

## **MSAC Application 1775**

# **Newborn bloodspot screening for mucopolysaccharidosis Type I (MPS I; Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome)**

**Applicant: Department of Health and Aged Care**

## **PICO Confirmation**

## Summary of PICO/PPICO criteria

A summary of the PICO criteria to define the questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC) are shown in Table 1 and Table 2.

**Table 1 PICO for newborn bloodspot screening (NBS) in mucopolysaccharidosis type I (MPS I): PICO Set 1**

Component	Description
Population	All newborn babies in Australia
Prior tests	No prior testing
Intervention	<p>Newborn bloodspot screening (NBS) to detect mucopolysaccharidosis type I (MPS I), based on a two-tier screening protocol:</p> <p>1<sup>st</sup> tier: quantification of the <math>\alpha</math>-L-iduronidase (IDUA) enzyme activity using tandem mass spectrometry (MS/MS) or a fluorometric assay</p> <p>2<sup>nd</sup> tier: endogenous biomarker method for measuring non-reducing end glycosaminoglycan (GAG) fragment analysis by liquid chromatography (LC)-MS/MS</p> <p><i>Note, the single tier screening protocol (GAG fragment analysis only) to also be included in the assessment (notwithstanding the available evidence may be a limiting factor).</i></p> <p>Diagnostic testing in those with a positive screening result (testing protocol as per the comparator)</p>
Comparator	<p>Current practice – Diagnostic testing for MPS I at the point of onset of phenotypic signs and symptoms; no universal newborn screening.</p> <p>Diagnostic testing:</p> <ul style="list-style-type: none"> <li>• Urine GAG analysis: <ul style="list-style-type: none"> <li>○ LC-MS/MS GAG fragment analysis</li> </ul> </li> <li>• Leukocyte IDUA enzyme activity test is conducted to confirm result if the urine GAG analysis is positive for MPS I</li> <li>• Those who are found to have MPS I after biochemical testing receive genetic testing (sequencing of the <i>IDUA</i> gene) to identify the pathogenic <i>IDUA</i> variants.</li> </ul>
Reference standard	A confirmed diagnosis following clinical assessment and diagnostic biochemical and genetic testing.
Outcomes	<p>Test performance:</p> <ul style="list-style-type: none"> <li>• Accuracy of the screening test (sensitivity, specificity, positive predictive value (what proportion of screen positive cases are MPS I rather than pseudodeficiencies), negative predictive value)</li> </ul>

Component	Description
	<ul style="list-style-type: none"> <li>• Diagnostic accuracy of confirmatory/diagnostic test (sensitivity, specificity, positive predictive value, negative predictive value)</li> <li>• Diagnostic yield and proportion of cases with a genotype that can predict a severe phenotype</li> </ul> <p>Change in management:</p> <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Age at treatment initiation (and whether prior to, or after phenotype onset)</li> <li>• Investigations/monitoring/treatments received (e.g. haematopoietic stem cell transplantation (HSCT))</li> </ul> <p>Clinical Effectiveness of NBS for MPS I:</p> <ul style="list-style-type: none"> <li>• Change in morbidity and mortality, quality of life, general functioning and disease manifestations (e.g. cognitive outcomes, progressive neurodegeneration) from earlier diagnosis, intervention, and/or avoidance of the diagnostic odyssey (either from studies assessing the impact of comparative change in management, or direct from test to health outcomes evidence)</li> </ul> <p>Safety of NBS for MPS I (physical harms to newborn from screening test, diagnostic test or subsequent early vs late treatment):</p> <ul style="list-style-type: none"> <li>• Psychological harm arising from NBS diagnosis and on-going monitoring for individuals with attenuated disease who may not become symptomatic for many years</li> <li>• Impact of false positive screening results (physical harms to the infant or psychological harms to the parents)</li> <li>• Impact of false negative results</li> <li>• Impact of diagnosing mild cases or variants of uncertain significance (VUS)</li> <li>• Safety of HSCT and enzyme replacement therapy (ERT)</li> <li>• Any potential risk of harm from ongoing monitoring and surveillance</li> </ul> <p>Economic and Financial Implications:</p> <ul style="list-style-type: none"> <li>• Cost-effectiveness of NBS for MPS I (cost per diagnosis; cost per quality adjusted life year (QALY))</li> <li>• Financial impact of screening, relative to existing practice (including impact of false positives, impact of screening-based treatment compared to treatment following diagnosis at phenotype presentation, impact of ongoing monitoring and surveillance for both diagnosed early onset cases and attenuated cases)</li> </ul> <p>Other relevant considerations:</p> <ul style="list-style-type: none"> <li>• Non health outcomes: Value of knowing (emotional benefits/harms to family, social benefits/harms to family)<sup>a</sup></li> <li>• Ethical considerations (equity of access, considerations regarding consent)</li> <li>• Organisational considerations (incremental impact of NBS on organisations, particularly the impact on services for monitoring late-onset</li> </ul>

Component	Description
	disease, or on the NBS programs itself including programmatic implementation considerations)
Assessment questions	What is the comparative safety, effectiveness and cost-effectiveness of NBS for MPS I versus current practice (no NBS, diagnosis on presentation of signs and symptoms)?

**Table 2 PICO for cascade testing of parents and affected siblings of a child diagnosed with MPS I: PICO Set 2**

Component	Description
Population	Biological parents, siblings, aunts and uncles of an individual (index case/proband)
Prior tests	Family history
Intervention	<p>Cascade testing after diagnosis of a newborn due to NBS:</p> <ul style="list-style-type: none"> <li>For parents, aunts and uncles: Genetic testing to determine the presence of specific familial P/LP <i>IDUA</i> variants. Parents may be referred for genetic counselling for family planning if requested.</li> <li>For siblings: biochemical testing (urine GAG analysis) or genetic testing.</li> </ul>
Comparator	<p>Cascade testing after diagnosis of a symptomatic child:</p> <ul style="list-style-type: none"> <li>For parents, aunts and uncles: Genetic testing to determine the presence of specific familial P/LP <i>IDUA</i> variants. Parents, aunts and uncles may be referred for genetic counselling for family planning if requested.</li> <li>For siblings: biochemical testing (urine GAG analysis) or genetic testing.</li> </ul> <p><i>(i.e. the same testing strategy as the intervention, differing only in the timing of the testing).</i></p>
Outcomes	<p>Test outcomes:</p> <ul style="list-style-type: none"> <li>Number of siblings with early diagnosis of MPS I</li> <li>Number of family members who uptake cascade testing</li> <li>Age at diagnosis/treatment of affected siblings</li> </ul> <p>Clinical Effectiveness:</p> <ul style="list-style-type: none"> <li>Effectiveness of early vs late monitoring/treatment (for affected siblings)</li> </ul> <p>Safety:</p> <p>Physical or psychological harms arising from earlier diagnosis, monitoring and treatment for siblings diagnosed with MPS I following cascade testing, including the impact of diagnosing siblings with attenuated disease who may not become symptomatic for many years</p> <p>Economic and Financial Implications:</p> <ul style="list-style-type: none"> <li>Cost-effectiveness</li> </ul>

Component	Description
	<ul style="list-style-type: none"> <li>• Financial impact of early vs late cascade testing</li> <li>• Total Australian Government health care costs</li> </ul> <p>Other relevant considerations:</p> <ul style="list-style-type: none"> <li>• Non health outcomes: Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family)<sup>a</sup></li> <li>• Ethical considerations (considerations regarding cascade testing, including notification of carrier status)</li> <li>• Organisational considerations</li> </ul>
Assessment questions	<p>What is the comparative safety, effectiveness and cost-effectiveness of cascade testing of family members of a newborn diagnosed with MPS I due to NBS versus cascade testing of family members following diagnosis of MPS I in the index case based after presentation with signs/symptoms?</p>

## Purpose of application

An application requesting that testing for mucopolysaccharidosis type I (MPS I) be added to Australia's newborn bloodspot screening (NBS) programs was developed by the Department of Health, following a request from the Hon Mark Butler MP, Minister for Health and Aged Care.

NBS programs are overseen and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS through the National Health Reform Agreement (NHRA). It announced funding of \$39.0 million under the 2022-23 Budget, of which \$25.3 million was provided to states and territories to support expansion of NBS programs. This application, as well as applications for NBS for glycogen storage disease type II (GSD II, commonly known as Pompe disease; application number 1774) and for mucopolysaccharidosis type II (MPS II; application number 1776) form part of this expansion. All three conditions are lysosomal storage disorders (LSDs) and there is overlap in the tests used to diagnose these three conditions. Therefore, other LSDs may be discussed when considering testing methodologies.

There are five laboratories that conduct tests on bloodspot cards, located in New South Wales, Victoria, Queensland, South Australia and Western Australia. Newborns born in states and territories without NBS testing laboratories have their dried bloodspots (DBS) sent interstate for testing. All NBS programs are underpinned by the Newborn Bloodspot Screening National Policy Framework (NBS NPF).

Proposals to add conditions to the NBS programs are considered by MSAC. In providing its advice MSAC considers the safety, effectiveness, cost-effectiveness and total cost of proposals for public funding, noting that for NBS applications alignment with the NBS NPF decision-making criteria (Appendix A) is a key additional policy consideration.

The clinical claim is that universal NBS for MPS I has superior safety and effectiveness compared to current practice (no universal screening; diagnosis upon symptomatic presentation) for diagnosis of MPS I. Early diagnosis of MPS I due to NBS rather than current practice (investigations following signs/symptoms of MPS I) results in earlier commencement of treatment, which can significantly extend the life of those with MPS I, delaying or preventing deterioration and maintaining a higher level of functioning/quality of life.

## PICO criteria (PICO Set 1):

### ***Population (PICO Set 1)***

The intended population for screening for MPS I as part of existing NBS programs is all newborns in Australia that participate in NBS. Over 99% of all newborn Australian babies participate in NBS screening (Huynh et al. 2022). There are no other eligibility criteria that apply.

*PASC noted the population was all newborns participating in the NBS programs.*

MPS I is an ultra-rare, genetic LSD that is inherited in an autosomal recessive manner. It is a progressive multisystem disorder with varying severity of symptoms, which are usually consistent with either severe or attenuated disease.

Lysosomes are located inside cells and are responsible for the breakdown and recycling of a range of complex cellular components including glycosaminoglycans (GAGs), sphingolipids, glycogen fragments, and proteins. The breakdown of these cellular components occurs through the concerted action of many different enzymes. If these enzymes are defective, it leads to intra-lysosomal accumulation of the non-degraded or partially degraded molecules, which causes cell destruction and eventually organ damage (Burlina and Gragnaniello 2022).

The condition MPS I is due to a pathogenic variant in the  $\alpha$ -L-iduronidase (*IDUA*) gene, which leads to a defective lysosomal IDUA enzyme. The defective enzyme is unable to degrade the GAGs, dermatan sulphate and heparan sulphate (Clarke 2002). GAGs (formerly known as mucopolysaccharides) are major components of the extracellular matrix, connective tissue (including cartilaginous structures such as joints and heart valves) and joint fluid (Clarke 2002).

#### *Natural history of the condition*

There are three clinical phenotypes classified under MPS I: the severe Hurler syndrome (MPS IH), and two attenuated syndromes: Hurler-Scheie syndrome (MPS IHS; of intermediate severity), and Scheie syndrome (MPS IS; the least severe). These phenotypes occur across a continuum of severity and vary in age of onset and rate of progression (Clarke et al. 2019; Keerthiga et al. 2023). Approximately 50% to 80% of cases fall within the severe form (Hurler syndrome), with signs/symptoms starting in the first year of life (Muenzer et al. 2009; Parini et al. 2017). Genotyping may be indicative of which phenotype people have.

The globally reported median age at diagnosis for MPS I (in general) varies between one and five years of age. However, when different clinical phenotypes are considered, the age at diagnosis varies significantly: for patients with the more severe Hurler phenotype, the median age at diagnosis is around one year of age, compared with approximately four years of age for Hurler-Scheie patients, and seven to nine years for those with the attenuated Scheie phenotype (Costello Medical 2019; Keerthiga et al. 2023).

#### *Hurler syndrome (MPS IH)*

Infants with Hurler syndrome may or may not appear normal at birth. Early manifestations are non-specific, with frequent upper respiratory tract infections before the age of one year. The repeated infections are due to upper airway obstructions caused by mucosal and adeno-tonsillar hypertrophy. Deceleration of growth is seen between 6-8 months and developmental delay begins in 12-24 months (Keerthiga et al. 2023). The condition is progressive with increasing deformity involving all bones (such as thoracolumbar gibbus, coarsening of the facial features, progressive skeletal dysplasia and progressive arthropathy involving most joints, known as dysostosis multiplex). Other symptoms include hepatosplenomegaly, umbilical or inguinal hernias, laryngeal and tracheal narrowing, coarsening of facial features, organomegaly, valve disease and cardiomyopathy, hearing loss, corneal clouding and progressive neurological disease with severe cognitive delay (Parini et al. 2017).

Without treatment, death usually occurs within the first ten years of life. Anterior C1-C2 subluxation occurs frequently and can cause cord compression and sudden death, while cardiac complications such as progressive cardiorespiratory failure due to cardiomyopathy, endocardial fibroelastosis, valvular regurgitation, and/or irregular and diffuse narrowing of the coronary arteries and irregular lesions of the aorta caused by GAG storage within the blood vessels are also common (Braunlin et al. 1992).

### Hurler–Scheie syndrome (MPS IHS)

Hurler–Scheie syndrome is intermediate in severity and has a lower incidence rate than Hurler syndrome. Symptoms usually start at around 2 years of age and is typically diagnosed at between two and six years of age, with joint stiffness as the most common presenting complaint (Vijay and Wraith 2005). Overall, there are common symptoms across the two attenuated subtypes (Hurler-Scheie and Scheie syndromes) involving the musculoskeletal, respiratory and cardiovascular systems (Vijay and Wraith 2005).

Hurler-Scheie progresses less rapidly than Hurler syndrome. Patients usually have normal intelligence, although static learning disabilities are not uncommon, and are usually due to increased intracranial pressure that can be corrected by ventriculoperitoneal shunting. However, patients typically die in their twenties of cardiac disease or respiratory failure (Roubicek et al. 1985).

### Scheie syndrome (MPS IS)

Scheie syndrome is the least severe form of MPS I. In the absence of NBS, the median age of diagnosis is around 9 years although some patients, with the mildest condition, may not be diagnosed until later in their adult years, due in part to their facial features being only mildly affected (Vijay and Wraith 2005). Patients with Scheie syndrome suffer from significant joint stiffness and pain, which can be debilitating. Aortic valve disease often requires valve replacement. Corneal clouding, optical nerve compression, or other related eye problems can lead to blindness. In general, the lifespan of patients with this syndrome is longer than with the other MPS I subtypes. Some Scheie patients have a normal lifespan, although they have significant disability. The average lifespan is limited to their middle decades (Vijay and Wraith 2005).

