

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1774 – Newborn bloodspot screening for glycogen storage disease, Type II (Pompe disease)

Applicant: Department of Health and Aged Care - Newborn bloodspot screening section

Date of MSAC consideration: 3-4 April 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting that glycogen storage disease type II (GSD II) be added to Australia's newborn bloodspot screening (NBS) programs was developed by the Department of Health and Aged Care, following a request from the Minister for Health and Aged Care. REDACTED, metabolic physician at REDACTED, metabolic physician at the REDACTED and REDACTED, clinical geneticist at REDACTED were supporting clinical expert co-applicants.

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 did not support the addition of glycogen storage disease, Type II (GSD II, Pompe disease) to the list of conditions screened as part of Australia's newborn bloodspot screening (NBS) programs because the potential harms of newborn screening for GSD II outweigh the potential benefits.

MSAC considered both its own Terms of Reference and the Newborn Bloodspot Screening National Policy Framework (NBS NPF) in providing its advice. MSAC considered the positive and negative impacts of newborn screening for the condition, and the potential for unintended negative impacts on the existing NBS programs.

MSAC noted that GSD II is a heterogenous condition. The infantile-onset GSD II (IOGSD II) is a severe, rapidly progressive condition that is fatal in the first year of life if not treated. However, late-onset GSD II (LOGSD II), the most common form of the condition, is mostly diagnosed in adults. Late-onset GSD II causes progressive muscle weakness, respiratory problems and worsening disability. Late-onset GSD II is less severe than infantile-onset GSD II and is associated with a significantly longer life expectancy.

MSAC considered that for infantile-onset GSD II, treatment with enzyme replacement therapy (ERT) during the newborn period may provide additional benefits compared with ERT commencement at symptom onset.

MSAC considered current screening and diagnostic testing for GSD II cannot accurately predict disease onset or prognosis for all cases of GSD II. MSAC noted screening followed by diagnostic testing and clinical examination can help differentiate IOGSD II cases from LOGSD II. MSAC considered the proposed 2-tier screening strategy (biochemical testing followed by genetic testing) will identify a disproportionately large number of late-onset cases and false positive

cases for each infantile-onset case detected. If implemented in 2025-2026, MSAC considered the first tier of screening would identify approximately 58 screen positive cases, who may be recalled for clinical review and diagnostic testing. Of these, approximately one newborn per year would be clinically diagnosed with infantile-onset disease. A further 10 newborns would be considered at risk of developing late-onset GSD II with an uncertain severity and age of onset while 47 would be false positive cases. In Australia, people with late-onset GSD II typically develop symptoms when aged 40 years or older.

Under current Life-Saving Drugs Program (LSDP) indications, any newborn diagnosed with late-onset disease who is screen positive (deficiency of acid alpha-glucosidase in dried bloodspot), and has a genetic variant in the GAA gene would be eligible to receive ERT whilst clinically asymptomatic and would potentially receive therapy for decades, despite there being no clinical evidence of health benefits associated with early treatment for late-onset GSD II.

MSAC also considered that late-onset GSD II is predominantly adult-onset, and diagnosis of adult-onset conditions in the newborn period does not align with the NBS NPF. MSAC considered there are ethical issues related to diagnosing newborns with a predominantly adult-onset condition, where there is no effective early intervention in childhood and the currently available tests cannot accurately determine the prognosis.

On balance, MSAC considered there to be a greater potential for harm than benefit from NBS for GSD II as, while one newborn per year may benefit from a diagnosis of infantile-onset GSD, a larger number of newborns will be recalled for testing, and newborns identified as at risk for late-onset disease may experience harms from screening such as: psychological harm (including anxiety) from the diagnosis of late-onset disease, overmedicalisation and overtreatment with no evidence of benefit, parental hypervigilance and burden from monitoring and medical procedures that may be of no benefit. MSAC considered that newborn bloodspot screening for GSD II could cause reputational damage to the NBS program if children are diagnosed for adult-onset conditions without an effective intervention. This may lead to distrust in the NBS programs and reduce overall participation in the programs. MSAC considered lower participation in NBS programs would result in worse health outcomes at the population level because other screened conditions that are more common and have effective evidence-based therapies, such as congenital hypothyroidism, phenylketonuria and cystic fibrosis would not be detected early.

MSAC noted that the incremental cost per screen was comparable to previously accepted costs per screen for other NBS conditions it had previously considered. However, MSAC considered the incremental cost per quality-adjusted life year (QALY) of screening for GSD II was very high and likely to be substantially underestimated. The economic model assumed that individuals diagnosed with late-onset disease would only be treated with ERT from symptom onset, however in clinical practice, a diagnosis would likely create expectation for earlier treatment with ERT, despite the absence of evidence to support this approach. MSAC considered that this would result in a much higher incremental cost per QALY.

MSAC considered the financial impact from NBS for GSD II was highly uncertain and likely substantial. MSAC considered the cost of providing ERT (primarily to the LSDP) would be approximately \$REDACTED in the first 5 years of screening should ERT be commenced for all newborns diagnosed with GSD II at birth (approximately 11 newborns per year), irrespective of the type of GSD II). MSAC advised the annual costs of ERT would continue to increase as more newborns are diagnosed with GSD II. MSAC noted that the financial impacts estimated in the DCAR also included the costs of first tier screening for the remaining 47 false positive screens.

MSAC advised the addition of infantile-onset GSD II to newborn screening programs could be reconsidered when i) new screening and diagnostic testing methodologies are developed that more accurately differentiate between infantile-onset GSD II versus late-onset GSD II; and ii)

additional higher quality evidence demonstrating that diagnosis following NBS and earlier treatment improves clinical outcomes compared with treatment following a symptomatic diagnosis.

Consumer summary

This application from the Department of Health and Aged Care (the department) requested advice about adding a screening test for glycogen storage disease type II (GSD II, also known as Pompe disease and Acid Maltase disease) to the Newborn Bloodspot Screening (NBS) programs. Newborn bloodspot screening programs are delivered by state and territory governments. The department is working with state and territory governments to increase the number and consistency of conditions screened. MSAC's advice provides input to the Health Ministers who make a decision at the Health Ministers' Meeting (HMM) on whether to implement new screening programs¹.

NBS programs involve collecting a tiny sample of blood from the heel of each newborn baby and using that sample placed on to special filter paper (also called dried bloodspot) to test for several severe childhood conditions, so that the baby may access treatment earlier. Although the NBS programs are optional, it has over 99% uptake across Australia. A positive initial screening test result, which identifies babies at risk for the condition of interest, does not make a diagnosis, but the baby is recalled for further clinical assessment and a separate diagnostic test. The diagnosis may be made before any detectable signs and symptoms of disease.

GSD II is a rare genetic (inherited) condition caused by very low levels of an enzyme called alpha glucosidase. This enzyme breaks down glycogen, a complex sugar, in the body. There are 2 forms of GSD II; one form is called infantile-onset GSD II, a life-threatening condition where affected babies can die without treatment, because of heart and breathing problems, due to weak muscles. Late-onset GSD II is mostly diagnosed in adults. In Australia, people with late-onset GSD II typically develop symptoms aged 40 years or older. People with late-onset GSD II can have trouble walking, breathing and experience severe disability. Late-onset GSD II progresses at slower rate than infantile-onset GSD II. Late-onset GSD II is much more common (80–90% of all cases) than infantile-onset GSD II (10–20% of all cases). People with GSD II who meet treatment guidelines can be treated with alglucosidase alfa or avalglucosidase alfa intravenous enzyme replacement therapies available in Australia through the Life Saving Drugs Program (LSDP).

The suggested screening test for GSD II would take place in 2 stages (tiers). The first-tier would be an enzyme activity test on the dried bloodspot. Babies with low enzyme levels would go on to have genetic testing to look for some alfa glucosidase genetic variants that are associated with a risk of developing GSD II.

If GSD II was included in Australia's newborn screening programs, approximately 58 babies each year would have abnormal screening test results and need clinical review and more testing. Most of these babies will not have GSD II but have a false positive test result. This may cause unnecessary anxiety for many families. Of the babies with abnormal screening test results, approximately one baby per year will have an early diagnosis of infantile-onset GSD II and may benefit from early treatment. An additional 10 babies will be diagnosed as having a late-onset version of GSD II. For these 10 babies, doctors and families will not know if, or when a child may develop symptoms, or how severe it will be. This is because the genetic tests and other tests used to diagnose GSD II cannot predict how the disease might develop in these children. MSAC noted that people in the same family with the same genetic variants can be affected differently, and some people do not ever develop symptoms.

¹ <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-nbs-our-national-decision-making-pathway-fact-sheet>

Consumer summary

MSAC considered that there is very little evidence that an early diagnosis of late-onset GSD II from newborn screening would improve health outcomes for these babies. In countries that already screen for GSD II, most children diagnosed with late-onset GSD II do not have treatment with enzyme replacement therapy. Instead, they are monitored to see if they develop symptoms of GSD II. MSAC considered that the evidence available does not show that children will have better health outcomes if they have an early diagnosis with late-onset GSD II through newborn screening. MSAC considered that 10 babies diagnosed as having a late-onset version of GSD II could have ongoing monitoring for decades. MSAC also considered that families would expect that conditions diagnosed through newborn screening would have an early treatment.

MSAC considered that diagnosing babies with late-onset GSD II may cause greater harm for babies and their families. MSAC considered having a diagnosis of a potentially serious illness may cause psychological harms for the child and their family because accurate information about if, or when they will develop the condition, or how severe it might be, may not be known. MSAC considered children diagnosed with late-onset GSD II could be harmed from medical procedures that may not improve their health. MSAC considered doctors usually do not test healthy children for medical conditions that cause problems in adulthood. This is because it takes away the child's ability to make their own informed decision. MSAC considered that many adults decide not to have genetic testing for conditions where there is no early treatment such as Huntington's disease. MSAC noted that most of the medical organisations who provided feedback also raised concerns about diagnosing late-onset GSD II in babies.

Therefore, MSAC did not support newborn screening for GSD II because it may cause greater harms than benefits. MSAC considered there is no effective early treatment for babies who are at risk of developing late-onset GSD II. MSAC further noted many of these babies may not develop signs and symptoms of GSD II in adulthood.

The Newborn Bloodspot Screening Policy Framework criteria require that there is a benefit to the baby by screening for the condition in the newborn period and an accepted early intervention. MSAC considered testing babies for a disease that may develop in adulthood does not benefit the newborn or their family. MSAC also considered that there is no accepted, effective early intervention for those diagnosed with late-onset GSD II.

MSAC considered adding GSD II to newborn screening programs could reduce trust in the newborn screening programs and lead to fewer babies having newborn screening. MSAC considered this may result in harm, as babies with other, more common conditions that are detected in screening, such as cystic fibrosis and congenital hypothyroidism would not be diagnosed at the earliest stage, where treatment is effective.

MSAC advised that newborn screening for infantile-onset GSD II should be considered when more accurate screening and diagnostic tests are available. These tests should clearly identify babies who have infantile-onset GSD II, but avoid identifying late-onset GSD II.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support newborn screening of GSD II because it may cause greater harms than health benefits. This was because the current screening tests and diagnostic tests (including genetic tests) will mostly identify babies who may develop the adult-onset (late-onset) form of GSD II. These children will not benefit from an early diagnosis because there is no effective early treatment. However, they may have psychological harms from being diagnosed with a potentially serious disease they might or might not develop in the future. MSAC advised that newborn screening for infantile-onset GSD II could be re-considered when a test is available that is able to accurately predict the type of GSD II.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from the Department of Health and Aged Care was to consider the addition of glycogen storage disease, Type II (GSD II, Pompe disease) to the list of conditions screened as part of Australia's newborn bloodspot screening (NBS) programs. MSAC considered both its own Terms of Reference and the Newborn Bloodspot Screening National Policy Framework (NBS NPF)² in providing its advice. MSAC noted that its advice would be considered at the Health Ministers Meeting, alongside advice from the Cancer and Population Screening Committee, the Health Chief Executives Forum and the NBS Program Management Committee.

MSAC noted that the NBS programs are underpinned by the NBS NPF, and implementation remains jurisdiction based, with screening provided by 5 NBS laboratories across Australia. For a condition to be included in Australia's NBS programs, it needs to align broadly with the NBS NPF, which outlines several criteria to be met including the following:

- The condition should be a serious health problem that leads to significant morbidity or mortality.
- There should be a benefit to conducting screening in the newborn period.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a suitable test protocol to identify the presence of the condition
- The protocol should, on balance, be socially and ethically acceptable to health professionals and the public.
- Health care services for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result. There should be an accepted intervention for those diagnosed with the condition.
- The benefit of screening a condition must be weighed against its impact on the program as a whole.

MSAC noted the consultation input received for this application, including from individuals with lived experience of having GSD II or having a family member with GSD II. MSAC noted individuals with GSD II experienced an extended period of time before diagnosis, and distress from the uncertainty about their health and dismissal of symptoms. MSAC further noted the psychosocial and physical burdens of disease impacted individuals' health or quality of life, ability to work and their ability to participate in hobbies or social activities. MSAC also acknowledged the devastating impact of having a child die from infantile-onset GSD II. MSAC noted that input from some medical organisations raised concerns about diagnosing late-onset GSD II in newborns.

MSAC noted that GSD II is an autosomal recessive lysosomal storage disorder, caused by a deficiency of alpha glucosidase (GAA), a lysosomal enzyme that is required to break down glycogen. GSD II is an inherited genetic condition caused by genetic variations in the GAA gene. The two main categories of clinically diagnosed GSD II are infantile-onset (IOGSD II) and late-onset (LOGSD II). IOGSD II is the most severe form of the disease and is associated with very low or no GAA activity. IOGSD II is characterised by symptoms that appear at birth or within the first few months of life. Symptoms of IOGSD II include hypotonia (low muscle tone), feeding and respiratory problems and cardiomyopathy (thickening of the heart muscle), that eventually require a ventilator. Without treatment, most individuals with IOGSD II have unremitting deterioration and die within the first year of life. MSAC noted LOGSD II is typically asymptomatic

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-policyframework?language=en>

at the time of newborn screening, with symptoms such as skeletal muscle weakness, respiratory problems, and exercise intolerance usually developing in adulthood. However, some individuals may be diagnosed before 18 years of age. MSAC noted the symptoms, severity and specific clinical features of LOGSD II can vary widely between individuals even if they have the same genetic variant.

MSAC noted that currently without the NBS, the timing of diagnosis for GSD II varies significantly depending on the disease form. Infantile-onset GSD II is typically diagnosed around 3 months of age (Pompe registry³) whereas LOGSD II is usually identified in adulthood. The most common type of GSD II is the late-onset form. MSAC considered Australian data showed that most people with LOGSD II develop symptoms in adulthood and are diagnosed when they are over 40 years of age. In Australia, the median age of diagnosis with of any form of GSD II is 36 years, ranging from 10 weeks to 69.7 years⁴. MSAC further noted data from the LSDP (2014-2024) indicated that for those with late onset disease who received ERT, the median age of symptom onset was over **REDACTED** of age and over **REDACTED** were adults (18 years or older). MSAC noted that people diagnosed with GSD II at a younger age have worse clinical outcomes.

Regarding the key health technology assessment (HTA) questions (Including the **availability of a suitable screening test (or tests) to accurately identify all newborns at risk for the proposed condition (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive) and whether disease subtype and prognosis can be determined from the screening and confirmatory tests to determine need for earlier treatment**), MSAC noted that proposed first-tier testing using a tandem mass spectrometry (MS/MS) or fluorometric assay on dried blood spot for GAA enzyme activity is unable to fully discriminate between IOGSD II (representing 10–20% of infants) and LOGSD II (affecting 80–90% of cases). MSAC noted that the levels of GAA enzyme activity in newborns overlaps for the infantile-onset and late onset forms of GSD II. The proposed second-tier rapid molecular (genetic) testing for common GAA variants is expected to diagnose most but not all IOGSD II infants and may help to exclude some pseudodeficiencies⁵ (a type of false positive result).

MSAC noted that this specific 2-tiered screening method has not been studied in international NBS programs and has no direct evidence to estimate how it would perform in practice. MSAC noted in many international jurisdictions, the first-tier screening method used to assess GAA enzyme activity is most commonly MS/MS. The majority of programs either do not have a second-tier screen, or use genetic testing as the second-tier screen or as part of confirmatory testing. MSAC noted that expert advice from South Australian NBS laboratory/National Referral Laboratory and NSW NBS laboratory indicated that currently there is no optimal screening protocol that could be used in Australia and that the number of pseudodeficiencies were high. MSAC considered there is no consensus on the most appropriate screening test protocol.

MSAC estimated that approximately 58 newborns would be recalled for further testing in 2025–26 should NBS be commenced. This was based on a screen positive rate of 0.019% from the NBS program in California where some newborns had genetic testing before they are recalled⁶. MSAC noted there were no reliable data for second-tier screening test proposed for Australia as

³ Kishnani, PS, et al 2013, 'Timing of diagnosis of patients with Pompe disease: data from the Pompe registry', *Am J Med Genet A*, vol. 161, no. 10, 2013.

⁴ Chin S, Fuller M. Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. *Lancet Reg Health West Pac*. 2022;19:100344.

⁵ Note: "Pseudodeficiency" refers to a genetic variant in the GAA gene that reduces alpha-glucosidase enzyme activity without causing clinical symptoms or disease.

⁶ Tang, H, et al. The First Year Experience of Newborn Screening for Pompe Disease in California. *International journal of neonatal screening*, 2020 6(1), 9.

at the time no established consensus existed on which GAA variants should be included for the Australian population. MSAC considered the number of newborns recalled in Australia could be substantially higher because higher screen positive rates have been reported in other NBS programs in the United States (0.022% in Pennsylvania⁷ and 0.06% Illinois⁸). MSAC considered that this was a relatively large number of newborns being recalled for further testing and will result in only one newborn per year being diagnosed with IOGSD II.

Screen positive newborns would be referred for further testing at the specialised paediatric metabolic clinics located in major capital cities. MSAC considered being recalled for further testing would cause undue stress and anxiety for many families as most newborns recalled will have a false positive screening test result. MSAC considered ensuring timely assessment of screen-positive newborns may be burdensome for paediatric metabolic clinics as they will need to examine many screen-positive, otherwise healthy newborns.

MSAC noted that newborns recalled for further testing would have a range of tests including molecular (genetic) testing and tests for cardiac and muscle function. MSAC considered that the results of genetic testing or normal GAA enzyme activity on repeat testing would confirm that some newborns do not have GSD II (false positive). This could be due to having a low enzyme level for a variety of reasons. These include having a pseudodeficiency variant (a known genetic variant that does not cause disease but causes low enzyme levels) or being an unaffected carrier (one pathogenic/likely pathogenic variant and one benign/likely benign variant). MSAC considered that newborns with evidence of cardiac involvement or hypotonia (low muscle tone) on clinical examination (including subsequent examinations) would be diagnosed as having IOGSD II.

MSAC considered that newborns with low enzyme levels and GAA variants that may cause GSD II (including one or more variants of unknown significance [VUS]), but do not have features of IOGSD II on examination may be diagnosed with LOGSD II. MSAC noted that there are over 900 known variants in the GAA gene and it is not always known which ones will cause disease in an individual. MSAC noted that in a 2021 study, there were 648 GAA variants identified that may cause GSD II and only 336 of these could be associated with a clinical disease-causing phenotype. The remainder of the variants were classified as “unknown” disease phenotype⁹. MSAC considered newborns diagnosed with LOGSD II would have ongoing testing, similar to some NBS programs in the United States^{6,7,8}. MSAC considered that families of most newborns diagnosed with LOGSD II will expect to be given information on their child’s phenotype, including a clear age of onset and predicted level of impact. Some newborns diagnosed with LOGSD II may never develop significant symptoms, either because some newborns with pathogenic variants will not develop symptoms or because they have a VUS that does not cause disease.

MSAC noted advice from the clinical co-applicants that suggested it is possible that newborns with VUSs could be excluded from reporting and diagnosis as there is potential harm to newborns from a diagnosis of GSD II and monitoring who would have otherwise remained asymptomatic. However, MSAC also noted that the clinical experts did not support this approach unanimously. MSAC considered this would miss some diagnoses of GSD II and missed diagnoses would occur more frequently for newborns with non-European ancestry as most genetic data are from people

⁷ Ficicioglu, C, et al., 'Newborn Screening for Pompe Disease: Pennsylvania Experience', *Int J Neonatal Screen*, vol. 6, no. 4, 2020

⁸ Burton, BK, et al, 'Newborn Screening for Pompe Disease in Illinois: Experience with 684,290 Infants', *Int J Neonatal Screen*, vol. 6, no. 1, 2020

⁹ de Faria et al., 'Update of the Pompe variant database for the prediction of clinical phenotypes: Novel disease-associated variants, common sequence variants, and results from newborn screening', *Human Mutation* 2021 42(2):119–34, doi:[10.1002/humu.24148](https://doi.org/10.1002/humu.24148).

with European ancestry. Similarly, MSAC considered newborns diagnosed with LOGSD II with non-European ancestry, including First Nations Australians, would be more likely to have an uncertain prognosis. MSAC noted a previous case in Australia, where a child from a population group not well represented in variant databases was initially identified with a VUS and later diagnosed with IOGSD II. MSAC considered this exemplified the limitations of the current GAA variant database and the incomplete understanding of the genetic variants that cause GSD II, especially in non-European populations. MSAC advised there was a need to collect information and establish a variant database for GSD II in Australia.

MSAC noted that the Australian population does not have common pathogenic founder variants in the GAA gene, unlike in countries such as Taiwan. MSAC considered this makes it more difficult to accurately screen and diagnose the condition in Australia. MSAC considered that if genetic testing reveals that the recalled newborn and one of their parents have the same two GAA gene variants, this could help clarify a potential diagnosis.

Overall, MSAC considered that genetic testing would not conclusively confirm or rule-out GSD II for a significant proportion of screen positive newborns, because there are many VUS in the GAA gene. For newborns with one or two pathogenic variants, genetic testing will not always identify whether they will develop IOGSD II, LOGSD II, or an unknown phenotype of GSD II. MSAC considered that other tests for GSD II such as urinary glucose tetrasaccharides are of limited use in screen-positive non-LOGSD II infants, as neonatal results are generally normal in LOGSD II.

MSAC estimated that, if NBS for GSD II was introduced, approximately 58 screen positive newborns for 2025-2026 would be recalled, further testing would identify one newborn with IOGSD II and approximately 10 newborns with LOGSD II (including those with VUS). This was based on the assumption that the birth prevalence of GSD II would increase due to NBS from 1/46,000 newborns to 1/29,000 newborns, estimated from the increase observed in California. However, MSAC noted that more recent data suggested a higher birth prevalence of 1/18,711¹⁰, and so it is possible that more than 100 screen positive newborns would be identified. MSAC considered the increasing prevalence reflected an incomplete understanding of the natural history of GSD II. MSAC considered the increasing reported prevalence of GSD II could reflect screening capturing people at risk of developing milder or asymptomatic forms of GSD II that may not otherwise be diagnosed, or lower penetrance of some variants. MSAC also considered the increasing reported prevalence of GSD II means it may no longer be considered an ultra-rare disease with a prevalence less than 1:50,000.

MSAC considered that NBS for GSD II would mostly lead to identifying a large number of newborns at risk of LOGSD II who may develop symptoms later in life. MSAC considered newborns diagnosed with LOGSD II may experience net harms from NBS for GSD II as they may experience psychological harms from being diagnosed with a potentially serious condition that does not have effective early intervention, over-medicalisation, and risks from medical procedures for ongoing monitoring.

