

MSAC Application 1774

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

Applicant: Department of Health and Aged Care

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

A summary of the PICO criteria to define the questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC) are shown in Table 1 and Table 2.

Table 1 PICO for newborn bloodspot screening (NBS) for glycogen storage disease type II (GSD II, Pompe disease): PICO Set 1

Component	Description
Population	All newborn babies in Australia
Prior tests	No prior testing
Intervention	<p>Newborn bloodspot screening (NBS) to detect glycogen storage disease type II (GSD II, also known as Pompe disease):</p> <p>1st-tier: quantification of the alpha-glucosidase (GAA) enzyme activity using tandem mass spectrometry (MS/MS) or a fluorometric assay on a dried bloodspot (DBS)</p> <p>2nd tier: rapid genetic testing for common GAA variants</p> <p>Diagnostic testing in those with a positive screening result (testing protocol as per the comparator)</p>
Comparator/s	<p>Current practice – diagnostic testing for GSD II at the point of onset of phenotypic signs & symptoms or a family history; no universal newborn screening for GSD II</p> <p>Diagnostic testing:</p> <ul style="list-style-type: none"> • History, clinical examination (may include electrophysiological testing for older children) • Cardiac assessment (chest radiography, echocardiogram or electrocardiogram) • GAA enzyme assay on DBS, or leukocytes, urinary tetrasaccharide (HEX4), which is required to meet LSDP eligibility criteria • Molecular genetic testing for common GAA variants • Respiratory function (age dependent) <p>If considered to have GSD II based on diagnostic testing and 2 GAA variants not identified during testing for common GAA variants:</p> <ul style="list-style-type: none"> • Extensive sequencing of the GAA gene to predict cross-reactive immunological material (CRIM) status in those with infantile-onset GSD II (IOGSD II) and allow cascade testing <p>If IOGSD II and GAA gene sequencing not informative on CRIM status:</p>

Component	Description
	<ul style="list-style-type: none"> Assessment of CRIM status using cultured skin fibroblasts
Reference standard	A confirmed diagnosis following clinical assessment and diagnostic biochemical and genetic testing.
Outcomes	<p>Screening test performance</p> <ul style="list-style-type: none"> Accuracy of the screening test (sensitivity, specificity, positive predictive value (what proportion of screen positive cases are GSD II rather than pseudodeficiencies), negative predictive value) Diagnostic accuracy of confirmatory/diagnostic test (sensitivity, specificity, positive predictive value, negative predictive value) Accuracy of classification (infantile vs late-onset) Diagnostic yield of screening <p>Change in management:</p> <ul style="list-style-type: none"> Age at diagnosis Age at treatment initiation (and whether prior to, or after phenotype onset) Time between phenotype onset and diagnosis (length of diagnostic odyssey) Investigations/monitoring/treatments received CRIM status Genetic counselling Psychological counselling <p>Clinical Effectiveness of NBS for GSD II:</p> <ul style="list-style-type: none"> Change in morbidity and mortality, quality of life, general functioning and disease manifestations from earlier diagnosis, intervention, and/or avoidance of the diagnostic odyssey (either from studies assessing the impact of comparative change in management, or direct from test to health outcomes evidence) <p>Safety of NBS for GSD II (physical harms to newborn from screening test, diagnostic test or subsequent treatment):</p> <ul style="list-style-type: none"> Impact of false positive screening results (physical harms to the infant or psychological harms to the parents or individual (age-dependent)) Impact of false negative results Impact of diagnosing late-onset cases at birth, creating “patients in waiting” Impact of detecting variants of uncertain significance (VUS) and novel variants Any potential risk of harm from ongoing monitoring and surveillance Safety of enzyme replacement therapy (ERT) <p>Economic and Financial Implications:</p> <ul style="list-style-type: none"> Cost-effectiveness of NBS for GSD II (cost per diagnosis; cost per quality adjusted life year (QALY))

Component	Description
	<ul style="list-style-type: none"> Financial impact of screening, relative to existing practice (including impact of false positives, impact of screening-based treatment compared to treatment following diagnosis at phenotype presentation, impact of ongoing monitoring and surveillance inclusive of genetic counselling and psychologist support) <p>Other relevant considerations:</p> <ul style="list-style-type: none"> Non health outcomes: Value of knowing (emotional benefits/harms to family, social benefits/harms to family) Ethical considerations (equity of access, considerations regarding consent) Organisational considerations (incremental impact of NBS on organisations, particularly the impact on services for monitoring late-onset disease, or on the NBS programs, including programmatic implementation considerations)
Assessment question	What is the comparative safety, effectiveness, cost-effectiveness and financial impact of NBS for GSD II versus current practice (no NBS, diagnosis on presentation of signs and symptoms)?

Table 2 PICO for cascade testing of family members of newborns diagnosed with GSD II via NBS: PICO set 2

Component	Description
Population	Biological parents and siblings of an individual (index case) with two pathogenic/likely pathogenic (P/LP) variants in the <i>GAA</i> gene
Prior tests	Family history
Intervention	<p>Cascade testing after diagnosis of a newborn due to NBS:</p> <ul style="list-style-type: none"> For parents: Genetic counselling and genetic testing for the specific familial variants in the alpha-glucosidase gene (<i>GAA</i>) identified in the newborn, using <i>GAA</i> gene sequencing. For siblings: <i>GAA</i> enzyme activity testing (on DBS, or leukocytes), followed by <i>GAA</i> gene sequencing for the familial variant if <i>GAA</i> enzyme activity below cut-off for suspected GSD II.
Comparator	<p>Cascade testing after diagnosis of a symptomatic child:</p> <ul style="list-style-type: none"> For parents: Genetic counselling and genetic testing of parents for the specific familial variants in the alpha-glucosidase gene (<i>GAA</i>) identified in the newborn, using <i>GAA</i> gene sequencing. For siblings: <i>GAA</i> enzyme activity testing (on DBS, or leukocytes) of siblings, followed by <i>GAA</i> gene sequencing for the familial variant if <i>GAA</i> enzyme activity below cut-off for suspected GSD II.

Component	Description
	<i>(i.e. the same testing strategy as the intervention, differing only in the timing of the testing).</i>
Outcomes	<p>Test outcomes:</p> <ul style="list-style-type: none"> • Number of siblings with early diagnosis of GSD II • Number of family members who uptake cascade testing • Age at diagnosis/treatment of affected siblings <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> • Effectiveness of early vs late monitoring/treatment • Effectiveness of immune modulation in CRIM negative probands <p>Safety:</p> <ul style="list-style-type: none"> • Physical or psychological harms arising from earlier diagnosis, monitoring and treatment for siblings diagnosed with GSD II following cascade testing, including the impact of diagnosing siblings with attenuated disease who may not become symptomatic for many years • Any potential risk of harm from ongoing monitoring and surveillance • Harms arising from immunomodulation in patients treated prior to defining their CRIM status. <p>Financial and economic outcomes:</p> <ul style="list-style-type: none"> • Cost-effectiveness • Financial impact of early vs late cascade testing • Total Australian Government health care costs <p>Other relevant considerations:</p> <ul style="list-style-type: none"> • Non health outcomes: Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family) • Ethical considerations (equity of access, considerations regarding consent, considerations regarding cascade testing, especially relating to identification of late-onset GSD II in asymptomatic newborns) • Organisational considerations such as discussing the impact of diagnoses on clinic visits, cardiology, metabolic laboratory, radiology and physiotherapy
Assessment question	What is the comparative safety, effectiveness, cost-effectiveness of cascade testing of family members of newborns identified with GSD II due to NBS, versus cascade testing of family members following diagnosis of GSD II in the affected individual after presentation with signs/symptoms?

Purpose of application

An application requesting that glycogen storage disease type II (GSD II, also known as Pompe disease) be added to the newborn bloodspot screening (NBS) programs was developed by the Department of Health, following a request from the Hon Mark Butler MP, Minister for Health and Aged Care.

NBS programs are overseen and managed by state and territory governments and operate independently of each other. The Australian Government contributes funding to hospital services, including those for NBS through the National Health Reform Agreement (NHRA). Funding of \$39.0 million was announced under the 2022-23 Budget, of which \$25.3 million was provided to states and territories to support expansion of NBS programs. This application, as well as applications for NBS for mucopolysaccharidosis type I and II (MPS I and II; application numbers 1775 and 1776) form part of this expansion. All three conditions are lysosomal storage disorders (LSDs) and there is overlap in the tests used to diagnose these three conditions. Therefore, other LSDs may be discussed when considering testing methodologies.

There are five laboratories that conduct tests on bloodspot cards, located in New South Wales, Queensland, South Australia, Victoria and Western Australia. Newborns born in states and territories without NBS testing laboratories have their dried bloodspots sent interstate for testing. All NBS programs are underpinned by the Newborn Bloodspot Screening National Policy Framework (NBS NPF).

Proposals to add conditions to NBS are considered by the Medical Services Advisory Committee (MSAC). In providing its advice MSAC considers the safety, effectiveness, cost-effectiveness and total cost of proposals for public funding, noting that for NBS applications alignment with the NBS NPF decision-making criteria (Appendix A) is a key additional policy consideration.

The overall claim is that universal NBS for GSD II has superior safety and effectiveness compared to current practice (no universal screening; diagnosis upon symptomatic presentation) for diagnosis of GSD II. Early diagnosis of GSD II due to NBS rather than current practice (investigations following signs/symptoms of GSD II) results in earlier commencement of treatment, which can significantly extend the life of those with infantile-onset GSD II (IOGSD II), delaying deterioration and maintaining a higher level of functioning/quality of life.

In addition to the detection of IOGSD II, NBS for GSD II would also detect cases of late-onset GSD II (LOGSD II). The benefit of identifying cases of LOGSD II in newborns is currently unclear, as although there may be benefits in avoiding the diagnostic odyssey and initiating treatment prior to symptom onset, it can be difficult to predict when symptoms would otherwise be likely to occur. Furthermore, there are some cases who may be diagnosed as having late-onset GSD II, who may never develop clinical features of the condition (i.e. these pseudodeficiencies are considered false positives). There is also a risk that early diagnosis could cause harms, due to the psychological impact of receiving a diagnosis, and physical harms of undergoing ongoing monitoring (and potentially treatment). Therefore while the clinical claim of the application is that NBS for LOGSD II has both superior effectiveness and non-inferior safety to current practice, these considerations suggest that a more reasonable clinical claim would be for superior effectiveness but inferior safety.

PICO criteria (PICO set 1)

Population (PICO Set 1)

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

PASC noted that the population was all babies who participated in universal NBS programs.

GSD II is a lysosomal storage disorder (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. The accumulation of glycogen disrupts the cytoarchitecture and function of affected cells, leading to multisystem disease and often, early death.

GSD II is a single gene disorder that has an autosomal recessive inheritance pattern. Pathogenic variants of the alpha-glucosidase gene (*GAA*) cause reduced activity of the gene and hence a deficiency of the enzyme, and in some cases virtually no enzyme is produced. The most severe cases of GSD II are associated with very low or no *GAA* activity, whereas milder cases of GSD II occur when there is some degree of enzyme production. Non-pathogenic variants, variants of uncertain significance (VUS) and pseudodeficiency variants are also identified through genetic sequencing. Pseudodeficiency and benign *GAA* variants are associated with lower *GAA* enzyme levels, but do not cause GSD II. A VUS may be reclassified as likely pathogenic (disease-causing), or benign (not disease-causing), in the future based on further information on the genotype-phenotype relationship for that variant, as it is acquired.

Treatment is available and funded through the Life Saving Drugs Program (LSDP) when eligibility criteria are met; more information is available in the intervention section of this document.

The two main categories of clinically determined GSD II are infantile-onset (which represents approximately one-third of cases) and late-onset (two-thirds of cases). All cases have the potential to be identified through universal NBS; however, screening will not always distinguish between the different categories of disease. NBS may also identify asymptomatic or uncertain cases that cannot be definitively determined as symptoms may develop late in life.

The most important category of GSD II to identify through screening is infantile-onset GSD II. This is the most serious form of the disease, with severe symptoms appearing within the first few months of life. Without treatment, most patients have unremitting deterioration and will die within the first year from cardiac insufficiency. Previous research had suggested that when initiated before 6 months, treatment with enzyme replacement therapy (ERT) extends survival, but may not extend this beyond early childhood. While registry data suggests that the median age of death while on ERT was 23.5 months (interquartile range 14.5 months to 44.5 months) (Kishnani et al. 2023) this was among the 26.5% (n= 88/332) patients that died within the study period.

Infantile-onset GSD II is further categorised into classic and non-classic types.

