

## SCREENING FOR DISEASE

### Screening for disease in the newborn: the evidence base for blood-spot screening

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#### Summary

This paper reviews the evidence of benefit resulting from newborn screening in Australia as well as for some of those disorders not yet included in the Australian panels, and discusses briefly disorders under active consideration for inclusion in the screening panels. There is solid evidence of benefit from newborn screening for phenylketonuria, congenital hypothyroidism, cystic fibrosis, and overall for the disorders included in tandem mass spectrometry screening. There is also some evidence of benefit for several disorders not screened for in Australia, including congenital adrenal hyperplasia. Harms resulting from screening include anxiety related to false positive results; adverse effects of unwarranted treatment for mild variants; unwanted genetic information; and the costs (opportunity costs) of screening. For well-run programs these harms are relatively small. Screening could become more effective with the development of good systems for rational consideration of disorders to be included, with the extended use of second tier testing to reduce the false positive rate, and with research on the most effective way to deal with mild variants. The most important aspect of increasing effectiveness is the full integration of the screening program, diagnostic laboratories, and the clinical service. This is already in place in Australasia.

**Abbreviations:** CAH, congenital adrenal hyperplasia; CDC, Centers for Disease Control; CH, congenital hypothyroidism; LSDs, lysosomal storage disorders; MCADD, medium-chain acyl CoA dehydrogenase deficiency (MCADD); MS/MS, tandem mass spectrometry; PKU, phenylketonuria; RCTs, randomised controlled trials.

**Key words:** Congenital adrenal hyperplasia, congenital hypothyroidism, cost analysis, cystic fibrosis, evaluation studies, lysosomal storage disorders, newborn screening, outcome assessment, phenylketonuria, tandem mass spectrometry.

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#### INTRODUCTION

Since mass newborn screening began in the 1960s with a dried-blood-spot test for phenylketonuria (PKU), the aim has been to detect newborns with serious but treatable disorders, facilitate early treatment and thus avoid or mitigate the adverse outcomes of the disorder. We recently reviewed current newborn screening in Australia, describing the conditions screened for and the tests employed.<sup>1</sup> Only briefly did we deal with costs and benefits, and how to evaluate them. But the core business of newborn screening is to provide a benefit to those affected with one of the disorders tested for. This paper will review the benefits so far documented, look at the objective data relating to

costs of diagnosis and treatment, and consider strategies that might make screening even more effective, both now and in the future. Only blood-spot screening is covered here, and other excellent point-of-care testing, such as hearing screening, is not included.

#### ASSESSING BENEFITS

It is difficult to assess the benefits of screening programs. In newborn screening, because of the rarity of disorders or a strong belief that screening would confer benefits, only screening for cystic fibrosis has been subjected to a randomised controlled trial. Other reports of outcome have been of lesser stringency, usually using historical controls for the unscreened comparison population, which introduces many biases. The main problem has been the increased detection of cases by screening, thus including cases with milder variants and excluding cases that died undiagnosed, and not being able to take into account incomplete penetrance. The natural history of a disorder, or of the cohort that would be detected by screening, cannot be completely known without retrospective screening studies, one of which is discussed below under congenital hypothyroidism. Thus, it is hard to compare like with like. One may need to estimate the occurrence of an outcome in affected children on a whole population basis for each cohort. That would mean, for example, comparing the numbers of children known to be affected by the disorder and suffering the outcome, say intellectual impairment, per 100 000 of the whole cohort (affected and unaffected) in both a screened and an unscreened population.<sup>2</sup>

#### BENEFITS ACCRUING FROM SCREENING PROGRAMS: DISORDERS SCREENED FOR IN AUSTRALIA

Screening for some disorders seems to have been so obviously beneficial that good trials are unlikely to take place. This of course includes the two earliest disorders screened for, PKU and congenital hypothyroidism (CH).

