

MSAC Application 1776

Newborn bloodspot screening for mucopolysaccharidosis type II (MPS II)

PICO Set 1

Population

Describe the population in which the proposed health technology is intended to be used:

The target population for mucopolysaccharidosis type II (MPS II) screening 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 II (Hunter syndrome) is a rare X-linked recessive lysosomal storage disorder (LSD). It is a chronic progressive multisystem disorder that affects many tissues and organs. Characteristics and symptoms vary in severity across a continuum ranging from milder attenuated disease to severe disease (Ream et al. 2023).

MPS II is caused by pathogenic variants in the *IDS* gene encoding the enzyme iduronate-2-sulfatase (I2S; OMIM 309900). Pathogenic variants in the *IDS* gene lead to a deficiency in the I2S enzyme resulting in the accumulation of two glycosaminoglycans (GAGs), dermatan sulphate (DS) and heparan sulphate (HS) in the lysosomes within cells. Accumulation of GAGs leads to lysosomal hypertrophy and an increase in the number of lysosomes within cells. Over time, this causes progressive, usually permanent, cellular damage in affected individuals. This leads to development of somatic manifestations and, in the more severe cases, neuronopathic manifestations of MPS II (Ream et al. 2023).

Natural history of MPS II

MPS II has historically been broadly divided into two forms:

- a severe (neuronopathic) form with CNS involvement and earlier onset
- a milder attenuated (non-neuronopathic) form with later onset

MPS II is a life-limiting disorder with life expectancy determined by symptom severity and neuronopathic involvement. Two thirds of individuals diagnosed with MPS II have the severe form characterised by earlier onset of symptoms, more rapid disease progression and neuronopathic involvement, leading to symptoms of significant neurological impairment including cognitive disability and behavioural problems (Ayodele et al. 2022).

At birth, newborns with MPS II do not present with obvious physical characteristics of the disorder. At around two to four years of age, facial features and somatic symptoms characteristic of MPS II start to appear. Coarseness of facial features, delayed development of motor and cognitive milestones, short stature, and abdominal distention are often the first characteristics observed by parents, prompting them to seek clinical advice. Over time affected children develop full lips, large cheeks, a broad nose, and a large tongue. The vocal cords enlarge which deepens the voice. They have frequent upper respiratory infections and sleep apnoea due to narrowing of the airway (D'Avanzo et al. 2020; Martin et al. 2008; MedlinePlus Genetics 2023). Between the ages of 6 and 8 years old, children with the severe form of MPS II begin to regress developmentally, losing their basic motor skills. As many organs and tissues are affected in MPS II, there are multiple characteristics and manifestations including a large head, hydrocephalus, short neck, an enlarged liver and spleen, umbilical or inguinal hernia, hearing loss, reduced vision, carpal tunnel syndrome, narrowing of the spinal canal compressing the spinal cord, and heart valve abnormalities leading to heart rhythm abnormalities and heart failure. Patients tend to be tall for their age until around 4 or 5 years of age. Growth of a child with MPS II slows at around 5 years old resulting in short stature.

Joint contractures develop that significantly affect mobility and multiple skeletal abnormalities called dysostosis multiplex are observed (D'Avanzo et al. 2020; Martin et al. 2008; MedlinePlus Genetics 2023). Without treatment, life expectancy is 10 to 20 years with death usually caused by obstructive airway disease and/or cardiac failure (Martin et al. 2008).

Compared to patients with severe MPS II, patients with attenuated MPS II have much later onset of symptoms, slower progression of peripheral signs/symptoms, and normal intelligence due to limited or no neuropathic involvement. Many of the symptoms of MPS II are similar between the severe and attenuated forms of MPS II (e.g., characteristic appearance and skeletal abnormalities) but are generally milder in the attenuated form. The main difference between the severe and attenuated forms is neurological involvement in the severe form including cognitive impairment and severe behavioural problems (D'Avanzo et al. 2020). Life expectancy for individuals with attenuated MPS II is significantly greater at around 60 to 70 years.

The Hunter Outcome Survey (HOS) is a voluntary registry that collects data regarding patients with MPS II in 29 countries, not including Australia. A study of 263 MPS II patients registered in the HOS reported that over 80% of patients experienced at least one neurological (84%) or cardiovascular (82%) symptom, as well as involvement in the abdomen, head and neck, skeleton, ear, mouth, and chest and lungs. At least 60% of patients additionally reported throat, skin, nose and gastrointestinal symptoms (Wraith et al. 2008). An analysis of patients from the HOS (treated and untreated) reported the median age of symptom onset at 1.5 years (ranging from 1.2 years for otitis media, to 6.1 years for cardiac valve disease), and a median age at diagnosis of 3.2 years (Burton et al. 2017).

As MPS II is a heterogenous multisystem condition, early characteristics and symptoms can overlap with other childhood syndromes or more common ailments. Consequently, a diagnosis can be difficult which may be exacerbated by lack of awareness and limited experience of this rare disorder. This can lead to misdiagnosis and/or delayed diagnosis (Wiśniewska et al. 2022). Patients and their families often endure a long diagnostic odyssey before receiving a definitive diagnosis with a typical diagnostic delay for MPS II of several years. Once a diagnosis of MPS II or similar condition is suspected, the patient is referred to a specialist metabolic disorders clinic for further clinical assessment and diagnostic testing to determine their I2S enzyme levels in blood and GAG levels in urine. These tests may be followed by genetic testing to identify the causative *IDS* gene variant.

Screening for this condition, currently performed in other countries such as the US and Taiwan, can be performed using comparable methods to diagnostic tests for MPS II.

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

MPS II is caused by deficiency of the lysosomal I2S enzyme that catalyses the first step in the breakdown of GAGs, HS and DS. The closely related condition MPS I is caused by deficiency of the lysosomal enzyme iduronidase (IDUA), catalysing the second step in the degradation of HS and DS (Filocamo et al. 2018). Both MPS I and MPS II result in accumulation of the GAGs DS and HS.

Genetics of MPS II

The *IDS* gene on the X chromosome spans 44 kb and has nine exons (D'Avanzo et al. 2020). A pseudogene of *IDS* called *IDSP1* is located close to the *IDS* gene. Some regions of the pseudogene are homologous to *IDS*, with exon 3 of the pseudogene being identical to exon 3 of the *IDS* gene

(D'Avanzo et al. 2020). This similarity increases the frequency of large gene rearrangements due to homologous recombination and makes genetic analysis of *IDS* variants more complex.

MPS II is characterized by high genetic heterogeneity as most of the *IDS* variants identified are private or novel. More than 700 *IDS* variants have been identified according to the Human Gene Mutation Database. It is estimated that approximately 10–33% of *IDS* variants identified are *de novo* rather than familial (Filocamo et al. 2018; NewSTEPs 2022; Pollard, Jones & Wood 2013). Around 50% of *IDS* variants identified to date are missense/nonsense mutations, followed in frequency by small deletions, splicing variants, gross deletions, complex rearrangements, small indels, and gross insertions (D'Avanzo et al. 2020). Large deletions of the *IDS* gene have also been identified that are not caused by homologous recombination.

