

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1737 – Newborn bloodspot screening for sickle cell disease and beta thalassaemia

Applicant: Australian Sickle Cell Advocacy Inc

Date of MSAC consideration: 27 July 2023

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

1. Purpose of application

An application requesting the addition of sickle cell disease (SCD) to newborn bloodspot screening (NBS) was received from Australian Sickle Cell Advocacy Inc by the Department of Health and Aged Care. During the initial review stage, the Sickle Cell Disease Expert Working Group recommended that beta(β)-thalassaemia, Haemoglobin E- β -thalassaemia and $\delta\beta$ -thalassaemia also be included in the application. These are all haemoglobinopathies, and this collective term will be used throughout this document (although not all haemoglobinopathies were included).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice regarding adding sickle cell disease (SCD) and beta (β)-thalassaemia to newborn bloodspot screening (NBS) programs. MSAC noted that SCD and β -thalassaemia are rare but severe conditions with high morbidity and mortality, especially SCD. MSAC considered that while adding these haemoglobinopathies to NBS would result in an earlier diagnosis than symptomatic presentation, the strength of existing healthcare in Australia including targeted testing of at-risk babies and pneumococcal vaccination rates, meant the incremental health outcome improvement from early diagnosis through universal NBS was uncertain. Additional evidence was required to quantify the change in management that would take place in Australia and resulting incremental health benefit from an earlier diagnosis through universal NBS as compared to diagnosis at symptom onset. MSAC considered that estimates of Australian incidence were highly uncertain, and overseas data had low applicability due to incidence differing by ancestry. Combined with uncertain screening costs, the rarity of these conditions, and the uncertain incremental diagnoses achieved through universal screening rather than existing targeted testing, MSAC considered the cost-effectiveness was highly uncertain. MSAC also considered the cost of testing may have been overestimated, and that using less costly methods would improve the cost-effectiveness and the financial impact.

Consumer summary

This was an application from Australian Sickle Cell Advocacy Inc requesting to add sickle cell disease and beta- (β -)thalassaemia to newborn bloodspot screening (NBS).

In Australia, states and territories offer bloodspot screening for all newborn babies. The screening is done by taking a heel prick blood sample from the baby in the first 48 to 72 hours of life, and drying it on a card. The blood sample is then tested for certain rare and serious genetic conditions and metabolic disorders. Detecting these conditions early allows for earlier monitoring and treatment, and therefore can lead to better health outcomes for the baby. If the condition is genetic, diagnosis can help the parents to make informed reproductive decisions for any future pregnancies.

Sickle cell disease and β -thalassaemia are inherited disorders of red blood cells, together called haemoglobinopathies. Red blood cells contain a protein called haemoglobin that carries oxygen throughout the body, and healthy red blood cells are flexible and shaped like a doughnut with a dent instead of a hole in the middle. Sickle cell disease is a genetic condition where a person has abnormal haemoglobin that causes the red blood cells to become rigid and sickle shaped. This makes it difficult for the red blood cells to move easily through blood vessels, and they can block blood vessels. People with sickle cell disease can experience episodes of severe pain, organ damage and increased infections, and sickle cell disease can be fatal. β -thalassaemia is a genetic condition where a person has less haemoglobin or the haemoglobin does not carry oxygen as well. People with β -thalassaemia tend to have lifelong anaemia (not enough haemoglobin), so often require regular blood transfusions, which in turn can lead to iron overload and other health complications. Testing for sickle cell disease and β -thalassaemia both look at haemoglobin, so a test for one can diagnose the other, and both conditions were included in this application.

The evidence showed that adding sickle cell disease and β -thalassaemia to the NBS was safe and would result in an earlier diagnosis than not adding them to NBS. However, in Australia, most babies with a haemoglobinopathy are already diagnosed at a relatively young age. The evidence presented showed not much difference in how babies would be treated if they were diagnosed earlier through NBS compared to diagnosis once symptoms present at the time when they first start to get symptoms. Additional evidence would be required to determine whether there would be a meaningful improvement in health outcomes from diagnosis through NBS for sickle cell disease and β -thalassaemia in Australia, relative to current practice. This was the main reason MSAC deferred its advice on NBS for sickle cell disease and β -thalassaemia. The evidence showed small differences in how babies are managed (including early antibiotic treatment and additional pneumococcal vaccinations), however these were not major differences, and the evidence came from countries where a greater proportion of people have sickle cell disease than in Australia due to ancestry and/or where the standard of healthcare is lower. Since the pneumococcal vaccine is on the National Immunisation Program, most babies in Australia are already vaccinated against pneumococcal disease starting at 2 months of age. Therefore, the benefits of a diagnosis in the first few days of life rather than when symptoms appear may not be as great as in other countries. MSAC considered that evidence was missing on what the change in management and resulting health improvement would be if sickle cell disease and β -thalassaemia were added to NBS in Australia.

MSAC considered the value-for-money of adding sickle cell disease and β -thalassaemia to NBS was highly uncertain. This was because the assessment was only able to look at the cost per early diagnosis, because the evidence in the literature did not allow the health improvement from an earlier diagnosis to be measured. The number of people with these conditions in Australia is at present highly uncertain, and the value-for-money particularly depended on this number, as well as on the cost of the screening test, which MSAC considered may have been

Consumer summary

overestimated. A cheaper test would reduce the financial cost to the NBS programs and make this screening better value for money.

MSAC deferred its advice on adding sickle cell disease and β -thalassaemia to NBS, because additional information would be needed to quantify changes in management and any improved health outcomes that would result, compared with the current situation in Australia.

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

MSAC deferred its advice on adding sickle cell disease and β -thalassaemia to NBS. MSAC acknowledged the seriousness of the conditions and that NBS would allow an earlier diagnosis, but considered the evidence had not shown that an earlier diagnosis, relative to current practice, would change healthcare of those babies or improve their health in the Australian context. The value for money and overall cost were also uncertain.

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

MSAC noted that this application from Australian Sickle Cell Advocacy was for adding sickle cell disease (SCD) and beta- (β -)thalassaemia to newborn bloodspot screening (NBS). MSAC noted that applications for adding and removing conditions from NBS were previously considered by the Standing Committee on Screening (SCoS). However, following its dissolution in 2021, applications for addition of conditions to NBS are now considered by other committees, including MSAC. This application (1737) and application 1710¹ are the first NBS applications to be considered by MSAC.

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

MSAC noted that the initial application from Australian Sickle Cell Advocacy Inc was only for SCD, but prior to entering the MSAC process, the SCD Expert Working Group recommended that other haemoglobinopathies (such as β -thalassaemia, haemoglobin E- β -thalassaemia and $\delta\beta$ -thalassaemia, but not α -thalassaemia) also be included, because abnormal haemoglobins other than HbS would also be detected during screening for SCD. Because the initial application was for SCD alone, the assessment was structured to use SCD as the base case and add β -thalassaemia as a scenario.

MSAC noted that newborns with SCD are at risk of serious symptoms as early as 8–10 weeks of age, and are at higher risk of mortality than the general population. Outcomes are poor if left

¹ MSAC application 1710 - Newborn bloodspot screening for X-linked adrenoleukodystrophy. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1710-public>

² Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework?language=en>

untreated, and many children with SCD die before the age of 3, or have disabling cerebrovascular disease (39% by age 18). For babies with β -thalassaemia major or intermedia, severe anaemia can cause serious symptoms in the first year of life. Treatments for SCD include hydroxyurea (HU), additional doses of pneumococcal vaccination in early childhood at 6 months and 4 years of age and early administration of prophylactic antibiotics. MSAC noted that the paediatric formulation of HU is not registered with the Therapeutic Goods Administration for use in Australia. MSAC noted that SCD and other haemoglobinopathies are categorised as a global public health problem by the World Health Organization. MSAC noted the applicant commented in its pre-MSAC response that a recent Lancet Haematology Commission had recommended “that by 2025, policies, resources, and facilities are in place to allow all babies worldwide to be tested for sickle cell disease”³.

MSAC noted that SCD is caused when a person is homozygous for the HbS variant (genotype HbSS), which is one specific variant in the beta haemoglobin *HBB* gene, HBB:p.(Glu7Val). This genotype results in rigid, sickle-shaped red blood cells that cannot move freely through blood vessels. SCD clinically manifest as acute pain episodes, and if left untreated results in progressive organ damage, including cerebrovascular disease, increased susceptibility to infections (especially invasive pneumococcal disease) and vaso-occlusive crisis. Heterozygous HbS genotype (“sickle carriers”) results in sickle cell trait disease (HbAS). HbS variants are inherited in an autosomal recessive (AR) manner, although it is also possible, but rare, for an HbS allele to arise *de novo*. β -thalassaemia is also an AR genetic condition, caused by any one of >1000 pathogenic genetic variants being present in both copies of a person’s beta haemoglobin (*HBB*) gene (and/or *HBD* gene for some types of β -thalassaemia). In β -thalassaemia, the quantity of beta chains produced is severely reduced, or the variant interferes with haemoglobin structure. Different variants have differing clinical severity, and people can be compound sickle/thalassaemia heterozygotes with a combination of SCD and β -thalassaemia variants, or compound heterozygotes with different types of β -thalassaemia variants (see 1737 PICO, Table 7).

MSAC noted the Department-contracted assessment report (DCAR) estimated the incidence of the included haemoglobinopathies in Australia at 0.53 per 100,000 births, based on data provided by the Australian Haemoglobinopathy Registry (HbR). MSAC noted ESC had considered the HbR data likely underestimated the incidence because they did not include stillbirths, terminated pregnancies or deaths before diagnosis. MSAC noted that currently, Western Australia is the only state that has a targeted testing program for infants at high risk. The incidence estimate from this program was about 8.6 per 100,000 births, which MSAC considered was substantially higher than the estimate based on HbR data. MSAC considered that the incidence of haemoglobinopathies in Australia was uncertain. MSAC also noted that migration to Australia from countries where SCD and β -thalassaemia are more prevalent has increased over time so, the incidence in Australia may be increasing.

MSAC noted that the population was all newborns undertaking NBS, and the proposed intervention was universal NBS within the first 48 to 72 hours of life. NBS was proposed to allow earlier diagnosis and facilitate better health outcomes for babies born in Australia. MSAC noted that the proposed screening protocols for SCD included a two-tier testing approach. The first-tier test would use a phenotypic method to detect abnormal haemoglobin, with second-tier confirmatory (usually genetic) testing to confirm diagnosis. Options for the first-tier methodology included isoelectric focusing (IEF), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE) and mass spectrometry (either electrospray ionization tandem mass

³ Piel FB et al. (2023) Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. *The Lancet Haematology*, 10(8): e633 - e686.

spectrometry (ESI-MS/MS) or Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry (MALDI-TOF)). MSAC noted that NBS is implemented locally, so each NBS laboratory determines which method of screening to use taking their local constraints into account. MSAC noted comments from some NBS laboratories that screening for SCD and β -thalassaemia could not be performed on current screening platforms (although one NBS laboratory stated they could use existing instrumentation to test for SCD but not β -thalassaemia). MSAC noted that there are existing Medicare Benefits Schedule (MBS) items for diagnosis of haemoglobinopathies that are used for testing people who present clinically, but that those MBS items would not be used in NBS. Cascade testing of biological relatives of newborns with a positive screening result was also part of the PICO, and would be funded by the states and territories.

MSAC noted that the primary comparator was no NBS for haemoglobinopathies and the secondary comparator was targeted testing of at-risk newborns. MSAC noted that targeted newborn testing currently takes place in Western Australia (which is ~11% of the national birth cohort), and that the DCAR stated the secondary comparator (targeted testing) better reflects current clinical practice in Australia. MSAC noted that Australian clinical practice guidelines also recommend targeted preconception and/or prenatal testing of potential parents and fetuses at risk for haemoglobinopathies respectively, but that these would not be replaced by NBS and were not part of the intervention nor the comparator. MSAC noted that the targeted testing that comprised the secondary comparator was only targeted testing of at-risk newborns, which would be replaced by NBS. Neonates are considered to be at increased risk of inheriting SCD if they have parents of indigenous African ancestry, or if at least one parent is known to have SCD. For β -thalassaemia, neonates are considered at risk if they have parents of Middle Eastern, Indian subcontinent or Asian ancestry, or if at least one parent is known to have β -thalassaemia. MSAC noted the DCAR cited expert opinion that because most Australian obstetric services include haemoglobinopathy screening for at risk couples, targeted neonatal testing currently detects approximately 95-99% of Australian newborns with a haemoglobinopathy. MSAC considered that only a small proportion of newborns are currently not diagnosed in the absence of universal newborn testing, but that because the Australian incidence was uncertain, the proportion of newborns currently detected in Australia was also uncertain.

MSAC noted cascade testing of family members of newborns detected through NBS was also assessed as part of the application (PICO set 2). MSAC considered cascade testing was important to inform the newborn's parents' reproductive decision-making.

MSAC noted the clinical claim was that early diagnosis (through universal NBS) was superior to diagnosis upon clinical presentation, as it would facilitate early intervention and improved health outcomes.

MSAC noted that the evidence base identified by the DCAR's systematic literature review included both direct and indirect evidence, and that MSAC's stated preference is for direct evidence from test to health outcomes for screening programs. MSAC agreed with ESC that the DCAR's separation of direct versus indirect evidence facilitated its consideration. MSAC noted the known limitations of evidence for rare diseases, consistent with the principles of the National Strategic Action Plan for Rare Diseases.

MSAC considered the main safety issue was the risk of adverse events associated with treatments for SCD or β -thalassaemia, such as HU. HU administration is associated with reduced neutrophil counts, which increase the risk of sepsis and bacteraemia, and require regular monitoring. MSAC considered safety outcomes from over-diagnosis or false positive screening test results were also possible but unlikely as the test accuracy was high. However, MSAC noted that the positive predictive value (PPV) and diagnostic yield (DY) were strongly influenced by the incidence.

MSAC noted that diagnosis of the included haemoglobinopathies currently takes place at an average age of 8.4 months (interquartile range 0.1 to 2.2 years) in Australia, and that NBS was proposed to result in earlier diagnosis. MSAC noted the DCAR commented that the age difference between diagnosis with universal NBS versus without NBS was likely to be smaller in Australia than that in the literature. MSAC agreed that NBS would result in earlier diagnosis of haemoglobinopathies, although considered how much earlier this would be in Australia was uncertain.

MSAC noted the direct evidence showed that earlier diagnosis of SCD led to earlier commencement of prophylactic antibiotics, reduced bacteraemia, and reduced mortality. MSAC noted that the applicant had commented in its pre-MSAC response that penicillin prophylaxis is recommended to start by age six weeks, and that parental education on palpation for splenomegaly may reduce mortality. MSAC also noted the direct evidence showed that early diagnosis of SCD reduced the number of hospitalisations and median days spent in hospital. However, MSAC considered that the change in management and improvements in health outcomes demonstrated by the evidence available for SCD were small. MSAC considered that most of the direct evidence was from countries where the incidence of SCD was much higher than in Australia, and so the evidence had low applicability to the Australian context. MSAC noted that direct evidence for the effectiveness of NBS for β -thalassaemia was scarce. MSAC considered that the effect of early diagnosis on health outcomes in Australia would likely be smaller than that reported in the literature, due to the strength of Australia's healthcare system, making the applicability of the direct evidence low. For example, Australia currently has high uptake of pneumococcal vaccination, meaning any infants with SCD who are not diagnosed by current targeted testing are therefore likely to be partially protected by routine pneumococcal vaccination, reducing the potential incremental benefit of NBS. MSAC noted no linked evidence additional to direct evidence was identified for any change in management from an early diagnosis through NBS. MSAC considered that potential changes in management for infants diagnosed with SCD or β -thalassaemia could be with respect to prophylactic antibiotics, genetic counselling, HU treatment, regular transfusion, and pneumococcal vaccination – but that changes in these had not been demonstrated by the evidence presented. MSAC considered the change in management and improvements in health outcomes demonstrated by the available evidence for SCD were small, and may not apply to Australia. MSAC also considered that superior effectiveness was highly dependent on the incidence of SCD and the effectiveness of existing targeted testing approaches, which were both uncertain for Australia. Overall, MSAC determined that additional evidence was required to demonstrate a meaningful change in management from NBS in Australia, with resulting measurable improvements to health outcomes.