MSAC considered the current screening and diagnostic tests cannot accurately predict disease onset or prognosis for all cases of GSD II. MSAC considered the current screening tests were not suitable because they have a high false positive rate and they cannot accurately discriminate between IOGSD II, LOGSD II and those who may not develop the condition.

In relation to **availability of effective treatment (or treatments) in Australia for at-risk newborns**, MSAC noted that the Australian Government funds enzyme replacement therapy (ERT), as alglucosidase alfa or avalglucosidase alfa, for management of IOGSD II and LOGSD II through the

¹⁰ Colburn R, Lapidus D. An analysis of Pompe newborn screening data: a new prevalence at birth, insight and discussion. *Front Pediatr.* 2024;11:1221140.

Life Saving Drugs Program (LSDP). MSAC noted that these ERTs are very high-cost treatments. For IOGSD II, the LSDP eligibility criteria are based on a laboratory diagnosis in children under 2 years of age, irrespective of symptoms. For LOGSD II, the LSDP eligibility criteria permit treatment in presymptomatic children 2–18 years of age with a laboratory diagnosis. Beyond 18 years of age, patients must have symptoms and meet the specific disease severity criteria to be eligible for ERT on the LSDP. MSAC considered the application of these criteria in the context of NBS for GSD II could lead to overtreating pre-symptomatic children diagnosed with LOGSD II who would potentially receive intravenous therapy for decades with no clear benefit on disease trajectory, based on the current evidence.

With respect to **effectiveness of treatment from the proposed earlier age of initiation following NBS screening and diagnosis (pre-symptomatic and early symptomatic) compared to age of initiation under current management pathway (established symptomatic presentation)**, MSAC considered that there was evidence that early ERT for patients with IOGSD II improves health outcomes, but that this evidence was of low quality. MSAC considered the available evidence showed improvements in overall survival and ventilator-free survival (VFS). MSAC considered earlier diagnosis and earlier treatment with ERT reduces cardiomyopathy and improves motor function (earlier independent walking) in IOGSD II. However, MSAC noted that ERT-treated patients with IOGSD II may later develop weakness, and bulbar dysfunction.¹¹ MSAC noted that the most recent evidence for the effectiveness of ERT on long-term motor function found that almost half of patients achieved the ability to walk independently (Pfrimmer et al 2024) and this was consistent with findings from other studies. However, MSAC noted that this study also reported that nearly 50% of children with IOGSD II lost an achieved motor milestone.

MSAC noted that most of the studies comparing outcomes of NBS for IOGSD II were based on a Taiwanese cohort diagnosed through newborn screening compared with a historical cohort. MSAC considered there were limitations in this evidence, including differences in screening algorithms, small sample sizes, potential loss to follow-up, high risk of bias, and variability in ERT timing and dosage. Additionally, historical cohorts generally commenced ERT later (around 6 months) than the Australian cohort (3 months), and there was limited information on the effectiveness of the supportive care provided that was unrelated to ERT. MSAC agreed with ESC that Taiwan has specific genetic variants that cause GSD II and variant frequency, and the Taiwanese experience may not be fully applicable to the Australian context. Overall, MSAC considered the available evidence demonstrated some benefits with earlier treatment of IOGSD II in terms of survival and ventilation-free survival, however the evidence was low-certainty.

MSAC noted the evidence base for LOGSD II consisted of 5 studies which were case series or non comparative studies. Of the LOGSD II cases identified in these studies, MSAC noted only 14 of 84 (17%) patients underwent ERT with variable commencement timing and dosage. In addition, most of these LOGSD II patients commenced ERT after developing symptoms. MSAC considered the findings had a high risk of bias due to methodological concerns, unknown loss to follow up, selection biases, outcomes reporting bias and publication bias. MSAC also noted evidence for early vs late ERT in IOGSD II and LOGSD II presented from retrospective case series and registry databases and concluded the findings were broadly consistent with those from screening programs. MSAC concluded that there was no high-confidence evidence that diagnosing newborns with LOGSD II and subsequent interventions improved health outcomes. MSAC considered that there is no consistently accepted intervention for newborns diagnosed with LOGSD II through newborn screening. MSAC noted this was supported by a clinical expert in the pre-MSAC response, who stated that ‘there is insufficient data about the long-term benefits of commencing treatment early in LOGSD II’. However, MSAC noted in clinical practice, a diagnosis

¹¹ Pfrimmer et al. , ‘Long-term outcome of infantile onset Pompe disease patients treated with enzyme replacement therapy – data from a German–Austrian cohort’, *J Neuromuscul Dis* 2024;11(1):167–77, doi:[10.3233/JND-230164](https://doi.org/10.3233/JND-230164).

would likely lead to an expectation for earlier treatment with ERT from families, despite the absence of evidence to support this approach.

MSAC noted that the key trial for pivotal trial of ERT with alglucosidase alfa for late onset disease. was conducted in patients aged 10-70 years (with a mean age in the 40s) with symptomatic LOGSD II. This study demonstrated disease stability over 78 weeks when treated with ERT ¹². MSAC considered the benefit from treatment was modest for people with symptomatic LOGSD II.

MSAC considered that there were adverse events associated with ERT, such as infusion reactions, long-term central venous access with infection risk, and formation of neutralising anti-drug antibodies. MSAC considered newborns diagnosed with LOGSD II could experience potential psychological harms (including anxiety), parental hypervigilance and 'sick role behaviour' as they have a diagnosis of a potentially severe disease. MSAC considered newborns diagnosed with LOGSD II could also experience harms from overmedicalisation and overtreatment, burden from monitoring and medical procedures that may be of no benefit.

Overall, MSAC considered there was limited evidence supporting effectiveness of earlier ERT treatment in children with LOGSD II. However, MSAC considered there is no accepted early intervention for newborns at risk of LOGSD II and no convincing evidence that an earlier diagnosis of LOGSD II during the newborn period would improve health outcomes. MSAC considered that without an effective early intervention, newborns diagnosed with LOGSD II may experience greater harm than benefits.

MSAC also considered that the intent of Australia's newborn screening programs is to identify babies' risk of becoming seriously ill from a rare condition in the newborn period and to improve the health of these babies by allowing early intervention. However, MSAC considered that most cases of GSD II identified through NBS would be late onset GSD II that would be expected to develop in adulthood. Therefore, MSAC considered NBS GSD II did not align with the intent of the newborn screening programs and several related criteria in the NBS NPF.

Regarding **cost-effectiveness of NBS screening compared to no newborn screening**, MSAC noted that a cost-utility analysis was presented that resulted in an uncertain and very high incremental cost-effectiveness ratio (ICER) of approximately \$REDACTED per quality-adjusted life year (QALY) that was mainly driven by the ERT costs. MSAC considered the estimated ICER was not informative and was highly underestimated due to the assumption that patients identified with LOGSD II via NBS will start ERT only when symptoms emerge (by age 2 years for approximately REDACTED% of patients with LOGSD II and at age 38 years for approximately REDACTED%). MSAC noted that no sensitivity analysis was presented where ERT is assumed to commence from birth in presymptomatic cases of LOGSD II. MSAC noted the cost per screen for the proposed screening strategy (\$REDACTED per newborn) was comparable to previously accepted costs per screen for other NBS conditions MSAC has previously considered.

MSAC further noted that the cost-effectiveness of ERTs funded through the LSDP were very high with uncertain ICERs of:

- \$REDACTED per life year gained (LYG) for LOGSD II patients treated with alglucosidase alfa
- \$REDACTED per QALY for LOGSD II patients and \$REDACTED per QALY for LOGSD II patients treated with avalglucosidase alfa.

MSAC noted that **the financial impact to the NBS programs** was \$REDACTED in Year 1 (including a one-off set-up cost) and approximately \$REDACTED annually from Years 2-6. Costs to state and

¹² van der Ploeg AT, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med*. 2010 Apr 15;362(15):1396-406. doi: 10.1056/NEJMoa0909859. PMID: 20393176.

territory budgets of adding GSD II to NBS would be \$42,555 in Year 1 to \$143,208 in Year 6 while the costs to the MBS would be \$27,980 in Year 1 to \$44,832 in Year 6.

Further, MSAC noted that the financial impacts for the LSDP could be very high due to the high likelihood that treatment with ERT would be sought on the LSDP for newborns with LOGSD II. In addition, the ERT costs (\$REDACTED in Year 1 to \$REDACTED in Year 6) are likely significantly underestimated, because the Department-contracted assessment report (DCAR):

- assumed that ERT starts 4.6 months earlier for IOGSD II
- assumed that all identified LOGSD II cases although they would commence ERT earlier, still only commenced ERT at symptom onset - the REDACTED% of cases who would otherwise commence ERT at age 12 years start at age 2 years for LOGSD II while the remainder of LOGSD II cases commenced ERT at age 38 years (instead of REDACTED)
- did not account for the increased duration of ERT use per patient (due to increased survival from earlier commencement) for all cases as it is assumed to occur beyond Year 6.

MSAC noted that additional financial analyses were developed which suggested that annual ERT costs by Year 6 could be as high as \$REDACTED assuming all newborns diagnosed with GSD II receive ERT from birth. MSAC considered this would increase each year as the number of newborns diagnosed with LOGSD II would increase each year and these cases would potentially use ERT for decades without clinical evidence supporting this use. MSAC also noted that the economic analysis and financial impact did not consider the costs of managing the harms that may result from ERT.

Regarding **relevant ethical (including equity), legal, social or organisational aspects specific to screening** for GSD II, MSAC considered there were significant ethical issues with screening newborns for GSD II. MSAC considered the current screening and diagnostic testing protocol may not be socially and ethically acceptable to health professionals and the broader public because it would mostly identify newborns at risk of developing an adult-onset condition that does not have an effective early intervention. MSAC noted that most medical and legal organisations do not support testing children for adult-onset diseases to preserve their autonomy and right to provide informed consent^{8,9,10,11}. MSAC noted that consultation input from health professionals and newborn screening laboratories raised concerns about identifying LOGSD II as it is mostly an adult-onset condition and limitations with the screening tests. MSAC considered that it was not known whether newborn screening for a mostly adult-onset condition, without an effective early intervention was acceptable to the Australian community.

MSAC noted that the majority (up to 90%) of individuals with a parent affected by Huntington's disease choose not to undergo predictive testing, largely due to the lack of an effective treatment and the fact that the knowledge of their genetic status cannot be unlearned once known¹³. MSAC considered there may not be benefits from the 'value of knowing' for newborns diagnosed with LOGSD II or their families because the results of the screening and diagnostic testing would not provide clear information about disease onset or severity.

MSAC considered there was a high likelihood that newborn screening for GSD II could cause reputational damage and distrust in the programs if diagnosing an adult-onset condition without an effective early intervention is not acceptable to the Australian community. MSAC considered this could negatively affect participation in the NBS programs. MSAC considered this may result in worse outcomes at the population level if participation levels drop, because some cases of

¹³ Anderson KE, et al. The choice not to undergo genetic testing for Huntington disease: Results from the PHAROS study. *Clin Genet*. 2019; 96: 28–34. <https://doi.org/10.1111/cge.13529>

more common conditions with effective evidence-based therapies, like cystic fibrosis and congenital hypothyroidism, would go undetected.

MSAC noted consent processes for NBS vary across jurisdictions in Australia and are not nearly as intensive as the consent procedures and genetic counselling offered for adults and children before genetic testing for severe conditions in clinical (i.e., non-screening) settings.

MSAC considered significant clinical resources will be required to manage the relatively large number of screen-positive newborns who will require clinical assessment, imaging (muscle MRI), and genetic and family counselling. MSAC considered that newborn screening for GSD II would require paediatric metabolic clinics to monitor an additional 10 asymptomatic newborns at risk of LOGSD II each year. However, even this relatively small number would have a compounding effect as by the end of 6 years the number of children monitored would be approximately 55. MSAC considered paediatric metabolic clinics may not have sufficient capacity to support the ongoing management of asymptomatic children diagnosed with LOGSD II.

Overall, MSAC did not support extending the NBS program to include GSD II because the potential harms of newborn screening for GSD II outweighed the potential benefits. NBS for GSD II would mostly identify newborns at risk of LOGSD II, a condition that is mostly diagnosed in adults. MSAC considered diagnosing adult-onset conditions in the newborn period does not align with the intent of Australia's newborn screening programs or the criteria in the NBS National Policy Framework.

MSAC considered there to be a greater potential for harm from NBS for GSD II as one newborn per year may benefit from a diagnosis of IOGSD II while a larger number of newborns diagnosed with LOGSD II may experience harms from screening. MSAC considered the current screening tests have a high false positive rate, and therefore a large number of newborns and their families would experience undue stress and anxiety being recalled for further testing as they will have false positive results.

MSAC advised the addition of infantile-onset GSD II to newborn screening programs could be reconsidered when:

- i) new screening and diagnostic testing methodologies are developed that more accurately differentiate between infantile-onset/severe GSD II versus late-onset/less severe GSD II. This would enable NBS for GSD II to be targeted to infants with the severe infantile-onset form who could then receive timely and appropriate treatments; and
- ii) additional higher quality evidence demonstrating that diagnosis of IOGSD II following NBS and earlier treatment improves clinical outcomes compared with treatment following a symptomatic diagnosis.

MSAC considered collecting information and establishing a variant database and outcomes registry for GSD II to determine the clinical significance of genetic variants would be beneficial to improve available evidence.

4. Background

This application is MSAC's first consideration of NBS for GSD II. Screening for GSD II may be multiplexed with NBS for MPS I (MSAC 1775), which MSAC considered in November 2024.

5. Prerequisites to implementation of any funding advice

NBS programs are underpinned by the Newborn Bloodspot Screening National Policy Framework (NBS NPF); however, these programs are managed by state and territory governments and

operate independently of each other. Prior to implementation of any funding advice, each state screening laboratory will be required to determine their preferred approach to screening for GSD II. There are five laboratories that conduct tests on bloodspot cards, located in New South Wales (NSW), Queensland, South Australia (SA), Victoria and Western Australia (WA). Babies born in states and territories without NBS testing laboratories have their dried bloodspots sent interstate for testing.

Expert advice from the NSW NBS laboratory and the SA NBS laboratory/National Referral Laboratory indicates that the optimal screening protocol is unknown in Australia. The methods currently in use internationally for NBS result in a high number of first-tier screen false positives, leading to a high number of second-tier tests. In addition, most patients identified by NBS will not have infantile-onset GSD II, that is, they will either have late-onset GSD II or pseudodeficiencies.

In addition to determining the preferred screening approach, NBS laboratories may be required to:

- Have or gain sufficient space for additional capital equipment, including mass spectrometry machines.
- Purchase additional mass spectrometry machines (adhering to local procurement policies including tender processes).
- Hire and train additional laboratory staff (in several cases moving to a different rostering system so the laboratory is in use 6 days per week instead of 5).
- Validate the screening protocols, determining normal and abnormal value ranges.
- Obtain National Association of Testing Authorities (NATA) accreditation.
- Add the new test to the Laboratory Information Management System¹⁴.

Guidelines on the management of patients with GSD II in Australia will be required to be updated, to incorporate recommendations on the management of patients identified through screening to have LOGSD II, who may not yet present with symptoms. Clinical capacity may also need to increase, to support the additional “patients in waiting” identified through screening, with their families requiring additional education and support.

To support these activities, direct funding is being provided to states and territories via a schedule to the Federation Funding Agreement (FFA) - Health, under which they can make decisions regarding the best use of funds for implementation in their own jurisdiction.

6. Proposal for public funding

The proposal is for GSD II to be added to the list of conditions screened through Australia’s NBS programs. If GSD II is diagnosed via NBS, then follow-on cascade testing of first-degree relatives is proposed although cascade testing will be covered by existing funding mechanisms for cascade testing. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). It is also directly investing \$107.3 million from 2022–23 to 2027–28 to support expansion of NBS programs. This includes:

- \$39 million from Budget 2022–23, including \$25.3 million for states and territories
- \$68.3 million from Budget 2024–25, including \$43.3 million for states and territories (announced through MYEFO 2024–25)

¹⁴ https://www.health.gov.au/sites/default/files/2024-06/newborn-bloodspot-screening-expansion-readiness-assessment-executive-summary_0.pdf

This application, as well as applications for NBS for mucopolysaccharidosis Type I and Type II (MPS I and MPS II; MSAC applications 1775 and 1776) form part of this expansion. The three conditions are lysosomal storage disorders (LSDs) and there can be overlap in the tests used to screen these three conditions.

Funding of newborn screening (PICO set 1)

Newborn screening for GSD II is currently not funded or conducted in Australia, and there are no Medicare Benefits Schedule (MBS) items specifically for the delivery of NBS services. This application is not seeking funding via MBS for NBS. MBS items may be used to confirm a GSD II diagnosis or to deliver downstream medical care.

Commercial kits, such as the NeoLSD™ MSMS Kit from Revvity, are available and would enable the detection of GSD II plus five additional LSDs (Gaucher Disease, Niemann-Pick A/B Disease, MPS I, Krabbe Disease and Fabry Disease). The estimated costs could be as follows.

- First-tier screening for GAA activity by the NeoLSD™ kit is estimated to cost REDACTED (960 reactions). Another option is the GelbChem [now known as Enfanos] SKU: CS5 (GAA) kit REDACTED (The detection of other LSDs simultaneously would improve the cost-effectiveness of an assessment of NBS for multiple conditions, but does not alter the assessment of NBS for GSD II alone).
- Second-tier screening conducted by short-panel genetic analysis is as yet uncoded.

Funding for the ongoing delivery of interventions for GSD II (noting this is one avenue for access) is provided for by the Australian Government through the Life Saving Drugs Program (LSDP), where eligibility criteria are met. The LSDP covers medicines for ultra-rare (1 case per 50,000 or fewer) and life-threatening diseases which could not be listed on the Pharmaceutical Benefits Scheme (PBS) on grounds of cost ineffectiveness but have been determined as being clinically effective by the Pharmaceutical Benefits Advisory Committee (PBAC).

Funding of testing of family members (PICO set 2)

New MBS items for testing of family members in relation to this application were not proposed; testing will continue to be funded by existing arrangements.

If GSD II is introduced into the NBS programs, additional resources would be required to implement the care and monitoring of individuals with asymptomatic late-onset GSD II, who would engage with the health system potentially decades earlier than they would have otherwise.

7. Population

There are two populations under consideration in this assessment: PICO Set 1 - newborns participating in universal newborn screening in Australia, and PICO Set 2 - family members of newborns diagnosed through NBS who are eligible for testing.

In the comparison of screening versus no screening, the populations eligible for the intervention and the comparators differ slightly, as summarised in Table 1.

Table 1 Description of populations included in the assessment

PICO set	Population for intervention	Population for comparator
PICO Set 1 - Newborns	All newborn babies in Australia screened through NBS	Affected individuals being investigated for GSD II due to signs/symptoms
PICO Set 2 – Family members	Biological parents and siblings of an index case ¹⁵ identified through NBS with two pathogenic/likely pathogenic (P/LP) variants, one P/LP variant and one variant of uncertain significance (VUS), or two VUSs in the GAA gene	Biological parents and siblings of a proband ¹⁶ identified after symptom onset with two pathogenic/likely pathogenic (P/LP) variants, one P/LP variant and one VUS, or two VUSs in the GAA gene (<i>noting that if 1 or 2 VUSs are identified in a symptomatic patient, they would be reclassified as P/LP</i>)

GAA = acid alpha-glucosidase; GSD II = glycogen storage disease Type II; NBS = newborn bloodspot screening; P/LP = pathogenic or likely pathogenic (variant); PICO = Population/Intervention/Comparator/Outcomes; VUS = Variants of uncertain significance

PICO Set 1: Newborns

The target population for screening is all babies born in Australia who participate in universal NBS programs. NBS uptake is currently estimated at 99.3% of Australian newborns (Huynh et al. 2022).

GSD II is an LSD that leads to progressive neuromuscular deterioration and often death when untreated. GSD II is caused by an inherited deficiency of the lysosomal enzyme alpha-glucosidase which is required to break down glycogen. Pathogenic/likely pathogenic (P/LP) variants of the alpha-glucosidase gene (GAA) cause reduced functionality of the gene and hence a deficiency of the enzyme. Benign variants, variants of uncertain significance (VUS) and pseudodeficiency variants are also identified through genetic sequencing. Pseudodeficiency GAA gene variants are associated with lower GAA enzyme levels, but do not lead to symptomatic disease – individuals with such variants do not require ERT and are ineligible for LSDP-funded ERT therapy.

The two main phenotypic categories of clinically determined GSD II are infantile-onset (IOGSD II) and late-onset (LOGSD II). All cases have the potential to be identified through universal NBS, however screening may also identify asymptomatic or uncertain cases that cannot be definitively predicted to develop symptoms later in life, or the severity of disease in those who do develop symptoms. Screening, followed by clinical assessment and further diagnostic testing, can differentiate between individuals with IOGSD II and LOGSD II, but cannot determine all individuals LOGSD II who will not become symptomatic (i.e. it cannot always distinguish between LOGSD II and a pseudodeficiency). The uncertainty around the risk of LOGSD II is due to the lack of information about some variants, and due to the highly variable individual phenotypic expression of some variants and genotypes. In Australia, the implementation of NBS may result in 1.28 cases per 308,000 births each year having a positive test for IOGSD II and 10 cases being diagnosed with LOGSD II.

IOGSD II is the most severe form of the disease and is associated with very low or no GAA activity (although noting some cases of LOGSD II also have low GAA activity). IOGSD II is distinguished by the presence of symptoms at birth or early development of cardiomyopathy. Severe symptoms, including severe cardiomegaly (enlarged heart), hypertrophic cardiomyopathy (thickening of the heart muscle), hypotonia (low muscle tone), and respiratory problems that eventually require a

¹⁵ Note: “index case” is used in this document to mean the first person in a family detected as having the condition (through diagnostic testing after NBS, but not following symptoms or cascade testing)

¹⁶ Note: “proband” is used in this document to mean an affected individual (i.e. a person who has signs and/or symptoms consistent with the disease phenotype) who has received a confirmatory (genetic, and/or other accepted diagnostic test) diagnosis.

ventilator, appear within the first few months of life. Without treatment, most patients have unremitting deterioration and will die within the first year.

LOGSD II, the second disease category, can be diagnosed at any age. An Australian study of children and adults being diagnosed with GSD II through the National Referral Laboratory between 2009 and 2020 reported the age at diagnosis to range from 10 weeks to 69.7 years (median age 36 years, Chin et al 2021). Symptom development is slower and variable, but they include muscle weakness, respiratory problems, difficulty exercising, and difficulty chewing or swallowing. Patients do not develop cardiomyopathy but can have significant morbidity and mortality due to skeletal muscle myopathy and diaphragmatic insufficiency. There is considerable variation in the age of symptom onset, and clinical presentation can range from asymptomatic to severe, with variability even in patients with identical genetic variants, suggesting that secondary factors may influence the clinical course.

In the absence of NBS, the diagnosis of the late-onset form is often difficult because of the variable and non-specific clinical picture, and it can resemble a range of other neuromuscular disorders. A high level of clinical awareness is needed for a timely diagnosis. Imaging and histologic studies suggest that there is muscle damage by the time that cases of LOGSD II are clinically detected.

PICO Set 2: Family members

GSD II has an autosomal recessive mode of inheritance, therefore both parents of an index case¹⁵ with two P/LP variants can be assumed to be carriers, with a one in four chance that future offspring would also be affected.

