MSAC Application 1775

Newborn bloodspot screening for mucopolysaccharidosis, Type 1 (MPS I)

PICO Set 1

Population

Describe the population in which the proposed health technology is intended to be used:
The intended population for screening for mucopolysaccharidosis type 1 (MPS I) as part of existing newborn bloodspot screening (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).

MPS I is a rare, genetic lysosomal storage disorder (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 organelles 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 & Gragnaniello 2022).

MPS I disease is due to a pathogenic variant in the α-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, L 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, L 2002).

Natural history of the condition

There are three clinical phenotypes classified under MPS I: the severe Hurler syndrome (MPS 1-H), and two attenuated syndromes: Hurler-Scheie syndrome (intermediate), and Scheie syndrome (least severe). These phenotypes occur across a continuum of severity and vary in age of onset and rate of progression (Clarke, LA 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).

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 ranges from around one year of age, compared around 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 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 disease 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, gargoyle facies, 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. It is typically diagnosed between two to six years of age, with joint stiffness as the most common presenting complaint (Vijay & Ed Wraith 2005). Overall, there are common symptoms across the two attenuated subtypes (Hurler and Hurler-Scheie syndromes) involving the musculoskeletal, respiratory and cardiovascular systems (Vijay & Ed 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 ventriculoperitoneal shunting. Their lifespan is shortened. 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. Patients may be diagnosed as late as in their teenage years, due in part to their facial features being only mildly affected (Vijay & Ed Wraith 2005). There is a considerable overlap in symptoms between affected children with Scheie and Hurler-Scheie syndromes. Scheie patients 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, lifespan 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 & Ed Wraith 2005).

Similarity between MPS I and mucopolysaccharidosis type II (MPS II)

MPS II is a closely related condition caused by deficiency of the lysosomal Iduronate-2-sulfatase (I2S) enzyme that catalyses the first step in the breakdown of two GAGs, known as heparan sulphate (HS) and dermatan sulphate (DS). MPS I is caused by deficiency of the lysosomal enzyme iduronidase (IDUA), which catalyses the second step in the degradation of HS and DS. Both MPS I and MPS II result in accumulation of DS and HS.

Genetics

Approximately 100 pathogenic variants in the *IDUA* gene that are associated with MPS I are reported in the Human Genome Database and MPS I Registry. Most known *IDUA* pathogenic variants are private, which makes the prediction of severity from uncertainties in genotype-phenotype correlation difficult. However, at least 7 to 9 pathogenic variants have been identified that occur with varying prevalence across different ethnicities and continents (Clarke, L 2002;

Clarke, LA et al. 2019; Kemper et al. 2015; Terlato & Cox 2003). Most of these mutations are associated with the severe Hurler phenotype, although some heterogenous mutations with W402X and Q70X have been associated with milder, attenuated forms. The most common reported MPS I pathogenic variants in North American patients are W402X (45%-60%), Q70X (17%) (Terlato & Cox 2003), and A75T (7%) and 474- 2a-->g (7%) (Clarke, LA et al. 1994).

Genetic testing of the *IDUA* gene would be undertaken in babies with a positive NBS screen for MPS I and whose diagnosis has been confirmed with leukocyte/fibroblast assays and urine GAG analysis to identify the specific pathogenic variants involved. This is important in the determination of the disease severity and may guide treatment decisions. Genetic cascade testing would also occur in close family members (siblings and parents) as warranted.

Pseudodeficiency

Some individuals will have lower enzymatic activity than the general population but remain clinically healthy; this is referred to as enzymatic pseudodeficiency (Burlina & Gragnaniello 2022). This 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 screening results. 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 & Gragnaniello 2022).

Incidence

Chin and Fuller (2022) reported that in Australia, 1 in 137,000 births are affected by MPS I with a prevalence of 0.73 per 100,000 live births between 2009 and 2020.

The incidence in Western Australia for the period 1969–1996 was estimated to be approximately 1 in 107,000 live births for Hurler syndrome (Nelson et al. 2003).

A review of the use of medicines listed on the Life Saving Drugs Program (LSDP) for MPS I was published in January 2023. In this report, the Expert Panel noted that the prevalence of MPS I was estimated to be 1.15 per 100,000 (1 in 86,957) births.

MPS Australia reported that Hurler syndrome represents about 1 in 88,000 births, Hurler-Scheie syndrome about 1 in 115,000 births and Scheie syndrome about 1 in 500,000 births (MPS Australia 2023).

However, these figures may be underestimates due to undiagnosed individuals with attenuated disease. Scott et al. (2013) reported that the prevalence of MPS I diagnosed via NBS and confirmed by DNA sequencing among 106,526 newborns included in the Washington State Newborn Screening program was 1 in 35,700 newborns. Gragnaniello et al. (2023) reported he 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.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:
Testing in the NBS program occurs in an unselected newborn population; no other eligibility criteria apply.

Provide a rationale for the specifics of the eligible population:
Testing for MPS I is proposed for addition to Australian NBS programs to enable early detection and treatment, prior to symptom onset, in affected babies and support improvement in clinical outcomes for these children.

A newborn with a positive MPS I screening test receives confirmatory diagnostic testing at a specialist metabolic disorders clinic and, if required, earlier access to treatment (HSCT and/or ERT) before the appearance of somatic or neurological damage due to GAG accumulation. Patients and their family would benefit from the value of knowing and a reduction in their diagnostic odyssey.

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 a rare recessive condition, the large majority of cases are not detected through this pathway and are consequently diagnosed clinically after onset of symptoms.