MSAC noted that the economic evaluation was a cost-effectiveness analysis, which measured effectiveness in terms of “additional early diagnosis of a clinically significant case”, because the DCAR had found insufficient evidence to translate the incremental benefit of the identified changes in management into patient-relevant outcomes beyond an early diagnosis. MSAC noted the uncertainty of the evidence used in the economic model for SCD was high, and the uncertainty of the evidence for β -thalassaemia was very high (Table 14). MSAC therefore considered that the economic results including β -thalassaemia were not credible.

MSAC noted the DCAR's reported incremental cost-effective ratios (ICERs) for SCD were \$141,338 per early diagnosis (vs no NBS / symptomatic identification), and \$13,833,958 per early diagnosis (vs targeted newborn testing). MSAC considered that these were higher than the cost per proband (and similar) ICERs measured in terms of diagnostic yield that it had previously supported, although the previous ICERs were not perfectly relevant for contextualisation: because cost-effectiveness may not be directly comparable between universal screening and testing of affected individuals, and also because in the affected individual context the diagnosis of a proband had demonstrable value in terms of prognosis and/or improving health outcomes,

whereas in this case the value of an earlier SCD diagnosis had not been demonstrated. MSAC therefore considered the cost-effectiveness of NBS for SCD was low and highly uncertain. MSAC advised the evidence had not demonstrated that NBS was comparatively cost-effective.

MSAC noted that the PICO had included a range of first tier methods (at a range of costs) in the intervention, and that the choice of method for the first tier test was the main driver of cost-effectiveness. MSAC noted policy advice that harmonisation of the methods used in different Australian NBS laboratories was unlikely, although considered that assessing multiple methods was impractical for the HTA, and while all methods that would be used in Australia are in-scope for the HTA and therefore need to be assessed, ideally in future the number of methods assessed should be reduced if possible. MSAC noted that the base case model had used MALDI-TOF, because this was the method for which NBS laboratories provided the cheapest costing (\$10). MSAC noted that when using the most costly first tier method, HPLC (\$96), the ICERs increased substantially. MSAC noted that ESC had commented that \$10 was a relatively low cost and the cost in Australia was unlikely to be lower than this, but that the applicant had commented that there are cheaper options in other parts of the world, and that Australian NBS laboratories may be able to progress more competitive quotes. MSAC considered that \$10 per test would be relatively costly for a universal screening program first tier test, and that less costly methods should be equally capable of providing a diagnosis of SCD and β -thalassaemia. MSAC queried whether less costly methods are available in Australia, and considered that using a less costly method would improve the cost-effectiveness. MSAC considered the highly uncertain data for incidence in Australia also added to the uncertainty of the economic results.

MSAC noted that the economic model used a 1-year time horizon, because this captured the difference between early diagnosis around the time of birth versus diagnosis at symptomatic presentation (average age 8.4 months). MSAC considered that it was possible that early diagnosis may have longer-term health benefits, but that the evidence presented had not demonstrated this.

MSAC noted the ICERs were lower against no NBS than against targeted testing. MSAC considered that targeted testing of at-risk neonates is conducted on a clinician-by-clinician basis and so will be variable. MSAC considered that it provides advice from the perspective of the healthcare system as a whole, and considered that it may be possible to make a better case for targeted testing, including from an economic perspective, although noted MSAC's advice on targeted testing was not being sought under this application. MSAC considered that if targeted testing of at-risk newborns were to be considered in future, the relevant clinical colleges and societies could be asked to define criteria for targeted testing.

MSAC noted utilisation was estimated using an epidemiological approach (assuming 99.3% NBS uptake), which it considered was appropriate. MSAC noted that the cost of the first tier test was the main driver of the overall financial impact, and the DCAR had estimated the financial cost to NBS programs was about \$3 million per year if the first tier screening test cost \$10 per newborn, and this increased to about \$30 million per year if the first tier screening test cost \$96 per newborn (Table 21). MSAC considered that the financial impact had likely been over-estimated due to a relatively costly method having been chosen, and that using a less costly first tier method would reduce the financial cost of NBS. MSAC noted that adding SCD to NBS would also affect other health budgets, including a potential cost-offset from reduced targeted neonatal testing. MSAC noted that the DCAR found there would be minimal incremental cost of cascade testing (PICO set 2), because targeted testing is estimated to detect 95-99% of neonates currently in Australia (although this proportion was informed by expert opinion). MSAC noted that in its experience cascade testing uptake is close to 100%, so considered that cascade testing for haemoglobinopathies already takes place to a nearly complete extent.

MSAC acknowledged the severity of SCD and β -thalassaemia, but considered that the evidence had not demonstrated health outcome improvement in Australia from earlier diagnosis through NBS. This was MSAC's primary concern, although it did also have other concerns. MSAC considered that key information was missing and additional evidence was required, so deferred its advice on adding SCD and β -thalassaemia to NBS. MSAC advised that the following evidence would be required to support its reconsideration:

- Quantify the change in management between NBS and current testing in Australia.
- Quantify the resulting effect on health outcomes in Australia.
- Provide a more reliable estimate of incidence in Australia.
- Investigate whether less costly screening methods are available in Australia, and if so determine their costs.
- Provide updated economic and financial analyses taking the above into account.

MSAC also considered that consultation with consumers and the SCD community may be able to provide better evidence on the non-health benefits from an earlier diagnosis, such as comments on access to health care. MSAC considered that a pilot study may be able to provide better quality incidence data for Australia.

MSAC considered that information for its reconsideration could be provided for SCD alone, because screening for SCD can also detect β -thalassaemia as a non-target condition.

MSAC noted that research is underway for genomic NBS, and that independent from this MSAC application the *HBB* gene has been identified by experts as relevant for genomic NBS.

4. Background

This is the first assessment of adding haemoglobinopathies to Australia's NBS programs to be considered by MSAC.

Applications to add a condition to NBS were previously considered by the Standing Committee on Screening (SCoS), and with the disbandment of SCoS the process changed in 2021 to MSAC providing advice instead. MSAC's July 2023 consideration of this application and MSAC Application 1710 (NBS for X-linked adrenoleukodystrophy) will be its first considerations of applications to add conditions to NBS.

5. Prerequisites to implementation of any funding advice

Each state and territory would determine which method of screening for SCD or SCD and β -thalassaemia they would implement. New conditions added to Australian NBS programs need to align with the Newborn Bloodspot Screening National Policy Framework (NBS NPF) decision-making criteria, which were considered as context for MSAC's advice.

Feedback from all Australian NBS laboratories indicated that screening for SCD and β -thalassaemia could not be performed on current screening platforms (although one laboratory stated they could use existing instrumentation to test for SCD but not β -thalassaemia). The full scope of considerations relevant to the NBS NPF criteria, such as detailed appraisal of all relevant implementation considerations, are outside the scope of MSAC's advice on NBS, however it is recognised that laboratories may require new equipment in order to perform testing.

6. Proposal for public funding

The proposal was for haemoglobinopathies to be added to the list of conditions screened for through Australia's NBS programs. If a hereditary haemoglobinopathy is diagnosed via NBS, then follow-on cascade testing of first-degree relatives is also proposed, however this is not covered by NBS program funding.

The Australian Government contributes funding to hospital services, including those for NBS through the National Health Reform Agreement (NHRA). It has also provided \$25.3 million over 4 years in direct funding to states and territories to support expansion and consistency of NBS programs.

There are five laboratories that conduct tests on bloodspot cards for NBS, located in New South Wales, Queensland, South Australia, Victoria and Western Australia. In Tasmania and the territories newborn dried bloodspot samples are sent interstate for testing. All NBS programs are underpinned by the NBS NPF. Babies screened through NBS programs have a small blood sample taken via a heel prick in the first 72 hours of life. The blood is collected and dried onto a filter card, which is then used for testing.

Screening protocols for SCD generally use a two-tier testing approach, whereby first-tier testing can identify the presence of abnormal haemoglobin (or not), and second-tier testing is performed to confirm the first result. Only samples found to have abnormal results in first-tier testing undergo second-tier testing. Each NBS laboratory would be responsible for deciding what screening protocol to use (i.e. which combination of test methods to use for first- and second-tier testing). Screening test methods assessed in this report include:

- isoelectric focusing (IEF);
- high-performance liquid chromatography (HPLC);
- capillary zone electrophoresis (CE);
- mass spectrometry (either Electrospray Ionization tandem mass spectrometry (ESI-MS/MS) or Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry (MALDI-TOF)); and
- quantitative polymerase chain reaction (qPCR).

Most testing protocols would then require genetic testing to confirm the diagnosis.

IEF, HPLC, CE and MS based assays are classified as phenotypic tests as they are based on the levels and/or relative proportions of haemoglobins present in a blood sample. Molecular based tests (qPCR, Sanger sequencing, and other genetic assays) are classified as genotypic tests, as they provide a genotype from the test sample. HPLC, CE and IEF are able to identify carriers of SCD and also some β -thalassaemia carriers, but MS assays are more limited in carrier identification as the technology is usually trained to identify a limited number of phenotypes accurately. Genotypic testing is capable of identifying all cases and carriers, within the scope of the test being performed.

IEF, HPLC, and CE are established for the diagnosis of haemoglobinopathies, and have MBS items available. The cost of testing will depend on the combination of tests chosen.

NBS in Australia does not currently include screening for haemoglobinopathies. Australian clinical practice guidelines recommend targeted preconception testing of potential parents for haemoglobinopathies in couples at risk, or in the prenatal period if a couple is already pregnant. Whilst this testing is recommended, it is not universal and cases are missed by this method; although the number of cases missed is unknown. Older data from the Victorian Birth Defects

Registry⁴ (1989-1998) indicated that the majority of thalassaemias identified prenatally resulted in pregnancy termination (39/63), highlighting the importance of timely identification to maximise choice. Targeted preconception and prenatal testing would continue even if NBS for SCD and β -thalassaemia were supported, so NBS would be *in addition* to this type of targeted preconception and prenatal testing. Limited targeted post-natal testing of the newborn is also performed in some Australian states. NBS would *replace* targeted post-natal testing of the newborn.

Cascade testing is likely to be performed by genetic testing of one or two familial variants. The cost of cascade testing is not covered by NBS funding however this is not a new service; cascade testing of family members already occurs when a person is diagnosed.

7. Population

There are two populations under consideration in this assessment: newborns participating in newborn screening in Australia, and family members of newborns diagnosed through NBS, eligible for cascade testing.

Population 1: Newborns

The conditions proposed for screening are inherited disorders in the structure or quantity of haemoglobin, or haemoglobinopathies. Haemoglobin (Hb), which is essential for oxygen transportation, is a protein normally constructed of two alpha and two beta chains (HbA). SCD and β -thalassaemia are two of the most severe haemoglobinopathies and the two conditions proposed to be added to the NBS.

SCD usually occurs with the inheritance of two HbS variants (or HbSS), one in each copy of the beta globin gene (*HBB* gene), but other variants are also known. People with SCD have rigid, sickle-shaped red blood cells that can block blood vessels particularly during hypoxia or dehydration, preventing tissue from getting sufficient oxygen. This can cause intense pain, infection, organ damage (lungs, kidneys, spleen and brain) and stroke (Genetic Science Learning Centre).

Since SCD impairs red cell production and is associated with increased red cell haemolysis, there is a potential lifelong requirement for blood transfusion (with increasing risk for alloimmunisation and reduction in availability of matched red cells for transfusion, over time) to ameliorate the disease effects. The American Society of Hematology guidelines suggests performing “extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion)” (Chou et al. 2020)⁵.

Stroke, silent cerebral infarcts (silent strokes), and cognitive morbidity are the most common permanent sequelae of SCD in children and adults, occurring in approximately 39% of children before their 18th birthday. Consequent to this risk for adverse neurodevelopmental outcome, children aged 2-16 years should have annual transcranial doppler (TCD) performed to assess risk for ischaemic stroke, and to direct transfusion need (see below). For suspected ischemic strokes,

⁴ Data contained in report “Beyond the crystal ball: the epidemiology of some genetic conditions in Victoria 2002” by Public Health Group, Rural and Regional Health and Aged Care Services Division, Victorian Government Department of Human Services

⁵ Chou, ST, et al. *Blood Adv* (2020), 'American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support', vol. 4, no. 2, pp. 327-355.

timely and appropriate red blood cell transfusion (within 2 hours of presentation to medical care) should be provided (DeBaun et al. 2020)⁶.

For children with SCD (ages 2-16 years) and abnormal TCD results who have been receiving transfusion therapy for at least 1 year and are interested in stopping transfusion, according to the clinical trial risk stratification with an MRI and magnetic resonance angiography (MRA) of the brain that hydroxyurea (HU) treatment at the maximum tolerated dose can be considered to substitute for regular blood transfusions (conditional recommendation based on low certainty in the evidence about effects (DeBaun et al. 2020). There are currently no official clinical recommendations for the use of HU in children with SCD in Australia, although it is recommended for prevention of stroke and acute chest syndrome (ACS) by some clinical groups (ASCA 2021; Greenway G).

In the general population, young children have a higher risk of severe pneumococcal infection, with pneumococcal vaccination being included in the routine vaccination schedule⁷. Individuals with SCD have a higher risk for pneumococcal infection than the general population and are eligible for additional vaccine doses in early childhood at 6 months and 4 years of age.

People with severe β -thalassaemia (intermedia and major) have also inherited variants in both *HBB* genes, which severely reduces the quantity of beta chains produced. The resultant excess of alpha chains can cause abnormal structures to form, and anaemia is common. Iron overload from regular transfusion causes iron toxicity and deposition in multiple organs with consequent impairment of function. A combination of SCD and β -thalassaemia variants can be inherited by the same individual. The target population for screening is all babies born in Australia who participate in universal newborn bloodspot screening programs. Included in the target population are infants at general risk (no known risk factors) and those at high risk of having SCD (including the homozygous HbSS form, heterozygous HbSC form, or HbS β -thalassaemia), or β -thalassaemia (including thalassaemia major, thalassaemia intermedia, HbE β -thalassaemia, or $\delta\beta$ -thalassaemia) due to factors such as ancestry or family history.

Newborns with SCD are at risk of serious symptoms as early as 8 to 10 weeks of age, and are at higher risk of mortality than the general population due to infection, and splenic infarction, which may occur during sickle crises. For babies with β -thalassaemia major or intermedia, severe anaemia can cause serious symptoms in the first year of life. It is proposed that NBS will diagnose neonates earlier than they are currently diagnosed in Australia, thereby reducing their morbidity and mortality. Babies with SCD can be given prophylactic penicillin and additional pneumococcal vaccination when diagnosed early, which are intended to lower the risk of sepsis, pneumonia, osteomyelitis, meningitis and death.

Early diagnosis brings awareness of the condition that enables commencement of monitoring for cerebrovascular disease risk, commencement of prophylactic interventions, undertaking baseline red cell antigen testing, and identification of symptoms in their earlier stages leading to earlier treatment. Hospitalisation should be reduced, and fewer downstream sequelae from severe anaemia, venous blockages and splenic sequestration should reduce the burden on the health system and improve health and social outcomes for children with severe haemoglobinopathies.

⁷ National Immunisation Schedule: <https://www.health.gov.au/sites/default/files/2023-03/national-immunisation-program-schedule.pdf>

Population 2: Family members

When a newborn is diagnosed with a haemoglobinopathy, both parents can be assumed to be carriers of pathogenic or likely pathogenic (P/LP) variants, and they are assumed to have a one in four chance of having an affected child with each subsequent pregnancy. It is proposed that cascade testing is offered to both parents as it can provide additional information for reproductive planning. While cascade testing is already offered to the relatives of cases identified through symptomatic presentation, the size of the population eligible for cascade testing may increase slightly if haemoglobinopathies were added to NBS. It is also proposed that siblings of a diagnosed child are eligible for cascade testing as they may be affected (and as yet undiagnosed) or carriers.

In the absence of a timely diagnosis of a newborn who has not yet become symptomatic, there is a risk the couple may have another affected child before the first child receives a formal diagnosis.

