Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1775 – Newborn bloodspot screening for mucopolysaccharidosis Type I (MPS I)

Applicant:	**Department of Health and Aged Care - Newborn bloodspot screening section**
Date of MSAC consideration:	**3-4 April 2025** **29 November 2024**

Context for decision: MSAC provides its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting the addition of mucopolysaccharidosis type I (MPS I) to Australia's newborn bloodspot screening (NBS) programs was developed by the Department of Health and Aged Care, following a request from the Minister for Health and Aged Care. REDACTED, metabolic physician at REDACTED, and REDACTED, metabolic physician and clinical geneticist REDACTED, were supporting clinical expert co-applicants.

2. MSAC's advice to the Minister

November 2024 and April 2025 MSAC consideration

MSAC considered the addition of mucopolysaccharidosis type I (MPS I) to newborn bloodspot screening (NBS) programs. In November 2024, MSAC noted that this was the first application considered after endorsement of the national decision-making pathway for the addition of conditions to the Australia's NBS programs by Health Ministers in November 2023. MSAC considered both its own Terms of Reference and the Newborn Bloodspot Screening National Policy Framework (NBS NPF) in providing its advice. MSAC considered the positive and negative impacts of newborn screening, and any potential for unintended negative impacts on the existing NBS programs.

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, in April 2025 MSAC supported adding MPS I to Australia's NBS programs because the potential benefits of newborn screening for MPS I outweigh the potential harms.

MSAC considered the following health technology assessment criteria were met. The proposed 2-tier screening strategy has acceptable clinical sensitivity to accurately identify newborns at risk for MPS I, with low rates of false positives and false negatives. If NBS for MPS I was implemented in 2025-26, approximately 4 newborns will have a positive screening test (and will be recalled for further testing). Of these, approximately 2 newborns will be diagnosed with Hurler syndrome (MPS IH) and one newborn will be at risk of developing Hurler-Scheie syndrome (MPS IHS). MSAC considered that one newborn will be at risk of developing Scheie syndrome (MPS IS) every two

years. MSAC considered that some newborns diagnosed as being at risk for an attenuated form of MPS I would not be expected to develop clinically significant or apparent symptoms of MPS I.

MSAC advised that there is evidence of additional benefit from an earlier diagnosis through NBS and earlier treatment for newborns with Hurler syndrome (MPS IH) and Hurler-Scheie syndrome (MPS IHS) compared with a diagnosis made after symptoms develop. MSAC considered that there is an effective treatment for these two subtypes of MPS I: enzyme replacement therapy [ERT] for MPS IHS (noting that ERT is funded for MPS IHS and requires several criteria to be met); and haematopoietic stem cell transplant (HSCT) usually preceded by ERT for MPS IH, although MSAC noted that ERT is currently not funded for this use in MPS IH through the Life Saving Drugs Program (LSDP) and that ERT for MPS IH was previously determined not to be clinically effective by the Pharmaceutical Benefits Advisory Committee (PBAC). LSDP eligibility criteria cannot be changed without reconsideration of clinical effectiveness by the PBAC. However, for newborns with Scheie syndrome (MPS IS, approximately one newborn every 2 years), the most attenuated and least severe form of MPS I, MSAC noted that there is no evidence of an effective treatment, and that the primary benefit of NBS would therefore be avoidance of diagnostic delay and a potential secondary benefit to identifying reproductive risk. MSAC considered the absence of an effective treatment raised complex ethical issues regarding adherence to the NBS NPF, and whether reporting results consistent with MPS IS should be resolved before screening is implemented.

MSAC noted that NBS for MPS I aligns with the primary objective of the NBS NPF decision-making criteria as MPS I is predominantly early-onset and severe, has a reliable screening test strategy with acceptable sensitivity and specificity, and there is an available treatment that can be commenced during the newborn period. MSAC considered the incremental cost per quality adjusted life year (QALY) gained for screening for MPS I was very high, the incremental cost per screen for MPS I was comparable to previously accepted costs per screen for other NBS conditions considered by MSAC, and the total cost to the NBS programs of screening for MPS I was modest.

MSAC noted that under the NBS decision-making pathway, Health Ministers make a decision at the Health Ministers' Meeting (HMM) on whether to implement screening for new conditions, and how it is implemented, after considering advice from MSAC, the NBS Program Management Committee (PMC), the Cancer and Population Screening (CAPS) Committee and the Health Chief Executives Forum (HCEF).

MSAC advised that a condition of its support for NBS for MPS I is that the following matters should be addressed prior to implementation of NBS for MPS I:

> (a) introduction of an appropriate consent process to ensure that parents are informed that their newborns may potentially be found to be at risk of a later onset form of MPS I with uncertain prognosis, to maintain trust in the NBS programs;
>
> (b) ethical analysis and consensus on reporting of screening results for cases with uncertain phenotype, or MPS IS (where determinable), noting that there is currently no treatment available for MPS IS;
>
> (c) development of Australian clinical practice guidelines, which may include consensus guidelines, for the monitoring and management of children who are pre-symptomatic but at risk of MPS I;
>
> (d) review of the eligibility criteria for ERT on the LSDP which currently provides access to individuals who meet eligibility criteria and are symptomatic, or for whom severe disease can be clearly predicted (noting reconsideration of eligibility is likely to require a submission to PBAC by the medicine sponsor) this review should also assess potential budget impact; and

(e) the parallel need to consider clinical service/workforce capacity and readiness, and establishment of a mechanism to collect national robust longitudinal data, including clinical outcomes data, to inform future reviews such as incidence of each subtype, to better define genotype-phenotype relationships in the Australian population, and potential benefits of earlier treatment for MPS I.

Addressing the above requirements may occur in parallel with the implementation processes to ensure timely screening of Australian newborns.

Consumer summary – November 2024 and April 2025

This application from the Department of Health and Aged Care (the department) requested advice about adding a screening test for mucopolysaccharidosis type 1 (MPS I) to Australia's Newborn Bloodspot Screening (NBS) programs. MSAC first considered the application in November 2024, and then re-considered it in April 2025, at which stage it supported the addition of MPS I to Australia's NBS programs, if a number of requirements are met before screening begins. MSAC's advice will be considered by the Health Ministers Meeting, alongside advice from the Cancer and Population Screening Committee, the Health Chief Executives Forum and the NBS Program Management Committee to determine whether MPS I should be added to the NBS programs delivered by the states and territories.

NBS programs are run Australia-wide, and involve a tiny sample of blood being taken from the heel of each newborn baby and placed on special filter paper, (resulting in a dried bloodspot). The sample is then used to test for several severe childhood conditions, so that an affected baby may access treatment earlier. Newborn screening is an optional program, and uptake across Australia is very high, at over 99.0%.

MPS I is an ultra-rare genetic (inherited) condition, with 0.73 babies currently diagnosed with MPS I per 100,000 live births in Australia (i.e. approximately 2 babies per year). This is expected to increase to around 1.15 babies in 100,000 live births (i.e. approximately 4 babies diagnosed per year) if newborn bloodspot screening for MPS I is introduced. This is because some people with milder symptoms are currently being missed and some people may not have symptoms significant enough to seek medical attention.

People with MPS I have low levels of an enzyme called alpha-L-iduronidase. Without enough enzyme, glycosaminoglycans (GAGs) - a type of sugar - builds up in their body and causes damage. People with MPS I can have problems in many parts of the body, including problems with the bones and joints, neurological problems, vision and hearing problems, heart problems, breathing problems and hernias.

There are 3 forms of MPS I. The most severe is Hurler syndrome. It is normally diagnosed in the first or second year of life after symptoms begin to show. The main treatment for Hurler syndrome is stem cell transplantation (also called bone marrow transplant). This treatment provides cells that produce the missing enzyme from a donor. Having a stem cell transplantation for Hurler syndrome at a younger age (before the age of 2 years) helps with neurological (such as intellectual disability) symptoms but may not prevent other problems such as heart, and bone and joint disease. Stem cell transplantation does not cure Hurler syndrome. Children with Hurler syndrome will need several surgeries later in life and support for disabilities they may have.

There are 2 less severe forms of MPS I, known as attenuated forms: Hurler–Scheie syndrome and Scheie syndrome. Babies with Hurler–Scheie syndrome can be treated with enzyme replacement therapy (ERT) called laronidase. This helps to increase the amount of enzyme in the body. MSAC considered early treatment with laronidase improves some symptoms of Hurler–Scheie syndrome.

Laronidase is a very expensive medicine. The Australian Government's Life Saving Drugs Program (LSDP) funds laronidase for some people with MPS I who meet certain criteria. MSAC

considered babies with Hurler syndrome waiting for a stem cell transplantation and all babies with Hurler- Scheie syndrome who are predicted to have severe disease may benefit from ERT. However, not all babies diagnosed with MPS I through the NBS would be currently eligible for treatment under the LSDP at the time of diagnosis. Current guidelines do not provide treatment for babies with Hurler–Scheie syndrome for whom severe disease cannot be predicted and are not yet symptomatic, or babies with Hurler syndrome waiting for a transplant.

MSAC considered that eligibility for laronidase treatment should be reviewed for babies diagnosed with MPS I by NBS.

Scheie syndrome is the least severe form, and some people with Scheie syndrome are not diagnosed until well into adulthood. MSAC considered there is no effective early treatment for Scheie syndrome.

An issue with screening for MPS I is that the severity of the disease cannot be predicted for some babies. There are different alterations to the genetic code that cause MPS I, and they are not all well-understood. This means that not all families of babies who are diagnosed with MPS I after newborn screening will know what to expect in terms of the course of their disease, and they may spend many years waiting for symptoms to appear. There is no effective early treatment for these babies.

The proposed newborn bloodspot screening test for MPS I would take place in 2 stages (tiers). The first tier would measure enzyme activity on the dried bloodspot sample. Those with low enzyme activity would go on to have a second tier test on their dried bloodspot sample to measure GAG (sugar) build-up. Any babies found to test positive for both tiers would go on to have a diagnosis confirmed by clinical examination, imaging and diagnostic genetic tests. MSAC considered the 2-tier screening strategy to be very effective (precise). That is, after both tiers of screening, MSAC considered that almost all babies who screen positive would go on to be diagnosed with MPS I.

MSAC considered newborn screening for MPS I was of acceptable value for money. The cost per screening test was low. MSAC noted that very costly, potentially life-saving treatments for very rare conditions have been considered good value for money.

MSAC supported newborn screening for MPS I if certain conditions are met. This is because MPS I mostly met the criteria for adding a condition to the newborn bloodspot screening programs, as described in the Newborn Bloodspot Screening National Policy Framework (NBS NPF). MSAC considered the potential benefits from newborn screening for MPS I were greater than the possible harms. However, MSAC advised its support for the addition of MPS I to the NBS programs is that the following issues should be addressed before babies are screened for MPS I. MSAC noted that the final decision on whether MPS I will be added to NBS programs lies with Health Ministers.

- Introduce an appropriate consent processes to ensure that parents are informed that their baby may potentially be diagnosed with MPS I. MPS I is different from conditions that are already screened because it is a complex condition. The consent process should include making sure parents are aware that for some forms of MPS I a disease course may not be predictable, that some babies may never have symptoms and that for some babies there may not be an effective early treatment. MSAC considered having clear and correct information in the consent process is important to maintain trust in the NBS programs. This will make sure that the high rate of participation in the NBS programs continue as new conditions are added.
- Undertake an ethical analysis and agree on whether screening results should be reported for babies who are found to have Scheie syndrome (if it can be determined) or babies whose MPS I type cannot be determined at the NBS stage, noting that clinical examination and confirmatory testing may provide a diagnosis. Scheie syndrome is

Consumer summary – November 2024 and April 2025

normally diagnosed in children and adults. For those affected, there is no effective early treatment. This may cause harm to these babies and their families because they will have the undue stress of a diagnosis and waiting to be sick without a benefit from early treatment. MSAC considered that experts need to consider the ethical issues with either option.

- Review suitability of funding of ERT with laronidase for babies diagnosed with MPS I via NBS, and who are likely to benefit from early treatment. Laronidase is an expensive medicine. Broader public funding of ERT is likely needed to achieve better health outcomes from NBS for MPS I and ensure there is equitable access to an effective early treatment.
- Develop Australian clinical practice guidelines, describing how to monitor and manage at-risk/pre-symptomatic babies whose disease onset and severity cannot be clearly predicted.
- Consider whether clinical services and workforce capacity are ready for the extra resources and work required if MPS I screening is added to NBS programs. This includes ensuring a system is set up and resourced to collect national, long-term data about people diagnosed with MPS I through NBS programs. This information would help to better understand the condition and to give people more certainty when they are diagnosed (for example, by understanding if certain gene alterations are more likely to result in more or less severe disease). This would also help record clinical outcomes and potential benefits of earlier treatment for MPS I.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported including MPS I in Australia's NBS programs. However, MSAC considered that there were a number of issues that must be addressed before MPS I screening begins. MSAC considered that the proposed 2-tier screening method was reliable for identifying babies with MSP I. MSAC considered early diagnosis and early treatment with enzyme replacement therapy or stem cell transplantation improved health outcomes for babies with the Hurler syndrome or Hurler-Scheie syndrome types of MPS I. MSAC considered the value for money of newborn screening for MPS I is acceptable. MPS I meets most of the Newborn Bloodspot Screening National Policy Framework and other health technology assessment criteria, such as safety and clinical effectiveness.

3. Summary of consideration and rationale for MSAC's advice

November 2024 and April 2025 MSAC consideration

MSAC noted that this application from the Department of Health and Aged Care was to consider the potential addition of mucopolysaccharidosis type 1 (MPS I) to Australia's Newborn Bloodspot Screening (NBS) programs. This application was requested by the Minister for Health and Aged Care, with input from 2 clinical co-applicants (**REDACTED**).

MSAC considered both its own Terms of Reference[1] and the Newborn Bloodspot Screening National Policy Framework[2] (NBS NPF) in providing its advice. MSAC first considered the application in November 2024. In April 2025, MSAC further considered the application and provided further advice. MSAC noted that Health Ministers decide whether to implement

[1] https://www.msac.gov.au/about-us/what-we-do/terms-reference

[2] Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policyframework?language=en

screening for conditions at the Health Ministers' Meeting (HMM). MSAC noted that its advice would be considered at HMM alongside advice from the Cancer and Population Screening Committee, the Health Chief Executives Forum and the NBS Program Management Committee to determine if MPS I should be a part of Australia's NBS programs.

MSAC noted that the NBS programs are underpinned by the NBS NPF, and implementation remains jurisdiction-based. Commonwealth funding supports the expansion of NBS programs, and screening is provided by 5 NBS laboratories across Australia. For a condition to be included in Australia's NBS programs, it needs to align broadly with the NBS NPF, which outlines several criteria the condition must meet. Some of these include:

- The condition should be a serious health problem that leads to significant morbidity or mortality.
- There should be a benefit to conducting screening in the newborn period.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a suitable test protocol to identify the presence of the condition.
- The protocol should, on balance, be socially and ethically acceptable to health professionals and the public.
- Health care services for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result.
- There should be an accepted intervention for those diagnosed with the condition.
- The benefit of screening a condition must be weighed against its impact on the program as a whole.

MSAC noted and welcomed the consultation input received from 9 professional organisations, 3 consumer organisations, one commercial organisation and one individual (clinical scientist at a NBS laboratory). MSAC also noted a summary of published studies compiled by the department, which highlighted the lived experiences of individuals diagnosed with MPS I, their families, carers and health professionals.

MSAC noted that MPS I is an ultra-rare lysosomal storage disease (LSD) caused by deficiency of the alpha-L-iduronidase (IDUA) enzyme, resulting in the build-up of glycosaminoglycans (GAGs) in lysosomes and a cascade of intracellular pathologic processes. It is a multisystem disorder and is usually categorised into 3 phenotypes: the severe form, Hurler syndrome (MPS IH), and 2 attenuated forms, Hurler–Scheie syndrome (MPS IHS) and Scheie syndrome (MPS IS). The median age of clinical diagnosis (after symptom onset) is approximately one year for MPS IH, 4 years for MPS IHS and approximately 14 years for MPS IS. Some individuals with MPS IS may be diagnosed in adulthood. Some people with mild MPS I may never be diagnosed.

Regarding the key health technology assessment (HTA) question of the **availability of a suitable screening test (or tests) to accurately identify all newborns at risk for the proposed condition (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive)**, MSAC noted that the proposed 2-tier screening method. The first tier screening would involve a test for IDUA enzyme activity on the dried bloodspot (DBS), and those with low enzyme activity would undergo second tier testing, which would be endogenous non-reducing end (NRE)-GAG analysis (either in-house or sent to the National Referral Laboratory [NRL] based in Adelaide). MSAC noted that those who screen positive would be recalled and clinically confirmed, including by examination and imaging.

MSAC noted that the current incidence of MPS I is 0.73 per 100,000 live births, or about 2 cases per year in Australia. Screening newborns for MPS I is expected to increase the incidence to around 1.15 cases per 100,000 live births, or about 3.69 cases each year, as it will bring forward

cases that would be diagnosed later and detect cases that otherwise would not be diagnosed, for example attenuated forms (asymptomatic or mild phenotypes). MSAC considered that the number of false positives found in single tier screening (IDUA enzyme activity below a threshold) would be decreased with the proposed 2-tier strategy, and therefore advised that it could be suitably sensitive and specific to accurately identify newborns at risk. However, MSAC noted that there was very limited evidence on the proposed 2-tier approach under consideration.

MSAC considered that, because different NBS laboratories may choose different enzyme assay methods and cut-off thresholds for further testing, screen positive rates may also vary between laboratories. MSAC considered differences in testing methods and thresholds will also affect the number of false positive tests and queried whether the tests will identify all newborns with an attenuated form of MPS I (i.e. MPS IHS or MPS IS). MSAC therefore advised that a national screening protocol should be agreed upon and concurrently implemented in all jurisdictions, to avoid variability in screening and reporting.

MSAC also considered **whether disease subtype and prognosis can be determined from the screening and confirmatory tests to determine the need for earlier treatment.** MSAC considered that, while the proposed 2-tier screening methodology can accurately detect babies with MPS I, it can only determine disease phenotype and prognosis precisely for some newborns who screen positive for MPS I.

MSAC noted that, based on experience from other centres, the proposed 2-tier screening method is expected to accurately predict phenotype in 50% of screen-detected attenuated cases. MSAC noted that molecular (genetic) testing could help to improve this, and allow prognosis to be predicted in up to 75% of cases and inform cascade testing. This would mean that at least 25% of newborns diagnosed would have MPS I of unknown phenotype, and would require clinical evaluation and, if that does not identify the features of MPS I, ongoing monitoring is needed until signs and symptoms appear. Thus, the NBS may not facilitate earlier ERT in at least 25% of attenuated cases.

If NBS for MPS I was implemented in 2025-26, MSAC considered approximately 4 newborns will have a positive screening test (and will be recalled for further testing). Of these, approximately 2 newborns will be diagnosed with Hurler syndrome (MPS IH) and one newborn will be at risk of developing Hurler-Scheie syndrome (MPS IHS). MSAC considered that one newborn will be at risk of developing Scheie syndrome (MPS IS) every two years. MSAC considered that some newborns diagnosed as being at risk for an attenuated form of MPS I would not be expected to develop clinically significant or apparent symptoms of MPS I.

MSAC noted that due to the uncertainties associated with diagnosis of an unknown phenotype, screening laboratories may choose not to report positive results where disease severity cannot be determined. However, MSAC considered there are ethical concerns around this. MSAC considered that all newborns who are recalled for diagnostic testing would be assessed via existing care pathways by expert metabolic physicians, which may identify and classify some cases with uncertain phenotype through clinical assessment. MSAC considered that other tests performed after an initial diagnosis of MPS I, such as X-ray or fibroblast testing, would provide additional information about disease subtype and prognosis. MSAC considered that the current evidence suggests fibroblast testing is superior to blood testing for predicting central nervous system disease.[3]

MSAC considered that a small number of newborns will be identified as having MPS I but will not have any clinical signs of MPS I at diagnosis. In the absence of known molecular genetic variants,

[3] Fuller et al., (2005), Prediction of neuropathology in mucopolysaccharidosis I patients, Mol Genet Metab 84(1):18–24.

these newborns will have an MPS I diagnosis with an uncertain clinical phenotype, meaning the severity and age of onset of symptoms would be unknown.

MSAC considered the screening and confirmatory tests would inform the need for earlier treatment for newborns diagnosed with MPS IH and some infants predicted to have attenuated MPS I (i.e. either MPS IS or MPS IHS). MSAC considered the screening and confirmatory tests would not inform the need for earlier treatment for those newborns diagnosed with MPS I of uncertain phenotype. MSAC considered there may be ethical issues and potential harms from identifying attenuated forms of MPS I and MPS I of uncertain phenotype.

