Consultation Survey on MSAC Application 1776

Newborn bloodspot screening for mucopolysaccharidosis, Type II (MPS II)

MSAC welcomes input on MSAC applications for public funding from individuals, organisations representing health professionals or consumers and/or carers, and from other stakeholders. Please use this template to prepare your input. You may also attach additional information if you consider it may be useful in informing MSAC and its sub-committees.

Sharing consultation input

Submitted consultation input will be routinely shared with the applicant and with MSAC and its sub-committees.

- The applicant will receive a summary of comments from individuals, with the individual's name and other identifying information removed.
- MSAC and its sub-committees will receive both the summary and copies of the comments, with the name of the individual and other identifying information removed.
- Consultation input from groups or organisations will be provided in a complete form to both the applicant and to MSAC and its sub-committees.

Consultation input may also be shared with HTA Assessment Groups from time to time to inform their reports to MSAC or with state and territory health representatives where the application is for a service to be delivered through public hospitals. Please do not include information in your input that you do not want shared as outlined above. In addition, to protect privacy, do not include identifying personal (e.g., name) or sensitive (e.g., medical history) information about third parties, such as medical professionals or friends/relatives.

How consultation input is used

MSAC and its sub-committees consider consultation input when appraising an application, including to better understand the potential impact of the proposed medical technology/service on consumers, carers, and health professionals. A summary of consultation input will be included in the Public Summary Document (PSD) published on the MSAC website once MSAC has completed its appraisal. The PSD may also cite input from groups/organisations, including the name of the organisation. As such, organisations should not include information or opinions in their consultation input that they would not wish to see in the public domain.

Consultation deadlines. Please ensure that your consultation input is submitted by the pre-PASC or pre-MSAC consultation deadline for this application. Consultation deadlines for each PASC and MSAC meeting are listed in the PASC, ESC, MSAC key dates available on the MSAC website. They are also published in the MSAC Bulletin. Consultation input received after the respective deadlines may not be considered.

For further information on the MSAC consultation process please refer to the MSAC Website or contact the Consumer Evidence and Engagement Unit on email: commentsMSAC@health.gov.au.
Thank you for taking the time to provide consultation input. Please return your completed survey to:

Email: commentsMSAC@health.gov.au

Mail: MSAC Secretariat,
MDP 960, GPO Box 9848,
ACT 2601.

PART 1 – PERSONAL AND ORGANISATIONAL INFORMATION

1. Respondent details

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2. Is the feedback being provided on an individual basis or by a collective group?

☐ Individual
☒ Collective Group

If an individual, specify the name of the organisation you work for

If a collective group, specify the name of the group

3. How would you best identify yourself?

☐ General Practitioner
☐ Specialist
☒ Researcher
☐ Consumer
☐ Care giver
☐ Other

If other, please specify

PART 2 – CLINICAL NEED AND PUBLIC HEALTH SIGNIFICANCE

4. Describe your experience with the medical condition (disease) and/or proposed intervention and/or service relating to the application summary.

Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, research and timelines of genomic research projects, and to support Commonwealth, State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy ad action for integrating genomic technologies into the health system. By interfacing with consumers, government, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Following the Genomic Health Futures Mission (GHFM) investment into five research projects exploring new models of genomic newborn bloodspot screening, Australian Genomics formed the Genomic Screening Consortium for Australian Newborns (GenSCAN), which includes the lead investigators of each of the five projects. GenSCAN was developed for the purpose of enabling improved efficiency and impact of the MRFF GHFM investment through complementary and collaborative research, as well as a cohesive national approach to the exploration of genomics into Australian newborn screening programs. Through GenSCAN, the GHFM funded projects are also exploring the opportunities to expand the conditions and genes currently screened. Under the GenSCAN Steering Committee there are five working groups collectively exploring technical platforms, bioinformatics and data, clinical matters and conditions to be screened, ethics, legal and social issues, and health policy and economic feasibility. In addition to investigators from the five research studies, these working groups are made of key subject matter experts, Department of Health and Aged Care representatives and patient advocacy members.

