

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1776 – Newborn bloodspot screening for mucopolysaccharidosis Type II (MPS II)

Applicant: Department of Health and Aged Care - Newborn
bloodspot screening section

Date of MSAC consideration: 3-4 April 2025

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 II (MPS II) 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 the REDACTED, and REDACTED, metabolic physician and clinical geneticist at the REDACTED, were supporting clinical expert co-applicants.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported adding mucopolysaccharidosis Type II (MPS II) to Australia's newborn bloodspot screening (NBS) programs because the potential benefits of screening newborns for MPS II outweigh the potential harms.

MSAC considered both its own Terms of Reference (TOR) and the NBS National Policy Framework (NPF) in providing its advice. MSAC considered the positive and negative impacts of screening newborns for MPS II, and the potential for unintended negative impacts on existing NBS programs.

MSAC considered that the following health technology assessment criteria were met. MSAC considered that the proposed 2-tier screening strategy has acceptable sensitivity to accurately identify newborns at risk of MPS II with low rates of false positives and false negatives. MSAC advised that there is evidence of additional benefit from an earlier diagnosis through NBS and earlier treatment. MSAC considered that an effective treatment is available for MPS II (enzyme replacement therapy [ERT]), although noted that this did not improve all disease signs or symptoms (e.g. neurological symptoms), and that current funding for ERT through the Life Saving Drugs Program (LSDP) would not allow access for pre-symptomatic newborns who screened positive without prediction of severe disease. LSDP eligibility criteria cannot be changed without reconsideration of clinical effectiveness by the Pharmaceutical Benefits Advisory Committee (PBAC).

MSAC noted that NBS for MPS II is aligned with the primary objective of the NBS NPF decision-making criteria, as the condition 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. By applying the average true positive rate of MPS II from overseas NBS programs to Australia, it was estimated that approximately 4 newborns would be diagnosed with MPS II via NBS in 2025-26. Of these approximately one newborn would be diagnosed with neuronopathic (more severe) MPS II and 3 newborns would be at-risk of developing non-neuronopathic MPS II, some of whom would not be expected to develop clinically significant or apparent symptoms of MPS II (and would therefore not be likely to be diagnosed in the absence of MPS II).

MSAC considered that the incremental cost per quality-adjusted life year (QALY) gained for screening for MPS II on its own was very high, noting however, that the estimated average cost per individual screened for MPS II 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 II was modest. MSAC further noted that, given its support for newborn screening of MPS I (MSAC application 1775), the incremental cost for newborn screening for MPS II would be minimal due to multiplexing (i.e. the same screening tests would be used for both MPS I and II).

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 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 II is that the following matters should be addressed prior to implementation of NBS for MPS II:

- (a) the introduction of an appropriate consent process to ensure that parents are informed that their newborns may potentially be found to be at-risk of or affected with an attenuated (non-neuronopathic) form of MPS II with uncertain prognosis who may not develop symptoms of MPS II, and to maintain trust in the NBS programs;
- (b) establishing a consensus on reporting of screening results for newborns with uncertain phenotype or for newborns without current access to treatment prior to symptom onset;
- (c) development of Australian clinical practice guidelines, which may include consensus guidelines, for the monitoring and management of children who are pre-symptomatic and whose disease onset and severity cannot be clearly predicted;
- (d) review by relevant authorities 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 that 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 II.

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

Consumer summary

This is an application from the Department of Health and Aged Care requesting advice about adding a screening test for mucopolysaccharidosis type 2 (MPS II) in Australia's Newborn Bloodspot Screening (NBS) programs. MSAC's advice will be considered by the Health Ministers Meeting alongside advice from the other committees in the new national decision-making pathway. These are the Cancer and Population Screening Committee, the Health Chief Executives Forum and the NBS Program Management Committee to determine if MPS II should be a part of the NBS programs delivered by the states and territories.

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

MPS II, also known as Hunter syndrome, is an ultra-rare condition, with approximately 0.62 babies currently diagnosed per 100,000 live births in Australia (i.e. approximately 2 babies diagnosed per year). This is expected to increase to around 1.42 babies diagnosed per 100,000 live births (i.e. approximately 4 babies per year diagnosed) if newborn bloodspot screening for MPS II is introduced, because people with mild symptoms who currently have undetected or undiagnosed disease would be picked up by screening.

People with MPS II cannot break down sugars called glycosaminoglycans (GAGs) because they are deficient in an enzyme, iduronate-2-sulfatase (IDS). The signs and symptoms vary, but affected people tend to have stiff joints, enlarged organs and tissues, including enlarged tongue and facial features, heart problems, neurological problems, and slowed growth. As a result of these complications, people with MPS II have a shortened lifespan. There are 2 forms of MPS II: a neuronopathic form (i.e. affected people have nervous system problems), which is normally more severe and often presents in babies aged 6–12 months; and a non-neuronopathic form (without nervous system involvement), which is normally less severe and may present in childhood or later in adulthood. Some people with this less severe form may never show symptoms or signs.

MPS II is a genetic condition caused by variations in a specific gene (the iduronate 2-sulfatase (*IDS*) gene), which is on the X chromosome (called "X-linked"). X-linked conditions are more likely to affect males, because they only inherit one copy of genes located on the X chromosome. Females very rarely have signs or symptoms of MPS II, and are instead more likely to be carriers of the condition (that is, if a female has one copy of an *IDS* gene variant, she may not have MPS II herself but may pass the variant on to a child, who may then go on to develop MPS II).

Newborn screening requires an initial screening test which identifies people at risk for the condition of interest – this test does not make a diagnosis. If the screening test identifies someone at-risk, they are recalled for further clinical assessment – a separate diagnostic test. The diagnostic laboratory test may make a diagnosis of a condition before any detectable signs and symptoms of disease are present.

The proposed screening method would measure enzyme activity on the dried bloodspot sample. Those with low enzyme activity would go on to have a "second-tier" test measuring GAG (sugar) build-up in the blood spot sample. MPS II is so rare that well over 99% of babies would be considered unaffected after the first tier of screening. The few newborns who receive a positive first tier screen result would go on to have the second-tier test. Any babies found to test positive for both tiers would go on to have a diagnosis confirmed by clinical examination, blood and urine tests, imaging tests and genetic tests.

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MSAC considered the 2-tier screening strategy to be very effective and that only true positives would be identified (that is, after both tiers of screening, MSAC considered that it was very unlikely any babies would be incorrectly diagnosed with MPS II who did not have the condition).

The available treatment for MPS II is idursulfase, an enzyme replacement therapy (ERT) that is currently accessed through the Life Saving Drugs Program (LSDP) in Australia. At the moment, not all babies and children with MPS II are eligible for ERT funded by the LSDP, as it is only available for children showing symptoms, or for those predicted to have a severe form of the disease (for example, if they have a sibling with severe disease). Babies who are diagnosed with MPS II through NBS may not yet show symptoms or might have uncertain disease progression, and so would not necessarily have access to treatment under the current LSDP criteria. MSAC advised that the LSDP criteria for access to therapy would need to be reviewed if MPS II screening was included as part of NBS. Because MPS II is so rare, there is also limited evidence about whether starting treatment before symptom onset will lead to better outcomes for all babies. Based on the evidence available, MSAC considered that ERT was at least partially effective for the most severe type of MPS II, and based on how ERT works, was likely to be at least partially effective for less severe disease, although no evidence for this was available. MSAC noted that ERT is not able to treat all symptoms (for example, it cannot reach the brain so cannot help with cognitive symptoms).

MSAC considered newborn screening for MPS II was 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 II if certain conditions are met. This is because MPS II mostly met the criteria for adding a condition to the newborn screening programs, as described in the Newborn Bloodspot Screening National Policy Framework¹ (NBS NPF). MSAC considered the potential benefits from newborn screening for MPS II were greater than the possible harms. However, MSAC advised that its support for the addition of MPS II to the NBS programs is that the following issues should be addressed before babies are screened for MPS II. MSAC noted that the final decision on whether MPS II will be added to NBS programs lies with the Health Ministers:

- Introduce an appropriate consent process to ensure that parents are informed that their babies may potentially be diagnosed with MPS II. MPS II 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 MPS II includes a later onset form, that course of disease may not be predictable, that some babies may never have symptoms, and that some babies may not have an early effective 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 babies will be recalled for MPS II if the severity of MPS II cannot be predicted at the NBS stage, noting that clinical examination and confirmatory testing may provide a diagnosis. For babies with uncertain phenotype there is no effective early treatment. This may cause harm to these children 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.

¹ <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework?language=en>

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- Review suitability of funding of ERT with idursulfase for babies diagnosed with MPS II via NBS, and who are likely to benefit from early treatment. Idursulfase is an expensive medicine. Broader public funding of ERT is likely needed to achieve better health outcomes from NBS for MPS II 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 II 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 II 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 II.

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

MSAC supported including MPS II in Australia's NBS programs. However, MSAC advised that there were a number of issues that should be addressed before MPS II screening begins. MSAC advised that the proposed 2-tier screening method was reliable for identifying true affected babies and that early access to enzyme replacement therapy was of benefit. MSAC considered the potential benefits from newborn screening for MPS II were greater than the possible harms. MSAC considered the value for money of newborn screening for MPS II is acceptable.

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

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

MSAC considered both its own Terms of Reference² and the Newborn Bloodspot Screening National Policy Framework³ (NBS NPF) in providing its advice. MSAC noted that its advice would be considered at 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 if MPS II 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:

² <https://www.msac.gov.au/about-us/what-we-do/terms-reference>

³ 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>

- 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 10 organisations and 2 individuals (one caregiver of an individual with MPS II and one health professional). MSAC also noted a summary of published studies compiled by the department, which highlighted the lived experiences of individuals diagnosed with MPS II, their families, carers and health professionals.

MSAC noted that MPS II is an X-linked recessive lysosomal storage disease (LSD) caused by an inherited deficiency or absence of the iduronate-2-sulfatase (IDS) enzyme required to break down glycosaminoglycans (GAGs) in the lysosomes within cells, leading to impaired cellular function. Clinical disease varies across a continuum, with two broad subtypes:

- A neuronopathic form, which is typically more severe, with central nervous system (CNS) involvement, including cognitive disability and childhood dementia. People with this form of MPS II generally have earlier onset (symptoms appear at 6–12 months old), and a lifespan of 10–20 years.
- A non-neuronopathic form, which is typically less severe and does not have CNS involvement. People with this form of MPS II generally have later (including adult) onset, and their lifespan can be 60–70 years.

MSAC noted that MPS II is an ultra-rare condition (defined as 1 or fewer cases per 50,000 births), with an estimated incidence in Australia (in the absence of NBS) of 0.62 per 100,000 live births (i.e. approximately 2 cases per year), although the actual incidence may be higher, where not all cases are currently detected.

MSAC noted the department-contracted assessment report (DCAR) estimated that, of cases currently clinically identified in Australia, approximately 75% are neuronopathic (severe), while 25% are non-neuronopathic (i.e. attenuated). This equates to an incidence of neuronopathic MPS II of approximately 0.47 per 100,000 live births (~1.43 cases per year), and an incidence of non-neuronopathic MPS II of approximately 0.15 per 100,000 live births (~0.47 cases per year).

MSAC noted that, if NBS for MPS II were to be implemented, incidence is expected to be approximately 1.42 cases per 100,000 live births, which equates to 4.33 MPS II cases detected per year (assuming 99.3% NBS uptake rate and using projected live births estimates). This would include 1.43 newborns (33%) diagnosed with severe [neuronopathic] MPS II, 0.47 newborns (11%) diagnosed with attenuated [non-neuronopathic] MPS II and 2.42 (56%) newborns diagnosed with very attenuated [non-neuronopathic] MPS II. MSAC considered that as only 0.47 cases of non-neuronopathic MPS II are diagnosed clinically each year, most of the newborns diagnosed with very attenuated MPS II diagnosed through NBS would not be expected to develop clinically significant or apparent symptoms of MPS II.

MSAC considered the **availability of a suitable screening test (or tests) to accurately identify all newborns at-risk of MPS II (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive)**, MSAC noted that the proposed newborn screening protocol for MPS II would be a 2-tier protocol. The first-tier screening would be a test for IDS enzyme activity on the dried bloodspot (DBS). Those with low enzyme activity would then 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 the second-tier test would be expected to rule out newborns with pseudodeficiency variants. MSAC noted that none of the 4 overseas NBS programs included a second-tier screening, and therefore that the positive- and negative-predictive values from these studies are not applicable to the proposed methodology. However, MSAC considered that the proposed 2-tier screen would be highly accurate and almost all newborns who test positive to the second-tier test will be diagnosed with MPS II. This is because a positive second-tier GAG test indicates that the patient has undegraded or partially degraded GAGs which suggests that the MPS II disease process is active. MSAC noted that over 99% of newborns would be expected to screen negative using the first-tier screening test (i.e. would not have low enzyme activity and would therefore be considered unaffected). Newborns who screen positive at first tier would go on to second-tier GAG testing, after which diagnosis for those who screen positive would be clinically confirmed, by examination and imaging. MSAC noted the DCAR estimated that approximately 88 newborns per year would screen positive at first-tier screening and proceed to second-tier testing, which of whom 84 would test negative (false positives). Approximately 4 newborns will test positive on both screening tests be recalled for further testing. Of these, approximately one newborn will be diagnosed with severe MPS II. The remaining 3 newborns will be diagnosed with, or at risk of developing attenuated MPS II most of whom would not be expected to develop clinically significant or apparent symptoms of MPS II.

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 MPS II. 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 considered **whether MPS II disease subtype and prognosis can be determined from the screening and confirmatory tests to determine the need for earlier treatment**. MSAC considered the disease subtype and prognosis can be determined for some patients after screening and diagnostic tests. MSAC considered genetic testing is needed to predict subtype of MPS II. However, MPS II is characterised by high genetic heterogeneity making it difficult to identify genotype-phenotype associations and predict the subtype and prognosis. Most of the *IDS* variants identified are either private or novel, with >700 *IDS* pathogenic variants identified. MSAC noted that different phenotypes have been observed in unrelated patients who carry the same variant. MSAC considered that imaging (x-rays) and clinical examination of a newborn can detect early signs of disease in the joints, and assist in predicting severe early-onset phenotypes, particularly in newborns with unknown or novel genetic variants. However, phenotype prediction may also be inaccurate and MSAC considered that families are likely to expect phenotype prediction at the time of diagnosis, rather than months afterwards.

Therefore, MSAC noted that, of those who ultimately screen positive and are diagnosed with MPS II, only 20–30% of newborns would be expected to have known pathogenic variants in a population with primarily European ancestry. For the remaining newborns, MSAC advised that severity cannot be predicted after initial testing and ongoing follow-up is required for newborns with a normal clinical examination, normal imaging and genetic variants that cannot accurately predict the subtype and prognosis.

MSAC noted that there are some founder variants in Southeast Asian populations, and therefore considered that studies on MPS II diagnosed via NBS from Southeast Asia are less applicable to predicting the subtype and severity of MPS II diagnosed through NBS in the Australian context.

MSAC further noted that, prior to implementation, there should be a consensus whether results should be reported for those identified as at-risk of attenuated MPS II as most of these newborns would not be expected to develop clinically significant or apparent symptoms of MPS II. MSAC therefore considered that, while the proposed 2-tier screening method would be reliable for diagnosing MPS II, it (alongside confirmatory tests) cannot always predict the age of sign/symptom onset or severity of disease.

MSAC considered the **availability of effective treatment (or treatments) in Australia for at-risk newborns.**

MSAC noted that idursulfase, an intravenous ERT, is available for treatment in Australia. MSAC noted that the available evidence was for the severe form of MPS II, while no evidence was available on the benefit of earlier treatment with ERT in attenuated cases. MSAC noted that earlier ERT initiation appeared to result in some improvement in somatic manifestations of the disease, but because ERT cannot cross the blood–brain barrier (BBB), it has no effect on cognitive impairment. MSAC considered that ERT was at least partially effective in the severe form of MPS II.

MSAC noted that the Australian Government currently funds idursulfase for some patients with MPS II under the LSDP. Patients need to meet general and condition-specific criteria to be eligible, including at least one of the complications of MPS II. MSAC noted that pre-symptomatic infants and children aged <5 years may also be eligible where there has been a diagnosis of MPS II, for example by genotyping, with clear prediction of progress of the disease, or if, on the basis of a sibling's disease progression, severe disease can be predicted. MSAC considered the current requirement of clear prediction of severe disease in pre-symptomatic infants/children aged <5 years to access LSDP-funded ERT may prevent many newborns identified by NBS from accessing treatment until significant symptoms have developed.

MSAC noted that there was some evidence of the benefit of idursulfase treatment for those with MPS II for some aspects of the disease but not all. MSAC noted that idursulfase does not cross the blood-brain barrier (BBB) and therefore is ineffective for CNS disease for individuals with neuronopathic MPS II. However, MSAC considered that there may be possible benefits for other disease manifestations. MSAC advised that public funding for idursulfase for newborns diagnosed with MPS II through NBS be considered to ensure that diagnosis of MPS II through NBS 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 implemented prior to implementing NBS for MPS II. 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 idursulfase for MPS II. MSAC also noted that there are no national clinical management guidelines to guide the use of ERT in children who are presymptomatic but whose disease onset and severity cannot be 'clearly predicted'.

MSAC noted that haematopoietic stem cell transplantation (HSCT) has been used for MPS II in some cases, but is considered experimental and is not currently funded by the Commonwealth as treatment for MPS II.

MSAC noted that the pre-MSAC response commented that intrathecal ERT may be of benefit for neurological involvement, and that some of these therapies are currently in phase 3 trials. However, these emerging therapies are not yet currently available outside clinical trials, nor are

there publicly funded mechanisms for affected newborns diagnosed through NBS. MSAC considered that it was important to ensure the availability of mechanisms to incorporate new evidence into the MPS II clinical practice guidelines as it becomes available. MSAC considered that both the LSDP EP and pharmaceutical sponsors have a role in ensuring that the LSDP eligibility criteria are aligned with up-to-date clinical practice guidelines.

MSAC considered the evidence on the **effectiveness of treatment from the proposed earlier age of initiation following NBS screening and diagnosis (pre-symptomatic and early symptomatic), compared to age of treatment initiation under current management pathway (established symptomatic presentation)**. MSAC noted that evidence regarding the benefits of earlier treatment initiation was very limited, largely due to the rarity of the condition. MSAC noted that there was no direct evidence comparing ERT initiation in the context of NBS compared to no NBS. Instead, the DCAR presented data from case series and sibling studies. For example, evidence from a US NBS program (Illinois) showed that, of 3 newborns treated with ERT only within 3 months of birth, there appeared to be a slowed progression of symptoms normally seen in children with MPS II. However, all 3 children were still displaying developmental delays at the time of reporting. In another case series reporting on the NBS program in Taiwan, MSAC noted that all 4 newborns identified as having MPS II were treated with ERT and 3 received additional HSCT (before age 2) making it difficult to estimate the incremental benefit of earlier ERT. MSAC noted clinical findings, particularly imaging outcomes, were reported, but that predicted phenotypes were not, and that ages at treatment and follow up varied. Due to the small sample, use of HSCT, and the variable reporting, MSAC did not consider the Taiwanese study to be informative regarding the effectiveness of earlier treatment with ERT in the Australian context.

MSAC noted the limited evidence available to assess the safety of earlier administration of ERT, but that ERT has a known side effect profile that includes infusion-related reactions. MSAC also noted long-term monitoring of presymptomatic patients identified through NBS may have safety risks, as surveillance often involves imaging (e.g. x-ray or computed tomography) requiring exposure to radiation and sedation, which can be potentially harmful, especially in young children. For patients with attenuated MPS II, an early pre-symptomatic diagnosis through NBS would lead to years of clinical surveillance before symptoms appear, without evidence of an effective early intervention or evidence of improved health outcomes. MSAC considered newborns at risk of developing attenuated disease may experience harm from having a diagnostic label including psychological distress and 'sick role behaviour' without the potential for improved health outcomes.

MSAC considered the **cost-effectiveness of NBS for MPS II compared to no newborn screening**. MSAC noted that all newborns would be screened at an estimated average cost of \$REDACTED per screen, and that while very few newborns would be detected, the cost per screen remained low. MSAC considered the low cost per screen combined with the potential benefits of early diagnosis and treatment access for affected individuals, supported the cost-effectiveness of NBS for MPS II in the context of high ICERs in the other economic analyses.

MSAC considered the results of the cost-utility analysis (CUA) and noted that although it was exploratory and was associated with significant uncertainty due to limited evidence, it was nonetheless informative for the committee. The CUA explored the possible additional benefits (survival gains in severe MPS II, avoiding the diagnostic delay in attenuated MPS II) and incorporated the costs associated with NBS for MPS II for all newborns, confirmatory and monitoring costs for all newborns who screened positive for MPS II, and treatment (ERT) costs for severe MPS II cases. The resulting incremental cost-effectiveness ratio (ICER) was very high, at approximately \$REDACTED per quality-adjusted life year (QALY) gained for severe MPS II. A CUA for all MPS II cases (any subtype) was not presented due to data limitations. MSAC noted that the QALY benefits were generated based on early ERT-related survival benefits in severe MPS II from

a case series of 6 patients from Japan with an 11-year follow-up. The very small number of patients and limited evidence was a key source of uncertainty in the economic modelling.

