NEWBORN SCREENING: PRESENT AND FUTURE

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NEWBORN SCREENING SUMMARY: PRESENT AND FUTURE

Newborn babies are screened for a selected panel of serious, early onset genetic disorders. Metabolic newborn screening is the screening of a specific population (neonates) using indirect measures of genetic disorders, rather than direct genetic (DNA) testing.

Metabolic screening looks for evidence of an existing disorder, whereas DNA testing is a risk assessment (i.e. predictive, not diagnostic) for a disorder.

The indirect measures used in newborn screening are of chemical compounds (metabolites) found in the bloodstream, which are part of metabolism (the process of using food).

These metabolites are analysed in a blood sample taken two to three days after birth. This allows enough time for the baby's own metabolism to take effect, without the influence of the maternal metabolism left over from pregnancy. Abnormal levels (those outside a defined range) are considered suggestive of a disorder. Such results are followed up with retesting and/or further investigation.

Not all positive results are true positives: some are termed false positives upon further investigation. A small number of negative results may turn out to be false too.

Pre-2007, the metabolites were analysed using a combination of biochemical and antibody-based detection techniques. Seven rare disorders were tested for in New Zealand until recently: phenylketonuria (PKU), maple syrup urine disease (MSUD), galactosaemia (GALT), biotinidase deficiency (BIOT), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), and cystic fibrosis (CF). It was estimated that this newborn screening detected thirty to thirty-five affected babies per annum.[1]

The New Zealand screening panel has recently been expanded by the introduction of a mass spectrometry system (tandem mass spectrometry). This technology can simultaneously measure many metabolites. The number of disorders in the screening panel will increase by twenty-one (in addition to the seven disorders on the old panel).

Direct genetic (DNA) testing is sometimes used as a follow-up to a positive result. There are currently, however, no genetic tests that are more efficient and cost effective than indirect metabolic screening. DNA screening technology is likely to become cheaper and more effective in the future.

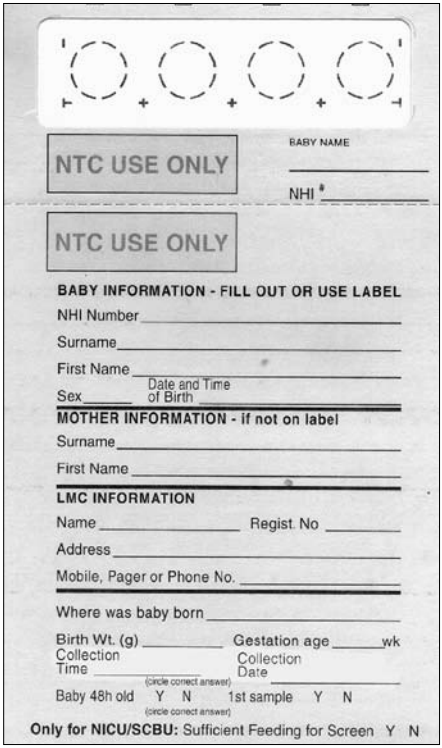
A disorder may be caused by one change (or more) out of many different changes to DNA sequence or structure. Some changes have more severe consequences than other changes, and severity can vary from person to person, even for those with the same causative mutations.

Difficulties with direct screening of DNA include assessment of the risk of developing a disorder based on a positive result, and gaps in knowledge regarding the different causes of a particular disorder.

Direct genetic screening of newborns is a possibility for the future. In the near to medium term future, DNA screening (as opposed to diagnostic or follow-up testing) may be used as an adjunct to newborn metabolic screening, but is unlikely to replace it altogether. Long-term, it is likely that unanticipated technologies will exist and may be used for the purpose.

Figure 1: *The Guthrie card is used to collect blood samples for testing by the newborn metabolic screening programme in New Zealand*

Source: *Screening Matters newsletter*[2]



1 INTRODUCTION

Screening programmes are public health initiatives to enable early detection – and usually treatment – of various medical conditions. This section will focus on newborn metabolic screening in New Zealand: the theoretical basis of population screening; the current screening programme; and what is possible or likely in the future from a scientific and clinical perspective.

Newborn screening *per se* is not limited to metabolic disorders: it includes any screening test performed on neonates, including for heart defects, deafness and hip dysplasia. The current newborn metabolic screening regime (often abbreviated to newborn screening) uses changes in the levels of normal blood compounds to indicate the possible presence of early onset, serious, treatable genetic disorders.

New Zealand has recently increased the number of metabolic disorders on the newborn metabolic screening panel. New Zealand is following Australia and parts of the United States in the evolution and expansion of our newborn metabolic screening programme, so we have access to a great deal of international data to guide the development and improvement of our programme. Much has been written already on newborn metabolic screening internationally so, to prevent repetition, readers will be referred to some of these documents for more detail or a different perspective.

This report will also examine the potential of direct genetic (DNA) screening of newborns, and its possible place in a future New Zealand newborn screening programme. DNA screening is currently not feasible in the public health context, although this may change as the technology improves and the costs reduce. In addition, interpretation of genetic information, unlike metabolic results, can be imprecise. The ability to understand the implications of particular genetic results will have to improve as well. Whilst both indirect (metabolic) and direct (DNA) newborn genetic screening have some benefits in common (early detection and treatment), DNA screening is thought to have wider implications – medical and in particular social – for the person undergoing testing.

2 MEDICAL SCREENING PROGRAMMES

The object of screening for disease is to discover those among the apparently well who are in fact suffering from disease.[3]

2.1 Screening is public health

Prevention is better than cure.

Screening programmes are public health measures. Public health focuses on populations, rather than individuals, and is typically the responsibility of government. It is in the public (and political) interest that as many people as possible are healthy and contributing to society. There is generally a limited budget with which to achieve this goal so spending is prioritised in favour of strategies that give the most health benefit for the cost.

Encouragement of good population health can be approached in a number of ways. It may involve strategies such as prevention of illness, control or treatment of illness, physical aids to enable high function, environmental monitoring and accident prevention.

Public health encompasses diverse areas of population health including (but not limited to) food safety, vaccination programmes, epidemic control, health inequities, safety and injury control, hygiene and sanitation control and screening for early detection and treatment of disease. The wide focus of population health potentially impacts on autonomy, liberty, privacy and property.[4] In exceptional circumstances, public health can be and has been used to justify the restriction of all four of these individual aspects in serious risk situations, including detention and compulsory treatment for tuberculosis and closing (and prosecution of) unhygienic food premises.

As a public health initiative, medical screening has a fundamentally different basis from that of an individual medical investigation, although many of the testing techniques are the same. Investigative medical testing is prompted either by physical symptoms (i.e. it is diagnostic) or by a strong family history of a disorder, which suggests an increased likelihood of developing the disorder. Testing is personal medicine, for the benefit of the individual (and family); screening will have this effect ultimately, but it is aimed primarily at the good of a population. Any benefits resulting from screening are measured from the point of view of population health and include reduction of disease burden (incidence, morbidity and mortality) and the (eventual) reduction of national health costs from early detection and intervention.

Health screening involves testing ostensibly healthy people for a disorder that they may be unlikely ever to have (or pass on), in the hope of detecting the unlucky few who have or will develop it. Often, the screen is a simple indicative test and is a

springboard for more extensive testing to investigate and verify any positive result; that is, a diagnosis. Screening a healthy population imposes extra responsibilities on the programme that may not be relevant for more personal, diagnostic investigations.

Screening programmes aim to detect as many people as possible with a particular undiagnosed health issue, in the most cost-effective way and with the least number of negative implications (missed diagnoses, unnecessary investigation and/or treatment and psychological suffering). As a cost-reduction tool, a screening programme must reduce disease incidence, morbidity or mortality in a cost-efficient manner.

Despite the population health perspective, however, there is a duty to minimise negative personal and/or social consequences for populations and the individual, particularly when there is little risk to others (as opposed to, for example, a deadly contagious disease). Criteria for a successful screening programme with respect to newborn metabolic screening, and the risks and responsibilities associated with such programmes, will be examined in this section.

Active national health screening programmes in New Zealand are BreastScreen Aotearoa (breast cancer), National Cervical Screening Programme (cervical cancer) and the Newborn Metabolic Screening Programme.[5] Programmes under investigation or in the process of being implemented are universal newborn hearing screening, antenatal HIV screening, screening for chlamydia infection, colorectal cancer screening and antenatal screening for fetal aneuploidy.[6]

2.2 Selective screening

The vast majority of screening programmes are selective or targeted in some way, rather than being mass or whole-population screening for serious disease. Some programmes are selective for particular age groups or developmental stages; others are selective for ethnicity or environmental factors. Population subgroups are selected on level of risk, based on epidemiological data.[7] The higher the risk to a selected population, the more likely a programme is to be cost effective.

Breast cancer, for example, rarely develops in men and young women, so the targeted population for BreastScreen Aotearoa is women between the ages of forty-five and sixty-nine.[8] This means that men and younger women who do develop breast cancer will be detected through other means and possibly with more advanced cancer. The cost of regularly screening the whole population would be prohibitively expensive, however, as well as being a drain on specialised personnel and equipment. Psychologically, it is also a source of worry for those people with false positive results who require follow-up screening. This latter group (false positives) is likely to be principally made up from the groups of men and younger women as, in women, younger breast tissue is often more difficult to screen accurately using current X-ray

technologies.[9] Limiting the population screened to those who are most likely to have detectable cancer constitutes the balance between coverage and cost efficiency. This does not mean that people with a known higher risk of breast cancer are excluded from screening entirely; merely that they may not be included in a formal population screening programme.

In New Zealand, some ethnic populations also have higher incidence of and death from breast cancer, whether through inherited genetic susceptibilities, environmental factors or late detection (often because of delayed reporting of symptoms).[10] Advertising campaigns and other mechanisms target susceptible populations, in the hopes of further lowering the breast cancer morbidity and mortality rates in these populations and therefore overall.

The newborn metabolic screening programme, by contrast, consists of a one-off test: screening for multiple conditions that have serious (life-threatening) consequences for newborns and young infants. Newborn screening is, on one level, a mass-screening programme as every individual newborn is offered screening and, ultimately, most of the population will be screened. It is also a time when almost every child will be in contact with medical personnel. As such, it represents a convenient opportunity for screening for slightly later onset (months rather than weeks) disorders, in addition to disorders with very early onset.

A selective aspect of the newborn screening programme is that the disorders currently on the screening panel manifest initially at this very early stage in life, with identifiable signs around day two after birth, and are most effectively treated early. Later onset disorders (e.g. Duchenne muscular dystrophy (DMD)) are not currently considered for the screening panel, as they can be detected later in the child's life or are currently untreatable. Newborns in New Zealand are screened for hip dysplasia, heart defects and a number of metabolic, endocrine and exocrine disorders. Hearing testing will soon be introduced in the whole of New Zealand.

All newborns in New Zealand are tested with the same metabolic screening panel, although this is not necessarily the case overseas. Until recently, testing for sickle-cell anaemia and thalassaemia in the United Kingdom was restricted to particular ethnicities with a higher incidence of these disorders, although screening is shortly to become available to all newborns.[11]

3 NEWBORN METABOLIC SCREENING PROGRAMMES

… early diagnosis is better than diagnosis made late in the natural course of a disease process.[12]

3.1 What is newborn metabolic screening?

A brief summary of all the disorders included in the New Zealand newborn metabolic screening programme is available on the National Screening Unit website.[13] For more information on individual disorders, see National Newborn Screening and Genetics Resource Center,[14] the March of Dimes website[15] or the Financial, Ethical, Legal and Social Issues website.[16] For extensive descriptions of the various disorders, see 'Newborn Screening Fact Sheets',[17] published by the American Academy of Pediatrics and the ACMG report on standardising newborn screening.[18]

Newborn metabolic screening is a public health programme in which the majority of newborns are screened for a select group of early-onset, severe and (currently) treatable disorders. Four blood spots (from a heel prick) are taken at approximately forty-eight hours after birth. These blood spots are sent to a testing facility, where small circles of the dried blood samples are punched out and analysed for various chemical compounds in the blood. Particular biological molecules, where found at unexpected concentrations (whether too high or too low), can indicate a disorder. An abnormal screening result is followed up with more precise testing to reach a more conclusive diagnosis.