At least half of newborns diagnosed with MPS I will have the severe Hurler syndrome and are likely to benefit from an earlier diagnosis via NBS. Diagnosis will allow earlier pre-symptomatic treatment with hematopoietic stem cell transplant (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 indicates earlier treatment with HSCT improves survival at 1 year post-transplant and neurological outcomes, a systematic review by Kemper et al. (2015) found that the results may be confounded because more severe cases were more likely to be diagnosed earlier but are also likely to have worse outcomes because of the higher level of underlying disease.

Newborns diagnosed with the attenuated forms of MPS I 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.

However, some newborns with the mildest attenuated form of Scheie syndrome may not present with any symptoms until adulthood. These babies are likely to undergo years of anxiety and follow-up testing for the development of symptoms that may never manifest.

Intervention

Name of the proposed health technology:
The proposed health technology is universal NBS for MPS I through Australia's NBS programs.

All families are offered NBS for their newborn within 48 to 72 hours of birth. Over 99% of newborns receive NBS, which screens for up to 32 rare conditions (The Department of Health and Aged Care 2023).

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).

NBS is performed in five laboratories across Australia that conduct tests on dried bloodspot (DBS) cards, located in New South Wales, Queensland, South Australia, Victoria and Western Australia. Dried bloodspots collected in states and territories without NBS laboratories are sent interstate for testing. All NBS programs are underpinned by the Newborn Bloodspot Screening National Policy Framework (The Department of Health and Aged Care 2018).

It is proposed that MPS I be added to existing programs to support early diagnosis and intervention to improve clinical outcomes, particularly for individuals with types that require intervention during their first few years of life.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The identification of individuals at risk of developing MPS I is to be based on:

- A screening test, carried out in NBS laboratories
- Clinical assessment and confirmatory diagnostic testing for newborns with abnormal screening results.

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

Currently, NBS is conducted by collecting blood samples from all newborns onto filter cards. In the laboratory, the bloodspots are punched out and used in reagents required for the various screening tests. Testing for MPS I will utilise the same DBS samples and is expected to employ a two-tiered method in Australian newborn screening laboratories based on:

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

<u>Measurement of IDUA enzyme activity in DBS samples</u>

Most lysosomal enzymes are active in rehydrated DBS samples, thus permitting their activities to be measured. Enzymatic assays generally involve the addition of lysosomal enzyme substrates in buffer to a DBS punch. The mixture is then incubated at 37°C for a prescribed period prior to measuring the enzymatic activity. The enzyme activity is usually measured by fluorometry or MS/MS in DBS samples for applications in NBS programs (Gelb et al. 2022).

Fluorometric assays:

The 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 multiplex assays. 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) reported 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 enzymatic activity related to Pompe, 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. 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.

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).

State and territory screening laboratories will be consulted to determine their preferred approach for screening, to inform the health technology assessment for MSAC consideration during the PICO development stage. The use of a commercially available kit from Revvity or developing in-house methods was considered previously. If a collaborative national approach to procure the kit is used, it is estimated to cost approximately [redacted]. Some of the reactions however will be required for quality control samples, therefore will not equate to screening for [redacted] babies. The incremental cost of screening per child would be [redacted]. The kit is capable of detecting five other lysosomal storage disorders simultaneously (Gaucher Disease, Niemann-Pick A/B Disease, Pompe disease, 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 MPSII alone.

<u>Measurement of GAG (dermatan sulphate and heparan sulphate) levels in DBS samples</u>

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 measurement 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 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%).

Identify how the proposed technology achieves the intended patient outcomes:
The key aim of NBS for MPS I is to identify babies with the condition before symptoms appear, to support initiation of treatment(s) that may delay or prevent complications associated with the condition. The recommended treatment for Hurler syndrome is HSCT using either bone marrow or cord blood cells and enzyme replacement therapy (ERT) for attenuated forms of MPS I.

Timely diagnosis and intervention for severe MPS I is critical. When left untreated, children with Hurler syndrome are unlikely to survive beyond 10 years of age. Peri-transplant administration of laronidase as a supportive/adjuvant treatment in addition to initiating treatment with HSCT has been shown to be beneficial in terms of respiratory and cardiovascular functions (de Ru et al. 2011; Ghosh et al. 2016). Treatment with HSCT is much more likely to achieve better outcomes if initiated prior to the occurrence of complications (Ghosh et al. 2016; Staba et al. 2004).

Children with Hurler-Scheie and Scheie syndromes may have relatively longer life-expectancy, compared to those with Hurler syndrome. However, it is associated with severe co-morbidities. Based on the evidence that ERT is beneficial in MPS I patients, and due to its progressive nature, it has been recommended that ERT should be initiated at diagnosis to achieve the best clinical outcomes (Muenzer 2014; Parini et al. 2017).

<u>Clinical assessment and diagnostic testing</u>

Newborns receiving a positive screening result need to be referred for clinical assessment and diagnostic testing, including urine GAG analysis (both measurement of the GAG concentration using a colorimetric detection method and GAG subtype analysis using LC-MS/MS), peripheral blood leukocyte IDUA enzyme activity analysis; and *IDUA* gene molecular analysis.

Molecular genetic testing is best suited for confirmatory testing due to allelic heterogeneity and the need for expert interpretation, in the context of clinical and metabolic assessment, to provide appropriate therapeutic options to the family. This includes the availability of cascade testing.

Currently, it may take over 6 weeks to obtain genetic testing results (expert opinion), which is unfavourable given earlier diagnosis and intervention can improve clinical outcomes for babies.