8. Comparator

Population 1: Newborns

The primary comparator to universal NBS for haemoglobinopathies is no screening. In the absence of universal NBS, individuals who have the disease would only be investigated after presenting with clinical symptoms of a haemoglobinopathy (i.e. the comparator would be clinical diagnosis). As an example, the investigations may consist of HPLC and CE (using MBS items 65078 and 65081), followed by genetic testing. This scenario does not reflect current clinical practice in Australia.

A secondary comparator to universal NBS is targeted testing of neonates suspected or known to be at high risk. Testing of at-risk couples (preconception or prenatal) is recommended clinical practice in Australia, as mentioned above, and this would continue if NBS was introduced. However targeted testing of newborn babies missed through preconception or prenatal testing would be replaced by NBS. Reliable, recent data on the number of babies missed by targeted antenatal or neonatal testing were not available, so a range of estimates have been used, informed by older data and clinical experts. Targeted testing on cord blood currently takes place in Western Australia. Neonates are considered to be at high risk of inheriting SCD if they have parents of indigenous African origin, or if at least one parent has SCD. For β -thalassaemia, neonates are considered at risk if they have parents of Middle Eastern, Indian subcontinent or Asian origin or if at least one parent has β -thalassaemia. There are other ancestries that are also at risk.

Population 2: Family members

The comparator to cascade testing using a genetic test, is genetic counselling and cascade testing using phenotypic HPLC, CE or IEF.

9. Summary of public consultation input

Consultation feedback was received from eight (8) professional organisations, three (3) consumer organisations and four (4) health professionals. The organisations that submitted input were:

- The New South Wales NBS Programme and CHW Haematology Department (NSW NBS Programme)
- Thalassaemia and Sickle Cell Australia (TASCA)
- Genetic Undiagnosed and Rare Disease Collaborative Australia (GUARD)
- South Australia Women's and Children's Hospital, department of Haematology/oncology (WCH)
- The Newborn Screening Committee of the Human Genetics Society of Australia (HGSA)
- Rare Voices Australia
- Royal Children's Hospital/Royal Women's Hospital, Victoria (RCH/RWH)
- PathWest Haemoglobinopathy Reference Laboratory and Perth Children's Hospital Haematology Department (PathWest)
- Victorian Clinical Genetics Service (VCGS)
- Australian Haemoglobinopathy Registry (HbR)
- Haematology Society of Australia and New Zealand (HSANZ)

Additional targeted comments were provided by the NSW NBS Program following PASC consideration.

The consultation feedback received was mixed. Most respondents acknowledged potential benefits of NBS for SCD and β -thalassaemia. However, several respondents were not supportive of the proposed service.

The consultation feedback raised concerns in relation to the proposed test method, the detection of genetic carriers, and the detection of non-paternity.

The main benefits of public funding received in the consultation feedback included:

- Benefits from earlier diagnosis. This included earlier initiation of treatment and monitoring which could reduce disease complications and improve quality of life. Some respondents considered public funding would help reduce disease associated mortality and morbidity and may therefore reduce grief experienced by families.
- Improved access to testing and avoiding diagnostic odyssey.

The main disadvantages of public funding received in the consultation feedback included:

- Identifying carriers who will not develop disease
- Potential to identify people with mild disease. Analytical screening results may not predict the phenotypic variability seen with the beta-thalassaemias.
- Potential for false positives (e.g. other haemoglobinopathies).
- Infants with beta-thalassaemia are less likely to benefit from early intervention.

10. Characteristics of the evidence base

The Health Technology Assessment (HTA) group conducted a systematic review (SR) of the peer reviewed literature published in PubMed and MEDLINE databases. A large body of direct evidence assessing NBS for SCD was identified. A 2016 HTA (IHE 2016) with broad study inclusion criteria formed the basis of direct evidence, with later published evidence included from the SR. The highest level of evidence overall was comparative cohort study (level III-3) although most studies were cohort studies without concurrent controls (level III-3). The studies were rated from low to moderate for risk of bias and were conducted in settings of low to high socioeconomic status. Many were performed in areas of high SCD prevalence, often associated with high malaria prevalence. Historically, high rates of malaria infection have driven a high

prevalence of SCD, as carriers of SCD have been protected against the worst impacts of the plasmodium (*P. falciparum*) that causes malaria. The studies assessing NBS in high SCD prevalence countries do not have good applicability to the Australian healthcare setting. The *P. falciparum* is rarely present in Australia, and malaria is not endemic, Countries with endemic malaria and high SCD prevalence are often of low socioeconomic status, with poor healthcare, and the combination of these factors has led to poor health outcomes for those with either disease.

Linked evidence was included to address the questions not covered in the direct evidence. There are also specific criteria for new applications for additions to NBS that must be addressed. Studies were included that assessed diagnostic accuracy, and treatment effectiveness. The evidence on treatment effectiveness was the highest-level evidence (level I) of this assessment as it came from a systematic review of RCTs of SCD treatments. This study was rated moderate for risk of bias, and the settings for the four relevant RCTs were France, Netherlands, and the United States. Of 31 diagnostic accuracy studies conducted on dried blood spots, the majority were rated high risk of bias, and only six rated low risk of bias. Once again, many of the studies were conducted in settings of high SCD prevalence and therefore have reduced applicability to Australia.

There was very limited evidence identified on β -thalassaemia, family members undergoing cascade testing, and change in management.

A rapid review conducted by Abt Associates for Application 1737 provided an additional source of studies (Abt Associates 2022).

The key features of the direct evidence are summarised in Table 1 and for linked evidence in Table 2.

Table 1 Key features of the included direct evidence (Population 1)

References	k n	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
NBS for haemoglobinopathies vs no screening						
(IHE 2016)	k=5 n=NR	Ret Coh Up to 15 y	<i>Low to high</i>	Newborns participating in NBS	Mortality Diagnostic accuracy	
(Le et al. 2018)	n=260	Ret comparative Coh	<i>Low</i>	SCD patient register (diagnosis by NBS)	Time to diagnosis from first event 15-year survival from diagnosis Likelihood of severe events	

Coh = cohort study; NBS = newborn bloodspot screening; Ret = retrospective; SCD = sickle cell disease
Source: DCAR Table 1.

Table 2 Key features of the included linked evidence (Population 1)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	Coh and CS		High
	Accuracy for SCD screening	☒ k=24 n= 3,751,356	
	Accuracy for β -thalassaemia screening	☒ k=8 n=4,921,990	
Health outcomes	SR	☒ k=5 n=932	Moderate

Coh = cohort study; CS = case series; NA = not applicable; SCD = sickle cell disease; SR = systematic review
Source: DCAR Table 2.

11. Comparative safety

Population 1: Newborns

Physical harms associated with screening

NBS is performed on peripheral blood extracted from a heel prick onto filter paper, and as such is a very safe screening test. Newborns already undergo a heel prick for blood collection for NBS, and adding haemoglobinopathies to the NBS schedule will not require an extra heel prick. Other potential safety considerations for screening are associated with over-diagnosis or false positive test results, but given the type of disease and the accuracy of the tests, both of these are unlikely. There may also be psychological and social impacts associated with receiving positive test results; again, these impacts are experienced earlier than with clinical diagnosis, but are not additional. The main safety issues relating to NBS therefore are those associated with treatments for SCD or β -thalassaemia received by newborns diagnosed early by NBS that are over and above those received by babies diagnosed at a later age,

Physical harms associated with treatment

There was some evidence for treatment safety for SCD. One SR identified two RCTs (447 children) that reported the treatment-related complications and adverse events in children <5 years old with SCD who were randomised to either antibiotic (penicillin) prophylaxis or placebo/no prophylaxis. There was no difference in the number of adverse events between those given penicillin and those given placebo or no prophylaxis. There were some local reactions in children given penicillin intramuscularly.

IHE (2016) noted that some children may have an allergic reaction to penicillin, however there were no cases reported in the studies in that HTA.

One randomised controlled trial (RCT) showed that the absolute neutrophil count was three times more likely to drop in the children treated with HU compared with placebo, possibly placing those children at higher risk of infection. Persistent or recurrent neutropenia led to a reduced dosage of HU in some children and a change to placebo in others. The higher risk of infection was not reflected in the sepsis or bacteraemia rates in the trial, which were more frequent in the children who received placebo than HU (Table 3).

Table 3 Adverse effects of HU in children with SCD in the BABY HUG trial

Adverse effect	HU	Placebo	Difference
Absolute neutrophil count (500-120/mm ²)	107 events/45 children	34 events/18 children	HR 3.0 (95% CI 1.7, 5.1) p<0.001
Sepsis or bacteraemia	3 events/2 children	6 events/5 children	HR 0.4 (95% CI 0.08, 2.06) p=0.26

CI = confidence interval; HR = hazard ratio; HU = hydroxyurea; SCD = sickle cell disease
Source: (Meremikwu & Okomo 2016) Table source: DCAR Table 3.

In another RCT, skin rash occurred in 10% of cases that received HU but did not occur in the placebo group. Despite this outcome, the trial reported that no participants had any major adverse events.

There was no reliable evidence of physical harms associated with β -thalassaemia treatments.

Harms from false positive or false negative results

There may be harms related to false positive result. There was a psychological impact associated with test results, and waiting for confirmation of diagnosis may be associated with parent anxiety (IHE, 2016). No data were reported.

False negative results leave newborns with undiagnosed SCD, and consequently at risk of serious bacterial infection until diagnosis, as they will not receive prophylactic penicillin, nor additional doses of pneumococcus vaccination that are given to babies diagnosed with SCD. False negative results are likely to have been infrequent, however no data were identified in the HTAs or primary studies.

Physical harms associated with no screening

For individuals who do not have a haemoglobinopathy, the absence of NBS for the disorders will have no negative impact. However, for those with a haemoglobinopathy, the absence of NBS would mean a delayed clinical diagnosis and delayed treatment, which results in inferior health outcomes. The implications of this are discussed more in “Clinical utility summary”.

Population 2: Family members

No physical harms are expected from cascade testing of family members, as testing is performed to identify carriers only. The phenotypic tests performed only require a blood sample, and genetic testing requires either a blood sample or sample collected non-invasively such as a buccal sample. Cascade testing itself is therefore considered very safe. There may be psychological or social impacts associated with receiving a positive test result. There was no reliable evidence identified for these outcomes.

In the absence of NBS for haemoglobinopathies, family members would only be offered cascade testing after the clinical diagnosis of cases. The safety outcomes would be identical for early versus late cascade testing.

12. Comparative effectiveness

Population 1: Newborns

Direct evidence

The direct evidence compared health outcomes between ‘early’ and ‘late’ diagnosed cohorts of babies with SCD, defined below. IHE (2016) was the main source of evidence up to 2014, and the SR conducted by the HTA group provided the source of studies from 2014 until the search date (4 October 2022). Included studies were designed to assess the performance of NBS for SCD, so ‘early’ diagnosis meant diagnosis of newborns by universal NBS. ‘Late’ diagnosed cohorts were babies diagnosed prior to the initiation of NBS (i.e. diagnosed at a later age symptomatically), or were defined by symptomatic diagnosis. There were also studies that compared data from a time period early in the establishment of NBS and later, when NBS was well established, to determine if there was an improvement in health outcomes over that period. The mean age of diagnosis for children in late cohorts was not clear in most studies (IHE 2016).

Safety

IHE (2016) reported harms from testing from the HTA by Blancquaert et al (2009)⁸. There was no evidence of physical harms associated with sample collection (almost all newborns in Australia undergo NBS in any case) or test performance. There was no evidence of harm from early treatment, but the rare possibility of an anaphylactic reaction was noted by the authors. There were no data on anaphylactic reactions⁹.

IHE (2016) found that harms related to false positive results were associated with the psychological impact of the test results. Waiting for confirmation of diagnosis may be associated with parent anxiety. No data were reported.

False negative results leave newborns with undiagnosed SCD, and consequently at higher risk of a number of sequelae until diagnosis, one of the most common being serious bacterial infection as they will not receive prophylactic penicillin. No data were identified in the HTAs. There was no safety data reported in primary studies identified in the SR literature.

Effectiveness

The main effectiveness outcome reported in the direct evidence was mortality. Other outcomes reported were morbidity, hospitalisation time and time to first consultation.

The primary studies reported in IHE (2016) (four in total) all found that earlier age at diagnosis lowered the mortality rate in children. The age of children included in the various analyses ranged from <2 years to <15 years for long term analyses. Two studies found statistically significant differences in favour of early diagnosis. The study by King et al (2007)¹⁰, provided comparative analyses for the 1st, 2nd, 3rd, 5th, and 10th year of life for children diagnosed with SCD either by NBS or by symptom presentation. There was a statistically significant improvement in mortality for children up to their 5th year of life ($p < 0.001$ for the 1st, 2nd, 3rd, and 5th years), but in their 10th year ($p = 0.176$), there was no difference in mortality between early and late diagnosed groups (Table 5). This data came from two Jamaican cohorts, one diagnosed by NBS, and one from an earlier study who were diagnosed symptomatically. The authors concluded that prophylactic penicillin given soon after newborn diagnosis, and education for parents about signs of infection and splenic sequestration were responsible for the improvement in survival between early and late diagnosed groups, but after 5 years of age, children were less vulnerable. This effect in children with SCD under 5 years of age is consistent with a higher susceptibility at younger age to serious infections (particularly from encapsulated bacteria such as *Streptococcus pneumoniae*) that can lead to death, as a consequence of splenic dysfunction and poorer immunity than older children (IHE 2016). NBS and the interventions that follow diagnosis appear to have a protective effect against these impacts. With older age, the development of immunity and maturity of the spleen place children with SCD at lower risk of serious consequences of infection.

⁸ https://www.inspq.qc.ca/pdf/publications/1171_AnemieFalciforme.pdf

⁹ The risk of penicillin-induced anaphylaxis (type 1 hypersensitivity) in the general population is reported as 0.02% to 0.04% of recipients. Source: <https://www.ncbi.nlm.nih.gov/books/NBK459320/#:~:text=The%20incidence%20of%20anaphylaxis%20to,IgE%20antibodies%20decrease%20over%20time>

¹⁰ King, L, et al. *J Med Screen* (2007), 'Newborn sickle cell disease screening: The Jamaican experience (1995-2006)', , vol. 14, 02/01, pp. 117-122.

Table 4 Mortality of children with SCD diagnosed by NBS and treated in Jamaica, compared to children diagnosed and treated at a later age (Runkel et al. 2020)

Age	Intervention (n=395 ^a) vs control (n=105 ^c)		
	OR ^b	95% CI ^b	P value ^b
1st year of life	0.09	0.03, 0.30	<0.001
2 nd year of life	0.06	0.02, 0.20	<0.001
3 rd year of life	0.05	0.02, 0.15	<0.001
5 th year of life	0.09	0.04, 0.22	<0.001
10 th year of life	0.33	0.07, 1.64	0.176

CI = confidence interval; NBS = newborn screening program; OR = odds ratio; SCD = sickle cell disease

Notes: a. Parents of 40 of the newborns did not attend the initial consultation. Therefore, 395 newborns were included in the intervention program

b. IQWiG's own calculations approximately determined from the data on mortality rates in the groups and self-estimated number n.

c. Data taken from IQWiG's own calculation of the mortality rate from data on survival probability which is given in King et al (2007). Information on the method used to estimate survival probability was missing in King et al (2007). No absolute numbers of deaths or survivors available.

Source: DCAR Table 4, adapted from (Runkel et al. 2020).

Overall, the studies with comparative results (level III-3) reported by IHE (2016) found mortality to be reduced by the implementation of NBS (Table 5).

Table 5 Mortality of children diagnosed with SCD by NBS compared with those diagnosed at a later age (IHE 2016)

Study ID	Intervention N	Mortality outcome description	Absolute difference (reduction with NBS)
(Yanni et al. 2009) US	NBS N=1,354	Mortality in children <3 y Mortality in children <4 y caused by infection	68% (95% CI 58%, 75%) 24% (95% CI NR)
(Frempong & Pearson 2007) Connecticut, US	NBS with comprehensive follow-up care N not stated	SCD-related deaths in children <15 y	13 deaths
(Vichinsky et al. 1988) California, US	NBS with strong emphasis on parental education and no prophylactic penicillin N=81	HbSS SCD-related mortality	6.2%
(King, L et al. 2007) (Lee et al. 1995) Jamaica	NBS with prophylactic penicillin, parental education and close monitoring N=455	Early NBS (1973-1975) vs late NBS (1995-2006): Mortality in children <2 y Mortality in children <10 y Mortality caused by splenic sequestration	 13.41% 15.2% 27.47%

CI=confidence interval; HbSS = homozygous haemoglobin S disease; NBS = newborn bloodspot screening; NR = not reported; SCD = sickle cell disease

Source: DCAR Table 5.