##### Phenylketonuria

The natural history is fairly well known, although as pointed out above, it is not known with certainty in its entirety. Without early diagnosis by screening most affected patients will suffer significant mental retardation, a high proportion requiring institutional care. Penetrance seems high but not complete. An informative 1974 study by Smith and Wolff was of sibling pairs, one of whom had been diagnosed because of mental retardation, and the other discovered by chemical testing of sibs.<sup>3</sup> Of 18 affected sibs investigated, three had

an IQ >80. The remaining 33 PKU patients had a mean IQ of 39, the majority having an IQ below 55. It is apparent that early diagnosis and appropriate treatment (diet and phenylalanine-free supplements) avoids this. Compliant patients have IQs within the normal range, and may progress to university. However, there are deficits even in well-treated patients, but these are subtle.<sup>4</sup> There is clear evidence that good control of phenylalanine levels in the first 14 years of life leads to a good outcome.<sup>5</sup> There are few adverse effects: currently the false positive rate is low, and a recent study<sup>6</sup> showed that even at the start of PKU screening, adverse effects were few—far fewer than had been postulated. However, there is one which was not anticipated at all: the possibility of the maternal phenylketonuria (MPKU) syndrome. Elevated circulating phenylalanine levels are teratogenic. The MPKU syndrome comprises intrauterine growth retardation, irreversible intellectual retardation, microcephaly, facial dysmorphism, and sometimes congenital heart disease in babies whose mothers have PKU and poor or no dietary control during the pregnancy. This problem remains<sup>7</sup> and slightly reduces the undoubted benefits of screening.

### Congenital hypothyroidism

Screening was first described in 1974 in Quebec, using a test for thyroxine in dried blood spots.<sup>8</sup> Later, the assay for thyroid stimulating hormone (TSH) gradually became the preferred first-line test. One of the most interesting early studies of outcome was the Swedish retrospective study.<sup>9</sup> In this 1980 investigation, 100 239 dried blood spots were retrieved and TSH was assayed 5 years after the spots were drawn. At that time Sweden was not screening for CH. Samples from 32 children had elevated TSH levels; 31 of the 32 children were traced. Fifteen had already been diagnosed to have CH and were on treatment. Seven were found to be hypothyroid, but had not been diagnosed. Nine were euthyroid. All children had a measurement of developmental quotient (DQ). The clinically diagnosed had a mean DQ of  $87 \pm 20$ ; the undiagnosed but affected had a mean DQ of  $100 \pm 12$ , and the euthyroid children a DQ of  $107 \pm 6$ . A control group had a DQ of 103. The authors concluded that if there was newborn screening, '...overdiagnosis of about a quarter of patients considered to have true positive findings...(would be) outweighed by the early identification of all infants with the disease'. Their study showed the apparent birth incidence in Sweden without screening of 1:6700, in line with the recent findings in a review by Grosse and Van Vliet from the Centers for Disease Control<sup>10</sup> who reviewed published surveys from developed countries, including the above study. Six prevalence studies from Northern Europe and the United Kingdom for the period 1963–1978, before screening was undertaken, revealed very consistent results: the prevalence was 1:6100 to 1:6900 (mean 1:6500). With the advent of newborn screening, the birth prevalence recorded has been around 1:3500 in most parts of the world, with a trend to increasing detection.<sup>11</sup> This increase is likely to be due to modification to cut-off levels, with screening tests detecting babies with much milder hypothyroidism (and probably less benefit). In the Grosse and Van Vliet paper<sup>10</sup> four studies had data on cognitive test scores of unscreened children aged 5 to 7 years. The mean IQ recorded in these clinically diagnosed patients ranged from 82 to 88, with 8–27% having an IQ below 70. The range of IQs was 40–116. By contrast, reports of intellectual attainments in screened children only show about 1% with an IQ below 70. The authors conclude that

in unscreened populations overt intellectual disability (IQ < 70) was less common, at around 25%, than previously published estimates of 35–40%, but that with a mean IQ in the 80s, a much higher number had suffered significant loss of potential. Screened children on the whole perform within the normal range of intellectual ability, but those with delayed bone age and other indications of prenatal effect performed less well in respect to IQ and motor skills than those with less severe hypothyroidism.<sup>12,13</sup> Starting treatment earlier and with higher thyroxine dosages appears to minimise this effect.<sup>14</sup> Rovet, in a careful study of siblings, found that children with early-treated CH nevertheless had lost an average of 8 IQ points on the McCarthy scale and 6 IQ points on the Wechsler Intelligence Scale for Children-Revised (WISC-R).<sup>15</sup>

