

Nomination forms for requesting the assessment of a condition for addition to or removal from newborn bloodspot screening

Overview

This document contains the nomination forms provided in the [Newborn Bloodspot Screening National Policy Framework](#) (the Framework) and described in Policy Area 5: Decision-making process. These forms must be completed in order to request the assessment of a condition for addition to or removal from newborn bloodspot screening.

Before submitting a nomination form, please consider the following information.

Completing a nomination form

The Standing Committee on Screening (SCoS) will consider conditions for assessment once a year. Nomination forms must be completed and submitted to SCoS@health.gov.au by **no later than 1 November** each year. Nominations received after this date will be considered as part of the following year's submissions.

Anyone in Australia can nominate a condition (either for addition to screening or removal from screening) by completing the appropriate nomination form. It is recommended that nominees seek the advice and guidance of an Australian newborn bloodspot screening program prior to completing the form. This will help to ensure that conditions appropriate for nomination and assessment have not already been considered for inclusion, and reduce the chance of duplication if multiple groups or jurisdictions are working on similar applications. Contact details for the newborn bloodspot screening programs may be sought from the national Newborn Bloodspot Screening Program Management Committee, via the SCoS email address listed above.

Consideration of the nomination form

Once the completed nomination forms have been received, the Program Management Committee will make an initial assessment of all applications and provide a recommendation to SCoS as to which of the nominated conditions merit more detailed assessment. The recommendation reached by the Program Management Committee is primarily based on the information provided in the nomination forms. As such, it is important that the nomination form is as complete, comprehensive and accurate in its responses as possible. If insufficient evidence is provided in the nomination form, applicants will be advised after this first assessment and may wish to resubmit once all the required information is obtained.

Recommendations for further assessment

After considering the recommendation from the Program Management Committee, SCoS will determine which conditions merit detailed review. A detailed review involves an assessment of all available evidence on screening for the condition in question, in line with the decision-making criteria in the Framework.

Progression to and timing of the detailed review are dependent on a number of considerations, including: availability of staff and resources to support the review; the level of evidence available in Australia and internationally; the complexity of the issues being considered; and whether an economic analysis is conducted.

Final recommendation

Based on the outcome of the detailed review, SCoS will arrive at one of the final recommendations shown in the box below. If SCoS recommends screening (or ceasing screening) for a condition, the relevant recommendation, accompanied by preliminary cost implications where necessary, will be submitted to the Australian Health Ministers' Advisory Council (AHMAC) for consideration, via the relevant Principal Committee.

If the recommendation is supported by AHMAC, state and territory governments are then responsible for funding and establishing any other requirements around adding conditions, taking into account local contexts. It may not be appropriate for all states and territories to screen for all conditions due to differences in local populations, priorities and/or feasibility.

Recommendations that can be made following assessment of the evidence for screening a condition

1. **When considering including a condition in newborn bloodspot screening**, possible recommendations include:
 - Screening is recommended.
 - A pilot is recommended, and specific issues flagged for investigation.
 - Based on the current evidence and understanding of a condition, screening is not recommended at this time. However, there may be merit in revisiting this condition in the future if further evidence emerges.
 - Screening is not recommended.

2. **When considering removing a condition currently screened**, possible recommendations include:
 - Continue screening.
 - Cease screening.

More information

For more information regarding the decision-making process for adding or removing conditions from newborn bloodspot screening programs, see Policy Area 5: Decision-making process in the [Newborn Bloodspot Screening National Policy Framework](#).

Any specific questions regarding the nomination or assessment process can be submitted to the Program Management Committee, via SCoS@health.gov.au.

**Nomination form requesting assessment of a condition for
addition to newborn bloodspot screening**

Please submit to the Newborn Bloodspot Screening Program Management Committee
via SCoS@health.gov.au

Date received: (to be completed by secretariat)

Questions	Response
Name of nominator(s)	REDACTED
Organisation(s) (if applicable)	Australian Sickle Cell Advocacy Inc
Contact details (address, phone, email)	REDACTED
Role(s) (for example, clinician, researcher, parent, advocate etc.)	Advocates and clinicians
Condition nominated for assessment (specifying form(s), if applicable)	Sickle Cell Disease
OMIM* or other names for the condition	603903

*Online Mendelian Inheritance in Man: <http://www.omim.org/>

Instructions for completion

- Please complete as many of the 'response' sections within this form as possible, citing relevant references within the text by number, then list and attach all references at section 6.
- It is recommended that a nominee who is not from a newborn bloodspot screening program seeks the advice and guidance of their jurisdiction's newborn bloodspot screening program regarding the required documentation and evidence in order to make a submission for the addition or removal of a condition.
- When the nomination form is complete, it should be submitted to the Newborn Bloodspot Screening Program Management Committee.