Metabolic refers to the process of digesting food into smaller chemical compounds (metabolites) that the body can use for energy and for growth. Protein catalysts called enzymes, which are encoded in DNA by genes, produce metabolites by breaking down food. If an enzyme for breaking food into reuseable components is faulty or absent, because of a harmful genetic mutation, then a metabolic disorder can result. Symptoms may be because of a deficiency in or toxic accumulation of a particular metabolite.

There are three main groups of metabolic disorders relating to dietary protein and fat digestion: amino acid, organic acid and fatty acid disorders respectively. For this reason, a variety of metabolites can be used as a measure of 'normal' metabolism. For the metabolites measured in newborn screening, the 'normal' or healthy concentration ranges are known for each particular disorder and newborns with a result outside this range are investigated further.

As metabolic disorders relate to food processing, many of the health effects can be ameliorated and even eliminated through modification or supplementation of diet. In phenylketonuria, for example, a liver enzyme involved in the processing of the amino acid phenylalanine is non-functional. By almost completely removing

phenylalanine from the diet, the severe health effects of the disorder (developmental delay, seizures, speech abnormalities) can be greatly reduced, although there are still some residual effects.

The phrase newborn metabolic screening is slightly misleading, as it is not solely metabolic disorders that are screened for. Whilst metabolic disorders comprise the majority of disorders in the panel (particularly in the recently introduced expanded screening), two endocrine disorders[19] (congenital hypothyroidism and congenital adrenal hyperplasia) and an exocrine[20] disorder (cystic fibrosis) are also commonly included.

In the case of endocrine disorders, missing hormones that would normally be produced by the body can be used as the treatment. There is no treatment to eliminate all the symptoms of the exocrine disorder, cystic fibrosis; although antibiotics and physiotherapy are used to try to prevent infection and move thickened mucus in the lungs. Secreted pancreatic enzymes can be replaced in the form of pills and attention to and supplementation of diet can reduce growth impairment and malnourishment often seen in children with cystic fibrosis. This treatment can improve quality of life and extend the lifespan of an affected person through to their thirties or even forties.

3.2 Newborn metabolic screening is genetic screening

Genetic testing is not strictly limited to DNA-based analysis. Any test that can indicate a genetic disorder is generally termed a genetic test. In this way, newborn metabolic screening is genetic screening, although no DNA is examined directly in the initial screen. To avoid confusion and differentiate between direct genetic screening and (non-DNA) metabolic screening, genetic testing through direct interpretation of DNA sequence will be referred to as DNA testing or screening throughout this report.

Virtually all the disorders on the metabolic newborn screening panels internationally are autosomal recessive genetic disorders. Both parents must contribute a non-functional copy of the (same) gene to give rise to an affected child. In cystic fibrosis, for example, an affected child will have two non-functional copies of the CFTR gene, one inherited from the mother and one inherited from the father.

Some non-functional gene versions (alleles) are more common in certain populations than others. In populations of Northern European origin (often called Caucasian), non-functional CFTR gene alleles are more common than in other (e.g. Asian) populations. This higher frequency in a population increases the chance of both parents being carriers (i.e. both have one functional and one non-functional copy of the particular gene). A carrier couple has a one in four chance of having an affected child. If the non-functional alleles of genes are very rare, then the chance of both parents being carriers is very small, unless they are related to one another.

Most metabolic disorders are very rare because the non-functional alleles are rare in the population. The more common non-functional alleles, for example in cystic fibrosis, may have some evolutionary advantage when present in a single copy (i.e., in a carrier), although the actual advantage conferred by a non-functional CF allele is unknown.

Other disorders have a genetic basis but are often *de novo* (new) mutations rather than inherited. Congenital hypothyroidism is most commonly a sporadic (non-inherited) endocrine condition. Approximately 15 per cent of occurrences are thought to be genetic[21] but the overwhelming cause is thought to be thyroid dysgenesis (failure to develop normally). This is an error of early development, as identical twins are mostly not both affected;[22] but it is difficult to estimate the genetic component of thyroid dysgenesis.[23]

DNA testing of individuals may be used, once the metabolic test results are confirmed, to ascertain the diagnosis or cause. Testing enables future family planning by the parents and wider family – in particular, in New Zealand, for the relatively common and well-characterised disorder, cystic fibrosis. Testing may also have a research benefit. DNA screening is not currently in use in newborn programmes as the initial screen.

The fact that newborn metabolic screening is genetic screening has implications for the screening criteria that have not been recognised until recently – in particular, the implications for the wider family. This is discussed further in the fourth section, 'Criteria for the newborn screening panel'.

3.3 Newborn screening is symptomatic screening

Whilst newborn metabolic screening involves testing apparently healthy newborns, the screen is actually for an existing disorder. Although there are usually no obvious physical symptoms at that early stage in life, there is an existing, detectable phenotype by the time the blood sample is taken: the altered level of the key metabolite or hormone in the blood. All metabolic testing is symptomatic screening based on the blood screen.

This is in sharp contrast to DNA testing, where the presence of a disease-causing allele (or two) is only predictive of the development of a disorder. DNA analysis can give a numerical risk that the disorder will develop (this may be high or low depending on the disorder) and may give an indication of the severity of the disorder that does manifest. As we will see later in this section, however, there are no guarantees that DNA results predictive of disease will translate into a severe health disorder. There are currently no official nationwide newborn DNA screening programmes. Additional reasons for this will be discussed later in this report.

3.4 A brief history of metabolic screening

In 1934, Følling published his discovery that phenylketonuria (PKU) was likely to be caused by an 'anomaly', probably related to the metabolism of a protein component (amino acid) phenylalanine.[24] This led to the idea that dietary restriction could reduce the severity of PKU.[25] Development of commercial diets for those children with PKU was well underway by the late 1950s.[26] Unfortunately, PKU was often not detected until severe neurological damage was already evident in at least one child in affected families.

A test developed by microbiologist Robert Guthrie and Ada Susi, and eventually published in 1963, was an early reliable test for PKU. It was also a revolutionary method of collecting the blood sample for testing: the blood was spotted onto filter paper and allowed to dry. The test itself was a bacterial growth assay, whereby dried blood spot samples containing elevated levels of the amino acid phenylalanine (an indication of PKU) promoted bacterial growth on selection media.[27] Those with 'normal' levels of phenylalanine did not allow growth of the bacteria (inhibition). The development of a reliable test meant that treatment, i.e. dietary restriction, could begin early, minimising the neurological damage characteristic of the disorder.

Less than 1 per cent of residents in United States institutions for intellectual impairments were known to have PKU at this time, although universal screening was promoted as a way of significantly reducing developmental delay and mental retardation in the population.[28] The first infant affected with PKU was detected in New York State in 1962, after only 800 screening tests had been performed.[29] This early find, other early successes[30] and vigorous promotion compelled more and more States to introduce newborn testing and many made it mandatory. Newborn testing slowly spread internationally and new tests were added to what become a screening panel for newborns. The bacterial inhibition assay is no longer in use, as new technologies have improved detection sensitivities and replaced older methods. The cards used to collect newborn blood spots are still often called Guthrie cards, and the cotton-based 'paper' card technology has changed little since first developed.

3.5 Modern newborn metabolic screening programmes

Newborn metabolic screening programmes vary from country to country and, in some countries, from State to State. There is a wide variation in programmes internationally, ranging from no screening in many developing nations, through to forty-five specific tests offered by New York State in the United States.[31]

3.5.1. International programmes

3.5.1.1 The United Kingdom (UK)

There is substantial and more detailed information available on the United Kingdom newborn screening programme website.[32] The United Kingdom programme, formed in 2002, is accountable to the Department of Health and reports to the National Screening Committee. Screening is funded by the National Health Service (NHS) and currently covers approximately 600 000 newborns per annum. Parental consent is required for newborn screening.[33]

The United Kingdom currently only screens for two disorders universally: PKU and congenital hypothyroidism. Sickle-cell anaemia and thalassaemia have recently been added to the universal screening panel, although non-selective screening has yet to begin. These two groups of haemoglobin disorders are more common in those of African and Caribbean descent and, until recently, were only offered to these ethnicities. Now, because of intermarriage etc., [i]t is no longer possible to assume who may or may not be affected'.[34]

Cystic fibrosis (CF) screening is currently offered in some NHS trust areas and not others. Universal CF screening is being rolled out across the country and the newborn screening programme aims for screening to be offered 'to all babies born in England by April 2007'.[35] It is already available to those in Scotland, Wales and Northern Ireland.[36]

Aside from a negative report in 1997,[37] the United Kingdom did not appear to be contemplating expanding its screening programme,[38] despite there being possible justification for the use of tandem mass spectrometry to screen for glutaric aciduria type 1 (GA1), based on its own evidence.[39] This was also true of medium-chain acyl CoA dehydrogenase (MCAD) deficiency, but the screening programme recently announced its addition to the newborn screening panel.[40]

3.5.1.2 Australia

Screening in Australia is fully publicly funded and parental consent is required for participation. '[A]pproximately 258,000 newborn screening cards are processed in Australian laboratories' every year.[41]

Screening in Australia is superficially dictated and performed State by State (under State health departments), although there is a degree of co-ordination between the centres. There are five principal screening laboratories: '… Western Australia (WA), South Australia (SA) that also covers Tasmania (TAS) and part of the Northern Territory (NT); Victoria (VIC); New South Wales (NSW) that also covers the Australian Capital Territory (ACT) and Queensland covering part of the Northern Territory.'[42] All centres had adopted tandem mass spectroscopy (MSMS) screening by 2004, with WA being the final State to implement extended screening.[43]

State newborn screening is based upon and guided by national and Australasian policies, for example the joint Human Genetics Society of Australasia (HGSA) and Royal Australasian College of Physicians (RACP) policy statements.[44] As such, New Zealand and Australian screening programmes are now aligned and there is co-operation between the programmes.

Each State decides a number of operational aspects.[45] Whilst the latest HGSA/RACP guidelines suggest a number of disorders that States could choose to include in State screening panels, the programmes are now 'essentially aligned'.[46] To facilitate a more standardised programme in other operational areas (such as retention of Guthrie cards), the Australian Health Minister's Advisory Council (AHMAC) Advisory Group on Human Gene Patents and Genetic Testing has recently undertaken a consultation on what this standardised programme might look like.[47]

3.5.1.3 The United States of America (US)

Screening programmes are run at the State level in the US. Programmes vary enormously from State to State, at all levels. Funding is from a variety of sources: it usually comprises varying combinations of State, insurance and 'user pays'. Screening is compulsory in most States (48/51) so consent is often not sought and the level of information provided to parents is variable.[48] Some States have opt-out clauses 'for (1) religious reasons (33/51), (2) any reason (13/51)'.[49] Almost four million newborns are screened per annum.[50]

There is a move in the US to standardise the screening tests available in each State, and to upgrade all screening programmes to tandem mass spectrometry. This move is led by the Department of Health, which commissioned an American College of Medical Genetics analysis.[51] The ACMG report recommends a core-screening panel of twenty-nine disorders through the widespread introduction of MSMS screening. The State-based funding of newborn screening programmes compromises this initiative, due to different levels of funding and support, and there is therefore a push to introduce at least partial federal funding of these programmes.

3.5.2 New Zealand

Screening was established in New Zealand in the mid-1960s. Guthrie took sabbatical leave to Dunedin, New Zealand in 1968 and Professor Arthur Veale started up newborn screening from the Otago School of Medicine as a result. The programme was moved in 1973, when he moved to the new medical school in Auckland.[52]

The National Screening Unit (NSU) now oversees and is responsible for the newborn metabolic screening programme, from within the Ministry of Health.[53] This chain of responsibility is a relatively recent occurrence.[54] The NSU contracts the Auckland

District Health Board and its medical testing laboratory LabPLUS to provide the newborn screening services.[55]

The Starship Foundation (a national children's health charity) recently gifted the funds for a Tandem Mass Spectrometer (MSMS) to the Auckland District Health Board, to enable expanded screening in New Zealand. The screening panel was extended from seven disorders to approximately twenty-nine disorders (depending how they are classified) and extended screening began on 1 December 2006. The disorders on the New Zealand screening panel are described and summarised by the NSU.[56] Phenylketonuria (PKU) and maple syrup urine disease (MSUD) screening has been transferred to the MSMS; the other individual tests continue to be performed using existing technologies. The disorders on the panel are now aligned with Australia. Extended screening is estimated to be able to detect five to ten more affected infants per year, in addition to the approximately thirty-five newborns already identified annually.[57] It can be estimated that approximately one in 1500 New Zealand children is affected by one of the seven disorders on the original panel.[58]

New Zealand has an extremely high rate of coverage in screening newborns, estimated by the newborn metabolic screening programme to be between 99 and 100 per cent of the approximately 59 000 or more children born annually.[59] Informed consent by parents is required, although anecdotal evidence is that the informed part of the consent process is not occurring consistently. There is also recent evidence from Australia showing a low level of knowledge of the programme, even amongst parents.[60] The New Zealand situation is likely to be similar. (See the section in this Report by Kirsty Dobbs and Richman Wee, 'Newborn Screening and Related Legal Issues', for further discussion regarding parental consent.)