MSAC considered that, while the ICER was high, this was largely driven by the high cost of treatment and the relatively modest demonstrated benefits of earlier treatment. MSAC also considered that cost-effectiveness might potentially be improved if MPS II were to be included in a multiplexed screening panel alongside a condition such as MPS I (Application 1775), although the ICERs would likely remain high. MSAC noted that the ICERs for ultra-rare conditions are often very high. MSAC also noted that a 2007 PBAC submission for idursulfase for MPS II treatment reported an incremental cost in the range of \$15,000- \$45,000 per additional metre walked in a six-minute walk test (6MWT)⁴. The 6MWT measures cardiac and respiratory as well as joint function. MSAC noted that treatments such as ERT for MPS II are funded through the LSDP, despite having ICERs higher than those typically considered to be cost-effective by the PBAC. MSAC considered that the cost-effectiveness of ERT may need to be assessed by the PBAC to support any potential expansion of LSDP funding.

MSAC considered cost-effectiveness analyses reporting the cost per diagnosis of MPS II were less informative because MPS II is a very rare condition making the cost per diagnosis very high when the cost per newborn screened and overall cost to the NBS programs is acceptable.

MSAC considered **the likely financial impact of adding MPS II to NBS to all relevant budget holders**. MSAC noted the financial impact to the NBS programs was estimated to be \$REDACTED in Year 1 (including a one-off set up cost) and approximately \$REDACTED annually in Years 2-6 of listing. MSAC noted that the Assessment Group's rejoinder presented analyses that included the costs of ERT use in cases of MPS II that are already present at the time of NBS implementation, and presymptomatic ERT use in attenuated MPS II cases. MSAC noted the resulting cost of ERT use to the LSDP increased by almost 7-fold by Year 6 (increasing from \$REDACTED in Year 1 to \$REDACTED in Year 6) if LSDP criteria was expanded to include attenuated and very attenuated cases (see Table 24). MSAC noted that other budget impacts were relatively minor, with an anticipated net cost to states/territories health budgets of \$REDACTED in Year 1 to \$REDACTED in Year 6, and to the MBS of \$41,941 in Year 1 to \$168,031 in Year 6.

MSAC considered the **relevant ethical (including equity), legal, social or organisational aspects specific to screening** for MPS II.

MSAC considered that there are significant ethical implications of screening newborns for MPS II, which should be considered by other relevant bodies on the NBS national decision-making pathway and resolved prior to implementation.

MSAC noted that the ethical issues associated with NBS for MPS II are different from the vast majority of currently screened conditions. This is because MPS II has different subtypes with different prognoses. Although NBS for MPS II will enable earlier diagnosis and intervention for newborns who will develop the most severe, earlier-onset form of MPS II, screening will also identify newborns at risk of developing attenuated forms of MPS II. MSAC considered some newborns at risk of developing attenuated forms of MPS II may not benefit from screening in the newborn period because symptoms may not develop until later in childhood or in adulthood. MSAC noted that some of those newborns diagnosed with an attenuated form of disease may have no or very mild symptoms that may not have led to a diagnosis of MPS II in the absence of screening. For some newborns with attenuated MPS II, an early pre-symptomatic diagnosis through NBS would lead to years of clinical surveillance before symptoms appear, without an effective early intervention to improve health outcomes. MSAC considered newborns at risk of

⁴ Idursulfase Public Summary Document, November 2007 PBAC meeting. <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2007-11/Idursulfase%20rhu%20ELAPRASE%20Genzyme%205%203%20PSD%20Nov%2008%20FINAL.pdf>

developing attenuated disease may experience harm from having a diagnostic label including psychological distress and 'sick role behaviour' without the potential for improved health outcomes.

MSAC therefore considered that while an earlier diagnosis may potentially help some newborns and their families avoid a 'diagnostic odyssey,' it may not benefit some newborns at risk of developing attenuated MPS II who may never develop significant symptoms. MSAC considered that an earlier diagnosis of attenuated MPS II through NBS 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 potential treatment options may not be immediately 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 to the entire process of MPS I newborn screening⁵. MSAC considered that due to the similarities between NBS for MPS I and MPS II there is potential for anxiety and stress for families of newborns diagnosed with MPS II if there is an uncertain prognosis, without the potential benefits of early treatment.

MSAC considered that carrier testing of at-risk family members can provide valuable information to support informed reproductive decisions.

MSAC considered that there are ethical issues associated with screening newborns for conditions where some individuals may not develop the condition until adulthood and if there is no effective intervention in childhood. Most professional and legal organisations do not support testing children for adult-onset diseases to preserve the child's autonomy and right to provide informed consent^{6,7,8,9}. MSAC noted that many adults choose 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 as not all newborns would be eligible to access to pre-symptomatic treatment with idursulfase on the LSDP.

MSAC advised that consideration could be given to only reporting diagnoses of MPS II where some benefits from early treatment. MSAC noted that NBS laboratories could limit reporting to known phenotypes with 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

⁵ 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.

⁶ 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.

⁷ 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.

⁸ 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.

⁹ 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/>

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 II to NBS programs has ethical considerations that warrant updates to consent processes when MPS II screening is implemented. MSAC noted that, currently, there is no national consensus about the requirement for written consent for newborn screening and written consent is not universally required in all states and territories. MSAC therefore advised that appropriate consent processes must be updated with the implementation of screening newborns for MPS II. MSAC considered the consent process should inform families of the potential for a diagnosis of MPS II with an uncertain prognosis (if these are reported), and that some newborns diagnosed may not develop significant symptoms or may develop symptoms in late childhood or adulthood. MSAC considered this consent should inform families of the availability (or not) of a publicly funded effective early treatment so they can provide informed consent. MSAC advised that this consent should incorporate the consensus on reporting diagnoses of MPS II.

MSAC considered that this is essential to minimise any potential negative impact on the existing public trust in the NBS programs, as evidenced by the near universal uptake (over 99.0%). MSAC considered there may be a risk in diagnosing children with adult-onset conditions, or conditions with no early intervention as this can potentially discourage parents from participating in NBS programs. 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, as fewer newborns would be diagnosed earlier and receive effective earlier treatment for more common conditions such as cystic fibrosis and congenital hypothyroidism.

MSAC advised that, if NBS for MPS II is implemented, a registry should be developed to enable long-term follow-up to establish incidence of each disease subtype and genotype–phenotype relationships (including the proportion of individuals with each MPS II subtype in the Australian context), and collect clinical outcomes data on the potential benefits of earlier treatment. MSAC also considered that a national screening protocol for MPS II should be agreed upon and implemented concurrently across all jurisdictions to ensure equitable access to screening.

MSAC advised that adding LSDs to newborn screening programs as part of an agreed multiplexed panel would be more efficient and preferable.

Overall, MSAC supported the addition of MPS II to the NBS programs, provided the following issues are addressed before implementation:

- A consensus is reached regarding whether a diagnosis of MPS II should be reported for newborns predicted to develop attenuated or later onset form of MPS II or for newborns who would not have access to treatment at diagnosis (i.e. before symptom onset). MSAC considered this would require an ethical analysis.
- Review expanded public funding for ERT with idursulfase for newborns diagnosed with MPS II and who are likely to benefit from early treatment. Idursulfase is a high-cost medicine. Public funding of ERT is needed to achieve better health outcomes from NBS for MPS II and ensure there is 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 newborns may be found to be at-risk of, diagnosed with an attenuated (non-neuronopathic) form of MPS II or MPS II with an

uncertain prognosis. The consent process must inform parents of the uncertainty in prognosis associated with such a finding, including an uncertainty in the timing of symptom onset, potential for adult-onset disease, the presentation of only mild or even no symptoms and the lack of an effective early intervention. This consent process would need to be informed by the consensus on reporting results.

- Australian clinical practice guidelines, which may include consensus guidelines, are developed for the monitoring and management of presymptomatic newborns/infants/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 II) and clinical outcomes to inform future reviews of NBS for MPS II (noting that 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.

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.
- Acceptable cost-effectiveness
- The total cost to NBS programs is acceptable (but there are high cost impacts to the LSDP).

Additionally, MSAC considered that the primary decision-making criteria of the NBS NPF were met as the condition is predominantly early-onset (the median age of clinical diagnosis 3.2 years) and severe with an effective early intervention, noting current restrictions on access to publicly funded ERT must be resolved as a part of implementation.

4. Background

MSAC has not previously considered adding MPS II to NBS programs. Addition of one related lysosomal storage disorder (LSD) to NBS programs is being considered by MSAC alongside this application (MSAC application 1774 – NBS for glycogen storage disorder, type II [GSD II]). MSAC considered the addition of MPS I to NBS programs (MSAC application 1775) at its November 2024 meeting.

5. Prerequisites to implementation of any funding advice

Each state and territory would determine which method of screening for MPS II they would implement. 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 have already been determined to be met, by the other committees in the NBS decision-making governance process. 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 II to be added to the NBS programs, NBS laboratories would be required to:

- Have or gain sufficient space for additional capital equipment, including mass spectrometry machines.
- Purchase additional mass spectrometry machines (adhering to local procurement policies including tender processes).
- Hire and train additional laboratory staff (in several cases moving to a different rostering system so the laboratory is in use 6 days per week instead of 5).
- Validate the screening protocols, determining normal and abnormal value ranges,
- Obtain National Association of Testing Authorities (NATA) accreditation and
- Add the new test to the Laboratory Information Management System¹⁰.

The NBS laboratories have estimated it would take at least 6 months to implement NBS testing using a commercial kit, such as the NeoLSD2™ kit from Revvity. This would require set-up of the new machine, to validate the screening test, undertaking a pilot 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, these could be sent to the National Referral Laboratory (NRL) for Lysosomal, Peroxisomal and Other Related Disorders, which may need to purchase an additional mass spectrometry machine.

Guidelines on the management of patients with MPS II 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 and support.

To support these activities, direct funding is being provided to states and territories via a schedule to the Federation Funding Agreement (FFA) - Health, under which they can make decisions regarding the best use of funds for implementation in their own jurisdiction.

6. Proposal for public funding

The proposal is for MPS II 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. Babies born in states and territories without NBS testing laboratories have their dried bloodspots (DBS) sent interstate for testing.

¹⁰ https://www.health.gov.au/sites/default/files/2024-06/newborn-bloodspot-screening-expansion-readiness-assessment-executive-summary_0.pdf

Each laboratory may choose their preferred screening protocol. For MPS II, the NBS laboratories were consistent that:

- First-tier screening should be done by testing for iduronate 2-sulphatase (IDS) enzyme activity on the DBS (using either the NeoLSD2™ kit from Revvity or a REDACTED kit [due to be available from REDACTED]).
- 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 protocol is not currently in use in any other country.

If a case of MPS II is diagnosed due to NBS, then testing of family members such as maternal aunts, maternal uncles and siblings if appropriate is also proposed (testing of fathers and other paternal relatives would occur only under certain circumstances¹¹). 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 male siblings (if deemed clinically relevant) would be by either the use of endogenous NRE-GAG analysis on urine 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 testing of family members. Female siblings would only undergo testing if symptomatic or for family planning purposes, as the condition is very rare in females and knowledge of carrier status is not always desired in people prior to reproductive age¹². Testing of relatives already occurs when a person is diagnosed with MPS II, so this is not a new service.

7. Population

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 people 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 1.

¹¹ Paternal relatives would only receive cascade testing if the index case is a female at risk of MPS II due to X-chromosome anomaly or skewed X-chromosome inactivation.

¹² Vears, DF et al. (2023). Human Genetics Society of Australasia Position Statement: Genetic Carrier Testing for Recessive Conditions. *Twin Res Hum Genet* 26(2):188-194. DOI:10.1017/thg.2023.15.

Table 1 Description of populations included in the assessment

PICO set	Population for intervention	Population for comparator
PICO Set 1 - Newborns	All newborn babies in Australia who participate in universal NBS programs.	Affected individuals being investigated for MPS II due to signs/symptoms
PICO Set 2 – Family members	Biological mothers, and siblings of an individual (index case) identified through NBS with a pathogenic/likely pathogenic (P/LP) variant(s) in the <i>IDS</i> gene Where the mother tests positive, also her parents and siblings	Biological mothers, and siblings of a proband identified after symptom onset with a pathogenic/likely pathogenic (P/LP) variants or VUS (reclassified as P/LP) in the <i>IDS</i> gene Where the mother tests positive, also her parents and siblings

IDS = iduronate 2-sulphatase; MPS II = mucopolysaccharidosis Type II; 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 screening is over 99%¹³. The population proposed for MPS II screening is the same as would undergo NBS in the absence of MPS II being part of NBS programs (i.e. approximately 300,000 newborns per year). Sufficient DBS samples are currently taken, meaning that there would be no additional impact to the process of taking heel prick samples on a filter card within the first 48-72 hours of life to screen for MPS II.

MPS II is an ultra-rare (defined as 1 case per 50,000 births or fewer) LSD. A 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 II, the lysosomal enzyme Iduronate-2-sulphatase (*IDS* or *I2S*), 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.

MPS II is inherited in an X-linked recessive manner, as the *IDS* gene (OMIM 309900) is located on the X chromosome, and consequently predominantly affects males. Females are usually carriers and very rarely develop clinical signs of MPS II unless there is skewed X-chromosome inactivation (XCI), which can lead to inactivation of the normal copy of the *IDS* gene. It is estimated that between 10–33% of *IDS* variants identified in affected individuals are *de novo* rather than familial in origin.

At birth, newborns with MPS II do not appear to be affected by the condition. For children affected by the most severe form of MPS II, the first symptoms characteristic of MPS II start to appear as early as 4 to 12 months of age. They may have subclinical deterioration prior to first signs and symptoms, such that there is usually a delay in manifestation of the disease (i.e. between when deterioration first starts, and when symptoms develop)¹⁴. The first signs may be non-specific respiratory and ENT issues. In the first few years of their life, children with severe MPS II do not meet developmental milestones. As MPS II progresses, children regress developmentally, losing much of their cognitive function and develop behavioural issues including hyperactivity. Growth slows at around 5 years of age, resulting in short stature. As many organs and tissues are affected in MPS II, there are multiple characteristics and clinical features

¹³ 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* 60(10): 1551-1561. DOI 10.1515/cclm-2022-0403.

¹⁴ Shapiro, EG, Jones, SA & Escolar, ML (2017). Developmental and behavioral aspects of mucopolysaccharidoses with brain manifestations — Neurological signs and symptoms. *Mol Genet Metab* 122: 1-7.

associated with this disease that require treatment, including frequent upper respiratory infections, sleep apnoea due to narrowing of the airway, hernias. In later childhood, hydrocephalus, hearing loss, reduced vision, heart valve and heart rhythm abnormalities and skeletal abnormalities become evident. Life expectancy with the severe form of MPS II is between 10 to 20 years of age with death usually caused by obstructive airway disease and/or cardiac failure.

Many of the systemic symptoms of late-onset attenuated MPS II are similar to those experienced by patients with severe MPS II but are generally milder and with limited or absent neurological involvement (cognitive impairment and/or behavioural problems). However, as life expectancy is significantly greater at up to 60 to 70 years for individuals with attenuated disease, they may ultimately be as greatly affected as severe patients due to the cumulative somatic manifestations progressing over a longer period of time.

Individuals with *IDS* gene variants linked to IDS pseudodeficiency exhibit reduced IDS enzyme activity (~5–15% of normal levels) but maintain normal urinary GAG levels and show no symptoms of MPS II. These individuals remain asymptomatic because the gene variants reduce the activity of the enzyme as detected by laboratory testing but do not reduce it to a disease-causing level, as sufficient IDS function prevents GAG accumulation. NRE-GAG analysis, proposed as a second-tier test, can effectively distinguish between individuals with MPS II and those with IDS pseudodeficiency. This distinction is crucial as it minimises false positive cases in newborn screening, reducing unnecessary recalls for confirmatory testing and improving the positive predictive value (PPV) of the screening process.

The true birth prevalence of MPS II in Australia is unknown, as the number of clinically diagnosed patients may be an underestimate due to undetected cases of attenuated disease (or death before diagnosis for severe disease cases). Based on those clinically diagnosed between 2009 and 2020 in Australia, the estimated incidence of MPS II was 0.62 per 100,000 live births. The weighted average worldwide birth prevalence of MPS II from 4 NBS programs from Japan, Taiwan and the United States (Illinois and Missouri) is 1.42 per 100,000 live births.

PICO Set 2 – Family members

Based on the X-linked inheritance pattern of MPS II, it is proposed that genetic testing will be offered to the mother of male newborns diagnosed with pathogenic or likely pathogenic variants of *IDS*. If the mother tests positive, then testing of her parents and siblings is indicated (i.e. the newborn's maternal grandparents, aunts and uncles). MPS II is familial (inherited) in most cases, but *de novo* variants are reported to occur in 10–33% of MPS II cases. When MPS II is familial, the biological mother of affected male offspring with a pathogenic variant is a carrier, with a 50% chance that other male offspring would be affected.

Older male siblings of index cases born before the implementation of NBS for MPS II may remain undiagnosed until symptom onset, which in MPS II patients with severe disease is typically at 1-3 years of age, or later for patients with attenuated disease. It is recommended that these individuals undergo biochemical testing, such as urine GAG analysis. If results are positive, further diagnostic testing, including genetic testing, would be offered.

Genetic testing for young female siblings is generally deferred unless medically indicated, according to the Human Genetics Society of Australasia (HGSA) guidelines, to allow informed decision-making. The clinical expert advice suggested cascade testing at any age with proper counselling, but ethical guidance is needed on communicating results.

8. Comparator

PICO Set 1 Individuals undergoing diagnostic testing after symptom onset

The comparator to adding MPS II to Australian NBS programs is no screening for MPS II, and diagnostic testing as it currently occurs after symptom onset.

Diagnostic tests currently performed in individuals suspected of having or being at risk of MPS II include:

- A urinary NRE-GAG analysis using liquid chromatography (LC)-tandem mass spectrometry (MS/MS).
- A leukocyte IDS enzyme activity test.
Although not required for diagnosis, it is still useful to predict the severity of disease. Additionally, the eligibility criteria to access idursulfase through the LSDP requires that the diagnosis of MPS II be confirmed by the demonstration of a deficiency of IDS enzyme activity in white blood cells with the assay performed in a NATA-accredited laboratory, or for siblings of a known patient, detection of a disease-causing variant.

Those who are found to have MPS II following the above diagnostic testing undergo genetic testing.

Tests performed for diagnostic confirmation of suspected MPS II are not listed on the MBS and are currently funded by state and territory health budgets.

PICO Set 2 – Family members

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

1. Genetic testing for the specific familial P/LP variants is offered to mothers (fathers, aunts and uncles, if appropriate) after the diagnosis of a symptomatic child within the hospital 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 may be referred to an appropriate clinic.
2. Male siblings of the affected patient considered to be at risk of having MPS II have biochemical testing (urine GAG analysis) or genetic testing. Female siblings would only have testing if they were symptomatic, as the X-linked recessive condition is very rare in females.

Female siblings are not proposed to be offered testing to determine carrier status, unless they are considered competent to consent to being tested to gain information that may be used for their own reproductive planning.

9. Summary of public consultation input

Consultation input was received from 10 organisations and 2 individuals, one caregiver of an individual with MPS II and one health professional. The organisations that provided input were:

- Western Australian Newborn Bloodspot Screening Program (WA NBS)
- Australasian Society of Inborn Errors of Metabolism (ASIM) [special interest group of Human Genetics Society of Australasia (HGSA)]
- Rare Voices Australia (RVA)
- Genetic Alliance Australia (GAA)

- Royal College of Pathologists of Australasia (RCPA)
- Australian Genomics
- Childhood Dementia Initiative (CDI)
- Statewide Biochemical Genetics Service within SA Pathology (SA Pathology)
- Sanofi-Aventis Australia
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

Level of support for public funding

The consultation feedback received was supportive of public funding for newborn bloodspot screening (NBS) for MPS II. The consultation feedback highlighted concerns regarding potential testing methods and their accuracy, and also that NBS for MPS II may lead to overdiagnosis and ‘medicalisation’ of newborns who may never develop MPS II.

Perceived Advantages

- Timely diagnosis.
- Avoidance of the ‘diagnostic odyssey’, and subsequently reduced financial burden on both families and the healthcare system that would otherwise result from searching for a diagnosis.
- Earlier treatment, prior to onset of significant and irreversible disease manifestations (particularly in individuals with the severe neuronopathic form of MPS II), which will potentially improve outcomes.
- Equitable access, since all families will have equal access to early diagnosis.

Perceived Disadvantages

- Limitations of the proposed screening tests, including potentially poor positive predictive value, and the limitations on genotyping to assist with diagnosis and/or phenotype prediction (due to the large number of private variants in the relevant gene).
- Screening may identify newborns who may have only mild symptoms or never have symptoms with consequent ethical implications.
- Initial testing is unlikely to distinguish between patients who will develop neuronopathic or non-neuronopathic forms of MPS II.
- Ethical issues were raised about screening newborns for a condition that may not present until adulthood.

Support for Implementation /issues

The consultation feedback identified a number of other services that would need to be delivered before or after the intervention. These included resourcing of NBS labs (e.g. for staffing, equipment, and facilities), confirmatory diagnostic testing, genetic counselling, specialised multidisciplinary care from metabolic services, cascade testing, prenatal testing, and support for families (education material, assistance navigating the health system). Consultation feedback also highlighted the additional healthcare and allied health services needed to care for people with symptomatic MPS II.

The feedback also highlighted equity issues, raising concerns that not all newborns who screen positive for MPS II would have the same access to treatments and services (e.g. where metabolic services and HSCT are not available in all states and territories).

10. Characteristics of the evidence base

The key characteristics of the evidence base is summarised in Table 2.

