Newborn Bloodspot Screening Condition Assessment Summary
Congenital adrenal hyperplasia (CAH)

Background

About newborn bloodspot screening in Australia

Newborn bloodspot screening (NBS) is a public health initiative that aims to protect newborn babies from the life-threatening effects of rare, congenital conditions. In Australia, NBS programs involve a blood sample being collected from newborns within the first 48 to 72 hours of life. This bloodspot sample is dried and sent to specialised laboratories for testing. Babies with a positive screening result are then referred on for diagnosis of the suspected condition and management if the condition is confirmed.

In Australia, each state and territory is responsible for funding and operating their own program and over 99% of babies born in Australia are screened each year. Australian NBS programs provide timely results to families to enable early intervention that minimises or avoids the serious impacts of the conditions screened. Of those screened, about one in every thousand babies born is diagnosed with a condition that, without timely intervention as a result of screening, would have been undetected and may have caused severe intellectual or physical disability, or death.

While NBS programs have been operating successfully across Australia for around 50 years, there were no national policies supporting the programs or a decision-making process for assessing conditions for inclusion on NBS panels. To address this, the Standing Committee on Screening (SCoS) developed the *Newborn Bloodspot Screening National Policy Framework* (NBS Framework), which was endorsed by Australian Health Ministers' Advisory Council (AHMAC) and released in 2018. The Framework provides national policy guidance on the elements needed to support the ongoing success of NBS in Australia, and aligns the programs with AHMAC's *Population Based Screening Framework*. The NBS Framework also provides a robust, transparent process for national decision-making regarding conditions screened as part of NBS.

About the decision-making process

The decision-making process included in the NBS Framework provides a single national mechanism for assessing conditions for inclusion in, or removal from, NBS programs, to which states and territories can contribute. The outcome of these assessments can then be used to inform all states and territories regarding the conditions included in their NBS programs, thereby avoiding any duplication of effort. Having a clearly articulated process means that the programs are transparent and accountable, and each condition is assessed in the same way. It also supports a continued high level of consistency for conditions screened.

A robust decision-making process is vital to ensuring that a decision to include or remove a condition from NBS is only ever reached after a careful assessment of the available evidence. In particular, screening should only be offered for a condition when the evidence indicates that the benefits of screening will outweigh the harms. Furthermore, given that health care funding is finite, it is important that the benefits of screening for a condition justify the associated costs.

The decision making process is overseen by SCoS, which is responsible for making a recommendation about the addition or removal of a condition to NBS programs in Australia. A

condition can be nominated by anyone in Australia by completing a nomination form. Nomination forms are reviewed by the inter-jurisdictional national NBS Program Management Committee (PMC). Depending on the recommendations from the PMC and relevant clinical expertise, SCoS may request a detailed review by a time-limited Working Group and economic analysis to inform their final recommendations. If screening for a particular condition is recommended by SCoS, the relevant recommendation, accompanied by preliminary cost implications where necessary, will be submitted to AHMAC for consideration.

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.

Assessing CAH

In 2013, the Human Genetics Society of Australasia wrote to all Australian Health Ministers requesting that CAH be considered for inclusion in Australian NBS programs. Following the development of the NBS framework, CAH was identified as a suitable test case to assess the feasibility of the decision making process prior to the Framework's endorsement by AHMAC. In 2016, SCoS established the time-limited CAH Working Group (Working Group) to conduct a detailed review of the evidence for NBS for CAH. An economic analysis was conducted simultaneously to inform advice on the cost-effectiveness of screening for CAH as part of Australian NBS programs.

About this document

This document is a summary of the evidence used by the Working Group, SCoS and AHMAC, to provide a national recommendation on adding CAH to Australian NBS programs.

Detailed review of congenital adrenal hyperplasia (CAH)

About the condition

Congenital adrenal hyperplasia (CAH) is a rare, genetic condition that affects around 1 in 15,000 persons in Australia. CAH affects the production of hormones from the adrenal glands. The adrenal glands sit on top of the kidneys and produce three types of hormones: cortisol, aldosterone, and androgens (e.g. testosterone). CAH impairs the conversion of cholesterol into cortisol by the adrenal glands. The low cortisol levels stimulate the adrenal glands to attempt to make more of the missing cortisol, which leads to them producing too many androgens.

