

# Medical Services Advisory Committee (MSAC) Public Summary Document

## ***Application No. 1737.1 – Newborn bloodspot screening for sickle cell disease***

**Applicant:** Australian Sickle Cell Advocacy Inc

**Date of MSAC consideration:** 23-24 November 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.

### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported adding SCD to NBS. Although the new data had limitations, MSAC was satisfied the evidence demonstrated that an early diagnosis of SCD through NBS would change management in the Australian context, and would improve health outcomes for babies screened through NBS programs. Existing targeted testing detects less than half of SCD cases before symptoms develop, so NBS would result in more early diagnoses. NBS for SCD can also detect beta-thalassaemia and potentially other haemoglobinopathies as non-target conditions. The updated estimate of SCD incidence in Australia was substantially higher than in the previous assessment and likely closer to the truth than previous calculations, noting also that incidence is likely to increase further over time due to immigration. NBS for SCD had non-inferior safety, with the main potential harms from side effects of hydroxyurea treatment and false results, although false results were unlikely. The main remaining uncertainty was the cost of screening, as this will vary depending on which screening method each NBS laboratory chooses and its staffing and instrument capacity to introduce new tests. Based on its analytical validity and the updated estimate of incidence, MSAC advised electrospray ionisation tandem mass spectrometry had acceptable cost-effectiveness in terms of cost per early diagnosis of SCD at a first-tier screening cost to \$8.23 per test. The financial cost of NBS for SCD was likely reasonable, but was also uncertain as it depended on the cost of first-tier screening. Implementation costs for program changes were not part of this application.

## Consumer summary

This was an application from Australian Sickle Cell Advocacy Inc requesting to add sickle cell disease to newborn bloodspot screening (NBS) programs.

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. The blood sample is then tested for certain rare but 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 also help the parents to make choices for any future pregnancies.

Sickle cell disease is an inherited disorder of red blood cells. Red blood cells contain a protein called haemoglobin, which carries oxygen throughout the body. Healthy red blood cells are flexible and shaped like a doughnut, with a dent 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 small blood vessels, which can become blocked. People with sickle cell disease often require blood transfusions and can experience episodes of severe pain, organ damage and increased infections. In severe cases, people can die from having sickle cell disease.

MSAC previously considered this application in July 2023. The evidence from the scientific literature that was presented to MSAC in July showed that NBS would allow an earlier diagnosis, but did not show that an earlier diagnosis would change health care provided to those babies or improve their health, in the Australian context. The value for money and overall cost were also uncertain. This time, a new assessment was presented to MSAC that used Australian registry and unpublished data, and a less costly but equally effective screening method. The July application proposed testing for both sickle cell disease and beta-thalassaemia (another inherited blood disorder) by NBS, but the new application looked at sickle cell disease screening alone because MSAC advised in July that most NBS for sickle cell disease can also detect beta-thalassaemia.

Adding sickle cell disease to NBS would result in more early diagnoses before signs and symptoms start to emerge, compared to the current situation where less than half of all people with sickle cell disease are diagnosed before symptoms appear. The new evidence showed that diagnosing sickle cell disease before symptoms appear did change how patients were managed in Australia, and made it less likely they would need to go to the emergency department due to sickle cell disease, or be admitted to hospital. The new evidence also showed that early diagnosis of sickle cell disease reduced the proportion of patients who get sepsis (a serious life-threatening condition caused by the body's extreme response to an infection, which damages its own organs and tissue). Patients diagnosed before they get sick were also more likely to take preventative medicine, and be checked for risk of stroke as part of routine monitoring for SCD. MSAC accepted that even though the evidence had limitations, overall the addition of sickle cell disease to NBS would enable people who have this condition to be detected earlier, which would change the treatments they receive and improve their health outcomes.

In terms of safety, overall MSAC considered that adding sickle cell disease to NBS was acceptably safe. The main potential harms were likely to be side effects of treatments for sickle cell disease, and harms from false positive or false negative screening results although these were unlikely. MSAC considered the potential harms from SCD treatment to be less serious than from the effects of the disease itself.

When it first considered this application, MSAC was concerned that the incidence of sickle cell disease in Australia was highly uncertain, and this also made the value-for-money of screening for it uncertain. This second assessment calculated a new estimate of incidence incorporating ancestry estimates, which was higher than before, and MSAC advised this estimate was more reasonable.

## Consumer summary

Another concern MSAC had when it considered this application in July was that the cost of the main method proposed for screening may have been overestimated. There are a range of different methods that can be used in screening for sickle cell disease, and it is up to each NBS laboratory to choose which method they use. This second assessment used a different main method and tested a range of potential costs for it, because the exact cost would depend on which method the laboratory chooses and how many newborns it was screening. While MSAC considered that this made the cost per screen uncertain, at the re-calculated incidence MSAC advised that NBS for sickle cell disease was acceptable value for money at a costing of up to \$8.23, and the financial cost was likely reasonable.

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

After considering the strength of the evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported adding sickle cell disease to NBS programs. MSAC acknowledged that NBS for sickle cell disease can also detect beta-thalassaemia and potentially other haemoglobinopathies.

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

MSAC noted that this resubmission from Australian Sickle Cell Advocacy Inc requested the addition of SCD to NBS programs. MSAC recalled it had previously considered this application at its July 2023 meeting<sup>1</sup>, when it deferred its advice regarding the addition of SCD and  $\beta$ -thalassaemia pending additional evidence on incidence, change in management and improvement in health outcomes from that change, and updated economic and financial analyses.

While the first health technology assessment of this application (the 1737 Department-contracted assessment report (DCAR)) examined adding both SCD and beta-thalassaemia to NBS, in July 2023 MSAC advised that *"information for its reconsideration could be provided for SCD alone because screening for SCD can also detect  $\beta$ -thalassaemia as a non-target condition"* (1737 PSD, pg 8). NBS for SCD alone was therefore proposed for reconsideration, and the 1737.1 fit-for-purpose (FFP) overview was contracted seeking to use new evidence to address MSAC's concerns.

MSAC noted that the Newborn Bloodspot Screening National Policy Framework (NBS NPF)<sup>2</sup> 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, is 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 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

<sup>1</sup> Public Summary Document (PSD) for MSAC application 1737 – Newborn bloodspot screening for sickle cell disease and beta thalassaemia. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1737-public>

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

genotype results in rigid, sickle-shaped red blood cells that cannot move freely through blood vessels. SCD clinically manifests 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.

MSAC noted that consultation feedback on application 1737 was received from eight professional organisations, three consumer organisations and four health professionals. The consultation feedback received was mixed. Most respondents acknowledged potential benefits of NBS for SCD (and  $\beta$ -thalassaemia), however, there were concerns in relation to the proposed test method, the detection of genetic carriers and the detection of non-paternity.

MSAC noted that while the 1737 DCAR's assessment was based on a systematic review of the published literature, the 1737.1 FFP overview provided an assessment that was updated mainly based on Australian Haemoglobinopathy Registry (HbR) analyses for MSAC<sup>3</sup>, but also included unpublished data from the HbR and analyses of HbR data from Nelson et al. 2023<sup>4</sup>. No new direct evidence was provided. MSAC noted analyses of registry data were provided by the HbR for Australian-born patients diagnosed with SCD (all ages) who could be categorised as diagnosed before vs after symptom onset (n=109, of which n=52 early diagnosis and n=57 late diagnosis). MSAC noted these data did not use the proposed intervention (universal NBS), but instead compared patients diagnosed early (through targeted testing) versus late (at or after the point of symptom onset), on the assumption that an early diagnosis through the proposed intervention would not have meaningfully different consequences for management and health outcomes than an early diagnosis through targeted testing. The FFP overview used the HbR and Australian data from Nelson et al. (2023) and an unpublished manuscript to provide an updated linked evidence assessment. MSAC noted that for universal screening programs it has a stated clear preference for direct from test to health outcomes evidence, however it considered that the international evidence for SCD was of low applicability to the Australian context, and that the assessment informed by the HbR data was a more accurate reflection of what the consequences of NBS would be in Australia. MSAC considered there were limitations to the HbR data, because the registry is voluntary for both patients and sites and so not comprehensive. The sample size was small, its data were observational, and subject to selection bias, although it is unknown in what direction the bias would influence the results. However, despite its limitations, MSAC considered the registry data were an acceptable evidentiary basis on which it could provide its advice, especially in the context of SCD being a rare disease.

Regarding incidence, MSAC recalled that based on the 1737 DCAR it had considered the estimated Australian incidence of SCD and beta-thalassaemia (0.53 to 8.6 per 100,000 newborns) was highly uncertain, and that overseas data had low applicability due to incidence differing by ancestry. MSAC noted the 1737.1 FFP overview provided a new estimate of incidence that combined HbR data on ancestry of SCD cases from Sub-Saharan Africa as a key high-prevalence region (Nelson et al., 2023) with incidence among populations with high SCD prevalence, and the proportion of births in Australia to parents from these high-risk countries (then extrapolating to account for births to couples from outside this region). MSAC noted the applicant's concern in its pre-MSAC response that ancestries other than Sub-Saharan Africa had been excluded from the calculations, but considered that the extrapolation meant this had not been the case. MSAC noted the 1737.1 FFP overview's calculations estimated the Australian incidence of SCD to be 34.2 per 100,000 (or 106 cases per year), and considered this was higher than the 1737 DCAR's estimates and likely to be closer to the true incidence. MSAC noted the pre-MSAC response from the applicant stated that there is a clear trend of increased

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<sup>3</sup> Australian Haemoglobinopathy Registry (HbR) Brief report for MSAC (2023).

<sup>4</sup> Nelson, A, et al. (2023) 'Sickle cell disease in Australia: A snapshot from the Australian Haemoglobinopathy Registry. *Int Med J*, 2023 Dec 8, doi: 10.1111/imj.16297. Epub ahead of print. PMID: 38064543.

migration of people from countries with high incidences of SCD, and MSAC agreed that migration to Australia from countries where SCD is more prevalent is increasing over time, so the Australian incidence was likely to increase further in the future.

MSAC recalled that the 1737 DCAR had estimated based on expert opinion that current targeted testing of at-risk neonates detected 95-99% of haemoglobinopathy cases before symptom onset, however noted that HbR data showed current targeted testing in Australia only identified 47.7% of cases of SCD before symptom onset. MSAC considered that despite its limitations the HbR data were more reliable than expert opinion, and therefore that the incremental proportion of cases that would be diagnosed pre-symptomatically by NBS compared to targeted testing was greater than had previously been estimated. MSAC noted that at an incidence of 34.2 per 100,000 the FFP overview estimated current targeted testing diagnosed 51 cases of SCD per year prior to symptom onset, whereas NBS would detect an additional 55 cases of SCD per year pre-symptomatically.

Regarding safety, MSAC considered there to be no additional direct harm from adding another condition to NBS as it would use part of the same bloodspot already collected. MSAC considered there may be psychological and social impacts associated with receiving a positive diagnosis through NBS, although these impacts would be experienced earlier with NBS but would not be additional. Potential harms could also arise from false positive or false negative test results, but given the accuracy of two-tiered screening, MSAC considered false results were unlikely. The main safety issues relating to NBS for SCD were therefore potential harms associated with treatments for SCD received by newborns diagnosed early by NBS that are over and above those received by babies diagnosed at a later age, however MSAC considered the harms associated from SCD complications due to non-receipt of guideline recommended prophylaxis were likely to be greater than from the prophylactic interventions themselves. Overall, MSAC advised NBS for SCD was comparatively safe.

MSAC noted the HbR report showed the median age of diagnosis was 2.4 months in the pre-symptomatically diagnosed group, versus 15.6 months in patients diagnosed at symptom onset. MSAC recalled it had previously accepted that NBS would result in an earlier diagnosis than at symptomatic presentation, and considered that while the HbR evidence was based on existing targeted testing rather than universal NBS it also supported the reasoning that adding SCD to universal NBS would result in earlier diagnosis of SCD cases. MSAC further noted that the median age at symptomatic diagnosis of SCD was substantially older than age at diagnosis in countries such as the USA where SCD is more prevalent, which it considered aligned with its experience that Australian healthcare services are less attuned to SCD given its rarity in Australia and supported the clinical need to add SCD to NBS in Australia.

