



## The failure to diagnose inborn errors of metabolism in New Zealand: the case for expanded newborn screening

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### Abstract

**Aims** Expanded newborn screening uses a new technology, tandem mass spectrometry, to diagnose an additional 20 plus rare treatable inborn errors of metabolism based on the further analysis of the current newborn Guthrie card blood sample. The purpose of this study was to investigate the incidence of these disorders in New Zealand, based on clinical diagnosis rates, and compare these to the incidence, based on the established expanded newborn screening programme, in New South Wales, Australia.

**Methods** Over a 3-year period, the cases of inborn errors of metabolism notified to the New Zealand Paediatric Surveillance Unit and/or identified by the relevant metabolic laboratories were recorded and compared to the incidence rates during the same period in New South Wales.

**Results** There were 175,000 and 270,000 births in New Zealand and New South Wales respectively during the study period. Eight cases of treatable inborn errors (potentially diagnosable by newborn screening) were diagnosed in New Zealand compared to 41 (including two prior to screening) in New South Wales. The disorder medium chain acyl Co-A dehydrogenase deficiency was diagnosed twice in New Zealand and in 24 newborn infants in New South Wales.

**Conclusions** Without expanded newborn screening, inborn errors of metabolism are under-diagnosed in New Zealand. This study supports the recent establishment of screening in New Zealand.

Inborn errors of metabolism are genetic defects of biochemistry that may result in clinical illness. Individually they are rare conditions, but collectively they are not uncommon with an overall prevalence approaching 1:1000.<sup>1,2</sup>

A group of conditions—disorders of intermediary metabolism—involve the catabolism of fats and protein. These are the fatty acid oxidation disorders and the amino and organic acidopathies. The former involve defects in the mitochondrial oxidation of fatty acids and present (classically) with hypoglycaemia, inappropriately low ketones, and subsequent encephalopathy often following a period of fasting and/or intercurrent illness in a child. The latter result in massive accumulation of specific amino and organic acids, sometimes with associated hyperammonaemia, and clinically often present with neonatal encephalopathy or alternatively with varied presentations later in life.

Because the diseases are rare, and the clinical phenotypes encountered are much more frequently seen in conditions such as sepsis, the correct underlying diagnosis is frequently missed. This leads to catastrophic outcomes, as death is likely if an accurate diagnosis is not made. In fact even when a correct diagnosis is made during

the initial presentation the outcome can be poor as neurological damage has already occurred. Thus diagnosis and treatment prior to clinical illness is ideal.

Expanded newborn screening (ENBS), using tandem mass spectrometry, accurately detects marker compounds in the dried blood spot from the neonatal Guthrie card. The technique is highly sensitive and specific and, once initial setting up costs are met, is relatively cheap when added to an existing newborn screening service.<sup>3</sup>

ENBS allows for the identification of around 30 different disorders—provided the sample is taken at the correct time, transported quickly to the screening laboratory, and analysed appropriately, and treatment is started prior to the child becoming unwell.<sup>4</sup> The newborn screening service in New South Wales, one of the pioneers of ENBS, has recently shown that this leads to significant improvements in diagnostic rates and outcome.<sup>5,6</sup>

The purpose of this study was to evaluate the incidence rates of the disorders of intermediary metabolism in New Zealand (NZ), based on the numbers of clinical diagnosis, from January 2004 till the commencement of ENBS in December 2006 and to compare these to the incidence rates, obtained mostly via EBNS, in New South Wales (NSW).

## Method

From January 2004, paediatricians in NZ were sent monthly questionnaires (via email or regular post) from the New Zealand Paediatric Surveillance Unit (NZPSU). It asked whether they had diagnosed an inborn error of metabolism over the previous month. If they had then they were sent a further questionnaire regarding the exact diagnosis along with aspects of the clinical presentation and immediate outcome.

This study was approved by the Lower South Regional Ethics Committee. In addition the Auckland, Wellington, and Christchurch laboratories (that either perform the relevant metabolic investigations or facilitate samples being sent to the appropriate tertiary laboratories in Australia) were contacted and ask to report cases.

The numbers of patients diagnosed with disorders of intermediary metabolism diagnosed clinically (thus excluding PKU which is diagnosed by already established screening methods) in NZ from 2004–2006 were compared to those obtained from childhood clinical presentations and the expanded newborn screening programme (see Table 1 for a list of diseases screened that can be diagnosed by ENBS) based at The Children's Hospital at Westmead in Sydney, New South Wales during the same period.

