Consultation Survey on MSAC Application 1775

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

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

Australian Genomics

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 medical service would facilitate earlier diagnosis of mucopolysaccharidosis, Type 1 (MPS I) than would occur without the intervention. Earlier identification would offer the opportunity for the individual to have more treatment options available that have confirmation of a positive indication via NBS. The current clinical care model does not provide an opportunity for early detection of MPS I, other than genetic testing of relatives coupled with prenatal screening where there is a family history. NBS facilitates early detection, and consideration for Hematopoietic Stem Cell Transplant (HSCT) and/or Enzyme Replacement Therapy (ERT). For the severe Hurler syndrome phenotype, earlier detection via NBS will allow for earlier HSCT treatment which would likely result in slower neurological decline and prevent and/or reverse clinical features severe MPS I (Muenzer et al., 2009). There is evidence that if HSCT treatment starts before complications occur, better outcomes are achieved (Ghosh et al., 2016; Staba et al., 2004).

ERT treatment is recommended for patients with attenuated forms of MPS I with early treatment being recommended. There is evidence of less severe symptoms (cardiac, sleep apnoea, liver size, linear growth, mobility range and visual activity Muenzer et al., 2009).

We support the proposal of a two-tiered approach as outlined in the application, making use of IDUA enzyme activity (tier 1) and subsequent measurement of GAG on samples with a positive first tier result. There is a strong evidence base from overseas centres adopting this approach that there is a reduction in the false positive rate (Clarke et al., 2020).

There is a gene therapy trial currently underway for patients with MPS I where eligibility is from four months of age. This highlights the importance of early diagnosis for potential access to novel treatments (https://clinicaltrials.gov/study/NCT03580083https://www.research.chop.edu/rgx-111-gene-therapy-in-patients-with-mucopolysaccharidosis-type-i-mps-i).

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?

The proposed tier 1 test for MPS I is done with a kit purchased from Revvity. A conservative estimate would suggest that Australia would require around 650 kits per year (not accounting for controls). Presumably this diagnostic kit is not manufactured in Australia, which raises concerns about potential impacts on the availability of assay kit and supply chain issues. These issues arise given factors like geopolitical instability and impacts we have recently experienced from the COVID-19 pandemic. Building sovereign capability and capacity for a testing program as critical as the NBS would ensure self-sufficiency for Australia.

There may be adverse side effects of treatment with HSCT. (Noh and Lee, 2014; Guidelines for treatment of MPS I through LSDP 2022). There may be complications from graft versus host disease for example (PICO Set 1).

For some milder Scheie syndrome cases, ERT treatment is not recommended until later in life when symptoms appear – in these cases appropriate support services would need to be made available for families due to the prolonged delay and uncertainty of the commencement of symptoms.

For those patients who are identified to have MPS I and are eligible to receive ERT through the LSDP this may raise further complications for families. These may be long, uncomfortable treatments, with potential adverse reactions. These difficulties would be amplified for families where specialists who can administer the treatment are not available in every state/territory and they must travel to receive therapy.

PICO Set 1 indicates there are some genetic variants with differing prevalence across ethnicities. 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 I affects several organs, individuals who test positive after confirmation will have a range of health professionals involved in their care including cardiologists, neurologists, respiratory physicians, psychologists and genetic counsellors.

Where an individual has had their bloodspot screening result confirmed, genetic testing via a genetic service would be offered, including genetic counselling around reproductive options for carriers of MPS I disease causing variants.

PICO Set 1 refers to a consultation process to determine how laboratories would prefer to conduct testing for MPS I (e.g. in house versus Revvity kit, mass spec versus fluorometry). This, combined with GAG assay, *IDUA* sequencing, and

the important role clinical assessment make it a complicated diagnostic pathway. It will be very important for Australian Government to lead the development of coordinated harmonised approaches across testing laboratories in different jurisdictions. National consistency of screening programs is an objective of the National Newborn Bloodspot Screening Policy Framework and the Australian Society of Inborn Metabolism. This can only be achieved through collaboration between the health departments in each state and territory, including the five national NBS programs and subsequent referral pathways to ensure appropriate clinical models of care and clinician support.

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 (Newborn Bloodspot Screening Policy Framework).

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

- ☒ Yes
- ☐ No

Please explain:

The intervention is NBS for MPS I plus cascade testing for relatives.

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 is no universal screening for MPS I through NBS.

