Health Policy Advisory Committee on Technology

Technology Brief

Neonatal screening for lysosomal storage disorders

August 2012

HealthPACT
emerging health technology
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This brief was prepared by Ms Karen Humphreys from the Australian Safety and Efficacy Register of New Intervventional Procedures – Surgical (ASERNIP-S).
Technology brief

Register ID  WP115

Name of technology  Neonatal screening for lysosomal storage disorders

Purpose and target group  Detection of lysosomal storage disorders in the neonate population

Stage of development in Australia

☐ Yet to emerge  ☐ Established
☐ Experimental  ☐ Established but changed indication or modification of technique
☒ Investigational  ☐ Should be taken out of use
☐ Nearly established

Australian Therapeutic Goods Administration approval

☐ Yes  ☐ ARTG number
☐ No
☒ Not applicable

International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused*</th>
</tr>
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<tbody>
<tr>
<td>Australia</td>
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<tr>
<td>USA</td>
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</table>

* While the required technology is widely diffused, widespread population screening has only been conducted in the context of trials

Impact summary

Laboratories that perform routine analysis of heel prick tests may have the necessary equipment to provide additional screening for lysosomal storage disorders (LSDs) in neonates; however should a national neonatal screening program be introduced in Australia and New Zealand, additional investment in both technology and staffing would be required. In addition to these economic considerations, there are ethical considerations that also surround the uptake of this technology. Newborn screening for selected genetic disorders using dried blood spots (DBS) is currently occurring in Australia at a population level, but does not routinely include LSD screening. A small
technical feasibility study for newborn LSD screening has been published using DBS cards collected from the South Australian Screening Centre; however, the feasibility of including LSD screening as part of a national neonatal screening program has not been assessed in Australia.5

Background

LSDs comprise more than 50 serious, progressive diseases that arise due to an inherited dysfunction in the lysosome. The lysosome is an intracellular organelle with the primary function of degrading substrates through a variety of pathways including endocytosis, phagocytosis and autophagy.1 Lysosomes contain a range of hydrolytic enzymes to undertake degradation. Loss-of-function mutations in one or more of the hydrolytic enzymes, or other integral lysosomal proteins, can lead to substrate accumulation and storage within the lysosome.2 The stored substrate is specific to each disorder, and traditionally the LSDs have been categorised according to the type of substrate stored (for example, mucopolysaccharidoses, oligosaccharidoses, sphingolipidoses, gangliosidoses).2, 3 They may also be classified based on the nature of the defective protein.3 The majority of LSDs are recessively inherited autosomal traits, with several that are recessively inherited X-linked traits. Examples of LSDs include Gaucher’s disease, Fabry’s disease, Tay-Sach’s disease, Pompe’s disease, and Niemann-Pick disease types A and B.4

The accumulation of substrates in LSDs can alter many cellular processes, including lysosomal pH regulation, synaptic release, endocytosis, vesicle maturation, autophagy and exocytosis.1, 3 Progressive lysosomal substrate deposition can occur in cells throughout the body.4 This accumulation can result in the deterioration of cellular and tissue function, and the dysfunction of vital organs, muscles and neurons.1-3 The clinical presentations of LSDs vary, and can be affected by the underlying genetic mutation. The onset of most LSDs occurs in childhood, after the achievement of early developmental milestones; however, some LSDs present in utero or during the newborn period, while others present in late adulthood. Early symptoms can include neurological disorders and slowing of developmental progress, dysmorphic facial appearance, cardiac disease or enlargement of the liver and/or spleen.3 Many disorders affect the central nervous system and most patients have a decreased lifespan and significant morbidity.2

Treatment is generally directed towards symptomatic care of secondary complications; however, for some LSDs, haematopoietic stem-cell transplantation (from bone marrow or cord blood) and enzyme replacement therapy are emerging as promising treatments.2, 4 Due to the progressive nature of these disorders, the effectiveness of these therapies relies heavily on early detection and treatment.
Haematopoietic stem-cell transplantations may be more successful in neonates due to the natural immaturity of the immune system.5