The latter facility screens all newborns in New South Wales and the Australian Capital Territory (these two areas will be referred to as 'NSW' in this document).

## Results

From 2004–2006 inclusive there were approximately 175,000 births in NZ<sup>7</sup> and 270,000 births in NSW.<sup>8</sup>

During the 3-year study period, 15 cases of disorders of intermediary metabolism were reported in NZ (Table 2). One of these (Maple Syrup Urine Disease, MSUD) was diagnosed by the newborn screening programme (NZ is somewhat unusual internationally in that it had an established screening programme specific for this disorder during the period 2004–6); one was diagnosed prenatally (ornithine transcarbamylase deficiency, OTC) following a sibling diagnosis; and in 13 cases the diagnosis was made following metabolic investigations performed during the clinical investigation of a symptomatic patient. Eight cases (including one adult) were

diagnosed with disorders on intermediary metabolism that could have been detected by ENBS.

**Table 1. Inborn errors of metabolism that can be diagnosed by expanded newborn screening**

**Fatty acid oxidation disorders**

Carnitine uptake defect  
Carnitine palmitoyltransferase 1 deficiency (CPT1)  
Carnitine palmitoyltransferase 2 deficiency (CPT2)  
Carnitine-acylcarnitine translocase deficiency  
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)  
Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)  
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)  
Trifunctional protein deficiency  
Multiple acyl-CoA dehydrogenase deficiency (MADD)

**Aminoacidopathies**

Phenylketonuria (PKU)  
Homocystinuria (Hcy)  
Maple syrup urine disease (MSUD)  
Argininase deficiency  
Argininosuccinic acidaemia  
Citrullinaemia type 1 (CIT I)  
Citrullinaemia type 2 (CIT II)  
Tyrosinaemia type II (TYR)

**Organic acidopathies**

Glutaric acidaemia type 1 (GA1)  
Beta ketothiolase deficiency  
Isovaleric acidaemia  
Methylmalonic acidaemia (Cobalamin disorders- CblC)  
Methylmalonic acidaemia (mutase deficiency) (MMA)  
Holocarboxylase synthetase deficiency (HCS)  
Propionic acidaemia  
HMG-CoA lyase deficiency  
2 Methyl 3 hydroxybutyric acidaemia  
3 Methyl glutaconic acidaemia  
3 Methylcrotonyl carboxylase deficiency (3-MCC)

**Other**

Vitamin B-12 deficiency

**Table 2. Disorders of intermediary metabolism diagnosed in New Zealand: 2004–06**

Disease	Method of initial diagnosis	Age of diagnosis	Outcome	Ability to diagnose on expanded newborn screening	Early diagnosis likely to improve outcome
MCAD	Clinical	9 months	Good	Yes	Yes
MCAD	Clinical	34 months	Good	Yes	Yes
MSUD	NBS	1 week	Good	Yes	Yes
GA1	Clinical	5 months	Poor	Yes	Yes
Ketothiolase	Clinical	6 months	Good	Yes	Yes
HCS	Clinical	1 week	Poor	Yes	No
MADD	Clinical	1 month	Poor	Yes	No
VLCAD	Clinical	40 years	Good	Yes	Yes
NKH	Clinical	1 week	Poor	No	No
NKH	Clinical	2 months	Poor	No	No
NKH	Clinical	1 week	Poor	No	No
NKH	Clinical	1 week	Poor	No	No
OTC	Prenatal	Antenatal	Poor	No	No
OTC	Clinical	10 years	Good	No	Yes
OTC	Clinical	14 years	Good	No	Yes

MCAD=Medium chain acyl Co-A dehydrogenase deficiency; GA1=Glutaric acidemia type I; HCS=Holocarboxylase synthetase (deficiency); MADD=Multiple acyl Co-A dehydrogenase deficiency; VLCAD=Very long-chain acyl-CoA dehydrogenase deficiency; NKH=Non-ketotic hyperglycaemia; OTC=Ornithine transcarbamylase (deficiency).

**Table 3. Disorders of intermediary metabolism diagnosed in New South Wales: cohort born 2004-06 (N=45)**

Disease	Method of initial diagnosis	Number of children	Early diagnosis likely to improve outcome
MCAD	NBS	24	Yes
CblC	NBS	1	Yes
MMA	Clinical-pre NBS	1	Yes
MMA	Prenatal	1	Yes
MSUD	NBS	1	Yes
VLCAD	NBS	3	Yes
CIT I	NBS	1	Yes
CIT II	NBS	1	Yes
TYR	NBS	1	Yes
OTC	Clinical	1	Yes
OTC	Prenatal	1	Yes
Hcy	NBS	1	Yes
GA1	NBS	4	Yes
MADD	NBS	2	Sometimes
3-MCC	Maternal	3	No
NKH	Clinical	2	No
B-12 deficiency	NBS	2	Yes

CblC=Cobalamin C deficiency; MMA=Methylmalonic acidemia; CIT I=Citrullinaemia type I; CIT II=Citrullinaemia type II; TYR=Tyrosinaemia; Hcy=Homocystinuria; 3-MCC=3-Methylcrotonyl carboxylase deficiency.

