



# **National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand**

**GUIDELINES DOCUMENT**

PUBLISHED 2024

## National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand

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NSW = New South Wales; NZ = Aotearoa New Zealand, QLD = Queensland; SA = South Australia; SAC = Scientific Advisory Committee; VIC = Victoria; WA = Western Australia

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## Glossary of terms

### **Accuracy**

(of measurement) closeness of agreement between a measured quantity value and a true quantity value of a measure.

### **Allele**

1) in genetics, any of several forms of a gene that is responsible for hereditary variation; 2) one of the alternate forms of a polymorphic DNA sequence that is not necessarily contained within a gene; 3) one of the alternative forms of a gene that may occupy a given locus.

### **Analyte**

component represented in the name of a measurable quantity.

### **Assay**

1) assay - to analyse or measure a sample of a specimen to determine the amount, activity, or potency of a specific analyte or substance; 2) qualitative assay - reports only the presence or absence of the analyte, without quantitation; 3) quantitative assay - generates a spectrum of signal responses that correlate with the concentration of the analyte of interest

### **Carrier screening**

the identification of asymptomatic individuals of both sexes who are heterozygous for a common recessive disorder or females heterozygous for an X-linked recessive disorder and at risk to have an affected child.

### **Clinical evaluation**

(of in vitro diagnostic devices) an investigation of the clinical performance characteristics of a new (or new indication for use of) in vitro diagnostic assay in controlled clinical settings

### **Clinical sensitivity**

(for newborn screening) the proportion of newborns in the screened population who have the target disease and who have positive screening test results.

### **Clinical validity**

the accuracy with which a test predicts the presence or absence of a clinical condition or predisposition.

### **Confirmatory test**

(for newborn screening) a test to prove or disprove the presence of a specific disease, group of diseases, or phenotypic difference suspected because of screening test results.

### **Copy number variant**

an insertion or deletion that involves a DNA fragment of 1 kb or larger.

### **Diagnostic accuracy**

the ability of a diagnostic test method to discriminate between diseased and non-diseased subjects or between two or more clinical states.

### **Diagnostic test**

a measurement or examination of a diagnostic specimen for the purpose of diagnosis, prevention, or treatment of any disease or the assessment of health or impairment of health of an individual patient.

### **Digital polymerase chain reaction**

dPCR separates the sample into a large number of partitions, and the polymerase chain reaction is carried out in each partition individually. In the dilution range where some partitions do not contain any copies of the template, the partitioning of the sample allows one to count the template molecules by estimating according to Poisson distribution. This estimate gives an absolute count of template copies without reference to any independent standard, and its accuracy may be improved in principle to any desired level by counting more partitions.

### **Discrepant result (also discordant result)**

result that is inconsistent to a medically significant degree with another result obtained from the same sample, with a result from another measurement procedure, or with a well-substantiated medical diagnosis.

### **Dried blood spot**

a specimen collected for laboratory testing, using an approved medical device composed of a specified filter paper, on which printed circles indicate the area to be filled with whole blood and air-dried for transport or storage.

### **Ethylene diamine tetraacetic acid (EDTA)**

(EDTA) one of a class of aminopolycarboxylic acids that act as sequestering (also referred to as “chelating”) agents.

### **Exon**

a transcribed region of a gene that is present in the mature messenger RNA.

### **False-negative screening result**

screen-negative result in an affected newborn. A screen-negative result indicates an individual is not at increased risk for the primary target disease when the individual is found later to be affected.

### **False-positive screening result**

screen-positive result in an unaffected newborn. A screen-positive result indicates an individual is at increased risk for the primary target disease when the individual is found later to be unaffected.

### **First-tier screen**

(for newborn screening) a single assay, combination of assays, physiological measurement, or assessment performed on all newborns to screen for a disease, group of diseases, or phenotypic difference as the first step in the laboratory screening algorithm.

### **Follow-up**

(for newborn screening) actions taken to ensure that a newborn whose specimen is unacceptable or whose screening result warrants additional action receives evaluation and/or intervention.

### **Gene**

a chromosomal segment that codes for a single polypeptide chain or a structural molecule.