However, if expanded reproductive genetic carrier screening becomes more broadly available in Australia, the comparator will likely be adjusted to newborns that have not been born following reproductive interventions carried out due to identified *IDUA* carrier status in both genetic parents. This, along with the alternative comparator (couples with known family history or ancestry indicating targeted testing) will influence the definition of the comparator and population over time.

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 I 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 I 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:

It is not possible to comment on the service fee of the kit due to redaction. The Revvity MSMS kit referenced in the application screens for MPS I and five other LSDs, including GSD II (MSAC application 1774). We note that other lysosomal storage disorders that this assay can detect (Gaucher disease, Niemann-Pick A/B, Fabry disease and Gaucher disease) are conditions identified for NBS technical advice (https://www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened). The ability for an assay to detect multiple conditions in parallel, relates to item 4.5, pg 39 of the NBS National Policy Framework, in terms of multiplexing within existing panels.

The proposed price of supply for cascade testing for sequencing *IDUA* (mainly for family planning) is consistent with the reimbursement cost associated with existing Medicare item numbers for cascade testing per pathogenic/likely pathogenic variant. As the number of disease-causing variants for this condition >100 the price of service may be increased as several variants may need to be reviewed. 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.

NBS testing for this condition is in place in the USA and Taiwan (Chan et al., 2019; Clark et al.,2020), 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.
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 conditions to screening programs, and in the delivery of screening programs more generally, in a harmonised way to achieve health equity.

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

Again, thank you for taking the time to provide valuable feedback.

References

Australian Government Dept of Health and Aged Care 2022. Guidelines for the treatment of mucopolysaccharidosis type I (MPS I) through the Life Saving Drugs Program. https://www.health.gov.au/sites/default/files/2022-11/life-saving-drugs-program-mucopolysaccharidosis-type-i-mps-i-guidelines_0.pdf

Chan MJ, Liao HC, Gelb MH, Chuang CK, Liu MY, Chen HJ, Kao SM, Lin HY, Huang YH, Kumar AB, Chennamaneni NK, Pendem N, Lin SP, Chiang CC. Taiwan National Newborn Screening Program by Tandem Mass Spectrometry for Mucopolysaccharidoses Types I, II, and VI. J Pediatr. 2019 Feb;205:176-182. doi: 10.1016/j.jpeds.2018.09.063. Epub 2018 Nov 6. PMID: 30409495; PMCID: PMC6623979.

Clarke LA, Dickson P, Ellinwood NM, Klein TL. Newborn Screening for Mucopolysaccharidosis I: Moving Forward Learning from Experience. Int J Neonatal Screen. 2020 Nov 19;6(4):91. doi: 10.3390/ijns6040091. PMID: 33227921; PMCID: PMC7712368.

Ghosh A, Miller W, Orchard PJ, Jones SA, Mercer J, Church HJ, Tylee K, Lund T, Bigger BW, Tolar J, Wynn RF. Enzyme replacement therapy prior to haematopoietic stem cell transplantation in Mucopolysaccharidosis Type I: 10 year combined experience of 2 centres. Mol Genet Metab. 2016 Mar;117(3):373-7. doi: 10.1016/j.ymgme.2016.01.011. Epub 2016 Jan 27. PMID: 26832957; PMCID: PMC5177791.

Gragnaniello V, Cazzorla C, Gueraldi D, Puma A, Loro C, Porcù E, Stornaiuolo M, Miglioranza P, Salviati L, Burlina AP, Burlina AB. Light and Shadows in Newborn Screening for Lysosomal Storage Disorders: Eight Years of Experience in Northeast Italy. Int J Neonatal Screen. 2023 Dec 25;10(1):3. doi: 10.3390/ijns10010003. PMID: 38248631; PMCID: PMC10801488.

Muenzer J, Wraith JE, Clarke LA; International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009 Jan;123(1):19-29. doi: 10.1542/peds.2008-0416. PMID: 19117856.

Noh H, Lee JI. Current and potential therapeutic strategies for mucopolysaccharidoses. J Clin Pharm Ther. 2014 Jun;39(3):215-24. doi: 10.1111/jcpt.12136. Epub 2014 Feb 25. PMID: 24612142.

Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P, Allison-Thacker J, Wood S, Wenger DA, Rubinstein P, Hopwood JJ, Krivit W, Kurtzberg J. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med. 2004 May 6;350(19):1960-9. doi: 10.1056/NEJMoa032613. PMID: 15128896.