When a case of IOGSD II is diagnosed, it is proposed that segregation testing is offered to biological parents to confirm either the inheritance of variants (whether 2 detected variants have been inherited from separate parents) and allow for reproductive decision making and planning, or de novo variant(s) that have no additional risk for subsequent offspring. Due to the severity and early presentation of IOGSD II, it is unlikely that any older siblings would be considered at risk of having IOGSD II. However, older siblings may be carriers of GSD II and should be offered genetic counselling and carrier testing upon reaching reproductive age. Other family members may also request carrier testing to inform their reproductive decision making.

When a case of LOGSD II is identified, it may be appropriate to also offer cascade and carrier testing to other members of the broader family and their children, as LOGSD II symptoms may not yet have been observed or diagnosed.

Prevalence in Australia

GSD II has an estimated birth prevalence of 1 per 46,000 live births in Australia, based on diagnostic testing after presentation with symptoms or family history, between 2009 and 2020, Chin et al 2021). However, it varies based on ancestry. A recent global estimation of incidence was 1/23,000¹⁷. Based on data provided by the LSDP, it was estimated that approximately **REDACTED** babies would be diagnosed with GSD II per year, if NBS programs are introduced. Of these, **REDACTED** were predicted to have IOGSD II. NBS for GSD II is expected to mostly identify LOGSD II, in which most patients have symptom onset in late childhood or adulthood (although some patients do present with severe symptoms in early childhood). The proportion of LOGSD II

¹⁷ Park KS. Carrier frequency and predicted genetic prevalence of Pompe disease based on a general population database. *Mol Genet Metab Rep.* 2021;27:100734.

to IOGSD II cases is predicted to increase with NBS as additional non-symptomatic/very mild cases of LOGSD II will be identified.

In addition to IOGSD II and LOGSD II, screening is predicted to detect a similar number of pseudodeficiency cases per year. These would be considered as false positive if reported, but a second-tier genetic panel may identify some common pseudodeficiency alleles and therefore rule out some false positive cases.

A small number of cases may be diagnosed prenatally (2/81 diagnosed between 2009 and 2020 in Australia (Chin & Fuller 2022)), and the introduction of NBS for GSD II is not expected to alter the management or outcomes in this group. However, they are still considered part of the target population, as any babies born with prior diagnoses would still undergo NBS and incur the costs of the first-tier screening.

8. Comparator

PICO Set 1: Diagnostic testing for GSD II following symptom onset

The comparator for universal newborn screening for GSD II is no newborn screening with diagnosis made following symptom onset, as is performed currently.

In babies with IOGSD II, symptom onset would usually occur in the first few weeks or months of life. In the absence of screening, the process of determining a diagnosis of IOGSD II can take 1 – 3 months. In LOGSD II, symptom onset may occur at any time from childhood until old age. The delay from symptom presentation to diagnosis has been reported to vary from less than one year to 32 years, and in another study, more than half of the patients were diagnosed more than five years from symptom onset (Lisi, E et al. 2016).

The proposed diagnostic testing of infants found to be positive on NBS is similar to the process of diagnostic testing for GSD II after symptom onset. Testing would normally start with assessing GAA enzyme activity on dried bloodspot (DBS), or leukocytes, but as this result is not always conclusive, further testing that includes urinary glucose tetrasaccharide (HEX4) analysis, genetic analysis and clinical assessment is likely to also be performed. Testing of symptomatic individuals may occur in a different order, depending based on the specific clinical presentation of the child.

The range of tests performed includes:

- History, clinical examination (may include electrophysiological testing for older children)
- Cardiac assessment (chest radiography, echocardiogram or electrocardiogram, particularly in younger children)
- GAA enzyme assay on DBS or leukocytes, urinary HEX4, which is required to meet LSDP eligibility criteria, should access to treatment be required via the LSDP
- Respiratory function (age dependent). This is not required in children <5 years of age for LSDP eligibility consideration
- Molecular genetic testing of GAA gene
- Muscle MRI.

PICO set 2: Family members

The comparator is testing offered to the family members of a presenting individual diagnosed with GSD II following the onset of symptoms as follows:

- Parents would be offered testing for P/LP variants to determine segregation of the identified variants,
- Siblings would be offered biochemical testing to detect GAA enzyme levels followed by genetic testing if they have low enzyme levels.

The testing protocol for family members itself would be identical, regardless of whether the proband or index case is identified through NBS or after symptom onset; the only thing that would differ is the timing of testing, due to the difference in timing of diagnosis of the index cases/probands with GSD II. The difference in timing would be less than a year when the index case/proband has IOGSD II, but may be decades if the index case/proband has LOGSD II.

9. Summary of public consultation input

Consultation input was received from 12 organisations and 19 individuals, 7 of whom were individuals with the condition, 10 identified as carers or other interested individual, one researcher and one specialist. The organisations that provided input were:

- Australian Pompe Association
- Western Australian Newborn Bloodspot Screening Program (WA NBS)
- Australasian Society of Inborn Errors of Metabolism (ASIM) [special interest group of Human Genetics Society of Australasia (HGSA)]
- Rare Voices Australia (RVA)
- Genetic Alliance Australia (GAA)
- Genetic Support Network Victoria (GSNV)
- Australian Genomics
- Statewide Biochemical Genetics Service within SA Pathology (SA Pathology) – the national diagnosis service for GSD II.
- Sanofi-Aventis Australia (Sanofi) x 2
- New South Wales Newborn Screening Programme (NSW NBS)
- Royal College of Pathologists of Australasia (RCPA)
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

Level of support for public funding

The consultation feedback received was supportive of public funding for Newborn bloodspot screening (NBS) for GSD II. The consultation feedback highlighted concerns regarding the testing methods and also raised that LOGSD II (an adult-onset condition) will be the main condition diagnosed through NBS for GSD II.

Perceived Advantages

- Timely diagnosis.
- Avoiding diagnostic odyssey.
- Earlier treatment to reduce symptoms, reduce disease progression, reduce disability, improve quality of life and prevent deaths.
- Improve equity of access.
- Allowing preconception testing and cascade testing to ensure that families are aware of genetic diseases like Pompe.

Perceived Disadvantages

- Limitations with the proposed screening tests.

- NBS currently captures the full spectrum of GSD II and is unable to differentiate between IOGSD II and LOGSD II.
- Ethical concerns related to identifying LOGSD II in newborns due to limited evidence to support very early diagnosis of LOGSD II cases.
- Complexities also include ethical issues associated with screening a baby for an adult disease, managing counselling and future expectations of the patient.

Support for Implementation /issues

Other services identified in the consultation feedback requiring resourcing before or after the intervention included staffing, equipment, facilities for NBS labs, resources for first and second tier testing, services to manage false positives, confirmatory diagnostic testing (including genetic testing), genetic counselling, clinical guidelines and treatment algorithms specific for Australia, counselling for families of newborns identified as having LOGSD II, tertiary metabolic services and multidisciplinary care for GSD II including ERT. Consultation input also noted that a range of health services may be required to care for people with symptomatic GSD II.

Consumers who responded included people with GSD II (predominantly late onset or not specified) and family members caring for or friends of people with GSD II. Several respondents stated there is a long, difficult and costly process before being diagnosed with GSD II and during this time some developed worsening symptoms. Consumers supported the service and highlighted the 'value of knowing' being important to them as it would inform reproductive decision making, lead to parents being better prepared for a child's disabilities, and people with LOGSD II being able to make decisions that accommodate future disability.

10. Characteristics of the evidence base

The summary of included evidence is presented in Table 2.

PICO Set 1: Newborns

One systematic review (SR) published in 2013 met inclusion criteria. Kemper et al. (2013)¹⁸ made indirect comparisons between sub-populations that had undergone NBS and that had been diagnosed following symptom onset from Taiwan, and the Pompe registry population data sets. An additional 11 primary studies evaluating NBS published from 2013 onwards were also included for direct test to health outcome evidence; these were based in Taiwan, Italy, Japan and the United States. Four publications were cohort studies with historical comparators, and two studies were case series with naïve indirect comparisons. Two of the comparative studies evaluated enzyme replacement therapy (ERT) administered fortnightly at higher doses than the approved dose regimen in Australia of 20mg/kg of body weight. The remaining seven publications were case series, including the Italian study. There was overlap between the patients included in the Taiwanese studies, but the publications were still included for their separate analyses. Risk of bias was assessed as high for the SR using the Assessing the Methodological Quality of Systematic Reviews – 2 (AMSTAR 2) checklist for SRs. The risk of bias was rated moderate for the primary studies in the direct evidence section that provided comparative evidence, because of the use of historical controls, comparator populations from other jurisdictions, and lack of control for confounding factors.

There were 40 case series that met the inclusion criteria for evidence on test accuracy. The case series reporting on NBS programs were assessed using the Quality Assessment of Diagnostic

¹⁸ Kemper AR, et al. Evidence Report: Newborn Screening for Pompe Disease. USA: Duke University; 2013.

Accuracy Studies–2 (QUADAS-2) checklist for test accuracy studies. Twenty-nine case series provided evidence on test results from NBS programs from 21 different jurisdictions. The SR by Kemper et al. (2013) contributed data from three countries. The protocols used either tandem mass spectrometry (MS/MS) or fluorometry methodology for first-tier screening and a range of follow-up retesting, second-tier screening and/or confirmation methods. There were no protocols that matched the proposed method for Australian NBS, with a ‘rapid genetic test’ to rule out common pseudodeficiencies. The populations ranged in size from 3,000 to 994,975 newborns, and the studies were assessed as low to moderate for risk of bias.

Change in management evidence came from a naïve indirect comparison of 28 case series. Eight case series included IOGSD II cases identified through NBS, and two of the eight also included LOGSD II cases. One of the case series was based on Pompe registry data. There were 20 case series that reported on cases identified in symptomatic populations. The case series studies were not assessed for bias although a naïve indirect comparison of case series studies is inherently highly at risk of bias due to confounding factors (such as differences between healthcare systems that may lead to differences in timing of diagnosis or availability of ERT). Consequently, the findings from these studies should be interpreted with some caution, as the direction of effect of any bias is unknown.

A total of 11 studies (two SRs and nine primary studies) met the inclusion criteria for assessing evidence on health outcomes resulting from early compared to late ERT for IOGSD II. The SR by Kemper et al. (2013) provided data from the Pompe Registry and two articles published in 2009 of the Taiwanese NBS-screened cohort. Four case series conducted retrospective longitudinal evaluations in IOGSD II patients. A further five case series were conducted in LOGSD II cases. One additional SR met the inclusion criteria as it assessed the long-term survival and other health outcomes for LOGSD II patients given ERT upon presentation with signs and symptoms of progression. A comparison of early versus late treatment effectiveness conducted on effect modifiers of ERT outcomes was included from the SR. The DCAR considered studies were assessed as moderate to high for risk of bias using the National Heart, Lung and Blood Institute (NHLBI) Tool for cohort and cross-sectional studies. The DCAR considered data from the SR was based on a naïve comparison of case series data so was also assessed using the NHLBI Tool and found high for risk of bias.

PICO Set 2: Family members

There were no comparative studies identified that fulfilled the inclusion criteria, reporting on the safety and effectiveness of testing of family members following NBS for GSD II.

Nine case series met the inclusion criteria for assessing the outcomes of cascade testing in family members following a diagnosis of IOGSD II or LOGSD II in probands or index cases. The case series included either patients diagnosed by NBS, or individuals diagnosed following symptom onset by genetic testing of patient populations at risk of GSD II. The case series ranged in size from 1 to 18 index cases or probands. Given the high risk of bias due to a number of confounding factors, the DCAR considered these studies represent very low-level evidence and appraisal of risk of bias was not conducted.

Table 2 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
PICO Set 1: Newborns			
Direct from test to health outcomes	SR Cohort studies with historical control Case series with naïve comparison Case series	☒ k=1 SR n=14 ☒ k=11 ps n= 441	Moderate
Accuracy and performance of the test (cross-sectional accuracy)	SR Case series with historical control Case series	☒ k=1 SR n=548,561 ☒ k=40 ps n=4,831,438	Moderate
Change in patient management	Case series	☒ k=28 n=1,146	Not conducted
Health outcomes	SRs Case series with naïve comparison Case series	☒ k=2 SR n=966 ☒ k=9 ps n=535	High
PICO Set 2: Family members			
Cascade test outcome	Case series	☒ k=9 n=40	Not conducted

k = number of studies; n = number of patients; PICO = Population/Intervention/Comparator/Outcomes; ps = primary study; SR = systematic review

11. Comparative safety

PICO Set 1 – Newborns

There were no studies that met the inclusion criteria that presented direct from test to health outcomes evidence for harms of NBS for GSD II.

Safety of NBS screening

The DCAR considered there were no issues with the safety of the screening tests. These are performed on DBS samples. The blood is typically collected from a heel prick in newborns onto blotting paper which is considered a safe way to collect whole blood from newborns, and is already performed for NBS. Screening on older populations is also performed using DBS for GAA enzyme activity determination as laboratories are adapted to using these for MS/MS and fluorometry.

Safety of ERT

There was low level evidence of adverse events associated with ERT given to patients diagnosed with IOGSD II. In addition to published evidence, the product information for alglucosidase alfa (Myozyme®) indicated that infusion related reactions occur in 14% of patients, with higher rates in younger children¹⁹. A higher rate is found to occur in association with avalglucosidase alfa

¹⁹ Myozyme Product Information: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2010-PI-07179-3&d=20241108172310101>

(Nexviazyme®)²⁰. Infants are usually given immunosuppression medications prior to enzyme replacement therapies.

Adverse events were categorised as follows:

- Development of anti-rhGAA antibodies
- Elevated B-type natriuretic peptide (BNP) levels.
- Infusion-related reactions (cardiovascular: hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, nodal rhythm, peripheral coldness; Respiratory: tachypnoea, wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnoea, cough, respiratory tract irritation, oxygen saturation decreased; Cutaneous: angioneurotic oedema, urticaria, rash, erythema, periorbital oedema, pruritus, hyperhidrosis, cold sweat, livedo reticularis
- Arrhythmias (bradycardia and tachycardia)
- Risk of Acute Cardiorespiratory Failure
- Risk of immune suppression

Cross-reactive immunological material (CRIM) status (investigated either through GAA sequencing or Western blot analysis of cultured skin fibroblasts) is a critical feature of IOGSD II patients, and those who test CRIM-negative are known to respond poorly to ERT²¹. However, among CRIM-positive patients, it is common for patients receiving ERT to develop anti-rhGAA antibodies. Patient titres are monitored, as high levels of antibodies can reduce ERT effectiveness. In the evidence presented, most patients' titres did not reach critical levels and in most cases, immune tolerance induction treatment (ITI) resulted in the reduction of anti-rhGAA antibodies. The remaining three adverse event categories are related to cardiac status which can be critical in IOGSD II patients. There was no comparison of adverse events between early ERT (following NBS diagnosis of IOGSD II) versus late ERT (following IOGSD II symptom onset and diagnosis).

Infants with IOGSD II have a high mortality risk in their first year without treatment, so the risk of adverse events associated with ERT is usually considered acceptable. There may also be adverse events for LOGSD II patients given ERT, and the risk of these could be weighed against the effectiveness of treatment if their symptoms are less than severe.

NBS for GSD II could lead to harms associated with identifying individuals with a laboratory/genetic diagnosis who are currently asymptomatic but at risk for clinically detectable disease, the identification of patients with LOGSD II and the creation of "patients-in-waiting" if asymptomatic at diagnosis. This would include individuals who develop symptoms, and others who do not develop symptoms; this latter group would then be classified as having a pseudodeficiency (which would be a false positive result). Although false positive results of NBS can be reduced through effective diagnostic testing protocols, due to the disease characteristics there will be cases identified with risk for LOGSD II that will have an unknown prognosis. In addition, some variation in phenotypic expression was observed within families having the same genotype, which adds to uncertainty regarding when to initiate ERT treatment – but LSDP-subsidised ERT can be started from 24 months of age in presymptomatic individuals. The DCAR noted there may be psychological impacts from these scenarios such as increased anxiety, or

²⁰ Nexviazyme Product Information: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2021-PI-02382-1>

²¹ ABS. Births, Australia Canberra, Australia: Australian Bureau of Statistics; 2022 [Available from: <https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>.

parental hypervigilance, and other psychosocial implications such as stigma, discrimination, and increased financial burdens.

PICO Set 2 - Family members

Safety issues associated with testing family members are similar to those for PICO Set 1, particularly for asymptomatic family members who may receive a diagnosis of LOGSD II because of testing and the consequent creation of “patients-in-waiting”. Factors to consider include unknown prognoses, and variations in phenotypic expression within families with identical variants. There are a range of psychological impacts of LOGSD II diagnoses for asymptomatic individuals regarding medicalisation of asymptomatic individuals, increased parental vigilance, potential for stigma and discrimination, inequity of access to follow-up and increased financial burdens associated with monitoring. However, patients with LOGSD II have reported deterioration in health status during diagnostic delays. Therefore, the DCAR noted that the psychological impacts of LOGSD II diagnoses require some consideration alongside benefits that include the avoidance of prolonged diagnostic delays, the ability to obtain treatment, ability of individuals to make life decisions informed by diagnoses, and potentially gain greater life satisfaction.

12. Comparative effectiveness

PICO Set 1 – Newborns

Early diagnosis and treatment of GSD II by NBS compared with late diagnosis and treatment following symptom onset

Health outcomes for IOGSD II

Data from studies of direct from test to health outcome evidence in Taiwanese studies showed that early diagnosis of IOGSD II by NBS, followed by early initiation of ERT is associated with improved survival and improved ventilation-free survival (VFS) compared to late diagnosis and ERT. There was a statistically significant benefit observed for overall survival at 50 months of follow-up with 100% (13/13 patients) compared with 50% (5/10 patients) survival. (Kaplan-Meier analyses for patients diagnosed via NBS compared to presentation with clinical signs and symptoms gave $p=0.028^{22}$). In addition, 100% survival up to 3.5 years was observed in the non-comparative studies of other programs of NBS-diagnosed patients with IOGSD II and early commencement of ERT.

VFS was also evaluated in Taiwanese studies; there were statistically significant benefits observed for infants diagnosed by NBS with early initiation of ERT compared to those diagnosed clinically and treated later at 50 months of follow-up. Results from the most recent study identified patients receiving standard doses reached statistical significance⁶. The relative risk (RR) for VFS was 0.05 (95% CI 0.003, 0.716; $p = 0.03$).

Comparisons of early (before 3 months of age) versus late (after 3 months) ERT in IOGSD II patients from symptomatic population supported the direct evidence overall, for survival and VFS, i.e. improved survival associated with early ERT. Other naive comparisons of early versus late treated patients showed similar trends. One case series found patients who were given earlier treatment had worse survival; however, some patients in the early treatment group had severe,

²² Chien YH, et al. Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth. *J Pediatr.* 2015;166(4):985-91.e1-2.

late-stage cardiomyopathy which potentially skewed the results. Results from small case series were largely impacted by the severity of patient symptoms at diagnosis.

Improvements were also observed in motor function for patients diagnosed via NBS and who commenced ERT within the first month of life, or within days of diagnosis. More patients achieved independent walking when diagnosed by NBS and treated early (59%) compared to patients who were diagnosed via symptom presentation and commenced ERT later (17%). In addition, the mean age of walking was younger for those diagnosed by NBS (11.9 ± 1.0 months) than those diagnosed clinically (16.57 ± 1.6 months). Statistical analyses were not performed, but these results were supported in other measures. However, the DCAR noted motor function was observed to decline over time in a recent study of patients with LOGSD II who were diagnosed via NBS; by early adolescence, some patients experienced difficulty with climbing or walking, and a minority of patients were confined to wheelchairs.

Health outcomes for LOGSD II

There was a paucity of studies that reported direct from test to health outcomes evidence of NBS for the diagnosis of LOGSD II. From the limited available evidence, the principal benefits of NBS for the diagnosis of LOGSD II was the diagnosis and earlier initiation of ERT treatment in patients who developed symptom progression, decreased time to diagnosis, and the avoidance of prolonged diagnostic delays. In the non-comparative studies, individuals diagnosed via NBS were undergoing monitoring and some patients had commenced ERT; at last follow-up, the treated patients remained alive at an age range of 3-9 years. Other health benefits for patients with LOGSD II who were treated with ERT upon symptom presentation were improvements in respiratory function and achievement of independent walking. However, some patients experienced delays in psychomotor development, and persistent abdominal and pelvic muscle weakness. In recent studies of patients with LOGSD II, some patients were receiving higher doses of ERT; however, the applicability of these results to the Australian setting is unknown because higher doses of ERT have not been approved under LSDP criteria.

There was also little evidence comparing outcomes based on timing of initiation of ERT in symptomatic LOGSD II populations. The DCAR considered the outcomes reported were likely to be highly influenced by the severity of symptoms at the time of ERT initiation, and there was some risk of publication bias.

Test accuracy

There were no studies identified that compared screening protocols between newborns and symptomatic populations.

Newborns

The newborn screening protocol in the ratified PICO for MSAC application 1774 was GAA enzyme activity testing, followed by a rapid genetic test to rule out any cases with exclusively pseudodeficiency variants (i.e. any cases with at least one P/LP variant, VUS or no variants would still undergo confirmatory testing). No studies (or NBS programs) were identified that used this approach. Some jurisdictions used GAA enzyme activity testing followed by GAA gene sequencing, where any case with at least one P/LP variant or VUS was referred.

Most NBS programs for GSD II use either MS/MS or fluorometric assay for GAA activity as a first-tier (or single-tier) screen. Screening protocols using MS/MS as first-tier screen followed by genetic analysis as a second-tier assay or confirmation, have a lower first-tier screen positive rate range and correspondingly higher positive predictive value (PPV) range compared to other protocols that use MS/MS only. Genetic assays have better specificity compared to other assays, and therefore contribute to a higher PPV. A summary of first-tier positive and retest positive

results with respective PPV for MS/MS followed by a genetic assay prior to recall is given in Table 3. No studies followed up screen negative results, so data on the sensitivity and specificity of NBS for GSD II were unable to be reliably determined.

Table 3 Summary of screen positive results for MS/MS first-tier screening followed by genetic analysis

Results	NBS programs N (n cases)	Range	PPV
First-tier screen positive	7 (856)	0.015% - 0.41%	3.5% - 50%
Retest positive	5 (204)	0.008% - 0.15%	15% - 80%

MS/MS = tandem mass spectrometry; N=number of NBS programs; n = number of patients; NBS = newborn bloodspot screening; PPV = positive predictive value

Protocols that used a MS/MS assay as a first-tier (or single-tier) screen tended to have a lower screen positive rate and higher PPV than those using fluorometry. There were many missing data in the studies, so summary statistics are not reliable.

NBS programs have developed their own methods (e.g. stratified cut-offs for GAA activity; synthetic substrates, and neutral GAA activity ratios) for reducing false positive rates and improving the PPV, and this is an acknowledged challenge for GSD II screening. There is no clear first and/or second-tier methodology that can do this, due to the large number of pseudodeficiency variants and variability in LOGSD II variant expression. There is increasing knowledge on the likely prognosis associated with specific variants, but the large range in disease severity remains unpredictable (i.e. there is variable expressivity) and is likely to be multifactorial.

The DCAR noted, NBS results in this assessment illustrated that screen positive rates improved (reduced) with each tier of screening or retesting added to the protocol. With NBS however, cost and practicality of screening large sample numbers also come into consideration of adding screening tiers and other changes to protocols.