During the same period, 45 children were diagnosed in NSW (Table 3). Thirty-nine cases were disorders of intermediary metabolism diagnosed via ENBS. An additional two cases, potentially diagnosable by ENBS, were diagnosed prior to screening; one prenatally and one symptomatically in the first few days of life. Of the other four cases, three were diagnosed clinically after screening (two of non-ketotic hyperglycaemia [NKH] and one of ornithine transcarbamylase [OTC] deficiency, and one prenatally [OTC]).

Three mothers were diagnosed, based on the results' of their children's newborn screening, with the probably benign condition 3-methylcrotonylcarboxylase (3-

MCC) deficiency. In addition, the ENBS programme diagnosed two neonates with vitamin B-12 deficiency.

Specifically looking at the disorder—medium chain acyl Co-A dehydrogenase deficiency (MCAD)—two cases were diagnosed in NZ (1 in 87,500) and 24 in NSW (1 in 11,250).

## Discussion

The duration of this study and the numbers involved are not sufficient to prove or disprove the effectiveness of ENBS. However larger studies (many of them from the NSW screening programme) have addressed this issue.<sup>4-6</sup> This study does, however, illustrate a number of important points pertaining to the recent introduction of ENBS in NZ.

MCAD is by far the most prevalent disorder of intermediary metabolism (excluding PKU which has been screened for separately in NZ since the late 1960s), and thus the most important condition clinically. Classically it presents with hypoketotic hypoglycaemia and encephalopathy, following a period of catabolic stress such as a viral gastroenteritis, during the early childhood years.

Without screening, approximately 25% of cases die from MCAD prior to or without a diagnosis.<sup>9-11</sup> A slightly smaller percentage have at least one admission with characteristic clinical features (hypoglycaemia, encephalopathy) prior to a correct diagnosis being made. This is unfortunate as treatment is simple and cheap, and once a diagnosis is made, the outcome is excellent with a very low mortality and morbidity.<sup>6, 10</sup>

The key to treatment is patient/parent education. Parents are instructed to make sure the child has a regular oral energy intake, especially when they are unwell and prior to going to sleep at night. During times of intercurrent illness they should commence the emergency regimen (Table 4). While some of the other disorders of intermediary metabolism require somewhat more complicated diets and medications, the emergency regimen is an important aspect in the treatment of all.

Perhaps a third of children with MCAD do not present clinically. They are the subgroup that for whatever reason (most likely an avoidance of significant childhood illnesses) are never subjected to significant catabolic stress and thus avoid situations where they are fully reliant on their bodies' ability to metabolise fatty acids.

It could be argued that ENBS is in fact harmful to these patients as it potentially introduces psychological stress to a family that were never going to have problems. However the ability to prevent mortality in the symptomatic children outweighs this probably minor concern. Increasing evidence also shows that the initial presentation of MCAD is not confined to the childhood years—and events such as self-induced alcohol intoxication, prolonged labour with unexpected fasting, and unrelated medical illnesses can precipitate metabolic decompensation in adulthood.<sup>12, 13</sup> There is also evidence that some patients with MCAD can have chronic problems with fatigue, muscle pain, and exercise intolerance.<sup>11</sup>

**Table 4. The Emergency Regimen for the initial home treatment of suspected metabolic decompensation in disorders of intermediary metabolism**

<p>Children who are unwell but are still alert, feeding well and are not having recurrent vomiting should be commenced on the following emergency regimen.</p> <p>Stop normal solid feeds. Continue on any special formulas. Continue to take usual medications.</p> <p>Commence glucose polymer drink (e.g. maltodextran, polycose or similar) as prescribed by doctor/dietician. Every two hours during the day and every 2–4 hours during the night</p>		
Age (years)	Glucose polymer concentration (g/100ml)	Total daily volume
0-1	10	120-200 ml/kg
1-2	15	95 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml
<p>Continue to assess the child every two-four hours. If they improve, slowly recommence the normal diet. If they are unwell but stable continue with the emergency regimen. Contact doctor and/or metabolic service if child remains on the emergency regimen for more than 36–48 hours</p> <p><b>If the child becomes significantly unwell, drowsy and/or is having recurrent vomiting then they should be seen at the nearest hospital immediately. Contact your doctor or the metabolic service if concerned.</b></p>		