Neonatal screening programs have been in use for decades and are generally intended to differentiate asymptomatic newborns from those without a disease for disorders in which early detection and presymptomatic treatment are required to avoid serious clinical harm. A disorder must also have a high enough prevalence to justify inclusion in such programs.4 Several studies have been published that implemented pilot screening for LSDs to assess the practicality and appropriateness of including these disorders in neonatal screening panels.4 In addition, several states in the USA have passed legislation to include some LSDs in their neonatal screening programs, while regional neonatal screening programs are commencing in parts of Europe.4

Screening for LSDs typically involves the collection of DBS, with subsequent enzyme activity analysis, using such technology as electrospray ionisation tandem mass spectrometry (ESI-MS).4 First introduced in 1993, ESI-MS has been shown in multiple studies to be technically feasible.6-11 ESI-MS enables the simultaneous screening of several enzyme activities related to LSDs from DBS samples and high-throughput, multiplex assays have been developed to simplify and expedite workflow.9-13 More advanced DNA-based genetic mutation analysis is generally used to confirm a suspected positive result from an enzyme activity screen4; however, one study by Chien et al (2012) has indicated that mutation analysis as a primary screening method may be more sensitive than the enzyme-based technique.14 Numerous genetic and biomarker studies for the detection of LSDs are currently being conducted.15

**Clinical need and burden of disease**

There are more than 50 different forms of LSDs. While each individual disorder is rare, when considered as a group, the prevalence in Australia has been estimated at 1 in 7,700 births.5 More recent estimates are available from other countries, such as a recent screening study in Austria which put the combined incidence of LSDs at approximately 1 in 2,315 births.4

Due to the rarity of LSDs, there are limited data available on the burden of disease in Australia. Most LSDs can be classified by ICD-10-AM code as either ‘E74 Other disorders of carbohydrate metabolism’ or ‘E75 Disorders of sphingolipid metabolism and other lipid storage disorders’. In Australia in 2009 – 2010, there were 490 hospital separations for the disease classification ‘Other disorders of carbohydrate metabolism’ and 1,864 hospital separations for the disease classification ‘Disorders of sphingolipid metabolism and other lipid storage disorders’. More specific LSD data are not available.16
Diffusion of technology in Australia

Newborn screening for selected genetic disorders using DBS is currently occurring in Australia at a population level, but does not routinely include LSD screening. A small technical feasibility study for newborn LSD screening has been published using DBS cards collected from the South Australian Neonatal Screening Centre. Since 1998, an LSD pilot project has been in operation at the South Australian Neonatal Screening Centre to determine the effectiveness of the test for identifying neonates at risk of having an LSD.

Comparators

The comparator for the introduction of widespread neonatal LSD screening is diagnosis once clinical symptoms have emerged. Issues around widespread screening implementation versus the comparator of no widespread screening are predominantly economic and ethical, rather than technical.

Safety and effectiveness

Study description

An Austrian study provided the first evidence for the introduction of a screen for multiple LSDs into a nation-wide neonatal screening program. Additional population-wide screening studies for single selected LSDs have been conducted in several countries (Table 1).

Mechtler et al (2012) implemented a multiplex high-throughput screening assay for Gaucher’s disease, Pompe’s disease, Fabry’s disease, and Niemann-Pick disease types A and B in an anonymous prospective nation-wide screening study in Austria. The aim of the study was to assess the practicality and appropriateness of including these disorders in neonatal screening panels; these issues could be considered the main effectiveness measures for the introduction of LSD screening.