High genetic heterogeneity associated with MPS II means that identifying genotype–phenotype relationships has been difficult (Filocamo et al. 2018; Vollebregt et al. 2017). While affected family members with the same variant tend to share a similar phenotype, there are different phenotypes in unrelated MPS II patients carrying the same variant suggesting that genetic modifying processes or environmental factors may be involved (D'Avanzo et al. 2020). However, some variants have been linked to specific phenotypes. For example, complete deletion of the *IDS* gene has been consistently associated with severe MPS II (Seo et al. 2020; Vollebregt et al. 2017).

Some individuals have *IDS* gene variants associated with I2S pseudodeficiency. When these patients are tested, they exhibit low I2S enzyme levels (~ 5–15% of normal activity) but normal urinary GAG levels and no symptoms of MPS II (NewSTEPs 2022). These patients are asymptomatic because they have sufficient I2S activity to prevent accumulation of GAGs. Both the proposed NBS method and the current testing method for MPS II diagnosis can differentiate between individuals with MPS II and those with pseudodeficiency, preventing misdiagnosis and unnecessary treatment.

Genetic testing of the *IDS* gene would be carried out in babies positive for MPS II on NBS screening as part of the confirmatory diagnostic testing to identify the specific variants involved. While current understanding of genotype/phenotype associations are limited for MPS II, some variants have been linked to the more severe form of MPS II and may guide treatment decisions. Cascade genetic testing would also be available to family members (siblings and parents) if a causative variant is identified.

Inheritance of MPS II

As an X-linked recessive disorder, MPS II primarily affects males. MPS II is usually inherited from a mother carrying an *IDS* pathogenic variant (carrier). In line with X-linked inheritance patterns, a carrier biological mother and unaffected biological father have a 50% chance that a daughter will be a carrier (50% chance that she will not be a carrier) and a 50% chance that a son will be affected (50% chance that he will be unaffected and not a carrier). All daughters of an affected father would be carriers, while all sons would be unaffected and not carriers.

While most females that are MPS II carriers are asymptomatic, they can have slightly lower I2S enzyme levels compared to normal females (non-carriers), although often within the normal range. Females are rarely diagnosed with MPS II, and when they are it is usually due to abnormalities in the structure of the X-linked chromosome or the inactivation process of the X-chromosome (Kemper 2022).

Genetic counselling, reproductive advice, and prenatal testing would benefit all individuals who are planning to have children and have been diagnosed with MPS II or identified as a carrier for MPS II.

Incidence in Australia

The distribution and incidence of MPS II is variable based on geographical region and/or ethnic background (Çelik et al. 2021).

A study of the Western Australian population from 1969-1996 reported an estimated incidence of MPS II of 0.31 per 100,000 live births and 0.6 per 100,000 male live births. The incidence rate was calculated by dividing the total number of cases diagnosed prenatally and postnatally by the total number of live births or total number of male live births during the study period. In all cases, the diagnosis was confirmed by one dimensional electrophoresis of urinary GAGs and/or by enzyme assay on leucocytes or fibroblasts (Nelson et al. 2003).

Another Australian study of the incidence and prevalence of LSDs reviewed data from the national referral laboratory for LSD diagnosis in Australia over 12 years (2009 to 2020). The laboratory diagnosis of MPS II was made by a combination of biochemical assessments (deficient I2S enzyme and/or elevated GAG biomarkers) and genetic testing. The number of live births was obtained from the Australian Bureau of Statistics. The estimated incidence of MPS II was 0.57 per 100,000 live births, with all cases diagnosed being male (Chin & Fuller 2022).

The Expert Panel for the Life Saving Drugs Program (LSDP) review of the enzyme replacement therapy (ERT) idursulfase (ELAPRASE®) reported that the best prevalence estimate for MPS II in Australia is between 0.13 and 0.3 per 50,000 people, which is below the 1:50,000 threshold for a rare disease under the LSDP (Australian Government Department of Health and Aged Care 2023a).

A study based on an international assessment of all MPS disorders estimated the birth incidence of MPS II to be in the range of 0.13 (Norway) to 2.16 (Estonia) cases per 100,000 births (Çelik et al. 2021). The prevalence in Japan and Taiwan based on clinical identification has been reported to be 0.84 to 1.07 per 100,000 births (Çelik et al. 2021). In the US, NBS programs in Illinois and Missouri published preliminary, estimates of 0.9 and 1.3 diagnosed MPS II cases per 100,000 newborns screened (Bilyeu et al. 2020; Burton, Hickey & Hitchins 2020).

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 II as part of the newborn screening program would allow for early detection and treatment in affected babies and support improvement in clinical outcomes for these children.

The potential advantage of NBS for MPS II is that newborn babies with MPS II will be identified shortly after birth before they develop characteristic features and symptoms of the disease caused by accumulation of GAGs. A newborn with a positive MPS II screening result would receive confirmatory diagnostic testing at a specialist metabolic disorders clinic and, if required, earlier access to MPS II treatment 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.

A systematic review by the US Health Resources and Service Administration (HRSA) was commissioned for the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in 2022 to consider the potential inclusion of MPS II in the Recommended Uniform Screening Panel (RUSP). This report investigated the benefit of early (less than 1 year of age) versus late (greater than 1 year of age) initiation of ERT for MPS II (Kemper 2022). In February 2022, the ACHDNC recommended the addition of MPS II to the RUSP based on the accuracy of screening, the likely benefit of pre-symptomatic treatment, and the feasibility of implementing MPS II NBS. The recommendation was accepted by the Secretary of Health and Human Services. The committee concluded that early detection could lead to early treatment, which has clinical benefit for somatic non-CNS complications, including musculoskeletal progression and organ involvement. The Secretary of Health and Human Services requested a follow-up report in 5 years reviewing the status of US state implementation of MPS II screening, access, and cost of treatment for infants diagnosed with MPS II and the impacts on families (Kemper 2022).

The evidence review reported that there were no prospective studies that directly compared the benefit of pre-symptomatic ERT to the benefits for patients who commence ERT when already symptomatic, but retrospective studies where treatment was stratified by age and description of siblings with MPS II were identified. A number of sibling case studies reported that earlier initiation of ERT was associated with improved health outcomes, including reduced severity of symptoms, less reliance on family for day-to-day activities and comparatively better IQ than the sibling who started treatment at a later age (Kemper 2022; Tajima et al. 2013; Tomita et al. 2021; Tyłki-Szymanska et al. 2012; Vashakmadze et al. 2021).