Two cases of MCAD were diagnosed in NZ during the study period and thankfully both had a good outcome. However, presuming a similar incidence as NSW, it is likely that 16 children (95% confidence interval: 9–22) were born with the condition during the study period. Of these, 3-4 children would have died.<sup>9,10</sup>

We are aware of two NZ children dying from confirmed MCAD over the last 6 years. Thus purely for this one condition it is possible to make a good case for ENBS in NZ. A cost-benefit analysis commissioned by the New Zealand National Testing Centre in 2002 found that (over a 7-year period) the cost per death avoided would be \$11,500 and the cost per life year gained \$590.<sup>14</sup>

Another problem that has emerged with the advent of MCAD screening is the realisation that the mutation profile of patients with MCAD deficiency diagnosed by ENBS is somewhat different from that of those diagnosed clinically, in that the proportion of alleles with the common MCAD mutation in children who are diagnosed symptomatically is greater than in those that are diagnosed via ENBS.<sup>15,16</sup>

This suggests that there are a group of MCAD patients identified by screening who, while having the typical blood biochemical profile, are at a lesser risk than those with the 'classical' form of the condition. This is hardly surprising as several other metabolic diseases (for instance MSUD and PKU) are known to have milder or intermediate forms. This phenomenon is likely to be seen in other conditions and illustrates the evolving nature of ENBS knowledge.

Most of the other fatty acid oxidation disorders (FAODs) are also readily diagnosed by ENBS. They tend to present in a similar manner to MCAD. Some, such as LCHAD, have an even poorer prognosis without screening.<sup>17</sup> Others such as late-onset VLCAD tend not to present with childhood hypoglycaemia—but (as seen with

the case diagnosed in NZ during the study period) with exercise induced rhabdomyolysis in adulthood. Thus, while still a useful disease to diagnose early (the patient in question had many years of exercise induced muscle problems that could have been prevented with a high calorie oral carbohydrate intake prior to and during activity), one may encounter a situation in which a disease that is not going to cause problems for many years is diagnosed soon after birth.

While the case for ENBS for the FAODs (in particular MCAD) is strong, the situation is less clear for some of the amino and organic acidopathies.<sup>18</sup> These disorders of protein catabolism generally present with encephalopathy and the long-term outcome is often dependent on the degree of neurological damage suffered during the first presentation.

Some, such as glutaric aciduria type 1 (GA I) and beta ketothiolase deficiency, tend to present after the neonatal period, and as treatment is available and screening can easily be added (with minimal additional cost to the screening programme for the FAODs), a good case for screening can be made.

The known case of GA I that presented during the study period in NZ resulted in severe disability that could have been prevented with early detection. Based on the NSW figures, it is possible (even likely) that there are were other similar cases in NZ—although they remain undiagnosed and thus remain unreported.

NSW reported 41 children (1 in 6585) with treatable inborn errors of metabolism that can be detected by ENBS; 2 of these were diagnosed prior to screening. In NZ we diagnosed 7 children (1 in 25,000) during the same period, 1 (MSUD) by established screening, and 1 clinically in the first few days of life.

Assuming a similar incidence in both populations, as well as the 14 ‘missed’ cases of MCAD described above, there may have been an additional 6 (95% confidence interval: 2–10) cases of other inborn errors that were not diagnosed correctly, or (less likely) have not yet presented clinically.

In some conditions, such as the classical severe forms of methylmalonic aciduria and MSUD, the children are likely to be becoming sick within the first few days of life. This is illustrated by the NZ patient with MSUD who was diagnosed by the existing screening programme on the day following the child’s admission to hospital with encephalopathy. While an even earlier diagnosis would have been optimal, the screening diagnosis allowed for a much earlier diagnosis than would have been obtained on clinical grounds and thus undoubtedly improved the child’s outcome.

Thus in order to optimise outcome and screening programme effectiveness it is critical that the Guthrie card is obtained early (as soon is practical after 48 hours of age) and just as importantly transported quickly to the screening laboratory.

There are some disorders that ENBS cannot reliably diagnose. This is because the key metabolites in affected patients are not in a range that is significantly different from the extremes of the normal population and thus NBS is not sufficiently specific.