MSAC recalled its primary concern at its July 2023 consideration of this application had been that the evidence had not demonstrated an early diagnosis through NBS would result in meaningful change in management in the Australian context with resulting health outcome improvement. MSAC noted there was no new direct evidence, and the FFP overview presented an updated linked assessment for comparative effectiveness. MSAC noted the observational data from the HbR indicated compared to those diagnosed at or after symptom onset, those who were diagnosed pre-symptomatically were more likely to receive prophylactic antibiotics (67% vs 47%) and were more likely to have a transcranial Doppler performed to predict the risk of stroke (84% vs 56%). Some differences in the management were statistically significant between patients diagnosed early versus late, although this was not a comparison between the intervention and the comparator. MSAC also noted that stem cell transplantation is currently a treatment option for severe SCD and new therapies for SCD including gene therapies have recently been approved internationally, so considered that change in management from an early SCD diagnosis in

Australia may be greater in the future. Overall, MSAC considered the evidence showed NBS for SCD would result in meaningful change in management in the Australian context.

Regarding health outcomes, MSAC noted the HbR report showed higher rates of a range of complications amongst patients diagnosed late compared to those diagnosed early (Table 11). MSAC noted the differences were statistically significant between patients diagnosed early versus late for some outcomes (e.g. sepsis, cholecystectomy), although for nearly all complication outcomes the differences were too small to be statistically significant, and this was not a comparison between the intervention and the comparator (because the comparator includes nearly half of SCD patients being diagnosed pre-symptomatically, so the difference between intervention and comparator will be less than the difference between early versus late diagnosis). Compared to diagnosis at or after symptom onset, pre-symptomatic diagnosis was associated with changes to health outcomes including reduced SCD-related emergency department presentations in the past 12 months (0 presentations in 63% vs 47% of cases) and hospital admissions in the past 12 months (0 admissions in 69% vs 46% of cases; excluding planned transfusion admissions), and reduced history of sepsis (4% vs 31%) and cholecystectomy (8% vs 25%). MSAC noted the registry data showed early diagnosis was associated with both change in management and improved health outcomes, but did not directly show that the change in management caused the improved health outcomes. MSAC considered that causality could reasonably be inferred because international evidence-based guidelines recommend various changes in management for patients with SCD, because they are well established to improve health outcomes. Overall, MSAC advised the registry evidence demonstrated health outcome improvement from a pre-symptomatic diagnosis of SCD.

The 1737 DCAR used matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF) as the base case first-tier screening method, and at its July 2023 meeting, *“MSAC considered that \$10 per [MALDI-TOF] 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”* (1737 PSD, pg 7). MSAC noted that an expert consulted during preparation of the FFP overview advised that electrospray ionisation tandem mass spectrometry (ESI MS/MS) would be a more appropriate method for the first-tier test than MALDI-TOF, and also provided costing estimates for this method, which varied depending on whether or not new infrastructure was required to add screening for SCD, and the number of newborns screened by the laboratory. MSAC noted NBS laboratories may also opt for a different method than ESI-MS/MS depending on their current instrumentation and methodologies used, capacity and workload. MSAC considered that all of the methods assessed by the 1737 DCAR and 1737.1 FFP overview had acceptable analytical validity, although IEF was unlikely to be used in practice. The FFP overview used \$2 as its base case cost of first-tier testing, which was the estimated cost if laboratories had mass spectrometry capacity available. However, if laboratories did not have spare capacity and would have to purchase a new mass spectrometer, with its accompanying costs, then the weighted national average cost per ESI-MS/MS test was estimated to be \$7.09 (Table 13). MSAC considered the cost of first-tier screening was therefore the main area of uncertainty for this application, as it was likely to vary by laboratory.

MSAC noted the 1737.1 FFP overview updated the 1737 DCAR’s economic modelling with revised assumptions for effectiveness of the comparator (47.7% rather than 99% of cases detected pre-symptomatically), incidence of SCD (34.2 rather than 0.53 per 100,000), and cost per first-tier ESI-MS/MS. It also updated the average age at symptomatic diagnosis from 8.4 months to 15.6 months based on data from the HbR report, which increased the duration of additional treatments and ongoing management in the additional patients diagnosed with SCD before symptom onset, using some costs informed based on analyses of unpublished data from the HbR. MSAC noted sensitivity analyses were provided for a range of estimated costs of first-tier screening (Table 13), including the weighted national average (\$7.09) and median (\$8.23)

cost per ESI-MS/MS if no laboratories have the current capacity to accommodate SCD screening. MSAC noted that at a first-tier cost of \$2 (which excluded fixed costs to add capacity) the incremental cost-effectiveness ratio (ICER) was \$12,280 per additional case of SCD identified earlier, however MSAC advised fixed costs should be included in the economic modelling in order to more accurately reflect the resource use and opportunity cost (for example in terms of machine time and labour), therefore this ICER excluding fixed costs was not appropriate. MSAC noted that at the weighted national average first-tier cost of \$7.09 including fixed costs the ICER was \$40,257 per early diagnosis, which it considered was acceptably cost-effective. MSAC considered that screening was acceptably cost-effective up to a costing of \$8.23 per first-tier screen, which had an ICER of \$46,523 per early diagnosis of SCD. MSAC noted the key drivers of the ICER were incidence of SCD, cost of first-tier testing and proportion of cases identified pre-symptomatically at present.

MSAC noted the 1737.1 FFP overview presented a financial analysis that was updated from the 1737 DCAR's analysis to reflect the updated costing for first-tier screening, updated incidence, and costs to other funding sources arising from the evidenced changes in management (such as the cost of prophylactic antibiotics to the PBS), including some costs estimated by unpublished data from the HbR. MSAC noted the financial cost to NBS programs of adding SCD was approximately \$700,000 per year (excluding fixed costs). MSAC noted there would also be direct costs to other funding sources, including cost-offsets from testing no longer needed of approximately \$50,000 per year from current targeted testing avoided and \$11,000 per year from testing upon symptom onset avoided, as well as small increased costs to the MBS and PBS from increased treatment and monitoring in the period before a symptomatic diagnosis. MSAC noted the total financial cost to Government (including to NBS programs, states and territories, the MBS and the PBS) of NBS for SCD was \$638,955 in year 1 increasing to \$661,059 in year 6 (Table 22). MSAC noted analyses had also been provided estimating the indirect cost-offset to states and territories from hospitalisations avoided that indicated a net saving, however MSAC considered the estimated indirect cost-offset was highly uncertain and so this analysis was unreliable for decision-making and its advice on the financial impact was based on the direct analyses.

MSAC considered that there are also significant program costs (such as education and training) to add conditions to NBS that were not captured by the HTA. MSAC considered that a large body of education must accompany any change in the NBS programs. This information is targeted both to health professionals and patients, with written and usually video information on the conditions being screened, and is published in multiple languages. MSAC considered in terms of implementation that it would be least disruptive to NBS laboratories and maternity and primary care services to add multiple new conditions to NBS at one time. MSAC noted that an in-depth consideration of implementation issues was beyond its ToRs, but that policy advice from the Department indicated bundling conditions for implementation will be considered, where possible.

MSAC acknowledged that depending on the method used for screening, NBS for sickle cell disease can also detect most cases of beta-thalassaemia and potentially other haemoglobinopathies, as non-target conditions (also known as additional findings).

## **4. Background**

MSAC previously considered the addition of SCD and  $\beta$ -thalassaemia to NBS programs, including the 1737 DCAR, at its July 2023 meeting. Based on the evidence provided, MSAC deferred its advice due to requiring additional evidence to support the addition of SCD and  $\beta$ -thalassaemia. Specifically, the MSAC advised the evidence outlined in Table 1 would be required to support its reconsideration. A fit-for-purpose (FFP) overview was developed to address these concerns.

**Table 1 Summary of key matters of concern to MSAC/MSAC Executive**

Component	Matters of concern	How the current FFP overview addressed the concern
Population	MSAC considered that information for its reconsideration could be provided for SCD alone because screening for SCD can also detect $\beta$ -thalassaemia as a non-target condition (1737 PSD, p8).	FFP overview assessed only SCD (including HbSS, HbSC and HbS $\beta$ -thalassaemia).
	MSAC considered that the incidence of haemoglobinopathies in Australia was uncertain (1737 PSD, p4). Provide a more reliable estimate of incidence in Australia (1737 PSD, p8).	Incidence has been estimated by applying the incidence from a key high-risk region, and applying the incidence to the proportion of births in Australia to parents from these high-risk countries (then extrapolating to account for cases to couples from outside of this region).
Proposal for public funding	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 $\beta$ -thalassaemia. MSAC queried whether less costly methods are available in Australia, and considered that using a less costly method would improve the cost-effectiveness (1737 PSD, p7). Investigate whether less costly screening methods are available in Australia, and if so determine their costs (1737 PSD, p8).	An expert consulted during preparation of the assessment provided advice that electrospray ionisation tandem mass spectrometry (ESI MS/MS) would be a more appropriate method for the first-tier test, and also provided costing estimates based on the number of newborns screened by the laboratory. The base case of \$2.00 per first-tier test was used, assumed appropriate where laboratories have mass spectrometry and staffing capacity available.
Linked evidence – performance of targeted testing	MSAC Executive noted that Australian Haemoglobinopathy Registry (HbR) data indicated that only 47.7% of SCD cases are currently diagnosed prior to symptom onset, not 95-99% as reported in DCAR 1737 based on expert opinion. (MSAC executive minutes, 22 September 2023).	These data are incorporated in Section 10 and influence the estimates of the incremental benefit of NBS.
Linked evidence – change in management	Quantify the change in management between NBS and current testing in Australia (1737 PSD, p8).	HbR data included in Section 10, demonstrating differences in management between those diagnosed early vs late.
Linked evidence – effectiveness of change in management	Quantify the resulting effect on health outcomes in Australia (quantify the incremental health benefit from an earlier diagnosis through universal NBS as compared to diagnosis at symptom onset) (1737 PSD, p8).	HbR data included in Section 10, demonstrating differences in health outcomes in those diagnosed early vs late.
Economic evaluation and financial/ budgetary impacts	Provide updated economic and financial analyses taking the above into account (1737 PSD, p8).	The economic and financial analyses have been updated to reflect the lower cost per screen and proportion of cases, as per the HbR data, who receive a diagnosis prior to symptom development. While data on the effect of change in management were able to be incorporated to an extent in the financial analysis, the economic analysis could not easily be extended to a CUA. This was acknowledged by the MSAC Executive (item 5.1, MSAC Executive Minutes, 22 September 2023), which considered that, under revised assumptions regarding the test cost, if the costing were sufficiently low then the financial cost of screening may not justify the cost of a second DCAR to conduct a CUA.

CUA = cost-utility analysis; DCAR = Department Contracted Assessment Report; FFP = fit-for-purpose; HbR = Australian Haemoglobinopathy Registry; MSAC = Medical Services Advisory Committee; NBS = Newborn bloodspot screening; PSD = Public Summary Document; SCD = sickle cell disease



## 5. Prerequisites to implementation of any funding advice

Each state and territory laboratory would determine which method of screening for SCD they would implement. MSAC considered that the Newborn Bloodspot Screening National Policy Framework (NBS NPF) provides context for its advice, but noted that a detailed appraisal of the full scope of considerations relevant to the NBS NPF criteria, such as a detailed appraisal of all relevant implementation considerations, is 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 (1737 PSD, p3).

## 6. Proposal for public funding

The proposal was for SCD to be added to the list of conditions screened for through Australia's NBS programs. If SCD 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.

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, using a different test. Only samples found to have abnormal results in first-tier testing undergo second-tier testing. Each NBS laboratory may choose which combination of test methods to use for first- and second-tier testing. Screening test methods assessed in DCAR 1737 and this FFP overview included:

- isoelectric focusing (IEF);
- high-performance liquid chromatography (HPLC);
- capillary zone electrophoresis (CE);
- mass spectrometry (either Electrospray Ionisation 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.

The method used for first-tier testing in this FFP overview was ESI-MS/MS, based on expert advice received during development of the overview that it would be the most appropriate method in the majority of Australian NBS laboratories. While other methods may have acceptable analytical validity, they were not explored in sensitivity analyses for this assessment as MSAC previously "*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  $\beta$ -thalassaemia*" (1737 PSD, pg 7), and no updated lower costings were available for other methods.