The effects of CAH vary significantly from person to person, depending on the gene mutation present. Males and females are equally at risk of CAH. Most babies diagnosed with the condition have one of the two 'classic' forms: salt-wasting CAH or simple virilising CAH. Salt-wasting CAH is a particularly serious form of the condition that requires treatment from birth and affects approximately 75% of babies with classic CAH. If undiagnosed, infants with this form are at risk of life-threatening adrenal 'crisis' within the first few weeks of life, caused by very low blood glucose, low blood pressure, salt loss and dehydration. Simple virilising CAH mainly affects the development of the genitals in females and causes early puberty (sometimes at 2 – 4 years of age) in both sexes. Simple virilising CAH can also cause less severe forms of adrenal 'crisis'.

In addition to the 'classic' forms of CAH, there is a non-classic or 'late-onset' form. This form usually causes milder effects than classic CAH, with signs and symptoms varying from person to person. Many people with non-classic CAH do not display symptoms of the condition until adolescence or early adulthood, while some may never develop symptoms. The review summarised here only focused on the 'classic' forms of CAH.

Outcomes of the detailed review

The CAH assessment working group conducted a detailed review of the evidence available to assess screening for classic CAH against the criteria set out in the Newborn Bloodspot Screening National Policy Framework (Box 1). The following section provides a summary of the key evidence against each criterion, and the relevant benefits and harms of screening for classic CAH identified by the working group.

Box 1. Decision-making criteria for adding or removing conditions from Australian newborn bloodspot screening programs

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

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

Criterion 1: The condition should be a serious health problem that leads to significant morbidity and mortality

The incidence of classic CAH in Australia is estimated to be around 1 in 15,000. This is consistent with incidence figures reported internationally. Mortality associated with classic CAH is assumed to be low in Australia. This is consistent with other countries that have a similarly high quality of health care. Despite this, morbidity can be significant unless the condition is diagnosed and treatment is commenced shortly after birth. In particular, newborns with undetected salt-wasting CAH are often diagnosed when they present with adrenal crisis in the first few weeks of life. Salt-wasting crises occur at a crucial time of brain development and may lead to neurological damage and intellectual disability. Morbidity associated with classic CAH also includes: genital virilisation in females; and rapid growth and accelerated sexual maturation (generally between the ages of 2 and 5 years) in males with undetected simple virilising CAH.

Benefits	Harms
• Screening minimises morbidity associated with the condition. • Screening supports timely access to health care services for diagnosis and intervention. This is particularly important in regional and remote communities that do not have immediate access to these services. The impact of this is particularly serious for salt-wasting CAH.	*No issues identified*

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

Early detection of classic CAH through screening in the newborn period supports the commencement of treatment as early as possible, to help avoid or minimise morbidity and mortality associated with the condition. In particular, early detection of salt-wasting CAH minimises the risk of newborns suffering an adrenal crisis. In addition to the health benefits to the newborn, early detection through screening can assist families by reducing the anxiety and stress of having a baby with a life-threatening condition. There is some evidence of possible harm to the emotional state of parents associated with early detection through newborn screening in the case of false positive results.

Benefits	Harms
• Screening reduces the likelihood of adrenal crisis in the newborn period. This minimises the number of emergency presentations and time in ICU, and the associated anxiety and distress to parents.	• There is a risk of increased parental anxiety associated with false positives. **Note:** false positives are minimised using a two-tiered test protocol, with immunoassay followed by tandem mass spectrometry.

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

Signs and symptoms of classic CAH vary across individuals and between males and females. Females with classic CAH are often identified at birth due to virilised genitalia. Females with severe virilisation

may be incorrectly identified as males at birth, and therefore the diagnosis will be missed until they present with other signs of CAH. Males and missed females with salt-wasting CAH are usually detected when they present with adrenal crisis within the first three weeks of life. Males with simple virilising CAH normally do not present with adrenal crisis. These males are usually detected within the first 60 months of life, with faster growth and early sexual development.