### *Treatments available for MPS I*

The recommended treatment for Hurler syndrome is hematopoietic stem cell transplantation (HSCT) using either bone marrow or cord blood cells in the first year to 2.5 years of life if a suitable donor is available (Staba et al. 2004; Stapleton et al. 2019). HSCT can prevent and/or reverse many, but not all, of the clinical features of severe MPS I (Muenzer et al. 2009). The outcome for individual patients is dependent on the disease burden at the time of diagnosis and time taken to undergo HSCT. HSCT can improve cognitive outcomes, increase survival, improve growth, reduce facial coarseness and hepatosplenomegaly, improve hearing and prevent hydrocephalus. HSCT has lesser effects on the skeletal and joint manifestations, corneal clouding, and cardiac involvement. It is recommended that patients receive enzyme replacement therapy (ERT) in the time between diagnosis and HSCT to prevent further deterioration of non-central nervous system (CNS) manifestations (Muenzer et al. 2009), although, it is not available through the Life Saving Drugs Program (LSDP) for this indication, as laronidase has not been assessed for subsidy purposes on the LSDP for these patients<sup>1</sup>. ERT alone is not recommended as it cannot cross the blood-brain barrier and thus has no effect on neurological disease manifestations.

Successful engraftment (colonisation of the donated stem cells) would result in the production of the deficient enzyme in cells that circulate in the body and can cross the blood-brain barrier. Enzyme is released by these cells into the bloodstream and is taken up by the cells in various organs where GAGs are metabolised (Hampe et al. 2021). After a successful HSCT, normal IDUA activity can be measured in blood cell lysates and there is a corresponding rapid reduction of heparan sulphate and dermatan sulphate in the

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<sup>1</sup> Life Saving Drugs Program Medicines: Mucopolysaccharidosis Type I (MPS I) Expert Panel Evaluation Overview



blood and urine in most patients (Hampe et al. 2021). However, GAG levels (especially for dermatan sulphate) generally remain above normal reference levels. This is likely due to partial GAG degradation in difficult-to-reach organs; these GAGs will diffuse into the circulation and will eventually be excreted in the urine. Dermatan sulphate stems predominantly from hard-to-reach organs and tissues, such as bone, cartilage, and heart valves. This correlated with the observations that most physical abnormalities, except cardiac valvular and skeletal deformities, are either stabilised or even slowly resolved after successful HSCT. Similarly, the eye is a difficult to reach organ for donor cells, thus HSCT has a limited effect on corneal clouding.

In the brain, donor monocytes differentiate into microglia or brain macrophages after crossing the blood brain barrier to enable the breakdown of GAGs in the CNS, resulting in the preservation of intellectual development. However, replacement of the recipient's microglia by donor-derived cells takes up to one year and deterioration in intellect and development may continue during this transitional period. This emphasises the importance of early treatment in preventing cognitive impairment.

The HSCT procedure has risks for morbidity and mortality associated with it (Keerthiga et al. 2023). Complications such as incomplete colonisation and graft vs host disease can impact the outcomes. Several studies reported that the survival rates for patients with severe MPS I who received HSCT ranged from 63% to 100% at 1-year, and from 78% to 100% at 5-years (Kemper et al. 2015). Without treatment these children would be unlikely to live beyond ten years of age (Braunlin et al. 1992). Further specialist treatments for individual disease manifestations may be required, especially orthopaedic interventions for skeletal deformities and valve replacement surgery (Keerthiga et al. 2023).

ERT by intravenous administration of the recombinant enzyme, laronidase, is the recommended treatment for children who have the attenuated forms of MPS I and is indicated by the TGA for the treatment of non-neurological manifestations of the disease<sup>2</sup>. However, in the current setting, laronidase is only available through the LSDP for MPS IHS and not MPS IH or MPS IS, based on the recommendation of the PBAC. HSCT is discouraged for children with MPS IS because it offers no therapeutic advantage over ERT. ERT has been shown to improve cardiac manifestations, sleep apnoea, liver size, linear growth, range of mobility and visual acuity (Keerthiga et al. 2023; Muenzer et al. 2009). Starting treatment early, before cellular damage occurs is preferred, as once the damage occurs and symptoms become apparent, many disease manifestations are not reversible (Muenzer 2014). Patients with attenuated disease receiving ERT will still require management by a specialist team to treat evolving disease manifestation. In some milder Scheie syndrome cases, where symptoms do not become apparent until adolescence or adulthood, ERT would not be started until these symptoms become apparent. Infusion-related reactions are very common. Thus, pretreatment with antihistamines and antipyretics is recommended (Concolino, Deodato and Parini 2018).

Laronidase does not cross the blood-brain barrier and is therefore ineffective in treating any CNS symptoms. However, trials on the effectiveness of intrathecal delivery of ERT in combination with standard treatment (HSCT) for severe MPS I have shown a reduction in cerebrospinal fluid (CSF) abnormalities

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<sup>2</sup> <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2010-PI-04490-3&d=20240322172310101>

(Eisengart et al. 2019). Another approach taken is to use a IDUA fusion protein, where the fusion partner facilitates the crossing of the blood-brain barrier.

Fusion of IDUA to a monoclonal antibody targeting the human insulin receptor was used in two clinical trials that investigated its effect on cognitive function. One trial enrolled children with severe neurocognitive impairment (NCT03071341). The other trial enrolled children with attenuated MPS I with CNS complications, such as spinal cord compression and/or learning disabilities (NCT03053089). Both trials reported improved or stabilised CNS function (Hampe et al. 2021).

In the absence of either HSCT or ERT, the only other available treatment options for patients with MPS I are to be treated for the individual manifestations of the condition that will appear as the it progresses (Bay et al. 2021; Keerthiga et al. 2023). These may include:

- infant learning programs/special education for developmental delay
- physical therapy
- orthopaedic surgery as needed
- joint replacement for progressive arthropathy
- atlanto-occipital stabilisation
- spinal cord decompression for cervical myelopathy
- cerebrospinal fluid shunting for hydrocephalus;
- early median nerve decompression for carpal tunnel syndrome based on nerve conduction studies before clinical manifestations develop
- special attention to anaesthetic risks
- hats with visors/sunglasses to reduce glare
- corneal transplantation for ophthalmologic involvement
- cardiac valve replacement as needed and bacterial endocarditis prophylaxis for those with cardiac involvement
- tonsillectomy and adenoidectomy for eustachian tube dysfunction and/or upper airway obstruction
- tracheostomy and ventilatory support
- hearing aids as needed
- continuous positive airway pressure (CPAP) for sleep apnoea
- gastrointestinal management for diarrhoea and constipation
- tongue reduction.

#### *Eligibility of accessing ERT in Australia*

Laronidase is listed on the LSDP for treatment of MPS I.

The current LSDP funding conditions for MPS I state that diagnosis must be confirmed by the demonstration of a deficiency of IDUA activity in white blood cells with the assay performed in a NATA-accredited laboratory; or, for siblings of a known patient, detection of two disease-causing variants in the *IDUA* gene.

The patient must present with at least one of the following complications of MPS I to be eligible for treatment with laronidase:

- Sleep disordered breathing: Patients with an apnoea/hypopnoea incidence of > 5 events/hour of total sleep time or > 2 severe episodes of desaturation (oxygen saturation < 80%) in an overnight sleep study.
- Respiratory function tests: Patients with forced vital capacity (FVC) < 80% of predicted value for height.
- Cardiac: Myocardial dysfunction as indicated by a reduction in ejection fraction to < 56% (normal range 56-78%) or a reduction in fraction shortening to < 25% (normal range 25-46%).
- Joint contractures: Patients developing restricted range of movement of joints of > 10 degrees from normal in shoulders, neck, hips, knees, elbows or hands.
- Infants and children aged < 5 years: Applications may be submitted for infants and children not yet demonstrating symptoms consistent with other eligibility criteria where there has been a diagnosis of MPS I, for example by genotyping, with clear prediction of progress of the disease, or if severe disease can be predicted on the basis of a sibling's disease progression.

Note that the Therapeutic Goods Administration (TGA) Product Information for laronidase indicates that its safety and effectiveness in patients below the age of 5 has not been established.

Patients who are not eligible for subsidised treatment with laronidase for the treatment of MPS I through the LSDP are:

- Patients with confirmed MPS IH (including those patients who do not have a suitable HSCT donor) or MPS IS.
- Patients who have significant learning difficulties and/or neuropathic involvement with their disease indicating MPS IH.
- Patients with the presence of another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by ERT.
- The presence of another medical condition that might reasonably be expected to compromise a response to ERT.

The LSDP undertook a review of the use of laronidase, which was considered by the LSDP Expert Panel (the Expert Panel) at its October 2020 meeting and published in 2023 (Department of Health and Aged Care 2023). The Expert Panel found that the current eligibility criteria for access to subsidised laronidase for MPS I are more restrictive than those applying internationally, particularly for use in:

- combination with HSCT
- patients with mild disease (MPS IS)
- patients with presymptomatic disease; or
- patients with severe forms of the disease that includes low cognitive function (MPS IH).

Thus, in the current setting without NBS for this condition, only a proportion of MPS I patients (those with MPS IHS) would be eligible for treatment with ERT through the LSDP. Any expansion to the currently approved LSDP population would require a submission to the PBAC, which would need to assess the medicine as clinically effective in the expanded population before the medicine could be considered for LSDP listing by the Expert Panel.

### Genetics

More than 200 pathogenic variants in the *IDUA* gene that are associated with MPS I are reported in the Human Genome Database and MPS I Registry (Poletto et al. 2018). However, most cases have at least one of 9 pathogenic variants which occur with varying prevalence across different ancestries and continents

(Clarke 2002; Clarke et al. 2019; Kemper et al. 2015; Terlato and Cox 2003). Most of these variants are associated with the severe Hurler phenotype, although some heterogenous variants with W402X and Q70X have been associated with milder, attenuated forms. The most common reported MPS I pathogenic variants in North American, European and Australian patients are W402X (up to 63% of cases) and Q70X (17%); A75T (7%) and 474- 2a-->g (7%) are also frequent in Northern and Eastern Europe (Clarke et al. 1994; Poletto et al. 2018; Terlato and Cox 2003). P533R accounts for 90% of all variants in Morocco and c.1190-1G>A, p.A79V, p.L346R and c.613\_617dupTGCTC are the most frequent variant found in Asian populations (Poletto et al. 2018). Many more *IDUA* pathogenic variants are private (that is, only found in one individual or family), which makes the prediction of severity difficult due to uncertainties in genotype-phenotype correlation in these cases.

Genetic testing of the *IDUA* gene would be undertaken in babies with a positive NBS screen for MPS I. This is important in the prediction of the disease severity and may guide treatment decisions, as well as allowing cascade testing. Best practice guidelines suggest use of genotyping to predict whether patients will have a severe or attenuated phenotype (Kubaski et al. 2020).

### *Pseudodeficiency*

Some individuals will have lower enzymatic activity than the general population, which is referred to as enzymatic pseudodeficiency, but they remain clinically healthy (Burlina and Gragnaniello 2022). This condition is due to polymorphic genetic variants in the *IDUA* gene with reduced function, albeit sufficient function to avoid disease. However, depending on the test methodology and the chosen cut-off level, the reduced function may lead to false-positive NBS screening results (that is, clinically healthy individuals may be falsely classed as NBS positive and would require further testing to diagnose the pseudodeficiency). Pseudodeficiency alleles have a higher frequency than MPS I-causing alleles in the normal population of approximately 0.01–0.02% of screened samples (Burlina and Gragnaniello 2022). Introducing a second-tier test increased the specificity of NBS by reducing the false positives (Polo et al. 2020).

### *Incidence*

Chin and Fuller (2022) reported that in Australia, 1 in 137,000 births are affected by MPS I with a prevalence rate of 0.73 per 100,000 live births between 2009 and 2020. An earlier publication (Nelson et al. 2003) reported that the incidence rate in Western Australia for the period 1969–1996 was estimated to be approximately 1 in 107,000 live births for Hurler syndrome.

According to the MPS Australia website approximately 1 in 80,000 births are affected by MPS I, with Hurler syndrome occurring in about 1 in 88,000 births, Hurler-Scheie syndrome in about 1 in 115,000 births and Scheie syndrome in about 1 in 500,000 births, although they do not provide a source for this information (MPS Australia 2023). The US MPS I<sup>3</sup> website indicates that 61% of MPS I cases are Hurler syndrome, 23% are Hurler-Scheie syndrome and 13% are Scheie syndrome, however no source is referenced.

A review of the use of medicines listed on the LSDP for MPS I was published in January 2023 (Department of Health and Aged Care 2023). The use of laronidase (Aldurazyme®) for MPS I was listed on the LSDP on 1 August 2007. In this report, the Expert Panel noted that the prevalence of MPS I, as estimated in the

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<sup>3</sup> MPSALLFORONE. TYPES OF MPS I. URL: <https://www.mps1disease.com/understanding-mps1/types-of-mps1> [accessed 15 February 2024]

Report, was 1.15 per 100,000 (1 in 86,957) births. This correlates with the data on the MPS Australia website. However, this prevalence may be an underestimate due to undiagnosed individuals with attenuated disease. Scott et al. (2013) reported that the prevalence of MPS I diagnosed via the NBS and confirmed by DNA sequencing among 106,526 newborns included in the Washington State Newborn Screening program was 1 in 35,700 newborns. Another report on the prevalence of MPS I diagnosed via NBS among 248,616 newborns in Italy over an eight-year period to be 1 in 62,154 newborns (Graganiello et al. 2023).

#### *Expected utilisation*

The utilisation of NBS is not expected to alter if MPS I screening is added to the NBS program. However, it is imperative that the addition of new conditions does not adversely impact existing trust and participation.

Uptake of NBS is very high in Australia, with 99.3% of babies screened (Huynh et al. 2022). The number of babies born in Australia has been relatively consistent since 2010, with figures varying between 295,976 in 2020, to 312,548 in 2014 (AIHW 2022), as the population size increases, but the fertility rate (births per woman) decreases. The ABS registered births (ABS 2022) was used to project the estimated number of births per year, 2024–2028.

The total number of babies likely to be referred for diagnostic testing for MPS I after a positive NBS can be estimated based on the following:

The estimated number of newborns diagnosed with MPS I:

- An incidence of 0.73 per 100,000 live births, taken from Chin and Fuller (2022), was used to estimate the number of affected babies (true positives, TP) that would be identified by screening. This would result in 2 babies per year being TP.
- If current diagnostic rates for MPS I are underestimated due to very mild cases that do not become symptomatic until later in adulthood, the incidence may be as high as 2.8 per 100,000 live births (Scott et al. 2013). This would result in 9 babies per year being TP.

Based on these incidence figures, the number of babies receiving each tier of testing in Year 1 has been estimated as follows:

- The number of babies provided first-tier testing is 311,651.
- The false positive (FP) rate for the first-tier enzyme activity analysis was estimated to be 0.008% (Schielen, Kemper and Gelb 2017), meaning 27-34 babies would require second-tier testing.
- The FP rate for the second-tier GAG quantification analysis was estimated to be 0.03% (Schielen, Kemper and Gelb 2017), meaning 3-10 babies would be referred for confirmatory diagnostic testing.
- However, this number may increase if the incidence of MPS I is underestimated due to misdiagnosis of patients with very late onset MPS IS.

*PASC noted the incidence of MPS I was estimated to be between 0.73 and 2.8 per 100,000 live births, and considered the incidence of MPS I was likely underreported due to attenuated MPS IS, which may go*

undiagnosed. PASC noted the PICO estimated that NBS for MPS I would potentially identify 2 to 9 babies per year.

## **Intervention (PICO Set 1)**

### *Screening*

The proposed intervention is the addition of testing for MPS I to the NBS programs. All families are offered NBS for their newborn within 48 to 72 hours of birth. Over 99% of newborns receive NBS, which currently screens for up to 32 rare conditions (The Department of Health and Aged Care 2023).

