# **Medical Services Advisory Committee (MSAC)Public Summary Document**

Application No. 1710 – Newborn bloodspot screening for X-linked adrenoleukodystrophy

**Applicant:** **Leukodystrophy Resource & Research Organisation Inc.**

**Date of MSAC consideration: 27 July 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

## 1. Purpose of application

An application requesting the addition of X-linked adrenoleukodystrophy (X-ALD) to newborn bloodspot screening (NBS) was received from the Leukodystrophy Resource & Research Organisation by the Department of Health and Aged Care. Dr ||||||||, Associate Professor in Paediatric Neurology at the | | || |, was a supporting co-applicant.

## 2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported adding X-linked adrenoleukodystrophy (X-ALD) to newborn bloodspot screening (NBS) programs. MSAC considered that adding X-ALD to NBS would provide superior effectiveness through allowing early genetic diagnosis before symptom onset, thus allowing monitoring of children at risk of developing X-ALD, and early treatment including stem cell transplant for patients with cerebral ALD, which improves health outcomes. MSAC also supported cascade testing of the families of newborns identified through NBS as being at risk of X-ALD, as this will support families’ reproductive decision-making. MSAC considered that the evidence for health outcome improvement from NBS was clear in males but much less certain for females diagnosed through screening due to their predominantly adult-onset disease, and that the decision to report NBS results for males only versus all newborns was a complex consideration. MSAC considered there were arguments each way and, on balance, supported X-ALD NBS results being reported for all newborns, because reporting results for all newborns would equitably allow all families of children identified through screening to make informed reproductive decisions. It was assumed by MSAC that reporting results for only one sex would likely be unacceptable in the Australian context, and reporting results for all babies would make for simpler screening implementation.

MSAC considered that adding X-ALD to NBS was acceptably safe, with potential harms from undergoing monitoring where clinical disease may not eventuate due to low penetrance, psychological harm from a positive result, and only symptomatic treatment being available for some X-ALD manifestations. MSAC considered that two tiered mass spectrometry was not necessary prior to genetic testing if testing examined multiple species of very long chain fatty acids and their ratios, because this would have higher specificity without adding an extra tier to screening. MSAC considered that the recommended screening method had been defined too narrowly for the assessment, but that the updated cost-effectiveness analysis and financial estimates were acceptable.

| Consumer summary |
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| This was an application from the Leukodystrophy Resource & Research Organisation Inc requesting to add X-linked adrenoleukodystrophy (X-ALD) to newborn bloodspot screening (NBS).In Australia, states and territories offer bloodspot screening for all newborn babies. The screening is done by taking a heel prick blood sample from the baby in the first 48 to 72 hours of life and drying it on a card. The blood sample is then tested for certain rare and serious genetic conditions and metabolic disorders. Detecting these conditions early allows for earlier treatment and therefore can lead to better health outcomes for the baby. If the condition is genetic, diagnosis can help parents to make informed reproductive decisions for any future pregnancies.The X and Y chromosomes, also known as the sex chromosomes, determine the biological sex of an individual. Typically, biological males have one X chromosome (and one Y chromosome) per cell, and biological females have two X chromosomes per cell. Newborns are also assigned a 'phenotypic' sex at birth based on the appearance of their genitalia. Sometimes the newborn might have ambiguous genitalia and then their sex is not classifiable as either male or female. Rarely, a newborn may be born with a condition in which their biological sex is inconsistent with phenotypic sex. Throughout this document, sex relates to the person’s number of X chromosomes (biological sex).X-ALD is a genetic condition that is caused by differences in the *ABCD1* gene, which is on the X chromosome (called “X-linked”). X-linked conditions affect males more, because they only inherit one copy of genes located on the X chromosome, and X-ALD is a debilitating disease in boys. In X-ALD, chemicals called very long chain fatty acids build up in the body. X-ALD can present in a range of different ways, including adrenal insufficiency (Addison’s disease), spinal cord dysfunction (adrenomyeloneuropathy) and rapid degeneration of neurons (cerebral ALD). Having a disease-causing genetic variant in *ABCD1* means a person is at risk of developing X-ALD, however not all people with a variant develop disease. Variation in the signs and symptoms of X-ALD can even occur within the same family, where people share a genetic variant. Without early treatment, the health outcomes for affected boys are poor. Females with X-ALD can have progressive spinal nerve damage (called myelopathy), but symptoms are usually not seen until mid-to-late adulthood.MSAC considered adding X-ALD to NBS was clinically safe as it only involves a heel prick, and would use the same bloodspot already collected. There were some potential harms of adding X-ALD to NBS: mainly for monitoring boys who may may never develop X-ALD, and psychological harm from a positive result, including for people with types of X-ALD where only symptomatic treatment is available. Adding X-ALD to NBS would allow diagnosis around the time of birth, rather than delaying diagnosis until the child presents with symptoms of X-ALD. The evidence showed that adding X-ALD to NBS was clinically effective, because it allowed early monitoring of at-risk children and potentially allowed early stem cell transplant for boys with cerebral ALD, which had better health outcomes when performed early in the disease. In the Netherlands, NBS for X-ALD also includes a test called an “X-counter” to allow reporting results for boys only, and one question was whether this should be used in Australia. In the Netherlands all newborns are screened, but before reporting on any results for X-ALD they run a test that counts the number of X chromosomes per cell. Then, they only report the X-ALD result for newborns with one X chromosome. Although girls are not affected by X-ALD until typically decades later, and there are no early interventions available for females with X-ALD, on balance MSAC considered it appropriate to report X-ALD results for all newborns. This was mainly because the parents of baby girls carrying an X-ALD variant identified through NBS can have further testing and use this information to inform their reproductive planning, including any future pregnancies. Couples who have a girl with an X-ALD variant have a much higher risk than the general population of having a baby with X-ALD in any future pregnancy (1 in 4 chance where the mother is a carrier), so this is important information for those couples. Also, MSAC assumed that reporting results for only one sex would likely not be acceptable in the Australian context, and the screening process would be simpler without an X-counter. The benefit of reporting results for female babies is therefore primarily to the family, which is similar to the benefits of cascade testing for some cancer genes and aligns with the principles behind NBS.There are many ways that screening for X-ALD can be performed in the NBS laboratories. Using more than one step of testing is routine for newborn bloodspot screening, and the main options for X-ALD screening involve the use of two to three tests one after the other (called “tiers”) for each newborn bloodspot sample (called two-tier or three-tier screening). Two-tier screening involves an initial screening test, with those newborns identified at high risk by that test then having a second, more sensitive test. For X-ALD, the method options for the tiers were two different types of mass spectrometry and genetic testing. Mass spectrometry is a method that can be used to work out how much of a given chemical (such as a fatty acid) is present in a sample. Depending on the choice of first-tier mass spectrometry method, a second tier test could be a different type of mass spectrometry test, and for the last tier a genetic test would be used to confirm diagnosis prior to reporting the result. MSAC recommended that screening could efficiently use a method called FIA (flow injection analysis) tandem mass spectrometry for the first tier, then genetic testing for the second tier. An extra tier of screening (using a different type of mass spectrometry) would not be necessary if the FIA mass spectrometry looks at not only a fatty acid called C26:0 but also at related fatty acids and their ratios. MSAC considered adding X-ALD to NBS was acceptable value-for-money, and would come at a financial cost that was acceptable.MSAC’s advice to the Commonwealth Minister for Health and Aged CareAfter considering the strength of the evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported adding X-ALD to NBS programs. |

## 3. Summary of consideration and rationale for MSAC’s advice

MSAC noted that this application from the Leukodystrophy Resource & Research Organisation Inc was for adding X-linked adrenoleukodystrophy (X-ALD) to newborn bloodspot screening (NBS). MSAC noted that applications for adding and removing conditions from NBS were previously considered by the Standing Committee on Screening (SCoS). However, following its dissolution in 2021, applications for addition of conditions to NBS are now considered by other committees, including MSAC. This application (1710) and application 1737[[1]](#footnote-2) are the first NBS applications to be considered by MSAC.

MSAC noted that the Newborn Bloodspot Screening National Policy Framework (NBS NPF)[[2]](#footnote-3) was developed through the SCoS in 2018, but NBS implementation remains state-based, with screening provided by five NBS laboratories across Australia. MSAC considered the NBS NPF decision-making criteria as context for its advice, but noted that the full scope of considerations relevant to the NBS NPF criteria, such as a detailed appraisal of all relevant implementation considerations, are outside MSAC’s terms of reference (ToRs). MSAC noted that its advice within its ToRs would be used in conjunction with advice from others in the overall decision-making process for NBS in Australia.

MSAC noted that X-ALD is an X-linked neurological disorder of peroxisomal very long chain fatty acid (VLCFA) transport that presents clinically with a range of phenotypes in males, ranging from Addison’s disease and spinal cord dysfunction (adrenomyeloneuropathy) to rapid neurodegeneration (childhood cerebral ALD [CCALD]). X-ALD is rare, with incidence somewhat uncertain but about 1 in 9,000. MSAC noted that X-ALD is caused by pathogenic or likely pathogenic (P/LP) variants in the *ABCD1* gene, but that variants are typically private (unique to each family), with incomplete penetrance (Table 5) and variable expressivity. As is typical for X-linked conditions, the condition is more commonly found in males and is more severe in males.

MSAC noted that the population was all newborns undertaking NBS, and the proposed intervention was newborn bloodspot screening within the first 48 to 72 hours of life. NBS was proposed to allow earlier diagnosis and management. The Department-contracted assessment report (DCAR) assessed four main screening strategies (plus variations involving the X-counter test for a total of nine strategies altogether), comprised of various combinations of flow injection analysis tandem mass spectrometry (FIA-MS/MS), (high-performance) liquid chromatography ((HP)LC)-MS/MS, and genetic testing:

1. FIA-MS/MS, then HPLC-MS/MS
2. FIA-MS/MS, then *ABCD1* genetic testing
3. HPLC-MS/MS, then *ABCD1* genetic testing
4. FIA-MS/MS, then HPLC-MS/MS, then *ABCD1* genetic testing

MSAC noted that the most sensitive biomarker for detection of high VLCFA levels during screening is the VLCFA C26:0, but it is in low abundance. MSAC considered an additional tier of HPLC-MS/MS (strategy IV) was unnecessary, as a single tier of FIA-MS/MS (strategy II) can be optimised to achieve the same result by quantifying more species of VLCFA than only C26:0 (such as C24:0 and C22:0) and their ratios. MSAC considered that using FIA-MS/MS to measure multiple VLCFA species would improve specificity for X-ALD, however this would require optimisation of the mass spectrometer. MSAC noted that each Australian NBS laboratory determines the instrumentation used for testing as well as the local cut-offs. MSAC noted that in its experience diagnosing affected individuals displaying signs and/or symptoms of X-ALD, classical X-ALD diagnosis uses HPLC (gas chromatography or tandem mass spectrometry) and measures C26:0 and C24:0 and the ratios C26:22 and C24:22. MSAC considered that this was supported by the literature, for example Natarajan 2019[[3]](#footnote-4) found that C26:0-LPC, C26:0-C20:0 ratio and C24:0-LPC were significantly elevated in the blood of people with X-ALD compared to controls, by 6, 3.5 and 3 folds respectively. MSAC therefore advised that the method used for X-ALD screening should be first tier FIA-MS/MS to measure multiple species of VLCFAs and their ratios, as this would offer sufficient specificity without adding another tier of mass spectrometry screening, followed by a second tier using *ABCD1* genetic testing (strategy II).

MSAC noted that most *ABCD1* genetic variants are private, but agreed with ESC that genetic testing was unlikely to result in a variant of uncertain significance (VUS) because the abnormal VLCFA levels from the prior tier of screening can be taken into account when classifying the pathogenicity of the detected genetic variant. MSAC noted that approximately 7-9% of female heterozygotes for a P/LP *ABCD1* variant have normal VLCFA levels due to non-random X-inactivation. MSAC considered cascade testing would need to use genetic methods in females as VLCFA levels are not definitive for them.

MSAC noted that the comparator was no universal NBS for X-ALD, with X-ALD diagnosis delayed until symptom onset. Genetic testing of the *ABCD1* gene is part of current standard of care for children diagnosed at symptom onset. Following a diagnosis of a pathogenic or likely pathogenic variant in *ABCD1*, monitoring and treatment takes place. The nature of monitoring and treatment for X-ALD is not proposed to be altered by NBS, but monitoring would commence earlier to permit earlier haematopoietic stem cell transplant (HSCT). Management of CCALD includes neurological/MRI monitoring and HSCT once the early stage of cerebral disease is clinically and/or radiologically detected. MSAC noted the likelihood of future additional interventions, as the United States Food and Drug Administration approved the lentiviral gene therapy Skysona in 2022. MSAC noted that the European Medicines Agency granted marketing authorisation for the same therapy in 2021, but this has since been withdrawn.

MSAC noted the DCAR used a linked evidence approach. The DCAR’s systematic literature review identified no studies examining the change in health outcomes due to a change in clinical decisions, no studies comparing treatment at early versus late progression, and no studies on health outcomes for AMN or adrenal insufficiency. Key studies identified through the DCAR’s systematic literature review included two studies comparing HSCT versus no HSCT as a treatment for cerebral ALD (CALD) (and AMN with cerebral/cerebellar involvement), both judged to be at high risk of bias, and ten studies comparing HSCT at early versus late CALD progression, of which three were judged to be at high risk of bias and seven at moderate risk.

Regarding safety, MSAC considered there to be no additional direct harm from adding another condition to NBS as it would use the same bloodspot already collected. MSAC noted the applicant stated in its pre-MSAC response that NBS for X-ALD “does no harm”, however MSAC considered there were potential indirect harms from adding X-ALD to NBS. MSAC considered that the harms of NBS for X-ALD included risks from undergoing monitoring where clinical disease may not eventuate in some children due to low penetrance (monitoring uses magnetic resonance imaging [MRI], which requires general anaesthetic in young children). MSAC considered that while early HSCT improved survival, potential harms from HSCT include mortality, graft failure, and graft-versus-host disease. Further potential harms from adding X-ALD to NBS also included the psychological harm from a positive result (true or false positive), and the psychological harm from receiving a diagnosis where management is only symptomatic treatment, as opposed to treatment that can halt disease progression. However, MSAC considered that the psychological harm from a positive result would likely be similar to that for other serious conditions already included in NBS programs. On balance, MSAC considered these potential harms were acceptable, and so advised that adding X-ALD to NBS was comparatively safe.

MSAC noted the DCAR stated that about 50% of boys at risk of X-ALD will develop primary adrenal insufficiency by the age of 10, and 30–35% will develop CCALD in childhood (Table 5). MSAC noted the DCAR assumed that AMN and AI had no effect on overall survival, but considered that this did not align with its anecdotal clinical experience – and noted that one patient died from adrenal crisis in a clinical trial. MSAC noted the applicant’s pre-MSAC response disagreed with the age of presentation reported by the DCAR, and MSAC considered that anecdotal evidence supported earlier diagnosis in some cases, suggesting the DCAR had overestimated the age of X-ALD presentation in males. MSAC considered the evidence demonstrated that X-ALD is a serious condition in males. MSAC noted that the DCAR reported about half of women with X-ALD will present with AMN from age 40 to 65 years, and considered this aligned with its experience that more than 80% of females develop a chronic progressive myelopathy over their lifetime and are unlikely to develop any symptoms until they are well into adulthood. MSAC noted that adrenal insufficiency is not seen in females with X-ALD, and CALD is rare.

MSAC considered that NBS would allow a biochemical and genetic diagnosis of risk for X-ALD (as the condition has incomplete penetrance) made around the time of birth, rather than delaying diagnosis to the point of symptom onset, as is currently the case. MSAC considered that the evidence demonstrated HSCT was more effective (i.e. resulted in higher overall survival) when performed earlier in X-ALD progression, compared to later (Table 7, Figure 2). MSAC noted that guidelines recommend ongoing monitoring in childhood for only male patients with X-ALD and not for females. MSAC noted the applicant stated in its pre-MSAC response that some females will develop X-ALD symptoms, and so they should be referred to as “females with X-ALD" rather than “female carriers”. MSAC agreed that some females develop symptoms, however considered that this would happen in adulthood and the evidence presented did not demonstrate that NBS would result in any change in management with resulting health outcome improvement for female newborns. MSAC advised that NBS for X-ALD had superior effectiveness in males.

MSAC considered that sex assigned at birth (or phenotypic sex) was not an appropriate surrogate for the number of X chromosomes, and agreed that reporting of results for individuals with one X chromosome (referred to as males for simplicity) would therefore require an X-counter or similar test. MSAC noted that NBS for X-ALD in the Netherlands includes an X-counter, but that other countries report results for all newborns. MSAC considered that there were both advantages and disadvantages of reporting results for only males, and that the decision was an ethically complex one. MSAC considered that the ethical analysis in the DCAR was informative but it was not a formal ethical analysis. MSAC noted consultation comments that reporting results for females would not be aligned with the NBS NPF criteria, because there is no childhood treatment and their X-ALD phenotype does not manifest until decades later. MSAC noted the applicant stated in its pre-MSAC response that NBS for X-ALD “will allow families to make reproductive decisions that could prevent further needless deaths in their extended families”. MSAC considered that identifying female heterozygote newborns would support the parents’ reproductive decision-making, and allow couples to make informed reproductive decisions for any future pregnancies. Heterozygote mothers would pass on their P/LP allele to 50% of children, of which 50% would be female heterozygotes and 50% would be male hemizygotes at risk of X-ALD; and hemizygote fathers would pass on their P/LP allele to 100% of their female children and 0% of their male children. MSAC considered that it was important to inform couples who had a female heterozygote newborn detected through NBS, to allow them to receive genetic counselling and cascade testing to allow them to make informed reproductive decisions for any future pregnancies. MSAC considered the tension between public health ethics and medical ethics in the context of reporting results for males versus all newborns in NBS, and in the absence of an empirical analysis, assumed that reporting results for only one sex would likely be unacceptable in the Australian context, because Australian society places considerable value on being egalitarian, and in not withholding information that may be of personal importance to the screened individual and their family. MSAC discussed the ethical issues, including that for NBS the target population is unable to give consent therefore the primary potential benefit of screening is for the health of the newborn, and that standard practice is to not report adult-onset conditions in people who cannot consent to receive such information. MSAC considered that limiting reporting to male newborns would mitigate harm, however that the ability to inform reproductive decision-making was greater if results were reported for all newborns. MSAC also considered that laboratory workflows would be simpler without the addition of an X-counter tier to screening. MSAC considered that the benefit of reporting X-ALD results for female newborns would accrue primarily to the family, and recalled it had previously supported cascade testing arising out of cancer genetic testing, which similarly has benefits to individuals other than the person tested, although in this case an adult consents to NBS on behalf of the newborn rather than the testing individual consenting to it themselves. MSAC noted that such ‘secondary benefits’ of NBS are allowed for in the NBS NPF decision-making criteria. On balance, MSAC recommended that NBS for X-ALD report screening results for all newborns rather than only males, primarily due to the value of reproductive decision-making benefits to the family from reporting results for female newborns. However, MSAC noted that it was providing advice within its ToRs and it was not the final decision-maker for NBS. MSAC considered that its advice to report results for all newborns rather than males only for X-ALD NBS was not necessarily generalisable to other conditions where there is no identifiable health outcome improvement for a subgroup of patients, and so the potential addition of each condition to NBS needs to be considered on its merits.