Benefits	Harms
• The natural history of CAH is understood, along with the benefits of treatment.	*No issues identified*
• Some infants with CAH can quickly become sick because of differences in how their symptoms appear. Screening will help families to identify that their infant could be sick and support decision-making around taking their child to a doctor or emergency department.	
• Currently, males with simple virilising CAH are not being diagnosed until they present with signs, normally between the ages of 2 and 5 years.	

Criterion 4: **There should be a suitable test protocol to identify the presence of the condition**

There are a number of different test protocols that may be used to identify the presence of CAH. The most appropriate test protocol for the Australian setting is a two-tiered approach using immunoassay and tandem mass spectrometry. This test protocol is estimated to have an average positive predictive value (PPV) across programs of at least 50%, meaning that 50% of the babies who receive a positive test result actually do have the condition. It is simple and reliable, and both methods are currently used to test for other conditions included as part of newborn bloodspot screening. The test cannot be included within existing newborn bloodspot screening testing panels, but can be performed separately on current dried bloodspots. There is a diagnostic test available for newborns with an abnormal screening result.

Benefits	Harms
• The test protocol is already defined, available and familiar to newborn bloodspot screening laboratories. The equipment, techniques and technology are available and the ability to perform the test exists.	• There are some false positives associated with the screening test. Note: false positives are minimised using a two-tiered test protocol, with immunoassay followed by tandem mass spectrometry.
• The test is simple and has good clinical and analytic validity.	
• Diagnostic testing is available nationwide.	
• The test protocol can be performed on the same dried bloodspot that is already collected for newborn bloodspot screening.	
• Results would be available within the timeframe required for screening to be effective.	

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

Potential harms associated with the test protocol were considered, including whether other conditions can be identified, and potential physical and psychological impacts of the test or the results of the test. A two-tiered test protocol for CAH using immunoassay and tandem mass spectrometry does not detect other conditions of clinical or unknown significance. There are no obvious harms that are associated with adding this test protocol to newborn bloodspot screening programs.

Benefits	Harms
• There are no obvious harms associated with the test protocol.	*No issues identified*

Criterion 6: Facilities for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result

Facilities are in place to support the diagnosis and management of classic CAH through health care services across Australia. Generally, health care services have indicated that they have capacity to support diagnostic testing for newborns with abnormal screening results following a screening test that has a PPV of at least 50%. High quality facilities to support diagnosis and management of classic CAH already exist within the current health care system. There are processes in place for newborns in rural and remote communities to support diagnosis and management.

Benefits	Harms
• Facilities already exist for diagnosis and management, and they are of sufficient quality. Only minimal extra resources would be required.	*No issues identified*
• Treatment would be responsive rather than reactive; diagnosis and management would be routine and semi-urgent rather than urgent or an emergency, particularly for salt-wasting CAH. This means fewer babies would need to be admitted to hospital for adrenal crisis.	
• Pathways exist for all patients to access health care services for diagnosis and management.	

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

Treatment of salt-wasting CAH with hydrocortisone, fludrocortisone and sodium chloride is highly effective for treating or preventing adrenal crisis. While commencing treatment is effective for managing symptoms of CAH at any point, outcomes are improved the earlier the treatment is initiated. If males with simple virilising CAH are not diagnosed and do not commence treatment until they present with rapid growth in early childhood, adult height may be compromised. Treatment is readily available and accessible for families through all health care services and pharmacies, including in regional and remote areas.

Benefits	Harms
• Treatment is essential and urgent for salt-wasting cases. The treatment is highly effective at treating or preventing adrenal crisis, and minimising long-term morbidity.	*No issues identified*
• The treatment is readily available and affordable for families.	
• There is the potential to significantly benefit the quality of life for patients with both forms of classic CAH through early and effective treatment.	
• The treatment pathway is well-understood.	