DBS samples were collected consecutively from 34,736 newborns from January to July 2010, as part of the routine national Austrian newborn screening program which covers more than 99% of births. All samples successfully screened with the regular screening panel for endocrine and metabolic disorders were additionally analysed for four different lysosomal enzyme activities: acid β-glucocerebrosidase (GBA; deficient in Gaucher’s disease), α-galactosidase A (GLA; deficient in Fabry’s disease), α-glucosidase (GAA; deficient in Pompe’s disease), and acid sphingomyelinase (ASM; deficient in Niemann-Pick disease type A and B). The DBS screen for LSDs was performed using ESI-MS. The authors adapted a direct multiplex assay to allow for use of automated sample preparation and pipetting steps with liquid handling stations to enable high-throughput screening. Quality control measures were implemented in line with neonatal screening procedures for other metabolic disorders.
disorders, and 32 blood samples from affected individuals served as controls. DBS from potentially enzyme-deficient infants were retested in duplicates, and positive results were diagnostically confirmed by subsequent mutational analysis of genomic DNA.4

**Safety**

Safety aspects of screening for LSDs were not specifically reported. The study made use of DBS samples that are routinely collected from neonates for screening for other disorders, and presumably no additional safety issues applied to the LSD screen.4

**Effectiveness**

The adapted biochemical multiplex screening assay for the selected LSDs was successful for all 34,736 samples. The 32 control samples from known affected patients had low enzyme activities that could be clearly distinguished from healthy controls. The first line ESI-MS screening identified 124 samples with low enzyme activity. When the samples were retested in duplicates from the same DBS card, 38 neonates were found to have low enzyme activity (4 had low GBA, 5 had low GAA, 28 had low GLA, and 1 had low ASM).

Mutation analysis was subsequently performed in the 38 suspected cases, and 15 were positive by genetic testing and classed as confirmed cases. The confirmed cases included two for Gaucher’s disease (low GBA), four for Pompe’s disease (low GAA) and nine for Fabry’s disease (low GLA), with no confirmed cases of Niemann-Pick types A/B disease (low ASM). This gave a combined incidence of 1 per 2,315 births (95% confidence interval (CI) of 1 per 1,403 to 1 per 4,136 births), and individual disorder incidence rates of 1 per 17,368 births for Gaucher’s disease, 1 per 8,684 births for Pompe’s disease, and 1 per 3,859 births for Fabry’s disease, with Niemann-Pick types A/B disease not found in the tested population.

Most mutations (75%) were associated with a mild phenotype related to later onset and slow disease progression. The positive predictive value (PPV) for the ESI-MS screening test was 40% (95% CI 24 – 57%) overall for the LSDs screened, 50% (95% CI 7 – 93%) for Gaucher’s disease, 80% (95% CI 28 – 99%) for Pompe’s disease, 32% (16 – 95%) for Fabry’s disease, and 0% (95% CI 0 – 95%) for Niemann-Pick types A/B disease. The false positive rate per million was 660 (95% CI 420 – 990) overall for the LSDs screened, 60 (95% CI 10 – 210) for Gaucher’s disease, 30 (95% CI 1 – 160) for Pompe’s disease, 550 (95% CI 330 – 850) for Fabry’s disease, and 30 (95% CI 1 – 160) for Niemann-Pick types A/B disease.4
## Table 1  Population-wide screening studies in single selected lysosomal storage disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Number screened</th>
<th>Number detected</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pompe’s disease</strong></td>
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<tr>
<td>Chien et al (2008)(^{19}), Chien et al (2009)(^{20}), Labrousse et al (2010)(^{22})</td>
<td>Taiwan Pilot screening program (~45% of all newborns in Taiwan). GAA measured from DBS via fluorescence assay, with confirmatory DNA analysis.</td>
<td>132,538 newborns</td>
<td>121 initially identified with standard technique (0.09%), of which 113 had low GAA upon further testing, and at least four has confirmed disease (~1 in 33,000).(^{18}) 107 of the 113 suspected cases consented to additional DNA analysis, of which 69 had GAA mutations. Of the remaining 38 with no GAA mutations, 36 were homozygous for the pseudodeficiency allele, which causes low GAA activity in normal individuals.(^{22})</td>
<td>The screening program was shown to improve clinical outcomes in infants identified by screening compared with infants identified by clinical signs and symptoms.(^{20})</td>
</tr>
<tr>
<td><strong>Fabry’s disease</strong></td>
<td></td>
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<tr>
<td>Spada et al (2006)(^{25})</td>
<td>Italy Pilot screening program of consecutive newborn males in a region in Italy. GLA measured from DBS via a fully automated system, with confirmatory DNA analysis.</td>
<td>37,104 male newborns</td>
<td>12 detected with standard technique and confirmed with DNA analysis (0.03% of screened males; ~1 in 3100 males).</td>
<td>Four novel mutations were identified. Of the 12 cases, most had mutations consistent with the later-onset disease phenotype.</td>
</tr>
<tr>
<td>Hwu et al (2009)(^{21})</td>
<td>Taiwan Pilot screening program of consecutive newborns (~40% of all newborns in Taiwan) GLA measured from DBS, with further confirmatory analysis.</td>
<td>171,977 newborns</td>
<td>94 initially identified with standard technique (0.055%), of which 75 had low GLA activity and GLA mutations upon further testing (~1 in 1250 males and ~1 in 40,840 females).</td>
<td>Most cases had mutations consistent with the later-onset disease phenotype.</td>
</tr>
<tr>
<td>Lin et al (2009)(^{23})</td>
<td>Taiwan Pilot screening program of consecutive newborns (~55% of all newborns in Taiwan) GLA measured from DBS, with further confirmatory analysis.</td>
<td>110,027 newborns</td>
<td>67 initially identified with standard technique, of which 45 had low GLA activity and GLA mutations upon further testing (~1 in 1400 males).</td>
<td>More of the known mutations were consistent with the later-onset disease phenotype than with the classic phenotype.</td>
</tr>
<tr>
<td>Chien et al (2012)(^{14})</td>
<td>Taiwan Pilot screening program of consecutive newborns in Taiwan DNA-based mutation analysis as primary screen, for specific GLA mutation linked to late-onset disease.</td>
<td>20,063 newborns</td>
<td>12 of 10,499 males (0.114% or ~1 in 875) and 24 of 9564 females (0.25% or ~1 in 399) had the specific GLA mutation IVS4+919G&gt;A.</td>
<td>Traditional GLA activity screening using DBS would only have identified 67% of the mutation-positive male newborns and only 17% of the mutation-positive female newborns.</td>
</tr>
</tbody>
</table>
Krabbe’s disease

