropriate method for ensuring that people who undergo testing as children are informed of the fact for the following reasons. First, it would encourage parents and health professionals to disclose test results to children – as the fact of testing will be disclosed to them anyway. Secondly, it gives the person tested a choice regarding whether or not to access the information (assuming that he or she has not already been told). Thirdly, it avoids the difficulties of imposing a new disclosure duty that may have unwieldy and undesirable consequences in terms of monitoring, enforcement and sanctions.

Genetic counselling would be required to assist minors in deciding whether to access their test results, and to support them whatever their choice. The privacy of the register and its information must be strictly maintained.

Parents will usually be aware of their children's results and can treat that information as their own for the purposes of disclosure. Health professionals are bound by confidentiality duties to the child and may not disclose the results except to those entitled to receive them (usually the guardians) or pursuant to applicable statutory or regulatory exceptions.

The child's privacy interests need to be weighed against the interests served by allowing parents to disclose their child's genetic test results to certain people or agencies, for example to school or caregivers (so that they can be alert for early symptoms, etc.), and against the parents' rights to freedom of expression under section 14 of the New Zealand Bill of Rights Act 1990.

Competent minors who have had genetic testing on the basis of their own informed consent are entitled to the same rigorous protection of their privacy and confidentiality as are adults. This is particularly important in genetic testing because of the greater family interest in the information, and the current lack of any legal duty on parents or others to keep such information private.

COMMUNITY GENETICS: WITH PARTICULAR EMPHASIS ON ESTABLISHING A MĀORI ETHICAL FRAMEWORK FOR GENETIC RESEARCH WITH MĀORI

Genetic testing of whole communities is a way of picking up disease trends within that community. The diseases will not necessarily be genetically based. They will also be influenced by environmental factors. However, long-term studies hold out the hope that patterns of living combined with the genetic markers could lead to medical break-throughs to improve the health of whole communities. The major question here is whether, once a whole community gives up the genetic material for study and analysis, they lose control over the information in that material and whether they may be harmed by the ways in which the outcomes of the research are interpreted or released. We all remember the 'warrior gene' news headline in New Zealand when it was suggested that a certain gene that was prevalent in Māori predisposed people to act more violently and aggressively. This had potential to deter people from wanting to release their genetic material for study. In this Report, we set out an ethical protocol so that communities are aware of how their genetic material will be used in research and are consulted about the release of the research findings before they are made public.

Indigenous communities have unique concerns in relation to genetic research. The impact of genetic information on them as communities is potentially greater than the impact on other, less defined, groups. Greater assurance needs to be given that the research will be conducted in accordance with robust ethical guidelines and that it will meet their expectations. Any research relationship must respect indigenous cultural beliefs and be in keeping with their values.

We recommend that researchers explain to the community what the research is about and the potential likely findings, and how they would be released, so that the particular community can make a choice as to whether or not to be involved. Genetic samples should be considered to be 'on loan' to the researchers for the specific purposes for which consent was obtained. Guidelines for ethics committees in New Zealand require researchers to take steps to minimise potential harm to participants. The best way to achieve this is to work in partnership with participants to ensure that they fully understand what is happening and the researcher fully understands the participants and their potential concerns.

In New Zealand, any research on Māori health burdens should take steps to minimise harm to Māori arising out of the research. Researchers are required to minimise harms, which generally fall into four categories: physical; psychological; social; and economic. For research involving Māori, researchers are additionally obliged under the current Operational Standard for Ethics Committees to minimise harms that may occur to the whānau (family or community), hinengaro (emotional well-being and state of mind), wairua (spirit) and tinana (the body or physical self). The concept of harm is broad enough to include 'pain, stress, fatigue, emotional distress, embarrassment, cultural dissonance and exploitation'.

The guidance proposes that minimisation of harm be achieved through inclusion of Māori as 'partners and participants in the design, implementation, management, and analysis of research about Māori or Māori health'. Any research on Māori conducted in New Zealand should be based on the principles of partnership, participation and protection.

Partnership involves working with iwi, hapū, whānau and Māori communities to ensure Māori individual and collective rights are respected and protected. Participation involves including Māori in the design, governance, management, implementation and analysis of research. Protection involves actively protecting Māori individual and collective rights; Māori data; and Māori culture, cultural concepts, values, norms, practices and language in the research process.