Symptomatic populations

Test-positive and PPV values were higher in populations with signs and symptoms of GSD II, than NBS populations, as expected. The symptomatic populations were much smaller, sometimes highly selected, and considered high-risk for GSD II. The number needed to test to diagnose one GSD II case ranged between 34 and 121 symptomatic patients across all studies.

The highest PPV range was in the group of studies conducted in those with unexplained elevated creatine kinase (CK) and/or undiagnosed limb-girdle weakness in patients older than 1 year of age, based on first-tier screen positive results (PPV range 17.5% - 100%). First-tier MS/MS or fluorometric assay of GAA activity was used in most studies, but two studies used a multigene panel, which may explain the higher PPVs in the group. The higher diagnostic rate in the symptomatic populations could be seen to favour screening high-risk populations over NBS screening. However, this strategy is likely to miss cases, and cause diagnostic delays, particularly for LOGSD II.

Estimation of Australian NBS cases

The results from one study that reported on an NBS program in California²³ was used to predict estimates of GSD II cases identified by Australian NBS, as it had a similar pre-NBS birth prevalence and NBS protocol similar to the one proposed for Australia. The Californian protocol used flow injection analysis (FIA)-MS/MS followed by GAA gene sequencing prior to recall of the baby and family for confirmation. **REDACTED**.²⁴ Following NBS, the prevalence increased in California, as has been the case in other countries and would be expected in Australia (see Table 4).

Table 4 Birth prevalence estimates of GSD II in California and Australia

NBS program	Birth prevalence estimate			
	Prior to NBS		After NBS	
California	2.5 cases / 100,000	1/40,000 newborns	3.97 cases / 100,000	1/25,000 newborns
Australia ^a	2.19 cases / 100,000	1/46,000 newborns	3.48 cases / 100,000	1/29,000 newborns

GSD II = glycogen storage disease Type II; NBS = newborn bloodspot screening

a. Prevalence estimate in Australia after proposed NBS is based on the proportional increase in California following NBS (3.97/2.5).

Based on diagnostic data from the Californian NBS²³, prevalence data for NBS in Australia³, over 99.0% uptake rate and a projected number of live births based on ABS data, it was estimated that there would be approximately one ILOGSD II case and 10 LOGSD II cases diagnosed by NBS per year in Australia. In a scenario where a small genetic GAA screening panel is used as a second-tier screen to rule out pseudodeficiency cases that do not require further assessment (and all other first-tier positive cases go on to clinical assessment and gene sequencing), a similar specificity might be found in Australian NBS to the California NBS data. Alternatively, if a larger panel is used and only those with P/LP variants are referred on for confirmatory testing, some rarer variants may be missed, and there may be fewer GSD II cases diagnosed by NBS in Australia than in the Californian program. There may be a higher number of false negative results because of the lower specificity in this alternative scenario, which would be identified later when symptoms appeared. If, however, only those with at least one common pseudodeficiency variant are excluded after the small panel (i.e. those without any variants are referred for confirmatory testing), then all cases should be identified.

²³ Tang H, et al. The First Year Experience of Newborn Screening for Pompe Disease in California. *Int J Neonatal Screen*. 2020;6(1).

²⁴ **REDACTED**

Change in management due to early compared with late diagnosis of GSD II

Evidence for change in management was poor quality, but consistent in showing a diagnostic delay for both symptomatic IOGSD II and LOGSD II patients.

Early compared with late diagnosis of IOGSD II

For IOGSD II infants who were not diagnosed until after symptom onset, data from the Pompe Registry showed delays from symptom onset to diagnosis of a median of 1.4 (range 0.0 to 13.9) months. This evidence was supported by three smaller studies that found diagnosis was delayed (compared to age at symptom onset) by approximately 1.4 months (median of medians), and occurred at an age of 3 months (median of medians). The DCAR considered this has the potential to delay ERT treatment and impact health outcomes including survival for these infants.

Early compared with late diagnosis of LOGSD II

Across the case series included ($k = 4$), the median of median diagnostic delays (for all LOGSD II cases, regardless of age of onset) was 8 years.

Data from the Pompe Registry provided a median interval from the point of symptom onset to diagnosis of 12.6 (range 0 to 60) years; the median age of symptom onset was 6.2 years, with the median age of diagnosis of 18.5 years. The age range of the children in the Pompe registry was 12 months to 12 years. As this was the largest data set for children with LOGSD II ($n=118$) it was likely to be the most accurate, although the range was very broad. Other small studies ($k = 3$) supported the evidence but found smaller median diagnostic delays between 0.9 (range 0 to 5.8) years to 6.5 (range 0 to 11) years. Some children were diagnosed prior to symptom onset in the study populations (hence the ranges start at zero), either because of a family history of GSD II, or possibly incidental detection in other cases.

Data from a single study indicated that symptomatic children were more often misdiagnosed than affected adults, and it is possible that individuals diagnosed with LOGSD II who become symptomatic as children would benefit more from the implementation of NBS than those who become symptomatic as adults. Those who are symptomatic at a younger age are at risk of delayed motor development, worse pulmonary outcomes, and worse prognosis than those who are symptomatic at a later age. In some cases, ERT may be warranted if they have a known severe genotype.

Data from the Pompe Registry found a median diagnostic delay of 6 (range 0 to 49) years for adults and children aged over 12 years at the point of symptoms onset diagnosed with LOGSD II ($n=426$). Median age at symptom onset was 35 years, and median age at diagnosis was 43 years. Again, the diagnostic delay had a broad range, likely due to non-specific symptoms, occurring within a broad age-range and varying degrees of severity. Other studies ($k = 3$) found median delays ranged from 5 to 21.5 years in adults. Adults received up to four misdiagnoses prior to their final GSD II diagnosis but most LOGSD II adults experience one to two misdiagnoses, and potentially inappropriate treatment for a non-existent condition. This can impact their access to appropriate treatment.

Data from low level evidence from studies that reported whether symptomatic patients were treated or monitored after diagnosis of LOGSD II, 75% patients were given ERT, 33% were given ventilation assistance (invasive or non-invasive), however these rates would vary by the severity of symptoms in the populations. Notably, in the longest single study of monitoring of patients with NBS-diagnosed LOGSD II, 8.22% were treated with ERT, and 82.6% were monitored up to 7 years (the longest study period that reported monitoring).

Summary of the clinical findings for PICO Set 1

The DCAR considered based on the literature review findings, results from the Californian NBS program (Tang et al. 2020) and Australian data (Chin & Fuller 2022), for every 1 million babies tested, approximately 189 patients would test positive on GAA enzyme testing and be referred for diagnostic testing²⁵.

Of those referred for diagnostic testing (n = 189), there would be approximately:

n = 35 true positives -

- 3 newborns would have LOGSD II and receive earlier ERT, and have likely survival, respiratory and motor benefits,
- 32 would have LOGSD II and would be regularly monitored to determine when they should receive ERT (LSDP criteria require they be over age 2 years to become eligible), whether symptomatic or not),
- 12 of those diagnosed with LOGSD II would have a VUS (and therefore a more uncertain prognosis) and would be regularly monitored to receive timely ERT if required, but some may experience harm from knowledge of uncertain future health, or hyperawareness of their health (while others would find a benefit in that knowledge).

n = 154 false positives -

- 39 would have pseudodeficiency of which 19 individuals would be assumed to be ruled out due to finding a variant known to be associated with a pseudodeficiency.
- 66 carriers,
- 50 would have no GSD II variant.

PICO Set 2 - Family members

There were very little data on the uptake of testing in family members of individuals diagnosed with GSD II upon diagnosis by either NBS or presentation with signs and symptoms of GSD II.

As a clinical diagnosis of LOGSD II is made within the first 12 months, the timing of cascade testing following NBS or following a clinical diagnosis would also differ by a year at most. In most cases, the testing of parents would occur early enough to be informative for reproductive planning of subsequent children, regardless of the presence of NBS or no NBS. It is assumed that the uptake of genetic testing after the diagnosis of a child with LOGSD II would be the same, regardless of the method of diagnosis.

No data were available on the proportion of parents or siblings of someone diagnosed through NBS to have LOGSD II, who underwent testing. Family members diagnosed with LOGSD II were only reported if they received treatment with ERT which made it difficult to know what proportion of individuals diagnosed with LOGSD II via NBS gained benefit from diagnosis via NBS. One study (of 18 probands and 42 siblings) reported that only 29% of eligible siblings completed cascade testing following the clinical diagnosis of LOGSD II²⁶ when the proband was an adult. Small case series were identified describing the cascade testing (and subsequent management) of siblings, which identified some additional affected individuals. These siblings either commenced ERT or were regularly monitored for symptoms. The very limited evidence available suggests that

²⁵ Figures are approximate and have been rounded down in cases where the associated fractions are ≤ 0.5 and rounded up where the fractions are > 0.5 .

²⁶ Ausems MG, et al. Phenotypic expression of late-onset glycogen storage disease type II: identification of asymptomatic adults through family studies and review of reported families. *Neuromuscul Disord.* 2000;10(7):467-71.

cascade testing may assist in the earlier diagnosis of siblings, and this had an impact on the clinical management of these siblings. Although ERT is likely to be beneficial (as there is evidence that ERT is superior to no ERT), the advantage of earlier ERT is uncertain.

If a child is diagnosed through NBS, parents would be able to use this information for reproductive planning and elder siblings may benefit from cascade testing. Patients diagnosed on clinical presentation with symptoms of LOGSD II may have both older and younger siblings who would benefit from cascade testing.

What remains unknown, is the extent to which LOGSD II is currently undiagnosed because of substantial heterogeneity of clinical presentation, and the similarity of symptoms to those of other myopathies. As such, the DCAR noted it is possible that some additional parents would be tested if these currently undiagnosed cases are detected through NBS.

Clinical claim

PICO Set 1: Newborns

The use of NBS for IOGSD II resulted in superior effectiveness and noninferior safety compared with no NBS. The statistically significant benefits in survival and ventilation-free survival arise through the facilitation by NBS of earlier treatment with ERT than following a diagnosis after symptomatic presentation.

The use of NBS for LOGSD II resulted in potentially superior effectiveness compared with no NBS (due to avoidance of the diagnostic delay and uncertain but possible benefits of earlier ERT). However, the use of NBS for LOGSD II has potentially inferior safety compared to no NBS (due to the psychological impact of creating patients-in-waiting, and potential harms following earlier commencement of ERT).

PICO Set 2: Family members

Based on logic and a limited evidence base, testing of family members after NBS (when the index cases or probands have IOGSD II) likely results in non-inferior safety and effectiveness compared to testing of family members after clinical diagnosis due to symptom onset.

The DCAR considered testing of family members after NBS (when the index case has LOGSD II) may result in superior effectiveness and non-inferior safety compared to testing after clinical diagnosis due to symptom onset. For parents, the information is more likely to be gained at a time when it may be used for reproductive planning. In addition, cascade testing of siblings may allow siblings to be monitored and receive earlier ERT on presentation with signs and/or symptoms of disease.

13. Economic evaluation

A cost-effectiveness analysis (estimating cost per diagnosis) and cost consequences analysis were presented to evaluate the addition of GSD II to the NBS programs. An exploratory cost-utility analysis translated the possible additional benefits of adding GSD II to NBS into upper and lower range estimates of the survival/QALY gains expected in IOGSD II patients, and also incorporated the costs and disutility associated with unmanaged symptoms during the diagnostic delay in LOGSD II patients.

The clinical evaluation suggested that testing of parents and siblings following NBS is likely to be superior to testing of parents and siblings following symptom onset, however there is no evidence

available to demonstrate this. Therefore, a cost consequence analysis was conducted to estimate the costs per couple informed for GAA carrier status associated with testing of family members per affected newborn.

A summary of the key components of the economic evaluation is presented in Table 5.

Table 5 Summary of the economic evaluation for NBS for GSD II

Component	Description
Perspective	Australian health care system perspective
Population	<u>PICO Set 1</u> : All newborns participating in NBS programs <u>PICO Set 2</u> : Family members of the cases diagnosed with GSD II
Comparator	Current practice <u>PICO Set 1</u> : Diagnostic testing for GSD II at the point of onset of phenotypic signs and symptoms; no universal newborn screening for this disease. <u>PICO Set 2</u> : Testing of family members after the clinical identification of probands
Type(s) of analysis	<u>PICO Set 1</u> : Newborns: Cost-effectiveness analysis (CEA), cost consequences analysis (CCA), exploratory cost-utility analysis (CUA) <u>PICO Set 2</u> : Testing: Cost analysis and/or cost consequences analysis
Outcomes	<u>PICO Set 1</u> : Newborns: <ul style="list-style-type: none"> • Direct effect (primary analysis for CEA): clinically relevant early diagnoses • Associated intermediate health consequences: reduced diagnostic delay, faster access to treatment, improved likelihood of treatment effectiveness, improved survival, reduced recurrence in families • Exploratory CUA: life years gained, QALYs gained <u>PICO Set 2</u> : Testing of family members: <ul style="list-style-type: none"> • Cost of additional testing + qualitative description of health outcomes
Time horizon	50 years
Computational method	<u>PICO Set 1</u> : <ul style="list-style-type: none"> • Decision tree model for base case analysis and cost-consequences • Additional partitioned survival model added to the decision tree for the exploratory analysis <u>PICO Set 2</u> : <ul style="list-style-type: none"> • Cost analysis and/or cost consequence analysis
Generation of the base case	<u>PICO Set 1</u> : Modelled stepped analysis, incorporating aspects of the direct and linked evidence and other key model assumptions sequentially. <u>PICO Set 2</u> : Cost consequence analysis added to the PICO Set 1 model
Health states	None relevant for the base case CEA, CCA and testing of family members Exploratory CUA: IOGSD II: mild symptoms, severe symptoms, and dead
Cycle length	One year in base case analysis and one month in exploratory analysis
Transition probabilities	<u>PICO Set 1</u> : <u>All analyses</u> : <ul style="list-style-type: none"> • Prevalence of GSD II and subtypes: in the absence of NBS based on the Australian study ⁴(Chin and Fuller 2022) and LSDP registry data. Post NBS based on proportional increase in prevalence of GSD II post-NBS in California NBS study²³. • Test performance: Performance of first-tier and second-tier screening was as per table below. <u>Exploratory analysis</u> : extended model estimates ICERs associated with assumptions of minimum and maximum potential effectiveness associated with early access to ERT, translated into survival and health related quality of life gains based on evidence review presented in the DCAR. Estimates were informed by:

Component	Description
	<ul style="list-style-type: none"> Invasive ventilation free survival and overall survival related to early treatment in IOGSD II diagnosed through NBS vs non NBS²⁷ and alternative extrapolations of curves Age specific all-cause mortality in Australian population²⁸
Discount rate	5% per annum for both costs and outcomes (rates of 0% and 3.5% per annum assessed in the sensitivity analysis)
Software	Excel

Parameter	Value	Source
<u>IOGSD II</u>	4 years	Linked evidence of change in management for newborns Section of DCAR
<u>LOGSD II</u> : onset age ≤12years	7 years	
<u>LOGSD II</u> : onset age >12years		
Survival and disease progression associated with late and early ERT in IOGSD II	Multiple inputs – as in model transition probabilities, variables and extrapolation Section of DCAR	Extrapolation of survival and ventilation free survival data from ²⁷ and cost-utility study
Costs		
NBS costs		
First-tier NBS	\$Redacted	Estimated cost of LC-MS/MS GAA enzyme assay using the GelbChem SKU: CS5 kit (estimated using consultation feedback provided by the NBS laboratory experts during the evaluation process). PICO Confirmation
Second-tier NBS	\$500	
Cost of diagnostic confirmation after second-tier test	\$3,158 ^c	Healthcare resource use and costs section of DCAR
Known familial variant analysis	\$400	PICO confirmation
Annual ERT costs alglucosidase alfa and avalglucosidase alfa	<u>IOGSD II</u> Redacted <u>LOGSD II</u> Redacted	Average weighted cost over 52 weeks for individuals diagnosed with IOGSD II. Fixed monthly cost for individuals diagnosed with LOGSD II. Product costing provided by Department of Health and Aged Care
Annual monitoring cost ^a	\$3,034.59	See Table 7 below
Annualised diagnostic delay cost per patient in the absence of diagnosis through NBS ^b	\$12,826.72	See Table 7 below
Cost associated with mild disease health state for IOGSD II (per month)	\$1,135.20	Resource use for medical services, allied health services, imaging and pathology sourced from economic study by Richardson 2021 ³⁰ .
Cost associated with severe disease (ventilation-assisted) health state for IOGSD II (per month)	\$10,755.80	Resource use for medical services, hospitalisations, allied health services, imaging and pathology sourced from economic study by Richardson 2021 ²⁴ .
Cost associated with health state transition (from mild disease to ventilation-assisted health state, once off)	\$98,604	Resource use for medical services, hospitalisations, and medical equipment sourced from economic study by Richardson 2021 ²⁴ .
Health Outcome utility values (exploratory analysis only)		
Utility in well health state	0.829 – 0.910	Mean (SD) utility observed in Australian children aged 11–17 years (Chen 2015) ³¹ and in adults >18years (McCaffrey 2016) ³²
GSD II with mild symptoms	0.799 – 0.853	Age specific (Richardson et al. 2021; Simon et al. 2019)

³⁰ Richardson, JS, et al 2021, 'Health and economic outcomes of newborn screening for infantile-onset Pompe disease', *Genet Med*, vol. 23, no. 4, Apr, pp. 758-766.

³¹ Chen, Get al 2015, 'Assessing the Health-Related Quality of Life of Australian Adolescents: An Empirical Comparison of the Child Health Utility 9D and EQ-5D-Y Instruments', *Value in Health*, vol. 18, no. 4, 2015/06/01/, pp. 432-438

³² McCaffrey, N, et al 2016, 'Health-related quality of life measured using the EQ-5D–5L: South Australian population norms', *Health and Quality of Life Outcomes*, vol. 14, no. 1, 2016/09/20, p. 133.

Parameter	Value	Source
GSD II with severe symptoms	0.399 – 0.536	Age specific (Richardson et al. 2021; Simon et al. 2019)
Disutility during diagnostic delay (pre-diagnosis)	0.030 –0.057	Difference between utility in health states 'well' and 'mild symptoms'.

ERT = enzyme replacement therapy; FPR = false positive rate; GAA = acid alpha-glucosidase; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LC-MS/MS = liquid chromatography- tandem mass spectrometry; LSDP = Life Saving Drugs Program; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; PICO = Population/Intervention/Comparator/Outcomes; SD = standard deviation

^a Additional health-care utilization for patients diagnosed with GSD II but without symptoms, annual estimate: GP visit, outpatient visit; lab work including creatine kinase-MB, comprehensive panel, and urine hex4, cardiac studies, respiratory studies, specialist visits.

^b Additional costs of prolonged evaluation and diagnostic testing (diagnostic delay) for cases identified clinically in the absence of NBS included additional outpatient and emergency room visits and lab tests.

^c Figure is not inclusive of cost of segregation testing of parents.

The costs associated with disease monitoring in asymptomatic probable LOGSD II and costs associated with diagnostic delay in those diagnosed through clinical identification after symptom presentation are provided in Table 7.

Table 7 Estimated resource use and costs associated with annual surveillance and diagnostic delay for GSD II

Description	Cost	Cost per unit	Units	Source
Diagnostic delay				
GP consultation for referral and review	\$165.80	\$82.90	2	Scheduled fee for MBS item 36
Specialist metabolic clinic visit	\$4,397.57	\$2,198.79	2	NHCDC Tier 2 code 20.08
Eye review	\$582.24	\$582.24	1	NHCDC Tier 2 code 20.17
Skeletal survey	\$100.25	\$100.25	1	Scheduled fee for MBS item 58306
ENT/hearing assessment	\$618.65	\$618.65	1	NHCDC Tier 2 code 20.18
Sleep studies	\$799.60	\$799.60	1	Scheduled fee for MBS item 12210
Occupational therapy	\$2,195.41	\$548.85	4	NHCDC Tier 2 code 40.06
Electrocardiogram	\$83.80	\$20.95	4	Scheduled fee for MBS item 11707
Electromyography	\$170.75	\$170.75	1	Scheduled fee for MBS item 11021
Chest X-ray	\$69.00	\$69.00	1	Radiology services catalogue published by Australian Diagnostic Imaging Association
Serum creatine kinase	\$10.00	\$10.00	1	Scheduled fee for MBS 66500
Liver function tests	\$18.00	\$18.00	1	Scheduled fee for MBS 66512
Cardiac echocardiograms	\$258.70	\$258.70	1	Scheduled fee for MBS item 55126
HEX4	\$122.00	\$122.00	1	SA Pathology Catalogue
Leucocyte Lysosomal Enzyme Studies	\$432.00	\$432.00	1	SA Pathology Catalogue
Alpha-Galactosidase Activity DBS 4MU	\$116.00	\$116.00	1	SA Pathology Catalogue
Respiratory studies (including 6 minute walk test)	157.95	\$157.95	1	Scheduled fee for MBS item 11503
GP visits	\$829.00	\$82.90	10	Scheduled fee for MBS item 36
Specialist appointment for referral	\$1,132.80	\$283.20	4	Scheduled fee for MBS item 132
Specialist appointment for delivery of results	\$567.20	\$141.80	4	MBS item 133
<i>Total cost of diagnostic delay</i>	\$12,826.72			
Annual surveillance				
GP consultation for referral and review	\$165.80	\$82.90	2	Scheduled fee for MBS item 36
Specialist metabolic clinic visit	\$2,198.79	\$2,198.79	1	NHCDC Tier 2 code 20.08
HEX4	\$122.00	\$122.00	1	SA Pathology Catalogue
Leucocyte Lysosomal Enzyme Studies	\$432.00	\$432.00	1	SA Pathology Catalogue
Alpha-Galactosidase Activity DBS 4MU	\$116.00	\$116.00	1	SA Pathology Catalogue
<i>Total cost of annual surveillance¹</i>	\$3,034.59			

4MU = 4-methylumbelliferyl-alpha-glucopyranoside substrate; DBS = dried bloodspot; GSD II = glycogen storage disease Type II; HEX4 = Glucose tetrasaccharides; MBS = Medicare Benefits Schedule; NHCDC = National Hospital Cost Data Collection; SA = South Australia

¹ Services costed in annual surveillance based on Richardson et al 2021 and include 2 GP visits, Metabolic clinic visit, lab work including enzyme studies and HEX4

Source: IHACPA 2024, Appendix K – Price weights for non-admitted patients, Table 16. Non-admitted price weights, MBS online Schedule for 2024, SA Pathology Catalogue

The economic evaluation is presented in stepped manner in Table 8 for a cohort of 100,000 newborns. All diagnoses through NBS are assumed to be early diagnoses compared with diagnosis after symptom onset in the no NBS strategy. Step 1 includes the costs associated with screening (NBS) and diagnostic confirmation testing (in both NBS and no NBS strategies) and the cost of diagnostic delay for the duration of diagnostic delay (IO: 4.6 months, LO at age ≤12 years: 4 years, and LO >12 years: 7 years) in the absence of NBS. The average cost per diagnoses of GSD II was REDACTED/3.48 diagnoses) with NBS and REDACTED/2.19 diagnoses) in the absence of NBS. The ICER was \$REDACTED per additional diagnoses of GSD II cases.