### **Gene sequencing**

process of recording the exact sequence of nucleotides in a given gene fragment.

### **Genetic counselling**

process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following: 1) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; 2) education about inheritance, testing, management, prevention, resources, and research; and 3) counselling to promote informed choices and adaptation to the risk or condition.

### **Genetic variant**

a DNA sequence that varies from a reference DNA sequence.

### **Genotype**

the genetic makeup of an organism or group of organisms, with reference to a single trait, set of traits, or an entire complex of traits.

### **Genotype phenotype correlation**

the association between the presence of a certain genetic variant or variants (genotype) and the resulting pattern of abnormalities (phenotype).

### **Gestational age**

time since conception, measured in weeks and days or in completed weeks only.

### **Gold standard**

a nonspecific term that indicates that a process or material(s) is the best available approximation of the truth.

### **Homozygous deletion**

the deletion of two alleles at corresponding loci on homologous chromosomes identical for one or more loci. A homozygous pathogenic sequence variant is the presence of the identical variant on both alleles of a specific gene. However, when both alleles of a gene harbour variants, but the variants are different, these are called compound heterozygous. This is important, for example, in recessive diseases in which each allele carries a different genetic variant, one from each parent.

### **Intervention**

(for newborn screening) specific newborn screening follow-up activity (e.g., clinical assessment, medical management, monitoring, treatments) aimed at preventing morbidity and mortality in at-risk or affected newborns.

### **Jurisdiction**

the area for which a newborn screening program has legal authority and/or responsibility.

### **Loci**

1) the position of a gene on a chromosome; 2) the position on a chromosome of a DNA sequence that is not necessarily contained within a gene

### **Multiplex**

simultaneous detection of two or more nucleic acid targets in a single reaction.

### **Multiplex assay**

the simultaneous quantitative or qualitative analysis of multiple analytes.

### **Newborn dried blood spot screening**

process of collecting blood onto the blood collection (specified filter paper) section of a specimen collection device (for newborn screening), testing defined analytes by approved laboratory methods, and reporting results as appropriate.

### **Newborn screening program**

a health program, which is one part of a greater newborn screening system, that operates with the goal of reducing morbidity and mortality in newborns with congenital diseases through early detection and intervention and consists of the jurisdiction's health service components, which might include policies and regulations, planning and audits, specimen collection and transport, laboratory testing, and short- and long-term follow-up.

### **Next-generation sequencing**

DNA sequencing, encompassing several high-throughput approaches, that uses miniaturized and parallelized platforms for sequencing of thousands to millions of short reads ( $\approx 50$  to 400 bases).

### **Phenotype**

the observed biochemical, physiological, and/or morphological characteristics of an individual, as determined by the genotype and the environment in which it is expressed.

### **Polymerase chain reaction**

a method for producing multiple copies of a segment of genomic DNA or coding DNA to test for the presence or expression of the sequence of the gene of interest or to obtain adequate amounts of the sequence of interest for additional analysis.

a common method of DNA amplification, using pairs of oligonucleotide primers as start sites for repetitive rounds of DNA polymerase-catalysed replication and alternating with denaturation in successive heating-cooling cycles.

### **Protocol**

the defined procedure by which a patient with a particular condition should be handled.

### **Quality-adjusted life years**

an outcome measure that incorporates the quality or desirability of a health state with the duration of survival.

### **Quantitative**

a characterization applied to laboratory tests that give results expressing a numerical amount or level (i.e., concentration) of an analyte in a specimen.

### **Repeat screening (requested)**

any subsequent screening test(s) performed on an additional specimen that was collected because the previous screening specimen had an out-of-range or screen-inconclusive result or was deemed unacceptable for testing.

### **Repeat screening (routine)**

any subsequent screening test(s) performed on an additional specimen that was collected as part of the screening program's routine practices.

### **Retest**

the same test applied to a punched sample from the same dried blood spot (DBS) specimen to obtain replicate results as part of the activity within the newborn screening laboratory process.

### **Screening**

the systematic application of a test or inquiry, to identify individuals at sufficiently high risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder.