It is proposed that MPS I be added to existing programs to support early diagnosis and intervention to improve clinical outcomes, noting that under current LSDP criteria, treatment can only be initiated after complications of MPS I have occurred.

Screening for MPS I can be achieved through analysis of the DBS. Currently most international NBS laboratories use a two-tiered screening protocol, with the first tier being an IDUA enzyme activity assay. The two-tiered screening protocol as follows:

- Measurement of IDUA enzyme activity using tandem mass spectrometry (MS/MS) or fluorometry (first-tier screening test)
- Quantification of GAG (dermatan sulphate and heparan sulphate) levels on samples returning a positive first-tier test result (second-tier screening test).

Expert advice has suggested that laboratories are moving towards the use of GAG fragment analysis as the second-tier screen (instead of GAG quantification)<sup>4</sup>.

The NBS enzymatic activity and GAG quantification assays are not considered definitive and confirmatory tests are still required. However, expert advice suggests that the single-tier GAG fragment analysis is definitive. Genetic testing would be performed for the purpose of predicting the severity of disease (whether Hurler syndrome or one of the more attenuated versions); and to facilitate cascade testing in the parents.

A diagnosis will lead to intervention where appropriate, and/or ongoing monitoring and surveillance of at-risk individuals.

*PASC noted that the majority of MPS I is Hurler Syndrome which can be treated by HSCT, where a suitable donor is available, however patients diagnosed with MPS IH or MPS IS through NBS would usually not be eligible to access ERT on the LSDP (as per above description of eligibility for accessing ERT in Australia). PASC therefore considered a key question was whether the proposed screening for MPS I met the decision-making criteria of the NBS NPF, as these include that “there should be an accepted intervention for patients with recognised disease” – yet for some patients diagnosed with MPS I through NBS there would currently be no treatment available for asymptomatic individuals. PASC considered that it is not MSAC’s role to*

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<sup>4</sup> Expert advice received via email on 23/03/23 from the Head of the National Referral Laboratory

*advise on whether the NBS NPF criteria are fulfilled, but that the existence of a therapy and change in management form part of consideration of effectiveness under MSAC's terms of reference.*

#### *Measurement of IDUA enzyme activity in DBS samples (first-tier screening)*

Most lysosomal enzymes are active in rehydrated DBS samples, thus permitting their activities to be measured on samples collected for NBS programs, by either fluorometry or MS/MS (Gelb et al. 2022). A DBS card is punched, and the sample is placed in a tube with buffer containing lysosomal enzyme substrates. The mixture is then incubated at 37°C for a prescribed period prior to measuring the enzymatic activity.

#### *Fluorometric assays:*

Fluorometric assays measure individual enzymatic activity using 4-methylumbelliferyl (4-MU)-glycoside substrates. There is an increase in fluorescence when 4-MU-glycosides are acted on by lysosomal enzymes, enabling quantification of the enzyme products by fluorescence. However, the intrinsic fluorescence of the 4MU-glycoside substrates results in higher background noise than MS/MS assays (Kumar et al. 2015), reducing their analytical range.

#### *Tandem mass spectrometry:*

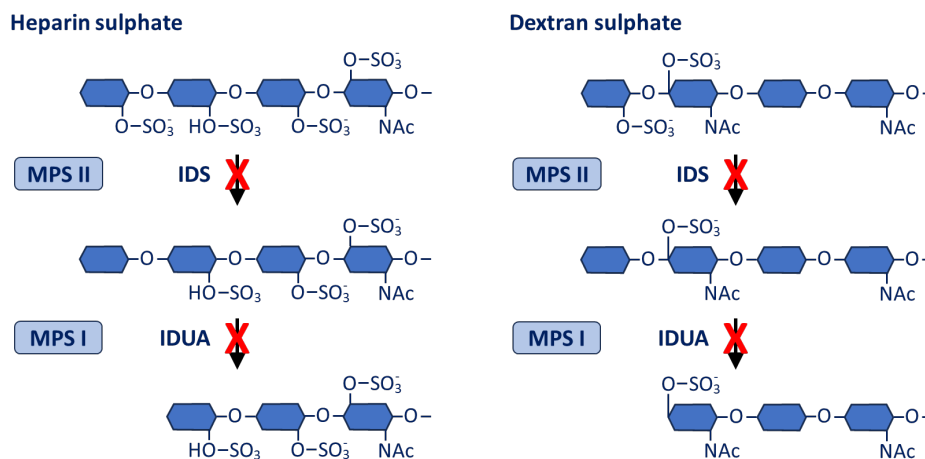
MS/MS-based assays allow for multiplexing (the measurement of multiple analytes at once). There are two MS/MS methods used in NBS for LSDs:

- Flow-injection analysis (FIA)-MS/MS, where the sample is introduced as a bolus injection into the mass spectrometer without the prior fractionation of analytes.
- Liquid chromatography (LC)-combined with MS/MS (LC-MS/MS) where the analytes are fractionated using a liquid–liquid extraction step with ethyl acetate.

Gelb et al (2022) report that the maintenance of LC-MS/MS and FIA-MS/MS instrumentation is similar, and LC-MS/MS has the advantage of allowing for a larger number of diseases to be cost-effectively screened in a high throughput, multiplex assay with an adequate turnaround time. The authors also noted that LC-MS/MS is the 'preferred' method used in commercial production of reagents and kits.

The first laboratory to use LC-MS/MS to quantitate enzyme products as a primary screening test was the Illinois NBS laboratory with a 6-plex LSD assay that measured enzymic activity related to GSD II, MPS I, Krabbe, Fabry, Niemann-Pick-A/B, and Gaucher diseases. This was recently expanded with the addition of iduronate-2-sulfatase (IDS) for MPS-II. There is a requirement for a second assay for MPS II, because the product of IDS enzymic activity is the substrate for IDUA (MPS I), as shown in Figure 1. One 3 mm DBS punch is incubated in an assay cocktail for all enzymes except IDS. A second 3 mm DBS punch is used for the IDS assay. The two assay mixtures are combined prior to analysis in a single LC-MS/MS run per newborn.





**Figure 1 Relationship between the substrate and product of the IDUA and IDS enzymes that are associated with MPS I and MPS II disease**

IDUA =  $\alpha$ -L-iduronidase; IDS = iduronate sulphatase, MPS = mucopolysaccharidosis

Source: Modified from Filocamo et al. (2018)

Screening for MPS I currently occurs in NBS laboratories in the USA, Taiwan, the Netherlands and regions of Italy, using FIA-MS/MS, except Illinois and Utah, where LC-MS/MS is used (Gelb et al. 2022).

### *Analysis of GAG (dermatan sulphate and heparan sulphate) levels and/or subspecies in DBS samples (second-tier screening)*

#### *Determination of endogenous GAG subspecies in the dried bloodspot*

GAG fragment analysis using LC-MS/MS with the derivatising agent, 1-phenyl-3-methyl-5-pyrazolone, can be used on dried bloodspots to identify endogenous non-reducing end GAG subspecies that are reflective of the respective enzyme deficiency, enabling the identification of 10 MPS subtypes, including MPS I (i.e. the same method currently used on urine samples by the National Referral Laboratory, based at the Adelaide Women's and Children's Hospital (AWCH), Genetics and Molecular Pathology laboratory (Herbst et al. 2023)).

#### *Quantification of GAGs in the dried bloodspot*

As the assays to detect IDUA enzyme activity have a low positive predictive value due to the detection of individuals with pseudodeficiencies, samples returning a positive first-tier test result (i.e., samples with low IDUA enzyme activity) would undergo a second tier NBS test to determine the level of GAGs in the DBS samples.

LC-MS/MS assays are used by most NBS programs for second tier testing to improve the specificity of screening tests affected by low positive predictive values (Gelb et al. 2022). This reduces the number of false-positives as a normal result of the second-tier test overrules the first-tier test result. For MPS I, a large proportion of below-cutoff enzyme activity levels detected by first-tier enzymatic activity assays are due to pseudodeficiencies. The quantification of GAGs in a separate punch from the same DBS readily separates true deficiencies from pseudodeficiencies. Individuals with pseudodeficiencies would have normal levels of GAGs in the DBS sample whereas individuals with true deficiencies would have elevated levels.

Schielen et al. (2017) found that the false positive rate for GAG MS/MS quantification analysis for MPS I and MPS II was approximately 0.03%. This is much higher when compared to the false positive rate for the



MS/MS enzyme activity assay (<0.008%). These results suggest that GAG quantification analysis is more appropriate for second-tier analysis following measurement of the enzymatic activity in the DBS.

#### *Single-tier screening protocol:*

With the advent of GAG fragment analysis using DBS samples, at the pre-PASC meeting with co-applicants on 5 March 2024 the clinical expert co-applicants suggested that GAG fragment analysis should be the screening method of choice. This would enable the detection of 10 MPS subtypes, including MPS I (Herbst et al. 2023).

*PASC noted that different screening protocols could be used for identifying MPS I. PASC noted that enzyme levels and GAG quantification were not considered definitive (although GAG fragment analysis is definitive). PASC noted each of the NBS screening laboratories may decide what protocol to use, so there may be variation in methods across Australia. However, for the purposes of enabling assessment, PASC advised that the chosen screening protocol was two-tier screening comprised of first-tier screening for IDUA enzyme activity (using LC-MS/MS), followed by second-tier GAG fragment analysis (either in-house or sent to the National Referral Laboratory). It was noted that most laboratories would not be able to perform the GAG fragment analysis, as it requires a quadruple linear ion trap (QTRAP) and is even more expensive and specialised than other forms of MS/MS. PASC considered that all laboratories would require additional mass spectrometry equipment to provide this screening. PASC noted that two-tiers of screening could be done on one bloodspot, as the bloodspots are 10-11 mm (may depend on jurisdiction), and a 3 mm punch is used.*

*PASC noted a single-tier screening protocol (GAG fragment analysis only) was also raised as a potential future tool for screening. PASC considered that it would be informative to MSAC if the DCAR were able to include a cost analysis and any other relevant evidence on single-tier screening for MPS I, although accepted there was likely to be very little evidence to inform fulsome assessment and so this was more likely to be a discussion piece.*

#### *Method preferred by the Australian NBS laboratories*

The Western Australian NBS Laboratory has indicated that they would use the commercially available NeoLSD™ kit from Revvity<sup>5</sup>. Some form of quality control is required to ensure equal effectiveness across in scope methods used by all five screening laboratories regardless of the screening methodologies used by different laboratories.

*PASC discussed that although commercial kits such as the Revvity NeoLSD kit may be more expensive than in-house tests, they are simpler and faster to implement than developing an in-house test, and there may be benefits from multiplexing with other conditions (e.g. multiplexing MPS I and GSD II).*

The Western Australian NBS Laboratory also indicated that a locally performed second-tier test is not warranted due to the small number of positive screening results expected. Instead, second tier testing of the DBS (GAG analysis) would be referred to the Adelaide Women's and Children's Hospital (AWCH) Genetics and Molecular Pathology, National Referral Centre for LSD. They have also indicated that third

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<sup>5</sup> NeoLSD™ MSMS Kit [URL: https://www.revvity.com/product/neolsd-msms-kit-3093-0020](https://www.revvity.com/product/neolsd-msms-kit-3093-0020) last updated 2023. Accessed 11 December 2023.

tier genetic sequencing would also be performed. However, it is unclear if this would be on the original DBS sample or if a new sample would be required.

Targeted consultation feedback from the National Referral Laboratory (the same laboratory that performs NBS for South Australia, the Northern Territory and Tasmania) reported that they would use a single-tier screen for the specific GAG fragments (see Single-tier screening protocol above). This is able to distinguish between different types of MPS.

*PASC discussed that although the Northern Territory, the Australian Capital Territory and Tasmania do not have their own NBS screening laboratories, equitable access to NBS is not a problem, as samples are sent interstate. PASC considered equity of access to downstream diagnostic testing and ongoing care is a greater equity concern, although telehealth assists with that.*

#### *Confirmatory diagnosis of MPS I*

Babies with a positive screening test would be referred to a metabolic clinic for further testing. If GAG fragment analysis has not been performed, then confirmatory testing would include urine GAG fragment analysis or quantification of GAG levels and leukocyte IDUA enzyme activity testing, as per the comparator. Only those who are positive on further testing would be diagnosed with MPS I.

Diagnostic testing would involve enzyme assay and/or genetic testing, which can be useful for predicting the severity of disease, and genetic testing can also be useful for facilitating cascade testing. Hurler syndrome (where there is a complete loss of IDUA enzyme activity) is often associated with two common variants, so rapid genotyping could be useful to detect the variant/s in some patients (allowing faster turnaround of results than sequencing).

*PASC noted that although the head of the National Referral Laboratory had advised that assessing IDUA enzyme levels in leukocytes was not required for diagnostic purposes (if GAG fragment analyses have been performed), the actual enzyme level provides some useful prognostic information. Given the need for a confirmatory test and that the subsidised treatment, laronidase via the LDSP (if eligible), is very expensive, the cost of the test for the enzyme activity test seemed reasonable. It is also currently required for access to laronidase for ERT via the LSDP.*

Tertiary care for MPS I requires ongoing care and counselling from specialised metabolic clinics to determine the best clinical management pathway for each child. This includes initial treatment with HSCT or ERT (as appropriate for the disease subtype) and ongoing care from multidisciplinary teams through the public hospital system to treat specific symptoms as they emerge.

If MPS I is added to the NBS programs in Australia, additional funding would be required for metabolic clinics, to enable them to handle the additional workload, especially that generated by babies diagnosed with late onset MPS I disease.

#### **Comparator (PICO Set 1)**

The comparator to universal NBS for MPS I is no screening for MPS I through NBS programs. Diagnosis would occur as per current clinical practice, following presentation with symptoms consistent with MPS or

being investigated due to having a family history of MPS I (e.g. a sibling with a diagnosis of MPS I). Those investigated due to symptoms are considered under PICO set 1, and those investigated due to having a family history of MPS I are considered under PICO set 2.

Current diagnostic tests include:

- Urine GAG analysis:
  - Quantification of urinary GAGs (elevated urinary GAGs measured by colorimetric detection reaction is usually the first diagnostic indicator of a MPS disorder) and/or
  - A urinary GAG fragment analysis using LC-MS/MS with the derivatising agent, 1-phenyl-3-methyl-5-pyrazolone, is conducted to identify endogenous non-reducing ends from the GAGs that are reflective of the respective enzyme deficiency, enabling the identification of 10 MPS subtypes, including MPS I. This method has been used in AWCH, Genetics and Molecular Pathology laboratory, since receiving NATA accreditation in 2017 (Fuller 2020).
- A leukocyte IDUA enzyme activity test is conducted to confirm a positive result from the urine GAG analysis<sup>6</sup>. Typically, the substrate used is a synthetic analogue harbouring a fluorescent label which is released as a result of enzyme action. The enzymatic reaction is stopped, and the intensity of fluorescence is measured.
- Those who are found to have MPS I receive genetic testing (sequencing of the *IDUA* gene) to identify the *IDUA* variants responsible for the disease. In the majority of cases, the genotype may assist in the prediction of the phenotype.