The guidance describes consultation as the 'key component' in developing research on a Māori health issue and is a 'dynamic and flexible process' involving a 'two way communication process for presenting and receiving information before final decisions are made, in order to influence those decisions'.

Consultation means:

- setting out a proposal not fully decided upon,
- adequately informing a party about relevant information upon which the proposal is based,
- listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal),
- undertaking that task in a genuine and not cosmetic manner, and
- reaching a decision that may or may not alter the original proposal.

The guidance calls for Māori participation 'in the governance and management of research', particularly research focusing on Māori health, and for researchers to ensure that Māori participants have 'the same protection as all other participants in research,

with particular acknowledgement of cultural diversity for Māori'. The guidance specifically states that this is to include 'protection of individual and collective rights and ownership of data as well as protection from harm'. Researchers are obliged to 'support' and 'protect' Māori culture, language, cultural beliefs, practices, values and norms. Importantly in the context of genetic research, ethics committees are asked to consider whether mechanisms are in place 'to ensure the Māori individuals and groups are not marginalised in the research process or by the presentation of the research results'.

This Report responds to trends around research on genetic variation and the potential for such research to reveal information linking genetic variation to common diseases amongst Māori. The focus is on what has been referred to as the 'new genetics', or the expanding nature of research on genetic variation that analyses the genetic links to common diseases, for example cancer and diabetes, as opposed to single-gene disorders and genetic diseases such as Huntington disease. 'New genetics' is a phrase developed to emphasise the expanding role and rapid development of genetics. Shickle defines it as 'applications resulting from development in techniques for locating genes, their products and functions'. The key for this Report about the term 'new genetics' is that it is specifically about studying and identifying the genetics of more common diseases (and is not just a study of rare diseases). It involves the possibility of much more rapid and large-scale analysis of factors contributing to diseases that Māori and other indigenous peoples suffer disproportionately.

This part of the Report explores the broader context of Māori health by discussing Hauora Māori frameworks and knowledge systems for addressing health disparities and contrasts these with the philosophical and scientific ideals driving 'new genetics'. As links between genetic variation and the health of certain populations, particularly indigenous and ethnic populations, continue to be made the issues that arise are primarily driven by ethical, cultural, social and political influences. This research involved analysing the relationships between potential health benefits from genetic testing of newborns and any cultural, spiritual or ethical issues this testing may raise. It looked at the tensions between Māori collective tribal responsibilities and individual rights with regard to the access to and use of human genetic material. This Report proposes that genetic testing research could have significant benefits for Māori and other communities particularly if a broad approach to establishing and implementing moral, ethical and spiritual frameworks to drive such research is adopted.

This part of the Report introduces the Mana Protocols for genetic research and outlines how such protocols could be developed and used to assist Māori (whānau, hapū and iwi), researchers, funders and regulators of genetic research.

We recommend that a Māori ethical framework for genetics, to be administered by a Māori ethics committee or similar body, should be established. While legitimate concerns have been raised about the genetic testing of ethnic and indigenous communities, equally strong sentiments have been expressed warning that we should be careful 'not to throw the baby out with the bath water'. The key is to ensure that the approach to genetic research is balanced in terms of its risks and benefits, and that we do not give genetics a more negative or positive spin than is justified. The need for honesty is paramount. There are many talented and committed Māori and non-Māori genetic researchers who believe their science can make a significant contribution to the improvement of community well-being. If genetic research is to be conducted with kaupapa wairua Māori as its foundation, the benefits will be significantly enhanced.

NEW GENETIC TESTING TECHNOLOGIES

The use of microarrays allows many genetic tests to be done simultaneously on one genetic sample and changes (mutations) to be found that are currently not detected. Microarrays are being used predominantly in the research sector. There has been some movement into the clinical testing and diagnostics arena internationally, but its eventual utility in clinical screening remains to be seen. The diagnostic aspect of microarrays has been enthusiastically reported in the clinical and scientific literature and remains one of the most likely uses of the technology as the cost comes down.