Cascade testing is likely to be performed by genetic testing for the familial variants. The cost of cascade testing is not covered by NBS funding. Cascade testing of family members already occurs when a person is diagnosed, hence, it is not a new service. No new data on cascade testing were identified for this FFP overview.

## 7. Population

The population under consideration in this assessment is newborns participating in newborn screening in Australia.

Sickle cell disease is an inherited disorder that affects the structure of haemoglobin. Haemoglobin (Hb), which is essential for oxygen transportation, is a protein normally constructed of two alpha and two beta chains (HbA).

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 such as HbS combined with HbC (HbSC), or a  $\beta$ -thalassaemia variant (HbS $\beta$ -thalassaemia). 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<sup>5</sup>.

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)”<sup>6</sup>.

Stroke, silent cerebral infarcts (silent strokes), and cognitive morbidity are the most common permanent sequelae of SCD in children and adults. 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, timely and appropriate red blood cell transfusion (within 2 hours of presentation to medical care) should be provided<sup>7</sup>.

Hydroxyurea (HU) treatment at the maximum tolerated dose can be considered to substitute for regular blood transfusions for children with SCD (ages 2-16 years) and abnormal TCD results who have been receiving transfusion therapy for at least 1 year. This approach is based on the clinical trial risk stratification with an MRI and magnetic resonance angiography (MRA) of the brain (conditional recommendation based on low certainty in the evidence about effects). A liquid formulation of HU for paediatric use is not approved by the Therapeutic Goods Administration (TGA) for the prophylactic treatment of SCD; however patients may obtain this product through the Authorised Prescriber scheme. HU is not reimbursed through the Pharmaceutical Benefits Scheme. HU is recommended for prevention of stroke and acute chest syndrome (ACS) by Australian clinical haematology groups<sup>8</sup>.

In the general population, young children have a higher risk of severe pneumococcal infection, with pneumococcal vaccination being included in the routine vaccination schedule<sup>9</sup>. Individuals

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<sup>5</sup> Genetic Science Learning Centre, Hemoglobin Disorders, University of Utah, viewed 30th September 2022, <<https://learn.genetics.utah.edu/content/genetics/hemoglobin>>.

<sup>6</sup> Chou, ST, et al. (2020), 'American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support', *Blood Adv*, vol. 4, no. 2, pp. 327-355. DOI 10.1182/bloodadvances.2019001143.

<sup>7</sup> DeBaun, et al (2020), 'American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults', *Blood Adv*, vol. 4, no. 8, pp. 1554-1588. DOI 10.1182/bloodadvances.2019001142.

<sup>8</sup> ASCA 2021, *Hydroxyurea in Treating Sickle Cell Disease*, Victoria, Australia.

Greenway A *Sickle Cell Anaemia*, The Royal Children's Hospital, Melbourne, University of Melbourne.

<sup>9</sup> National Immunisation Schedule: <https://www.health.gov.au/sites/default/files/2023-03/national-immunisation-program-schedule.pdf>

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.

The target population for screening is all newborns born in Australia who participate in universal newborn bloodspot screening programs. Included in the target population are infants at high risk of having SCD (including the homozygous HbSS form, heterozygous HbSC form, or HbS $\beta$ -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 cell crises. 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 receive prophylactic penicillin and additional pneumococcal vaccinations when diagnosed early, that have the potential 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, early parental education for identification of signs of splenic sequestration, 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.

### **Estimation of the incidence of SCD**

In the absence of reliable data for the incidence of SCD, one method of estimating the incidence within Australia was to use data from the countries of origin where there is a high prevalence of SCD and consider the rate of immigration to Australia from those sources (Nelson et al). A meta-analysis of studies on the incidence of SCD (either HbSS, HbSC, or HbS $\beta$ -thalassaemia) found that in people from Sub-Saharan Africa, there were 1125.49 cases of SCD per 100,000 live births (95% CI 680.43, 1570.5)<sup>10</sup>. Although a similar approach could be used for people from India, where the incidence in the meta-analysis was found to be 447.90 (95%CI 111.69, 783.91) per 100,000 live births, these data are unlikely to be representative of immigrants who enter Australia. For people who migrate to Australia for non-humanitarian reasons, the pre-arrival screening process includes a full blood examination/film, which has the potential to detect cases and carriers of SCD. Sickle cell anaemia is on the list of conditions deemed to impose significant costs and/or demands, which means that a visa will not be granted, unless a health waiver is given<sup>11</sup>.

Data from Sub-Saharan Africa were therefore extrapolated. The HbR data as a whole reported that 77.6% of paediatric cases have a self-reported ancestry from Sub-Saharan Africa (Nelson et al., 2023). If the assumption is made that the distribution of ancestry of cases remains stable when restricting to cases born in Australia, then it could be assumed that 82 cases per year represents 77.6% of SCD cases, which would equate to a total of 106 cases per year, or an incidence of 34.2 per 100,000 (Table 2). This is a highly uncertain assumption, as patterns of migration (and the reasons for migration) can differ largely over time.

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<sup>10</sup> Wastnedge E, et al. (2018) The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. *J Glob Health*. 2018 Dec;8(2):021103. DOI: 10.7189/jogh.08.021103.

<sup>11</sup> Joint Standing Committee on Migration (2009). 'Inquiry into immigration treatment of disability'. Submission from the Department of Immigration & Citizenship. Canberra. [https://aphref.aph.gov.au/\\_house\\_committee\\_mig\\_disability\\_subs\\_sub066](https://aphref.aph.gov.au/_house_committee_mig_disability_subs_sub066) accessed 19/10/23.

**Table 2 Estimated SCD incidence**

	Total births in 2021 <sup>1</sup>	Estimated no. with SCD
Mother from Sub-Saharan African	6,933	82 (95%CI 50, 115) <sup>2</sup>
Father from Sub-Saharan African	7,322	
Australia	309,996	106 <sup>3</sup> Incidence of 34.2 per 100,000

<sup>1</sup>Australian Bureau of Statistics, Births, Australia 2021

<sup>2</sup>Based on the incidence of SCD reported by Wastnedge et al. (2018) and the no. of births in Australia to a father born from a region at high risk of SCD

<sup>3</sup>Assuming that the SCD cases from Sub-Saharan African background constitutes 77.6% of cases reported by Nelson et al. (2023)

## 8. Comparator

The comparator is current practice in Australia, which is a combination of:

- targeted testing of newborns at high risk (where available); and
- no screening (for those at general risk, or where the high risk status is missed by the healthcare provider or testing not available).

Neonates are considered to be at high risk of inheriting SCD if they have parents of indigenous African origin, or from a country with high SCD prevalence, or if at least one parent has SCD. Australian clinical practice guidelines recommend targeted preconception and/or prenatal testing of potential parents and fetuses at risk for haemoglobinopathies respectively. Preconception and prenatal testing would not be replaced by NBS and are not considered part of the intervention nor the comparator. Targeted neonatal testing on cord blood currently takes place in Western Australia and would be replaced by NBS if implemented.

In the absence of prenatal or neonatal testing, individuals who have SCD would only be investigated after presenting with clinical symptoms (i.e. part of the comparator is clinical diagnosis). As an example, the investigations may consist of HPLC and CE (using MBS items 65078 and 65081), followed by genetic testing.

## 9. Summary of public consultation input

Please refer to the 1737 PSD (pg 12-13).

## 10. Characteristics of the evidence base

Additional evidence for the FFP overview was provided by the Australian Haemoglobinopathy Registry (HbR). Analyses of HbR data were provided for the subset of patients born in Australia and diagnosed with SCD who could be categorised into diagnosis before symptoms vs at or after symptom onset (n = 109). The data from the registry were observational, not comprehensive and were subject to selection bias as the registry is not comprehensive (although it is unknown in what direction the bias would influence the results). Those who were diagnosed at or after symptom onset were not only diagnosed at a later age than those identified from targeted testing, but are also currently older on average (15.0 years vs 12.1 years). This may suggest an improvement in the rate of targeted testing over time, and possible confounding between the groups as the management of SCD used at the time when the participants were first born or were

diagnosed may have differed. It is unknown if there were systematic differences between those diagnosed early vs later that may have biased the results. Some of the results may be biased (favouring targeted testing) as the outcome measures relate to whether the individuals have ever experienced certain outcomes (e.g. history of sepsis, history of splenectomy etc), and the difference in age between the groups means those in the late diagnosis group have had a longer time period to experience the events. It is also unknown why such a high proportion of patients were missed by targeted screening, and whether there were any confounding factors which may also influence health outcomes. The size of the registry cohort was also small (n=109), which may be a consequence of the rarity of SCD and/or the registry not being comprehensive. All this being noted, the HbR data represent the best currently available dataset on current practice, and the differences in management and health outcomes between those diagnosed early and late in Australia.

The evidence included in DCAR 1737 was derived from systematic review (SR) of the peer reviewed literature identified in PubMed and Embase databases. A large body of direct evidence assessing NBS for SCD was identified. A 2016 HTA with broad study inclusion criteria formed the basis of direct evidence, with later published evidence included from the SR<sup>12</sup>. 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 did 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. 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 24 diagnostic accuracy studies conducted on dried blood spots, the majority were rated high risk of bias, and only two rated low risk of bias, due to the absence of verification bias. Once again, many of the studies were conducted in settings of high SCD prevalence and therefore had reduced applicability to Australia.

A rapid review conducted by Abt Associates for Application 1737 provided an additional source of studies<sup>13</sup>.

The key features of the direct evidence are summarised in Table 3 and for linked evidence in Table 4.

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<sup>12</sup> IHE 2016, Newborn blood spot screening for galactosemia, tyrosinemia type I, homocystinuria, sickle cell anemia, sickle cell/beta-thalassemia, sickle cell/hemoglobin C disease, and severe combined immunodeficiency, Edmonton (AB), Institute of Health Economics, Canada.

<sup>13</sup> Abt Associates 2022, A Rapid review of the Newborn Blood Screening in Sickle Cell Disease and b-thalassemia.

**Table 3 Key features of the included direct evidence**

References	k n	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>NBS for haemoglobinopathies vs no screening</b>						
(IHE 2016) <sup>14</sup>	k=5 n=NR	Retrospective cohort Up to 15 years	<i>Low to high</i>	Newborns participating in NBS	Mortality Diagnostic accuracy	No
(Le et al. 2018) <sup>15</sup>	n=260	Retrospective cohort	<i>Low</i>	SCD patient register (diagnosis by NBS)	Time to diagnosis from first event 15-year survival from diagnosis Likelihood of severe events	No

k = number of studies; n = number of participants; NBS = newborn bloodspot screening; NR = not reported; SCD = sickle cell disease;

**Table 4 Key features of the included linked evidence**

Criterion	Type of evidence supplied	Extent of evidence supplied		Overall risk of bias in evidence base
Accuracy and performance of the SCD screening	Cohorts and case series	☒	k=24 n= 3,751,356	High
Change in management	Registry	☒	k=1 n=108	High
Health outcomes	Systematic review and registry data	☒	k=6 n=1,040	Moderate

k = number of studies; n = number of participants; SCD = sickle cell disease

## 11. Comparative safety

### *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 universal NBS, and adding haemoglobinopathies to the universal NBS schedule should 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 received by newborns diagnosed early by NBS that are over and above those received by babies diagnosed at a later age (but noting the harms associated from SCD complications due to non-receipt of guideline recommended prophylaxis are likely to be greater than from the prophylactic interventions themselves).

<sup>14</sup> IHE 2016, Newborn blood spot screening for galactosemia, tyrosinemia type I, homocystinuria, sickle cell anemia, sickle cell/beta-thalassemia, sickle cell/hemoglobin C disease, and severe combined immunodeficiency, Edmonton (AB), Institute of Health Economics, Canada.

<sup>15</sup> Le, PQ, et al. (2018), 'Neonatal screening improves sickle cell disease clinical outcome in Belgium', *J Med Screen*, vol. 25(2), 01 Jun, pp. 57-63. DOI: 10.1177/0969141317701166

## 12. Comparative effectiveness

### **Direct evidence**

No new direct evidence data were identified for this FFP overview. For a summary of the direct evidence, please refer to the 1737 PSD (pg 16-20).