Expert opinion from the Head of the National Referral Laboratory has suggested that the use of GAG fragment analysis would mean confirmatory diagnosis using leukocyte IDUA enzyme activity level would not be required. However, the current eligibility criteria for laronidase through the LSDP requires that the diagnosis of MPS I be confirmed through by the demonstration of a deficiency of IDUA enzyme activity in white blood cells with the assay performed in a NATA-accredited laboratory; or, for siblings of a known patient, detection of 2 disease-causing variants.

*PASC accepted that the comparator is diagnostic testing following onset of signs and symptoms or a family history of MPS I (no universal NBS).*

### **Reference standard (PICO Set 1)**

In order to determine the accuracy of screening, the suggested reference standard would be diagnostic testing (both biochemical and genetic testing) following clinical assessment.

*PASC accepted that the reference standard is existing diagnostic testing following diagnosis based on signs and/or symptoms.*

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<sup>6</sup> SA Pathology. Pathology Collection Guide. URL:

<https://www.sapathology.sa.gov.au/wps/wcm/connect/SA+Pathology+Internet+Content+New/Content/Clinicians/Pathology+Collection+Guide/> [accessed 20 February 2024]

## **Outcomes (PICO Set 1)**

Screening test performance:

- Diagnostic accuracy of the screening test (sensitivity, specificity, positive predictive value)
- Diagnostic yield and proportion of cases with a genotype that can predict a severe phenotype

Change in management:

- Age at diagnosis
- Age at treatment initiation (and whether prior to, or after symptom onset)
- Investigations/monitoring/treatments received (e.g. HSCT)

Clinical Effectiveness:

- Impact of the change in management (i.e. Improvement in morbidity and mortality, quality of life, general functioning and disease manifestations from early diagnosis, intervention, and/or avoidance of the diagnostic odyssey)
- Value of knowing (harms/benefits to the individual or family members from earlier diagnosis)

Safety (physical harms to newborn of screening test, diagnostic test or subsequent treatment):

- Impact of false positive screening results (physical harms to the infant or psychological harms to the parents)
- Impact of false negative results
- Impact of diagnosing mild cases or private variants not previously associated with MPS I
- Safety of haematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT)
- Any potential risk of harm from ongoing monitoring and surveillance

Economic and Financial Implications:

- Cost-effectiveness (cost per diagnosis; cost per quality adjusted life year (QALY))
- Financial impact of screening, relative to existing practice (including impact of false positives, savings from early intervention and/or change in treatment approach, ongoing monitoring and surveillance of patients with MPS I and any potential risk of harm)

Other relevant considerations:

- Value of knowing (harms/benefits to the individual or family members from earlier diagnosis)
- Ethical considerations (equity of access, considerations regarding consent)
- Organisational considerations (incremental impact of NBS on organisations, particularly the impact on services for monitoring late-onset disease, or on the NBS programs, including programmatic implementation considerations)

The Expert Panel reviewing the use of laronidase through the LSDP found that the clinical treatment outcomes that are most important to patients and their families include improvement in symptoms, general functioning and quality of life (Department of Health and Aged Care 2023). These outcomes were

reported to be aligned with the clinical trial outcomes. The Expert Panel reported that the data available to estimate the survival benefit of treatment with laronidase was limited.

*PASC noted that issues such as workforce capacity are out of scope of this assessment.*

*PASC noted that the LSDP criteria as they stand are outside the scope of the MSAC process, so the DCAR should use the current LSDP criteria. PASC noted changes to the LSDP criteria require a submission to both the PBAC and the LSDP Expert Panel. PASC advised that in future, where NBS applications involve a corresponding change to a therapy, a codependent application is required. Currently, for index cases with MPS IHS, ERT is only available after disease complications occur, which limits the potential benefit of early diagnosis due to NBS in this subgroup. If MPS IHS cases have a genotype with an established genotype-phenotype correlation of severe disease then ERT may be accessed through the LSDP. The assessment should therefore consider what proportion of cases with MPS IHS would have a genotype corresponding to a known severe phenotype. Out of session, PASC noted the clinical expert co-applicant advice that if a newborn is identified with the severe form of MPS I they would be considered for bone marrow transplantation and not long-term enzyme therapy. There may be a request for enzyme therapy for the period of pre-transplantation only – which is current practice, although not funded through the LSDP for these patients as above.*

## **PICO criteria (PICO Set 2)**

When an individual is diagnosed with MPS I, current practice for cascade testing is genetic testing of the parents and biochemical testing or genetic testing of their siblings. This would also occur if the index case is identified via NBS. However, earlier identification of disease in a newborn may lead to earlier detection of a condition in asymptomatic siblings or earlier intervention with assisted reproduction techniques such that future siblings would be free of the condition. The clinical claim is that cascade testing after a diagnosis of MPS I based on NBS would have superior effectiveness and non-inferior safety to cascade testing after diagnosis of MPS I due symptomatic presentation.

### ***Population (PICO Set 2)***

MPS I is autosomal recessive, therefore, both parents of an affected newborn with two pathogenic variants can be assumed to be carriers, with a one in four chance that any siblings and future offspring would also be affected.

When a newborn is diagnosed with MPS I, it is proposed that genetic testing to detect the variants identified in the child is offered to parents, aunts and uncles to allow for further reproductive planning.

Older siblings of the affected newborn may themselves also be affected, most likely with attenuated disease, as the median age at diagnosis of severe disease is around one year of age. When unaffected siblings reach reproductive age, they may elect to undergo cascade testing for carrier status, and if required, partner testing through an appropriate clinic for family planning purposes. This would most likely occur at a cost to the sibling.

It may be appropriate for members of the broader family (the parents' siblings and/or biological nieces and nephews) to also seek cascade testing to determine carrier status for reproductive planning purposes.

### *Expected utilisation*

According to calculations conducted for PICO Set 1, the number of babies diagnosed with MPS I per year was estimated to be 2 - 9 babies (see expected utilisation in the population section for PICO Set 1 above).

Thus, the parents of the 2-9 babies would be offered cascade testing in the first year. That would be a total of 4-18 cascade tests.

The average number of dependent children in an Australia household was reported to be 1.2 in 2020 according to the CEIC Global Database<sup>7</sup>. Thus, each family is expected to have 1-2 children. If we take a conservative approach and assume that each positive baby had one sibling, no more than 2-9 siblings would require cascade testing. According to Mendelian recessive inheritance patterns, 25% of the tested siblings would be expected to have MPS I and an additional 50% would be carriers.

Thus, it would be expected that 0-3 siblings of babies diagnosed via the NBS would be diagnosed with MPS 1 after biochemical testing and would be offered cascade testing. Under the current and proposed cascade testing scenarios, between 4 and 21 cascade tests would therefore be conducted per year. However, this number may be higher if the incidence of MPS I is currently underestimated.

*PASC noted that if there are 2 – 9 babies diagnosed with MPS I per year due to NBS, there would be 4 to 18 parents to be eligible for cascade testing. If there is also one sibling per index case, this suggests 2 – 9 siblings may be eligible for cascade testing per year.*

*PASC agreed that cascade testing for parents and siblings would be assessed. Out of session, PASC considered that in practice the aunts and uncles of an NBS-diagnosed case also commonly seek testing, as they are usually of a similar age and have reproductive concerns for their own families. PASC therefore advised the cascade testing population considered for the assessment should also include the newborn's parents' siblings.*

### **Intervention (PICO Set 2)**

The proposed intervention of cascade testing is the same as the comparator, which is current clinical practice. The key difference is the timing of cascade testing, which would occur earlier when the index case<sup>8</sup> is diagnosed due to NBS rather than presenting with signs/symptoms.

The intervention for the parents, aunts and uncles of a newborn diagnosed with MPS I through NBS is genetic testing for the specific pathogenic variants identified in the newborn. Genetic testing to determine the presence of specific pathogenic *IDUA* variants is usually conducted using targeted sequencing

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<sup>7</sup> CEIC. Australia Average Number of Dependent Children in Household: Multiple Family. Available from URL: <https://www.ceicdata.com/en/australia/survey-of-income-and-housing-average-number-of-dependent-children-in-household-by-family-composition/average-number-of-dependent-children-in-household-multiple-family#:~:text=Bureau%20of%20Statistics-,Australia%20Average%20Number%20of%20Dependent%20Children%20in%20Household%3A%20Multiple%20Family,of%201.400%20Person%20for%202018> Accessed 8 February 2024.

<sup>8</sup> Note: "index case" is used in this document to mean the first person in a family detected as having the condition (through diagnostic testing after NBS, but not following symptoms or cascade testing)

methods. Referral for genetic counselling and reproductive advice, as well as assisted reproductive technology would be provided if desired.

Siblings would be offered biochemical testing (urine GAG fragment analysis) or genetic testing if considered at risk of having MPS I.

*PASC noted the proposal for cascade testing of siblings was that biochemical testing precede genetic testing, however in out-of-session input on the clinical management algorithms following the PASC meeting, clinical expert co-applicant advice was that siblings could receive cascade testing using either method, because two P/LP variants will not always be identified in the index case or proband. However PASC noted (out of session) DNA sequencing detects 97% of disease-causing variants in MPS I<sup>9</sup>, therefore considered that not detecting two P/LP variants would be rare. PASC considered that when the index case initially has 1 P/LP variant and 1 VUS, biochemical and functional analysis during diagnostic testing may provide evidence to re-classify the VUS as a LP variant. PASC agreed with the clinical expert co-applicants that if the VUS was unable to be re-classified, then genetic testing of at-risk siblings for the one known P/LP variant would not distinguish carrier siblings from affected siblings, although urinary GAG fragment analysis could. PASC (out of session) therefore accepted the clinical expert advice and advised the cascade testing intervention for siblings was biochemical testing or genetic testing.*

The number of parents tested may increase by 50-100% if MPS I is currently underdiagnosed. Particularly if babies with very late onset attenuated MPS I are identified as newborns; parents are more likely to be concerned about their disease progression in early childhood and may still be planning on having another child, compared to when diagnosis occurs when the child is a teenager or young adult. Additionally, there may be some initial shift towards earlier cascade testing in the first few years for some families if screening for MPS I is added to the NBS program, as the babies would be diagnosed prior to the onset of clinical symptoms.

*PASC noted that the method of cascade testing would differ between the parents (where the intention is to detect carrier status) and the siblings (where cases but not carriers are detected). PASC discussed that if only one parent is identified as a carrier, the second variant in the index case could be a de novo variant or could be due to a non-paternity event.*

*PASC discussed if cascade testing results are positive, that advice and referrals for family planning would be required. Additional multi-disciplinary team care would be required, and PASC noted that some of the additional funding announced for the expansion of NBS was for the downstream implications of screening (i.e. not only for the screening itself).*

### **Comparator (PICO Set 2)**

Currently, cascade testing involves a two-step approach.

1. Genetic testing for the specific familial pathogenic variants is offered to parents, aunts and uncles after the diagnosis of a symptomatic child within the hospital system. Genetic counsellors are rarely

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<sup>9</sup> Clark LA. Mucopolysaccharidosis Type I. 2002 Oct 31 [Updated 2024]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1162/>

associated with metabolic clinics in current practice in Australia. If the parents, aunts and uncles wish for further family planning advice, they may be referred to an appropriate clinic.

2. Older siblings of the affected newborn considered to be at risk of being affected receive biochemical testing (urine GAG analysis) or genetic testing. If the sibling is diagnosed with MPS I, it will most likely be attenuated disease, as the median age at diagnosis of severe disease ranges from 0.8 to 1.0 year of age.

Siblings are not proposed to be offered cascade testing to determine carrier status.

*PASC noted that the comparator was the same as the intervention, with the only difference being the timing.*

### **Outcomes (PICO Set 2)**

Test outcomes:

- Number of family members who uptake cascade testing
- Age at diagnosis/treatment of affected siblings

Clinical Effectiveness of cascade testing:

Effectiveness of early vs late monitoring/treatment (for affected siblings) Safety of cascade testing:

- Physical or psychological harms arising from earlier diagnosis, monitoring and treatment for siblings diagnosed with MPS I following cascade testing, including the impact of diagnosing siblings with attenuated disease who may not become symptomatic for many years.

Economic and Financial Implications of cascade testing:

- Cost-effectiveness
- Financial impact of early vs late cascade testing
- Total Australian Government health care costs

Other relevant considerations:

- Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family)
- Ethical considerations (considerations regarding cascade testing, including notification of carrier status)
- Organisational considerations

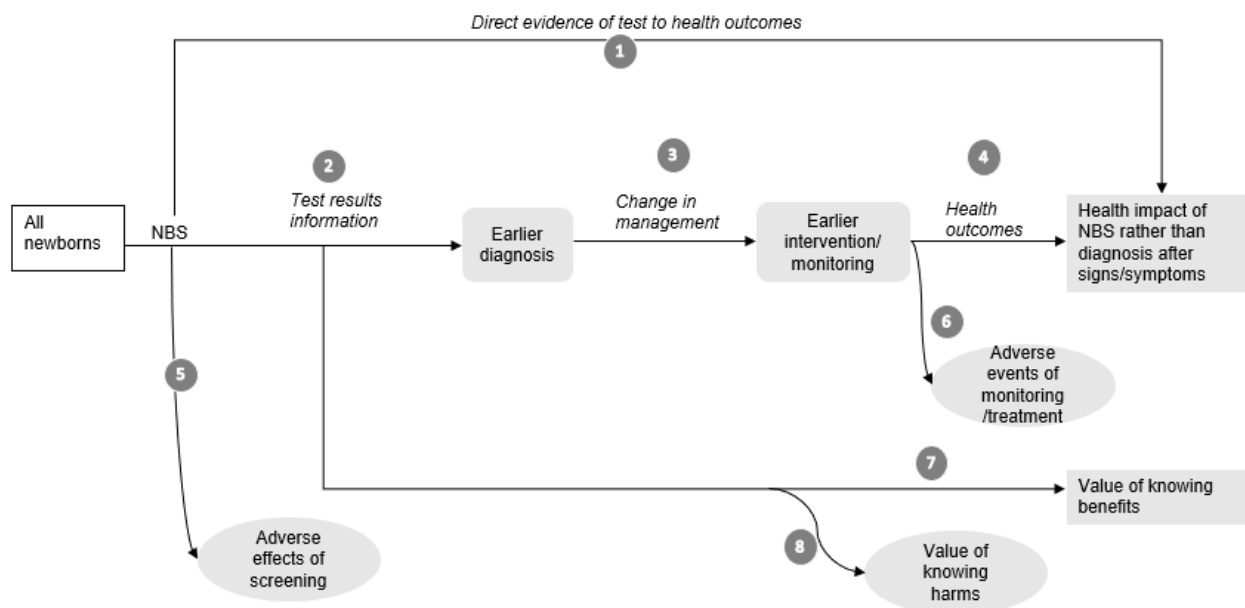
*PASC acknowledged that the outcomes included the ability for family members to use the information for reproductive purposes.*

## **Assessment framework (for investigative technologies)**

The NBS programs are a form of universal (or population) screening. As universal screening programs are considered to be associated with a high financial risk, MSAC has a clear preference for 'direct from test to health outcomes' evidence (MSAC 2021). However, the NBS NPF (Appendix A) also provides a set of



guiding criteria to be addressed in the assessment of adding or removing conditions from the NBS programs that include elements of linked evidence. Therefore, although limited 'direct from test to health outcomes' evidence is available on this topic, a linked evidence approach will also be used.