Studies published later than 2014 on the whole showed better health outcomes for more recent cohorts diagnosed by NBS compared to cohorts diagnosed in the early stages of NBS, supporting an overall improvement in babies' health with the establishment and development of NBS.

One Belgian study (level III-3) conducted Kaplan-Meier analyses for 15-year estimates of the likelihood of outcomes of SCD and compared them between those who were diagnosed by NBS

and those who were diagnosed following a clinical event. The median age at diagnosis was 0 and 1.0 (range 0.1-15.3) years for the NBS and later diagnosed groups, respectively. There was no significant difference in the likelihood of ACS, acute anaemia, severe infection or vaso-occlusive crisis (VOC) between NBS and later diagnosed groups. Similarly, the authors found no significant difference in mortality between groups (NBS 1.2% [0.18 deaths per 100 patient-years] versus comparator 1.1% [0.10 deaths per 100 patient-years]). An analysis of the outcome of bacteraemia was the only one that showed a statistically significant difference between NBS and later diagnosed children, finding that those diagnosed by NBS were less likely to experience bacteraemia, an effect of serious infection.

The findings of Le et al (2018)¹¹ support earlier results that show early implementation of prophylactic antibiotics can reduce the risk of death due to serious infection in babies with SCD. The access to other maintenance and treatments for the later diagnosed children may have reduced differences in mortality between groups over time. The dilution of the impact of early intervention over time is similar to that seen in mortality in the Jamaican study between 5 and 10 years of life.

Further analyses in the study by Le et al (2018) showed that the mean age at first event for severe symptoms such as ACS, severe infection, and VOC, was significantly younger in children diagnosed by NBS than in those diagnosed at later age. These results were unexpected, but the authors explained it was likely due to parents and clinicians being aware of the child's condition once they were diagnosed, and therefore recognising the symptoms of SCD. Prior to diagnosis symptoms may have been missed, or not recorded as related to SCD. This argument was supported by the data for hospitalisation (Table 6). The data showed that while NBS-diagnosed children have earlier recorded first events, they are hospitalised less often and spend less time in hospital than babies diagnosed later, which could be a considerable advantage to both the babies with SCD and to the health system. The median hospitalised days per 100 patient-years was significantly lower in the NBS screened group compared to the children diagnosed at symptom onset (median [range]: NBS 1.25 [0-21, 42] versus comparator 2.82 [0-35, 28]; $p < 0.0001$).

Table 6 Number of hospitalisations and days spent in hospital for children diagnosed with SCD

Hospitalisation	Diagnosed at NBS	Diagnosed at later age	p-value
Median days/100 patient-years (range)	1.25 (0-21.42)	2.82 (0-35.28)	<0.0001

NBS = newborn screening; SCD = sickle cell disease

Source: DCAR Table 6, from (Le et al. 2018).

In Australia, the age difference between proposed NBS diagnosis and that made through current practice of targeted neonatal testing and symptomatic diagnosis, is likely to be smaller than that in the published studies. The median age of diagnosis of SCD in children is approximately 8.4 months (0.7 years, interquartile range, IQR 0.1, 2.2 years) without NBS, according to data from the Haemoglobinopathy Registry (HbR) (Abt Associates 2022). Therefore, the impact of early diagnosis on population-level mortality is likely to be reduced, although it is acknowledged that this does not mitigate the mortality risk for those individuals who are not identified before symptom onset. The health system in Australia in 2023, is likely to offer health benefits for survival that would largely mitigate the impact of early infection and splenic sequestration on

¹¹ Le, PQ, et al., *J Med Screen* (2018), 'Neonatal screening improves sickle cell disease clinical outcome in Belgium', , vol. 25(2), 01 Jun, pp. 57-63.

mortality, when compared to earlier studies in Jamaica, or the US. In addition, the prevalence of SCD in this country is much lower than the studied settings, so any impact on mortality would be small and difficult to determine accurately.

The evidence for inclusion of β -thalassaemia in NBS programs was scarce. One study provided direct evidence that compared the frequency of osteopenia in children with β -thalassaemia major or intermedia between those diagnosed by NBS and those diagnosed later. Vitamin D had been given to 15% of the whole group as a prophylactic measure against osteopenia, but there was insufficient information in the study to draw any conclusions.

Linked evidence

Test accuracy

Studies reporting test accuracy data constituted the largest body of evidence in this assessment. There were 31 studies that met the inclusion criteria for test accuracy that used a newborn bloodspot from heel pricks, 24 of which assessed screening tests for SCD as the primary target, and seven assessed thalassaemia as the primary target.

Most studies compared the results of first-tier screening against second-tier screening or confirmatory testing, and used the pragmatic design of only performing second-tier screening/confirmatory testing on those who were first-tier screen-positive. This study design does not allow determination of whether the screening test missed any cases.

Eight of the 31 studies compared one screening method against another method in all participants, and were therefore able to provide sensitivity and specificity for the first-tier screening method. No studies were able to provide the accuracy of the screening program as a whole (the first- and subsequent tiers of screening combined).

For SCD screening (in five of the eight studies), methods used either two tier testing or two-tier testing plus confirmation by genetic testing. Two studies could report only presumptive sensitivity and specificity as not all babies were given second tier testing. Three of the NBS programs amongst the five studies used HPLC as the first-tier screening test followed by either CE, IEF, or HPLC repeated at 2 to 3 months. One NBS program used ESI-MS/MS followed by CE, with the addition of genetic testing performed on suspected cases. A fifth study did not report the two-tier test strategy, but rather that an alternative complementary test was used for second tier testing. The study did not report false negative results, so specificity could not be calculated. For SCD diagnosis overall, sensitivity was 100%, and specificity ranged from >99% to 100% across the studies (Table 7). The overall GRADE for the accuracy of first-tier testing for SCD was moderate for certainty, rated down due to the risk of bias, with two out of five studies having verification bias.

For β -thalassaemia (four of the eight studies), screening methods are usually chosen based on the prevalence of variants in the population undergoing NBS. In the programs which were explicit about the test order, first tier testing was HPLC, CE or IEF, and second tier testing was DNA analysis (methods varied) or MS/MS. Sensitivity for the diagnosis of β -thalassaemia ranged from 88.78% to 98.5%, and specificity ranged from 98.73% to 100% (Table 7). The overall GRADE for the accuracy of first-tier testing for β -thalassaemia was rated as low certainty, rated down due to indirectness (the two studies which provided most of the results were from populations with very different prevalence of β -thalassaemia to Australia), and the results were imprecise due to the small number of cases.

Table 7 Summary of sensitivity and specificity of NBS for SCD and β -thalassaemia

Disease screened	Sensitivity	Specificity	PPV ^a	NPV ^a
SCD	100%	>99% - 100%	100%	100%
B-thalassaemia	88.78% - 98.5%	98.73% - 100%	0% - 100% ^a	100%

NBS = newborn bloodspot screening; NPV = negative predictive value; PPV = positive predictive value; SCD = sickle cell disease

Notes: a. Calculated for the Australian setting. When a prevalence of <0.01% is applied (as is the case in Australia) the PPV is 0, if the sensitivity is less than 100%

Source: DCAR Table 7.

Both the positive predictive value (PPV) and diagnostic yield are highly influenced by the prevalence of the disorder in the population. Variability between studies is likely due to difference in baseline prevalence of haemoglobinopathies rather than differences in the accuracy of the screening tests, and therefore these outcomes are of little value.

With the low prevalence of disease in Australia (estimated at <0.01% of the general population), tests which have less than perfect sensitivity result in a PPV of 0% (when rounding is applied). That is, for every true positive case identified, at least 100 further cases are suspected of having disease, and require second-tier testing to confirm. However, most studies had complete concordance between tests, meaning that nearly everyone identified as having disease from first-tier testing truly had disease. Compared to no universal screening, the very small possibility of cases being missed by NBS is greatly reduced from the risk associated with no universal screening.

Change in management

The key change in management that would be expected from NBS is earlier initiation of prophylactic treatment (such as antibiotics) and parental education to improve recognition of early symptoms, pneumococcal vaccination appropriate for individuals with SCD and initiation of other treatments (such as hydroxyurea), pre-symptomatic extended blood group typing, and surveillance (such as transcranial doppler) in a timely manner.

No studies were identified additional to direct evidence studies that examined the timeliness of treatment initiation based on diagnosis. One explanation for this is that NBS screening for SCD and thalassaemia is well established in other parts of the world, so there has been little comparative research on the associated changes in management for many decades.

To inform this assessment, studies that reported on rates of clinical treatment in children identified in their NBS programs were discussed, with data from Australia compared where available. This included a study of the SCD NBS screening program in the UK and a study on a smaller cohort from the US. Data from Australia were provided by the Australian Haemoglobinopathies Registry, but these data were only broadly comparative as the age range of the children was wider and detail was lacking. Results are shown in Table 8.

This high rate of vaccination in Australia may not be improved by adding SCD to NBS. However, it is acknowledged that ancestry is a critical factor in identifying SCD risk, and limited English language or other social or cultural barriers may impact the access to vaccination in this population.

Table 8 Intervention rates for children diagnosed with haemoglobinopathies

Intervention	Haemoglobinopathy Registry data (Australia) ^a	US cohort n=198 (Meier et al 2020)	UK cohort n=1317 (Streetly et al 2018)
Age at diagnosis of SCD	Median 0.7 IQR 0.1, 2.2 years ^b (equates to a median of 8.4 months)	Mean 25.3 days offered genetic counselling	80.3% by 3 months 97% by 6 months
Age of symptom onset for SCD	Median 1.0 IQR 1.0, 3.0 years	-	-
Children with SCD using prophylactic antibiotics	57.2% age <18 years	Mean age at first dose HbFS: 27.2 days Other HbS: 34.0 days	80.3% by 3 months 97.3% by 6 months
Children with SCD using HU	56.7% age <18 years	21.4% - 81.3% (within 1 year fu)	-
Children with SCD receiving regular transfusions	15.1% age <18 years	-	-
Children with SCD who have undergone doppler screening	-	25% - 69% (age 2-3 years)	-
Age at diagnosis of β -thalassaemia	Within 1 month	-	-
Children with β -thalassaemia using prophylactic antibiotics	63.0% age <18 years	-	-
Children with β -thalassaemia using prophylactic antibiotics	>50% age <18 years	-	-
Children with β -thalassaemia receiving regular transfusions	64.2% age <18 years	-	-
Children who have received pneumococcal vaccine	95.70% by 1 year ^c 95.27% by 2 years ^c	97.5% at least one vaccine (within 1 year fu)	-

fu = follow-up; HbFS = combination of fetal and sickle haemoglobin giving a milder version of SCD; HbS = sickle haemoglobinopathies; HU = hydroxyurea; IQR = interquartile range; SCD = sickle cell disease

Notes: a. Data provided for the rapid review (Abt Associates 2022), except for pneumococcal vaccination rates.

b. This is the diagnostic age reported for children with SCD under 18 years of age by the Registry. Less severe cases such as non HbSS cases (19.4% of paediatric cases) are likely to be diagnosed at the higher end of the age range. Immigrants (17% of cases have a listed country of birth other than Australia) may be diagnosed at a later time point.

c. Data from Department of Health, 2022 (<https://www.health.gov.au/topics/immunisation/immunisation-data/childhood-immunisation-coverage/current-coverage-data-tables-for-all-children>)

Source: DCAR Table 8.

Treatment effectiveness

Treatments recommended for babies with SCD or β -thalassaemia up to 12 months of age were considered. Treatments recommended after that age are not likely to be impacted by earlier diagnosis by NBS. A SR published in 2016 provided data on treatments for SCD. There were no additional primary studies that provided more data on SCD. There was little evidence identified that reported on treatments for β -thalassaemia. One small level IV study provided inconclusive data.

The SR reviewed RCT evidence for effectiveness for the following SCD treatment comparisons: antibiotic prophylaxis versus placebo or no prophylaxis in children up to 5 years of age; antibiotic prophylaxis versus placebo or no prophylaxis in children over 5 years of age; and HU versus placebo in children.

The effectiveness of prophylactic penicillin was investigated in two RCTs in children aged 6 to 36 months (total n = 447). One RCT (n = 215) compared oral penicillin with placebo, and the other RCT (n = 242) compared monthly penicillin injections with no prophylaxis. The trials were conducted in the 1980s in the US, and Jamaica respectively. The US trial was ended prematurely, after four deaths occurred in the placebo arm. The difference in mortality between trial arms did not reach significance (OR 0.11; 95% CI 0.01, 2.11; p = 0.14). There were no deaths in the Jamaican trial (followed for 5 years), and mortality overall was no different between those given penicillin and those who were not.

Pneumococcal infections were compared between arms in both RCTs. The authors of the SR conducted an analysis of results from both trials, including available data from the early terminated US trial. The analysis found that infection rates were lower in the prophylaxis arms compared to no prophylaxis. Results are summarised in Table 9.

Table 9 Comparison of pneumococcal infections between children with SCD < 5 years of age who received antibiotic prophylaxis and those who received placebo or no prophylaxis (Meremikwu & Okomo 2016)

Total N	Antibiotic prophylaxis	Placebo/ no prophylaxis	Difference ^a
457 In combined analysis for Jamaican trial (John et al, 1984) and US trial (Gaston et al, 1986)	9 infections (9/248; 4%)	19 infections (19/209; 9%)	OR 0.37 (95% CI 0.16, 0.86) p=0.02 Heterogeneity: I ² =69%

CI = confidence interval; OR = odds ratio; RCT = randomised controlled trial; SCD = sickle cell disease

Notes: a. Combined analysis conducted by Meremikwu et al (2016) amongst children who were receiving pneumococcal vaccine
Source: DCAR Table 9.

All children in the US trial had also been given the polysaccharide pneumococcal vaccine (participants received the 14-valent pneumovax, which was substituted for the 23-valent vaccine when it became available), whereas only half of children in the Jamaican trial received the 14-valent polysaccharide pneumococcal vaccine ¹². A sub-group analysis performed by the SR authors found that this may have increased the effect of the penicillin prophylaxis. For those who received the vaccine there was a significant reduction in pneumococcal infections amongst those who received penicillin compared with those who did not (OR 0.41; 95% CI 0.17, 0.96; I² = 76%), whereas for those who did not get the vaccine there was no significant difference between penicillin and no penicillin arms (OR 0.15; 95% CI 0.01, 3.28). Clinical advice provided in the SR recommended that both penicillin prophylaxis and pneumococcal vaccination are given to children with SCD. Where there is high incidence of *S. pneumoniae* antibiotic resistance the effectiveness and penicillin prophylaxis can be reduced, but pneumococcal vaccination can help prevent the infection to begin with.

One RCT conducted in the US assessed penicillin prophylaxis compared with placebo in children older than 5 years. All children in the trial had previously been given antibiotic prophylaxis for 2 years or more. There was no difference in mortality between trial arms. There was no significant difference in the incidence of pneumococcal infections between arms (penicillin 2/201 [1%] versus placebo 4/199 [2%]; OR 0.49; 95% CI 0.09, 2.71; p = 0.41). A carry over effect of penicillin prophylaxis in the placebo arm could not be ruled out.

¹² As a comparison, the Australian National Immunisation Program schedule for children recommends the conjugate pneumococcal vaccine Prevenar 13 at 2, 4, and 12 months of age. Children with SCD would be eligible for an additional dose of Prevenar 13 at 6 months of age. Children with SCD would be also eligible for an additional dose of the polysaccharide-based vaccine Pneumovax 23 at 4 years of age. Source: [National Immunisation Program](#)

Hydroxyurea (HU) therapy was compared to placebo in three RCTs, conducted in Belgium (n = 25 children, age not specified), the US (the BABY HUG trial, n = 193 children aged 9 to 18 months), and India (n = 60 children aged 5 to 18 years). There were a number of outcomes compared in the SR: mortality, incidence of crisis (mean hospital stay, hospitalisation events, pain - all reports, pain alone, mean VOC per patient), and disease related complications (number of blood transfusions, stroke, dactylitis, ACS, splenic sequestration).