### **Linked evidence**

#### Performance of current testing strategies

New data from the HbR indicated that only 47.7% of SCD cases are currently diagnosed prior to symptom onset. Those identified through targeted testing were diagnosed at a median age of 0.2 years (interquartile range, IQR = 0.0, 0.5 years) or 2.4 months, whereas those diagnosed after symptom onset were diagnosed at a median of 1.3 years (IQR = 0.8, 3.0) or 15.6 months. This median age of 15.6 months for symptomatic diagnosis was an increase from the 9.6 months used in the 1737 DCAR. These data were derived from SCD cases born in Australia, either children or adults, and may not be comprehensive. The median current age of the cases included was 15.0 years (IQR 7.6, 25.0) for those diagnosed at or after symptom onset, and 12.1 years (IQR 7.1, 15.2) for those diagnosed through targeted testing. It is unclear the degree to which clinical practice, or the rate of targeted testing has changed since this cohort was born (given some participants were older than 25 years of age, and older cases may have been diagnosed after symptom onset rather than by targeted testing).

#### Performance of NBS for SCD

No new data on the accuracy of screening for SCD were collated for this FFP overview. From DCAR 1737, the evidence suggests that NBS for SCD is likely to detect 100% of cases, with only a very small number of “false positives” (due to other haemoglobin abnormalities being detected).

Five studies were identified that provided an estimate of the sensitivity and specificity of first-tier SCD screening. Three studies could report only presumptive sensitivity and specificity as not all babies were given second tier testing (the absence of false negatives was presumed by the lack of children being diagnosed upon symptom onset at a later date). For SCD diagnosis overall, sensitivity was 100%, and specificity ranged from >99% to 100% across the studies (Table 5). 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 three out of five studies having verification bias.

**Table 5 Studies reporting the sensitivity and specificity of NBS for SCD**

Study Population (n)	1 <sup>st</sup> tier screen 1 <sup>st</sup> tier results	2 <sup>nd</sup> tier screen 2 <sup>nd</sup> tier results	Sensitivity	Specificity	PPV / NPV <sup>a</sup>
(Frommel et al. 2014) <sup>16</sup> Germany N=34,084 newborns	<b>HPLC</b>	<b>CE</b> If +ve: genetic analysis	100% (presumptive) <sup>a</sup>	100% (presumptive) <sup>a</sup>	100% / 100%
	14 SCD +ve 34,070 SCD -ve (including 236 heterozygous for Hb variants)	CE: 14 SCD +ve Genetic: 13 SCD +ve 1 SCD/ $\beta$ -thalassaemia No -ve babies known to have SCD.			
(Campbell, Henthorn & Davies 1999) <sup>17</sup> UK N=25,750 newborns	<b>HPLC (on SCD program)</b>	<b>IEF</b> (Babies without HbA or with variant other than HbS or HbC were recalled for retesting at 6 weeks)	SCD or HbS/HbC carrier 100%	SCD or HbS/HbC carrier 100%	100% / 100%
	32 SCD +ve	32 SCD +ve			
(Garcia-Morin et al. 2020) <sup>18</sup> Spain N=1,048,222 newborns	<b>HPLC</b>	<b>HPLC after 2-3 months</b>	100% (presumptive) <sup>a</sup>	99.99% (presumptive) <sup>a</sup>	96.9% / 100%
	197 possible SCD +ve	187 SCD +ve 10 false +ve (9 carriers, 1 benign condition)			
(Lobitz et al. 2019) <sup>19</sup> Germany N=29,079 newborns	<b>ESI-MS/MS</b>	<b>CE (on all)</b> <b>Genetic testing</b> (those with suspected disease)	100%	100%	100% / 100%
	7 suspected SCD +ve	7 SCD +ve			
(Streetly et al. 2018) <sup>20</sup> UK N= approximately 3.25 million newborns	<b>Unspecified (HPLC, CE, MS or IEF)</b>	<b>Alternative procedure</b> using a different principle	100% (presumptive) <sup>a</sup>	>99% (presumptive) <sup>a</sup>	98.0% / 100%
	1,447 SCD +ve	1,427 SCD +ve 20 false +ve (abnormal findings but clinically insignificant)			

CE = capillary electrophoresis; DNA = deoxyribonucleic acid; Hb = haemoglobin; HbA = adult haemoglobin; HbC = haemoglobin C; HbS = sickle haemoglobin; HPLC = high performance liquid chromatography; IEF = isoelectric focusing; ESI-MS/MS = Electrospray ionization tandem mass spectrometry; NBS = newborn bloodspot screening; PPV = positive predictive value; S $\beta$  = sickle beta-thalassaemia; SCD = sickle cell disease; SCT = sickle cell trait

a. long term follow-up has not detected any additional cases; PPV and NPV calculated for the Australian setting using a prevalence of 0.03%.

<sup>16</sup> Frömmel, C et al. (2018), 'Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies: A Short Review on Classical Laboratory Methods-Isoelectric Focusing, HPLC, and Capillary Electrophoresis', *Int J Neonatal Screen*, vol. 4, no. 4, Dec, p. 39. doi:10.3390/ijns4040039

<sup>17</sup> Campbell, M, et al (1999), 'Evaluation of cation-exchange HPLC compared with isoelectric focusing for neonatal hemoglobinopathy screening', *Clin Chem*, vol. 45, no. 7, Jul, pp. 969-975.

<sup>18</sup> Garcia-Morin, et al. (2020), 'Fifteen years of newborn sickle cell disease screening in Madrid, Spain: an emerging disease in a European country', *Ann Hematol*, vol. 99(7), 01 Jul, pp. 1465-1474. <https://dx.doi.org/10.1007/s00277-020-04044-z>

<sup>19</sup> Lobitz, S, et al. (2019), 'Newborn screening by tandem mass spectrometry confirms the high prevalence of sickle cell disease among German newborns', *Ann Hematol*, vol. 98(1), 30 Jan, pp. 47-53. <https://dx.doi.org/10.1007/s00277-018-3477-4>

<sup>20</sup> Streetly, et al. (2018), 'Evaluation of newborn sickle cell screening programme in England: 2010-2016', *Arch Dis Child* vol. 103(7), 01 Jul, pp. 648-653. <https://dx.doi.org/10.1136/archdischild-2017-313213>



## Change in management

The key change in management that would be expected from universal NBS for SCD 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.

The DCAR 1737 did not identify any studies additional to direct evidence studies that examined the timeliness of investigations/treatment initiation based on diagnosis. One explanation for this is that NBS screening for SCD and thalassemia 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.

In the absence of good quality evidence comparing the management strategies following NBS versus no NBS, observational data from the HbR were reported. These data did not include any patients diagnosed through universal NBS but showed the difference in the types of management required when patients are diagnosed early through targeted testing, versus late diagnosis (at the point of symptoms). The HbR data suggested that those who were diagnosed early (with diagnosis at median of 2 months old and prior to symptom onset) were more likely to receive prophylactic antibiotics and were more likely to have a transcranial Doppler performed to predict the risk of stroke, than those diagnosed at or after symptom onset (with diagnosis at median 1.3 years). The differences in the management were statistically significant between patients diagnosed early versus late, although this was not a comparison between the intervention and the comparator.

**Table 6 Differences in management of SCD in patients diagnosed early (targeted testing) vs late (at symptom onset)**

Change in management	Diagnosed at or after symptom onset (n=57)	Diagnosed before symptom onset (n=51)	p-value
Prophylactic antibiotics	27/57 (47.4%)	34/51 (66.7%)	0.043
Hydroxyurea	34/57 (59.7%)	28/51 (54.9%)	0.62
Transcranial Doppler performed	31/55 (56.4%)	43/51 (84.3%)	0.002
Brain MRI performed	20/56 (35.7%)	14/51 (27.5%)	0.36
Age at first transfusion, years, median (IQR)	5.0 (2.0, 7.0)	5.0 (3.0, 7.0)	0.67

IQR = interquartile range; MRI = magnetic resonance imaging; SCD = sickle cell disease

Source: Australian Haemoglobinopathy Registry data

## Effectiveness of change in management

The most directly applicable evidence assessing the health impact of early versus late diagnosis came from the HbR. The HbR data compared the outcomes for those who were diagnosed at or after symptom onset, versus those diagnosed prior to symptom onset. The rates of complications were higher in the group diagnosed later, for nearly all outcomes, although the differences were too small to be statistically different. A statistically significantly higher proportion of patients in the late diagnosis group had a history of sepsis and cholecystectomy than the group diagnosed early, although this was not a comparison between the intervention and the comparator. There was also a non-significant trend towards a higher proportion of the late-diagnosed patients having had a splenectomy (compared to those diagnosed early by targeted testing).

Over a 12-month period, patients diagnosed at or after symptom onset had an average of 1.18 SCD-related presentations to the emergency department (ED), whereas those diagnosed early through targeted testing, had on average 0.41 SCD-related ED presentations each year. Nearly every instance of ED presentation was followed by hospital admission.

**Table 7 Complications due to SCD in those diagnosed after symptom onset or due to targeted testing**

<b>Complications in past 12 months</b>	<b>Diagnosed at or after symptom onset (n=57)</b>	<b>Diagnosed before symptom onset (n=51)</b>	<b>p-value</b>
Vaso-occlusive crisis	49/57 (86.0%)	40/51 (78.4%)	0.30
Splenic sequestration	13/57 (22.8%)	11/51 (21.6%)	0.88
Aplastic crisis	4/57 (7.0%)	3/51 (5.9%)	0.81
Stroke – silent	1/57 (1.8%)	0/51 (0.0%)	0.34
Stroke – overt, clinical	0/57 (0.0%)	0/51 (0.0%)	-
Neurocognitive impairment	3/57 (5.3%)	3/51 (5.88%)	0.89
<b>Medical history</b>	<b>Diagnosed at or after symptom onset (n=57)</b>	<b>Diagnosed before symptom onset (n=52)</b>	<b>p-value</b>
History of sepsis	17/54 (31.48%)	2/49 (4.08%)	<0.001
History of dactylitis	12/47 (25.53%)	7/47 (14.89%)	0.20
History of splenectomy	15/57 (26.32%)	7/50 (14.00%)	0.12
History of cholecystectomy	14/57 (24.56%)	4/50 (8.00%)	0.022
Bone marrow/ peripheral blood stem	2/57 (3.51%)	1.51 (1.96%)	0.63
<b>Estimated SCD-related presentations to ED in past 12 months</b>	<b>Diagnosed at or after symptom onset (n=57)</b>	<b>Diagnosed before symptom onset (n=51)</b>	<b>p-value</b>
0	27/57 (47.4%)	32/51 (62.8%)	0.009
1	12/57 (21.1%)	17/51 (33.3%)	
2	5/57 (8.8%)	2/51 (3.9%)	
3	8/57 (14.0%)	0/51 (0.0%)	
4	4/57 (7.0%)	0/51 (0.0%)	
5+	1/57 (1.8%)	0/51 (0.0%)	
<b>ED presentation not related to SCD</b>	9/30 (30.00%)	5/19 (26.3%)	0.78
<b>Estimated admissions to hospital in past 12 months (excluding planned transfusions)</b>	<b>Diagnosed at or after symptom onset (n=57)</b>	<b>Diagnosed before symptom onset (n=51)</b>	<b>p-value</b>
0	26/57 (45.6%)	35/51 (68.6%)	<0.001
1	10/57 (17.5%)	15/51 (29.4%)	
2	12/57 (21.1%)	1/51 (2.0%)	
3	6/57 (10.5%)	0/51 (0.0%)	
4	3/57 (5.3%)	0/51 (0.0%)	
Other acute complication(s)	9/30 (30.00%)	5/19 (26.3%)	0.78

ED = emergency department; SCD = sickle cell disease

Source: Australian Haemoglobinopathy Registry data

The HbR data do not compare the intervention against the comparator, although supplement the evidence that was used in DCAR 1737 to establish the effectiveness of the management and treatment strategies for babies diagnosed early by NBS. The DCAR's evidence came from a 2016

SR that 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 8.