There is still a technology block regarding the use of microarrays with PGD for aneuploidy screening in the form of whole genome amplification. If this problem can be overcome, microarrays could conceivably make a positive difference to implantation rates and reduce miscarriage rates for those who choose to use PGD for this purpose. PGD requires, however, that in vitro fertilisation (IVF) be used to generate embryos for testing. It is therefore unlikely that it will ever be used outside fertility clinics and, even then, only for a subset of clients. Future use remains debatable.

As the cost comes down, microarrray technologies will likely supersede the existing cytogenetic technologies as a first-line prenatal test. Arrays are faster and potentially offer more detailed screening for disorder-causing chromosomal changes. This does not preclude simultaneous karyotyping as a method of confirming any larger abnormalities, or the use of other techniques for later confirmation of an abnormal result. All cytogenetic results should be confirmed, preferably by using another method. As knowledge increases regarding the effects of medium to large chromosomal changes, (ironically) through increased testing as well as new research data, uncertainty about the seriousness of particular changes will be reduced.

There remains, however, the difficulty of explaining the technology and results to a lay audience. A number of other ethical issues have been raised around the use of microarrays for prenatal screening. In addition, microarray use in prenatal screening currently requires an invasive procedure to obtain fetal material for testing. Again, unless there are developments in non-invasive testing, this technology will be limited to those women already undergoing amniocentesis or chorionic villus sampling.

A debate is underway regarding how much genetic information is useful and the advantages and disadvantages of selective versus whole genome screening. There is a corollary with the use of whole-body CAT and MRI scans for simple health 'check-ups'. Abnormalities may be detected that have no effect on the quality of life but, because they have been found, they are investigated or treated unnecessarily. The more targeted the microarrays to specific clinical questions, the less likely this is to occur.

Genetic services in New Zealand are currently stretched. Introduction of the routine use of microarrays would require a substantial investment, not only in technology and laboratory staffing, but also in clinical genetics and counselling personnel.

Implementation of new testing technologies in New Zealand currently appears to be driven by the clinical testing laboratories, on a cost recovery basis. There appears to be no national strategy for monitoring and introducing new techniques and technologies. While this is not necessarily a negative, it may preclude a national push for the introduction of new genetic testing tools; particularly if this were to be based in a single laboratory in competition with others. In addition, private genetic testing services have not been established in New Zealand or Australia. This may or may not affect whether laboratories offer new services. The promised follow-up to the 2003 report by DHBNZ on molecular genetic testing in New Zealand is said to be underway. We await the report with some anticipation.

Beyond microarray technologies, rapid whole genome sequencing is being touted as the next revolution in genetic testing. It is likely that rapid whole genome sequencing will become viable in the medium to long term. This technology reveals the ultimate genetic information – the exact sequence of the genomic DNA. This information is superior to the limited data from microarrays, although it is likely to need more interpretation. It is unlikely, however, to detect ploidy changes, such as trisomies, without additional analysis. Detection of chromosomal copy number variation (CNV) is the principal driver of most current and future PGD, prenatal and diagnostic testing.

Array comparative genomic hybridisation (aCGH) represents a major advance in the field of cytogenetics and offers tremendous promise in prenatal diagnosis for the detection of genetic alterations leading to serious genetic conditions. This technology, also sometimes known as molecular karyotyping, can detect differences in DNA

copy number at hundreds or thousands of points in the genome simultaneously. This technology promises to replace standard karyotyping, which uses standard microscopy to view chromosomes directly in order to detect structural variations that lead to conditions such as Down syndrome (which can be caused by trisomy 21, that is three copies of chromosome 21 instead of two, or a joining of chromosomes 21 and 14) or Turner syndrome (loss of one copy or part of one copy of the X chromosome in girls), or genetic duplications, deletions, insertions or translocations (some of which can be associated with hereditary diseases or cancers). Compared to standard karyotyping, aCGH can detect genetic variations at a much higher resolution.

Array comparative genomic hybridisation was initially studied and utilised in cancer genetics to determine how chromosome structure and function contributed to tumour development. Although it is still used for this purpose, it is hoped that aCGH will be valuable in other clinical contexts, including prenatal screening and diagnosis. In research, aCGH has demonstrated an unparalleled ability to perform comprehensive, high-resolution scans of both the whole genome and specific chromosomal regions. Physicians are looking to aCGH to increase their ability to detect clinically significant genetic alterations. Although it is already a powerful research tool, the technology is still in its early stages and has not fully transitioned to clinical use. However, in the United States, aCGH is already being offered as a clinical test in postnatal and prenatal settings. More research is necessary to determine how and in what capacity aCGH technology can and should be used for clinical prenatal screening or diagnosis. A necessary aspect of this development is a thorough consideration of the ethical implications of the new technology; this will come to the forefront as clinical use of aCGH increases.