PICO Set 1 - Newborns

No evidence was identified that directly compared any outcomes after NBS for MPS II versus current practice (diagnosis after symptom onset, or due to family history). A naïve indirect comparison was therefore performed, based on a large number of retrospective case series (k=86) of MPS II cases diagnosed without NBS, and a small number of case series (k=5) that screened a large number of neonates, but diagnosed only a very small number of MPS II cases, in line with the rarity of the condition. The data were therefore highly uncertain. The naïve indirect comparison was highly biased, as the newborn screening data have been collated over a more recent time period (2017 - 2023) than the studies on diagnosis without NBS (1977 - 2024), and improvements made to healthcare systems worldwide over time may therefore bias the comparison in favour of NBS.

A total of 16 studies (10 case-control studies, 2 retrospective cohort studies and 3 prospective cohort studies and 1 study that included both case-control data and prospective cohort data for a NBS program) met the inclusion criteria for assessing the test accuracy of NBS methodologies for the detection of newborns with MPS II. 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 68 studies (61 case series, 4 case reports, 2 case-control studies and 1 retrospective cohort study) were included in the section on 'Linked evidence of change in management'. The bulk of the evidence was reporting on the age at diagnosis or treatment of patients with MPS II 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.

PICO Set 2 – Family members

Only one publication by Burton et al (2023) reported on the effectiveness and safety of testing of family members following identification of the index case by NBS for MPS II.

A further 25 studies (case series and case reports) reported on results of family member testing following diagnosis of the proband with symptoms of MPS II and how this information was used.

Table 2 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
PICO Set 1			
Direct from test to health outcomes	No direct comparative evidence. NBS screening studies that reported on outcomes for those MPS II cases diagnosed Hunter Outcome Survey – MPS II registry data	☒ k=5 case series (4 NBS, 1 no NBS n= 10 (NBS); n= 800 (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=10 n=10,946 ☒ k=4 n=1,479,601 ☒ k=2 n=133,491	High risk of verification bias
Change in patient management	Case series Case report Historical control study Retrospective cohort study	☒ k=61 n= 4,945 ☒ k=4 n=4 ☒ k=2 n=184 ☒ k=1 n=20	High risk of bias
Health outcomes	Case Series Historical control study Retrospective cohort studies	☒ k=25 n= 1,682 ☒ k=2 n=47 ☒ k=3 n=97	High risk of bias
PICO Set 2			
Testing of family members	Case Series	☒ k=26 n= 509	High risk of bias

k = number of studies; n = number of patients; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening

11. Comparative safety

PICO Set 1 - Newborns

Safety of testing

No direct evidence was identified on the safety of NBS for MPS II. 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 II, the safety impact of the test itself is likely to be negligible.

Safety of surgery with/without knowledge of MPS II status

Serious manifestations and complications that develop in individuals diagnosed with MPS II often require surgical intervention. Risks associated with surgery have been identified for individuals with MPS II, as airway management and tracheal intubation in MPS II patients are reported to be challenging, interfering with their ability to remain sufficiently ventilated during anaesthesia. The analysis of approximately 100 patients in the Hunter Outcome Survey (HOS) registry indicated that 22% of patients were reported to have difficulties with intubation during surgical procedures. 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 II. Nevertheless, if a patient is recognised preoperatively to have MPS II, a well-prepared team of anaesthesiologists and

surgeons can be primed for any surgical intervention required and would know to use specific ventilatory support techniques that are recommended for patients with MPS II.

The rate of surgical procedures performed without knowledge of MPS II status is expected to reduce to zero once sufficient time has passed after the introduction of NBS for MPS II. 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 II diagnosis), should reduce.

Safety of having a diagnosis prior to symptom-onset

The harms associated with knowing a diagnosis or being a “patient in waiting” for patients with attenuated disease, especially those with the late onset attenuated forms of MPS II, 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 conditions that have a late/adult-onset subtype. However, recent publications argue that providing parents with information about later-onset subtypes of genetic conditions, especially when potential harms can be mitigated and lead to better management of the condition, can be beneficial and serve the child's best interests. The earlier diagnosis, coupled with adequate and appropriately delivered information, would permit parents and patients to face their diagnosis, empowered not only in the decision-making process and facilitated access to treatment, but also in the potential to make more informed family planning decisions.

In addition to the potential psychological harm of creating “patients in waiting”, long-term monitoring of presymptomatic patients identified through NBS may carry physical safety risks. Monitoring procedures, such as imaging modalities, often involve exposure to radiation or sedation, which can be potentially harmful, especially in young children. For patients with attenuated MPS II, early diagnosis through NBS leads to years of clinical surveillance before symptoms appear, subjecting them to repeated investigations. Without NBS, these individuals would only undergo diagnostic and monitoring procedures after symptom onset, potentially reducing their cumulative exposure to the risks associated with early and prolonged monitoring.

Safety of early vs late ERT

The safety of early versus late ERT was considered, and fewer infusion-related adverse events (IRAEs) were observed in older patients (cut-off 6 - 12 years). Studies indicated that one of the factors associated with the occurrence of IRAEs was the immunogenic response to ERT treatment. Although not all IRAEs are antibody-mediated, immunogenicity can increase the risk of IRAEs. Two articles showed that more than half (53 – 59%) of younger patients (< 12 years of age) were antibody-positive (Ab+) at baseline, and therefore had a greater risk of experiencing IRAEs than antibody-negative (Ab-) patients. Additionally, the severity of MPS II was also associated with a higher risk of IRAEs; younger patients were more likely to have null variants resulting in both the severe form of disease and the increased likelihood of developing antibodies, and to experience higher proportion of IRAEs. It is unknown whether the higher rate of IRAEs observed in younger patients diagnosed following early symptom onset and treated with ERT would also be observed if the patients were to be diagnosed via NBS.

Safety of early vs late HSCT

Insufficient information on early versus late HSCT was available to make a comparison regarding the impact that the timing has on the safety of the procedure. In Taiwan, 2 of 4 patients

identified through NBS reported adverse events after treatment with HSCT following ERT. One of these two patients died at the age of 0.6 years after infection and sepsis¹⁵.

In Australia, REDACTED out of REDACTED patients with MPS II who received HSCT had graft vs host disease, and no transplant-related deaths were recorded.

PICO Set 2 - Family members

Testing of family members after NBS is expected to have no additional safety concerns compared to testing of family members after clinical identification of the index/proband after symptom onset.

12. Comparative effectiveness

PICO Set 1 - Newborns

Direct from test to health outcomes evidence

No comparative direct evidence was available.

Four case series were identified on NBS programs, with a total of 1,479,601 newborns screened. From these studies, a total of 21 newborns were identified to potentially have MPS II. Of these 21 cases:

- 5 were identified to have a neuronopathic phenotype and 4 were non-neuronopathic based on genotype and/or evaluation of other family members. In 12 cases, the phenotypes could not be established due to the patients having variants of uncertain significance (VUS).
- Only 10 received treatment (all received ERT) and had their management described in literature. 3 patients also received HSCT afterwards, one of whom died at 0.8 years of age due to infection and sepsis. All other patients were still alive at the end of follow-up (differed for each patient).

In comparison, data on survival in those who did not undergo NBS were gained from the HOS registry, which reported that 84% of those who had received ERT were alive at the last recorded routine visit in 2016. The median follow-up time from birth to last visit was 13 years (95% CI: 12.3 - 13.8 years) for treated patients. Due to the small amount of data from those diagnosed due to NBS, it was difficult to compare the health outcomes of patients diagnosed through NBS and without NBS. This naïve indirect comparison was at risk of bias given the potential for confounding factors that may influence the results (in either direction) and the risk that healthcare systems have improved over time (favouring NBS).

A linked-evidence assessment was therefore used to supplement the direct evidence.

¹⁵ Lin, HY et al. (2022). Newborn Screening Program for Mucopolysaccharidosis Type II and Long-Term Follow-Up of the Screen-Positive Subjects in Taiwan. *J Pers Med* 12(7):6-21.

Linked evidence of test accuracy

Diagnostic accuracy of first-tier fluorometric enzyme activity testing for detecting MPS II as part of a NBS program

Five case-control studies reported on the diagnostic accuracy of the fluorometric assay compared with a clinical confirmatory diagnosis. Two studies used an automated digital microfluids (DMF) platform to perform the fluorometric test. Four studies used control DBS samples from newborns. The other study used healthy controls aged over 18 years. The positive DBS samples all came from MPS II patients who had been clinically diagnosed, but the age range and severity of disease were not reported for all of these patients.

None of the studies reported a false negative result and only 2 of the 5 studies reported any false positive results. A meta-analysis using STATA 18.0 was conducted to determine the pooled specificity of NBS using a fluorometric IDS enzyme assay compared with a clinical diagnosis. The pooled sensitivity was 100% for all studies (data not shown) and the pooled specificity value (Figure 1) was 99.8% (95% CI 90, 100).

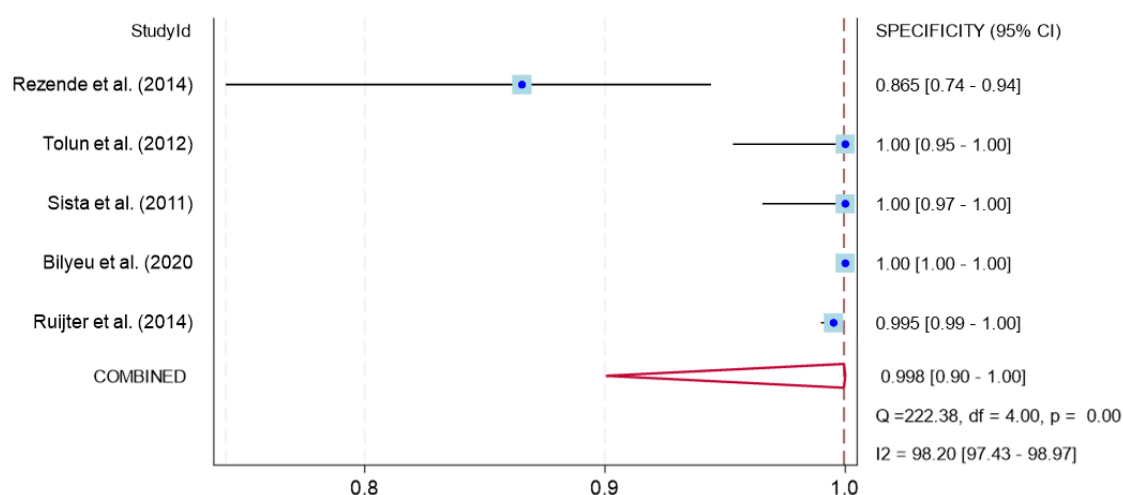


Figure 1 Forest plot showing the pooled specificity of the fluorometric IDS enzyme assay compared with a clinical diagnosis.

CI = confidence interval

Diagnostic accuracy of first-tier MS/MS enzyme activity testing for detecting MPS II as part of a NBS program

Two case-control studies reported on the diagnostic accuracy of first-tier LC-MS/MS enzyme activity testing compared with a clinical confirmatory diagnosis. The 2 x 2 data from each study were summarised in Table 3. Both studies used control DBS samples from newborns. The positive DBS samples all came from MPS II patients who had been clinically diagnosed, but the age range and severity of disease were not reported for all patients.

There were no false negative results, giving a sensitivity of 100% for both studies. Only 3 out of a total of 816 newborn DBS samples were false positive, giving an overall specificity of 99.6%.

Table 3 The sensitivity and specificity of MS/MS enzyme activity testing for MPS II

Study Country	Population	MS/MS test cutoff	Confirmatory Diagnosis	TP	FP	FN	TN	Sensitivity	Specificity
Oguni et al (2020) Japan	N=762 DBS from newborns collected during routine NBS N=14 DBS from patients diagnosed with severe MPS II	LC-MS/MS Cutoff NR	Tests NR	14	3	0	759	100%	99.6%
Wang et al. (2007) USA	N=57 DBS from randomly chosen newborns. N=13 DBS from MPS II patients	EIS-MS/MS Cutoff value NR	Tests NR	13	0	0	57	100%	100%

CI = confidence interval; DBS = dried bloodspot; EIS-MS/MS = electrospray ionisation mass spectrometry; FN = false negative; FP = false positive; LC = liquid chromatography; LC-MS/MS = liquid chromatography- tandem mass spectrometry; MPS II = mucopolysaccharidosis Type II; MS = mass spectroscopy; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NR = not reported; TN = true negative; TP = true positive; USA = United States of America

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

Four studies provided results from 4 NBS programs from Japan, Taiwan and 2 USA states that enabled the screen positive rate (SPR), false positive rate (FPR) and the positive predictive value (PPV) to be calculated ^{14,16,17,18}. The difference between the SPR and the FPR did not equal the true positive rate (TPR), as this included newborns that did not yet have a definitive diagnosis or were lost to follow-up. The PPV was calculated by dividing the TPR (per 100,000) by the SPR (per 100,000). The results from these studies were summarised in Table 4.

¹⁶ Bilyeu, H et al. (2020). Validation and Implementation of a Highly Sensitive and Efficient Newborn Screening Assay for Mucopolysaccharidosis Type II. *Int J Neonatal Screen* 6(4).

¹⁷ Burton, BK et al. (2023). Newborn screening for mucopolysaccharidosis type II: Lessons learned. *Mol Genet Metab* 140(1):107557.

¹⁸ Hattori, Y et al. (2023). Frequency of iduronate-2-sulfatase gene variants detected in newborn screening for mucopolysaccharidosis type II in Japan. *Mol Genet Metab Rep* 37:101003.

Table 4 The SPR, FPR, TPR and PPV for MPS II detection for NBS programs

Study/Country	Population	Test	Number TP and FP	Screen positive and FP rates
Bilyeu et al. (2020) Missouri, USA	N= 146,954 DBS from newborns	Fluorometric enzyme assay Retest in duplicate	2 MPS II (also had positive family history) 22 FP 5 lost to follow-up	SPR=29/146,945 (0.02%) FPR=22/146,945 (0.015%) TPR=1/73,477 or 1.4/100,000 newborns
Burton et al. (2023) Illinois, USA	N=586,323 DBS from newborns	UPLC-MS/MS IDS enzyme assay	8 MPS II (3 severe, 4 attenuated, 1 unknown) 63 FP 5 unresolved	SPR=76/586,323 (0.012%) newborns FPR=63/586,323 (0.011%) TPR=1/73,290 or 1.4/100,000 newborns
Hattori et al. (2023) Japan	N=197,700 DBS from newborns	Fluorometric enzyme assay Recall for second DBS sample	1 MPS II 111 FP 10 lost to follow-up	SPR=122/197,700 (0.062%) FPR=111/197,700 (0.056%) TPR=1/197,700 or 0.5/100,000 newborns
Lin et al (2022) Taiwan	N=548,624 DBS from newborns	LC-MS/MS IDS enzyme assay	10 MPS II 192 FP (normal GAGs)	SPR=202/548,624 (0.037%) FPR=192/548,624 (0.035%) TPR=1/54,862 or 1.8/100,000 newborns
All NBS programs	N=1,479,601 DBS from newborns k=4		21 MPS II	SPR=0.029% (0.012–0.062) =29/100,000 newborns FPR=0.026% (0.011–0.056) =26/100,000 newborns TP=21; TPR=1.42/100,000 newborns PPV=4.89%

DBS = dried bloodspot; FP = false positive; FPR = false positive rate; IDS = iduronate 2-sulphatase; LC = liquid chromatography; LC-MS/MS = liquid chromatography- tandem mass spectrometry; MPS II = mucopolysaccharidosis Type II; MS = mass spectroscopy; MS/MS = tandem mass spectrometry; k = number of studies; N = number of study participants; NBS = newborn bloodspot screening; PPV = positive predictive value; SPR = screen positive rate; TP = true positive; TPR = true positive rate; UPLC-MS/MS = ultra-pure liquid chromatography- tandem mass spectrometry; USA = United States of America

The median SPR for all 4 NBS programs was 0.029% (range 0.012–0.062%). This equated to 29 positive NBS screens per 100,000 newborns tested. The median FPR for all 4 NBS programs was 0.026% (range 0.011–0.056%). Overall, the NBS programs had a PPV of 4.89%.

There were 21 newborns with MPS II detected among a total of 1,479,601 newborns screened. This equated to 1.42 per 100,000 newborns being diagnosed with MPS II via NBS 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 1776. 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 yet been published. The only published report of using NRE-GAG analysis on DBS is a case-control study with a small sample size (n=45; 7 with MPS I), reporting 100% sensitivity and specificity¹⁹. Thus, the accuracy of using this methodology for second-tier screening is uncertain due to the limited volume of data.

¹⁹ Herbst, ZM et al. (2022). Evaluation of Two Methods for Quantification of Glycosaminoglycan Biomarkers in Newborn Dried Blood Spots from Patients with Severe and Attenuated Mucopolysaccharidosis Type II. *Int J Neonatal Screen* 8(1).

However, one study reported on the use of GAG digestion (another method of GAG disaccharide analysis) as a second-tier assay in an NBS program²⁰. The FPR in this study was 0%. This would improve the PPV from the current 4.89% to 100%. Thus, GAG disaccharide analysis could provide a promising second tier assay that would largely, if not entirely, eliminate false positives and reduce the number of newborns requiring clinical evaluation.

Summary

Australian NBS programs would most likely use an IDS enzyme assay as a first-tier test and include retesting of any DBSs with low enzyme activity as part of the screening algorithm. When the outcomes from the four NBS programs included in this report were analysed, it was found that 29/100,000 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 87 DBS samples using a second-tier test, which would most likely be the NRE-GAG test and would most likely occur in the NRL in Adelaide. The NRE-GAG test is expected to eliminate all false positive results such that only those who have MPS II would be recalled for clinical confirmatory diagnosis. This would result in the NBS programs in Australia having a PPV and NPV of (or very close to) 100%. Worldwide, 1.42 cases of MPS II per 100,000 newborns screened were detected via NBS programs. Assuming that the overseas data are applicable to Australia, this would indicate that approximately 4 cases of MPS II per year would be identified across Australia via the NBS programs.

Linked evidence of change in management

A total of 68 studies met the inclusion criteria for assessing change in management following diagnosis of MPS II through NBS (k=5) compared with no NBS (k=63).

Time to diagnosis

No studies were identified that reported on the presence of a diagnostic delay in patients with MPS II who were diagnosed through NBS. On the contrary, 13 case series were identified that reported on the length of time from the onset of clinical signs and symptoms to diagnosis for patients with MPS II who were diagnosed without NBS (Table 5). The median time between symptom onset and diagnosis for severe (neuronopathic) cases from 4 case series involving 350 cases was 1.5 years (range 0 – 9.2 years). The median time between symptom onset and diagnosis for attenuated (non-neuronopathic) cases from 6 case series involving 284 cases was 2.03 years (range 0 – 18 years). From 3 small case series reporting on 26 patients in which cases were not classified into severe or attenuated types, the overall median time to diagnosis was 2.5 years (range 0 – 19 years).

Those affected with the attenuated phenotype of MPS II experienced a longer diagnostic delay (by around 6 months longer median time and almost double the upper limit of the range), compared to those with the severe phenotype. Moreover, individuals with attenuated disease also experience mild neurocognitive impairment without regression which can manifest as poor adaptive skills, neurocognitive difficulties, and attention difficulties, therefore, classification of cases as attenuated/non-neuronopathic varied across studies.

²⁰ Stapleton, M et al. (2020). Newborn screening for mucopolysaccharidoses: Measurement of glycosaminoglycans by LC-MS/MS. *Mol Genet Metab Rep* 22:100563.

Table 5 Time to diagnosis in the absence of NBS

Phenotype	Number of studies	Number of patients	Median time from symptom onset to diagnosis
Neuronopathic (severe)	4	350	1.5 years (range 0 – 9.2 years)
Non-neuronopathic (attenuated)	6	284	2.03 years (range 0 – 18 years)
Not Specified	3	26	2.5 years (range 0 – 19 years)

NBS = newborn bloodspot screening

Age at Diagnosis via NBS compared to no NBS

A naïve comparison of the age of diagnosis in the presence or absence of NBS was undertaken. One study reported on the median age at diagnosis since the introduction of NBS in Taiwan in 2016. This included 6 patients diagnosed with MPS II due to NBS at a median age of 0.15 years (range: 0.1 – 0.2 years) between 2016 and 2019²¹.

Based on data from a case series (n=6)²², the Australia and New Zealand Transplant & Cellular Therapies (ANZTCT) registry patients who received HSCT (n=REDACTED), and MPS II patients who received ERT via the LSDP from 2014 – 2024 (n=REDACTED), the median age at diagnosis of MPS II was REDACTED (range REDACTED) in Australia.

Globally, in 12 case series (n = 402), the median age at diagnosis for severe disease cases was 3.1 years (range 0.5 – 14). The median age at diagnosis for cases of attenuated disease was reported in 9 case series (n= 130) was significantly higher than severe disease cases (median 6 years, range 2.9 – 14). In 9 case series where cases were not classified into severe or attenuated type, the median age of diagnosis was 3 years (range 0 – 59.7 years). Two patients were diagnosed at the age of 53 and 59.7 years; these may be considered outliers. If these are excluded, the age range was 0 – 22 years. The results are summarised in Table 6.

NBS would result in earlier diagnosis for all three phenotypes, but the length of time between when individuals would be diagnosed due to NBS and when they would be diagnosed without NBS varied between phenotypes. Given the age at diagnosis for attenuated MPS II types, some of these individuals may require decades of follow-up before symptoms emerge.