There are various reasons for the success of the New Zealand programme, not least of which is the commitment of the staff. New Zealand has a small population with a State-funded, central testing laboratory. The publicly funded health system also supports the follow-up testing and treatment of affected children. Being small allows New Zealand the flexibility to modify the programme quickly as new evidence and best practice is reported; although the small size (and level of funding) also makes it more difficult to innovate in the way that some larger countries do. Additionally there is a mandated single point of contact for each newborn in New Zealand, the Lead Maternity Carer (LMC), which allows for efficient follow-up and retesting if required.

4 CRITERIA FOR THE NEWBORN SCREENING PANEL

In 1968, a set of principles was published under the auspices of the World Health Organisation to guide screening programmes (Box 1). This early set of criteria, proposed by Wilson and Jungner, was aimed at '… the chronic non-communicable diseases prevalent in the more advanced countries …'[61] – such as adult-onset cancer – so some aspects are not necessarily applicable to newborn screening. These principles are still in general use today, however, although there are many variations on the theme. Some precepts appear to be more universal than others and all are, to some extent, subjective.

Box 1: Wilson-Jungner principles of early disease detection[62]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The total cost 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.
10. Case-finding should be a continuous process, not a 'once and for all' project.

Most programmes now state the criteria on which they (claim to) have been based. In the main these criteria draw heavily on the Wilson-Jungner principles, including those of the National Screening Unit in New Zealand (again these were written with adult-onset cancers in mind, not newborn screening).[63] Another criterion that has been added subsequently is a requirement for evidence of effectiveness, although this is possibly implicit in the original principles. New Zealand also requires 'consideration of social and ethical issues', which presumably includes such issues as education and consent, although this is unclear.[64]

As more disorders are added to newborn screening panels through improvements in technology, the threshold for inclusion appears to be evolving, and the older criteria are being modifyied or challenged. In the case of 'acceptable treatment', for example, there is much discussion (and seemingly less published research)[65] about the efficacy of some treatments in preventing health crises and providing benefits to the child.

The benefit to populations and affected individuals is larger and varied. Affected individuals with non-treatable disorders can still benefit from newborn screening. However benefits are mostly indirect (i.e. to the family unit rather than medically to the individual), and may be accompanied by (somewhat intangible) harms of varying magnitude, such as stress, anxiety and changes in behaviour.

Various commentators are starting to challenge aspects of the Wilson-Jungner criteria for newborn screening. Wilcken, who has gone the farthest, attempts to reformulate the criteria into something more suited to the heterogeneity of newborn screening programmes. Wilcken[66] has gone back to first principles to examine the older criteria, looking at four broad principles: beneficence, non-maleficence, autonomy and justice. She concludes that, in the absence of harm, screening may be beneficial even when there is no direct benefit to the newborn.

This section will loosely examine some of these principles as well as more scientific aspects in relation to modern newborn metabolic screening.

4.1 Prevalence and severity of disorder

Wilson and Jungner specify that the condition should be an 'important' health disorder – a subjective criterion. Importance will vary depending on the point of view (personal, family, community, health system, economic) from which this criterion is assessed.

An unusual feature of newborn metabolic screening is that the individual disorders are rare across the population and the number of children affected by a single disorder can be as low as one in 100 000 newborns or less. The combined detection rate for the whole screening panel is, however, comparatively high (one in 1500 in New Zealand using the old screening panel).[67] Testing for a number of rare disorders increases the number of children who are helped significantly, thereby increasing the benefit to society. The principal advantage of newer screening methodologies is that very rare disorders are easily added to the screening panel, at little extra cost, providing incremental benefits to population health and a significant benefit to those few children and families affected.

Individual benefit from screening is small because of the rarity of these disorders (although, when combined, they become much less rare). On this basis, parents can seemingly opt out with relatively little risk. Some justify opting out of the scheme on the basis that their child's pain, from obtaining the blood sample, outweighs any benefit from screening.[68] It has been estimated, however, that a 1 per cent drop in screening coverage in Australia would result in '… two or three babies per year with a treatable disorder [who] could die or suffer permanent damage'.[69]

The severity of the disorder to be screened for must be considered; the more severe the disorder, the greater the cost benefit ratio to the child and society. This criterion

is subjective and more relevant where individual tests are performed, as opposed to expanded screening where an additional metabolite is easily examined in a two-minute screen. If a disorder is not considered 'important'[70] as far as childhood health goes, but can be definitely and cheaply detected and treated, then it still may be considered for inclusion on the panel. This has not yet occurred in metabolic screening and newborn screening panels comprise only serious (often lethal), very early onset disorders.

Prevalence can also affect the validity of a screening test through its 'positive predictive value'. This is discussed more fully in section 4.2, 'Valid screening test'.

4.2 Valid screening test

This criterion is one of the most important and underlies the whole basis of screening. Without an effective screening test, extra cost is incurred as well as possible psychological harm to parents whilst a large number of families wait for confirmation of a positive screening result, which may turn out to be a false positive. Alternatively (or additionally), a number of affected children may not be identified from the screen, losing the opportunity for early treatment and, consequently, public confidence.

The validity of a test can be defined by two concepts: sensitivity and specificity. Sensitivity is the ability to identify accurately all those children affected by a particular disorder (true positives). Specificity is the ability to identify accurately all those child *not* affected by a particular disorder (true negatives). With most newborn screening tests, as with any other, there is often a trade-off between sensitivity and specificity: the more affected children that are detected, the more unaffected children that return a false positive screening result.

Testing for chemical compounds in a blood sample rarely yields a simple yes or no answer. In a group of healthy people, the molecule of interest will be present in a variety of concentrations, known as a normal range. These concentrations may even change within an individual, on a daily or even hourly basis. If the molecule is at a concentration within the normal range, it is likely (but not certain) that the individual will be healthy. If the level of the compound is outside the normal range, this could (but not definitely) indicate a disorder.

The problems with balancing sensitivity and specificity can be illustrated using a theoretical example as in Figure 2. The average concentration for unaffected people is approximately 5 units and approximately 8 units for affected people. Until the graph is examined, this initially seems sufficiently different to enable diagnosis. Unaffected people may have a blood concentration of the compound ranging from approximately 2.75 to 7.25 units. Affected people may be in the range from approximately 4.5 to 11.25 units. As can be seen, the affected and unaffected ranges

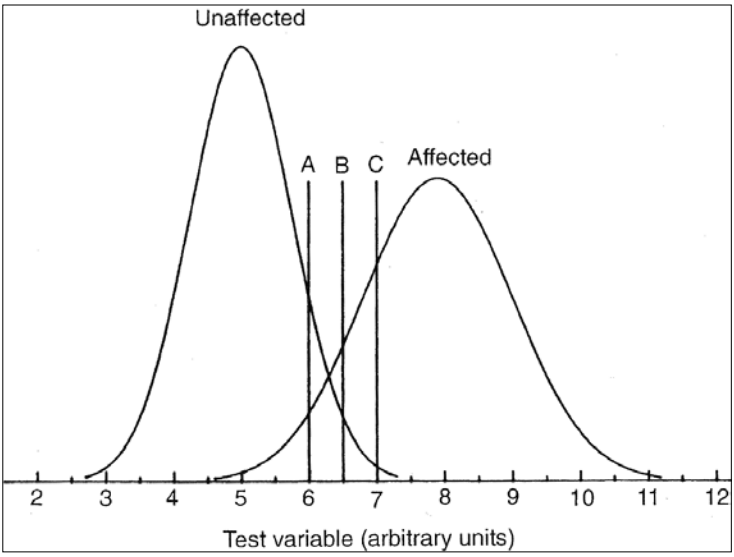
overlap, so if a screening test gives a result of 6 units, additional tests must be done to try and determine disease status. If the result is 10 units, then it is very likely that the individual is affected, as there were no unaffected people with this concentration in the population.

In a screening test, a cut-off point is used, below or above which there will be further investigation. If point A (6 units or more) is used then most affected people will be followed up, but a proportion of unaffected people will also be investigated (high sensitivity, low specificity). If point B (6.5 units or more) is used, then a lot of affected people and fewer unaffected people will be investigated (lower sensitivity, higher specificity). If point C is used (7 units or more), then up to a quarter of affected people will be missed, but almost no unaffected people will be investigated (low sensitivity, high specificity).

Figure 2: *The results of a hypothetical screen and the balance between sensitivity and specificity.*

The chemical compound of interest (test variable) can be detected in overlapping ranges in unaffected and affected individuals. The Y axis (not shown) is number of people. A, B and C are three potential cut off points for further investigation, each with differing specificities and sensitivities.

Source: *Wald and Leck, 2000*[71]



The cut-off value used depends on how important it is to identify affected newborns. For a disorder such as PKU, where early identification and treatment are crucial to a good outcome, the cut-off point may be set to capture more newborns (more false positives) than a disorder such as cystic fibrosis, where children are sometimes identified at birth (outside the screening process) and where prophylactic treatment is helpful, but not crucial to a good outcome.

One result of the large crossover between healthy and affected, for cystic fibrosis testing in particular, is that unaffected carriers (with one functional copy and one non-functional copy of the CFTR gene) may be detected in the affected range. Carrier detection in itself is relatively harmless,[72] as there is no actual disease present, but may cause distress to parents, particularly when the concept of 'carrier' is misunderstood. Parents and relatives who may also be carriers should subsequently be offered testing for carrier status, to discover whether there is a risk to future children of actual cystic fibrosis.

By themselves, however, sensitivity and specificity are not enough to ensure an acceptable screening test, and an effective diagnostic test may not necessarily be an effective screening test. A calculation called positive predictive value can take into account sensitivity and specificity, and the overall prevalence of a disorder in a population.[73] Positive predictive value is a measure of the probability that someone with a positive result for a disorder is actually affected. Conversely, negative predictive value gives a measure of the proportion of people with negative test results who do not have the disorder.

The more common a disorder is in a population, the more favourable is the positive predictive value. Positive predictive value also changes from one population to another. Hence, even with a good, reliable screen, if the disorder is rare in a population, there will be a higher number of false positive results than true positives. This factor must be taken into account when managing follow-up services for those with positive tests.

Whilst sensitivity, specificity and positive predictive value are crucial, a number of other factors are also important. To be useful as a population screen, a test must be simple, reliable and consistent, easily automated and inexpensive.

4.3 Treatment: Is this necessary for screening?

The availability of an efficacious treatment is a now a contentious criterion for inclusion of a disorder in a screening panel. The disorders screened for in New Zealand, for now, are 'treatable'. Wilson and Jungner's original criteria suggested treatment was necessary for inclusion and, indeed, they state that it is probably the most important criterion.[74] Whilst treatment is an important aspect of newborn screening, nevertheless there is still value in very early detection of a disorder in the

absence of a treatment, from the points of view of the child, the family and public health. This is not necessarily the case with the chronic disorders that Wilson and Jungner had in mind, although lifestyle planning is still a relevant factor for those with chronic adult diseases.

The definition of 'accepted treatment'[75] does not necessarily mean that the treatment is cost effective (in a public health context), widely available or even particularly efficacious; it is just the best treatment available, preferably with minimal side effects. Treatment is, in the main, not a permanent cure in the context of inherited newborn metabolic disorders. The ease and cost of treatment vary enormously depending on the severity of the disorder and the efficacy of treatment, which may mitigate a few, some, many or all symptoms. Treatment can range from simply avoiding fasting (e.g. medium-chain acyl-CoA dehydrogenase deficiency (MCAD)), dietary supplementation (e.g. biotinidase deficiency) or severe dietary restriction (e.g. PKU) to, more extremely, a liver transplant (e.g. methylmalonic academia), a heart and lung transplant or gene therapy (e.g. cystic fibrosis or CF).