<u>Treatment and ongoing management</u>

Once a diagnosis is confirmed, disease severity must be determined to guide the management plan. Clinical management of individuals diagnosed with MPS I is described in the proposed clinical management algorithm (Figure 2).

The preferred treatment for babies with severe MPS I is HSCT in the first 2-2.5 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 ERT in the time between diagnosis and HSCT to prevent further deterioration of non-cerebrospinal fluid (CSF) manifestations (Muenzer et al. 2009). 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 with the most significant benefit being the preservation of intellectual development. Most physical abnormalities, except cardiac valvular and skeletal deformities, are either stabilised or even slowly resolve after successful HSCT. However, the HSCT procedure is risky with increased 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. HSCT is discouraged for these children 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 appear until adolescence or adulthood, ERT would not be started until these symptoms become apparent.

Infusion-related reactions are very common. Thus, pre-treatment with antihistamines and antipyretics is recommended (Concolino, Deodato & Parini 2018).

Laronidase does not cross the blood-brain barrier and is therefore ineffective in treating any central nervous system (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 CSF abnormalities (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 stabilized CNS function (Hampe et al. 2021).

Additional treatment of individual manifestations will most likely be required throughout the course of disease (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 stabilization;
- 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;
- ventilating tubes;
- hearing aids as needed;
- CPAP for sleep apnoea;
- gastrointestinal management for diarrhea and constipation.

These treatments would occur as needed in patients identified as part of NBS, and those currently identified after the onset of symptoms. However, the early pre-symptomatic treatments may mitigate symptom development and reduce the requirement for these interventions as the disease progresses.

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 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.

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

- with confirmed MPS IH or MPS IS.
- who have significant learning difficulties and/or neuropathic involvement with their disease indicating MPS IH.
- with the presence of another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by ERT.
- where the presence of another medical condition that might reasonably be expected to compromise a response to ERT.

Thus, currently only a proportion of MPS I patients (those with MPS IHS) would be eligible for ERT with laronidase through the LSDP. It is noted that the TGA Product Information for laronidase indicates its safety and effectiveness in patients below the age of 5 has not been established.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
☐ Yes
☒ No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
☒ Yes
☐ No

Provide details and explain:
All families are offered NBS for their newborns. Screening is dependent on parental consent.

To implement screening, the adopted testing protocol would need to be implemented by the Australian NBS laboratories. Further, the screening protocol will need to be accredited by NATA prior to implementation. Associated training will also be required for laboratory staff. Funding for screening will also need to be sought by NBS laboratories from their respective state budget cycles to procure necessary equipment and reagents.

If there is a significant increase in the number of patients diagnosed with MPS I (and other LSDs) that require surveillance, including mild cases or people with variants of unknown significance, further resourcing would be needed for providing adequate clinical care for these patients. For

example, expert advice indicated that limited or no LSD specialists in Western Australia, Tasmania or Northern Territory, meaning these states rely on resources from other jurisdictions with sufficient expertise. Additional resources for follow-up annual testing, such as cardiac evaluations, to meet LSDP eligibility guidelines may also be required to remain within the required timeframe.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Screening for MPS I via NBS would occur through the existing NBS programs across Australia.

The health professionals required to screen for MPS I as part of NBS may vary from jurisdiction to jurisdiction; however, below is a potential list of key health professionals who may be needed:

1) Nurses/midwives who obtain parental consent and collect blood samples on NBS dried bloodspot cards. They may also be required to collect repeat samples if the results of the initial NBS tests are inconclusive. These processes already occur routinely to screen for other conditions.

2) Screening laboratory scientist/pathologist – these professionals are needed to undertake the screening, and will be required to develop and implement the screening test and analyse the data for MPS I.

3) Clinical nurse consultants/ screening laboratory support staff will need to assist with recalls, parent notification or early notification of clinicians where there are abnormal results, and referrals into care. These processes already occur for other conditions.

4) If abnormal, follow up diagnostic testing may be necessary through a relevant clinic or hospital department, an appropriate physician for diagnosis or through a genetic counsellor. While it is noted that diagnostic testing already occurs for MPS I, there may be an increase in the number of diagnostic tests conducted overall associated with false positives and the possible detection of mild / benign cases.

5) If MPS I is confirmed, a multi-disciplinary team will be needed as it affects multiple body systems. The multi-disciplinary team may include neurologists, orthopaedic surgeons, physiotherapists, cardiologists, ophthalmologists, and ear, nose and throat specialists, among others.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
N/A

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
☒ Yes
☐ No

Provide details and explain:
All Australian newborn screening laboratories are NATA accredited under ISO 15189:2022 to perform human pathology services on patient samples. This process includes an independent

assessment of pre-analytical, analytical and post-analytical processes associated with the screening tests for each condition. NATA evaluation of all new tests implemented by the newborn screening laboratories to screen for MPS I will be required prior to the commencement of universal screening.

A multiple clinical chemistry constituent IVD product produced by Revvity for the quantitative measurement of alpha-L-idruronase (IDUA) which can be used as a first-tier screening test for MPS I, is listed on the Australian Register of Therapeutic Goods (ARTG) under ARTG ID 295864 as a Class 2 IVD (low public health risk or moderate personal risk). Laboratory developed tests utilised by thew newborn screening laboratories do not require TGA approval.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☒ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☒ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Blood samples can be taken in many clinical settings and at home by qualified staff. Analysis of the samples will be undertaken by NBS laboratories.