Table 6 Age at diagnosis of MPS II in the presence or absence of NBS

Phenotype	Number of studies	Number of patients	Median age at diagnosis
Without NBS			
Neuronopathic (severe)	12	402	3.1 years (range 0.5 – 14 years)
Non-neuronopathic (attenuated)	9	130	6 years (range 2.9 – 14 years)
Not Specified	11	1,032	3 years (range 0 – 59.7 years)
With NBS			
Not Specified	1	6	0.16 years

NBS = newborn bloodspot screening

²¹ Lin, HY et al.(2020a). Survival and diagnostic age of 175 Taiwanese patients with mucopolysaccharidoses (1985-2019). *Orphanet J Rare Dis* 15(1): 314.

²² Crowe, L et al. (2017). Cognitive and behaviour profiles of children with mucopolysaccharidosis Type II. *Cogn Neuropsychol* 34(6):347-356.

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

A naïve comparison of the age at treatment initiation in the presence or absence of NBS was undertaken. The results are summarised in Table 7.

Four case series (1 from Taiwan, 1 from Japan and 2 from US (Illinois)) reported on the median age at treatment initiation for MPS II patients diagnosed through NBS. The overall median age at treatment initiation after diagnosis via NBS was 0.25 years (range 0.08 – 1 years).

In Australia and New Zealand, the median age at first HSCT between 2009 and 2024 was **REDACTED** (range **REDACTED**), which was on average **REDACTED** after diagnosis (range **REDACTED**) in the absence of NBS (ANZTCT registry data). Furthermore, the median age at treatment initiation for ERT in MPS II patients in Australia was also calculated using the LSDP data for **REDACTED** patients from 2014 – 2024 in the absence of NBS. The median age of MPS II patients when they first receive ERT was estimated to be **REDACTED** (range **REDACTED**), which was on average **REDACTED** after diagnosis (range **REDACTED**).

Globally, from 8 case series (n= 144) the median age at treatment initiation for patients diagnosed with the severe (neuronopathic) form of MPS II was 5.1 years (range 0.13 – 12.1 years). On the contrary, 6 studies (n=88) reported the median age at treatment initiation for patients with the attenuated (non-neuronopathic) form of MPS II in the absence of NBS to be 7.5 years (range 0.13 – 25.3 years).

The difference in age at time of treatment initiation 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 II receiving treatment (ERT ± HSCT) at an earlier age.

However, as treatment of MPS II in Australia is limited to treatment of symptoms as they occur, it is uncertain what health benefit earlier diagnosis via the NBS would provide for patients diagnosed with the attenuated phenotype, 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 II attenuated disease, there is likely to still be value in having an early diagnosis of attenuated disease, due to the avoidance of diagnostic delay).

Table 7 Age at treatment initiation in the presence or absence of NBS

Phenotype	Number of studies	Number of patients	Median time from symptom onset to diagnosis
Without NBS			
Neuronopathic (severe)	8	144	5.1 years (range 0.3 – 12.1 years)
Non-neuronopathic (attenuated)	6	88	7.5 years (range 0.13 – 25.3 years)
Not Specified	11	1,237	7 years (range 0 – 32.2 years)
With NBS			
Not Specified	4	6	0.25 years (range 0.08 – 1 year)

NBS = newborn bloodspot screening

Is genotype predictive of phenotype in MPS II?

A total of 27 studies met the inclusion criteria for assessing the relationship between genotype and phenotype in mostly males with MPS II. A further 17 studies were identified to assess the genotype/phenotype relationship in females with MPS II. If genotype is predictive of the severity

of MPS II, this information could be used for earlier access to ERT via the LSDP (for patients aged under 5 not yet displaying symptoms) and may guide other management decisions.

Overall, 64–75% of patients with an identifiable variant in the *IDS* gene had severe disease. Only those with major changes, such as recombination events between *IDS* and the *IDS2* pseudogene and large deletions and/or insertions (of at least 1 exon) of the *IDS* gene were much more likely to have severe disease (92.8–100%) than attenuated disease.

However, predicting the phenotype for small deletions/insertions leading to frameshift variants, intronic or splicing variants, nonsense variants and missense variants (e.g. the splicing variant, c.1122C>T, the nonsense variants, R172* and R443*, and the missense variants, S333L and R468Q) was complicated because these occurred in patients with different phenotypes, i.e. in those diagnosed with severe or attenuated disease, and in those with or without cognitive impairment. That is, the same genotype was associated with multiple different phenotypes, meaning that phenotype could not be predicted with any confidence based on the genotype. The reasons for this are uncertain. It may partly be due to differences in the definitions of severe and attenuated disease, and cognitive impairment. Variable penetrance may also indicate the involvement of other factors, such as genetic modifiers or environmental influences. Overall, small deletions/insertions leading to frameshift variants, intronic or splicing variants, nonsense variants and missense variants had similar probabilities of having severe disease (48.8–87.2%) to the overall population (64.1–75.4%).

Thus, predicting the severity of MPS II based on the genotype of a newborn, with no family history of MPS II, is uncertain and may be insufficient for gaining earlier access to ERT via the LSDP, which requires a clear prediction of disease severity, before symptoms arise.

Females with MPS II are most likely to be heterozygous with skewed X chromosome inactivation, that inactivates the normal *IDS* gene. Moreover, the types of pathogenic variants found in females with MPS II are similar in type and proportion (when allowing for the extremely small sample size) to those identified in males. This suggests that the carrier status of female newborns with low *IDS* enzyme activity and a heterozygous phenotype should be confirmed using NRE-GAG analysis and emphasises the importance of including second-tier NRE-GAG testing for detection of MPS II via the NBS.

Linked evidence of health outcomes

Worldwide, 1.42 cases of MPS II per 100,000 newborns were detected via NBS programs, indicating that approximately 4 cases of MPS II per year would be identified across Australia via the NBS programs. Two to three of these cases would have the severe phenotype and one to two cases every year would have the attenuated phenotype.

Effectiveness of early vs late ERT in MPS II

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

Severe Disease

Most of the studies reporting on the impact of early versus late initiation of ERT focused on MPS II patients with severe disease only.

A case series investigated the possible survival benefit of early initiation of ERT in 17 MPS II patients. The authors defined “early” treatment group based on the disease stage rather than the age at treatment initiation. The early treatment group (stage 2) patients had mild developmental

delays due to physical or motor disabilities and could independently perform tasks in daily life, whereas the late treatment group was defined as patients for whom the treatment was initiated at stage 4 or later (when patients were already bedridden and required advanced medical care). Only 1 out of 9 patients in the early treatment group had disease progression with no mortality whereas in the late treatment group 6 out of 8 patients had further disease progression and 3 of them died. This suggested that late initiation of ERT (after the patient is already stage 4 or more severe) may have a limited impact on slowing progression. Furthermore, the improved survival in the early treatment group observed in this study may also be due to the lead time bias as patients at an earlier stage of disease are less likely to die regardless of the treatment.

One case series reported on the influence of age at time of ERT initiation on quality of life. In a sibling pair case series, parents perceived better quality of life in the younger sibling who was diagnosed pre-symptomatically due to cascade testing and started ERT at 13 months of age, compared to his older brother who started ERT at 3.9 years.

Two sibling case series analysed the impact of pre-symptomatic versus post-symptomatic treatment on neurological manifestations in younger versus older siblings. These studies reported that younger siblings who had ERT at an earlier age (pre-symptomatically) were significantly more likely to have better cognitive development than those who had ERT at a later age (post-symptomatically). In these studies, two elder siblings had a low developmental and intelligent quotient score at baseline. After receiving treatment at 3 years and 7.5 years of age respectively, no stabilisation or improvement in neurological symptoms was observed with ERT in elder siblings. On the contrary, their younger siblings who were diagnosed pre-symptomatically and received treatment at 3 and 4 months of age continued to have normal psychomotor development after 3 - 4 years of follow-up.

Only limited data on the impact of ERT on different health outcomes such as growth or motor development in younger children (usually < 5 years of age) were available due to the difficulty in performing meaningful evaluations in young children. Limited data from the sibling studies showed that, although the use of ERT did not prevent somatic and neurological manifestations of MPS II in general, earlier treatment can slow the progression of the disease. ERT improved growth rates to a similar degree in younger versus older groups, but the benefits tended to be slightly higher in those who had treatment initiated at an earlier age. Early initiation of ERT may also slow the progression of cardiovascular disease, but due to limited data the benefits could not be quantified. One recent study reviewed the medical charts of MPS II patients across 19 sites in the US and identified an overall trend for lower cardiovascular disease burden in patients who initiated ERT before 3 years of age as compared to other patients who started ERT at an older age (> 3 years of age)²³.

Attenuated Disease

There was a scarcity of evidence on the impact of early versus late initiation of ERT in MPS II cases with attenuated disease. Overall, four case series were identified that reported on the impact of ERT on health outcomes of MPS II patients with attenuated disease.

Shapiro et al. assessed quality of life using the Child Health Questionnaire PF-50. Psychosocial wellbeing was similar to population norms (for all MPS II patients with attenuated disease) but physical functioning differed based on the age at time of HSCT, with physical wellbeing lower than the normative average for children older than 12 years of age (mean (standard deviation, SD): 26.53 (9.45)).

²³ Yee, KS et al. (2022). Impact of the Timing of Enzyme Replacement Therapy Initiation and Cognitive Impairment Status on Outcomes for Patients with Mucopolysaccharidosis II (MPS II) in the United States: A Retrospective Chart Review. *J Health Econ Outcomes Res* 9(2):67-76.

Two case series identified greater improvement in growth patterns in patients with attenuated disease as compared to patients with severe disease. The ERT may have less impact on patients with a severe form due to the severe dysostosis multiplex, hepatosplenomegaly and malnutrition caused by poor oral intake due to dysphagia observed in MPS II patients with severe disease.

Conversely, Tomanin et al.²⁴ identified that the positive impact of early initiation of ERT on organomegaly was more pronounced in severe MPS II cases. The authors indicated that these results could be explained by the presence of more advanced clinical signs in severe patients at start of treatment, for which an amelioration due to ERT could be more evident. For example, there were no significant signs of organomegaly in patients with attenuated cases at baseline, thus no improvement or deterioration was seen after ERT.

Overall, the applicability of these findings to the comparison of NBS vs no NBS is unknown, as in the absence of NBS, the median age of ERT initiation is **REDACTED** years. Both early and late treatment groups in these studies were later than the current practice.

Effectiveness of early vs late HSCT in MPS II

The states and territories fund the use of domestically-sourced haematopoietic stem cells (HSCs) (autologous or allogeneic) whereas the Commonwealth holds responsibility for funding overseas-sourced HSCs. The current guidelines for the Commonwealth Bone Marrow Transplant Program state that MPS II is not a condition which meets the eligibility for routine funding of overseas transplant searches and costs of collection and transport of transplant tissue - any application would need to be considered on individual merit.

There is limited information available regarding the long-term outcomes of early versus late initiation of HSCT for MPS II patients who were diagnosed after the onset of symptoms. Three case series (including two sibling studies) provided data on the impact of early versus late initiation of HSCT on health outcomes. From the ANZTCT registry, **REDACTED** patients received HSCT for MPS II from 2009 – 2024 at a median age of **REDACTED** (range **REDACTED**). The median time from diagnosis to receiving HSCT was **REDACTED**. There were insufficient data from the registry to be able to compare health outcomes for patients with MPS II who had received HSCT at different ages.

The very limited data available did not identify any clear benefit of early initiation of HSCT on the outcomes of survival, quality of life, hearing, vision, cardiac disease, respiratory disease, or organomegaly. In two sibship studies, two younger siblings had pre-symptomatic initiation of HSCT at 2 years and 70 days, whereas older siblings received transplant at 5 and 6 years, respectively. The pre-symptomatic initiation with HSCT tended to have a positive impact on the physical and motor development of patients with MPS II. In comparison to older siblings who were diagnosed after the onset of symptoms, younger siblings who were diagnosed and initiated HSCT pre-symptomatically had normal motor development and met the majority of growth milestones.

One case series assessed the cognitive development in 18 MPS II patients with a severe phenotype who received HSCT using the Activities of Daily Life (ADL) questionnaire. This questionnaire assessed the basic motor skills needed for movement, daily activities and cognition. Patients who received HSCT at ≤ 5 years of age had better cognitive and neurodevelopment scores than patients older than 5 years of age at treatment initiation²⁵.

²⁴ Tomanin, R et al. (2014). Clinical efficacy of enzyme replacement therapy in paediatric Hunter patients, an independent study of 3.5 years. *Orphanet J Rare Dis* 9:129.

²⁵ Tanjuakio, J et al. (2015). Activities of daily living in patients with Hunter syndrome: impact of enzyme replacement therapy and hematopoietic stem cell transplantation. *Mol Genet Metab* 114(2):161-169.

Clinical claim

For individuals with severe MPS II, the addition of MPS II to NBS programs would result in superior effectiveness and non-inferior safety to diagnosis after symptom onset, due to the superior effectiveness of earlier treatment, and the benefit in avoiding a diagnostic delay.

For individuals with attenuated MPS II, use of NBS would result in potentially superior effectiveness (due to avoidance of a diagnostic delay and possible benefits of earlier ERT) and inferior safety compared to no NBS (due to some risks associated with continuous clinical surveillance (i.e. radiation, sedation) and psychological impact of an uncertain diagnosis and creating patients-in-waiting).

PICO Set 2 - Family members

From the case series identified, it was not possible to draw any conclusion regarding the uptake rate of testing by families of a proband/index case, because for index cases (confirmed laboratory diagnosis in the absence of signs/symptoms), the number of family members tested for each newborn was not stated, whereas for probands (confirmed diagnosis including signs/symptoms and laboratory diagnosis), many studies reporting testing included segregation analysis of the *IDS* variant identified in family members as part of the diagnostic follow-up of individuals with or at risk of MPS II.

Studies also showed that testing of family members proved valuable in confirming *IDS* pseudodeficiency in certain newborns. This was highlighted by a case in which the maternal grandfather, who exhibited no clinical signs of MPS II, shared the same biochemical and molecular test results for MPS II as the screened newborn, indicating a predicted *IDS* pseudodeficiency.

In the case series reporting outcomes of testing mothers of symptomatic probands diagnosed with MPS II, approximately 70–80% were confirmed as carriers, aligning with the known frequency of familial and *de novo IDS* variants²⁶. Studies suggested that the prevalence of somatic and/or germline mosaicism in single MPS II cases caused by *de novo IDS* variants may be underestimated. Therefore, genetic testing should be extended to all at-risk family members and that prenatal diagnosis should be offered, even when the mother of an isolated MPS II case has a normal *IDS* genotype.

The case series reviewed indicated that when parents were aware that their child had MPS II, they would use reproductive planning options, such as preimplantation genetic diagnosis (PGD) or prenatal testing, for future pregnancies. Advancements in diagnosis, multidisciplinary care, and treatments like ERT and HSCT have improved life expectancy of individuals with MPS II. As a result, a growing number of adult MPS II patients are starting families or exploring their family planning options. When the index case is diagnosed due to NBS, no subsequent children would have been conceived prior to the parents' receiving information regarding the mother's carrier status. However, if the proband is diagnosed due to clinical symptoms (at a median of 3.1 years of age), there is the possibility of further children having been conceived/born prior to receiving this information. The ability for genetic testing to occur at an earlier timepoint due to NBS rather than clinical symptoms is therefore important for allowing reproductive planning.

For mothers confirmed as MPS II carriers, PGD and prenatal testing are offered for future pregnancies. However, due to the possibility of germline mosaicism, even non-carrier mothers should receive family planning advice, including access to PGD or prenatal testing. If a proband is

²⁶ Vafiadaki, E et al.(1998). Mutation analysis in 57 unrelated patients with MPS II (Hunter's disease). *Arch Dis Child*79(3):237-241.

diagnosed with MPS II, and their mother is pregnant again already, prenatal testing may be necessary, to diagnose/rule out the condition in the foetus. All siblings of the index case who could be affected or carriers of MPS II would likely be older than the newborn.

In 2021, the average fertility rate for Australian women who had at least one child, was 1.9 children²⁷. It could therefore be assumed that in approximately half of cases where a child is identified as having MPS II, the family would already have had one prior child (and their family would be complete), and in the remaining cases, the family wishes to have a subsequent child. Therefore, if four MPS II cases are diagnosed annually in Australia, it is estimated that in two of these cases, the parents may explore reproductive planning for future children, and in the other two cases of a newborn diagnosed with MPS II, there may be an older sibling who would benefit from an earlier diagnosis.

Clinical claim

Based on the evidence identified, testing of family members after index case identification through NBS is superior to testing of family members after proband identification after symptom onset. This is because the information is obtained at an earlier timepoint, which increases the likelihood of it being useful for reproductive planning.

13. Economic evaluation

Overview

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

A cost analysis was conducted to estimate the costs associated with testing of family members per affected newborn. MSAC acknowledged that the potential for family members to use carrier status to alter reproductive decisions or allow prenatal testing should be considered, but the extent to which this would occur was not quantified in the DCAR.

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

NBS for MPS II would result in a diagnosis within the first month or two of life, which is earlier than the usual time of diagnosis through clinical identification for all MPS II phenotypes (severe and attenuated).

A literature review was performed to identify any published economic evaluations relevant to the economic question or to inform the structure and/or inputs for an economic model; no studies were identified that were relevant to inform the economic evaluation.

The economic evaluation was a decision tree analysis incorporating estimates of the prevalence of MPS II with and without NBS, the performance of screening tests and at the conclusion of the diagnostic process, those with MPS II are classified into severe, attenuated and very attenuated phenotypes. The modelled time horizon for the decision tree analysis was REDACTED years at

²⁷ Qu, L & Baxter, J 2023, Births in Australia, Australian Government, Canberra.

which time all affected cases of MPS II who would be identified are diagnosed either through NBS or clinical identification.

It is expected that the prevalence of MPS II in Australia would increase if NBS for MPS II is implemented, as seen in other jurisdictions (Table 4). As NBS does not increase the true underlying prevalence of MPS II, the economic model assumes that clinical identification of MPS II does not identify a certain proportion of MPS II cases. The model further assumes that these unidentified cases are “very attenuated” MPS II cases, based on reports in the literature that these cases were identified through cascade testing initiated by a familial index case (rather than due to presentation of signs or symptoms), and speculation that NBS identifies a greater proportion of attenuated cases by scholars in NBS jurisdictions^{14,28,29}.

An exploratory extension to the decision analytic model assumed that there are survival benefits associated with early diagnosis of severe MPS II, and attempted to quantify these over a lifetime time horizon (100 years). Attenuated patients are not modelled in the exploratory analysis (in either arm) as it is assumed that NBS would not result in survival benefits or improved quality of life for these patients. This was based on the LSDP’s criteria that, unless a severe phenotype can be predicted for patients under 5 years of age, only symptomatic patients are eligible for access to treatment. Hence, the only difference in the timing of ERT initiation for attenuated patients between the modelled arms would be the length of the diagnostic delay (as NBS patients would be able to start ERT immediately following sufficient symptom onset whereas attenuated patients in the no NBS arm may only start the diagnostic delay process after symptom onset and then receive ERT on completion of the diagnostic delay or, in some cases of very attenuated disease, may not be correctly diagnosed and would not receive ERT). There was no data to support additional survival for attenuated patients based on this uncertain and relatively small difference in the timing of ERT initiation. Similarly, differences in survival or quality of life for very attenuated patients were not modelled.

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

²⁸ Burton, BK et al.(2023). Newborn screening for mucopolysaccharidosis type II: Lessons learned. *Mol Genet Metab* 140(1):107557.

²⁹ Quaio, CR et al. (2012). Report of a Large Brazilian Family With a Very Attenuated Form of Hunter Syndrome (MPS II). *JIMD Rep* 4:125-128.

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 cases diagnosed with MPS II
Comparator	PICO Set 1: Diagnostic testing for MPS II 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: Cost-effectiveness analysis, cost consequences analysis, cost-utility analysis PICO Set 2: Cost consequences analysis
Outcomes	PICO Set 1: Newborns: <ul style="list-style-type: none"> • Direct effect (primary analysis for CEA): 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: <ul style="list-style-type: none"> • Early identification of affected cases and carriers. • Costs of additional testing of family members
Time horizon	Redacted years in the base case evaluation and for testing of family members. Based on the eldest age of diagnosis for an MPS II case in Australia reported in Redacted . A lifetime time horizon in the exploratory analysis (i.e. 100 years).
Computational method	Decision tree model for base case analysis and cost-consequences. Time-dependent state-transition Markov cohort model for the exploratory analysis.
Generation of the base case	Performed in one step as the structure of the model did not rely on building layers of uncertainty or multiple translations of the clinical evidence.
Health states	Not defined for the base case CEA, CCA and testing of family members Exploratory CUA: <ul style="list-style-type: none"> • Severe MPS II: alive, dead • Very attenuated MPS II: alive, dead
Cycle length	One year in the exploratory CUA.
Probabilities	<u>Base case analysis:</u> <ul style="list-style-type: none"> • Prevalence of MPS II: Prevalence of MPS II was based on the TPR of NBS of MPS II, sourced from the evidence review of published MPS II NBS studies. • Test performance: Performance of first-tier screening was as per linked evidence for test accuracy presented in the DCAR. Second-tier screening was assumed to have 100% sensitivity and specificity. <u>Exploratory analysis:</u> includes survival and health related quality of life gains associated with early access to ERT following NBS for severe MPS II patients based on the evidence review presented for health outcomes in the DCAR. Estimates were informed by: <ul style="list-style-type: none"> • The duration of 100% survival for early ERT treated patients (Tomita et al. 2021). • HR of late treated severe versus attenuated patients (Ueda & Hokugo 2020). • Late treated disease specific mortality (Burton et al. 2017). • ABS lifetables.
Discount rate	5% for both costs and outcomes (discounting rate of 0% and 3.5% applied in sensitivity analyses).
Software	Excel

ABS = Australian Bureau of Statistics; CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ERT = enzyme replacement therapy; HR = hazard ratio; LSDP = Life Saving Drugs Program; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; PICO = Population/Intervention/Comparator/Outcomes; TPR = true positive rate.

A high-level summary of the inputs used in the economic evaluation is presented in Table 9.

Table 9 Summary of the inputs used in the economic evaluation

Parameter	Value	Source
Population and health-related variables		
Estimated prevalence of MPS II in Australian newborns	1.42 per 100,000 newborns	Median true positive rate of NBS for MPS II in 4 jurisdictions (2 US states, Taiwan, Japan) which conduct NBS for MPS II (Table 4).
Clinical identification rate of MPS II in Australia	0.62 per 100,000 newborns	Prevalence rate among Australian live births (Chin & Fuller 2022) where cases were identified clinically.
Proportion of severe MPS II cases	33%	(75% of cases identified through clinical identification) ^a / true MPS II prevalence.
Proportion of attenuated MPS II cases	11%	(25% of cases identified through clinical identification) ^a / true MPS II prevalence.
Proportion of very attenuated MPS II cases	56%	(True MPS II prevalence minus cases identified through clinical identification) / true MPS II prevalence.
Test performance of LC-MS/MS IDS enzyme assay	Sensitivity: 100% FPR: 0.028%	Median screen positive rate minus the median true positive rate for all NBS studies using LC-MS/MS or fluorometric IDS enzyme assay as a first-tier test (Table 4) ^b .
Test performance of NRE-GAG analysis	Sensitivity: 100% FPR: 0%	The NRE-GAG assay has a reported sensitivity and specificity of 100%.
Family member tests per proband	5.22 (includes FDRs and SDRs)	Australian fertility rates and the prevalence of <i>de novo</i> IDS variants.
Costs		
Cost of first-tier testing with NBS	\$Redacted per screen	Based on the cost of testing by LC-MS/MS IDS enzyme assay using Redacted kit; estimated using consultation feedback provided by the NBS laboratory experts during the evaluation process.
Cost of second-tier testing with NBS	\$167.00	Price listed on SA Pathology 'Pathology Collection Guide' for NRE-GAG fragmentation analysis.
Cost for clinical diagnosis of MPS II (including the diagnostic delay costs)	\$3,282.38	Specialist consults required for MPS II diagnosis (2.95 consults at \$541 per consult), whole body MRI with sedation (\$1,688) and GAG analysis (\$167).
Confirmatory MPS II diagnostic cost	\$766.00	Price listed on the SA Pathology 'Pathology Collection Guide' for confirmatory mucopolysaccharidosis enzymes test (\$388) and full gene variant analysis for MPS II (\$378).
Cost of testing of family members	\$500.00	PASC advised for the assessment to use a cost of \$500 for cascade testing (1776 PICO).
Annual cost of monitoring in MPS II cases (all phenotypes, symptomatic or asymptomatic)	\$1,568.07 - \$9,408.40	Based on monitoring tests outlined in the European recommendations for the diagnosis and multidisciplinary management of MPS II and the LSDP continuing eligibility criteria ³⁰ . The frequency of monitoring differed depending on age and phenotype based on the 1776 PICO.
Annual ERT costs	\$Redacted - \$Redacted	Cost of idursulfase treatment and administration for patients aged 0 – 18 (weight-based dosing).
Transition probabilities and utilities used in the exploratory analysis		

³⁰ Scarpa, M et al. (2011). Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis* 6:72.

Parameter	Value	Source
Survival for no NBS severe patients	Time-dependent probabilities derived from applying a hazard ratio ^c to extrapolated OS data from a treated pooled cohort (severe and attenuated) MPS II patients enrolled in the HOS registry to estimate late treated severe MPS II survival.	
Survival for NBS severe patients	Adding 7 years of 100% survival to the no NBS severe patients OS curve (above), based on 7 year event-free survival apparent in Tomita et al. (2021) when compared to Burton et al. (2017).	
Survival for NBS very attenuated patients	Survival in line with ABS lifetables as reports indicate that these cases have near-normal life-expectancy (ABS 2023a; Guffon et al. 2015; Quaio et al. 2012; Wraith et al. 2008b). This impacts monitoring costs only in the analysis.	
Health utility value for severe patients (in either arm)	0.520	Mean overall HRQoL utility score (derived through the HUI3 instrument reported in Raluy-Callado et al. (2013). the same utilities are applied for the entire duration severe patients are alive based on the rapid rate of disease progression for severe patients outlined in Tomita et al. (2021) for both early and late treated patients.

ABS = Australian Bureau of Statistics; ERT = enzyme replacement therapy; FDRs = first-degree relatives; FPR = false positive rate; GAG = glycosaminoglycan; HOS = Hunter Outcome Survey; HRQoL = health-related quality of life; HUI3 = health utility index mark 3; IDS = iduronate 2-sulphatase; LC = liquid chromatography; LC-MS/MS = liquid chromatography- tandem mass spectrometry; LSDP = Life Saving Drugs Program; MPS II = mucopolysaccharidosis Type II; MRI = magnetic resonance imaging; MS = mass spectroscopy; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan; OS = overall survival; PASC = PICO Confirmation Advisory Sub-Committee of the MSAC; PICO = Population/Intervention/Comparator/Outcomes; SA = South Australia; SDRs = second-degree relatives.

^a The evidence review found that 75% of MPS II cases are likely to have the severe phenotype based on studying reviewing patients who were mostly diagnosed through clinical identification.

^b The FPR (0.026%) from the evidence review does not include newborns those with inconclusive results who, in clinical practice, would move on to NRE-GAG fragmentation analysis. As this input impacts the number GAG analyses only, the screen positive rate minus the true positive rate was considered to be more accurate.

^c Hazard ratio calculated during the assessment based off severe vs a pooled cohort of severe and attenuated MPS II patients OS data³¹.

PICO set 1

The population and health-related variables for the base case analysis and the transition probabilities and utility inputs for the exploratory analysis are presented in Table 9 with their respective sources and derivations.

Costs

Costs included in the base case model were diagnosis costs (NBS and confirmatory costs in the NBS arms and diagnostic delay and confirmatory costs in the no NBS arm), and treatment and monitoring costs upon diagnosis for severe patients. For attenuated patients, monitoring costs were included upon diagnosis, and treatment costs were included upon diagnosis in the no NBS arm and upon symptom onset in the NBS arm (noting that diagnosis is after symptom onset in the no NBS arm due to the diagnostic delay). Only monitoring costs are included for very attenuated patients in the NBS arm as they are undiagnosed in the no NBS arm. MSAC noted that costs of segregation testing of parents should have been included in the confirmatory testing costs, instead of being included in testing of family members.

The exploratory analysis extends the treatment and monitoring costs for severe patients and monitoring costs for very attenuated patients in the NBS arm until death. As mentioned above

³¹ Ueda, K & Hokugo, J (2020). Safety and efficacy of idursulfase in the treatment of mucopolysaccharidosis II (Hunter syndrome): a post-marketing study in Japan. *Expert Opin Drug Saf* 19(7):891-901.

there was inadequate evidence to suggest that there are significant differences (in the costs and outcomes) for attenuated patients beyond the base case time horizon.

Diagnostic delay and clinical identification costs

Due to the rarity of the disease as well as the variability of clinical manifestations, MPS II poses a challenge for diagnosis. The cost of diagnostic delay was based on the number of physician consultations received before an MPS II diagnosis and diagnostic costs of MPS II in the absence of NBS for MPS II.

Based on the distribution of the number of physicians consultations received before an MPS II diagnosis for patients in the Guffon et al. (2015)³², it was assumed that each MPS II patient would require 2.95 different specialist consults-each consult assuming to include a GP visit for a referral (MBS item 36: \$82.90), a specialist visit (MBS item 132: \$305.15), and a review consult with a specialist (MBS item 133: \$152.80).

Studies have also reported that skeletal surveys are often conducted for patients suspected to be affected by MPS II due to skeletal abnormalities observed in the first 18-months to four years of life^{30,33,34}. In the economic modelling the costs for a full body MRI (MBS 63564) with sedation (MBS 63494 and 25013) were applied as costs for the skeletal surveys. Upon suspicion of MPS II, it is expected that a GAG analysis (\$167) would be performed as this is currently how the majority of cases in Australia are currently identified³⁵.

The total cost of diagnostic delay and clinical identification (\$3,282) is likely a substantial underestimate as various investigative tests (aside from skeletal surveys) would accompany specialist visits; however, there is a paucity data to inform this. It is also necessary to consider that some of the investigations that would occur in the clinical diagnostic process would still be conducted following diagnosis after NBS (e.g. MRIs) to identify a baseline and track disease progression. Therefore, not all investigative healthcare costs associated with the delay in clinical diagnosis would be expected to be offset following an NBS initiated diagnosis. Alternative diagnostic delay costs were tested, and the model was not sensitive to these costs (see Table 12).

Monitoring costs

All diagnosed patients in both arms are expected to incur monitoring costs. The types of monitoring tests and services are expected to be consistent across the three classifications of MPS II (severe, attenuated and very attenuated) based on guidelines (for patients on and off treatment)^{18, 36}. The frequency of monitoring differs depending on the patient's age and their MPS II phenotype as indicated by the expert advice provided by the PASC (1776 PICO). All identified cases are monitored every 3 months for the first 2 years of life. This frequency of monitoring is continued for severe patients beyond 2 years of age, while those with the attenuated or very attenuated phenotype require monitoring every 6 months until age 6, and every 18 months for ages 6+.

³² Guffon, N et al. (2015). Diagnosis, quality of life, and treatment of patients with Hunter syndrome in the French healthcare system: a retrospective observational study. *Orphanet J Rare Dis* 10:43.

³³ Scarpa, M (1993). Mucopolysaccharidosis Type II, in MP Adam, J Feldman, GM Mirzaa, RA Pagon, SE Wallace, LJH Bean, KW Gripp & A Amemiya (eds), *GeneReviews*(®), University of Washington, Seattle

³⁴ Tenorio, F & de Souza, CFM (2023). A Retrospective Study of Mucopolysaccharidosis Type II in Brazil - Data from Brazilian Health System (DATASUS). *J Inborn Errors Metab Screen*11: e20230003.

³⁵ Chin, SJ & Fuller, M (2022). Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. *The Lancet Regional Health – Western Pacific* 19.

³⁶ Żuber, Z et al. (2023). Diagnosis and Management of Mucopolysaccharidosis Type II (Hunter Syndrome) in Poland. *Biomedicines* 11(6).

Monitoring tests and services were estimates based on the European recommendations for the diagnosis and multidisciplinary management of MPS II and the continuing eligibility criteria for ERT treatment under the LSDP, and were assumed to include a GP appointment (MBS 721: \$164), echocardiogram (MBS 55132: \$259), electrocardiogram (MBS 11707: \$21), abdominal ultrasound (MBS 55036: \$125), whole body MRI (MBS 63564: \$1616), sleep study (MBS 12210: \$72) and an NRE-GAG analysis (\$167). The total cost per monitoring cycle was \$2,352.³⁰

Results

The generation of the base case analysis was done in one step, as the structure of the model did not rely on building layers of uncertainty or multiple translations of the clinical evidence. The clinical evidence utilised in the base case analysis includes the prevalence of MPS II and the distribution of MPS II phenotypes. Costs included diagnosis costs (NBS and confirmatory costs in the NBS arms and diagnostic delay and confirmatory costs in the no NBS arm), treatment costs for severe patients only and monitoring costs once diagnosed until the end of the time horizon. (REDACTED years).

The ICERs were substantial (\$REDACTED per early diagnosis of severe MPS II case or \$REDACTED per early diagnosis of any MPS II case) reflecting the very low rate of diagnosis per individual screened. The ICER was driven predominantly by the costs of screening. Although the costs and time durations associated with diagnostic delay were uncertain, these were likely to have very low impact on the ICERs. The ICER reduced to \$REDACTED per early diagnosis of MPS II case when the first-tier screening assays were multiplexed in a two-tier screening strategy (where the cost of screening was shared between MPS I and MPS II).

The results of the base case economic evaluation (with discounted costs) are presented in Table 10.

Table 10 Results of base case economic evaluation using REDACTED kit (costs and outcomes are discounted)

	NBS for MPS II	No NBS for MPS II	Increment
Step 1: Time horizon: Redacted years			
Using two-tier screening protocol			
<u>Health outcome:</u>			
Early diagnosis of severe MPS II case			
Early diagnosis of MPS II case			
<u>Costs:</u>			
NBS: Costs associated with NBS for MPS II for all newborns, confirmatory and monitoring costs for MPS II cases and treatment costs for severe MPS II cases.			
No NBS: Diagnostic delay, confirmatory diagnosis and monitoring costs (once diagnosed) for MPS II cases and treatment costs (once diagnosed) for severe MPS II cases.			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
Early diagnosis of severe MPS II case	0.00000468 4.7 per million	0	0.00000468 4.7 per million
Early diagnosis of MPS II case	0.00001420 14.2 per million	0	0.00001420 14.2 per million
ICER (\$/early diagnosis of severe MPS II case)			\$Redacted
ICER (\$/early diagnosis of MPS II case)			\$Redacted
Single-tier screening protocol using NRE-GAG assay			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
Early diagnosis of severe MPS II case	0.00000468 4.7 per million	0	0.00000468 4.7 per million
Early diagnosis of MPS II case	0.00001420 14.2 per million	0	0.00001420 14.2 per million
ICER (\$/early diagnosis of severe MPS II case)			\$Redacted
ICER (\$/early diagnosis of MPS II case)			\$Redacted
Multiplexed single-tier screening for MPS I and MPS II			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
Early diagnosis of severe MPS II case	0.00000468 4.7 per million	0	0.00000468 4.7 per million
Early diagnosis of MPS II case	0.00001420 14.2 per million	0	0.00001420 14.2 per million
ICER (\$/early diagnosis of severe MPS II case)			\$Redacted
ICER (\$/early diagnosis of MPS II case)			\$Redacted

GAG = glycosaminoglycan; ICER = incremental cost-effectiveness ratio; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan

Disaggregated and aggregated base-case results

The disaggregated costs and outcomes for the two-tier screening strategy are presented in Table 11. The incremental costs were driven by the costs associated with NBS.

Table 11 Disaggregated summary of cost and outcome impacts in the economic evaluation

	NBS	No NBS	Increment
Costs (discounted)	\$Redacted	\$Redacted	\$Redacted
- NBS	\$Redacted	\$Redacted	\$Redacted
- Diagnostic delay and clinical identification diagnosis	0	\$0.02	-\$0.02
- Confirmatory testing	\$0.01	\$0.00	\$0.01
- Monitoring until the time horizon	\$Redacted	\$Redacted	\$Redacted
- Treatment until the time horizon	\$Redacted	\$Redacted	\$Redacted
Early diagnosis	0.00001420 14.2 per million	0	0.00001420 14.2 per million
- Severe MPS II cases	0.00000468 4.7 per million	0	0.00000468 4.7 per million
- Attenuated MPS II cases	0.00000152 1.5 per million	0	0.00000152 1.5 per million
- Very attenuated MPS II cases	0.00000800 8.0 per million	0	0.00000800 8.0 per million

MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening

Sensitivity analysis: base case model

Sensitivity analyses conducted on the base case model are presented in Table 12. The results were sensitive to the approach and costs of first-tier screening and the prevalence of MPS II.

Table 12 Sensitivity analysis for base case model (using two-tier screening protocol)

	Incremental costs	Increment early diagnosis	ICER/early diagnosis	% Change
Base case analysis	\$Redacted	0.0000142	\$Redacted	0%
<i>Strategy and cost of 1st tier screening (base case: \$Redacted for Redacted kit)</i>				
Revvity MPS7plex MS/MS kit: \$Redacted	\$Redacted	0.0000142	\$Redacted	147%
Revvity MPS4plex MS/MS kit: \$Redacted	\$Redacted	0.0000142	\$Redacted	90%
Redacted multiplex for MPS I, MPS II, Pompe: \$Redacted	\$Redacted	0.0000142	\$Redacted	-42%
Single-tier screening using NRE-GAG assay: \$Redacted	\$Redacted	0.0000142	\$Redacted	7%
Single-tier NRE-GAG assay multiplex for MPS I, MPS II: \$Redacted	\$Redacted	0.0000142	\$Redacted	-32%
<i>Prevalence of MPS II with NBS (base case: 1.42 per 100,000 newborns)^a</i>				
Equal to the clinical identification rate in Australia (0.62 per 100,000 newborns).	\$Redacted	0.0000062	\$Redacted	113%
<i>Cost of the diagnostic delay (base case: \$1,282)^b</i>				
\$18,200 ^c	\$Redacted	0.0000142	\$Redacted	1%

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

^a Median TPR of NBS for MPS II from NBS jurisdictions.

^b Based on 2.95 different specialist visits (as per Guffon et al.), a full body MRI and a GAG analysis.³²

^c Based on the total upper estimate for diagnostic delay costs presented in Wu et al. for paediatric mitochondrial disease patients³⁷.

³⁷ Wu, Yet al. (2022). Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation. *Eur J Hum Genet* 30:577–586.

Exploratory scenario analysis

The modelled results for the exploratory analysis are presented in a stepped manner in Table 13.

The results of this analysis should be interpreted with caution due to the uncertainty associated with limited and uncertain comparative data for the survival and quality of life benefits.

The key drivers of the exploratory analysis were the additional years of survival for patients who were diagnosed through NBS and hence receive earlier treatment, and the utility value for severe patients.

Table 13 Stepped results of the exploratory economic evaluation using two-tier screening protocol

	NBS for MPS II	No NBS for MPS II	Increment
Step 1: Base case analysis Using two-tier screening protocol <u>Health outcome:</u> Early diagnosis of severe MPS II case Early diagnosis of MPS II case <u>Costs:</u> NBS: Costs associated with NBS for MPS II for all newborns, confirmatory and monitoring costs for MPS II cases and treatment costs for severe MPS II cases. No NBS: Diagnostic delay, confirmatory diagnosis and monitoring costs (once diagnosed) for MPS II cases and treatment costs (once diagnosed) for severe MPS II cases.			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
Early diagnosis of severe MPS II case	0.00000468 4.7 per million	0	0.00000468 4.7 per million
ICER (\$/early diagnosis of severe MPS II case)			\$Redacted
ICER (\$/early diagnosis of MPS II case)			\$Redacted
Step 2: CEA (cost per life year gained) Extends the base case analysis to a lifetime time horizon for severe and very attenuated patients only. ^a <u>Health outcome:</u> Life years gained for severe MPS II cases <u>Costs:</u> Treatment and monitoring costs for severe disease cases until death. Monitoring costs for very attenuated patients in the NBS arm until death. ^b			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
Life years gained	0.00006788 67.9 per million	0.00005553 55.5 per million	0.00001235 12.4 per million
ICER (cost per life year gained)			\$Redacted
Step 3: CUA (cost per QALY gained) Utilities applied to life-years accrued for severe MPS II patients.			
Costs (on average, per person)	\$Redacted	\$Redacted	\$Redacted
QALYs gained	0.00003462 30.6 per million	0.00002832 28.3 per million	0.00000630 6.3 per million
ICER (cost per QALY gained)			\$Redacted

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; QALY = quality-adjusted life year

^a As attenuated patients (in either arm) are only able to access treatment once symptoms arise (which would be the same irrespective of NBS or not), it was pragmatically assumed that there would be no difference in the costs or outcomes of attenuated patients beyond the base case analysis and hence these cases are not modelled in the exploratory analysis.

^b As very attenuated disease cases in the no NBS arm are not identified throughout their lifetime.

PICO set 2

Method

A cost analysis for testing of family members was performed for a cohort of 304,655 newborns that would be screened in the 2025–26 financial year. Based on the X-linked inheritance patterns of MPS II, it was assumed that testing would first be offered to first-degree relatives (biological mothers, fathers and siblings) of the proband and if the proband's variant was determined to be inherited (20% of cases, as per PASC advice), testing was extended to maternal second-degree relatives (maternal grandparents, aunts and uncles). The number of siblings and maternal aunts and uncles were calculated through Australian fertility rates and the probability of identifying additional carriers or cases from genetic testing was based on X-linked inheritance patterns³⁸.

Results

For 304,655 newborns screened (representing approximately one year), family member testing costs would be \$1,498 in the absence of NBS for MPS II and \$4,110 when NBS for MPS II is available when considering biological mothers and siblings of the proband only. When including biological fathers and maternal relatives of the proband (grandparents, aunts and uncles), family member testing costs would be \$4,116 without NBS and \$11,291 with NBS. The incremental cost is mainly attributable to the additional cases identified with NBS. However, this may also be off-set by the health benefit and cost-savings associated with preventing a recurrence of disease, though the extent to which that would occur in the Australian population is entirely unknown.

Conclusions

NBS was associated with a net incremental cost per MPS II case diagnosed compared with clinical identification in the absence of NBS. Some cost was offset due to avoidance of diagnostic delay, but this was relatively small in comparison to the increased screening costs. The ICERs (\$/early diagnosis and \$/early diagnosis of severe MPS II) 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 ERT for severe MPS II patients. 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, the relatively limited change in clinical management associated with early diagnosis and life-long monitoring implications for patients who would not have been identified without NBS. Earlier diagnosis through NBS would avoid diagnostic delay and increase timely treatment in many cases with MPS II; however, clinical benefits in cases of attenuated disease could not be quantified.

Testing of family members has the potential to inform reproductive planning but the associated health benefits cannot be quantified.

³⁸ Australian Bureau of Statistics 2022, Births, Australia, Australian Bureau of Statistics, Canberra, Australia, viewed 11 December 2023, <<https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>>.

14. Financial/budgetary impacts

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

As per the consultation feedback, all NBS laboratories would 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 II. Costs associated with program implementation included laboratory expansion and validation of the new screening protocol. These were considered as one-off set-up costs to NBS programs at the beginning. 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 presents the program implementation costs for introducing MPS II to the NBS programs.

Table 14 Program implementation costs for introducing MPS II to the NBS panel

	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	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total implementation cost per site	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total implementation cost to NBS					\$Redacted

MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; NT = Northern Territory; QLD = Queensland; SA = South Australia; WA = Western Australia

^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 REDACTED and projected live births for each state/territory ending June 2026 based on ABS population projections and registered births data³⁹. 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 II on the NBS panel were summarised in Table 15. The total cost to NBS programs for the addition of MPS II was \$REDACTED in the first financial year, including one-off implementation set-up costs. The total cost to NBS programs for years 2–6 was approximately \$REDACTED annually.

³⁹ ABS 2023, 'Table 1: Births, summary, Statistical Areas Level 4 of usual residence – 2011 to 2022', *Births, Australia*, Australian Bureau of Statistics, Canberra, ACT, <<https://www.abs.gov.au/statistics/people/population/births-australia/2022>>.

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

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Program implementation set-up costs for MPS II	\$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) ^b	310,748	310,907	311,065	311,223	311,381	311,539
Cost of first-tier screening (\$Redacted per sample screened) ^c	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total number of first-tier screen positives	88	88	88	89	89	89
Cost of second-tier screening (\$167.00 per test) ^d	\$14,746	\$14,763	\$14,763	\$14,780	\$14,780	\$14,780
Total cost to the NBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

MPS II = mucopolysaccharidosis Type II; 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.

^b Based on advice provided by NBS laboratories.

^c Cost per screen using the REDACTED kit and operational costs.

^d Based on GAG analysis cost outlined in the SA Pathology Collection Guide (<https://www.sapathology.sa.gov.au/clinicians/testing-screening/search-test-catalogue>). Advice provided by NBS laboratories is that second-tier GAG analyses will be sent to the NRL AWCH unless the second-tier testing load is very high.

Cost implications for other health budgets

NBS for MPS II is likely to affect other health budgets. There would be an increase in monitoring, treatment and family member testing costs as NBS will detect approximately 2 additional cases per year (based on prevalence rates with and without NBS, see Table 9). In addition to this, cases who would have been detected without NBS would have their diagnosis brought forward, which also brings forward monitoring and treatment initiation.

Costs to state and territory health budgets

There would be cost increases attributable to the additional number of confirmatory diagnosis, IDS variant and family member testing costs due to a greater detection of cases. There would also be an increase in GAG analyses and treatment administration services due to monitoring and treatment being brought forward.

These costs are offset by cost savings attributed to GAG analyses for a small number of cases who would have been clinically suspected of MPS II (i.e. without NBS) as these costs would shift to the NBS program. Net costs to state and territory health budgets are estimated in Table 16.

Table 16 Net costs to state and territory health budgets due to NBS for MPS II

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Additional cases diagnosed with NBS	2	2	2	2	2	2
Additional mucopolysaccharidosis enzymes test costs (\$388) ^a	\$936	\$935	\$935	\$934	\$934	\$934
Additional IDS genetic testing costs (\$378) ^a	\$911	\$911	\$911	\$910	\$910	\$910
Additional family member genetic testing costs (\$500) ^b	\$2,291	\$2,290	\$2,289	\$2,288	\$2,287	\$2,286
Patients receiving earlier treatment due to NBS ^c	1.42	2.85	4.28	4.28	4.75	5.21
Cost increase due to earlier ERT administration (\$Redacted/year of earlier Tx) ^d	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Cost increase due to earlier GAG analyses monitoring (\$167) ^{e,f}	\$2,872	\$5,745	\$7,657	\$8,617	\$9,578	\$10,538
Cost reduction due to NBS GAG analyses shifted to NBS program ^f	-\$315	-\$316	-\$316	-\$316	-\$316	-\$316
Total net costs to State and Territory health budgets	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; GAG = glycosaminoglycan; IDS = iduronate 2-sulphatase; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; Tx = treatment

^a Costs sourced from the SA Pathology Collection Guide. The NRL at the AWCH is the only facility who conduct diagnostic tests for MPS II.

^b Cost based on PASC advice in the 1776 PICO, each case is expected to have 1.90 family member tests (one for the biological mother and 0.9 for siblings based on fertility rates in 2022⁴⁰).

^c See Table 18.

^d Each administration is assumed to incur the cost of AR-DRF item 20.34 – endocrinology (\$336.83) and administrations occur weekly.

^e See Table 17 for the number of additional monitoring cycles with NBS (differs by age and phenotype).

^f Costs sourced from the SA Pathology Collection Guide. The AWCH is the only facility who conduct diagnostic tests for MPS II.

Costs to MBS

There are additional costs to the MBS due to an increase in the monitoring services as a result of earlier and greater detection of MPS II. The net increase in monitoring costs to the MBS have been estimated based on the monitoring services and frequency applied in the economic model, these are summarised in Table 17.

⁴⁰ ABS 2022, *Births, Australia*, Australian Bureau of Statistics, Canberra, Australia, viewed 11 December 2023, <<https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>>.

Table 17 Net increase in costs to the MBS due to NBS for MPS II monitoring

	2025-26	2026-27	2027-28	2028-29	2029-30	2030-31
Cases incurring net MBS monitoring costs due to NBS						
Additional monitoring cycles due to NBS ^a	17	34	46	52	57	63
Net increase in MBS services^b						
GP appointment (MBS 721)	17	34	46	52	57	63
Echocardiogram (MBS 55132)	17	34	46	52	57	63
Electrocardiogram (MBS 11707)	17	34	46	52	57	63
Abdominal ultrasound (MBS 55036)	17	34	46	52	57	63
Sleep study (MBS 12210)	17	34	46	52	57	63
Whole body MRI (MBS 63564)	17	34	46	52	57	63
Sedation (MBS 63494 and 25013) ^c	17	34	46	52	52	52
Net increase in MBS costs^d						
GP appointment costs (MBS 721 - \$164.35)	\$2,827	\$5,654	\$7,535	\$8,481	\$9,426	\$10,371
Echocardiogram costs (MBS 55132 - \$219.90)	\$3,782	\$7,564	\$10,082	\$11,347	\$12,611	\$13,875
Electrocardiogram costs (MBS 11707 - \$17.81)	\$306	\$613	\$816	\$919	\$1,021	\$1,124
Abdominal ultrasound costs (MBS 55036 - \$106.00)	\$1,823	\$3,646	\$4,860	\$5,469	\$6,079	\$6,688
Sleep study (MBS 12210 - \$679.66)	\$11,690	\$23,380	\$31,162	\$35,071	\$38,980	\$42,887
Whole body MRI (MBS 63564 - \$1,514.00)	\$26,041	\$52,082	\$69,417	\$78,125	\$86,830	\$95,534
Sedation (MBS 63494 and 25013 - \$60.90)	\$1,047	\$2,095	\$2,792	\$3,143	\$3,143	\$3,143
Total net increase in monitoring costs	\$47,517	\$95,034	\$126,665	\$142,555	\$158,090	\$173,621

ERT = enzyme replacement therapy; GP = general practitioner; LSDP = Life Saving Drugs Program; MBS = Medicare Benefits Schedule; MPS II = mucopolysaccharidosis Type II; MRI = magnetic resonance imaging; NBS = newborn bloodspot screening

^a Number of additional monitoring cycles differs by age and phenotype. In line with the economic analysis, among cases who would have been identified without NBS, it is assumed that 75% would have the severe phenotype and 25% would have the attenuated phenotype and all patients who would not have been identified without NBS have a (very) attenuated phenotype (see Table 9). Severe disease cases would have monitoring brought forward by three years as they would have been clinically diagnosed by age three without NBS and they are monitored 4 times a year (regardless of age) based on advice provided in the 1776 PICO. Attenuated disease cases would have monitoring brought forward by six years as they would have been clinically diagnosed by age six and they receive monitoring 4 times a year for ages 0 and 1 and twice year from ages 2 – 5 based on advice provided in the 1776 PICO. As very attenuated disease cases would not have been identified without NBS, their lifetime monitoring costs represent net costs to the MBS, frequency of monitoring for these cases are the same as attenuated disease cases.

^b Based on monitoring costs outlined in the European recommendations for the diagnosis and multidisciplinary management of MPS II and the continuing eligibility criteria for ERT under the LSDP.³⁰ With X-rays tests replaced with a whole body MRI to better reflect Australian practice

^c Sedation was assumed to be required for MRI scans for patients aged 0 -3 years.

^d MBS cost applied with a 85% MBS rebate, except for GP consults where the 100% benefit applies.

Costs to LSDP

Costs to the LSDP are expected to increase if MPS II is listed on the NBS panel as some patients (i.e. those with the severe phenotype) will be able to access treatment immediately upon diagnosis and attenuated patients would be able to access immediately upon symptom onset as per the current LSDP eligibility criteria. For cases who would not have been diagnosed without NBS, it is assumed that they will not incur any treatment costs within the 6-year financial analysis.

Table 18 Net costs to the LSDP due to NBS for MPS II

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Cases incurring net LSDP costs						
Severe disease cases receiving earlier treatment ^{a,b}	1.42	2.85	4.28	4.28	4.28	4.28
Attenuated disease cases receiving earlier treatment ^{a,c}	0.00	0.00	0.00	0.00	0.46	0.93
Net LSDP costs						
Severe disease cases net treatment costs ^d	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Attenuated disease cases net treatment costs ^e	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total net costs to the LSDP	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

LSDP = Life Saving Drugs Program; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening

^a In line with the economic analysis, among cases who would have been identified without NBS, it is assumed that 75% would have the severe phenotype and 25% would have the attenuated phenotype. For cases only identified with NBS, it is assumed they will not be symptomatic within the 6-year financial analysis and hence will not incur treatment costs.

^b Severe disease cases would have treatment brought forward by three years as they would have been clinically diagnosed by age three without NBS but with NBS they diagnosed at age 0 and eligible for treatment immediately as per the LSDP criteria.

^c As per the LSDP criteria, attenuated patients are only able to access treatment upon symptom onset. Given that the mean age of symptom onset for attenuated patients is age four, and their age of diagnosis without NBS is six years, with NBS there would be net treatment costs when the patient is aged four and five.

^d Treatment costs vary by age and phenotype as the treatment dosing is weight based. Treatment costs for severe patients aged zero and one are \$Redacted and aged two are \$Redacted.

^e Treatment costs vary by age and phenotype as the treatment dosing is weight based. Treatment costs for attenuated patients aged four and five are \$Redacted.

Sensitivity Analyses

Results of the sensitivity analyses performed on the costs to the NBS are presented in Table 19. Results were highly sensitive to the cost per screening. Number of births, prevalence of MPS II and false positive rate for the first-tier screening had a very low impact on the financial implications to NBS programs.

Table 19 Sensitivity analysis for costs to the NBS

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Base case	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Strategy and weighted average cost per screen of 1st tier screening (base case: \$Redacted for Redacted)						
Revvity MPS7plex MS/MS kit: \$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Revvity MPS4plex MS/MS kit: \$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Redacted multiplex for MPS I, MPS II, Pompe: \$Redacted ^a	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Single-tier screening using NRE-GAG assay: \$Redacted ^b	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Single-tier NRE-GAG assay multiplex for MPS I, MPS II: \$Redacted ^{b,c}	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Strategy and cost of 2nd tier screening (base case: \$167.00 conducted at the NRL AWCH)						
GelbChem SKU: BMKEG-3: \$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

AWCH = Adelaide Women's and Children's Hospital; GAG = glycosaminoglycan; MPS II = mucopolysaccharidosis Type II; MS = mass spectroscopy; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; NRE = nonreducing end; NRE-GAG = nonreducing end-glycosaminoglycan; NRL = National Referral Laboratory

^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 Using the GelbChem SKU: BMKEG-3 kit.

^c Multiplexed for MPS I and MPS II (i.e. cost per screen is halved).

Supplementary financial analyses 1 and 2 from the Rejoinder, which explored the potential impact on ERT expenditure associated with NBS for MPS II, are presented in Tables 20 to 23. These analyses were then combined in supplementary analysis 3, presented in Table 24.

Table 20 Derivation of the estimated size of MPS II cases born before MPS II NBS implementation but develop symptoms when MPS II NBS is implemented (for supplementary financial analysis 1)

Year	2018 - 19	2019 - 20	2020 - 21	2021 - 22	2022 - 23	2023 - 24	2024 - 25
Number of live births ^a	310,490	300,101	302,183	305,340	303,548	306,491	306,647
MPS II cases born and clinically identified (0.62 per 100,000 live births)	1.93	1.86	1.87	1.89	1.88	1.90	1.90
Attenuated cases (25% of clinically identified cases)	0.47	0.46	0.46	0.46	0.46	0.47	0.47
Expected year of diagnosis for attenuated cases (age six)	2024 - 25	2025 – 26	2026 - 27	2027 - 28	2028 - 29	2029 - 30	2030 - 31
Severe cases (75% of clinically identified cases)	1.45	1.40	1.41	1.43	1.42	1.43	1.43
Expected year of diagnosis for severe cases (age three)	2021 - 22	2022 - 23	2023 - 24	2024 - 25	2025–26	2026–27	2027–28

ABS = Australian Bureau of Statistics; DCAR = Department Contracted Assessment Report; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening

Note: NBS for MPS II assumed to be implemented in the 2025 – 26 financial year and all parameters sourced from the 1776 DCAR.

Bolded years include costs that are incurred during scope of the financial analysis (2025 – 26 to 2030 – 31).

^aNumber of live births based on observed and projected live births reported by the ABS.

Source: Rejoinder from the assessment group

Table 21 Additional ERT costs for clinically diagnosed populations after NBS implementation 2 (supplementary financial analysis 1)

Year	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Clinically diagnosed population (accumulated cases): attenuated aged 6 and 7	0.46	0.92	0.93	0.93	0.93	0.93
Clinically diagnosed population: attenuated aged 8+	0.00	0.00	0.46	0.92	1.38	1.84
Clinically diagnosed population: attenuated aged 6 and 7, cost	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Clinically diagnosed population: attenuated aged 8 - 13, cost	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Clinically diagnosed population: severe aged 2 - 5	1.42	2.85	4.29	4.29	4.29	4.29
Clinically diagnosed population: severe aged 2 - 5, cost	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total clinically diagnosed population:	1.88	3.77	5.67	6.13	6.60	7.07
Total costs for clinically diagnosed population	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; NBS = newborn bloodspot screening.

Source: Rejoinder from the assessment group

Table 22 Estimated size of MPS II cases who will not be able to access ERT under the LSDP immediately upon birth based on current criteria (for supplementary financial analysis 2)

Year	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Cases identified with NBS	4.30	4.30	4.30	4.30	4.30	4.30
Attenuated cases identified per year	0.46	0.46	0.46	0.46	0.46	0.47
Very attenuated cases identified per year	2.41	2.41	2.41	2.41	2.41	2.41

ERT = enzyme replacement therapy; LSDP = Life Saving Drugs Program; NBS = newborn bloodspot screening.

Source: Rejoinder from the assessment group

Table 23 Additional ERT costs for MPS II cases associated with reduced criteria for LSDP access (supplementary financial analysis 2)

Year	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Additional cases, aged below 0 – 1 (cumulative)	2.88	5.75	5.75	5.75	5.75	5.74
Additional ERT costs (cases aged 0 – 1)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Additional cases, aged 2 – 3 or very attenuated 3+ (cumulative)	0	0	2.88	5.75	8.16	10.57
Additional ERT costs (cases, aged 2 – 3 or very attenuated aged 3 – 7)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total additional non-symptomatic cases with ERT access (cumulative)	2.88	5.75	8.62	11.50	13.90	16.31
Total Additional Costs	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; LSDP = Life Saving Drugs Program; MPS II = mucopolysaccharidosis Type II
Source: Rejoinder from the assessment group

Table 24: Total ERT costs incorporating base case estimates and additional ERT use estimated in analyses 1 and 2

Year	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Analysis 1: Additional cases using ERT	1.88	3.77	5.67	6.13	6.60	7.07
Analysis 2: Additional cases using ERT	2.88	5.75	8.62	11.50	13.90	16.31
Analysis 1: Additional ERT costs	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Analysis 2: Additional ERT costs	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Base case LSDP costs associated with NBS for MPS II (as per DCAR 1776)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total cost for LSDP	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

DCAR = Department Contracted Assessment Report; ERT = enzyme replacement therapy; LSDP = Life Saving Drugs Program; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening.

Note: Analysis 1 refers to cases who were born prior to NBS implementation but are diagnosed within the scope of the six year financial analysis and Analysis 2 refers to attenuated and very attenuated MPS II cases who are diagnosed with NBS and would be able to access ERT immediately if the LSDP criteria requiring symptoms for access to ERT for MPS II cases is removed. ERT costs based on the 1776 DCAR.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

- 1. Is there a suitable screening test(s) (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive) to accurately identify all newborns at risk for all subtypes of the proposed condition?**

ESC noted that the sensitivity and specificity of 1st-tier fluorometric or tandem mass spectrometry (MS/MS) enzyme activity testing assessed in case-control studies are very high, but both screening methods risk identifying false positives (0.026%, range 0.011% to 0.056%), as reported in overseas NBS programs, Table 4).

ESC noted the limited published evidence available to inform the diagnostic accuracy of non-reducing end-glycosaminoglycan (NRE-GAG) analysis as a 2nd-tier test or as a single-tier test on the NBS protocol. ESC advised that the existence of a consensus threshold as a discriminatory diagnostic 2nd-tier test to rule out disease in individuals with pseudodeficiency needs clarification.

It is anticipated that, each year, NBS will identify 1.43 individuals with severe disease and 2.89 individuals at risk for later onset disease (comprising 0.47 cases at risk for attenuated disease - and 2.42 cases at risk for “very attenuated disease”).

ESC considered that screening may identify some individuals considered at-risk for future disease who may never progress to develop symptoms and signs. ESC considered these to be healthy over-diagnosed individuals rather than ‘patients in waiting’.

ESC noted that the National Pathology Accreditation Advisory Council (NPAAC) advised that screening tests for MPS II require specialist testing and are highly unlikely to be offered widely. Also, no External Quality Assessment (EQA) is offered for MPS II yet. ESC also noted that REDACTED has yet to receive NATA accreditation; however, the department advised that this would be sought closer to the implementation stage.

- 2. Can disease subtype and prognosis (with consideration of expressivity and penetrance) be determined from the screening and confirmatory tests and clinical assessment to determine the need for monitoring and/or earlier treatment?**

MPS II has 2 main subtypes: a severe (neuronopathic) subtype, characterised by earlier onset, more severe symptoms and neurocognitive involvement, and an attenuated subtype, which has a later onset and milder symptoms.

Screening and diagnostic testing may be able to differentiate between severe and attenuated disease in some individuals with MPS II, if a known pathogenic or likely pathogenic (P/LP) genotype can be identified. However, only a few of the >300 genetic variants described have confirmed phenotype/genotype associations due to the large number of novel or private variants associated with MPS II, meaning phenotype often cannot be determined.

ESC considered there is a need for clarification regarding the prognostic confidence of differentiating between each disease subtype. In particular, what proportion of the estimated 1.43 severe patients can be confidently differentiated from the estimated 2.89 cases at risk for attenuated disease based on clearly prognostic genetic results and what remaining proportion would have unclear prognostic genetic results. ESC also questioned whether it is possible to confidently differentiate the estimated 0.47 cases at risk for attenuated disease (who will manifest a milder form of the disease) from the 2.42 cases at risk for “very attenuated disease” (who may never manifest any signs or symptoms of the disease) based on genetic results alone.

The identification of a currently assigned variant of uncertain significance (VUS) may further impair the ability to differentiate between subtypes and preclude an accurate prognostic assessment of penetrance, the timing of disease onset and degree of expressivity. Advice is required on whether NBS laboratories will only report variants currently assigned P/LP, whether a VUS will be reported, and then whether that individual is monitored to ascertain pathogenicity, or whether VUS status would not be reported but these data held in a registry to allow for possible reclassification at a later time point should the individual develop symptomatic disease.

3. Is there is an effective treatment (or treatments) available in Australia for at-risk newborns? If the disease has subtypes are treatments available for each subtype?

ESC noted the management of MPS II comprises mainly of enzyme replacement therapy (ERT). Idursulfase is the only Life-Saving Drugs Program (LSDP)-funded drug as intravenous ERT for presymptomatic children <5 years of age with a diagnosis of MPS II and with “clear prediction of progress of the disease, or if, on the basis of a sibling's disease progression, severe disease can be predicted”.

ESC noted there is no LSDP-funded ERT for the presymptomatic children who would be identified through NBS and predicted to have attenuated disease, or for those whose disease onset and severity cannot be “clearly predicted”.

ERT does not cross the blood-brain barrier and is not expected to affect the onset or trajectory of central nervous system (CNS) disease in patients with severe MPS II. There is a paucity of evidence on the earlier use of ERT arising from an NBS-mediated diagnosis in patients with attenuated MPS II.

There are limited data on the use of haematopoietic stem cell transplant (HSCT) for patients with severe MPS II, which has a biologically plausible benefit, but the timing of transplant and extent of pre-existent disease can impact clinical outcomes. There is no evidence for the use of HSCT in attenuated MPS II. HSCT is provided through the states and territories, but there is no routine Commonwealth funding for stem cell collection and transportation from overseas donors. A variety of surgical procedures would be used for symptomatic individuals with MPS II, particularly those who have severe disease. There is a potential benefit from knowing an earlier diagnosis of MPS II relating to anaesthetic and surgical complexity/risk.

4. Is the available treatment effective from the proposed earlier age of initiation following NBS screening and diagnosis compared to symptomatic presentation?

There is no direct evidence for the comparative safety and effectiveness (improvement in survival or neurocognitive impairment) arising from a change in use of ERT following an earlier diagnosis of severe MPS II through NBS. Whether there is a possible survival benefit from earlier ERT in children with a high probability of developing symptomatic severe MPS II is highly uncertain due to the very limited observational data available (case series detected through NBS compared to historical registry data of clinical disease). Other indirect evidence (patients not identified through NBS) suggests possible benefits for earlier treatment on quality of life and slowing progression of the disease. Limited observational evidence suggests an increase in ERT-related adverse events arising from earlier ERT use.

There is no direct evidence for the comparative safety and effectiveness (overall survival) arising from earlier HSCT following an earlier diagnosis of severe MPS II by NBS. Limited observational evidence based on sibling pairs suggests possible benefit on neurocognitive impairment from HSCT delivered prior to symptom onset.

There are no data to support earlier treatment of children at risk of developing attenuated MPS II.

There are potential psychosocial harms associated with diagnostic labelling, clinical surveillance and follow-up testing and potential harms associated with surveillance imaging needed for monitoring children prior to therapy initiation.

5. Is the available treatment cost-effective from the proposed earlier age of initiation following NBS screening and diagnosis compared to symptomatic presentation?

The department-contracted assessment report (DCAR) evaluated the cost-effectiveness of expanding the NBS to include MPS II compared to current standard of care (management of MPS II at symptom onset in the absence of NBS for MS II). The estimated incremental overall survival (OS) benefit of an extracted case series of only six Japanese patients with clinically presenting severe MPS II who initiated ERT early and were then followed for a median of only 11 years. ESC considered this case series to be the key source of uncertainty in the exploratory QALY-based economic evaluation.

The DCAR estimated that it would cost \$REDACTED per additional case of severe MPS II diagnosed and \$REDACTED per additional case of MPS II (any subtype) diagnosed.

ESC noted the net costs to the LSDP appeared to be overestimated, as these should only be for the earlier use of ERT, and subsequent modelled incremental ERT costs in the economic model should only occur after year 9.

ESC noted the models' approach of reducing costs of screening to assess the impact on cost-effectiveness of multiplexing provides only a rough estimation. ESC considered that a revised "bundled" stepped evaluation of applications 1774, 1775 and 1776 should be considered to ensure any duplication of costs is addressed and cumulative diagnostic yield is appropriately captured across the three applications.

ESC noted that the one-off set-up costs for program implementation (\$REDACTED) were included in the financial impact but were excluded from the economic modelling.

6. What is the likely financial impact to all relevant budget holders for NBS screening for the condition?

The estimated cost of screening was \$REDACTED in year 1 and \$REDACTED in year 6, noting there may be additional LSDP expenditure not captured in the current assessment.

7. What are the relevant ethical (incl. equity), legal, social or organisational aspects specific to screening for this condition?

The newborn screening, diagnostic and clinical management pathway will identify individuals who are at-risk for attenuated disease. This includes cases where clinically apparent disease does not eventuate. There are no national clinical management guidelines to guide the use of ERT in children who are presymptomatic but whose disease onset and severity cannot be "clearly predicted".

If NBS for MPS II is implemented, there would need to be changes to the pre-test consent process informed by the approach of reporting and managing VUS, and in relation to managing uncertainty in the prognostic utility of screening in predicting disease subtype, age at onset and severity of disease (these issues may be common across NBS-related applications).

There would also be an ethical obligation to inform parents of a confirmed MPS II diagnosis in order to obtain their consent to proceed with further investigation of the child beyond the original bloodspot sample. Additionally, once further investigation is conducted, ethical principles of transparency and full disclosure would necessitate informing parents of the outcome of the further investigation.

ESC discussion

ESC noted that this application, from the Department of Health and Aged Care Newborn Bloodspot Screening (NBS) Section, sought the addition of mucopolysaccharidosis type II (MPS II, or Hunter syndrome) to the list of conditions screened as part of Australia's NBS programs. ESC noted that the Australian Government first announced funding under the 2022-23 Budget, with further provisions under the 2024-2025 Budget to support expansion of NBS programs.

ESC noted that the NBS is underpinned by the NBS National Policy Framework (NBS NPF)⁴¹, and implementation remains jurisdiction-based, with screening provided by five NBS laboratories across Australia. For a condition to progress to MSAC for assessment, it needs to align with the NBS NPF, which outlines several criteria the condition must meet. These include that: the condition is serious and benefits from early diagnosis in the newborn period; that there is a suitable screening test available; and having an effective intervention or treatment available. ESC further noted that the 9 Lysosomal Storage Disorders (LSD) have been considered to date by the National NBS Program Management Committee, out of which 3 have been referred to MSAC for assessment (MSAC applications 1774⁴², 1775⁴³ and 1776⁴⁴).

ESC noted that, as a starting premise for evaluation, newborn genetic screening needs to fulfil the same criteria for net benefit and cost-effectiveness as any screening program, and additionally must justify why screening should occur in the newborn period.

ESC noted and welcomed public consultation feedback from 9 organisations and 2 individuals (1 consumer and 1 health professional). ESC noted that the feedback was broadly supportive of screening for MPS II, but also raised some concerns around the test methodology and overdiagnosis of newborns who may never develop clinical signs or symptoms of MPS II. The feedback indicated that the main perceived benefit of screening for MPS II was earlier detection and diagnosis, and subsequent earlier intervention or monitoring, depending on the form of MPS II identified. Earlier diagnosis would also avoid the diagnostic delay and associated stress for both newborns and their families. ESC noted that feedback also considered the equity of access associated with NBS (i.e. that screening is without cost and accessible to all families) to be important. ESC noted that feedback stated that earlier access to treatment was likely to help slow disease progression and decrease morbidity, and that screening would also facilitate access to any future treatments on the horizon, which may be more effective or curative. However, ESC also noted that some feedback raised concerns about the limited evidence on the benefits of treatment, particularly for those under 1 year of age, and the associated risks of treatment, particularly with HSCT. ESC also noted concerns about the potential for false positive (FP) results, as well as the potential for individuals to be diagnosed with MPS II without full understanding of the condition or its associated impacts, particularly for the later onset form. Feedback highlighted the importance of education and counselling for affected families. ESC noted that feedback from families or carers of individuals with MPS II indicated that the benefits of screening were considered to outweigh any potential disadvantages.

ESC noted that MPS II is an X-linked recessive LSD caused by an inherited deficiency or absence of the iduronate 2-sulfatase (IDS) enzyme required to break down GAGs in the lysosomes within cells, leading to impaired cellular function. Clinical disease varies across a continuum, with two broad subtypes:

⁴¹ 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>

⁴² <https://www.msac.gov.au/applications/1774>

⁴³ <https://www.msac.gov.au/applications/1775>

⁴⁴ <https://www.msac.gov.au/applications/1776>

- A severe (neuronopathic) form with central nervous system (CNS) involvement, including cognitive disability, with earlier onset.
- A milder, attenuated (non-neuronopathic) form with later (including adult) onset.

ESC noted that the milder form is sometimes further categorised into 'attenuated' and 'very attenuated' subtypes. ESC noted that for those with the severe neuronopathic form, signs of MPS II are typically observed from 6-12 months of age, and life expectancy is 10-20 years of age. Those with severe MPS II do not meet developmental milestones within the first years of life, and later regress developmentally, losing cognitive function such as speech and language, and fine motor skills. Other characteristics or clinical features include hydrocephalus, frequent upper respiratory infections, sleep apnoea due to narrowing of the airway, an enlarged liver and spleen, hearing loss, reduced vision, narrowing of the spinal canal compressing the spinal cord, heart valve abnormalities leading to heart rhythm abnormalities, and skeletal abnormalities. For those with the late-onset form, the disease is similar but milder, without CNS involvement, and life expectancy is 60-70 years of age. ESC noted that while females are typically carriers, there are also rare instances in which females with a genetic variant may be symptomatic.

ESC noted that MPS II is an ultra-rare (defined as 1 or fewer cases per 50,000 births) condition, with an estimated incidence in Australia of 0.62 per 100,000 live births (i.e. approximately 2 cases per year), although the exact incidence of MPS II in Australia remains unknown. ESC noted estimates that, in Australia, 75% of cases diagnosed through clinical identification are severe, while 25% of cases are attenuated (i.e. attenuated or very attenuated). This equates to an incidence of severe MPS II of approximately 0.47 per 100,000 live births (~1.43 cases per year), and an incidence of attenuated MPS II of approximately 0.15 per 100,000 live births (~0.47 cases per year).

ESC noted the current and proposed clinical management algorithms. 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 2-tier testing strategy, with both tests performed on the dried bloodspot (DBS). The first-tier test would examine IDS enzyme activity on the DBS by liquid chromatography (LC)-tandem mass spectrometry (MS/MS), using either the NeoLSD2™ kit from Revvity or a **REDACTED** kit. Positive cases, i.e., cases with reduced IDS enzyme activity, would go through second-tier testing (GAG fragment analysis on the DBS by LC-MS/MS) either in-house or sent to the National Referral Laboratory (NRL) for Lysosomal, Peroxisomal and Other Related Disorders based in Adelaide, depending on the number of second-tier tests likely to be required. The second-tier test would rule out those who have reduced IDS enzyme activity, but do not have MPS II, such as those with IDS pseudodeficiency. These individuals exhibit low IDS enzyme levels (~5–15% of normal activity) but have normal GAG levels and no symptoms. ESC noted that a single-tier IDS-based test strategy would be impractical, because the assays used to detect IDS enzyme activity have a low positive predictive value (high FP rate). In the proposed two-tier screening method, a normal result for the second-tier test would overrule the first-tier test result and greatly reduce the final number of FP results. ESC noted that the kit from Revvity (NeoLSD2™) is not commercially available. ESC also noted that the DCAR stated that a **REDACTED** kit was expected to be available from **REDACTED**; however, this does not yet appear to be the case.

Overall, ESC noted the evidence base is mostly low quality, with high risk of bias, in the form of case-control studies, a case series, a case report and retrospective cohort studies. However, this is to be expected given the rarity of the condition. Study outcomes were health outcomes, accuracy and performance of the test, and change in patient management.

ESC noted the evidence for diagnostic accuracy of NBS for MPS II, which comprised case control studies with high risk of bias. The tests identified people with MPS II, possible MPS II and

possible pseudodeficiency. ESC noted that many people with pseudodeficiency were undergoing long-term monitoring and follow-up. Overall, ESC considered that the sensitivity of both the fluorometric and the LC-MS/MS IDS enzyme assays compared to clinical diagnosis was 100% in the case-control studies, suggesting no false negatives (FNs). Additionally, none of the overseas NBS programs have reported any FN patients (cases where the patient had undergone NBS, screened negative for MPS II, and was then later diagnosed with MPS II due to clinical symptoms), including the program that has been running the longest (since 2015). This suggests that the sensitivity of NBS screening using enzyme activity assays is likely enough to detect all newborns with severe forms of MPS II.

ESC noted that no information is available about the level of IDS enzyme activity in newborns with very mild attenuated MPS II, which does not become symptomatic until the patient is in early adulthood. Thus, the likelihood of a patient with low enzyme activity and a variant of uncertain significance (VUS) detected in the *IDS* gene causing a very mild form of MPS II being misdiagnosed with pseudodeficiency (and therefore misclassified as a FP) is unknown. However, using the GAG disaccharide analysis as a second-tier NBS test should detect those with mild disease, as they would have elevated GAG disaccharide profiles, reducing the likelihood of a misdiagnosis.

ESC also queried whether the GAG fragment analysis could be performed on a dried bloodspot as the first-tier test, as it is highly accurate and reliable on dried bloodspot samples, but noted that the evidence for this method was only for diagnosis, not screening.

ESC also noted advice that the required mass spectrometer would need to be much more sensitive than those typically used for first-tier enzyme activity analysis in NBS laboratories, and it would have to be maintained under optimal performance conditions, which is not practical for high throughput NBS laboratories.

ESC noted data from international NBS programs that showed that 21 newborns with MPS II were detected among a total of 1,479,601 newborns screened. This equated to 1.42 per 100,000 newborns being diagnosed with MPS II via NBS programs. The overall FP rate for these NBS programs was 0.030% (range of 0.011–0.058%). ESC noted that a few newborns who screened positive did not have a final diagnosis, mostly due to loss of follow-up. Based on an Australian annual birth rate of approximately 300,000 babies per year, if NBS for MPS II was implemented:

- 88 babies (includes 84 false-positives) would undergo second-tier testing per year (most likely the non-reducing end GAG test, and most likely at the NRL in Adelaide). The DCAR stated that the second-tier test would be expected to eliminate all FPs, and that only those who had MPS II would be recalled for clinical confirmatory diagnosis. However, ESC considered it likely that some FP babies would be recalled as well, noting the international FP rate.
- Of these 88 babies, based on the global incidence of 1.42 cases per 100,000, the DCAR estimated that 4.33 cases of MPS II per year would be identified across Australia via the NBS program (1.43 with severe disease and 2.89 at risk of attenuated disease). Of the 2.89 cases at risk of attenuated disease, the extra 2.42 cases that are predicted to be detected through the NBS would be at risk of “very attenuated disease”, that is, they would not necessarily be expected to develop clinically significant or apparent symptoms.

ESC considered that the proposed two-tier screening appears to have very high sensitivity and specificity, and is likely suitable to accurately identify all newborns at risk of having MPS II. However, ESC considered it important to ensure there was a consensus threshold to distinguish between possible MPS II and pseudodeficiency.

Regarding whether disease subtype and prognosis can be determined from screening and confirmatory tests to determine the need for earlier treatment, ESC noted that, although the proposed screening method can identify MPS II, it does not identify MPS II phenotype.

ESC noted that, in affected individuals, 10–33% of *IDS* variants are *de novo* rather than familial in origin. ESC noted that there is high genetic heterogeneity (>700 *IDS* pathogenic variants identified), making it difficult to identify genotype–phenotype associations.

ESC noted that while affected family members with the same variant tend to share a similar phenotype, different phenotypes in unrelated MPS II patients who carry the same variant have also been observed, which suggests that other factors may also play a role in determining phenotype. However, ESC noted some variants are consistently associated with a severe MPS II phenotype, such as deletion of the *IDS* gene.

Overall, ESC considered that severe MPS II can often be distinguished from attenuated MPS II using genotype and family evaluation, but noted that the prognosis for attenuated cases is uncertain, due to variable expressivity and the presence of VUSs.

ESC noted that the comparator for PICO set 1 is no NBS for MPS II, i.e. current practice where MPS II diagnosis only occurs at symptom onset. ESC noted that, globally, the current median age at diagnosis without NBS is 3.1 years (range 0.5 – 14 years) for severe cases and 6 years (range 2.9 – 14 years) for attenuated cases. In Australia, the median age at diagnosis of MPS II was REDACTED.

ESC noted that there are 2 main treatments available for MPS II: intravenous ERT (funded through the LSDP) and HSCT.

ESC noted that ERT is not currently publicly funded and available for all newborns who would be diagnosed with MPS II via NBS. ESC noted that NBS would identify babies with MPS II before they developed symptoms, but that some of the diagnosed individuals would not be able to access subsidised ERT via the LSDP due to the LSDP eligibility criteria. Currently, for those who are presymptomatic, ERT for MPS II is only funded by the LSDP for children <5 years of age with a diagnosis of MPS II and with “clear prediction of progress of the disease, or if, on the basis of a sibling's disease progression, severe disease can be predicted”. There is no LSDP-funded ERT for presymptomatic children identified through NBS predicted to have attenuated disease, or for those whose disease onset and severity cannot be “clearly predicted”. ESC noted that, since phenotype cannot always be predicted from genotype, and more attenuated cases would be detected via NBS than current clinical diagnosis, a number of babies identified as having MPS II via the NBS would not be immediately eligible for treatment, and would instead be monitored until symptomatic.

ESC further noted that, whilst there have been a limited number (REDACTED) of HSCTs performed domestically, funded by the states and territories, the Commonwealth does not fund the collection and transport of cells from overseas for HSCT for MPS II. No outcomes data were available for the Australian cohort of HSCT recipients.

ESC considered that, overall, there is a partially effective treatment available for severe MPS II, and for some cases of attenuated MPS II, although considered that the degree of effectiveness was uncertain.

In terms of whether these treatments are more effective if initiated at an earlier age (following NBS, compared to clinical diagnosis at symptom onset), ESC noted that limited evidence in babies with severe disease suggested that earlier (pre-symptomatic) initiation of ERT can improve health outcomes compared to initiation of ERT after symptom onset and clinical diagnosis. ERT was associated with improved growth rates to a similar degree in younger versus older groups

with severe disease, but the benefits tended to be slightly greater in those who had treatment initiated at an earlier age. Early initiation of ERT may also slow the progression of cardiovascular disease, based on limited data. Limited data from sibling studies also showed that, although the use of ERT did not prevent somatic and neurological manifestations of MPS II in general, earlier treatment can slow the progression of the disease. The limited evidence also suggested that pre-symptomatic initiation of ERT can lead to a better quality of life as it may significantly slow or prevent the development of irreversible disease manifestations such as physical disabilities. For other health outcomes such as survival, vision and hearing impairment, musculoskeletal disease and organomegaly, no clear benefit was identified.

ESC noted that ERT cannot cross the blood–brain barrier and therefore has no effect on CNS-related symptoms – one of the most debilitating aspects of neuronopathic MPS II. However, novel approaches of ERT delivery (e.g., intraventricular or intrathecal) and gene therapy are under development and may improve treatment outcomes for the neuronopathic MPS II.

ESC noted the limited evidence on the impact of early versus late initiation of ERT for babies with attenuated disease. A few studies identified that benefits of early ERT treatment are more pronounced in severe cases compared to attenuated MPS II cases. The applicability of these findings to the comparison of NBS vs no NBS is unknown, as these cases were not identified through an NBS program. In these studies, the early and late treatment groups were both older than those currently treated in practice in Australia.

For HSCT, ESC noted that the very limited available data suggested that early initiation of HSCT pre-symptomatically can improve health outcomes when compared to initiation of HSCT after the onset of symptoms. Unlike intravenous ERT, enzymes produced after HSCT can cross the blood–brain barrier, so may have a positive effect on CNS-related symptoms. Two case series based on sibling pairs indicated that pre-symptomatic initiation with HSCT tended to have a positive impact on physical and motor development. In one study, patients' activities of daily life appeared to be improved when HSCT occurred early in the course of their disease before onset of significant neurological symptoms, although the optimal timing of HSCT was unknown. For other health outcomes such as quality of life, cardiorespiratory disease, vision and hearing impairment, musculoskeletal disease and organomegaly, no evidence was identified comparing early versus late HSCT treatment. There was no evidence available for the benefits of earlier HSCT treatment in people with the attenuated form. ESC noted the limited Australian evidence related to survival outcomes. Of the REDACTED patients who received HSCT in Australia, REDACTED had graft versus host disease, and no deaths were recorded.

ESC noted the limited evidence from international NBS programs (Taiwan, US, Japan) showed that, of the 4 babies treated with either ERT alone or ERT + HSCT, 1 died from complications due to HSCT. In the remaining 3 babies, there appeared to be a slowing of the progression of symptoms normally seen in children with MPS II, up to 4.3 years of age. ESC acknowledged that this evidence is difficult to interpret with confidence given the variable clinical expression for the condition and the small sample size resulting from disease rarity. The 3 babies treated with ERT within 3 months of birth were still displaying developmental delays at the time of reporting. For attenuated cases identified through an NBS program, no signs or symptoms have been identified as part of regular monitoring.

Overall, ESC considered that there is limited evidence to suggest any survival benefit with earlier access to treatment, based on small sample sizes. However, ESC noted that there may be other benefits associated with earlier diagnosis via NBS, such as avoidance of surgery, or better preparation of the surgical team should an individual with MPS II require surgery (since those with undiagnosed MPS II may be more difficult to intubate). Additionally, ESC noted that earlier diagnosis may facilitate access to experimental or emerging therapies.

Overall, ESC considered NBS for MPS II to have superior effectiveness for the diagnosis of severe (early-onset) MPS II and probable superior effectiveness for attenuated MPS II, compared to no NBS.

ESC noted the proposed population for family member testing following diagnosis of an index case⁴⁵, which comprises biological mothers and siblings of the index case (PICO set 2). The proposed clinical management algorithm for this group involves genetic testing, starting with the mother of male newborns diagnosed with P/LP variants of MPS II. If the mother tests positive, testing will then be offered to the newborn's maternal grandparents, aunts and uncles.

ESC considered that the stepped economic evaluation was broadly reliable and appropriate for MSAC decision-making, and noted that its stepped approach was structurally similar to that used in the related NBS applications for MPS (applications [1774](#) and [1775](#)). ESC considered the time horizons to be appropriate (**REDACTED** years for cost per diagnosis and 100 years for cost per quality-adjusted life-years [QALYs]). ESC considered the model inputs to be mostly reasonable, but noted that the multiplexing sensitivity analysis was a rough estimate only. ESC considered the quality of life (QoL) data to be reasonable albeit simplistic. ESC noted that the one-off set-up costs for MPS II screening were excluded from the economic evaluation.