Criterion 8: The benefit of screening a condition must be weighed against its impact as a whole

There are no unique features of classic CAH that would require changes to the existing screening pathway should the condition be included in newborn bloodspot screening. There are no significant ethical considerations that are unique to CAH that would mean screening for the condition would require a separate consent process. It was noted that screening cannot be done within existing resources, as the current programs are at capacity. There are budgetary and resource requirements that must be provided to include CAH in newborn bloodspot screening programs.

Benefits	Harms
• Screening for CAH promotes equity of diagnosis, treatment and outcomes, particularly for Aboriginal and Torres Strait Islander, regional and remote communities.	• Screening cannot be done within existing resources, as programs are at capacity. There are budgetary and resource requirements plus minimal additional clinical time and resources associated with screening, which must be provided.
• Screening for CAH fits within the current screening pathway, and the consent process is consistent with the existing process.	
• CAH would not be the only time-dependent test in newborn bloodspot screening.	
• The treatment pathway is well-understood.	

Advice on the appropriateness of screening for CAH

The Working Group's advice to SCoS was that its assessment of the evidence demonstrated that screening for classic CAH as part of existing newborn bloodspot screening programs is appropriate. The Working Group identified and assessed the full range of benefits and harms associated with screening for classic CAH and concluded that, using a defined two-tiered test protocol, the benefits of screening for classic CAH outweigh the potential harms. The evidence reviewed indicates that screening for classic CAH would be effective in reducing serious morbidity associated with the condition. It is expected that there would also be mortality benefits from screening for classic CAH. Furthermore, the harms associated with screening, identified primarily as any false positives test results, can be minimised and differ little from those that currently exist for other conditions included in Australian newborn bloodspot screening programs.

Outcomes of the economic assessment

An economic analysis was conducted to evaluate the costs of including classic CAH in Australian NBS programs. The outcome from this analysis was that screening for classic CAH could be considered to be cost effective. The economic analysis estimated that compared to current practice, screening for classic CAH would cost an additional $2.14 per newborn screened. The incremental cost per additionally discounted lifetime quality adjusted life year (QALY) attained from newborn bloodspot screening for classic CAH was calculated to be $73,504. The World Health Organization advises an approximate guideline for a willingness to pay per QALY threshold of one to three times gross domestic product per capita, which in Australia equates to around $65,000 to $195,000.

Consideration of the evidence by SCoS and AHMAC

The SCoS reviewed both the detailed review and advice received from the Working Group as well as the economic analysis, and decided to recommend screening for classic CAH as part of Australian NBS programs.

This recommendation was endorsed by AHMAC and supported by the Council of Australian Governments' (COAG) Health Council.

Final SCoS recommendation

Screening is recommended.

Considerations for implementation

NBS programs are funded and operated by states and territories. Therefore each jurisdiction is responsible for considering the SCoS recommendation to add CAH screening to their NBS program. Detailed costing and implementation planning will need to occur at a jurisdictional level and take in to consideration the local context. It may not be appropriate for all states and territories to screen for CAH due to differences in local populations, priorities and/or feasibility.

Glossary

Analytical validity - How reliably the screening test is able to measure the small molecules in the bloodspot sample that is used to identify those at risk of a condition.

Clinical validity - How accurately the screening test predicts the presence, absence or risk of a condition.

False positive - A test result that incorrectly indicates a person has a condition when they do not have that condition.

Immunoassay - a biochemical test that measures the presence of small molecules.

Incidence - the number of new cases of the condition within a specified period of time, expressed as a proportion of the population.

Latent - not yet showing signs or symptoms of the condition.

Morbidity - sickness or disability associated with the condition.

Mortality - death associated with the condition.

Natural history - the course a condition takes in a person from onset to recovery or death, in the absence of any intervention.

Positive predictive value - the proportion of positive test results that are true positives, i.e. the proportion of persons tested who receive a positive test result indicating that they might have the condition that actually do develop the condition or have a diagnosis confirmed through other means.

Tandem mass spectrometry - an accurate method of measuring the presence of multiple small molecules.

Test protocol - a procedure or method to identify whether a person is likely to have the condition or not.

Two-tiered test protocol - a two-step approach in which two different methods are used, one after the other to identify whether a person is likely to have the condition or not.