In relation to the **availability of effective treatment (or treatments) in Australia for at-risk newborns**, MSAC considered that specific treatments are currently available for some, but not all, MPS I subtypes. MSAC noted that the Australian Government currently funds laronidase, an enzyme replacement therapy (ERT), for some patients with MPS IHS under the Life Saving Drugs Program (LSDP). This includes MPS IHS patients who meet specific criteria and who are symptomatic, or MPS IHS patients under 5 years old who are pre-symptomatic, if severe disease can be clearly predicted. MSAC noted that the LSDP review (2023)[4] identified that laronidase is high cost treatment, but that people with MPS I who were treated with laronidase appeared to live longer and had an improved quality of life. MSAC noted that, in terms of effectiveness, ERT does not cross the blood brain barrier (BBB), and therefore has no impact on the progression of neurocognitive symptoms in patients with MPS IH or IHS.

MSAC noted that some documented uses of ERT fall outside the uses funded via the LSDP. MSAC noted that ERT is not currently funded for those with MPS IH or MPS IS, and that the current LSDP eligibility criteria to access ERT would prevent some newborns with MPS IHS identified by NBS from accessing treatment until symptom onset (i.e. that pre-symptomatic newborns without a clear prediction of severe disease would not have access to ERT). MSAC noted that there was no evidence of benefit of laronidase treatment for those with MPS IS, and considered that laronidase was unlikely to be effective for treating the most common manifestations of this attenuated form of the disease (i.e. orthopaedic conditions) when treatment starts after symptom onset. MSAC considered laronidase would provide at least some benefit for those with MPS IH (particularly while awaiting HSCT) and MPS IHS, particularly when started before symptom onset. MSAC considered that public funding of laronidase for newborns diagnosed with MPS IH and MPS IHS through newborn screening is required so that the diagnosis of MPS I through newborn screening leads to newborns having access to an effective early intervention to improve health outcomes. MSAC advised that publicly funded access to ERT would need to be reviewed prior to implementing NBS for MPS I. MSAC considered this is necessary to ensure there is equitable access for families as it is a very high cost treatment. MSAC noted that if access was to be expanded via the LSDP, this would require a referral to the LSDP Expert Panel (LSDP EP) for further consideration, and noted that PBAC may be required to re-consider the effectiveness of laronidase.

MSAC noted that haematopoietic stem cell transplantation (HSCT) is also an approved treatment that is funded by Australian state/territory governments for patients with MPS IH. MSAC noted that these patients sometimes receive ERT prior to HSCT, but that this is not subsidised via LSDP. MSAC therefore considered that there was a treatment available in Australia for some newborns with MPS IHS and MPS IH who would be identified via NBS at diagnosis, but not for all MPS I cases.

[4] https://www.health.gov.au/sites/default/files/2023-01/life-saving-drugs-program-mps-i-review-summary-and-expert-panel-recommendations-for-consumers.pdf

MSAC considered there is currently no accepted, effective early invention available for those with MPS IS beyond symptom management.

With respect to **effectiveness of treatment from the proposed earlier age of initiation following NBS screening and diagnosis (pre-symptomatic and early symptomatic) compared to age of initiation under current management pathway (established symptomatic presentation),** MSAC noted that evidence was limited. MSAC considered that there was no evidence to show that earlier treatment would improve survival compared with starting treatment after developing symptoms and being diagnosed.

MSAC noted that the expected change in clinical management for those with MPS IH is earlier access to HSCT at a median age of 6 months, compared to a median age of **REDACTED** with no testing. For newborns diagnosed with MPS IH, MSAC considered that earlier treatment with HSCT would likely improve neurocognitive and physical outcomes based on the available evidence, because storage deficiencies develop *in utero* in babies with MPS IH, and it takes approximately 12 months for enough enzyme to accumulate in the brain after treatment.[5] However, MSAC acknowledged that the evidence supporting this is of low certainty. Australian data also showed an increased risk of graft-versus-host disease in patients who receive an earlier transplant. There are also no data to show that survival is improved with earlier access to HSCT, but it is biologically plausible as pre-clinical studies show that earlier treatment improves bone and cartilage outcomes in animal models of similar LSDs.[6] MSAC also noted that not all newborns will have a suitable donor for HSCT, and that HSCT does not cure MPS IH. MSAC noted patients will continue to experience other complications that are less or not amenable to HSCT, including bone, joint and eye complications. It is possible that these complications will be less significant following transplantation earlier in the disease trajectory, but patients with MPS IH continue to experience significant symptoms and disability after HSCT. MSAC noted that diagnosis of additional MPS IH cases may also increase the demand for ERT while awaiting HSCT, although it was also noted that the duration of any pre-HSCT ERT would be short, as HSCT initiation would be at an earlier age. MSAC noted advice that ERT for this purpose is currently funded by hospitals and is not available via the LSDP.

MSAC noted for newborns diagnosed with MPS IHS, earlier initiation of treatment with ERT may provide modest improvements in height and skeletal abnormalities for eligible individuals. MSAC noted expert advice that when ERT is commenced after disease is evident, it does not improve cardiac valve disease, corneal clouding or neurocognitive symptoms. MSAC further noted that, even with treatment, surgeries are often necessary to address ongoing complications. MSAC further noted the LSDP Expert Panel had reviewed the use of laronidase in 2023, and did not identify a survival benefit with ERT. The Expert Panel considered that ERT's benefits lie in the maintenance or slowing of deterioration (as opposed to an improvement) over time, which provides benefits to patients and their families.

MSAC noted there was no evidence of benefit for earlier therapy in MPS IS forms. MSAC noted that, as the least severe and most attenuated form of MPS I, MPS IS may not manifest until adulthood, or not at all. MSAC noted that the primary benefit of earlier diagnosis of MPS IS for the newborn would be avoidance of a diagnostic delay. In addition, the main clinical manifestation of MPS IS is orthopaedic conditions, for which ERT confers no benefit when started after symptom onset. Thus, MSAC considered that there is no clear effective treatment for MPS IS, and that those who choose to undergo ERT will receive no significant benefit and may be subject to overtreatment.

---

[5] Krivit, (2004), Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases, Springer *Semin Immunopathol* 26(1–2):119–32.

[6] Crawley et al., (1997), Enzyme replacement therapy from birth in a feline model of mucopolysaccharidosis type VI, *JCI* 99(4):651–62.

Overall, MSAC considered that earlier initiation of treatment was at least partially effective for MPS IH and MPS IHS. MSAC considered that the main benefit from earlier identification of MPS IS was avoidance of a diagnostic delay.

MSAC considered the **cost-effectiveness of NBS compared to no newborn screening**, and the economic implications of adding MPS I to the NBS. MSAC noted that the economic model considered MPS I overall, and also separately considered severe and attenuated forms of MPS I. The first step in the model was a decision tree (cost-effectiveness analysis [CEA]) that considered screening and identification of children with MPS I. A Markov model (cost-utility analysis [CUA]) then incorporated a longer time horizon and accrued benefits. The economic evaluation was focused on PICO set 1 (NBS testing), rather PICO set 2 (cascade testing), noting that the clinical management of cascade testing would remain unchanged with or without NBS.

MSAC considered that the most informative economic analysis presented for decision-making was the cost per screening test and cost-utility analysis (CUA). The CUA modelled the incremental cost per quality-adjusted life year (QALY) for all cases of MPS I detected, and included the costs of screening along with costs of ERT for patients with MPS IHS, and for MPS IH patients awaiting HSCT. However, MSAC noted no benefits of ERT were modelled due to lack of evidence of additional overall survival (OS) or quality of life (QoL) gains with earlier commencement of ERT. MSAC noted that the resulting ICER was $**REDACTED** per QALY. MSAC considered the ICER to be very high and well outside the range typically considered by MSAC to be cost-effective, but regarded this as acceptable in this setting given the totality of the context (ultra rare condition, very high cost therapy, existing access to ERT, accepted benefit in screen detected cases and the cost per screen is low). MSAC noted the ICER for the ERT laronidase, was considered by the PBAC to be well in excess of $**REDACTED** per QALY gained, and thus there is precedent for government accepting very high ICERs for highly specialised therapies for rare diseases. Sensitivity analyses showed that the ICERs were sensitive to the cost of the first-tier screening test and the modelled time horizon. MSAC noted that an additional analysis with a higher diagnostic delay cost was provided at ESC's request (using a cost of $18,200, which was the upper bound reported for mitochondrial disorders in Australia[7]). MSAC noted that the economic evaluation was not sensitive to significantly increased diagnostic delay costs, because the cost of whole-of-population screening continues to outweigh all disease-related costs.

MSAC noted that, based on the CEA, the ICER was approximately $**REDACTED** per confirmed diagnosis for a 2-tier screening method, but MSAC considered it inappropriate to include the equipment as part of the implementation costs if MPS II is added to the NBS as both conditions would be screened using the same kit. MSAC noted in such a case, equipment costs should only be accounted for once, since no additional equipment or reagents would be required to multiplex the 2 conditions. Removing these costs reduced the ICER to around $**REDACTED** per confirmed diagnosis. MSAC noted that this was much higher than ICERs for other NBS applications and prenatal testing it had considered, including for sickle cell disease, X-ALD and prenatal detection of trisomies. However, MSAC considered the cost per diagnosis comparisons were not necessarily relevant or useful due to the rarity of MPS I, where universal screening for ultra-rare conditions would always be expected to result in a high cost per diagnosis. MSAC considered there would be a small improvement in cost-effectiveness if multiple conditions were screened in a single multiplexed test (for example, MPS I and MPS II [MSAC application 1776]), but noted that the ICERs would remain high.

MSAC noted that **the financial impact to the NBS programs and other relevant budget holders.** MSAC noted that the expected financial impact to the NBS programs was $**REDACTED** in Year 1,

[7] Wu Y et al. (2022). Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation. *Eur J Hum Genet* 30(5):577-586. doi: 10.1038/s41431-021-00916-8.

which included one-off implementation costs, decreasing to approximately $**REDACTED** per year for Years 2–6. MSAC noted the expected impact to other budgets included a very small impact to the MBS in Year 1, and net savings to the MBS of approximately $3,000-$4,000 per year in Years 2-6. MSAC also noted that the expected impact to the LSDP budgets was approximately $**REDACTED** per year; MSAC considered that this was likely underestimated because it only included the cost of earlier ERT for one case per year. However, if disease course could be predicted, MSAC considered that it was highly likely that the net increase in costs to the LSDP for those with MPS IHS would increase by $**REDACTED** over 6 years. MSAC further noted that if access to ERT was made available for those with MPS IS, the total additional expenditure could be $**REDACTED** over 6 years. MSAC further noted, if ERT for MPS IH is subsidised and newborn screening for MPS IH is implemented, it could potentially decrease current ERT costs (to states and territories, as this use is not funded by the LSDP) by $**REDACTED** over 6 years as earlier HSCT would reduce the duration of pre-transplant ERT.

The estimated financial impact on ERT expenditure is further explored in the table below.

Table 1: Changes in enzyme replacement therapy (ERT) costs with laronidase

MPS I subtype	Impact of NBS on ERT use	Change in ERT use	Estimated financial impact from NBS on ERT expenditure over 6 years
MPS IH	Earlier blood stem cell transplant, reduces for the duration of pre-transplant ERT	Likely reduction in use per patient (state and territory funding, noting pre-HSCT ERT is not currently funded by the LSDP)	$**Redacted** [a]
MPS IHS (attenuated)	If the laboratory diagnosis **can** predict this subtype of future disease, these individuals receive LSDP-funded ERT from the time of NBS diagnosis	Highly likely increase in use per patient (LSDP funding for some patients)	$**Redacted** [b]
MPS IS (attenuated)	If the phenotype is predicted to be Scheie syndrome (MPS IS) then patients would be ineligible for ERT through the LSDP under current guidelines If disease severity **cannot** be predicted from the NBS diagnosis, individuals are monitored for the onset of signs and symptoms of disease. (There is an option for NBS laboratories to not report the NBS findings where the future disease state cannot be predicted satisfactorily)	Potential increase in use per patient (This would require an application to expand LSDP funding)	$**Redacted** [c]
Indeterminate	Most commonly this will be an individual with MPS IS	These individuals are not eligible for LSDP-funded ERT	$0 (but risk for potentially life-time cost of ERT if LSDP criteria permit use in MPS IS)

[a] Not funded by the LSDP. Net savings estimated as 6 months of laronidase treatment would occur earlier in the child's life. ~12 cases expected to be diagnosed over 6 years.

[b] An estimated 8.7 years of laronidase treatment at a cost of $**REDACTED** per year per case. <6 cases expected to be diagnosed over 6 years.

[c] Not funded by the LSDP. An estimated 50 years of laronidase treatment for MPS IS at a cost of $**REDACTED** per year per case. <6 cases expected to be diagnosed over 6 years

MSAC considered it was important that these additional costs of ERT be explored more carefully by government to ensure that the total financial impact is estimated as accurately as possible prior to implementation of MPS I screening.

MSAC noted that this application was not seeking funding for ERT and there are significant implications for the LSDP if MPS I screening is added to NBS programs, as screening will detect patients who are not currently eligible for therapy under the LSDP criteria. This will create a new pool of patients, both incident and prevalent, who will be seeking access to ERT, which is currently only available for MPS IHS patients who are symptomatic, or for whom there is a prediction of severe disease if they are under 5 years of age. MSAC considered that, where a child has already received a diagnosis, families will likely find it unacceptable to either not have access to treatment at all (in the case of MPS IS) or to wait for symptom presentation to access treatment (for MPS IHS). The LSDP Expert review concluded that ERT is not cost-effective but it may mitigate some symptoms of MPS I. MSAC noted that, without a submission to the LSDP to revise eligibility criteria for ERT, the modelled economic evaluations have incorporated use of ERT beyond current LSDP funding criteria. MSAC queried whether only MPS IH should be reported as part of the NBS, given that this is the only subtype for which all diagnosed individuals currently have access to an effective and approved treatment (HSCT) in Australia. MSAC noted that any proposed expansion in the use of ERT (either as a bridge to HSCT in MPS IH, which appears to be happening already; as a result of earlier treatment initiation in MPS IHS; or for the treatment of MPS IS, as suggested by the clinical co-applicants) was a matter for the LSDP Expert Panel to consider.

Regarding **relevant ethical (including equity), legal, social or organisational aspects specific to screening** for MPS I, MSAC considered that there were significant ethical implications of screening for MPS I that are different from the vast majority of currently screened conditions. NBS for MPS I will identify some newborns at risk of developing attenuated MPS I who may not benefit from screening in the newborn period because symptoms may not develop until later in childhood or in adulthood. NBS for MPS I may identify newborns who potentially may not ever develop symptoms. There is no effective early intervention for newborns with an early diagnosis of MPS IS or an indeterminate type of MPS I. However, MSAC considered an attenuated MPS I diagnosis may help newborns and their families through the 'value of knowing' and to avoid a 'diagnostic odyssey'. MSAC considered families may view the 'value of knowing' differently. MSAC considered that many families will consider there to be a 'value of knowing' for a diagnosis with predicted disease course. For others, there will be increased anxiety and stress associated with uncertain prognoses, where phenotype cannot be determined and/or treatment options may not be available. MSAC noted that in the United States (US) where NBS for MPS I has been implemented in some states, the National MPS Society receives 10–15 annual contacts from both distressed families and healthcare providers with experiences of inaccurate and false information related to the interpretation of the newborn screen result, as well as interpretation of subsequent testing. This confusion leads to anger and distrust related of the entire process of MPS I newborn screening[8]. MSAC noted the pre-ESC response, which also highlighted the need for clinical support for families after onset, particularly with regard to late or variable onset phenotypes. MSAC considered a presymptomatic diagnosis without an effective early intervention could cause harm to the newborn through excessive clinical monitoring and negative consequences from having a diagnostic label including psychological distress and 'sick role' behaviour without the potential for improved health outcomes.

MSAC noted there are positive benefits for carrier testing for at-risk family members to inform their future reproductive decisions.

[8] Clarke LA et al. (2020). Newborn Screening for Mucopolysaccharidosis I: Moving Forward Learning from Experience. *Int J Neonatal Screen* 19;6(4):91. doi: 10.3390/ijns6040091.

MSAC considered that there are ethical issues associated with screening newborns for conditions where some individuals may not develop the condition until adulthood if there is no effective intervention in childhood. Most professional and legal organisations do not support testing children for adult-onset diseases to preserve their autonomy and right to provide informed consent [9,10,11,12]. MSAC noted that many adults do chose to forgo genetic testing for conditions such as Huntington's disease, suggesting not all individuals want presymptomatic diagnosis when there are no effective treatment options available. MSAC considered there may also be implications for some types of insurance.

MSAC considered that there is a significant ethical and equity issue because not all newborns diagnosed with MPS IHS or MPS IH (awaiting transplant) will be eligible for publicly funded laronidase.

MSAC advised that there should be an ethical analysis of reporting MPS IS and MPS I with an uncertain phenotype before newborn screening for MPS I is implemented, because there is no effective early intervention. MSAC advised that one option would be to limit to reporting to diagnoses of MPS IH or MPS IHS (versus all MPS I diagnoses) where there are some benefits to the newborn from early treatment. MSAC noted that NBS laboratories could limit reporting to known phenotypes and an effective early intervention and not report results for unknown phenotypes (including VUSs) but considered there are ethical issues associated with not reporting abnormal test results, particularly as the testing methodology detects abnormal GAG storage. MSAC considered that further information on the acceptability of such an approach to the general population would be needed to inform consideration by the other bodies in the decision-making pathway, and that this issue should be resolved prior to implementation. MSAC acknowledged that clinical review would be required to determine phenotype and prognosis, so limiting reporting may not be possible in all cases.

MSAC advised that the addition of MPS I to newborn screening programs has ethical considerations that warrant updates to consent processes when screening for MPS I is implemented. MSAC noted that, currently, there is informed consent for newborn screening but no national consensus about the requirement for written consent across the states and territories. MSAC therefore advised that appropriate consent processes must be updated with the implementation of screening newborns for MPS I, as there is the potential to diagnose an infant with an uncertain phenotype. MSAC advised that this should incorporate the consensus on whether MPS IS and MPS I with uncertain phenotype would be reported. MSAC considered the consent process should inform families that some newborns may never develop significant symptoms MPS I and the availability of publicly funded effective early treatment so they can provide informed consent. MSAC considered this is essential to reduce any potential negative impact on public trust in NBS programs.

---

[9] Vears DF et al., 2024. Human Genetics Society of Australasia Position Statement: Predictive and Presymptomatic Genetic Testing in Adults and Children. *Twin Res Hum Genet*. 27(2):120-127. doi: 10.1017/thg.2024.9.

[10] European Society of Human Genetics, 2009. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. *Eur J Hum Genet*. 17(6):720-1. doi: 10.1038/ejhg.2009.26.

[11] COMMITTEE ON BIOETHICS; COMMITTEE ON GENETICS, AND; AMERICAN COLLEGE OF MEDICAL GENETICS AND; GENOMICS SOCIAL; ETHICAL; LEGAL ISSUES COMMITTEE, 2013. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 131(3):620-2. doi: 10.1542/peds.2012-3680.

[12] Australian Law Reform Commission & National Health and Medical Research Council (Australia) & Australian Health Ethics Committee. (2003). Essentially yours: the protection of human genetic information in Australia (Chapter 24 Population genetic screening programs). From https://www.alrc.gov.au/publication/essentially-yours-the-protection-of-human-genetic-information-in-australia-alrc-report-96/24-population-genetic-screening/population-genetic-screening-programs/

MSAC noted that the NBS programs have near universal uptake (over 99.0%), indicative of high levels of public trust in the programs. MSAC considered there may be a risk in diagnosing children with adult-onset conditions, or conditions with no early intervention as this can lead to distrust in newborn screening and potentially discourage parents from participation. Therefore, MSAC advised that the consent process would need to be carefully managed to ensure that trust in NBS programs is not diminished. MSAC advised that reduced participation in newborn screening would lead to worse health outcomes at a population level if newborns are not diagnosed and treated for other conditions that are more common than MPS I and where there are effective early interventions, such as cystic fibrosis, phenylketonuria and congenital hypothyroidism.

MSAC advised that, if NBS for MPS I is implemented, a registry should be developed and commenced simultaneously with newborn screening, to enable long-term follow-up to establish incidence of each disease subtype and their genotype–phenotype relationships (including the proportion of individuals with each MPS I subtype in the Australian context) and clinical outcomes data. MSAC advised that a publicly funded registry is preferred to ensure the data can be used to better understand clinical outcomes of MPS I.

