Australian Government

Department of Health

Consultation Survey on MSAC Application 1710

Nomination for X-ALD to be added to Newborn Bloodspot Screening program

MSAC welcomes feedback 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 feedback. You may also attach additional information if you consider it may be useful in informing MSAC and its sub-committees.

Sharing consultation feedback

Submitted consultation feedback will be 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 feedback from groups or organisations will be provided in a complete form to both the Applicant and to MSAC and its sub-committees.

Please do not include information in your feedback 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 feedback is used

MSAC and its sub-committees consider consultation feedback 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 feedback 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 feedback from groups/organisations, including the name of the organisation. As such, organisations should not include information or opinions in their feedback that they would not wish to see in the public domain.

Consultation deadlines. Please ensure that feedback 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 and MSAC and ESC calendars available on the MSAC website. They are also published in the MSAC Bulletin. Feedback 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 your feedback. 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

Name: Eloise Uebergang

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

☐ Individual
☒ Collective Group

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

If 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

Clinical research coordinator submitting a response on behalf of Australian Genomics in consultation with clinicians, researchers, and community representatives.

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 form

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, reach 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 and 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.

As part of its portfolio of project management, Australian Genomics administers the Massimo's Mission Leukodystrophy Flagship. Massimo's Mission brings together a multidisciplinary team focused on providing more diagnoses and better outcomes for families affected by leukodystrophies and white matter disorders through research and targeted precision treatments. Research projects include a national patient registry, natural history studies, disease modelling and clinical trials for specific leukodystrophies. Massimo's Mission works closely with local and international teams to promote new research projects and share scientific discoveries.

Massimo's Mission partners with organisations that support both leukodystrophy research and the leukodystrophy community and have a great depth of understanding of the lived experience of individuals and families affected by Adrenoleukodystrophy.

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 main benefit of newborn screening for ALD leading to the identification of **presymptomatic** infants is that these individuals can access effective clinical treatments for the cerebral forms and adrenal insufficiency at a much earlier stage, improving survival outcomes.

Cerebral ALD affects one-third of boys with ALD under the age of 12 and rapidly progresses to total disability and death if left untreated [1]. Hematopoietic stem cell transplantation (HSCT) is currently the only curative approach that can prevent the progression of brain degeneration; however, it is only effective in the early stages of Cerebral ALD, and can prevent onset altogether if treated whilst presymptomatic. Transplantation does not reverse neurological symptoms present at the time of HSCT nor does the cerebral disease stablise for up to 24 months post stem cell infusion. Therefore, presymptomatic or early detection for consideration of HSCT is critical. Gene therapy combined with autologous HSCT is emerging as a promising new treatment for Cerebral ALD, which has shown short-term central nervous system disease stabilisation in ALD without the morbidity and mortality associated with HSCT[2].

Adrenal insufficiency is a major clinical phenotype of ALD, with an estimated lifetime prevalence of over 80% [3]. The earliest manifestations are subclinical abnormalities of glucocorticoid secretion which can occur as early as 5 weeks [3]. Early detection (via newborn screening which leads to the patient being screened for adrenal function) is critical to provide life-saving treatment of chronic glucocorticoid replacement therapy with stress-dose steroids for acute physiologic stressors.

An early diagnosis can help avoid multiple imaging and associated anaesthesia and further invasive tests which may require long hospital stays. It can also facilitate referrals to the appropriate services to manage the condition and provide access to the NDIS and other financial and psychosocial support.

A diagnosis can help inform future reproductive decision making and guide the use of assisted reproductive therapies such as preimplantation genetic diagnosis to prevent a second child being affected. More broadly, a diagnosis can lead to screening of relatives via predictive genetic testing, particularly asymptomatic males who can be monitored for adrenal insufficiency and MRI imaging surveillance for cerebral disease [4]. Surveillance of at-risk family members is important as previous studies have found that ACTH levels can be abnormal in males at early stages prior to obvious adrenal disease [5]. Similarly, clinical neurologic disease can precede neuroimaging changes, demonstrating the benefit of early intervention via HSCT, prior to advanced disease on MRI.