MSAC noted that the economic evaluation was a cost-utility analysis, with the outcomes reported in terms of both screening cost per positive diagnosis (step 1), and incremental cost per quality-adjusted life year (QALY; step 2 includes all costs, i.e. monitoring etc in addition to NBS itself) (Table 10). MSAC considered both were informative. MSAC noted that strategy I excluded molecular testing, which it considered was not correct as it did not reflect that genetic testing will be performed at follow-up for screen-positive newborns, and so the cost would still be incurred (perhaps to the family rather than to NBS programs).

MSAC considered the main areas of uncertainty in the economic evaluation were:

* incidence of X-ALD – MSAC noted estimates in the DCAR ranged from 1 in 6,200 to 1 in 15,000, with a base case incidence of 1 in 9,000
* sensitivity and specificity of the screening test, including the cut-off and methodology used
* cascade testing uptake – MSAC estimated that 100% of families would take up cascade testing, informed by anecdotal experience. MSAC also considered that cascade testing would be incremental in many cases because the penetrance of X-ALD was not close to 100%, so the incidence through NBS would be higher than the clinically diagnosed incidence.
* the assumption that AMN and adrenal insufficiency did not affect the overall survival for patients with X-ALD – MSAC considered this may not be strictly correct, based on anecdotal reports.
* age of presentation and diagnosis – MSAC considered the age of presentation and diagnosis may have been over-estimated, based on anecdotal reports.

MSAC noted the DCAR reported the lowest ICERs for strategies I and IV, because those strategies had the fewest newborns receiving genetic testing. MSAC noted that for strategies I and IV, the DCAR reported the cost of screening per diagnosis was approximately $83,000 (step 1, where costs are only NBS itself), and the incremental cost per QALY was $8,000 (step 2, which includes other costs such as monitoring). For strategy II MSAC noted that the DCAR’s reported cost of NBS per newborn implied around 20% of newborns would receive second tier screening, which would not be appropriate for a first tier screening test and implied errors in the calculations. MSAC considered that the DCAR used a specificity of 78.33% (Natarajan 2019) for FIA-MS/MS, however this was for FIA-MS/MS of C26:0 alone, which was too narrow a definition of the method and did not align with classical X-ALD diagnosis based on multiple VLCFA species. MSAC further noted that Natarajan 2019 had reported a specificity of 98.33% for C24:0 alone, and considered that the specificity of FIA-MS/MS would be even higher than this for multiple species of VLCFAs and their ratios. MSAC noted the department’s calculations estimated that if the specificity of FIA-MS/MS for multiple species of VLCFAs was 99.5%, then the positive predictive value increased from 0.05% to 2.17%, and the proportion of newborns receiving second tier screening decreased to 0.5%. MSAC noted the DCAR HTA group provided post-MSAC updated modelling results using 99.5% specificity for FIA-MS/MS (and 3 million simulations to mitigate fluctuation due to X-ALD being a rare disease), which for strategy II showed a cost of screening per newborn of $8.76, an NBS cost per diagnosis of $81,886 (step 1), and an ICER per QALY of $116,226 (step 2) (Table 11). MSAC considered that 99.5% was the estimated lower bound for FIA-MS/MS specificity, so the updated results were therefore an upper bound estimate of the ICER. MSAC considered that the updated economic results were likely also conservative because first tier mass spectrometry tests should cost quite a bit less than the $5.44 per newborn used by the DCAR. MSAC commented that funding mass spectrometry for X-ALD NBS would also minimise the marginal cost of any future additions of other conditions that also use first tier mass spectrometry. Taking into account its advice that NBS for X-ALD should use FIA-MS/MS for multiple species of VLCFA to substantially improve specificity, followed by genetic testing, MSAC advised that adding X-ALD to NBS was cost-effective.

MSAC noted that utilisation was estimated using an epidemiological approach and 99% NBS uptake rate. MSAC considered the overly narrow definition of FIA-MS/MS had also resulted in the financial cost of strategy II having been overestimated by the DCAR. MSAC noted the DCAR had reported the financial cost of strategy II to NBS programs to be $10.5 million per year. MSAC noted that if the specificity of FIA-MS/MS was 99.5%, this resulted in an updated cost to NBS programs of $2.8 million per year for strategy II (Table 17). MSAC noted that adding X-ALD to NBS would also have costs to other existing funding sources from changes to patient management, to state and territory governments in particular ($145,000 increasing to $610,000 per year), but also to the MBS ($4,000 increasing to $114,000 per year) and the PBS ($3,000 per year) (Table 17). Early diagnosis through X-ALD would shift cascade testing of the relatives of males who would eventually present symptomatically to within the time horizon for financial analysis, and would add cascade testing for the relatives of males who would never present symptomatically and females. MSAC noted cascade testing would have an additional cost of $53,000 per year to states and territories (Table 18). MSAC advised the financial cost of adding X-ALD to NBS was acceptable.

MSAC noted that the NBS NPF decision-making criteria formed context for MSAC’s consideration of adding X-ALD to NBS. MSAC considered that although it was not being asked to advise on the fulfilment of specific decision-making criteria, its advice did not appear counter to any of the criteria.

MSAC noted that in the pre-MSAC response the applicant proposed that a coordinated strategy to collect, measure, build and translate data is needed to support quality improvement activities, monitoring of treatments and long-term outcomes, allowing revision of clinical care guidelines. MSAC agreed that creation of a national newborn screening registry that incorporated an X-ALD registry would be beneficial, although considered it would need to be funded.

## 4. Background

The MSAC has not previously considered the inclusion of X-ALD in NBS. X-ALD was the first NBS application considered by the PICO Advisory Sub-Committee (PASC) of the Medical Services Advisory Committee (MSAC) (August 2022) .

Applications to add a condition to NBS were previously considered by the Standing Committee on Screening (SCoS), and with the dissolution of SCoS the process changed in 2021 to MSAC providing advice instead. MSAC’s July 2023 consideration of this application and MSAC Application 1737 (NBS for Sickle cell disease and beta thalassaemia) will be its first considerations of applications to add conditions to NBS.

## 5. Prerequisites to implementation of any funding advice

Each state and territory is responsible for determining which method of screening for X-ALD they would implement. New conditions added to Australian NBS programs need to align with the Newborn Bloodspot Screening National Policy Framework (NBS NPF) decision-making criteria, which were considered as context for MSAC’s advice.

The proposed technology does not include a therapeutic good that requires TGA approval. The full scope of considerations relevant to the NBS NPF criteria, such as detailed appraisal of all relevant implementation considerations, are outside the scope of MSAC’s advice on NBS, however it is recognised that laboratories may require new equipment in order to perform testing.

## 6. Proposal for public funding

The proposal is for X-ALD to be added to the list of conditions screened for through Australia’s NBS programs. If a genetic diagnosis of being at risk of developing X-ALD is made via NBS, then follow-on cascade testing of first-degree relatives is also proposed.

NBS programs are overseen, funded and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). It has also provided $25.3 million over 4 years in direct funding to states and territories to support expansion and consistency of NBS programs.

Should X-ALD be included in the NBS program, there will be flow-on impacts to the healthcare system, including increased monitoring and surveillance of asymptomatic individuals identified as at risk for X-ALD from birth (e.g., specialists care, serial brain magnetic resonance imaging (MRI), genetic counselling services), treatments (e.g., HSCT) and the management of associated adverse events.

The PASC noted policy advice that there is no specific funding source for cascade testing arising out of NBS (p19, 1710 PICO Confirmation, August 2022 PASC Meeting). PASC subsequently also accepted that the MBS is not proposed to be the funding source for cascade testing (p32, 1737 PICO Confirmation, December 2022 PASC meeting). The Department’s policy advice was that cascade testing will continue to be funded by state and territory governments, in line with existing arrangements.

## 7. Population

PASC advised that the PICO for this application is comprised of two PICO sets: PICO set 1 for NBS, and PICO set 2 for cascade testing arising out of NBS. PICO set 1 is the primary purpose of this application.

### PICO set 1

The proposed population to be screened for risk of X-ALD is all newborn babies born in Australia.

The proposed target condition for addition to NBS is X-ALD.

The proposed technology would be used where no current technology is publicly funded (noting some of the proposed methods are already available, but are not funded for NBS for X-ALD) and in the context of a rare hereditary disease.

Current identification of cases of X-ALD relies on the symptomatic presentation of individuals prior to formal diagnosis. The proposed inclusion of X-ALD in the NBS program if supported would allow identification of cases in the pre-symptomatic stage, enabling earlier monitoring and earlier treatment (e.g., HSCT) if indicated, thereby potentially arresting disease progression with improved survival.

#### Potential screening strategies

Elevated C26:0-lysophosphatidylcholine (C26:0-LPC) levels may indicate the deregulation of lipid metabolism and are an established biomarker for assessing the risk of X-ALD (Moser et al., 2016[[4]](#footnote-5)).

The Application Form stated that there are several established methods for C26:0-LPC measurement and the screening laboratories in the USA use either three- or two-tier strategy (p5-6, Application Form).

The literature identified in the systematic review found that the analysis of C26:0-LPC by using flow injection analysis tandem mass spectrometry (FIA-MS/MS), performed in positive ion mode in the studies, is a fast, simple, and reliable method to screen for X-ALD from a dried blood spot (DBS) (Turgeon 2015[[5]](#footnote-6)). However, this method may yield high levels of false positives due to sample contamination or an interfering artefact/metabolite of unknown origin (Teber et al., 2022[[6]](#footnote-7), Hubbard et al., 2009[[7]](#footnote-8)).

Using high-performance liquid chromatography (HPLC-MS/MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) can ameliorate some of these issues. In HPLC-MS/MS, the sample is first separated by liquid chromatography, followed by tandem mass spectrometry to measure the levels of the target molecules such as C26:0-LPC (Hubbard et al., 2009). Using the same sample for the first and second tier analysis efficiently reduces false positive results in NBS applications (Turgeon et al., 2015). However, some positives from either tier may be associated with other disorders that result in elevated C26:0-LPC in the newborn DBS (Turgeon et al., 2015).

A third tier of molecular genetic testing for *ABCD1* gene is recommended to confirm the diagnosis. *ABCD1* genetic testing is the gold standard to confirm the diagnosis of X-ALD (expert adviser, a clinical geneticist)[[8]](#footnote-9).

In general, the applicant indicated that both C26:0-LPC biochemical testing and sequencing of the *ABCD1* gene can be conducted on the same DBS. In some cases, where the C26:0-LPC value is at the cut-off value for X-ALD newborn screening, a second test on a separately punched DBS can be used for confirmation before sequencing the *ABCD1* gene.

#### Scenario analyses (X-counter test)

The Health Council of the Netherlands considered that screening for the risk of X-ALD was useful only in male newborns and recommended only reporting results for males from screening for X-ALD. Consequently, a male-only screening algorithm, including an X-counter test, was developed and tested in a Dutch pilot study (the SCAN study). An X-counter test was integrated as the second tier in the pilot Dutch 4-tier screening algorithm (Albersen et al., 2023[[9]](#footnote-10)).

Sex determination is a complex screening algorithm challenge due to inconsistency between chromosomal sex and phenotypic sex, not classifiable male/female phenotype, and administrative errors. The X-counter test (various commercial kits available) determines the number of X chromosomes rather than the presence of a Y chromosome, because the chance that X-ALD will develop is determined by the number of X chromosomes. The X-counter test therefore enables the identification of individuals with one X chromosome at greatest risk for X-ALD but without unsolicited findings (e.g., sex chromosome disorders).

PASC considered that sex reported based on external genitalia was unreliable, and any advice to not report results for babies with a number of X chromosomes other than one would be based on the results of the X-counter test rather than sex reported on the bloodspot card. PASC also noted that no stakeholder had proposed using sex on the bloodspot card, and that the Victorian NBS laboratory had commented that this would be a departure from current practice that would have significant workflow changes and costs. PASC therefore agreed with the proposed population and advised that a scenario analysis of the population of only phenotypically male newborns is not required, because usingrecorded sex on the bloodspot card is not proposed, and the assessment’s examination of the X-counter will be addressed through scenario analyses of the intervention. (p7, 1710 PICO). Due to the position of the X-counter test in the screening algorithm for X-ALD, only a subset of all individuals with sex chromosome aneuploidy will be identified.

The PASC agreed that two-tier strategy should also be considered for X-ALD testing, with LC-MS/MS as the first tier, followed by *ABCD1* genetic testing (p2, 1710 PICO). LC-MS/MS methods have high sensitivity and specificity, but separating different LPC species limits its applicability to the wide-scale NBS program when this method is used alone (Turgeon et al., 2015). The PICO also included using FIA-MS/MS as the first tier, followed by *ABCD1* gene sequencing. However, FIA-MS/MS yields a high false positive rate and would lead to more samples proceeding to *ABCD1* sequencing, which can be time-consuming and costly.

Figure 1 presents an overview of the strategies considered in the current assessment. Table 1 presents a summary of the preferences of strategies from the state NBS laboratories.

Figure 1 Overview of the nine screening strategies of NBS for X-ALD considered in the assessment report, as advised by the PASC



FIA-MS/MS: flow injection tandem mass spectrometry; HPLC-MS/MS: high-performance liquid chromatography- mass spectrometry; PASC = PICO Advisory Sub-Committee of the MSAC.
Source: DCAR Figure 1.

Table 1 Summary of consultation feedback from the five state NBS programs in Australia

|  | Western Sydney Genetics Program (WSGP) (NSW NBS laboratory) | Victorian Clinical Genetic Services (VCGS) (Victorian NBS laboratory) | Queensland NBS program | Western Australia NBS program | SA Pathology (SA NBS laboratory) |
| --- | --- | --- | --- | --- | --- |
| Screening (universal vs. male-only) | Favours male-only NBS for X-ALD; considered screening for females not warranted; also, screening females introduces the risk of false positives and associated anxiety for families | Universal screening raised the controversy around the identification of adult-onset disorders as part of NBS programs and the individual’s right to know vs. the potential harm caused for patients in waiting. | No comment | No comment | No comment |
| Reporting of abnormal results (universal vs. male-only) | Favours male-only  | No comment | No comment | No comment | Favours male-only  |
| Preference of strategies | Plan to use “a 3-tier process, incorporating FIA-MS/MS as first tier…followed by a second tier ‘X-counter’ sex determination with male identified newborns proceeding to have *ABCD1* gene sequencing” (this description fits Strategy Ia in Figure 1). However, also stated that “should the kit they intend to use not be validated for use with HPLC-MS/MS, they will revert to the 4-tier screening algorithm as used by the Dutch programme” (p34, 1710 PICO) (i.e., Strategy IVa). | (HP)LC-MS/MS as confirmatory test instead of *ABCD1* genetic testing (p13, 1710 PICO) (Strategy I)Preferred 2-tier method; did not support 3-tier method (because does not add value, redundant) (p33, 1710 PICO). | Strategy I because no current capacity to do HPLC. | Strategy IV | No comment |
| Implementation issue(s) | Infrastructure required within the NBS programs needs to be adjusted as required to accommodate the increased workload. | Universal screening: workflow will fit into many of the current processes.Male-only screening: significant logistical considerations for the NBS laboratory including a totally separate workflow for samples identified as male; there will be significant costs for NBS laboratory related process management, staffing, equipment, and information technology costs. | No comment | Need to adopt the commercial PerkinElmer Neobase 2 kit (~$7). Testing would require no additional staff. | Infrastructure required within the NBS programs needs to be adjusted as required to accommodate the increased workload. |

FIA=Flow-injection analysis; HPLC=high performance liquid chromatography; MS/MS=tandem mass spectrometry; NBS = Newborn bloodspot screening; X-ALD = X-linked adrenoleukodystrophy.

Source: p31-34, 1710 PICO; feedback from the Queensland and Western Australia NBS programs (via the Department of Health and Aged Care).
Source: DCAR Table 1.

### PICO set 2

The proposed population for cascade testing was family members of newborns diagnosed with a pathogenic or likely pathogenic (P/LP) variant in *ABCD1* through NBS, with a scenario analysis of the cascade testing population being the family members of newborns with one X chromosome and a P/LP variant in *ABCD1*.

Under universal screening, “family members” refers to the parents (mother if the identified newborn is male, both parents if female) and siblings of the newborn, and first-degree relatives on the maternal side or paternal side, depending on inheritance. Under scenario analysis (male-only screening), “family members” refers to the mother and siblings of the identified male newborn and first-degree relatives on the maternal side if the mother is a carrier.

The proposed cascade testing of the relatives of newborns identified specifically through NBS would be used in the context of a rare hereditary disease.

## 8. Comparator

### PICO set 1

The comparator was no screening test (NBS for X-ALD is not currently available in Australia).

At present, identification of cases of X-ALD relies on the symptomatic presentation of individuals followed by formal diagnosis. Investigation and confirmatory tests are funded by the MBS (e.g., brain magnetic resonance imaging (MRI), adrenal function tests, specialist consultations) and the states and territories governments (e.g., plasma very long-chain fatty acid (VLCFA) levels, *ABCD1* genetic testing, cascade testing).

The reference standard used to determine the accuracy of the proposed NBS for X-ALD (including screening test/s and confirmatory *ABCD1* gene sequencing) is those individuals with clinical disease (i.e., clinical signs and symptoms of X-ALD, including radiology, pathology, histology) as well as a P/LP variant in the *ABCD1* gene.

### PICO set 2

The comparator was cascade testing offered to the family members of presenting individuals diagnosed with X-ALD. There is no relevant MBS item for cascade testing. The funding source is state and territory governments.

## 9. Summary of public consultation input

Consultation feedback was received from five (5) professional organisations, four (4) consumer organisations and one (1) individual health professional. The organisations that provided input were:

* Australian Pompe Association (APA)
* Human Genetics Society of Australasia (HGSA), Newborn Screening and Education Ethics and Social Issues Committees
* HGSA, Australasian Society for Inborn Errors of Metabolism (ASIEM) special interest group
* Australian Genomics
* Victorian Clinical Genetic Services (VCGS) (Victorian NBS laboratory)
* Better Access Australia
* Genetic Undiagnosed and Rare Disease Collaborative Australia (GUaRD)
* Rare Voices Australia (RVA)
* Western Sydney Genetics Program (WSGP) (NSW NBS laboratory)
* SA Pathology (SA NBS laboratory)

Further input was received following PASC from two organisations that had also provided input prior to the PASC consideration. The consultation feedback received was largely supportive of Newborn Bloodspot Screening for X-ALD. The consultation feedback raised a number of concerns, predominantly in relation to the population, i.e. whether only males should be screened.