The severe dietary restriction of phenylalanine that is the treatment for PKU, whilst very effective, is costly (if it is not State funded, as in the United States) and onerous for those on the diet. Even at the risk of severe neurological symptoms, a number of teens fail to maintain the strict diet required.[76]

The principal benefit of early detection, in the absence of treatment, is knowledge. An early diagnosis has a benefit to the newborn child, as it saves the so-called 'diagnostic odyssey'. This 'odyssey' is the process of wondering, waiting for medical consultations, examinations and testing to identify the cause of physical symptoms in an ill child. Whilst testing may be as innocuous as an additional blood sample, it can also be invasive and painful, depending on the tests required. It may also involve a series of tests over a long period. Some of these tests will still be required to confirm disorders detected through newborn screening but there are likely to be fewer tests if there is a specific disorder in mind.

Knowledge saves clinician time and health dollars in quickly diagnosing rare disorders, and may mitigate some of the worry for parents around an undiagnosed, inexplicably ill child. Some disorders are notoriously difficult to identify in the early stages and Duchenne muscular dystrophy (DMD), for example, may take up to two years from first symptoms to diagnosis.[77] As such, affected families tend to come out in favour of early diagnosis through screening rather than a wait-and-see approach.[78]

Disorders in newborn screening programmes typically are rare autosomal recessive conditions and, as such, there is usually no awareness of the disorder in the family until an affected child is born. Knowledge of the potential for a specific, severe genetic disorder in a family gives options for future family planning and testing of older

siblings (who potentially may be mildly affected or undetected). Family planning may (or may not) include reproductive planning (no more biological children, preimplantation genetic diagnosis or prenatal testing of future pregnancies). This may have indirect implications for the affected child in that an additional affected sibling may cause financial and/or emotional strain on a family, which in turn impacts on the child. Family planning also includes options regarding where and how to live, such as moving closer to support and medical services, a house with no stairs when there are mobility issues, special education options for the child, financial savings for future care and estate planning.

Wilcken[79] and others have argued that benefit to the family and absence of harm to the child still constitute grounds for testing newborns for disorders with no treatment, in some instances. Others argue that only direct benefit to the child in the form of treatment is appropriate,[80] as consent is not by the individual, but by the parent for the benefit of the child. This argument is more pertinent for later-onset disorders than for these very early to early onset, severe disorders that are already manifesting in some way. Issues that have been raised include problems bonding with a well but already diagnosed child, anxiety and stress, medicalisation of lifestyle and using untested, unproven and potentially expensive alternative therapies. There is also a risk of treating the child differently from the child's siblings; although this is not necessarily a negative, and benefits from a change in parental attitude (e.g. greater appreciation of all of their children) may flow through the whole family.[81] Nonetheless, there is much supposition and little evidence in this area.

The Human Genetics Society of Australasia (HGSA) policy statement (2004) on newborn screening makes no specific mention of treatment as a necessary criterion. There are, however, a few oblique (and contradictory) references to treatment:[82]

> *Timely intervention in these disorders significantly reduces morbidity, mortality and associated disabilities.*
>
> *1.1 There is benefit for the baby from early diagnosis (benefit to the family may also benefit the baby).*

There is a comment at the end of the document to the effect that screening for a number of (untreatable) disorders was not currently recommended, one of the reasons being 'proof of advantage from early diagnosis is absent or uncertain'.[83]

In the United States, where testing is often mandatory, testing for untreatable disorders can be interpreted as a problematic situation. This is because parents are, in some States, not given the choice of whether to screen or not. Whilst this may be thought to be appropriate for the current screening panel, some parents may not wish to know certain information if there is no direct action that they can take. Testing without

informed consent is neither appropriate nor current clinical practice, particularly for predictive testing of later-onset disorders.

In countries such as New Zealand, where informed consent is required, there may be fewer ethical and social issues regarding screening for untreatable disorders. Those who have an objection to screening for untreatable or later-onset disorders have the right to refuse in New Zealand, in accordance with standard genetic testing practices. This in turn means that their children will not be screened for treatable disorders, should they be added to the screening panel in the future. One option to diffuse this situation could be separate consent sections for 'treatable' and 'non-treatable' disorders. Education and informed consent also play a key role in the potential introduction of screening for untreatable disorders.

Parents with such knowledge could choose to use prenatal or preimplantation genetic testing in any future pregnancies or alternatives such as gamete donors or adoption, or could choose not to extend their biological family. Obviously, use of the above technologies should never be compulsory but, even if only a few parents choose to prevent a future affected birth, through whatever method, then there is some public health benefit.

As newborn screening is additionally for the benefit of the population and public health, it could be argued that any improvement to public health is a desirable aspect of newborn screening. This definition would include the potential for reduction of future affected births. Compulsion in testing and, more particularly, future reproductive planning is known as eugenics and is undesirable. Giving parents a choice and, potentially, options for future decisions is not eugenics.

There is little extra initial cost to adding more disorders to MSMS screening. Any cost is in follow-up and confirmation of diagnosis. If a test is discriminating enough then this cost should (intuitively) be less than later diagnosis. Whilst there is little direct benefit to the newborn (except avoiding many medical tests), there is greater benefit to the family as they know what to expect and can make reproductive and lifestyle decisions. There is a possible benefit to society in reduced numbers of tests and clinician time used for diagnosis, as well as a potential benefit if parents actively choose to avoid another affected birth.

Some have argued that parental or couples screening is a more logical approach if family planning options are an intended outcome of screening for untreatable disorders. This may be true but there are also arguments against this timing,[84] not least of which is the number of *de novo* mutations that occur during egg, sperm and/or embryo formation that would not be detected. One third of children born with Duchenne muscular dystrophy, for example, are a result of *de novo* mutations in the egg or embryo. Other arguments against parental screening include the lack

of planning in many pregnancies and the current difficulty in screening for one disorder, let alone many rare disorders.

4.4 Characterisation of disorders

It is important to have a thorough understanding of the natural history of disorders on any screening panel. Some disorders appear to be similar but in fact have differing causes, requiring different treatments. Information on the natural variability of disorders can also lead to a significant amount of information on the effectiveness of the various treatments. Ironically, some of this information may actually only be gained in the practice of screening, principally due to the rarity of many of the disorders.

Phenylketonuria (PKU) is the result of mutations to the phenylalanine hydroxylase (PAH) gene. It eventually became clear that, in a small percentage of cases, high levels of phenylalanine in the blood did not always mean that the child had PKU and that these children did not respond well to dietary restriction.[85] Approximately 1 per cent of high phenylalanine blood levels were the result of non-PAH mutations that affect how another factor participates in the phenylalanine-processing chain. Infants with perturbations in the levels of this tetrahydrobiopterin factor (BH4) have similar symptoms to PKU but do not response to the dietary restriction in the same way as newborns with classical PKU do. In fact, the severity of the dietary restriction actually caused substantial harm. PKU screening also detected mild variations of the disorder, where treatment may not be necessary at all and again could cause more harm than good.

The example of PKU illustrates the importance of a thorough understanding of the disorder in question. Due to the rarity of some of these disorders, however, it is difficult to gain this sort of detailed knowledge before the advent of a screening programme, because of the problems with diagnosing some of these affected children. Specialist research programmes and patient support groups have an important role to play in this aspect of screening programmes, through identifying affected families and carrying out more detailed research than can be undertaken by a screening programme.

4.5 Cost/benefit

Cost/benefit studies typically have not been very comprehensive in the past and are often based on direct costs to the screening programme. There are many costs, some of which are indirect and difficult to measure. Examples of costs include: population/parent education; the actual test (which can be further broken down into personnel, equipment purchase and maintenance, materials, overheads etc.); interpretation of ambiguous results by metabolic specialists; retesting or more specific confirmatory

testing for diagnosis of both affected and false positive samples; consequent testing of close family members; clinical management by metabolic specialists; direct treatment costs; and genetic counselling. These costs may or may not be offset by the early detection and treatment of affected children, and require careful evaluation.

Benefits include: reduced costs to the health system in hospital emergency departments; effective diagnostic processes; lower care needs (paid and unpaid) in disorders with developmental delay that can be prevented (including education); and ability to contribute to society and the economy.

Some costs and benefits, however, are more intangible and harder to put a monetary value on. Costs of this type include increased parental stress and time spent with children in medical clinics (both with and without screening). Benefits may include prevention of death of a child; informed decisions regarding future family plans; and lowered anxiety from early understanding of a condition.

One way to regard screening, given the difficulty of pricing a life, is in terms of effectiveness[86] and hence as a justifiable cost to the health system. It is obviously more difficult to justify in a health system such as that of the United States because of the strong cost drivers from an insurance-run structure.

5 THE SCREENING TECHNOLOGIES

No one technology can as yet cover all the disorders screened for in newborns. In centres using older technologies, each disorder is tested for individually, using the most appropriate specific test. The newer tandem mass spectroscopy (MSMS) technology enables simultaneous, high throughput testing of many metabolites. Not all disorders are detectable with MSMS technology so some disorders will continue to be tested for individually, even in expanded screening programmes. In New Zealand, only two tests from the old screening panel have been moved to the MSMS platform: phenylketouria (PKU) and maple syrup urine disease (MSUD). The other five remain as individual tests.

5.1 Biochemistry and immunohistochemistry

Biochemical and immunohistochemical testing are established technologies in newborn screening. As each test is for a specific molecule or protein, a new test must be developed for each new disorder to be screened for.

Biochemical testing involves testing the level of activity of a specific enzyme in a sample. Enzymes convert (catalyse) one molecule into another. Even if an enzyme is being made in the body, if it is not active, then the sample will give a positive test result for a disorder, as the enzyme is unable to catalyse the reaction.

The enzyme reaction occurs in this way:

Catalyst
Enzyme Z
X molecule → Y molecule
Precursor *Product*

All or part of molecule X fits into the active site of Enzyme Z, rather like a lock and key. Enzyme Z then converts X into the molecule Y. Sometime additional molecules are required as precursors and sometimes more than one product is produced.

Some biochemical testing measures the activity of an enzyme (e.g. phenylalanine hydroxylase) in a sample by either the appearance of a specific reaction product or the disappearance of a reaction precursor. Other biochemical testing involves testing for the presence and quantity of a specific metabolite (either a precursor or product). This testing is sometimes called spectrophotometry or colourimetric testing as the molecule being measured is detectable by a change in colour in a spectrophotometer machine compared to the colour in a control sample. The change in measured level of the molecule of interest is taken from the change in colour of the sample measured. From this measurement, the activity of the enzyme or quantity of a metabolite can be calculated. If the natural molecules involved in the reaction are not easily detectable by a spectrophotometer in the laboratory, then artificial 'analogues' are used (similar molecules that still fit like a key into the enzyme lock), which are detectable.

An immunoassay is the use of specific antibody/antigen recognition to perform a test. The biological sample can be tested either for the presence of the antigen (a specific protein) or antibodies to a specific protein.

An antibody is a molecule in the immune system that recognises a specific protein pattern. This recognition can also be described as a lock and key combination: only a particular key will fit in a specific lock. Specific (monoclonal) antibodies can be generated in the laboratory through cell culture. Antibodies for immunoassays may have fluorescent, coloured or radioactive molecules or enzymes artificially attached to one end, to enable detection.

One of the reactants is fixed to a solid support (e.g. a plastic tray) and any sample that has not bound to the fixed reactant can be washed away. This allows for more accurate quantification of the molecule of interest, e.g. the amount of immunoreactive trypsinogen in the blood sample when screening for cystic fibrosis.

5.2 High performance liquid chromatography

High performance liquid chromatography (HPLC) is not used in newborn screening in New Zealand.

HPLC techniques (and, in some programmes, isoelectric focusing) are used overseas to screen for blood disorders: the haemoglobinopathies, such as sickle-cell anaemia, and the thalassaemias. These disorders are predominantly found in populations of African, Mediterranean, Middle Eastern and Asia populations. They are thought to have become common in these populations because to have one copy of the relevant affected gene (allele) is protective for malaria. Having two copies of the relevant allele, however, causes severe symptoms from the effects on the morphology of red blood cells and generally results in premature death.

HPLC columns, specifically designed for haemoglobins, separate out the different types of haemoglobins according to how they travel through the HPLC column. The separation is measured according to the time each component (different type of haemoglobin) takes to come through the column and reach the detector. The column itself consists of a 'solid phase' that stays in the column and a liquid phase that travels through the column with the blood sample. Both the solid and liquid phases can be varied to ensure optimal separation of the sample being processed.