Clinical advice from the co-applicant had suggested that the term non-classic infantile-onset GSD II was no longer used (therefore patients with GSD II are either classified as classic infantile-onset GSD II or late-onset GSD II). PASC discussed that 'late-onset GSD II' may not always be an accurate description of the condition, as signs of disease may be found earlier than symptom-onset (if they are screened for/monitored), LSDP criteria categorises cases as infantile-onset or late-onset, therefore these categories align with existing clinical pathways to receive ERT.

IOPD usually has cardiomyopathy as a feature (85% of cases, (Kemper et al. 2013)) and leads to:

- severe cardiomegaly (a large heart)
- hypertrophic cardiomyopathy (thickening of the heart muscle)

- hepatomegaly (a large liver)
- general muscle weakness
- hypotonia (low muscle tone)
- feeding problems (due to low muscle tone in the face, a large tongue, tongue weakness, and/or difficulty moving the lips, tongue and jaw)
- breathing problems
- hearing problems and
- early death (from heart and lung failure due to the accumulation of glycogen).

Findings from clinical studies suggest that early identification and treatment of infantile-onset GSD II prior to the development of irreversible damage can lead to decreased morbidity and mortality compared to diagnosis at the time of clinical presentation (Kemper et al. 2013). Considering the rapid progression of the disease, timely diagnosis and treatment are important; even slight delays can remarkably alter the course of the disease (Hassnan et al. 2022). NBS can lead to an early diagnosis and enable access to presymptomatic enzyme replacement therapy (ERT) initiation. This has been shown to prevent cardiac and respiratory complications and helps in achieving normal growth and development in patients with infantile-onset GSD II (Hassnan et al. 2022).

The other category of GSD II is late-onset. This type of disease can be diagnosed at any age, with an Australian study of children and adults being diagnosed with GSD II through the National Referral Laboratory between 2009 and 2020 reporting the age at diagnosis to range from 10 weeks to 69.7 years (median age 36 years) (Chin & Fuller 2022). The late-onset type is characterised by slower disease progression, primarily impacting the skeletal muscles and often progressing to wheelchair confinement and eventual respiratory failure (Chin & Fuller 2022). Symptoms include:

- muscle weakness
- breathing problems
- difficulty exercising
- hepatomegaly (large liver) and
- difficulty chewing or swallowing.

Patients with late-onset GSD II do not develop cardiomyopathy but have significant morbidity and mortality due to skeletal muscle myopathy and diaphragmatic insufficiency. However, there is considerable variation in the age of symptom onset, and clinical presentation of late-onset GSD II can range from asymptomatic to severe. There is variability even in patients with identical genetic variants, suggesting that secondary factors may influence the clinical course (Winkel et al. 2005). The diagnosis of the late-onset form is often difficult because it can clinically resemble a range of other neuromuscular disorders (Cupler et al. 2012). Hence a high level of clinical suspicion is needed for a timely diagnosis, if not known previously (Kishnani et al. 2006). Imaging and histologic studies suggest that there is muscle damage by the time that cases of late-onset GSD II are clinically detected (Kemper et al. 2013).

GSD II has an estimated incidence of about 1/47,000 in Australia, based on diagnostic testing after presentation with symptoms, or family history (Chin & Fuller 2022). However, it varies based on ancestry. A recent global estimation of incidence was 1/23,000 (Park 2021). A large-scale pooled analysis of clinical studies from the US reported that 28% of GSD II cases were found to be infantile-onset, and most of those classic infantile-onset disease (Dasouki et al. 2014).

PASC noted that the prevalence of clinically diagnosed GSD II estimated in Australia (1/47,000) was too common to be considered 'ultra-rare' according to the criteria currently used for conditions being considered for the Life Saving Drugs Program (1/50,000) when including IOGSD II and LOGSD II cases. If GSD II is screened for, it is expected that overall prevalence would increase (consistent with what has been reported in other jurisdictions where screening programs have been introduced) with the increase being in LOGSD II and uncertain cases. It is expected that all IOGSD II cases are clinically detected under current management but would be diagnosed earlier with NBS.

It was estimated that approximately 6 – 17 babies would be diagnosed with GSD II per year, if introduced to NBS programs. It was estimated that 2 – 5 may have IOGSD II. Therefore, NBS for GSD II is expected to mostly identify LOGSD II – a condition that typically arises in adulthood or later childhood.

In addition to infantile-onset GSD II and late-onset GSD II, screening may detect known pseudodeficiency variants, where GAA enzyme activity is low in healthy newborns, who do not have or develop GSD II. These would be considered as false positive if reported, but addition of a second tier test for the common pseudodeficiency alleles may accurately identify the 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 stage of screening.

Intervention (PICO Set 1)

Screening

The proposed health technology is universal NBS for GSD II through Australia's NBS programs.

Newborn screening for GSD II is carried out using mass spectrometry (MS) or fluorometry on a dried bloodspot sample (DBS) collected onto filter paper in alignment with existing practice in the NBS programs. MS will be used to identify levels of alpha-glucosidase (GAA), an enzyme that is deficient or absent in GSD II. Enzyme analysis of blood samples is not specific enough to enable the differentiation between infantile-onset and late-onset GSD II. However, alpha-glucosidase activity levels >1% have generally not been noted in patients with classic infantile-onset GSD II, therefore levels <1% can support the diagnosis of infantile-onset GSD II (Kishnani et al. 2006). The test for GSD II can be conducted on the NBS sample as it is collected currently, so there is no additional resourcing required for sample collection, nor is there any additional risk to the baby associated with collection.

Screening for reduced blood alpha-glucosidase is often multiplexed with other lysosomal storage disorders (LSDs) (either via fluorometric, digital microfluidics, or tandem mass spectrometry-based technologies), given that treatment is also available for these disorders (Mechtler et al. 2012).

MSAC has previously advised that "*ideally in future the number of methods assessed should be reduced if possible*" (1737 PSD, pg 7). Each state screening laboratory is responsible for determining their preferred approach to screening for each condition on the NBS programs.

Expert advice from the New South Wales (NSW) NBS laboratory and the South Australian (SA) NBS laboratory/National Referral Laboratory, have expressed that the optimal screening protocol has not been determined. The methods currently in use result in a high number of false positives primarily caused by

pseudodeficiencies, and most patients identified will not have infantile-onset GSD II (that is, they will either have late-onset GSD II or pseudodeficiencies).

The Western Australian NBS laboratory indicated that they would use flow injection analysis (FIA) mass spectrometry (MS/MS) enzymology, using the commercial kit Revvity NeoLSD. This kit quantitatively measures the activity of the GAA enzyme, as well as the acid- β -glucocerebrosidase (ABG), acid-sphingomyelinase (ASM), β -galactocerebrosidase (GALC), α -galactosidase A (GLA) and α -L-iduronidase (IDUA). It can therefore be used to screen for GSD II at the same time as MPS I, Fabry disease, Gaucher disease, Niemann-Pick A/B and Krabbe disorders from a single punch. However, advice from REDACTED is that the kit is unnecessarily expensive, when a single enzyme assay is adequate.

Table 3 Methods of NBS for GSD II proposed to be used by different NBS programs in Australia

State	First-tier screen	Second-tier screen	Third-tier / Diagnosis
Western Australia	FIA-MS/MS enzymology using Revvity NeoLSD	Referred to Adelaide Women's and Children's Hospital National Referral Centre for Lysosomal storage diseases	GAA sequencing either in WA or AWCH using in-house test (refer to genotyping laboratory)
New South Wales	Assay to measure GAA activity	Not yet established	Urine HEX Molecular genetic testing
South Australia	Unclear. GAA enzyme activity insufficient. Recommending a pilot of enzyme activity, creatine/creatinine ratios, urinary HEX4 and genetic studies		

AWCH = Adelaide Women's and Children's Hospital; FIA MS/MS = flow injection analysis mass spectrometry; GAA = *alpha* glucosidase; HEX4 = glucotetrasaccharides; WA = Western Australia

Internationally, many different screening protocols for GSD II are available. For a summary, please see the table by Gragnaniello et al. (2022) provided in Appendix C. The first-tier screen is most commonly MS/MS to assess GAA enzyme activity (18 NBS programs). The majority of programs do not have a second-tier screen, or have genetic analysis as either the second-tier screen or confirmatory testing. After an abnormal single or second-tier screen, the parents would be contacted and the newborn would be referred for diagnostic testing.

PASC acknowledged that the assessment report will need to evaluate one screening protocol for the purposes of the economic analysis. PASC decided that the screening protocol (for evaluation, noting that states and territories may decide to implement a different screening protocol), should be GAA enzyme activity testing, followed by rapid genetic testing for common GAA variants (on the dried bloodspot) to facilitate timely ERT access for individuals with IOGSD II and rule out pseudodeficiencies.

Second tier testing is proposed using targeted sequencing of common GAA variants on a DBS sample collected at birth. Targeted sequencing can be performed with a short turn-around-time, and can frequently diagnose infantile-onset or late-onset GSD II through the identification of known P/LP variants, or identify common pseudodeficiency variants (and may therefore rule out GSD II). In addition, targeted gene panel testing may suggest CRIM status in a newborn. IOGSD II, LOGSD II and pseudodeficiency cases will not all be distinguishable by this method, as there are many rare variants and VUS.

One advantage of doing a rapid targeted genotype test is that it may determine CRIM status. It was noted that in New York, genetic testing is performed before reporting results to families. An expert advisor to

PASC explained that a single pseudodeficiency allele or single late-onset allele allows confident classifications to be made especially if a full gene sequencing is performed.

PASC requested expert advice be sought on whether HEX4 testing could be performed on DBS. PASC noted out of session clinical expert input was received that indicated that HEX4 testing had not been performed on DBS in their laboratory. Therefore this could not be used as an additional tier of testing at this time.

PASC noted that NBS for GSD II will identify cases of both infantile-onset GSD II and late-onset GSD II, and that it is not possible to accurately distinguish between the two for all cases prior to recalling the patient, which may contribute to uncertainty for patients and their families.

Diagnosis

Following second tier testing (targeted GAA sequencing), a newborn should be recalled for clinical examination unless GSD II has been ruled out through the identification of pseudodeficiency variants.

Signs of cardiomyopathy will be investigated to identify infantile-onset GSD II (chest X-ray, echocardiogram or electrocardiogram). The presence or suspicion of cardiomyopathy following a positive screening result requires urgent management to get confirmatory testing and ERT initiated as soon as possible. Babies with cardiomyopathy should have pathology tests performed to support the IOGSD II diagnosis. A urine glucose tetrasaccharide test (also known as hexose tetrasaccharide, or HEX4 test) will be requested concurrently with a repeat DBS for GAA activity. Glucose tetrasaccharide (Glc4) is a metabolite of glycogen and is raised in people with GSD II. Excess Glc4 is excreted in the urine and can be used to screen and monitor GSD II in the HEX4 test. However, Glc4 can also be elevated in other glycogen storage disorders, so should be used in conjunction with other tests if other GSDs are suspected. Creatinine kinase level (CK) is another test that can be supportive of a GSD II diagnosis.

In the current clinical setting, for access to ERT through the LSDP, a diagnosis of GSD II needs at least 2 of the following:

- GAA enzyme activity levels on dried bloodspot, lymphocytes and/or skin fibroblasts or skeletal muscle
- Documented urinary HEX4 indicating diagnostic elevation of glucose tetrasaccharides
- Documented disease-causing variant(s) in the GAA gene.

In those who are diagnosed with GSD II but do not have common variants identified in second tier screening, diagnostic GAA sequencing will be performed to identify the P/LP variant(s). The rate of detection of pathogenic, likely pathogenic, VUS, and pseudodeficiency variants in Australia will depend on the prevalence of specific variants in this country. GAA gene sequencing could be performed as the confirmatory test when the result is less urgent i.e. when there are no cardiomyopathy signs and/or late-onset GSD II is suspected. If a VUS is detected, segregation analysis and further testing to classify the pathogenicity of the VUS may be required. Segregation studies of the VUS associated with low GAA enzyme activity in the family would provide evidence towards the classification of pathogenicity of the VUS and its inheritance pattern. For cases where there is low enzyme activity but normal cardiac function, diagnosis of late-onset GSD II will depend on the GAA sequencing result, including analysis with parental DNA. Evaluation of symptoms such as muscle weakness, impaired pulmonary function, and subtle developmental delay would occur regularly. Sequencing results can provide input on whether P/LP variants, pseudodeficiency variants, VUS, or combination of variant types was present.

For screen positive individuals who do not have cardiomyopathy and are not identified with common variants for IOGSD II, there would be a need to perform non-rapid sequencing for uncommon variants.