Step 2 adds costs associated with monitoring in LOGSD II cases until symptom onset (LO at age ≤12 years : 2 years, and LO at age >12 years: 38 years) and additional use of ERT in symptomatic cases diagnosed earlier for the duration of diagnostic delay (IO: 4.7 months, LO at age ≤12 years: 4 years, and LO at age >12 years: 7 years) in the NBS strategy. The ICER was \$REDACTED per additional diagnoses of GSD II cases.

Table 8 Results for base case economic evaluation using Redacted kit (per cohort of 100,000 newborns)

Stepped analysis	Universal NBS	No universal NBS	Increment
Step 1: Diagnostic costs only (includes NBS and confirmatory tests in the NBS arm and diagnostic delay and confirmation tests in the no NBS arm).			
Total cost	\$Redacted	\$Redacted	\$Redacted
Number of diagnoses	3.4796	2.1900	1.2896
ICER (\$/additional diagnosis)			\$Redacted
Step 2: Step 1 + immediate change in management costs: <i>costs associated with annual surveillance and earlier access to ERT (due to earlier diagnosis) in cases diagnosed through the NBS</i>			
Total cost	\$Redacted	\$Redacted	\$Redacted
Number of diagnoses	3.4796	2.1900	1.2896
ICER (\$/additional diagnosis)			\$Redacted
Multiplexed first-tier screening for MPS I, MPS II and GSD II^a			
Total cost	\$Redacted	\$Redacted	\$Redacted
Number of diagnoses	3.4796	2.1900	1.2896
ICER (\$/additional diagnosis)			\$Redacted

ERT = enzyme replacement therapy; ICER = incremental cost-effectiveness ratio; glycogen storage disease Type II; MPS I = mucopolysaccharidosis Type I; MPS II = mucopolysaccharidosis Type II; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening

^a From October 2024 Redacted kit is available for multiplexing MS/MS enzymatic assays for MPS I, MPS II and Pompe disorders which are currently under MSAC consideration for NBS panel extension. If these tests were multiplexed, the screening cost per sample attributed to MPS I detection will be one-third as the running cost (all the operational costs, equipment costs and kit costs) would remain same but will perform detection of three disorders at the same time.

The base case result indicated that NBS for GSD II costs an additional \$REDACTED and would result in an additional (\$/earlier) diagnosis for 0.0000219 GSD II cases per newborn screened; in a cohort of 100,000 newborns, the cost would be \$REDACTED and identify on average 1.29 additional cases. As expected with all rare disease screening applications both within Australia and internationally, the ICERs were substantial (\$REDACTED per additional diagnosis of GSD II case) reflecting the very low rate of diagnosis per individual screened. The ICER was predominantly driven by the cost per screening and cost associated with additional use of ERT. Although the costs and time durations associated with the diagnostic delay were uncertain, these were likely to have very low impact on the ICERs.

The ICER reduced to \$REDACTED per additional diagnosis of GSD II case when the first-tier screening assays were multiplexed in a two-tier screening strategy ('sharing' the cost of screening between three disorders MPS I, MPS II and GSD II).

Model validation

Data for observed age-specific and long-term survival in the proposed population were not available. Figure 1 and Figure 2 show the modelled and observed VFSi and OS curves for IOGSD II, both when diagnosed through NBS (early diagnosis and early treatment) or diagnosed through clinical identification. The modelled VFSi and overall survival are reasonably consistent with the limited data in the literature for the no-NBS arm and shows the two extremes, upper and lower bounds, for NBS arm.

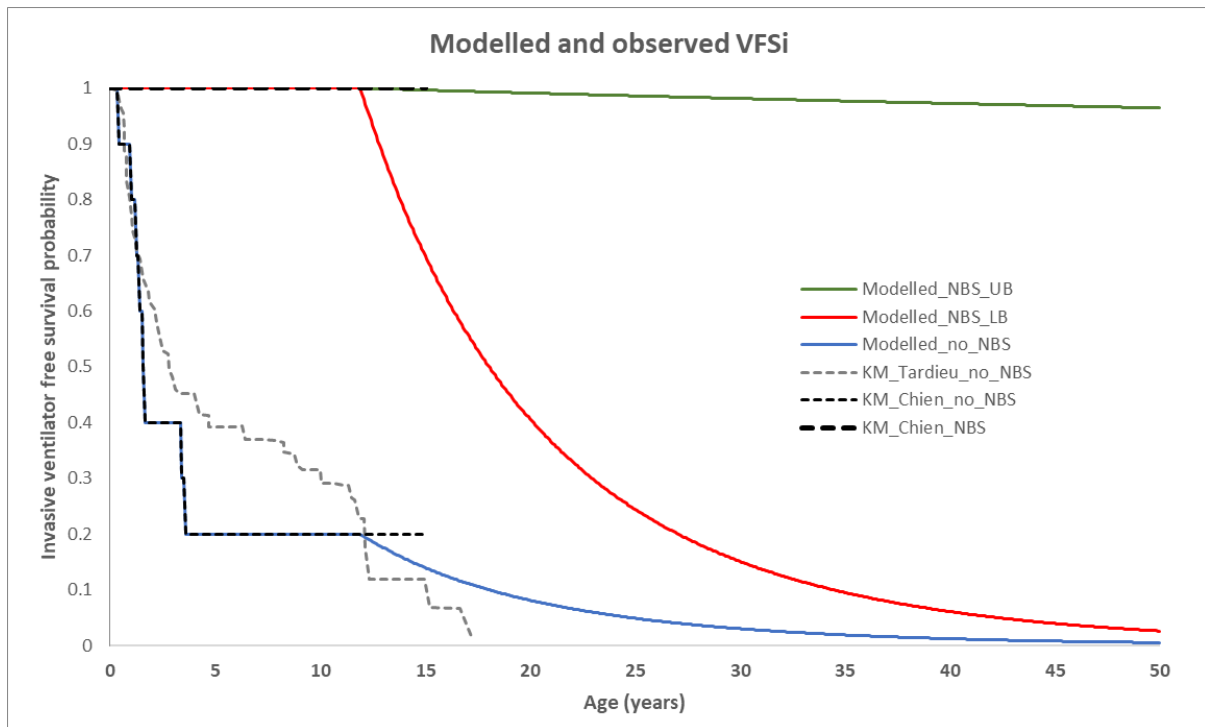


Figure 1 Modelled and observed invasive ventilator free survival (VFSi) curves for infantile onset GSD II
 GSD II = glycogen storage disease type II; KM = Kaplan-Meier; LB = lower bound; NBS = newborn bloodspot screening; UB = upper bound

Source: Kaplan-Meier survival curves digitised from published studies (Tardieu et al. 2023) and (Chien, Y-H, Hwu & Lee 2019)

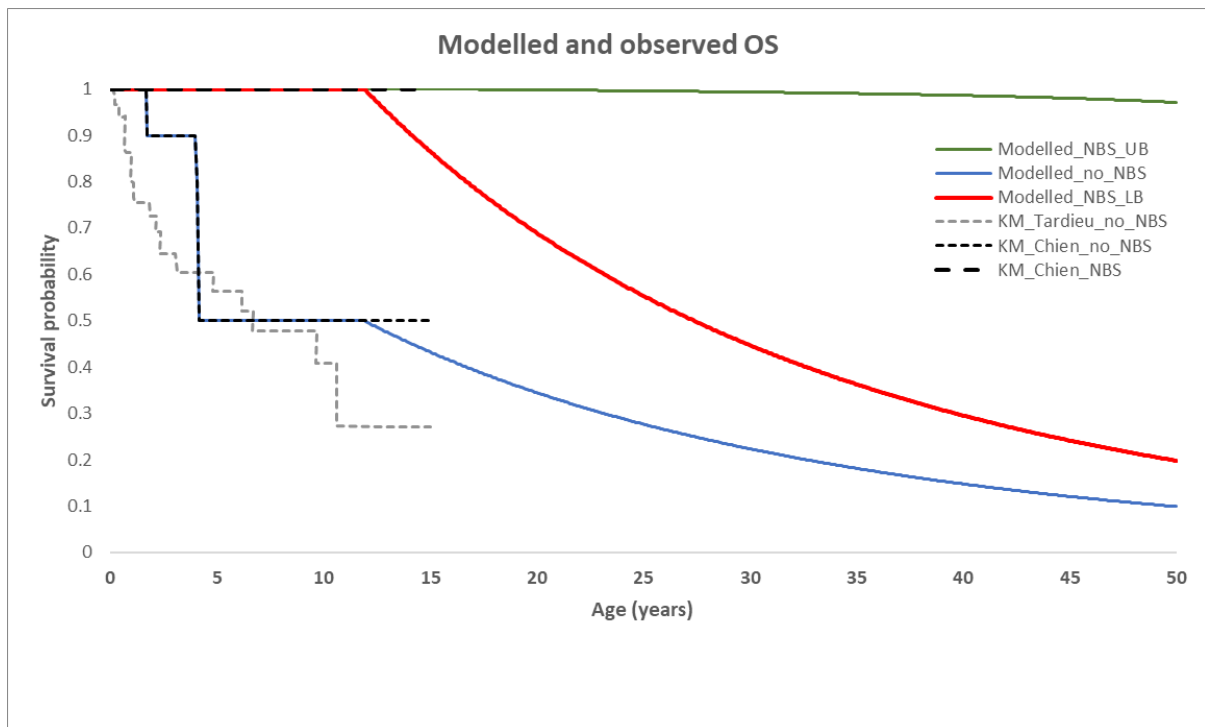


Figure 2 Modelled and observed overall survival (OS) curves for infantile onset GSD II

GSD II = glycogen storage disorder type II; KM = Kaplan-Meier; LB = lower bound; NBS = newborn bloodspot screening; UB = upper bound

Source: Kaplan-Meier survival curves digitised from published studies (Tardieu et al. 2023) and (Chien, Y-H, Hwu & Lee 2019)

Exploratory scenario analysis

Table 9 presents the modelled results for exploratory scenario analyses (per cohort of 100,000 newborns) in a stepped manner; with Steps 3-5 replicated for each of the assumptions regarding the upper and lower bounds of ERT benefit (in terms of IOGSD VFSi and OS in the NBS cohort) based on the 23 patients in the Taiwanese study (see Figure 1 and Figure 2). Integrating the survival and quality of life benefits for early access to ERT in IOGSD II and avoiding the diagnostic delay and early access to ERT in LOGSD II results in the ICERs in the range **\$REDACTED** to **\$REDACTED** per QALY gained. Although the overall survival and VFSi is improved in IOGSD II cases in NBS arm due to early access to ERT, it would mean longer duration of treatment with ERT and higher treatment and disease management costs compared with no NBS strategy.

The ICER reduced to likely within the range of **\$REDACTED** to **\$REDACTED** per QALY gained when the first-tier screening assays were multiplexed in a two-tier screening strategy ('sharing' the cost of screening between three disorders MPS I, MPS II and GSD II (Step 5 in Table 9).

The results for this analysis should be interpreted with caution due to the uncertainty associated with limited or uncertain comparative data for the survival and quality of life benefits.

Table 9 Results of exploratory economic evaluation using “upper” and lower” bounds for IO survival estimates for NBS strategy two-tier screening protocol (per cohort of 100,000 newborns)

	Universal NBS	No universal NBS	Increment
Assuming LOWER BOUND of effectiveness of early access to ERT following NBS			
Step 3: Extended base case analysis to integrate VFSi and OS long-term survival rates for early vs late ERT in IOGSD II (ERT, disease management costed accordingly), and general population survival for all other groups, modelled over a 50 year time horizon.			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
LYs (discounted)	1,904,189.51	1,904,187.56	1.9422
ICER (\$/LY gained)			\$Redacted
Step 4: Utility values applied to different health states			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
QALYs (discounted)	1,633,752.41	1,633,750.30	2.1131
ICER (\$/QALY gained)			\$Redacted
Step 5: Multiplexed first-tier screening for MPS I, MPS II and GSD II) ^a			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
QALYs (discounted)	1,633,752.41	1,633,750.30	2.1131
ICER (\$/QALY gained)			\$Redacted
Assuming UPPER BOUND of effectiveness of early access to ERT following NBS			
Step 3: Extended base case analysis to integrate, long-term VFSi and OS survival rates for early vs late ERT in IOGSD II (ERT and disease management costed accordingly), and general population survival for all other groups, modelled over a 50 year time horizon			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
LYs (discounted)	1,904,190.79	1,904,187.56	3.2253
ICER (\$/LY gained)			\$Redacted
Step 4: Utility values applied to different health states in life years			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
QALYs (discounted)	1,633,753.74	1,633,750.30	3.4370
ICER (\$/QALY gained)			\$Redacted
Step 5: Multiplexed first-tier screening for MPS I, MPS II and GSD II) ^a			
Total costs (average, per 100,000 persons) (discounted)	\$Redacted	\$Redacted	\$Redacted
QALYs (discounted)	1,633,753.74	1,633,750.30	3.4370
ICER (\$/QALY gained)			\$Redacted

ERT = enzyme replacement therapy; GSD II = glycogen storage disorder Type II; ICER = incremental cost-effectiveness ratio; IO = infantile onset; LO = late onset; LY = life years; MPS I = mucopolysaccharidosis Type I; MPS II = mucopolysaccharidosis Type II; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening; QALY = quality adjusted life years

^a From October 2024 Redacted kit is available for multiplexing MS/MS enzymatic assays for MPS I, MPS II and Pompe disorders which are currently under MSAC consideration for NBS panel extension. If these tests were multiplexed, the screening cost per sample attributed to MPS I detection will be one-third as the running cost (all the operational costs, equipment costs and kit costs) would remain same but will perform detection of three disorders at the same time.

Segregation and cascade testing in family members of the index cases (PICO set 2)

Most diagnosed cases of GSD II would be associated with familial screening (biological parents and siblings of an affected individual). The testing strategy is the same irrespective of the

diagnostic pathway, differing only in the timing of the testing. Uptake rate of cascade testing for LOGSD II diagnosed after symptom onset at older age, is lower compared to the uptake in family members of cases diagnosed through NBS. Table 10 provides a cost analysis for the cascade tests associated with a cohort of 100,000 newborns. Overall, for an incremental increase in expenditure of \$REDACTED (of which \$7,831 is for additional cascade testing); an additional 2.23 couples (4.46 individuals) are informed for reproductive planning in addition to the 1.29 incremental diagnoses of index cases due to the NBS.

Table 10 Results for the segregation and cascade tests associated with a cohort of 100,000 newborns

	Universal NBS	No universal NBS	Increment
Number of segregation tests (couples)	3.48	1.25	2.23
Cost associated with segregation tests	\$4,377	\$640	\$3,737
Number of cascade tests (siblings)	3.48	3.48	0.00
Cost associated with cascade tests	\$4,795	\$701	\$4,094
Total number of family members tested	10.44	5.98	4.46
Total costs of sibling testing (PICO set 2)	\$9,172	\$1,341	\$7,831
Total costs (average, per 100,000 persons) (PICO set 1)	\$Redacted	\$Redacted	\$Redacted
Total costs per 100,000 persons and tests in family members of proband	\$Redacted	\$Redacted	\$Redacted

PICO = Population/Intervention/Comparator/Outcomes; NBS = newborn bloodspot screening

Sensitivity analysis

Table 11 presents the sensitivity analysis around key parameters in the base case model. The results were sensitive to the cost of first-tier screening, discounting rate applied to costs and outcomes and prevalence of GSD II.

Table11 Sensitivity analysis for base case model (using two-tier screening protocol) for a cohort of 100,000 persons

	Increment in cost	Increment in number of diagnosis	ICER/additional diagnosis	Percent change in ICER
Base case analysis	\$Redacted	1.2896	\$Redacted	–
<i>Cost of 1st tier screening (base case: \$Redacted for GelbChem kit)</i>				
Revvity NeoLSD™ MS/MS kit: Redacted	\$Redacted	1.2896	\$Redacted	30%
Revvity kit multiplexed for MPS I and GSD II: Redacted	\$Redacted	1.2896	\$Redacted	–10%
Redacted kit multiplexed: Redacted ^a	\$Redacted	1.2896	\$Redacted	–34%
<i>Discounting rate for costs (base case: 5% per annum)</i>				
0%	\$Redacted	1.2896	\$Redacted	219%
3.5%	\$Redacted	1.2896	\$Redacted	28%
<i>Prevalence of GSD II per 100,000 (base case: no NBS: 2.19 and NBS: 3.48)</i>				
Low (no NBS: 2.00, NBS: 2.19)	\$Redacted	0.1900	\$Redacted	451%
High (no NBS: 2.19, NBS: 5.56)	\$Redacted	3.3700	\$Redacted	–50%

GSD II = glycogen storage disease type II; ICER = incremental cost-effectiveness ratio; MPS I = mucopolysaccharidosis Type I; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening

^a From October 2024 Redacted kit is available to multiplex MS/MS enzymatic assays for MPS I, MPS II and GSD II which are currently under MSAC consideration for NBS panel extension. If these tests are multiplexed, the screening cost per sample attributed to MPS I detection will be one-third as the running cost (all the operational costs, equipment costs and kit costs) would remain same but will perform detection of three disorders at the same time.

Sensitivity analysis: extended model

Table 12 presents the summary results for sensitivity analysis of exploratory economic evaluation using “upper” and lower” bounds for infantile onset survival (VFSi and OS) estimates for NBS strategy (per cohort of 100,000 newborns) depicting the impact on ICER per QALY gained of varying parameter values for key uncertain parameters. The key drivers in the exploratory analysis were cost of first tier screening, prevalence of GSD II, cost of ERT and discounting rate applied to future costs and outcomes.

Table 12 Sensitivity analysis of exploratory economic evaluation using “upper” and lower” bounds for IO survival estimates for NBS strategy (per cohort of 100,000 newborns)

	Using upper bound for IO survival effectiveness		Using lower bound for IO survival	
	ICER/QALY	Percent change	ICER/QALY	Percent change
Base case analysis	\$Redacted	–	\$Redacted	–
<i>Cost of 1st tier screening (base case: \$Redacted for GelbChem kit)</i>				
Revvity NeoLSD™ MS/MS kit: \$Redacted	\$Redacted	15%	\$Redacted	18%
Revvity kit multiplexed for MPS I and GSD II: \$Redacted	\$Redacted	–5%	\$Redacted	–6%
Redacted kit multiplexed: \$Redacted ^a	\$Redacted	–17%	\$Redacted	–21%
<i>Annual surveillance cost (base case: \$3,035)</i>				
Doubled (\$6,069)	\$Redacted	7%	\$Redacted	8%
<i>Annual cost associated with diagnostic delay (base case: \$12,827)</i>				
Halved (\$6,413)	\$Redacted	1%	\$Redacted	1%
Doubled (\$25,653)	\$Redacted	–1%	\$Redacted	–1%
<i>Cost of ERT (weight based for IOGSD II and fixed monthly cost for LOGSD II)</i>				
Halved (multiply cost per vial for IO and ERT cost per month for LO by 0.5)	\$Redacted	–35%	\$Redacted	–31%
<i>Discounting rate for costs and outcomes (base case: 5% per annum)</i>				
0%	\$Redacted	8%	\$Redacted	34%
3.5%	\$Redacted	0%	\$Redacted	5%
<i>Prevalence of GSD II per 100,000 (base case: no NBS: 2.19 and NBS: 3.48)</i>				
Low (no NBS: 2.00, NBS: 2.19)	\$Redacted	–14%	\$Redacted	–17%
High (no NBS: 2.19, NBS: 5.56)	\$Redacted	31%	\$Redacted	35%
<i>Annual cost associated with extensive surveillance disease management for LOGSD II (base case: excluded)^b</i>				
Extensive follow-up every 3 months (annual: \$21,699)	\$Redacted	3%	\$Redacted	4%
Extensive follow-up every 6 months (annual: \$10,850)	\$Redacted	1%	\$Redacted	2%

GSD II = glycogen storage disease type II; ICER = incremental cost-effectiveness ratio; IOGSD II = infantile onset GSD II; LOGSD II = late onset GSD II; MPS I = mucopolysaccharidosis Type I; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening

^a From October 2024 Redacted is available to multiplex MS/MS enzymatic assays for MPS I, MPS II and GSD II which are currently under MSAC consideration for NBS panel extension. If these tests are multiplexed, the screening cost per sample attributed to MPS I detection will be one-third as the running cost (all the operational costs, equipment costs and kit costs) would remain same but will perform detection of three disorders at the same time.

^b Analyses added from Rejoinder

Conclusions

NBS was associated with a net incremental cost per affected GSD II case diagnosed compared with clinical identification in the absence of NBS. Some cost was offset due to reduced diagnostic delay but this was relatively small in comparison to the increased screening costs. The DCAR considered the ICERs (\$/confirmed GSD II diagnosis) were high primarily due to the rarity of the disease.

The limited evidence indicated possible survival and quality of life benefits associated with early access to ERT in cases with IOGSD II. When the improved survival and quality of life associated with early access to treatment were integrated in the model, the ICER (\$/QALY) was also relatively high due to the rarity of the disease and also the relatively limited change in clinical management associated with early diagnosis in LOGSD II. The DCAR considered earlier diagnosis through NBS would avoid the diagnostic delay and increase timely treatment in many cases with LOGSD II, however clinical benefits could not be quantified beyond reducing the costs and disutility associated with unmanaged symptoms during the diagnostic delay in LOGSD II cases.

The DCAR considered the potential impact of testing of parents and other adult family members after NBS is that it allows more information to inform reproductive planning, which may reduce the occurrence of GSD II in future siblings or cousins.

14. Financial/budgetary impacts

An epidemiological approach was used to estimate the resource utilisation and financial implications of incorporating GSD II screening into existing NBS programs.

As per the consultation feedback, all NBS laboratories will need some building expansion to accommodate for new equipment, validation and verification of the new screening protocol and hiring of additional workforce to expand the NBS programs to include GSD II. Costs associated with program implementation included laboratory expansion and validation of the new screening protocol. These were considered as once-off set-up costs to NBS programs at the beginning. Direct funding is being provided by the Commonwealth to states and territories to support expansion of NBS programs and consistency in screening across Australia. States and territories can determine how to allocate this funding within their jurisdiction to best support implementation in line with the terms of the Federation Funding Agreement (FFA) schedule.

Table 13 presented the program implementation costs for introducing GSD II to the NBS programs.

Table 13 Program implementation costs for introducing GSD II to the NBS programs

	WA	QLD + half of NT	NSW	SA + Tasmania + half of NT	Victoria
Laboratory capacity and capability (not necessarily assay specific)					
Space expansion ^a	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Costs associated with specific assay verification and validation					
Validation costs (reagents and staff) ^b	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total implementation cost per site	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total implementation cost to NBS					\$Redacted

GSD II = Glycogen storage disease Type II I; NBS = newborn bloodspot screening; NSW = New South Wales; WA = Western Australia

Source: Assumptions based on expert advice provided by NBS laboratories.

^a Estimates for laboratory expansion were only provided by the WA and QLD NBS laboratory experts. For other NBS programs costs were these were assumed to be similar to WA and QLD based on the volume of tests run.

^b As per NBS laboratory expert advice validation costs for reagent/kit is generally one-third of the annual cost of reagents for each lab. These were estimated using use and cost of GelbChem SKU CS5 kit (**Redacted** per kit for 100 assays) and projected live births for each state/territory ending June 2026 based on ABS population projections and registered births data. Staff costs associated with validation process were only provided by QLD NBS laboratory. Based on this information it was assumed that at least two months of staff-time would be required for a validation process

Cost to NBS programs

The financial implications to the NBS programs resulting from the proposed inclusion of GSD II on the NBS panel were summarised in Table 14. The total cost to NBS programs for the addition of GSD II was **\$Redacted** in the first financial year including one-off implementation set-up costs. The total cost to NBS programs for years 2–6 was approximately **\$Redacted** annually.