Is the proposed health technology intended to be entirely rendered inside Australia?
☒ Yes
☐ No

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Please provide a name for your comparator:
The comparator for the proposed health technology is no screening for MPS I through NBS programs. Diagnosis would occur as per current clinical practice, following presentation with symptoms or having a family history of MPS I (e.g., a sibling with a diagnosis of MPS I).

Please provide an identifying number for your comparator (if applicable)
N/A

Please provide a rationale for why this is a comparator:
This is what occurs in the absence of MPS I screening.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:
Children who undergo NBS for MPS I should not require diagnostic testing on presentation with symptoms (the comparator) because they should have already been diagnosed.

The NBS enzymatic activity and GAG detection assays are not considered definitive and confirmatory tests are still required. The proposed confirmatory tests are the same tests as those currently used for diagnosis of children presenting with symptoms consistent with MPS I, in the absence of screening (the comparator).

However, as symptoms can mimic many other conditions, often the diagnostic odyssey would be simplified compared with diagnosis of a symptomatic child. The tests undertaken after a positive screening result in these presymptomatic children 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 symptoms would not be undertaken.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Health benefits

- Health outcomes from early diagnosis and intervention (improvement in morbidity and mortality, general functioning and disease manifestations)
- Quality of life (both the disease and the treatment may impact on quality aspects)
- Disease specific patient reported outcomes (PROs)

Health harms

- Impact of false positive results
- Impact of false negative results (noting this would mean the newborn is diagnosed clinically, which is the comparator. There is a potential that a diagnosis of MPS I may be overlooked if it is assumed it will be detected through NBS)
- Impact of diagnosing mild cases or variants of unknown significance
- Safety of HSCT and ERT, prior to or after symptom onset, short and long-term effects

Resources

- Financial impact of screening
- Financial impact of diagnosis, relative to existing practice (including false positives)
- Financial impact (including savings) of early intervention, relative to existing practice
- Financial impact of any change in clinical management following NBS (e.g., change in treatment approach when treatment occurs pre-symptomatically, genetic counselling, and other support services)
- Financial impact of ongoing monitoring and surveillance of patients with MPS I
- Cost effectiveness (cost per diagnosis; cost per QALY)

Other relevant considerations

- Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family, noting these are secondary to the outcomes delivered to the baby)
- Accuracy of the screening test (sensitivity, specificity, positive predictive value and diagnostic yield)
- Ethical considerations (equity of access, considerations regarding consent, considerations regarding cascade testing, including notification of carrier status)

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
Diagnosis of MPS I via the NBS programs would enable earlier diagnosis of the disease and consequently support timely access to intervention.

It is noted that the treatment choices would not change following the introduction of screening for MPS I as part of NBS. Newborns diagnosed with severe MPS I would continue to be referred for HSCT and those with attenuated disease may receive ERT. Newborns with IS may develop no disease manifestations until adulthood or even late adulthood. Thus, these children may receive regular monitoring for disease manifestations, and may not commence ERT until symptoms appear.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?
☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale
In terms of comparative benefits and harms, screening for MPS I as part of NBS to support early identification is claimed to be superior to the comparator of no NBS and diagnosis upon symptomatic presentation. The NBS program already acquires heel prick DBS samples from newborns, and this is considered to be an acceptably safe procedure. The addition of MPS I

screening to the NBS will not require any additional sampling, and thus, conducting the test does not raise any safety issues for the newborn.

Diagnosis of MPS I prior to the onset of symptoms supports timely access to intervention. Symptoms of MPS I occur due to cellular damage caused by accumulation of non-degraded GAGs in the lysosomes. If treatment commences before damage occurs, long-term health outcomes are improved.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
The aim of NBS is to identify individuals with disease before symptoms appear, so that early intervention can be implemented. This will decrease morbidity and mortality associated with the disease.

The test leads to the earlier diagnosis of MPS I (both the severe and attenuated forms). This allows clinicians to direct patient management, according to the severity of disease, for treatment with HSCT, with or without ERT, or ERT alone.

Identify how the proposed technology achieves the intended patient outcomes:
Please see response to the equivalent question under 'Intervention'.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? ☒ Yes ☐ No

Early diagnosis of MPS I changes management through allowing earlier access to treatment (see *Identify how the proposed technology achieves the intended patient outcomes*).

A change in health outcome? ☒ Yes ☐ No

Early intervention for MPS I would decrease morbidity and mortality associated with the condition (see *Identify how the proposed technology achieves the intended patient outcomes*).

Other benefits? ☒ Yes ☐ No

Please provide a rationale, and information on other benefits if relevant:
Earlier detection of MPS I enables the child and parents to receive genetic testing. With a definitive diagnosis, the family can seek advice from patient support groups before their child becomes symptomatic and access support services such a genetic counselling and reproductive technologies for family planning. Screening reduces or prevents the diagnostic odyssey and uncertainty associated with obtaining a definitive diagnosis for their child.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?
☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
As the comparator is no testing, the addition of a test will incur a cost. This cost would need to be considered against potential savings resulting from the reduction in cases presenting to health care facilities (e.g., emergency departments) with symptoms requiring urgent care, and associated testing (including possible misdiagnoses and retesting).