MSAC also considered a national screening protocol for MPS I should be agreed and implemented concurrently across all jurisdictions to ensure equity of access to screening. MSAC considered adding LSDs to newborn bloodspot screening programs as part of one agreed panel would be preferrable.

MSAC recalled that it first considered this application in November 2024. In April 2025, MSAC provided further advice on NBS for MPS I, and supported its inclusion in Australia's NBS programs. However, MSAC considered that there are significant policy, implementation and ethical issues that must be resolved prior to implementation. MSAC considered that these should be considered and advised upon by other committees in the national decision-making pathway. MSAC noted that Health Ministers will decide whether to implement newborn screening for MPS I after considering advice from MSAC and several other committees.

Overall, MSAC supported extending the NBS programs to include MPS I testing provided the following issues are addressed before implementation:

- A consensus is reached regarding whether screening results should be reported for newborns with an uncertain MPS I phenotype, or for newborns who would not have access to treatment at diagnosis (e.g. MPS IS, or MPS IHS before symptom onset without prediction of severe disease). MSAC considered this would require an ethical analysis.
- Review expanded public funding for ERT for newborns diagnosed with MPS IHS and MPS IH (awaiting transplantation) to ensure equitable access to an effective early intervention. This may require a review of the LSDP ERT eligibility criteria and the corresponding budget impacts for the LSDP (noting that reconsideration of eligibility criteria is likely to require a submission to PBAC by the medicine sponsor).
- To maintain trust in the NBS programs, appropriate consent processes are introduced to inform parents of the possibility that their newborn may be found to be at risk of an attenuated form of MPS I with uncertain prognosis and treatment availability.
- Australian clinical practice guidelines, which may include consensus guidelines, are developed for the monitoring and management of at-risk/presymptomatic children whose disease onset and severity cannot be clearly predicted.
- Clinical workforce capacity and readiness is established, along with a mechanism to collect national, robust, longitudinal data on genotype–phenotype relationships (especially for attenuated MPS I) and clinical outcomes to inform future reviews of NBS for MPS I (noting conditions can be, and have been, removed from the NBS programs).

Such data could also be used to track the benefits and harms of current and emerging treatments.

Addressing of the above requirements may occur in parallel with MPS I screening implementation process, to ensure timely screening of Australian babies.

Overall MSAC considered that the following key HTA criteria were met:

- False positive and false negative rates are low with the proposed 2-tier screening strategy.
- There is evidence of incremental benefit for screen-detected cases.
- The total cost for NBS is acceptable (but there is potential for significant financial impact to the LSDP).

Additionally, MSAC considered the primary criteria of the NBS NPF were met as the condition is predominantly early-onset and severe (the median age of clinical diagnosis is approximately one year for MPS IH and 4 years for MPS IHS) with an existing treatment, noting current restrictions to access.

4. Background

MSAC has not previously considered adding MPS I to NBS programs.

5. Prerequisites to implementation of any funding advice

Newborn screening laboratories would determine which method of screening for MPS I they would implement for their screening population. New conditions added to Australian NBS programs need to align with the Newborn Bloodspot Screening National Policy Framework (NBS NPF) decision-making criteria, which were considered as context for MSAC's advice. With the referral of a condition into the MSAC process, the other decision-making criteria of the NBS NPF (except cost-effectiveness) are assumed to be in alignment and have already been determined to be met, by the other committees in the NBS decision-making pathway. The full scope of considerations relevant to the NBS NPF criteria, such as detailed appraisal of all relevant implementation considerations, are outside the scope of MSAC's advice on NBS, as implementation is the role of the states and territories.

In order for MPS I to be added to the NBS programs, NBS laboratories would be required to:

- Have or gain sufficient space for additional capital equipment, including tandem mass spectrometry machines.
- Purchase additional tandem mass spectrometry machines (adhering to local procurement policies including tender processes).
- Hire and train additional laboratory staff (in several laboratories a different rostering system would be required so the laboratory is in use 6 days per week instead of 5).
- Validate the screening protocols, determining normal and abnormal value ranges.
- Ensuring the testing is added to their scope for National Association of Testing Authorities (NATA) accreditation.
- Add the new test to the Laboratory Information Management System[13].

[13] https://www.health.gov.au/sites/default/files/2024-06/newborn-bloodspot-screening-expansion-readiness-assessment-executive-summary_0.pdf

- Have access to second tier testing, either locally (in-lab) or referred to an Australian expert centre.

The NBS laboratories have estimated it would take at least 6 months to implement NBS testing using a commercial kit, such as the Revvity NeoLSD. This would require set-up of the new machine, validation of the screening test, piloting to minimise the risk of incorrect results, and checking the end-to-end pathway from receiving a sample to referral into care.

The number of cases positive on first-tier screening are unlikely to warrant each individual laboratory purchasing the equipment required for second-tier screening; rather, the samples could be sent to a central laboratory, the National Referral Laboratory (NRL) for Lysosomal Storage Diseases (LSDs) in South Australia for second-tier testing. If this occurred, the NRL may need to purchase an additional mass spectrometry machine.

The department contracted assessment report (DCAR) considered clinical guidelines for the management of patients with MPS I in Australia would be required to be updated, to incorporate recommendations on the management of patients identified through screening, who may not yet present with symptoms. Clinical capacity may also need to increase, to support the additional "patients in waiting" expected to be identified through screening, with their families requiring additional education, counselling and support. Additional education will also be required for their health care providers.

6. Proposal for public funding

The proposal is for MPS I to be added to the list of conditions screened for through Australia's NBS programs. NBS programs are overseen and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). It is also directly investing $107.3 million from 2022–23 to 2027–28 to support expansion of NBS programs. This includes:

- $39 million from Budget 2022–23, including $25.3 million for states and territories
- $68.3 million from Budget 2024–25, including $43.3 million for states and territories (announced through MYEFO 2024–25)

There are five laboratories that conduct tests on bloodspot cards, located in New South Wales, Victoria, Queensland, South Australia and Western Australia. Newborns born in states and territories without NBS testing laboratories have their dried bloodspots (DBS) sent interstate for testing. Each laboratory may choose their preferred screening protocol. For MPS I, the NBS laboratories were consistent that:

- First-tier screening should be done by testing alpha-L-iduronidase (IDUA) enzyme activity on the bloodspot (using a commercial kit such as the Revvity NeoLSD kit or GelbChem [now known as Enfanos] CS18 (IDUA) kit).
- Second-tier testing should be endogenous non-reducing end (NRE)-glycosaminoglycans (GAG) analysis on the DBS (either in-house or sent to the NRL for LSDs based in Adelaide, depending on the number of second-tier tests likely to be required).

The NRL and one of the clinical co-applicants recommended using endogenous NRE-GAG analysis as a single-tier screening method, so the PICO Advisory Sub-Committee (PASC) of the MSAC recommended that this screening protocol also be considered in the assessment. This method is not currently in use anywhere else in the world.

If a case of MPS I is diagnosed due to NBS, then cascade testing of aunts, uncles and siblings is also proposed. This testing would be outside NBS program funding. The testing of family members would involve genetic testing for the familial pathogenic/likely pathogenic (P/LP) variants identified in the index case/proband, and the testing of siblings (if deemed clinically relevant) would either be by the use of urine GAG analysis and/ or by genetic analysis, although MSAC noted segregation testing of parents should form part of the confirmatory testing and not be considered as part of cascade testing. MSAC noted that The Human Genetics Society of Australasia suggest the default position should be that carrier testing should not be provided until a child or young person can be supported to make an informed decision[14]). Testing of family members already occurs when a person is diagnosed with MPS I, so this is not a new service.

7. Populations

There are two different PICO sets that have been assessed in this report. In PICO set 1, the target population is newborns undergoing universal screening (although the population for the comparator is affected individuals of any age undergoing diagnostic testing). In PICO set 2, the target population is biological family members of someone diagnosed through either of the methods analysed in PICO set 1. In the comparison of screening versus no screening, the populations eligible for the intervention and the comparators differ slightly, as summarised in Table 2.

Table 2 Description of populations included in the assessment

PICO set	Population for intervention	Population for comparator
PICO Set 1 - Newborns	All newborn babies in Australia	Affected individuals being investigated for MPS I due to signs/symptoms
PICO Set 2 – Family members	Biological parents, aunts/uncles and siblings of an index case identified through NBS with two pathogenic/likely pathogenic (P/LP) variants or one P/LP variant and one VUS in the *IDUA* gene	Biological parents, aunts/uncles and siblings of a proband identified after symptom onset with two pathogenic/likely pathogenic (P/LP) variants or one P/LP variant and one VUS (reclassified as P/LP) in the *IDUA* gene

IDUA = *α-L-iduronidase*; MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening; P/LP = pathogenic or likely pathogenic; PICO = Population/Intervention/Comparator/Outcomes; VUS = variant of uncertain significance

PICO Set 1 – Newborns

In Australia, the uptake of newborn bloodspot screening is over 99%[15]. The population proposed for screening MPS I is the same as would undergo NBS in the absence of MPS I being part of the NBS programs (i.e. approximately 300,000 newborns per year). Sufficient dried bloodspots are currently made to enable this additional testing from the current heel prick samples placed onto a filter paper card in the first 48 -72 hours of life.

MPS I is an ultra-rare[16] lysosomal storage disorder that is inherited in an autosomal recessive manner. The disorder is caused by 2 pathogenic variants in the *α-L-iduronidase (IDUA)* gene. A

[14] Vears, DF, *et al.* (2023). Human Genetics Society of Australasia Position Statement: Genetic Carrier Testing for Recessive Conditions. *Twin Res Hum Genet*, vol. 26, no. 2, pp. 188-194. doi: 10.1017/thg.2023.15.

[15] Huynh, T *et al.* (2022). Fifty years of newborn screening for congenital hypothyroidism: current status in Australasia and the case for harmonisation. *Clin Chem Lab Med*, vol. 60, no. 10, Sep 27, pp. 1551-1561. doi: 10.1515/cclm-2022-0403.

[16] Defined as 1 case per 50,000 or fewer in Australian population https://www.health.gov.au/our-work/life-saving-drugs-program/about-the-lsdp

lysosome is a membrane bound organelle that occurs in nearly every cell in the body (excluding red blood cells). Lysosomes contain enzymes that are responsible for breaking down and recycling cellular waste. In MPS I, the lysosomal enzyme IDUA, which is responsible for breaking down the GAGs dermatan sulphate and heparan sulphate, is either missing or deficient. These undegraded/partially degraded GAGs therefore accumulate, causing the lysosome to enlarge, and rupture. This results in defects in the extracellular matrix, connective tissue (including joints and heart valves) and joint fluids.

There are three different subtypes of MPS I described that vary in severity and time of onset. Hurler syndrome (MPS IH) is the most common (50 – 80%) and severe subtype, with signs/symptoms occurring in the first year of life. Patients with MPS IH usually die within the first 10 years of life without treatment. Early symptoms are non-specific and involve frequent respiratory infections. However, deceleration of growth occurs between 6-8 months, and developmental delay begins at 12-24 months[17]. The condition is progressive, with increasing bone deformities, including coarsening of facial features, kyphosis in the spine and skeletal dysplasia, as well as abnormal enlargement of organs, valve disease, hearing loss and corneal clouding[18]. MPS IH is treated with haematopoietic stem cell transplantation (HSCT) if diagnosed before the age of 2.

Hurler-Scheie syndrome (MPS IHS) has a slower progression than MPS IH, with symptoms usually starting around age 2 years, with joint stiffness as the first problem noted. Cognitive development is not affected in the majority of patients with MPS IHS, or if learning difficulties are experienced, are typically much more slowly-progressive compared to that seen in MPS IH. In the absence of treatment, patients with MPS IHS often die in their twenties due to cardiac disease or respiratory failure[19]. The treatment for MPS IHS is enzyme replacement therapy with laronidase (Aldurazyme®), which is fully subsidised in Australia through the Life Saving Drugs Program (LSDP)[20] if patients meet the criteria for eligibility. The assessment group noted these criteria were developed at a time when patients were either diagnosed due to the development of symptoms, or due to having the same genotype as an older sibling with MPS IHS. In order for the criteria to be altered, in response to cases of MPS I being diagnosed due to NBS, the medicine sponsor would need to make a submission for altering/broadening the eligibility criteria for subsidised laronidase access via the LSDP.

The mildest form of MPS I is Scheie syndrome (MPS IS), which has very variable age of diagnosis (from childhood to the fifth decade). Patients with MPS IS may have joint stiffness and pain, aortic valve disease, corneal clouding and other eye problems, all of which may cause severe disability. The average lifespan is limited to the middle decades, although some patients with MPS IS have a normal lifespan.[21] There is no treatment available in Australia that slows the

---

[17] Keerthiga, M *et al.* (2023). Mucopolysaccharidoses: An overview and new treatment modalities. *Int J Clin Biochem Res*, vol. 10, no. 2, pp. 101-109

[18] Parini, R *et al.* (2017). Open issues in Mucopolysaccharidosis type I-Hurler. *Orphanet J Rare Dis*, vol. 12, no. 1, 2017/06/15, p. 112. doi: 10.1186/s13023-017-0662-9.

[19] Roubicek, M *et al.* (1985). The clinical spectrum of α-L-iduronidase deficiency. *Am J Med Genet*, vol. 20, no. 3, pp. 471-481. doi https://doi.org/10.1002/ajmg.1320200308.

[20] https://www.health.gov.au/resources/publications/life-saving-drugs-program-mucopolysaccharidosis-type-i-mps-i-guidelines

[21] Vijay, S & Wraith, J (2005). Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. *Acta Paediatrica*, vol. 94, no. 7, pp. 872-877 https://doi.org/10.1111/j.1651-2227.2005.tb02004.x.

progression of MPS IS, so treatments for this milder form are restricted to managing the individual manifestations of the condition as they appear.

The true birth prevalence of MPS I is unknown, as the rate clinically diagnosed may underestimate the number of attenuated cases (i.e. it is possible that some attenuated cases remain undiagnosed/misdiagnosed their whole lives). Based on those diagnosed between 2009 and 2020 in Australia, the DCAR estimated incidence of MPS I was 0.73 per 100,000 live births[22]. The worldwide birth prevalence of MPS I from 20 NBS programs from Brazil, Italy, Mexico, Japan, Taiwan and the United States is 1.23 per 100,000 live births.

PICO Set 2 – Family members

Following the identification of cases of MPS I, genetic testing would occur in both the index case/proband, as well as the parents, for segregation analysis. This is important to show that the 2 detected variants have been inherited from separate parents or de novo variant(s) that have no additional risk for subsequent offspring. Cascade testing of other family members may also occur, such as siblings (if considered clinically appropriate), and aunts/uncles (for the purposes of reproductive planning).

Nearly every case of MPS I will have both parents tested. In 2021, the average fertility rate for Australian women who had at least one child was 1.9[23]. It can be assumed that in half of families, the case diagnosed with MPS I would be the first-born and in half of families, the case diagnosed would be second-born. If the case diagnosed is first-born (and diagnosed at birth due to NBS), no siblings will yet be alive to test. The average number of siblings available per family for testing after NBS is therefore 0.5 (i.e. an older sibling available to test in half of families), and in the absence of NBS, it would be 1 (assuming either a younger or older sibling).

As both parents are obligate carriers, it can be assumed that their siblings (aunts and uncles of the proband/index case) would each have a 50% chance of also being carriers. It is estimated that each case will have an average of 1.68 aunts/uncles (based on data from the Australian Bureau of Statistics). The DCAR noted, no data on the uptake of cascade testing in aunts/uncles was identified for MPS I, but an Australian study identified that 11.5% of non-parent relatives underwent cascade testing after identification of cystic fibrosis in a newborn diagnosed due to NBS.[24] The DCAR therefore assumed that 0 – 1 aunts/uncles would be tested per family.

8. Comparator(s)

PICO Set 1 – After symptom onset

The comparator to adding MPS I to the NBS programs is no screening for MPS I and diagnostic testing after symptom onset.

Diagnostic tests currently performed in patients suspected of having or being at risk of MPS I include:

---

[22] Chin, SJ & Fuller, M (2022). Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. *Lancet Reg Health West Pac*, vol. 19. doi 10.1016/j.lanwpc.2021.100344.

[23] Qu, L & Baxter, J (2023). Births in Australia, Australian Government, Canberra.

[24] McClaren, BJ *et al.* (2010). Uptake of carrier testing in families after cystic fibrosis diagnosis through newborn screening. *Eur J Hum Genet*, vol. 18, no. 10, Oct, pp. 1084-1089. doi 10.1038/ejhg.2010.78.

- A urinary GAG analysis using liquid chromatography (LC)-tandem mass spectrometry (MS/MS).
- A leukocyte IDUA enzyme activity test.
  Although not required for diagnosis, it is still useful to predict the severity of disease. Additionally, the current eligibility criteria for laronidase through the LSDP requires that the diagnosis of MPS I be confirmed by the demonstration of a deficiency of IDUA enzyme activity in white blood cells with the assay performed in a NATA-accredited laboratory.

Those who are found to have MPS I have genetic testing, either by Sanger sequencing of the *IDUA* gene (for laboratories who have primers for this gene) or next generation sequencing.

PICO Set 2 – Family members

Currently, testing of family members involves a two-step approach.

1. Genetic testing for the specific familial P/LP/VUS variants is offered to parents, aunts and uncles after the diagnosis of a symptomatic child within the state clinical genetics system. Genetic counsellors are rarely associated with metabolic clinics in current practice in Australia. If the parents, aunts and uncles wish for further family planning advice, they are generally referred to a genetic clinic.

2. Siblings of the affected patient can undergo biochemical testing (urine GAG analysis) or genetic testing. If a sibling is diagnosed with MPS I by this testing (rather than due to symptom onset), this will most likely suggest an attenuated form of the disease, as the median age at diagnosis of severe disease is under one year of age.

Clearly unaffected siblings are not proposed to be offered carrier testing, unless they are old enough that this information may be used for reproductive planning.

9. Summary of public consultation input

MSAC welcomed consultation input received for this application and noted the period for public consultation closed on 11 October 2024. Consultation input was welcomed from nine (9) professional organisations, three (3) consumer organisations, one (1) commercial organisation and one (1) individual (clinical scientist at a newborn bloodspot screening [NBS] laboratory). The organisations that submitted input were:

- Western Australian Newborn Bloodspot Screening Program (WA NBS)
- Australasian Society of Inborn Errors of Metabolism (ASIEM, a special interest group of Human Genetics Society of Australasia [HGSA])
- Rare Voices Australia (RVA)
- Australian Genomics
- Childhood Dementia Initiative x 2
- Statewide Biochemical Genetics Service within SA Pathology
- Sanofi-Aventis Australia
- Genetic Alliance Australia (GAA)
- The Royal College of Pathologists of Australasia (RCPA)
- Australian College of Midwives
- Public Pathology Australia
- Sanfilippo Children's Foundation
- National Aboriginal Community Controlled Health Organisation (NACCHO)

Benefits

- Early diagnosis allows early intervention and equitable access to treatment, and optimises outcomes.
- Case series of severe MPS I (Hurler Syndrome) indicate benefit of early haematopoietic stem cell transplantation (HSCT) on neurocognitive outcomes.
- Increased support for patients and families, and reduced burden as a result of optimised treatment outcomes.
- Avoidance of the 'diagnostic odyssey' or misdiagnosis for patients, which may correspond to a reduced financial burden on the healthcare system.
- "Value of knowing" and reduction in psychological stress for patients, families and carers.

Disadvantages

- NBS for MPS I has previously shown a poor predictive positive value (PPV).
- Potential harms of screening should be considered for newborn screening.
- Potential loss of a number of months of bonding where parents would otherwise believe they have a baby who does not have the condition (noting it was considered that the improved health outcomes for the child would be likely to balance this).
- MPS I screening has been implemented in other countries but there may be issues with variants of unknown significance which can be challenging to manage, and issues with early determination of clinical phenotype.
- Risk of overtreatment for attenuated forms of MPS I should be considered.

Other

Consultation feedback also noted that not all patients diagnosed with MPS I would be eligible for subsidised treatment, with only some patients currently eligible for subsided enzyme replacement therapy (ERT) on the Life Saving Drugs Program (LSDP).

Consultation feedback from NACCHO also raised the importance of seeking further information around the cultural safety of NBS and systemic barriers that may preclude the equitable participation of Aboriginal and Torres Strait Islander families and babies in NBS programs in Australia. NACCHO highlighted that it is unclear what systems and processes are in place to ensure that NBS programs provide a culturally safe experience at all stages of the process, including during screening, clinical assessment, diagnostic testing, treatment and ongoing management.

The feedback from Sanfilippo Children's Foundation highlighted that there is currently no active MPS society within Australia, and stated that this places immense strain on families.

10. Characteristics of the evidence base

The key characteristics of the evidence base are summarised in Table 3.