### **Screen inconclusive**

a final, reportable result, based on the newborn screening result(s) and laboratory screening algorithm for a screened disease, group of diseases, or phenotypic difference, indicating the inability to accurately interpret the screening result, typically leading to a request for a repeat dried blood spot specimen.

### **Screen negative**

a final, reportable result for a disease, group of diseases, or phenotypic difference, based on the newborn screening result(s) and laboratory screening algorithm, indicating that the risk for that disease, group of diseases, or phenotypic difference is low and that no additional newborn screening follow-up is needed.

### **Screen positive**

a final, reportable result for a disease, group of diseases, or phenotypic difference, based on the newborn screening result(s) and laboratory screening algorithm, indicating that the risk for that disease, group of diseases, or phenotypic difference is higher and that additional follow-up is needed.

### **Second-tier screen**

(for newborn screening) additional assay, physiological measurement, or assessment, performed as a second step in a laboratory screening algorithm on a subset of newborns, that uses the initial screening specimen (i.e., specimen re-collection not necessary) when first-tier screening results are out of range.

**Venous blood sample**

blood collected after directly puncturing a vein, usually with a needle and syringe, or another collection device.

**Whole blood**

blood containing all its cellular components that has not been centrifuged nor had its plasma or serum removed.

*The glossary of terms is derived from The Clinical and Laboratory Standards Institute (CLSI) Harmonized Terminology Database (updated 2023).(1)*



## Abbreviations

AAV:	Adeno-Associated Virus
ANZCNS:	Australian and New Zealand Child Neurology Society
CALD:	Culturally and Linguistically Diverse
CHOP-INTEND:	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP:	Compound Muscle Action Potential
DBS:	Dried Blood Spot
ddPCR:	Digital Droplet Polymerase Chain Reaction
DMT:	Disease Modifying Therapies
EDTA:	Ethylenediaminetetraacetic Acid
EMG:	Electromyography
FDA:	USA Food and Drug Agency
GRADE:	Grading of Recommendations, Assessment, Development and Evaluations
HCP:	Healthcare Professional
HINE:	Hammersmith Infant Neurological Examination
HRM:	High Resolution Melting
MLPA:	Multiple Ligation dependent Probe Amplification
MND:	Motor Neuron Disease
NBS:	Newborn Bloodspot Screening
NHMRC:	Australian National Health and Medical Research Council
NGS:	Next Generation Sequencing
NLM:	New Line Method
PCR:	Polymerase Chain Reaction
PCR/CE:	Polymerase Chain Reaction-Capillary Electrophoresis
PICO:	Patient, Intervention, Comparison, Outcome

PBAC:	Pharmaceutical Benefits Advisory Committee
PBS:	Pharmaceutical Benefits Scheme
QI:	Quality Improvement
QoL:	Quality of Life
qPCR:	Quantitative Polymerase Chain Reaction
qRT-PCR:	Quantitative Reverse Transcription Polymerase Chain Reaction
RCT:	Randomised Control Trials
RFLP:	Restriction Fragment Length Polymorphism
RT-PCR:	Reverse Transcription Polymerase Chain Reaction
SAC:	Scientific Advisory Committee
SMA:	Spinal Muscular Atrophy
SMN:	Survival Motor Neuron
SMN1:	Survival Motor Neuron 1 gene
SMN2:	Survival Motor Neuron 2 gene
TGA:	Therapeutic Goods Administration

## Executive Summary

Spinal muscular atrophy (SMA) is a group of rare inherited genetic conditions, affecting around 1 in 10,000 individuals.(2) Considered as a predominantly childhood onset condition, SMA is caused by progressive loss of lower motor neurons from the spinal cord and brain stem.(3) The most common form of SMA is related to a deficiency of the survival motor neuron (SMN) protein and is the focus of this Guideline.