Sequencing has the potential to distinguish between infantile-onset and late-onset forms, and also distinguish pseudodeficiency of alpha glucosidase from genuine GSD II VUS as there are some variants with known associations (Dasouki et al. 2014; Mechtler et al. 2012; Sawada, Kido & Nakamura 2020). However, there are now more than 634 recorded variants in GAA and sequencing is therefore limited in its ability to differentiate. An additional complication is that there is a large degree of variation in symptom severity, particularly the late-onset cases. This is why clinical assessment is vital to diagnosis.

PASC discussed the importance of psychological support and education for families of diagnosed newborns, particularly those diagnosed with late-onset GSD II, who may be living with anxiety for many years.

Although NBS for GSD II has been introduced into some jurisdictions internationally, PASC noted that there was uncertainty about the optimal screening protocol, as many screening protocols used to have a high rate of false positives and a low positive predictive value. One exception is Taiwan, which performs NBS using enzyme testing as a first-tier screen, followed by common variant testing. The reason that this testing strategy has reasonable predictive value, is that there are some very common variants found in people of Taiwanese ancestry for late-onset GSD II and pseudodeficiencies. The success of the Taiwanese screening program may therefore not be applicable elsewhere, where there are more heterogeneous variants observed in the GAA gene.

PASC noted that although a rapid genetic test may be useful for assessing common variants, the spectrum of variants is very diverse, and the ability to determine that a variant is pathogenic/likely pathogenic is ancestry-dependent (if the patient has non-Caucasian ancestry, they are more likely to have variants of uncertain significance than Caucasians). PASC noted that there is currently no Australia-wide registry data for GSD II.

Table 4 shows an estimate of case numbers which will be detected by screening in Australia, based on a projection provided by Kemper et al (2013) in a US population is given in Table 4. The data are also based on an estimated incidence of 2.14 cases per 100,000 of GSD II taken from Chin and Fuller (2022), and an annual birth estimate of 312,380 for the 2025-2026 financial year. The positive predictive value of screening will be highly dependent on the screening methods employed by the laboratories, including the choice of second tier test or the use of repeat screening.

Table 4 Estimated cases detected through NBS for GSD II in Australia for the financial year 2025-2026

Screening results in 312,380 newborns	Rate	Number
Total positive screens	0.00655%	20
True positives	51.1% of positives	10
False positives (pseudodeficiencies)	48.9%	10
Total negative screens	99.99%	312,360
True negatives	99.99%	312,359
False negatives	0.00025%	1

¹ US projected data are reported in Kemper et al (2013), (Table C.6). The US data was calculated using screening rates identified in the Taiwan NBS program for GSD II which uses a fluorometric assay for DBS GAA. The data may not apply in an Australian setting.

Treatment

There is currently no cure for GSD II, but treatment with ERT has been found to delay symptom onset, slow the rate of progression of the disease, lengthen survival and improve motor development and cardiac function. Those with infantile-onset GSD II are likely to have cardiomyopathy at birth, but other forms of

GSD II may be diagnosed pre-phenotypically (for instance through cascade testing) and treated prior to signs of disease though any pre-phenotypic ERT treatment would be subject to numerous conditions (discussed further below).

In Australia, alglucosidase alfa (Myozyme®) and avalglucosidase alfa (Nexviazyme®), are listed on the Australian Register of Therapeutic Goods (ARTG) for the long-term treatment of patients with a confirmed diagnosis of GSD II and can be administered for both infantile-onset GSD II and late-onset GSD II. However, Nexviazyme® is only indicated for patients aged one year and older.

The management of GSD II requires a team of specialists, including a metabolic genetics expert, a cardiologist, a respiratory physician, neurologist/neuromuscular specialist, immunologist, general paediatrician, general practitioner, speech therapist, gastroenterologist, ENT surgeon, audiologist, orthopaedic surgeon, radiologist, orthotist, rehabilitation specialist and a genetics counsellor (STAR-G 2024). In the Australian context, a dietitian and social worker would also be involved in care. Treatments for GSD II include:

- enzyme replacement therapy (ERT)
- respiratory support, and as symptoms progress, may require non invasive or mechanical ventilation
- cardiac care (medications to treat cardiomyopathy)
- physiotherapy (help strengthen muscles, improve motion, develop motor skills)
- psychosocial support (individual and family counselling, disease education, support groups for managing the emotional and psychological impact of the disease)
- general medical care (nutrition advice, tube feeding if required) (STAR-G 2024).

In cases of infantile-onset GSD II, immunomodulation, followed by ERT would be initiated immediately after diagnosis, while cross-reactive immunological material (CRIM) status is investigated (either through GAA sequencing or Western blot analysis of cultured skin fibroblasts). In CRIM-positive babies, the immunomodulation may be ceased, if indicated, while in CRIM-negative babies, it is usually continued. Follow-up programs are begun, to review tolerance of ERT, and evaluate the progression of disease. Treatments are adjusted when required.

Some cases are diagnosed with late onset GSD II via investigations following NBS in asymptomatic infants; these patients are monitored or may receive treatment with ERT if there are signs of a severe phenotype. Signs and symptoms of late-onset GSD II typically present during the second and sixth decade of life. Currently, ERT is available through LSDP for late-onset GSD II for patients aged between 2 and 18 years prior to the onset of signs or symptoms. After 18 years severe clinical manifestations are required to access ERT as per LSDP criteria.

In the current setting without NBS for GSD II in Australia, there are currently no agreed guidelines for monitoring late-onset GSD II. Individuals with late onset GSD II will be potentially diagnosed early through NBS when implemented and there is a need to develop appropriate guidelines for the monitoring of these patients. Expert opinion suggests that there is currently an unmet need for individuals who are diagnosed after the age of 18, who have not yet developed either severe respiratory symptoms, sleep disordered breathing or significant muscle weakness (i.e. patients who could potentially benefit from ERT prior to

deterioration, but are ineligible for subsidised ERT on the LSDP¹). The introduction of NBS for GSD II should result in the earlier detection of late-onset GSD II, leading to a concurrent decrease in the population being diagnosed after age 18 years. Although ERT can slow the progression of symptoms, treatment does not entirely prevent disease progression, particularly if commenced after symptoms are present as, at this stage, muscle damage is already present. The current LSDP criteria (in the setting of no NBS for GSD II) requires that the patient must demonstrate clinical improvement or stabilisation of the condition, and evidence to support ongoing eligibility for the treatment of infantile-onset or late-onset GSD II.

There are potential harms associated with ERT. Babies who are cross-reactive immunological material (CRIM) negative form antibodies against replacement enzyme, rendering the treatment less effective. To avoid this, pre-sensitisation immunomodulation (such as rituximab, methotrexate and immunoglobulin) is given with ERT to CRIM negative infantile-onset GSD II patients. Because of the long turn-around-time in getting CRIM status results back from the laboratory, immunomodulants are given to all infants starting ERT in current clinical practice (according to expert clinical advice). By doing so, the delay in administering ERT can be minimised. Any harms from immunomodulation and ERT (side effects, adverse events) need to be weighed against their benefits.

Comparator(s) (PICO Set 1)

Screening

The comparator for universal newborn screening for GSD II is no newborn screening (diagnosis delayed to the point of symptom onset).

Diagnosis

In the absence of screening, individuals with GSD II would only be identified once they present with symptoms of GSD II or after the diagnosis of a direct family member (although individuals diagnosed due family history are categorised as PICO set 2). In babies with infantile-onset GSD II, this initial presentation would usually occur in the first few weeks or months of life. In late-onset GSD II, there is often a delay of several years between symptom onset and diagnosis because of the non-specific nature of the symptoms.

The process of diagnostic testing for GSD II after symptom onset is like the diagnostic testing of infants found to be positive on NBS, including testing GAA enzyme activity (on DBS, or leukocytes).

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 tetrasaccharide (HEX4), which is required to meet LSDP eligibility criteria
- Respiratory function (age dependent)
- Molecular genetic testing of GAA gene

PASC noted that the comparator is diagnostic testing after the onset of phenotypic signs and symptoms.

¹ Received via personal communication in teleconference with clinical co-applicants 5 March 2024

Treatment

In the comparator scenario, patients with GSD II are only diagnosed after having symptoms of disease (within the first year for infantile-onset GSD II, or at any age for late-onset GSD II). This results in the treatment of GSD II being initiated later than would be the case if diagnosed through NBS. However, after diagnosis, the treatment options are the same in the intervention and comparator arms:

- enzyme replacement therapy (ERT)
- immunomodulation for CRIM negative infants
- respiratory support, and as symptoms progress, mechanical ventilation
- cardiac care (medications to treat cardiomyopathy)
- physiotherapy (help strengthen muscles, improve motion, develop motor skills)
- psychosocial support (individual and family counselling, disease education, support groups for managing the emotional and psychological impact of the disease)
- general medical care (nutrition advice, tube feeding if required) (STAR-G 2024).

In the case of late-onset GSD II, there is often a delay of several years between symptom onset and diagnosis because of the non-specific nature of the symptoms. For those with signs/symptoms suggestive of GSD II, ERT may be administered if clinically indicated. Patients who are diagnosed when they are older than 18 years, are only eligible for ERT through the LSDP if they have severe symptoms (either <80% of predicted respiratory function; sleep disordered breathing with oxygen saturation <80% or significant muscular weakness).

The Pharmaceutical Benefits Advisory Committee (PBAC) considered that for infantile-onset GSD II, ERT extends survival compared to palliative care, although not beyond early childhood ([alglucosidase alfa PSD, July 2008 PBAC meeting](#)). ERT may also prolong invasive ventilation-free survival (Newton et al. 2015).

If treatment is initiated only after irreversible damage of the muscle has occurred, due to lysosomal dysfunction resulting in cellular damage, then the symptoms are likely to be more severe than if treatment is initiated pre-symptomatically. The management of the condition may therefore be more resource-intensive in the no screening arm than the screening arm. The Pharmaceutical Benefits Advisory Committee (PBAC) may need to consider how safe and effective ERT is in patients detected due to NBS, compared to patients detected after symptom-onset.

The LSDP subsidises medicines submitted by a pharmaceutical company if:

- they are clinically effective, but not cost effective (and therefore not listed on the PBS)
- they treat life threatening and ultra-rare conditions (defined as 1 case per 50,000 people or fewer in the Australian population)

Reference standard (PICO Set 1)

The accuracy of the NBS test for GSD II will be assessed using all available diagnostic information as the reference standard. This is an imperfect reference standard, as even long-term studies may be unable to distinguish between pre-phenotypic late-onset GSD II and pseudodeficiencies.

PASC noted that the laboratory reference standard (GAA enzyme activity, HEX4 and genotype) is for a phenotypic presentation. However, following screening, with genotyping of asymptomatic individuals, it may be very difficult to accurately predict disease trajectory or severity given variable penetrance and affectedness, and/or uncertain impact of variants of unknown significance.

Outcomes (PICO Set 1)

PASC noted that there were a wide range of relevant outcomes to be assessed.

Screening test performance:

- Accuracy of the screening test (sensitivity, specificity, positive predictive value)
- Diagnostic accuracy of confirmatory/diagnostic test (sensitivity, specificity, positive predictive value, negative predictive value)
- Accuracy of classification (infantile vs late-onset)
- Diagnostic yield of screening

Change in management:

- Age at diagnosis
- Age at treatment initiation (and whether prior to, or after phenotype onset)
- Time between phenotype onset and diagnosis (length of diagnostic odyssey)
- Investigations/monitoring/treatments received
- CRIM status
- Genetic counselling
- Psychological counselling

Clinical Effectiveness:

- Impact of the change in management (i.e. Improvement in morbidity and mortality, quality of life, general functioning and disease manifestations from early diagnosis, intervention, and/or avoidance of the diagnostic odyssey)

Safety (physical harms to newborn of screening test, diagnostic test or subsequent treatment):

- Impact of false positive screening results (physical harms to the infant or psychological harms to the parents)
- Impact of false negative results
- Impact of diagnosing late-onset cases at birth, creating “patients in waiting”
- Impact of detecting VUS and novel variants
- Any potential risk of harm from ongoing monitoring and surveillance
- Safety of enzyme replacement therapy (ERT)
- Safety of immunomodulation

PASC advised that the benefits and harms of diagnosis and management (including ERT) for newborns diagnosed with LOGSD II would have to be weighed against the benefits and harms of receiving a diagnosis of LOGSD II as a newborn or at phenotypic onset.