**Table 8 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)<sup>21</sup>**

Total N	Antibiotic prophylaxis	Placebo/ no prophylaxis	Difference <sup>a</sup>
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 <sup>2</sup> =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

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<sup>22</sup>. 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; I<sup>2</sup> = 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 of 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

<sup>21</sup> Meremikwu, MM et al. 2016, 'Sickle cell disease', *BMJ Clin Evid*, 1-24.

<sup>22</sup> 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](#)

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.

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 9.

**Table 9 Summary of treatment outcomes for hydroxyurea compared with placebo for children with SCD in the BABY HUG trial (Meremikwu et al. 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

Overall there are very few safety concerns, and significant effectiveness associated with guideline-directed treatments for young children with SCD. HU was effective in reducing morbidity in children with SCD, 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.

The evidence therefore demonstrated that when cases of SCD are detected early, preventative strategies are available that improve health outcomes for those affected, compared to starting treatment at a later time-point.

## Clinical utility summary

There were no prevalence or incidence data for haemoglobinopathies in Australia. Two methods of estimating the incidence were provided in DCAR 1737, based on laboratory input and data from Argent et al. 2012<sup>23</sup>). An additional estimate was calculated in this FFP overview, based on the birth prevalence of SCD within Sub-Saharan-Africa, the proportion of births in Australia to parents from Sub-Saharan-Africa, and the proportion of SCD cases on the HbR with Sub-Saharan-African ancestry (see Section 5 for more information). This provided a much higher estimate than those used in DCAR 1737 (34.2/100,000 rather than 0.53 or 8.6/100,000). However, uncertainty remained about the incidence of SCD in Australia.

Data from the HbR suggested that the current targeted testing approach in Australia only identifies 47.7% of cases of SCD, which was lower than estimated in DCAR 1737 (64% to 99%<sup>24</sup>). These changes suggested that the current targeted testing approach may result in 51 cases of SCD per year being diagnosed prior to symptom onset. With the proposed addition of SCD to NBS, it is estimated that 106 cases per year would be identified (with an additional 55 being identified soon after birth, rather than at or after the development of symptoms). The new estimates are provided in the unshaded cells in Table 10.

**Table 10 Incremental early diagnosis of SCD per year (based on 310,922 newborns expected to undergo NBS in 2023-24)<sup>a</sup>**

Estimated incidence	Diagnosed by NBS per year	Diagnosed by targeted testing			Incremental early diagnosis from NBS		
		47.7% <sup>b</sup>	64% <sup>c</sup>	99% <sup>d</sup>	52.3% <sup>b</sup>	36% <sup>c</sup>	1% <sup>d</sup>
0.53/100,000 <sup>e</sup>	2	1	1	2	1	1	0
8.6/100,000 <sup>f</sup>	27	13	17	27	14	10	0
34.2/100,000 <sup>g</sup>	106	51	68	105	55	38	1

NBS = newborn bloodspot screening

Notes: a. figures are rounded to whole numbers. Shaded cells use the incidence estimates and estimates of the proportion identified by targeted testing as presented in DCAR 1737. Unshaded cells are new data.

b. Source: HbR Brief report for MSAC (2023) (47.7% of SCD cases identified prior to symptoms)

c. Source: (DHS 2002) (64% of cases identified as at pregnancy)<sup>25</sup>

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

e. Source: (Argent et al. 2012)

f. Source: Based on data from PathWest

g. Source: Estimated using data from Wastnedge et al. (2018), Australian Bureau of Statistics (2022), and HbR (2023)

Early symptoms occurring prior to diagnosis in those missed by targeted testing could be severe, such as a vaso-occlusive crisis (VOC) leading to stroke or splenic sequestration, or death. HbR

<sup>23</sup> Argent E, et al. (2012), 'Australian Paediatric Surveillance Unit study of haemoglobinopathies in Australian children', *J Paediatr Child Health*, vol. 48, no. 4, Apr, pp. 356-360. doi: 10.1111/j.1440-1754.2011.02236.x

<sup>24</sup> Lower limit of range (64%) source: "Beyond the Crystal Ball – The Epidemiology of Some Genetic Conditions in Victoria, 2002". Department of Human Services, Victoria. <http://www.dhs.vic.gov.au/phd/genetics>  
Upper limit of range (99%) source: Clinical opinion from Monash Maternity Hospital (Meeting 21 Feb 2023 with DHA, clinical experts, and assessment group)

<sup>25</sup> DHS, V 2002, Beyond the Crystal Ball - The Epidemiology of Some Genetic Conditions in Victoria 2002, Rural and Regional Health and Aged Care Services Division, Victoria, <http://www.dhs.vic.gov.au/phd/genetics>

data showed that early diagnosis was associated with a higher proportion of patients receiving prophylactic antibiotics and having a transcranial Doppler performed to determine stroke risk (which can lead to intensification of treatment in those who require it). This reduces the likelihood of sepsis, VOC, and the requirement for surgical procedures such as splenectomy and cholecystectomy (removal of the spleen and gall bladder). Although the HbR data may be biased, due to the different age of patients with SCD in the group diagnosed early (median age 12, IQR 7.1, 15.2) versus late (median age 15, IQR 7.6, 25.0), the data suggested those in the targeted testing group had a 27.4% absolute risk reduction of having sepsis up to their most recent date of review.

HbR data comparing SCD cases diagnosed early vs late were used to construct a comparison of the intervention (universal NBS) against the comparator (no universal NBS). Using the incidence of 34.2 per 100,000, it was estimated that NBS would result in an additional 55 cases per year being diagnosed prior to symptom onset, which may result in:

- 15 cases of sepsis being avoided,
- 9 cholecystectomies being avoided,
- 7 splenectomies being avoided,
- 4 VOCs being avoided per year, and
- 42 SCD-related emergency department presentations avoided per year.

The calculations for the adverse events avoided are shown in Table 11 (varying by estimated incidence).

**Table 11 Estimated number of adverse events avoided due to universal NBS rather than 47.7% early diagnosis with targeted testing, per 310,922 newborns<sup>a</sup>**

Adverse event <sup>b</sup>	Early diagnosis	Late diagnosis	Absolute difference	No. of events avoided based on incremental early SCD diagnoses (varying by incidence per 100,000)		
				1 case (incidence 0.53)	14 cases (incidence 8.6)	55 cases (incidence 34.2)
Sepsis	4.08%	31.48%	27.40%	0	4	15
Cholecystectomy	8.00%	24.56%	16.56%	0	2	9
Splenectomy	14.00%	26.32%	12.32%	0	2	7
VOC per 12 months	78.4%	86.0%	7.6%	0	1	4
SCD-related ED presentations per 12 months	Mean 0.41	Mean 1.18	0.76	1	11	42

ED = emergency department; NBS = newborn bloodspot screening; SCD = sickle cell disease; VOC = vaso-occlusive crisis

Notes: a. figures are rounded to whole numbers

b. Source: HbR Brief report for MSAC (2023)

c. Source: (Argent et al. 2012)

d. Source: Based on data from PathWest

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

## Clinical claim

The clinical claim is that early diagnosis (due to universal NBS) and early intervention, education and genetic counselling are superior to late diagnosis (without universal NBS). There was no explicit claim regarding the comparative safety of adding SCD to the NBS programs.

The evidence supported the clinical claim that universal NBS for SCD has superior effectiveness compared to no universal NBS for SCD (targeted testing for those at high risk, and diagnosis upon symptom onset for those at general risk or those at high risk missed by targeted testing).

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

### 13. Economic evaluation

The economic analysis presented in the 1737 DCAR was a cost-effectiveness analysis (CEA) that reported the incremental cost for an additional early diagnosis of a clinically significant case. A cost-utility analysis (CUA) was unable to be presented due to insufficient evidence available to translate the incremental benefit of these changes into patient-relevant outcomes and quality-adjusted life years gained.

The additional data from the HbR may provide evidence of a change in management and improved health outcomes in an Australian dataset, noting the limitations of these data described in '10. Characteristics of the evidence base'. Given that the CEA presented in the 1737 DCAR cannot easily be extended to a CUA, the MSAC Executive considered that, under revised assumptions regarding the test cost, if the costing were sufficiently low then the financial cost of screening may not justify the cost of a second DCAR to conduct a CUA (MSAC Executive, 22 September 2023).

On this basis, the 1737 DCAR economic evaluation was updated to reflect the following changes:

- First-tier test method was changed to ESI-MS/MS, with a test cost of \$2.00 per screen (previously MALDI-TOF at a cost of \$10 per screen)
- The comparator reflected the secondary comparison presented previously (i.e. a mix of parental, prenatal, neonatal and no screening), however the proportion of cases identified through targeted testing activities was reduced to 47.7% based on HbR data (99% previously)
- Increased age with symptomatic diagnosis (15.6 months), based on HbR data (HbR Brief report for MSAC (2023)) (previously 9.6 months)
- Updated use and costs of additional treatment and monitoring associated with earlier diagnosis, based on unpublished data from the HbR.
- Alternate SCD incidence estimates applied (34.2 per 100,000, as per Table 2, previously 7.1 per 100,000)

Based on MSAC advice that information for its reconsideration could be provided for SCD alone (1737 PSD, p8),  $\beta$ -thalassemia cases and haemoglobinopathy carriers have been removed from the analysis as their inclusion affects interpretation of absolute costs and outcomes across model arms. Minor errors in the cost of SCD monitoring and prophylaxis in cases identified and missed through universal NBS were also corrected.

A stepped approach was used to generate the updated base case analysis, which incorporated the key changes separately to distinguish their respective effect on the results presented to MSAC in the 1737 DCAR previously.

A summary of the key components of the economic evaluation is presented in Table 12.

**Table 12 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	Targeted testing available (including parental, fetal and neonatal) along with symptomatic identification of disease in cases missed through targeted testing
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Additional early diagnosis of clinically significant cases
Time horizon	Age at diagnosis through symptomatic identification only (median 15.6 months)
Computational method	Decision tree analysis
Generation of the base case	Modelled stepped analysis, incorporating the key changes separately to distinguish the effect of each of these on the results.
Transition probabilities	Incidence of haemoglobinopathy: Derived assuming the birth prevalence of SCD in Sub-Saharan Africa, the number of births in Australia to people from Sub-Saharan Africa and the proportion of cases from the HbR from Sub-Saharan Africa (Table 2). Cases identified through current targeted testing: HbR data ('Performance of current testing strategies') Test performance: Performance of first-tier screening (100%) 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	5% per annum
Software	Excel

Note: Shaded cells depict those elements that are unchanged from the previous DCAR.

HbR = Australian Haemoglobinopathy Registry; NBS = newborn bloodspot screening; SCD = sickle cell disease

An expert consulted during preparation of the assessment advised that ESI-MS/MS would be the most appropriate test method to assume for first-tier screening of SCD in Australia, however that the cost per screen would vary depending on whether the respective laboratories do or do not have the current capacity (in terms of instrumentation and staff) to incorporate additional testing. Where there is capacity, the expert advised that test costs would be up to \$2 per newborn screened, including instrument amortisation and staff time.

In the instance where laboratories do not have the capacity, the expert advised additional costs of instrumentation, maintenance and staff would need to be considered. This would result in a variable cost per first tier ESI-MS/MS test based on the number of tests performed at each site per year. For a laboratory operating 100,000 tests per year, the cost per test was estimated as \$4.30<sup>26</sup>. However where fewer tests were performed, the cost per test was estimated to be higher (e.g. \$13.50<sup>27</sup> for a laboratory running 22,000 tests per year). Using this information, and projections of the number of births nationally in 2023 (estimated in the 1737 DCAR, Figure 12B), a weighted average (\$7.09) and median (\$8.23) cost were estimated ('Approach 1', Table 13) to account for the number of tests performed per site, assuming no labs have the current capacity to accommodate SCD screening. Alternate estimates based on population projections published by the ABS have also been estimated ('Approach 2', Table 13) (noting that, as per DCAR 1737,

<sup>26</sup> Cost per test for the instrument (amortised over 5 years) \$0.60, plus \$1.20 for staff, \$2.00 for the test and \$0.50 for comms

<sup>27</sup> Cost per test for the instrument (amortised over 5 years) \$3.00, plus \$6.00 for staff, \$2.00 for the test and \$2.50 for comms



the currently available ABS population projections are substantially higher than the number of registered births observed).