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It should be noted that the proposed NBS screening strategy for MPS II does not identify newborns that are MPS II genetic carriers, as although these patients may have lower I2S enzyme activity, they usually have GAG levels within the normal range. Similarly, newborns with pseudodeficiency also have low I2S activity but GAG levels that fall within the normal range. The screening approach used in current NBS programs is designed to exclude these “pseudodeficient” newborns as false positives.

Genetic testing to identify the causative variant in the *IDS* gene currently has limited prognostic utility due to poor genotype/phenotype correlation (Vollebregt et al. 2017). However, earlier genetic testing following a positive NBS result for MPS II allows cascade testing of parents and siblings to confirm if they are MPS II carriers or are affected by MPS II if they have not been previously diagnosed. However, a causative variant identified by genetic testing in an index case may be *de novo* in origin rather than familial.

Intervention

Name of the proposed health technology:

The proposed health technology is universal NBS for MPS II 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 (Australian Government Department of Health and Aged Care 2023b; Huynh et al. 2022).

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 (NBS NPF) (O'Leary & Maxwell 2015).

It is proposed that MPS II be added to existing programs to support early diagnosis and intervention to improve clinical outcomes for both the severe and attenuated forms of MPS II.

Describe the key components and clinical steps involved in delivering the proposed health technology:

The identification of individuals at risk of developing MPS II 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 II will utilise the same DBS samples and is expected to employ a two-tiered method in Australian newborn screening laboratories based on:

- Measurement of I2S enzyme activity using liquid chromatography tandem mass spectrometry (LC-MS/MS) or fluorometric enzymatic assay (first-tier screening test)
- Measurement of GAG (dermatan sulphate and heparan sulphate) levels using a dried bloodspot sample and LC-MS/MS is carried out in patients with a positive first-tier test result (second-tier screening test).

Use of the two-tier screening approach proposed should decrease the number of false positive results for MPS II (due to pseudodeficiency) identified through NBS that are referred for subsequent confirmatory diagnostic testing (Herbst et al. 2022).

Measurement of I2S enzyme activity in DBS samples (first-tier screening test)

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 dried bloodspot punch. The mixture is then incubated at 37°C for a prescribed period prior to measuring the enzymatic activity. In NBS programs, I2S enzyme activity is usually measured by fluorometry or tandem mass spectrometry (MS/MS) in dried bloodspot samples (Gelb et al. 2022).

Fluorometric assays

Fluorometric enzyme assays identify samples with reduced enzyme activity by using an artificial substrate with a fluorescent tag, 4-methylumbelliferyl (4-MU)-glycoside. 4-MU-glycosides are acted on by lysosomal enzymes enabling quantification of the enzyme products by fluorescence. Kumar et al (2015) reported that the intrinsic fluorescence of the 4MU-glycoside substrates results in higher background noise than tandem MS/MS assays, reducing their analytical range (Kumar et al. 2015). However, pilot results from Taiwan, Illinois, and Missouri for MPS II NBS indicate that both tandem MS/MS and fluorometry can be effective (Arunkumar et al. 2020).

Tandem mass spectrometry (MS/MS)

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 analytes are fractionated using a liquid-liquid extraction step with ethyl acetate.

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

The Illinois NBS laboratory was the first to use LC-MS/MS to quantitate enzyme products as a primary screening test 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 test was recently expanded to include I2S for MPS-II. A second assay is used for MPS II because the product of I2S enzymatic activity is the substrate for IDUA (MPS I). One 3 mm dried bloodspot punch is incubated in an assay reagent for all enzymes except IDS. A second 3 mm dried bloodspot 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.

Measurement of GAGs (dermatan sulfate and heparan sulfate) levels in dried bloodspot samples (second-tier screening test)

As the assay to detect I2S enzyme activity has a low positive predictive value due to the detection of individuals with pseudodeficiencies, samples with a positive first-tier test result (i.e., samples with low I2S enzyme activity) would undergo a second NBS test to determine the level of GAGs in the dried bloodspot 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. This reduces the number of false-positives as a normal result of the second-tier test overrules the first-tier test result.

For MPS II, a high proportion of below-cutoff enzyme activity levels (< 10% of median normal activity) detected by the first-tier I2S activity assay are due to pseudodeficiency. The measurement of GAGs in a separate punch from the same dried bloodspot sample differentiates between true I2S deficiency due to MPS II and pseudodeficiency (Herbst et al. 2022). Individuals with pseudodeficiency have normal levels of GAGs in the dried bloodspot sample whereas individuals with I2S deficiency due to MPS II have elevated GAG levels.

Identify how the proposed technology achieves the intended patient outcomes:

The key aim of NBS screening for MPS II is to identify newborns with the condition before symptoms appear, so that a diagnosis can be confirmed, and treatment can be started that might delay or prevent complications associated with the MPS II. Evidence will be provided in the assessment report that early intervention leads to health benefits for patients.

Currently individuals are referred for further clinical assessment and diagnostic testing when the clinician has a suspicion that the patient has MPS II based on signs, symptoms, and prior clinical investigations/interventions suggestive of MPS II or after the detection of an affected family member. If diagnosis only occurs after symptomatic presentation, a patient already has complications associated with accumulation of excess GAGs in the lysosomes.

Clinical assessment and diagnostic testing

Newborns receiving an abnormal or indeterminate screening result for MPS II need to be referred for clinical assessment and confirmatory diagnostic testing, including plasma or peripheral blood leukocyte I2S enzyme activity analysis, analysis of GAG levels in urine, testing for another sulfatase to exclude multiple sulfatase deficiency and genetic analysis to identify the causative *IDS* gene variant.

Genetic testing is not essential for a confirmed diagnosis of MPS II. Due to genetic heterogeneity and the need for expert interpretation due to the presence of the *IDS^{P1}* pseudogene, genetic testing is used for confirmatory testing, in the context of clinical and metabolic assessment. Genetic testing may identify an *IDS* variant of unknown significance (VUS). Identification of the causative variant permits cascade genetic testing to identify other affected family members or genetic carriers of MPS II. This may inform future treatment and reproductive options.

Treatment and ongoing management

In cases where a MPS II diagnosis is confirmed or uncertainty remains regarding the diagnosis following confirmatory testing, the patient and their family should be referred to a metabolic disorders clinic to discuss the MPS II diagnosis, treatment options and cascade genetic testing for family members (for parents and siblings initially) with a metabolic disease specialist and clinical geneticist.

Individuals with a confirmed diagnosis of MPS II require ongoing clinical management and monitoring of symptoms by a multidisciplinary team (Muenzer et al. 2009). Expert advice has indicated that regular clinical surveillance of the baby would be carried out during childhood (at ~6 month intervals) to monitor for symptoms consistent with development of the severe form of MPS II. Many patients with the severe form of MPS II will develop potentially life-threatening manifestations by the second decade of life. Beyond childhood, clinical assessment would only occur if a patient presented with symptoms of MPS II, as the patient would be more likely to have the later onset slowly progressing attenuated form of MPS II. Regular monitoring during childhood and uncertainty

around the implications of an MPS II diagnosis (e.g., severity at presentation) places an additional burden on both the patient and family particularly as a newborn with MPS II appears normal at birth when NBS is carried out.