There are a number of types of haemoglobin chain that combine to form a haemoglobin compound (Hb). The combination of four chains changes over time and a newborn profile is different from that of an adult. The predominant combination in newborns is called fetal haemoglobin or Hb F, with a small amount of the adult form, Hb A. The absence of Hb A and the presence of the sickle-cell form of haemoglobin (Hb S) is diagnostic for sickle-cell anaemia.

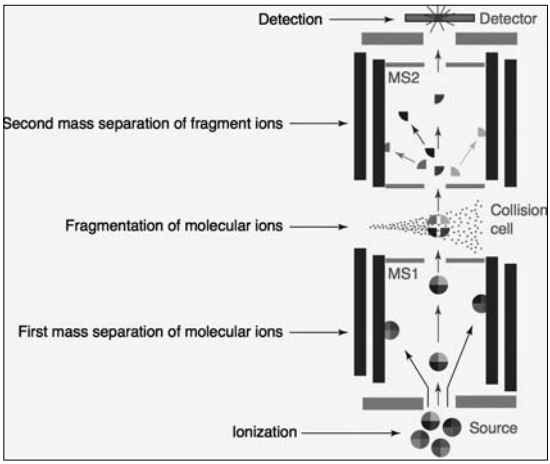
5.3 Tandem mass spectrometry

Tandem mass spectrometry (MSMS) is a method to separate and detect molecules on the basis of both size (mass) and electric charge. (For more detail on MSMS technology, see Chace et al., 2002.)[87] These molecules can be electrically separated, using positively and negatively charged plates in the chambers, to alter their course through the chambers. This separation is used to remove molecules that are not going to be measured and to ensure that known fragments of interest are aimed at the detector.

Figure 2: *The results of a hypothetical screen and the balance between sensitivity and specificity.*

The chemical compound of interest (test variable) can be detected in overlapping ranges in unaffected and affected individuals. The Y axis (not shown) is number of people. A, B and C are three potential cut off points for further investigation, each with differing specificities and sensitivities.

Source: *Wald and Leck, 2000*[71]



In newborn screening, the MSMS is used to measure individual amino acids and acylcarnitines in the heel prick blood sample. Amino acids, such as phenylalanine, are the building blocks of proteins. Carnitine is used to transport fatty acids (a component of fats and oils) around cells. A fatty acid attached to the transporter molecule carnitine is called an acylcarnitine. Acylcarnitines are named according to the length of fatty acid involved, e.g. C8 (octanoylcarnitine) is the fatty acid measured in particular in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and it has a backbone of eight carbons. They are sometimes more simply referred to as short, medium and long chain.

The tandem mass spectrometer is essentially two mass spectrometers lined up together and connected by a 'collision cell'. The blood sample can be fed into the first chamber in a number of different ways to make it, for example, a gas-phase electrospray. MSMS equipment sometimes takes its name from this step in the chemical analysis. The sample is separated according to the constraints programmed into the computer. Molecules that get directed into the collision cell, by the first mass

spectrometer (MS), are broken up into smaller pieces and passed through the second MS chamber. The molecules are again separated according to the parameters of the test and those molecules of interest are directed towards the detector. The result is a graph as shown in Figure 4.

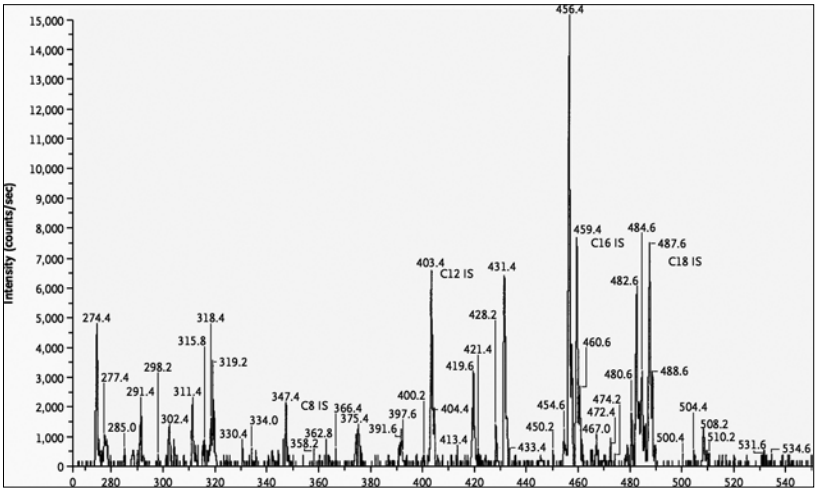
The two mass spectrometers can be loosely thought of as increasingly fine sieves: the coarse unwanted material is held back by the top sieve, allowing the more specific, finer material to proceed to the next step. The collision chamber breaks the material up further before it is separated again in the second sieve, allowing the 'purified' material of interest to pass through to the detector and directing unwanted material away from the detector.

Many types of acylcarnitines and amino acids can be measured within minutes, enabling the detection of many disorders.

Figure 4: *MSMS readout for acylcarnitines, showing MCAD. The first result is from an individual affected by medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency showing the accumulated acylcarnitine C8 molecule at around 345, the molecule diagnostic for the disorder. The second is from an unaffected control individual. Note the absence of a major peak for the C8 molecule. Intensity (vertical axis) indicates the amount of each molecule, by the height and width of each peak. IS indicates the internal standards used to guide peak identification*

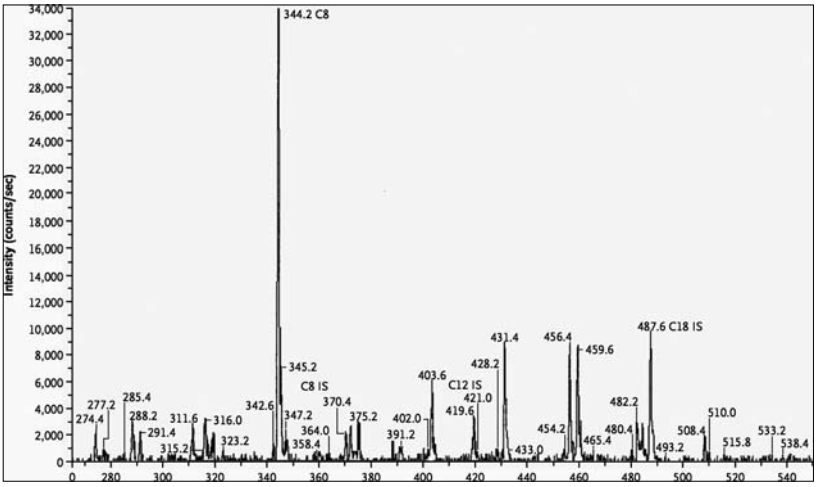
Source: *Khoury et al., 2003*[89]

MCAD profile:



Acylcarnitines (mass-to-charge ratio)

Unaffected control profile:



Acylcarnitines (mass-to-charge ratio)

6 WHAT DOES EXPANDED SCREENING MEAN FOR NEW ZEALAND?

There seems little doubt now that expanded NBS using MSMS technology is a positive development for New Zealand. New Zealand would be following other countries in this respect, particularly Australia and the United States. More children with rare disorders are detected for little extra cost in testing, reducing mortality and morbidity.[90] New Zealand is likely to follow international recommendations on how to screen and what to screen for, and there is much international experience to draw on, particularly from Australia.

Ostensibly, expanded metabolic screening is not very controversial anymore and few of the negative aspects of expanded screening are new. There is still sparse, but increasing, evidence that early detection can mitigate various effects of these disorders in young children.[91] The main issues highlighted by the introduction of the MSMS would appear to be deciding which disorders are most effectively included in the screening panel and ensuring sufficient State resourcing (financial and medical) of the programme.

6.1 Main scientific and clinical issues

Expanded screening has been added to a well-established newborn screening programme. This programme already has quality assurance, audit and evaluation aspects in place, with oversight by the newborn metabolic screening programme Advisory Group, the National Screening Unit and the relevant professional bodies. Whilst there have been additional requirements in terms of equipment and laboratory and clinical personnel, these were put in place well before expanded screening was offered. The equipment was tested using affected samples from the established New South Wales (Australia) programme and New Zealand has followed Australia's lead with regard to the disorders on the screening panel.[92]

A factor that may or may not have some bearing on the future newborn screening panel is changing national demographics through immigration. In other words, 'what does the population profile look like?' This issue has prompted Britain to introduce universal screening for sickle-cell anaemia, moving from the previous screening that targeted those of African or Caribbean descent. With an increasing proportion of the New Zealand population being of Asian descent, it may be worth considering disorders such as the thalassaemias or glucose-6-phosphatase dehydrogenase deficiency for screening in the future.

Issues of cost/benefit and effectiveness can be guided by data from Australia and internationally. There is certainly data on effectiveness of early detection for MCAD and cystic fibrosis from Australia,[93] but it would be useful to see New Zealand data to gauge the effectiveness of the programme in this respect.

The main issues of expansion are not new, but in some instances are amplified. These concerns include, but are not limited to, unaffected carrier detection, which is already an issue for cystic fibrosis; false positives, resulting in stress for parents and increased use of clinical services for investigation; false negatives, meaning that the disorder may be excluded from future diagnosis; increased cost of following up anomalous results, because of increased testing; and incidental detection of untreatable disease.

6.2 Other New Zealand issues

A number of other issues have peripheral interest from a scientific/clinical point of view.

The recent purchase of the New Zealand MSMS equipment was funded by a children's charity, the Starship Foundation. Aside from the versatility of the equipment (used in both screening and diagnostics), it seems that the newborn metabolic screening programme is a core health service, worthy of State-funded support. This should include upgrades and support for new and improved technology, particularly as

this move aligned the New Zealand programme with the Australian screening programmes.

Education of consumers about newborn metabolic screening, from anecdotal reports, appears patchy at best. There is a requirement for 'informed consent' on the part of parents before the newborn's heel blood sample may be taken. Up until now, there have been no major issues reported in New Zealand with respect to the lack of information provided, either before or at the time of sampling. As the programme continues to expand, as will invariably happen, the informed part of the consent process will become more crucial. The introduction of screening for untreatable disorders or even expansion to DNA screening requires that parents come to a considered conclusion about testing their newborn, in keeping with any other genetic testing processes. Awareness on the part of lead maternity carers, prenatal education courses, maternity/neonatal services and even parents must be raised. It may be easier to achieve this through gradual changes to education curricula and medical systems before any further expansion, rather than having a sudden change in processes later.

The use of the blood samples on stored Guthrie cards is about to undergo a consultation process. Currently Guthrie cards are stored indefinitely and most New Zealanders born since 1968 will have a card in storage. There appears to be official provision and support for using older samples for quality control and screen development, directly relating to the primary purpose of the screening programme, i.e. the detection of newborns with serious, early onset disorders. Allowing the stored blood samples to be accessed without consent for purposes unrelated to the screening programme is more problematic and has implications for the integrity of the programme.

Participation in the newborn metabolic screening programme is extremely high in New Zealand: over 99 per cent of newborns are tested.[94] Yet, each year, a small but increasing number of parents are requesting their child's Guthrie card back after screening. [95] Is there a perception of risk in segments of the community regarding the way in which their child's DNA might be used in the future? Until now, the NMSP Advisory Group has carefully guarded the integrity of the programme by an extremely limited release of cards to the police (for forensic identification only), although the Courts can order access for paternity testing, for example. The Advisory Group has so far refused all requests to use the cards for scientific research unrelated to the programme.

Guthrie cards are a potentially valuable resource for many and varied lines of research by scientists and clinicians. Some such research may even answer important health questions for New Zealanders. Is there, however, a possibility of reduced screening coverage due to a perceived risk in the storage of cards evolving into a perceived risk in screening? Hopefully, the public consultation will go some way towards answering this and other questions.

In the meantime, any perception of secrecy or concealment with regard to use of the cards outside the primary purpose of the programme has the potential to severely damage the programme. Information and consent processes need to be consistent and of good quality to allay any possible fears. These processes are largely outside the control of the newborn screening programme.

There is a possible corollary to be found in vaccination programmes, where a small number of vocal people are able to alter vaccination rates through wide dissemination of selective information or misinformation. If there is any threat to the success of the primary purpose of the programme in this manner, then secondary uses of the Guthrie cards must be continue to be stringently controlled or even stopped.