Prior to the introduction of treatments over the last decade, SMA was the leading genetic cause of infant death in the Western world, with only 10% of children with the severest, infantile onset form, surviving past their second birthday.(4)

With the introduction of SMN augmenting treatments, SMA has changed from a progressive condition with limited survival and increasing challenges in motor function, feeding and breathing, to one where an affected individual has the potential to survive, gain motor skills and live life with greater independence. The greatest magnitude of benefit on health outcomes are observed when treatment is given early, particularly before the signs and symptoms of the condition develop i.e. in the presymptomatic or clinically silent stage.(5-9)

Newborn screening for SMA has been recognised as a population wide health program that can facilitate early diagnosis, timely treatment and improvements in health and psychosocial outcomes for affected children and their families.(5, 10-12)

In 2022, after a period of evidence gathering and consultation from the first Australian pilot program for SMA (which ran in New South Wales and the Australian Capital Territory 2018-2022), the Commonwealth Department of Health endorsed the inclusion of SMA on routine newborn screening panels.(13) This was followed in 2023 by Te Whatu Ora (Health New Zealand) endorsing routine inclusion of SMA onto routine newborn screening panels.(14)

Decentralisation of newborn screening in Australia and a separate centralised system in Aotearoa New Zealand may give rise to regional differences in newborn screening programs.(15, 16) To address this barrier, a best practice Guideline that is founded in evidence and that aligns with an Australasian healthcare landscape is essential.(17) Of note, access to multidisciplinary care services for children and families with rare diseases such as SMA, can be challenging, particularly in outer regional, remote, and very remote parts of Australia, generating a potential for inequity for all Australians. This is perpetuated by specialist services, clinical genetics and genomics that centre on urban areas with limited investment in regional and rural areas.(18, 19) These factors have the potential to create inequity in the access to diagnosis, treatment, care, and potential outcomes of affected children.

This Guideline was developed to provide a child and family focussed approach to newborn screening for SMA across Australia and Aotearoa New Zealand. It was intended to span the entire healthcare journey of the newborn, from screening, through to diagnosis and immediate post-diagnosis assessment and care for the newborn and their family. The Guideline was considered essential to give all Australian and Aotearoa New Zealand children with SMA, equitable access to an expedient diagnosis of SMA and best care, based on evidence. It is envisaged that the recommendations therein will serve to improve health and psychosocial outcomes for affected children, and to support their families through this process.

The Guideline has been formulated using a validated methodology for searching, appraising and grading evidence.(20-26) Recommendations have been developed using systematic evidence synthesis in combination with expertise and evidence from an Australian and Aotearoa New Zealand multidisciplinary national committee, with state and territory representation across (newborn) screening, diagnostics, clinical care, advocacy and lived experiences from consumer domains.

The Guideline is applicable to individuals involved in the (newborn) screening and diagnosis process (including scientists and laboratory staff) and healthcare professionals (neurologists, paediatricians, general practitioners, clinical geneticists, nurses, allied health therapists) involved in the management of individuals with SMA and their families as identified through

a newborn screening for SMA process (collectively defined for the purpose of the Guideline as healthcare practitioners). Targeted secondary end users included health system planners, managers and administrators whose organisations provided services for population screening and care of individuals with SMA and their families. It is recommended that the Guideline be reviewed and updated at minimum every five years.

## Plain language summary

This Guideline explains to healthcare practitioners involved in (newborn) screening, diagnostics and clinical care of newborns and infants with SMA, how to practice in ways that are accurate, timely and helpful to individuals with the condition and their families.

### Background

SMA is a genetic condition that results in progressive muscle weakness. The most common form of SMA is caused by an absence of a part of both copies of the survival motor neuron 1 (*SMN1*) gene which leads to deficiency of a protein called survival motor neuron (SMN) and loss of nerve cells (motor neurons) that control muscle movement.(3) In a minority of individuals, SMA is caused by other changes (pathogenic variants) in the *SMN1* gene, which are not identified by current newborn screening methods. There are other forms of SMA not related to SMN protein deficiency and these are not covered in the Guideline.