**Table 13 Estimated cost per first tier ESI-MS/MS test assuming sites require additional instrumentation and staff**

Screening Laboratory	No. screened per site (%)	Change in newborns screened <sup>a</sup>	Estimated reduction in cost <sup>b</sup>	Cost per test
Approach 1: Proportions of newborns screened per site, based on ABS registered births by state or territory of registration 2022 <sup>c</sup> , applied to national projections of the registered births per year, 2023, estimated in DCAR 1737 (Figure 12B)				
NSW (screens newborns in ACT and NSW)	106,279 (34.0%)	383.1%	73.6%	\$3.56
VIC (screens newborns in VIC)	79,280 (25.3%)	260.4%	50.0%	\$6.74
SA (screens newborns in SA, TAS and half of those from NT)	27,876 (8.9%)	26.7%	5.1%	\$12.81
QLD (screens QLD and half of those from NT)	66,704 (21.3%)	203.2%	39.1%	\$8.23
WA (screens newborns in WA)	32,752 (10.5%)	48.9%	9.4%	\$12.23
Median no. samples tested	66,704	203.2%	39.1%	\$8.23
Weighted average				\$7.09
Approach 2: ABS population projections (Series B) of persons in Australia, age 0, in 2023 <sup>d</sup>				
NSW (screens newborns in ACT and NSW)	121,224 (34.3%)	451.0%	86.7%	\$2.00
VIC (screens newborns in VIC)	94,567 (26.8%)	329.9%	63.4%	\$4.94
SA (screens newborns in SA, TAS and half of those from NT)	28,956 (8.2%)	31.6%	6.1%	\$12.68
QLD (screens QLD and half of those from NT)	72,877 (20.6%)	231.3%	44.5%	\$7.50
WA (screens newborns in WA)	35,801 (10.1%)	62.7%	12.1%	\$11.87
Median no. samples tested	72,877	231.3%	44.5%	\$7.50
Weighted average				\$5.80

Note: Based on the information provided by the expert consulted, with an increase in the no. of newborns screened of 354.5% (from 22,000 to 100,000), the cost per test reduced by 68.1% (from \$13.50 to \$4.30). The cost per test was assumed to have a minimum cost of \$2.00 (no lower than the cost per test assuming laboratories have current capacity to test).

<sup>a</sup> Relative to 22,000

<sup>b</sup> Relative to \$13.50. Calculated as the change in newborns screened / 354.5% × 68.1%

<sup>c</sup> Australian Bureau of Statistics [ABS] 2023, Births, Australia. Commonwealth of Australia, Canberra, viewed 30 October 2023. Available from: <https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>.

<sup>d</sup> Australian Bureau of Statistics [ABS] (2018) Population Projections by Region, 2017-2066, age 0 [Data Explorer], accessed 30 October 2023. Available from:

[https://explore.data.abs.gov.au/vis?fs\[0\]=People%2C0%7Cpopulation%23POPULATION%23&pg=20&fc=People&df\[ds\]=PEOPLE\\_TOPI\\_CS&df\[id\]=POP\\_PROJ\\_REGION\\_2012\\_2061&df\[ag\]=ABS&df\[vs\]=1.0.0&pd=2022%2C2026&dq=8%2B7%2B6%2B5%2B4%2B3%2B2%2B1.3.0.2.2.2.2.A&ly\[cl\]=TIME\\_PERIOD&ly\[rw\]=REGION](https://explore.data.abs.gov.au/vis?fs[0]=People%2C0%7Cpopulation%23POPULATION%23&pg=20&fc=People&df[ds]=PEOPLE_TOPI_CS&df[id]=POP_PROJ_REGION_2012_2061&df[ag]=ABS&df[vs]=1.0.0&pd=2022%2C2026&dq=8%2B7%2B6%2B5%2B4%2B3%2B2%2B1.3.0.2.2.2.2.A&ly[cl]=TIME_PERIOD&ly[rw]=REGION)

The extent of current laboratory capacity to accommodate proposed SCD screening was unavailable for the assessment and will need to be determined by each laboratory. The base case estimates assumed an average test cost of \$2.00, given this reflected the incremental cost of introducing SCD screening (excluding any costs to increase capacity), however sensitivity analyses were presented assuming alternate costings that also account for additional instruments and staff.

The results of the stepped analysis to generate the updated base case economic evaluation are presented in Table 14. The resulting ICER was sensitive to most of the changes made (excluding minor model updates). Incidence of SCD, test cost and impact of targeted testing remained the key drivers of the analysis, as they were in the 1737 DCAR.

**Table 14 Results of the stepped economic analysis**

	Universal NBS	No Universal NBS	Increment
<b>ICER presented in 1737 DCAR</b>			
Step 6, Table 15 of the 1737 PSD, universal NBS identifies SCD only, compared to symptomatic presentation. Step 6 included the incorporation of targeted testing, screening performance, NBS uptake, cost of prophylactic treatments and monitoring, and the incorporation of cascade testing.			
Costs	\$10.35	\$0.33	\$10.02
Early diagnosis of affected cases	0.00007	0.00000	0.00007
<b>ICER</b>			<b>\$141,338</b>
<b>Step 1 – Minor model updates</b>			
Based on MSAC advice that information could be provided for SCD alone, $\beta$ -thalassaemia cases and haemoglobinopathy carriers were removed from the analysis. Minor errors in the cost of SCD monitoring and prophylaxis in cases identified and missed through universal NBS were also corrected.			
The average age at symptomatic diagnosis was updated (from 8.4 months to 15.6 months) based on data from the HbR in Australian-born SCD patients included in the registry. This increased the duration of additional treatments (prophylactic antibiotics and hydroxyurea) and ongoing disease management resources in the additional patients diagnosed with SCD before symptom development through universal NBS. Some costs were updated or added based on unpublished data from the HbR. <sup>a</sup>			
Costs	\$10.12	\$0.07	\$10.05
Early diagnosis of affected cases	0.00007	0.00000	0.00007
<b>ICER</b>			<b>\$141,707</b>
<b>Step 2 – Updated test method and cost.</b>			
The test method was updated from MALDI-TOF to ESI-MS/MS based on expert consultation. The cost per test was also reduced from \$10.00 per screen to \$2.00. As performance of testing is unchanged in this step (100% sensitivity, 99.99% specificity), only the incremental costs change.			
Costs	\$2.18	\$0.07	\$2.11
Early diagnosis of affected cases	0.00007	0.00000	0.00007
<b>ICER</b>			<b>\$29,707</b>
<b>Step 3 – Incorporate targeted testing</b>			
The impact of targeted testing (including parental, prenatal and neonatal testing) was included. Data from the HbR reported that of Australian-born SCD patients included in the registry, 52/109 (47.7%) were diagnosed before development of symptoms, and so this was used to inform the proportion identified through current targeted testing processes. A slight reduction in the absolute cost following universal NBS was observed due to targeted testing reducing the number of second tier and cascade tests assumed.			
Costs	\$2.17	\$0.13	\$2.04
Early diagnosis of affected cases	0.00007	0.00003	0.00004
<b>ICER</b>			<b>\$54,980</b>
<b>Step 4 – Update SCD incidence</b>			
Incidence was increased from 7.1 per 100,000 (Pathwest: 2.5/35,000) to 34.2 per 100,000 based on the birth prevalence of SCD in Sub-Saharan Africa, the number of births in Australia to people from Sub-Saharan Africa and the proportion of cases from the HbR from Sub-Saharan Africa.			
Costs	\$2.69	\$0.50	\$2.18
Early diagnosis of affected cases	0.00034	0.00016	0.00018
<b>ICER</b>			<b>\$12,280</b>

ESI-MS/MS = Electrospray Ionization tandem mass spectrometry; HbR = Australian Haemoglobinopathy Registry; ICER = incremental cost-effectiveness ratio; MALDI-TOF = Matrix Assisted Laser Desorption/Ionization time-of-flight mass spectrometry; SCD = sickle cell disease.

<sup>a</sup> Annual cost and uptake of antibiotic prophylaxis were updated, hydroxyurea cost was added and additional monitoring (vitamin D and abdominal ultrasound) was applied annually.

The key drivers of the model are presented in Table 15. The values chosen for each of these parameters were associated with considerable uncertainty, and the ICER was sensitive to changes in these estimates.

**Table 15 Key drivers of the model**

Description	Method/Value	Impact Base case: \$12,280 per additional case of SCD identified earlier
Incidence	The incidence of SCD modelled was 32.4 per 100,000. This was derived from the birth prevalence of SCD in Sub-Saharan-Africa, the number of births in Australia to people from Sub-Saharan Africa and the proportion of cases in the HbR from Sub-Saharan Africa (Table 2). The applicability of this estimate was uncertain as patterns of migration (and the reasons for migration) can differ largely over time. For comparison birth prevalence through the UK NBS program was estimated to be 39 per 100,000 births <sup>a</sup> . Published data on incidence in Australia have limited applicability to the current setting due to their age. Contemporary estimates provided by PathWest suggested incidence in the range 5.7–8.6 per 100,000.	High, likely favours universal NBS. Reducing the incidence to 5.7 per 100,000 and 8.6 per 100,000 increased the ICER to \$68,643 and \$45,835, respectively.
Cases identified through current targeted testing	47.7% based on an analysis of Australian-born SCD patients in the HbR who had their diagnosis prior to development of symptoms (52/109). As described in 'Performance of current testing strategies', due to concerns regarding the comprehensiveness and age of the patients included in the HbR, these estimates are likely associated with a high degree of uncertainty. Expert advice provided during the preparation of DCAR 1737 suggested that most cases (95–99%) were identified through existing practices.	High, uncertain direction of bias. Reducing the proportion to 25%, reduced the ICER to \$8,867, whereas increasing it to 75% increased the ICER to \$24,587. Further increases to 95% increased the ICER to \$118,903.
Cost of first-tier screening	The base case assumed first-tier screening test cost of \$2.00, based on the incremental cost of introducing SCD screening using ESI-MS/MS, assuming costs of additional instrumentation and staff to expand NBS are not required/included. Figures were based on estimates provided by an expert consulted during the preparation of the assessment.	High, uncertain direction of bias. Assuming no laboratories currently have the capacity to accommodate SCD screening (average cost per screen of \$7.09) increased the ICER to \$40,257.

ESI-MS/MS = electrospray ionisation tandem mass spectrometry; HbR = Australian Haemoglobinopathy Registry; ICER = incremental cost-effectiveness ratio; SCD = sickle cell disease.

<sup>a</sup> Streatly, A, Sisodia, R, Dick, M, Latinovic, R, Hounsell, K & Dormandy, E 2018, 'Evaluation of newborn sickle cell screening programme in England: 2010-2016', Archives of disease in childhood, vol. 103(7), 01 Jul, pp. 648-653.

The results of key sensitivity analyses are presented in Table 16.

**Table 16 Results of key sensitivity analyses (ICERs in terms of cost per early diagnosis of an affected case)**

	Inc. cost	Inc. effect	ICER	% change
<b>Base-case</b>	<b>\$2.18</b>	<b>0.00018</b>	<b>\$12,280</b>	<b>-</b>
<b>Cost of ESI-MS/MS first-tier screening test (base case: \$2.00)</b>				
\$4.30	\$4.43	0.00018	\$24,922	103%
\$7.09	\$7.15	0.00018	\$40,257	228%
\$8.23	\$8.26	0.00018	\$46,523	279%
\$13.50	\$13.41	0.00018	\$75,490	515%
<b>SCD incidence (base case: 34.2 per 100,000)</b>				
0.53 per 100,000 births	\$2.00	0.00000	\$728,409	5832%
5.7 per 100,000 births	\$2.03	0.00003	\$68,643	459%
8.6 per 100,000 births	\$2.05	0.00004	\$45,835	273%
<b>Proportion of cases identified through targeted testing (base case: 47.7%)</b>				
0%	\$2.34	0.00034	\$6,902	-44%
25%	\$2.26	0.00025	\$8,867	-28%
65%	\$2.12	0.00012	\$17,850	45%
75%	\$2.09	0.00008	\$24,587	100%
85%	\$2.05	0.00005	\$40,306	228%
95%	\$2.02	0.00002	\$118,903	868%
99%	\$2.01	0.00000	\$590,488	4709%

ESI-MS/MS = Electrospray ionisation tandem mass spectrometry; ICER = incremental cost-effectiveness ratio; Inc. = incremental; SCD = sickle cell disease.