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Screening test accuracy					
1.	Population study	Burton et al. (2017). "Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience." The Journal of Pediatrics 190: 130-135.	MS/MS was used to assay for the 5 LSD-associated enzymes in DBS specimens obtained from 219,973 newborn samples sent to the Newborn Screening Laboratory of the Illinois Department of Public Health in Chicago. The incidence of MPS I was comparable with previously published estimates. Only 1 definite case of MPS I was detected. At age 6 weeks, she had symptoms consistent with severe MPS I.	https://doi.org/10.1016/j.jpeds.2017.06.048	2017
2.	Population study	Chan et al. (2019). "Taiwan National Newborn Screening Program by Tandem Mass Spectrometry for Mucopolysaccharidoses Types I, II, and VI." The Journal of Pediatrics 205: 176-182.	130,237 DBSs were collected consecutively as part of the national Taiwan newborn screening programs. Enzyme activities were measured MS/MS from DBS punches. If the first test was positive a second sample second DBS sample was tested. 120 (0.09%) newborns had enzyme activities lower than the cutoff value and were recalled for a second DBS. Most of the cases were ruled out based on the normal enzyme activities from their second DBS. This left only 5 (0.004%) newborns with decreased enzyme activity from both DBSs.	https://doi.org/10.1016/j.jpeds.2018.09.063	2019
3.	Population study	Chuang et al. (2018). "Status of newborn screening and follow up investigations for Mucopolysaccharidoses I and II in Taiwan." Orphanet Journal of Rare Diseases 13(1): 84.	294,196 infants were screened using MS/MS for MPS I. Of these infants, 8 suspected cases were referred for confirmation. Four were strongly suspected of having MPS I.	https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0816-4	2018
4	Review	Costello Medical (2019). Newborn Screening for Mucopolysaccharidosis Type I. External review against programme appraisal criteria for the UK National Screening Committee. UK, UK National Screening Committee.	This review looked at screening in newborn babies for MPS I. The review updated the previous UK NSC review, looking at all new evidence published since 2014.	https://view-health-screening-recommendations.service.gov.uk/mps-i/	2019
5	Pilot study	Elliott et al. (2016). "Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry." Molecular Genetics and Metabolism 118(4): 304-309.	Pilot study to identify enzyme deficiency in 6 LSDs 43,000 de-identified newborn DBS using FIA- MS/MS. For MPS I, the mean activity was 6.56 µmol/h/L. With a screen cutoff of 10% of the daily mean, 6 samples screened positive. After genotyping two babies carried variants with resultant enzyme activity at 4% of the daily mean were identified.	https://doi.org/10.1016/j.ymgme.2016.05.015	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6	Population study	Gragnaniello et al. (2023). Light and Shadows in Newborn Screening for Lysosomal Storage Disorders: Eight Years of Experience in Northeast Italy. Preprints, Preprints.	Report of 8-years experience of screening and follow up on 248,616 neonates screened for four lysosomal storage diseases (Pompe disease, mucopolysaccharidosis type I, Fabry disease, Gaucher disease), using enzyme activity assay by tandem mass spectrometry, and biomarker quantification as second tier test. 29 were positive for MPS I and 4 were confirmed to have the disease. Of the remaining 25 cases, 21 were pseudodeficient, 2 had VUS and 2 were carriers.	https://www.preprints.org/manuscript/202311.0727/v1	2023
7	Review	Schielen et al. (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 3(2): 6.	Screening for several LSDs is now feasible. Methods are available, both commercially and laboratory-developed and -validated, for up to 10 LSDs, sometimes in multiplex assays. Second-tier methods including biomarker quantification and rapid targeted DNA sequencing to help stratify the positives from first-tier newborn screening are being rapidly advanced.	https://www.mdpi.com/2409-515X/3/2/6	2017
Treatment outcomes					
8	Retrospective cohort study	Aldenhoven et al. (2015). "Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study." Blood 125(13): 2164-2172.	The goal of this international study was to identify predictors of the long-term outcome of patients with MPS IH after successful HSCT. Two hundred seventeen patients with MPS IH successfully engrafted with a median follow-up age of 9.2 years were included. Primary endpoints were neurodevelopmental outcomes and growth. Secondary endpoints included neurologic, orthopaedic, cardiac, respiratory, ophthalmologic, audiologic, and endocrinologic outcomes. Considerable residual disease burden was observed in the majority of the transplanted patients with MPS IH, with high variability between patients. Preservation of cognitive function at HSCT and a younger age at transplantation were major predictors for superior cognitive development posttransplant. A normal α-L-iduronidase enzyme level obtained post-HSCT was another highly significant predictor for superior long-term outcome in most organ systems.	https://ashpublications.org/blood/article/125/13/2164/33988/Long-term-outcome-of-Hurler-syndrome-patients	2015
9	Clinical study	Ghosh et al. (2016). "Enzyme replacement therapy prior to haematopoietic stem cell transplantation in Mucopolysaccharidosis Type I: 10year combined experience of 2 centres." Molecular Genetics and Metabolism 117(3): 373-377.	A report of the combined 10 year experience of ERT plus HSCT in two paediatric metabolic and transplant centres. Of 81 patients who underwent a first transplant procedure for Hurler, 88% (71/81) survived and 81% (66/81) were alive and engrafted at a median follow-up of 46 months (range 3–124 months). The incidence of grade II–IV acute and any chronic graft versus host disease was 17% and 11% respectively. Urinary GAGs were significantly reduced after a period of enzyme replacement therapy. In several individuals with decreased cardiac contractility, an improvement of their condition during enzyme replacement therapy enabled them to undergo transplantation.	https://doi.org/10.1016/j.ymgme.2016.01.011	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
10	Systematic review	Kemper et al. (2015). "Newborn screening for mucopolysaccharidosis type 1 (MPS I): a systematic review of evidence. Report of final findings." Final Version 1: 3-60.	The systematic evidence review of the potential benefits and harms associated with NBS for MPS I compared to usual care based on published and unpublished data. Observational data suggest that detection through screening compared to usual clinical case detection will not alter mortality in the first three- years of life. However, indirect observational data suggest that there may be an impact of early HSCT on cognitive development. NBS would be estimated to detect 44 cases of MPS I (range: 22-89) in the USA annually, with at least 29 (range:13-62) being severe.	https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/mps1-external-evidence-review-report.pdf	2015
11	Case report	Munoz-Rojas et al. (2008). "Intrathecal enzyme replacement therapy in a patient with mucopolysaccharidosis type I and symptomatic spinal cord compression." American Journal of Medical Genetics Part A 146A(19): 2538-2544.	Case report on the use of intrathecal (IT) laronidase in a MPS I patient with SCC who refused the surgical treatment. There were no clinically significant changes in serum chemistries. CSF GAG results revealed pretreatment values slightly above normal standards: 13.3 mg/L (NV<12 mg/L) which after IT laronidase infusions were within normal levels (10.3 mg/L). 12MWT presented a 14% improvement, with better performance on stability and gait control.	https://doi.org/10.1002/ajmg.a.32294	2008
12	Clinical study	Sauer et al. (2009). "Allogeneic blood SCT for children with Hurler's syndrome: results from the German multicenter approach MPS-HCT 2005." Bone Marrow Transplant 43(5): 375-381.	12 children with a median age of 14 months had HSCT. At a median follow-up of 29 months (range 2-85 months), all children were engrafted and had either stabilized or improved neurological function. One developed acute GVHD ≥grade II. RRT ≥grade II was observed in two patients.	https://www.nature.com/articles/bmt2008328	2009
13	Clinical study	Staba et al. (2004). "Cord-Blood Transplants from Unrelated Donors in Patients with Hurler's Syndrome." New England Journal of Medicine 350(19): 1960-1969.	20 consecutive children with Hurler's syndrome received busulfan, cyclophosphamide, and antithymocyte globulin before receiving cord-blood transplants from unrelated donors. The children were subsequently evaluated for engraftment, adverse effects, and effects on disease symptoms. Cord blood from unrelated donors appears to be an excellent source of stem cells for transplantation in patients with Hurler's syndrome. Sustained engraftment can be achieved without total-body irradiation. Cord-blood transplantation favourably altered the natural history of Hurler's syndrome in this study.	https://www.nejm.org/doi/full/10.1056/NEJMoa032613	2004