It is clear that screening for CH has delivered major benefit, even if this is a little less than first thought. Many puzzles remain, especially as to whether there is any need to treat babies with subclinical hypothyroidism detected by more stringent screening tests,<sup>16</sup> and what is the optimal management of transient hypothyroidism or short-lasting neonatal hyperthyrotropinaemia.<sup>17</sup>

### Cystic fibrosis

Newborn screening for cystic fibrosis is a fascinating case of various jurisdictions coming to completely different decisions about screening, over a period of 30 years, while the evidence of benefit gradually accumulated and strengthened. This delay contrasted greatly to the rapidity with which screening by tandem mass spectrometry was taken up (see below) when there was, initially, no evidence of benefit.

A dried blood spot method for screening for cystic fibrosis was first described in 1979.<sup>18</sup> Several programs started soon thereafter, and evidence of nutritional and other early health benefits were published.<sup>19,20</sup> Screening was very controversial, and in 1985 two randomised controlled trials (RCTs) were begun, the only RCTs in newborn screening history.<sup>21,22</sup> Much evidence of benefit has finally come out of the Wisconsin RCT.<sup>21</sup> This was an interesting study, in which all newborns were tested, but randomly assigned to have either immediate analysis of results, with confirmation and treatment in positive cases, or storage of the results in the computer unanalysed, until 4 years had elapsed. Parents gave informed consent to this procedure. Several chance differences emerged between the groups, causing unfortunate biases, but comparing those with similar characteristics (principally only those who in either screened or unscreened groups had pancreatic insufficiency but no meconium ileus) the researchers showed clear evidence of nutritional, growth and intellectual advantage.<sup>23</sup> This strong evidence of benefit was also found in well-conducted observational studies.<sup>24</sup> Screening, after a long pause of up to 30 years, is now universal throughout the USA, UK, most of Canada and Europe and parts of South America. It has been conducted in Australia since 1981, and has been universal throughout Australasia for over 11 years.

Table 1 shows some very early data of ours from New South Wales, Australia. This study looked at rates of hospitalisation in the first 2 years of life in screened and unscreened patients.<sup>20</sup> The unscreened were a historical cohort, from 3 years before screening started, and so biases were possible. However, the striking change occurring with the onset of screening, with no trend with time, made the data rather compelling.

**Table 1** Cystic fibrosis screening NSW admissions to hospital in first 2 years of life (excluding birth episode) for CF related illness in patients attending The Children's Hospital, Camperdown

Cohort	Born	Number	Mean hospital days <2 years of age*
Unscreened, no MI	1978–1979	24	27.5 (range 0–112)
Unscreened, no MI	1979–mid-1981	24	27.0 (range 0–240)
Screened, no MI	Mid-1981–1982	17	3.4 (range 0–20)
Screened, no MI	1982–1983	17	4.4 (range 0–31)
MI	1978–1983	16	16

\*No admissions: unscreened 15/48 (31%), screened 24/34 (71%),  $p < 0.0005$ . More than 21 days of admission: unscreened 20/48 (42%), screened 1/34 (3%),  $p < 0.0005$ . MI, meconium ileus.

### 'Expanded newborn screening' using tandem mass spectrometry

Over 40 disorders are currently detectable simultaneously on a single, 3 mm dried blood spot using tandem mass spectrometry (MS/MS).<sup>25</sup> The technology relies on identifying marker compounds by separating and quantifying ions, based on their mass-to-charge ratio. So far this has principally been used to detect disorders of amino acid, organic acid and fatty acid metabolism, by quantifying amino acids and acylcarnitines. This ability to multiplex testing has revolutionised newborn screening, making it feasible, for the first time, to test for extremely rare disorders which would never have been considered on a one-test-one-disorder basis. When this screening was first described in the mid-1990s, there was much pressure from US parent groups, and much interest from clinicians, and over a period of 10 years MS/MS screening was very widely implemented for a large number of disorders, ahead of any formal evidence of benefit.