No evidence was identified that directly compared any outcomes after NBS for MPS I versus current practice (diagnosis after symptom onset, or due to family history). The DCAR therefore performed, a naïve indirect comparison, based on a large number of retrospective case series of MPS I cases diagnosed without NBS, and a small number of case series that screened a large number of neonates, but diagnosed only a very small number of MPS I cases. The data were therefore highly uncertain. The DCAR considered naïve indirect comparison was highly biased, as the newborn screening data have been collated over a more recent time period than the studies on diagnosis without NBS, and improvements made to healthcare systems worldwide over time may therefore bias the comparison in favour of NBS.

A total of 32 studies (6 case-control studies, 7 retrospective cohort studies and 19 prospective cohort studies) met the inclusion criteria for assessing the test accuracy of NBS methodologies for the detection of newborns with MPS I. However, as the reference standard was only used to verify whether newborns with a positive screen were true or false positives, and all negative screens were not verified, all of the studies were subject to verification bias.

A total of 60 case series and 6 case reports in MPS I patients were included in the section on 'Linked evidence of change in management' (as well as a single historical control study in MPS in general). The bulk of the evidence was reporting on the age at diagnosis or treatment of patients with MPS I in the absence of NBS. The resultant naïve indirect comparison (between more recent NBS studies and decades of historical case series prior to NBS) is highly biased.

The impact of the expected changes in management (early HSCT and early ERT) was assessed by using case series that compared early versus late treatment (i.e. treated like cohort studies). Studies on HSCT were potentially biased in that patients with related donors may have been able to receive HSCT earlier than those without related donors, and this was also a predictor of more favourable outcomes. E.g. Boelens et al. (2013) reported that 5-year event free survival was 81% in human leukocyte antigens (HLA) matched sibling donor, and 66% in HLA-matched unrelated donor. For studies on ERT, all the evidence came from sibships (sibling pairs or trios, where the youngest in each family was diagnosed pre-symptomatically). This evidence was very limited, with small study sizes due to the rarity of the disease and subtype.

The DCAR considered main evidence on the value of knowing came from a series of interviews with parents whose child had MPS I, and people with MPS I, discussing their experiences with the 'diagnostic odyssey'.

Table 3 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Direct from test to health outcomes	NBS screening studies that reported on outcomes for those MPS I cases diagnosed MPS I registry data	☒ k=4 case series n=5 (NBS); n=188 (no NBS)	Very high
Accuracy and performance of the test (cross-sectional accuracy)	Case-control studies Prospective cohort studies of NBS programs Retrospective cohort studies of NBS programs	☒ k=6 n=4,692 ☒ k=19 n=3,793,487 ☒ k=7 n=306,001	High risk of verification bias
Change in patient management	Case series Case report Historical control study	☒ k=60 n=5,480 ☒ k=6 n=6 ☒ k=1 n=175	High (no RoB checklist used)
Health outcomes	Case report Cohort studies	☒ k=3 n=7 ☒ k=28 n=1,977	High risk of bias
Value of knowing	Qualitative study	☒ k=1 n=17	Likely applicable to Australian setting

k = number of studies; MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening; RoB = risk of bias

11. Comparative safety

PICO Set 1 - Newborns

No direct evidence was identified on the safety of NBS for MPS I. Given bloodspots are already currently collected for existing conditions on the NBS programs, and collection of additional bloodspots should not be required for the purposes of testing for MPS I, the DCAR considered the safety impact of the test itself is likely to be negligible.

Risks associated with surgery have been identified for MPS I patients due to airway obstruction interfering with their ability to remain sufficiently ventilated during anaesthesia. However, no evidence was identified on the benefits/risks of using a tailored surgical plan to minimise complications when the patient is known to have MPS I. Nevertheless, it is recommended that a specialist in MPS should be consulted to collaborate with the surgical team.

The rate of surgical procedures performed without knowledge of MPS I status is expected to reduce to zero once sufficient time has passed after the introduction of NBS for MPS I. It is hypothesised that with early diagnosis, both the requirement for surgical procedures (due to early treatment reducing the severity of symptoms), and the risks associated with surgical procedures (due to severity of the condition as well as knowledge of the MPS I diagnosis), should reduce.

The harms associated with knowing a diagnosis or being a "patient in waiting" for patients with attenuated MPS I, were mostly related to parental and patient fears and anxiety in the face of uncertainty. This has historically been one of the main arguments against screening and genetic testing of newborns and children for later/adult-onset conditions. However, evidence considered in 'Other relevant information' suggests that many parents would prefer to know the diagnosis and avoid the 'diagnostic odyssey', despite concerns of creating "patients in waiting" and the impact this may have on being able to have a "carefree childhood".

PICO Set 2 - Family members

Testing of family members for known variants after NBS is expected to have no additional safety concerns over testing of family members after the index/proband is identified after symptom onset.

12. Comparative effectiveness

PICO Set 1 - Newborns

Direct from test to health outcomes evidence

No comparative direct evidence was available.

Six case series were identified on NBS programs, with a total of 2,017,236 newborns screened. From these studies, a total of 41 newborns were identified to potentially have MPS I. Five were classified as having MPS IH. All five cases of MPS IH diagnosed through NBS and treated early with HSCT were still alive (up to 6 years follow-up). In the absence of NBS, overall survival rates reported from the MPS I registry in outcomes of HSCT in cases of MPS IH were 90.4% 12-month

survival and 73.4% 5-year survival[25]. The small amount of data from those diagnosed due to NBS means that the comparison should be considered hypothesis-generating, but too uncertain to use as the basis of any conclusions. A linked-evidence assessment was therefore used to supplement the direct evidence.

Linked evidence of test accuracy

Screen positive rate for methodologies used in various NBS programs

Ten publications reported on the outcomes from thirteen different international NBS programs that screened for MPS I using a fluorometric assay to determine the IDUA enzyme activity level in DBS from the newborns. When used as a first-tier test, the fluorometric measurement of IDUA enzyme activity has a median screen positive rate of 0.24% (range 0.0095–0.4%; k=8). Any retesting of samples with low IDUA activity, or the addition of a second-tier test, greatly reduced the number of false positives recalled for follow-up diagnostic testing. The median screen positive rate for all studies that retested samples with initial low activity was 0.052% (range 0–0.92%; k=9). In individual studies reporting both initial and retesting results, this represented a 40–97% reduction in the number of newborns requiring follow-up confirmatory diagnostic testing.

Sixteen studies reported on the outcomes from NBS programs that screened for MPS I using a MS/MS-based enzyme assay to determine the IDUA enzyme activity level in DBS from the newborns. Twelve studies used flow injection analysis (FIA)-MS/MS and four studies used LC-MS/MS. When used as a first-tier test without retesting of samples with low IDUA enzyme activity, the median screen positive rate for FIA-MS/MS and LC-MS/MS was 0.11% (range 0.0085–2.05%; k=8) and 0.24% (range 0.069–0.27%; k=3), respectively. The use of any retesting protocol or a second-tier test reduced the median number of false positives recalled for follow-up diagnostic testing with a median screen positive rate of 0.011% (range 0.0036–0.036%, k=9) for FIA-MS/MS and 0.015% (range 0.014–0.092%; k=3) for LC-MS/MS. The use of repeat testing or a second-tier test reduced the screen positive rate by 33–98% in individual studies when compared to the initial test positive rate.

The screen positive and false positive rates for various NBS programs in detecting MPS I

Fifteen studies provided results from 21 NBS programs from Brazil, Italy, Japan, Mexico, Taiwan and 13 USA states that enabled the screen positive rate, false positive rate and the positive predictive value (PPV) to be calculated (Table 4). The PPV was calculated by dividing the true positive rate (TPR) (per 100,000) by the screen positive rate (SPR)(per 100,000).

[25] Kemper, A *et al.* (2015). Newborn screening for mucopolysaccharidosis type 1 (MPS I): a systematic review of evidence. Report of final findings. Final Version, vol. 1, pp. 3-60

Table 4 The median screen positive rate, false positive rate, PPV and the number of true positive cases for various NBS programs by country and choice of 1st tier test

Country	1st tier test	Population	Median SPR (range) Median FPR (range) Number of TP, TPR, PPV
All NBS programs	Fluorometric IDUA enzyme assay FIA-MS/MS IDUA enzyme assay LC-MS/MS IDUA enzyme assay	N=3,569,166 DBS from newborns k=21	SPR=0.024% (0–0.40) =24/100,000 FPR=0.022% (0–0.399) =22/100,000 TP=44; TPR=1.23/100,000 PPV=5.1%
US NBS programs	Fluorometric IDUA enzyme assay FIA-MS/MS IDUA enzyme assay LC-MS/MS IDUA enzyme assay	N=3,034,647 DBS from newborns k=13	SPR=0.055% (0.0036–0.04) =55/100,000 FPR=0.055% (0.0018–0.399) =55/100,000 TP=32; TPR=1.05/100,000 PPV=1.9%
non-US NBS programs	Fluorometric IDUA enzyme assay FIA-MS/MS IDUA enzyme assay LC-MS/MS IDUA enzyme assay	N=534,519 DBS from newborns k=8	SPR=0.0090% (0–0.024) =9/100,000 FPR=0.0062% (0–0.022) =6/100,000 TP=12; TPR=2.25/100,000 PPV=25.0%

DBS = dried bloodspot; k = number of studies; FIA-MS/MS = flow-injection analysis-tandem mass spectrometry; FP = false positive; FPR = false positive rate; IDUA = α-L-iduronidase; LC-MS/MS = liquid chromatography- tandem mass spectrometry; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; PPV = positive predictive value; SPR = screen positive rate; TP = true positive; TPR = true positive rate; US = United States

The median screen positive rate, which includes all true positives and false positives, for all NBS programs was 0.024% (range 0–0.40%; k=21). This equates to 24 positive NBS screens per 100,000 newborns tested. The median false positive rate for all NBS programs was 0.022% (range 0–0.399%; k=21). This equates to 22 false positive NBS screens per 100,000 newborns tested. Overall, the NBS programs had a PPV of 5.1%.

The wide range in the screen positive rate between NBS programs is due to the wide range in the false positive rate. False positives were mainly due to setting the detection limit too high, resulting in the detection of newborns with either pseudodeficiency *IDUA* variants or carriers of a single P/LP *IDUA* variant. The frequency of pseudodeficiency varies by ancestry: African and African American populations have a high incidence of pseudodeficiency compared to European and Asian populations[26].

To date, no NBS program has reported a false negative screening result. However, one out of four case-control studies[27] did report a single false negative case. This patient was 33 years old at diagnosis of attenuated MPS I, and the DBS IDUA activity for this patient (5.5 µmol/L/h) fell just above the cutoff value (5.2 µmol/L/h). However, as the age and severity of disease for the other MPS I patients in these studies is unknown, it is uncertain if the very late onset form of attenuated MPS I is the cause of the false negative result.

Nevertheless, newborns with very attenuated forms of MPS IS who will not develop symptoms until later in life (i.e. in their 30s to 60s) could potentially be misdiagnosed in an NBS program with a false negative screening result. As no NBS program has yet reported a false negative result, all newborns with severe (MPS IH) and intermediate (MPS IHS) forms of disease have most likely been identified correctly. However, the DCAR considered programs have not been running long enough to know if all newborns with very attenuated forms of MPS IS have likewise

[26] Polo, G *et al*. (2020). The combined use of enzyme activity and metabolite assays as a strategy for newborn screening of mucopolysaccharidosis type I. *Clin Chem Lab Med,* vol. 58, no. 12, pp. 2063-2072.

[27] Hirachan, R *et al.* (2024). Evaluation, in a highly specialised enzyme laboratory, of a digital microfluidics platform for rapid assessment of lysosomal enzyme activity in dried blood spots. *JIMD Rep*, vol. 65, no. 2, pp. 124-131.

been correctly identified via NBS. It is also possible that newborns with very attenuated forms of MPS IS were misdiagnosed as false positives, even though they were true positives, especially if *IDUA* gene sequencing revealed one variant of uncertain significance (VUS) and a P/LP variant, or even two VUSs, and the infant was symptom free at follow-up (i.e. the newborn may truly have the condition, be detected on first-tier screening, and inappropriately ruled out after second-tier or genetic testing).

There were 44 newborns with MPS I detected among a total of 3,569,166 newborns screened. This equates to 1.23 per 100,000 newborns being diagnosed with MPS I via newborn screening programs.

LC-MS/MS to measure GAG disaccharides as a second-tier NBS test

NRE-GAG analysis is the preferred second-tier test according to the ratified PICO for MSAC application 1775. Although this test is being used as a second-tier test for NBS in some states in the USA, no results from these programs have as yet been published. The only published report of using NRE-GAG analysis on DBS is a case-control study with a very small sample size (n=45; 7 with MPS I), reporting 100% sensitivity and specificity. Thus, the accuracy of using this methodology for second-tier screening is uncertain at this time.

However, 3 studies have reported on the use of other GAG disaccharide analysis methods (GAG methanolysis and GAG digestion) as a second-tier assay in 3 NBS programs. The median false positive rate in these NBS programs was 0% (range 0–0.0018%). This would improve the PPV from the current 5.1% to 100%. Thus, GAG disaccharide analysis does provide a promising second tier assay that will largely, if not entirely, eliminate false positive results and reduce the number of newborns requiring clinical evaluation.

Summary

Australian NBS programs will most likely use an IDUA enzyme assay as a first-tier test and include retesting of any DBSs with low enzyme activity as part of the first-tier screening algorithm. Overall, the 21 NBS programs included in this report indicate that a median of 24 per 100,000 newborns would have a positive first-tier screening result. With an annual birth rate of approximately 300,000 babies per year, Australian NBS laboratories would be testing approximately 72 DBS samples using a second-tier test, which will most likely be the NRE-GAG test. This volume of second-tier testing would not warrant each individual laboratory purchasing the relevant equipment and validating their protocols for testing NRE-GAG analysis. It is therefore likely that the second-tier testing would occur in the NRL for LSDs in Adelaide. The NRE-GAG test is expected to eliminate all false positive results such that only those who have MPS I will be recalled for clinical confirmatory diagnosis. This would result in the Australian NBS programs having a PPV and negative predictive value (NPV) of (or very close to) 100%. Worldwide, 1.23 cases of MPS I per 100,000 newborns were detected via NBS programs, suggesting that approximately 4 cases of MPS I per year would be identified across Australia via the NBS.

Linked evidence of change in management

A total of 66 case series or case reports met the inclusion criteria for assessing change in management following diagnosis of MPS I through NBS (k=5) or in the absence of NBS (k=61).

Age at diagnosis via NBS compared with no NBS

A naïve comparison of the age of diagnosis in the presence or absence of NBS was undertaken. Several case series reported on the median age of diagnosis for Hurler, Hurler-Scheie and Scheie syndromes. Diagnosis in the absence of NBS occurs after the child becomes symptomatic or due to a family history of MPS I. One study reported on the median age at diagnosis of any MPS type

(including 7 MPS I patients) since the introduction of NBS in Taiwan in 2016. This study also noted that there was a reduction in age at diagnosis over time even in the absence of NBS. The results are summarised in Table 5.

One patient was much older than expected for the diagnosis of Hurler syndrome. This patient was diagnosed at age 23.8 years in India, which is more than double the life expectancy for a child with Hurler who had received no specific treatment. No other details about this patient were available, making the actual diagnosis in this case uncertain. The median age of diagnosis in the absence of NBS was calculated using case series with 3 or more patients.

Table 5 Age at diagnosis of MPS I in the presence or absence of NBS

Syndrome	Number of studies	Number of patients	Median age at diagnosis
In the absence of NBS			
Hurler (MPS IH)	11	1,051	11 months (range 0–87 months)
Hurler-Scheie (MPS IHS)	6	234	4.05 years (range 0–38.7 years)
Scheie (MPS IS)	6	128	13.5 years (range 0–54 years)
With NBS			
All MPS types (not only MPS I)	1	7	2.4 months

MPS I = mucopolysaccharidosis Type I; MPS IH = mucopolysaccharidosis Type I Hurler syndrome; MPS IHS = mucopolysaccharidosis Type I Hurler-Scheie syndrome; MPS IS = mucopolysaccharidosis Type I Scheie syndrome; NA = not applicable; NBS = newborn bloodspot screening

Data from the Australia and New Zealand Transplant & Cellular Therapies (ANZTCT) registry, specific to patients with Hurler syndrome who received HSCT between 2008 and 2024, reported that median age at diagnosis was **REDACTED**, this was in the absence of NBS.

Conclusion: The DCAR concluded NBS would result in earlier diagnosis for all three phenotypes, but the length of time between when patients would be diagnosed due to NBS and when they would be diagnosed without NBS varies between phenotypes. Given the age at diagnosis for attenuated MPS I types, some of these patients, especially those with Scheie syndrome, may require decades of follow-up before symptoms emerge.

Age at treatment initiation after diagnosis via NBS compared with no NBS

A naïve comparison of the age at treatment initiation in the presence or absence of NBS was undertaken. It should be noted that the interval between diagnosis and treatment has reduced over time (in the absence of NBS), associated with improvements in the healthcare system. This introduced a bias to any naïve indirect comparisons made. Several case series reported on the median age at treatment initiation for ERT and HSCT. The results are summarised in Table 6.

In Australia and New Zealand, the median age at first HSCT between 2008 and 2014 was **REDACTED** in the absence of NBS.

Table 6 Age at treatment initiation in the presence or absence of NBS

Syndrome	Number of studies	Number of patients	Median age at treatment initiation
In the absence of NBS			
HSCT for MPS IH	20	1,051	16.75 months (range 1 month-31.2 years)
ERT for MPS IHS	4	228	8.8 years (range 15 days–55 years)
With NBS			
HSCT for MPS IH	4	6	6 months (range 2.5–7 months)
ERT for MPS IHS	1	1	1 month

ERT = enzyme replacement therapy; HSCT = haemopoietic stem cell transplantation; MPS I = mucopolysaccharidosis Type I; MPS IH = mucopolysaccharidosis Type I Hurler syndrome; MPS IHS = mucopolysaccharidosis Type I Hurler-Scheie syndrome; NBS = newborn bloodspot screening

Conclusion: The DCAR considered difference in age at time of HSCT between the NBS and no NBS case series was substantial, such that even despite the risk of bias, it can still be confidently concluded that diagnosis via NBS leads to patients with MPS IH undergoing HSCT at an earlier age.

Treatment details after diagnosis of MPS IHS via NBS has only been reported for a single newborn, to date. This patient started ERT at 1 month, which was much earlier than the median 8.8 years derived from the case series reporting this information.

No information on the treatment of newborns diagnosed with MPS IS was available. However, as treatment of MPS IS in Australia is limited to treatment of symptoms as they occur, the DCAR considered it is uncertain what health benefit earlier diagnosis via the NBS would be for these patients, other than routine surveillance for the onset of symptoms, which may not occur for several decades in some cases. (Note, even in the absence of a clear change in management for patients with MPS IS, there is likely to still be value in having an early diagnosis of MPS IS, due to the avoidance of a diagnostic delay, see 'Other relevant information').

Proportion of those with MPS IHS potentially eligible for earlier ERT (genotype predictive of phenotype)

Applications can be submitted to request access to subsidised ERT via the LSDP for infants and children aged less than 5 years who are not yet demonstrating symptoms. The disease progression in these children must be predictable. For example, if the infant or child has the same genotype as an affected sibling, and the course of disease may be predicted on the basis of the sibling's disease progression.

The proportion of infants detected through NBS who had genotypes known to be associated with MPS IHS was estimated from five case series reporting on genotype/phenotype associations for MPS IHS patients. The median proportion of patients with 2 known P/LP variants associated with MPS IHS was 50% (range 37.5–79.9%). It is assumed that the proportion of genotypes able to be linked to particular phenotypes would increase with time, meaning that the estimates from the literature (published between 2001 and 2019) likely underestimate the proportion potentially eligible for subsidised access to ERT.

Conclusion: The DCAR considered It is possible that applications may be made so that newborns diagnosed due to NBS, who have a genotype known to be associated with MPS IHS, can access subsidised ERT. As only 4 newborns are expected to be diagnosed with MPS I per year in Australia, and 2–3 of these patients are likely to have MPS IH, no more than one patient every one or two years would be diagnosed with MPS IHS, and half of these patients will be able to apply based on their genotype.

Time to diagnosis

Nine case series or case reports were identified that reported on the time between symptom onset and diagnosis for those with MPS I in the absence of NBS. The severity of the condition had a large influence on the length of diagnostic delay (the more severe the condition, the shorter the time to diagnosis). The median time to diagnosis is summarised in Table 7.