The collaborative approach of GenSCAN works towards the aim of achieving national consistency for Newborn Bloodspot Screening especially with respect to any introduction of genomic sequencing as part of the program. Australian Genomics supported research has a strong emphasis on bioethics as well as exploring questions of implementation in a national setting.

5. What do you see as the benefit(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

The proposed service would facilitate earlier diagnosis of mucopolysaccharidosis, Type II (MPS II) and in turn for affected individuals and their families to support earlier access to interventions including Enzyme Replacement Therapy (ERT) and Hematopoietic Stem Cell Transplant (HSCT). For MPS II, this would potentially mean that treatment can begin prior to symptoms. This reduces the chance of complications associated with MPS II. Expert consensus from the American College of Medical Genetics and Genomics recommended that ERT should start at the time of diagnosis and prior to the onset of symptoms in individuals with a severe MPS II genotype or anyone with MPS II symptoms (McBride et al., 2020). There is evidence that treatment with ERT (for example idursulfase) improves patient outcomes (PICO Set 1). A study by Burton et al., (2017) found a 54% lower risk of death in MPS II patients that had received idursulfase treatment. There is also evidence of increased joint mobility after ERT (Muenzer et al., 2006). We note that testing for MPS II is available via the Life Saving Drugs Program, increasing equity of access for this treatment.

Where a genetic diagnosis has been made for MPS II (noting difficulties associated with the pseudogene *IDSP1*), cascade testing of mothers and older male siblings is recommended. This will provide more information for the family regarding reproductive options and more certainty around diagnosis for other family members.

Regenxbio has a gene therapy trial for MPS II currently underway. The inclusion criteria for the age of participants is 4 months to 5 years of age. This highlights the importance of early diagnosis for potential access to novel treatments (https://www.clinicaltrials.gov/study/NCT03566043).

6. What do you see as the disadvantage(s) of the proposed medical service, in particular for the person involved and/or their family and carers?

Unlike the proposed tests in applications 1774 and 1775, there is no commercially available test kit for MPS II. Therefore, the work up of tests in the individual testing laboratories may result in variability in the methodology used, in turn influencing other factors including costing and turnaround times. Given that 78% of tier 1 tests give false positive results (due to pseudodeficiency), the volume of tier 2 GAG testing is expected to be large compared to other conditions being screened via NBS.

Eligibility to ERT through the LSDP has strict eligibility criteria and initial applications must be followed by annual reapplications to ensure continued eligibility is met. This would be a highly stressful process for families, especially for the small number who do not meet or do not continue to the meet the criteria. At the same time HSCT is not a risk-free procedure and would also cause considerable stress to families.

As outlined in the PICO Set 1, there is limited data on the benefits and risks of ERT treatment in babies under 1 year old. We encourage further work on this evidence base. As reviewed by Concolino et al., (2018), ERT is generally well tolerated and has an acceptable safety profile. The treatment has been available since 2006 for MPS II (Concolino et al., 2018). There is a risk of death with HSCT treatment and a lack of efficacy for CNS symptoms (Ream et al., 202).

Australia's lack of participation in the Hunter outcome survey – a registry collecting data about MPS II in 29 countries – disadvantages Australian newborns diagnosed with MPS II via the NBS program. The collection of data for Australian patients would help contribute to the natural history of the condition, making diagnosis, prognosis and treatment more accurate for this complex condition with a typically long diagnostic odyssey.

PICO Set 1 outlines variable incidence of MPS II based on geography and ethnicity. The introduction of genetic testing as part of any screening program raises the critical importance of genetic databases representing the diversity of Australians, to determine the prevalence of specific variants in different ethnic groups to inform variant classification. This will impact the prevalence of VUS in some individuals and will affect equity of service delivery in non-Caucasian populations including Aboriginal and Torres Strait Islander people. Projects such as ourDNA (https://populationgenomics.org.au/projects-ourdna/) should contribute to a more complete genetic variant database for Aboriginal and Torres Strait Islander People. This MRFF funded program aims to increase genomic representation of Australian communities from a variety of backgrounds including African, Asian, Middle Eastern, Oceanic and Aboriginal and Torres Strait Islander communities. Australian Genomics encourages further work in this area to achieve equitable and best practice standard of care access.