For some disorders benefit was extremely likely. Medium-chain acyl CoA dehydrogenase deficiency (MCADD), a fatty-acid oxidation disorder and the most common disorder detected by MS/MS after PKU, was associated with a considerable death rate in young children suffering episodes of catabolic stress, such as intercurrent illness, whereas in survivors or affected siblings of survivors, after diagnosis had been made and proper management of illness put in place, mortality appeared vanishingly low.<sup>26</sup> This likely benefit was eventually shown to be real; newborn screening resulted in far fewer episodes of metabolic decompensation or death in MCADD<sup>27,28</sup> but to demonstrate this required a very large screened and unscreened population. Screening, as always, results in a much higher detection rate of many disorders than does detection following clinical presentation. For some disorders this was a very surprising increase, and it is now considered that certain enzyme deficiencies are benign or nearly so, rarely if ever present with clinical illness, and inflate the numbers of 'cases' detected by expanded newborn screening. So far, benefit has been unequivocally shown for two disorders: MCADD and glutaric aciduria type I (GAI, glutaryl CoA dehydrogenase deficiency), a devastating disorder with very high morbidity (damage to the basal ganglia) and mortality, but which can be successfully treated by diet and medications to avoid this damage.<sup>29</sup>

No-one has produced hard evidence showing benefit for other individual disorders currently sought by MS/MS although early diagnosis is almost certainly beneficial for some. In 2003 we started an Australia-wide study of overall outcomes at 6 years of age for screened and unscreened cohorts. We made use of the fact that not all states were screening during 1998 to

2002, and we were able to have historical and contemporaneous control groups. We excluded PKU from our analysis, and analysed separately patients who had presented clinically in the first 5 days of life, and those who had disorders that we had come to believe were benign, as neither of these groups could be expected to benefit from newborn screening. The outcome at 6 years of age for MCADD, and for all other disorders taken together as a group, was analysed. We found fewer deaths and fewer clinically significant disabilities in the screened cohort, on a population basis, thus negating the problem of over-diagnosis by screening.<sup>30</sup> It is really not possible to obtain high-order evidence for benefit in individually very rare disorders, and this does present problems unless anecdotal evidence is very compelling.

### BENEFITS SHOWN FOR DISORDERS NOT INCLUDED IN SCREENING IN AUSTRALIA

#### Congenital adrenal hyperplasia

Screening for congenital adrenal hyperplasia (CAH) has been carried out for over 30 years. All of the United States and over 20 other countries now screen. New Zealand has been screening since 1986, but screening is not yet undertaken in any Australian state. This has been largely because until recently there has been doubt about the magnitude of the benefit. CAH is caused by the deficiency of any one of several enzymes required for the biosynthesis of adrenal steroids. Over 95% of cases are due to a deficiency of 21-hydroxylase, which results in cortisol deficiency, androgen excess, and accumulation of 17-OH progesterone, the marker used for newborn screening. The live birth incidence is around 1:14 000. Two-thirds of babies with classical CAH have salt-wasting, the remaining one-third having a simple virilising type. The rationale for screening is the avoidance of early male deaths due to an adrenal crisis occurring in the first weeks of life, avoidance of intellectual deficit in those who survive such a crisis, and avoidance of wrong sex assignment in girls, who have ambiguous external genitalia. Although there is curiously little compelling evidence to give strong support to screening, and much of that is old, as screening has been so widespread for so long, more evidence is emerging. For example, a recent study in the UK, where there is no CAH screening, found a statistically significant deficit of boys with severe (null) mutations in one large clinic, implying deaths of undiagnosed infant boys.<sup>31</sup> Girls are likely to be diagnosed because of the ambiguous genitalia, but boys may suffer a crisis and death without the relevant tests ever being undertaken. A CDC study also found evidence of averted mortality,<sup>32</sup> but felt that case-control

studies of stored residual dried blood spot specimens would be needed for conclusive evidence.<sup>33</sup> Screening is highly recommended by Australian endocrinologists,<sup>34</sup> and screening strategies have improved.<sup>1</sup>