Overall, consultation feedback demonstrated broad agreement that the main benefit of X-ALD for NBS is early detection and treatment. The benefits of genetic knowledge to the families of carrier girls, and for their own knowledge when older was also noted. The other main benefits of NBS for X-ALD stated in the consultation feedback were:

* Reduced financial burden
* Gives families opportunity to plan lifestyle and set goals for treatment
* Allows for further genetic characterisation and phenotyping
* Identification of these disorders in the family would allow for cascade testing and identification of further affected family members
* Wilson and Jungner criteria for screening clearly met for male babies
* PEX disorders may also be detected
* Symptom awareness
* Lack of publicly funded screening means many tests are not even available to be privately purchased, publicly funding the proposed service may improve this.
* Increased innovation in screening and testing technology
* Reduced need for higher cost genetic sequencing
* Reduced diagnostic odyssey
* Reduced trauma from misdiagnosis and protracted medical assessments
* Reduces presentations of adrenal crisis associated with X-ALD

The main disadvantages of NBS for X-ALD in the consultation feedback included:

* Inability to predict phenotype from lab tests
* Potential for a prolonged period of medical follow up
* Not enough data on risk of screen-positive babies to develop classical X-ALD, raising questions on whether screening results overall benefit or harm families
* Poor family compliance with prolonged medical follow up could lead to poorer than expected outcomes in screen-detected cases
* False positives and associated harms
* No preventative treatment for affected females
* Additional resources needed for genetic counselling, treatment and monitoring services for both symptomatic and asymptomatic patients, and for longer term follow up in adult onset disease
* Uncertainty on how to manage novel variants with uncertain significance in *ABCD1*
* Currently no treatments for AMN apart from steroid replacement therapy in affected females
* Potential harms and emotional burden from the knowledge of a rare disease developing later in life
* Ambiguity around clinical outcomes
* Transplant does not protect against the manifestation of adrenal insufficiency adult-onset AMN
* Paediatric HSCT services are not available in all states and territories therefore inter-jurisdictional policies are required to be in place.
* Concerns that adding X-ALD to NBS may result in the use of a controversial low-fat diet in association with Lorenzo’s oil in delaying the onset or prevention of potential childhood onset of CALD, as one centre still manages patients with a low-fat diet with Lorenzo’s oil and several centres have provided this treatment in the past. ASIEM raised concerns that there is no international consensus on the use of Lorenzo’s oil in CALD prevention and the low-fat diet used is nutritionally incomplete for an infant and young child. Lorenzo’s oil has side-effects, requires monitoring, is contra-indicated by aspiration risk, and is not currently funded on the PBS but is available to buy in Australia.

Additional input from the NSW NBS program in regard to the proposed population confirmed their disagreement with the proposed population including female newborns, and considered there was merit in the Dutch NBS programme for X-ALD (Barendsen et al, 2020[[10]](#footnote-11)), wherein screening results are only reported for male newborns. They considered that screening female newborns will have its inherent risk of false positives, and the associated anxiety created for families.

## 10. Characteristics of the evidence base

No direct evidence was identified showing a direct link between NBS for X-ALD and improvement of health outcomes. A linked evidence approach was therefore used to assess the clinical efficacy and safety of NBS for X-ALD compared to no screening. This assessment included two populations, population 1 (PICO set 1) was all newborns in Australia, including both female and male. For PICO set 1, an additional scenario analysis was also presented of newborns with one X chromosome (typically males and hereafter for simplicity referred to as “male newborns”, though recognising that this would include a small proportion of newborns with karyotypes other than 46,XY). Population 2 (PICO set 2) was family members of individuals genetically diagnosed with X-ALD as a result of NBS. Most of the evidence was identified for PICO set 1 (Table 2).

### Test accuracy

Test accuracy studies were assessed using the QUADAS 2 checklist for diagnostic accuracy studies, and the majority of studies were rated low or moderate for risk of bias. Nine studies of implemented NBS programs for X-ALD met the inclusion criteria (six retrospective/pilot studies, two case-control, and one Dutch study).

**PICO set 1: All Australian newborns**

Six studies were international retrospective analyses or pilot NBS programs in the USA. These studies assessed a three-tier screening strategy (FIA-MS/MS+LC-MS/MS + *ABCD1* gene testing) or two-tier screening strategy (LC-MS/MS + *ABCD1* gene testing). All the studies used different cut-off values, which may have impacted the estimated positive predictive value (PPV). Two case-controlled studies (Natarajan et al., 2018[[11]](#footnote-12), Natarajan et al., 2019[[12]](#footnote-13)) assessed the sensitivity and specificity of FIA‑MS/MS and LC-MS/MS and had a moderate study bias. The cut-off value of both FIA-MS/MS (≥0.42 µmol/L) and LC-MS/MS (≥0.13 µmol/L) were higher than the cut-off values used in all the international NBS programs for X-ALD presented in this assessment. Thus, the international NBS programs may have more positive patients, including more false positive patients compared to the case-controlled studies.

No studies examined the test accuracy of *ABCD1* genetic testing directly, given it is considered the gold standard to confirm a genetic diagnosis (Wanders and Eichler, 2023). All international NBS programs for X-ALD reported in this assessment used *ABCD1* genetic testing as a confirmational test to ensure patients had a genetic variation.

**PICO set 1a: Scenario analysis of male newborns only**

One study (SCAN study) (N=71,208) was carried out by the Dutch health council (Albersen et al., 2023), which recommended screening only male newborns for ALD without identifying untreatable conditions associated with elevated C26:0-LPC, like Zellweger spectrum disorders and single peroxisomal enzyme defects. The SCAN study used a four-tier screening strategy, which included an X-counter test to determine newborn males only.

The SCAN study positioned X-counter in the second tier because the first tier FIA-MS/MS is a sensitive test for identifying elevated C26:0-LPC, and most of the girls would have been excluded prior to this test (Barendsen et al., 2020). The X-counter test used a modified commercial test to determine the number of X-chromosomes present in a one-tier screen positive dried blood sample (DBS) (Barendsen et al., 2020). The risk of bias of the SCAN study was considered low as the testing laboratory was blinded and the study strategy aligned with the four-tiers reference standard.

**PICO set 2: Cascade testing of family members of newborns diagnosed with X-ALD via NBS**

No studies that met the inclusion criteria for assessing the test accuracy for cascade testing for family members of newborns genetically diagnosed with X-ALD as a result of NBS identified. Two international NBS programs for X-ALD reported their follow up results of cascade testing.

### Penetrance of the biomarker

No evidence was identified on the proportion of babies diagnosed as positive through NBS who will go on to develop X-ALD clinically – no NBS programs have been running for long enough to capture this data.

### Change in clinical management

**PICO set 1: All Australian newborns**

No studies were identified that examined the change in management evidence from implementing NBS for X‑ALD.

Twelve guidelines and reviews were identified that described the progressive conditions of X-ALD, current clinical management (including surveillance and monitoring) and the effectiveness of available treatment (for positively diagnosed individuals and their relatives). Four studies were retrospective (Liberato et al., 2019[[13]](#footnote-14), Mahmood et al., 2007[[14]](#footnote-15), Peters et al., 2004[[15]](#footnote-16), Raymond et al., 2019[[16]](#footnote-17)). One prospective study (Matsukawa et al., 2020[[17]](#footnote-18)), three reviews (Barendsen et al., 2020, Kemp et al., 2012[[18]](#footnote-19), Turk et al., 2020[[19]](#footnote-20)) and four expert opinions and reports (Engelen et al., 2022[[20]](#footnote-21), Gupta et al., 2022[[21]](#footnote-22), Regelmann et al., 2018[[22]](#footnote-23), Vogel et al., 2015[[23]](#footnote-24)) were identified.

**PICO set 1a: Scenario analysis of male newborns only**

Twelve studies described the difference between clinical management pathways for males and females.

**Health outcomes**

Cohort studies, retrospective chart reviews, and cross-sectional studies comparing health outcomes were assessed using the Cochrane Risk of Bias In Non-randomised Studies ‑Interventions (ROBINS-I) and were rated moderate to high risk of bias.

No studies were identified linking change in management due to the identification of X-ALD to health outcomes or adverse events. No studies compared early treatment arising from NBS for X-ALD and diagnosis with late treatment at disease sign/symptom onset. There were no studies identified that assessed evidence on health outcomes for X-ALD phenotypes AMN or adrenal insufficiency.

Two studies compared health outcomes for HSCT versus no HSCT as a treatment of cerebral adrenoleukodystrophy (CALD) (Matsukawa et al., 2020)(N=45), (Raymond et al., 2019) (N=137). Nine studies compared early HSCT versus late HSCT as treatment of CALD, where ‘early’ and ‘late’ were based on clinical assessment of disease progression at the time of transplant.

When appraised for risk of bias using the Cochrane ROBINS-I, both studies comparing HSCT with no HSCT were rated high due to the potential for confounding. When appraised for risk of bias using ROBINS-I, three of the ten studies comparing early and late HSCT were rated high, and seven were rated moderate. Studies were conducted in the USA, UK, Europe and Japan.

One study (Schwan et al. 2019[[24]](#footnote-25)) was identified that presented qualitative evidence on the impact of a positive newborn bloodspot screening result for X-ALD, including the impact of cascade testing. The study was assessed as having a high risk of bias using the Critical Appraisal Skills Program (CASP) checklist for qualitative studies.

Table 2 Key features of the included evidence

| **Population** | **Test results (diagnostic yield)** | **Change in management decisions** | **Health outcomes (OS, MFD-free survival, disease progression)** | **Non-health outcomes (e.g., value of knowing)** |
| --- | --- | --- | --- | --- |
| All newborns in Australia (PICO set 1) | k = 9n = 3,454,646Pilot studies and case control studies Rob: Low – moderate [RoB]  | Recommended earlier monitoring surveillance and treatment. K = 12n = 541Retrospective and prospective studies. Review and expert opinion. Rob: Low – High | k = 12n = 502Cohort, retrospective chart review, cross-sectional studiesRoB: moderate-high | k = 0n = 0  |
| Cascade testing for family members of newborns diagnosed with X-ALD (PICO set 2) | 0  | 0 | 0 | k = 1n = 10Qualitative cross-sectional studiesRoB: high |

k=number of studies, MFD = major functional disability; n=number of patients; OS = overall survival; RoB = risk of bias; X-ALD = X-linked adrenoleukodystrophy.
Source: DCAR Table 2.

## 11. Comparative safety

### NBS safety

There was no direct safety evidence comparing the addition of X-ALD to NBS against no NBS for X-ALD. Collecting dried blood spot (DBS) specimens is performed routinely through the NBS program. It involves pricking the skin of the foot and gently squeezing and releasing the area to be pricked until it is ready to be bled. Gentle pressure is applied to stop the bleeding, ensuring the wound is clean and bleeding has stopped (clinical expert advice). The NBS for X-ALD will use the same DBS from the NBS card. There is no extra step involved in collecting DBS just for X-ALD, so there is no incremental direct harm to patients.

### Cascade testing safety

There was no direct safety evidence of cascade testing (PICO set 2). Currently, genetic testing for the *ABCD1* familial variant is offered to family members of patients with signs and symptoms of X‑ALD. The cascade genetic testing is through a blood or saliva test, therefore considered safe (clinical expert advice).

### HSCT complications

Table 3 outlines mortality, graft failure and graft versus host disease (GVHD) for patients receiving HSCT in the included studies.

Table 3 Results of mortality, engraftment failure and GVHD across the included studies

| Trial/Study | Matsukawa 2020 | Raymond 2019 |
| --- | --- | --- |
| Stem cell donor source |  Bone marrow: | Related donor, BM/PBSCs | Unrelated donor, BM/PBSCs | Unrelated Cord Blood | All sources |
| HSCT cohort (N) | 12 | 19 | 14 | 31 | 65 |
| Mortality at 1 year, n (%) | 0 (0.0) | 2 (10.5) | 4 (28.6) | 6 (19.4) | 12 (18.5) |
| Graft failure, n (%) | NR | 2 (10.5) | 4 (28.6) | 6 (19.4) | 12 (18.5) |
| GVHD eligible population (n) | 12 | 18 | 12 | 27 | 58 |
| Acute GVHD |
| Grade II-IV, n (%) | 1 (8.3) | 3 (16.7) | 4 (33.3) | 11 (40.7) | 18 (31.0) |
| Grade III-IV, n (%) | 1 (8.3) | 1 (5.6) | 2 (16.7) | 3 (11.1) | 6 (10.3) |
| Chronic GVHD |
| Any | 2 (16.7) | NR | NR | NR | NR |
| Grade II-IV, n (%) | NR | 2 (11.1) | 1 (8.3) | 1 (3.7) | 4 (6.9) |
| Grade III-IV, n (%) | NR | 2 (11.1) | 0 | 1 (3,7) | 3 (5.2) |

Source: DCAR Table 3. From Table 2, Matsukawa 2020; Table 4, Raymond 2019.
BM = bone marrow; GVHD = graft versus host disease; HSCT = haematopoietic stem cell transplantation; n = number of patients who experienced an event; N = number of study participants in the treatment arm; NR = not reported; PBSCs = peripheral blood stem cells.

Table 4 suggests that early intervention with HSCT reduced HSCT complications such as transplant related mortality, graft failure, and GVHD when compared with late HSCT. Some of the included studies did not present safety data in terms of ‘early’ and ‘late’ HSCT.

Table 4 Results of transplant complications across the included studies

| Disease severity threshold/ Study | Cohort | Analysis point, years | Earlyn/N, % (95% CI) | Laten/N, % (95% CI) | HR | p-value |
| --- | --- | --- | --- | --- | --- | --- |
| Transplant related mortality |
| Chiesa et al. (2022) a | Children | 2 | NR, 7.0 (1.1, 20.5) | NR, 22.1 (4.9, 47.1) | 0.214 (0.035, 1.317) | 0.094 |
| Kuhl et al. (2017) b | Adults | NR | 1/9, 11.1 | 2/5, 40.0 | NR | NR |
| Waldhüter et al. (2019) c | Adults | 1 | 0/9, 0.0 | 3/6, 50.0 | NR | NR |
| Graft failure/rejection |
| Yalcin et al. (2021) d | Children | 3.5 | 1/15, 6.7 | 1/10, 10.0 | NR | NR |
| Chiesa et al. (2022) a | Children | 2 | NR, 23.2 (11.2, 37.4) | NR, 6.3 (0.4, 25.5) | 3.847 (0.487, 30.372) | 0.153 |
| Acute GVHD – Grade II-IV, % (95% CI) |
| Chiesa et al. (2022) a | Children | 2 | NR, 15.4 (6.1, 28.5) | NR, 25.6 (7.4, 49.0) | 0.0673 (0.190, 2.388) | 0.423 |
| Kuhl et al. (2017) b | Adults | NR | 0/9, 0.0 | 1/5, 20.0 | NR | NR |
| Waldhüter et al. (2019) c | Adults | 1 | 0/9, 0.0 | 2/6, 33.3 | NR | NR |
| Acute GVHD – Grade III-IV, % (95% CI) |
| Chiesa et al. (2022) a | Children | 2 | NR, 10.3 (3.2, 22.2) | NR, 13.0 (1.9, 34.8) | 0.935 (0.171, 5.113) | 0.815 |
| Kuhl et al. (2017) b | Adults | NR | 0/9, 0.0 | 1/5, 20.0 | NR | NR |
| Waldhüter et al. (2019) c | Adults | 1 | 0/9, 0.0 | 1/6, 16.7 | NR | NR |
| Chronic GVHD – overall, % (95% CI) |
| Chiesa et al. (2022) a | Children | 2 | NR, 19.3 (3.3, 33.7) | NR, 7.4 (0.4, 29.6) | 2.634 (0.323, 21.502) | 0.304 |
| Waldhüter et al. (2019) c | Adults | 1 | 3/9, 33.3 | 0/6, 0.0 | NR | NR |

Source: DCAR Table 4. From Table 2, Chiesa (2022); Table 2, Kuhl (2017); Table 2, Waldhüter (2019); Supplementary 1, Yalcin (2021).
CI = confidence interval; EDSS = Expanded Disability Status Scale; GVHD = graft versus host disease; HR = hazard ratio; HSCT = haematopoietic stem cell transplantation; MRD = matched related donor (includes bone marrow and peripheral blood); MUD = matched unrelated donor (included bone marrow and peripheral blood); n = number of patients with event; N = number of patients in the group; NR = not reported; n.s = not significant; UCB = umbilical cord blood; URD = unrelated donor (includes bone marrow and peripheral blood.

a Chiesa R, et al. 2022. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. *Blood Advances,* 6**,** 1512-1524. Donor source n (%); early disease: MRD + matched UCB = 11 (28.2), URD = 14 (35.9), unrelated UCB = 14 (35.9); late disease: MRD + matched UCB = 1 (6.3), UR = 4 (25.0), unrelated UCB = 6 (37.5), haploidentical = 5 (31.9).

b Kuhl JS, et al. 2017. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. *Brain,* 140**,** 953-966. Donor source n (%); early disease: MRD = 1 (11.1), MUD = 7 (77.7), UCB = 1 (11.1); late disease: MRD = 2 (40.0), MUD = 2 (40.0), UCB = 1 (20.0).

c Waldhüter N, et al. 2019. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy. *J Inherit Metab Dis,* 42**,** 313-324. Donor source n (%); early disease: MRD = 2 (22.2), MUD = 7 (77.7); late disease: MRD = 1 (16.7), MUD = 5 (83.3).

d Yalcin K, et al. 2021. Allogeneic hematopoietic stem cell transplantation in patients with childhood cerebral adrenoleukodystrophy: A single‐center experience “Better prognosis in earlier stage”. *Pediatric Transplantation,* 25. Donor source n (%); early disease: MRD = 4 (26.7), MUD = 9 (60.0), haploidentical = 1 (6.7); late disease: MRD = 3 (30.0), MUD = 5 (50.0); haploidentical = 2 (20.0).

## 12. Comparative effectiveness

A linked evidence approach was taken to show the effectiveness of the addition of X-ALD to NBS compared to no NBS for X-ALD, as no direct evidence was identified. Of note, it is common to have lack of data and research output in NBS for X-ALD as X-ALD is a rare disease.

### Test accuracy

**PICO set 1: Australian newborns**

Five pilot studies of NBS for X-ALD conducted in the USA used a three-tier strategy, Baker (2022, N=82,920) reported the highest positive predictive value (PPV) after the second tier (93%), 80% for males and 100% for females. This is likely because the study had the lowest cut-off from the second tier using HPLC-MS/MS (0.15 µmol/L) among all five studies. Matteson (2021[[25]](#footnote-26)) had the largest screening population (N=1,854,631), and reported the lowest PPV after the second tier (68%).

Natarajan (2019, N=310), which measured C26:0-LPC using FIA-MS/MS with a cut-off level of 0.42µmol/L, reported that FIA-MS/MS a sensitivity and specificity of 100% and 78.33% respectively. Natarajan (2018, N=396), which measured C26:0-LPC level using LC-MS/MS with a cut off level of 0.13 µmol/L, reported that LC-MS/MS had a sensitivity and specificity of 100% and 100%, respectively.