Economic and Financial Implications:

- Cost-effectiveness of NBS for GSD II (cost per diagnosis; cost per quality adjusted life year (QALY))
- Financial impact of screening, relative to existing practice (including impact of false positives, savings from early intervention and/or change in treatment approach, ongoing monitoring and surveillance of individuals diagnosed with GSD II)

Other relevant considerations:

- Non-health outcomes: Value of knowing (harms/benefits to the individual or family members from earlier diagnosis)
- Ethical considerations (equity of access, considerations regarding consent, ethics of identifying late-onset GSD II prior to being eligible for ERT).
- Organisational considerations (incremental impact of NBS on organisations, particularly the impact on services for monitoring late-onset disease, or on the NBS programs itself including programmatic implementation considerations).

PASC acknowledged that there are important ethical issues for discussion regarding NBS for GSD II. One ethical issue is related to LOGSD II diagnoses through NBS as the benefits of diagnosis in the newborn period are not clear and there is a lack of clinical agreement on the appropriate management of newborns diagnosed with LOGSD II. Newborns diagnosed with LOGSD II will require long-term follow-up, and this may cause anxiety or psychological problems in parents and/or the child, while also giving the opportunity to get earlier treatment if they subsequently meet eligibility criteria for treatment on the LSDP. In addition, although false positive results will hopefully be minimised through the choice of appropriate screening protocol and tests, these diagnoses will be unavoidable because of the presence of pseudodeficiency variants and VUS. PASC advised that the ethical considerations associated with identifying risk for LOGSD II must also be weighed against the need for prompt intervention for newborns with IOGSD II.

PASC noted that access to ERT may be more difficult for patients in rural areas and hence there may be an unintended inequity of access to treatment. Similarly, there may be barriers in rural areas' access to monitoring and other therapies.

PASC noted that detailed appraisal for all relevant implementation considerations that may include workforce capacity issues are out of scope for MSAC's terms of reference (ToRs). However, PASC noted expert advice that additional clinical infrastructure will be needed to support newborns and their families who are diagnosed with GSD II through newborn screening.

PASC noted that changes to LSDP funding ERT for GSD II are outside the scope of this MSAC application, so the safety/effectiveness of changing the LSDP criteria will not be assessed. Any changes to the LSDP funding ERT for GSD II criteria would require a submission to the PBAC.

PICO criteria (PICO set 2)

Population (PICO Set 2)

GSD II has a recessive mode of inheritance, therefore both parents of an index case² with two pathogenic/likely pathogenic (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 infantile-onset GSD II is diagnosed, it is proposed that cascade testing is offered to biological parents to allow for further reproductive planning. Older siblings of the index case (born prior to the implementation of NBS for GSD II) may themselves also be affected or carriers and should also receive genetic counselling and cascade testing.

² 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)

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

Cascade testing of unaffected siblings to determine carrier status may not be offered in all cases (e.g., older siblings that are asymptomatic). However, when the child reaches reproductive age, they may elect to undergo cascade testing, and if required, reproductive partner testing, through an appropriate clinic for family planning purposes. This would most likely occur at a cost to the sibling.

PASC noted that if 6-17 babies with GSD II are identified through NBS, that there would be 12-34 parents eligible for cascade testing. It could also be assumed that if each baby identified with GSD II had one sibling, then there would be 6-17 siblings eligible to undergo cascade testing. Of these, it is estimated that 1 in 4 will be positive on enzyme testing, and uptake genetic testing. It is therefore estimated that 1 to 5 siblings per year may access genetic testing for the familial GAA variant. PASC noted that there could be an estimated 13-39 cascade tests per year including parents and siblings and assuming an incidence of GSDII of between 1:47,000 and 1:18,000. However, the uptake of cascade testing is unclear as parents may choose not to seek cascade testing for siblings of an index case with LOGSD II. Siblings may choose to get tested later in life.

Intervention (PICO Set 2)

The intervention for parents of a newborn identified through universal NBS with GSD II is genetic counselling and cascade testing for the specific familial variants identified in the index case. GAA gene sequencing is likely to be the method used for cascade testing. Carrier status is determined by the presence of the familial pathogenic/likely pathogenic variant identified through screening and confirmation in the index case.

Siblings would first receive GAA enzyme activity testing (either on DBS, or leukocytes), to determine whether they have GSD II. If unaffected, no further testing would occur, unless they wish to undergo carrier testing once they are an adult. If they are found to have signs of GSD II based on their GAA enzyme levels (e.g. low enzyme activity), then they would be offered GAA sequencing to confirm the diagnosis. If two pathogenic/likely pathogenic variants are identified, then they would undergo monitoring and/or treatment.

Any cases identified through cascade testing after their siblings have undergone NBS, would likely be diagnosed much earlier than if they underwent diagnostic testing after symptom-onset, or after cascade testing after the index case has developed symptoms.

PASC noted that the intervention for PICO set 2 (cascade testing) was the same as the comparator (current clinical practice), with the key difference in the timing of testing. The number of cascade tests performed may be higher in the intervention arm than the comparator arm because in addition to identifying more cases due to the earlier timing of testing, NBS may also identify LOGSD II variants that may not cause (early) disease manifestation.

Reference standard (PICO Set 2)

The methods chosen for genetic testing for identified familial variants can be assumed to be 100% sensitive and specific, so no reference standard is required for genetic testing.

The reference standard for the clinical diagnosis for siblings would be all available information.

Comparator (PICO Set 2)

The comparator is cascade testing offered to the family members of a presenting individual diagnosed with GSD II based on signs or symptoms (proband). Parents would be offered testing for P/LP variants to determine carrier status, and siblings would be offered biochemical testing to detect GAA enzyme levels followed by genetic testing if they have low enzyme levels. That is, the cascade testing protocol 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 case. Given the median age of diagnosis of GSD II in Australia in the absence of NBS has been 36 years (Chin & Fuller 2022), it is unclear if this higher median age will have different implications for the numbers of family members that may be interested in taking up cascade testing.

PASC noted that the comparator for PICO set 2 was testing of parents for pathogenic/likely pathogenic variants to determine carrier status, and biochemical testing of siblings of the proband to detect GSD II cases. If siblings have low enzyme activity levels, then they may receive genetic testing for the familial GAA variant.

Outcomes (PICO Set 2)

For most family members tested, the expected test results will be that they either are, or are not a carrier of, or affected by, GSD II. For the parents, a major benefit of cascade testing is to inform further reproductive decision-making.

A small proportion of siblings who did not themselves get tested for GSD II through newborn screening (due to being born outside of Australia or born prior to the introduction of LSDs to the NBS programs) may be identified as being clinically affected with GSD II (infantile-onset GSD II or late-onset GSD II) due to cascade testing. Older family members may be identified with late-onset GSD II or as a carrier of late-onset GSD II if cascade testing is offered to a broader family group following the diagnosis of a newborn with late-onset GSD II.

Test outcomes of cascade testing:

- Number of siblings with early diagnosis of GSD II
- Number of family members who take up cascade testing
- Age at diagnosis/treatment of affected siblings

Clinical Effectiveness of cascade testing:

- Clinical outcomes from an early vs late diagnosis and intervention (for affected siblings)
- Effectiveness of immune modulation in CRIM negative probands

Safety of cascade testing:

- Impact of diagnosing siblings with late-onset disease that may not become symptomatic for many years (including psychological impact to siblings or parents, and harms from investigations and treatments).
- Any potential risk of harm from ongoing monitoring and surveillance

- Harms arising from immunomodulation in patients treated prior to defining their CRIM status.

Economic and Financial Implications:

- Cost-effectiveness
- Financial impact of an increase in cascade testing (if previously underdiagnosed)
- Total Australian Government health care costs

Other relevant considerations:

- Non-health outcomes: Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family, noting these are secondary to the outcomes delivered to the baby)
- Ethical considerations (considerations regarding cascade testing, including notification of carrier status; ethics of diagnosing late-onset GSD II where the optimum management prior to symptom development is unclear)
- Organisational considerations such as discussing the impact of diagnoses on clinic visits, cardiology, metabolic laboratory, radiology and physiotherapy.

PASC noted that the outcomes for PICO set 2 were test outcomes, clinical effectiveness outcomes, safety outcomes, cost-effectiveness and financial implications, and other relevant considerations (value of knowing, ethical considerations and organisational considerations). Organisational considerations include discussing the impact of diagnoses on clinic visits, cardiology, metabolic laboratory, radiology and physiotherapy.

Assessment framework (for investigative technologies)

The NBS programs are a form of universal (or population) screening. As universal screening programs are considered to be associated with a high financial risk, MSAC has a clear preference for 'direct from test to health outcomes' evidence (MSAC 2021). Scoping searches have identified only limited comparative direct evidence of test to health outcomes. Furthermore, the Newborn Bloodspot Screening National Policy Framework (NBS NPF) also provides a set of guiding criteria to be addressed in the assessment of adding or removing conditions from the NBS programs that include elements of linked evidence. Therefore, both 'direct from test to health outcomes' evidence and a linked evidence approach will be sought in the assessment. The approach is illustrated in Figure 1.

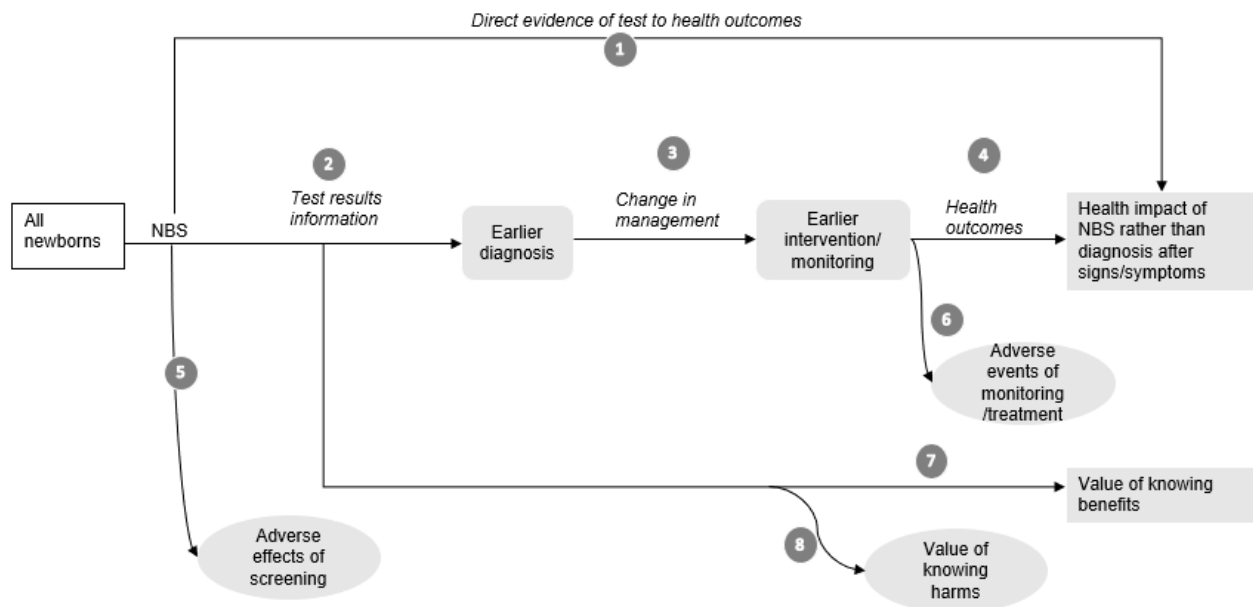


Figure 1: Assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: adverse events due to screening; 6: adverse events due to treatment/monitoring; 7: benefits of knowing; 8: harms of knowing

The assessment questions related to the HTA assessment framework are:

1. Is there direct from screening to health outcomes evidence to support the claim that NBS leads to improved health outcomes?
2. Test accuracy: When compared with diagnostic testing of symptomatic children as the reference standard, what is the accuracy of NBS for identifying patients with GSD II? What are the implications of discordances among the test results?
What proportion of patients are diagnosed with GSD II prior to symptom development due to NBS or no NBS?
3. How does the NBS test results impact the clinical management of the individual (in either the timing or the type of monitoring/treatments used), compared with diagnosis after symptom onset (or due to family history)?
4. Does the change in the clinical management (monitoring and early treatment with ERT) improve health outcomes (morbidity, mortality, QoL)?
5. What are the adverse events associated with NBS for detection of GSD II, when compared to the current practice of no screening and diagnosis after symptom onset? (*no incremental safety issues expected for the baby as bloodspots already collected, but any additional false positive results may result in psychological harms to the parents and child*)
6. What are the adverse events associated with the monitoring and treatment of individuals diagnosed with GSD II through NBS?
7. What value of knowing is there for patients with an GSD II diagnosis, diagnosed early due to NBS? (*this may be relevant for late-onset GSD II not otherwise diagnosed prior to symptom onset*)
8. What harms come from the knowledge of GSD II status? (*this may be relevant for late-onset GSD II prior to symptom onset*)

Other relevant considerations

Proposals considered by MSAC can have aspects that are unique to the proposed technology, circumstances of use or funding arrangement, such that MSAC is unlikely to have considered the factors previously in the same context. Other relevant considerations should be explored in section 5 of the assessment report.