Table 7 Time to diagnosis in the absence of NBS

Syndrome	Number of studies	Number of patients	Median time from symptom onset to diagnosis
Hurler (MPS IH)	4	43	14.25 months (range 0–59 months)
Hurler-Scheie (MPS IHS)	3	11	25 months (range 5 months–14.5 years)
Scheie (MPS IS)	4	86	7.5 years (range 0–50 years)

MPS I = mucopolysaccharidosis Type I; MPS IH = mucopolysaccharidosis Type I Hurler syndrome; MPS IHS = mucopolysaccharidosis Type I Hurler-Scheie syndrome; MPS IS = mucopolysaccharidosis Type I Scheie syndrome; NBS = newborn bloodspot screening

From four small case series involving 43 patients with Hurler syndrome, the median time between symptom onset and diagnosis was 14.25 months (range 0–59 months). The median time from symptom onset to diagnosis was longer than the median age at time of diagnosis reported in Table 5, due to the small number of studies being easily influenced by outlying results.

The overall median time to diagnosis for 11 patients (from three case series) with Hurler-Scheie syndrome was 25 months (range 5 to 174 months). From 4 case series reporting on 3 or more patients (N=86) with Scheie syndrome the overall median time to diagnosis was 7.5 years, however, the range was very large (from not existing, to 50 years).

Linked evidence of impact of change in management

Worldwide, 1.23 cases per 100,000 were detected via NBS programs (44 newborns were detected as having MPS I among a total of 3,569,166 newborns screened), suggesting that approximately four cases of MPS I would be diagnosed each year in Australia due to NBS, if introduced to NBS programs. Two to three of these cases would have MPS IH and one case every year or two would have MPS IHS.

Effectiveness of early vs late HSCT in MPS I

In the absence of sufficient evidence of outcomes in patients who underwent HSCT after being detected by NBS versus in the absence of NBS, evidence was sought on whether those patients who receive HSCT “early” versus “late” have different health outcomes.

Nine studies reported on survival following HSCT in patients with Hurler syndrome, using cut-offs between 8 months and 24 months. The largest case series (reporting data from the MPS I registry) reported superior survival in those treated prior to 8 months, but hypothesized that this was due to more severe cases being detected earlier. When studies that reported hazard ratios (HRs) were meta-analysed (Figure 1), there was a non-significant trend suggesting that early HSCT (prior to 12 months or prior to 18 months) was associated with improved survival (5 to 13 years), compared to late HSCT (after 12 or 18 months).

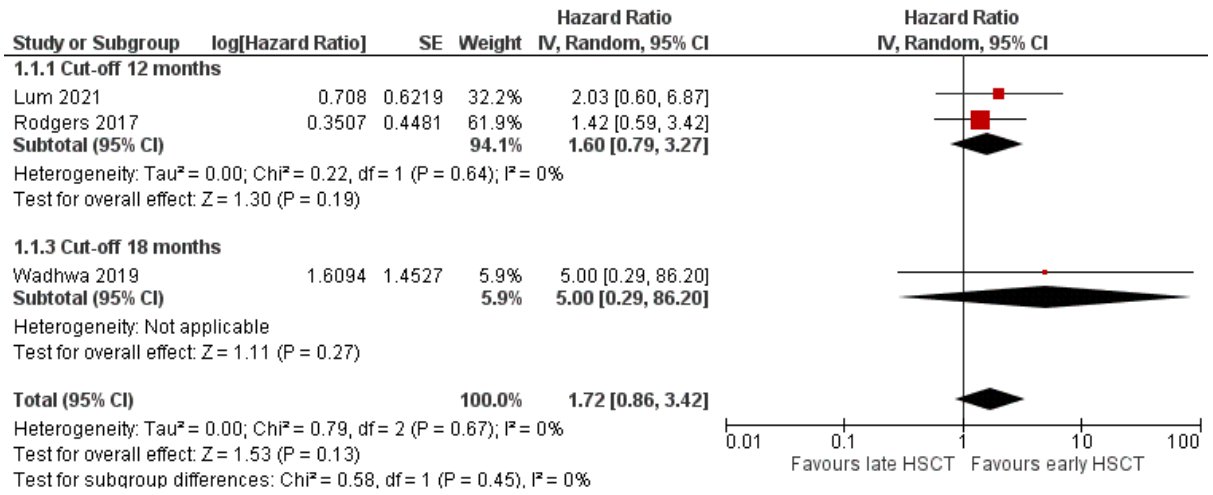

Figure 1 Survival benefit for early vs late HSCT

CI = confidence interval; HSCT = haematopoietic stem cell transplantation; SE = standard error

Six out of seven articles that assessed the influence of age at HSCT on cognitive outcomes, reported that those who had HSCT at an earlier age were significantly more likely to have better cognitive development than those who had HSCT at a later age. Poe et al. (2014) reported that those who underwent HSCT at 4 months could be expected to have normal cognitive development. However, those who had HSCT at 12 months old could be expected to have the average cognitive development age of 10.3 years by age 12, and if transplanted at age 25 months, they could be expected to have developmental age of 7 years old by age 12, [28]. Similar results were reported by Shapiro et al., who reported that every year of delay in receiving HSCT was associated with an 8-point reduction in intelligence quotient (IQ). Peters et al. (1996, 1998) and Guffon et al. (2021) also reported benefits in earlier HSCT, but a larger proportion of the patients treated in these studies had HSCT after the age of 2 years. It is unclear why the results of Bjoraker et al. (2006) differed from the other studies (possibly through chance, or due to different outcome measurement tools).

One article reported on the influence of age at time of HSCT on quality of life. Kunin-Batson et al. (2016) reported that on the Child Health Questionnaire PF-50, psychosocial wellbeing was similar to population norms (for all MPS I patients) but physical functioning differed based on the age at time of HSCT, with every year older being associated with almost one standard deviation poorer physical functioning (-8.10, 95% CI 13.16 to 3.05, p= 0.002).[29]

The safety of early versus late HSCT was considered, but conflicting results were found regarding whether early or late HSCT is associated with higher rates of graft vs host disease (GvHD).

Conclusion:

The DCAR considered 2-3 people per year are expected to be diagnosed with MPS IH due to the NBS are likely to receive HSCT approximately a year earlier than in the absence of NBS, and this

[28] Poe, MD *et al.* (2014). Early treatment is associated with improved cognition in Hurler syndrome. *Ann Neurol*, vol. 76, no. 5, 2014-11, pp. 747-753. doi:10.1002/ana.24246.

[29] Kunin-Batson, AS *et al.* (2016). Long-Term Cognitive and Functional Outcomes in Children with Mucopolysaccharidosis (MPS)-IH (Hurler Syndrome) Treated with Hematopoietic Cell Transplantation. *JIMD Rep*, vol. 29, 2016, pp. 95-102 doi:10.1007/8904_2015_521.

has the potential benefit of assisting them to live longer, have normal or near-normal cognitive functioning, and better physical functioning outcomes than they would have otherwise.

Effectiveness of early vs late ERT in MPS IHS

Six articles were identified that reported on a total of 27 cases of MPS IHS from 13 sibships (sibling pairs or trios, where one (or two) siblings each was diagnosed post-symptomatically, and the younger sibling was diagnosed pre-symptomatically).

The very limited data available did not identify any clear benefit of early initiation of ERT on the outcomes of survival, quality of life, cognitive development, hearing, vision, cardiac disease, respiratory disease, or organomegaly. However, the evidence was suggestive that early ERT has benefits in outcomes relating to bone growth. Early initiation of ERT results in cases of MPS IHS having a more-normal stature compared to their later-diagnosed siblings, with a slower progression of dysostosis multiplex, preventing it from becoming as severe. Early ERT also slows the progression of joint stiffness.

No difference in the rate of adverse events related to ERT were reported from early versus late initiation of ERT. MSAC considered, the highly uncertain data (due to the rarity of the disease and limited evidence-base) meant that no firm conclusions could be drawn on the outcomes of early initiation of ERT.

Conclusion:

The DCAR estimated that one MPS IHS case every one or two years may benefit from being identified early due to NBS and receiving early treatment with laronidase.

Clinical claim

The DCAR considered addition of MPS I to NBS programs would result in superior effectiveness and non-inferior safety to diagnosis after symptom onset, due the superior effectiveness of early treatment, and the benefit in reducing the time to diagnosis.

PICO Set 2 - Family members

There was very little data on the uptake of testing in family members of someone diagnosed with MPS I. What was clear from the case series identified, was that in cases where parents knew they had a child with MPS I, they would make use of reproductive planning options to assist with subsequent children. These options include oocyte testing (testing for carrier status, prior to fertilisation and implantation), pre-implantation genetic testing, and prenatal testing.

If four cases of MPS I are diagnosed per year in Australia, it can be assumed that in two of these cases, their parents may wish to have further children, and make use of reproductive planning options. It can also be assumed that in the first few of years of NBS implementation, in half of the families with a newborn identified with MPS I, there may be other siblings who also receive some benefit from earlier diagnosis.

Clinical claim

The DCAR considered , based on logic and a limited evidence base, testing of family members after index case identification through NBS is superior to testing of family members after proband identification after symptom-onset, as the information is gained at an earlier timepoint, increasing the likelihood of this information being useful for reproductive planning.

13. Economic evaluation

A cost-effectiveness analysis (estimating cost per diagnosis of MPS I) and a cost consequence analysis were presented to evaluate the addition of MPS I to NBS programs. A cost utility analysis explored the possible additional benefits of adding MPS I to NBS programs, including survival gains in severe MPS I and avoiding the diagnostic delay in attenuated MPS I.

A cost analysis was conducted to estimate the costs associated with testing of family members per affected newborn. The potential for family members to use carrier status to alter reproductive decisions or allow prenatal testing is a potential benefit of NBS, but the extent to which this would occur for MPS I could not be quantified.

The general rationale of NBS for rare conditions is that (i) earlier diagnosis – potentially prior to symptom onset - may result in faster access to treatment and may improve treatment outcomes and (ii) the diagnostic delay can be avoided.

NBS for MPS I would result in a diagnosis within the first month or two of life for all MPS I cases, which is earlier than the usual time of diagnosis for all MPS I phenotypes, but the relative difference in the length of time between when cases would ordinarily be diagnosed without NBS, and the implications of early diagnosis, vary considerably across the three phenotypes.

Although NBS can identify MPS I, there may be uncertainty regarding phenotype classification. While babies with the most severe form (MPS IH) will have clinical features that may be detected at the first investigations (when clinicians know what to look for), distinguishing between the two attenuated forms of MPS I (MPS IHS and MPS IS) may be more difficult. Therefore, in the assessment model these diagnostic classifications are combined and referred to as an NBS diagnosis of "attenuated".

The economic evaluation takes the form of a decision tree analysis incorporating estimates of the prevalence of MPS I (categorised by subtypes) and performance of screening tests. The modelled time horizon for the decision tree analysis was 10 years at which time all affected cases of MPS I were assumed to be diagnosed (with or without NBS).

An extension to the simple decision analytic model assumes that there are survival and quality of life benefits associated with early diagnosis of MPS IH and attempts to quantify these over the modelled time horizon of 30 years and translate the effect of earlier diagnosis through NBS into life years/quality adjusted life years (QALYs) gained. It was noted that the underlying premise behind some of the modelled relationships is uncertain, and translations cannot be performed with any degree of certainty.

A summary of the economic evaluation is provided in Table 8.

Table 8 Summary of the economic evaluation

Component	Description
Perspective	Australian health care system perspective
Population	PICO Set 1: All newborns participating in NBS programs PICO Set 2: Family members of the affected cases
Comparator	Current practice PICO Set 1: Diagnostic testing for MPS I at the point of onset of phenotypic signs and symptoms; no universal newborn screening. PICO Set 2: Testing in family members after the clinical identification of affected cases
Type(s) of analysis	PICO Set 1: Newborns: Cost-effectiveness analysis (CEA), cost consequences analysis (CCA), cost-utility analysis (CUA) PICO Set 2: Testing of family members: cost-analysis only

Component	Description
Outcomes	PICO Set 1: Newborns: • Direct effect (primary analysis for CEA): clinically relevant early diagnoses • Associated intermediate health consequences: reduced diagnostic delay, faster access to treatment, improved likelihood of treatment effectiveness, reduced recurrence in families • Exploratory CUA: life years gained, QALYs gained PICO Set 2: Testing of family members: • Cost of additional cascade testing (cost analysis)
Time horizon	Base case evaluation and testing of family members: Time to reach a diagnosis: 10 years Chin et al. (2022) reported that the median age of diagnosis of MPS I in Australia between 2009 and 2020 was 1.3 years (range, 0.01 to 54.7 years) Exploratory CUA: 30 years (up to 50 years assessed in sensitivity analysis)
Computational method	PICO Set 1: Decision tree model for base case analysis and cost-consequences Decision analytic Markov cohort model for the exploratory analysis PICO Set 2: Cost comparison
Generation of the base case	PICO Set 1: Modelled stepped analysis, incorporating different aspects of the linked evidence and other key model assumptions separately to distinguish the effect of each of these on the results. PICO Set 2: cost comparison
Health states	None relevant for the base case CEA, CCA and testing of family members Exploratory CUA: • severe MPS I: No HSCT, post-HSCT and dead • attenuated MPS I: Alive, dead • MPS I unidentified: Alive, dead • No MPS I: Alive, dead
Cycle length	6 months for exploratory CUA for PICO Set 1
Transition probabilities	PICO Set 1: All analyses: • Prevalence of MPS I and subtypes: Prevalence of MPS I (and subtypes) in the absence of NBS was based on the evidence review of published MPS I registry data and other published studies. Prevalence of MPS I (and subtypes) post NBS was based on mean prevalence of MPS I in newborns from published NBS studies. • Test performance: Performance of first-tier screening was as per linked evidence for test accuracy presented in DCAR. Second tier screening was assumed to have 100% sensitivity and specificity. Exploratory analysis the extended model includes survival and health related quality of life gains associated with early access to HSCT in the MPS IH based on evidence review presented in for health outcomes in the DCAR. Transition probabilities were informed by: • Age specific all-cause mortality in Australian population [30] • Disease specific mortality [31]

[30] ABS (2023). Life expectancy, Table 1.9 Life Tables, Australia, 2020-2022, in ABS (ed.), *Births, Australia*, Australian Bureau of Statistics, Canberra, ACT, viewed 21 May 2024, <https://www.abs.gov.au/statistics/people/population/life-expectancy/latest-release#cite-window1>.

[31] Wadhwa, A *et al.* (2019). Late Mortality after Allogeneic Blood or Marrow Transplantation for Inborn Errors of Metabolism: A Report from the Blood or Marrow Transplant Survivor Study-2 (BMTSS-2). *Biol Blood Marrow Transplant*, vol. 25, no. 2, 2019-2, pp. 328-334.

Component	Description
	• Treatment related mortality associated with HSCT [32] • The relative hazard of death for early versus late HSCT [33]
Discount rate	5% for both costs and outcomes in exploratory scenario analysis (discounting rate of 0% and 3.5% per annum assessed in the sensitivity analysis)
Software	Excel, TreeAge Pro

HSCT = haemopoietic stem cell transplantation; MPS I = mucopolysaccharidosis Type I; MPS IH = mucopolysaccharidosis Type I Hurler syndrome; NBS = newborn bloodspot screening; QALY = quality-adjusted life years

Table 9 provides a high-level summary of the inputs used in the economic evaluation.

Table 9 Summary of the inputs used in the economic evaluation

Parameter	Value	Source
Transition probabilities		
Estimated prevalence of MPS I in Australia (no NBS)	1.15 per 100,000	LSDP report (Department of Health and Aged Care 2023)
Estimated prevalence of MPS I post NBS (Australia)	1.23 per 100,000	There were 44 newborns with MPS I detected among a total of 3,569,166 newborns screened worldwide. This equates to 1.23 per 100,000 newborns being diagnosed with MPS I via newborn screening programs.
Proportion of affected cases that are severe (MPS IH)	Pre NBS: 61% Post NBS: 57%	The absolute number of MPS IH (severe cases) diagnosed is assumed to remain the same irrespective of the availability of NBS. Proportion of severe cases of MPS I post NBS was estimated using current prevalence of MPS I and proportion of severe cases.
Test performance	First-tier test (LC-MS/MS IDUA enzyme assay) Sensitivity: 100% FPR: 0.022% Second-tier test (NRE-GAG assay) Sensitivity: 100% FPR: 0%	The proportion of MPS I cases identified was assumed to be 100% and did not vary by the method used to detect MPS I, given the different first-tier test methods employed and consistency in sensitivity reported in the studies included in linked evidence for test accuracy presented in DCAR. Based on 21 studies reviewed in linked evidence for test accuracy presented in DCAR, the median false positive rate for all NBS programs was 0.022% (range 0–0.399%). The NRE-GAG assay for second tier screening has a reported sensitivity and specificity of 100%
Costs		
Cost of first-tier NBS	$**Redacted**	Based on the cost of testing by LC-MS/MS IDUA enzyme assay using the GelbChem SKU: CS18 kit (estimated using consultation feedback provided by the NBS laboratories during the evaluation process).
Cost of second-tier NBS	$167	Price listed on SA Pathology 'Pathology Collection Guide' for NRE-GAG fragmentation analysis. Currently this test is only available at Adelaide Women's and Children's Hospital National Referral Centre for Lysosomal storage diseases. If the second-tier referral load is high, additional laboratories may need to develop processes for second-tier testing for MPS I and MPS II endogenous GAG analysis in house, otherwise all second tier testing will be referred to South Australia.

[32] Mitchell, R *et al.* (2013). Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: A report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. *Pediatric Transplantation*, vol. 17, no. 6, pp. 582-588.

[33] Bhatia, S *et al.* (2021). Trends in Late Mortality and Life Expectancy After Allogeneic Blood or Marrow Transplantation Over 4 Decades: A Blood or Marrow Transplant Survivor Study Report. *JAMA Oncology*, vol. 7, no. 11, pp. 1626-1634.

Parameter	Value	Source
Cost of diagnostic confirmation after second-tier test	$1,482.85	Price listed on SA Pathology 'Pathology Collection Guide' is $388 for Mucopolysaccharidosis Enzymes test and $554 for full gene variant analysis (total: $942) and a consultation with general physician and a specialist.
Cost of known familial variant analysis	$378	Price listed on SA Pathology 'Pathology Collection Guide'
Cost for various medical consults with general physician or specialist.	$82.90 – $305.15	MBS Scheduled Fees (August 2024) Item 36, Item 132, Item 133, Item 721.
Additional inputs used only in exploratory analysis		
Age specific mortality rate	Life table	Age specific mortality rates sourced from Australian life table
Relative risk of mortality in MPS IH who have late HSCT (after 18 months) compared with general population	37	Estimated from study by Wadhwa *et al.* (2019)
Hazard Ratio for mortality associated with late vs early HSCT	1.72	Meta-analysis of survival data reported for early vs late HSCT
Treatment related mortality (TRM) for HSCT	Late HSCT: 19.0% Early HSCT: 13.2%	Australia and New Zealand HSCT registry data (Mitchell et al. 2013) Better disease status before HSCT had lower TRM (HR: 0.694 for all cause mortality) (Bhatia et al. 2021)
Cost of HSCT	$**Redacted**	Cost associated with donor workup and collection, cost of tissue typing and hospital transplant cost
Average annual cost of treatment with laronidase (Aldurazyme) in children of age <2 years	$**Redacted**	Included cost of administration $336.83 (AR-DRG item 20.34-endocrynology) and average cost of laronidase (Aldurazyme) per week (over 52 weeks) from LSDP registry data
Utility in well health state	0.829 (0.185)	Mean (SD) utility observed in Australian children aged 11–17 years (Chin *et al.* 2022)
Disutility associated with progressive cognitive impairment in MPS IH	–0.430	Difference of utility in severe disease (Pompe) health state in infants 6 months old (0.399) [34]and utility in well health state (0.829).
Disutility associated with HSCT	–0.26	Difference between mean health state utilities for transplant year (0.47) and pre-transplant year (0.73) in patients with ß-thalassemia [35]

FP = false positive; FPR = false positive rate; GAG = glycosaminoglycan; GP = General Physician; HSCT = haemopoietic stem cell transplantation; IDUA = α-L-iduronidase; LC-MS/MS = liquid chromatography- tandem mass spectrometry; LSD = lysosomal storage disorder; LSDP = Life Saving Drugs Program; MBS = Medicare Benefits Schedule; MPS I = mucopolysaccharidosis Type I; MPS IH = mucopolysaccharidosis Type I Hurler syndrome; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NR = not reported; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan; SD = standard deviation

The costs included in the base case model are the cost of screening newborns and costs associated with diagnosis either after screening or after symptom onset (including the cost associated with a diagnostic delay in the absence of NBS) and monitoring in presymptomatic MPS I cases identified through NBS. MSAC considered that the costs associated with donor workup and collection for matched unrelated donor for HSCT would possibly be higher. The cost-utility analysis extended the model in a stepped manner to include health outcomes associated with early diagnosis of MPS I, costs associated with treatment for severe cases (HSCT for MPS IH), and additional costs associated with ERT for MPS IHS.