**Lysosomal storage disorders**

This group of complex disorders is a new target for newborn screening, which has raised several ethical and practical concerns. Lysosomal storage disorders (LSDs) comprise over 50 distinct disorders associated with intra-lysosomal accumulation of a metabolic product, with consequent impaired lysosomal function, and tissue and organ damage. Treatments have recently been developed for some LSDs, and early experience suggests that these improve the long-term outcome if they are started before irreversible damage has occurred. Much developmental work is being undertaken. Newborn screening for LSDs has already started for a few disorders in Taiwan, in a few states in the USA, and in Northern Italy.

Treatments in routine use in some disorders and in some circumstances are haemopoietic stem cell transplantation, enzyme replacement therapy (ERT), and substrate reduction therapy. There are several emerging therapies that are now being trialled, including further forms of ERT, gene therapy, and mutation specific therapies such as stop-codon read-through and pharmacological chaperone therapy. Not all types of therapy are beneficial in all types of disorder or for all aspects of any one disorder.

- Benefits from early diagnosis by screening are clear for MPS I<sup>35</sup> and for infantile Pompe's disease, although the long-term outcome for treated infantile Pompe's disease remains unknown.<sup>36,37</sup>
- In some other LSDs there are improvements in mortality in the short term, but evidence suggests that there may merely be conversion from rapidly progressing lethal diseases to chronic but significantly progressive conditions with unclear outcome.<sup>38</sup>
- Several disorders, e.g., Gaucher's and Fabry's diseases, show undoubted benefit from treatment, but there is as yet no compelling evidence that treatment needs to start in infancy.

Major problems include the very high cost of enzyme replacement therapy—a lifelong need once started, and currently reaching \$200 000–\$400 000 per annum for each adult patient<sup>39</sup>—and the difficulty of distinguishing infantile

and later onset phenotypes in screen positive patients, with consequent uncertainty about management. One example is Fabry's disease.<sup>40</sup>

**Other disorders**

Amongst other disorders screened for around the world, there is clear evidence of benefit only for the sickling disorders<sup>41</sup> and for severe (but not partial) biotinidase deficiency. Australian programs should be considering screening for sickle cell anaemia because of our changing population. Biotinidase deficiency is another disorder widely screened for elsewhere (including New Zealand). Severe deficiency is associated with deafness, retinal disease, intellectual disability, ataxia and other neurological problems, and these are avoidable with early diagnosis and oral biotin treatment.<sup>42</sup> Newborn screening for severe combined immunodeficiency seems likely to be beneficial also,<sup>43</sup> although the test is somewhat expensive. This is a disorder which has recently been approved for screening in the US, using their new process for assessment of the suitability of disorders for screening.<sup>44</sup> For several other disorders sought by newborn screening elsewhere for many years, evidence of benefit is only recently being published, for example for glucose-6-phosphatase deficiency.<sup>45</sup> Such screening would not be beneficial everywhere, depending on the locally prevalent mutation, but the sheer number of cases found has tended to overwhelm some screening programs (C. Padilla, personal communication).

**DISORDERS UNDER CONSIDERATION FOR SCREENING**

With the development of new treatments and new screening technologies, so many disorders are being considered or reconsidered that possibilities seem limitless. Duchenne muscular dystrophy is one disorder under active consideration because of the increasing possibility of the use of molecular techniques for therapy such as read-through of stop codons, and exon skipping.<sup>46</sup> These and other therapies such as use of pharmacological chaperones of course apply widely, not to specific disorders, but rather for specific mutations within disorders. Table 2 shows some of the disorders under consideration for inclusion in screening programs at present.

