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Position Statement

Title:	**X-linked Adrenoleukodystrophy (X-ALD) Newborn screening**
Document Number:	2025PS05
Publication Date:	October 2025
Replaces:	Nil
Review Date:	October 2026

Introduction

In November 2023, the Health Ministers' Meeting (HMM) endorsed the national newborn screening (NBS) decision-making pathway, providing a consistent and transparent approach for determining which conditions are included in the NBS programs across Australia. Through this decision-making pathway, the Medical Services Advisory Committee (MSAC) supported the addition of X-linked Adrenoleukodystrophy (X-ALD) to Australia's NBS programs for all newborns, including males and females.

Concerns were raised by relevant treating clinicians regarding universal screening (males and females) because the medical risks for males with X-ALD are significantly different to the risks for females with X-ALD, due to the way the condition is inherited. Less than 1% of women with ALD will develop the treatable complications arising from X-ALD, namely cerebral ALD or adrenal insufficiency. Instead, adult females with X-ALD develop a different condition, adrenomyeloneuropathy (AMN) (a degenerative disease of the spinal cord) with general age of onset between the age of 40–60 years. Currently, there is no curative treatment for myelopathy.

On 6 December 2024, all Australian Health Ministers agreed to add X-ALD to Australia's NBS programs for male newborns, and noted additional work was required to "*explore the ethical considerations and social acceptability of screening and reporting abnormal results for female newborns*", due to the later onset and less severe manifestation of the condition compared to males.

The Human Genetics Society of Australasia (HGSA) understands that a report on X-ALD screening in females including ethical implications and social acceptability was prepared by an external agency to support the HMM make their final decision on whether screening for X-ALD in female newborns should be included in Australia's NBS programs.

Recommendation

The Human Genetics Society of Australasia supports sex-specific newborn screening (males only) as detecting female newborns with an adult-onset neurodegenerative disorder (AMN) is inappropriate and inconsistent with Australasian newborn screening principles.

Australia's Newborn Screening Policy Framework[1] (NPF) outlines several pertinent criteria for considering conditions for screening:

[2] There should be a benefit to conducting screening in the newborn period
[7] There should be an accepted intervention for those diagnosed with the condition
[8] The benefit of screening a condition must be weighed against its impact on the program as a whole

Australia's NPF also notes the potential secondary benefits of screening conditions through newborn screening:

"While the benefit to the baby must always be the first consideration, for some conditions a benefit for the family and/or community, as well as the benefit to the baby, may also be important and warrant consideration. This might include benefits to the family for conditions where there is currently no intervention and which will be likely to lead to early mortality but where a definitive diagnosis might be aided by a screening test".

Screening newborn males for X-ALD will support a definitive diagnosis and the opportunity for early intervention and treatment.

This is however not relevant for newborn females with X-ALD as the presentation is adult onset and the condition cannot be treated. Therefore, screening for X-ALD in newborn females does not meet the agreed NPF criteria that there should be a benefit to conducting screening in the newborn period, and there should be an accepted intervention for those diagnosed with the condition.

The NPF also advises decision-makers to consider why the newborn period is the best time to screen a condition (Criteria 2.2), the utility of the information to assist reproductive decision-making (Criteria 2.3), and harms from reporting this information (Criteria 2.5).

Once a newborn male has been identified as having X-ALD through NBS, other family members, including the child's mother, will be offered genetic testing for X-ALD (cascade testing). Individuals and families will then have the opportunity to use this information for future reproductive decision making.

Background information on X-linked adrenoleukodystrophy (X-ALD).
X-ALD is a devastating neurometabolic disorder affecting the adrenal glands, brain and spinal cord. It has an estimated prevalence of 1 in 17 000 births[2]. The most severe form, childhood cerebral adrenoleukodystrophy (CCALD), affects between 31 and 57% of hemizygous males, typically

presenting between 2 and 10 years of age, and is associated with rapid neurologic decline; untreated, death or severe disability typically occurs within approximately 3 years[3]. The lifetime prevalence of adrenal insufficiency in male X-ALD patients is 80–90%; with 50% between the age of 5 months to 10 years[4]. Failure to recognise adrenal insufficiency at an early stage, and delayed treatment can lead to death even from minor illnesses. The adult spinal cord disease, AMN occurs in affected males with the age of onset in the 20s and 30s (60%)[2].

In contrast, women with X-ALD have a very low risk (<1%) for developing adrenal insufficiency or CCALD[5]. In contrast 80% of female carriers develop neurological symptoms of AMN by the age of 60, ranging from mild to severe disability, which are untreatable[4].

Hence, NBS for X-ALD in males will enable early diagnosis, prospective monitoring and timely therapeutic intervention, thereby preventing irreversible neurological damage and saving lives. NBS is not warranted in newborn females as X-ALD carriers are at very low risk for adrenal insufficiency or CCALD. Diagnosis of the disorder in newborn males will facilitate cascade testing and identification of affected family members, facilitating future informed reproductive planning.

Currently, few countries screen for X-ALD, with Japan and the Netherlands choosing sex-specific screening. The Dutch NBS programme for X- ALD only reported male newborns, for the reasons cited above, i.e. adult females with X-ALD have a very low risk (<1%) for developing adrenal insufficiency or CCALD[5]. Additionally, most female carriers (~ 80%) develop neurological symptoms of AMN much later in life (by the age of 60), and there are no specific treatments available currently for AMN.

The overarching ethical consideration relevant to population screening is preventing collective harm by identifying those who will not benefit from early detection and follow-up monitoring[6]. This is particularly important when there is a lack of surveillance protocols for heterozygote females with X-ALD. Other ethical considerations include the potential psychosocial harm impacting the child's wellbeing, removing the child's right to autonomously decide for themselves whether to be tested in the future, the potential for discrimination, and implications for personally risk-rated insurance products such as life insurance.

There is a lack of long-term data on the impact of X-ALD screening, particularly on female newborns and their families, as it is a recent inclusion in several global NBS programs. Useful insights and potential challenges of screening X-linked recessive disorders could be learnt from Fabry disease. NBS for Fabry disease was first initiated in 2003 as a pilot study in Italy and subsequently by several other jurisdictions. NBS for Fabry disease is complex due to inconclusive results and late-onset presentations, resulting in 'patients in waiting' and a risk of loss to follow-up. Ethical concerns arise due the potential for overmedicalisation and misdiagnosis[7]. The inclusion of Fabry disease in Australian NBS was not recommended for Medical Services Advisory Committee (MSAC) consideration. Similarly, Fabry is not included in the US Recommended Uniform Screening panel, although some US states have independently mandated its inclusion following patient advocacy.

Screening female newborns for X-ALD will have its inherent risk of false positives, and the associated anxiety created for families. Reproductive autonomy is not an acceptable benefit to screening female newborns without a direct benefit to the female newborn in the immediate future.

The HGSA position statement on "Genetic Carrier Testing for Recessive Conditions"[8] supports this view stating:

"*Unless there is direct medical benefit in the immediate future, the default position should be to postpone carrier testing until the child or young person can be supported to make an informed decision*."

While the HGSA acknowledges the desire for females to have information about their carrier status to inform reproductive decision making, the known challenges with screening for X-ALD in females outweighs the potential benefits of including female newborns in the screening program.

Reproductive genetic carrier screening (RGCS) is recommended for all people planning a pregnancy and X-ALD is currently included as a condition screened for through several RGCS options.

References:

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