There is no international standard for which strategy to use for NBS for X-ALD. There are no international guidelines for any NBS program, in terms of the clinical conditions included for testing, the way screening is organised and conducted. Each country/ state has different operation systems, resources, infrastructure, and demographics. Both FIA-MS/MS and LC-MS/MS had high sensitivity (100%), while FIA-MS/MS had a lower specificity (78.33%) compared to LC-MS/MS (100%) (Natarajan et al 2018, Natarajan et al 2019). Studies that used the two-tier strategy (Matteson et al., 2021, Wiens et al., 2019[[26]](#footnote-27)) had higher PPV compared to those that used a three tier strategy, but the sample size was relatively small in these two studies.

**PICO set 1a: scenario analysis of males only**

The SCAN study (Albersen et al., 2023) reported that the X-counter test (using Devyser Resolution XY v2 kit to match the number of X chromosomes to sex as recorded on the bloodspot card) had 100% accuracy after correction of administrative errors in the recorded sex. Two samples out of 507 had discrepancies and after investigation both dried bloodspot cards were found to have been discordant for assigned sex due to administrative error, and so using X-chromosome analysis with Devyser Resolution XY v2 kit was able to provide 100% accuracy.

The SCAN study did not report the true negative and false negative test results. This is reasonable given X-ALD is rare and no follow-up was designed into the protocols for test-negative patients. The PPV after the third tier was 20%, and it increased to 100% after the fourth tier of genetic sequencing test.

### Penetrance of the biomarker

No evidence was identified on the proportion of babies diagnosed as positive through NBS who will go on to develop X-ALD clinically, however comparing incidence data from clinical presentation against positive NBS diagnosis rates gave an estimated penetrance of 9.8% to 37.7%.

The economic model included the percentage of patients with incident phenotypic presentation by sex and age (Table 5).

Table 5 Proportion of patients of developing phenotypic presentation per year, by sex and age

| Sex | Phenotypic presentation | Age | Mean phenotypic presentation incidence (%) | Source |
| --- | --- | --- | --- | --- |
| Male | Cerebral ALD | 0 to <3 years | 0% | Turk 2020 |
| 3 to <11 years | 33% |
| 11 to <21 years | 5.5% |
| ≥21 years | 20% |
| Adrenal insufficiency | 0 to 10 years | 47% | Huffnagel 2019 |
| 11 to 40 years | 29% |
| > 40 years | 5.7% |
| AMN | 0 to <30 years | 0% | Turk 2020 |
| ≥30 years | 100% |
| Female | Cerebral ALD |  | 0% | Turk 2020 |
| Adrenal insufficiency |  | 0% | Turk 2020 (rare in females and does not precede AMN phenotype as seen in males) |
| AMN | 0 to <40years | 0% | Turk 2020 |
| ≥40 to <65 years | 50% |
| ≥65 years | 65% |

ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy

Source: DCAR economic model for PICO set 1, tab “Probabilities” and DCAR Table 99.

### Change in clinical management

Clinical experts advised that the implementation of NBS for X-ALD would result in the same clinical management decisions, but would change the clinical pathway where earlier monitoring of newborns with X-ALD will occur instead of monitoring disease progression commencing only after the onset of symptoms. Early monitoring may lead to earlier treatment before patients become symptomatic and potentially untreatable, reducing mortality and morbidity rates.

Most of the guidelines and reviews concluded that HSCT could halt the progression of CALD, with superior outcomes obtained when HSCT is performed early in the disease progression. Engelen et al. (2022) (an expert opinion) mentioned that adrenal insufficiency could be treated with hormone replacement therapy. Regelmann et al. (2018) (an expert opinion) indicated that early detection and treatment for adrenal insufficiency could prevent life-threatening adrenal crises. Detailed analysis is presented on the effectiveness of HSCT. Peters et al. (2004)[[27]](#footnote-28) stated that boys with early-stage cerebral X-ALD (childhood CALD) treated with HSCT have a clear survival and function advantage over boys not receiving HSCT who, therefore, experience the progressive changes associated with the natural history of the disease.

The clinical management pathways were different between males and females. Eight studies reported the monitoring and surveillance guidelines for boys diagnosed with X-ALD. Seven studies proposed regular brain MRI (to monitor the development of cerebral ALD) for neurologically asymptomatic boys with X-ALD. Vogel et al. (2015) recommended brain MRI surveillance from the age of six months onwards. Two studies suggested that brain MRI examinations should be performed under general anaesthesia until age seven (Bladowska et al. 2015)[[28]](#footnote-29) or until children can lie still for the MRI (Mallack et al., 2021)[[29]](#footnote-30). Four studies indicated that tests for primary adrenal insufficiency should be conducted for serum adrenocorticotropic hormone and cortisol from birth for males.

Four studies reported the surveillance guidelines for females with positive X-ALD genetic test at birth, and concluded that no routine screening for cerebral disease in female patients is required (Engelen et al. 2022, Kemper et al. 2017[[30]](#footnote-31), Vogel et al. 2015, Zhu et al. 2020[[31]](#footnote-32)) as ALD in females is an adult-onset disorder (typically 30 years and later) without current treatment options.

The current clinical practice for cascade testing is to test eligible first-degree relatives of patients diagnosed with X-ALD. The clinical practice for cascade testing would be to test eligible first-degree relatives of patients diagnosed positive at NBS with a risk of developing X-ALD. If NBS for X-ALD is listed as an additional service of the NBS program, cascade testing for relatives of genotype positive male babies may not increase initially while the male baby has not developed any symptoms, but it may increase after the onset of symptoms (depending on parents’ consents).

If NBS for X-ALD is listed to include testing female babies, the cascade testing uptake will increase for relatives of genotype positive female babies at any time after the NBS program. Genotype positive females do not present symptoms until later in life and their relative would not otherwise known the risk of developing X-ALD unless they choose to undertake a cascade test. Detection of at-risk individuals through extended family testing compared with clinical detection was associated with improved survival and less neurologic involvement post HSCT based on MRI ratings for individuals with CCALD (Brosco et al. 2015[[32]](#footnote-33)).

### Effectiveness of HSCT

Two studies were identified that compared HSCT with no HSCT for patients with CALD. Matsukawa (2020) included patients with CALD or AMN with cerebral/cerebellar involvement while Raymond (2019) included patients with childhood CALD only. Given the differences in patient populations, the results were not meta-analysed.

Table 6 shows that treatment with HSCT improved the survival of patients with CALD (and AMN with cerebral/cerebellar involvement).

Table 6 Results of OS across the included studies comparing HSCT and no HSCT

| Outcome | HSCT | No HSCT |
| --- | --- | --- |
| Matsukawa 2020N=12 a | Raymond 2019N = 65 b | Matsukawa 2020N=8 | Raymond 2019N=72 |
| KM analysis point (months) c | 69.1 | 24 | 60 | 69.1 | 24 | 60 |
| Alive (%, 95% CI) | 100 (NA) | 82 (69.8, 89.1) | 74 (59.3, 83.6) | 25 (NA) | 74 (62.5, 83.0) | 55 (4.2., 65.7) |
| Median OS (months) | not reached | not reached | 70.8d | 92 |

Source: DCAR Table 5. From p6 and Figure 2, Matsukawa 2020; pp540-541 Raymond 2019.
CI = confidence interval; HSCT = hematopoietic stem cell transplant; KM = Kaplan-Meier; MRI = magnetic resonance imaging; N = number of patients; NR = not reported; OS = overall survival.
a All patients received bone marrow transplants; ten from unrelated donors and two from related donors.

b Survival estimates stratified by donor type were not presented in the publication.

c KM analysis in Matsukawa (2020) conducted from the earliest time of either the onset of cerebral/cerebellar/brainstem MRI lesions or the onset of clinical symptoms attributable to cerebral/ cerebellar/brainstem lesions. KM analysis in Raymond (2019) conducted from diagnosis.

d Matsukawa (2020) reported that six of the eight patients who did not undergo HSCT died 69.1 months (median period; range 16.0–104.1months) after the onset of cerebral/ cerebellar/brainstem involvement but did not provide median OS. The Kaplan Meier analysis (Figure 2 of the publication) was digitised to estimate median OS of 70.8 months.

Nine studies were identified that compared ‘early’ and ‘late’ HSCT for patients with CALD, where ‘early’ and ‘late’ were based on clinical assessment of disease progression at the time of transplant (Beckmann et al., 2018[[33]](#footnote-34), Bladowska et al., 2015, Chiesa et al., 2022, Kuhl et al., 2018[[34]](#footnote-35), Kuhl et al., 2017, Miller et al., 2011[[35]](#footnote-36), Waldhüter et al., 2019, Yalcin et al., 2021).The included studies used two different assessment methods (Loes score and extent of motor dysfunction) and a variety of thresholds to define ‘early’ and ‘late/advanced’ disease. The studies also considered different patient populations (children and adults) and conducted analyses at different timepoints. Given these differences, the results were not meta-analysed.

Table 7 indicates that ‘early’ treatment with HSCT, across a range of assessment methods and thresholds improved the survival of patients with CALD compared to those treated with ‘late/advanced’ HSCT. Kaplan-Meier estimates from studies were consistent with those presented by Chiesa et al (2022) (Figure 2).

Table 7 Results of OS across the included studies comparing ‘early’ and ‘late’ HSCT.

| Disease severity threshold/ Study | Cohort | KM analysis point, years | OS, % (95% CI) | HR (95% CI) | p-value |
| --- | --- | --- | --- | --- | --- |
| Early disease | Late disease |
| Loes <9 vs Loes ≥9 |
| Kuhl (2018) a | Children | 10 | NR | NR | 0.48 (0.06-4.0) | 0.484 |
| Peters (2004) b | Children  | 5 | 92 (81, 100) | 45 (23, 67) | NR | < 0.01 |
| Yalcin (2021) c | Children | 3 | 93.3 (80.7, 100) | 40.0 (9.6, 70.4) | NR | 0.004 |
| Loes ≤9 vs Loes >9 |
| Chiesa (2022) d | Children | 2 | 81.9 (57.8, 93.0) | 53.0 (23.3, 75.9) | 0.207 (0.058, 0.743) | 0.008 |
| Loes <10 vs Loes ≥10 |
| Miller (2011) e | Children | 5 | 89 (70, 96) | 60 (34, 78) | NR | 0.03 |
| EDSS < 6 vs EDSS ≥ 6 |
| Kuhl (2017) f | Adults | NR | 77.8 (SD: 13.9) | 20.0 (SD: 17.9) | NR | 0.048 |
| Waldhüter (2019) g | Adults | 5 | NR | 50 (SD: 20) | NR | n.s |

Source: DCAR Table 6. FromTable 2, Kuhl (2018); p863, Peters (2004); p4, Yalcin (2021); Table 2, Chiesa (2022); p1973, Miller (2011); p957 Kuhl (2017); Table 4, Waldhüter (2019).
BM = bone marrow; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; KM = Kaplan-Meier; MRD = matched related donor (includes bone marrow and peripheral blood); MUD = matched unrelated donor (included bone marrow and peripheral blood); NR = not reported; n.s = not significant; OS = overall survival; SD = standard deviation; UCB = umbilical cord blood; vs= versus.

a Donor source stratified by early/late disease was not presented. For the entire cohort (N=36) the donor sources were n (%): related BM = 9 (25), unrelated BM = 17 (47), unrelated peripheral blood stem cells = 9 (25); unrelated cord blood = 1 (3).

b Donor source stratified by early/late disease was not presented. For the entire cohort (N=94) the donor sources were n (%): related BM = 42 (44.7), unrelated BM = 40 (42.5), unrelated UCB = 12 (12.8).

c Donor source n (%); early disease: MRD = 2 (22.2), MUD = 7 (77.7); late disease: MRD = 1 (16.7), MUD = 5 (83.3).

d Donor source n (%); early disease: MRD + matched UCB = 11 (28.2), URD = 14 (35.9), unrelated UCB = 14 (35.9); late disease: MRD + matched UCB = 1 (6.3), UR = 4 (25.0), unrelated UCB = 6 (37.5), haploidentical = 5 (31.9).

e Donor source stratified by early/late disease was not presented. For the entire cohort (N=60) the donor sources were n (%): related BM = 18 (30), unrelated BM = 10 (17), unrelated UCB 32 (53). The authors reported that no significant difference in survival was noted for HSCT graft source.

f Donor source n (%); early disease: MRD = 1 (11.1), MUD = 7 (77.7), UCB = 1 (11.1); late disease: MRD = 2 (40.0), MUD = 2 (40.0), UCB = 1 (20.0).

g Donor source n (%); early disease: MRD = 2 (22.2), MUD = 7 (77.7); late disease: MRD = 1 (16.7), MUD = 5 (83.3).



Figure 2 Kaplan-Meier analyses of overall survival

Source: DCAR Figure 2. From Figure 1A Chiesa (2022).

AD = Loes > 9 and NFS >1; ED = Loes ≤ 9 and NFS ≤1; ED1 = Loes ≤ 4 and NFS ≤ 1; ED2 = Loes >4 to 9 and NFS ≤1; HSCT = hematopoietic stem cell transplant; NFS = neurological function score.

Raymond et al. (2019) classified loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, and complete loss of voluntary movement as MFDs. These disabilities were deemed clinically significant functional deficits resulting from CALD.

Results for major functional disability (MFD) free survival and disease progression were consistent with the findings for overall survival. However, one study (Kuhl 2018, n = 36, moderate risk of bias) found that patients with early disease were more likely to experience an event (defined as a gain in ALD-disability rating score, including MFD) than patients with advanced disease.

**PICO set 2: Cascade testing**

Two international NBS programs for X-ALD reported their follow up results of cascade testing. Baker et al. (2022)[[36]](#footnote-37) found 13 X-ALD positive patients through NBS. All 4 males demonstrated maternal inheritance of their variant, of which two families had known X-ALD, and two did not have a family history. 26 newly identified at risk males were identified among 1st to 3rd degree relatives. One of 13 newborns family refused follow up, the rest of the newborn families were provided with cascade testing and genetic counselling. Long-term follow-up data were not provided. There were no discussions in terms of what type of cascade testing was provided and testing accuracy.

Priestley et al. (2022)[[37]](#footnote-38) reported 44 infants with X-ALD, of which 34 infants’ family cascade testing results were available. Most of the cases were maternally inherited (28/34, 82%), one pathogenic variant identified in a female patient was inherited from her asymptomatic father and three females carried de novo pathogenic variants. Additionally, for two female patients, maternal testing was negative, but paternal testing was not available.

A qualitative study by Schwan et al. (2019) interviewed 10 mothers of children who were screened positive via NBS as being at risk of X-ALD. Key themes discussed during the interviews were stress, uncertainty, desire for more information about the disease, mental health support, and carrier testing.

Four out of 10 mothers reported that their children being at risk of X-ALD had a negative impact on the relationship with their spouse. Two families reporting a negative impact found through cascade testing that the father also possessed the pathogenic *ABDC1* variant, which raised concerns for the father’s and daughter’s health. Mental health challenges and concerns regarding future children were reported as contributing to the negative impact on family relationships. Three out of 10 mothers reported a positive impact, noting the diagnosis created stronger bonds within the family. Three mothers asked for information on financial resources for cascade testing and other services not covered by health insurance.

Some family members of female newborns screen positive via NBS as being at risk of X-ALD may have misunderstood the impact on their daughter’s long-term health given that there is no treatment for female newborns and their symptoms may develop later in life (this is discussed further in Section 5). From the interview conducted by Schwan et al. (2019), ‘60% of mothers reported feeling moderately or very hopeful about their child’s future, and 70% reported a positive progression in their emotions about their child’s diagnosis, even though much sadness and uncertainty remained.

Differences in emotional progression were noted in mothers of sons versus daughters, with the former generally reporting more hopefulness and acceptance of their son’s result and possible ALD diagnosis when compared to mothers of daughters. This discrepancy may be explained by mothers’ misunderstanding of their daughter’s NBS result. Two of the three mothers with daughters expressed concern that their child may become severely disabled or die in childhood despite receiving genetic counselling, even though females generally develop only the milder symptoms of myelopathy in adulthood.’

Clinical claim

The use of NBS for X-ALD resulted in superior effectiveness compared with no screening for Australian newborns. There was no evidence supporting that implementing NBS for X-ALD would affect the current clinical management of X-ALD-related diseases, such as CALD. The lack of data and research was an expected shortfall for all NBS and rare diseases such as X-ALD. However, studies from expert opinion and guidelines suggest that NBS for X-ALD would lead to earlier diagnosis of X-ALD and earlier ongoing monitoring and treatment. Early monitoring may lead to earlier treatment before patients become symptomatic and potentially untreatable, reducing mortality and morbidity rates.

Studies identified through this assessment concluded that HSCT could halt the progression of CALD, with superior outcomes obtained when HSCT was performed early in disease progression. Early treatment for HSCT improved the overall survival, MFD-free survival for patients with CALD, and had a positive impact on disease progression. (MFDs are classified loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, and complete loss of voluntary movement. These disabilities were deemed clinically significant functional deficits resulting from CALD (Raymond et al. 2019)).

Guidelines suggest ongoing monitoring for only male patients with X-ALD and not for females. Boys with early-stage cerebral X-ALD (childhood CALD) treated with HSCT have a clear survival and function advantage over boys not receiving HSCT who, therefore, experience the progressive changes associated with the natural history of the disease. (Peters et al. 2004).

13. Economic evaluation

PICO set 1

The clinical evidence presented suggests that adding X-ALD to the NBS program was superior to the current practice of no screening in Australia. Based on this clinical conclusion, the type of economic evaluation used was a cost-effectiveness analysis and a cost-utility analysis. The outcomes considered were incremental cost per positive diagnosis and QALYs. Table 8 summarises the key components of the economic evaluation for PICO set 1.