Additional information relevant to decision-making that is not captured elsewhere in the assessment is anticipated to include organisational and infrastructure components that are outside the HTA (such as the impact on healthcare services downstream of the screening laboratories).

Clinical management algorithms

PASC acknowledged the clinical management algorithms and noted the amendments required to align with classifications of GSD II as per LSDP criteria. PASC advised the agreed screening protocol should be reflected in the algorithms.

Current clinical management for infantile-onset GSD II

In the current management for infantile-onset GSD II, children less than 24 months of age are assessed once signs (or symptoms in older children) occur that are suggestive of GSD II. Once a clinical examination has been conducted, a GAA enzyme activity assay is performed on a dried blood spot sample. In those with low enzyme activity and cardiomyopathy (infantile-onset GSD II), CRIM status should be determined and ERT can be started in the patient following immunomodulation. GAA sequencing will also be performed for confirmation, but treatment should not wait for the results as the early implementation of ERT is critical to avoid worsening symptom development. In babies without cardiomyopathy and low alpha glucosidase activity, confirmatory testing can be performed by urine Glc4 assay or GAA sequencing. Once two tests are positive for GSD II, ERT should be started after immunomodulation if CRIM positive status cannot be confirmed. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

As a proportion of newborns initially classified as infantile onset GSD II may ultimately be classified as late onset GSD II if cardiomyopathy is not detected, the figure also included a pathway for diagnosis of late onset GSD II or atypical infantile onset GSD II.

Current management for late-onset GSD II

Late-onset GSD II occurs in children over 2 years of age and adults. The severity of symptoms and the rate of development is usually dependent on the level of enzyme activity in the individual. In adults, symptoms can develop slowly and may not be diagnosed for some time as the symptoms are often non-specific to GSD II. Sometimes a muscle biopsy is performed and there may be histopathological features of GSD II. Often a broad neuro-muscular panel of genes may be sequenced, and the diagnosis ascertained using this method. Alternatively, an alpha glucosidase enzyme assay may be ordered, typically on DBS. Once one test identifies the condition, other confirmatory tests using a different technique is usually performed e.g., HEX4 assay. If late-onset GSD II is confirmed and the patient is between 2 and 18 years of age, ERT can be started per LSDP criteria, without waiting for the onset of symptoms. Alternatively, diagnosed children between the ages of 1 and 18 years can enter a monitoring pathway prior to the onset of symptoms. If those aged 1 to 2 years develop symptoms they are assumed to have atypical late onset GSD II and are

eligible for treatment funded through the LSDP. Adults diagnosed with late-onset GSD II can be offered ERT after symptoms appear, per the LSDP criteria. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

The current management algorithm for infantile onset GSD II and late onset GSD II is in Figure 2.

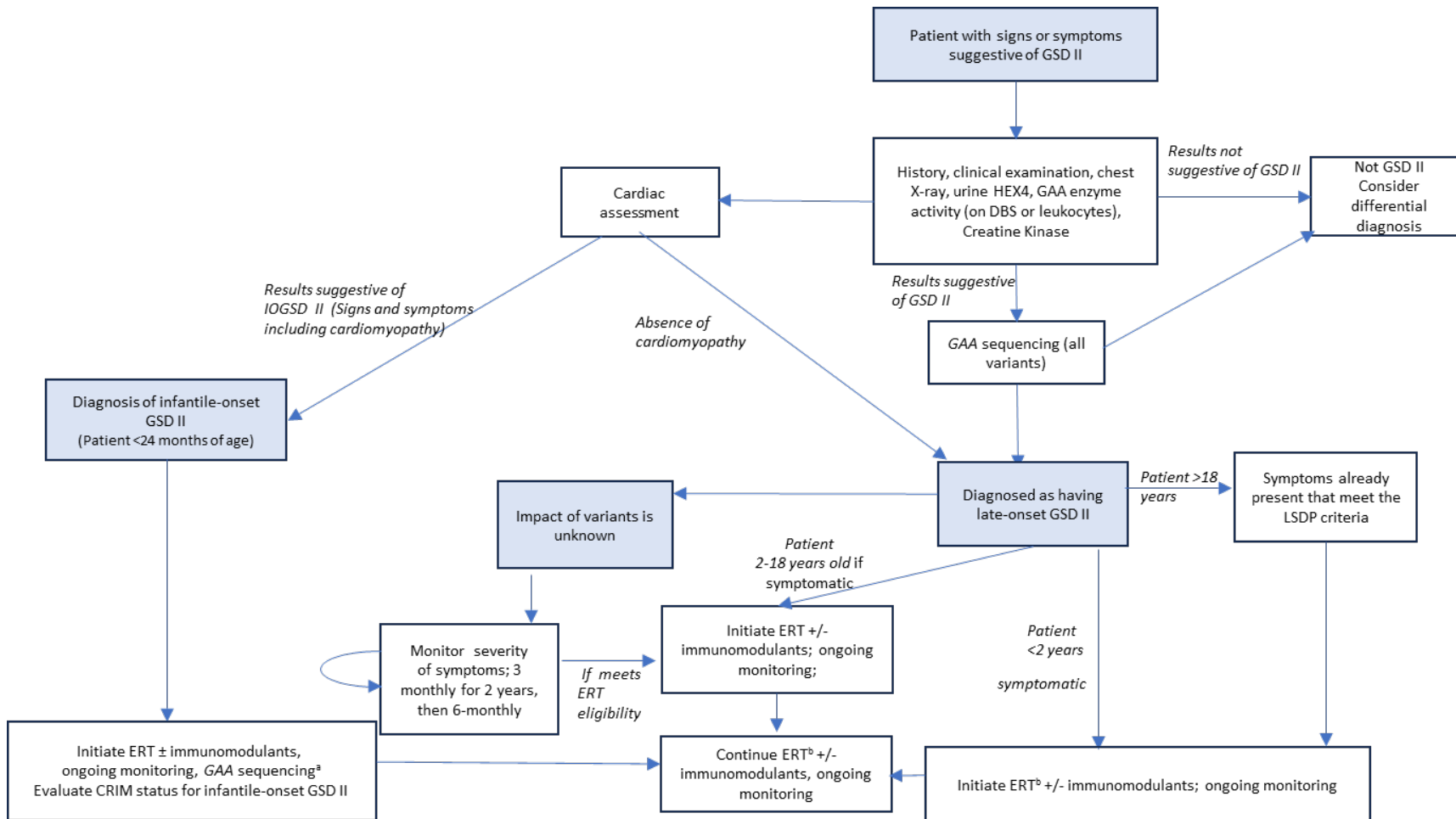


Figure 2: Current clinical management algorithm for infantile-onset and late-onset GSD II

^aGAA sequencing not required for the diagnosis of GSD II if GAA enzyme activity documented and tetrasaccharide testing (from urine HEX4) indicates a diagnostic elevation of glucose tetrasaccharides, but may be desired to facilitate cascade testing of family members or to predict CRIM status

^bERT for infantile-onset GSD II available through the LSDP is alglucosidase alfa (Myozyme) if <12 months, or alglucosidase alfa or avalglucosidase alfa (Nexviazyme) if >12 months /ERT if diagnosed with late-onset GSD II, ERT is only available after age 24 months for late-onset GSD II

CRIM = cross-reactive immunological material; DBS = dried bloodspot; ERT = enzyme replacement treatment; GAA = acid alpha-glucosidase; GSD II = glycogen storage disease type II; HEX4 = hexose tetrasaccharide; LSDP = Life Saving Drugs Program

Proposed management of infantile-onset and late-onset GSD II

Diagnosis of infantile-onset GSD II following NBS would occur in most cases prior to symptom development, although for those with infantile-onset GSD II, there is likely to be evidence of (undiagnosed) cardiomyopathy at birth. Following a positive first-tier screen test, confirmation with second tier testing is performed by targeted *GAA* sequencing for common IOGSD II variants. Identification of two or more pseudodeficiency variants can rule out GSD II. If the infant is either found to have one or two common P/LP variants, or no common variants, then clinical assessment/diagnostic testing should be performed. If there are signs of cardiomyopathy, ERT can be started, after immunomodulation while CRIM status is being determined. Molecular confirmation of GSD II can be made by full *GAA* sequencing. If infantile-onset GSD II is confirmed, ERT can begin. If there is no cardiomyopathy and the infant remains asymptomatic, ERT can begin after 2 years of age, according to current LSDP criteria. Because testing is performed in newborns, it is anticipated that ERT can start earlier than in the absence of NBS. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

In people at risk for late-onset GSD II identified through NBS, a laboratory diagnosis would occur as a newborn possibly decades before symptoms develop. After a positive screening result, a clinical assessment would typically detect no signs of GSD II. *GAA* sequencing will then be requested for diagnostic confirmation. The presence of two pathogenic variants is diagnostic of GSD II but does not determine the age of onset of signs and symptoms. Patients between 2 and 18 years of age genetically diagnosed can be treated and monitored pre-symptomatically, but those under 2 or over 18 years should be monitored clinically and for biomarker change (in CPK concentration) until symptom development. At first signs of disease or threshold change in biomarker concentration, ERT may be considered. Per LSDP criteria, ERT is not usually offered to adults until first signs of symptoms or change in biomarker levels. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are carriers.

The proposed management algorithm is shown in Figure 3.

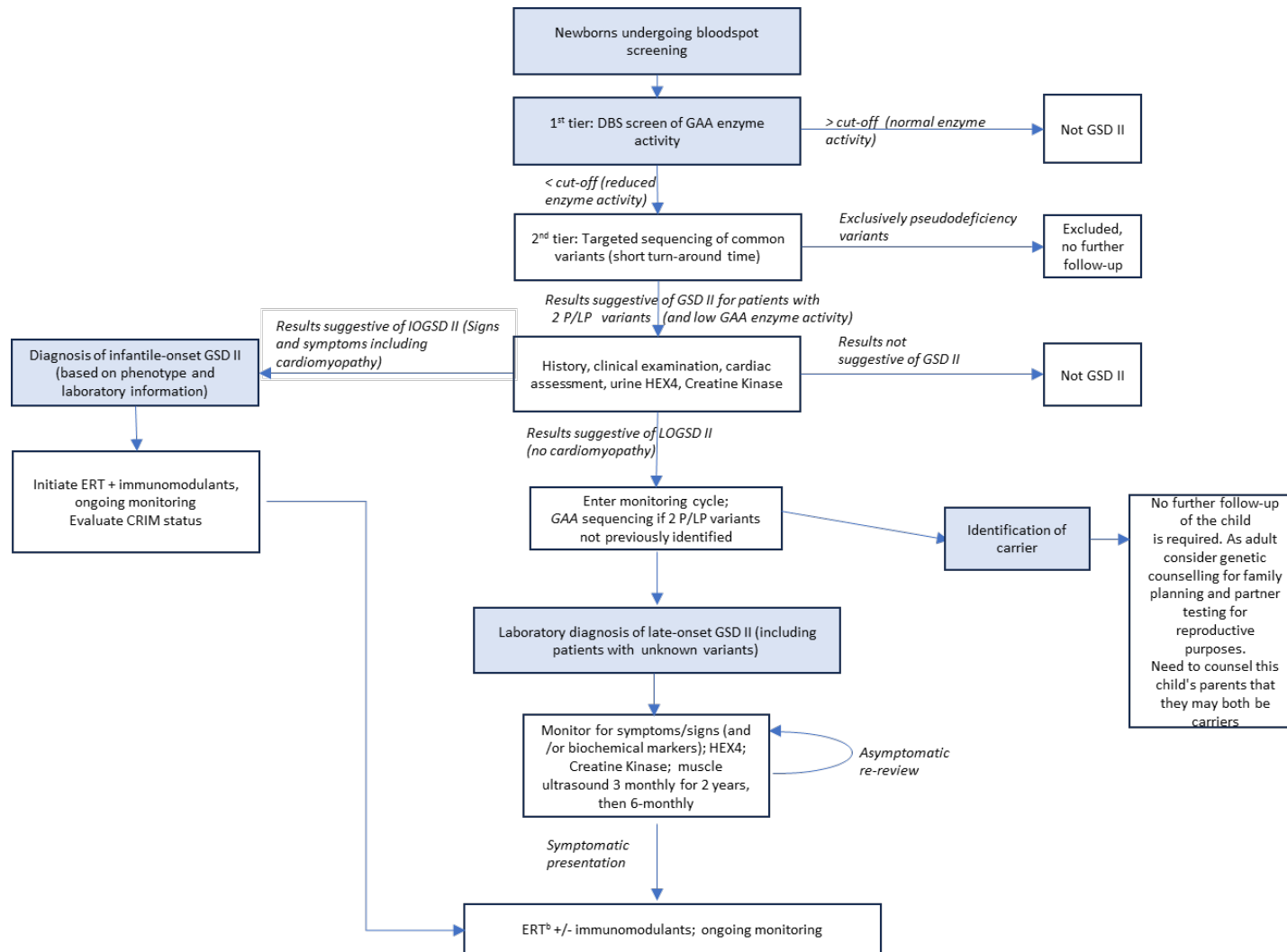


Figure 3: Proposed clinical management algorithm for infantile-onset and late-onset GSD II