**Figure 2 Assessment framework showing the links from the test population to health outcomes**

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: adverse events due to testing; 6: advents due to changes in management (monitoring/treatment); 7: value of knowing (benefits) 8: value of knowing (harms)

The assessment questions related to the HTA assessment framework for PICO set 1 are:

1. Is there direct from screening to health outcomes evidence to support the claim that NBS leads to improved health outcomes?
2. Test accuracy: When compared with diagnostic testing as the reference standard, what is the accuracy of NBS screening for identifying patients with MPS I? What are the implications of discordances among the test results?  
What proportion of patients are diagnosed with MPS I prior to symptom development due to NBS or no NBS?
3. Do the NBS test results impact the clinical management of the individual (in either the timing or the type of monitoring/treatments used), compared with diagnosis after symptom onset?
4. Does the change in the clinical management (monitoring and early treatment with HSCT, and/or ERT (as appropriate) improve health outcomes (morbidity, mortality, QoL)?
5. What are the adverse events associated with NBS for detection of MPS I, when compared to the current practice of no screening and diagnosis after symptom onset? (*no incremental safety issues expected for the baby as bloodspots already collected, but any additional false positive results may result in psychological harms to the individual and/or their parents*)
6. What are the adverse events associated with the monitoring and treatment of individuals diagnosed with MPS I through NBS?

7. What value of knowing is there for patients with an MPS I diagnosis, diagnosed early due to NBS? *(this may be relevant for attenuated MPS subtypes not otherwise diagnosed prior to symptom onset)*
8. What harms come from the knowledge of MPS I status? *(this may be relevant for attenuated MPS subtypes not otherwise diagnosed prior to symptom onset)*

### ***Other relevant considerations***

Proposals considered by MSAC can have aspects that are unique to the proposed technology, circumstances of use or funding arrangement, such that MSAC is unlikely to have considered the factors previously in the same context. Other relevant considerations should be explored in section 5 of the assessment report.

Additional information relevant to decision-making that is not captured elsewhere in the assessment is anticipated to include:

- Are there any additional implementation issues, such as:
  - The costs of purchasing equipment and training additional personnel, that are required for screening for this condition?
  - Additional resources and personnel required by metabolic clinics for the increased workload for managing and counselling babies identified pre-symptomatically via the NBS and who may not develop symptoms until adulthood.

*PASC noted that the outcomes for assessment were structured in such a way assuming a linked evidence assessment.*

*PASC noted that the assessment should be underpinned by the NBS NPF criteria.*

## **Clinical management algorithms**

### ***Current clinical management algorithm (PICO Set 1)***

The current clinical management algorithm is based on the general guide published by Muenzer et al. (2009). The authors noted that specific patient circumstances, such as treatment availability and the patient's unique clinical situation, must always be factored into treatment decisions. They indicated that a child of 2 years of age with a developmental quotient (DQ) under 70 could still be a good candidate for HSCT if his or her DQ was decreased by very poor motor skills resulting from non-CNS manifestations of severe MPS I.

HSCT has also been used to treat patients with Hurler-Scheie who are at risk of progressive neurocognitive impairment (Parini et al. 2017). Expert opinion indicated that this is not used in Australian clinical practice, therefore, it has not been included in the algorithm.

In the current management algorithm, children presenting with symptoms consistent with MPS I undergo diagnostic testing. The level of urinary GAGs is elevated in patients with any MPS disorder, so detection of increased urinary GAGs has historically been the first diagnostic indicator of an MPS disorder. However,

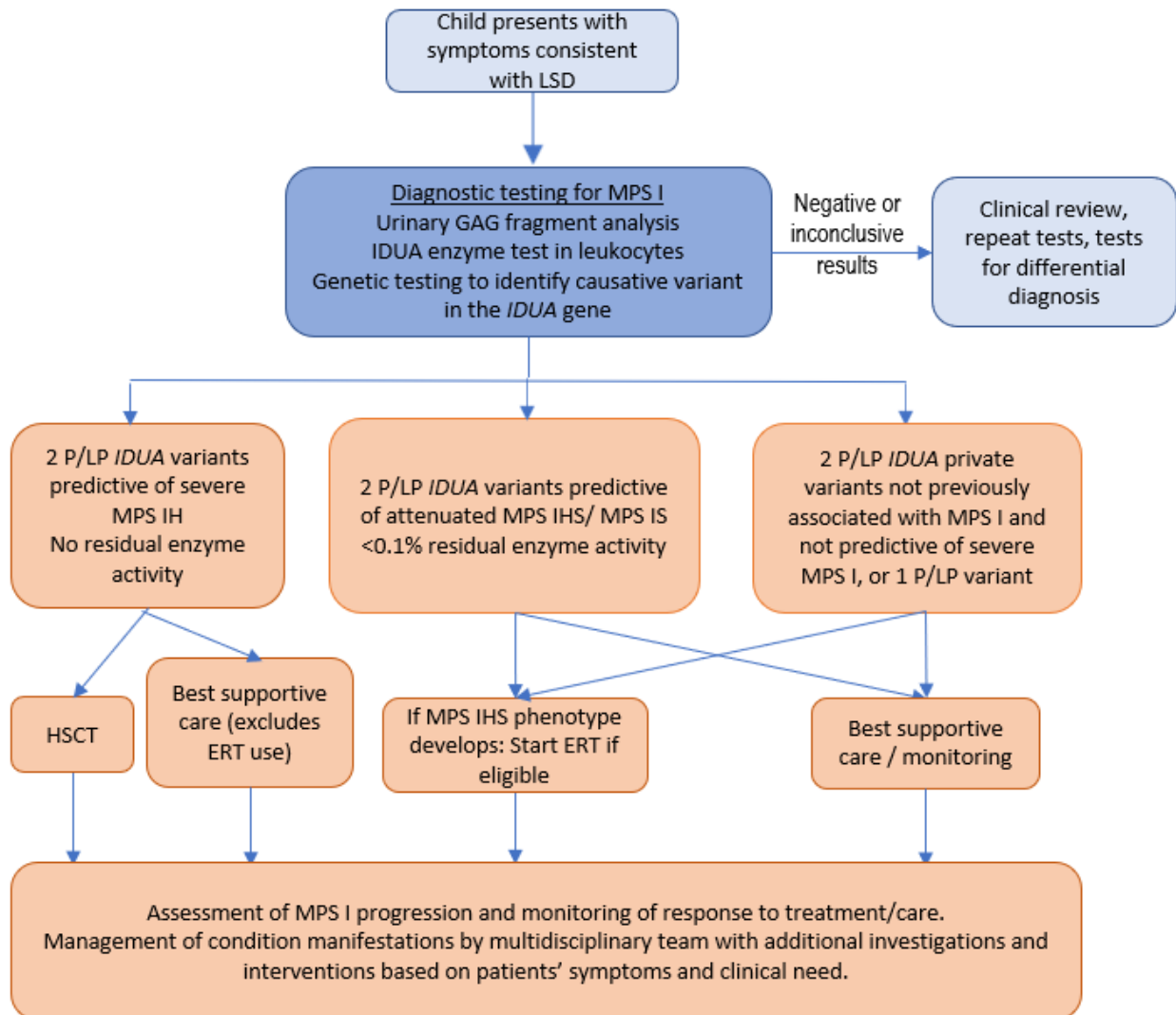
elevated urinary GAGs are not diagnostic. This has been removed from the algorithm, in favour of urinary GAG fragment analysis.

The National Referral Laboratory is now performing urinary GAG fragment analysis using LC-MS/MS with a derivatising agent to detect the non-reducing ends and measure the level of native GAG fragments present. Each MPS type have a specific non-reducing end reflective of the respective enzyme deficiency. This approach allows identification of 10 subtypes, including MPS I.

A leukocyte enzyme activity test may then be conducted. Those with very low or no enzyme activity (0-0.1%) are considered to have MPS I. Advice from the National Referral Laboratory has suggested that this is no longer required for diagnostic purposes. However, in order for patients with MPS IHS to be eligible for access to laronidase through the LSDP, they need to have a documented deficiency of IDUA enzyme activity. Those who are found to have MPS I receive genetic testing to identify the pathogenic *IDUA* variants responsible for the disease. Some patients will have *IDUA* variants immediately identifiable as pathogenic or likely pathogenic, but others will have VUS significance. This is due to most *IDUA* pathogenic variants being private (note: although most variants are private, the majority of patients have at least one common pathogenic variant). Thus, the VUS identified in patients who have been biochemically diagnosed with MPS I (i.e. elevated GAGs and no or very low enzyme activity) may be able to be reclassified as being pathogenic or likely pathogenic.

Individuals diagnosed with MPS IH are assumed to be treated with HSCT if a suitable donor is available, and those with MPS IHS may receive ERT if their symptoms are severe enough to meet the LSDP criteria. Alternatively, if they have MPS IHS and a genotype that predicts severe disease (e.g. if they have the same variants as a sibling with severe disease), they may also be eligible for ERT (Figure 3) prior to the onset of symptoms. It may not be appropriate to treat some patients with mild, very late onset forms of MPS IS with ERT, and these patients cannot access ERT through the LSDP. As MPS I is a progressive disease, further treatments for specific manifestations will be required. In the absence of either HSCT or ERT, these specific treatments are the only other available treatment options for MPS I. These treatments may involve surgery, physical therapy, and/or developmental stimulation.

Those who are found to not have MPS I will undergo further evaluation for other diseases with similar or overlapping symptoms.



**Figure 3 Current clinical management algorithm**

ERT = enzyme replacement therapy; DQ = developmental quotient; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA =  $\alpha$ -L-iduronidase; LSD = lysosomal storage disorder; MPS I = mucopolysaccharidosis type I; VUS = variants of uncertain significance. Source: modified from Bay et al (2021), Fuller (2020), Muenzer et al (2009), and Stapleton et al (2019); and updated Post PASC (out of session) in response to advice received from clinical expert co-applicant on 22/05/24

### **Proposed clinical management algorithm (PICO Set 1)**

The proposed clinical management algorithm is shown in Figure 4. Testing for MPS I as part of the NBS programs allows for early detection and treatment, prior to symptom onset, in affected babies to support improvement in clinical outcomes for these children.

There are no other feasible mechanisms currently available for supporting early diagnosis of MPS I beyond cascade screening of relatives of known cases and prenatal testing of subsequent pregnancies. As an ultra-rare recessive condition, the large majority of cases are not detected through this pathway and are consequently diagnosed clinically after onset of symptoms.

Newborns who receive an abnormal screening result for MPS I through NBS would receive confirmatory diagnostic testing at a specialist metabolic disorders clinic. The confirmatory diagnostic tests used for the proposed algorithm are the same as the diagnostic tests used for the current algorithm (urine GAG fragment analysis, leukocyte IDUA enzyme activity test).

Those who are diagnosed with MPS I receive genetic testing to identify the pathogenic *IDUA* variants responsible for the disease. VUSs identified in patients who have been biochemically diagnosed (i.e. elevated GAGs or GAG fragments that indicate MPS I and no or very low enzyme activity) may be able to be reclassified as being pathogenic or likely pathogenic. In most cases, the genotype may help predict whether the phenotype is severe (Hurler syndrome) or milder (either Hurler-Scheie or Scheie) (Kubaski et al. 2020). However, prediction of disease severity is unlikely to be made on the basis of the private variants previously not associated with MPS I.

Those found to not have MPS I after confirmatory testing require no further intervention (false positive NBS) but their parents may require psychological support and follow up.

Those diagnosed with MPS I would receive clinical care, including earlier access to treatment with HSCT and/or ERT where (and when) appropriate, before the appearance/progression of somatic or neurological damage due to GAG accumulation. Those with known mild forms of MPS I, where symptoms are not expected to appear until later in life, would receive continued surveillance. Patients and their family would benefit (or be harmed) from the value of knowing and a reduction in their diagnostic odyssey.

Approximately two thirds of the newborns diagnosed with MPS I will have the severe Hurler syndrome (Kemper et al. 2015) and are expected to benefit from an earlier diagnosis via the NBS. Diagnosis will allow earlier pre-symptomatic treatment with HSCT which will likely prevent or significantly slow neurological decline. The extent of this benefit is difficult to define. Although there is some evidence that indicated earlier treatment with HSCT improved survival at 1-year post transplant and neurological outcomes, a systematic review by Kemper et al. (2015) found that, without newborn screening, the results may be confounded because more severe cases were more likely to be diagnosed earlier but are also more likely to have worse outcomes because of the higher level of underlying disease.

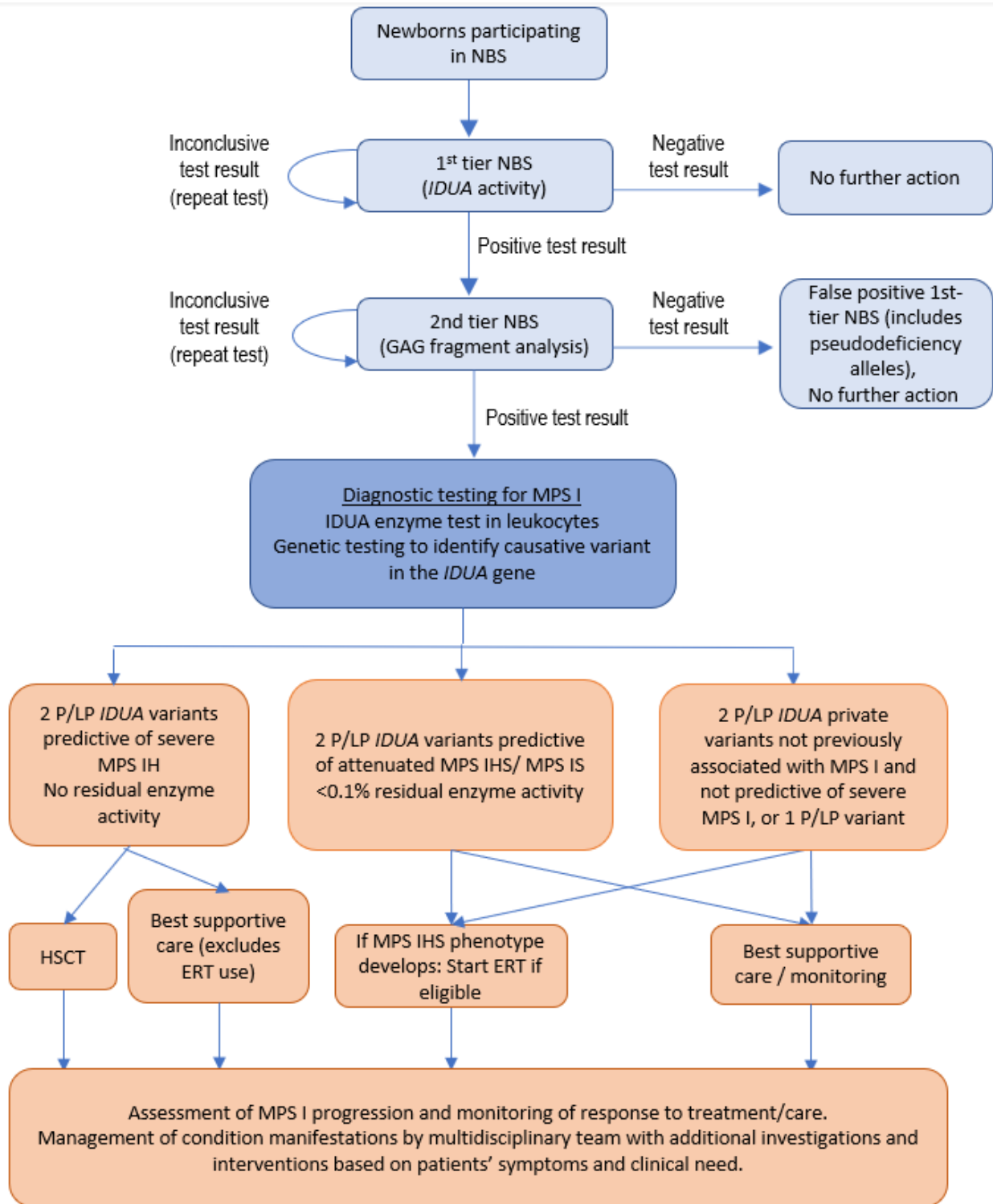
Newborns diagnosed with the MPS IHS may also benefit from earlier ERT. The systematic review by Kemper et al. (2015) reported on two case reports on siblings diagnosed with attenuated MPS I. In both cases the symptomatic diagnosis of the older sibling enabled the pre-symptomatic diagnosis of the younger sibling. Both reports found that when ERT was started in the younger sibling prior to the

development of symptoms (at 4 and 5 months of age), the disease progression was greatly reduced compared to the older sibling. At 5-years follow-up both younger siblings showed minimal clinical evidence of disease, compared to their older siblings who started treatment at 5 and 6 years of age.