ESC considered the model transition probabilities, variables and extrapolation to be the source of greatest uncertainty in QALY modelling, as multiple assumptions were used with poor transitivity. In particular, ESC noted that the overall survival curve for all MPS II types without NBS testing was first extrapolated beyond the observed median follow-up of 35 years in 800 patients with MPS II in the global Hunter Outcomes Study (with no patient assumed to die before 9 years of age). To better estimate the OS curve for severe MPS II cases without NBS testing, a derived hazard ratio (HR) of severe only Japanese patients to mixed (51% severe, 49% attenuated) Japanese patients was applied to this extrapolation. The upper 95% confidence limit (CI) of this HR was selected rather than the point estimate because it generated more plausible mean OS in severe MPS II patients. To generate the extra OS curve for severe MPS II patients detected earlier with NBS testing, the model assumed that none of these screened patients would die before 16 years of age, and thus shifted their entire subsequent OS curve 16 minus 9 = 7 years to the right of the derived OS curve for severe MPS II patients who received late ERT. This last key assumption was based on a case series of 6 Japanese patients extracted from a retrospective cohort study (Tomita et al. 2021) who received early ERT, with a median follow-up of 11 years and only one patient who was followed for 16 years, making the modelled incremental OS highly uncertain and showing that the model is highly sensitive to this assumption.

ESC noted that the incremental cost-effectiveness ratio (ICER) was **\$REDACTED** per early diagnosis of severe MPS II case from the step 1 base case model over **REDACTED** years (per newborn screened), including associated costs of testing, diagnostic delay, monitoring and ERT treatment. ESC noted that the ICER was **\$REDACTED** per early diagnosis of any subtype of MPS II.

An exploratory ICER of **\$REDACTED** per QALY gained was calculated by adding discounted quality-adjusted survival gains, prolonged monitoring and prolonged ERT costs for severe patients. ESC noted this decreased the ICER to **\$REDACTED** per QALY gained if using another HR from Burton 2017, and decreased to **\$REDACTED** per QALY gained if using a different utility value from Beusterien (2012). Decreasing the annual discount rate also decreased the ICER.

ESC also noted that the modelled health increments mostly arose from earlier treatment of severe MPS II, and any attenuated MPS II health trade-offs were not quantified.

⁴⁵ 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 family member testing)

ESC concluded that the ICERs are high, but acknowledged this is a reflection of the rarity of the condition being screened. ESC advised that MSAC may wish to consider the ICERs for treatments for rare conditions accepted by the LSDP Expert Panel, to provide context for acceptable ICERs for rare diseases. ESC further noted that MSAC should also be aware that the rule of rescue, which influences LSDP decision-making, is driven by small numbers of identifiable individuals in extremely severe circumstances, which may apply to some of the diagnosed cases, but not to all those screened.

ESC noted that the economic model does not estimate any decreased disutility from minimising the diagnostic delay of detected patients who do develop symptoms, nor any increased disutility from monitoring, including lifelong monitoring of those detected patients who do not develop symptoms. However, ESC considered that these omissions are likely to have a small effect on the estimated ICER per QALY, which is driven more by the estimated overall survival gains than by utility changes.

ESC considered the financial impact calculations were appropriate and largely based on verifiable facts, such as the newborn population, NBS uptake rates, annual incidence rates and literature-based clinical management protocols. In addition, ESC considered the estimated use and financial implications of the proposed NBS expansion to be largely reasonable, except that:

- Net costs to the LSDP appear to have been overestimated, as these should only be for the earlier use of ERT; subsequent modelled incremental ERT costs in the economic model should only occur after year 9.
- The DCAR's approach to estimating the effects of expanding via a multiplex test is incorrect; MSAC should consider which costs will not be duplicated if 2 or more of applications [1774](#), [1775](#) and 1776 are supported and NBS-implemented (such as some of the "once-off set up" program implementation costs and some of the non-test-kit costs of tier 1 screening).

ESC noted that the difference between an LC-MS/MS machine and an electrospray ionisation MS/MS machine was considered and the costs of purchasing the former machine appropriately added to the implementation costs for this application. ESC recalled that MSAC supported the use of the latter machine in its consideration of sickle cell disease testing on the NBS (Application 1737.1).

ESC noted the largest financial impact would be to the NBS (\$REDACTED in year 1 to \$REDACTED in year 6), with a total cost to government health budgets of \$REDACTED in year 1 and \$REDACTED in year 6.

ESC noted the two supplementary financial analyses supplied by the rejoinder. ESC considered that the supplementary financial analysis 2 is informative because it is similar to MSAC's previous requests to assess the consequence of both changing the NBS and changing the LSDP Guidelines to allow increased access to ERT for presymptomatic MPS II patients. ESC considered that the supplementary financial analysis 1 was not informative for MSAC because adding MPS II to the NBS would not cause an increase in the number of diagnoses of MPS II patients who were born before the NBS implementation, as this analysis implied.

ESC noted the complex ethical issues associated with the application. NBS for MPS II would increase the detection of individuals with the attenuated form of the disease, who otherwise might not be diagnosed without screening. However, early screening for certain conditions may have limited value, as the knowledge of a potential future illness can cause undue stress and anxiety. In addition to adverse effects from treatment, there are further potential harms resulting from early diagnosis particularly for those with attenuated MPS II, which include those from surveillance imaging (such as oncogenic risk from multiple CTs, risk from general

anaesthetic/sedation with magnetic resonance imaging), as well as potential psychosocial harms from diagnostic labelling, clinical surveillance and follow-up testing.

ESC also noted that some studies argue that testing newborns for adult-onset conditions may infringe on an individual's right to decide if and when they want to learn about their health. Specifically, ESC identified an ethical obligation to inform parents of a possible diagnosis of glycogen storage disease type II (target condition in application [1774](#)), which may arise once further investigation of the child requires parental consent to proceed beyond the original bloodspot sample. In such cases, an ethical obligation subsequently arises to inform parents of the outcome of the further investigation, in accordance with ethical principles of transparency and full disclosure.

ESC noted that sharing information about later-onset conditions with parents – especially when potential harms can be managed – can benefit the child and support their best interests. There is still limited evidence on the experiences of patients and parents involved in MPS II identification through NBS. Early diagnosis, combined with clear and well-delivered information, could empower parents and patients, enhancing their decision-making abilities, improving access to treatment and enabling more informed family planning choices. In addition, ESC noted the benefits associated with avoiding multiple tests as part of the diagnostic delay that often happens with patients with MPS II. ESC noted a possible benefit of gaining access to future therapies, but considered that access to these therapies is many years away and out of scope for a health technology assessment to consider.

ESC queried whether the Revvity multiplex kit options should be excluded from consideration for use as part of the NBS given that they are dominated by the **REDACTED** options (that is, they are more expensive but are not more accurate). Further, the MPS7plex kit may also report results for LSD conditions (e.g., CLN2, MPS III) that health ministers have agreed should not progress to MSAC for possible inclusion in the NBS⁴⁶, thus creating ethical difficulties for the reporting pathologist that could be avoided by not using this test kit. However, the department clarified that pathologists have the option of not testing for all 7 enzymes on the panel when using the MPS7plex kit⁴⁷ which may eliminate this ethical issue.

ESC noted that the pre-ESC response argued that the term 'patients in waiting' is not appropriate, because these patients will develop signs and symptoms even if these are milder than for severe cases. However, ESC considered that while this may be true for some individuals with attenuated MPS II, others (particularly those considered to have "very attenuated" MPS II) may never develop symptoms, and are in fact healthy people who are over-diagnosed, over-monitored and potentially over-treated.

ESC noted the PASC comments, particularly regarding the additional equipment and staff that would be required if MPS II screening was to be implemented in NBS laboratories (currently only provided through the NRL), as well as that not all patients would be eligible for access to ERT on the LSDP. ESC noted that the MSAC Executive had requested that the assessment group explore the potential economic and financial impacts of changes to LSDP criteria to expand treatment to more patients who may be identified through NBS.

⁴⁶ Available: <https://www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened#conditions-agreed-as-nontarget->

⁴⁷ This test evaluates the activity of 7 enzymes associated with the following lysosomal storage diseases: MPS II (Hunter syndrome), MPS IIIB (Sanfilippo syndrome), MPS IVA (Marquio A syndrome), MPS IVB (Marquio A syndrome B), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly syndrome) and CLN2 (Neural Ceroid Lipofuscinoses syndrome) (available: <https://apps-omics.revvity.com/test/test-pdf/?test-code=B2041>).

ESC advised that the following additional information may be needed to inform MSAC consideration:

- Revise the current approach to assessing the effects of multiplexing through undertaking a “bundled” stepped evaluation of applications 1774, 1775 and 1776 whereby any duplication of costs is addressed and cumulative diagnostic yield is appropriately assessed across the three applications.
- Clarify whether the unit cost of the proposed NBS Tier 1 testing should be benchmarked (as per the public summary document (PSD) for MSAC application 1737.⁴⁸) and if so which test components are to be included in the benchmark (MSAC should also be aware that this approach will not accurately reflect comparative cost-effectiveness because the ICER/diagnosis will vary by the genotypic prevalence of each disease and other incremental costs, and the ICER/QALY will also vary by the incremental health gains.).
- Obtain expert clinical advice on how all screen positive cases would be followed up and managed, including severe cases, cases at risk of attenuated diseases, cases at risk of very attenuated disease, and those assumed to have pseudodeficiency (noting many undergo long-term surveillance after NBS detection as per international evidence).

⁴⁸ <https://www.msac.gov.au/applications/1737-1>

Table 25 Summary table ESC compiled to facilitate MSAC consideration

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
1) Suitable NBS tests?			
Availability	<p>Partially (c.f. Main Issues box). 2-tier protocol:</p> <ul style="list-style-type: none"> Tier 1 screening options include the Redacted (NATA approval is yet to be obtained). Tier 2 testing involves reflex endogenous NRE-GAG analysis on DBS, same method as currently used on urine samples by the NRL for LSDs. <p>Little evidence for NRE-GAG as a single-tier test is available and it is not recommended due to the need for a sensitive mass spectrometer maintained under optimal performance conditions which is impractical in the high throughput context of the NBS.</p> <p>Family member test options are already used.</p>	-	<p>MSAC should consider whether to advise that possible Revvity multiplex test options be excluded from this expansion of the NBS because they are dominated by other test options:</p> <p>(a) they are more expensive (b) they are not more accurate (c) the Revvity MPS7plex kit reports results for conditions agreed by health ministers not to progress to MSAC for possible inclusion in the NBS, <i>thus creating avoidable ethical difficulties for the reporting pathologist.</i></p>
Accuracy ranges	<p>First-tier, combining fluorometric and mass spectroscopy methods (k=4), median (range): screen positive rate: 0.029% (0.012–0.062) false positive rate: 0.026% (0.011–0.056) true positive rate: 0.00142% positive predictive value: 4.89%</p> <p>Second-tier (NRE-GAG): few direct results, so 100% true positive rate extrapolated from GAG digestion (a similar testing method)</p>	<p>Sensitivity and specificity both accepted as 100%. From a total of 723 subjects including 630 controls, all 93 MPS patients (13 with MPS II) were correctly identified as 1 of 10 subtypes by urinary NRE-GAG. (Urinary NRE-GAG is also accepted as providing additional diagnostic information over NRE-GAG performed on a bloodspot sample.)</p>	<p>MSAC may wish to note that there could be an ethical obligation to inform parents of a confirmed MPS II diagnosis (and to obtain their consent) if there is a need to proceed with further investigation of the child beyond the original bloodspot sample, and therefore also an additional ethical obligation to subsequently inform the parents of the outcome of the further investigation.</p>
2) Determination of disease subtype and prognosis following NBS?			

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
	<p>Partially for disease sub-type (c.f. Main Issues box). MPS II is distinguishable from pseudodeficiency by the second-tier test on the bloodspot sample, although there is uncertainty whether there is consensus on the diagnostic threshold that is used to rule out MPS II. Neuronopathic (severe) MPS II is confidently distinguishable only if “major changes” to the <i>IDS</i> gene, or if there are family members with known genotype and phenotype. Otherwise not able to confidently predict whether individual may develop neuronopathic or non-neuronopathic (later onset attenuated) MPS II.</p> <p>No for prognosis.</p>	Severity determined based on clinical presentation.	The current treated life expectancy is 10-20 years for severe MPS II (median 17 years, range 14-21 years in one study) and 60-70 years for attenuated MPS II.
3) Effective treatment of each MPS II subtype?			
Neuronopathic (severe), including presymptomatic if <5 years of age	<p>Uncertain effectiveness:</p> <ol style="list-style-type: none"> Intravenous ERT (idursulfase) available via the LSDP: is ineffective for CNS disease (does not cross blood brain barrier), possible beneficial effects on other outcomes. <p>HSCT potentially available via states and territories (no routine Commonwealth funding for stem cell collection and transportation from overseas donors): possible beneficial effects on CNS disease and other outcomes</p>	As for with NBS – ERT available after diagnosis. HSCT potentially available via states and territories.	
Non-neuronopathic (later onset, attenuated), symptomatic only	Unknown effectiveness for both ERT and HSCT	-	Idursulfase is the only Life-Saving Drugs Program (LSDP)-funded drug as intravenous ERT for presymptomatic children <5 years of age with a diagnosis of MPS II and with “clear prediction of progress of the disease, or if, on the basis of a

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
			<p>sibling's disease progression, severe disease can be predicted".</p> <p>There is no LSDP-funded ERT for presymptomatic children identified through NBS predicted to have attenuated disease, or for those whose disease onset and severity cannot be "clearly predicted".</p> <p>There is no evidence for the use of HSCT in attenuated MPS II.</p>
4) Increased effectiveness of earlier treatment start?			
Evidentiary basis = Linked evidence: earlier diagnosis => earlier management change => better health outcomes			
Age at symptom onset in years, median			
Neuronopathic (severe)	-	1-3	No change expected
Non-neuronopathic (later onset, attenuated)	-	4	No change expected
Age at diagnosis in years, median (range)		Redacted	
Neuronopathic (severe)	0.16	3.1 (0.5 – 14)	
Non-neuronopathic (later onset, attenuated)	0.16	6 (2.9 – 14)	
Age at ERT treatment initiation after diagnosis in years, median (range)		Redacted	
Neuronopathic (severe)	Likely 0.25 (0.08 – 1)	5.1 (0.3 – 12.1)	Age at treatment initiation with NBS was not reported separately for each phenotype; however, given the LSDP criteria for ERT access, the reported age at ERT initiation would likely only apply to severe cases in the Australian context.
Non-neuronopathic (later onset, attenuated)	Not reported separately from severe cases 4 (estimated using age at treatment initiation in the absence of NBS, minus the median length of diagnostic delay).	7.5 (0.13 – 25.3)	Age at treatment initiation with NBS was not reported separately for each phenotype; however, given the LSDP criteria for ERT access, the reported age at ERT initiation would likely only apply to severe cases in the Australian context.

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
Time to diagnosis in years, median (range)			
Neuronopathic (severe)	–	1.5 (0 – 9.2)	
Non-neuronopathic (later onset, attenuated)	–	2.03 (0 – 18)	
Proportion with diagnostic delay			
Neuronopathic (severe)	–	Assumed to be 100%	
Non-neuronopathic (later onset, attenuated)	–	Assumed to be 100%	
Number of MPS II affected cases monitored			
Neuronopathic (severe)	0	–	
Non-neuronopathic (later onset, attenuated)	2.89	–	
Treatment effectiveness			
Early vs late ERT (idursulfase 0.5 mg/kg weekly) in neuronopathic (severe) MPS II not reported quantitatively	The economic model claims 7 extra years of 100% overall survival (assumption based on very uncertain effectiveness data for early use of ERT from a case series of 6 Japanese children with severe MPS II who received “early” ERT in a retrospective cohort study of 17 Japanese children compared with modified overall survival data from a cohort of 800 patients receiving late ERT in the global Hunter Outcomes Study).		Concerns about the poor transitivity across single-arm studies hinders the drawing of any robust quantified comparison. There is no direct evidence for the comparative safety and effectiveness arising from the change in use of ERT or HSCT following an earlier diagnosis of severe MPS II through NBS. The possible survival benefit from earlier ERT is highly uncertain due to the very limited observational data available.
Early vs late ERT in non-neuronopathic (later onset, attenuated) MPS II not reported quantitatively	The economic model makes no incremental health outcome claim.		Concerns about the poor transitivity across single-arm studies hinders the drawing of any robust quantified comparison.
5) Cost-effectiveness?			
Step 1 Base case model (per newborn screened), Redacted-year time horizon^a			
ICER (\$/early diagnosis of severe MPS II)	Cost: \$Redacted Early severe MPS II diagnoses: 0.00000468	Cost: \$Redacted Early severe MPS II diagnoses: 0	Increment: \$Redacted Increment: 0.00000468 (4.7 per million) ICER: \$Redacted

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
ICER (\$/early diagnosis of any subtype of MPS II)	Cost: \$Redacted Early diagnoses of MPS II (any subtype): 0.00001420	Cost: \$Redacted Early diagnoses of MPS II (any subtype): 0	Increment: \$Redacted Increment: 0.00001420 (14.2 per million) ICER: \$Redacted
Step 3 Exploratory model (per newborn screened), lifetime (100 years) time horizon^b (exploratory costs included costs of NBS, confirmatory testing, treatment and monitoring)			
ICER (\$/QALY gained)	Cost: \$Redacted QALYs: 0.00003462 (34.6 per million) Intravenous ERT and monitoring started in first year of life.	Cost: \$Redacted QALYs: 0.00002832 (28.3 per million) Intravenous ERT and monitoring started from year of diagnosis (aged 3 years).	Increment: \$Redacted Increment: 0.00000630 (6.3 per million) ICER: \$Redacted Exploratory treatment costs included costs of intravenous weekly ERT and administration (assumed 100% compliance and no discontinuation of treatment while alive). Monitoring every 3 months
Utilisation – incident cases			
Number of MPS II affected cases diagnosed per year	4.33 = 1.42/100,000 (which is less than 1/50,000)	1.89 = 0.62/100,000	
Proportion neuronopathic (severe)	33%	75%	
Proportion non-neuronopathic (later onset, attenuated)	11%	25%	
Proportion “very attenuated”	56%	–	
Number with neuronopathic (severe) MPS II	1.43	1.42	
Number with non-neuronopathic (later onset, attenuated) MPS II	0.47	0.47	
Number with “very attenuated” MPS II	2.42	0	
6) Financial estimates for each budget holder?			
Program implementation costs	\$Redacted (Year 1)		\$Redacted (Year 1)
Total cost to the NBS	\$Redacted (Year 1) to \$Redacted (Year 6)	–	\$Redacted (Year 1) to \$Redacted (Year 6)
Cost to States and Territories			\$Redacted (Year 1) to \$Redacted (Year 6)
Cost to the MBS (Commonwealth)			\$0.05 million (Year 1) to \$0.17 million (Year 6)
Cost to the LSDP (Commonwealth)			\$Redacted (Year 1) to \$Redacted (Year 6)

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for MPS II	Current (No universal NBS for MPS II) – diagnosis at symptom onset	Other/Increment/Comment
Cost to government health budgets			\$Redacted (Year 1) to \$Redacted (Year 6)

Source: Compiled by ESC with the assistance of the department based on the 1776 Department-Contracted Assessment Report.

^a The NBS arm includes costs for expanding NBS to include MPS II for all newborns, confirmatory and monitoring costs for MPS II cases and treatment costs for severe MPS II cases. The no NBS arm includes costs for diagnostic delay, confirmatory diagnosis and monitoring costs (once diagnosed) for MPS II cases and treatment costs (once diagnosed) for severe MPS II cases.

^b Both arms include treatment and monitoring costs for severe disease cases until death. The NBS arm also includes monitoring costs for “very attenuated” patients until death. The no NBS arm does not include any costs for any “very attenuated” disease cases because they are not identified throughout their lifetime.

Abbreviations: DBS = dried blood spot; ERT= enzyme replacement therapy; GAG = glycosaminoglycans; HSCT = haematopoietic stem cell transplant; ICER= incremental cost-effectiveness ratio; LSD = Lysosome Storage Disorder; LSDP= Life Saving Drugs Program; m = month(s); MBS = Medicare Benefits Schedule; MPS II = mucopolysaccharidosis Type II; NATA = National Association of Testing Authorities; NBS = newborn bloodspot screening; NRE-GAG = non-reducing end-glycosaminoglycans; NRL = National Referral Laboratory; QALY= quality-adjusted life year.

Table 26 Summary table of estimated annual consequences of Newborn Bloodspot Screening for MPS II (Hunter syndrome)

Screened	NBS result to parents	Subsequent diagnosis to parents	Incremental consequence of screening for patients ^b	Health outcome consequences for patients	Incremental cost-effectiveness outcomes for patients
305,000	304,996 no	–	–	–	–
	4.33 yes ^a	1.43 severe	Patient diagnosed ~3 years earlier	Earlier ERT treatment suggested to improve intermediate and symptomatic health outcomes and overall survival	\$Redacted/QALY
		0.47 later onset, attenuated 2.42 “very attenuated”	2.4 more “very attenuated” patients diagnosed; all diagnosed years earlier	Earlier ERT treatment not shown to improve outcomes; may cause harms such as developing antibodies; later diagnostic delay shortened, extra monitoring (with associated harms) required.	Up to 2.42 extra patients receiving prolonged monitoring at \$2,101.13 per monitored patient per year

^a MSAC should consider whether to advise that a new informed consent be obtained from parents at this point to enable subsequent testing beyond the bloodspot sample based on the positive NBS result.

^b These consequences do not include any estimates of incremental consequences from family member testing

Abbreviations: ERT= enzyme replacement therapy; MPS II = mucopolysaccharidosis Type II; NBS = newborn bloodspot screening; QALY= quality-adjusted life year

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)