Current treatments are not curative but aim to manage the symptoms of MPS II. The goals of managing MPS II are to improve quality of life, slow down progression, and to prevent permanent tissue and organ damage (Scarpa et al. 2011). Early intervention may help prevent irreversible damage.

While patients may benefit from earlier diagnosis and treatment, they are also exposed to the burdens and risks of treatment prior to the appearance of symptoms associated with MPS II and this also places an additional burden on the family. Treatment options for MPS II are currently limited to ERT requiring weekly attendance at a clinic for IV infusions, which is well tolerated, and/or hematopoietic stem cell transplantation (HSCT) which risks serious adverse events such as graft versus host disease and mortality. There is currently limited evidence to support use of either treatment in young babies or the impact of long-term treatment on morbidity or mortality. Additionally, ERT has limited treatment efficacy for neurological symptoms in patients with the severe form of MPS II that occurs in around two thirds of babies with MPS II. ERT does not cross the blood/brain barrier and therefore has little or no impact on symptoms due to neurological involvement. However, there is some evidence that ERT treated babies with severe MPS II may still benefit from improvements in some of their somatic symptoms (Scarpa et al. 2011).

Enzyme replacement therapy (ERT)

Intravenous ERT with idursulfase (ELAPRASE®; ARTG 129481), a human recombinant I2S enzyme, is currently the preferred treatment for MPS II. It is indicated for the long-term treatment of patients with MPS II. The recommended dosage regimen is 0.5 mg/kg of body weight administered every week as an intravenous infusion. The recommended infusion time is 3 to 8 hours. Treatment should be supervised by a physician or healthcare professional experienced in the management of patients with MPS II or other inherited metabolic disorders (Therapeutic Goods Administration 2008). ERT is generally well tolerated. The most common treatment related adverse events associated with use of ERT are infusion-related reactions and hypersensitivity reactions that can in some cases be life threatening (Therapeutic Goods Administration 2008). Patients may also develop antibodies, including neutralising antibodies, to idursulfase although these antibodies do not always impact on treatment efficacy.

A phase II/III trial of idursulfase in individuals with attenuated MPS II over the age of 8 years who were cognitively intact demonstrated improvement in some somatic manifestations (Muenzer et al. 2006). There were significant improvements in the six-minute walk test (6MWT) distance and forced vital capacity on pulmonary function tests (PFT), but not in percentage of predicted forced vital capacity in the treated group when compared to the placebo group at 53 weeks (Muenzer et al. 2006). In the two-year extension study, statistically significant increases in 6MWT distance and absolute forced vital capacity were observed at the end of the study. There were also improvements in mean liver and spleen volumes, while the shoulder joint range of motion improved and remained stable in other joints. The authors concluded that ERT resulted in sustained clinical improvement during 3 years of treatment in the study population (Muenzer et al. 2011).

The studies on idursulfase included patients with attenuated MPS II and excluded patients with neuronopathic involvement (Muenzer et al. 2011; Muenzer et al. 2007; Muenzer et al. 2006). Idursulfase does not cross the blood-brain barrier and therefore does not affect the cognitive and behavioural manifestations associated with the severe form of MPS II (Scarpa et al. 2011). ERT has been associated with somatic improvements in the most severe patients but has not resulted in cognitive benefits (Muenzer et al. 2012). Thus, ERT might benefit the newly identified cases of MPS II even with the severe form of MPS II, but not those with end-stage brain disease. Novel approaches (e.g., intraventricular or intrathecal) of ERT delivery and newer therapies currently under development may improve treatment outcomes for the neuronopathic aspects of severe MPS II (Kemper 2022).

In the review of idursulfase treatment funding by the Australian LSDP, the Expert Panel noted there were many positive aspects to idursulfase treatment as experienced by patients, their families and treating physicians. Important outcomes for adult and paediatric patients with MPS II were stabilisation and reduction of respiratory symptoms, improved mobility and range of motion, improved tolerance for and reduced need for surgery, reduced liver size, improved quality of life (QoL), improved sleep, and increased life expectancy (Australian Government Department of Health and Aged Care 2023a). These observations are in line with other evidence reviews of ERT treatment (da Silva et al. 2016; Kemper 2022; McBride, Berry & Braverman 2020; Ream et al. 2023; Scarpa et al. 2011; Žuber et al. 2023).

There is limited data on the benefits and risks of ERT treatment in babies aged under 1 year as most data published for young children are derived from retrospective studies, mainly family and matched sibling case reports and case series (Kemper 2022). However, as MPS II is a rare disorder these studies provide some insight into the benefits of treatment for individual patients.

There are no treatment guidelines for MPS II in Australia. Guidance has been developed in Europe and the US (McBride, Berry & Braverman 2020; Scarpa et al. 2011). The current European guidelines were developed in 2011 by the Hunter Syndrome European Expert Council (HSEEC). The guidance recommends that patients are closely monitored and undergo a comprehensive physical, biochemical, and behavioural evaluation, ideally at a specialist LSD clinic, every 6 to 12 months, or more frequently if they have signs or symptoms of MPS II that are progressing rapidly (Scarpa et al. 2011).

Recent US guidance on treatment of MPS II from a Delphi derived practice resource from the American College of Medical Genetics and Genomics (ACMG) made consensus-based treatment recommendations as a previous systematic evidence-based review of treatment for MPS II was unable to create a definitive practice guideline based solely on published evidence (McBride, Berry & Braverman 2020). Regarding ERT treatment, the Delphi study recommended:

- All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting ERT, prior to showing signs or symptoms.
- Individuals with signs or symptoms with either attenuated or severe MPS II warrant ERT.
- Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.

Given that newborns identified by NBS appear normal (i.e., without apparent symptoms) at birth and it is not possible to reliably distinguish between the severe and attenuated forms of MPS II based on

biochemical and genetic testing, it might be difficult to predict whether the disease will progress to the severe form prior to a child becoming symptomatic.

The European guideline considers that because there is a clear relationship between progressive GAG storage and clinical manifestations in MPS II, ERT should be initiated as early as possible after diagnosis. The consensus opinion of the authors was that due to the heterogeneous nature of MPS II and the variable rate of progression, it would be reasonable to offer ERT to all patients for at least 12-18 months, regardless of MPS II phenotype, after which a decision would be made as to whether to continue in consultation with the parents. The primary concern would be impact on the patient's quality of life. Evidence of central nervous system (CNS) disease progression would be taken into consideration when deciding to continue treatment (Scarpa et al. 2011).

There are no predefined discontinuation rules for ERT. The decision to stop treatment is based on a patient's individual circumstances and clinical judgement. A decision in the best interests of the patient is made following discussions with the patient and/or their family (Scarpa et al. 2011). In Australia, funding for ERT through the LSDP is contingent on continuing to meet eligibility criteria, as described below.