7. What other benefits can you see from having this intervention publically funded?

There may be a reduction in financial cost to the health system through early detection of MPS I. This would be in terms of the affected individual (allowing for early detection and more informed treatment options compared to clinical diagnosis), and the risk assessment of family members by determining carrier status (by providing certainty around the need for ongoing monitoring and surveillance).

8. What other services do you believe need to be delivered before or after this intervention, e.g. Dietician, Pathology etc?

The initial NBS test will mainly be facilitated by the neonatologist, nurse and midwife team. As MPS II affects several organs, individuals who test positive after confirmation will have a range of health professionals involved in their care, including specialist physicians and allied health professionals including genetic counsellors.

Genetic testing is complicated the presence of a pseudogene which may be encountered in the confirmatory testing process. There are more than 700 pathogenic variants described and up to 30% are *de novo* (PICO Set 1). For this X-linked condition, if there is a referral to a genetic service, the female parent and any older male siblings of an affected newborn would be offered genetic testing.

Given the presence of the *IDS* pseudogene, interpretation of variants can be challenging. Secondly, as is the case with all genes, variants of uncertain significance will inevitably be identified. However, there are specific biochemical investigations (that state biochemical genetics labs have set up or could set up), and specific enzymology that can be performed in easily accessible tissues (available from the Adelaide reference laboratory), that can assist with interpretation of variants.

PART 3 – INDICATION(S) FOR THE PROPOSED MEDICAL SERVICE AND CLINICAL CLAIM

9. Do you agree or disagree with the proposed population(s) for the proposed medical service?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

The population indicated is all newborns in Australia, as they are eligible for NBS, although 99.3% of newborns in Australia do undergo NBS (National Newborn Bloodspot Screening Policy Framework).

PICO Set 2 outlines the population for cascade testing to be performed on the female parent of male newborns with disease-causing variants. There is also a consultation question about whether male parents should be tested in the rare case of affected female newborns. MSAC should consider the clinical and system implications of further cascade testing as part of their deliberations.

10. Have all the associated interventions been adequately captured in the application summary?

- ☒ Yes
- ☐ No

Please explain:

The intervention is NBS for MPS II plus cascade testing for the female parent.

11. Do you agree or disagree that the comparator(s) to the proposed medical service?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Please explain:

The comparator of no universal screening for MPS II through NBS**.**

The Application Summary suggests that there are no genetic counsellors associated with metabolic clinics in current practice in Australia. Although this is true, most metabolic clinics are either part of a more

comprehensive genetics service or have readily accessible clinical genetics services, and so could access genetic counsellors as needed. It should also be noted that most metabolic specialists have been trained or accredited by the RACP under its Clinical Genetics training board, so should have the requisite skills to deliver genetic diagnoses.

12. Do you agree or disagree with the clinical claim made for the proposed medical service?

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

The claim is that NBS MPS II testing is superior to no testing, based on a summary of evidence presented in the application that earlier treatment is more effective than later commencement of treatment at symptom onset and diagnosis.

PART 4 – COST INFORMATION FOR THE PROPOSED MEDICAL SERVICE

13. **Do you agree with the proposed service descriptor?**

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

There is no service descriptor for NBS MPS II screening as it is not a proposed addition to the MBS.

14. **Do you agree with the proposed service fee?**

- ☐ Strongly Agree
- ☒ Agree
- ☐ Disagree
- ☐ Strongly Disagree

Specify why or why not:

The proposed price of supply for the screening test is based on the cost of the MPS I test. This information is redacted so it is not possible to comment.

The proposed price of supply for cascade testing for sequencing *IDS* (mainly for family planning) is consistent with the reimbursement cost associated with existing Medicare item numbers for cascade testing per pathogenic/likely pathogenic variant. Over 700 variants have been identified in the *IDS* gene for this condition and the price of service may be increased as several variants may need to be reviewed. Complex genotype-phenotype relationships and a pseudogene contribute to diagnostic complexity. Expectation for this to cost to be covered by family would introduce inequity and the NBS testing pathway should be publicly funded from end to end.