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
14	Review	Taylor et al. (2019). "Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future." Biology of Blood and Marrow Transplantation 25(7): e226-e246.	HSCT has proven to be an effective therapeutic option for various types of MPS. Previous concerns about the safety of the procedure have kept HSCT from being more widely used on different types of MPS patients. However, with the increased medical technology and awareness of the disease, the survival rates for HSCT has significantly improved. The more frequent use of HSCT in various types of MPS should be considered with careful selection of the patients since HSCT has proven to correct more clinical manifestations of the disease than only ERT. Also, one-time administration of the procedure allows for HSCT to be a more cost-effective option.	https://www.sciencedirect.com/science/article/pii/S1083879119301375	2019
15	Observational study	Wraith et al. (2007). "Enzyme Replacement Therapy in Patients Who Have Mucopolysaccharidosis I and Are Younger Than 5 Years: Results of a Multinational Study of Recombinant Human α-l-Iduronidase (Laronidase)." Pediatrics 120(1): e37-e46.	A prospective, open-label, multinational study of 20 patients who had MPS I and were <5 years old (16 with Hurler syndrome, 4 with Hurler-Scheie syndrome) and were scheduled to receive intravenous laronidase at 100 U/kg (0.58 mg/kg) weekly for 52 weeks. Investigators reported improved clinical status in 94% of patients at week 52. The mean urinary GAG level declined by approx.. 50% at week 13 and was sustained thereafter. The liver edge was reduced by 69.5% in patients with a palpable liver at baseline. The proportion of patients with left ventricular hypertrophy decreased from 53% to 17%. Global assessment of sleep studies showed improvement or stabilization in 67% of patients.	https://publications.aap.org/pediatrics/article/120/1/e37/70481/Enzyme-Replacement-Therapy-in-Patients-Who-Have?autologincheck=redirected	2007

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).
None identified.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
N/A

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
☐ Yes
☒ No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
N/A

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
The test can be undertaken on the sample already collected through the NBS program; additional costs depend on the type(s) of laboratory testing that is undertaken.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Nil.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
The comparator is no screening for MPS I; therefore, the difference in resource use is associated with the incremental cost of screening for MPS I as part of existing NBS programs.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
Newborns who receive an abnormal screening result for MPS I through NBS would receive confirmatory testing (leukocyte IDUA enzyme activity test, urine GAG analysis, sequencing of the *IDUA* gene). Those found to not have MPS I require no further intervention (false positive NBS). Those diagnosed with MPS I would receive clinical care, including treatment with HSCT and/or ERT where (and when) appropriate. Those with known mild forms of MPS I, where symptoms are not expected to appear until later in life, would receive continued surveillance. 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.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
Children presenting with symptoms consistent with MPS I undergo diagnostic testing (leukocyte IDUA enzyme activity test, urine GAG analysis, sequencing of the *IDUA* gene).