Eligibility for subsidised ERT (idursulfase; ELAPRASE®) treatment in Australia

ERT (idursulfase; ELAPRASE®) has been funded in Australia since 2008. Funding is provided for eligible individuals diagnosed with MPS II through the Commonwealth LSDP. A patient must continually meet the LSDP funding conditions in order to remain eligible for ERT (Australian Government Department of Health and Aged Care 2022). The LSDP for idursulfase treatment was reviewed by an Expert Panel in 2020 (Australian Government Department of Health and Aged Care 2023a). The patient must present with at least one of the following complications of MPS II to be eligible for treatment with idursulfase:

- Sleep disordered breathing: Patients with an Apnoea/Hypopnoea Incidence of >5 events/hour of total sleep time or more than 2 severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
- Respiratory function tests: Patients with FVC less than 80% of predicted value for height.
- Cardiac: Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 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 greater than 10 degrees from normal in shoulders, neck, hips, knees, elbows or hands.
- Infants and children aged less than 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 II, for example by genotyping, with clear prediction of progress of the disease, or if, on the basis of a sibling's disease progression, severe disease can be predicted.

The LSDP guidelines for initial application and annual reapplication for subsidised treatment for MPS II state that "a patient must not be suffering from any other medical condition, including complications or sequelae of MPS II, that might compromise the effectiveness of the drug treatment".

The LSDP Expert Panel review report of the LSDP idursulfase treatment guidelines estimated that approximately 90% of patients with MPS II in Australia have symptoms of end-organ damage and were therefore eligible for access to LSDP-subsidised treatment. The majority (85%) of these eligible patients accessed treatment on the LSDP (Australian Government Department of Health and Aged Care 2023a). Newborns identified with a severe form of MPS II following NBS will be asymptomatic in the majority of cases and will fall into the current LSDP criteria for infants and children aged <5 years (Australian Government Department of Health and Aged Care 2022). To maintain eligibility for LSDP funding, the patient's clinician must reapply annually demonstrating clinical improvement in the patient or stabilisation of the patient's condition attributable to idursulfase treatment (Australian Government Department of Health and Aged Care 2022). Expert advice suggests that when treatment is initiated in an asymptomatic baby diagnosed following NBS, some outcome assessments required as part of subsequent reapplication process may not be considered appropriate for assessment of very young babies.

Hematopoietic Stem Cell Transplantation (HSCT)

ERT cannot cross the blood-brain barrier and therefore has a limited impact on CNS symptoms. HSCT has been investigated and used to treat patients with the severe form of MPS II characterised by CNS involvement because peripheral blood monocytes can cross the blood-brain barrier and may establish in the CNS as microglial cells (Taylor et al. 2019). Recipients of HSCT can use donor cells from bone marrow, peripheral blood, or umbilical cord blood. An allogeneic HSCT (i.e., using bone marrow from a donor who does not have MPS II) can increase I2S activity. Patients with MPS II who receive HSCT may need additional treatment including ERT.

The number of patients that have received HSCT for MPS II in Australia is very small based on expert advice. HSCT is not often recommended as an initial treatment for MPS II as it is a serious medical procedure associated with potentially life-threatening adverse events. Risks include serious infections after the procedure and other problems, such as graft versus host disease.

Authors of a recent review of early versus late treatment with HSCT therapy concluded that HSCT has a disease modifying effect and that early HSCT can positively impact on neurological disease progression in patients with severe MPS II. It may offer an effective treatment strategy for children diagnosed with the severe form of MPS II through NBS if clinical assessment, biochemical testing, and genetic testing have utility for predicting severe MPS II. However, further research is required to establish how long HSCT remains effective in children with MPS II (Sreekantam et al. 2022).

A retrospective study in Japan to evaluate the efficacy and benefit of HSCT in MPS II patients assessed activities of daily living (ADL), IQ, brain magnetic resonance image (MRI) lesions, cardiac valvular regurgitation, and urinary GAG over a follow-up period of 9.6 ± 3.5 years. They concluded that the utility of HSCT should be re-evaluated for the treatment for MPS II and that HSCT may be beneficial when it is performed before signs of brain atrophy appear on MRI and before heart valvular regurgitation occurs (Tanaka et al. 2012). It is difficult to estimate the cost of HSCT because of many factors impacting on the cost (e.g., age at transplantation, the type of donor, preconditioning regimen used, potential complications, and other out-of-pocket expenses).

Disease specific treatments under development

Because idursulfase does not significantly cross the blood-brain barrier, the role of delivery of ERT directly to the CNS, either intrathecally or intraventricularly, for individuals with severe MPS II is an active area of research (Muenzer et al. 2022a, 2022b; Seo et al. 2023).

Gene therapy for MPS II is focused on delivery of the *IDS* gene using viral vectors (e.g., adeno-associated viruses, lentiviruses or retroviruses) or *in vivo* gene therapy based on genome editing (Wood & Bigger 2022; Zapolnik & Pyrkosz 2021).

Other interventions

Additional treatment of individual manifestations will most likely be required throughout the course of the disease. Common interventions required as the symptoms of MPS II become apparent during disease progression include developmental, occupational, and physical therapy; shunting for hydrocephalus; tonsillectomy and adenoidectomy; continuous positive pressure ventilation (or tracheostomy); carpal tunnel release; cardiac valve replacement; inguinal hernia repair; and hip replacement (Joseph, DiCesare & Miller 2018).

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

All families are offered NBS for their newborn. Screening is dependent on parental consent.

To implement screening, the adopted testing protocol would need to be added to 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 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 II via NBS would occur through 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:

- 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.
- Screening laboratory scientist/pathologist – these professionals are needed to undertake the screening and will be required to develop and implement a screening and data analysis protocol for MPS II.
- 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.
- If abnormal follow up, diagnostic testing may be necessary through the children’s hospital, an appropriate physician for diagnosis or through a genetic counsellor. While it is noted that diagnostic testing already occurs for MPS II, 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.
- If MPS II is confirmed, a multi-disciplinary team will be needed as it affects multiple body systems. The tertiary and quaternary hospitals in Australia are equipped with the adequate resources for multidisciplinary management of MPS II.

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 II will be required prior to the commencement of universal screening.

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 II through NBS programs. Diagnosis of MPS II would occur as per current clinical practice, following either presentation with symptoms consistent with MPS II or a family history of MPS II (e.g., sibling with a diagnosis of MPS II or mother that has been identified as a carrier).