Orsini et al (2009)24

USA

- Pilot screening program of anonymous newborns in the USA.
- GALC measured from DBS via a high-throughput system.

139,074 newborns
One detected with standard technique and confirmed with DNA analysis (also 100% detection of all positive controls).

DBS: dried blood spot; GAA: α-glucosidase; GLA: α-galactosidase A; GALC: galactocerebrosidase

Cost impact

Mechtler et al (2012) reported that to add the detection of several LSDs to routine neonatal screening, an additional tandem mass spectrometry system and at least one extra laboratory worker for sample preparation were needed. The total analysis time for 100 samples was approximately three hours. The reagent costs were about €1 per sample for all four multiplexed LSDs, which the authors stated was much the same as for other screening assays.4 Other costs associated with the test include labour, equipment maintenance (for both sample preparation and screening) and writedown.

Downstream costs that also need to be considered include those to confirm the diagnosis, input from specialist clinical consultants, genetic counselling services; as well as participation in paediatric metabolic programs following a positive diagnosis.

LSD treatment costs are also relevant, as the detection of more LSDs at birth may result in earlier uptake of available treatments. While the majority of treatments are directed towards symptomatic care, primary therapies such as haematopoietic stem cell transplantation and recombinant enzyme replacement therapies could enable early treatment before irreversible damage occurs.2,18 For many countries, expense is a large consideration in the treatment of LSDs as most new therapies have a high cost, require considerable expertise, and often lack sufficient evidence of effectiveness.2

Ethical, cultural or religious considerations

As with any screening program, there are many ethical considerations around neonatal screening for LSDs.2 Such ethical considerations include how best to treat presymptomatic individuals with positive screen results, and how best to inform parents of the likely outcomes for the affected individual and also of future reproductive risks. Many countries have adopted a conservative approach to neonatal screening, possibly due to the scarcity of formal evidence of benefit and the fear of harm of false positive or negative screening results.18