[34] Simon, NJ *et al*. (2019). Health utilities and parental quality of life effects for three rare conditions tested in newborns. *J Patient Rep Outcomes*, vol. 3, no. 1, Jan 22, p. 4.

[35] Matza, LS *et al*. (2020). Health state utilities associated with treatment for transfusion-dependent β-thalassemia. *Eur J Health Econ*, vol. 21, no. 3, Apr, pp. 397-407.

Cost of confirmatory testing

The cost of confirmatory diagnostic tests, according to the SA Pathology 'Pathology Collection Guide' was $167 for a mucopolysaccharides Urine Screen, $388 for a mucopolysaccharidosis enzymes test and $554 for full gene variant analysis. It was assumed that after diagnosis through NBS, the MPS I cases will require a general practitioner (GP) visit for referral, specialist consult and review for confirmatory diagnostic testing and disease management. MSAC noted that the GP visit cost for referral was included in error, as after diagnosis through NBS, the MPS I cases would typically not require a GP referral for confirmatory testing. MSAC considered this would not have a material impact on the costs. MSAC further noted costs of segregation testing of parents should have been included as part of the confirmatory testing costs, instead of being included in testing of family members.

It was assumed that as an NRE-GAG test would be performed as a part of the NBS process, confirmatory tests for MPS I cases identified through NBS would only include a mucopolysaccharidosis enzymes test ($388) and full gene variant analysis ($554). Therefore, the cost of confirmatory testing for the universal NBS arm was $1,482.85 and for no universal NBS it was $1,217.17 (cost of GP visits and specialist consultations are accounted as part of the cost of a diagnostic delay in the absence of NBS).

Cost of monitoring

It was assumed that once diagnosed (irrespective of being symptomatic or presymptomatic), the MPS I cases would undergo periodic surveillance and disease monitoring. MSAC noted although monitoring would generally be undertaken by a metabolic physician in a public hospital clinic, attendance by a GP for preparation of a GP management plan for a patient with chronic disease (MBS item 721, $164.35) was used as the annual cost of disease monitoring up until the time to symptom onset. Time to symptom onset considered in the model was 12.5 months, 1.5 years and 5.3 years in MPS IH, MPS IHS and MPS IS respectively. It was assumed that the cost of disease monitoring would be identical across NBS or clinical identification arms after the disease diagnosis, and therefore was not included beyond time to symptom onset.

Cost of diagnostic delay

Due to the rarity of the disease as well as the variability of clinical manifestations, MPS I poses a challenge for diagnosis. One study based on patient and physician real-world surveys reported that patients saw a mean of 4.7 (severe subtype) or 4.5 (attenuated subtypes) specialists prior to receiving a diagnosis of MPS I, with most cases seeing paediatricians, geneticists/metabolic disease specialists and general practitioners[36]. The costs associated with inappropriate treatment (due to misdiagnoses) and other diagnostic tests could not be ascertained due to the lack of information and are not included in the model. It is assumed that each specialist visit (MBS item 132: $305.15) will incur an additional GP visit for a referral (MBS item 36: $82.90) and a review consult with the specialist (MBS item 133: $152.80). The sum of these three costs is $540.85. The cost of diagnostic delay is estimated by multiplying $540.85 with the mean number of specialist visits (MPS IH: $540.85 × 4.7 = $2,542; and MPS I attenuated: $540.85 × 4.5 = $2,433.83).

[36] Bruni, S *et al*. (2016). The diagnostic journey of patients with mucopolysaccharidosis I: A real-world survey of patient and physician experiences. *Mol Genet Metab Rep*, vol. 8, 2016-9, pp. 67-73.

The total cost of diagnostic delay and confirmatory testing for MPS IH and MPS I attenuated is estimated as $3,651 and $3,543, respectively. These costs are applied to the modelled year equal to time to symptom onset for each subtype in the no universal NBS strategy.

NBS for MPS I is not expected to reduce the costs of the diagnostic delay for other conditions with overlapping symptoms to MPS I (such as other forms of MPS). In the proposed scenario where MPS I may have been excluded (following NBS), the current diagnostic tests (mucopolysaccharides urine screen and enzymes test) are still likely to be performed because these are diagnostically informative across the broader disease spectrum, not used exclusively to identify MPS I.

Results

The economic evaluation was presented in stepped manner in Table 10. The most important health outcome for NBS of MPS I was earlier detection of severe MPS I cases enabling earlier HSCT. At step 1, the health outcome and time horizon is early diagnosis of severe MPS I at 6 months. This step includes the costs associated with screening (NBS) and early diagnosis (≤6 months) of severe MPS I (confirmatory testing in both NBS and no NBS, and diagnostic delay in no NBS). The average cost per early diagnosis of severe MPS I case was $REDACTED ($REDACTED/0.0000072 diagnoses) with NBS and $3,651 ($REDACTED/REDACTED diagnoses) in the absence of NBS. The ICER was $REDACTED per additional early diagnosis of severe MPS I cases.

Step 2 extends the time horizon to 10 years and captures all MPS I diagnosis (early/late severe or attenuated MPS I) with or without NBS. This ICER is higher, at $REDACTED per additional confirmed diagnosis of MPS I (any form). This is primarily due to the assumption that all severe cases of MPS I would be diagnosed irrespective of NBS by 10 years, and so the difference in the number of confirmed diagnoses is driven solely by the number of unidentified attenuated MPS I cases (see Table 11). The cost of NBS screening for MPS I includes the costs associated with NBS, confirmatory diagnostic testing and routine surveillance (until symptom presentation– 12.5 months for MPS IH, 1.5 years for MPS IHS and 5.3 years for MPS IS); the additional costs are negligible and (with rounding) the cost still appears as $REDACTED per individual screened. The average cost per confirmed diagnosis of MPS I was $REDACTED ($REDACTED/0.0000123 diagnoses) with NBS.

The cost of no universal NBS (diagnosis through clinical identification, including the costs of a diagnostic delay and confirmatory diagnostic testing) was $REDACTED per individual (i.e. averaged over an identical cohort as in the NBS screening arm, including approximately 300,000 individuals with no symptoms of MPS I and having no further investigations). The average cost per confirmed diagnosis of MPS I was $3,351 ($REDACTED/REDACTED diagnoses) in the absence of NBS.

The ICERs were very high ($REDACTED per additional early diagnosis of severe MPS I or $REDACTED per additional confirmed diagnosis of MPS I), reflecting the low rate of diagnosis per individual screened. Although the costs and time durations associated with surveillance and diagnostic delay were uncertain, these were likely to have very low impact on the ICERs. The ICER reduced to $REDACTED per confirmed diagnosis of MPS I when the first-tier screening assays were multiplexed in a two-tier screening strategy (essentially 'sharing' the cost of screening between the 2 disorders of MPS I and MPS II).

Table 10 presents the results of the base case economic evaluation (costs are discounted).

Table 10 Results of base case economic evaluation using GelbChem kits (costs are discounted)

	Universal NBS	No universal NBS	Increment
Step 1: Time horizon: 6 months Health outcome: Early diagnosis of severe MPS I cases (≤6 months) Costs: Universal NBS: Costs associated with newborn screening, confirmatory diagnostic tests in cases identified No universal NBS: diagnostic delay [b] and confirmatory diagnostic tests [c] in cases identified			
Using two-tier screening protocol			
Costs (average, per person)	$**Redacted**	$**Redacted**	$**Redacted**
Early MPS I diagnosis (≤6 months)	0.0000007 7.0 per million	**Redacted**	**Redacted**
ICER ($/additional early diagnosis of severe MPS I)			$**Redacted**
Step 2: Time horizon: 10 years Health outcome: All MPS I diagnosis (including severe and attenuated MPS I cases diagnosed up to 10 years) Costs: Universal NBS: Costs associated with newborn screening, confirmatory diagnostic tests in cases identified, periodic surveillance [a] (in presymptomatic attenuated or unknown MPS I) No universal NBS: diagnostic delay [b] and confirmatory diagnostic tests [c] in cases identified			
Using two-tier screening protocol			
Costs (average, per person)	$**Redacted**	$**Redacted**	$**Redacted**
Confirmed MPS I diagnosis	0.0000123 12.3 per million	**Redacted**	**Redacted**
ICER ($/confirmed diagnosis)			$**Redacted**
Single-tier screening protocol using NRE-GAG assay			
Costs (average, per person)	$**Redacted**	$**Redacted**	$**Redacted**
Confirmed MPS I diagnosis	0.0000123 12.3 per million	**Redacted**	**Redacted**
ICER ($/confirmed diagnosis)			$**Redacted**
Multiplexed single-tier screening for MPS I and MPS II			
Costs (average, per person)	$**Redacted**	$**Redacted**	$**Redacted**
Confirmed MPS I diagnosis	0.0000123 12.3 per million	**Redacted**	**Redacted**
ICER ($/confirmed diagnosis)			$**Redacted**

ICER = incremental cost-effectiveness ratio; MPS I = mucopolysaccharidosis Type I; MPS II = mucopolysaccharidosis Type II; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NRE-GAG = nonreducing end-glycosaminoglycan

[a] The cost of one GP consult (MBS item 721: $164.35) for preparation of a chronic disease management plan.

[b] The costs associated with diagnostic delay included; consultation with GP (MBS item 36) and specialist consult and review (MBS items 132 and 133). These were multiplied by the mean number of physician consultations in the absence of NBS (4.7 for severe sub type and 4.5 for attenuated form). The cost of diagnostic delay was estimated as MPS IH: $540.85 × 4.7 = $2,542; and MPS I attenuated: $540.85 × 4.5 = $2,433.83.

[c] Confirmatory tests for MPS I include: $167 for a mucopolysaccharides Urine Screen, $388 for mucopolysaccharidosis enzymes test, $554 for full gene variant analysis, visit to a GP, specialist consults and a review consult. It is assumed that NRE-GAG won't be repeated after NBS. Therefore, cost of confirmatory testing for universal NBS arm was $1,482.85 and for no universal NBS was $1,217.17 (in the absence of NBS cost of GP visit and specialist consults are accounted as part of the cost of diagnostic delay).

Disaggregated and aggregated base-case results

Disaggregated costs and outcomes are presented in Table 11. The incremental cost was driven by costs associated with the newborn screening tests.

Table 11 Disaggregated modelled costs and outcomes over 10 years with two-tier screening (Step 2) (discounted costs, undiscounted and discounted 'diagnoses' outcomes)

	Universal NBS	No universal NBS	Increment
Costs (discounted)	**$Redacted**	**$Redacted**	**$Redacted**
• Cost of NBS	**$Redacted**	**$Redacted**	**$Redacted**
• Cost associated with confirmatory diagnostic test (including diagnostic delay in the absence of NBS)	$0.02	**$Redacted**	**$Redacted**
• Cost associated with surveillance	$0.0029	$0.00	$0.0029
Diagnoses (undiscounted)			
Confirmed MPS I diagnoses	**0.0000123 (12.3 per million)**	**Redacted**	**Redacted**
Severe MPS I	0.0000070 (7 per million)	**Redacted**	**Redacted**
• Severe MPS I cases with early HSCT: diagnosed in first ≤6 months	0.0000070 (7 per million)	**Redacted**	**Redacted**
Attenuated MPS I	0.0000053 (5.3 per million)	**Redacted**	**Redacted**
Diagnoses (discounted)*			
Confirmed MPS I diagnoses	**0.0000123 (12.3 per million)**	**Redacted**	**Redacted**
Severe MPS I*	0.0000070 (7 per million)	**Redacted**	**Redacted**
• Severe MPS I cases with early HSCT: diagnosed in first ≤6 months	0.0000070 (7 per million)	**Redacted**	**Redacted**
Attenuated MPS I	0.0000053 (5.3 per million)	**Redacted**	**Redacted**

HSCT = haemopoietic stem cell transplantation; MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening
*Note: 'discounted' diagnoses are presented for methodological completeness but can only be interpreted as an abstract unit. A count of diagnoses represents a scalar value which, on applying discounting becomes distorted and no longer represents a count. The reduced number of diagnoses of MPS I cases attributable to discounting represents a reduction in the 'value of the diagnoses' due to it being deferred, rather than a difference in actual cases diagnosed.

Exploratory scenario analysis

Table 12 presents the modelled results for exploratory scenario analysis in a stepped manner.

When interpreting the results of this analysis, MSAC noted the uncertainty associated with limited or uncertain comparative data for the survival and quality of life benefits.

Table 12 Results of exploratory economic evaluation using two-tier screening protocol

Stepped analysis	Universal NBS	No universal NBS	Increment
Step 1: Cost of early diagnosis of severe MPS I			
Costs (on average, per person)	$**Redacted**	$**Redacted**	$**Redacted**
Early MPS I diagnosis (≤6 months)	0.0000007 7.0 per million	**Redacted**	**Redacted**
ICER ($/additional early diagnosis of severe MPS I)			$**Redacted**
Step 2: Cost of Diagnosis (base case)			
Total costs (discounted)	$**Redacted**	$**Redacted**	$**Redacted**
Confirmed MPS I diagnosis (undiscounted)	0.0000123 (12.3 per million)	**Redacted**	**Redacted**
ICER ($/confirmed diagnosis)			$**Redacted**
Step 3: Extended base case analysis to integrate cost of HSCT, survival data for MPS I (severe), attenuated MPS I and no MPS I over 30 years modelled time horizon and half-yearly cycle length. * assuming that there is no difference in short-term or long-term survival following early vs late HSCT.			
Costs (on average, per person) (discounted)	$**Redacted**	$**Redacted**	$**Redacted**
Number of MPS I H cases identified early and accessing early HSCT (undiscounted)	0.0000070 (7 per million)	**Redacted**	**Redacted**
ICER ($/additional case accessing early HSCT)			-
LYs (discounted)	29.857348	29.857345	-[a]
Step 4: Applying a differential to the short-term risk of mortality associated with HSCT, and a differential to the ongoing long-term survival rate for early vs late HSCT in severe MPS I			
Costs (on average, per person) (discounted)	$**Redacted**	$**Redacted**	$**Redacted**
LYs (discounted)	29.857364	29.857345	0.000018659 (represents an increased 2.948 LY in each additional case obtaining early HSCT)
ICER ($/LY gained)			$**Redacted**
Step 5: Utility values applied to different health states in life years			
Costs (on average, per person) (discounted)	$**Redacted**	$**Redacted**	$**Redacted**
QALYs (discounted)	13.008578	13.008555	0.00002303 (represents an increased 3.638 QALYs in each additional case obtaining early HSCT)
ICER ($/QALY gained)			$**Redacted**
Step 6: Additional ERT costs (associated with earlier access) for MPS IHS added (no additional benefit)			
Costs (on average, per person) (discounted)	$**Redacted**	$**Redacted**	$**Redacted**
QALYs (discounted)	13.008578	13.008555	0.00002303
ICER ($/QALY gained)			$**Redacted**

[a] *In the economic model, when early vs late HSCT relative mortality risks are set to 1, there is a residual difference in life years (0.0000027) generated due to the omission of background mortality occurring for cases whilst in the cycle of HSCT. For the purposes of interpreting the economic analysis at step 2, it should be assumed that there are no incremental life years associated with NBS.*

HSCT = haemopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; LY = life years; MPS I = mucopolysaccharidosis Type I; MPS IHS = mucopolysaccharidosis Type I Hurler Scheie syndrome; NBS = newborn bloodspot screening; QALY = quality adjusted life years; QoL = quality of life

A cost analysis for testing of family members was performed. This identified that for 304,655 newborns screened (representing approximately one year) testing of family members costs will be $5,492 in the absence of NBS for MPS I and $6,329 when NBS for MPS I is available. The

cost of additional testing of family members has the potential to be off-set by the health benefit and cost-savings associated with preventing a recurrence of disease, however the DCAR considered the extent to which that would occur in the Australian population is entirely unknown.

Sensitivity analysis: base case model

Table 13 presents sensitivity analyses around key parameters in the base case model. The results were sensitive to the costs of first-tier screening and the prevalence of MPS I.

Table 13 Sensitivity analysis for base case model (using two-tier screening protocol)

	Increment in cost	Increment in number of diagnoses	ICER/additional diagnosis	Percent change
Base case analysis	$**Redacted**	**0.0000008**	$**Redacted**	**-**
*Cost of 1st tier screening (base case: $**Redacted** for GelbChem kit)*				
Revvity NeoLSD MS/MS kit: $**Redacted**	$**Redacted**	0.0000008	$**Redacted**	59%
Revvity kit multiplexed for MPS I and Pompe disease: $**Redacted**	$**Redacted**	0.0000008	$**Redacted**	–21%
Redacted kit multiplexed: $**Redacted** [a]	$**Redacted**	0.0000008	$**Redacted**	–67%
Prevalence of MPS I per 100,000 (base case: no NBS: 1.15 and NBS: 1.23)				
Low (no NBS: 0.73, NBS: 1.10)	$**Redacted**	0.0000037	$**Redacted**	–78%
High (no NBS: 1.85, NBS: 3.34)	$**Redacted**	0.0000149	$**Redacted**	–95%

ICER = incremental cost-effectiveness ratio; LSD = lysosomal storage disorder; MPS I = mucopolysaccharidosis Type I; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening

[a] From **Redacted** kit would be able to multiplex MS/MS enzymatic assays for MPS I, MPS II and Pompe disorders which are currently under MSAC consideration for NBS panel extension. If these tests are multiplexed, the screening cost per sample attributed to MPS I detection will be one-third as the running cost (all the operational costs, equipment costs and kit costs) would remain same but will perform detection of three disorders at the same time.

The DCAR considered the key drivers in the exploratory analysis were the modelled time horizon, cost of first tier screening, prevalence of MPS I, risk reduction in mortality due to early access to HSCT, and disutility associated with later treatment.

Conclusions

NBS was associated with a net incremental cost per affected MPS I case diagnosed compared with clinical identification in the absence of NBS. Some cost was offset due to reduced diagnostic delay, but this was relatively small in comparison to the increased screening costs. The ICERs ($/confirmed MPS I diagnosis and $/additional early diagnosis of severe MPS I) were high due to the rarity of the disease.

The limited evidence indicated possible survival and quality of life benefits associated with early access to HSCT in cases with MPS IH. When the improved survival and quality of life associated with early access to treatment were integrated in the model, the ICER/QALY was also relatively high due to the rarity of the disease and also the relatively limited change in clinical management associated with early diagnosis. Earlier diagnosis through NBS would avoid diagnostic delay and increase timely treatment in many cases with MPS I, however clinical benefits in attenuated cases could not be quantified.

The DCAR considered testing of family members has the potential to inform reproductive planning but the associated health benefits could not be quantified.

14. Financial/budgetary impacts

An epidemiological approach was used to estimate the resource utilisation and financial implications of incorporating MPS I screening into existing NBS programs.

As per the consultation feedback, all NBS laboratories will need some building expansion to accommodate for new equipment, validation and verification of the new screening protocol and hiring of additional workforce to expand the NBS programs to include MPS I. The projections included costs associated with program implementation included laboratory expansion and validation of the new screening protocol, but did not include costs that would be required to develop and deliver education materials for consumers and health care providers. These were considered as once-off set-up costs to NBS programs in Year 1 of the projections. It was noted that direct funding is being provided by the Commonwealth to states and territories to support expansion of NBS programs and consistency in screening across Australia. States and territories can determine how to allocate this funding within their jurisdiction to best support implementation in line with the terms of the Federation Funding Agreement (FFA) schedule.

Table 14 presented the program implementation costs for introducing MPS I to the NBS programs.

Table 14 Program implementation costs for introducing MPS I to the NBS programs

	WA	QLD + half of NT	NSW	SA + Tasmania + half of NT	Victoria
Laboratory capacity and capability (not necessarily assay specific)					
Space expansion [a]	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Costs associated with specific assay verification and validation					
Validation costs (reagents and staff) [b]	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Total implementation cost per site	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Total implementation cost to NBS					$**Redacted**

MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening; NSW = New South Wales; WA = Western Australia
Source: Assumptions based on expert advice provided by NBS laboratories.
[a] Estimates for laboratory expansion were only provided by the WA and QLD NBS laboratory experts. For other NBS programs costs were these were assumed to be similar to WA and QLD based on the volume of tests run.
[b] As per NBS laboratory expert advice validation costs for reagent/kit is generally one-third of the annual cost of reagents for each lab. These were estimated using use and cost of GelbChem kit and projected live births for each state/territory ending June 2026 based on ABS population projections and registered births data. Staff costs associated with validation process were only provided by QLD NBS laboratory. Based on this information it was assumed that at least two months of staff-time would be required for a validation process

Cost to NBS programs

The financial implications to the NBS programs resulting from the proposed inclusion of MPS I on the NBS panel is summarised in Table 15. The total cost to NBS programs for the addition of MPS I was estimated in the DCAR as being $**REDACTED** in the first financial year (including one-off implementation set-up costs) and approximately $**REDACTED** annually. in years 2–6.