**Table 8 Summary of the economic evaluation (PICO set 1)**

| **Component** | **Description** |
| --- | --- |
| Perspective | Australian health care system perspective |
| Population | All newborns in Australia |
| Prior testing | None |
| Comparator | Current strategy (no screening test) (NBS for X-ALD is not currently available in Australia) |
| Type of analysis | Cost-utility analysis |
| Outcomes | Cost per positive diagnosis, cost per QALY  |
| Time horizon | Lifetime in the model base case  |
| Computational method | Model-based economic evaluation: combining a decision tree and an individual-level state-transition model (microsimulation). |
| Generation of the base case | Proposed strategies (Strategy I, II, III, IV) versus no screeningModelled stepped economic evaluation.Step 1: Decision-trees reflecting NBS to identify newborns at risk of developing X-ALD (positive diagnosis). Costs incurred included screening costs only. Estimation of the incremental cost per positive diagnosis. (Note 1)Step 2: Modelled state transitions between 5 health states: asymptomatic, symptomatic pre-HSCT, HSCT, post-HSCT and death. Costs incurred included pre-symptomatic monitoring, treatment costs for AI and AMN, HSCT and treatment for complications. Baseline utilities were based on population norms. Disutilities incurred included symptomatic HSCT, HSCT, complications from HSCT, and post-HSCT. |
| Scenario analyses: Incorporation of an X-Counter testProposed strategies (Strategy Ia, IIa, IIIa, IVa and IVb) versus no screeningModelled stepped economic evaluation as per above. |
| Health states | Asymptomatic, symptomatic pre-HSCT, HSCT, symptomatic post-HSCT, death |
| Cycle length | One year |
| Transition probabilities | Prevalence of ALD at birth (Matteson et al., 2021)Test accuracy of NBS screening tests (FIA-MS/MS, HPLC-MS/MS) based on (Natarajan et al., 2018), (Natarajan et al., 2019).Test accuracy of *ABCD1* genetic tests was assumed to be 100% (sensitivity/specificity).Probability of developing CALD and AMN, by age and gender (Turk et al., 2020).Probability of developing AI by age and gender (Huffnagel et al., 2019).Probability of death (no HSCT, HSCT) (Raymond et al., 2019) (Chiesa et al., 2022).Probability of death, no X-ALD, asymptomatic and no CALD, and post-HSCT (ABS National Life Tables 2022) |
| Utilities | Asymptomatic, by age (McCaffrey et al., 2016)Utility decrement associated with ALD, by disease severity (Bessey et al., 2018)Utility decrements associated with HSCT, acute GVHD and chronic GVHD (Matza et al., 2020) |
| Discount rate | 5% for both costs and outcomes |
| Software | TreeAge Pro 2023 |

AI = adrenal insufficiency; ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy; CALD = cerebral adrenoleukodystrophy; FIA=Flow-injection analysis; HPLC=high performance liquid chromatography; HSCT= haematopoietic stem cell transplantation; MS/MS=tandem mass spectrometry; NBS = Newborn Bloodspot Screening program; PICO = Population, Intervention, Comparison, Outcomes; QALY = quality-adjusted life years; X-ALD=X-linked adrenoleukodystrophy.

Note 1: The positive diagnoses from Strategies I and Ia were not genetically confirmed.
Source: DCAR Table 7.

Key assumptions used in the economic model for NBS are described in Table 9.

**Table 9 Summary of assumptions used in the model (PICO set 1)**

|  | **Assumptions** |
| --- | --- |
| Population | The "birth prevalence" of X-ALD (i.e., the incidence of X-ALD at birth for all newborns from Matteson 2021 is the same as the prevalence of X-ALD in the population in Australia. |
| The "birth prevalence" of X-ALD will not change over time (throughout the model duration). |
| The proportion of males among newborns will remain the same over time. |
| Structure | The development of CALD, AI or AMN are mutually independent events. |
| Parameters | There is no difference in the uptake of NBS under the current or proposed policy. |
| There is no difference in the uptake of NBS for X-ALD across screening strategies. |
| There is no loss to follow-up after diagnosis of X-ALD (biochemical or genetic). |
| *ABCD1* genetic test is assumed to have 100% sensitivity and 100% specificity *(compared to FIA-MS/MS 100% sensitivity and 78.33% specificity, and HPLC-MS/MS 100% sensitivity and 100% specificity)*. |
| Females do not develop CALD or AI. |
| Complications from HSCT last one cycle. |
| *Change in management is assumed in terms of the percentage of patients meeting the criteria for early HSCT from 50% to 85%* |
| Utilities | No disutilities are associated with false positive or false negative test results. |
| *The utility decrements associated with various functional levels as assessed by the ALD-Disability Rating Scale in the UK Bessey 2018 study were applicable to Australia.**The utility decrement associated with HSCT was assumed to be the same as the utility difference between allogeneic HSCT and gene therapy.**It was assumed that disease stabilised (progression halted) after HSCT.**The utility decrements associated with acute and chronic GvHD post-HSCT for transfusion-dependent β-thalassemia were the same as that for CALD.* |

AI = adrenal insufficiency; AMN = adrenomyeloneuropathy; CALD = cerebral adrenoleukodystrophy; *GvHD = graft versus host disease;* HSCT= haematopoietic stem cell transplantation; NBS = Newborn Bloodspot Screening; X-ALD = X-linked adrenoleukodystrophy.

Source: DCAR Table 52. ESC’s additions are shown in blue italics.

Under the base case, the least costly screening strategy was Strategy I ($7.64 per individual), which did not involve *ABCD1* genetic testing (Table 10). This was followed by Strategy IV ($7.70 per individual), which involved screening individuals with FIA-MS/MS, HPLC-MS/MS, and finally *ABCD1* genetic testing. This is because it involved the fewest individuals receiving *ABCD1* genetic testing, which was the most expensive test ($673.20 per test). Strategy II had the highest costs ($149.60 per individual). This was because it involved the most individuals receiving *ABCD1* genetic testing.

As is the case for all rare disease/screening both within Australia and internationally, the cost per positive diagnosis was high across all of the strategies, reflecting the low rate of diagnoses per individual screened. Strategy I had the lowest cost per positive diagnosis ($83,027.85 per positive diagnosis), closely followed by Strategy IV ($83,701.05 per positive diagnosis). These results largely reflected the testing costs per individual, as there was little variation in terms of the number of individuals receiving a positive diagnosis. Strategy I dominated the other strategies (less costly, more or similar number of diagnoses).

When considering comparative cost-effectiveness across all four strategies not including an X-counter test, Strategy IV was the most cost-effective, followed closely by Strategy I (incremental cost $8,077 and $8,315 per additional QALY gained respectively). These strategies were found to have more positive diagnoses than strategies including an X-counter, although this included positive diagnoses in (heterozygote) female newborns where ALD in females is an adult-onset disorder.

Under scenario analyses where an X-counter test was incorporated, the least costly screening strategy was Strategy IVb ($7.68 per individual), with the X-counter test positioned after the second-tier test of HPLC-MS/MS. This was followed by Strategy IIIa ($10.47 per individual), where the X-counter test was positioned after HPLC-MS/MS but before the *ABCD1* genetic testing. When considering comparative cost-effectiveness across all four strategies, Strategy IVb was the most cost-effective, followed closely by Strategy IVa (incremental cost $7,676 and $30,631 per additional QALY gained respectively).

Overall, considering all nine strategies, Strategy IVb was the most cost-effective, followed closely by Strategy IV.

Disaggregated diagnosis results are presented inTable 12. None of the strategies gave false positive or false negative results, which reflected the assumptions that both HPLC-MS/MS and *ABCD1* genetic testing had 100% testing accuracy. However, Strategies II and IIa resulted in variants of uncertain significance (VUSs) being detected, as more patients who were true negative received *ABCD1* genetic testing.

One-way sensitivity analyses were conducted on a range of variables. Across almost all one-way sensitivity analyses, the ICER of Strategy IV remained the lowest, with Strategy I the second lowest. When the X-counter test was included in strategies, the ICER of Strategy IVb was the lowest. Table 13 presents the variation of the cost per positive diagnosis across the strategies and across a range of variables. The cost per positive diagnosis was lowest for Strategy I, with Strategy IV the second lowest. When the X-counter test was included in strategies, the cost per positive diagnosis of Strategy I remained the lowest. The cost per positive diagnosis was higher in any strategies that included FIA-MS/MS (paying for unnecessary subsequent tests for false positive results).

Table 10 Economic evaluation results by screening strategy (PICO set 1) – DCAR

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Screening Strategy** | **I** | **Ia** | **II** | **IIa** | **III** | **IIIa** | **IV** | **IVa** | **IVb** | **Current** |
| **Step 1:** |  |  |  |  |  |  |  |  |  |  |
| Diagnostic cost ($) | 7.64  | 27.96  | 149.60  | 100.75  | 10.48  | 10.47  | 7.70  | 28.01  | 7.68  | - |
| Positive diagnoses | 0.000092 | 0.000064 | 0.000092 | 0.000064 | 0.000092 | 0.000064 | 0.000092 | 0.000064 | 0.000048 | - |
| Cost ($) per positive diagnosis | 83,028 | 436,919 | 1,626,093 | 1,574,244 | 113,863 | 163,528 | 83,701 | 437,593 | 160,002 | - |
| **Step 2:** |  |  |  |  |  |  |  |  |  |  |
| Cost | 8.93  | 29.21  | 233.72  | 146.79  | 11.76  | 11.71  | 8.96  | 29.43  | 8.75  | 0.75  |
| QALYs | 19.020577  | 19.020447  | 19.020577  | 19.020447  | 19.019372  | 19.019256  | 19.020609  | 19.020529  | 19.020635  | 19.019593  |
| Incremental costs | 8.18  | 28.46  | 232.97  | 146.03  | 11.01  | 10.96  | 8.21  | 28.67  | 8.00  |  |
| QALYs gained | 0.000983  | 0.000854  | 0.000983  | 0.000854  | -0.000222  | -0.000338  | 0.001016  | 0.000936  | 0.001042  |  |
| ICER (cost per QALY gained) | **8,315**  | **33,322**  | **236,945**  | **170,998**  | **-49,710**  | **-32,442**  | **8,077**  | **30,631**  | **7,676**  |  |
|  | **Dominated** | **Dominated** | **Dominated** | **Dominated** | **Dominated** | **Dominated** |  | **Dominated** | **Dominated** |  |

Source: DCAR Table 8. ICER = Incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

Notes: 250,000 simulations. Across all strategies, Strategy IV had the lowest ICER, so all other strategies were labelled ‘dominated’. Positive diagnoses from Strategies I and Ia were not genetically confirmed.

Table 11 Economic evaluation results by screening strategy (PICO set 1) – post-MSAC updated analyses

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Screening Strategy*** | ***I*** | ***Ia*** | ***II*** | ***IIa*** | ***III*** | ***IIIa*** | ***IV*** | ***IVa*** | ***IVb*** | ***Current*** |
| ***Step 1:*** |  |  |  |  |  |  |  |  |  |  |
| *Diagnostic cost ($)* | *5.44* | *5.91* | *8.76* | *7.61* | *10.49* | *10.46* | *5.51* | *5.95* | *5.49* |  |
| *Positive diagnoses* | *0.000107* | *0.000056* | *0.00010700* | *0.000056* | *0.000107* | *0.000056* | *0.000107* | *0.000056* | *0.000055* |  |
| *Cost ($) per positive diagnosis* | *50,829* | *106,246* | *81,886* | *136,718* | *98,015* | *187,971* | *51,502* | *106,919* | *99,754* |  |
| ***Step 2:*** |  |  |  |  |  |  |  |  |  |  |
| *Cost* | *6.79* | *7.06* | *12.00* | *9.79* | *11.84* | *11.61* | *6.86* | *7.13* | *6.64* | *0.66*  |
| *QALYs* | *19.021710* | *19.021754* | *19.021710* | *19.021754* | *19.021729* | *19.021738* | *19.021701* | *19.021772* | *19.021740* | *19.021613*  |
| *Incremental costs* | *6.13* | *6.40* | *11.34* | *9.13* | *11.18* | *10.95* | *6.20* | *6.47* | *5.98* |  |
| *QALYs gained* | *0.000098* | *0.000141* | *0.000098* | *0.000141* | *0.000117* | *0.000126* | *0.000088* | *0.000160* | *0.000127* |  |
| *ICER (cost per QALY gained)* | *62,793* | *45,369* | *116,226* | *64,715* | *95,883* | *87,122* | *70,216* | *40,478* | *47,084* |  |
|  | ***Dominated*** | ***Dominated*** | ***Dominated*** | ***Dominated*** | ***Dominated*** | ***Dominated*** | ***Dominated*** |  | ***Dominated*** |  |

*Source: Post-MSAC modelling results provided by the DCAR HTA group to align with MSAC’s advice: assuming FIA-MS/MS specificity increased from 78.33% to 99.5%, and using 3 million simulations to reduce the effect of chance in the context of rare disease. ICER = Incremental cost-effectiveness ratio; QALY = quality-adjusted life years.*

*Notes: 3 million simulations. Across all strategies, Strategy IVa had the lowest ICER, so all other strategies were labelled ‘dominated’. Positive diagnoses from Strategies I and Ia were not genetically confirmed.*

**Table 12 Outcomes: disaggregated summary of diagnoses and phenotypes in the economic evaluation (PICO set 1)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Screening Strategy** | **I** | **Ia** | **II** | **IIa** | **III** | **IIIa** | **IV** | **IVa** | **IVb** | **Current** |
| Positive diagnoses | 0.00010667 | 0.00007000 | 0.00010667 | 0.00007000 | 0.00010667 | 0.00007000 | 0.00010667 | 0.00007000 | 0.00005667 | - |
| False positives | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | - |
| False negatives | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | - |
| VUS | 0.00000000 | 0.00000000 | 0.11635667 | 0.06284667 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | 0.00000000 | - |
| Cases that develop AI | 0.00004000  | 0.00005600  | 0.00004000  | 0.00005600  | 0.00004000  | 0.00005600  | 0.00004800  | 0.00004800  | 0.00003600  | 0.00004400  |
| Cases that develop AMN | 0.00008400  | 0.00007200  | 0.00008400  | 0.00007200  | 0.00008400  | 0.00007200  | 0.00008400  | 0.00008400  | 0.00008400  | 0.00008000  |
| Cases that develop CALD | 0.00005600  | 0.00006800  | 0.00005600  | 0.00006800  | 0.00005600  | 0.00006800  | 0.00005600  | 0.00006800  | 0.00005200  | 0.00005600  |
| HSCT | 0.00004400  | 0.00006400  | 0.00004400  | 0.00006400  | 0.00004400  | 0.00006400  | 0.00005600  | 0.00006400  | 0.00004800  | 0.00004400  |

AI = adrenal insufficiency; AMN = adrenomyeloneuropathy; CALD = Cerebral adrenoleukodystrophy; HSCT= haematopoietic stem cell transplantation; VUS: Variant of uncertain significance

Notes: 250,000 simulations. Positive diagnoses from Strategies I and Ia were not genetically confirmed. Source: DCAR Table 9.

Table 13 One-way sensitivity analyses, cost ($) per positive diagnosis (PICO set 1)

| **Screening Strategy** | **I** | **Ia** | **II** | **IIa** | **III** | **IIIa** | **IV** | **IVa** | **IVb** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Base case** | **83,028** | **436,919** | **1,626,093** | **1,574,244** | **113,863** | **163,528** | **83,701** | **437,593** | **160,002** |
| FIA-MS/MS sensitivity = 90% (base case = 100%) | 136,396 | 776,637 | 2,671,005 | 2,798,032 | 113,863 | 163,528 | 137,069 | 777,311 | 239,541 |
| FIA-MS/MS specificity = 90% (base case = 78.33%) | 69,766 | 245,896 | 777,451 | 765,230 | 113,863 | 163,528 | 70,439 | 246,570 | 134,584 |
| HPLC-MS/MS sensitivity = 95% (base case = 100%) | 90,935 | 466,047 | 1,626,093 | 1,574,244 | 145,305 | 217,771 | 91,608 | 466,721 | 174,468 |
| HPLC-MS/MS specificity = 95% (base case = 100%) | 706 | 5,167 | 1,626,093 | 1,574,244 | 470,396 | 502,039 | 162,202 | 493,847 | 259,770 |
| X-ALD, birth prevalence = 0.0042%, Priestly 2022 (base case = 0.0111%, Matteson 2021) | 146,889 | 698,986 | 2,876,519 | 2,518,374 | 200,933 | 261,141 | 147,562 | 699,659 | 273,653 |
| X-ALD, birth prevalence = 0.01622%, Wiens 2019 (base case = 0.0111%, Matteson 2021) | 63,656 | 367,959 | 1,246,783 | 1,325,741 | 87,452 | 137,851 | 64,330 | 368,632 | 120,217 |
| *ABCD1* genetic test, unit cost = $378 (SA NBS program estimate) (base case = $1,053.50; simple average of QLD and WA estimates) | 83,028 | 436,919 | 938,713 | 1,067,607 | 113,568 | 163,233 | 83,406 | 437,297 | 159,706 |
| *ABCD1* genetic test, unit cost = $1,200 (WA NBS program estimate) (base case = $1,053.50; simple average of QLD and WA estimates) | 83,028 | 436,919 | 2,852,758 | 2,478,364 | 114,390 | 164,055 | 84,228 | 438,119 | 160,528 |
| X-Counter test, unit cost, $200 (base case =$100) | 83,028 | 771,644 | 1,626,093 | 1,908,969 | 113,863 | 163,672 | 83,701 | 772,318 | 160,193 |
| X-Counter test, unit cost, $50 (base case =$100) | 83,028 | 269,557 | 1,626,093 | 1,406,881 | 113,863 | 163,456 | 83,701 | 270,230 | 159,906 |

FIA–MS/MS: flow injection tandem mass spectrometry; HP LC-MS/MS: high-pressure liquid chromatography- mass spectrometry; X-ALD=X-linked adrenoleukodystrophy.

Notes: Positive diagnoses from Strategies I and Ia were not genetically confirmed. Simplified model (250,000 simulations). Source: DCAR Table 10.

PICO set 2

No studies that assessed the test accuracy or long-term outcomes of cascade testing for family members of the X-ALD positively diagnosed individual were identified during the assessment. Minimal evidence was identified on the real-world implementation of international NBS programs. The economic evaluation conducted for PICO set 2 was therefore limited to estimating the average expected cost per positive diagnosis from cascade testing. Table 14 summarises the key components of the economic evaluation for PICO set 2.

**Table 14 Summary of the economic evaluation (PICO set 2)**

| **Component** | **Description** |
| --- | --- |
| Perspective | Australian health care system perspective |
| Population | Family members\* of newborns diagnosed with a P/LP variant(s) in *ABCD1* through NBS, and the family members of presenting individuals diagnosed with signs and symptoms of X-ALD (if not already tested following identification through NBS). Scenario analysis: family members\* of newborns with one X chromosome and a P/LP variant in *ABCD1*. |
| Prior testing | Medical and family history |
| Comparator | Current practice of no cascade testing (cascade testing offered to the family members of presenting individuals diagnosed with signs and symptoms of X-ALD). |
| Type of analysis | Cost-effectiveness analysis |
| Outcomes | Cost per positive diagnosis (identification of the familial P/LP variants from cascade testing) |
| Computational method | Decision tree analysis  |
| Generation of the base case | Modelled analysisStep 1: Decision tree reflecting cascade testing of the mother of the newborn with positive genotype if male, or both the father and the mother of the newborn if female, then extending to cascade testing to the relevant parent’s first-degree relatives (FDRs) upon positive diagnosis. Costs incurred included testing costs only. Estimation of the incremental cost per positive diagnosis. |
| Health states | None |
| Cycle length | Not applicable |
| Transition probabilities | The probability of inheriting the familial variant was based on the X-linked pattern of inheritance. The uptake rates of the mother, father and FDRs were assumed to be the same, using the uptake rate of cystic fibrosis cascade testing as a proxy (as advised by the Department)Only the father’s daughter(s) aged 16 years and over were offered cascade testing.The proportion of newborns with positive genotype who are male was assumed to be the same as the sex distribution in newborns. |
| Discount rate | None |
| Software | TreeAge Pro 2023 |

FDRs = First degree relatives; NBS = Newborn bloodspot screening; P/LP = pathogenic or likely pathogenic; X-ALD = X-linked adrenoleukodystrophy.

Source: DCAR Table 11.