Some newborns with the mildest attenuated form of Scheie syndrome may not present with any symptoms until adulthood. These individuals are likely to undergo years of anxiety and follow-up testing for the development of symptoms that may never manifest. It should be noted that testing children for adult-onset genetic diseases is not usually considered appropriate (Botkin et al. 2015).

As MPS I is a progressive disease, further treatments for specific manifestations would occur as required. These treatments may involve surgery, physical therapy, and/or developmental stimulation. However, the early pre-symptomatic treatments may mitigate symptom development and reduce the requirement for these interventions as the disease progresses.

As the symptoms of MPS I can mimic many other conditions, the current method of diagnosis after symptoms develop is associated with a diagnostic odyssey. Conversely, for a presymptomatic child with a positive NBS screening test, the diagnostic odyssey would be avoided. The tests undertaken after a NBS positive result would be specifically directed towards a diagnosis of MPS I and other tests that would have been used to diagnose or rule out other diseases that have similar or overlapping symptoms would not be undertaken.



**Figure 4 Proposed clinical management algorithm (PICO Set 1)**

ERT = enzyme replacement therapy; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA =  $\alpha$ -L-iduronidase; NBS = newborn bloodspot screening; MPS I = mucopolysaccharidosis type I; VUS = variants of uncertain significance.  
 Source: modified from Costello Medical (2019), Bay et al (2021), Fuller (2020), Muenzer et al (2009), and Stapleton et al (2019); and updated Post PASC (out of session) in response to advice received from clinical expert co-applicant on 22/05/24

*PASC advised that the proposed clinical management algorithm for PICO set 1 should be amended, to remove the single-tier screening protocol (which was likely to have little evidence), leaving the chosen two-tier screening protocol.*

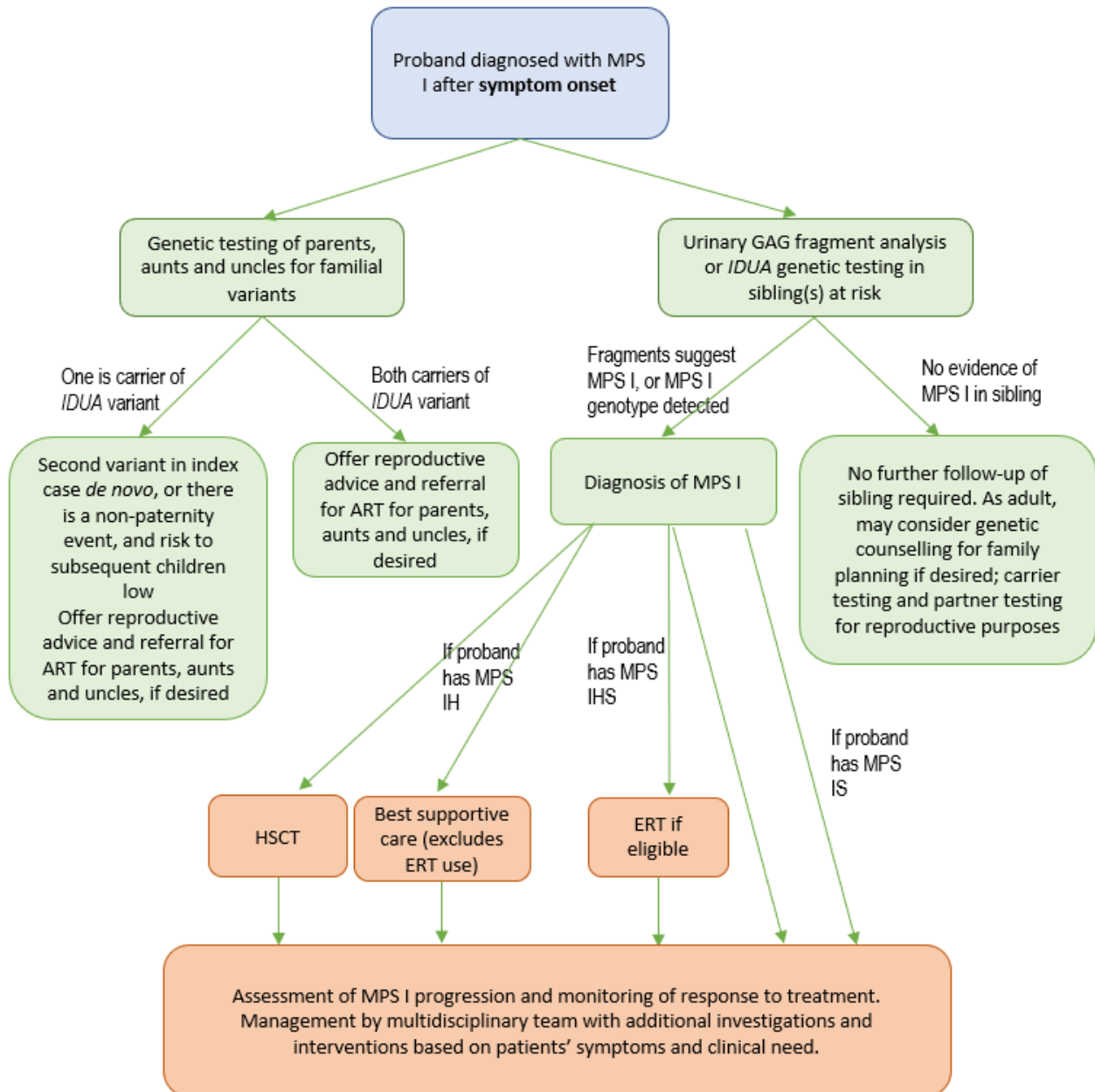
*The current and proposed pathways for PICO set 1 should incorporate the option of 'best supportive care', as there are some patients unsuitable for HSCT or ERT (with development below the DQ threshold).*

*PASC acknowledged that there are currently no Australian treatment/care guidelines for attenuated forms of MPS I identified early through NBS.*

### ***Current clinical management algorithm (PICO Set 2)***

The parents, aunts and uncles, of a child diagnosed with MPS I after symptom onset are offered cascade genetic testing for the familial variant/s. Siblings considered to be at risk would be offered biochemical testing or genetic testing. Siblings may be diagnosed with MPS I based on urine GAG analysis and/or leukocyte enzyme activity level and/or detection of a MPS 1 genotype.





**Figure 5 Current clinical management algorithm (PICO Set 2)**

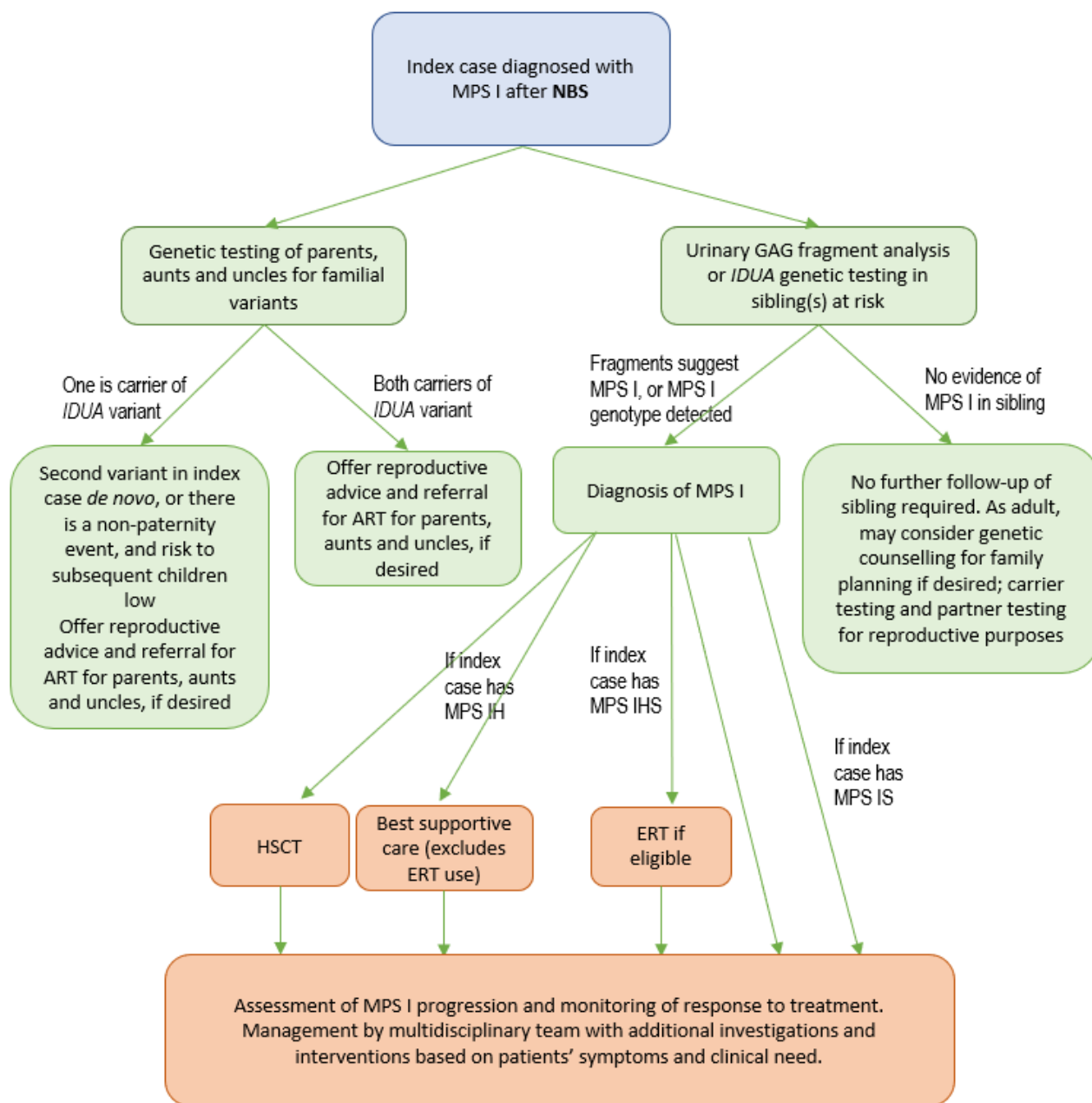
ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA =  $\alpha$ -L-iduronidase; MPS I = mucopolysaccharidosis type I.

Source: updated Post PASC (out of session) in response to advice received from clinical expert co-applicant on 22/05/24

**Proposed clinical management algorithm (PICO Set 2)**

The parents, aunts and uncles of a child diagnosed with MPS I after NBS are offered cascade genetic testing. Older asymptomatic siblings who test positive based on urine GAG fragment analysis or have P/LP variants of the *IDUA* gene diagnosed via cascade testing (biochemical testing or genetic testing) would most likely have attenuated MPS I as symptoms/manifestations for severe MPS I would be apparent at a median age of 0.8-1 year of age. However, in the first 1-2 years of the NBS program, or in families who

have recently migrated to Australia (that is, where the older sibling did not undergo NBS for MPS I themselves) it is possible that an older sibling aged 12-24 months may have undiagnosed severe MPS I.



**Figure 6 Proposed clinical management algorithm (PICO Set 2)**

ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA =  $\alpha$ -L-iduronidase; NBS = newborn bloodspot screening; MPS I = mucopolysaccharidosis type I  
 Source: updated Post PASC (out of session) in response to advice received from clinical expert co-applicant on 22/05/24

*The current and proposed pathways for PICO set 2 should acknowledge that if only one parent carries an IDUA variant, the second variant is either de novo, or there is a non-paternity event.*

PASC voiced its appreciation of the clinical expert co-applicants providing additional input out-of-session to correct the clinical management algorithms. PASC noted (out of session) the clinical management algorithms were updated in response to the advice received from the clinical expert co-applicant.

## Proposed economic evaluation

The expectation is that the evidence on NBS for detecting MPS I will demonstrate superior effectiveness and non-inferior safety, compared to no screening. The appropriate form of health economic evaluation is therefore a cost-utility analysis or cost-effectiveness analysis (Table 3).

**Table 3 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Non-inferior <sup>b</sup>	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior <sup>b</sup>	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

<sup>a</sup> 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

<sup>b</sup> An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Although there are three separate PICO confirmations for the three LSDs being considered for inclusion in the NBS programs for independent consideration of each condition (GSD II, MPS I and MPS II), there are potential efficiencies to be considered if all three are added to NBS programs at the same time.

The commercially available Revvity test can detect both GSD II and MPS I (as well as Krabbe, Fabry, Niemann-Pick-A/B, and Gaucher diseases), with MPS II assayed separately, but the two assay mixtures are then combined for analysis in a single LC-MS/MS run per newborn. The detection of other LSDs simultaneously, would presumably improve the cost-effectiveness of an assessment of NBS for multiple conditions, but does not alter the assessment of NBS for MPS I alone.

Likewise, if a GAG fragment analysis is done as the first-tier screen, 10 different MPS variants, including MPS I and II would be identified.

PASC noted that the costs of the screening protocols would differ depending on the assays chosen, as well as for either a single- or two-tier testing strategy. The chosen protocol for the economic evaluation is two-tiered screening, with a first tier IDUA enzyme activity screening followed by GAG fragment analysis.

*PASC commented that MSAC would also be interested in the single-tier screening protocol and requested a cost analysis of single-tier screening with GAG fragment analysis. PASC acknowledged that using the GAG fragment analysis would identify all the MPS subtypes.*

*PASC noted the potential for multiplexing NBS for multiple conditions. PASC considered that the assessment should allocate the whole cost of the first-tier screening to the assessment of this first condition, as per standard practice to assess the incremental cost (with sensitivity analyses adjusting the proportion of first-tier costs allocated to an individual condition if MSAC supports multiple conditions that can be multiplexed being introduced to NBS programs). Other costs will remain specific to each condition assessment, e.g. monitoring and treatment costs.*

## **Proposal for public funding**

### ***Funding of NBS for MPS I (PICO Set 1)***

Australian NBS programs are funded and delivered through public hospital services in all Australian jurisdictions and all NBS samples are tested by the newborn screening laboratories which are managed and funded within the public system.