Table 15 Financial impact to the Newborn Bloodspot Screening Program of adding MPS I

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Program implementation set-up costs for MPS I	$**Redacted**	–	–	–	–	–
Number of live births [a]	306,803	306,959	307,115	307,271	307,427	307,583
Number of babies who uptake NBS (99.3%)	304,655	304,810	304,965	305,120	305,275	305,430
Total number of first-tier tests (including 2% re-assays)	310,748	310,907	311,065	311,223	311,381	311,539
Cost of first-tier screening ($**Redacted** per sample screened)	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Total number of first-tier screen positives for MPS I	71	71	71	71	71	71
Cost of second-tier screening ($167.00 per test)	$11,807	$11,824	$11,840	$11,840	$11,857	$11,857
Total cost to the NBS programs	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**

MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening
[a] Based on projected number of births in Australia based on number of registered births data in 2008–2022 in Australia.

Cost implications for other health budgets

Medical services included in monitoring and treatment of newborns with MPS I detected through NBS programs may also use other Commonwealth funding sources such as the Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS), LSDP and other state/territory health budgets.

Cost to LSDP

An early diagnosis of MPS IHS cases may bring forward the use of subsidised ERT resulting in the additional costs to the LSDP: the estimated impact of this was uncertain but estimated to be equivalent REDACTED.

Costs to MBS

It was assumed that the patients diagnosed with pre-symptomatic MPS I through NBS will undergo additional disease monitoring that would not have otherwise occurred until they become symptomatic. Other costs of monitoring were offset by the costs associated with the likely diagnostic delay in the absence of NBS. Table 16 presents the estimated cost to the MBS due to NBS of MPS I.

Table 16 Cost to MBS due to NBS of MPS I

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Disease monitoring in affected cases (NBS)						
Number of MPS I affected cases monitored	1.59	3.18	3.88	4.58	5.25	5.27
Cost to MBS, disease monitoring [a]	$222	$444	$542	$639	$733	$736
Diagnostic delay in cases detected through clinical identification (no NBS)						
Number of severe MPS I affected cases diagnosed, no NBS	0.21	2.11	2.12	2.17	2.17	2.17
Number of attenuated MPS I affected cases diagnosed, no NBS	0.00	0.93	0.93	0.96	1.62	1.62
Cost to MBS, diagnostic delay [b]	$0	$3,955	$3,955	$4,062	$5,417	$5,417
Net financial implications to MBS						
Net cost to MBS	$222	–$3,511	–$3,413	–$3,423	–$4,684	–$4,681

MBS = Medicare Benefits Schedule; MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening
[a] The cost of one GP consult (MBS item 721: 85% rebate $139.70) for preparation of a chronic disease management plan.
[b] The costs included were; consultation with GP (MBS item 36) and specialist consult and review (MBS items 132 and 133). These were multiplied by the mean number of physician consultations in the absence of NBS (4.7 for severe sub type and 4.5 for attenuated form). The cost of diagnostic delay to the MBS (providing an 85% rebate was estimated as $2,161.06 and $2,069.10 per severe and attenuated MPS I cases respectively

Cost to state/territory health budgets

Tests performed for diagnostic confirmation of suspected MPS I cases and testing in family members of affected cases were not listed on the MBS and are currently funded by state and territory health budgets. It was estimated that for every affected MPS I case diagnosed, two parents, one uncle/aunt and one sibling may have genetic testing. The extent of increase in use of these services offered to the family members of affected newborns due to NBS for MPS I was uncertain. Net costs to state and territory health budgets were estimated based on the delay in diagnosis (Table 17).

Table 17 Cost to the State and Territories health budget due to NBS

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Confirmatory diagnostic testing in affected cases (NBS)						
Number of MPS I affected cases diagnosed	3.70	3.70	3.80	3.80	3.80	3.80
Cost of confirmatory diagnostic test ($388 + $554=$942)	$3,485	$3,485	$3,580	$3,580	$3,580	$3,580
Confirmatory diagnostic testing in affected cases (no NBS)						
Number of MPS I affected cases diagnosed	0.21	3.05	3.05	3.13	3.78	3.78
Cost of confirmatory diagnostic test ($388 + $554 + $167 = $1,109[a])	$234	$3,377	$3,383	$3,468	$4,195	$4,195
Tests in family members of the affected cases (NBS)						
Total number of tests for known familial variant analysis (2 parents and 1 uncles/aunts per affected case)	11	11	11	11	11	11
Cost of genetic testing ($378 per test)	$4,196	$4,196	$4,309	$4,309	$4,309	$4,309
Number of siblings tested (1 per affected case)	4	4	4	4	4	4
Cost of biochemical testing and NRE-GAG analysis in siblings ($167+$388 = $555 per test)	$2,054	$2,054	$2,109	$2,109	$2,109	$2,109
Tests in family members of the affected cases (no NBS)						
Total number of tests for known familial variant analysis (2 parents and 1 uncles/aunts per affected case)	0.63	9.14	9.15	9.38	11.35	11.35
Cost of genetic testing ($378 per test)	$239	$3,453	$3,460	$3,547	$4,289	$4,289
Number of siblings tested (1 per affected case)	0.21	3.05	3.05	3.13	3.78	3.78
Cost of biochemical testing and NRE-GAG analysis in siblings ($167+$388 = $555 per test)	$117	$1,690	$1,693	$1,736	$2,099	$2,099
Total cost to States and Territories health budget (NBS)	$9,735	$9,735	$9,998	$9,998	$9,998	$9,998
Total cost to States and Territories health budget (no NBS)	$590	$8,520	$8,536	$8,751	$10,583	$10,583
Net cost to States and Territories health budget						
Net cost to States and Territories health budget	$9,144	$1,214	$1,462	$1,247	–$585	–$585

GAG = glycosaminoglycan; MPS I = mucopolysaccharidosis Type I; NBS = newborn bloodspot screening; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan

[a] Figure is not inclusive of cost of segregation testing of parents.

The financial impact was driven by the cost per screening. The number of births, prevalence of MPS I and the false positive rate for the first-tier screening had very low impact on the financial implications to NBS programs. Table 18 presents the key sensitivity analyses.

Table 18 Sensitivity analysis

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Base case	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
*Cost of 1st tier screening (base case: $**Redacted** for GelbChem kit)*						
Redacted kit multiplexed [a]: $**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Revvity NeoLSD MS/MS kit: $**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Revvity kit multiplexed [b]: $**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**
Single-tier screening protocol using NRE-GAG assay (base case: two-tier screening)						
GelbChem kit: cost per screen- $**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**	$**Redacted**

GAG = glycosaminoglycan; MPS I = mucopolysaccharidosis Type I; MPS II = mucopolysaccharidosis Type II; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NR = not reported; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan

[a] **Redacted** kit multiplexed for MPS I, MPS II and Pompe disorders (i.e. cost per screen is one third the cost per screen in base case).

[b] Revvity kit multiplexed for MPS I and Pompe disorders (i.e. cost per screen is halved)

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Mucopolysaccharidosis, type 1 (MPS I) is an ultra-rare disease, which resulted in low volume, low-quality evidence and considerable uncertainty regarding the clinical claim of superior effectiveness and non-inferior safety of MPS I newborn bloodspot screening (NBS) compared to no NBS. The clinical claim is supported based on first principles and in the context of best available evidence. However, for individuals with the Hurler (MPS IH) and Hurler-Scheie (MPS IHS) disease phenotypes, evidence demonstrating a benefit for NBS-mediated diagnosis and earlier treatment (with haematopoietic stem cell transplantation [HSCT] and enzyme replacement therapy [ERT, laronidase] respectively) was limited, and benefits could not be quantified.
- MPS I NBS testing in the absence of genetic analysis does not differentiate between the three phenotypes. For individuals of different MPS I phenotypes, different eligibility and ineligibility requirements exist for access to ERT on the Life Saving Drugs Program (LSDP), making it difficult to identify the value of an early diagnosis for the individual identified by NBS. LSDP-funded therapy is currently only subsidised for individuals with Hurler-Scheie disease who meet the program's eligibility criteria.
- While there are genotypes that have been reported to demonstrate a genotype-phenotype relationship, notably for Hurler syndrome, most *α-L-iduronidase* (*IDUA)* variants are private within a family and cannot be used for prognostication. However, although most variants are private, the majority of patients have at least one of nine specific variants.
- For individuals identified with MPS IH, current clinical practice in Australia is treatment with HSCT. The LSDP does not subsidise use of laronidase prior to HSCT for MPS IH patients.

- There may be secondary benefits from identifying familial risk for MPS I, for informing reproductive decision-making and access to Medicare Benefits Schedule (MBS)-reimbursed pre-implantation genetic diagnosis.

Economic issues:

- ESC considered that the cost of diagnostic delay may have been underestimated, and requested that this be re-evaluated, and the economic analyses revised. Subsequently, the assessment group produced an Addendum, which included the revised analyses exploring higher costs of diagnostic delay.
- The cost-effectiveness analysis is relatively robust (given the evidence). Compared to previous NBS funding decisions, the incremental cost-effectiveness ratio (ICER) is likely to be very high.
- The cost-consequence analysis has limitations as it accounts for some but not all consequences. Defining effectiveness as all diagnoses made over a 10-year horizon may bias the analysis against the merits of NBS.
- The cost-utility analysis is highly uncertain and hence appropriately labelled as exploratory.
- Since the consideration of cost-effectiveness is secondary for ultra-rare conditions, the primary focus should be to understand the health and non-health effects/outcomes of early diagnosis where possible, noting that these are uncertain.

Financial issues:

- The approach to estimate the financial impact is appropriate. There is some uncertainty related to variation in the total number of births per year in Australia; however, sensitivity analyses demonstrated that financial impact was driven by the cost per screening, and that number of births had a very low impact on the financial implications to NBS programs.

Other relevant information:

- Although much of the disparity in health outcomes between metropolitan and non-metro settings can be attributed to social determinants, NBS for treatable conditions will likely have at least some positive impact on inequity (provided it is supported by standardised follow-up and treatment).
- There may be an ethical concern that the “value of knowing” for patients and families with MPS IH and MPS IHS occurs at the expense of those with MPS IS, for whom the knowledge of diagnosis brings with it a risk of considerable uncertainty and anxiety over an extended period of time, potentially life long. While MPS IS has historically been the least frequently detected phenotype, it is as yet unclear how MPS IS numbers might increase as a result of screening.
- There are questions around the impact of NBS consequences aside from health outcomes, such as information to support family planning, the value of knowing, and the avoidance of diagnostic delay, noting that its healthcare costs have already been considered.
- Other considerations include the potential to use multiplex assays, ethical arguments, codependency and emerging pathways to genetic diagnosis. Additionally, there are a number of potential implementation issues including set up costs and considerations around tiered testing, although these are outside the remit of the current health technology assessment (HTA).

ESC discussion

ESC noted this application, from the Department of Health and Aged Care Newborn Bloodspot Screening (NBS), sought the addition of mucopolysaccharidosis, type 1 (MPS I) to the list of conditions screened for as part of Australia’s NBS programs. ESC noted the Australian Government initially announced funding under the 2022-23 Budget, and then announced further

investment under the 2024-2025 Budget to support expansion of NBS programs. ESC noted NBS is underpinned by the NBS National Policy Framework (NBS NPF)[37] and implementation remains jurisdiction-based, with screening provided by five NBS laboratories across Australia.

ESC noted and welcomed public consultation feedback from eight professional organisations, two consumer organisations and one individual, which was supportive. ESC noted that peak bodies for rare diseases, including Rare Voices Australia supported the application, highlighting that early diagnosis enables early intervention, which can slow or halt disease progression and reduce the burden on family and carers. ESC noted feedback from the Childhood Dementia Initiative (CDI) organisation, which had conducted a survey among families of patients impacted by the condition. ESC noted the survey results emphasised that the earlier a diagnosis was received, the more disease impact was reduced, preventing future degeneration. The results of the survey also highlighted that an early diagnosis reduces the 'diagnostic odyssey' and psychological stress. ESC noted that feedback from Australian Genomics queried the type of screening proposed, stating that it was important that the proposed test should be the best option available, and supported two-tier screening. ESC noted that Australian Genomics also raised concerns about continuity of the proposed test, given the test kit is manufactured offshore, there may be possible supply issues. ESC noted stakeholders raised that genetic counselling and psychosocial support for families of an infant with an NBS-mediated diagnosis should be considered, as babies diagnosed with the condition will require extensive ongoing clinical management. ESC noted feedback that an earlier diagnosis was expected to enable earlier access to potential treatments as they become available in the future.

ESC noted MPS I is an autosomal recessive lysosomal storage disorder (LSD) caused by variants in the *IDUA* gene that leads to deficiency or absence of IDUA enzyme activity. MPS I can be divided into three separate phenotypes: Hurler syndrome (MPS IH), Hurler-Scheie syndrome (MPS IHS) and Scheie syndrome (MPS IS), listed from most to least severe. ESC noted that the life expectancy of patients with MPS IH, the most common and severe phenotype, is typically less than 10 years without treatment, and that clinical manifestations include facial and skeletal abnormalities, deafness, corneal issues, cardiac valve dysfunction, and cognitive and neurological impairment. ESC noted for the intermediate phenotype, MPS IHS, without treatment patients often die in their twenties due to cardiac disease or respiratory failure, but treatment with ERT offsets the effects of joint stiffness, respiratory problems and structural cardiac disease. For the mildest and least common form of the disease (MPS IS), ESC noted that patients generally live up to their fifties. The absolute incidence for this attenuated form is unknown because it appeared possible that some of these patients currently remain undiagnosed.

ESC noted that MPS I is an ultra-rare (defined as 1 case per 50,000 births or fewer) condition with an estimated incidence of MPS I in Australia of approximately 0.73 per 100,000 live births (i.e. approximately 2 cases per year diagnosed) although the absolute incidence of MPS I in Australia remains uncertain. ESC noted that in Australia, it is estimated that 61% of cases are MPS IH and 36% are attenuated MPS I (i.e. MPS IHS and MPS IS), while 3% of cases are of unknown phenotype. This equates to an incidence of MPS IH of approximately 0.45-0.57 per 100,000 live births (~3 cases every 2 years) and an incidence of attenuated MPS I of approximately 0.26 per 100,000 live births (~1 case per year).

ESC noted that the proposed population for NBS is all newborns (PICO set 1) participating in NBS programs in Australia. The proposed screening strategy for PICO set 1 is NBS using a two-tier testing approach, with both tests performed on the dried bloodspot (DBS). The first-tier test would examine IDUA enzyme activity on DBS using a Therapeutic Goods Administration (TGA)

[37] Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policyframework?language=en

approved kit, and positive cases would be confirmed through second-tier testing, which would be a non-reducing end glycosaminoglycan (NRE-GAG) analysis on DBS. This would be performed either in-house or sent to the National Referral Laboratory (NRL) in Australia, depending on the number of second-tier tests likely to be required. ESC noted advice from the head of the NRL indicated that single-tier screening using NRE-GAG could potentially be utilised for NBS. However, ESC noted that IDUA enzyme activity testing is required to meet current eligibility criteria to access ERT via the LSDP.

ESC also noted that, although the proposed screening can identify MPS I, it does not distinguish between phenotypes. Babies with the most severe form (MPS IH) will likely have clinical features that may be detected at initial clinical investigations, but distinguishing between MPS IHS and MPS IS may not be possible from an NBS-mediated diagnosis, and requires ongoing clinical assessment.

ESC noted that NBS programs are funded and delivered entirely through public hospitals via the National Health Reform Agreement and additional direct Australian Government funding, and thus does not require an MBS item. Similarly, ESC noted that there is an expectation that cascade testing would be funded via existing arrangements at public hospitals, as is currently done for families of babies diagnosed with MPS I, and would also not require any additional MBS item(s).

ESC noted the comparator for PICO set 1 is no NBS, i.e. current diagnostic practice where MPS I diagnosis is delayed until symptom onset. ESC noted that the current median time to diagnosis without NBS in Australia ranges from 11 months for MPS IH, 4.2 years for MPS IHS, to 13.5 years for MPS IS.

For individuals with MPS IH who underwent HSCT, the median age at diagnosis was REDACTED, and the median age at treatment initiation was REDACTED, which was on average REDACTED. Because MPS I is rare, children often undergo a diagnostic delay before a diagnosis is reached. The most severe phenotype (MPS IH) is the most common, but ESC considered that the incidence of the less severe phenotypes may increase if MPS I screening is included as part of Australia's NBS program because, currently, some people may reach adulthood without a diagnosis if they have late onset attenuated forms of MPS I. ESC noted that evidence presented in the department contracted assessment report (DCAR) suggested that an estimated 1-2 cases of an attenuated form would be detected per year with NBS.

ESC noted the clinical management algorithms for MPS I diagnosis (PICO set 1), where under the current algorithm, after a child presents with symptoms consistent with LSD, diagnostic testing for MPS I occurs. Under the proposed algorithm, all newborns participating in NBS programs in Australia would be screened for MPS I using the two-tier screening method described above. ESC noted that in both algorithms, treatment of MPS I is the same; babies and children diagnosed with MPS I may undergo ERT (laronidase), HSCT or best supportive care with or without NBS, depending on their MPS I phenotype.

ESC noted the proposed population for testing of family members following diagnosis of an index case[38] is biological parents, aunts, uncles and siblings of the index case (PICO set 2). ESC noted the estimate that approximately 3-4 family members would receive testing per positive index case identified, and therefore that 6-8 family members per year in Australia would be expected to receive testing overall, based on the estimated two MPS I diagnoses per year. ESC noted that, for testing of family members, the only difference between the current and the proposed clinical

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

management algorithm is whether the proband[39] or index case is diagnosed following symptom presentation or via NBS, respectively. After index case (with NBS) or proband (without NBS as is current practice) diagnosis, relatives undergo *IDUA* genetic testing (or urinary GAG fragment analysis in siblings). Follow-up (reproductive advice, genetic counselling, or treatment if diagnosed) is undertaken as appropriate.

ESC noted the clinical claim was that universal NBS for MPS I has superior safety and clinical effectiveness compared to current practice (i.e., no NBS). ESC noted that MPS IH is treated with HSCT as early as possible, which can prevent some clinical deterioration, with benefits for overall survival (OS), neurological and cognitive outcomes and facial appearance. However, ESC also noted HSCT does not improve skeletal, cardiac and corneal abnormalities for these patients. ESC noted that expert feedback indicated anecdotal evidence that outcomes have continued to improve with early HSCT for MPS IH patients, but that high quality evidence is limited. ESC noted that patients with MPS IH may apply for ERT while awaiting HSCT (as occurs currently), although ERT is not funded through the LSDP for this diagnosis; only MPS IHS (intermediate severity) cases are currently eligible for subsidised ERT under the LSDP criteria, and similar to HSCT, ERT is started as soon as possible. Currently, the median age at treatment initiation for individuals with MPS IHS is 8.8 years (range of 15 days to 55 years). ESC noted after diagnosis of MPS IHS via NBS, ERT initiation had only been reported for a single newborn, to date. This patient started ERT at 1 month, which was much earlier than the median 8.8 years. ESC noted that, because laronidase does not cross the blood-brain barrier, it does not improve neurological symptoms. ESC noted that the demand for ERT may potentially increase as a result of NBS for MPS I, due to the earlier detection of typically attenuated cases, but that the LSDP eligibility criteria may preclude these cases from accessing subsidised ERT.

ESC also noted that new therapies are on the horizon, such as monoclonal antibodies and gene therapy, although these therapies may not be available for several years.

ESC noted that the evidence base presented in the DCAR consisted of linked evidence, with no direct test-to-outcome data available and very small patient numbers due to the rarity of the condition, resulting in a high risk of bias. ESC noted that screening program data are available from 4 countries since approximately 2016, although in two of these countries, screening is regional and not national. ESC noted that because data are recent and the retrospective comparison data are historical, outcomes were potentially confounded by health system changes and improvements that likely occurred over time.