Table 15 presents the base case results and scenario analysis (male-only NBS screen for X-ALD) for PICO set 2.

The incremental cost-effectiveness of offering cascade testing to the family members of newborns diagnosed with a P/LP variant in *ABCD1* through NBS was estimated to be $8,789.16 per positive diagnosis through cascade testing. The expected cost-effectiveness decreased slightly to $6,688.91 per positive diagnosis when an X-counter was used prior resulting in considerations of the family members of male newborns with positive genotype only.

**Table 15 Base case results and scenario analysis (PICO set 2)**

|  | **Proposed**  | **Current** | **Increment**  |
| --- | --- | --- | --- |
| **Base case** |  |  |  |
| Cost | $2,373.07 | $0 | $2,373.07 |
| Positive diagnoses | 0.27 | 0 | 0.27 |
| **ICER** |  |  | **$8,789.16** |
| **Scenario analysis (Male-only NBS for X-ALD)** |
| Cost | $2,514.36 | $0 | $2,514.36 |
| Positive diagnoses | 0.38 | 0 | 0.38 |
| **ICER** |  |  | **$6,688.91** |

ICER = incremental cost-effectiveness ratio; NBS = newborn bloodspot screening; X-ALD = X-linked adrenoleukodystrophy.

Source: DCAR Table 12.

The results were most sensitive to the uptake rate of mother/FDRs, and the unit cost and frequency of use of genetic counselling (Table 16).

A key challenge in the economic evaluation of cascade testing of the family members of newborns diagnosed with P/LP variants in *ABCD1* at risk of X-ALD via the NBS program is that there is no relevant disease-specific Australian data/registry to inform the uptake or prevalence of variants among first-degree relatives. As a result, the current assessment relied on X-linked pattern of inheritance to estimate the likelihood of the presence of variants and assumptions on uptake rates.

**Table 16 Key drivers of the model (PICO set 2)**

| **Description** | **Method/Value** | **Impact****Base case: $8,789/additional positive diagnosis** |
| --- | --- | --- |
| Uptake rate of cascade testing among FDRs | Uptake rate of cascade testing of FDRs for X-ALD (37%, using the uptake rate for cystic fibrosis as a proxy (as advised by the Department). | High, favours comparator. Reducing the uptake rate of cascade testing among FDRs to 10% increased the cost per positive diagnosis to $18,838. |
| Cost of genetic counselling | The unit cost of genetic counselling in Australia ($1,056.09, estimate provided by Western Australia NBS laboratory) | Moderate, favours intervention. Reducing the unit cost from $1,056.09 to $236.82 (estimate provided by clinical expert in consultation with a state principal genetic counseller) reduced the cost per positive diagnosis to $2,831. |
| Frequency of genetic counselling | The number of genetic counselling sessions per positive diagnosis is uncertain (base case 3 sessions). | Moderate, favours comparator. Assuming 6 genetic counselling sessions per positive diagnosis increased the cost to $14,009 per additional positive diagnosis. |

*ABDC1* = ATP Binding Cassette Subfamily D Member 1; FDRs = first-degree relatives; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Source: DCAR Table 13.

14. Financial/budgetary impacts

NBS programs are overseen and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS through the National Health Reform Agreement (NHRA). It also announced funding of $39.0 million under the 2022-23 Budget, some of which will be provided direct to states and territories to support expansion of their NBS programs. It was assumed that testing for X-ALD through NBS programs would start in 2024.

An epidemiological approach was used to estimate the financial implications of screening all newborns (PICO set 1) in Australia for X-ALD through NBS. All newborns in Australia are eligible for NBS, and NBS uptake was estimated to be 99%. The estimated use and cost in PICO set 2 were based on the number of newborns (with positive genotype) diagnosed with X-ALD through NBS. PICO set 1 is the primary purpose of this application.

Financial estimates represent incremental costs compared to the current setting, where the X-ALD screening is not included in NBS programs. Based on literature, it was assumed within the financial modelling that no children would present symptomatically in the first six years after birth within the comparator. Consequently, no cost offsets were included in the financial estimates for PICO set 1, although financial implications of family members of newborns diagnosed with X-ALD as a result of NBS (PICO set 2) were also estimated.

There will likely be cost offsets beyond the six year time horizon of the financial analysis, which were not captured in the financial estimates. Children older than six years and adults diagnosed with X-ALD from symptomatic presentation will likely be originally misdiagnosed within their diagnostic odyssey due to the rarity of X-ALD. Including X-ALD in NBS programs will identify newborns with positive genotype and genetically (for strategies that include genetic testing) diagnose children as being at risk of developing X-ALD, eliminating the misdiagnosis and healthcare system costs associated with symptomatic presentation.

Due to the introduction of NBS for X-ALD, cascade testing will likely increase in the first six years. This resulted from a combination of bringing cascade testing forward for positive genotype male newborns compared to if they were diagnosed symptomatically, and from positive genotype female newborns (if results are reported for females) that would not otherwise have been picked up in the first six years after birth. Female newborns with positive genotype show signs and symptoms at a much later age than six years.

Table 17 shows the net financial implications to NBS programs and the Government for PICO set 1. Approximately 1.9 million newborns will receive NBS for X-ALD over six years. The total cost to NBS programs depended on the screening strategy implemented. Strategy I was estimated to have the lowest net financial impact on NBS programs at $11.1 million over six years. Strategy IVb had the next lowest financial impact at $11.2 million, while Strategy II had the greatest financial impact at $63.0 million over six years. Strategy II was the most costly because it had the highest number of newborns receiving *ABCD1* genetic testing compared to all other strategies.

There would also be a change in use of other health technologies associated with PICO set 1. This included $0.4 million over six years through the MBS to monitor for CCALD and AI, and $18,605 over six years through the PBS to treat GVHD and AI. State and territory governments were estimated to spend $3.0 million over six years for Strategies I to IV and $2.7 million over six years for Strategies Ia to IVb to treat CCALD with HSCT and to provide genetic counselling.

Table 17: Net financial implications to NBSa programs and other government budgets (PICO set 1)

| **Parameter**  | **Year 1(2024)** | **Year 2(2025)** | **Year 3(2026)** | **Year 4(2027)** | **Year 5(2028)** | **Year 6 (2029)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated use and cost of the proposed health technology** |
| Number of newborns eligible for NBS for X-ALD | 312,888 | 313,858 | 314,831 | 315,807 | 316,786 | 317,768 |
| Number of newborns who receive NBS for X-ALD (NBS uptake rate 99%) | 309,759 | 310,719 | 311,683 | 312,649 | 313,618 | 314,590 |
| **Total cost to NBS programs (PICO set 1) – DCAR** |
| Strategy I | $1,830,058 | $1,835,731 | $1,841,422 | $1,847,130 | $1,852,856 | $1,858,600 |
| Strategy Ia | $3,056,145 | $3,065,606 | $3,075,095 | $3,084,615 | $3,094,163 | $3,103,742 |
| Strategy II | $10,422,944 | $10,455,255 | $10,487,667 | $10,520,178 | $10,552,791 | $10,585,504 |
| Strategy IIa | $7,464,296 | $7,487,422 | $7,510,619 | $7,533,888 | $7,557,230 | $7,580,644 |
| Strategy III | $4,220,737 | $4,233,822 | $4,246,947 | $4,260,112 | $4,273,318 | $4,286,566 |
| Strategy IIIa | $3,893,847 | $3,905,905 | $3,917,999 | $3,930,132 | $3,942,301 | $3,954,509 |
| Strategy IV | $1,869,973 | $1,875,770 | $1,881,585 | $1,887,418 | $1,893,269 | $1,899,138 |
| Strategy IVa | $3,076,622 | $3,086,146 | $3,095,699 | $3,105,282 | $3,114,895 | $3,124,537 |
| Strategy IVb | $1,852,296 | $1,858,025 | $1,863,771 | $1,869,535 | $1,875,317 | $1,881,117 |
| ***Total cost to NBS programs (PICO set 1) – analyses updated to reflect MSAC’s advice*** |
| *Strategy I* | *$1,710,314* | *$1,715,616* | *$1,720,935* | *$1,726,270* | *$1,731,621* | *$1,736,989* |
| *Strategy Ia* | *$1,856,471* | *$1,862,213* | *$1,867,972* | *$1,873,749* | *$1,879,544* | *$1,885,357* |
| *Strategy II* | *$2,760,276* | *$2,768,833* | *$2,777,416* | *$2,786,026* | *$2,794,663* | *$2,803,326* |
| *Strategy IIa* | *$2,395,102* | *$2,402,513* | *$2,409,947* | *$2,417,404* | *$2,424,885* | *$2,432,388* |
| *Strategy IV* | *$1,715,192* | *$1,720,509* | *$1,725,842* | *$1,731,192* | *$1,736,559* | *$1,741,942* |
| *Strategy IVa* | *$1,858,973* | *$1,864,723* | *$1,870,490* | *$1,876,275* | *$1,882,077* | *$1,887,898* |
| *Strategy IVb* | *$1,709,373* | *$1,714,659* | *$1,719,961* | *$1,725,279* | *$1,730,614* | *$1,735,965* |
| **Change in use and cost of other health technologies (PICO set 1)** |
| Total cost implications to the MBS | $3,977 | $25,930 | $47,951 | $70,040 | $92,197 | $114,423 |
| Total cost implications to the PBS | $2,733 | $3,155 | $3,165 | $3,174 | $3,184 | $3,194 |
| Cost to state and territory Government (Strategy I to IV) | $145,533 | $524,411 | $545,768 | $567,190 | $588,679 | $610,235 |
| Cost to state and territory Government (Strategy Ia to IVb) | $92,720 | $471,435 | $492,627 | $513,885 | $535,209 | $556,599 |

AI= Adrenal insufficiency; CCALD= Childhood cerebral adrenoleukodystrophy; HSCT= Haematopoietic stem cell transplant; MBS= Medicare Benefits Schedule; NBS= Newborn Bloodspot Screening; PBS= Pharmaceutical Benefits Scheme; X-ALD= X-linked Adrenoleukodystrophy.

a NBS programs are overseen, funded and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). It also announced funding of $39.0 million under the 2022-23 Budget, some of which will be provided directly to states and territories to support the expansion of NBS programs.

Source: DCAR Table 14, andpost-MSAC modelling results provided by the DCAR HTA group to align with MSAC’s advice: assuming FIA-MS/MS specificity increased from 78.33% to 99.5%, toreflect MSAC’s advice that FIA-MS/MS should be for multiple VLCFAs (and their ratios) as this would have much higher specificity than FIA-MS/MS for C26:0 alone. 99.5% specificity of FIA-MS/MS resulted in a PPV of 2.17%, and 0.512% of newborns receiving second tier screening for strategy II. Strategy III and IIIa results were unchanged from those presented in the DCAR as these strategies do not include FIA-MS/MS.

Table 18 presents net financial implications to state and territory governments associated with NBS for X-ALD (PICO set 2). Approximately 180 family members were estimated to take up genetic counselling and cascade testing. For Strategies I to IV, family members of both male and female newborns with positive diagnosis through NBS would be eligible for genetic counselling and cascade testing. In contrast, with Strategies Ia to IVb, only family members of male newborns with a positive diagnosis through NBS would be eligible for genetic counselling and cascade testing.

The estimated total cost to the state and territory governments for PICO set 2 was $0.32 million for Strategies I to IV, and $0.13 million for Strategies Ia to IVb over six years.

Table 18: Net financial implications to state and territory government budgets associated with cascade testing arising from NBS for X-ALD (PICO set 2)

| **Parameter**  | **Year 1(2024)** | **Year 2(2025)** | **Year 3(2026)** | **Year 4(2027)** | **Year 5(2028)** | **Year 6 (2029)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated use of genetic counselling and cascade testing (PICO set 2)** |
| Total number of newborns who receive NBS for X-ALD | 309,759 | 310,719 | 311,683 | 312,649 | 313,618 | 314,590 |
| Number of newborns who receive NBS for X-ALD and identified with positive genotype (11.05 per 100,000) | 34 | 34 | 34 | 35 | 35 | 35 |
| Number of male newborns identified with positive genotype | 18 | 18 | 18 | 18 | 18 | 18 |
| Number of female newborns identified with positive genotype | 17 | 17 | 17 | 17 | 17 | 17 |
| Number of people eligible for cascade testing  | 81 | 81 | 81 | 81 | 82 | 82 |
| Number of people who receive cascade testing  | 30 | 30 | 30 | 30 | 30 | 30 |
| Number of people eligible for genetic counselling | 30 | 30 | 30 | 30 | 30 | 30 |
| Number of people who receive genetic counselling  | 30 | 30 | 30 | 30 | 30 | 30 |
| **Estimated total cost for PICO set 2** |
| Cost of cascade testing – Positively diagnosed males only (Strategy Ia to IVb) (*ABCD1* genetic test = $673.20) | $9,043 | $9,071 | $9,099 | $9,127 | $9,155 | $9,184 |
| Cost of cascade testing - Positively diagnosed females only | $12,544 | $12,583 | $12,622 | $12,661 | $12,700 | $12,740 |
| Cost of cascade testing - All persons (Strategy I to IV)  | $21,587 | $21,653 | $21,721 | $21,788 | $21,855 | $21,923 |
| Cost of genetic counselling - Positively diagnosed males only (Strategy Ia to IVb) (Cost of genetic counselling = $1056.09) | $13,205 | $13,246 | $13,287 | $13,328 | $13,369 | $13,411 |
| Cost of genetic counselling - Positively diagnosed females only | $18,318 | $18,375 | $18,432 | $18,489 | $18,546 | $18,604 |
| Cost of genetic counselling - All persons (Strategy I to IV) | $31,523 | $31,621 | $31,719 | $31,817 | $31,916 | $32,014 |
| **Estimated total cost to state and territory Government for PICO set 2 (Strategy I to IV)** | **$53,109** | **$53,274** | **$53,439** | **$53,605** | **$53,771** | **$53,938** |
| **Estimated total cost to the state and territories for PICO set 2 (Strategy Ia to IVb)** | **$22,248** | **$22,317** | **$22,386** | **$22,455** | **$22,525** | **$22,595** |

*ABCD1*= ATP Binding Cassette Subfamily D Member 1 gene; NBS= newborn bloodspot screening; X-ALD= X-linked adrenoleukodystrophy.

Note: Proportion of siblings who are eligible for cascade testing per newborn identified with a positive genotype is 0.7. Subsequent uptake rate of genetic counselling and cascade testing for PICO set 2 is 35%.

Source: DCAR Table 15.

There was some uncertainty in the financial estimates due to uncertain inputs for the prevalence of X-ALD in the Australian newborn population and the proportion of newborns expected to be positive after the FIA MS/MS test and the HPLC MS/MS tests. Increasing the prevalence of X-ALD from 0.01105% (Matteson et al., 2021) to 0.01622% (Wiens et al., 2019) increased the net financial impact on the NBS programs by $0.02 million (Strategy I to IVb) over six years. Decreasing the prevalence to 0.00424% reduced the net financial impact on the NBS programs by $0.03 million (Strategy I to IVb) over six years. In both these scenarios, Strategy I remained the least costly option.

Reducing the proportion of newborns expected to be positive after the FIA MS/MS test from 4.19% (Matteson et al., 2021) to 0.71% (Albersen et al., 2023) reduced the net financial impact on NBS programs. However, Strategy I was still the least costly option at $10.3 million over six years, followed by Strategy IVb at $10.4 million. Reducing the proportion of newborns expected to be positive after the HPLC MS/MS tests from 0.457% (Matteson et al., 2021) to 0.012% (Burton et al., 2022[[38]](#footnote-39)) reduced the net financial impact on NBS programs. However, Strategy I remained the least costly at $11.06 million, followed by Strategy IVb at $11.07 million over six years. With the higher cost of the *ABCD1* genetic test ($721.25 and $1,200), Strategy I remained the least costly option (as the strategy did not include the test, which would still be funded by state governments for public patients seen in their genetics clinics).

Reducing the uptake rate for genetic counselling to 50% reduced, and increasing the uptake rate of cascade testing to 90% increased, the cost implications for state and territory governments. Cost implications for the state and territory governments were estimated to increase by $3.35 million over six years if all newborns with CCALD underwent HSCT. Increasing the number of siblings eligible for cascade testing (per positively diagnosed newborn) to 2 increased the cost of state and territories government by $0.22 million (Strategy I to IV) and $0.12 million (Strategy Ia to IVb) over six years. Irrespective of the price of the X-counter test ($50 or $100), Strategy I ($11.0 million) remained the least costly option (as the strategy did not include the test), followed by Strategy IVb ($11.20 million or $11.24 million).

Overall, Strategy I remained the least costly testing strategy to NBS programs and Strategy II remained the most costly testing strategy across all sensitivity analyses (see Table 19).

**Table 19: Summary of sensitivity analysis impacts on least costly and most costly strategies to NBS programs**

| **Input**  | **Base case value** | **SA value** | **Least costly** | **Most costly** |
| --- | --- | --- | --- | --- |
| Prevalence of X-ALD in Australia | 0.0111% | 0.00424% | Strategy I | Strategy II |
| 0.01622% | Strategy I | Strategy II |
| Proportion of patients positive after FIA-MS/MS test | 4.19% | 0.71% | Strategy I | Strategy III |
| Proportion of patients positive after HPLC-MS/MS test | 0.457% | 0.012% | Strategy I | Strategy II |
| Uptake rate of cascade testing | 37% | 90% | Strategy I | Strategy II |
| Uptake rate of genetic counselling | 100% | 50% | Strategy I | Strategy II |
| Proportion CCALD newborn for whom HSCT is indicated and feasible | 35% | 100% | Strategy I | Strategy II |
| X-counter test cost  | $100 | $50 | Strategy I | Strategy II |
| $150 | Strategy I | Strategy II |
| Number of siblings eligible for cascade testing | 0.7 | 2 | Strategy I | Strategy II |
| Cost of *ABCD1* genetic test | $673.20 | $721.25 | Strategy I | Strategy II |
| $1,200.00 | Strategy I | Strategy II |

*ABCD1*= ATP Binding Cassette Subfamily D Member 1 gene; ALD= Adrenoleukodystrophy; CCALD= Childhood cerebral adrenoleukodystrophy; HSCT= Haematopoietic stem cell transplant; FIA= Flow-injection analysis; HPLC-MS/MS= high performance liquid chromatography tandem mass spectrometry; MS/MS= Tandem mass spectrometry; SA = sensitivity analysis.Source: DCAR Table 16.

## 15. Other relevant information

Other relevant considerations for this application included ethical issues, the value of knowing, patient and social aspects, organisational aspects and fulfilment of the Newborn Bloodspot Screening National Policy Framework (NBS NPF) criteria.

### Ethical issues

Ethical issues in undertaking newborn bloodspot screening (NBS) for X-ALD can be considered against a backdrop of screening ethics in general and specifically related to the use of genetics in screening, and the overarching ethical issues in NBS. Analysis of ethical issues involves a consideration of a theoretical claim or position that has been made, e.g., whether something ought to be done. For NBS, the ethical framing draws predominantly on public health ethics, although as a screening participant moves from screening to follow-up diagnosis (if indicated), then considerations of clinical ethics will also become relevant.