The newborn metabolic screening programme is not a DNA bank or a biobank. It has not been designed in this way and does not have the processes and safeguards in place to be used in this manner. In addition, these samples are from predominantly healthy newborns. They are not taken because of apparent disease and they are not pathology samples or any other type of sample taken for specific medical purposes; so there is no emotional or other link between the purposes of the research and the family. Members of the public have not consented to their samples or their children's samples being used in any way outside the screening programme. The programme must not be used as a tissue or DNA repository simply because it is the easiest way to answer a particular research question. There are almost always other paths that can be followed to answer the same research question.

7 MOLECULAR GENETIC SCREENING – THE INEVITABILITY?

For more detail on the implications of newborn DNA screening, please to refer to articles by Green and Pass,[96] Kerruish and Robertson,[97] the Human Genetics Commission[98] and Wilcken.[99] For more detail on microarray whole genome screening, please refer to 'Genetic testing and microarray technologies' by Genevieve Matthews in this Report.

Whilst molecular genetic (DNA) newborn screening ostensibly has the same aims as metabolic screening, i.e. detection of potential medical problems, it has far greater potential to detect medical issues far into the future. DNA screening can detect conditions that may not arise until middle age or even later, whereas metabolic screening is currently limited to the early years of life (or around the time when the blood sample is taken).

DNA screening has the potential to predict a wider range and greater number of disorders, an advantage from a purely public health perspective. There are, however, many issues left to deal with from scientific, clinical, ethical, legal and policy points of view. This section will focus on the scientific and clinical limitations and future promise of DNA screening.

7.1 What is different?

Newborn DNA screening would involve analysing the DNA contained in the blood spots, rather than the metabolic molecules. Testing could even move from blood to some other bodily sample, such as a cheek cell swab. By examining the DNA for changes (mutations) known to cause specific disorders, it would be hoped that, if the screening were performed early enough, more disorders would be *predicted* before any symptoms or damage were detectable. Early detection enables early treatment, if available, or modification of environment for those disorders that respond to such changes.

Short of creating an entirely new population-screening regime, with different screening times, the time of newborn screening remains convenient for undertaking additional screening. It is also a time where many, but not all, disorders have not yet begun to develop. Conversely, there is much controversy around the idea of predictive genetic screening for later-onset disorders, even for people with a known risk. This may provide the impetus to drive a more selective screening programme with various screening points over time; perhaps even integrating existing (non-DNA) screening programmes such as breast cancer screening.

Newborn genetic screening using DNA analysis of newborn blood spots is likely to be considered more seriously in the future as genetic testing technologies improve and become cheaper. Concomitant with improvements in technology are improvements in knowledge regarding the basis of genetic disorders. Advances include identification of disease-causing mutations and interpretation of genetic data to give a more accurate estimation of risk.

High throughput, massively parallel (microarray) technology in particular is a likely candidate technology for screening in the future. Microarray systems can screen from hundreds to hundreds of thousands of specific genetic variants in a short time, but are only just starting to move from research trials into clinical use. Whole genome sequencing is also a possibility in the longer term. Microarray technologies are explained in more detail in the prenatal whole genome screening sections of this Report.[100]

There are, however, some issues with the use of DNA screening that do not exist with the indirect metabolic screening. So, what are the differences between newborn genetic (DNA) screening and newborn metabolic screening?

7.1.1 Metabolic versus genetic screening

Concerns typically raised around DNA screening relate to overlapping aspects of various screening criteria: test validity; availability of treatment; the predicted severity and the natural history of the disorder; and, specifically, the risk of developing a disorder (penetrance and expressivity). Penetrance is the percentage of people who are at risk and who actually go on to exhibit symptoms. Expressivity is the degree to

which the symptoms manifest, i.e. severity. Issues of cost will likely resolve themselves as the technology improves and becomes more common.

The crucial difference between the two types of screening is that metabolic testing is symptomatic, whereas DNA screening is predictive. Metabolic screening detects abnormal levels of molecules in the body, which may be as a result of genetic disease. If there is no disease present then these metabolites will usually be within the normal concentration range. DNA screening, with our current level of knowledge and technology, detects *some* mutations that *probably* cause disease. In both types of screening, further investigation of an at-risk result would be required.

The measurement of abnormal metabolite levels is symptomatic testing; in other words, there are possible signs of disease development that can be followed up. Even when the obvious physical symptoms have not developed, the abnormal metabolite levels themselves are a symptom or phenotype (physical result of a DNA genotype) and evidence of a disorder that will likely develop further.

DNA screening is predictive; but the existence of a specific genotype (DNA sequence) is not deterministic, merely indicative of what may occur in the future. A number of factors must be taken into account before a risk prediction of a future disorder can be made from DNA sequence alone. With a few disorders, this risk assessment is straightforward because a particular change in a single gene invariably results in the symptoms of the disorder, e.g. Huntington disease.

For other disorders, using current knowledge, it is impossible to predict accurately that a person will develop symptoms and a higher follow-up rate may be expected. For example, in one study of the most serious haemochromatosis mutation, two copies caused one person of a group 152 homozygotes to go on to develop the blood disorder.[101] This demonstrates a low penetrance[102] and, whilst the treatment is relatively simple (regular blood donation), it may be unnecessary if a person never develops any symptoms. Children with DNA mutations known to cause particular conditions occasionally receive negative test results under the metabolic screening programme. Guthrie cards in New Zealand are stored indefinitely, partly to follow up on these rare occurrences, potentially enabling staff to refine the metabolic test further. The lack of development of symptoms (penetrance) or reduced severity of the disorder (expressivity)[103] may be because of a weak genotype/phenotype link and/or many (known and unknown) modifiers. Until more is known about such disorders, they are unlikely to be included on a screening panel, even if there is a simple treatment as with haemochromatosis.[104]

DNA screening, using a limited panel of serious or common mutations, is likely to miss some children with rare or uncharacterised mutations leading, in theory, to a lower detection rate. This issue is discussed further in section 7.4.1 on cystic fibrosis.

If DNA screening were introduced today as a replacement for metabolic screening, a DNA genotype would be a signal for close monitoring of the child – in all probability looking for changes in metabolite levels. Some children would not be detected at all, as not all causative mutations have been identified.[105] These children could develop symptoms without any early recognition or treatment, if in fact treatment exists.

DNA screening, however, may be able to detect those with later-onset variants of those disorders in newborn screening panels.

Sometimes children, such as those with some neonatal-onset classical organic acidurias, have a medical crisis before their disorder is identified through metabolic screening.[106] DNA screening of, particularly metabolic, disorders could exacerbate the number of these occurrences due to the time (currently) taken to complete the DNA screening and follow-up analysis. This risk of an early crisis is lower for some of the disorders currently being considered for DNA screening (e.g. fragile X syndrome) as they are, for the most part, slightly later onset. Children may not exhibit symptoms for months or a few years after birth. Technological advances may eventually minimise this risk, through some combination of improvement in the speed of screening and shifting of the time of screening.

Other children who could be disadvantaged by DNA screening alone are those inadvertently detected through the current metabolic screening programme. These are children, with disorders that are not specifically tested for, who have an abnormal result for one or more metabolites using metabolic screening.[107] Currently, in New Zealand, these children will be followed up by a metabolic physician; but, unless the problem is actually of genetic origin and there is detailed screening of the newborn genome, it is possible that DNA screening will not detect at least some of these children. This non-specific detection 'feature' of metabolic screening is not regarded by everyone as an advantage, however, and this information can be specifically excluded by focusing solely on the metabolic molecules of interest. Alternatively, more children with disorders may be identified using new DNA screening technologies, depending on how the technology is used.

The heel prick to obtain blood for metabolic testing cannot be performed at birth: a short wait of approximately twenty-four hours is required to allow the maternal influences on the child's metabolism to subside. DNA screening on the other hand may be performed at birth, and potentially may be performed before birth. An amniocentesis sample, for example, is tested for major chromosomal abnormalities including whole chromosome changes (aneuploidy) and large deletions and duplications (segmental aneuploidy). Amniocentesis is currently used as a *de facto* aneuploidy screen in New Zealand, due to the lack of any other comprehensive, reliable screening programme. There is no physical reason why this sample could not be used for other genetic analyses. On the other hand, there is a risk of miscarriage

from the amniocentesis procedure, so screening of all fetuses is not feasible unless non-invasive sampling techniques can be developed.

DNA screening, as opposed to metabolic screening, is not affected by such factors as an early blood transfusion and prematurity.[108] These aspects can and do affect metabolic screening results, sometimes masking an existing disorder. An obstructed bowel (meconium ileus), for example, can mask the detection of cystic fibrosis in a newborn, although this symptom is in itself a signal for further investigation.

In addition, all known disease-causing mutations can be added to a microarray screen for a specific disorder. This ability could certainly benefit non-Northern European populations in the case of cystic fibrosis, where the delta F508 mutation is a far less common cause of the disorder. Whilst it is possible that some children would miss being diagnosed, even screening with all ~1500 known mutations, the risk is particularly small compared to using only twenty-three mutations, as with the United States cystic fibrosis prenatal screening programme. There is also certainly an opportunity for application of microarrays in diagnostics.

There are currently some serious limitations to widespread DNA screening:

- Not all disorders are of primarily genetic cause. An excellent example of this is congenital hypothyroidism (see section 3.2). Whilst a small proportion of cases have a heritable genetic cause, most do not. Congenital hypothyroidism would necessarily continue to be screened for metabolically. DNA screening would also not replace newborn screening for hip or heart defects and hearing deficits, although it could be used in conjunction with traditional screening for the last two issues.
- Not all DNA mutations that cause disease are known; not all modifiers of mutations are known either. This may lead to great difficulty interpreting any information derived from DNA screening. A person's genetic background is not immediately relevant for primary metabolic screening and it is only when the characterisation part of the diagnostic process starts that genetics become pertinent.
- The presence of specific DNA mutations does not automatically lead to a disease state. In comparison, metabolic testing only attempts to detect the developing disease state. DNA screening will inevitably lead to the detection of children with very mild or no symptoms, who require no treatment.
- Short of sequencing the whole genome, not all disease-causing mutations are able to be detected (technological limitations) and not all should necessarily be automatically detected (for ethical reasons), for example, because they have high environmental influences (lessening the predictive value) or are very late onset. There is much debate around the latter issue.

- There is the potential to widen DNA screening to sequences in the genome that have no direct bearing on physical health status, such as behavioural or psychological traits. Traits such as these typically have a very high environmental component. The effects and long-term consequences of using DNA screening in this manner are unknown but are generally predicted to be unhelpful to the individual.
- There is a lot of evidence to suggest that the medical system is not currently equipped to deal with genetic information such as this,[109] particularly at the primary health-care level, but also in more specialised areas. Substantial investment in training and additional recruitment of trained personnel (such as laboratory staff, genetic counsellors/associates and clinical geneticists) would be required even to start pilot programmes, let alone widespread screening.

Many of the current scientific limitations of DNA screening will be mitigated, if not solved, in the future. Improvements in technology are widely predicted and, with increasing use of genetic testing or screening technologies, genetic information will be more easily interpreted through the use of information in extensive databases.

The question of benefit to the child from newborn screening becomes much more equivocal in these situations, even ignoring the presence or absence of a treatment and more complex issues such as privacy and autonomy. Significant benefit and cost effectiveness will need to be comprehensively demonstrated before DNA screening is introduced across-the-board in any programme.

7.1.2 Genotype/phenotype relationships

The general perception of autosomal recessive disorders is that, if an individual has two non- or sub-functional copies of a gene, then they will exhibit a standard single gene trait or disease. Unfortunately (or fortunately), genetics is not as straightforward as this, and many factors can modify whether the expected phenotype is exhibited or not.

There are many reasons why a disease genotype, revealed by DNA testing, may not manifest as a disorder phenotype. Influences from other parts of the genome and the environment are responsible for this variation; but, for many disorders, the specific reasons behind the variation are unknown.

7.1.2.1 Haemochromatosis

Haemochromatosis is an iron-overload disorder, due to a failure in normal iron metabolism. Excess iron in the body is deposited in various organs over time, potentially (but not necessarily) causing damage including cirrhosis and cancer (liver), diabetes (pancreas) and heart failure. It is easily treated by regular withdrawal of blood, for example, by donating to blood banks. There are four main types of inherited haemochromatosis, caused by mutations in different genes.[110]

Classical haemochromatosis (the focus in this section) is an adult-onset, recessive disorder. There is one very common disease allele of the HFE gene in Northern European populations, the C282Y allele. Two copies of this allele are also associated with the highest risk of the disorder.[111] Because of the ease of treatment, it has been suggested as a good candidate for population screening.