Abbreviations: CK = creatinine kinase assay; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

^aGAA sequencing not required for the diagnosis of GSD II if GAA enzyme activity documented and tetrasaccharide testing (from urine HEX4) indicates a diagnostic elevation of glucose tetrasaccharides, but may be desired to facilitate cascade testing of family members or for determination of CRIM status

^bERT for IOGSD II available through the LSDP is alglucosidase alfa (Myozyme) if <12 months, or alglucosidase alfa or avalglucosidase alfa (Nexviazyme) if >12 months; ERT if diagnosed with late-onset GSD II, ERT is only available after age 24 months

CRIM = cross-reactive immunological material; DBS = dried bloodspot; ERT = enzyme replacement treatment; GSD II = glycogen storage disease type II; HEX4 = hexose tetrasaccharide

Current cascade testing of family members

After a proband is diagnosed with GSD II and pathogenic/likely pathogenic variants are identified, family members are offered cascade testing. If VUS are identified in the proband, parental testing (enzyme activity in DBS and molecular testing) should be performed – this segregation analysis requires parental counselling and consent for testing. This is for the purpose of detecting carrier status in the parents, to assist with reclassification of VUS and to assess for cases of GSD II in siblings. The clinical management algorithm is shown in Figure 4. Given that in Australia, the median age of diagnosis across both infantile-onset and late-onset GSD II is 36 years (Chin & Fuller 2022), it is unknown how many parents would seek carrier testing.

Siblings of someone with GSD II are eligible for cascade testing to determine if they have GSD II. If they are found to not have GSD II, as an adult they may choose to undergo carrier testing.

Proposed cascade testing of family members

The methods used for cascade testing of family members is not expected to differ, with the proposed introduction of NBS for GSD II. However, as the index cases via NBS will be identified earlier than the probands are without NBS, there will also be earlier cascade testing opportunities, and potentially a higher uptake of cascade testing. The clinical management algorithm that is proposed to follow an identified case is identified through an NBS program is shown in Figure 5.

Following NBS, untested older siblings identified as having risk for GSD II through cascade testing are likely to be diagnosed much earlier than if they were investigated after their symptom-onset, or after the index affected individual had been diagnosed after symptom-onset.

For PICO set 2, it was suggested that if only one parent of an index case has a GSD II variant, this may be due to a 'non-parental event', e.g. conception through donor egg or non-paternity or de novo mutations. The incidence of gonadal mosaicism is unknown and segmental uniparental disomy has been reported (Stijm et al 2020).

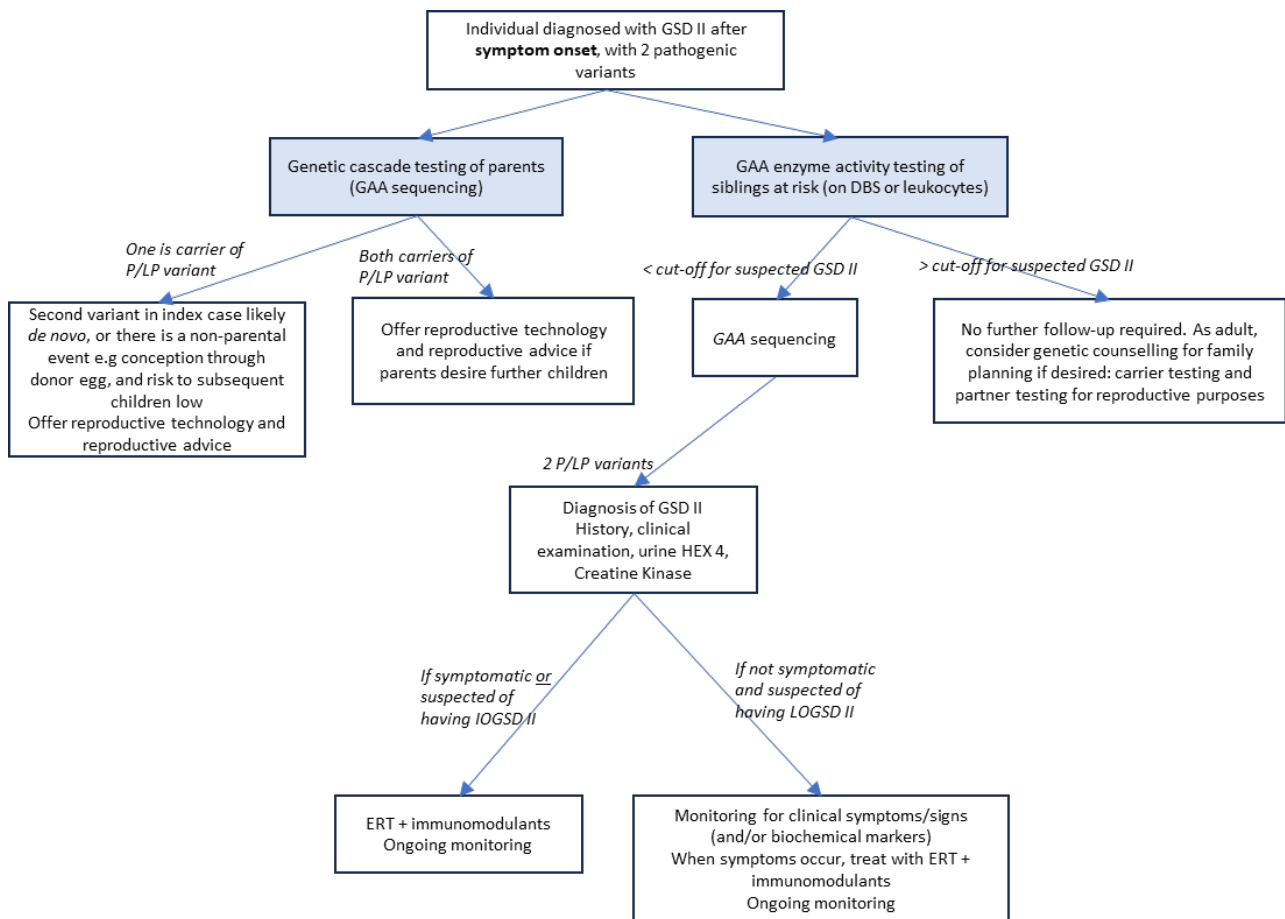


Figure 4: Current clinical management algorithm for cascade testing of family members

Abbreviations: CK = creatinine kinase assay; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

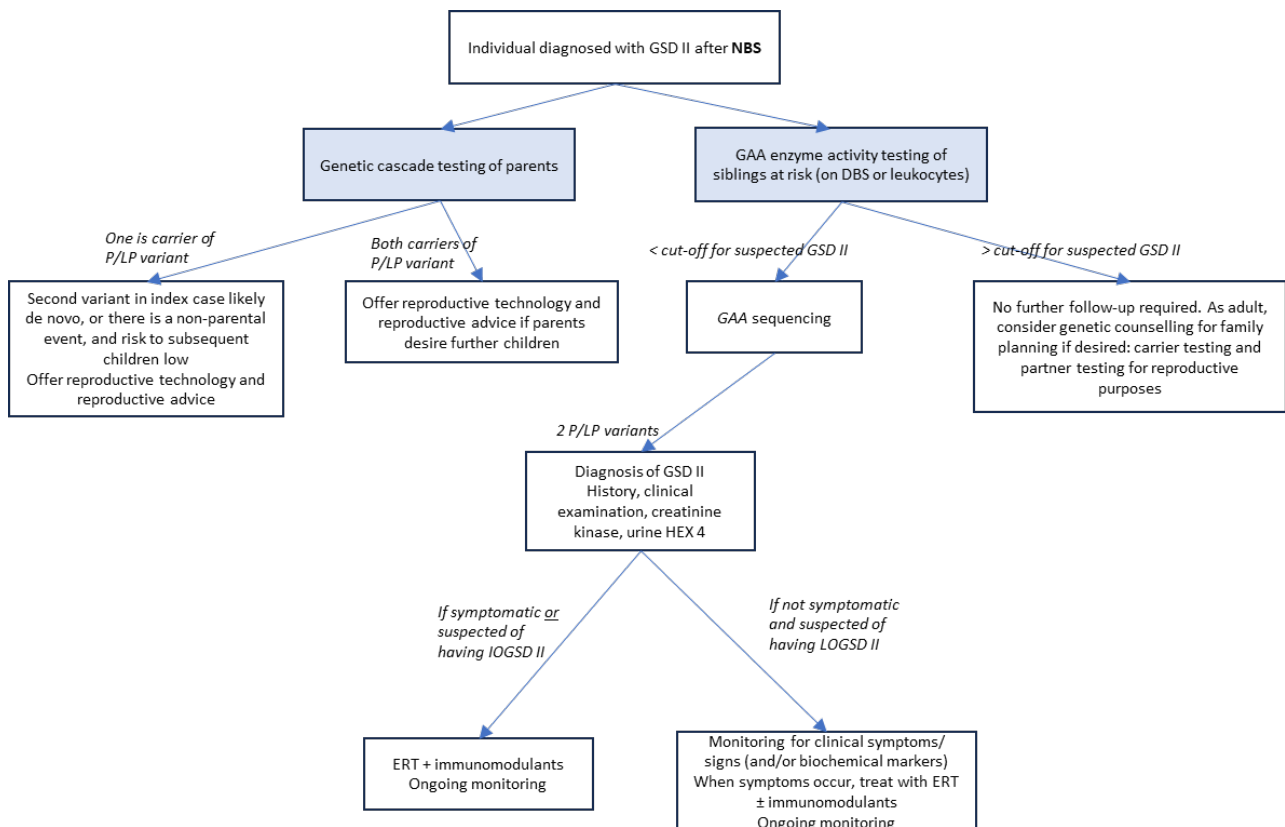


Figure 5: Proposed clinical management algorithm for cascade testing of family members

Proposed economic evaluation

PASC noted that the economic assessment should be considered in the context of the NBS National Policy Framework criteria.

It is likely that NBS for GSD II will demonstrate superior effectiveness and non-inferior safety compared to no universal newborn screening for index cases with infantile-onset GSD II. The appropriate form of health economic evaluation is therefore a cost-utility analysis or cost-effectiveness analysis (see Table 5). However, for each case of infantile-onset GSD II detected, there are many more cases of either late-onset GSD II or pseudodeficiencies detected, in whom it is possible that NBS will cause harm. If the overall comparative safety is considered inferior, and comparative effectiveness is superior, then the appropriate form of health economic evaluation is considered to likely still be a cost-utility analysis. It is noted that in such a cost utility model, providing a model which incorporates the expected utilities of early intervention for cases of infantile-onset GSD II as well as disutilities from false positive diagnoses and early diagnoses of late-onset GSD II will be difficult.

PASC noted that it was possible that screening for GSD II may result in inferior safety, due to the detection of “patients in waiting” (either LOGSD II or VUS). PASC noted that if overall comparative safety is considered inferior and comparative effectiveness is superior, then the appropriate economic evaluation is a cost-utility analysis but the modelling for this may be difficult.

The methods used to perform cascade testing are identical in the two scenarios with and without NBS for GSD II, although cascade testing could occur earlier in the NBS scenario. If any cases of late-onset GSD II

are detected through cascade testing, it is expected that earlier cascade testing would be superior to late cascade testing in regard to effectiveness, and non-inferior in regard to safety. If no additional cases are detected through cascade testing, then non-inferior safety and effectiveness would be expected from early vs late cascade testing. A cost-minimisation analysis would be more appropriate in this scenario.