Testing urinary GAG levels

The level of urinary GAGs are elevated in patients with any MPS disorder, so detection of increased urinary GAGs measured by colorimetric detection reaction is usually the first diagnostic indicator of an MPS disorder. However, elevated urinary GAGs are not diagnostic.

In Australia, if elevated GAGs are detected, a urinary GAG subspecies LC MS/MS test for the non-reducing end that measures the native GAG fragments is performed. Each MPS type will have a specific non-reducing end reflective of the respective enzyme deficiency. This approach allows identification of 10 subtypes, including MPS I. This method has been used in the Women's and Children's Hospital, Genetics and Molecular Pathology, Adelaide, since receiving NATA accreditation in 2017 (Fuller 2020).

Leukocyte enzyme activity testing

If the initial urine screening is negative, a leukocyte enzyme activity test is conducted. 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.

Genetic testing

Those who are found to have MPS I receive genetic testing to identify the pathogenic variants responsible for the disease.

Clinical care

Individuals diagnosed with MPS I may be treated with HSCT and/or ERT, as appropriate. As MPS I is a progressive disease, further treatments for specific manifestations occur as required. 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 symptoms.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
The confirmatory tests (leukocyte/fibroblast IDUA enzyme activity test, urine GAG analysis, sequencing of the IDUA gene) used for the intervention are the same as the diagnostic tests used for the comparator.

If MPS I was added to NBS programs, more individuals will receive confirmatory testing with the proposed health technology than with the comparator health technology. This is due to the testing of newborns with false positive NBS results. With the comparator health technology only children presenting with symptoms consistent with MPS I would be tested. The use of healthcare resources would also be associated with monitoring and surveillance of diagnosed cases, particularly for those with variants of unknown significance or with mild forms of the condition (where time to symptomatic presentation is unknown).

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Current clinical management algorithm

This algorithm was originally designed as a general guide (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 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-CSF 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). This is not captured in the algorithm.

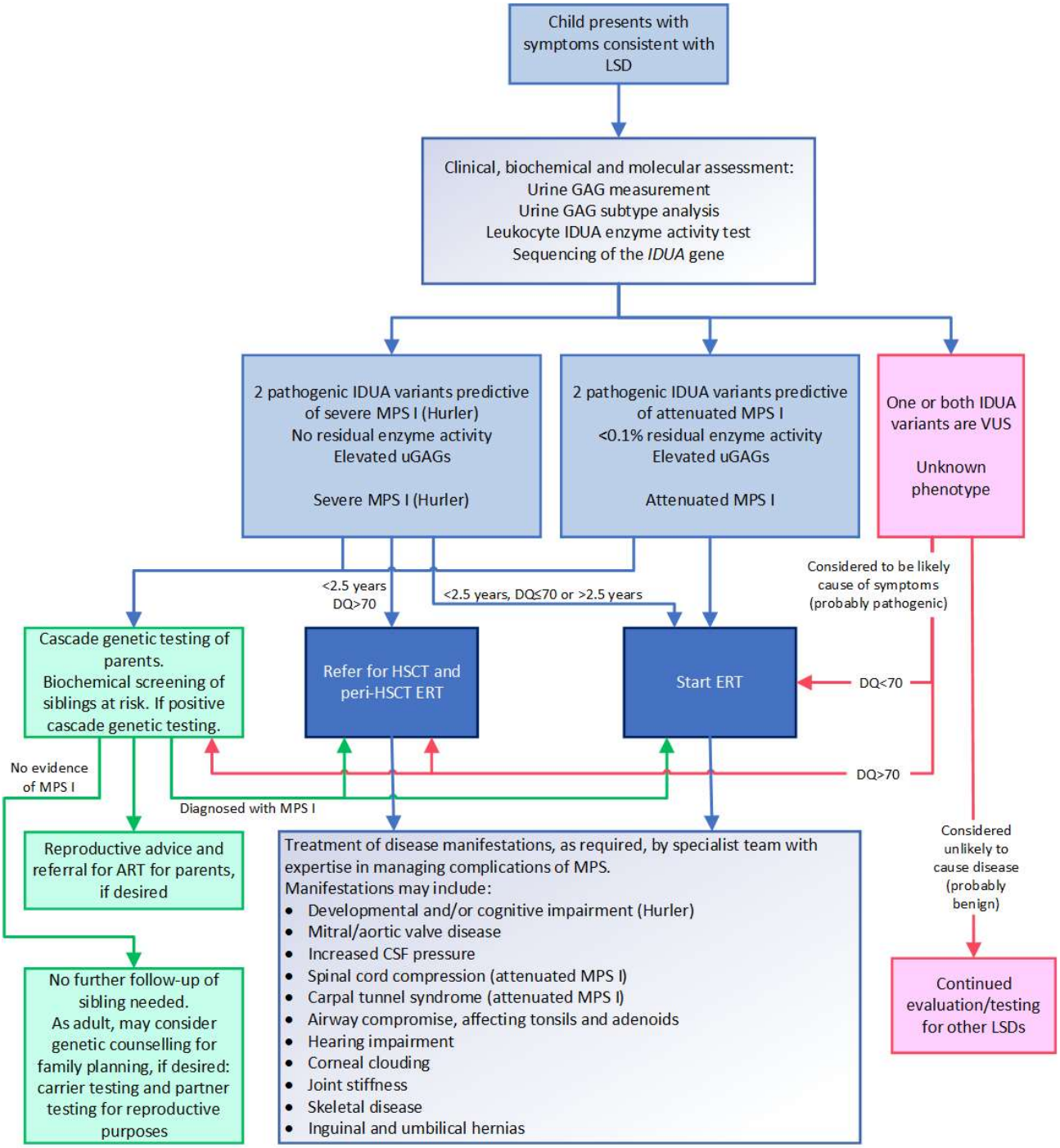

Figure 1 Current clinical management algorithm

ART = assisted reproductive technology; CSF= cerebrospinal fluid; ERT = enzyme replacement therapy; DQ = developmental quotient; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA = α-L-iduronidase; LSD = lysosomal storage disorder; MPS I = mucopolysaccharidosis type I; uGAG = glycosaminoglycans detected in urine; VUS = variants of unknown significance.