The mortality rate was not different between those who received HU or placebo – there were no deaths in the two trials reporting this outcome.

All measures of hospitalisation favoured HU over placebo, in that children administered HU experienced fewer hospital admissions and spent less time in hospital.

Incidences of crisis outcomes were reported by the BABY HUG trial. All results but one favoured the children receiving HU, who experienced statistically significantly fewer painful crisis events (alone or in conjunction with other symptoms), dactylitis, ACS, and transfusions than children who received placebo. The exception was incidence of splenic sequestration, which was similar between trial arms. The lower number of transfusions in children given HU was supported by a second RCT, which found similar results to BABY HUG. Results from the BABY HUG trial are summarised in Table 10.

Table 10 Summary of treatment outcomes for hydroxyurea compared with placebo for children with SCD in the BABY HUG trial (Meremikwu & Okomo 2016)

Outcome	HU	Placebo	Difference	Favoured arm
Hospitalisation	232 events/69 children	324 events/84 children	HR 0.73 (95% CI 0.53, 1.00) p=0.05	HU
Pain (all reports)	177 events/62 children	375 events/75 children	HR 0.59 (95%CI 0.42, 0.83) p=0.002	HU
Pain alone	63 events/37 children	121 events/55 children	HR 0.54 (95%CI 0.36, 0.83) p=0.004	HU
Blood transfusions	35 events/20 children	63 events /33 children	HR 0.55 (95%CI 0.32, 0.96) p=0.03	HU
Dactylitis	24 events/14 children	123 events/42 children	HR 0.27 (95%CI 0.15, 0.50) p<0.0001	HU
ACS	8 events/7 children	27 events/18 children	HR 0.36 (95%CI 0.15, 0.87) p=0.02	HU
Splenic sequestration	12 events/8 children	12 events/9 children	HR 0.88 (95% CI 0.34, 2.27) p=0.79	None

ACS = acute chest syndrome; CI = confidence interval; HR = hazard ratio; HU = hydroxyurea; SCD = sickle cell disease
Source: DCAR Table 10.

Overall there are very few safety concerns, and significant effectiveness associated with treatments for young children with SCD. HU was effective in reducing morbidity in children with HU, but its effectiveness should be weighed against the safety concern of reduced absolute neutrophil count, which has the possibility of increasing the risk of infection. Children can be managed by adjustment of their HU dosage if side effects occur.

Population 2: Family members

There was little evidence for Population 2 that met the inclusion criteria. There was no direct evidence identified for cascade testing of family members of children diagnosed with SCD or β -thalassaemia by NBS. Five studies reporting linked evidence data met the inclusion criteria for this population.

Linked evidence

Test accuracy

If a baby is diagnosed with SCD or β -thalassaemia, then it can be assumed that both parents are carriers. In some instances, for example compound heterozygotes of SCD and milder forms of β -thalassaemia, a carrier may be affected by mild symptoms of the disease. Reporting of results for family members following NBS was rare in the literature, despite authors often commenting that cascade testing was performed.

One small study was identified that compared first tier screening with confirmatory testing for detecting SCD in six family members. The first-tier screen was performed using a MinION DNA sequencing assay of the *HBB* locus, and the confirmatory testing was Sanger sequencing. The results of the assay were fully concordant with the results of Sanger sequencing. Given the size and the risk of bias within the study, it does not contribute to consideration of the usefulness of cascade testing.

The accuracy of cascade testing may be assumed to be very close to 100% (allowing for human error/sample contamination). The methods for cascade testing, whether phenotypic or genetic, should be chosen based on the particular haemoglobins or variants with which the newborn is identified.

Change in management

Linked evidence was sought, however there was no evidence that met the eligibility criteria for change in management related to cascade testing. The inclusion criteria were broadened to include non-comparative evidence, but still no studies were identified.

Treatment effectiveness

No evidence was identified. As cascade testing only identifies carriers, no treatments are likely to be necessary.

Clinical utility summary

There are no prevalence or incidence data for haemoglobinopathies in Australia. In the absence of real data, estimates have been made in the following scenarios. There is considerable uncertainty around these estimates, as demonstrated by the wide range of possible cases.

If NBS for SCD with/without β -thalassaemia was conducted in Australia, for every 1,000,000 newborns tested, between 5 and 86 babies would be diagnosed with one of the disorders (based on an estimated incidence range of 0.53 to 8.6 per 100,000 from laboratory input and Argent et al (2012)¹³. This would therefore be the incremental benefit of additional newborns diagnosed by NBS over the primary comparator – no NBS (diagnosis delayed until symptom onset). In this

¹³ Argent, E, et al. *J Paediatr Child Health* (2012), 'Australian Paediatric Surveillance Unit study of haemoglobinopathies in Australian children', , vol. 48, no. 4, Apr, pp. 356-360

scenario it is assumed that in the comparator arm, no cases would be picked up through testing for anaemia (or other conditions) or would be detected because parents are known to be carriers. In the primary comparator scenario, all babies with SCD would be identified at presentation with symptoms (late diagnosis). Estimated incremental benefit is given in Table 11.

Table 11 Suggested incremental benefit of adding the nominated haemoglobinopathies to NBS per 1,000,000 newborns screened^a

Estimated incidence	Diagnoses by NBS (n)	Diagnosed if there is no testing or screening (n)	Impacted by late diagnosis (n) (incremental benefit)
0.53/100,000 ^b	5	0	5
8.6/100,000 ^c	86	0	86

NBS = newborn bloodspot screening

Notes: a. figures are rounded to whole numbers

b. Source: (Argent et al. 2012)

c. Source: Based on data from PathWest

Table source: DCAR Table 11.

The secondary comparator scenario, where targeted testing is undertaken, was informed by clinical advice in the absence of data. The identification rate of cases by targeted testing is high using both prenatal and neonatal settings. If 64%¹⁴ to 99%¹⁵ of all cases are identified by targeted testing, the incremental benefit of additional newborns diagnosed by NBS would be between 2 and 31 more newborns per 1,000,000 newborns screened (worst case scenario of 64% identified by targeted testing) and 0 to 1 more newborn per 1,000,000 newborns screened (best case scenario of 99% identified by targeted testing). It should be noted that data for prenatal and neonatal testing could not be separated, therefore the incremental benefit has not accounted for targeted newborn testing in the comparator, and could be underestimated.

It is expected that in the absence of NBS a proportion of babies missed by targeted testing would only be diagnosed after developing symptoms, approximately 6 months to 2 years later, and there is a chance that these early symptoms could be severe (such as a VOC leading to stroke or splenic sequestration, or death). Expert opinion from state laboratories, the HbR, and clinical advice indicates that at most, the proportion not diagnosed until severe symptoms may be 50% of babies missed by targeted testing. This equates to an estimated 1 to 16 babies per 1,000,000 screened that may be impacted by late diagnosis. Although treatments for SCD are effective, the likelihood of the early diagnosis and intervention avoiding significant clinical impact (compared to diagnosis after symptoms develop, in the Australian setting) is unknown.

The numerators used in these estimates are highly subjective and variable and cannot be relied upon to represent the true numbers diagnosed in Australia. The suggested estimates presented are summarised in Table 12.

¹⁴ Lower limit of range (64%) source: "Beyond the Crystal Ball – The Epidemiology of Some Genetic Conditions in Victoria, 2002". Department of Human Services, Victoria.

¹⁵ Upper limit of range (99%) source: Clinical opinion from Monash Maternity Hospital (Meeting 21 Feb 2023 with DHA, clinical experts, and assessment group)

Table 12 Suggested incremental benefit of adding the nominated haemoglobinopathies to NBS over targeted testing per 1,000,000 newborns screened^a

Estimated incidence	Diagnoses by NBS per 1,000,000 newborns(n)	Diagnosed by comparator testing (n)		Impacted by late diagnosis (n) (incremental benefit)	
		64% ^e	99% ^c	20%	50%
0.53/100,000 ^b	5	3	5	0-0	0-1
8.6/100,000 ^d	86	55	85	0-6	1-16

NBS = newborn bloodspot screening

Notes: **a.** figures are rounded to whole numbers

b. Source: (Argent et al. 2012)

c. Source: Expert opinion from Monash Medical Centre (99% of cases identified by targeted testing)

d. Source: Based on data from PathWest

e. Source: (DHS 2002) (64% of cases identified as at pregnancies)

Table source: DCAR Table 12.

There were insufficient data to estimate the clinical utility separately for the diagnosis by NBS for SCD and β -thalassaemia.

There were insufficient data to estimate the clinical utility for cascade testing of family members.

Clinical claim

Newborns participating in NBS programs

The use of NBS for SCD (early diagnosis) resulted in superior effectiveness compared with no NBS for SCD (late diagnosis) in infants and children up to 5 years of age. This outcome was highly dependent on the prevalence of SCD and the effectiveness of targeted testing approaches.

The use of NBS for SCD (early diagnosis) resulted in noninferior safety compared with no NBS (late diagnosis).

There were insufficient data to determine the incremental effectiveness or safety of NBS for SCD over targeted neonatal screening.

There were insufficient data to determine the incremental effectiveness or safety of NBS for SCD and β -thalassaemia over NBS for SCD alone for infants and children up to 5 years of age. However, it could be assumed that additional β -thalassaemia cases would be identified early by NBS.

Family members eligible for cascade testing

There was insufficient data to determine the safety and effectiveness of cascade testing of family members of newborns diagnosed with SCD or β -thalassaemia.

A key benefit of cascade testing is likely to be the value of knowing, so that family members can make informed future reproductive choices. There is also the potential of identifying children with SCD who are pre-symptomatic.

13. Economic evaluation

While the use of NBS for SCD was associated with a clinical claim of superior effectiveness and noninferior safety, the evidence base had limited applicability to the current Australian context

due to the availability of pneumococcal vaccinations in all newborns as early as two months and early diagnosis through prior parental testing of high-risk couples. It was recognised that current targeted testing methods did miss some affected cases, and so there would be a benefit in terms of earlier diagnoses through universal NBS, but the extent of this benefit could not be quantified to the Australian context. Likely change in management that could be expected in practice included additional vaccinations (at 6 months and 4 years) and parental education on symptoms resulting in better management of SCD. However, insufficient evidence was available to translate the incremental benefit of these changes into patient-relevant outcomes, beyond early diagnosis of a clinically significant case. Therefore, the outcome modelled was limited to the incremental cost per additional early diagnosis of a clinically significant case.

No clinical claims could be made regarding the further expansion of the program to include both SCD and β -thalassemia. Therefore, further analyses based on expansions to include β -thalassemia could be considered as exploratory only, as the benefits quantified in terms of additional early diagnoses were more difficult to interpret. As such, alternate funding scenarios were presented for the decision to add SCD screening alone to the NBS, to adding both SCD and β -thalassemia to the NBS. Marginal analyses would be presented, in line with what was proposed in the PICO Confirmation, for moving between these scenarios.

As suggested in the PICO confirmation, the primary comparator to universal NBS for the haemoglobinopathies was no NBS. In the absence of universal NBS, those individuals who were affected were assumed only to be investigated after presenting with clinical features of a haemoglobinopathy. The effect of prenatal or neonatal testing where parents' carrier status had previously been identified, and targeted newborn screening (based on ancestry only, in the absence of parental risk assessment) was therefore considered only in the secondary comparison. Expert opinion provided during the development of the DCAR had suggested that symptomatic identification occurred only in the minority of cases, and as such the results of the analyses against both comparisons were presented side-by-side.

A stepped approach was used to generate the base case analysis that incorporated key assumptions and different aspects of the linked evidence separately to distinguish the effect of each of these on the results.

A summary of the key components of the economic evaluation is presented in Table 13.

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Newborn testing: All newborns born in Australia Cascade testing: Immediate family members of affected and carrier newborns
Comparator	Primary: No NBS Secondary: Targeted testing of high-risk newborns along with symptomatic identification of disease in cases missed through targeted testing
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Newborns: <ul style="list-style-type: none"> • Additional early diagnosis of clinically significant cases • Additional carriers identified Cascade: <ul style="list-style-type: none"> • Additional carriers identified
Time horizon	Average age at diagnosis through symptomatic identification only (one year)
Computational method	Decision tree analysis
Generation of the base case	Modelled stepped analysis, incorporating different aspects of the linked evidence and other key model assumptions separately to distinguish the effect of each of these on the results.
Transition probabilities	Incidence of haemoglobinopathy: Expert opinion to reflect the contemporary setting. Estimates of the incidence of carriers of haemoglobinopathy in newborns was not identified. The ratio of carriers per affected newborn case (23.2 : 1) based on the studies included in report was used to estimate the incidence of carriers in the cohort for screening. Current targeted testing (secondary comparison only): Based on published estimates and expert opinion Test performance: Performance of first-tier screening (100% for SCD and 98.5% for β -thalassaemia) was as based on reported evidence. Second tier screening was assumed to have 100% sensitivity and specificity. Yield of cascade screening: Mendelian inheritance was assumed and varied by newborn status.
Discount rate	Not applied (time horizon less than one year)
Software	Excel

NBS = newborn bloodspot screening; SCD = sickle cell disease

Source: DCAR Table 13.

A number of the inputs used in the model were based on expert opinion or have been assumed. These have been summarised in Table 14 with a depiction of the extent of uncertainty associated.

Table 14 Summary of key inputs and assumptions used in the economic evaluation

Input/assumption	Estimate (source)	
	SCD	β -thalassaemia
Incidence	7 per 100,000 (consultation on Nomination Form from PathWest) Range tested: 0.62 to 7 per 100,000 births	17 per 100,000 (expert opinion provided during preparation of the DCAR) ^{a,b} Range tested: 6 to 71 per 100,000 births
Extent of targeted screening (applicable only to secondary comparison)	99% (expert opinion provided during preparation of the DCAR) ^a Range tested: 99% in base case and 25% and 95% in sensitivity analyses	99% (expert opinion provided during preparation of the DCAR) ^a Range tested: 99% in base case and 25% and 95% in sensitivity analyses
Screening strategy	First-tier: MALDI-TOF Second-tier: DNA sequencing (based on the screening strategy proposed by WA NBS during the preparation of the DCAR) ^c Alternate screening strategies explored	First-tier: MALDI-TOF Second-tier: DNA sequencing (based on the screening strategy proposed by WA NBS during the preparation of the DCAR) ^c Alternate screening strategies explored
Cost of screening	First-tier: \$10.00 (up to \$96.60), based on the cost of testing by mass spectrometry as indicated by providers of NBS in WA. ^d Second-tier: \$500.00	First-tier: \$10.00 (up to 96.60), based the cost of testing by mass spectrometry as indicated by providers of NBS in WA. ^d Second-tier: \$500.00
Sensitivity of screening methods	100% assumed across all methods ('Test accuracy' evidence which was consistent across varied methods)	98.5% assumed across all methods for β -thal major ('Test accuracy' evidence which varied by study and method). Some test strategies were assumed to be unable to identify β -thal intermedia
Specificity of screening	99.99% ('Test accuracy' evidence reported >99-100% specificity). Though high concordance was also noted (so screen-positives were highly likely to be truly positive and so very high specificity has been assumed)	99.99% ('Test accuracy' evidence reported 98.7% to 100% specificity). Though high concordance was also noted (so screen-positives were highly likely to be truly positive and so very high specificity has been assumed)
Benefit from the clinical evidence	Early identification leads to prophylactic antibiotic treatment and pneumococcal vaccination and increased awareness about symptoms. Initiation of transfusion, monitoring by cranial doppler, and commencement of hydroxyurea may be additional benefits, however this was not supported by evidence identified in the clinical evaluation.	Unknown
Likely benefit in Australian clinical practice	Expert opinion ^a suggests that the majority of cases are identified through current targeted testing. In cases missed, universal pneumococcal vaccination is also available, which may reduce the benefit of universal NBS observed in practice	Unknown
Benefit modelled	Cases identified earlier – noting that there is a likely benefit (e.g. additional vaccinations) for identifying these cases earlier, however this cannot be quantified in the proposed setting	Cases identified earlier – however this should be interpreted with caution

Note: Colour shading of cells depict the extent of uncertainty in the estimate or assumption applied. **Red** denotes high uncertainty, **orange** denotes moderate uncertainty, and **green** denotes low uncertainty.