1. The condition

The condition should be a serious health problem that leads to significant morbidity or mortality. There should be a benefit to conducting screening in the newborn period; and the natural history of the condition, including development from latent to declared disease, should be adequately understood.

Guiding questions	Response
What is the incidence of the condition in Australia? Is this determined clinically or through screening studies in other countries?	<ul style="list-style-type: none"> • >300,000 babies are born with SCD every year and >100 million have sickle cell trait every year [1] • There are 256 SCD patients in Australian Registry, but true incidence is not known. However, it is expected to raise due to migration. Global number of migrants with HbS increased from 1.6 million in 1960 to 3.6 million in 2000 [2,3]. The incidence is determined by screening.

Guiding questions	Response
What is the burden of disease associated with the condition, including morbidity and mortality? What is the spectrum of disease—in particular, are there mild or late-onset forms?	The burden of SCD is huge on personal and family level, as well as on community economics. the community. SCD is a chronic debilitating disease with high mortality and a long list of morbidities including, but not limited to: chronic haemolytic anaemia, recurrent vaso-occlusive crisis resulting in multiple organs damage, life threatening acute chest syndrome, aplastic anaemia, acute splenic sequestration, ischaemic stroke and silent infarcts, avascular necrosis of femoral head, priapism, cognitive impairment and psycho-social harms [1 - 31]. Life expectancy is reduced (54 vs 76 years [8] and 50 - 90% of affected children in low-income countries die before their 5th birthday [16]. Mild forms exist.
At what age would the condition usually be detected clinically?	Generally from 6 months of. However complications such as acute splenic sequestration can occur from 3 months of age with 50% recurrence rate, and encapsulated bacterial infections and can occur from early childhood [5,9].
What are the benefits of early diagnosis and intervention/treatment? (Consider such benefits as early intervention, prevention of symptoms, reduction of disease severity, provision of a definitive diagnosis, emotional and social benefits and provision of information that would assist families with reproductive decision making.)	There is good evidence of the benefits of early diagnosis followed by early intervention. A RCT by Gaston et al showed a 84% reduction in infection in Penicillin prophylaxis group started at 4 months of age vs placebo group [7,25]. A Cochrane review 2002 showed SCD infants on Penicillin prophylaxis had significantly lower risk for pneumococcal infections (odds ratio = 0.37, 95% CI 0.16 - 0.86) [7]. An observational study showed a 10-fold reduction in mortality related to splenic sequestration when early parental education on spleen size was provided (Edmond et al. 1985) [1]. Additional benefits include pneumococcal conjugated vaccine, prompt clinical intervention for infection or splenic sequestration, early education, access to comprehensive medical care, genetic counselling for future pregnancies. The mortality has dropped by 50% in 1 - 4 years old SCD patients and life expectancy has improved from 14.3 years to in 40's and 50's in USA and Canada since implementation of universal NBS [1].
What are the possible harms of screening and/or early diagnosis?	Potential psycho-social harms due to incidental detection of sickle cell carrier status, of haemoglobinopathies of unknown clinical significance, possible exposure of non-paternity, stigmata, and potential discrimination [5].

2. The test

There should be a suitable test protocol to identify the presence of the condition, and the test protocol should be socially and ethically acceptable to health professionals and the public.

Guiding questions	Nominator's response
Describe a detailed methodology for the test (for example, tandem mass spectrometry, immunoassay, molecular), including any second-tier testing required. Provide reference to a published methodology and describe any modifications required.	<p>- Two-tiered approach is still used by most NBS programs. The following methodologies can be used as initial or second-tier screening: High Performance Liquid Chromatography (HPLC), Isoelectric Focusing (IEF), Capillary Electrophoresis (CE). The principle of the above tests is based on the separation of haemoglobin (Hb) species and quantification of their respective fractions from dried blood spot (DBS) or cord blood samples. - A robust quality insurance program, reporting and referral systems must be in place.</p> <p>- Tandem Mass Spectrometry (MS/MS) has also been used in other countries. We suggest using HPLC and CE/IEF as initial and second-tier screening [1,12,13,14,15,17,18,19,20,21,22,23,24]</p>

Guiding questions	Nominator's response
Can the test be performed on the same dried bloodspot specimen that is used currently? If not, what additional sample would be required?	Yes
For the proposed testing protocol, comment on the:	
clinical and analytic validity	Good
sensitivity	Close to 100%
specificity	Close to 100%
false positive rate	Close to 0%, but can be increased by prematurity
false negative rate	Close to 0%, but can be increased by recent blood transfusion
positive predictive value	Close to 100%
negative predictive value	Close to 100%
What other conditions may be detected (clinical or of unknown significance)?	Sickle cell trait and other haemoglobinopathies
What would be the cost of the test?	The cost for HPLC has been reported in USA and Germany between 2 - 6 US \$ + costs Labour + Equipment. However in Australia the cost for HPLC ranges between 90 - 100 AU \$
If DNA analysis is required, would testing include common mutations, a panel or full sequencing?	Yes, whole exome sequencing (Panel sequencing), targeting the protein-coding portions of the beta globin gene followed by copy number variation analysis of the beta globin locus to determine normal vs sickle cell mutation [20].
What are the potential harms associated with the test protocol?	Potential psychological harms related to non-paternity disclosure, stigmata and discrimination

3. The intervention

There should be an accepted intervention for patients with recognised disease, and facilities for diagnosis and management should be available so that these services can be offered if there is a positive screening result.