PART 5 – ADDITIONAL COMMENTS

15. Do you have any additional comments on the proposed intervention and/or medical condition (disease) relating to the proposed medical service?

The proposed medical services align with key objectives outlined in the program overview of the NBS National Policy Framework, pg 9, with the objectives of newborn screening including: quality, timely and evidence informed screening; enables early detection to reduce morbidity and mortality of conditions; support timely communication of relevant information to families.

The proposed interventions also relate to pre-symptomatic identification of a health condition, which supports the policy aspirations of a more proactive health system for Australia.

The US Secretary of Health and Human Services added MPS II to the Recommended Uniform Screening Panel (conditions recommended for newborn screening (Ream et al., 2023). the proposed intervention would align Australia with similar NBS programs in other countries.

Broader current Australian health system issues that need to be considered alongside the NBS program include:

1. The important role that an expanded reproductive carrier screening program for Australia could play in the proactive, upstream prevention of genetic health conditions. Also, the inclusion of a potential expanded carrier screening program in the health economic modelling and other HTA aspects when considering diagnostic and therapeutic interventions for genetic conditions.
2. The need for genetic registries for accurate and complete data collection with respect to pathogenicity of variants, variant frequency, genotype-phenotype relationships, and effectiveness of high-cost novel therapies. With gene therapies under development for MPS II, the importance of registries to track the impact of therapies over time becomes increasingly important.
3. The critical role that having a complete picture of the genetic diversity of Australians will have in accurate screening and diagnosis of genetic conditions in Australia, making access to novel health technologies and therapies equitable for our First Nations people and our diverse population.
4. The importance of states and territories in working together to introduce new health conditions to screening programs, and in the delivery of screening programs more generally, in a harmonised way to achieve health equity.

16.Do you have any comments on this feedback survey? Please provide comments or suggestions on how this process could be improved.

<u>Again, thank you for taking the time to provide valuable feedback.</u>

References

Burton BK, Jego V, Mikl J, Jones SA. Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). J Inherit Metab Dis. 2017 Nov;40(6):867-874. doi: 10.1007/s10545-017-0075-x. Epub 2017 Sep 8. PMID: 28887757.

Concolino D, Deodato F, Parini R. Enzyme replacement therapy: efficacy and limitations. Ital J Pediatr. 2018 Nov 16;44(Suppl 2):120. doi: 10.1186/s13052-018-0562-1. PMID: 30442189; PMCID: PMC6238252.

McBride KL, Berry SA, Braverman N; ACMG Therapeutics Committee. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 Nov;22(11):1735-1742. doi: 10.1038/s41436-020-0909-z. Epub 2020 Aug 3. PMID: 32741966.

Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, Vellodi A, Martin R, Ramaswami U, Gucsavas-Calikoglu M, Vijayaraghavan S, Wendt S, Puga AC, Ulbrich B, Shinawi M, Cleary M, Piper D, Conway AM, Kimura A. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med. 2006 Aug;8(8):465-73. doi: 10.1097/01.gim.0000232477.37660.fb. Erratum in: Genet Med. 2006 Sep;8(9):599. Wendt, Suzanne [corrected to Wendt, Susanne]; Puga, Antonio [corrected to Puga, Ana Cristina]; Conway, Ann Marie [corrected to Conway, Anne Marie]. PMID: 16912578.

National Bloodspot Screening National Policy Framework. Australian Health Ministers Advisory Council May 2018. https://www.health.gov.au/sites/default/files/documents/2020/10/newborn-bloodspot-screening-national-policy-framework.pdf

Pollard LM, Jones JR, Wood TC. Molecular characterization of 355 mucopolysaccharidosis patients reveals 104 novel mutations. J Inherit Metab Dis. 2013 Mar;36(2):179-87. Epub 2012 Sep 14. PMID: 22976768.

Ream MA, Lam WKK, Grosse SD, Ojodu J, Jones E, Prosser LA, Rosé AM, Comeau AM, Tanksley S, Powell CM, Kemper AR. Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. Genet Med. 2023 Feb;25(2):100330. doi: 10.1016/j.gim.2022.10.012. Epub 2022 Nov 29. PMID: 36445366; PMCID: PMC9905270.