For NBS as a program, public health ethics as applied to other forms of screening is generally appropriate because the concepts and issues that form the focus for analysis reflect the status of the intervention as a population-level health program; one that needs to be sustainable to deliver to a whole population at high quality. However, in contrast to many other forms of screening, the target population is unable to give consent. This means that the health of the newborn is considered as the primary benefit of screening.

There are multiple ethical considerations relevant to population screening. The overarching consideration is preventing collective harm by identifying those who may benefit from follow-up monitoring or treatment. At the same time, harm is also prevented by not identifying those who will not benefit (or may be harmed) by follow-up monitoring. Getting this balance right may be challenging for X-ALD.

Further considerations relating to screening ethics include the tension between public health and clinical ethics, getting the balance right between severity and prevalence in a screening context (i.e., if detecting a very rare but severe condition gives rise to excessive costs), tensions between screening program sustainability and the welfare of individuals who participate in that program, and the importance of defining appropriate and defensible goals for screening; ones that balance individual and societal interests.

NBS is a very successful screening program with high uptake and high public trust. Ethical considerations in NBS relate to choosing appropriate conditions to screen, ensuring appropriate consent, providing support post-screening and managing bloodspot collections appropriately.

The question of whether to add X-ALD to NBS raises ethical questions. A comparison of benefits and harms illustrates the complexity involved. The main benefit of detecting X-ALD via NBS is the identification of male children who, if not identified, would have developed the most severe cerebral form of X-ALD (leading to significant morbidity and/or mortality). NBS will enable monitoring and treatment as required, aiming to achieve better survival rates for these children (e.g., through a reduced clinical presentation with adrenal crisis). This small group of newborns and their families may also avoid a diagnostic odyssey and/or psychological or financial harm through delayed diagnosis. While treatment (hematopoietic stem cell transplant; or HSCT) may not necessarily have to take place early in life, screening in the newborn period (as part of NBS rather than as a separate stand-alone screening program) will ensure high screening coverage. Additional benefits include adding to the evidence base about genetics and X-ALD, enabling innovation in screening, and increasing professional and public awareness of this condition.

The main harms of NBS for X-ALD identified were the lack of treatment intervention in early childhood (as would usually be the case for other conditions detected on NBS), that not all male newborns detected as at risk will necessarily be able to access treatment such as HSCT, and the possibility that screening will place a family into uncertainty, which may cause psychological distress. Further, screening is also likely to identify a proportionally large number of newborns who will never go on to develop the cerebral form of the disease. Identifying males will also make their mothers presumptive carriers, which will inform them of a risk to their own health later in life. Receiving such information is less common in NBS, although (as noted in the following paragraph) it could also inform subsequent reproductive decisions of the children identified through NBS and, more immediately, their parents (this information is arguably warranted irrespective of whether the child identified is male or female). Preimplantation genetic diagnosis and IVF are currently MBS-funded where a family has an affected child identified. Additional harms include possible loss to follow-up, the incidental detection of other non-target conditions that would not meet NBS NPF screening criteria, and incomplete penetrance.

One key issue in whether to screen for X-ALD in NBS is whether a test should be used to exclude females from such screening. If females are not excluded, the question is, then, whether results should be reported. There are no implications for a carrier female newborn’s health in childhood and several states raised concerns with reporting results for females. However, this information can also benefit parents of screen-positive female newborns, as they may use it in future reproductive decisions, and evidence in other countries suggests parents are in favour of being told. And while it would be unusual to routinely provide this information without consent so early in life, newborn females themselves could also use this knowledge to inform their own future reproductive decision-making. However, the information is something that adults have the right *not* to know about.

One overseas jurisdiction has shown it is feasible to include an X-counter in NBS, enabling the reporting of X-ALD results for males only. While this may cost more in the lab, identifying female carriers carries greater genetic counselling costs. Limiting reporting to male newborns also mitigates harm. While the penetrance of X-ALD is incomplete in both males and females, in females it will also be detecting an incompletely penetrant, adult-onset condition and so seems unlikely to meet NBS NPF criteria. Not reporting an adult-onset condition is also consistent with the approach in clinical practice – endorsed by professional societies – not to undertake carrier testing in young people who cannot consent to receive such information.

An additional issue is whether to offer cascade testing to older female siblings of screen-positive newborns. As above, carrier testing is not routinely offered to young people (here, females; as testing in males would be considered diagnostic). However, family communication and education about risk factors should be encouraged, as should access to continuing care with relevant health providers.

Concerns about information from screening being ‘withheld’ can be partially addressed by reiterating the screening paradigm, including that it is not the point of screening to identify and report all information. Rather, the aim is to provide a feasible and sustainable, high-quality test to implement at a population scale. Upholding feasibility could include not reporting variants of uncertain significance (around 19% of variants are of this type) because of the uncertainty regarding how to manage care for the child in light of this information. The incidence of VUS may decrease with time as knowledge improves.

### Value of knowing

The potential value of knowing information about X-ALD from NBS had three elements: (i) shortening the diagnostic odyssey with the aim of mitigating morbidity and/or mortality, (ii) enabling cascade testing and (iii) informing future reproductive decisions. Regarding the latter two, cascade testing is important and potentially valuable, yet not as developed in the health system as it could be. Cascade testing should not be assumed to be an efficient or perfect process. The follow-on costs of additional testing and counselling are also relevant. Any justification of NBS for X-ALD on the grounds that it informs future reproductive decisions should be made while also recognising the *ABCD1* gene’s incomplete penetrance and variable expressivity, and the impact this may have on reproductive confidence. There is also some evidence (in relation to other conditions) that reproductive intentions following receipt of information from NBS actually have limited influence on future reproductive behaviours.

### Patient and social aspects

Existing (but limited) evidence on the patient and social aspects of NBS for X-ALD suggested that patients and carriers generally support NBS for X-ALD and desire maximal information, but that they may not fully understand the complexity of screening. Evidence about harm from earlier detection is limited, with one study suggesting that parental depression may be lower in those whose child's diagnosis was made via NBS. Stress levels, however, were the same regardless of when a child was diagnosed.

NBS for X-ALD presents unique challenges in counselling families, as families may experience anticipatory anxiety due to incomplete penetrance. A psychosocial study conducted in parents who participated in NBS for Duchenne Muscular Dystrophy in Wales showed that they supported the availability of screening for preparedness and reproductive choice, and there was no significant impact on parent-child bonding.

### Organisational aspects

Organisational aspects of NBS for X-ALD included standard considerations relating to laboratory resourcing, staff expertise, follow-up genetic counselling and so on. A specific consideration related to whether NBS for X-ALD should have separate consent (i.e., as a means to address some of the ethical issues, or to engage with parents about an X-counter test if one is used). A separate consent process would introduce additional costs while being unlikely, on balance, to make a significant difference to uptake rates. A rationale for separate consent may be better supported if a decision is made to report results for females, given that the information being provided is something that will not have relevance for many years, and that reporting carrier status in the newborn period is contentious.

A further consideration relates to reanalysis. Overall, screening is a ‘point in time’ test. With reanalysis and reinterpretation still in the early stages of development, it may not yet be feasible to do this in a screening context (given the volume of results). However, as innovations such as automated reanalysis becomes a reality, this could make the reanalysis of results more feasible.

## 16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

* A three-tiered approach to screening (strategy IV) appeared preferable to two-tiered screening, because the first two tiers combined provide evidence of a newborn having elevated very long chain fatty acid levels, which would increase confidence in the pathogenicity of any VUSs detected, given most X-ALD genetic variants are ‘private’ (family-specific).
* X-ALD is an X-linked condition: many female carriers will not develop symptoms, and those who do will generally do so in adulthood and receive best supportive care. The majority of consultation input received was against reporting results for female newborns, as reporting results for female newborns may not meet the NBS NPF criteria of screening in order to identify an individual for whom intervention is required in early childhood. Reporting results for screened male newborns only may, on balance, be preferable, although whether results should be reported for males only versus all newborns is a complex ethical issue that requires fulsome consideration. The reporting of NBS results for males only would preclude information for parental reproductive decision-making where the first born children are carrier females, but with risk for affected males in subsequent pregnancies. On the other hand, reporting results for all newborns would enable all families to make informed reproductive decisions for future pregnancies via cascade testing –the NBS NPF allows for the consideration of this benefit to the family, however it is secondary to the benefit to the newborn. If reporting results for screened females is deemed inappropriate, then the X-counter test would need to be included at any point after the first tier FIA-MS/MS.
* Cascade testing of the parents of infants identified through NBS would facilitate informed reproductive decision-making, and enable identification of a familial variant in asymptomatic mothers who may become symptomatic in the future.
* There were limited data from Australia and overseas on X-ALD prevalence and change in management as a result of NBS for X-ALD.

Economic issues:

* Four strategies (plus variations to include an X-counter) were assessed, and NBS for X-ALD appeared to be cost-effective compared to no NBS for X-ALD for at least some strategies. Cost-effectiveness differed between the strategies: strategies I and IV were the most cost-effective.
* When an X-counter was included NBS appeared to remain cost-effective, although the cost-effectiveness was determined by the test(s) preceding the X-counter. The most cost-effective strategies that included an X-counter were strategies Ia, IVa and IVb.
* Using the original DCAR data, the cost-effectiveness was most sensitive to the sensitivity, specificity and cost of the tests used in screening, because X-ALD is a rare condition. Most QALY gains arose from early access to HSCT (between 4 and 8 years), which was associated with an increase in utility post HSCT, until death occurs in the model.
* The structure and approach of the model were consistent with the literature, however in the context of X-ALD being a rare disease, the model was overcomplicated, which made it hard to interrogate and interpret the results. MSAC may wish to consider that the uncertainty in the ICER be considered in the context of evidence generation challenges associated with rare diseases.
* The DCAR reported lower QALYs for strategy III compared to no NBS, which differed from strategy II although the basis for the difference could not be identified. The reported reduced effectiveness could not be verified by ESC’s validation of the model, and so ESC considered the reported cost-effectiveness of strategy III to be unreliable. The reported negative effectiveness was perhaps a result of natural variation in the microsimulation draws due to very small numbers because X-ALD is a rare disease, or may relate to slightly different death rates for this strategy. The ICER for strategy III should be interpreted with caution.
* Key uncertainties in the economic model included the estimated prevalence of X-ALD positive diagnosis through NBS, which had a wide range of estimates (including estimates based on small sample sizes, and none from Australia). There were also limited data to inform estimates of the proportion of patients receiving early HSCT, and different data sources of death rates for X-ALD and HSCT, but these had minimal effect on the ICER.
* There were limited data to inform the economic model for cascade testing arising from NBS, which made the results inherently uncertain. Cascade testing improved in cost-effectiveness when an X-counter was included.

Financial issues:

* There was considerable uncertainty in the financial estimates. This was because of uncertainty in the prevalence of a positive diagnosis of X-ALD through NBS, cost of *ABCD1* genetic testing and the X-counter, positive predictive value of FIA-MS/MS and HPLC-MS/MS, proportion of newborns for whom HSCT would be feasible, and the uptake rate of cascade testing.

Other relevant information:

* While a comprehensive narrative summary of the ethical issues was presented, a formal ethical analysis may be necessary to inform over-arching consideration of the ethical aspects of NBS for X-ALD, especially for the complex ethical issue of whether results should be reported for males only versus all newborns.
* The low penetrance of *ABCD1* variants to cause clinical X-ALD may result in psychological distress for male individuals and their families due to the need for surveillance monitoring. NBS for X-ALD could also be harmful because the incomplete penetrance of a positive result through NBS means many ‘positive’ female newborns will not develop X-ALD until adulthood, if at all, which may cause psychological distress for their families. Harm could also arise from the lack of currently registered treatment options for some disease manifestations.

**ESC discussion**

ESC noted that this application from the Leukodystrophy Resource & Research Organisation Inc was for including X-linked adrenoleukodystrophy (X-ALD) in Australia’s newborn bloodspot screening (NBS) programs. ESC noted that with the dissolution of the Standing Committee on Screening (SCoS) applications for inclusion/removal of conditions from NBS programs are now considered by MSAC, and that applications 1710 and 1737 were the first NBS applications to be considered by ESC and MSAC.

ESC noted that the genetic basis for X-ALD is variants in the *ABCD1* gene, which is located on the X chromosome. Patients with X-ALD have very high levels of certain fatty acids, particularly C26:0-lysophosphatidylcholine (C26:0 LPC), however most *ABCD1* variants are ‘private’ (family-specific), with almost every kindred having a different variant. ESC noted the genotype–phenotype correlation is weak, with many people who have a genetic variant not developing clinical signs or symptoms of X-ALD, and in some cases the same variant causing different presentation, severity and onset even within the same kindred. ESC noted that although the variation in X-ALD clinical phenotypes is great, neurologic manifestations are present in nearly all males by adulthood[[39]](#footnote-40), and considered that it is difficult to estimate at which age males will become symptomatic, and if symptomatic what their phenotype will be. ESC considered that the applicability of the DCAR’s penetrance estimates (Table 5) depended on the test method(s) used to define the population in whom manifestation was subsequently examined. Onset of disease in males (or more correctly, in individuals with one X chromosome – hereafter referred to as males for simplicity) can occur at various stages of childhood or adulthood, and with various degrees of severity of phenotype. The three main phenotypes in males are childhood cerebral ALD (CCALD, also known as CALD), adrenomyeloneuropathy (AMN) and adrenal insufficiency (AI, also known as Addison’s disease). The signs and symptoms of AMN may include progressive stiffness and weakness of the legs (paraparesis), ataxia, speech difficulties, sexual dysfunction and loss of bladder or bowel control. Male onset of AMN often occurs in the early twenties to late thirties and in approximately 40% AMN affected males the disease may progress to have cerebral involvement. Treatment for CCALD is by haematopoietic stem cell transplant (HSCT) if diagnosed early. HSCT does not prevent AMN or reverse AI, although AI can be managed in other ways. Around 50% of females with an X-ALD genotype develop mild symptoms later in life.

ESC noted that NBS programs are delivered by state and territory governments, and that screening takes place in five laboratories across Australia. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). The Australian Government also announced funding of $39.0 million in the 2022–23 Budget, of which $25.3 million has been offered directly to states and territories through a Schedule under the Federation Funding Agreement – Health to support expanding the number of conditions included in NBS programs and increasing consistency between the states and territories. ESC also noted the NBS National Policy Framework (NBS NPF)[[40]](#footnote-41) and its decision-making criteria, which provided context for ESC’s consideration of this application.

ESC noted that the UK National Screening Committee had assessed NBS for X-ALD in 2021 but did not recommend screening because there was very limited information on the outcome of treatment and its comparative effectiveness in asymptomatic individuals versus symptomatic individuals. Also, the UK Committee was uncertain regarding the impact of early diagnosis, especially for individuals who would be directed to undergo surveillance monitoring but will not develop CCALD, and separately, for babies that could be identified with other disorders of fatty acid oxidation but for which there are no treatments. However, ESC also noted that the Netherlands (reporting of results for males only) and some US states (reporting of results for all newborns, on the basis of supporting reproductive planning) have opted to include X-ALD in their NBS programs.

ESC noted that the PICO proposed assessing the risk of X-ALD through quantification of the fatty acid C26:0-lysophosphatidylcholine (C26:0-LPC) in newborn dried bloodspots, by flow-injection analysis (FIA) tandem mass spectrometry (MS/MS) and/or (high-performance) liquid chromatography ((HP)LC)-MS/MS, and/or *ABCD1* genetic testing (PICO set 1). The PICO also included options for an X-counter test, which determines the number of X chromosomes. ESC noted the resulting nine screening strategies that were assessed (Figure 1) included variations on if and when an X-counter was included, based around four screening strategies:

1. FIA-MS/MS, then HPLC-MS/MS
2. FIA-MS/MS, then *ABCD1* genetic testing
3. HPLC-MS/MS, then *ABCD1* genetic testing
4. FIA-MS/MS, then HPLC-MS/MS, then *ABCD1* genetic testing

ESC considered that strategy I, which was the UK-based strategy described in some literature, was fast and reliable, although had a higher rate of false positives because of the lower specificity of FIA-MS/MS. ESC noted C26:0-LPC is also elevated in other peroxisomal disorders, such as Zellweger spectrum disorder. ESC considered that strategies II and III that included the “gold standard” *ABCD1* genetic testing for confirming a genetic diagnosis, and may ameliorate any potential false positive issues arising in strategy I. ESC noted that strategy IV was for three-tiered screening, which had a higher positive predictive value (PPV) in international studies, but required access to a different mass spectrometer.

ESC considered the clinical benefit of X-ALD NBS was primarily to shorten or prevent diagnostic delay, allowing earlier ongoing monitoring and potentially early HSCT. ESC noted that overall survival appeared higher in patients who received early HSCT than late or no HSCT, but that this treatment was only for the 31-35% of males developing the CCALD phenotype of X-ALD at age 3-10. ESC noted the potential benefits of early diagnosis and HSCT for males with CCALD phenotype, however considered the availability of treatment only available once symptomatic for other disease manifestations (and females), and the potential for psychological distress for families due to uncertainty about symptom onset arising from incomplete penetrance of *ABCD1* variants are potential harms. ESC considered X-ALD NBS would also enable cascade testing, and support informed future reproductive decisions of both the children identified through NBS and (more immediately) their parents. However, the incomplete penetrance, impact on reproductive confidence, and potential limited influence on future reproductive behaviours are uncertain.

ESC noted that where NBS identifies a newborn as being at risk of X-ALD (through high fatty acid levels for strategy I and through a genetic diagnosis for strategies II-IV), clinical practice is to next test the biological relatives of the newborn to see if they are also at risk of X-ALD (PICO set 2). ESC noted that the comparator for cascade testing of newborns detected as being at risk of X-ALD through NBS was cascade testing of the relatives of patients clinically presenting with X-ALD. ESC noted that 4.1% of X-ALD variants arise *de novo* (i.e., are not inherited), which it considered supported the need for cascade testing of the mother following a positive diagnosis through NBS (and if results for females were also to be reported, then also cascade testing of the father to identify men with a genetic variant that has not led to X-ALD manifesting), then other first-degree relatives of the parent as applicable. ESC noted PASC had considered cascade testing was not appropriate when a variant of uncertain significance (VUS) is identified in the newborn, however ESC considered that evidence of the newborn having high fatty acid levels (from the one or two previous tiers of screening) may provide sufficient functional evidence to classify VUSs as pathogenic or likely pathogenic (P/LP) variants. ESC considered genetic counselling would support families following a positive diagnosis through NBS.