Disorders of adult onset could be screened for in the newborn, since screening can be efficiently accomplished in this 'captive' population. One adult onset condition that has been considered for newborn screening is haemochromatosis,

**Table 2** Examples of disorders for which newborn screening has been suggested

Lysosomal storage disorders	Screening for Pompe's, Gaucher's, Fabry's, Krabbe's, MPS I disorders in a few areas (see text)	Methodology satisfactory for many disorders. Problems of desirability and benefit (see text)
Severe combined immunodeficiency	Screening recommended in USA. Five states were screening by 04/2011	Benefit appears likely. Test is rather expensive
Diabetes mellitus type I susceptibility	Several studies in USA, and Scandinavia, with specific parental consent	No proven preventive measures, and low predictive value; some benefit likely
Duchenne muscular dystrophy	Screening for several years in Wales; <sup>60</sup> other small programs	Effective treatment now likely to become available for some; increased interest in screening
Fragile X syndrome	No screening current; several small pilot projects	Expensive methods. No treatment current, but genetic advice considered helpful
Haemochromatosis	No newborn screening; some carrier testing pilot studies	Low penetrance. Adult onset
Long QT syndrome	No newborn screening	Molecular testing possible in the future
Spinal muscular atrophy	No newborn screening	No current specific therapy. Molecular testing possible in the future
Genome-wide screening	Possible for many conditions including for susceptibility and adult onset diseases	Testing currently too expensive, but becoming cheaper. Ethical concerns widespread

with one group suggesting the use of 'reverse cascade testing' following newborn screening to identify affected adults.<sup>47</sup> The clinical penetrance of this iron storage condition is quite low, however, and there are other reasons too against this approach.<sup>48</sup> So far, there is no enthusiasm for including adult onset disorders in newborn screening panels.

## HARMS AND COSTS OF SCREENING PROGRAMS

### Harms

There is no point in considering benefits without a careful consideration of possible harms of screening. Overall, these can be summarised as: anxiety related to false positive results; adverse effects of unwarranted treatment; unwanted genetic information; and the costs (opportunity costs) of screening. There are other possible harms, but these are in practice the main ones encountered.

Anxiety related to false positive results may in the past have been over-estimated. A recent study<sup>49</sup> showed that there was a good tolerance for false positive results, provided that there was good information about the screening tests. The need for good information and communication has been shown in many studies, and provision of information to the general public, parents in particular, and to health professionals has to be an integral part of any screening program. Even with the best information, there is anxiety for a few days while the clinical diagnosis is resolved, so reduction of the false positive rate and speeding of the diagnostic process are both important aims for screening programs.

Possible harms from over-diagnosis, the adverse effects of unwarranted treatment, and the medicalising of babies with very mild forms of disease, is not a new problem<sup>50</sup> but has been brought very much to the fore with MS/MS screening. It is certainly an important issue in some instances. One case in point is short-chain acyl-CoA dehydrogenase deficiency (SCADD). This disorder was known for some time, but rarely diagnosed before MS/MS screening. Clinically diagnosed cases had very varied symptoms, with no consistent pattern, while cases diagnosed by newborn screening were asymptomatic. There is now much evidence to suggest that this is a benign condition.<sup>51</sup> Isobutyryl CoA dehydrogenase deficiency is detected on screening by the same marker (C4, butyrylcarnitine) and is also apparently benign, and these are two conditions for which there is no evidence at present to warrant their inclusion in screening panels. Both are excluded now from screening in Australasia, but patients with these 'disorders' and others that seem benign are routinely detected in screening programs elsewhere, and are often subjected to dietary modification and medication.

Unwanted genetic information, mainly the identification of carriers, for example in CF screening, has been largely considered as unfortunate, although it does allow for genetic counselling for the family. This problem will become much more apparent if molecular methods are used in first-line screening in the future. This problem in particular, and indeed all harms, are minimised if the identified babies are referred to experienced metabolic services and if there is good information given to parents.