β -thal = beta-thalassemia; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; NBS = newborn bloodspot screening; SCD = sickle-cell disease.

^a Received from Monash by teleconference, 21/2/23.

^b Total incidence in VIC/TAS estimated to be approx. 20 affected cases per year of 82,400 births (24 per 100,000). The difference between the total incidence estimated and the incidence noted by PathWest is assumed to be the incidence of β -thalassemia

^c Received 13/1/23 by email.

^d Received 13/2/23 by email.

Source: DCAR Table 14.

The PICO Confirmation suggested that the base case economic analysis should adopt the most cost-effective test strategy. The different strategies available in Australia were noted to have trade-offs. The most expensive options (HPLC and CE) were more comprehensive in the haemoglobinopathies they were able to detect (all SCD and most β -thalassemia cases, in addition to carriers), whereas the least expensive options (ESI-MS/MS, MALDI-TOF and HbS allele-specific PCR) were more limited in what they were able to detect (all SCD cases, and most β -thalassemia cases). Given these trade-offs, the assessment of cost-effectiveness is subjective and remains for MSAC consideration of the additional value alternate test options provide for additional cost. The base case adopts MALDI-TOF (at a cost of \$10 per screen) based on the screening strategy proposed by WA NBS provided during the preparation of the DCAR.¹⁶

The results of the stepped analysis to generate the base case economic evaluation is presented in Table 15. For the primary comparison (i.e. compared to symptomatic identification only), very little change was observed in the ICER when incorporating the key assumptions and different aspects of the linked evidence. Expansion of the program to include identification of β -thalassemia cases had the largest impact on the results.

For the secondary comparison, including the effects of targeted testing had the largest impact on the results (as this was associated with a substantial decrease in the additional cases identified early through universal NBS), followed by the identification of β -thalassemia cases (which increased the additional cases identified).

Table 15 Results of the stepped economic analysis

	Primary Comparison: Symptomatic identification only			Secondary Comparison: Targeted testing available ^a		
	Universal NBS	No Universal NBS	Increment	Universal NBS	No Universal NBS	Increment
Step 1 – Identification of SCD affected cases only.						
Costs include only those related to universal NBS (or the cost of testing on symptomatic diagnosis), assuming first-tier screening using MALDI-TOF. No targeting testing is assumed in either comparison, nor are costs related to monitoring or treatment in cases of SCD identified earlier. Assumes 100% uptake of universal NBS and 100% test performance. Incidence of SCD is assumed to be 7 per 100,000 births.						
Costs	\$10.12	\$0.12	\$10.00	\$10.12	\$0.12	\$10.00
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00007	0.00000	0.00007
ICER			\$140,022			\$140,022

¹⁶ Received 13/2/23 by email

	Primary Comparison: Symptomatic identification only			Secondary Comparison: Targeted testing available ^a		
	Universal NBS	No Universal NBS	Increment	Universal NBS	No Universal NBS	Increment
Step 2 – Incorporation of targeted testing (only applicable to secondary comparison)						
Costs and outcomes of targeted testing (i.e. parental, fetal and neonatal) included in the secondary comparison only. 99% of affected cases are assumed to be identified through targeted testing. Cost of targeted testing includes fetal testing, testing of neonates (predominantly based on prior parental identification, though to a lesser extent based on ancestry)						
Costs	\$10.12	\$0.12	\$10.00	\$10.39	\$0.55	\$9.83
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00024	0.00024	0.00000
ICER	\$140,022			\$13,765,301		
Step 3 – Incorporation of screening performance						
Test performance estimates from 'Test accuracy' are included (100% sensitivity and 99.99% specificity). While specificity ranged >99-100%, high concordance was also noted (so screen-positives were highly likely to be truly positive and so very high specificity has been assumed)						
Costs	\$10.17	\$0.12	\$10.05	\$10.44	\$0.55	\$9.88
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00024	0.00024	0.00000
ICER	\$140,718			\$13,834,898		
Step 4 – Applying uptake of current newborn testing (99.3% newborn testing, based on Huynh et al. 2022)						
Costs	\$10.10	\$0.12	\$9.98	\$10.37	\$0.55	\$9.81
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00024	0.00024	0.00000
ICER	\$140,718			\$13,833,338		
Step 5 – Incorporating cost of prophylactic treatments and monitoring						
In cases of SCD identified earlier, the cost of prophylactic treatment (consisting of penicillin) and monitoring (consisting of routine health checks and specialist outpatient visits) were included.						
Costs	\$10.28	\$0.26	\$10.02	\$10.66	\$0.84	\$9.81
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00024	0.00024	0.00000
ICER	\$141,338			\$13,833,958		
Step 6 – Incorporation of cascade testing						
The cost of cascade testing in relatives of affected cases and carriers is included. Each newborn is assumed to have two parents and one sibling eligible for cascade testing. 100% uptake is assumed in relatives of affected cases.						
Costs	\$10.35	\$0.33	\$10.02	\$10.72	\$0.91	\$9.81
Early diagnosis of affected cases	0.00007	0.00000	0.00007	0.00024	0.00024	0.00000
ICER	\$141,338			\$13,833,958		
Step 7 – Expansion of the screening program to also include β-thalassaemia						
Incidence of β -thalassaemia assumed to be 17 per 100,000 births and screening (by MALDI-TOF) is assumed to identify 74.25% of affected cases. No changes in management (in terms of prophylactic treatment or management) are assumed in these additionally identified cases						
Costs	\$10.34	\$0.32	\$10.03	\$10.61	\$0.80	\$9.81
Early diagnosis of affected cases	0.00020	0.00000	0.00020	0.00024	0.00024	0.00000
ICER	\$50,867			\$4,977,386		

ICER = incremental cost-effectiveness ratio; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; NBS = newborn bloodspot screening; SCD = sickle cell disease.

^a Secondary comparison includes parental, fetal and neonatal testing of haemoglobinopathies

Source: DCAR Table 15.

The marginal cost-effectiveness of expanding the program to include identification of β -thalassaemia cases and carriers is presented in Table 16. While the marginal ICERs are low for the expansion of the program to include β -thalassaemia, as described above, the interpretation of the additional earlier diagnoses of β -thalassaemia is less certain.

Table 16 Marginal analyses of expanding the NBS to include SCD and β -thalassaemia over SCD alone

	Incremental Cost	Incremental earlier diagnoses	Marginal costs	Marginal earlier diagnoses	Marginal ICER of expanding the program
Primary comparison: symptomatic identification only					
SCD only	\$96.35	0.00007			
SCD + β -thal	\$99.63	0.00024	\$3.29	0.00016	\$19,940
Secondary comparison: targeted testing available^a					
SCD only	\$81.81	0.00001			
SCD + β -thal	\$82.04	0.00003	\$0.23	0.00002	\$9,494

β -thal = β -thalassaemia, ICER = incremental cost-effectiveness ratio; NBS = newborn bloodspot screening; SCD = sickle cell disease

^a Secondary comparison includes parental, fetal and neonatal testing of haemoglobinopathies

Source: DCAR Table 16.

Disaggregated costs are presented in Table 17. The incremental cost is driven by the cost of first-tier screening, and to a lesser extent, in the primary comparison to symptomatic identification alone, second-tier screening. The primary cost offsets were due to a reduction in symptomatic identification.

In the secondary comparison, incremental costs were again driven by the cost of first-tier screening, with some costs due to second-tier screening (though this was noted to be less than observed under the primary comparison). Cost offsets were driven by a reduction in the cost of targeted newborn testing based on ancestry alone (assumed to be replaced by universal NBS).

Table 17 Disaggregated modelled costs

Type of resource item	Primary Comparison: Symptomatic identification only			Secondary Comparison: Targeted testing available ^a		
	Universal NBS	No Universal NBS	Increment	Universal NBS	No Universal NBS	Increment
First-tier screening costs	\$9.93	\$0.00	\$9.93	\$9.93	\$0.00	\$9.93
Second-tier screening costs	\$0.15	\$0.00	\$0.15	\$0.05	\$0.00	\$0.05
Symptomatic testing	\$0.02	\$0.12	-\$0.09	\$0.00	\$0.00	-\$0.00
Targeted fetal testing	\$0.00	\$0.00	\$0.00	\$0.10	\$0.10	\$0.00
Targeted newborn testing	\$0.00	\$0.00	\$0.00	\$0.29	\$0.46	-\$0.17
SCD antibiotic prophylaxis	\$0.05	\$0.02	\$0.03	\$0.05	\$0.05	\$0.00
SCD monitoring	\$0.05	\$0.03	\$0.02	\$0.05	\$0.05	\$0.00
Cascade testing	\$0.15	\$0.15	\$0.00	\$0.14	\$0.14	\$0.00
Total	\$10.34	\$0.32	\$10.03	\$10.61	\$0.80	\$9.81

NBS = newborn bloodspot screening; SCD = sickle-cell disease.

^a Secondary comparison includes parental, fetal and neonatal testing of haemoglobinopathies

Source: DCAR Table 17.

Disaggregated outcomes are presented in Table 18. Fewer affected cases identified earlier were observed in the primary versus secondary comparison. This was because the test strategy chosen was assumed to be unable to identify all affected cases. Where targeted testing was allowed, these cases that were not able to be identified through universal NBS were also identified. Therefore, the analysis assumes no degradation in the use of targeted testing, particularly if a less sensitive test method is chosen for universal NBS.

Table 18 Disaggregated health outcomes

	Primary Comparison: Symptomatic identification only			Secondary Comparison: Targeted testing available		
	Universal NBS	No Universal NBS	Increment	Universal NBS	No Universal NBS	Increment
Early diagnosis of affected cases	0.000197	0.00000	0.000197	0.000242	0.000240	0.000002
• Identified through NBS	0.000197	0.000000	0.000197	0.000002	0.000000	0.000002
• Identified through targeted testing	0.000000	0.000000	0.000000	0.000240	0.000240	0.000000

NBS = newborn bloodspot screening.

Source: DCAR Table 18.

The key drivers of the model are presented in Table 19.

Table 19 Key drivers of the model

Description	Method/Value	Impact Base case: \$50,867 per additional case of SCD or β -thalassaemia identified earlier
Extent of targeted testing	As data were not available to estimate the incidence of cases of haemoglobinopathy missed through current targeted testing (i.e. predominantly fetal or neonatal testing where parental risk is known), the approach to quantify the extent of benefit from universal NBS was to estimate the overall incidence of haemoglobinopathies and then apply best estimates of targeted testing uptake. However, the primary comparison scenario assumes no targeted testing (i.e. no fetal testing or neonatal testing either where parental risk is known, or through targeted screening of newborns based on ancestry alone). Expert opinion ^a suggests that the majority of cases are identified through current targeted testing.	High, favours universal NBS. Inclusion of targeted testing in the comparator increased the ICER to \$4,977,386.
Incidence	The incidence of hemoglobinopathies modelled was 24 per 100,000, comprised of 7 per 100,000 SCD and 17 per 100,000 β -thalassaemia. This was based on consultation on the Nomination Form (from PathWest on SCD incidence) and expert opinion ^a provided during the preparation of the DCAR. The only published data on the incidence in Australia identified (Modell 2008) was based on data collected 1953–84 (Crighton et al. 2016; Modell & Darlison 2008) and so may have limited applicability to the current setting. Lower and upper estimates of incidence are explored using the Modell (2008) data – either directly, or by applying the distribution of haemoglobinopathy type to contemporary estimates from PathWest.	High, direction unknown. When the Modell (2008) data were used directly (total incidence 7 per 100,000), the ICER was observed to increase to \$192,631; however when the distribution of haemoglobinopathy type to contemporary estimates from PathWest (total incidence 78 per 100,000), the ICER reduced to \$16,701.

Description	Method/Value	Impact Base case: \$50,867 per additional case of SCD or β -thalassaemia identified earlier
Cost of first-tier screening	The base case assumes first-tier screening using MALDI-TOF. This was based on consultation on the Nomination Form received from the NSW NBS laboratory and that testing may be able to detect SCD and some β -thalassaemia, whereas other less expensive options (e.g. quantitative PCR) may currently be only able to detect SCD. The cost of MALDI-TOF was assumed to be \$10, based on the cost of testing by mass spectrometry as indicated by providers of NBS in WA. In	High, favours universal NBS. When higher first-tier test costs are assumed, the ICER increased to: <ul style="list-style-type: none"> • \$101,238 with a test cost of \$20; • \$252,351 with a cost of \$50; and • \$487,081 with a cost of \$96.60.

^a Received from Monash by teleconference, 21/2/23.

ICER = incremental cost-effectiveness ratio; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; NBS = newborn bloodspot screening; PCR = polymerase chain reaction; SCD = sickle cell disease.

Source: DCAR Table 19

The results of key sensitivity analyses are presented in Table 20 for the primary comparison. Analyses around the secondary comparison were similarly affected by the analyses explored.

Table 20 Results of key sensitivity analyses, primary comparison (symptomatic identification only)

	Inc. cost	Inc. effect	ICER	% change
Base-case	\$10.03	0.00020	\$50,867	-
First-tier screening test (base case: MALDI-TOF, \$10)				
IEF, \$49.05	\$48.81	0.00024	\$204,763	303%
HPLC, \$96.60	\$96.02	0.00024	\$402,863	692%
CE, \$96.60	\$96.02	0.00024	\$402,863	692%
ESI-MS/MS, \$10	\$10.03	0.00020	\$50,867	0%
HbS allele-specific PCR, \$13	\$13.00	0.00007	\$183,338	260%
Haemoglobinopathy incidence (base case: VIC/TAS total incidence and PathWest SCD incidence: 7 per 100,000 SCD; 17 per 100,000 β-thal)^a				
Modell (2008) 1 per 100,000 SCD; 6 per 100,000 β -thal	\$9.98	0.00005	\$192,631	279%
PathWest, assuming proportions from Modell (2008) 7 per 100,000 SCD; 71 per 100,000 β -thal	\$9.99	0.00060	\$16,701	-67%
PathWest for SCD, Modell (2008) for β -thal 7 per 100,000 SCD; 6 per 100,000 β -thal	\$10.04	0.00012	\$86,089	69%
VIC/TAS total incidence, proportions from Modell (2008): 2 per 100,000 SCD; 22 per 100,000 β -thal	\$9.98	0.00018	\$54,099	6%
Sensitivity of β-thal screening (base case: 98.5%)				
88.8%	\$10.03	0.00018	\$54,288	7%

β -thal = beta-thalassaemia; CE = capillary electrophoresis; ESI-MS/MS = Electrospray Ionization tandem mass spectrometry; HbS = haemoglobin S; HPLC = high performance liquid chromatography; ICER = incremental cost-effectiveness ratio; Inc. = incremental; IEF = isoelectric focusing; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; PCR = polymerase chain reaction; SCD = sickle cell disease.

^a Total incidence estimated to be 24 per 100,000 (from 20 cases of haemoglobinopathy identified each year of approx. 82,400 births). Incidence of SCD was assumed as for PathWest, with the remaining incident cases assumed to be β -thal. The distribution of β -thal major to β -thal intermedia was assumed as for the Modell's Almanac (2008) data.

Source: DCAR Table 20.

14. Financial/budgetary impacts

An epidemiological approach is presented to estimate the use and financial impact of expanding NBS programs to include haemoglobinopathies. This includes the estimated use and cost of first- and second-tier testing (including genetic testing, where used as the second-tier test). The financial impact for other changes to state budgets (including changes in the use of current targeted testing) is presented separately.

The financial implications to the NBS resulting from the proposed addition of haemoglobinopathies to the screening program are summarised in Table 21.