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 Australia in the absence of MPS II 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:

All children who undergo NBS for MPS II should not require diagnostic testing on presentation with symptoms (the comparator) because they should already have received confirmatory diagnostic testing following NBS. It is noted that the confirmatory diagnostic tests undertaken on babies identified through NBS or when presenting with symptoms are the same. The NBS I2S enzymatic activity and GAG detection assays are not considered definitive and confirmatory testing using the

current diagnostic tests would still be required. However, as symptoms can mimic many other conditions, in some cases the diagnostic odyssey would be simplified compared with diagnosis of a symptomatic child. The tests undertaken after a NBS positive screen in these presymptomatic children would be specifically directed towards a diagnosis of MPS II. Other tests that would have been used to diagnose or rule out other diseases that have similar symptoms would not be undertaken except in cases where the NBS test results for MPS II and subsequent diagnostic tests were inconclusive (e.g., borderline test results, no family history of MPS II and identification of a VUS in the *IDS* gene during genetic testing). In these cases, additional tests and further clinical investigation may be required to exclude other conditions (e.g., childhood syndromes, other LSDs or metabolic disorders).

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

- Impacts from false positive results
- Impacts from false negative results leading to a delayed or missed diagnosis of MPS II (noting this would mean the newborn is diagnosed clinically, which is the comparator. There is a potential that a diagnosis of MPS II may be overlooked if it is assumed it will be detected through NBS)
- Impacts from identifying variants of unknown significance in the *IDS* gene where the impact of the variant on phenotype is uncertain
- 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 presymptomatically, requirements for MPS II symptom monitoring and surveillance, genetic counselling, and other support services)
- Financial impact of ongoing monitoring and surveillance of patients with MPS II
- 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 II via the NBS programs could enable earlier diagnosis of the disease and may allow for earlier commencement of ERT prior to the development of symptoms for individuals with predicted disease progression. There is evidence to indicate earlier initiation of ERT improves some of the clinical outcomes related to improvement in symptoms, general functioning and quality of life. There is also some evidence to suggest that earlier commencement of ERT can slow the progression of the disease and can extend life expectancy.

Although treatment would commence earlier after a positive NBS, the treatment choices may not change, with newborns diagnosed with MPS II being treated with ERT to improve symptoms of somatic manifestations of MPS II. It is unclear whether earlier treatment of asymptomatic patients would impact on the use of HSCT to reduce the ongoing burden of weekly ERT infusions, and to slow development of symptoms associated with neuronopathy in babies at increased risk of the severe form of MPS II. Ongoing research is focused on improving treatment options for neuronopathic symptoms and to also provide longer term treatments, such as gene therapy, which can be considered as “curative”.

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 health outcomes, screening for MPS II as part of NBS to support early identification is claimed to be superior to the comparator of no NBS and diagnosis upon symptomatic presentation. Early diagnosis supports timely access to intervention. The symptoms occur due to cellular damage caused by accumulation of non-degraded GAGs in the lysosomes. If treatment commences before this damage occurs, both short and long-term health outcomes are improved.

NBS requires a dried blood spot from the newborn for testing. The process for obtaining the bloodspot is via a heel prick and is considered acceptably safe. The current blood spot collection is considered adequate to accommodate the addition of this test so poses no extra risk to the baby.

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 MPS II before symptoms appear, so that early intervention can be implemented. This will decrease morbidity and mortality associated with the disease.

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

A change in clinical management? Yes No

Newborns identified by NBS for MPS II as being at risk of having MPS II are offered earlier confirmatory biochemical and genetic testing to confirm the diagnosis prior to becoming symptomatic. Treatment (either ERT or HSCT) would be available to patients affected by MPS II as appropriate. Currently, patients would only be diagnosed based on clinical suspicion and subsequent diagnostic biochemical and genetic testing to confirm the diagnosis once they had become symptomatic. This would be around 2 to 4 years of age for a patient with the severe form of MPS II but in the second decade of life for patients with the late onset milder attenuated form of MPS II. The time of diagnosis impacts on the time treatment can be initiated. Patients receiving earlier diagnosis and treatment may require fewer investigations and interventions due to reduction in or stabilization of their MPS II manifestations over their lifetime.

A change in health outcome? Yes No

Evidence to date suggests that health outcomes for patients with MPS II are improved by early initiation of treatment. These observations apply to both treatment with ERT and HSCT. A reduction in or stabilisation of their MPS II manifestations may not improve mortality rates but may increase life expectancy and quality of life. However, as diagnosis of MPS II and subsequent initiation of treatment occurs earlier, a patient and their family are exposed to the burden and risks of treatment for a longer period.

Other benefits? Yes No

Please provide a rationale, and information on other benefits if relevant:

Patients and their family would benefit from the value of knowing and a reduction in their diagnostic odyssey. Earlier detection of MPS II enables parents to be genetically tested (cascade testing) and gain access to reproductive technologies for family planning. The family can access support services such as genetic counselling and seek advice from patient support groups before their child develops the characteristic symptoms of MPS II. 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
1.	Systematic review	Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States, <i>Genet Med</i> , 25 (2): 100330 Ream et al.	A systematic review of evidence reporting the accuracy of screening, the benefit of presymptomatic treatment compared with usual case detection, and the feasibility of implementing MPS II newborn screening.	https://pubmed.ncbi.nlm.nih.gov/36445366/	2023
2.	Systematic review report	Evidence-Based Review of Newborn Screening for Mucopolysaccharidosis Type II: Final Report (02/20/2022), Health Resources and Administration (HRSA) Kemper, AR, et al. The Evidence-Based Review Group	Report summarising the evidence regarding the benefits and harms of NBS for Mucopolysaccharidosis Type II (MPS II) and the capability of state NBS programs to offer comprehensive testing and follow up for the condition. This report is the data source for Ream et al (2023) in row above.	https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/mps-ii-final-report-3-28-2022.pdf	2022
3.	RCT	A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome)', <i>Genet Med</i> , vol. 8, no. 8, Aug, pp. 465-473. Muenzer et al.	An RCT to evaluate the safety and efficacy of recombinant human iduronate-2-sulfatase (idursulfase) in the treatment of mucopolysaccharidosis II in 96 MPS II patients between 5 and 31 years of age.	https://pubmed.ncbi.nlm.nih.gov/16912578/	2006
4.	RCT	Long-term, open-labelled extension study of idursulfase in the treatment of Hunter syndrome', <i>Genet Med</i> , vol. 13, no. 2, Feb, pp. 95-101. Muenzer et al.	Open-label extension study enrolling 94 patients who completed the phase II/III study of idursulfase (Muenzer et al, 2006). Clinical outcomes and safety were assessed.	https://pubmed.ncbi.nlm.nih.gov/21150784/	2011
5.	Registry	Initial report from the Hunter Outcome Survey', <i>Genet Med</i> , vol. 10, no. 7, Jul, pp. 508-516. Wraith et al.	An international, multicentre, long-term observational survey of 263 MPS II patients (24% receiving ERT). Observations reported include vital signs, laboratory values, signs and symptoms of organ involvement, and the results of selected functional tests.	https://pubmed.ncbi.nlm.nih.gov/18580692/	2008
6.	Registry	Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). Burton et al.	Data from the HOS (July 2016) were used to compare survival in idursulfase-treated (n = 800) and untreated (n =95) male patients followed prospectively in this multinational, observational registry.	https://pubmed.ncbi.nlm.nih.gov/28887757/	2017