### Costs

Cost is an ethical issue. There should always be consideration of opportunity costs: what other health gain could result from

use of the money otherwise devoted to screening? Most estimates of the costs of screening, and cost-benefit analyses have been based on theoretical consideration and necessarily include many assumptions. All costings and assessments of cost-benefit are difficult.<sup>52</sup> For some disorders there is a clear decision. For example, Geelhoed and colleagues evaluated the costs and benefits of screening for PKU and CH in Western Australia, and concluded: 'Neonatal screening...is a cost saving use of resources, and the emergence of maternal PKU has not had a significant effect on economic outcomes.'<sup>53</sup> However, in general it is not so easy. Norman *et al.* examined the economic evidence in relation to MS/MS screening from an international perspective.<sup>54</sup> They found that among 13 studies, differences in structure and approach (either from a health care or societal perspective) of interventions and outcome measures that were included, as well as the limit of studies to developed countries, made any generalisations impossible and '...assumptions regarding disease progression and subsequent health care utilisation suggests that further work needs to consider the importance of longer-term follow-up'. Where newborn screening saves lives, but costs more than not screening,<sup>55</sup> it does raise the question of whether and how to use cost benefit analyses for decision making about newborn screening.

## STRATEGIES TO MAKE NEWBORN SCREENING MORE EFFECTIVE

Newborns are largely a captive population, and screening applied to newborns has some inherent efficiencies. In order to increase the effectiveness it is vital that the disorders included in the screening program are appropriate, that the testing is done accurately, in the most effective way, that confirmatory diagnosis and referral for treatment are done well and quickly, and that long-term follow-up is undertaken so that outcomes can be investigated and any problems quickly identified. In fact, all elements of the whole newborn screening system must be perfectly tuned. Some aspects of this need special mention.

### Inclusion of disorders in screening programs

There is a wild divergence of views on which disorders should be included in screening.<sup>56</sup> Systems for rational consideration of the likely merits of various disorders will be more and more needed and are, happily, already being developed in Australia and elsewhere.<sup>44</sup>

### Screening laboratory organisation

Screening should not be too complicated, with relatively simple algorithms, but improvements such as the use of second-tier testing<sup>57</sup> should be adopted as appropriate. There must be some tolerance for a few false negative test results, in order to keep false positive rates low. This balancing act should be disorder-specific. For certain disorders, for example PKU or glutaric aciduria type I, a false negative result must not happen, as the outcome would be likely to be catastrophic. On the other hand, there would be more tolerance for a false negative result for mild hypothyroidism, which might not result in severe harm with a delayed diagnosis.

### Integration of screening, diagnosis and treatment, with centre-based follow-up

The major aspect that impairs the effectiveness of newborn screening is lack of a coordinated system for screening,

diagnosis and management, which also incorporates long-term follow-up. Collaboration among people involved in all the aspects of screening is crucial to improve efficiency and effectiveness. In Australia we have been lucky to have inherited such a system. Elsewhere it is not so, with diagnostic testing being referred to a variety of laboratories, and treatment spread among many physicians. In cystic fibrosis the beneficial effect of centre-based treatment has been clearly demonstrated, for example, in France;<sup>58</sup> for rare metabolic diseases, although there is as yet no published evidence, it appears likely that centres of excellence provide the most accurate and efficient final diagnosis and most effective treatment.

### Information for parents and health professionals

As already mentioned, this is crucial for allaying parental anxiety, and ensuring the correct testing, referral and follow-up is undertaken.<sup>49</sup> Education, provision of information, and counselling must be part of the whole newborn screening system.

### Mild cases, probably needing no treatment

Strategies for dealing well with this problem should be developed. All inherited disorders cover a spectrum of severity and many disorders have been found that include those with apparently very mild mutations, who seem not at any risk. However a few cases of mild citrullinaemia, now easily diagnosed by newborn screening, have been found to have severe, sometimes fatal, decompensations for the first time in adulthood.<sup>2</sup> The same is true of MCADD.<sup>59</sup> Mild phenotypes need to be followed in a skilled but non-intrusive way.

## THE FUTURE OF NEWBORN SCREENING

Newborn screening is driven in part by new technologies and discovery of new marker compounds that make testing possible, and in part by new treatments that make testing desirable. With rapid advances on these fronts future newborn screening seems limitless. Certainly first-line molecular testing will become affordable, and there will be pressure to screen newborns for disease susceptibility and for adult onset disease. This will greatly increase the complexity, and will increase also the need for evaluation of benefit. For the future it will be extremely important to consider at an early stage all the lessons from the past.

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