Table 21 Net financial implications of adding haemoglobinopathies to NBS programs

	2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
No. babies born	313,259	313,993	314,727	315,462	316,196	316,930
No. babies who uptake NBS (99.3%)	310,922	311,651	312,380	313,109	313,837	314,566
Cost of first-tier (MALDI-TOF) screening (\$10.00 per test)	\$3,109,219	\$3,116,508	\$3,123,797	\$3,131,086	\$3,138,375	\$3,145,663
No. with SCD that is correctly identified (7 per 100,000 ^a , of which 100% identified ^b)	22	22	22	22	22	22
No. with β -thal that is correctly identified (17 per 100,000 ^c , of which 74.25% identified ^b)	40	40	40	40	40	40
No. false-positive screens (0.01% of true negatives) ^d	31	31	31	31	31	31
No. SCD second-tier screens ^e	38	38	38	38	38	38
Cost of second-tier SCD screening (by CE) (\$96.60 per test)	\$18,832	\$18,876	\$18,920	\$18,964	\$19,008	\$19,053
No. β -thal second-tier screens ^f	55	55	55	55	55	56
Cost of second-tier β -thal screening (sequencing) (\$500.00 per test)	\$27,486	\$27,551	\$27,615	\$27,680	\$27,744	\$27,808
Total cost of second-tier screening	\$46,318	\$46,427	\$46,535	\$46,644	\$46,752	\$46,861
Total cost to the NBS	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524

^a Based on incidence of SCD reported in Consultation on the Nomination Form (PathWest)

^b Sensitivity estimates reported in the evidence for 'Test accuracy'

^c Total incidence of haemoglobinopathies was estimated from expert opinion provided from Monash (by teleconference, 21/2/23) to be 24 per 100,000 (based on 20 affected cases of approx. 82,400 births each year in VIC/TAS). The difference between the total incidence and incidence of SCD was estimated to be β -thalassaemia incidence.

^d While test specificity in the evidence for 'Test accuracy' ranged >99-100% for SCD and 98.7-100% for β -thalassaemia, the estimate applied was 99.99% as near complete concordance between tests was also observed (i.e. positives on the first-tier test were highly likely to truly have disease).

^e The sum of SCD cases identified, SCD carriers identified and 50% of false positive screens.

^f The sum of β -thal cases identified, β -thal carriers identified and 50% of false positive screens.

β -thal = beta-thalassaemia; CE = capillary electrophoresis; HPLC = high-performance liquid chromatography; NBS = newborn bloodspot screening; SCD = sickle-cell disease.

Source: DCAR Table 21

The financial impact was driven by the cost of first-tier screening. Given that the data available to inform the extent of use of first-tier screening (i.e. the number of newborns and uptake of NBS) were reasonably robust, the main driver of total first-tier screening costs was the test strategy chosen. Second-tier screening costs made up a small proportion of the estimated cost to the NBS.

Relevant alternate funding scenarios are presented in Table 22, varying the haemoglobinopathy screened for (i.e. SCD only or SCD and β -thalassaemia) and varying the first-tier screening strategy. Scenarios were additionally explored in the DCAR where carrier status was also reported.

Table 22 Net financial impact to NBS programs, alternate funding scenarios

	First-tier screen cost	Proportion first-tier screening identifies				Net cost to the Newborn Bloodspot Screening program					
		SCD cases	β thal cases	SCD carriers	β thal carriers	2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
Haemoglobinopathy identified											
- SCD only	\$10.00	100.0%	0.0%	0.0%	0.0%	\$3,135,779	\$3,143,130	\$3,150,481	\$3,157,832	\$3,165,183	\$3,172,534
- SCD and β -thal (major only)	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524
- SCD and β -thal (major and intermedia) [base case]	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524
First-tier screening strategy ^a											
- IEF	\$49.05	100.0%	98.5%	0.0%	0.0%	\$15,303,491	\$15,339,366	\$15,375,242	\$15,411,117	\$15,446,992	\$15,482,868
- HPLC	\$96.60	100.0%	98.5%	0.0%	0.0%	\$30,087,829	\$30,158,363	\$30,228,896	\$30,299,430	\$30,369,964	\$30,440,497
- CE	\$96.60	100.0%	98.5%	0.0%	0.0%	\$30,087,829	\$30,158,363	\$30,228,896	\$30,299,430	\$30,369,964	\$30,440,497
- ESI-MS/MS	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524
- MALDI-TOF [base case]	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524
- HbS allele-specific PCR	\$13.00	100.0%	0.0%	0.0%	0.0%	\$4,068,609	\$4,078,147	\$4,087,684	\$4,097,222	\$4,106,760	\$4,116,298
Second-tier SCD screening strategy											
- IEF	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,138,553	\$3,145,911	\$3,153,268	\$3,160,626	\$3,167,983	\$3,175,341
- HPLC	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,140,344	\$3,147,706	\$3,155,067	\$3,162,429	\$3,169,791	\$3,177,153
- DNA sequencing [base case]	\$10.00	100.0%	74.3%	0.0%	0.0%	\$3,155,537	\$3,162,935	\$3,170,332	\$3,177,730	\$3,185,127	\$3,192,524

^a Second-tier screening for all scenarios was assumed to be by DNA sequencing.

β -thal = β -thalassaemia; CE = capillary electrophoresis; ESI-MS/MS = Electrospray Ionization tandem mass spectrometry; HbS = haemoglobin S; HPLC = high performance liquid chromatography; IEF = isoelectric focusing; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; PCR = polymerase chain reaction; SCD = sickle-cell disease.

Source: DCAR Table 22

Little variation was observed across the scenarios that explored the haemoglobinopathy identified. This was because first-tier screening costs were unchanged across these analyses (i.e. affected only the extent of use of second-tier screening) and because the test assumed in the base case (i.e. MALDI-TOF) is not able to detect β -thalassemia intermedia. Expanding second-tier screening from SCD affected cases only to also include those with β -thalassemia was associated with an additional annual cost of approximately \$20,000.

The results of the alternate first-tier screening scenarios were more variable and ranged from \$3–30 million per year. The most expensive options (HPLC and CE) were more comprehensive in the haemoglobinopathies they were able to detect (all SCD and most β -thalassemia cases). The least expensive options (ESI-MS/MS, MALDI-TOF and HbS allele-specific PCR) were more limited in the haemoglobinopathies they were able to detect (all SCD cases and the majority of β -thalassemia cases).

The addition of haemoglobinopathies to the NBS program would also affect other health budgets, due to the change in current targeted testing practices. The extent of the change in the use (and therefore cost) of testing is unclear and will likely be influenced by the test method chosen for NBS e.g. if MALDI-TOF is used for NBS this may not identify all cases of β -thalassemia, and so as current testing is targeted to those at high-risk or who are demonstrating symptoms, more comprehensive testing (e.g. HPLC) may be used. Further, the timing of testing may also affect the extent in the change in use of current testing (as testing during pregnancy will be unchanged, and so universal NBS would likely be performed in addition to prenatal testing). Given the small number of cases per year, the impact is likely to range from a small reduction in cost to other health budgets (~\$46,000 per year, assuming a reduction in a higher cost first-tier targeted testing) to no difference in cost (assuming current testing practices remain in place due to the requirement for a more sensitive test and/or timing of testing).

No change was expected in the use or cost of cascade testing of relatives of affected cases (as all affected cases are currently identified).

The net effect of these changes is estimated to range from a reduction of up to approximately \$46,000 per year, assuming the maximum reduction in the use and cost of current testing, to no change, assuming current testing practices remain in place (due to the test method requested and/or timing of testing).

15. Other relevant information

Ethics review

Ethical considerations concern equity of access; consent; emotional, social and family impacts; notification of sickle cell trait (SCT, i.e., carrier status), especially for newborns; and reproductive planning.

In the US, families of children with SCD tend to be socioeconomically disadvantaged. This suggests that, in the US, screening for SCD, where beneficial, may be of additional value by virtue of especially helping disadvantaged populations and thereby helping to reduce existing health inequities.

There is mixed evidence concerning parental knowledge of SCD in affected populations prior to newborn screening. This suggests that particular attention should be paid to adequately informing parents as part of the newborn screening consent process. It may also be justifiable for health professionals to "nudge" people toward screening (e.g., by emphasising its benefits) where treatment effectiveness warrants this.

UK parents who received a SCD-positive test result after newborn bloodspot screening experienced fears about SCD-related stigma. These fears often led to parents withholding the SCD diagnosis from family or friends, which may reduce cascade testing. This suggests that tailored genetic counselling following an SCD-positive test result may be important.

In the Netherlands the introduction of hemoglobinopathy into newborn screening did not result in expected increases in parents getting cascade testing.

Multiple studies discuss how to best notify parents of an SCD-positive or SCT-positive result following newborn bloodspot screening. Face-to-face notification from a confident and knowledgeable healthcare professional seems recommended.

Most healthcare providers and parents support the disclosure of SCT-positive results. Healthcare providers often see the results as belonging to the patient, while parents emphasise that their child has a right to know. Many parents want more information about SCT, especially rare symptomatology. Parents often seek to inform their child, with professional support, generally from adolescence, though the best timing seems difficult to pinpoint. Parents are often ambivalent about how the information will affect their child, with “the value of knowing being balanced against the burden of responsibility” placed on their child [13]. There is evidence that parents also value SCT results to inform their own future reproductive intentions.

Organisational issues

Feedback was sought from the laboratories conducting NBS throughout Australia regarding the type of testing platform they would be likely to use, should SCD and/or β -thalassaemia screening be implemented, and any additional concerns they may have. Consistent feedback indicated that there was no impact on uptake of NBS expected through the implementation of SCD and/or β -thalassaemia screening, but this should be monitored for changes.

States and territories would make individual choices regarding their preferred testing protocol, taking into account factors including each NBS laboratory's needs. Laboratories choosing testing platforms for SCD screening should keep in mind the capabilities of the test for identifying carriers, as this has major implications for the options that follow screening for families and individuals at risk of SCD. Additionally, identification of carriers can increase the workload significantly through the follow up testing of family members.

All the NBS laboratories in Australia have expressed they could only introduce screening for haemoglobinopathies if additional funding was provided (for staff and reagents), and most laboratories also suggested they would require new space capital equipment, and training.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The proposed haemoglobinopathies have an uncertain but low incidence in Australia, estimated to be 0.53 per 100,000 births. The incidence may be increasing over time with demographic change due to migration from countries that have a higher sickle cell disease (SCD) and haemoglobinopathy incidence. Australian registry data may underestimate the incidence.
- The use of newborn bloodspot screening (NBS) for SCD (early diagnosis) had superior effectiveness and non-inferior safety compared with no NBS for SCD (late diagnosis) (primary comparator). However, this outcome was highly dependent on the prevalence of SCD and the effectiveness of targeted testing approaches.
- Earlier diagnosis through NBS could lead to early interventions such as commencement of prophylactic antibiotics and administration of additional vaccinations over routine schedule, and engagement with specialist services, thereby improving health outcomes. Changes in clinical management upon a positive diagnosis of haemoglobinopathy through NBS may be broader than those assessed in the DCAR, and there may also be non-health benefits such as parental education and value of knowing.
- Targeted neonatal testing of infants at high risk (secondary comparator) currently occurs only in Western Australia (comprising ~11% of the national birth cohort), although expert opinion suggested the majority of cases are already detected through targeted testing. There were insufficient data to determine the incremental effectiveness or safety of NBS for SCD over targeted neonatal testing. Other states and territories are not actively considering targeted neonatal testing at this time.
- There were insufficient data to determine the incremental effectiveness or safety of NBS for β -thalassaemia and SCD compared to SCD alone. However, it can be assumed that NBS would identify additional β -thalassaemia cases in the pre-symptomatic period.
- There were insufficient data to determine the safety and effectiveness of cascade testing of the family members of newborns diagnosed with SCD or β -thalassaemia. The key benefit of cascade testing is to inform future reproductive choices, and identify first-degree relatives who are pre-symptomatic, which may include those with carrier state.

Economic issues:

- Given the limited availability of high-quality data due to the small patient population with this rare condition, the estimated cost-effectiveness was uncertain. Universal newborn screening is unlikely to demonstrate cost-effectiveness in the Australian context, given the current strategy of targeted neonatal testing and pneumococcal vaccination availability to newborns, which resulted in an uncertain clinical claim of superiority. However, NBS may lead to administration of the additional pneumococcal vaccinations required for management of identified newborns at increased risk for pneumococcal disease.
- NBS for SCD had a very small incremental benefit but was also of modest cost, resulting in an ICER of \$141,000 per affected case diagnosed earlier against the comparator of no NBS. Against targeted neonatal testing, NBS for SCD had an ICER of \$14 million per affected case diagnosed earlier. Adding NBS for β -thalassaemia improved the ICERs, however also made them even more uncertain.
- The economic model used a time horizon of 1 year as this captured the differences from the comparator while maintaining the robustness of the model given highly uncertain inputs, although may have underestimated the long-term health benefits and long-term costs.

- The cost of the tier 1 test and the haemoglobinopathy incidence were uncertain, and were the main drivers of the cost-effectiveness.

Financial issues:

- The cost of the tier 1 test in the test strategy chosen was the main driver of the total financial cost. The total financial cost was estimated to be \$3 million per year, though this increased to \$30 million per year when a more costly tier 1 test was used.

ESC discussion

ESC noted that this application from the Australian Sickle Cell Advocacy Inc was for inclusion of sickle cell disease (SCD) and beta (β) thalassaemia in the Australian newborn bloodspot screening (NBS) programs. ESC noted that applications 1737 and 1710 were the first applications to be considered for inclusion in the Australian NBS programs by ESC and MSAC, and following disbandment of the Standing Committee on Screening (SCoS) in 2021.

ESC noted that SCD is an autosomal recessive genetic blood disorder associated with episodes of acute illness and progressive organ damage. Complications of SCD result in frequent hospitalisation for treatment, lead to poor health outcomes, and are burdensome for families and healthcare systems. Anaemia, acute chest syndrome, cerebrovascular disease, infections (invasive pneumococcal disease), and veno-occlusive crisis are the most prevalent co-morbidities. β -thalassaemia is an autosomal recessive genetic disorder that causes iron overload and lifelong anaemia due to reduced levels of functional haemoglobin. ESC noted that the initial application was for SCD only; the Sickle Cell Disease Expert Working Group recommended that β -thalassaemia, haemoglobin E- β -thalassaemia and $\delta\beta$ -thalassaemia also be included (note that this application excludes α -thalassaemia). Collectively, these conditions are referred to as haemoglobinopathies, which for the purposes of this document excludes α -thalassaemia.

ESC noted that NBS programs are delivered by state and territory governments, and that screening takes place in five laboratories across Australia. The Australian Government contributes funding to hospital services, including those for NBS, through the National Health Reform Agreement (NHRA). The Australian Government also announced funding of \$39.0 million in the 2022–23 Budget, of which \$25.3 million has been offered directly to states and territories through a Schedule under the Federation Funding Agreement – Health to support expanding the number of conditions included in NBS programs and increasing consistency between the states and territories. ESC noted the NBS National Policy Framework (NBS NPF)¹⁷ and its decision-making criteria, which provided context for ESC's consideration of this application.

ESC noted that the true incidence of haemoglobinopathies in Australia was uncertain, but was estimated by the Department-contracted assessment report (DCAR) to be 0.53 per 100,000 births based on data from the Australian Haemoglobinopathy Registry. ESC considered that these registry data were likely to be an underestimate as they did not include still births, terminated pregnancies or deaths before diagnosis. ESC also noted that the incidence of haemoglobinopathies may be increasing in Australia due to increased migration from places where these conditions are more prevalent (i.e. people of African ancestry for SCD, and of Middle Eastern and Asian ancestry for β -thalassaemia). ESC noted that PathWest data indicated a much higher incidence of the nominated haemoglobinopathies of 8.6 per 100,000 births.