For some LSDs, there is some limited evidence that presymptomatic diagnosis and early treatment can favourably alter the natural history of the disease.24 For example, in the Taiwanese screening study for Pompe’s disease, the screening
program was shown to improve clinical outcomes in infants identified by screening, compared with infants identified by clinical signs and symptoms.\textsuperscript{20}

For many LSDs, effective primary therapies have not yet been found, and a presymptomatic diagnosis may have little effect on disease progression. Detection of a known mutation can provide guidance on the likelihood of a classic or late-onset disease phenotype; however, precise genotype-phenotype correlations are not possible for many LSDs, particularly when novel mutations are detected.\textsuperscript{18} Uncertainty regarding how a disease will manifest translates into uncertainty regarding the appropriate age to commence treatment.\textsuperscript{18} Identification of adult-onset variants and variants of uncertain significance could potentially be identified in greater numbers than the early infantile forms of LSDs, and some patients with these variants may never develop symptoms or require therapy.\textsuperscript{2}

The manner in which trials to display the feasibility of neonatal screening are conducted also raises ethical issues. Anonymous study designs, such as those performed by Mechtler et al (2012)\textsuperscript{4} and Orsini et al (2009)\textsuperscript{24} where routine DBS samples were de-identified for the additional LSD screen, preclude clinical assessment of neonates identified as having a disorder by the screening process. Future studies without informed consent and clinical assessment could be deemed unethical.\textsuperscript{18}

Other issues

Fletcher & Wilcken (2012)\textsuperscript{18} noted that assessing the benefit of neonatal screening for LSDs is difficult due to the rarity of the disorders. Frameworks are being developed to systematically assess the merits of screening for additional disorders.\textsuperscript{26}

Many of the studies included were sponsored by the manufacturer or distributor of enzyme(s) used in the treatment of LSDs, with employees of these companies included as study authors.

Summary of findings

From the primary study by Mechtler et al (2012)\textsuperscript{4}, nation-wide neonatal screening for several LSDs using ESI-MS was technically feasible. More accurate confirmation of an LSD could be obtained after repeated biochemical screening and genetic testing. Mechtler et al (2012)\textsuperscript{4} stated that the combined incidence of the four LSDs screened was higher than expected (1 per 2,315 births). This was in agreement with some of the additional screening studies for single LSDs that also noted that neonatal screening produced higher incidence rates than previously recorded clinical diagnosis rates.\textsuperscript{14, 21, 23, 25} The mutation analyses in the studies by Mechtler et al (2012)\textsuperscript{4}, Chien et al (2012)\textsuperscript{14}, Hwu et al (2009)\textsuperscript{21}, Lin et al (2009)\textsuperscript{23}, and Spada et al (2006)\textsuperscript{25} detected a high proportion of mutations linked with late-onset disease
symptoms. Individuals with such mutations are likely to appear asymptomatic in early years, and without neonatal screening would only be identified later in life or not at all.

Whilst LSD screening is technically effective, and holds no more safety risk than current screening programs using DBS, the introduction of an expanded nation-wide neonatal screening program for LSDs is associated with both economic and ethical issues. The value of detecting an LSD at birth is clear when favourable outcomes are dependent on early initiation of treatments. More ethical issues surround the detection of LSDs where treatments are less effective, or where the likelihood and timing of symptom development is unknown. Economic considerations include the downstream costs associated with confirmatory diagnosis, specialist clinical consultant input, genetic counselling services and participation in paediatric metabolic programs following a positive diagnosis.

HealthPACT assessment:

Based on the increasing availability of evidence for population-wide neonatal LSD screening, and the economic and ethical issues surrounding this technology, HealthPACT recommended that the technology be monitored for 24 months.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 9
Total number of level IV studies: 9

References


**Search criteria to be used (MeSH terms)**

(lysosomal storage disorders OR lysosomal storage disease OR Gaucher’s disease OR Gaucher disease OR Pompe’s disease OR Pompe disease OR Fabry’s disease OR Fabry disease OR Niemann-Pick disease)

AND

(screening OR diagnosis)

AND

(neonatal OR neonate* OR baby OR babies OR infant* OR newborn*)

AND

(population OR nationwide)