Table 14 Financial impact to the Newborn Bloodspot Screening Program of adding GSD II

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Program implementation set-up costs for GSD II	\$Redacted	–	–	–	–	–
Number of live births ^a	306,803	306,959	307,115	307,271	307,427	307,583
Number of babies who uptake NBS (99.3%)	304,655	304,810	304,965	305,120	305,275	305,430
Total number of first-tier tests (including 2% re-assays)	310,748	310,907	311,065	311,223	311,381	311,539
Cost of first-tier screening (\$Redacted per sample screened) (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Total number of first-tier screen positives for GSD II	58	58	58	58	58	58
Cost of second-tier screening (\$500 per test)	\$28,850	\$28,850	\$28,850	\$28,850	\$28,900	\$28,900
Total cost to the NBS program (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted

GSD II = Type I; NBS = newborn bloodspot screening

^a Based on projected number of births in Australia based on number of registered births data in 2008–2022 in Australia.

Cost implications for other health budgets

Medical services included in monitoring and treatment of newborns with GSD II detected through NBS programs may also use other Commonwealth funding sources such as the Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS), LSDP and other state/territory health budgets.

The estimated cost of monitoring, diagnostic delay and confirmatory testing were disaggregated based on the potential funding providers. Total costs for services that are listed on MBS were aggregated and MBS rebates were estimated. MBS rebates 85% of the scheduled fee for Medicare services which have an MBS fee of \$683 or less, for those with fee equal or higher than \$683 attracts the rebate of difference of MBS fee and greatest permissible gap (GPG) set at \$102.40 from 1 November 2024. Cost of services that were not listed on MBS and were provided by state pathology or as outpatient or inpatient hospital services were attributed to state and territories health budgets. This included services such as HEX4 test, enzyme studies, GAA activity test, visit to metabolic clinics, genetic testing in probands and family members.

Table 15 and Table 16 present the estimated net cost implications to the state and territories health budgets and net cost to MBS due to the introduction of GSD II on the NBS panel.

Table 15 Cost implications to state and territory (S/T) health budgets due to NBS of GSD II ^a

	2025-26	2026-27	2027-28	2028-29	2029-30	2030-31
Universal NBS						
Number of GSD II cases diagnosed	10.60	10.60	10.60	10.60	10.60	10.60
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	9.60	9.60	9.60	9.60	9.60	9.60
Cost of confirmatory diagnostic test	\$9,423	\$9,423	\$9,423	\$9,423	\$9,423	\$9,423
Cost of treatment monitoring (uptake in LOGSD II - 82.6%)	\$22,752	\$45,504	\$66,823	\$88,142	\$109,461	\$130,779
Segregation tests in parents (one couple per affected case)	\$8,480	\$8,480	\$8,480	\$8,480	\$8,480	\$8,480
Cascade tests in siblings (one sibling per affected case)	\$9,423	\$9,423	\$9,423	\$9,423	\$9,423	\$9,423
Total cost to S/T health budgets due to NBS	\$50,079	\$72,831	\$94,150	\$115,469	\$136,787	\$158,106
Current practice						
Number of GSD II affected cases diagnosed	6.67	6.68	6.68	6.68	6.69	6.69
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	5.67	5.67	5.68	5.68	5.68	5.69
Cumulative number of LOGSD II cases symptomatic at age 2 years	0.00	0.00	0.37	0.74	1.12	1.49
Cost of confirmatory diagnostic test (only IO diagnosed)	\$890	\$890	\$891	\$891	\$892	\$892
Cost of diagnostic delay	\$4,944	\$4,947	\$6,787	\$8,627	\$10,469	\$12,312
Segregation tests in parents (one couple per affected case)	\$801	\$801	\$801	\$802	\$802	\$803
Cascade tests in siblings (one sibling per affected case)	\$890	\$890	\$891	\$891	\$892	\$892
Total cost offset to S/T health budgets	\$7,524	\$7,528	\$9,369	\$11,211	\$13,054	\$14,898
Net costs to S/T health budgets	\$42,555	\$65,303	\$84,781	\$104,257	\$123,733	\$143,208

GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; NBS = newborn bloodspot screening

^a Cost of services that were not listed on MBS and were provided by state pathology or as outpatient or inpatient hospital services were attributed to state and territories health budgets. This included services such as HEX4 test, enzyme studies, GAA activity test, visit to metabolic clinics, genetic testing in probands and family members and other allied health services not provisioned for Medicare benefits.

Table 16 Cost implications to MBS due to NBS of GSD II

	2025-26	2026-27	2027-28	2028-29	2029-30	2030-31
Universal NBS						
Number of GSD II cases diagnosed	10.60	10.60	10.60	10.60	10.60	10.60
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	9.60	9.60	9.60	9.60	9.60	9.60
Cumulative number of LOGSD II cases symptomatic at age 2 years	0.00	0.00	0.63	1.26	1.89	2.52
Cost of administration associated with excess ERT infusion, IOGSD II first year	\$3,410	\$3,410	\$3,410	\$3,410	\$3,410	\$3,410
Cost of administration associated with excess ERT infusion, LOGSD II	\$0	\$0	\$5,532	\$11,064	\$16,597	\$22,129
Cost of confirmatory diagnostic test	\$21,269	\$21,269	\$21,269	\$21,269	\$21,269	\$21,269
Cost of annual monitoring (uptake in LOGSD II - 82.6%)	\$1,118	\$1,118	\$1,118	\$1,118	\$1,118	\$1,118
Segregation tests in parents (one couple per affected case)	\$4,127	\$4,127	\$4,127	\$4,127	\$4,127	\$4,127
Cascade tests in siblings (one siblings per affected case)	\$4,406	\$4,406	\$4,406	\$4,406	\$4,406	\$4,406
Total cost to MBS due to NBS	\$34,330	\$34,330	\$39,862	\$45,395	\$50,927	\$56,459
Current practice						
Number of GSD II affected cases diagnosed	6.67	6.68	6.68	6.68	6.69	6.69
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	5.67	5.67	5.68	5.68	5.68	5.69
Cumulative number of LOGSD II cases symptomatic at age 2 years	0.00	0.00	0.37	0.74	1.12	1.49
Cost of confirmatory diagnostic test (only IO diagnosed)	\$2,008	\$2,009	\$2,010	\$2,011	\$2,012	\$2,013
Cost of diagnostic delay	\$3,537	\$3,538	\$4,854	\$6,171	\$7,488	\$8,806
Segregation tests in parents (one couple per affected case)	\$390	\$390	\$390	\$390	\$390	\$391
Cascade tests in siblings (one siblings per affected case)	\$416	\$416	\$416	\$417	\$417	\$417
Total cost offset to MBS	\$6,350	\$6,353	\$7,671	\$8,989	\$10,307	\$11,627
Net costs to MBS	\$27,980	\$27,977	\$32,192	\$36,406	\$40,619	\$44,832

GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; MBS = Medicare Benefits Schedule; NBS = newborn bloodspot screening

Earlier diagnosis of GSD II cases through NBS may result in earlier access to ERT. For IOGSD II it is expected there will be additional 4.6 months of treatment in the first year of birth. Although ERT costs may be higher in later years due to improved survival with early access to ERT, these are not accounted for in the financial model. For LOGSD II, around REDACTED% of the cases present with symptoms by age 12 years and will be eligible for ERT. These cases are assumed to start ERT (additional years of ERT treatment in NBS compared to diagnosis on symptom presentation). Table 17 presents the estimated cost implications to LSDP budgets due to NBS for GSD II.

Table 17 Cost implications to LSDP budgets due to NBS for GSD II

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Universal NBS						
Number of GSD II affected cases diagnosed	10.60	10.60	10.60	10.60	10.60	10.60
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	9.60	9.60	9.60	9.60	9.60	9.60
Cumulative number of LOGSD II cases symptomatic at age 2 years	0.00	0.00	0.63	1.26	1.89	2.52
ERT costs, IOGSD II first year only (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
ERT costs, LOGSD II (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Total costs to LSDP due to NBS (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Current practice (offsets)						
Number of GSD II affected cases diagnosed	6.67	6.68	6.68	6.68	6.69	6.69
Number of affected cases with IOGSD II	1.00	1.00	1.00	1.00	1.00	1.00
Number of affected cases with LOGSD II	5.67	5.67	5.68	5.68	5.68	5.69
Cumulative number of LOGSD II cases symptomatic at age 2 years	0.00	0.00	0.37	0.74	1.12	1.49
ERT costs, IOGSD II first year only (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
ERT costs, LOGSD II (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Total costs to LSDP (current practice) (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Net costs to LSDP due to NBS (\$)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted

ERT = enzyme replacement therapy; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; LSDP = Life Saving Drugs Program; NBS = newborn bloodspot screening

The financial impact was driven by the cost per screening. Number of births, prevalence of GSD II and the false positive rate for the first-tier screening had very low impact on the financial implications to NBS programs. Table 18 presents the key sensitivity analysis.

Table 18 Sensitivity analysis

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Base case	\$ Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Cost of 1st tier screening (base case: \$Redacted for GelbChem kit)</i>						
Redacted kit multiplexed^a: \$ Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Revvity NeoLSD™ MS/MS kit: \$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Revvity kit multiplexed ^b : \$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

GSD II = glycogen storage disease Type II; MPS I = mucopolysaccharidosis Type I; MPS II = mucopolysaccharidosis Type II; MS/MS = tandem mass spectrometry; NBS = newborn bloodspot screening

^a **Redacted** kit multiplexed for MPS I, MPS II and GSD II (i.e. cost per screen is one third the cost per screen in base case).

^b Revvity kit multiplexed for MPS I and GSD II (i.e., cost per screen is halved)

Three additional scenario analyses from the Rejoinder for the potential impact on ERT expenditure associated with NBS screening for GSD II, under alternative scenarios are presented in Table 19 to Table 23 . ESC considered that Scenario 1 analysis informs MSAC by matching similar requests made previously by MSAC to assess the consequence of both changing the NBS and changing the LSDP Guidelines to allow an increase in the ERT dose for IOGSD II patients.

Table 19 Implication to LSDP budget associated with NBS for GSD II using high dose ERT (Scenario 1)

	2025-26	2026-27	2027-28	2028-29	2029-30	2030-31
<u>Universal NBS</u>						
<i>Number of GSD II affected cases diagnosed</i>	10.60	10.60	10.60	10.60	10.60	10.60
<i># with IOGSD II</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i># with LOGSD II</i>	9.60	9.60	9.60	9.60	9.60	9.60
<i>Cumulative number of LOGSD II cases symptomatic at age 2 years</i>	0.00	0.00	0.63	1.26	1.89	2.52
<i>ERT costs, IOGSD II and treated with high dose</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP with NBS and high dose ERT</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<u>Current practice (offsets)</u>						
<i>Number of GSD II affected cases diagnosed</i>	6.67	6.68	6.68	6.68	6.69	6.69
<i># with IOGSD II</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i># with LOGSD II</i>	5.67	5.67	5.68	5.68	5.68	5.69
<i>Cumulative number of LOGSD II cases symptomatic at age 2 years</i>	0.00	0.00	0.37	0.74	1.12	1.49
<i>ERT costs, IOGSD II and listed doses (see Table 22)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP (current practice)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Net costs to LSDP due to NBS</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; LSDP = Life Saving Drugs Program; NBS = newborn bloodspot screening

Source: Rejoinder from assessment group

Table 20 Total ERT costs for IOGSD II cases, diagnosed through NBS and assuming high dose ERT (Scenario 1)

	Average cost of high dose ERT (weight based dosing)						
		2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Age 0–1 (Tx for 0.93 year)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 1–2	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 2–3	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 3–4	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 4–5	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 5–6	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

Source: Rejoinder from assessment group

Table 21 Total ERT costs for IOGSD II cases diagnosed clinically & treated with listed doses (current practice) (Scenario 1)

	Average cost of ERT listed dose of 20mg/kg (weight based dosing)						
		2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Age 0–1(Tx for 0.54 year)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 1–2	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 2–3	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 3–4	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 4–5	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Age 5–6	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Total	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

Source: Rejoinder from assessment group

Table 22 Cost implications to LSDP budgets due to NBS for GSD II and LOGSD II treated from birth (Scenario 2)

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
<u>Universal NBS</u>						
<i>Number of GSD II affected cases diagnosed</i>	10.60	10.60	10.60	10.60	10.60	10.60
<i>Number of affected cases with IOGSD II</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i>Number of affected cases with LOGSD II</i>	9.60	9.60	9.60	9.60	9.60	9.60
<i>Cumulative number of LOGSD II cases treated from birth</i>	9.60	19.20	28.80	38.40	48.00	57.60
<i>ERT costs, IOGSD II (first year of birth only)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP due to NBS</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<u>Current practice (offsets)</u>						
<i>Number of GSD II affected cases diagnosed</i>	6.67	6.68	6.68	6.68	6.69	6.69
<i>Number of affected cases with IOGSD II</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i>Number of affected cases with LOGSD II</i>	5.67	5.67	5.68	5.68	5.68	5.69
<i>Cumulative number of LOGSD II cases symptomatic at age 2 years</i>	0.00	0.00	0.37	0.74	1.12	1.49
<i>ERT costs, IOGSD II (first year of birth only)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP (current practice)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<u>Net costs to LSDP due to NBS</u>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; LSDP = Life Saving Drugs Program; NBS = newborn bloodspot screening

Source: Rejoinder from assessment group

Shaded cells represent those with changed values from the DCAR base case.

Table 23 Cost implications to LSDP budgets due to NBS for GSD II (including incident cases born prior to NBS implementation [Scenario 3])

	2025–26	2026–27	2027–28	2028–29	2029–30	2030–31
Universal NBS						
<i>All GSD II affected cases diagnosed (NBS)</i>	10.60	10.60	10.60	10.60	10.60	10.60
<i>Number of affected cases with IOGSD II (9.43%)</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i>Number of affected cases with LOGSD II (90.57%)</i>	9.60	9.60	9.60	9.60	9.60	9.60
<i>Incident cases born prior to NBS implementation</i>	6.67	5.67	5.68	5.68	5.68	5.69
<i>ERT costs, IOGSD II (first year of birth only)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, for cumulative incident cases born prior to NBS implementation</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP with NBS¹</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Current practice offsets						
<i>All GSD II affected cases diagnosed (current practice)</i>	6.67	6.68	6.68	6.68	6.69	6.69
<i>Number of affected cases with IOGSD II (9.43%)</i>	1.00	1.00	1.00	1.00	1.00	1.00
<i>Number of affected cases with LOGSD II (90.57%)</i>	5.67	5.67	5.68	5.68	5.68	5.69
<i>ERT costs, IOGSD II (first year of birth only)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>ERT costs, LOGSD II</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<i>Total costs to LSDP (current practice)</i>	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Net total cost to LSDP with NBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

ERT = enzyme replacement therapy; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; LSDP = Life Saving Drugs Program; NBS = newborn bloodspot screening

¹ERT costs for IOGSD II are included for the year of diagnosis only as the costs for subsequent years would be similar across both strategies.

Source: Rejoinder from assessment group

Shaded cells represent those with changed values from the DCAR base case.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

1. **Is there a suitable screening test(s) (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive) to accurately identify all newborns at risk for all subtypes of the proposed condition?**

First-tier screening based on acid alpha-glucosidase (GAA) enzyme activity cannot detect ILOGSD II without also detecting a proportion of individuals at risk for LOGSD II (which is predominantly an adult-onset condition), individuals with low GAA enzyme activity who do not develop clinical features of the condition (pseudodeficiency), and individuals who may develop mild phenotypic disease that is currently not diagnosed in the absence of NBS.

Second-tier genetic screening will identify those with commonly occurring pathogenic/likely pathogenic variants and will rule-out the need for further testing in some children with pseudodeficiency, although ESC was uncertain if this was a categorical test outcome. This second-tier screening will not exclude individuals who may develop mild phenotypic disease that is currently not diagnosed.

It is estimated that screening 304,655 Australian newborns per year (which was the projected number of newborns to be screened in the first year of NBS for GSD II if implemented in 2025-26) will identify 1.0 case of ILOGSD II and 9.6 children at-risk for LOGSD II. In addition, this screening could identify 11.8 cases of pseudodeficiency (additional to those ruled out by the second-tier screening test), 20.1 carriers, and 15.2 individuals who would not progress to develop clinical GSD II. Although cases of ILOGSD II would be rapidly confirmed by detecting cardiomyopathy, ESC considered further advice is needed about whether individuals in the other four groups (totalling 57 cases per year) can be clearly distinguished from each other at the conclusion of all diagnostic steps following an initial screen positive result.

There were limited data on the accuracy and prognostic ability of these screening tests and based on the information provided to ESC there is no clear first-tier and/or second-tier methodology that could reduce false positives (FPs) and increase the positive predictive value (PPV), due to the large number of pseudodeficiency variants, variants of uncertain significance (VUS), and phenotypic variability for LOGSD II genetic variants. However, ESC noted expert advice from international screening programs that suggests some improvements have occurred over time due to refinement of cut off values and increases in classified variants in international registries.

2. **Can disease subtype and prognosis (with consideration of expressivity and penetrance) be determined from the screening and confirmatory tests and clinical assessment to determine the need for monitoring and/or earlier treatment?**

Screening will identify children at risk for GSD II, including those with one or two common variants, and false positives. Diagnostic testing may predict the subtype of disease for variants that have a reported genotype:phenotype relationship. For a proportion of children at risk for LOGSD II, diagnostic testing cannot predict if clinically apparent disease will occur, or if it does, its likely severity or time of onset – this can only be ascertained through subsequent long-term clinical follow-up.

All children recalled for diagnostic testing after a screen positive result will be assessed for clinically apparent symptoms and signs, including the presence of cardiomyopathy which confirms ILOGSD II. For other children identified as at-risk for GSD II, there will be individuals

who ultimately remain disease-free. These individuals may be considered overdiagnosed (i.e. there is no prognostic or clinical utility associated with the genetic diagnosis).

Given these unknowns, ESC considered that there was a need for further expert clinical advice on how all individuals with a positive result at the end of all the diagnostic steps would be managed, including how many (if any) at risk of future disease might be ruled out of ongoing clinical surveillance.

3. Is there is an effective treatment (or treatments) available in Australia for at-risk newborns? If the disease has subtypes, are treatments available for each subtype?

Enzyme replacement therapy (ERT) for management of IOGSD II and LOGSD II is funded by the Australian Government through the Life Saving Drug. Program (LSDP). For IOGSD II, the eligibility criteria permit use based on a “diagnosis” in children under 2 years of age.

The LSDP eligibility criteria for LOGSD II permit ERT use in presymptomatic children aged 2-18 years of age with a “diagnosis” (meaning laboratory diagnosis only), and without a need to have predicted the severity of disease phenotype. Application of these criteria in the context of NBS for GSD II is associated with the possibility of overtreatment of children identified at-risk of LOGSD II who would never develop clinical disease, or would only develop mild symptoms (i.e. these children would not have presented in the absence of screening).

Newborn screening, diagnosis and clinical assessment will likely lead to earlier diagnosis and avoidance of the diagnostic delay for some of those individuals who would go onto develop clinical LOGSD II.

There are no national clinical practice guidelines for the management of presymptomatic children at-risk of LOGSD II identified through newborn screening, but advice from the clinical experts supporting this application is that in practice ERT would only be commenced when symptoms and signs of the disease become apparent, in alignment with international guidelines. If so, further clinical expert advice is needed on whether this means an additional 57 individuals per year will need to undergo long term monitoring for symptoms and signs of possible disease, potentially for the rest of their lives.

4. Is the available treatment effective from the proposed earlier age of initiation following NBS screening and diagnosis compared to symptomatic presentation?

Comparative effectiveness and safety of ERT in IOGSD II following NBS:

There is observational evidence of likely greater effectiveness (before irreversible signs and symptoms develop) from starting ERT earlier for IOGSD II cases where current LSDP eligibility criteria are met.

There is a lack of direct evidence on the comparative risk of developing ERT related adverse events (AEs) and neutralising antibodies (especially in Cross-reactive immunological material (CRIM) positive patients) from starting ERT earlier. ESC noted the clinical advice that initiation of immunomodulation therapy prior to ERT reduces the potential for developing neutralising autoantibodies to ERT.

Comparative effectiveness and safety of ERT in LOGSD II following NBS:

There is observational evidence of likely greater effectiveness in patients with symptomatic LOGSD II from starting ERT earlier. However, there are no direct data to support presymptomatic use of ERT in children identified as at risk of LOGSDII, and there are likely harms associated with such use. ESC noted that LSDP-funded ERT is permitted for these

children after 24 months of age. Monitored individuals who develop clinical LOGSD II may also benefit by potentially avoiding a diagnostic delay.

There is emergent evidence for use of ERT at doses higher than is currently funded via the LSDP for individuals who experience insufficient disease control with the recommended dose. However, ESC considered that the safety, effectiveness, cost-effectiveness and financial impact of such use is out of scope for the current MSAC application.

5. Is the available treatment cost-effective from the proposed earlier age of initiation following NBS screening and diagnosis compared to symptomatic presentation?

Cost-effectiveness of ERT in GSD II following NBS:

ESC noted that the cost-effectiveness analysis is relatively robust (given the paucity in evidence). ESC noted that the incremental cost-effectiveness ratio (ICER) (base case ICER **\$REDACTED** per additional GSD II diagnosis) is very high compared with earlier MSAC considerations for NBS, but also noted that there is no agreed national or international benchmarks for cost-effectiveness for NBS for rare diseases. However, ESC was of the view that it would be informative for MSAC to consider the ICERs for treatments listed on the LSDP to provide context for the current consideration. If doing so, ESC also advised that MSAC should be aware that the rule of rescue, which influences LSDP decision-making, is driven by small numbers of identifiable individuals in extremely severe circumstances, and that the ICERs previously accepted by the LSDP Expert Panel may apply to some of the diagnosed cases, but not to all those who would be screen positive.

The ICER increased to **\$REDACTED** per additional diagnosis when the costs for annual surveillance and ERT were taken into account. The ICER per Quality Adjusted Life Year (QALY) was estimated to be between **\$REDACTED** and **\$REDACTED** when the discounted survival, quality of life gains, and prolonged ERT costs were included. ESC noted these ICERs were driven predominantly by ERT costs. ESC also noted that most of the modelled incremental health gains arose from survival gains rather than quality of life gains.

ESC noted two key uncertainties associated with these ICERs:

- i) the hazard ratio of overall survival from the Taiwan cohort comparison was a key uncertainty associated with the health increment in the ICER per QALY estimate. However, given the limited comparative data on survival benefits, the extent of this uncertainty is not easy to quantify so was not explored in sensitivity analyses
- ii) the magnitude of the incremental costs, due to the assumption that NBS-identified patients who are identified with LOGSD II will start ERT only when symptoms emerge.

ESC noted that the **\$REDACTED** one-off program implementation costs were applied in year 1 of the financial analysis, but were excluded from the economic evaluations. ESC considered it would be useful for MSAC to be presented with two separate sets of economic analyses that (i) excluded the program implementation costs, and (ii) included the program implementation in the first year of the economic evaluations (after being adjusted to the 100,000-member cohort size).