ESC noted that both SCD and β -thalassaemia are clinically significant diseases, and the burden of disease for these conditions is high. If untreated, outcomes are poor and many children with SCD

¹⁷ Newborn Bloodspot Screening National Policy Framework (NBS NPF), Department of Health, 2018. Available at: <https://www.health.gov.au/resources/publications/newborn-bloodspot-screening-national-policy-framework?language=en>

die before the age of 3, or have disabling silent, or overt, cerebrovascular disease. Children with SCD have high mortality rates due to splenic sequestration-mediated pneumococcal sepsis and also have high disease-related morbidity requiring frequent hospitalisation. ESC noted, the American Society of Hematology (ASH) Guidelines for sickle cell disease for the prevention, diagnosis and treatment of cerebrovascular disease (2020) recommend annual transcranial doppler (TCD) imaging for children aged 2-16 years, and for those with abnormal TCD doppler to have 3-4 weekly transfusions to maintain the maximum HbS level <30% and maintain the haemoglobin concentration >9.0 g/dL. ESC noted recommendations from the ASH Guideline for stem cell transplantation in SCD include consideration of transplantation in patients with neurological injury where a matched related sibling is available, and consideration of transplantation where frequent painful crises or acute chest syndrome (ACS) occur despite optimised medical therapy.

ESC noted that most public consultation feedback acknowledged the benefits of addition of the conditions to Australian NBS program and were supportive of the application. However, there were also several respondents that were not supportive of implementing the proposed service. Feedback highlighted that a targeted testing approach based on ancestry can result in missed cases, as people's ancestry or family history are not always known, and this is especially true in a multicultural country like Australia. Feedback also noted that an earlier treatment leads to improved health outcomes. Some feedback also highlighted that cascade testing may result in a need for genetic counselling.

ESC noted that the application had two PICO sets:

1. NBS for all newborns in Australia, which is the focus of the application, and
2. Cascade testing of family members of newborns who test positive through NBS.

ESC considered a further issue for consumers was potential inequity of access if the follow-on monitoring and treatment required after a diagnosis were not available nationwide, including remote and rural areas in particular. Also if NBS for SCD and β -thalassaemia were not implemented nationwide, this also risks inequity for families in accessing effective screening services. Further accessibility concerns were around access to genetic counselling and clinical expertise in remote and rural areas.

ESC considered the comparators for both populations were appropriate: for PICO set 1, the primary comparator was no NBS and the secondary comparator was targeted testing of at-risk newborns, and for PICO set 2 the comparator to cascade testing using genetic methods was cascade testing using phenotypic methods. ESC noted the DCAR stated that targeted testing of at-risk neonates is current clinical practice in Australia, which according to expert opinion already detects 95-99% of babies with haemoglobinopathies, and that the vaccination program already has high uptake so babies would likely still be protected in the absence of NBS. However, ESC noted Department advice that targeted neonatal testing likely only takes place at present in Western Australia (comprising ~11% of the national birth cohort), not nationally. Given its effectiveness ESC queried whether other states or territories were considering taking up targeted testing, and noted Department advice that the other states and territories are not actively considering taking up targeted neonatal testing at this time. ESC considered that although targeted neonatal testing is not nationwide, that did not mean it should not be compared against, and considered there was merit in both comparators.

ESC noted the current and proposed clinical management algorithms for SCD and β -thalassaemia. The current algorithms identified babies who present clinically with signs and symptoms of a haemoglobinopathy, who then undergo diagnostic testing followed by confirmatory genetic testing. High-risk neonates identified by family history undergo targeted

testing on cord or venous blood (in Western Australia). ESC noted that under the proposed clinical management algorithms all newborns receive tier 1 (and tier 2, depending on the strategy) screening, followed by confirmatory genetic testing for babies who have a positive result. Family members of newborns found to have a haemoglobinopathy through NBS would have access to cascade testing (PICO set 2), genetic counselling, and reproductive planning if appropriate.

ESC noted that there were several bloodspot screening testing methodologies available for the tier 1 testing, but most studies used high-performance liquid chromatography (HPLC). The available methods varied substantially in cost: from \$10 for matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF, the base case method), to \$96 for HPLC.

ESC noted that the evidence base included both direct and indirect evidence, and considered that the DCAR's separation of the evidence into direct versus indirect evidence was useful because for universal screening programs MSAC has a clear preference for direct from test to health outcomes evidence as stated in the MSAC Guidelines. ESC noted the clinical claim that early diagnosis (through NBS) and early intervention, education and genetic counselling are superior to late diagnosis (without NBS). ESC noted most of the direct evidence was from countries where the incidence of SCD was much higher than in Australia, which ESC considered had low applicability to the Australian context. ESC noted that direct evidence for the effectiveness of including β -thalassaemia in NBS programs was scarce.

ESC noted that there was no explicit claim regarding the comparative safety of adding haemoglobinopathies to the NBS programs. However, ESC considered that there were no additional safety issues regarding the test itself, as newborns already undergo a heel prick test, and no additional heel prick would be required. ESC considered the main safety consideration was risk associated with treatments for SCD or β -thalassaemia, such as hydroxyurea (HU), received by newborns diagnosed early by NBS that are over and above those received by babies clinically diagnosed at a later age. HU administration is associated with reduced neutrophil counts, which require regular monitoring, and consequent risk for sepsis or bacteraemia. Other safety considerations included overdiagnosis or false positive test results, but given the type of disease and the accuracy of the tests ESC considered both of these were unlikely. The psychological and social impacts associated with receiving a positive result were also potential safety concerns, however ESC considered given the high penetrance these were not incremental, and with NBS would only be experienced earlier than with diagnosis upon clinical presentation.

ESC noted that the direct evidence showed that earlier diagnosis led to earlier commencement of prophylactic treatments significantly reducing mortality for children with SCD. On morbidity, ESC noted direct evidence that NBS for SCD reduced the number of hospitalisations and median days spent in hospital. ESC considered that, in Australia, the age difference between proposed NBS diagnosis and diagnosis made through targeted neonatal testing or symptomatic diagnosis is likely to be smaller than that in the published studies. Therefore, the impact of early diagnosis on population-level mortality would likely be smaller in Australia. ESC considered that, when compared to earlier studies in Jamaica or the United States, the Australian healthcare system was likely to offer health benefits for survival that would largely mitigate the impact of early infection and splenic sequestration on mortality.

ESC noted indirect or linked evidence on the clinical effectiveness of screening was also presented. On test accuracy, ESC noted the sensitivity and specificity of testing were 100% and >99–100% respectively for SCD and 88.8–98.5% and 98.73–100% respectively for β -thalassaemia, and considered that the test accuracy was high for both conditions. ESC noted that the positive predictive value (PPV) and negative predictive value (NPV) of testing were 100%,

however considered this should be interpreted with caution because the PPV was 0% if prevalence is <0.01% (as is the case in Australia) and sensitivity is <100%. In considering the linked evidence for changes in clinical management, ESC noted that earlier access to prophylactic antibiotics, risk-based pneumococcal vaccination and HU treatment did result in improved outcomes for newborns with SCD. However, ESC considered that the clinical utility in Australia may be lower than reported in the literature, because Australia has high uptake of the standard pneumococcal vaccine schedule for the general population-risk individuals as part of the National Immunisation Program. ESC considered that NBS would result in earlier prophylactic antibiotic treatment for babies found to be positive for a haemoglobinopathy and access to additional vaccination administered for high-risk children with SCD, and treatment with HU, which trial data showed significantly improved multiple outcomes. ESC noted that there is no liquid formulation of HU either currently registered or reimbursed in Australia that is required for young children – access is required through the Authorised Prescriber pathway or Special Access Scheme to an imported product. ESC noted that antibiotic prophylaxis reduced infections in children with SCD aged <5 years. According to data from the Australian Haemoglobinopathy Registry, the median age of diagnosis of SCD in children was 8.4 months, indicating that prophylactic antibiotic therapy is likely started within the first year of birth. ESC noted that there was little evidence that reported on treatments for β -thalassaemia (one small level IV study provided inconclusive data), but that these patients can receive prophylactic antibiotics and regular transfusions. Treatments recommended for babies with SCD or β -thalassaemia up to 12 months of age were considered because treatments after that age were not likely to be changed by earlier diagnosis via NBS.

ESC considered that the uncertainty around the incidence of haemoglobinopathies in Australia resulted in considerable uncertainty in the estimated clinical utility and incremental benefit of NBS, as demonstrated by the wide range of estimated numbers of incremental diagnoses. ESC noted that NBS would result in an incremental 5-86 diagnoses per 1,000,000 newborns screened against no NBS (and no targeted testing). However, if 64–99% of all cases are identified by targeted neonatal testing (Table 12; although this may be an overestimate if targeted testing is only done in Western Australia), then the incremental benefit of additional newborns diagnosed by NBS would be between:

- 2 to 31 more newborns diagnosed per 1,000,000 newborns screened (worst case scenario of 64% identified by targeted testing)
- 0 to 1 more newborn diagnosed per 1,000,000 newborns screened (best case scenario of 99% identified by targeted testing).

ESC noted that there were little data (direct or linked) regarding comparative safety or effectiveness for population 2 (cascade testing), but considered that the key benefit of cascade testing was to inform reproductive choices and identify siblings who are pre-symptomatic.

Overall, ESC considered the clinical evidence supported superior effectiveness of NBS for SCD compared to no NBS (late diagnosis), however this was highly dependent on the incidence of SCD and the effectiveness of targeted testing. ESC considered the evidence also supported non-inferior safety of NBS for SCD compared to no NBS. ESC considered there were insufficient data to accurately determine the incremental effectiveness or safety of NBS against targeted testing, of NBS for SCD and β -thalassaemia over NBS for SCD alone, and of cascade testing.

ESC noted that the economic model used a decision tree analysis incorporating estimates of the incidence of haemoglobinopathies, performance of screening tests and extent of current testing (where appropriate). The DCAR commented that insufficient evidence was available to translate the incremental benefit of a diagnosis into patient-relevant outcomes beyond early diagnosis, therefore conducted a cost-effectiveness analysis (CEA) with effectiveness measured in terms of

the incremental cost per additional early diagnosis of a clinically significant case. ESC considered cost-utility analyses are preferred as they are in general more informative for MSAC, but considered that a CEA was reasonable for this assessment. ESC noted the base case assumed that universal NBS will not report on carrier status, in line with the Department's policy position that carrier results should not be reported in NBS.

Overall, ESC considered the uncertainty of the evidence used in the economic model for SCD was high, and the uncertainty of the evidence for β -thalassaemia was very high (Table 14). ESC noted that the key areas of uncertainty in the economic evaluation were:

- Applicability, as ESC considered there was uncertainty about the superiority claim: because missed cases would likely be treated and protected by pneumococcal vaccination anyway, noting newborns with SCD need more doses than those offered through routine vaccination, and targeted neonatal testing already detects most cases, noting only Western Australia has targeted testing (WA representing 11% of Australian births).
- Many of the data inputs were of low-quality:
 - There was a paucity of data for incidence of SCD and β -thalassaemia in Australia. Estimates were largely based on pathology data, expert opinion, or international data.
 - The choice of tier 1 testing methodology was the main driver of the cost-effectiveness, as costs ranged from \$10 to \$96, and all newborns screened receive the tier 1 test.
 - The PPV heavily depended on the estimates of incidence, which were highly uncertain.

ESC noted the most recent Australian estimates of incidence were 10 years old, and considered the incidence in Australia may be increasing over time, with demographic change due to migration from countries that have a higher incidence of SCD (Africa) and haemoglobinopathies (Middle East and Asia). ESC considered that an alternate estimate of current Australian incidence constructed using demographic data from the most recent census data would require further assumptions around nationality and ancestry and only add to the uncertainty.

Given the cost of the tier 1 test was the main driver of cost-effectiveness and the applicant had commented that there were 'much cheaper test options' in other parts of the world, ESC contemplated whether more competitive quotes would improve the ICER, but considered \$10 was already relatively low cost and the cost in Australia was unlikely to be lower than this.

ESC noted the incremental benefit was small, and considered this was mainly because the population of affected newborns is small while the population of tested newborns is large.

ESC noted that ICERs were presented for comparisons against the primary and secondary comparator, screening for SCD or SCD and β -thalassaemia, and considered that the cost-effectiveness differed substantially across these scenarios and also depended on the method used for tier 1 screening. ESC noted the reported ICERs in terms of incremental cost per incremental early diagnosis were, for SCD \$141,000 (against no NBS) and \$13.8 million (against targeted neonatal testing), and for SCD and β -thalassaemia \$51,000 (against no NBS) and \$5 million (against targeted neonatal testing) (Table 15). ESC considered that comparisons against the primary comparator were more cost-effective, and that while on face value adding β -thalassaemia improved the cost-effectiveness, introducing data for β -thalassaemia increased the uncertainty of the ICERs. ESC's interrogation of the model for SCD only (given the very high uncertainty when β -thalassaemia was added) showed that when more costly tier 1 screening methods were used the ICERs increased substantially (to \$1.4 million against no NBS and to \$133 million against targeted neonatal testing), and that using alternative estimates of incidence also substantially increased the ICERs (to \$4.4 million against no NBS and \$431 million against targeted neonatal testing). ESC considered the substantial increase to ICERs in these sensitivity analyses highlighted that there was substantial uncertainty in the model.

In contextualising these ICERs ESC noted that previous economic analyses for Australian NBS had been published in some cases, but that these had not been considered by MSAC. ESC

considered that NBS was a new area of screening for MSAC to assess, and that while MSAC had previously considered the cost-effectiveness for genetic testing in terms of cost per proband or similar measures, the willingness to pay (WTP) threshold may differ for NBS compared to non-screening testing of affected individuals.

ESC considered the model's 1-year time horizon was appropriate, as it reflected the timeframe within which affected babies would be identified and interventions initiated, in both a world with NBS and without it. ESC considered that using the shorter time horizon had made the model more robust, however also meant the model may not have fully captured the longer-term benefits of NBS (potentially including reduced mortality), and may also have underestimated the longer-term incremental costs (such as increased long-term monitoring costs) and cost-offsets. However, ESC considered that extending the time horizon would only increase uncertainty due to the low-quality inputs. ESC considered that because NBS conditions are typically rare conditions, low incidence and low quality and uncertain inputs were likely to be a recurring issue for future assessments, which may make striking the appropriate balance between time horizon and level of robustness a recurring complexity in economic modelling of NBS.

ESC noted that utilisation was estimated using an epidemiological approach that assumed approximately 310,000 to 315,000 babies born each year, with an NBS uptake of >98% based on current uptake, which ESC considered was reasonable. ESC noted the financial cost was \$3.2 million per year, assuming the tier 1 test method was MALDI-TOF (approximately \$10 per test). ESC considered that using a more costly tier 1 method substantially increased the financial cost, for example if HPLC was used instead (approximately \$96 per test) then the financial impact increased to \$30 million per year (Table 22).

ESC also speculated on developments that may be relevant to NBS for haemoglobinopathies in the future. ESC commented that if expanded reproductive carrier testing (as proposed in MSAC application 1637¹⁸) were implemented in Australia, then this would screen for conditions including haemoglobinopathies, which may result in their incidence decreasing over time. ESC also commented that if or when genomic newborn screening is introduced this would be a substantial shift, and may improve the cost-effectiveness of NBS. ESC commented that gene therapies such as CRISPR-based treatment are emerging, and Australian patients may be able to access these through the Medical Treatment Overseas Program.

Lastly, ESC commented that at present HU is not a Therapeutic Goods Administration (TGA)-registered therapy for SCD in Australia, but if SCD were to be included in NBS then this could motivate registration of HU.

17. Applicant comments on MSAC's Public Summary Document

There is evidence that universal screening for SCD has significantly improved outcomes even in the countries comparable to Australian standards although the prevalence of the disease may not be the same. The average age of diagnosis of SCD in Australia is currently beyond the recommended age for initiation of interventions.

SCD prevalence was found to be higher than all of the conditions being screened on NBS programs in France, Italy, and Germany in pilot studies. Sweden and Ireland both have a smaller sickle cell populations than Australia, and yet they have NBS for SCD. Historically this condition occurs in people who originate from Sub-Saharan Africa; with immigration this pattern is

¹⁸ Public Summary Document for MSAC application 1637 – Expanded Reproductive Carrier Screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1637-public>

changing and the number of SCD cases is steadily growing. Although the current prevalence of SCD in Australia is unknown or presumed low, the current data available are inaccurate as not all centres contribute to the haemoglobinopathy registry.

18. Further information on MSAC

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