Guiding questions	Nominator's response
What diagnostic testing is necessary? Is it available and reliable? What is its associated cost?	- Every abnormal result will require a confirmation by one of the following tests with an alternative principle: HPLC, IEF, CE. MS/MS or DNA-based assay can also be used. These tests are available and reliable. - DNA-based assay in Victoria costs about 300 AU \$.
What is the established intervention/treatment for this condition?	Early initiation of Penicillin prophylaxis soon after diagnosis, preferably by 2 months of age and Pneumococcal conjugated vaccine, comprehensive medical care, early parental education, genetic counselling for future pregnancies, and monitoring of complications. Disease modifying therapies: Hydroxyurea, longterm regular transfusion and curative therapy: bone marrow transplant.
Do all patients require an intervention or treatment upon diagnosis? If not, can those who require treatment be distinguished from those who do not?	Yes, particularly: <ul style="list-style-type: none"> • Early Penicillin prophylaxis and Pneumococcal vaccine • Comprehensive medical care • Parental education and genetic counselling for future pregnancies • Monitoring of complications

Guiding questions	Nominator's response
How effective is the intervention/treatment? (Does it alleviate symptoms, slow/halt progression?)	Very effective <ul style="list-style-type: none"> • Good evidence that early intervention prevents complications, particularly encapsulated bacterial infections/sepsis, reduce morbidities and hospital admission requirement, reduced mortality, and has improved life expectancy [1,7,8,9, 12,13,14, 25] • Hydroxurea, longterm regular transfusion, BMT: very effective [31].
What are the impacts on quality of life?	Positive: significant reduction in morbidities and hospital admissions.
How urgent is the intervention/treatment? Must it be initiated before symptoms present?	Interventions need to be initiated and implemented early , soon after the diagnosis has been made, and as indicated. A retrospective cohort study by Rankine-Mullings et al showed 43% and 40% reduction in vaso-occlusive crisis and acute chest syndrome in early care group vs late care group [13].
What are the potential harms of the intervention/treatment?	Generally well tolerated, however some interventions have side-effects, which need to be monitored.
What is the cost of the intervention/treatment	It is difficult to accurately determine the cost without knowing the accurate incidence of the disease in Australia for a meaningful costing analysis.
What facilities are required to deliver the intervention/treatment? Do current health care facilities in each state and territory have capacity, and are they of sufficient quality, to support the intervention/treatment? Is there equitable access to the intervention/treatment?	In Australia, SCD patients are managed by specialized Haematology Units mainly located within tertiary health facilities, providing a comprehensive medical care model. Most of the states in Australia have Haematology Units of acceptable standard to support the intervention/treatment, including comprehensive medical care of SCD patients.

4. Cost-effectiveness

Guiding questions	Nominator's response
Provide any available evidence for the cost-effectiveness of screening for this condition, either from Australia or internationally.	A cost-effective analysis using a Markov simulation model by Panepinto et al, considering the costs and outcomes associated with the prevention and treatment of sepsis in SCD patients: targeted screening of African American vs no screening: 6709 \$ per additional year of life saved. Universal screening vs targeted screening: 30,760 \$ per additional year of life saved. Targeted screening is always cost-effective compared to no screening. Universal screening always identifies more infants with disease, prevents more deaths, and is cost-effective [27].

5. Any Other Comments

The demographic threshold for cost-effectiveness occurs if the population at risk live births in a given population reaches about 5% (Springkle et al. 1994). However universal screening in Italy found incidence of 1.16% (0.07% SCD, 0.68% with sickle cell trait) similar to other European countries with high immigration (Martella et al. 2017) [21]. In Berlin pilot study, 14/34,084 returned positive for SCD (4.11/10,000) [19], and in 2016, 431 returned positive in French NBS (Birth prevalence of 1:1836) [21]; both the highest among all targeted diseases in NBS programs in Germany and in France. many European countries have already approved universal NBS for SCD: UK, France, Spain, The Netherlands, Malta [31].

US Preventive Services Task Forces found universal NBS for SCD approved in all 50 states and DC in 2006, to be cost effective [25].

6. References

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