Haemochromatosis is a partially penetrant disorder, however, and not all homozygotes for the above mutation will go on to develop iron overload, let alone disease of the various organs. Whilst quality data is lacking, it is estimated in one review that 38 per cent to 50 per cent of homozygotes with the C282Y allele will develop iron overload and 10 per cent to 33 per cent will develop disease in the long term.[112] In other words, over 50 per cent of people at risk will never develop symptoms. Another study estimates the risk of serious disease to be substantially lower at ~1 per cent; although there was later some scientific criticism of the methods used.[113] The risk of disease is lower for people with less penetrant haemochromatosis-causing HFE alleles.

The basis upon which some people develop disease and others are asymptomatic is unknown. There is also no consensus regarding whether or how to treat asymptomatic homozygotes, although closer monitoring of health will allow intervention where serious disease might have otherwise been missed.[114] Besides the possible psychological effects introduced by a positive genetic test for susceptibility (shown to be unfounded in one Australian study),[115] there may be implications for health insurance eligibility in some countries. For these reasons, population screening has never been implemented, despite the ease of treatment. It is a likely candidate, however, if widespread DNA screening should ever be introduced.

7.1.2.2 Phenylketonuria (PKU)

PKU was one of the first disorders to be screened for in newborns. It has been observed that, even with this classically Mendelian (single-gene) disorder, the severity of the symptoms may vary between siblings who have the same genetic origins.

Clearly, PKU shows variability in severity because it can be caused by a number of mutations in different parts of the phenylalanine hydroxylase (PAH) gene. This variation is due to the differing effects of the individual mutations on the active site of the enzyme produced from the gene, as well as changes to regulation, protein folding, protein aggregation and/or protein stability.[116] It has been demonstrated, however, that these properties can be modified in the laboratory by changes to proteins that help other proteins fold correctly (chaperonins), as well as by changes in environmental temperature. It is entirely possible that these same changes could help modulate the PAH enzyme in people too, explaining at least some of the variation seen in people with the same causative mutations.[117]

A more expansive explanation is postulated by Scriver.[118] He suggests that the phenotype (physical effects) seen in PKU can be further divided into the enzyme phenotype, the metabolic phenotype and the cognitive phenotype. The enzyme phenotype, aside from variability from the causal mutation(s), is modified by variability in protein folding and degradation systems in the body; the metabolic phenotype is where there may be variation in phenylalanine transport and processing; and the cognitive phenotype is subject to variation in phenylalanine transport into the brain. These three different phenotypes probably have some genetic basis, not just in the PAH gene. All of these phenotypes are in turn modified by the environment, diet being the major influence in the case of PKU.

7.1.3 Whole genome screening versus selective screening

There is potential to screen for many more disorders simultaneously with DNA screening than with current technologies. There is the capability to target early onset, serious disorders, as in current screening programmes, or to expand the screening panel to all known single-gene disorders or even more widely in the future. Some of these conditions may not be 'serious' or may not manifest themselves in the early childhood period, two criteria that are widespread in many newborn screening programmes. Commentators in the literature are only now starting to explore some of the implications of extending 'newborn' screening in this way. Although many of these issues are not new for individual genetic testing in those with a known risk, they are greatly magnified when looked at from the viewpoint of a low-risk population.

There are three basic alternatives for the use of DNA screening of populations: keep to same criteria currently used in newborn screening and limit screening to a small number of high-risk newborn disorders; screen for many disorders at newborn stage; or expand the screening, but adopt different time points according to when a disorder is most likely to develop. There is also a choice to be made about whether to limit screening to serious, single-gene disorders or all single-gene disorders, or whether to expand into more complex genetic disorders such as heart disease and Alzheimer's disease. This type of widespread screening has many more ethical, psychological and social implications than does targeted newborn screening, as many more factors are involved in causation of disorders and accurately predicting risk is far less precise.

The use of whole genome screening or even whole genome sequencing can be likened to a genetic health scan. On the one hand, there may be value in knowing that there is a future risk. On the other hand, a genetic health scan has similar pitfalls to the use of a whole body screen, such as a computerised tomography (CT) scan, as a general health measure (rather than for diagnostics) including false results.[119] Merely by having a scan, there may be risks to physical and psychological health and well-being through possibly unnecessary investigation as a follow-up to any unfavourable results, whether high or low risk.

The pros and cons of each strategy will have to be seriously considered and balanced against available health resources before comprehensive genetic screening is offered to the general population.

7.2 Practical considerations of DNA screening

A number of practical considerations may affect whether and how whole or targeted genome screening might be used.

Microarray screening of the genome is similar to MSMS screening, in that it is easy and relatively cheap to add new disorders to a screening microarray. Additional screening is even easier for whole genome sequencing as the data is already available: the data simply needs to be identified and analysed.

Potentially the major factor regarding if and how genetic screening is used is the issue of intellectual property ownership and licensing of patented genetic information or tests. This issue is already affecting how genetic tests are used in general, including which tests are available on diagnostic microarrays.[120] Tests that are protected by intellectual property (IP) rights may be freely available and are sometimes patented solely to ensure this availability. Alternatively, the information that is the basis of the IP may be restricted either by pricing or even by limited availability to particular licensees. Limiting access in either manner tends to restrict the availability of tests on comprehensive microarray screens for some genetic mutations or even whole genes.

'Informed' consent will still need to be obtained to perform this type of genetic screening in New Zealand. Whilst it is, for the most part, impractical to obtain consent for each test on a microarray, the tests could be grouped in some way and separate consent obtained for each group. Tests could be grouped, for example, by age of onset, severity or complexity (e.g. heart disease, with multiple genes and environmental influences, versus hereditary breast cancer, with one or few genes and low environment effects). Separate consent for DNA screening as part of a multiplatform screen, for example of newborns, is also desirable.

If the usual genetic testing standards are to be adhered to, then there are extra counselling requirements to be met for genetic screening. Counselling should be performed by persons trained in genetic counselling, further increasing the demand for genetic clinicians and counsellors. This increase in demand would require training of additional staff, or education of alternative personnel such as general practitioners and midwives. General practitioners' knowledge of genetic services has already been shown to be in need of improvement, so counselling and communication of results would require a substantial investment.[121]

Partial or whole genome screening and sequencing generates large quantities of data. If this data is to be kept for some future use, then a number of factors need to be considered in this storage. There must be enough capacity physically to store and back up the raw and/or processed data. There must also be systems for accessing and analysing this information in a meaningful way. Additionally, the security of the data must be protected at least as well as any other personal information. Some would argue that protection systems should be better than for other personal information. Alternatively, if costs are reduced enough, the data could be regenerated each time it is required. The requirement for storage would be reduced; although other factors such as analytical capacity and security for the duration of the existence of the data would still be required. Security would at some stage have to be assumed by those holding that individual's medical records.

7.3 Children's issues

The debate around testing children for genetic disorders is vigorous. This issue is comprehensively covered in the section of this Report entitled 'Genetic testing of children who cannot give a valid consent' by Deborah Lawson. Diagnostic DNA testing is generally considered acceptable, as there is (in theory) already an existing disorder. Where there is demonstrable, direct benefit to a child, in terms of treatment or cure, then predictive DNA testing for early onset disorders is also considered acceptable – although when this testing should be performed is more contentious.

When and whether to test for later-onset and untreatable disorders is where the debate polarises, with much speculation and little evidence on both sides. There appears to be a continuum of acceptability, with screening for earlier-onset disorders typically considered more acceptable than screening for adult-onset disorders. Early testing for later-onset breast cancer (BRCA 1 and 2 mutations), for example, is more controversial than screening for earlier-onset (often in the teens) colorectal cancer (familial adenomatous polyposis).

Some commentators consider that screening should not be refused out of hand and that clinicians and counsellors should carefully consider requests for early genetic testing.[122] Factors to be considered include ease of psychological adjustment in young children, ability to access new treatments or research trials and parental knowledge of the capacity to understand and temperament of the child. Others consider that privacy issues (including the ability to stop parents telling anyone, compulsory disclosure for insurance and employment problems), potential pressure to participate in research and the later autonomy of child override any desire on the part of the parents for early genetic testing.

There appears to be a consensus in the literature that any testing or screening should be 'in the best interests' of the child. There is no consensus on what this phrase actually means. Best interests can be narrowly construed, focusing on available medical treatment; or it can be interpreted more widely, looking, for example, at the child in the context of the family unit, psychological adjustment, opportunities to enrol in treatment research programmes and educational opportunities.

As mentioned, this is a polarising debate, with little actual evidence on either side. Any attempt to introduce widespread DNA screening will need to be considered on the basis of well-designed, small pilot programmes and carefully analysed data.

7.4 Genetic programmes in use

A small number of DNA screening programmes have been employed internationally, such as those for type 1 diabetes (IDDM).[123] They are, for the most part, small research or pilot trials but one, cystic fibrosis screening, is being routinely offered to couples planning or starting a family in the United States. Positive and negative aspects of these programmes have been discussed and can inform the debate on newborn molecular genetic screening.

7.4.1 Cystic fibrosis prenatal screening programme

Typical cystic fibrosis (CF) is a recessive disorder, resulting from mutations in the 'cystic fibrosis transmembrane conductance regulator' (CFTR) gene. Richards and Grody,[124] Watson et al.,[125] Farrell and Fost[126] and Uphoff and Highsmith[127] offer more detail on the United States cystic fibrosis screening programme. Two (asymptomatic) carriers of CF mutations have a one in four chance of having an affected child. There are currently 1523 documented mutations in the CFTR gene worldwide,[128] although most of these are extremely rare or unique. This gene codes for a chloride ion channel in epithelial cells (cells that are in contact with the outside environment). If the protein is non-functional or absent, due to degradation of the abnormal protein, then the lack of chloride ion transportation affects many organs.

Cystic fibrosis, in its most serious form, is a condition that affects the lungs, pancreas, digestive system and male fertility, amongst other bodily systems. Although severe CF is now survivable past childhood, using physiotherapy and pharmaceutical treatment, it can still substantially shorten the lifespan. The average lifespan for someone with serious CF is now just over thirty years.[129]

The most common and severe mutation is a three-nucleotide deletion that removes a phenylalanine amino acid from the protein (deltaF508), resulting in a protein that misfolds and degrades in the endoplasmic reticulum. More than 80 per cent of cystic fibrosis cases are due to this single amino acid deletion in CFTR in those of Northern European descent.[130] This incidence is lower in other ethnicities.

Cystic fibrosis is a variable disorder although some mutations are classically associated with characteristic symptoms. The deltaF508 phenotype is typically coupled with severe pulmonary symptoms and pancreatic insufficiency. Puzzlingly, however, some homozygotes for this mutation do not have any lung disease.[131] Pancreatic insufficiency does seem to be more closely correlated with particular mutations and the severity and age of onset of lung symptoms may be affected by environmental factors such as exposure to tobacco smoke, pollution and pathogens.[132] Even amongst affected siblings with the same genotype (deltaF508/D614G), however, there is variation in the severity of pulmonary and pancreatic symptoms.[133]

Some sequence variants may be modified by another mutation. One example of this influence is the 5T polymorphism effect on the R117H polymorphism. Whilst the 5T is a common variant in the population, its presence transforms the often-mild R117H variant into one with more severe effect.

In 2001, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynaecologists (ACOG) recommended[134] that DNA testing for common, serious cystic fibrosis-causing mutations be *offered* to all prospective parents (planning a family or currently pregnant), as a standard of care. This followed a 1997 NIH report[135] to the same effect. If both parents are found to carry a CF-causing mutation, they can choose to test the fetus for CF status or, if not yet pregnant, to use preimplantation genetic diagnosis to screen embryos before transfer and implantation – or even to not have biological children.

The original report recommended a core panel of twenty-five mutations for general population screening, each with a minimum cystic fibrosis population frequency of 0.1 per cent. These mutations were selected for their ability to cause severe disease, as well as their frequency in the United States population. The panel was later reduced to twenty-three mutations, as early testing revealed the actual frequencies of cystic fibrosis-causing mutations in a population of such mixed ethnicities. There are also four modifying mutations screened for as reflex[136] tests, depending on the primary screening results, e.g. the presence of the R117H allele.[137] The screening programme should only test for the presence of these four modifying alleles (including the 5T allele) after a positive screen for the allele that they modify – the R117H variant in the case of the 5T allele. When screening parents for carrier status, the 5T and R117H variations must be on the same chromosome to pose a risk of cystic fibrosis to a future child.