Although there are three separate PICO confirmations for the three LSDs being considered for inclusion in the NBS programs for independent consideration of each condition (GSD II, MPS I and MPS II), there are potential efficiencies to be considered if all three are added to NBS programs. The commercially available Revvity test can detect both GSD II and MPS I (as well as Krabbe, Fabry, Niemann-Pick-A/B, and Gaucher diseases), with MPS II assayed separately, but the two assay mixtures are then combined for analysis in a single LC-MS/MS run per newborn.

PASC noted that if the Revvity kit is used to screen for GAA enzyme activity level, there may be efficiencies in combining the testing with the other conditions (such as MPS I), although the base case should assume all the costs are allocated to GSD II.

PASC noted that the economic evaluation will need to take account of HEX4 which can support identification of pseudodeficiencies (and therefore refute the screen-positive diagnosis of possible GSD II) and is required to access ERT through the LSDP alongside genetic testing which is required to check for alleles associated with IOGSD II, LOGSD II and pseudodeficiencies to predict severity, and to facilitate cascade testing.

Table 5 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Non-inferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

^b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

Funding of NBS for MPS II (PICO Set 1)

NBS for GSD II disease is currently not funded or performed in Australia.

Australian NBS programs are funded and delivered through public hospital services in all Australian jurisdictions. Patients and families can choose to utilise services through the private system at their own

cost for postpartum care and any necessary ongoing intervention for rare diseases. However, all NBS samples are tested by the newborn screening laboratories which are managed and funded within the public system.

Each jurisdiction has unique arrangements for the funding and delivery of NBS services to align with specific local health system structures. Funding for the Australian NBS programs comes from a mix of jurisdictional and national funds. The Australian government contributes funds for public hospital services, including typical sample collection, testing and downstream care in the NBS programs, under the 2020-25 National Health Reform Agreement (NHRA). The NHRA recognises the states and territories as system managers of public hospitals. In addition to these standard funding mechanisms, the Australian Government has directly contributed \$25.3 million to states and territories to support the expansion of the NBS programs through a schedule to the Health Federation Funding Agreement.

PASC noted that direct funding is being provided by the Commonwealth to states and territories to support expansion of Australia's NBS programs and support 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.

There are no Medicare Benefits Schedule (MBS) items specifically for the delivery of NBS services; however, MBS items may be used in the delivery of downstream medical care or to confirm diagnoses.

Funding for the ongoing delivery of interventions for GSD II is also provided for by the Australian Government through the LSDP, where eligibility criteria are met. The LSDP covers medicines for ultra-rare conditions (1 case per 50,000 or fewer) which could not be listed on the Pharmaceutical Benefits Scheme (PBS) on grounds of cost effectiveness but have been determined as being clinically effective by the PBAC, where the sponsor has applied for LSDP listing and the medicine has been assessed as meeting LSDP eligibility criteria.

PASC noted that the LSDP criteria for ERT was outside the scope of the assessment. However, PASC advised that in future, where NBS applications involve a corresponding change to a therapy, a codependent application is required.

If using a commercially available kit, such as the NeoLSD MSMS Kit from Revvity, which 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. REDACTED the kit is estimated to cost approximately \$ REDACTED, according to expert advice. The incremental cost of screening per child would be \$ REDACTED as some of the reactions would be required for quality control samples. The detection of other LSDs simultaneously, would presumably improve the cost-effectiveness of an assessment of NBS for multiple conditions, but does not alter the assessment of NBS for GSD II alone.

Funding of cascade testing (PICO Set 2)

New MBS items for cascade testing in relation to this application are not proposed. The Department's advice was that cascade testing will continue to be funded by existing arrangements. Cascade testing is available on the MBS for other conditions, such monogenic conditions (73361), familial hypercholesterolaemia (73353) and mitochondrial disease (73462). GSD II is a monogenic condition.

The MBS fee for genetic testing a close biological relative of a child with a known pathogenic or likely pathogenic disease variant for all three of these conditions is \$400.00 (Benefit: 75% = \$300.00 85% = \$340.00) and indeed this is the fee for almost all cascade testing MBS items, except for 73423 for neuromuscular disorders which has a fee of \$500.00 (Benefit: 75% = \$375.00 85% = \$425.00). For NBS of SCD, PASC previously advised that the cost for a laboratory to conduct genetic testing of the *HBB* gene or the *HBB* and *HBD* genes (for confirmatory testing for the newborn and for cascade testing of family members) was approximately \$500 (1737 PICO, pg. 32; 1737 and 1737.1 PSDs).

Thus, the cost of cascade testing for close relatives of a newborn diagnosed with GSD II would likely be the same. The total cost for this service would be small as the incidence was 2.14 per 100,000 (1 per 47,000 live births over the period 2009 to 2020) in a recent Australian publication (Chin & Fuller 2022).

Expert advice has suggested that if GSD II is introduced into the NBS programs, in addition to funding the screening and diagnostic testing steps, additional resources would be required to implement the care and monitoring of patients with late-onset GSD II, who would engage with the health system potentially decades earlier than they would have otherwise.

PASC noted the NBS NPF criteria and questioned to what extent GSD II fulfilled the NBS NPF criteria if NBS for GSD II would mostly identify newborns who may develop LOGSD II – a predominantly adult-onset condition.

Summary of public consultation input

PASC noted and welcomed consultation input from 11 organisations and 18 individuals, 17 of whom were consumers and one health professionals (clinical scientist at a NBS laboratory). The 11 organisations that submitted input were (list in dot points):

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

The consultation feedback received predominately supportive of public funding newborn screening for GSD II. The consultation feedback raised concerns about testing methods and concerns that LOGSD II (an adult-onset condition) will be the main condition diagnosed through newborn screening for GSD II.

Clinical need and public health significance

The main perceived benefits of public funding noted in the consultation feedback included timely diagnosis, avoiding diagnostic odyssey and earlier treatment. Respondents considered earlier treatment

would reduce symptoms, reduce disease progression, reduce disability, improve quality of life, and prevent deaths from GSD II.

The main disadvantages of public funding received in the consultation feedback included limitations with the proposed screening tests and concerns related to identifying LOGSD II in newborns. The main limitations with the proposed screening tests were that further studies are needed to determine the optimal tests for screening, high rates of false positive results leading to recall and unnecessary anxiety for families, and that genetic testing may report unclear or benign variants. Concerns related to the identification of LOGSD II in newborns was that it is an adult-onset condition (median age of diagnosis is 36 years), the results of testing will not inform when symptoms may develop (or if they will ever develop symptoms), 'medicalisation' of children before symptoms develop, lack of evidence for early interventions for LOGSD II following a diagnosis in newborns, and ethical concerns about testing newborns for an adult-onset condition.

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. Care for people with GSD II requires care from a range of health services including cardiology, respiratory, rehabilitation, surgery, psychology, genetic counselling, dietetics, neurology, occupational therapy and speech therapy. The consultation input stated that there are no metabolic services in NT, ACT and Tasmania however referral pathways are established.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback largely agreed with the proposed population and proposed comparator.

The consultation feedback was mixed regarding the clinical claim. Several respondents considered that the benefits from NBS for GSD II had been shown in other countries where it is included in their NBS program. However other respondents disagreed and considered the optimal method of screening had not been determined, that enzyme activity is insufficient and further studies were needed.

Cost information for the proposed medical service

The consultation feedback mostly agreed with the proposed service descriptor; however, one respondent disagreed and considered the proposal test would result in too many false positives.

The consultation feedback was mixed for the proposed service fee which was redacted in the published application form. The main points of disagreement were the costs for confirmatory testing was not included, the proposed test kit is more costly than alternatives, and that downstream health costs have not been captured such as further testing, clinical care, psychological support and cascade testing.

Additional comments

Additional consultation feedback was provided on genomic newborn screening, genetic registries to improve variant classification (and improve equity for non-Caucasian people underrepresented in databases) and response of treatments, and reproductive carrier screening. Sanofi (supplier of two ERT therapies for GSD) stated it has the capacity to support the provision of treatment for newly diagnosed patients who meet the eligibility criteria for the supply of the ERTs through the LSDP pathway.

Consumer Feedback

Consumers who responded included people with GSD II (predominantly late onset or not specified) and family members and friends of people with GSD II. Several respondents stated there is a long, difficult and costly process before being diagnosed with GSD II. Several respondents with LOGSD II stated it took several years (sometimes over 10 years) before they were diagnosed. During this time, they developed severe symptoms and disability, felt dismissed by healthcare professionals, and traumatised by having a severe unexplained illness. One respondent stated that a newborn with IOGSD II was considered 'non-thriving'. Another stated that an infant with a late diagnosis of IOGSD II had been assessed as to whether they were 'viable' to receive treatment – a distressing experience for the family.

Several respondents highlighted the impact of LOGSD II and IOGSD II. This included muscle weakness, loss of mobility, needing to use a wheelchair, needing help to breathe, and being unable to participate in normal activities due to muscle weakness making it difficult or impossible to walk, use standard toilets, or take stairs. Responses stated a child with IOGSD II had damage to several major organs, was unable to move, sit or feed due to GSD II. Another response described the mother of a child with IOGSD II having to quit work to provide continuous care while also paying for specialised medical equipment and long stays away from home. Consumers also highlighted the importance of the value of knowing including being better prepared for a child's disabilities, informed reproductive decision making, and people with LOGSD II being able to make decisions that accommodate future disability.

PASC noted that 29 responses were received from targeted consultation. Feedback received varied between favouring screening for IOGSD II only, or screening for both IOGSD II and LOGSD II. Expert advice indicated that currently available tests are not able to screen only for IOGSD II without also detecting LOGSD II. PASC noted that the Human Genetics Society of Australasia (HGSA) were not supportive of screening newborns for adult-onset conditions. A suggestion was made that the assessment would need input from individuals with lived experience, and expertise in bioethics.

PASC noted input that GAA enzyme activity testing is not appropriate as a single-tier screening test as it will detect a high number of individuals with pseudodeficiency. PASC noted that respondents suggested various potential second tier screening tests – the WA NBS laboratory indicated a preference for glucotetrasaccharide (Glc4/HEX4) quantification as a second tier test prior to genetic testing while the SA NBS laboratory suggested that pilot studies are required to confirm the appropriate screening protocol. Laboratories also confirmed the suitability of urine tetrasaccharide (HEX4) testing for the diagnosis of screen-positive cases and agreed that this would result in more timely diagnosis required for IOGSD II cases relative to genetic testing. PASC noted that glucotetrasaccharide (Glc4/HEX4) quantification on DBS is not yet available.

Expert advice indicated that urine HEX4 testing was supportive, and not diagnostic, but agreed that it was required to access intervention through the LSDP according to current eligibility criteria. PASC noted out-of-session input from a clinical expert that HEX4 testing had not been performed on DBS in their laboratory.

PASC noted that feedback suggested that there is a lack of evidence for the long-term management of LOGSD II, and the importance of counselling and education materials for LOGSD II. Feedback noted that those with IOGSD II may survive beyond early childhood if they commence ERT at an early age.

PASC considered further consumer input from the broader population who would be screened would be informative for MSAC's consideration. PASC considered that to inform a balanced perspective it would also be beneficial to have consumer input regarding the acceptability of screening for a condition for which there may be no treatment. PASC noted out of session that consumer views on the acceptability of this could depend on a number of factors such as why the screening information is being gathered, how invasive the screening methodology is, how the data will be held and by whom, and whether consumers' details will be held on a list to be contacted if treatment is developed in future. Out of session, PASC considered that NBS for this condition would be no more invasive than is NBS for other conditions (at most

it might require a few more drops of blood), that the National Pathology Accreditation Advisory Council (NPAAC) requires the original report for genetic testing to be held for 100 years, and that consumers' details will not be held on a list to be contacted if a treatment is developed in the future. PASC noted out of session that other factors that may require consideration include whether consumers would be supported to connect with other parents with children who have also tested positive for this condition and likely push for action or treatment. PASC considered (out of session) that this was a likely outcome of counselling and support that must form part of the NBS programs, and should be costed. PASC considered (out of session) that psychological counselling and support will likely be very important to ensure that consumers can make an informed decision.

Next steps

The assessment will proceed as a Department Contracted Assessment Report.

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Appendix A NBS National Policy Framework (NBS NPF) Criteria

NBS National Policy Framework Criteria

The condition

1. The condition should be a serious health problem that leads to significant morbidity or mortality.

1.1 What data are there on the incidence of the condition, including in the Australian population? How is this incidence determined—through screening studies, international programs, cases identified clinically, modelled estimates based on data from variant databases or some other means? Are there any known differences in incidence in Australian sub-populations?

1.2 What is the burden of disease associated with the condition, including morbidity and mortality? Does the burden of disease vary between individuals?