All of us have a related gene, located near to *SMN1*, called survival motor neuron gene 2 (*SMN2*) that can produce some functional SMN protein to partially make up for the loss of the *SMN1* gene. The number of copies of *SMN2* can vary between people and change the severity of SMA. Generally, people who have a higher copy number of *SMN2* have a milder form of SMA.(27) The number of *SMN2* copies can be important to predict when an individual with SMA might get symptoms and how severe their condition may be.(27)

Newborn screening can identify conditions that may affect a child's long-term health or survival. Newborn screening aims to identify children at risk of serious but treatable conditions, such as SMA that if managed early can prevent or reduce death, illness and/or disability and provide the best outcomes for affected children. In 2022 and 2023, the governments of Australia and Aotearoa New Zealand respectively, agreed that SMA should be part of routine national newborn screening programs i.e. be offered to all babies born within Australasia. (14, 28) Children identified by SMA newborn screening are urgently

referred for confirmatory testing, discussion of treatments and care. A summary of the recommendations from the Guideline include:

### Section 1: The process of newborn screening for spinal muscular atrophy

Newborn screening for SMA should be completed on the few drops of blood (usually) taken from the baby's heel within the first few days of life. The screening method should look for the most common genetic change that is found in 95% of people with SMA i.e. the missing part of the *SMN1* gene called exon 7. A positive screen is when there is no exon 7 on *SMN1* detected on the blood spot.(29)

As *SMN2* copy number is important to predict how quickly the baby might develop signs of SMA and guide the need for quick treatment,(30, 31) *SMN2* copy number testing should ideally be done on the same blood spot, or as soon as possible during the process of diagnosis. Newborn screening for SMA should be completed in state (newborn) screening laboratories, using testing methods that are suitably approved and certified.

### Section 2: The process of confirming a diagnosis for spinal muscular atrophy

The newborn screening test, although very accurate, indicates whether a particular baby is at increased risk of having SMA. The condition needs to be confirmed (that is diagnosed) through additional blood tests from a screen positive newborn. These blood tests should include looking for exon 7 on *SMN1* and confirming the *SMN2* copy number.(12, 32, 33) Diagnostic blood tests should be completed using testing methods that are suitably approved and certified.

### Section 3: The process of providing care and advocating for children and families undertaking the process of newborn screening for spinal muscular atrophy

As SMA can progress quickly, it is important that all healthcare practitioners communicate and work together to make sure that the screen positive newborn has a molecular genetic diagnosis confirmed accurately and quickly, and that treatment plans are considered early. Healthcare practitioners should be competent and provide high quality services that are safe and supportive. They should collect, use, and share information in ways that are helpful, respectful, and accessible. Families of screen positive newborns should be referred to supports when needed and desired at any point of the newborn screening for SMA pathway.



## Guideline purpose, scope, population and setting

### Purpose

The Guideline has been developed to provide a set of recommendations that align with the evidence base, which can be used to inform the processes of screening, diagnostic and immediate post-diagnostic clinical management for all newborns/infants undertaking newborn screening for SMA in Australia and Aotearoa New Zealand (for the purpose of the Guideline considered as Australasia).

It is envisaged that adopting best practice recommendations will streamline and standardise these processes across Australasia to ensure efficiency of access to diagnosis, treatment and care for affected children. The recommendations have been developed to optimise access to information, care and support for families going through the healthcare journey with their children. It is envisaged that the Guideline will lead to adoption of high-quality care which will improve the health and psychosocial outcomes of affected children and the wellbeing of their families.

The purpose of the Guideline is therefore to provide informed guidance for screening, diagnostic and clinical care service providers to standardise the implementation of national newborn screening for SMA in a manner that is equitable, feasible and sustainable across Australasia. The Guideline's purpose has also been developed to meet the needs and expectations of children screening positive for SMA through newborn screening programs, and their families.

### Scope

The Guideline takes the view of the healthcare journey for the newborn and family from screening for SMA, through to confirmation of a diagnosis, and clinical care and support after the diagnostic period. The consenting process for (newborn) screening has been considered outside the scope of this Guideline.

The Guideline is intended to inform and guide but does not replace clinical reasoning or acumen. It is linked with and thus do not replace the National Screening Policy Framework (34) and internationally developed Standards of Care for SMA.(35, 36) It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and Aotearoa New Zealand.

As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address access to healthcare and treatment pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded healthcare. Furthermore, it does not include recommendations for medicines or services that are unavailable or restricted in these jurisdictions.