Whilst this panel will detect many or even most couples at risk, a low-risk test result is not a guarantee of a child free from CF, as there are numerous different, rare alleles not screened for. As the panel is based on allele frequency in the whole United States population, minority populations with different CF allele frequencies are likely to be disadvantaged. Any increase to the screening panel, for example through use of

microarray screening, will reduce the chance of being misclassified as low risk. On the other hand, interpretation of risk or expected severity of CF from the extra data may cause additional problems. In some areas or even practices in the United States screening is offered routinely; in others it is not offered at all, depending on factors present in the medical community.

There does seem to be some confusion generated by the programme, both in those being tested and those communicating the test results. There is growing evidence that many people undergoing testing do not truly understand and/or remember what they are being told. In some older studies, 'confusion amongst carriers has exceeded 50 per cent'.[138] Although there is a duty to communicate information at a level that can be understood by those to be screened, some of this information is sufficiently complicated that some practitioners themselves are not equipped to grasp the details.[139] Whilst informed consent is important, because there are possible implications for insurance or non-paternity, most confusion appears to arise from interpreting and communicating results to those screened.

In one unfortunate incident, approximately thirty women underwent an unnecessary amniocentesis after mistakenly being screened for the 5T polymorphism as a primary test, rather than a follow-up (reflex) screen.[140] The presence of the 5T allele in the absence of the R117H allele is not a risk factor for CF.[141] Amniocentesis carries a ~0.5 per cent risk of miscarriage. This incident is thought to have arisen through guidelines not being followed. 'There have also been "unconfirmed anecdotal reports" of mothers aborting fetuses based on bad information, said Michael Watson …'[142] Watson repeated this assertion about the cystic fibrosis screening programme at a recent symposium on prenatal testing.[143]

Despite these reported problems with the screening programme, '[i]t is increasingly clear that CF carrier screening can be carried out in some primary care settings with a high degree of patient satisfaction, high levels of patient understanding, and high levels of interest among pregnant couples …'[144] It seems that this is a screening programme that laboratories and medical professionals will grow into with time.

7.4.2 Complex genetic disorders

Complex genetic disorders, also known as quantitative or multifactorial disorders, are those with multiple and often variable contributing factors. These causes can be different genetic factors, as well as environmental influences. The genetic factors may also predispose the individual to react to a particular environment in a certain way. In the case of heart disease, for example, those individuals with a genetic predisposition to atherosclerosis (narrowing of the arteries) are more likely to develop severe fatty plaques in their arteries when they have a poor-quality diet – high in saturated fat – than those without a genetic predisposition.

As there are multiple factors involved in complex genetic disorders, often many unknown, it is very difficult to make predictions of future health based on just one factor, i.e. a single genetic test. As we have seen, even so-called 'simple' genetic disorders can be difficult to predict from this information.

Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM) is one such complex disorder that develops in young children. Genetic susceptibility involves a major single-gene contribution and multiple smaller contributions from many other genes. In addition, there are, as yet unknown, environmental factors that influence the development of the disorder. The challenges of using genetic testing for prediction of type 1 diabetes are discussed more thoroughly in the section of this Report entitled 'New possibilities for newborn genetic screening: Screening for genetic susceptibility to common disease' by Nikki Kerruish.

7.5 Future of newborn DNA screening

In the near future, DNA screening will most likely be used as an adjunct to, not as a replacement for, metabolic testing for specific disorders. In the longer term, it seems likely that there will be some form of genome screening as the technology and the knowledge to interpret this type of information improves.

It would seem to be a mistake to replace a successful metabolic screening programme simply because there is a newer technology available. Whilst it is likely that the metabolic screening technology will continue to evolve, it is unlikely that it will be replaced entirely by DNA genetic screening in the immediate future. The body of knowledge with regard to causes and particularly modifiers of genetic disorders is growing; but it is currently modest and is likely to remain so for some time, particularly for very rare diseases (such as those typically in the screening panel) and disorders with multiple genetic and/or environmental factors.

It is far more likely that, as the costs of DNA testing come down, new disorders will be added to the screening panel, whose tests are based on DNA analysis. There are a number of more common (non-metabolic) genetic disorders that develop in childhood and which were considered by the ACMG screening report.[145] Whilst they did not score highly enough to be recommended for inclusion in the screening panel, this time at least, it is probable that these disorders will be reconsidered for inclusion in the future (with others). With the rapid evolution of appropriately predictive and cost-effective tests, they will likely be added to the screening panel before long.

One example of such a candidate genetic disorder is fragile X syndrome, which is almost solely caused by a trinucleotide repeat expansion in the FMR1 gene. Testing for one known and well-characterised mutation is more straightforward than testing for the ~1500 mutations characterised (so far) for CF. Whilst there is no known

treatment (in common with many of these non-metabolic disorders), early detection would enable reproductive choices for parents, minimise the 'diagnostic odyssey' and enable planning for future education, e.g. specialised learning programmes.

Aside from practical issues in the use of genetic screening, social issues exist, with DNA screening being perceived as riskier than metabolic screening. There are potential issues of public trust and confidence in the areas of science, privacy, discrimination and general understanding of genetics etc.[146] In addition, there are concerns associated with the accurate communication and evident misinterpretation of results, both by consumers and, in some instances, providers. Many of the problems postulated around public acceptance and comprehension are ill defined and may be overestimated,[147] as there is little evidence either way. Personal and public understanding of risk relating to genetic information is likely to be linked to all these factors, as well as to personal and group experiences.[148]

Many predict that microarray technologies or even whole genome sequencing will eventually (and perhaps sooner rather than later) become sufficiently inexpensive and rapid as to be used as a profiling technique. As information about the causes of genetic disorders becomes increasingly detailed, it is likely that this profiling will be performed shortly after birth. This idea has recently been discussed in the United Kingdom and dismissed, but only for the meantime.[149]

There are two possible uses of this detailed information. One involves profiling the individual for all possible genetic risks and possibly attempting to reduce or mitigate the risks from birth, either medically (pharmacologically or surgically) or through lifestyle modifications. One commentator observes of lifestyle changes:

> *… the pious hope that knowledge might lead to beneficial lifestyle alterations seems likely to remain just that – a pious hope. We have not yet learned how to ensure that people take advice about harmful lifestyles.*[150]

The other usage of genetic profiling information involves interrogating the genetic data only as needed. For example, a newborn's sequence could be examined only for risk of early-onset, serious conditions. It could also be examined for serious, later-onset, single-gene disorders (such as some cancers) in the interests of monitoring, prophylaxis and/or family planning. Having said that, for many dominant familial cancers, there is generally already a family awareness of risk and this usage could merely supplant testing already performed at various developmental stages. Genetic information could be examined at later, defined, times for risk of progressive later-onset disorders. The timing would have to be carefully considered, however, as tissue damage may start well before symptoms manifest. The psychological and social aspects of this information must also be considered, preferably on the basis of credible evidence generated by pilot projects rather than speculation about possible harms and benefits.

Stored genetic information could be used diagnostically, if the individual were showing possible symptoms of a specific disorder, presumably not already screened for. The information could also be used to optimise treatment, by examining which drug or drug dosage might be most effective, based on the genetic data (pharmacogenetics).

The reasons given for dismissing newborn DNA profiling in the United Kingdom were principally to do with the state and cost of current technology.[151] Ethical and social concerns were raised but the report recommended that the issue be re-examined in five years' time. This finding does not speak to irreconcilable flaws in the idea, although the other concerns will assume increasing importance as the technological and cost concerns are resolved.[152]

8 CONCLUSIONS

1. The Wilson-Jungner criteria that have been used as a foundation for newborn screening are not necessarily entirely relevant to newborns and their families, having originally been formulated in 1968 for chronic adult disorders. Changes in technology and society and differences peculiar to newborn screening, as well as scientific and clinical evidence, must be taken into account in reformulating criteria specifically for newborn screening.
2. Much of the controversy (although not all) around newborn screening in the United States is unique to and driven by that particular political environment. The absence of federal funding means that the State, insurance companies and consumers must fund the programmes and that each programme is determined State by State. Many programmes also have an element of compulsion, as opposed to New Zealand where parents must actively consent. In addition, the health system that supports these potentially expensive treatments is driven by private health insurance for those who can afford it (and are not judged a liability), limited State-funded care for the very disadvantaged and little for those outside these two groups. An insurance-driven health system is central to many of the heightened concerns around data privacy, employment discrimination and future access to affordable health insurance.
3. The current New Zealand newborn metabolic screening programme appears by any available measure[153] to be a competent and successfully run programme, given the good detection and participation rates. The 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 staff and Advisory Board have thus far been careful to avoid negative publicity and have carefully managed access to the Guthrie cards in the interests of public confidence in the programme. 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 State funding.

4. New Zealand is following international trends in newborn screening but not in too hurried a fashion. Even before expansion, New Zealand 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 and experience of these new technologies from overseas countries and to put in place adequate support services, e.g. to employ a clinical metabolic specialist, before launching MSMS screening.

5. 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 NMSP is shortly to consult on various aspects of the programme and the storage and use of the Guthrie cards in particular. This consultation is a positive move given the apparent (anecdotal) growing distrust and misinformation surrounding the use of DNA samples and, therefore, Guthrie cards. The small but growing number of parents requesting the return of the cards[154] evidences some distrust and sensitivity around potential uses of the DNA samples. This may have implications in the future for the screening programme when DNA screening is introduced (in whatever form).

   It could be productive to make more education and information available regarding the programme, particularly in antenatal classes and on the internet, but also amongst the general population, for example popular science reporting in the media[155] or in the context of a 'future screening' public consultation. Education of parents-to-be in the third trimester of pregnancy is not a new idea but has been slow to be implemented by maternity service providers.

   Within copyright bounds, it would also be useful to see publications, whether scientific or popular, being made available to those parents and members of the public who are seeking more information than is contained in the educational pamphlet.

6. It would be useful to see more audit, epidemiological and cost-effectiveness data and/or research (amongst other topics) coming out of the programme. This would be best undertaken by the programme itself but, given the apparently constrained levels of financial support and small number of key staff, this research might be most easily done in association with other researchers, rather than solely internally. Collaborative reports may also mitigate any conflict of interests concerns.

7. 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.[156] The MSMS is also to be used as a metabolic diagnostic tool (outside newborn screening). Given the expansion of newborn screening, the versatility of the new technology and its potential for disease prevention, the purchase of the MSMS was perhaps worthy of better governmental support, rather than the programme's needing to rely on a children's charity for financial support.

8. The newborn metabolic screening programme can justifiably be classed as a genetic service. At present, there is seemingly unofficial and *ad hoc* national co-ordination with respect to genetic services. There is currently a review of the 2003 NHC report on co-ordination of genetic testing in New Zealand[157] by the New Zealand District Health Boards, presumably with a view to implementation of at least some of the report, although there is no other information available on this review currently. Newborn metabolic screening should at least be acknowledged in future genetic co-ordination initiatives; although, equally, the programme legitimately belongs within the mandate of screening services.

9. Once scientifically accurate, clinically useful, cost-effective, high-throughput screens are available for the more controversial disorders, such as early onset, untreatable genetic disorders, e.g. some lysosomal or peroxisomal storage disorders, it would be positive to see public discussion of the pros and cons of inclusion of untreatable disorders. This could be a function of the Ministry of Health, a genetic services overview, screening services and the Bioethics Council, etc. If screening for untreatable disorders were to be introduced then there must be improved education (of and by providers) so parents are aware of the implications of screening for this type of disorder. Separate consent, although consuming more time and resources, might also be desirable in the implementation period, at least.

10. Any future expansion of DNA screening will require sound scientific and clinical justification and an extensive education campaign, including perhaps public consultation. Whilst the majority of the population appears to be comfortable with at least some aspects of genetic testing,[158] failure to inform and discuss may be seen in a suspicious light by a small yet vocal section of the population, resulting in distrust in the programme and, potentially, a lowered participation rate in newborn screening.

11. Eventually, it seems likely that DNA screening for individual disorders will be introduced as adjunct tests to the metabolic screening programme. With the speed at which science is developing and innovating 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 longer term, although how and when this information might be used, after the initial sequencing process, remains to be seen.

12. 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. If any were identified, there would be merit in evaluating them for screening.

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