Research suggests that individuals and families affected by ALD are supportive of NBS. A recent study conducted interviews with the mothers of 10 children who were identified via newborn screening for ALD in California [6]. There was overwhelming support from these mothers that ALD should be included on the newborn screening panel for both males and females. 60% believed that testing for ALD in males should be offered prenatally and 40% believed it should be offered at birth, whilst 30% believed that testing for females should be offered prenatally and 70% believed that if should be offered at birth. Unpublished preliminary findings from an ongoing Australian qualitative study of people affected by ALD (n=6) suggest support for NBS, citing the benefits of early diagnosis in reducing uncertainty. When asked about her views of NBS, one participant commented, 'Perhaps you'll be able to prepare for it better from a medical perspective as well as from a kind of emotional psychological perspective'.

Whilst the proposed service could facilitate improved outcomes in clinical management, treatment, and quality of life for individuals and families affected by the cerebral forms and adrenal insufficiency, these benefits need to be carefully balanced with the issues discussed below.

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?

ALD has a variable clinical spectrum and neither the biochemistry nor patient mutation in *ABCD1* can predict the clinical course. Families can experience anxiety living with this uncertainty [7].

Genetic testing has brought other challenges, including the high proportion of cases with novel variants of uncertain significance in *ABCD1*. This challenge, in conjunction with poor genotype-phenotype correlation, has created uncertainty in how to diagnose and subsequently manage these cases.

Detection of carrier females via NBS continues to be controversial. Females may experience symptoms such as myelopathy and neuropathic pain, however onset is typically from 30 years of age, and there are currently no treatments for Adrenomyeloneuropathy (AMN) apart from steroid replacement therapy if needed. In some newborn screening programs such as New York State, Minnesota, and North Carolina, ALD status for female infants is disclosed with the justification that it facilitates testing and timely diagnosis of at-risk family members and to help inform reproductive planning in the future. Strategies for screening only male infants, are being explored in the Netherlands[8] and Japan[9].

HSCT as a treatment option is limited by matched donor availability and is associated with significant morbidity and mortality [1]. However, gene therapy trials with autologous HSCT have shown promising results that do not have the associated morbidity and mortality of HSCT.

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

Reduced primary financial and psychosocial impact on families affected by the cerebral forms and adrenal insufficiency.

The identification of ALD patients through newborn screening offers the opportunity for further genetic characterisation and phenotyping.

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

After early identification via NBS it is very important that the infant and family should receive diagnoses and counselling in a timely fashion. As more individuals with ALD are identified at birth, there will be an **increasing** need for various clinical services (e.g. neurometabolic, endocrine, haematology, oncology, genetics, imaging) in conjunction with the availability of matched donors for HSCT and transplant centres, and potentially gene therapy centres. This will have a range of implications on health system resourcing and associated costs.

Guidelines for monitoring boys diagnosed with ALD from newborn screening have been published and include expedited referral to an endocrinologist and a schedule for MRI monitoring [10, 11]. Protocols for long term surveillance and intervention (where needed) will be essential for appropriate management. Overseas NBS programs have suggested that the initial encounter with the family should be provided by a program that has experience with ALD and that follow-up can be provided by a multidisciplinary team that can coordinate all aspects of care [4].

For elevated VLCFA or abnormal ratios of VLCFA, a referral should be placed to genetics for genetic counselling and genetic testing to confirm the diagnosis of ALD. After genetic confirmation in the proband, genetic counselling and targeted testing can be provided for broader family members to identify at risk family members and provide reproductive information.

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 – which is all babies born in Australia?

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

Specify why or why not:

Section 5 of the application seems to suggest screening only males rather than 'all babies'. This should be clarified so there is no ambiguity regarding the proposed population. If proposing to also screen females, the balance of universal screening and intrusion into the autonomy of an asymptomatic female carrier who does not develop any childhood disease needs to be further considered as much of the application is focused around males with cerebral disease.

10. Do you have any additional information regarding the test protocol outlined in Part 2 of the nomination form?

The costs suggested for VLCFA ($80 AUD) and *ABCD1* sequencing ($1000 AUD) is an appropriate estimate.

11. Do you agree or disagree that the comparator(s) to the proposed medical service – which is no screening – is correct?

☒ Strongly Agree
☐ Agree
☐ Disagree
☐ Strongly Disagree

Please explain:

The comparator is no screening.

12. Have all the associated interventions been adequately captured in Part 3 of the nomination form?

☒ Yes
☐ No

Please explain:

However more consideration is needed regarding clinical follow-up and management of identified cases and the impact on health services.

PART 4 – COST INFORMATION FOR THE PROPOSED MEDICAL SERVICE

13. Do you have any comments or additional details regarding the proposed cost effectiveness as per Part 4 of the nomination form?

No additional studies that we are aware of describing cost effectiveness since the 2018 study referenced in the original application.

PART 5 – ADDITIONAL COMMENTS

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

There are clear merits to X-ALD newborn screening, the major benefit would be to boys who will develop cerebral disease. There is a treatment available but unfortunately most patients at present

are too progressed for this to be a beneficial option. Newborn screening and appropriate radiological surveillance would make this treatment option accessible to many more patients. These benefits need to be carefully balanced with the problem that most people diagnosed on NBS will not develop cerebral disease. This process will lead to the diagnosis of people who will develop adult-onset disease, and the anxiety that this causes. Unfortunately, there is no biomarker or genotype/phenotype concordance to predict which people diagnosed on newborn screening will develop cerebral disease vs late onset disease.

Collection of long-term outcome data will be essential to demonstrate and improve quality of care of individuals affected by adrenoleukodystrophy.

15. **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

1. Zhu, J., et al., *The Changing Face of Adrenoleukodystrophy.* Endocr Rev, 2020. **41**(4): p. 577-93.
2. Eichler, F., et al., *Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy.* New England Journal of Medicine, 2017. **377**(17): p. 1630-1638.
3. Huffnagel, I.C., et al., *The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration.* J Clin Endocrinol Metab, 2019. **104**(1): p. 118-126.
4. Moser, A.B., E. Seeger, and G.V. Raymond, *Newborn Screening for X-Linked Adrenoleukodystrophy: Past, Present, and Future.* Int J Neonatal Screen, 2022. **8**(1).
5. Dubey, P., et al., *Adrenal insufficiency in asymptomatic adrenoleukodystrophy patients identified by very long-chain fatty acid screening.* J Pediatr, 2005. **146**(4): p. 528-32.
6. Schwan, K., et al., *Family Perspectives on Newborn Screening for X-Linked Adrenoleukodystrophy in California.* Int J Neonatal Screen, 2019. **5**(4): p. 42.
7. Schwan, K., et al., *Family Perspectives on Newborn Screening for X-Linked Adrenoleukodystrophy in California.* International Journal of Neonatal Screening, 2019. **5**(4): p. 42.
8. Barendsen, R.W., et al., *Adrenoleukodystrophy Newborn Screening in the Netherlands (SCAN Study): The X-Factor.* Front Cell Dev Biol, 2020. **8**: p. 499.
9. Shimozawa, N., et al., *Advanced Diagnostic System and Introduction of Newborn Screening of Adrenoleukodystrophy and Peroxisomal Disorders in Japan.* Int J Neonatal Screen, 2021. **7**(3).
10. Regelmann, M.O., et al., *Adrenoleukodystrophy: Guidance for Adrenal Surveillance in Males Identified by Newborn Screen.* J Clin Endocrinol Metab, 2018. **103**(11): p. 4324-4331.
11. Mallack, E.J., et al., *MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: Meta-analysis and consensus guidelines.* J Inherit Metab Dis, 2021. **44**(3): p. 728-739.