ESC noted that, from the evidence available, it appeared that the time from diagnosis to treatment with HSCT or ERT has significantly reduced in countries and jurisdictions with an NBS program for MPS I, typically by months or years. ESC noted that earlier access to HSCT (prior to 12 or 18 months of age) is associated with an increase in life expectancy and reduced physical and cognitive impairment. ESC also noted earlier diagnosis by NBS could optimise the therapeutic window for HSCT as the average time from diagnosis to HSCT is currently approximately 6 months for children diagnosed in the absence of NBS (Table 20). Similarly, early access to ERT for MPS IHS cases appears to improve outcomes. ESC noted that evidence for improvements in outcomes resulting from the early diagnosis of MPS IS is unclear, but that it would result in the avoidance of diagnostic delay, which ESC noted was considered to be of significant value by parents and carers. ESC considered the applicability of these results to the Australian population to be unclear.

[39] Note: "proband" is used in this document to mean an affected individual (i.e. a person who has signs and/or symptoms consistent with the disease phenotype) who has received a confirmatory (genetic, and/or other accepted diagnostic test) diagnosis.

Overall, ESC considered that there was considerable uncertainty in any conclusions that may be drawn from the available evidence; however, ESC recognised that the lack of evidence was due to the rarity of the condition.

Because of the two-tier approach to screening, ESC considered false positive test results to be unlikely and the sensitivity and specificity to be close to 100%. ESC noted that the maximum time to follow up after any screening in the published literature was 6.5 years, which ESC considered was not sufficient follow up time to determine the risk of potential false negative or the impact of subsequent delayed diagnoses; however, ESC noted that to date, no NBS has yet reported a false negative result using the proposed two-tier screening approach.

ESC noted that no direct safety evidence was available for NBS for MPS I, although it considered that no additional risk was associated with sample collection given that bloodspots are already collected as part of Australia's NBS programs. ESC noted that, with the likelihood of earlier HSCT uptake, there was a theoretical risk associated with surgery on babies with complex airways, although clinical advice was that appropriate risk management planning would improve with knowledge of the condition. ESC also noted that there was a potential risk of anxiety and overwhelming information for parents and carers associated in particular with attenuated MPS I forms; however, ESC noted that most evidence suggested this was outweighed by the value of knowing and avoidance of diagnostic delay. ESC therefore considered the claim of non-inferior safety to be uncertain but supported based on first principles.

For the testing of family members population (PICO set 2), ESC noted there was no evidence for health outcomes. However, ESC noted that the knowledge of the test results would result in a change in management, for example aiding in reproductive planning and perhaps leading to oocyte testing, pre-implantation genetic testing and prenatal testing, regardless of whether it followed from NBS or current clinical practice (in the absence of NBS). In addition, ESC noted that there was an expectation that test information would be more useful for reproductive planning following NBS, because it would be accessible earlier. ESC noted that these claims were largely based on logic rather than on any specific evidence, but acknowledged that affected family members considered test results to be valuable information for family reproductive planning. Any older siblings identified as having MPS I as a result of cascade testing would enter a treatment pathway similar to the proband/index case. On balance, ESC considered that the evidence for the clinical claim is uncertain but supported based on first principles.

ESC noted that to be eligible for ERT on the LSDP for MPS IHS a number of conditions are required to be met including documented diagnosis of disease and clinical manifestations as outlined in the LSDP guidelines (Table 19). ESC noted that NBS may lead to an increase in the number of diagnoses particularly for attenuated forms of MPS I and, thus, the number of MPS IHS cases who are eligible to access ERT. Further to this, ESC noted the birth prevalence observed in other countries and jurisdictions where MPS I NBS has been implemented; for example, ESC noted that in California, birth prevalence of MPS I after screening was 1 in 61,691 (if patients with MPS I with variants of unknown significance were included, which was considered reasonable noting these patients were all designated for long term follow-up). Therefore, ESC questioned whether an increase in diagnoses due to NBS could lead to an increase in prevalence of MPS I in Australia making the condition no longer being classified as an 'ultra-rare' disease, which might affect its eligibility for funding via LSDP; however, assuming a birthrate of 307,000 per year, this would equate to an incident number of cases of 6 per year to exceed the ultra-rare definition of 1:50,000. ESC noted that evidence presented in the DCAR suggested that approximately 4 cases of MPS I per year would be identified across Australia via the NBS, and therefore that NBS is not expected to impact on eligibility of funding for MPS I treatment via the LSDP.

Table 19 Current initial eligibility and ineligibility criteria for LSDP-funded laronidase

Patient characteristics	LSDP criteria
Diagnosis of MPS IH	Ineligible for LSDP-funded laronidase
Diagnosis of MPS IHS	Initially eligible for LSDP-funded laronidase if: The diagnosis of MPS I (is) confirmed by the demonstration of a deficiency of alpha-L-iduronidase in white blood cells with the assay performed in a NATA-accredited laboratory; or, for siblings of a known patient, detection of 2 disease-causing mutations. A deficiency of alpha-L-iduronidase in white blood cells should be confirmed by either an enzyme assay in cultured skin fibroblasts or by detection of 2 disease-causing mutations in the alpha-L-iduronidase 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 FVC < 80% of predicted value for height. • 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%). • 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.
Diagnosis of MPS IS	Ineligible for LSDP-funded laronidase
Patients with significant learning difficulties and/or neuropathic involvement with their disease indicating MPS IH	Ineligible for LSDP-funded laronidase
Patients with another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by enzyme replacement therapy	Ineligible for LSDP-funded laronidase
Patients with another medical condition that might reasonably be expected to compromise a response to ERT	Ineligible for LSDP-funded laronidase

Source: LSDP guidelines for MPS I, 2024 [40]

Abbreviations: ERT= enzyme replacement therapy; FVC= forced vital capacity LSDP= Life Saving Drugs Program; MPS I = Mucopolysaccharidosis, type 1; MPS IH = MPS I Hurler; MPS IHS = MPS I Hurler-Scheie; MPS IS = MPS I Scheie; NATA = National Association of Testing Authorities.

[40] https://www.health.gov.au/sites/default/files/2024-09/life-saving-drugs-program-mucopolysaccharidosis-type-i-mps-i-guidelines_0.pdf

ESC also considered it would be helpful for MSAC decision-making to have estimates on the number of patients who would access HSCT after a MPS I diagnosis, when they would be likely to access HSCT and what the benefits are of accessing HSCT earlier due to an earlier diagnosis. ESC noted that if MPS I was included in Australia's NBS program, patients diagnosed with MPS IH (~2 patients per year with NBS) are expected to access treatment within approximately 6 months of diagnosis, at 8-9 months of age, rather than at >2 years of age as occurs currently (Table 20). ESC noted that earlier access to HSCT may result in improved cognitive outcomes, but that patients would still need to undergo future cardiac surgery and that HSCT would not improve corneal clouding, as GAG will still accumulate. Therefore, ESC considered that costs associated with these procedures should be accounted for.

ESC noted that the uncertainties in the clinical evidence carried through to the economic evaluation, which included a cost-effectiveness analysis (CEA), a cost-consequences analysis (CCA) and an exploratory cost-utility analysis (CUA) for the newborn population (PICO set 1). For testing of family members population (PICO set 2), a cost analysis was performed.

For severe cases of MPS I, ESC considered there to be some evidence of benefit (short-term OS related to HSCT and long-term benefits for cognitive and physical functioning) of accessing HSCT early vs late. However, there is insufficient certainty to include these in the base case analysis. For attenuated cases, ESC considered the benefit to be less clear, as there were queries regarding eligibility to access ERT and the benefits of earlier access.

ESC noted that the cost of screening was driven by the program implementation and operation costs, with operational costs comprising approximately 79% of the screening cost. HSCT and ERT costs were applied based on assumptions regarding eligibility and access to treatment. ESC considered all model input costs to be reasonable. The weighted average cost per sample screened was $REDACTED, which ESC considered to be high compared to other screening tests on the NBS.

ESC considered that the stepped CEA provided the simplest, most robust analysis of the three presented, because it addressed the key advantage of the NBS, namely, early diagnosis. ESC noted that the CEA resulted in an ICER of $REDACTED per additional early diagnosis of severe MPS I. For the CCA, ESC considered that it may be biased against NBS MPS I in that it does not reward early diagnosis and instead considers the total number of diagnoses reached over 10 years; however, ESC also noted that currently, diagnoses typically occur after the 6 month time horizon used in the CEA (Table 20), and that these would be captured in the CCA. As a result, the ICER is unfavourably high at $REDACTED per confirmed diagnosis using the 2-tier screening approach. ESC noted that sensitivity analysis undertaken to include screening for two additional lysosomal storage disorders (MPS II and Pompe disease) using the same kit demonstrated a reduction in the ICER to $REDACTED; however, adopting this multiplex assay would be dependent on the inclusion of the two additional disorders as part of the NBS programs, pending MSAC's future considerations. ESC acknowledged that an NBS program would likely increase the total number of diagnoses over 10 years, although this is not its primary objective.

Compared to other NBS for other conditions, MPS I NBS screening is very high cost due to the relatively high tier-one test cost and the rarity of the condition. ESC noted that directly comparing costs between previous NBS applications was difficult due to the high uncertainty of ICER calculations. The cost per measure of diagnostic yield (DY) compared to other germline genetic testing on the MBS or NBS is also very high for MPS I.

ESC noted the exploratory CUA provided an ICER of $REDACTED per quality-adjusted life year (QALY) gained (time horizon of 30 years), but considered that the model had considerable sources of uncertainty, including the structure of the model, uncertainty in the input parameters

which were based on other conditions, and assumptions regarding treatment timing and access. These issues largely resulted from the uncertain evidence, and also because the nature of the disease progression varies between phenotypes.

ESC noted the concerns raised in the applicant's pre-ESC response that the cost of the diagnostic delay in current clinical management (i.e. prior to NBS implementation) may have been underestimated. ESC noted that the total cost of diagnostic delay and confirmatory testing for MPS IH and MPS I attenuated forms had been estimated as $3,651 and $3,543, respectively. ESC considered it was likely that these costs had been underestimated, and noted that the costs were based on a single study only, so reliability may have been limited. ESC considered that in practice, diagnostic delay was likely to be over a longer period of time and also that it presents a larger financial burden than was accounted for. ESC considered that along with specialist visits, costs of symptom management and medical interventions prior to diagnosis should be factored into the cost of diagnostic delay, although ESC did note that, if NBS was implemented, some intervention and symptom management costs would not be averted. For example, where HSCT does not reduce all complications associated with MPS IH, treatments associated with skeletal, eye and cardiac complications would still be required in both the intervention and comparator arms. ESC advised that the diagnostic delay costs (and therefore also the economic base case and downstream analyses) should be re-evaluated, taking into account further evidence from similar rare conditions if possible.

ESC noted that the cost analysis for the testing of family members population resulted in an incremental cost of testing of $836.76 per year if NBS is introduced for MPS I; however, ESC considered that this does not reflect important consequences such as family planning and related potential cost offsets, although ESC acknowledged that these costs would have been highly uncertain. Benefits to older siblings is assumed to be time-limited. Therefore, ESC considered it difficult to draw conclusions regarding the cost-effectiveness for testing of family members but noted that testing of family members already occurs for families of babies who are diagnosed through the current clinical pathway (that is, not through the NBS) and will continue to occur.

ESC noted the sensitivity analysis and that the cost of the tier-one test was the main driver of the ICERs. Extending the time horizon to beyond 30 years does not appear to have a substantial impact on the ICERs. ESC also noted that there are multiple lysosomal storage disorders being considered for funding, which the sensitivity analysis considered through multiplex testing. This would split the costs across multiple conditions, which is also an important driver, and would reduce the overall cost of screening. However, ESC noted that this was dependent on all conditions being added to the NBS programs. ESC noted that the caveat to these sensitivity analyses was whether MSAC accepts the CUA base case.

ESC noted that the net financial impact to NBS programs would be approximately $REDACTED in Year 1 (including ~$REDACTED of program implementation costs) and $REDACTED in Year 6. ESC noted that the current uptake of the NBS is over 99% of newborns, although the number of live births per year is variable. Other budgets impacted by including MPS I screening on the NBS are the LSDP, MBS (negligible, comprising additional monitoring costs expected to be offset by avoiding diagnostic delay) and state and territory budgets (also negligible, as cascade testing is currently performed). The finances are largely impacted by the cost of the test kit. ESC noted that in the pre-ESC response the applicant expressed concerns that the costs of monitoring had been underestimated, and that subsequently the financial impact may have also been underestimated. However, ESC also noted that additional analyses provided in the pre-ESC rejoinder indicated that increasing the cost of monitoring has a very low impact on the base case ICER (+1.0% in cost/confirmed diagnosis).

ESC noted that an alternative diagnostic pathway to biochemical NBS may include up-front genomic screening for newborns; however ESC also noted that this is still on the horizon and is not currently part of routine clinical practice. ESC therefore considered that, while genomic screening may supersede biochemical MPS I NBS (if implemented), it is not currently a practical alternative to NBS and as a future potential alternative only, would not impact on the consideration of the current application, and likely would not result in a higher diagnostic yield.

ESC noted that there are several ethical considerations associated with NBS, such as value of knowing, and parent and family wellbeing, as well an increased quality of life for children. ESC noted the implications and potential non-financial "costs" of moving from a clinically-based paradigm for diagnosis, to a screening-based approach for MPS-I, are unclear. In particular, there is a potential 'disutility' of knowing for patients and families associated with the MPS IS phenotype (including those with variants of unknown significance). This is because diagnosis for these patients brings with it considerable and potentially ongoing uncertainty and anxiety, and even after symptom presentation. ESC noted there are challenges associated with providing early diagnoses of a condition for which treatment is not subsidised for all patients, and/or symptoms may not present until later in life, creating 'patients-in-waiting'. There are also implications for any older or future siblings. However, given the small number of MPS I diagnoses expected per year, and that MPS IH is the most common form and has early symptom presentation, ESC noted that the number of 'patients-in-waiting' created was expected to be approximately 1-2 patients per year.

ESC noted that males with MPS I tend to have poorer neurological development compared to females, but agreed that the proposed population should include all newborns participating in NBS programs regardless of sex, because MPS I is an autosomal condition.

Overall, ESC noted that there was significant difficulty associated with assessing the clinical effectiveness and cost-effectiveness for an earlier diagnosis of such a rare disease. The difficulty is compounded by the fact that not all subtypes of the condition have access to the same treatments.

Table 20 Summary table at request of ESC discussion

Parameter	Proposed – Universal Newborn Screening	Current (No universal NBS) – diagnosis at symptom onset	Other/Increment/Comment
Direct evidence			
MPS registry, Overall Survival		12 m: 90.4% 5 y: 73.4%	
Linked evidence, change management			
Age at diagnosis, median			
Hurler (MPS IH)	2.4 m All MPS types	11 m (0-87 m) **Redacted**	
Hurler-Scheie (MPS IHS)		4.1 y (0-39 y)	
Scheie (MPS IS)		13.5 y (0-54 y)	
Age at treatment initiation after diagnosis, median	–		
Hurler (MPS IH)	HSCT: 6 m (2.5-7 m)	HSCT: 16.8 m (range 1 m-31.2 y) **Redacted**	
Hurler-Scheie (MPS IHS)	ERT: 1 m	ERT: 8.8 y (15 d-55 y)	
Time to diagnosis			
Hurler (MPS IH)	–	14 m (0-59 m)	
Hurler-Scheie (MPS IHS)	–	25 m (5 m-14 y)	
Scheie (MPS IS)	–	7.5 y (0-50 y)	
Treatment effectiveness			
Early vs late HSCT in MPS I			Meta analysis showed a non significant trend suggesting early HSCT (prior to 12 m or prior to 18 m) was associated with improved survival (5 to 13 y compared to late HSCT (after 12 or 18 m).
Early vs late ERT in MPS IHS			Six articles (27 cases of MPS IH) The very limited data available did not identify any clear benefit of early initiation of ERT on the outcomes of survival, quality of life, cognitive development, hearing, vision, cardiac disease, respiratory disease, or

Parameter	Proposed – Universal Newborn Screening	Current (No universal NBS) – diagnosis at symptom onset	Other/Increment/Comment
			organomegaly. However, the evidence was suggestive that early ERT has benefits in outcomes relating to bone growth and joint health.
Economic evaluation			
ICER ($/additional early diagnosis of severe MPS I) Step 1 base case model	$**Redacted** Early MPS I diagnosis (≤6 months): 7.0 per million	$**Redacted** Early MPS I diagnosis (≤6 months): **Redacted**	Incremental cost: $**Redacted** Incremental effect: **Redacted** ICER: $**Redacted**
Treatment/management costs in CEA	Costs associated with newborn screening, confirmatory diagnostic tests in cases identified	Diagnostic delay and diagnostic tests in cases identified	
ICER ($/additional confirmed diagnosis) Step 2 base case model	$**Redacted**	$**Redacted**	Incremental cost: $**Redacted** Incremental effect: **Redacted**
ICER ($/QALY gained) Stepped evaluation (6 steps)	$**Redacted** QALY: 13.008578	$**Redacted** QALY: 13.008555	Incremental cost: $**Redacted** Incremental QALY: 0.00002303 ICER: $**Redacted**
Treatment/management costs in CUA			
HSCT total cost per transplant ($**Redacted**) Step 3 exploratory model, Extended base case analysis to integrate cost of HSCT, survival data for MPS I (severe), attenuated MPS I and no MPS over 30y	Costs (average per person, discounted) = $**Redacted** Number of MPS I H cases identified early and accessing early HSCT (undiscounted): 7 per million	Costs (average per person, discounted) = $**Redacted** Number of MPS I H cases identified early and accessing early HSCT (undiscounted): **Redacted**	Incremental cost: $**Redacted** Incremental benefit: **Redacted** MPS IH cases identified early and accessing early HSCT ICER ($/additional case accessing early HSCT): –
ERT, Annual cost of Aldurazyme® (laronidase) for <2 y old ($**Redacted**) in CUA Step 6 Additional ERT costs (associated with earlier access) for MPS IHS added (no additional benefit)	$**Redacted** QALYs: 13.008578	$**Redacted** QALYs: 13.008555	Incremental cost=$**Redacted** Incremental QALYs = 0.00002303 ICER: $**Redacted**
Utilisation – incident cases			
Number of MPS I affected cases diagnosed per year	3.70 (Year 1) to 3.80 (Year 6)	0.21 (Year 1) to 3.78 (Year 6)	
Proportion severe (MPS IH)	57%	61%	
Proportion attenuated	43%	36%	
Proportion of attenuated as MPS IHS	58%	23%	
Proportion of attenuated as MPS IS	41%	13%	

Parameter	Proposed – Universal Newborn Screening	Current (No universal NBS) – diagnosis at symptom onset	Other/Increment/Comment
Hurler (MPS IH)	2.11 (Year 1) to 2.17 (Year 6)	0.21 (Year 1)[a] to 2.17 (Year 6)	
Hurler-Scheie (MPS IHS)	0.93 (Year 1) to 0.96 (Year 6)	0 (Year 1)[b] to 0.96 (Year 6)[b]	
Scheie (MPS IS)	0.65 (Year 1) to 0.67 (Year 6)	0 (Year 1)[c] to 0.65 (Year 6)[c]	
Number of MPS I affected cases monitored	1.59 (Year 1) to 5.27 (Year 6)	–	
Hurler (MPS IH)	0	–	
Hurler-Scheie (MPS IHS)	0.93 (Year 1) to 1.92 (Year 6)	–	
Scheie (MPS IS)	0.65 (Year 1) to 3.34 (Year 6)	–	
Diagnostic delay	–	0.21 (Year 1) to 3.78 (Year 6)	
Hurler (MPS IH)	–	0.21 (Year 1) to 2.17 (Year 6)	
Attenuated (MPS IHS and MPS IH)	–	0 (Year 1) to 1.61 (Year 6)	
Financial estimates			
Program implementation costs	$**Redacted** (Year 1)		
Total cost to NBS	$**Redacted** (Year 1) to $**Redacted** (Year 6)	–	
Cost of HSCT			Cost of HSCT were not assumed to differ but may be delayed by year
Cost of ERT			**Redacted**

[a] 10% cases detected in each year and 90% remaining cases detected in following year

[b] Each year, cases detected 12 months later

[c] Each year, cases detected 5 years later

Source: Compiled by department from 1775 department contracted assessment report and financials spreadsheet "04. DCAR 1775 - Financials-Final"

Abbreviations: ANZTCT= Australia and New Zealand Transplant & Cellular Therapies; CEA= cost effectiveness analysis; CUA= cost-utility analysis; ERT= enzyme replacement therapy; HSCT = haematopoietic stem cell transplantation; ICER= incremental cost-effectiveness ratio; m = month(s); LSDP= Life Saving Drugs Program; MPS I = Mucopolysaccharidosis, type 1; MPS IH = MPS I Hurler; MPS IHS = MPS I Hurler-Scheie; MPS IS = MPS I Scheie; NBS = newborn bloodspot screening; QALY= quality-adjusted life years; y = year(s

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website