OTC deficiency—the most common of the urea cycle disorders and thus a disease in which it would be beneficial to screen for—is probably the most important of these. Therefore it is vital that clinicians remain alert for the possibility of an inborn error of metabolism in sick children and do not assume that just because the child has had a normal newborn screen that they do not have a metabolic disorder.

Direct communication with the screening laboratory and/or the related clinical metabolic service can be very useful in these cases. Based on the numbers of metabolic investigations performed there appears to be lesser index of suspicion of metabolic disease in symptomatic individuals in NZ compared to Australian centres.

Some disorders cannot be diagnosed by ENBS and in addition there is no effective treatment. Classical NKH, a condition characterised by early neonatal seizures and encephalopathy, is the best example of this. This is particularly relevant in New Zealand where NKH appears to have a high incidence in the Māori population as illustrated by the four cases diagnosed during the study period.

Another condition with a high incidence in New Zealand is biotin-resistant holocarboxylase synthetase (HCS) deficiency.<sup>19</sup> Typically classical HCS presents in the first few months of life, is easily treated with oral biotin, and is thus a good candidate disease for NBS. However in the Samoan population, due to the presence of a particularly pathogenic common mutation, it presents (on day 1 of life) with severe lactic acidosis and encephalopathy and treatment with biotin is overall disappointing. (However, newborn screening may assist families, by ensuring that a diagnosis is made, if all children are tested.)

Additional early evidence shows that several other metabolic diseases occur with particularly high frequency in the Pacific communities, probably due to a gene founder effect.<sup>20</sup> Similarly, ethnic groups where consanguinity is not uncommon also have a high incidence. Thus the unique ethnic demographics of the NZ population need to be considered when interpreting international recommendations regarding ENBS

Some metabolic diseases detectable by ENBS are probably benign conditions in most patients. 3-methylcrotonyl coxylase (3-MCC) and short chain acyl Co-A dehydrogenase deficiency are two such conditions. The NSW screening programme diagnosed three mothers with 3-MCC deficiency by detecting the relevant raised metabolites in the Guthrie card of the newborn infant. The child's metabolism had not yet had a chance to clear these maternal compounds that had accumulated *in utero*.

SCAD deficiency has now been removed from the list of screened conditions. Similarly, although more clinically significant, woman who are vitamin B-12 deficient can be detected by noting a raised propionyl carnitine levels in their child's Guthrie card sample. The children are also B-12 deficient and are at significant risk as they are likely to be exposed to a low B-12 diet during infancy.

There have been a small but regular number of infants suffering from catastrophic complications of B-12 deficiency in NZ in recent years and hopefully ENBS will help to address this problem.

A high degree of specificity is important in all screening programmes. ENBS measures a number of key metabolites (corresponding to one or more disease), each with cut-off limits, outside of which a second sample is requested. Thankfully the highly accurate nature of mass spectrometry means that despite screening for 20 plus diseases, the cumulative false positive rate is only around 0.2%. Thus in NZ we may expect to ask for second samples in around 120 patients annually. The second sample is nearly always normal and reflects the normalisation of the neonates biochemistry rather than an inaccurate first test.

Nevertheless false positives can lead to heightened parental anxiety,<sup>21</sup> and improved communication and education of all parties involved in screening has been suggested as the optimal strategy in reducing this.<sup>22</sup>

Expanded newborn screening using tandem mass spectrometry is an important recent development in screening and paediatrics. Unlike most screening programmes whereby a single test is used to screen for a single disease, ENBS uses a single sample to measure a large number of compounds to look for a range of diseases.

With some of these diseases there is good evidence that current clinical detection methods are inadequate and likely to be leading to unnecessary mortality and thus a strong case can be made for newborn screening.

With other conditions the supporting evidence for screening is not yet available, usually because of the rarity of the individual disease, although clinical experience suggests there are likely to be benefits provided unnecessary delay is avoided in the collection, transport, and processing of the samples.

The change from a 'one test-one disorder' to a 'one test-many disorders' paradigm has added complexity to decision making in newborn screening. The National Screening Unit of the Ministry of Health, who have governance over the Newborn Metabolic Screening Programme, was required to examine in detail the implications of ENBS. Securing the required capital to purchase the tandem mass spectrometer was problematic and required a generous contribution from the Starship Foundation.<sup>23</sup>

For these reasons, and despite evidence supporting the benefits of ENBS accumulating since the mid-1990s,<sup>24,25</sup> NZ was the last (commenced in December 2006) of the newborn screening programme countries in the Asia-Pacific region to introduce ENBS.

**Competing interests:** None.

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