ESC considered the approach in the DCAR to exploring the potential impact of 'multiplexing' the proposed testing across the conditions covered by applications 1774, 1775 and 1776. ESC considered that the approach of reducing costs of screening to assess the effect of multiplexing provides only a rough estimation of adjusted cost-effectiveness. ESC discussed an alternative approach to conducting a stepped economic evaluation of multiplexing across

applications 1774, 1775 and 1776, to ensure cumulative diagnostic yield is appropriately assessed across the three applications, and to avoid any double-counting of costs.

6. What is the likely financial impact to all relevant budget holders for NBS screening for the condition?

ESC noted that the largest financial impact would be to the NBS programs (\$REDACTED in Year 1 to \$REDACTED in Year 6), with a total cost to government health budgets inclusive of these program costs of \$REDACTED in Year 1 and \$REDACTED in Year 6.

7. What are the relevant ethical (including equity), legal, social or organisational aspects specific to screening for this condition?

ESC noted that the screening diagnostic and clinical management pathway will identify individuals who are at-risk for late, even adult-onset disease, and also cases where clinically apparent disease will not eventuate (i.e. overdiagnosis). There are no national clinical practice guidelines to guide the use of ERT (which is permissively worded in the LSDP criteria) in a proportion of children at-risk for LOGSD II and who are currently asymptomatic.

Given the number of children who would be identified as at-risk of LOGSD II from screening but who would have currently assigned variants of unknown significance, ESC advised that MSAC consider whether reporting of screening results should be limited to known pathogenic or likely pathogenic variants, or whether VUSs could also be reported. ESC highlighted the need to collect more genotype:phenotype information (e.g. clinical outcomes registry and variant database), especially if VUSs are to be reported.

ESC considered that a number of ethical questions arise regarding NBS for GSD II, regarding the type and timing of information provided to parents and process(es) for obtaining consent for screening and further testing. ESC considered these ethical issues relate to the reporting and managing of variants of unknown significance noting there may be an ethical obligation to inform parents of a potential diagnosis of GSD II); uncertainty in the prognostic utility of screening in predicting disease subtype, age at onset or severity of disease; and further investigation of the child requiring further parental consent to proceed beyond the original bloodspot sample.

Additionally, once further investigation is conducted, ethical principles of transparency and full disclosure would necessitate informing parents of the outcome of the further investigation.

ESC noted that these ethical issues may also be relevant to other NBS applications

The pattern of GAA variants expected in Australian sub-populations cannot be assumed as the same for populations where NBS has been implemented, or representative of variants reported in literature.

ESC noted that the establishment of a national registry for the NBS program could help address clinical and ethical issues with variants and reporting.

ESC advised that MSAC may wish to refer the following matters to the LSDP Expert Panel in the context of its avalglucosidase alfa 24 Month Review:

- the prevalence of GSD II is already beyond the LSDP threshold, and is projected to increase further with the proposed inclusion of GSD II in NBS programs.
- whether to consider the basis for current LSDP criteria to permit ERT initiation in asymptomatic patients between the ages of 24 months and 18 years for individuals diagnosed via the NBS and suggestive of GSD II

- whether to (continue to) permit a dose of 40 mg/kg/eow (every other week) for patients with IOGSD II who experience insufficient control, or declining response to ERT at the TGA-approved initial dose, as evidence suggested possible benefits associated with higher doses of ERT, compared to the recommended dose.

ESC discussion

ESC noted this application, from the Department of Health and Aged Care Newborn Bloodspot Screening (NBS) Section, sought the addition of glycogen storage disease, type II (GSD II; Pompe disease) to the list of conditions screened as part of Australia's NBS programs. ESC noted the NBS programs are overseen and managed by state and territory governments. ESC noted the Australian Government initially announced funding under the 2022-23 Budget, followed by additional funding in the 2024-25 Budget to support expansion of NBS programs.

ESC noted the NBS is underpinned by the NBS National Policy Framework (NBS NPF)³³. For a condition to progress to MSAC for assessment, it needs to align broadly with the NBS NPF which lays out multiple criteria including: the condition is serious and benefits from early diagnosis in the newborn period; having a suitable screening test available, which is socially and ethically acceptable; and having an effective intervention or treatment available. ESC further noted that 9 Lysosomal Storage Disorders (LSD) have been considered to date by the National NBS Program Management Committee, out of which 3 have been referred to MSAC for assessment (MSAC applications 1774³⁴, 1775³⁵ and 1776³⁶).

ESC noted that as a starting premise for evaluation, newborn bloodspot screening needs to fulfil the same criteria for net benefit and cost-effectiveness as any screening program and additionally justify why screening should occur in the newborn period.

ESC noted and welcomed public consultation feedback from 11 organisations and 19 individuals (7 individuals with the condition, 10 identified as carers or other interested individuals, one researcher and one specialist). ESC noted the public consultation feedback was supportive, including from peak bodies such as Genetic Alliance Australia and Rare Voices Australia. Feedback from consumers highlighted that NBS would enable earlier diagnosis and timely access to enzyme replacement therapy (ERT) which would slow disease progression, reduce morbidity, and save families from a diagnostic odyssey. Additionally, including GDS II in NBS would allow equity of access for screening. Concerns were raised about false positives (FPs) and the identification and management of late onset disease, with feedback highlighting the need for clear guidelines around monitoring of these patients. ESC noted some feedback also raised logistical issues, such as the additional need for education, staff and genetic counselling for patients and their families.

ESC noted that GSD II is an autosomal recessive LSD, caused by a deficiency of alpha-glucosidase (GAA), a lysosomal enzyme that is required to break down glycogen. The 2 main phenotypic categories of clinically determined GSD II are infantile-onset (IOGSD II) and late-onset (LOGSD II). IOGSD II is the most severe form of the disease and is associated with very low or no GAA activity. IOGSD II is characterised by symptoms at birth or during early development. Severe symptoms, including severe cardiomegaly (enlarged heart), hypertrophic cardiomyopathy (thickening of the heart muscle), hypotonia (low muscle tone), and respiratory problems that eventually require a ventilator, appear within the first few months of life. Without treatment, most individuals have unremitting deterioration and die within the first year of life from cardiac insufficiency.

³³ 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-policyframework?language=en>

³⁴ <https://www.msac.gov.au/applications/1774>

³⁵ <https://www.msac.gov.au/applications/1775>

³⁶ <https://www.msac.gov.au/applications/1776>

LOGSD II can be diagnosed at any age (median age of 36 years in Australia; range of 10 weeks to 69.7 years)³⁷, with slower progression of symptoms than IOGSD II. Individuals do not develop cardiomyopathy but can have significant morbidity and mortality due to skeletal muscle myopathy and diaphragmatic insufficiency. There is considerable variation in the age of symptom onset, and severity of signs and symptoms. Variability in disease features can exist between individuals with identical genetic variants, suggesting that unknown secondary factors influence the clinical course of disease. ESC noted that symptoms in individuals with LOGSD II often vary and may include muscle weakness, respiratory problems, difficulty exercising, and difficulty chewing or swallowing. LOGSD II diagnosis can be difficult, as it can resemble many other types of neuromuscular conditions, requiring a high level of clinical awareness for a timely diagnosis. By the time LOGSD II cases are clinically detected, muscle damage is typically already present.

ESC noted the estimated prevalence of GSD II in Australia of 1 per 46,000 live births (based on diagnostic testing after presentation with symptoms, or family history between 2009 and 2024, Chin et al 2021). ESC also noted that the prevalence varies by ancestry, as the recent global estimated prevalence is 1 per 23,000.

ESC noted estimates that the NBS programs would diagnose at least 10.6 babies with GSD II per year. Of these, one baby is predicted to have IOGSD II. NBS for GSD II is expected to mostly identify LOGSD II, in which most individuals have symptom onset in late childhood or adulthood (although some patients present with severe symptoms in early childhood). The proportion of LOGSD II to IOGSD II cases is predicted to increase if GSD II screening is added to the NBS, as additional non-symptomatic or very mild cases who would otherwise not present clinically will be identified. In addition to IOGSD II and LOGSD II, ESC noted that screening is predicted to detect a similar number of individuals with pseudodeficiency per year. These may be considered as false positive (FP) if reported, but a second-tier genetic panel screening could identify some common pseudodeficiency alleles and therefore rule out some FP cases. ESC recommended that clinical expert advice be sought as to how pseudodeficiency and FP cases would be managed clinically, and in particular the proportion of cases where disease is considered to be ruled out and who could avoid long term clinical surveillance.

ESC noted that a small number of cases may be diagnosed prenatally (2/81 were diagnosed between 2009 and 2020 in Australia, [Chin & Fuller 2022]), and the introduction of NBS for GSD II is not expected to alter the management or outcomes in this group. However, these newborns are still considered part of the target population, as any babies born with prior diagnoses would still undergo NBS (to screen for any other co-existing conditions that may be identified through the NBS) and thus incur the costs of screening.

ESC noted the current and proposed clinical management algorithms. ESC noted that the proposed population is all newborns (PICO set 1) participating in NBS programs in Australia and the comparator for PICO set 1 is standard of care (defined as no NBS for GSD II). The proposed screening strategy for PICO set 1 is a 2-tier screening strategy with both tests performed on the dried bloodspot (DBS). The first test is a screen of GAA enzyme activity using mass spectrometer (MS)/MS or fluorometric assay. Positive cases would then undergo targeted sequencing of common GAA gene variants to rule out cases with known exclusively pseudodeficiency variants.

ESC noted that one of the key health technology assessment (HTA) questions encompassing NBS assessments is whether there is a suitable screening test (or tests) to accurately identify all newborns at risk for the proposed condition (with acceptable clinical sensitivity and specificity according to consensus thresholds for what is considered positive). ESC noted there was a paucity of data for screening of GSD II. ESC further noted that protocols that use an MS/MS assay as a first-tier (or single-tier) screen tended to have a lower screen positive rate and higher positive predictive value (PPV) than those using fluorometry. Positive rates decrease with each tier of screening or retesting added to the protocol. However, ESC noted that the cost and practicality of screening large sample numbers must also be considered when adding screening

³⁷ Chin S, Fuller M. Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. *Lancet Reg Health West Pac*. 2022;19:100344..

tiers and other changes to protocols. ESC noted that the summary statistics reported in studies of diagnostic accuracy were unreliable. For instance, ESC noted that the range of PPV for first - tier screen positive and retest positive results was 3.5%-50% and 15%-80% respectively.

ESC also noted that many international NBS programs have developed their own screening methods (such as stratified cut-offs for GAA activity, synthetic substrates, and neutral GAA activity ratios) for reducing FP rates and improving the PPV, and this is an acknowledged challenge for GSD II screening. There is no clear first-tier and/or second-tier methodology that can reduce FPs and increase the PPV, due to the large number of pseudodeficiency variants, variants of uncertain significance (VUS), and variability in variant expression in LOGSD II.

ESC agreed with the pre-ESC response that there is a need for a clinical outcomes registry coupled with a variant database to improve the longitudinal assessment of the genotype–phenotype relationship for individuals with VUS. ESC noted that following positive screening results, infants would be recalled to undergo diagnostic testing (testing protocol as per the comparator).

Regarding the diagnostic testing, ESC queried:

- whether a molecular diagnosis would be made for an infant without symptoms/signs if they have 2 GAA VUS
- what the threshold is for calling a variant likely pathogenic in the screening case compared to the clinical presentation case
- whether there is expert consensus about the ability to differentiate between pseudodeficiency and individuals at-risk for LOGSD II, noting the lower pre-test probability in a screening case than with a clinical presentation case
- what work has been done to develop a clinical outcomes registry, as previously recommended by MSAC for addition of other conditions to the NBS.

In addition, ESC queried how accurately future disease status can be predicted for newborns without symptoms and signs. ESC also noted that index and comparator tests are incorporated in the reference standard, which may overestimate accuracy.

ESC noted that for equity of access to these services, all of the screening and diagnostic tests/assessments for GSD II need to be publicly funded.

Regarding whether disease subtype and prognosis can be determined from the screening and confirmatory tests to determine the need for earlier treatment (with consideration of expressivity and penetrance), ESC advised that the 2-tier screening approach cannot completely differentiate those with IOGSD II from those at risk of LOGSD II. For those at-risk of LOGSD II, screening cannot predict if an individual will become symptomatic or remain asymptomatic, because of the lack of information about some variants and the highly variable phenotypic expression of some variants and genotypes. However, clinical assessment of children during recall for diagnostic testing can differentiate IOGSD II from LOGSD II based on clinical signs and symptoms, including the presence of cardiomyopathy which may help determine timing of ERT initiation. ESC noted diagnostic testing may also predict the subtype of disease for variants that have a reported genotype:phenotype relationship. ESC further noted that, for a proportion of LOGSD II cases, the likely severity or time of onset cannot be predicted and can only be ascertained through long-term follow-up of individuals.

ESC noted in relation to the availability of an effective treatment (or treatments) for at-risk newborns in Australia, the main treatment available is ERT via the Life Saving Drugs Program (LSDP) that covers medicines for ultra-rare (≤ 1 case per 50,000), life-threatening diseases. ERT is subsidised through the LSDP for patients with a laboratory diagnosis of GSD II. Infants with a diagnosis of IOGSD II can access ERT without an age restriction. In contrast, individuals with a laboratory diagnosis and a risk of developing LOGSD II can access ERT while presymptomatic between the ages of 2-18 years (but noting this may lead to over-treatment of some at-risk LOGSD II cases). For those presenting with LOGSD II beyond 18 years of age, additional clinical criteria must be met for ERT access.

ESC noted that introduction of NBS for GSD II will likely lead to an earlier diagnosis of GSD II, thereby sparing some individuals a prolonged diagnostic delay. ESC noted due to the lack of national clinical practice guidelines for asymptomatic children at-risk of LOGSD II identified through the NBS, the clinical advice is that, in practice, ERT would likely be commenced when signs and symptoms of disease become apparent in these individuals. In light of this clinical advice, ESC noted:

- a lack of direct evidence of comparative effectiveness in these patients for earlier ERT
- the expected development of ERT adverse effects
- the expected development of neutralising antibodies to ERT (especially in CRIM+ve patients)
- this approach is not recommended in international treatment protocols
- this approach could represent ineffective use of ERT (however, given current LSDP subsidy guidelines, this is unlikely to influence prescribers or parents).

However, given the importance of this uncertainty to the economic evaluation, ESC also considered that there were several reasons why ERT may be commenced pre-symptomatically:

- an assumption that pre-symptomatic ERT for LOGSD II may have greater benefits (before irreversible organ damage occurs) as demonstrated in IOGSD II
- the current LSDP subsidy guidelines do not necessarily preclude it.

ESC noted the key clinical evidence of NBS for GSD II vs current management and change in management was largely from observational studies such as case series and cohort studies, resulting in an evidence base with at least a moderate risk of bias. Regarding whether the available treatment is effective from the proposed earlier age of initiation following NBS screening and diagnosis (asymptomatic and early symptomatic) compared to symptomatic presentation, for individuals with IOGSD II, ESC noted the evidence presented was a naïve comparison of NBS cohorts with historical control cohorts that did not adjust for potential differences in confounders between populations. The studies looking at Taiwan's experience of the GSD II screening program suggested that for both overall survival and ventilation-free survival there was extra benefit from earlier treatment, although ESC noted that the patient numbers were small. At 50 months, the differences were statistically significant based on a Kaplan-Meier survival analysis ($p=0.028$ for overall survival and $p<0.001$ for ventilation-free survival). Therefore, ESC considered that there is probable benefit from starting treatment earlier for IOGSD II cases.

ESC noted for the late onset disease subtype, the limited available evidence came from non-comparative studies. Among individuals diagnosed with LOGSD II via NBS, 17% had commenced ERT, while 83% were undergoing monitoring for up to 7 years (the longest study period). Additionally, ESC noted there was limited comparative evidence on outcomes such as motor function which was based on the timing of initiation of ERT in symptomatic LOGSD II populations, making the benefits uncertain.

Regarding safety, ESC considered there are known adverse effects from ERT given to patients diagnosed with IOGSD II, which are expected to proportionately increase if GSD II testing is introduced to the NBS programs and results in earlier ERT access for more individuals. Adverse events (AEs) are associated with ERT given to patients diagnosed with both IOGSD II and LOGSD II. In addition to published evidence, product information for alglucosidase alfa (Myozyme®) indicated infusion-related reactions occur in 14% of patients, with higher rates in younger children. A higher rate was reported with avalglucosidase alfa (Nexvazyme®). The majority of infusion-related reactions were mild to moderate in severity and associated with high flow rates. AEs were categorised as:

- development of neutralising anti-rhGAA antibodies
- elevated B-type natriuretic peptide (BNP) levels
- infusion-related reactions
- risk of acute cardiorespiratory failure.

ESC considered there are additional safety issues relating to the need for central venous access, which can result in long-term complications (infections, thrombosis and progressive loss of access). ESC considered these risks to be particularly relevant if ERT is used among the asymptomatic population at risk for LOGSD II.

In addition, ESC considered the potential psychosocial and financial harms from a laboratory/genetic diagnosis, especially for a proportion of babies who are asymptomatic but at risk for clinical LOGSD II, as some would develop symptoms later, but some would never develop symptoms. Although the literature described these individuals as ‘patients in waiting’ ESC considered that some proportion may be more appropriately described as overdiagnosed healthy people. The testing will also identify people at risk for LOGSD II who will have an unknown prognosis. In addition, variation in phenotypic expression was observed within families with the same genotype, adding to uncertainty on when to initiate ERT treatment. However, ESC noted that the Department-contracted assessment report (DCAR) does not present any empirical evidence about these harms.

ESC noted the applicant’s comment that expert clinical advice highlights it may not be accurate to regard LOGSD II as a predominantly adult-onset condition as approximately one fifth of children with supposed LOGSD II can have biochemical, muscle ultrasound and physical signs of the disease process starting in infancy. However, ESC considered that this advice is based on clinically determined disease and under NBS it is likely that babies will be identified with variants who would otherwise never have presented clinically (as children or adults) – because they are either completely asymptomatic or have very mild symptoms.

ESC considered the overall net benefit versus harms of GSD II screening, based on the Californian NBS program and some Australian data. For every 304,655 newborns screened annually (which was the projected screening population of the first year of NBS for GSD II if implemented in 2025-26), Australian NBS programs would identify:

- 10.6 true positives who would be eligible for ERT
 - 1 newborn with LOGSD II would receive earlier ERT and have likely survival, respiratory and motor benefits
 - 9.6 diagnosed with LOGSD I (3.5 with a VUS) with a proportion of those at risk who would be monitored regularly to determine whether and when they should receive ERT.
- 47.1 FPs who would not be monitored, and ultimately not require treatment
 - 11.8 would have pseudodeficiency variants, of which 5.9 would be ruled out from having the condition. However, ESC considered it was uncertain if this meant the other 5.9 out of the 11.8 with pseudodeficiency variants would not be ruled out from having the condition, which means they are not actually FP
 - 20.1 would be carriers. ESC noted that such individuals are not really FPs and queried whether the carriers would be reported, and whether they would all be carriers for a pathogenic/likely pathogenic variant (or whether number also includes carriers of VUSs).
 - 15.2 with no known GSD II variant found. ESC noted that these might not really be FPs if developing the condition in the future was still possible. ESC questioned if this result would be more likely for babies with non-European ancestry (as VUS are more common in people with non-European ancestry due to underrepresentation in genetic databases). ESC considered the distinction between no known variant found vs LOGSD II to be unclear, and it was uncertain how these infants would be clinically managed.

ESC considered that, based on this analysis, out of 304,655 newborns screened annually, fewer than 6 individuals (1 with LOGSD II, 4.8 with LOGSD I) are likely to benefit from NBS early diagnosis and treatment. ESC considered that more than 4 people are likely to be harmed through being labelled as having a condition that will likely never be symptomatic or only causes mild symptoms. This was based on the assumption that only half of “at risk for LOGSD II” cases would eventually become symptomatic based on current GSD II incidence. In addition, ESC considered that more than 47 individuals and their families would likely experience net harm through unnecessary worry, clinical visits and tests. It is also unclear how many of these

individuals would be managed clinically over the long term. ESC considered it important to confirm whether these different subgroups can be distinguished from each other, particularly those at risk for LOGSD II, pseudodeficiency, carriers and no GSD II cases.

Overall, ESC agreed with the clinical claim that NBS for GSD II has superior effectiveness and noninferior safety for the IOGSD II cases. However, for individuals at risk for LOGSD II, ESC concluded that clinical effectiveness is potentially superior, while safety may be inferior compared to no screening.

For the the relevant ethical (including equity), legal, social or organisational aspects specific to screening for GSD II, ESC noted the screening, diagnostic and clinical management pathway will identify individuals who are at-risk for late, including adult-onset disease, and also cases where disease does not eventuate. ESC acknowledged there are benefits of avoiding a diagnostic delay resulting in delaying the diagnosis by 5 years or more, as commonly occurs for the late onset form of the disease. Other non-health benefits of the NBS include autonomy, reproductive decision-making and an ability to address the diagnosis throughout the person's life. However, ESC noted potential burdens to families of late-onset patients diagnosed through the NBS, such as unnecessary medicalisation and parental vigilance, stigma and discrimination, inequity of access to follow-up care, and financial issues.

ESC noted possible higher rate of survival, ventilation-free survival and motor function improvement associated with higher doses of ERT, compared to the recommended dose for alglucosidase alfa and avalglucosidase alfa, which is 20 mg/kg administered every other week (eow). The Therapeutic Goods Administration (TGA) states that dose escalation to 40 mg/kg/eow may be considered for patients with IOGSD II who experience insufficient control. However, ESC noted higher doses of ERT have not been approved for subsidised access in Australia according to current LSDP criteria, and any potential change to LSDP criteria is out of scope of this application. ESC considered that MSAC may wish to refer these and other matters to the LSDP Expert Panel (see discussion below).

ESC noted and agreed with many aspects of the pre-ESC response, including that early access to ERT benefits infants with IOGSD II. However, ESC reiterated that this benefit does not extend to all patients diagnosed with LOGSD II, or to those who have FPs or pseudodeficiencies. ESC also recommended caution about placing too much emphasis on the Taiwan NBS outcomes, as Taiwan has unique variants and variant frequency, and numerical estimates cannot be applied directly to the Australian context.

ESC noted the pattern of GAA variants in Australian sub-populations may differ from those observed in populations where NBS has been implemented or those reported in the literature and cannot be assumed to be the same.

ESC noted that it is unclear how VUS will be reported and/or reanalysed and reported on. ESC recalled MSAC's previous recommendation in application 1775 that a national registry be established for the NBS programs, which would also need to incorporate a variant database to ensure follow up is able to link uncertain genotypes to phenotype. ESC noted that this registry does not yet exist, but that its establishment could help address some clinical and ethical issues with variants and reporting. ESC further noted that the pre-test consent process would need to be informed by the approach to variant reporting and the need for longitudinal follow-up in relation to managing the uncertainty of predicting future disease phenotype and severity.

ESC noted the proposed population for cascade testing following diagnosis of an index case is biological parents and siblings of the index case with two pathogenic/likely pathogenic (P/LP) variants in the GAA gene (PICO set 2). ESC noted that, with GSD II being an autosomal recessive condition, both parents of an index case with two P/LP variants can be assumed to be carriers, with a one in four chance that future offspring would also be affected. For IOGSD II cases, cascade testing may inform biological parents for reproductive decision making and planning. For the older siblings who may also be carriers, ESC advised genetic counselling and carrier testing upon reaching reproductive age should be considered.

ESC considered for LOGSD II cases, it may be appropriate to also offer cascade testing to other members of the broader family and their children, as LOGSD II symptoms may not yet have been observed or diagnosed.

ESC noted the evidence presented for cascade testing was based on case series. Overall, ESC agreed that for PICO set 2 for IOGSD II cases the claim is likely non-inferior effectiveness and non-inferior safety. However, ESC considered that when the index case has LOGSD II the clinical claim is potentially superior effectiveness and inferior safety.

ESC considered that the stepped economic evaluation in the DCAR was broadly reliable for MSAC decision-making, and its stepped approach is structurally similar to related NBS applications 1775 (MPS I) and 1776 (MPS II). The model structure (comparing 100,000 newborns) and time horizon (50 years) were reasonable, as were the validity of model inputs and appropriateness to the Australian setting. However, ESC highlighted that the current approach of accounting for reduced costs from multiplexing (essentially by dividing the screening cost per sample by three) provides a rough approximation only of the effect of multiplexing on the cost-effectiveness estimates. ESC considered that a better approach for taking account of multiplexing would have been to undertake a bundled economic evaluation of screening for all three conditions covered in the three NBS applications before MSAC (mucopolysaccharidosis Type 1, mucopolysaccharidosis Type 2, GSD II) taking account of the joint (shared) incremental costs of screening for the added conditions and the 'true' (i.e. not double counted) incremental costs and health increments associated with screening for each condition to derive the Incremental Cost Effectiveness Ratio (ICER) of screening for each condition and the average ICER of screening for all three. ESC also noted that the **\$REDACTED** program implementation costs calculated for the financial analysis were not included in the economic evaluations (after adjusting for the 100,000-member cohort size).

ESC considered the model transition probabilities, variables and extrapolation were all reasonable, including the estimated increase in LOGSD II incidence only and the 'upper bound' and 'lower bound' survival extrapolations. ESC considered the health outcomes and quality of life data to be mostly reasonable, except that sensitivity of the modelled ICER to the trial results was not assessed. The health care resource use and costs were mostly reasonable, except for the omission of the one-off **REDACTED** program implementation costs of NBS and the likely underestimate of ERT costs for patients identified via NBS who do not have IOGSD II. ESC concluded that the model validation was reasonable although it would have been preferable if the DCAR also reported Markov traces for the modelled health states.

ESC noted that the modelled and observed survival curves showed a survival benefit associated with a GSD II NBS programs, albeit based on low sample sizes. A partitioned survival analysis demonstrated similar ventilation-free survival benefits.

ESC noted that the health increments captured in the model mostly arise from treating IOGSD II while the health effects from LOGSD II are not quantified with the exception of the reduced disutility of diagnostic delay under NBS which had a miniscule impact on health increments. ESC noted that cascade testing also only had a miniscule impact on incremental costs. ESC noted that the main drivers of incremental costs in the model are Tier 1 screening and ERT.

ESC noted that the ICERs were high – the base case ICER that included the test costs for diagnostic delay was **\$REDACTED** per additional GSD II diagnosis. This ICER increased to **\$REDACTED** per additional diagnosis when the annual surveillance and ERT costs were taken into account. The ICER per Quality Adjusted Life Year (QALY) was between **\$REDACTED** and **\$REDACTED** when the discounted survival and quality of life gains and prolonged ERT costs were included (mostly driven by ERT costs). ESC noted that most modelled incremental health gains arose from survival gains rather than quality of life gains.

ESC noted that, if using a multiplex kit such as the **REDACTED** kit (which can screen for multiple conditions, including those covered by applications 1775 and 1776), the screening costs and hence resulting ICERs decreased. However, using a Revvity NeoLSD™ MS/MS multiplex kit increased the costs (and ICERs) as it is significantly more expensive than the **REDACTED** multiplex kit.

ESC noted the pre-ESC response's observation that the DCAR's costing of annual surveillance of LOGSD II cases is insufficient, and that most centres do not have multidisciplinary teams or access to support staff. ESC acknowledged that the cost of intensive surveillance of symptomatic cases diagnosed via NBS (that occurs during the period that cases without a diagnosis via NBS are in a diagnostic delay) will contribute to an incremental cost difference between the modelled arms. ESC noted that the rejoinder presented a revised model that included these aforementioned increased costs of surveillance of symptomatic cases: this increased the ICER to **\$REDACTED** per quality-adjusted life year.

ESC noted that the greatest uncertainty in generating the ICER/QALY estimate is the hazard ratio of overall survival from the Taiwan cohort comparison. As noted previously, this was not assessed in the sensitivity analyses because the extent of this uncertainty is not straightforward to quantify. ESC also noted that the greatest cost uncertainty in the model is the best-case assumption that no NBS-identified patient with at-risk LOGSD II would commence ERT until symptoms emerge. However, ESC noted that the second scenario in the Rejoinder estimated the financial implications of a highest cost assumption that all NBS patients with at risk LOGSD II would commence ERT at birth.

ESC concluded that the ICERs are very high, but acknowledged this is a reflection of the rarity of the condition being screened. ESC advised that MSAC may wish to consider the ICERs accepted by the LSDP Expert Panel to provide context for ICERs for rare diseases. ESC further noted that MSAC should also be aware that the rule of rescue, which influences LSDP decision-making, is driven by small numbers of identifiable individuals in extremely severe circumstances, which may apply to some of the diagnosed cases, but not to all those screened.

ESC noted the applicant's request that ESC and MSAC not directly compare the ICER per QALY of previous NBS applications, due to the high uncertainty of ICER calculations. However, ESC considered that the 'exploratory' analyses reported in the DCAR gives MSAC a basis for comparison with these other applications whilst being mindful of their uncertainties. While ESC acknowledged that the CEA per additional GSD II diagnosis was primarily used as the base case analysis due to high uncertainty in the comparative data for survival and quality of life benefits of NBS for GSD II, it considered that even the base case analysis was difficult to interpret. ESC acknowledged the applicant's argument that although the monitoring of individuals identified with LOGSD II is an added cost to the health system, it offers several benefits that are difficult to quantify including avoidance of the diagnostic delay. However, ESC noted that the economic model already includes increased utility from minimising the diagnostic delay.

ESC considered the financial impact calculations to be appropriate and largely based on verifiable facts, such as the newborn population, NBS uptake rates, annual incidence rates and literature-based clinical management protocols. In addition, ESC considered the estimated use and financial implications of the proposed NBS expansion to be largely reasonable, except that:

- use of ERT in patients identified via NBS who are identified with LOGSD II is likely underestimated, and thus, the financial impact to the LSDP is also likely underestimated
- the DCAR's approach to estimating the effects of expanding via a multiplex test is only an approximation. As noted previously, MSAC should consider which costs will not be duplicated if 2 or more of applications 1774, 1775 and 1776 are supported and NBS implemented (such as some of the "once-off set up" program implementation costs and some of the non-test-kit costs of tier 1 screening).

ESC noted that the difference between a liquid chromatography (LC)-MS/MS machine and an electrospray ionisation MS/MS machine was considered and the costs of purchasing the former machine appropriately added to the implementation costs for this application. ESC recalled that MSAC supported the use of the latter machine in its consideration of sickle cell disease testing on the NBS (Application 1737.1).

ESC noted the largest financial impact would be to the NBS (**\$REDACTED** in Year 1 to **\$REDACTED** in Year 6), with a total cost to government health budgets inclusive of the NBS of **\$REDACTED** in Year 1 and **\$REDACTED** in Year 6.

ESC recognised an ethical obligation to inform parents of a potential diagnosis of GSD II, because further investigation of the child would require parental consent to proceed beyond the original bloodspot sample. Additionally, once further investigation is conducted, ethical principles of transparency and full disclosure would necessitate informing parents of the outcome of the further investigation including results indicating an adult-onset condition.

ESC queried whether the Revvity multiplex kit options should be excluded from consideration for use as part of the NBS given that they are dominated by the **REDACTED** options (that is, they are more expensive but are not more accurate) and may also report results for MPS conditions that health ministers have agreed should not progress to MSAC for possible inclusion in the NBS. Given the last point, ESC queried whether this may create ethical difficulties for the reporting pathologist that could be avoided by not using this test kit. However, the applicant clarified that pathologists have the option of not testing for all disorders when using the Revvity multiplex kits options, which may eliminate this ethical issue.

ESC noted the LSDP Expert Panel's avalglucosidase alfa 24-month review³⁸ in December 2024, and raised that MSAC may wish to refer the following matters to the LSDP Expert Panel:

- the prevalence of GSD II is already beyond the LSDP threshold, and projected to increase further with proposed expansion of the NBS
- whether to consider the basis for current LSDP criteria to permit ERT initiation in asymptomatic patients between the ages of 24 months and 18 years for individuals diagnosed via the NBS and suggestive of GSD II
- whether to (continue to) permit a dose of 40 mg/kg/eow (every other week) for patients with IOGSD II who experience insufficient control, or declining response to ERT at the TGA-approved initial dose as evidence suggested possible benefits associated with higher doses of ERT, compared to the recommended dose.
- ESC considered a revision to the current approach to assess the effects of multiplexing through undertaking a “bundled” stepped evaluation of applications 1774, 1775 and 1776. This approach should address any duplication of costs and ensure an appropriate assessment of cumulative diagnostic yield across the three applications. ESC recommended this work could be undertaken after MSAC has considered all three NBS applications and provided advice regarding the order in which the analyses should be stepped. ESC noted that ideally the order would be based on the base case ICER for each application (with the application having the lowest ICER included as the first step, then the next highest ICER). However, ESC recognised that MSAC may have an alternative view where it may prefer to nominate the application with the strongest case for NBS as the first step.

ESC further recommended that the following additional work be undertaken before MSAC consideration:

- Clarify whether the unit cost of the proposed NBS Tier 1 testing should be benchmarked (as per PSD for Application 1737.1) and if so which test components are to be included in the benchmark. MSAC should also be aware that this approach will not accurately reflect comparative cost-effectiveness because the ICER/diagnosis will vary by the genotypic prevalence of each disease and other incremental costs, and the ICER/QALY will also vary by the incremental health gains.
- obtain expert clinical advice on how all screen positive results would be managed, including
 - pseudodeficiency variants (are there some patients for whom disease would not be ruled out and would require monitoring?)
 - carriers
 - no GSD II variant found, and if this result is more likely in individuals with non-European ancestry.

³⁸ <https://www.health.gov.au/resources/publications/avalglucosidase-alfa-terms-of-reference-and-protocol-questions?language=en>

ESC noted that out of approximately 304,655 newborns screened a year it is estimated based on results of previous studies that 58 will screen positive at Tier 1 and of these, 1.0 will be diagnosed with IOGSD II, 9.6 with LOGSD II, 11.8 will be identified with pseudodeficiency, 20.1 will be identified as carriers while a remaining 15.2 will be confirmed as false Tier 1 positives. ESC sought further comment on the prognostic confidence of these respective subtypes at completion of NBS diagnostic confirmation i.e.

- Of the screen positive individuals identified with IOGSD II (1) vs LOGSD II (9.6) what percentage will have clear 'yes/no' cardiomyopathy results and what percentage will have unclear results?
- Of the screen positive individuals identified with LOGSD II (9.6) vs pseudodeficiency (11.8) vs 'carriers' (20.1) vs 'no GSD II' (15.2) what percentage of this combined group is likely to develop symptoms?

ESC noted that on 11 September 2024, the government announced it 'will end the ability to discriminate based on adverse predictive genetic test results by banning their use in life insurance underwriting'; however, as of 4 February 2025, the appropriate legislation had not yet been introduced and public consultation is ongoing.

Table 5 Summary table for the key Health Technology Assessment (HTA) questions for MSAC consideration

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for GSD II	Current (No universal NBS for GSD II) – diagnosis at symptom onset	Other/Increment/Comment
1) Suitable NBS tests?			
Availability	Partially. Tier 1 screening options include the GelbChem SKU: CS5 (GAA) Kit (although NATA approval is yet to be obtained). Tier 2 options involve small-panel genetic analysis targeting GAA sequencing, but these are yet to be defined. Tier 3 options such as urinary HEX4 may also be indicated. Cascade test options are already used and are determined by the proband's results.	-	MSAC should consider whether to advise that possible Revvity multiplex test options be excluded from this expansion of the NBS because they are dominated by other test options: (a) they are more expensive (b) they are not more accurate (c) they report results for conditions agreed by health ministers not to progress to MSAC for possible inclusion in the NBS, thus creating avoidable ethical difficulties for the reporting pathologist.
Accuracy ranges	First-tier screen positive: 0.015% - 0.41% positive predictive value: 3.5% - 50% sensitivity: 100% false positive rate: 50% - 96.5% Re-test positive: 0.008% - 0.15% positive predictive value: 15% - 80% sensitivity: 100% false positive rate: 20% - 86%	Positive GSD II cases of symptomatic patients tested: 0.8% - 2.9% positive predictive value: 17.5% - 100% (these are the best results, which came from patients older than 1 year of age who presented with unexplained elevated CK and/or undiagnosed limb-girdle weakness)	MSAC should consider whether to advise that an ethical obligation to inform parents of a possible GSD II diagnosis arises once further investigation of the child needs their consent to proceed beyond the original bloodspot sample and therefore an ethical obligation subsequently arises to inform the parents of the outcome of the further investigation.
2) Determination of disease subtype and prognosis following NBS?			
	Partially for disease sub-type. IOGSD II is determined via clinical evidence of cardiomyopathy, but for all other identified cases, LOGSD II cannot always be distinguished from pseudodeficiency. No for prognosis.	-	The current treated prognosis for IOGSD II is a median of life expectancy of 23.5 months (interquartile range 14.5 months to 44.5 months), but this result is among the 88/332 Pompe Registry ^a patients who died within the study period, so is right-censored (that is, younger than the expected overall median and interquartile range). The current treated prognosis for LOGSD II is not reported. Pseudodeficiency remains asymptomatic for life.

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for GSD II	Current (No universal NBS for GSD II) – diagnosis at symptom onset	Other/Increment/Comment
3) Effective treatment of each GSD II subtype?			
IOGSD II	Yes, ERT (alglucosidase alfa or avalglucosidase alfa) via the LSDP if the initial application is made before 24 months of age	-	Avalglucosidase alfa is not LSDP-approved before 12 months of age.
LOGSD II, presymptomatic	Yes, alglucosidase alfa or avalglucosidase alfa via the LSDP if the initial application is made after 24 months and before 18 years of age	-	
LOGSD II, symptomatic	Yes, alglucosidase alfa or avalglucosidase alfa via the LSDP if the initial application is made after 24 months of age	-	
Pseudodeficiency	Not required	-	
4) Increased effectiveness of earlier treatment start?			
Evidentiary basis = Linked evidence: earlier diagnosis => earlier management change => better health outcomes			
Age at symptom onset, median			
IOGSD II		26 days (economic model), compared to 2.0 months (Pompe Registry ^a)	
LOGSD II		in children ≤12 years: 2 years in adults and children >12 years: 38 years (economic model), compared to in children ≤12 years: 6.2 years in adults and children >12 years: 35 years (Pompe Registry ^a)	
Age at diagnosis, median			
IOGSD II	26 days (economic model)	Redacted (economic model and LSDP Registry ^b), compared to 4.6 months (Pompe Registry ^a)	
LOGSD II	26 days (economic model)	in children ≤12 years: Redacted in adults and children >12 years: Redacted (economic model and LSDP Registry ^b) compared to in children ≤12 years: 18.5 years in adults and children >12 years: 43 years (Pompe Registry ^a)	Redacted % of LOGSD II “onset” (present with diagnosis before 12 years of age Redacted % of LOGSD II “onset” after 12 years of age (economic model and LSDP Registry ^b) compared to 30% and 70% respectively (Pompe Registry ^a) derived from Table 65 in the DCAR (It appears the modeller has interpreted this as onset of

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for GSD II	Current (No universal NBS for GSD II) – diagnosis at symptom onset	Other/Increment/Comment
			symptoms rather than diagnosis, which is inconsistent with the basis of an LSDP application, , which may explain the greater – but largely inconsequential – discrepancy between the model estimates and the Pompe registry estimates of age of symptom onset, age at diagnosis and length of diagnostic delay for LOGSD II children ≤ 12 years)
Age at ERT treatment initiation after diagnosis			
IOGSD II	assumed to be immediate after diagnosis	assumed to be immediate after diagnosis	
LOGSD II	assumed to be immediate after (delayed) symptom onset	assumed to be immediate after (delayed) diagnosis	
Time to diagnosis (length of diagnostic delay). median			
IOGSD II	–	4.6 months (economic model) compared to 1.4 (range 0.0 to 13.9) months (Pompe Registry ^a)	
LOGSD II	–	in children ≤ 12 years: 4 years in adults and children >12 years: 7 years (economic model), compared to children ≤ 12 years: 12.6 (range 0 to 60) years, in adults and children >12 years: 6 (range 0 to 49.8) years (Pompe Registry ^a)	
Proportion with diagnostic delay	–	100% (economic model)	
IOGSD II	–	100% (economic model)	
LOGSD II	–	100% (economic model)	
Proportion of GSD II affected cases monitored		–	
IOGSD II	0	–	
LOGSD II	82.6% (economic model)	–	
Treatment effectiveness			
Early vs late ERT (20 mg/kg alglucosidase alfa or avalglucosidase alfa every other week) in IOGSD II (retrospective cohort study in Taiwan which initially used a different NBS algorithm)	At 50 months' follow-up: 100% (13/13) alive 100% (13/13) ventilation-free	At 50 months' follow-up: 50% (5/10) alive 20% (2/10) ventilation-free	Based on Kaplan Meier analysis (test not specified, but likely a log-rank test): $p=0.028$ for the overall survival difference $p<0.001$ for the ventilation-free overall survival difference.

Parameter	Proposed – Universal Newborn Bloodspot Screening (NBS) for GSD II	Current (No universal NBS for GSD II) – diagnosis at symptom onset	Other/Increment/Comment
Early vs late ERT in LOGSD II			No robust data reported to enable any comparison.
5) Cost-effectiveness?			
ICER (\$/extra diagnosis of GSD II) Step 1 base case model (per 100,000), test costs only (including diagnostic delay costs)	Cost: \$Redacted GSD II diagnoses: 3.48	Cost: \$Redacted GSD II diagnoses: 2.19	Incremental cost: \$Redacted Incremental diagnoses: 1.29 ICER: \$Redacted
ICER (\$/extra diagnosis of GSD II) Step 2 base case model (per 100,000), adding annual surveillance and earlier ERT costs	Cost: \$Redacted GSD II diagnoses: 3.48	Cost: \$Redacted GSD II diagnoses: 2.19	Incremental cost: \$Redacted Incremental diagnoses: 1.29 ICER: \$Redacted
Exploratory ICER (\$/QALY gained) Step 4, adding discounted survival and quality of life gains and prolonged ERT costs	Cost: \$Redacted to \$Redacted QALY: 1,633,752.41 to 1,633,753.74	Cost: \$Redacted QALY: 1,633,750.30	Incremental cost: \$Redacted to \$Redacted Incremental QALY: 2.1131 to 3.4370 ICER: \$Redacted to \$Redacted
Utilisation – incident cases			
Number of GSD II affected cases diagnosed per year	10.60 (Year 1 to 6) = 1.74/50,000, which is greater than 1/50,000	6.67 (Year 1) to 6.69 (Year 6) = 1.09/50,000, which is greater than 1/50,000	
Proportion IOGSD II	9% (economic model)	15% (economic model)	
Proportion LOGSD II	91% (economic model)	85% (economic model)	
Number with IOGSD II	1.00 (Year 1 to 6)	1.00 (Year 1 to 6)	
Number with LOGSD II	9.60 (Year 1 to 6)	5.67 (Year 1) to 5.69 (Year 6)	
Number with pseudodeficiency	11.8	–	
Number of carriers	20.1	–	
6) Financial estimates for each budget holder?			
Program implementation costs	\$Redacted (Year 1)		\$Redacted (Year 1)
Total cost to the NBS	\$Redacted (Year 1) to \$Redacted (Year 6)	–	\$Redacted (Year 1) to \$Redacted (Year 6)
Cost to States and Territories	\$0.05m (Year 1) to \$0.16m (Year 6)	\$0.01m (Year 1) to \$0.01m (Year 6)	\$0.04m (Year 1) to \$0.14m (Year 6)
Cost to the MBS (Commonwealth)	\$0.03m (Year 1) to \$0.06m (Year 6)	\$0.01m (Year 1) to \$0.01m (Year 6)	\$0.03m (Year 1) to \$0.04m (Year 6)
Cost to the LSDP (Commonwealth)	\$Redacted (Year 1) to \$Redacted (Year 6)	\$Redacted (Year 1) to \$Redacted (Year 6)	\$Redacted (Year 1) to \$Redacted (Year 6)
Cost to government health budgets	\$Redacted (Year 1) to \$Redacted (Year 6)	\$Redacted (Year 1) to \$Redacted (Year 6)	\$Redacted (Year 1) to \$Redacted (Year 6)

^a The Pompe Registry is a multinational (including 6 Australian sites), on-going, long-term (to 2034), observational registry collecting data on GSD II patients registered since 2004. It is sponsored and administered by Genzyme, a Sanofi company (Cambridge, MA) and contains the largest collection of data on these patients in the world. ^b The LSDP Registry is an ongoing collection of data on patients receiving therapy via the LSDP, including patients with GSD II since 2010. It includes data on at least REDACTED IOGSD II patients and REDACTED LOGSD II patients

Source: Compiled by the Department from the 1774 Department Contracted Assessment Report and financials spreadsheet “04. DCAR 1774 - Financials-Final”

Abbreviations: ERT= enzyme replacement therapy; GSD II = glycogen storage disease Type II; HEX4 = glucose tetrasaccharides; ICER= incremental cost-effectiveness ratio; m = month(s); IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; LSDP= Life Saving Drugs Program; MBS = Medicare Benefits Schedule; NBS = newborn bloodspot screening; QALY= quality-adjusted life year

Table 6 Summary table of estimated annual consequences of Newborn Bloodspot Screening for GSD II (Pompe disease)

Screened	Tier 1 result to parents	Subsequent diagnosis to parents	Incremental consequence of screening for patients ^c	Health outcome consequences for patients	Incremental cost-effectiveness outcomes for patients
304,655 ^a	304,597 no	—	—	—	—
	58 yes ^b	1.0 IOGSD II	Patient diagnosed 1.4 to 4.6 months earlier	Earlier ERT treatment shown to improve ventilation-free survival and overall survival	\$Redacted /QALY to \$Redacted /QALY
		9.6 LOGSD II	4 more patients diagnosed, all diagnosed years earlier	ERT treatment given before symptoms appear not shown to improve outcomes; may cause harms such as developing antibodies; later diagnostic delay shortened	Redacted
		11.8 pseudodeficiency	11.8 patients identified with pseudodeficiency	None shown and no intervention needed	—
		20.1 carriers	20.1 patients identified as carriers	Helps inform reproductive decisions	—
		15.2 no GSD II	15.2 patients confirmed as false Tier 1 positives	None shown and no intervention needed	—

^a Figure chosen to align with projected number of births in 2025-26 and 99.3% uptake rate which is aligned with utilisation estimates in financials

^b MSAC should consider whether to advise that a new informed consent be obtained from these parents at this point to enable subsequent testing beyond the bloodspot sample based on the positive Tier 1 result.

^c These consequences do not include any estimates of incremental consequences from cascade testing

Abbreviations: ERT= enzyme replacement therapy; GSD II = glycogen storage disease Type II; IOGSD II = infantile-onset glycogen storage disease Type II; LOGSD II = late-onset glycogen storage disease Type II; QALY= quality-adjusted life year

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)