Source: modified from Bay et al (2021), Fuller (2020), Muenzer et al (2009), Stapleton et al (2019)

Proposed clinical management algorithm

Older asymptomatic siblings who have pathogenic variants of the *IDUA* gene diagnosed via cascade 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, it is possible that an older sibling aged 12-24 months may have undiagnosed Hurler syndrome.

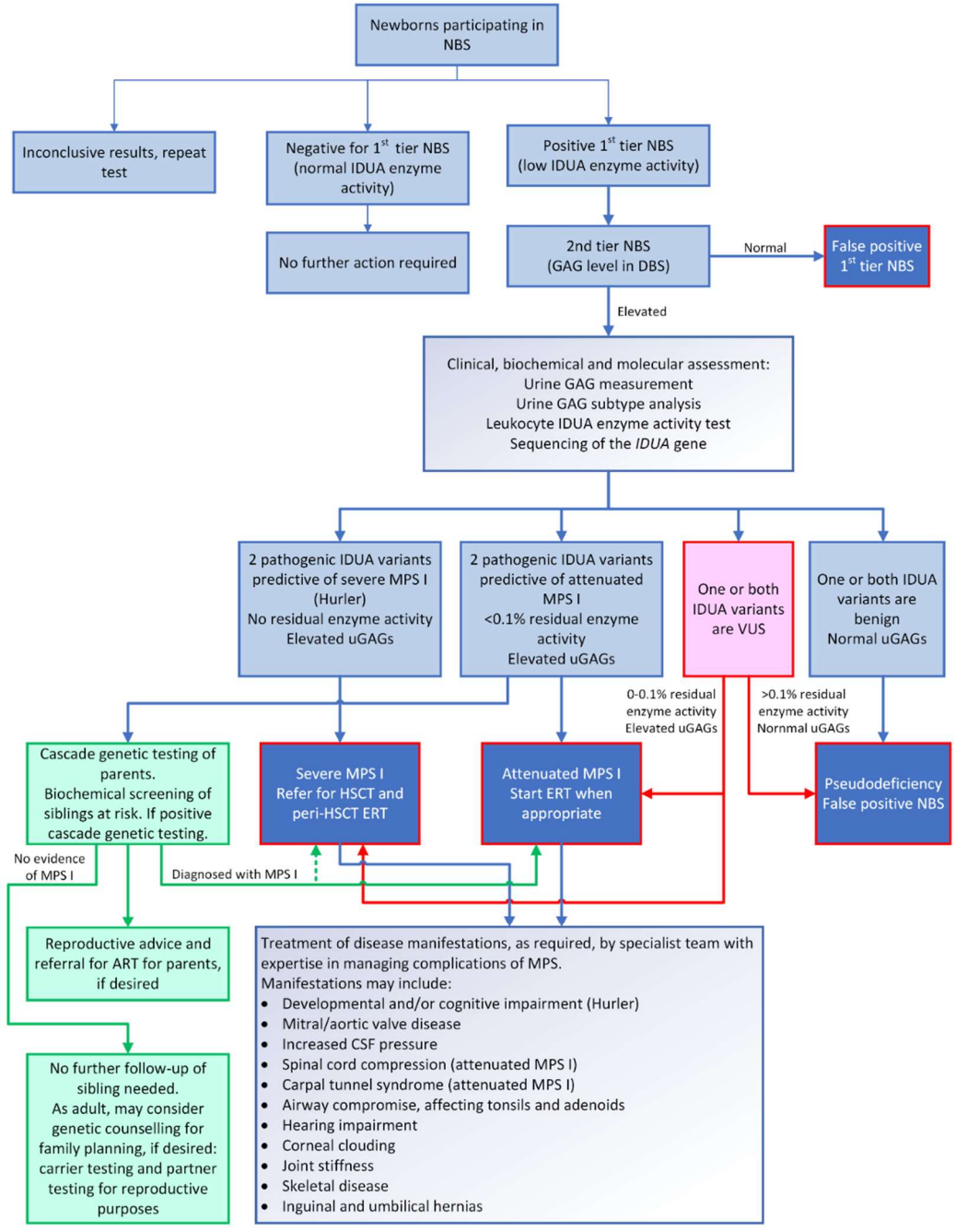

Figure 2 Proposed clinical treatment algorithm

ART = assisted reproductive technology; CSF= cerebrospinal fluid; DBS = dried blood spot; ERT = enzyme replacement therapy; GAG = glycosaminoglycan; HSCT = hematopoietic stem cell transplantation; IDUA = α-L-iduronidase; NBS = newborn bloodspot screening; MPS I = mucopolysaccharidosis type I; uGAG = glycosaminoglycans detected in urine; VUS = variants of unknown significance.

Source: modified from Costello Medical (2019), Bay et al (2021), Fuller (2020), Muenzer et al (2009), Stapleton et al (2019)