Each jurisdiction has unique arrangements for the funding and delivery of NBS services to align with specific local health system structures. Funding for the Australian NBS programs comes from a mix of jurisdictional and national funds. The Australian government contributes funds for public hospital services, including typical sample collection, testing and downstream care in the NBS programs, under the 2020-25 National Health Reform Agreement (NHRA). The NHRA recognises the states and territories as system managers of public hospitals. In addition to these standard funding mechanisms, the Australian Government is directly contributing \$25.3 million to states and territories to support the expansion of the NBS programs through a schedule to the Health Federation Funding Agreement. This funding can be used by jurisdictions at their discretion.

If a collaborative national approach to procure the commercially available kit from Revvity is used, it is estimated to cost approximately \$ REDACTED per kit (960 reactions)<sup>10</sup>. Some of the reactions however are required for quality control (usually one QC test per batch tested), therefore will not equate to screening for 960 babies. The incremental cost of screening per child would be \$ REDACTED AUD. The kit is capable of detecting five other lysosomal storage disorders simultaneously (Gaucher Disease, Niemann-Pick A/B Disease, GSD II, Krabbe Disease and Fabry Disease), which would presumably improve the cost-effectiveness of an assessment of NBS for multiple conditions but does not alter the assessment of NBS for MPS I alone. The additional costs for personnel to conduct the test, other equipment required, etc. that would also be incurred would also be subject to the same cost-effectiveness measures, depending on the number of conditions tested for.

The WA NBS laboratory has estimated the cost per annum of first tier screening for MPS I in WA would be:

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<sup>10</sup> NeoLSD™ MSMS Kit URL:<https://www.revvity.com/product/neolsd-msms-kit-3093-0020> last updated 2023. Accessed 11 December 2023.

- Assay: Revvity NeoLSD @ \$ REDACTED per kit (inc GST), REDACTED required per year \$ REDACTED
- Consumables: ~\$ REDACTED
- Fixed costs: MS/MS service costs ~\$ REDACTED  
1 senior managing scientist and 2 medical scientists ~\$ REDACTED
- Total costs per annum: ~\$ REDACTED

The set-up costs for the WA NBS laboratory were estimated to be:

- Purchasing of Mass spectrometer \$ REDACTED
- Laboratory alterations for equipment and staff ~\$ REDACTED
- Total ~\$ REDACTED

This cost would remain the same if screening was for both MPS I and GSD II. If MPS II was also included there would be an additional cost of \$ REDACTED per annum for the MPS II assay (Revvity NeoLSD2).

The WA NBS laboratory commented that the relatively low (expected) incidence of positive samples does not warrant a local second tier service and that analysis would occur at the AWCH. It would be billed but the cost is uncertain.

The diagnostic tests used to confirm a diagnosis of MPS I are currently funded by the state and territory governments through the public hospital system. The cost of confirmatory diagnostic tests, according to the SA Pathology 'Pathology Collection Guide'<sup>11</sup> is \$167 for a Mucopolysaccharides Urine Screen and \$388 for Mucopolysaccharidosis Enzymes test. This arrangement would continue if MPS I is added to the NBS programs. However, it is possible that the number of diagnostic tests required could increase by 50-100% if the incidence of MPS is underreported due to undiagnosed individuals with attenuated MPS IS (Gragnaniello et al. 2023; Scott et al. 2013).

Funding for the ongoing delivery of interventions for MPS I is provided for by the Australian government (for HSCT) and the LSDP (for ERT), where eligibility criteria are met. The LSDP covers medicines for ultra-rare conditions (1 case per 50,000 or fewer) which could not be listed on the Pharmaceutical Benefits Scheme (PBS) on grounds of cost effectiveness but have been determined as being clinically effective by the PBAC, where the sponsor has applied for LSDP listing and the medicine has been assessed as meeting LSDP eligibility criteria. Medical services included in monitoring and treatment of newborns detected through NBS may also use other Commonwealth funding sources such as the MBS and PBS, and State/Territory funding.

There would also be additional use of healthcare resources associated with monitoring and surveillance of cases of attenuated disease, where time to symptomatic presentation is unknown.

*PASC noted that direct funding is being provided by the Commonwealth to states and territories to support expansion of Australia's NBS programs and support consistency in screening across Australia. States and*

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<sup>11</sup> SA Pathology. Pathology Collection Guide. URL: <https://www.sapathology.sa.gov.au/wps/wcm/connect/SA+Pathology+Internet+Content+New/Content/Clinicians/Pathology+Collection+Guide/> [accessed 20 February 2024]

*territories can determine how to allocate this funding within their jurisdiction to best support implementation in line with the terms of the Federation Funding Agreement (FFA) schedule.*

*PASC discussed that NBS laboratories would be required to purchase new LC-MS/MS machines in order to perform the NBS for MPS I, as the types of MS/MS machines currently in use in NBS laboratories would not be suitable. PASC estimated that every laboratory would need at least one (additional) LC-MS/MS machine, and NSW and Victoria would require two. PASC noted the funding source for this would be “NBS programs”, and that economic analyses include relevant costs across all funding sources.*

### **Funding of cascade testing (PICO Set 2)**

Cascade testing is available on the MBS for other conditions, such monogenic conditions (73361), familial hypercholesterolaemia (73353) and mitochondrial disease (73462).

The MBS fee for testing a close biological relative of a child with a known pathogenic or likely pathogenic disease variant for all three of these conditions is \$400.00 (Benefit: 75% = \$300.00 85% = \$340.00) and indeed this is the fee for almost all cascade testing MBS items, except for 73423 for neuromuscular disorders which has a fee of \$500.00 (Benefit: 75% = \$375.00 85% = \$425.00). For NBS of SCD, PASC previously advised that the cost for a laboratory to conduct genetic testing of the *HBB* gene or the *HBB* and *HBD* genes (for confirmatory testing for the newborn and for cascade testing of family members) was approximately \$500 (1737 PICO, pg 32; 1737 and 1737.1 PSDs).

Thus, the cost of cascade genetic testing for close relatives of a newborn diagnosed with MPS I would likely be the same. The cost of biochemical testing of siblings would be less; \$167 for a Mucopolysaccharides Urine Screen. However, if this test is positive there would be an additional cost of \$388 for a confirmatory Mucopolysaccharidosis Enzymes test.

New MBS items for cascade testing in relation to this application are not proposed. The Department’s advice was that cascade testing will continue to be funded by existing arrangements.

*PASC considered that for a symptomatic child, cascade testing could reasonably be claimed under MBS item 73361 (cascade testing of the sibling of a child with a known monogenic condition).*

The total cost for this service would be small as the incidence of MPS I in Australia is estimated to be between 0.73 and 1.2 per 100,000 live births (Chin and Fuller 2022; MPS Australia 2023). However, it is possible that the number of families requiring cascade tests could increase by 50-100%, if the incidence of MPS is underreported due to undiagnosed individuals with attenuated MPS IS (Graganiello et al. 2023; Scott et al. 2013).

## **Summary of public consultation input**

*PASC noted and welcomed consultation input from 9 organisations and 1 individual (clinical scientist at a NBS laboratory). The 9 organisations that submitted input were:*

- Western Australian Newborn Bloodspot Screening Program (WA NBS)
- Australasian Society of Inborn Errors of Metabolism (ASIAM) [special interest group of Human Genetics Society of Australasia (HGSA)]

- Rare Voices Australia (RVA)
- Genetic Alliance Australia (GAA)
- Australian Genomics
- Childhood Dementia Initiative (CDI)
- Statewide Biochemical Genetics Service within SA Pathology (SA Pathology)
- Sanofi-Aventis Australia (Sanofi)
- Royal College of Pathologists of Australasia (RCPA)

The consultation feedback received was mostly supportive of public funding newborn screening for MPS I. The consultation feedback raised several concerns, mostly in relation to the ability of available tests to predict disease course and severity, limitations of testing methods and limited subsidised access to ERT on the LSDP.

### **Clinical need and public health significance**

The main benefits of public funding identified in the consultation feedback was that newborn screening would allow earlier diagnosis of MPS I, avoiding diagnostic odyssey (and associated stress on families and patients), enabling early MPS I-specific treatments (ERT and HSCT), improving quality of life for children with MPS I, additional time to find a donor for HSCT, benefits from the value of knowing and access to new therapies (including gene therapies).

The main disadvantages of public funding received in the consultation feedback included difficulty predicting the disease course, including the severity and when symptoms may develop. This may result in some children having extended clinical follow-up before they develop symptoms. Some patients have private variants of the *IDUA* gene (unique to patient and their family). Additionally, people with non-Caucasian ancestry are more likely to have VUS due to underrepresentation on genetic databases, affecting equity of service delivery. Consultation feedback outlined disadvantage of test methods including high false positive rates with enzyme testing and high accuracy of GAG fragment analysis which can also detect all MPS disorders. Only some patients diagnosed with MPS I through newborn screening would be eligible for subsidised ERT on LSDP.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included resourcing of NBS labs (for staffing, equipment, facilities), confirmatory diagnostic testing, genetic counselling, specialised multidisciplinary care from metabolic service, cascade testing and support for families (disease education, psychosocial support). Consultation feedback highlighted that MPS I is a multi-system disorder and medical care for people with MPS I extends beyond metabolic services to orthopaedic, respiratory, developmental paediatrics, clinical genetics, cardiology, surgery, anaesthetic and HSCT services. The consultation input also noted limitations in access to treatment, stating that there are no local metabolic services in NT, ACT and Tasmania, no HSCT provision in these regions as well as in SA, and that First Nations Australians in isolated geographical regions will need to have access to services.

### **Indication for the proposed medical service and clinical claim**

The consultation feedback mostly agreed with the proposed population.

The consultation feedback mostly agreed with the proposed comparator.

The consultation feedback was mixed regarding the clinical claim. Consultation input that agreed with the clinical claim agreed that earlier diagnosis of MPS I through newborn screening will improve health

outcomes. Consultation input that disagreed with the clinical claim raised issues related to the most appropriate testing method.

### **Cost information for the proposed medical service**

The consultation feedback mostly agreed with the proposed service descriptor.

The consultation feedback was mixed regarding the proposed service fee. Consultation feedback that disagreed considered alternative testing options were less costly and that downstream costs had not been captured.

### **Additional comments**

Additional consultation feedback stated cascade testing should also be funded to minimise inequity and emphasised the importance of data collection and genetic registries. Consultation feedback queried the ethics of screening for a condition that may not present until adulthood. Consultation feedback considered the screening test could be used to monitor disease and decide when to start treatment for patients with attenuated disease as this is current practice for other lysosomal disorders when asymptomatic family members are identified through cascade testing. Sanofi (sponsor of ERT laronidase) stated it has the capacity to support the provision of treatment for newly diagnosed patients who meet the eligibility criteria for the supply of this ERT through the LSDP pathway.

### **Consumer Feedback**

Consumer feedback stated that a family with a child with MPS I wished their child was diagnosed earlier to prevent worsening illness, had trouble reaching a diagnosis, experienced distress as to whether their child was a good candidate for transplant due to advanced disease. Consultation input also outlined the effects of MPS I on several organ system and that it can result in small stature, mobility problems, intellectual limitations, differences in physical appearance and social problems. Several organisations highlighted the importance of the value of knowing including the importance of having a diagnosis, ability to make decision, benefits to the broader family by determining carrier status, and the potential to benefit from future advances even if conditions may have later onset or an unclear disease course.

*PASC noted that the public consultation responses were positive about the incorporation of MPS I to the NBS programs, and suggested that NBS would result in early intervention and better health outcomes. However, it was acknowledged that there would be challenges in predicting the severity of disease.*

*PASC noted the Royal College of Pathologists of Australasia (RCPA) commented that GAG fragment analysis was superior to other methods of screening for MPS I. A potential benefit is that this method can detect other forms of MPS.*

*PASC considered that broader consumer input from the families of newborns likely to be screened would be informative for MSAC's consideration. PASC considered that to inform a more balanced perspective it would also be beneficial to have consumer input regarding the acceptability of screening for a condition for which there may be no treatment. PASC noted out of session that consumer views on the acceptability of this could depend on a number of factors such as why the screening information is being gathered, how invasive the screening methodology is, how the data will be held and by whom, and whether consumers' details will be held on a list to be contacted if treatment is developed in the future. Out of session, PASC considered that NBS for this condition would be no more invasive than is NBS for other conditions (at most it might require a few more drops of blood), that the National Pathology Accreditation Advisory Council*

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*(NPAAC) requires the original report for genetic testing to be held for 100 years, and that consumers' details will not be held on a list to be contacted if a treatment is developed in the future. PASC noted out of session that other factors that may require consideration include whether consumers would be supported to connect with other parents with children who have also tested positive for this condition and likely push for action or treatment. PASC considered (out of session) that this was a likely outcome of the counselling and support that must form part of NBS programs, and should be costed. PASC considered (out of session) that psychological counselling and support will likely be very important to ensure that consumers can make an informed decision.*

## **Next steps**

*The assessment will proceed as a Department Contracted Assessment Report.*

## References

ABS 2022, *Births, Australia*, Australian Bureau of Statistics, Canberra, Australia, viewed 11 december 2023, <<https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>>.

AIHW 2022, *National Perinatal Data Collection annual update 2020 - data tables*.

Bay, L, Amartino, H, Antacle, A, Arberas, C, Berretta, A, Botto, H, Cazalas, M, Copiz, A, De Cunto, C, Drelichman, G, Espada, G, Eiroa, H, Fainboim, A, Fano, V, Guelber, R, Maffey, A, Parisi, C, Pereyra, M, Remondino, R, Schenone, A, Spécola, N, Staciuk, R and Zuccaro, G 2021, 'New recommendations for the care of patients with mucopolysaccharidosis type I', *Arch Argent Pediatr*, vol. 119, no. 2, pp. e121-e128.

Botkin, Jeffrey R, Belmont, John W, Berg, Jonathan S, Berkman, Benjamin E, Bombard, Y, Holm, Ingrid A, Levy, Howard P, Ormond, Kelly E, Saal, Howard M, Spinner, Nancy B, Wilfond, Benjamin S and McInerney, Joseph D 2015, 'Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents', *The American Journal of Human Genetics*, vol. 97, no. 1, pp. 6-21.

Braunlin, EA, Hunter, DW, Krivit, W, Burke, BA, Hesslein, PS, Porter, PT and Whitley, CB 1992, 'Evaluation of coronary artery disease in the Hurler syndrome by angiography', *The American Journal of Cardiology*, vol. 69, no. 17, pp. 1487-1489.

Burlina, AB and Gragnaniello, V 2022, 'Newborn screening of mucopolysaccharidosis type I', *Critical Reviews in Clinical Laboratory Sciences*, vol. 59, no. 4, pp. 257-277.

Chin, SJ and Fuller, M 2022, 'Prevalence of lysosomal storage disorders in Australia from 2009 to 2020', *The Lancet Regional Health – Western Pacific*, vol. 19.

Clarke, L 2002, *Mucopolysaccharidosis Type I*, University of Washington, Seattle, Seattle (WA), viewed 21/11/23, <<https://www.ncbi.nlm.nih.gov/books/NBK1162/>>.

Clarke, L, Giugliani, R, Guffon, N, Jones, SA, Keenan, HA, Munoz-Rojas, MV, Okuyama, T, Viskochil, D, Whitley, CB, Wijburg, FA and Muenzer, J 2019, 'Genotype-phenotype relationships in mucopolysaccharidosis type I (MPS I): Insights from the International MPS I Registry', *Clinical Genetics*, vol. 96, no. 4, pp. 281-289.