At this stage of the development of aCGH technology, a number of recommendations can be made for clinical use. These recommendations should be revisited as information about its clinical validity and utility is obtained, and as the accuracy, resolution and cost of aCGH-based tests evolve.

First, aCGH should be used for prenatal testing only under research protocols where other data necessary for learning how to interpret aCGH data are also collected.

This information might include the results of other prenatal screening tests (such as nuchal translucency and multiple-marker blood tests) and clinical data on parents. The aCGH data should be validated by and compared to data from some other method such as standard karyotyping, FISH and QF-PCR.

Secondly, before clinical use as a prenatal test, aCGH should be used and evaluated under conditions that allow assessment of the clinical significance of the results (i.e., where phenotype and clinical information about the patient are available from newborns, children or adults).

Given the large amount of copy-number variation in the general population, even among apparently healthy people, the finding of copy-number variants may in itself be of unclear clinical significance. In the prenatal setting, very little clinical information can be obtained to aid in the interpretation of aCGH results, and it is thus not the optimal setting in which first to bring the technology to clinical use.

Thirdly, laboratories beginning to use aCGH should adopt uniform and transparent technical standards, including standards regarding what constitutes the 'normal' control samples with which patient samples are compared.

Fourthly, research and clinical laboratories using aCGH should anticipate the possibility of uncovering 'incidental' findings and make plans for handling them.

For example, if parental samples are tested, in order to interpret the findings from a fetal sample tested to detect trisomy 21, the laboratory should make advance plans for whether and how to report unexpected findings of major clinical significance that arise in the parental samples. Laboratories should also decide whether any results will be withheld.

Fifthly, informed consent to aCGH in research or clinical settings should include provision for how research subjects or patients want to handle 'incidental' findings, the possibility of unwanted results and results of unknown clinical significance.

The diagnostic power of aCGH technology offers an exciting and revolutionary approach to prenatal diagnosis, providing a much more fine-tuned tool for genetic analysis than other currently available technologies. The detection capability, as a result of increased resolution, the comprehensive nature of the tests and the potential for faster reporting times, makes aCGH a promising new technique. However, despite the documented successes of this technology so far, more research is needed to understand its scope fully so that aCGH can be implemented as a clinical tool in prenatal diagnosis. Because the technique has not yet transitioned to clinical use, there are as yet no established standards for its application. To be sure, ethical difficulties and ambiguities will attend its clinical use. Research will no doubt continue to improve the technology; but it is also important that the ethical, legal and social implications are given serious consideration as aCGH transitions to clinical use.

CONCLUSION

The main finding which comes through in all aspects of this Report is the current lack of awareness and understanding of the benefits that genetic testing can bring to the health of individuals, families and communities. This lack of understanding and awareness is not simply within the general population but also among the medical profession, because many doctors were trained before the discovery of the human genome. Discovery of the human genome raises a whole new and different way of looking at the current and future health of individuals and communities. While genetic testing technologies are still emerging, their potential to provide information which will help people understand their health status in a better light is clear. The information that is obtained as a result of genetic testing has the potential to be misused or misunderstood. However, that is true of any information and should not be cited as a reason to deter us as a society from obtaining the information and subjecting it to careful analysis.

The full impact of the discovery of the human genome has not yet fulfilled the potential promise to help us understand the genetic structure of all diseases because the nature of disease and the interaction of genetics with the environment is complex. For the advancement of society, we must continue to explore the full potential of the meaning of our genetic make-up with an open mind. Throughout this Report, we provide legal and ethical frameworks to ensure that the potential for misuse of genetic information is avoided as much as possible. Overall, the benefits of genetic testing for the health of individuals and populations outweigh the potential harms and we hope that the frameworks in this Report will minimise the impact of those harms.

Mark Henaghan & Sheila McLean
(with thanks to all project members for their input)
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