Multivariate analyses were conducted exploring the effect of varying both first-tier ESI-MS/MS test cost and SCD incidence (Figure 1).

**Figure 1 Multivariate analyses for the ICER per additional case of SCD identified earlier, varying first-tier ESI-MS/MS test cost and SCD incidence**

		Test cost						
		\$1.50	\$2.00	\$4.30	\$5.80	\$7.09	\$7.50	\$8.23
Incidence (per 100,000)	0.53	\$551,068	\$728,409	\$1,544,174	\$2,076,195	\$2,533,733	\$2,679,152	\$2,938,069
	5.7	\$52,153	\$68,643	\$144,495	\$193,963	\$236,506	\$250,028	\$274,103
	8.6	\$34,906	\$45,835	\$96,109	\$128,897	\$157,094	\$166,056	\$182,012
	34.2	\$9,532	\$12,280	\$24,922	\$33,167	\$40,257	\$42,511	\$46,523

ESI-MS/MS = electrospray ionisation tandem mass spectrometry; ICER = incremental cost-effectiveness ratio; SCD = sickle cell disease.

## 14. Financial/budgetary impacts

The approach to estimate the use and financial impact of expanding NBS programs to include haemoglobinopathies was updated from that presented in the 1737 DCAR. This included:

- Changing the base case test method (and cost) used for first-tier screening to ESI-MS/MS (assumed test cost of \$2.00)
- Restricting the analysis to the impact of identifying SCD (i.e. no second-tier screening in those with first-tier screens suggestive of  $\beta$ -thalassaemia)
- Increasing the incidence of SCD to 34.2 per 100,000 births

- Updating the financial impact to other health budgets based on MSAC’s advice on application 1737 in July 2023 and on unpublished data provided by the HbR.
- A summary of the data sources used in estimating the updated financial impact for the addition of SCD to NBS programs is presented in Table 17.

**Table 17 Data sources and parameter values applied in the utilisation and financial estimates**

Data	Source and value	Justification
No. of births per year, 2008–2021	ABS registered births (ABS 2022) <sup>a</sup>	Used to project the estimated number of births per year, 2022–2030, as ABS projections for the number of births per year (2017–2066) (ABS 2018) <sup>b</sup> , appear to overestimate the annual number of registered births.
No. babies who uptake NBS, 2016–2020	Huynh et al. (2022) <sup>c</sup>	The total number of babies screened through NBS programs 2016–2020 was divided by the number of registered births over the same time period to estimate the rate of uptake of NBS (99.3%).
Incidence of SCD in newborns	34.2 per 100,000 (Table 2)	Derived assuming the birth prevalence of SCD in Sub-Saharan Africa, the number of births in Australia to people from Sub-Saharan Africa and the proportion of Australian-born cases from the HbR with ancestry from Sub-Saharan Africa. The applicability of this estimate was uncertain as patterns of migration (and the reasons for migration) can differ largely over time. For comparison birth prevalence through the UK NBS program was estimated to be 39 per 100,000 births (Streetly et al. 2018) <sup>d</sup> . Alternate estimates applied in DCAR 1737 were tested in sensitivity analyses (0.53–8.6 per 100,000).
Sensitivity of first-tier screening	100%	100% sensitivity was reported across multiple studies using varied methods.
Specificity of first-tier screening	Assumption. 99.99%	While specificity of testing ranged from >99–100% for SCD, an estimate close to 100% is applied for consistency with the clinical evidence which observed near complete concordance between tests
Cost of screening and confirmatory testing in newborns	First-tier: \$2.00 Second-tier: \$500	First-tier screening by ESI-MS/MS and second-tier by DNA sequencing. First-tier screen costs for ESI-MS/MS were estimated by an expert consulted during the preparation of the assessment. Alternate estimates were also provided (or derived from expert advice) (Table 13).
Use of current targeted newborn testing	1.69%	Assumed to occur in WA only (representing 11% of births nationally) and in those with high-risk ancestries (15.4% of births) (Section 3.2.4 of the 1737 DCAR)
Cost of targeted newborn testing	\$10.00 (expert opinion) <sup>e</sup>	WA NBS for targeted newborn testing
Proportion of SCD cases currently missed before symptom onset	52.3% (HbR, see ‘Performance of current testing strategies’)	Analyses of the Australian-born SCD patients in the HbR suggest that 57/109 patients did not receive a diagnosis until after presentation of symptoms.
Cost of testing on symptom development	\$193.20	No information was available to inform the resource use required to treat symptoms at the time of delayed diagnosis, and so the analysis assumed only the use and cost of phenotypic testing (one HPLC and one CE, each with a cost of \$96.60)
Cost per year of hydroxyurea treatment	\$█	Unpublished data from the HbR estimated an average cost of hydroxyurea treatment in SCD patients of \$█ per annum. In this study, █% of patients used hydroxyurea treatment, therefore, the cost for one year of treatment was estimated to be \$█.

Data	Source and value	Justification
Additional use of hydroxyurea treatment in patients diagnosed earlier	6.6 months in 57.4% of patients (HbR, Table 6)	Additional treatment due to earlier diagnosis was based on the time between the recommended age for commencement of hydroxyurea (9 months) and the median age of diagnosis after symptom development (15.6 months) (HbR, 'Change in management'). The proportion assumed to uptake hydroxyurea was not assumed to vary in those with an earlier diagnosis, and so uptake across all Australian-born patients reported in the HbR data was assumed.
Cost per year of prophylactic antibiotic treatment	\$█	Unpublished data from the HbR estimated an average cost of prophylactic antibiotic treatment in SCD patients of \$█ per annum. In this study, █% of patients use prophylactic antibiotic treatment, therefore, the cost for one year of treatment was estimated to be \$█.
Additional use of prophylactic antibiotic treatment in patients diagnosed earlier	12.6 months additional in 66.7% of patients (HbR, Table 6) 19.3% higher use ongoing (HbR, Table 6)	Additional treatment due to earlier diagnosis was based on the recommended age for commencement of hydroxyurea (3 months) and the median age of diagnosis after symptom development (15.6 months) (HbR, 'Change in management'). HbR data also reported higher use of prophylactic antibiotics (66.7% vs 47.4%). It is unclear whether these data reflect current (i.e. ongoing) use, or a history of use. If these reflect the extent of current use, differences in age across groups may confound these differences.
Increase in TCD use in patients diagnosed earlier	28.0% (HbR, Table 6)	HbR data reported a higher proportion of TCD screening performed. It was unclear based on these data when screening started or how frequently patients were screened. The analyses therefore assumed a 28.0% increase in adherence to recommended screening (i.e. annually from age 2).
Cost per TCD	\$82.90 (MBS item 11614)	All assumed in outpatient setting (85% benefit, \$70.50)
Reduction in hospitalisations in patients diagnosed earlier	0.79 per patient per year (HbR, Table 7)	HbR data reported a significant reduction in hospital admissions in the preceding 12 months in patients who received their diagnosis prior to symptom development. It is unclear whether the extent in the reduction of hospitalisation use reported would apply from birth and how this may vary over time given that patients in the registry had a median current age of 15.0 (IQR: 7.6, 25.0) and 12.1 (IQR: 1.7, 15.0) years, for those diagnosed at/after symptoms and those diagnosed from targeted testing respectively. Further, differences in age across groups may confound these differences. Given these uncertainties, analyses that assume the reduction in hospitalisation applies from birth (and does not change over time) are presented, although should be interpreted with caution.
Cost per hospitalisation	\$█	Unpublished data from the HbR reported per SCD patient an average cost per year of hospitalisations of \$█ for █ admissions, therefore, the cost per hospital admission was estimated to be \$█.

Note: Shaded cells depict those elements that are unchanged from the 1737 DCAR.

CE = capillary electrophoresis; ESI-MS/MS = Electrospray Ionization tandem mass spectrometry; HbR = Australian Haemoglobinopathy Registry; HPLC = high performance liquid chromatography; SCD = sickle-cell disease; TCD = transcranial Doppler; WA = Western Australia.

<sup>a</sup> Australian Bureau of Statistics [ABS] 2022, Births, Australia. Births registered, 1933 to 2021(a), Commonwealth of Australia, Canberra, viewed 14 March 2023. Available from: <https://www.abs.gov.au/statistics/people/population/births-australia/latest-release>.

<sup>b</sup> Australian Bureau of Statistics [ABS] 2018, 3222.0 Population Projections, Australia, 2017 (base) – 2066, Commonwealth of Australia, Canberra, viewed 14 March 2023. Available from: <https://www.abs.gov.au/statistics/people/population/population-projections-australia/latest-release>.

<sup>c</sup> Huynh, T, Greaves, R, Mawad, N, Greed, L, Wotton, T, Wiley, V, Ranieri, E, Rankin, W, Ungerer, J, Price, R, Webster, D & Heather, N 2022, 'Fifty years of newborn screening for congenital hypothyroidism: current status in Australasia and the case for harmonisation', Clin Chem Lab Med, vol. 60, no. 10, Sep 27, pp. 1551-1561.

<sup>d</sup> Streetly, A, Sisodia, R, Dick, M, Latinovic, R, Hounsell, K & Dormandy, E 2018, 'Evaluation of newborn sickle cell screening programme in England: 2010-2016', Archives of disease in childhood, vol. 103(7), 01 Jul, pp. 648-653.

<sup>e</sup> Received by email 13/2/23

The financial implications to NBS programs resulting from the proposed addition of SCD to the screening program are summarised in Table 18.

**Table 18 Net financial implications of adding SCD 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
<b>Cost of first-tier screening (ESI-MS/MS) (\$2.00 per test)</b>	<b>\$621,844</b>	<b>\$623,302</b>	<b>\$624,759</b>	<b>\$626,217</b>	<b>\$627,675</b>	<b>\$629,133</b>
No. with SCD that is correctly identified (34.2 per 100,000, of which 100% identified)	106	107	107	107	107	108
No. false-positive screens (0.01% of true negatives)	31	31	31	31	31	31
No. SCD second-tier screens <sup>a</sup>	137	138	138	138	139	139
<b>Cost of second-tier screening (sequencing) (\$500.00 per test)</b>	<b>\$68,708</b>	<b>\$68,870</b>	<b>\$69,031</b>	<b>\$69,192</b>	<b>\$69,353</b>	<b>\$69,514</b>
<b>Total cost to NBS programs</b>	<b>\$690,552</b>	<b>\$692,171</b>	<b>\$693,790</b>	<b>\$695,409</b>	<b>\$697,028</b>	<b>\$698,646</b>

Note: Shaded cells depict those elements that are unchanged from the 1737 DCAR.

<sup>a</sup> The sum of SCD cases identified and false positive screens.

ESI-MS/MS = Electrospray Ionization tandem mass spectrometry; NBS = newborn bloodspot screening; SCD = sickle-cell disease.

The financial impact was driven by the cost per test 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 average cost per screen (as was also found in the 1737 DCAR). Second-tier screening costs made up a small proportion of the estimated cost to NBS programs. Sensitivity analyses around the financial impact to NBS programs are presented in Table 19. Expanding second-tier screening from SCD affected cases only to also include those with  $\beta$ -thalassaemia (major only) was associated with an additional annual cost of approximately \$18,000. Implementation costs were not included in these calculations.

**Table 19 Net financial impact to NBS programs, key sensitivity analyses**

	2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
<b>Base net impact to NBS programs</b>	<b>\$690,552</b>	<b>\$692,171</b>	<b>\$693,790</b>	<b>\$695,409</b>	<b>\$697,028</b>	<b>\$698,646</b>
SCD incidence (base case: 34.2 per 100,000)						
0.6 per 100,000 births	\$638,352	\$639,848	\$641,345	\$642,841	\$644,338	\$645,834
5.7 per 100,000 births	\$646,273	\$647,788	\$649,303	\$650,818	\$652,333	\$653,848
8.6 per 100,000 births	\$650,714	\$652,239	\$653,765	\$655,290	\$656,816	\$658,341

Cost of ESI-MS/MS first-tier screening (base case: \$2.00)						
\$4.30	\$1,405,673	\$1,408,968	\$1,412,263	\$1,415,559	\$1,418,854	\$1,422,149
\$7.09	\$2,273,145	\$2,278,474	\$2,283,803	\$2,289,131	\$2,294,460	\$2,299,789
\$8.23	\$2,627,596	\$2,633,756	\$2,639,915	\$2,646,075	\$2,652,235	\$2,658,395
\$13.50	\$4,266,155	\$4,276,156	\$4,286,156	\$4,296,157	\$4,306,158	\$4,316,159
Second-tier screening method (base case: DNA sequencing, \$500.00)						
HPLC (\$96.60)	\$635,118	\$636,607	\$638,096	\$639,585	\$641,074	\$642,563
Haemoglobinopathy identified (base case: SCD only)						
SCD and $\beta$ -thalassaemia (major only)	\$708,660	\$710,321	\$711,982	\$713,643	\$715,305	\$716,966

ESI-MS/MS = electrospray ionisation tandem mass spectrometry; HPLC = high performance liquid chromatography; NBS = newborn bloodspot screening; SCD = sickle cell disease.