It has been decided *a priori* that the risk-benefits of NBS for SMA (which have been predetermined through a pilot study),(10, 12, 37, 38) technical aspects of screening (as covered by the Clinical & Laboratory Standards Institute Guideline for Newborn Screening for SMA)(1) and diagnostic methodologies and ongoing management of individuals with SMA beyond the initial post-diagnostic period (as covered by international standards of care guidelines (35, 36) will not be covered in this guidance. Newborn screening is a public health program that fits alongside and within other public health initiatives such as reproductive carrier testing, and prenatal genetic screening. This Guideline acknowledges, compliments, and does not replace existing guidelines that encompass these domains.

It has been decided *a priori* that the Guideline will provide recommendations for newborn screening for SMA related to lack of survival motor neuron (SMN) protein (synonymous with 5q SMA or classic SMA) and thus SMA related to other causes will fall outside its scope.

## Population

Whilst incidence and prevalence varies between populations, SMA affects all ethnic groups.(39) During the development of the Guideline, the Guideline Development Group (GDG) acknowledged that whilst newborns ( $\leq 28$  days of age) generally undertook NBS for SMA within the first 2-3 days of life, in some jurisdictions and within some families, processes could occur after this defined period. Hence, NBS for SMA could technically also

occur in infants i.e. children (29 days to 12 months of age). Where newborns and infants were considered together, the GDG defined these two cohorts as synonymous with ‘children’.

During development, the GDG acknowledged the fact that the diagnosis of SMA within the early (newborn and infancy) period of life had effects on families. Accordingly, the Guideline extends to recommendations for family centred care, support and information provision.

The Guideline specifically provides best practice recommendations for the implementation of NBS for SMA in Australia and Aotearoa New Zealand, however, it may be used as a template in other health jurisdictions.

The Guideline applies to all newborns/infants undergoing NBS for SMA, and their families, inclusive of Aboriginal, Torres Strait and Pacific Islander, Māori and other First Nation peoples and culturally and linguistically diverse communities.

### Healthcare settings and clinical stage

The Guideline applies to the public health care setting (including primary, secondary and tertiary/specialist care) and clinical areas including hospitals and community health care services. The Guideline also applies to screening, diagnosis, assessment and treatment clinical stages.

### Target end users

Targeted primary end users of the Guideline include Australian and Aotearoa New Zealand healthcare practitioners, defined for the purpose of the Guideline as professionals working in the (newborn) screening and diagnosis process (including scientists and laboratory staff) and medical practitioners (paediatric neurologists, paediatricians, general practitioners, clinical geneticists, nurses, allied health therapists) involved in the care and management of individuals with SMA and their families as identified through an NBS for SMA process.

Targeted secondary end users include

1. Australian and Aotearoa New Zealand health system planners including public funding bodies, managers and administrators whose organisations provide services for population screening, diagnosis and care of individuals with SMA and their families.

2. Australian and Aotearoa New Zealand training providers including peak bodies and institutions that may use the Guideline to streamline educational and clinical resources.
3. Australian and Aotearoa New Zealand families of children undergoing and screening positive for SMA through newborn screening programs.

### Clinical questions to meet the needs of target end users

The GDG iteratively developed a set of broad questions within each domain of (newborn) screening, diagnosis and clinical care and advocacy. Broad questions to inform Guideline development included:

1. What processes should be used to screen for SMA in the newborn period?
2. Should prognostic tests be included in the newborn screening program for SMA?
3. What processes should be used to confirm the diagnosis of SMA after a screen positive result is received?
4. What diagnostic methods are available to predict or inform the age of onset or clinical severity of SMA and should these be included in diagnostic protocols?
5. If there are differences in screening and diagnostic test results (i.e. false positive, false negative or uncertain screening results) for a newborn identified as screen positive for SMA through newborn screening programs, how should these be resolved?
6. How, who and when should a screen positive result for SMA be communicated to families?
7. What assessments are required as part of the clinical diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program?
8. What educational materials or resources are required to support a family who receive a screen positive and diagnostic SMA result for their newborn through an NBS for SMA program?
9. Are there specific provisions that need to be considered in supporting families of Aboriginal, Māori or Torres Strait Islander descent and/or families of culturally and linguistically diverse groups as they navigate the NBS for SMA process?