7.	Registry	Clinical outcomes in idursulfase-treated patients with mucopolysaccharidosis type II: 3-year data from the hunter outcome survey (HOS). Muenzer et al.	Clinical outcomes following ≥ 3 years of ERT with idursulfase were investigated in 639 MPS II patients who had received idursulfase for ≥ 6 months enrolled in the HOS.	https://pubmed.ncbi.nlm.nih.gov/28974237/	2017
8.	RCT	Intrathecal idursulfase-IT in patients with neuronopathic mucopolysaccharidosis II: Results from a phase 2/3 randomized study. Mol Genet Metab. 2022 Sep-Oct;137(1-2):127-139. Muenzer et al.	Phase 2/3, open-label, RCT (NCT02055118) investigated the effects of intrathecally administered idursulfase-IT on cognitive function in 49 children > 3 years with MPS II and mild-to-moderate cognitive impairment; 47 completed the study.	https://pubmed.ncbi.nlm.nih.gov/36027721/	2022

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

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 II; therefore, the difference in resource use is associated with the incremental cost of screening for MPS II 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 II through NBS or would be referred for confirmatory diagnostic testing (leukocyte I2S enzyme activity test, urine GAG analysis, genetic analysis of the *IDS* gene). These are the same tests used to diagnose a patient presenting with symptoms of MPS II.

The following tests are used sequentially for confirmatory diagnostic testing of MPS II following a positive or borderline MPS II screening result:

Testing urinary GAG levels

The level of urinary GAGs are elevated in patients with any MPS disorder, so detection of increased urinary GAGs is usually the first diagnostic indicator of an MPS disorder. The presence of the two GAGs dermatan sulfate (DS) and heparin sulfate (HS) in urine indicates MPS II as a possible diagnosis; however, elevated urinary GAGs are not diagnostic and I2S enzyme activity assays are required for a definitive diagnosis.

GAGs are assessed qualitatively and quantitatively. Urine samples are analysed via chromatography or electrophoresis to identify abnormal GAG patterns, even if levels are not elevated. A negative GAG test does not necessarily rule out MPS II as a diagnosis.

Testing for level of I2S activity

Testing for absent or very low I2S activity is diagnostic for MPS II. Enzyme activity is measured in leukocytes, plasma or serum, or dried blood spots.

Second sulfatase testing

A second sulfatase should be measured to rule out multiple sulfatase deficiency and confirm the diagnosis of MPS II.

Genetic testing

Over 700 variants in the *IDS* gene have been reported in patients with MPS II. Once a likely causative variant has been identified, cascade testing of immediate family members (parents and siblings) is carried out to identify family members who may be carriers or at risk of the disease, and genetic counselling should be offered to all family members.

Clinical care

Patients who do not have MPS II after the confirmatory diagnostic testing require no further intervention (false positive NBS). Those who have a confirmed diagnosis of MPS II may be offered treatment, if appropriate, after consultation with the patient's family. Early treatment may be ERT (idursulfase) if the child meets the eligibility criteria of the Australian LSDP. An alternative treatment approach is HSCT (which may be combined temporarily with ERT) which may reduce the burden associated with weekly idursulfase infusions which are administered at a specialist metabolic clinic. Patients receiving treatment are regularly monitored by a multidisciplinary team to assess adverse events and treatment effectiveness. As MPS II progresses, further treatment and interventions for somatic or neuronopathic manifestations may be required and are managed by a multidisciplinary team.

Where a patient's diagnosis remains inconclusive after confirmatory testing, the patient may receive clinical assessments and further investigations or tests to exclude other potential diagnoses (e.g., other metabolic disorders or LSDs).

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 II undergo the same diagnostic testing and treatment pathways as children identified via NBS (as described above). The key difference is the time of confirmed diagnosis.

Describe and explain any differences in the healthcare resources used *after the proposed health technology* vs. the comparator health technology:

With NBS, more individuals will receive confirmatory testing than with the comparator. This is because newborns with false positive or inconclusive NBS results would require confirmatory diagnostic testing. With the comparator health technology only children presenting with symptoms consistent with MPS II would be tested, although some of these may not have MPS II

as the symptoms of MPS II are heterogenous and are common to other childhood syndromes and common conditions.

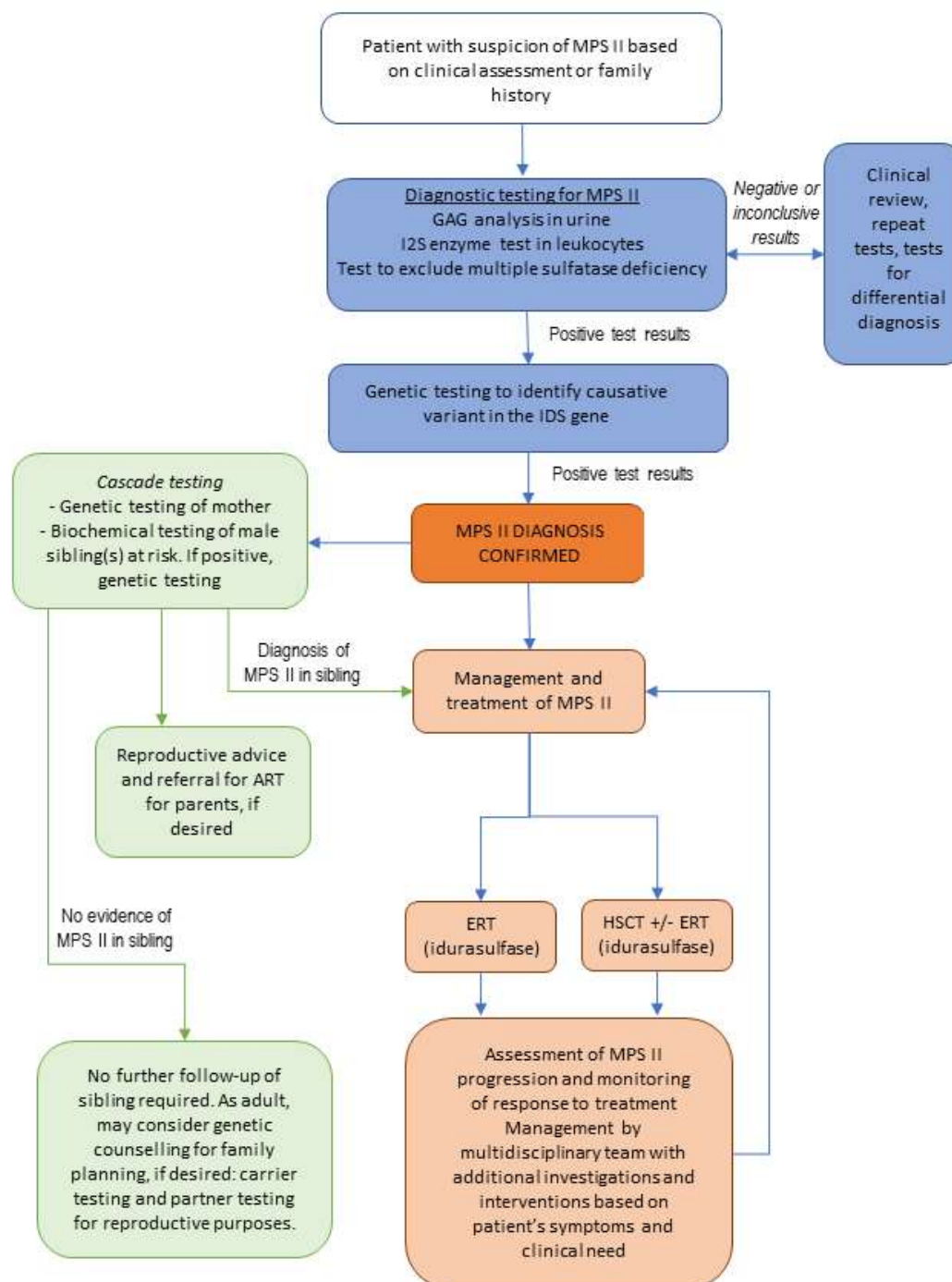
Treatment-related healthcare resources used will be affected by time of treatment initiation, type of treatment, benefits and risks associated with earlier treatment including reduction in somatic manifestations in patients treated at an early stage prior to these manifestations becoming apparent. As some evidence suggests that earlier treatment of MPS II is superior in terms of health outcomes, quality of life and life expectancy compared to treatment initiated after a patient develops somatic manifestations of MPS II, it might be reasonable to predict that patients may use fewer health resources across the course of the disease. However, as ERT would be initiated at an earlier stage, treatment costs and associated monitoring of treatment response are likely to be higher due to receiving treatment for a longer period.

Algorithms

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

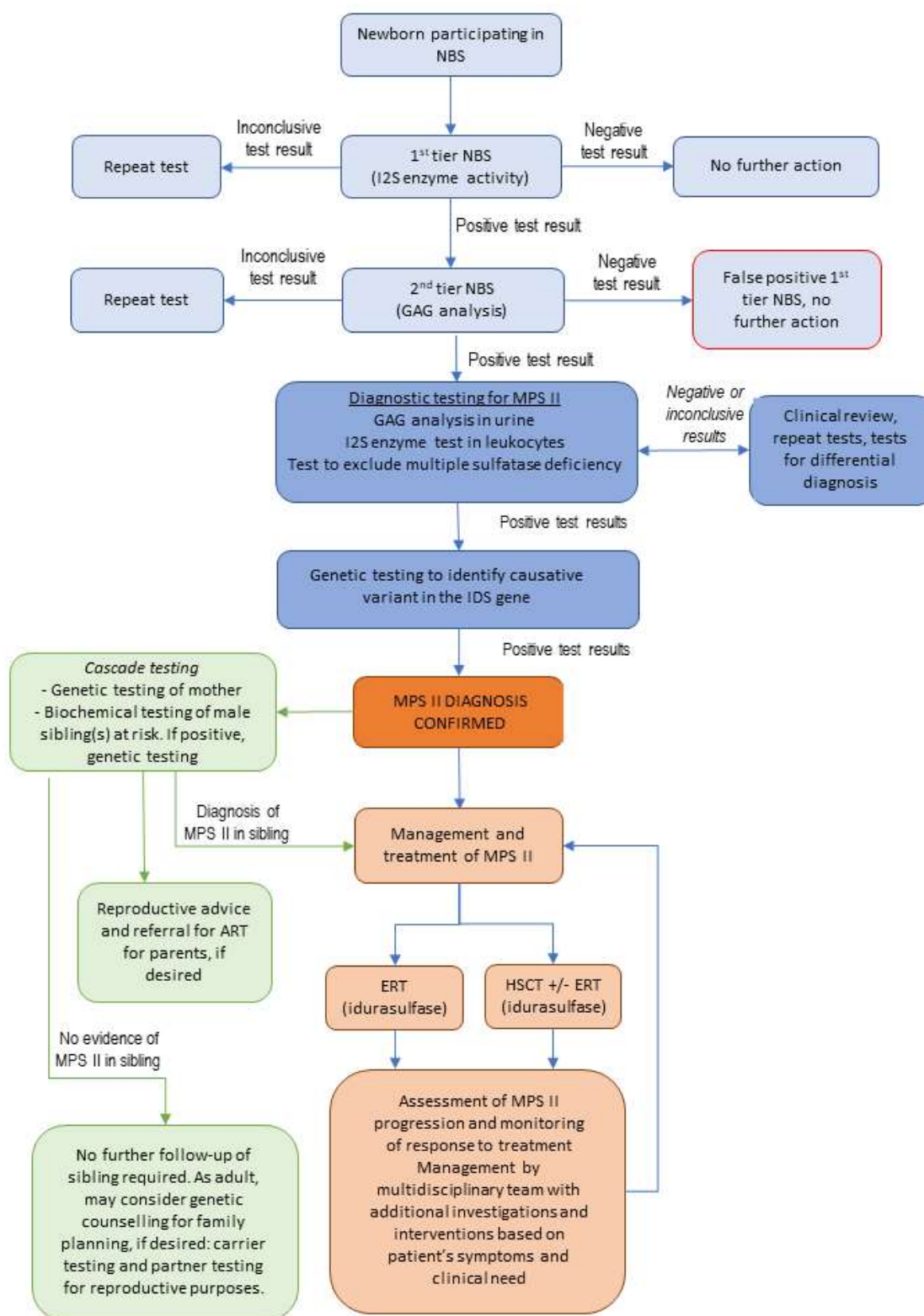
Current clinical management algorithm

Figure 1: Current management of MPS in the absence of MPS II screening as part of the universal NBS program



ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycans; HSCT = haematopoietic stem cell transplant; I2S = iduronate-2-sulfatase; IDS = iduronate-2-sulfatase gene; MPS = mucopolysaccharidosis.

Adapted from (Burton & Giugliani 2012; Scarpa et al. 2011)

Proposed clinical management algorithm**Figure 2: Proposed management of MPS after addition of MPS II screening to the universal NBS program**

ART = assisted reproductive technology; ERT = enzyme replacement therapy; GAG = glycosaminoglycans; HSCT = haematopoietic stem cell transplant; I2S = iduronate-2-sulfatase; *IDS* = iduronate-2-sulfatase gene; MPS = mucopolysaccharidosis; NBS = Newborn bloodspot screening. Adapted from (Arunkumar et al. 2020; Burton & Giugliani 2012; Scarpa et al. 2011)