2. There should be a benefit to conducting screening in the newborn period.

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

2.1 What are the known health benefits from early detection that exist, or can be achieved, through screening for the condition? This may include early intervention, prevention of symptoms or reduction in condition severity.

2.2 Why is screening for this condition during the newborn period the most beneficial method of early detection?

2.3 Does detection of this condition provide families with actionable information that assists them in making informed choices about reproduction in the future?

2.4 What emotional or social benefits does early detection provide?

2.5 What harms may arise from screening for the condition in the newborn period?

3. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

3.1 What information is known on the natural history of the condition in Australia or comparable international populations?

3.2 When would the condition usually be detected clinically?

3.3 Explore the current knowledge of penetrance of the condition. Are there known benign or milder late-onset forms?

4. There should be a suitable test protocol to identify the presence of the condition.

4.1 What test protocols could be used to identify the presence of the condition? Is there consensus on the most appropriate test protocol?

4.2 When considering the test protocol, what is the clinical and analytic validity based on a consideration of:

- Sensitivity;
- Specificity;
- False positive rate;
- False negative rate;
- Positive predictive value;
- Negative predicative value.

4.3 Is the test protocol simple and reliable?

4.4 Can the test protocol be performed on the available dried bloodspot?

4.5 Can the test be multiplexed within existing newborn bloodspot screening panels?

4.6 What is the cost of the test protocol?

4.7 Will genetic testing be used as part of the test protocol? If genetic testing is needed:

- Will this be by common mutations or sequencing?
- Which mutations would be tested?
- What is the penetrance of the mutations?
- Are there variants of uncertain significance?

5. The test protocol should, on balance, be socially and ethically acceptable to health professionals and the public.

5.1 Can the test protocol detect other conditions of clinical or unknown significance and/or carriers and, if so, what are the implications?

5.2 What are the potential benefits and harms associated with the preferred test protocol(s)?

The Intervention

6. Health care services for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result.

NBS National Policy Framework Criteria

- 6.1 What health care services are currently involved in the diagnosis and ongoing management of the condition?
- 6.2 What impact would screening for the condition have on the health care services that would be required to support diagnosis and management following an abnormal screening result?
- 6.3 Is diagnostic testing readily available and reliable?
- 6.4 Do current health care services have capacity to support the diagnosis and ongoing management of the condition?
- 6.5 Are current health care services of sufficient quality to support the diagnosis and ongoing management of this condition?
- 6.6 Is there equitable access to these health care services for families, including those from rural and remote areas?

7. There should be an accepted intervention for those diagnosed with the condition.

- 7.1 What accepted intervention(s) is (are) available for newborns that receive an early diagnosis through screening?
- 7.2 How well is the intervention and treatment pathway understood? Is there agreement on when intervention is required?
- 7.3 How effective is the intervention? Does it alleviate the symptoms of the condition or slow or halt its progression? What influence does the intervention have on quality and length of life?
- 7.4 How urgent is the intervention? Does the intervention need to be initiated before symptoms of the condition present?
- 7.5 Is the intervention readily available and accessible?
- 7.6 What are the potential harms associated with the intervention, and to what extent can these harms be mitigated or managed?
- 7.7 What is the cost of the intervention? What costs will be incurred for the diagnosis, management, and treatment of conditions, including the costs for false positives?
- 7.8 Is there equitable access to the intervention for families, including those from rural and remote areas?

Additional considerations

8. The benefit of screening a condition must be weighed against its impact on the program as a whole.

- 8.1 Can screening for this condition be achieved within the current screening pathway?
- 8.2 Is the addition of this condition likely to require ethical considerations that may warrant a separate consent process?
- 8.3 Would it be likely that screening for the condition would impact negatively upon other elements of the program? For example, could it be anticipated that participation rates might fall?
- 8.4 Are there any additional costs, such as the purchasing of new technology or training, which are associated with screening for this condition?
- 8.5 What is the economic impact of excluding/including the condition? Do benefits exceed costs? Is it cost-effective to screen? It may be necessary for a detailed economic evaluation to consider these questions and other relevant economic issues.

9. What other information relevant to decision making should be considered that has not been captured elsewhere?

Appendix B Current eligibility for ERT through the LSDP

Initial eligibility requirements for LSDP

Patient aged up to 24 months:

- Documented diagnosis of infantile-onset GSD II

Patient aged over 24 months and under 18 years:

- Documented diagnosis of late-onset GSD II

Patient aged over 18 years:

- Documented diagnosis of late-onset GSD II,

AND at least one of the following criteria:

- Respiratory function test: Patients with Forced Vital Capacity (FVC), either supine or erect, less than 80% of predicted value. Both supine and erect FVC should be performed.
- Sleep disordered breathing: Patients with an apnoea/hypopnoea incidence of >5 events/hour of total sleep time or more than two severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
- Significant muscular weakness: Patients with significant muscular weakness as evidenced by Manual Muscle Testing (MMT) (employing the MRC score) of 4 or less in either limb girdle accompanied by a 6 Minute Walk Test (6MWT).

Diagnosis of infantile-onset or late-onset GSD II must have been made using one of the following methods:

- Documented deficiency of alpha-glucosidase³ by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells; or
- At least 2 of the following confirmatory diagnostic tests from a NATA-accredited laboratory:
 - o Documented deficiency of alpha-glucosidase in dried blood spot or lymphocytes or mixed leukocytes or skin fibroblasts or skeletal muscle.
 - o Documented urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides.
 - o Documented molecular genetic testing indicating a disease-causing mutation in the alpha-glucosidase gene (*GAA* gene)

³ Note, the LSDP criteria use the term 'acid alpha-glucosidase' but the preferred term, according to the HUGO Gene Nomenclature Committee is 'alpha-glucosidase'

Appendix C Summary of NBS programs for GSD II

Table 6 Summary of published newborn screening programs for GSD II (Graganiello et al. 2022)

Program	Year(s)	Screened newborns	Screening method(s)	Second tier test(s)/postanalytical tool(s)	Other screened diseases	Total presumptive positive newborns	True positive (IOPD/LOPD) after genetic analysis	PPV %	Birth prevalence (IOPD/LOPD)
Europe									
Italy – Northeast	2015-2022	206,741	MS/MS	no	GD, FD, MPSI, NPA/B, KD	39	11 (3 IOPD, 8 LOPD)	28	1:18,432 (IOPD) 1:67,583, LOPD 1:25,344)
Austria (1)	2010	34,736 (deidentified)	MS/MS	no	GD, FD, NPA/B	5	4 (2 IOPD, 2 LOPD)	80	1:8,684 (IOPD) 1:17,368, LOPD 1:17,368)
Italy – Umbria region (2)	2010-2012	3,403	fluorometry	no	GD, FD, MPSI	3	0	/	/
Hungary (3)	N/A	40,024 (deidentified)	MS/MS	no	GD, FD, NPA/B	64	9 (2 LOPD)	14	1:4,447 (LOPD) 1:20,012)
United States									
Washington (4)	retrospective	111,544 (deidentified)	MS/MS	no	FD, MPSI	17	4 (LOPD)	24	1:27,886 (LOPD)
California (5)	2011-2013	89,508 (deidentified)	Comparative (DMF, MS/MS, immunocapture)	Fluorometry	GD, FD, MPSI	DMF: 412, immunocapture: 4478, MS/MS: 900	3	DMF: 0.728, immunocapture 0.067, MS/MS: 0.333	1:29,836
New York (6)	2013-2014	18,105	MS/MS	no	GD, FD, NPA/B	6	1 (LOPD)	17	1:18,105 (LOPD)

Program	Year(s)	Screened newborns	Screening method(s)	Second tier test(s)/postanalytical tool(s)	Other screened diseases	Total presumptive positive newborns	True positive (IOPD/LOPD) after genetic analysis	PPV %	Birth prevalence (IOPD/LOPD)
Washington (7)	N/A	44,074, (deidentified)	MS/MS	no	KD, FD, MPSI NPA/B, GD	2	1	50	1:44,074
Kentucky (8)	2016-2017	55,161	MS/MS	CLIR (6-plex/10-plex)	KD, MPSI	2	2 (LOPD)	100	1:27,580 (LOPD)
Georgia (9)	2017	52,332	MS/MS	CLIR (6-plex)	MPSI	6	3 (1 IOPD/2LOPD)	50	1:17,444 (IOPD 1:52,332, LOPD 1:34,888)
Missouri (10)	2013-2018	467,000	DMF	no	GD, FD, MPSI	274	46 (10 IOPD, 36 LOPD)	17	1:10,152 (IOPD 1:16,700, LOPD 1:12,972)
Illinois (11,12)	2014-2019	684,290	MS/MS	no	GD, FD, MPSI, NPA/B	395	29 (3 IOPD, 26 LOPD)	7.34	1:23,596 (IOPD 1228,096, LOPD 1:26,319)
Pennsylvania (13)	2016-2019	531,139	MS/MS	Genetic analysis	/	115	33 (2 IOPD, 31 LOPD)	29	1:16,095 (IOPD 1:265,569, LOPD 1:17,134)
California (14)	2018-2019	453,152	MS/MS	Genetic analysis	No	18	12 (2 IOPD, 10 LOPD)	66	1:25,200 (IOPD 1:226,576, LOPD 1:45,315)
New York (15)	N/A	260,620	MS/MS	Genetic analysis	KD	22	12	55	1:21,718
	N/A	262,467	MS/MS	CLIR (3-plex/7-plex); genetic analysis	KD	15	13	87	1:20,190
Latin America									
Brazil (16,17)	N/A	10,527	DMF	no	GD, FD, MPSI	1	0	/	/
Brazil (18)	N/A	834 deidentified	Fluorometry (modified)	No	GD, FD, MPSI, MPSVI	150 (25 after change of cutoff)	0	/	/

Program	Year(s)	Screened newborns	Screening method(s)	Second tier test(s)/postanalytical tool(s)	Other screened diseases	Total presumptive positive newborns	True positive (IOPD/LOPD) after genetic analysis	PPV %	Birth prevalence (IOPD/LOPD)
Mexico (19)	2012-2016	20,018	MS/MS	no	GD, FD, MPSI, NPA/B, KD	16	1	6.25	1:20,018
Asia									
Taiwan (20,21)	2005-2007	132,538	Fluorometry (NAG/GAA)	tGAA*	No	121	4 (3 IOPD, 1 LOPD)	3.3	1:33,134 (IOPD 1:44,179, LOPD 1:132,538)
Taiwan (22)	2005-2011	473,738	Fluorometry	No	no	250	28 (9 IOPD, 19 LOPD)	11	1:16,919 (IOPD 1:52,637; LOPD 1:24,933)
Taiwan (23)	2008-2012	402,281	Fluorometry, since 2010 MS/MS	no	/	321	27 (7 IOPD, 20 LOPD)	8.41	1:14,899 (IOPD 1:57,468, LOPD 1:20,114)
Taiwan (24)	2010-2013	191,786	MS/MS	no	GD, FD, MPSI	234	16 (5 IOPD, 11 LOPD)	6.83	1:11,986 (IOPD 1:38,357, LOPD 1:17,435)
Taiwan (25)	2017	64,147	MS/MS (ABG/GAA)	tGAA*	FD, GD, MPSI	20	6 (1 IOPD, 5 LOPD)	30	1:10,691 (IOPD 1:64,148, LOPD 1:12,830)
Taiwan (26)	2005-2018	994,975	Fluorometry	no	/	NA	55 (16 IOPD, 39 LOPD)	NA	1:18,090 (IOPD 1:62,186, LOPD 1:25,512)
Taiwan (27)	2018-2019	73,743	MS/MS	no	GD, FD, MPS I, MPS II, MPS IIIb, MPS IVa, MPS VI	6	4 (1 IOPD, 3 LOPD)	67	1:18,436 (IOPD 1:73,743, LOPD 1:24,581)

Program	Year(s)	Screened newborns	Screening method(s)	Second tier test(s)/postanalytical tool(s)	Other screened diseases	Total presumptive positive newborns	True positive (IOPD/LOPD) after genetic analysis	PPV %	Birth prevalence (IOPD/LOPD)
Japan (28,29)	2013-2020	296,759	Fluorometry	no	/	154	8 (1 IOPD, 7 LOPD)	5.2	1:37,095 (IOPD) 1:296,759. LOPD 1:42,394)
China (30)	N/A	38,945	MS/MS	no	GD, FD, MPSI, NPA/B, KD	180	3 (LOPD)	1.67	1:12,982 (LOPD)

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PASC noted that the birth prevalence of GSD II is more common than 1 in 50,000 in all jurisdictions where it is screened for.