Clarke, L, Nelson, PV, Warrington, CL, Morris, CP, Hopwood, JJ and Scott, HS 1994, 'Mutation analysis of 19 North American mucopolysaccharidosis type I patients: Identification of two additional frequent mutations', *Human Mutation*, vol. 3, no. 3, pp. 275-282.

Concolino, D, Deodato, F and Parini, R 2018, 'Enzyme replacement therapy: efficacy and limitations', *Italian Journal of Pediatrics*, vol. 44, no. 2, p. 120.

Costello Medical 2019, *Newborn Screening for Mucopolysaccharidosis Type I. External review against programme appraisal criteria for the UK National Screening Committee*, UK National Screening Committee, UK.

Department of Health and Aged Care 2023, *Life Saving Drugs Program (LSDP): Review of Medicines for Mucopolysaccharidosis Type I (MPS I)*, Canberra, Australia, <<https://www.health.gov.au/resources/collections/life-saving-drugs-program-resources-mucopolysaccharidosis-type-i-mps-i#medicines-review-documents>>.

Eisengart, JB, Pierpont, EI, Kaizer, AM, Rudser, KD, King, KE, Pasquali, M, Polgreen, LE, Dickson, PI, Le, SQ, Miller, WP, Tolar, J, Orchard, PJ and Lund, TC 2019, 'Intrathecal enzyme replacement for Hurler syndrome: biomarker association with neurocognitive outcomes', *Genet Med*, vol. 21, no. 11, pp. 2552-2560.

Filocamo, M, Tomanin, R, Bertola, F and Morrone, A 2018, 'Biochemical and molecular analysis in mucopolysaccharidoses: what a paediatrician must know', *Italian Journal of Pediatrics*, vol. 44, no. 2, p. 129.

Fuller, M 2020, 'Laboratory Diagnosis of Lysosomal Diseases: Newborn Screening to Treatment', *Clin Biochem Rev*, vol. 41, no. 2, pp. 53-66.

Gelb, MH, Basheeruddin, K, Burlina, A, Chen, H-J, Chien, Y-H, Dizikes, G, Dorley, C, Giugliani, R, Hietala, A, Hong, X, Kao, S-M, Khaledi, H, Klug, T, Kubaski, F, Liao, H-C, Martin, M, Manning, A, Orsini, J, Peng, Y, Ranieri, E, Rohrwasser, A, Szabo-Fresnais, N, Turgeon, CT, Vaz, FM, Wang, L-y and Matern, D 2022, 'Liquid Chromatography&ndash;Tandem Mass Spectrometry in Newborn Screening Laboratories', *International Journal of Neonatal Screening*, vol. 8, no. 4, p. 62.

Graganiello, V, Cazzorla, C, Gueraldi, D, Puma, A, Loro, C, Porcù, E, Stornaiuolo, M, Miglioranza, P, Salviati, L, Burlina, AP and Burlina, AB 2023, 'Light and Shadows in Newborn Screening for Lysosomal Storage Disorders: Eight Years of Experience in Northeast Italy', *Preprints*, Preprints, <<http://dx.doi.org/10.20944/preprints202311.0727.v1>>.

Hampe, CS, Wesley, J, Lund, TC, Orchard, PJ, Polgreen, LE, Eisengart, JB, McLoon, LK, Cureoglu, S, Schachern, P and McIvor, RS 2021, 'Mucopolysaccharidosis Type I: Current Treatments, Limitations, and Prospects for Improvement', *Biomolecules*, vol. 11, no. 2.

Herbst, ZM, Hong, X, Urdaneta, L, Klein, T, Waggoner, C, Liao, HC, Kubaski, F, Giugliani, R, Fuller, M and Gelb, MH 2023, 'Endogenous, non-reducing end glycosaminoglycan biomarkers are superior to internal disaccharide glycosaminoglycan biomarkers for newborn screening of mucopolysaccharidoses and GM1 gangliosidosis', *Mol Genet Metab*, vol. 140, no. 1-2, p. 107632.

Huynh, T, Greaves, R, Mawad, N, Greed, L, Wotton, T, Wiley, V, Ranieri, E, Rankin, W, Ungerer, J, Price, R, Webster, D and Heather, N 2022, 'Fifty years of newborn screening for congenital hypothyroidism: current status in Australasia and the case for harmonisation', *Clin Chem Lab Med*, vol. 60, no. 10, pp. 1551-1561.

Keerthiga, M, Chakraborty, A, Silvia, W, Atre, A and Shivakumar, P 2023, 'Mucopolysaccharidoses: An overview and new treatment modalities', *International Journal of Clinical Biochemistry and Research*, vol. 10, no. 2, pp. 101-109.

Kemper, A, Brosco, J, Green, N, Ojodu, J, Jones, E and Comeau, A 2015, 'Newborn screening for mucopolysaccharidosis type 1 (MPS I): a systematic review of evidence. Report of final findings', *Final Version*, vol. 1, pp. 3-60.

Kubaski, F, de Oliveira Poswar, F, Michelin-Tirelli, K, Matte, UDS, Horovitz, DD, Barth, AL, Baldo, G, Vairo, F and Giugliani, R 2020, 'Mucopolysaccharidosis Type I', *Diagnostics (Basel)*, vol. 10, no. 3.

Kumar, AB, Masi, S, Ghomashchi, F, Chennamaneni, NK, Ito, M, Scott, CR, Turecek, F, Gelb, MH and Spacil, Z 2015, 'Tandem Mass Spectrometry Has a Larger Analytical Range than Fluorescence Assays of Lysosomal Enzymes: Application to Newborn Screening and Diagnosis of Mucopolysaccharidoses Types II, IVA, and VI', *Clinical Chemistry*, vol. 61, no. 11, pp. 1363-1371.

MPS Australia 2023, *A Guide to Understanding Hurler, Hurler-Scheie And Scheie Syndromes (Mucopolysaccharidosis Type I; MPS I)*, Mucopolysaccharide & Related Diseases Society Aust. Ltd, viewed

22 November 2023, <<https://www.mpsociety.org.au/about-the-mps-and-related-diseases/mps-i/#:~:text=HOW%20COMMON%20IS%20MPS%20I,are%20affected%20by%20MPS%20I>>.

MSAC 2021, *Guidelines for preparing assessments for the Medical Services Advisory Committee*.

Muenzer, J 2014, 'Early initiation of enzyme replacement therapy for the mucopolysaccharidoses', *Molecular Genetics and Metabolism*, vol. 111, no. 2, pp. 63-72.

Muenzer, J, Wraith, JE, Clarke, LA, Management, atICPot and I, ToM 2009, 'Mucopolysaccharidosis I: Management and Treatment Guidelines', *Pediatrics*, vol. 123, no. 1, pp. 19-29.

Nelson, J, Crowhurst, J, Carey, B and Greed, L 2003, 'Incidence of the mucopolysaccharidoses in Western Australia', *American Journal of Medical Genetics Part A*, vol. 123A, no. 3, pp. 310-313.

Parini, R, Deodato, F, Di Rocco, M, Lanino, E, Locatelli, F, Messina, C, Rovelli, A and Scarpa, M 2017, 'Open issues in Mucopolysaccharidosis type I-Hurler', *Orphanet Journal of Rare Diseases*, vol. 12, no. 1, p. 112.

Poletto, E, Pasqualim, G, Giugliani, R, Matte, U and Baldo, G 2018, 'Worldwide distribution of common IDUA pathogenic variants', *Clin Genet*, vol. 94, no. 1, pp. 95-102.

Polo, G, Gualdi, D, Giuliani, A, Rubert, L, Cazzorla, C, Salviati, L, Marzollo, A, Biffi, A, Burlina, AP and Burlina, AB 2020, 'The combined use of enzyme activity and metabolite assays as a strategy for newborn screening of mucopolysaccharidosis type I', *Clin Chem Lab Med*, vol. 58, no. 12, pp. 2063-2072.

Roubicek, M, Gehler, J, Spranger, J, Opitz, JM and Reynolds, JF 1985, 'The clinical spectrum of  $\alpha$ -L-iduronidase deficiency', *American Journal of Medical Genetics*, vol. 20, no. 3, pp. 471-481.

Schielen, PCJI, Kemper, EA and Gelb, MH 2017, 'Newborn Screening for Lysosomal Storage Diseases: A Concise Review of the Literature on Screening Methods, Therapeutic Possibilities and Regional Programs', *International Journal of Neonatal Screening*, vol. 3, no. 2, p. 6.

Scott, CR, Elliott, S, Buroker, N, Thomas, LI, Keutzer, J, Glass, M, Gelb, MH and Turecek, F 2013, 'Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry', *J Pediatr*, vol. 163, no. 2, pp. 498-503.

Staba, SL, Escolar, ML, Poe, M, Kim, Y, Martin, PL, Szabolcs, P, Allison-Thacker, J, Wood, S, Wenger, DA, Rubinstein, P, Hopwood, JJ, Krivit, W and Kurtzberg, J 2004, 'Cord-Blood Transplants from Unrelated Donors in Patients with Hurler's Syndrome', *New England Journal of Medicine*, vol. 350, no. 19, pp. 1960-1969.

Stapleton, M, Hoshina, H, Sawamoto, K, Kubaski, F, Mason, RW, Mackenzie, WG, Theroux, M, Kobayashi, H, Yamaguchi, S, Suzuki, Y, Fukao, T, Tadao, O, Ida, H and Tomatsu, S 2019, 'Critical review of current MPS guidelines and management', *Molecular Genetics and Metabolism*, vol. 126, no. 3, pp. 238-245.

Terlato, NJ and Cox, GF 2003, 'Can mucopolysaccharidosis type I disease severity be predicted based on a patient's genotype? A comprehensive review of the literature', *Genetics in Medicine*, vol. 5, no. 4, pp. 286-294.

The Department of Health and Aged Care 2023, *About newborn bloodspot screening*, Commonwealth of Australia, Canberra, Australia, viewed 14 November 2023, <<https://www.health.gov.au/our-work/newborn-bloodspot-screening/about#conditions-screening-can-detect>>.

Vijay, S and Wraith, J 2005, 'Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I', *Acta Paediatrica*, vol. 94, no. 7, pp. 872-877.

# Appendix A NBS National Policy Framework (NBS NPF) Criteria

<i>NBS National Policy Framework Criteria</i>
<b>The condition</b>
<p><b>1. The condition should be a serious health problem that leads to significant morbidity or mortality.</b></p> <p>1.1 What data are there on the incidence of the condition, including in the Australian population? How is this incidence determined—through screening studies, international programs, cases identified clinically, modelled estimates based on data from variant databases or some other means? Are there any known differences in incidence in Australian sub-populations?</p> <p>1.2 What is the burden of disease associated with the condition, including morbidity and mortality? Does the burden of disease vary between individuals?</p>
<p><b>2. There should be a benefit to conducting screening in the newborn period.</b></p> <p>○ While the benefit to the baby must always be the first consideration, for some conditions a benefit for the family and/or community, as well as the benefit to the baby, may also be important and warrant consideration. This might include benefits to the family for conditions where there is currently no intervention and which will be likely to lead to early mortality but where a definitive diagnosis might be aided by a screening test.</p> <p>2.1 What are the known health benefits from early detection that exist, or can be achieved, through screening for the condition? This may include early intervention, prevention of symptoms or reduction in condition severity.</p> <p>2.2 Why is screening for this condition during the newborn period the most beneficial method of early detection?</p> <p>2.3 Does detection of this condition provide families with actionable information that assists them in making informed choices about reproduction in the future?</p> <p>2.4 What emotional or social benefits does early detection provide?</p> <p>2.5 What harms may arise from screening for the condition in the newborn period?</p>
<p><b>3. The natural history of the condition, including development from latent to declared disease, should be adequately understood.</b></p> <p>3.1 What information is known on the natural history of the condition in Australia or comparable international populations?</p>

## *NBS National Policy Framework Criteria*

3.2 When would the condition usually be detected clinically?

3.3 Explore the current knowledge of penetrance of the condition. Are there known benign or milder late-onset forms?

### **4. There should be a suitable test protocol to identify the presence of the condition.**

4.1 What test protocols could be used to identify the presence of the condition? Is there consensus on the most appropriate test protocol?

4.2 When considering the test protocol, what is the clinical and analytic validity based on a consideration of:

- Sensitivity;
- Specificity;
- False positive rate;
- False negative rate;
- Positive predictive value;
- Negative predicative value.

4.3 Is the test protocol simple and reliable?

4.4 Can the test protocol be performed on the available dried bloodspot?

4.5 Can the test be multiplexed within existing newborn bloodspot screening panels?

4.6 What is the cost of the test protocol?

4.7 Will genetic testing be used as part of the test protocol? If genetic testing is needed:

- Will this be by common mutations or sequencing?
- Which mutations would be tested?
- What is the penetrance of the mutations?
- Are there variants of uncertain significance?

### **5. The test protocol should, on balance, be socially and ethically acceptable to health professionals and the public.**

5.1 Can the test protocol detect other conditions of clinical or unknown significance and/or carriers and, if so, what are the implications?

5.2 What are the potential benefits and harms associated with the preferred test protocol(s)?

**The Intervention**

**6. Health care services for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result.**

- 6.1 What health care services are currently involved in the diagnosis and ongoing management of the condition?
- 6.2 What impact would screening for the condition have on the health care services that would be required to support diagnosis and management following an abnormal screening result?
- 6.3 Is diagnostic testing readily available and reliable?
- 6.4 Do current health care services have capacity to support the diagnosis and ongoing management of the condition?
- 6.5 Are current health care services of sufficient quality to support the diagnosis and ongoing management of this condition?
- 6.6 Is there equitable access to these health care services for families, including those from rural and remote areas?

**7. There should be an accepted intervention for those diagnosed with the condition.**

- 7.1 What accepted intervention(s) is (are) available for newborns that receive an early diagnosis through screening?
- 7.2 How well is the intervention and treatment pathway understood? Is there agreement on when intervention is required?
- 7.3 How effective is the intervention? Does it alleviate the symptoms of the condition or slow or halt its progression? What influence does the intervention have on quality and length of life?
- 7.4 How urgent is the intervention? Does the intervention need to be initiated before symptoms of the condition present?
- 7.5 Is the intervention readily available and accessible?
- 7.6 What are the potential harms associated with the intervention, and to what extent can these harms be mitigated or managed?
- 7.7 What is the cost of the intervention? What costs will be incurred for the diagnosis, management, and treatment of conditions, including the costs for false positives?

## *NBS National Policy Framework Criteria*

7.8 Is there equitable access to the intervention for families, including those from rural and remote areas?

### **Additional considerations**

**8. The benefit of screening a condition must be weighed against its impact on the program as a whole.**

8.1 Can screening for this condition be achieved within the current screening pathway?

8.2 Is the addition of this condition likely to require ethical considerations that may warrant a separate consent process?

8.3 Would it be likely that screening for the condition would impact negatively upon other elements of the program? For example, could it be anticipated that participation rates might fall?

8.4 Are there any additional costs, such as the purchasing of new technology or training, which are associated with screening for this condition?

8.5 What is the economic impact of excluding/including the condition? Do benefits exceed costs? Is it cost-effective to screen? It may be necessary for a detailed economic evaluation to consider these questions and other relevant economic issues.

**9. What other information relevant to decision making should be considered that has not been captured elsewhere?**