ESC noted the consultation feedback described the advantages of early diagnosis and treatment, but also the disadvantages of false positive results, which can lead to psychological distress. Consultation comments included that NBS aims to identify diseases that present in early childhood, which is not the case for X-ALD in females, so results should be reported for males only. ESC noted that consultation comments had been received mostly from professional organisations, and considered the perspectives of parents of children with X-ALD were underrepresented in consultation comments. ESC considered that while the DCAR included a narrative summary of the ethical issues for this application, a formal ethical analysis may be necessary to inform over-arching consideration of the ethical aspects of NBS for X-ALD, especially for the complex ethical issue of whether results should be reported for males only versus all newborns. ESC considered input from people who are living with or affected by X-ALD, including parents of affected children, would help inform further discussion of ethical issues. ESC considered a further issue for consumers was potential inequity of access if the follow-on monitoring and treatment required after a diagnosis were not available nationwide, including remote and rural areas in particular. Also if NBS for X-ALD were not implemented nationwide, this also risks inequity for families in accessing effective screening services. Further accessibility concerns were around access to genetic counselling and clinical expertise in remote and rural areas.

ESC considered the comparator of no NBS was appropriate. ESC considered that fatty acid-based screening was likely preferable for X-ALD, because of the weak genotype-phenotype correlation, and the increased difficulty of identifying *ABCD1* genetic variants as pathogenic or likely pathogenic when most variants in this gene are private. ESC considered that it was likely preferable to use a three-tiered screening approach: using FIA-MS/MS, followed by HPLC-MS/MS, then *ABCD1* genetic testing (strategy IV). A three-tiered approach appeared preferable because the first two tiers combined would provide evidence of raised fatty acid levels to increase confidence in the pathogenicity of any VUSs identified in the third tier, given most X-ALD genetic variants are private. Three-tier screening would also be more accurate because testing for C26:0-LPC can give false positives. ESC also noted expert consultation input that FIA-MS/MS followed by HPLC-MS/MS fits into existing laboratory workflows. ESC noted PASC’s advice that the X-counter test was unsuitable for Tier 1 screening for a rare disorder, and agreed that if an X-counter is to be included it should be used at some point after the first tier. ESC considered the preferred location of the X-counter test in the screening sequence may differ between laboratories.

ESC discussed the appropriateness of reporting results for female newborns, and the need to consider both public health ethics of screening and the ethics for diagnosed individuals and their families. ESC noted that the aim of NBS is to identify early childhood disease where there is a benefit to detection in the newborn period and secondary benefit to inform reproductive decision-making. ESC noted that females do not show symptoms until adulthood when they can make their own decisions about being tested for X-ALD, and there is no treatment for females beyond symptomatic treatment, but given the typical age of symptom onset her diagnosis may only be made after she has had children. ESC noted the majority of consultation input received was against reporting results for female newborns, and that the screening program in the Netherlands only reports X-ALD results for males. ESC considered that reporting results for females may not meet the NBS NPF criteria, in relation to the needs of the individual being screened. ESC queried whether screening but not reporting a female carrier result may create medicolegal risk for the provider, although considered this was unlikely because laboratories routinely do not report full results, for example because it is more efficient to run a panel test even when only one test on the panel is requested. On the other hand, ESC noted that if a female carrier is identified by NBS then a male infant in a subsequent pregnancy of the same reproductive partners has a 50% risk of being hemizygous for X-ALD, and considered that reporting results for all newborns would better support families to make informed reproductive decisions for future pregnancies. ESC noted comments that NBS would provide forewarning of adulthood disease in women, but considered this was a weak reason not aligned with the purpose of NBS, however would provide her the opportunity for informing reproductive decision-making if she were a carrier. Overall, ESC considered reporting results for males only may be preferable, although whether results should be reported for males only versus all newborns is a complex ethical issue that requires fulsome consideration. ESC noted that assessment of external genitalia in newborns as a surrogate for the number of X chromosomes can be unreliable, so an X-counter test (or equivalent) would be required if results for females were to not be reported.

ESC noted that NBS was the focus of the application, and considered the economic model for the NBS component (PICO set 1) comprehensively assessed the nine proposed screening strategies. ESC noted that the model was a two-step model: a decision tree including microsimulation, followed by a Markov state transition model including five health states. ESC considered the decision tree structure was based on a published model for the UK (Bessey 2018[[41]](#footnote-42)) with expansions to include microsimulation to account for heterogeneity in the inputs, and to explore the multiple proposed strategies. However, ESC considered that while this approach was consistent with the literature, the complex model overcomplicated the assessment and made it difficult to interpret results, particularly in the context of X-ALD being a rare disease, where there is often substantial uncertainty in the inputs. ESC noted both NBS applications being considered at this meeting had highly uncertain inputs, and contrasted the complex and longer time horizon model with substantial uncertainty for 1710, with the simpler and shorter time horizon model for NBS application 1737.

ESC considered the model showed that most utility gains and losses arose from early access to HSCT (Table 20). ESC considered that with NBS, a smaller proportion of people were in the asymptomatic state because of early HSCT. ESC considered the utility gains arose mainly from higher post-HSCT quality of life (QoL) and fewer deaths. Given the rare condition, ESC considered that while the results showed higher utility post-HSCT, this was for a small number of overall patients.

Table 20 Incremental utility across health states in the economic model (PICO set 1)

| **Health state** | **Utility of health state** | **Average incremental utility change with screening (Strategy II)** |
| --- | --- | --- |
| **Comparator** | **With screening** |
| Asymptomatic | 0.96 | 0.96 | -0.002 |
| Symptomatic pre-HSCT | 0.3145 | 0.3145 | -0.017 |
| HSCT (1 year) | 0.1645 | 0.1645 | 0.001 |
| Symptomatic post-HSCT | 0.5985 | 0.62755 | 0.056 |
| Death | 0 | 0 | -0.038 |

HSCT = haematopoietic stem cell transplant.
Source: ESC.

ESC noted the limited data from Australia and overseas on disease prevalence and change in management as a result of an X-ALD diagnosis through NBS. ESC noted the applicant’s pre-ESC response queried the use of 11.05 per 100,000 live births as the prevalence of X-ALD, and agreed the prevalence was uncertain (because the estimates ranged from 4.24 to 16.22 per 100,000, and there were no Australian estimates) but considered the uncertainty had been explored through sensitivity analyses of alternative estimates.

ESC confirmed that the key assumptions in the model were appropriate, but suggested adding that a change in management was assumed (that is, the percentage of patients diagnosed with CALD who would meet the criteria for HSCT increased from 50% to 85%), and that utility values associated with HSCT (before, during and after) should also be added to the list of assumptions. ESC noted the incremental cost-effectiveness ratios (ICERs) in step 1 of the economic evaluation (cost per positive diagnosis) for each strategy were largely driven by the sensitivity, specificity, and cost of each tier of screening, and there was very little variation in the number of individuals receiving a positive diagnosis across the strategies. ESC noted the cost-effectiveness of including X-counter testing in each strategy was determined by the preceding test(s). ESC noted that step 2 of the economic evaluation considered quality-adjusted life years (QALYs) and costs of earlier diagnosis, adding costs associated with neuroimaging surveillance, AI monitoring, and early HSCT, and the QoL associated with early HSCT (from 50% to 85%). ESC noted that the order of testing had an impact on overall cost-effectiveness, when an X-counter was used. ESC considered strategies I and IV were the most cost-effective strategies, with ICERs of $8,315 (I) and $8,077 (IV) per QALY respectively if an X-counter was not used, If an X-counter was used, the ICER was $33,322 (Ia) per QALY and $30,631 (IVa) per QALY if the X-counter was undertaken as a second test (before HPLC and ABCD1) or $7,676 (IVb) per QALY if the X-counter was undertaken as a third test (after HPLC and before ABCD1). The improved cost effectiveness in scenario IVb (compared with IVa) was due to less patients having to undergo expensive genetic testing (i.e they ended up in the correct treatment pathway earlier). ESC noted that economic analyses of NBS for other conditions in Australia had not been considered by MSAC.

ESC noted that the DCAR reported negative ICERs (northwest quadrant) for strategy III in step 2 – in this case implying this strategy was less effective (i.e. lower QALYs and higher costs when compared to no NBS). The DCAR attributed the reported negative ICER as being due to chance caused by slightly different death rates during and after HSCT, however ESC was unable to verify any difference in the death rates (or proportions in post HSCT) between strategies II and III. However, the uncertainty in cost-effectiveness of strategy III may hold less weight if MSAC considers strategies I and IV are preferred for clinical and applicability reasons.

Further, ESC was unable to verify superiority in any screening scenario (I to IV) based on a validity check on 1000 trials (rather, ESC’s validation showed that overall QoL was marginally lower when compared to no NBS, across all screening scenarios I to IV). ESC considered that it was more likely due to the small numbers in microsimulation draws because X-ALD is a rare disease. A post-ESC analyses by the HTA group confirmed that the negative ICERs in strategies III and IIIa were more due to chance and the rarity of the condition. Overall ESC considered that the reported ICERs should be interpreted with caution. MSAC may wish to consider that the uncertainty in the ICER be considered in the context of evidence generation challenges associated with rare diseases.

ESC noted the economic model for cascade testing was a decision tree analysis, with effectiveness expressed in terms of cost per positive diagnosis. ESC noted the cost-effectiveness of cascade testing was $8,789 per positive diagnosis without an X-counter, or $6,689 per positive diagnosis with an X-counter. ESC noted the cost-effectiveness of cascade testing was most sensitive to uptake rate, and the unit cost and frequency of genetic counselling. ESC noted limited data were available to inform the economic model for cascade testing, and considered the results for this model were highly uncertain.

ESC noted an epidemiological approach had been used to estimate utilisation based on the number of live births in 2021 with an annual growth rate of 0.31%, and considered this was slightly higher than the estimate used in the assessment report for NBS of sickle cell disease and beta thalassaemia (MSAC application 1737), but that it was nonetheless reasonable. ESC noted uptake of NBS was estimated to be ≥98% in line with current trends, which it considered was reasonable because NBS is an established and well accepted program in Australia.

ESC noted the financial impact to NBS programs of NBS for X-ALD using ESC’s preferred strategy IV was $1.9 million per year if an X-counter was not included, and if an X-counter was included $1.9 million (if 3rd tier) or $3.1 million per year (if 2nd tier) (Table 17). ESC noted the DCAR included extensive sensitivity analyses, and considered the financial estimates were highly uncertain because of the uncertainty of the prevalence of X-ALD, cost and PPV of the tests, and the proportion of newborns for whom HSCT would be feasible. For costs to funding sources other than the NBS programs, ESC noted that the costs of monitoring and treatments for newborns identified as being at risk of X-ALD by NBS would be borne by the states and territories, MBS and PBS (Table 17). ESC noted the annual cost to state and territory governments after the first year was comprised of monitoring and treatment costs of $520,000-$610,000 if an X-counter was not included or $470,000-$560,000 if an X-counter was included, and cascade testing costing $53,000 per year if an X-counter was not included or $22,000 if an X-counter was included.

## 17. Applicant comments on MSAC’s Public Summary Document

We found MSAC’s advice to be excellent and could not find any reasons for change that we could support with data. The detail regarding women is not the current thinking but there are no papers supporting the fact that ALD plays a major part in woman’s life from a much earlier time than current data shows.

## 18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](http://msac.gov.au/internet/msac/publishing.nsf/Content/Home-1)

1. MSAC application 1737 – Newborn bloodspot screening for Sickle Cell Disease and Beta Thalassaemia. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1737-public> [↑](#footnote-ref-2)
2. Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework?language=en> [↑](#footnote-ref-3)
3. Natarajan A, et al. 2019. Flow injection ionization-tandem mass spectrometry-based estimation of a panel of lysophosphatidylcholines in dried blood spots for screening of X-linked adrenoleukodystrophy. *Clin Chim Acta,* 495**,** 167-173. [↑](#footnote-ref-4)
4. Moser AB, et al. 2016. Newborn Screening for X-Linked Adrenoleukodystrophy. *Int J Neonatal Screen,* 2. [↑](#footnote-ref-5)
5. Turgeon CT, et al. 2015. Streamlined determination of lysophosphatidylcholines in dried blood spots for newborn screening of X-linked adrenoleukodystrophy. *Mol Genet Metab,* 114**,** 46-50. [↑](#footnote-ref-6)
6. Teber TA, et al. 2022. Newborn Screen for X-Linked Adrenoleukodystrophy Using Flow Injection Tandem Mass Spectrometry in Negative Ion Mode. *Int J Neonatal Screen,* 8. [↑](#footnote-ref-7)
7. Hubbard WC, et al. 2009. Newborn screening for X-linked adrenoleukodystrophy (X-ALD): validation of a combined liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. *Mol Genet Metab,* 97**,** 212-20. [↑](#footnote-ref-8)
8. Wanders RJA & Eichler FS, 2023. *X-linked adrenoleukodystrophy and adrenomyeloneuropathy. [Literature review current through: Feb 2023; topic last updated: 16 Nov 2022]*. Available: <https://www.uptodate.com/contents/x-linked-adrenoleukodystrophy-and-adrenomyeloneuropathy#H3329080115> [Accessed 10 March 2023]. [↑](#footnote-ref-9)
9. Albersen M, et al. 2023. Sex-specific newborn screening for X-linked adrenoleukodystrophy. *J Inherit Metab Dis,* 46**,** 116-128. [↑](#footnote-ref-10)
10. Barendsen RW, et al. 2020. Adrenoleukodystrophy Newborn Screening in the Netherlands (SCAN Study): The X-Factor. *Front Cell Dev Biol,* 8**,** 499. [↑](#footnote-ref-11)
11. Natarajan A, et al. 2018. Liquid chromatography-tandem mass spectrometry method for estimation of a panel of lysophosphatidylcholines in dried blood spots for screening of X-linked adrenoleukodystrophy. *Clin Chim Acta,* 485**,** 305-310. [↑](#footnote-ref-12)
12. Natarajan A, et al. 2019. Flow injection ionization-tandem mass spectrometry-based estimation of a panel of lysophosphatidylcholines in dried blood spots for screening of X-linked adrenoleukodystrophy. *Clin Chim Acta,* 495**,** 167-173. [↑](#footnote-ref-13)
13. Liberato AP, et al. 2019. MRI brain lesions in asymptomatic boys with X-linked adrenoleukodystrophy. *Neurology,* 92**,** e1698-e1708. [↑](#footnote-ref-14)
14. Mahmood A, et al. 2007. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *The Lancet Neurology,* 6**,** 687-692. [↑](#footnote-ref-15)
15. Peters C, et al. 2004. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood,* 104**,** 881-888. [↑](#footnote-ref-16)
16. Raymond GV, et al. 2019. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation,* 25**,** 538-548. [↑](#footnote-ref-17)
17. Matsukawa T, et al. 2020. Clinical efficacy of haematopoietic stem cell transplantation for adult adrenoleukodystrophy. *Brain Commun,* 2**,** fcz048. [↑](#footnote-ref-18)
18. Kemp S, et al. 2012. X-linked adrenoleukodystrophy: Clinical, metabolic, genetic and pathophysiological aspects. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease,* 1822**,** 1465-1474. [↑](#footnote-ref-19)
19. Turk BR, et al. 2020. X‐linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing, newborn screening and therapies. *International Journal of Developmental Neuroscience,* 80**,** 52-72. [↑](#footnote-ref-20)
20. Engelen M, et al. 2022. International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach. *Neurology*. [↑](#footnote-ref-21)
21. Gupta AO, et al. 2022. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. *Expert Opinion on Biological Therapy,* 22**,** 1151-1162. [↑](#footnote-ref-22)
22. Regelmann MO, et al. 2018. Adrenoleukodystrophy: Guidance for Adrenal Surveillance in Males Identified by Newborn Screen. *The Journal of Clinical Endocrinology & Metabolism,* 103**,** 4324-4331. [↑](#footnote-ref-23)
23. Vogel BH, et al. 2015. Newborn screening for X-linked adrenoleukodystrophy in New York State: Diagnostic protocol, surveillance protocol and treatment guidelines. *Molecular Genetics and Metabolism,* 114**,** 599-603. [↑](#footnote-ref-24)
24. Schwan K, et al. 2019. Family Perspectives on Newborn Screening for X-Linked Adrenoleukodystrophy in California. *Int J Neonatal Screen,* 5**,** 42. [↑](#footnote-ref-25)
25. Matteson J, et al. 2021. Adrenoleukodystrophy Newborn Screening in California Since 2016: Programmatic Outcomes and Follow-Up. *International Journal of Neonatal Screening,* 7. [↑](#footnote-ref-26)
26. Wiens K, et al. 2019. A report on state-wide implementation of newborn screening for X-linked Adrenoleukodystrophy. *Am J Med Genet A,* 179**,** 1205-1213. [↑](#footnote-ref-27)
27. Peters C, et al. 2004. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood,* 104**,** 881-888. [↑](#footnote-ref-28)
28. Bladowska J, et al. 2015. The Role of MR Imaging in the Assessment of Clinical Outcomes in Children with X-Linked Adrenoleukodystrophy after Allogeneic Haematopoietic Stem Cell Transplantation. *Polish Journal of Radiology,* 80**,** 181-190. [↑](#footnote-ref-29)
29. Mallack EJ, et al. 2021. MRI surveillance of boys with X‐linked adrenoleukodystrophy identified by newborn screening: Meta‐analysis and consensus guidelines. *Journal of Inherited Metabolic Disease,* 44**,** 728-739. [↑](#footnote-ref-30)
30. Kemper AR, et al. 2017. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. *Genetics in Medicine,* 19**,** 121-126. [↑](#footnote-ref-31)
31. Zhu J, et al. 2020. The Changing Face of Adrenoleukodystrophy. *Endocrine Reviews,* 41**,** 577-593. [↑](#footnote-ref-32)
32. Brosco J, et al. 2015. Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence. *In:* KEMPER, A. R. (ed.). UK: Maternal and Child Health Bureau. [↑](#footnote-ref-33)
33. Beckmann NB, et al. 2018. Quality of life among boys with adrenoleukodystrophy following hematopoietic stem cell transplant. *Child Neuropsychol,* 24**,** 986-998. [↑](#footnote-ref-34)
34. Kuhl JS, et al. 2018. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. *JAMA Netw Open,* 1**,** e180769. [↑](#footnote-ref-35)
35. Miller WP, et al. 2011. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood,* 118**,** 1971-8. [↑](#footnote-ref-36)
36. Baker CV, et al. 2022. Newborn Screening for X-Linked Adrenoleukodystrophy in Nebraska: Initial Experiences and Challenges. *Int J Neonatal Screen,* 8. [↑](#footnote-ref-37)
37. Priestley JRC, et al. 2022. Newborn Screening for X-Linked Adrenoleukodystrophy: Review of Data and Outcomes in Pennsylvania. *Int J Neonatal Screen,* 8. [↑](#footnote-ref-38)
38. Burton BK, et al. 2022. Newborn Screening for X-Linked Adrenoleukodystrophy: The Initial Illinois Experience. *Int J Neonatal Screen,* 8. [↑](#footnote-ref-39)
39. Huffnagel, I. C., et al. 2019. The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration. *J Clin Endocrinol Metab*, 104, 118-126. [↑](#footnote-ref-40)
40. Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework?language=en> [↑](#footnote-ref-41)
41. Bessey A, et al. 2018. Economic impact of screening for X-linked Adrenoleukodystrophy within a newborn blood spot screening programme. *Orphanet J Rare Dis,* 13, 179. [↑](#footnote-ref-42)