The impact on other health budgets affected by the addition of SCD to NBS programs was updated from the 1737 DCAR and separated into changes directly borne from the introduction of universal NBS and earlier diagnoses of SCD, and those due to the effects of changes in management (given the additional uncertainty inherent in these data and their applicability over time, as described in Table 17).

The direct effects from the introduction of universal NBS include the replacement of targeted newborn testing and testing upon symptom development. Additional costs are included due to earlier initiation – due to a reduced age at diagnosis (median 15.6 months following symptom development based on HbR data) – and/or higher uptake of treatment (i.e. prophylactic antibiotics, hydroxyurea and TCD).

The effects of changes in management included in the analysis have been restricted to the reduction in the annual number of hospitalisations (excluding planned transfusions). While significant reductions were also observed in the number of ED presentations it was also noted that the majority of ED presentations likely also required hospital admission (Nelson et al. 2023). Significant reductions were also observed in the history of certain events (sepsis and cholecystectomy, with a trend towards a reduction in a history of splenectomy). However these have not been included in the analysis as it was unclear when these events occurred (i.e. within forecast period) and what impact the differences in age across groups had on the extent of these differences. Further, management of these events would also likely be captured in the reduction in hospitalisations calculated above.

As per the 1737 DCAR, no changes were expected in the use or cost of cascade testing of relatives of affected cases (as all affected cases are currently identified  $\pm$  delay in diagnosis). This was consistent with MSAC's advice on application 1737 that, based on 95-99% detection through existing targeted testing and 100% uptake of cascade testing, cascade testing for haemoglobinopathies already takes place to a nearly complete extent.

Changes in use and cost of direct effects from the introduction of universal NBS to funding sources other than NBS programs are presented in Table 20. These changes in use and cost are borne across different health budgets, however the net effect across these funders was a small reduction in the annual cost (\$40,000–\$50,000 per year), driven by the reduction in current targeted newborn testing that would be replaced by universal NBS.



**Table 20 Impact on other health budgets, direct effects**

		2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
<b>Reduction in targeted newborn testing</b>							
A	No. newborns who uptake targeted newborn testing	310,922	311,651	312,380	313,109	313,837	314,566
B	No. newborns who currently undergo targeted newborn testing (A × 1.69%)	5,244	5,256	5,268	5,280	5,293	5,305
C	Reduction in cost of targeted newborn testing (B × \$10.00)	\$52,436	\$52,559	\$52,682	\$52,805	\$52,927	\$53,050
<b>Reduction in testing after symptom development</b>							
D	No. births Australia	313,259	313,993	314,727	315,462	316,196	316,930
E	No. newborns with SCD (D × 32.4 per 100,000)	107	107	108	108	108	108
F	No. identified through NBS (E × 99.3% uptake NBS × 100.0% sensitivity of screening)	106	107	107	107	107	108
G	No. who – in the absence of NBS – would not have been identified until after symptom development (F × 52.3%)	56	56	56	56	56	56
H	Reduction in cost of testing on symptom development (G × \$193.20)	\$10,743	\$10,768	\$10,794	\$10,819	\$10,844	\$10,869
<b>Changes in management due to earlier diagnosis</b>							
I	Increase in use of hydroxyurea in cases identified before symptom development (G × \$75.57 <sup>a</sup> )	\$4,202	\$4,212	\$4,222	\$4,232	\$4,241	\$4,251
J	Increase in prophylactic antibiotic use in cases identified earlier (G × \$132.71 <sup>b</sup> )	\$7,380	\$7,397	\$7,414	\$7,432	\$7,449	\$7,466
K	No. SCD cases identified earlier, age >1	-	56	111	167	223	279
L	Ongoing higher prophylactic antibiotic use (K × 19.3% × \$189.49)	-	\$2,034	\$4,072	\$6,115	\$8,163	\$10,216
M	Cumulative no. cases identified earlier (G + K)	56	111	167	223	279	336
N	Increase in annual TCD use (M × 28.0% in newborns from age 2)	-	-	16	31	47	62
O	Cost per TCD to the MBS (N × \$70.50)	-	-	\$1,096	\$2,194	\$3,295	\$4,398
<b>Net changes in cost to other health budgets</b>							
P	Net change in cost to State/Territories (I – C – H)	-\$58,977	-\$59,115	-\$59,253	-\$59,392	-\$59,530	-\$59,668
Q	Net change in cost to the PBS (J + L)	\$7,380	\$9,431	\$11,486	\$13,547	\$15,612	\$17,682
R	Net change in cost to the MBS (O)	-	-	\$1,096	\$2,194	\$3,295	\$4,398
	<b>Net effect to other health budgets due to direct effects of the expansion of NBS programs</b>	<b>-\$51,597</b>	<b>-\$49,685</b>	<b>-\$46,671</b>	<b>-\$43,651</b>	<b>-\$40,623</b>	<b>-\$37,588</b>

Note: Refer to Table 17 for the sources and justification for the parameters used in this table.

<sup>a</sup> 6.6 months (0.55 year) × \$233.93 annual cost of treatment × 57.4% use.

<sup>b</sup> 12.6 months (1.05 year) × \$189.49 annual cost of treatment × 66.7% use.

<sup>c</sup> To account for the cumulative number of patients aged >2, Row M two years prior are used e.g. in 2025-26 the increase in TCD use is derived by multiplying 28.0% by the cumulative number of patients two years prior in 2023-24 (i.e. 56).

SCD = sickle cell disease; TCD = transcranial Doppler.

The impact of changes in use and cost due to a reduction in hospital admissions is presented in Table 21. Given the assumption that the reduction in hospitalisation applies from birth (and does not change over time), by the sixth year after implementation in NBS programs –under the assumed incidence estimate of 34.2 per 100,000 births and that 52.3% of cases would be identified earlier due to universal NBS – an additional 336 patients with SCD are estimated to have been diagnosed prior to symptom development, resulting in a reduction of 265 hospital admissions and reduction in cost to States/Territories of \$1.8 million. For comparison, estimates

derived assuming a lower incidence estimate (8.6 per 100,000) are also presented, where the derived reduction in hospitalisations (66) and resulting reduction in cost (\$456,000) were substantially lower in the sixth year of the program. Additional sensitivity analyses are presented varying the proportion of cases missed, the reduction in hospitalisations assumed per patient per year and cost per hospitalisation.

**Table 21 Impact on other health budgets due to reduced hospitalisations (including sensitivity analyses)**

	2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
Cumulative no. cases identified earlier	56	111	167	223	279	336
Reduction in hospitalisations per year (0.79 per case identified earlier)	44	88	132	176	221	265
<b>Change in cost to State/Territories (\$6,867 per hospitalisation avoided)</b>	<b>-\$301,468</b>	<b>-\$603,642</b>	<b>-\$906,524</b>	<b>-\$1,210,111</b>	<b>-\$1,514,406</b>	<b>-\$1,819,407</b>
Sensitivity analyses						
Incidence of SCD (base case: 34.2 per 100,000)						
0.6 per 100,000 births	-\$5,455	-\$10,923	-\$16,404	-\$21,898	-\$27,404	-\$32,923
5.7 per 100,000 births	-\$50,371	-\$100,859	-\$151,466	-\$202,191	-\$253,034	-\$303,995
8.6 per 100,000 births	-\$75,556	-\$151,289	-\$227,199	-\$303,286	-\$379,550	-\$455,992
Proportion of SCD cases missed (base case: 52.3%)						
15%	-\$86,474	-\$173,150	-\$260,029	-\$347,111	-\$434,395	-\$521,883
25%	-\$144,123	-\$288,583	-\$433,382	-\$578,518	-\$723,992	-\$869,804
35%	-\$201,772	-\$404,017	-\$606,735	-\$809,925	-\$1,013,589	-\$1,217,726
Reduction in hospitalisations per patient diagnosed earlier per year (base case: 0.79)						
0.43	-\$164,199	-\$328,784	-\$493,753	-\$659,107	-\$824,847	-\$990,971
1.15	-\$439,138	-\$879,306	-\$1,320,503	-\$1,762,729	-\$2,205,985	-\$2,650,270
Cost per average hospital admission (base case: \$6,867)						
\$4,110	-\$180,442	-\$361,308	-\$542,596	-\$724,307	-\$906,441	-\$1,088,999
\$9,624	-\$422,493	-\$845,977	-\$1,270,451	-\$1,695,916	-\$2,122,371	-\$2,549,816

SCD = sickle cell disease.

The net cost to Government health budgets was therefore highly uncertain. The costs to Government were driven by the cost of expanding the screening program – primarily due to the cost per test of first-tier screening, which may be dependent on the current capacity of NBS laboratories to manage the proposed expansion and scale of screening operations.

The increase in cost of expanding the screening program may be offset by reduced hospitalisations in patients diagnosed prior to symptom development, from reduction of complications and morbidities. However the extent of these cost offsets was considerably uncertain, being driven by the incidence of SCD, proportion of cases missed through current targeted testing, and assumptions regarding the extent of the reduction in hospitalisations per year (and how this may change over time).

Estimated net cost to Government health budgets, with and without the impacts of reduced hospitalisations, are presented in Table 22 below.

**Table 22 Net impact to Government health budgets**

	2023-24	2024-25	2025-26	2027-28	2028-29	2029-30
Cost of adding SCD to NBS programs (Table 18)	\$690,552	\$692,171	\$693,790	\$695,409	\$697,028	\$698,646
Changes to other Government health budgets (excluding changes in hospitalisations) (Table 20)	-\$51,597	-\$49,685	-\$46,671	-\$43,651	-\$40,623	-\$37,588
<b>Net cost to Government health budgets (direct effects only)</b>	<b>\$638,955</b>	<b>\$642,487</b>	<b>\$647,119</b>	<b>\$651,758</b>	<b>\$656,405</b>	<b>\$661,059</b>
Changes in cost of hospital admissions (Table 21)	-\$301,468	-\$603,642	-\$906,524	-\$1,210,111	-\$1,514,406	-\$1,819,407
<b>Net cost to Government health budgets (including changes in hospitalisations)</b>	<b>\$337,487</b>	<b>\$38,844</b>	<b>-\$259,405</b>	<b>-\$558,354</b>	<b>-\$858,002</b>	<b>-\$1,158,349</b>

SCD = sickle cell disease.

## 15. Other relevant information

While program implementation costs were not considered in their entirety, some direct costs of implementing NBS for SCD (such as instrumentation and staffing costs) were included in this health technology assessment. However, broader programmatic implementation costs not captured by HTA will be significant, and maximum benefit/cost and minimum laboratory disruption will be achieved with bundling together the implementation of adding new conditions to screening programs. This will result in a single education program for all new conditions to be added to routine newborn blood spot screening, with separate information campaigns directed to health professionals, parents and the community.

## 16. Applicant comments on MSAC's Public Summary Document

Australia Sickle Cell Advocacy Inc welcomes the MSAC's advice to include screening for Sickle Cell Disease (SCD) as part of the Newborn Bloodspot Screening (NBS). This new listing will ensure early diagnosis of SCD in Australia, improving health outcomes for babies screened through NBS programs, where previous targeted tests detected less than half of SCD cases before symptoms developed. This is particularly important as the rates of SCD in Australia are substantially higher than previously thought, and noting the incidence of SCD in Australia is predicted to increase.

## 17. Further information on MSAC

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