10. For newborns diagnosed with SMA, what follow-up assessments are required that may modify health outcomes and quality of life for the newborn/infant and their families?
11. What are the standard treatments for SMA and evidence of their effectiveness to improve health outcomes and quality of life for newborns diagnosed with SMA?
12. For these treatments, are there any risks that need to be managed?
13. For newborns diagnosed with SMA through newborn screening programs, what is the best way of organising services in terms of integration of care, patient and family centred care, multidisciplinary assessment, and care management?
14. How do we consider equity of access to the NBS for SMA pathway, independent of health literacy, regional/remote location, gender, and cultural and language background of the family?



# Quick Reference List of Recommendations

## List of recommendations

The following are a reference list of Evidence and Consensus based recommendations, pertaining to the domains of screening, diagnostics and clinical care and advocacy within the newborn screening for SMA pathway that are included in the Guideline.

Each recommendation includes a ‘Grade of Recommendation.’ All Recommendations within the Guideline represent good practice and should be implemented. For evidence-based recommendations we provide a grade of A to D as defined by the quality and consistency of available evidence, generalisability, impact and applicability to the Australasian healthcare context of the evidence base available to support the recommendation. The grade of recommendations (strong, conditional) for consensus-based recommendations is intended to support users in considering a range of factors when implementing a given Recommendation, such as the benefits and harms, resources needed, and the acceptability to individuals, families, and practitioners. Here, where a Recommendation is strong, it is written as ‘*we recommend*’ and when a ‘conditional’ Recommendation has been made, it indicates that there are factors to consider during implementation and is written in the format of ‘*we suggest*’.

This approach to providing grades is consistent with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) framework.(20, 25) Further information about this approach is provided in the Administrative and Technical Report which can be found at <https://www.unsw.to/nbs-sma>.

[A more detailed explanation of the grading system behind the direction and strength of recommendations can be found here.](#)

## Section 1. Recommendations on screening for *SMNI* as part of (newborn) screening in SMA

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### Recommendation 1.1

Evidence based recommendation

We recommend that newborn screening for SMA should be performed on the routine newborn dried blood spot.

Grade of recommendation B

### Recommendation 1.2

Evidence based recommendation

We recommend that the target analyte of newborn screening for SMA is absence of exon 7 on *SMNI* i.e. zero copies of *SMNI*.

Grade of recommendation Grade B

### Recommendation 1.3

Consensus based recommendation

We recommend that the screening method selected by the screening program should have a sensitivity of  $\geq 95\%$  for the detection of *SMNI* exon 7 absence (0 *SMNI* copies).

Grade of recommendation Strong, Grade 1C

### Recommendation 1.4

Consensus based recommendation

We recommend that the screening test for SMA should determine the absence of exon 7 (0 *SMNI* copies), using suitably validated quantitative or qualitative assays.

Grade of recommendation Strong, Grade 1B



### Recommendation 1.5.

Consensus based recommendation

We suggest that screen positive samples (0 *SMN1* copies) should immediately be repeated on the same dried blood spot.

Grade of recommendation Conditional, Grade 2C

### Recommendation 1.6.

Consensus based recommendation

We recommend that the newborn screening process for SMA should **not** identify carrier status.

Grade of recommendation Strong, Grade 1C

### Recommendation 1.7.

Consensus based recommendation

We recommend that a screen positive result should be communicated to clinical services when the *SMN1* screening result is available (independent of the availability of *SMN2* copy number on screening assays), to reduce timelines to diagnosis and treatment.

Grade of recommendation Strong, Grade 1C

### Recommendation 1.8.

Consensus based recommendation

We recommend that if blood transfusion is considered, the dried blood spot (for purposes of screening for SMA) should be taken prior to transfusion of blood products.

Grade of recommendation Strong, Grade 1B

Recommendation 1.9.

Consensus based recommendation

We suggest that newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, and low or very low birthweight newborns should proceed using the same screening protocols as for term newborns.

Grade of recommendation Conditional, Grade 2B

## Section 2. