Consultation Survey on MSAC Application 1774

Newborn bloodspot screening for glycogen storage disease, Type II (Pompe disease)

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 Glycogen Storage Disorder-Type II (GSD II) than would occur without the intervention. Earlier identification would offer the opportunity for the individual to receive earlier access to treatment. Specifically, after further clinical assessment and a confirmatory diagnostic testing of individuals with abnormal screening results, enzyme replacement therapy (ERT) may be available via the Life Saving Drugs Program (LSDP). There is evidence that pre-symptomatic diagnosis and early treatment can delay onset of symptoms in infantile onset GSD II. In infantile-onset GSD II such early treatment has been linked to normal growth and development and presenting cardiac and respiratory function (Al-Hassnan et al, 2022). There is also evidence of lower mortality rates (Kemper et al., 2013).

For individuals with late-onset GSD II, the benefit still relates to early treatment for individuals who are monitored, and treatment commences as soon as the condition becomes symptomatic. There is evidence from late-onset GSD II patients that ERT improved walking distance (Sarah et al., 2022).

As outlined in the PICO Set 1 (also refer to Figure 1 and Figure 2), we understand that all patients with suspected GSD II will have *GAA* sequencing at some stage of their clinical management. For patients with suspected early-onset GSD, after a positive NBS result, urine HEX4 is used as the confirmatory test due to its shorter turn-around time. An indicative HEX4 assay result will be followed by *GAA* sequencing. For early-onset GSD II without cardiovascular complications and for late-onset GSD II where there is less clinical urgency, *GAA* sequencing will be used as the confirmatory test. This approach emphasises the need for standardised clinical and diagnostic pathways

and a multidisciplinary team approach to ensure testing and confirmation aligns with clinical urgency and treatment options.

Cascade testing of family members for variant(s) identified for GSD II will determine the carrier status of family members. This will provide certainty for non-carriers of not being at risk of developing the disease themselves, relieving them from any regular monitoring and surveillance processes. Additionally, for family members where carrier status is confirmed, it will permit reproductive options to be explored for further planned pregnancies.

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 GSD II 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. The consideration of these issues arises 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.

Table 6 in PICO Set 1 shows that almost half of positives identified from the NBS each year will be false positives, amounting to about 10 per year (e.g. due to pseudoinsufficiency variant). There will also be on average one false negative per year. As highlighted in the application, there will need to be rigorous processes associated with the timing and methodology of the second-tier test, as well as repeat screening. There will also need to be rigorous guidelines in place in relation to the timing of communication with the family – aligning with NBS objectives from the National Policy Framework, specifically timely communication of high-quality information to families on all aspects of newborn bloodspot screening.

There should also be consistent thresholds on the type of confirmatory testing used, depending on clinical urgency (i.e. urine HEX 4 for classic-consent GSD II is chosen due to its short turnaround time), for a consistent approach to the methodologies employed across different phenotypes.
It is outlined in the PICO Set 1 that *GAA* sequencing will be used for genetic diagnosis and identification of pathogenic variants. A turnaround time for test results of 6 weeks is quoted, following expert consultation by the applicant. There may be significant variation in this period between diagnostic laboratories. This may be the subject of further delays if there is a need to scale up to accommodate NBS tests. Overseas providers may be able to return results within a 3–4-week turnaround time.

The application states that there are currently 634 known variants causing the condition. Causing further complication, genotype-phenotype relationships are not straightforward and there is considerable variability in severity of symptoms. This adds to the likelihood of sequencing revealing variants of uncertain significance (VUS). It is interesting that the Missouri Newborn Screening criteria (Table 5 PICO Set 1) incorporate VUS into the assessment criteria. VUS will need to be considered as part of an NBS program for GSD II with expert review. The Australian Reproductive Carrier Screening Study (Mackenzie's Mission) convened a Variant Review Panel specifically to come together to review every variant to consider whether it should be reported, including VUS. Variant Review Panel meetings were held weekly by teleconference and attended by clinical and laboratory staff. Consensus on suitability for reporting was achieved during the meetings, which also served as a platform for recording all reported variants. Any changes in classification of variants over time were also discussed during the meetings. This Panel was an effective diagnostic activity but also a successful educational program. Such a model could be transferred to the NBS program. Note also that the preferred terminology in the field is now variant of uncertain significance rather than variant of unknown significance.

Particularly for newborns diagnosed with late onset GSD II, the psychosocial burden on families and the child themselves as they grow would be great (Crossen et al., 2022). Given that late onset GSD II may not become symptomatic until 60 years of age, this represents almost a whole lifetime of extensive monitoring and anticipation on the onset of symptoms. In addition to this, whether the systems to support families and resources for multi-disciplinary team monitoring are in place is unclear.

For those patients who are identified to have GSD II 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 suggests an incidence of GSD II in Australia of 1/47000, which is about half the global incidence of 1/23,000, and that the incidence rate varies based on 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 GSD II. 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). Health economics research done as part of the Australian Reproductive Carrier Screening Study (Mackenzie's Mission) modelled the lifetime cost of GSD II at more than $15.5M.

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

The initial newborn screening test will be facilitated by the neonatologist, nurse and midwife team. As outlined in PICO Set 1, where GSD II is confirmed, there will be a wide range of health specialists and disciplines involved (including cardiology; metabolic specialist; respiratory physician, dietician, psychology, genetic counsellor). As indicated by the figure presented, these are large multi-disciplinary teams involved in the management of patients, and to be effective this will require coordinated efforts through multi-disciplinary team review meetings and health data sharing between specialist services.

Where an individual has had their bloodspot screening result confirmed, genetic testing via a genetic service would be offered, including genetic counselling. Genetic counselling services would include full assessment of the impact and implications associated with a genetic GSD II diagnosis (Atherton et al., 2017) including reproductive options for carriers of GSD II causing variants.

PICO Set 1 refers to a consultation process to determine how laboratories would prefer to conduct both first and second tier testing for GSD II. There are several methods for second tier testing and a method will need to be worked up in diagnostic laboratories and NATA accreditation gained. This, combined with HEX4 assay, *GAA* 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 (National 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 GSD II 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 GSD II 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 *GAA* 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.

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 GSD II testing is superior to no testing, based on a summary of evidence presented in the application that earlier treatment is more effective than 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 GSD 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:

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 GSD II and five other LSDs, including MPS I (MSAC application 1775). 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 *GAA* (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 >634 the service fee 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 has been in place since 2015 in the USA, Taiwan and Italy (Klug et al., 2020; Chien et al., 2019; Parini et al., 2018); 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.

5. 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

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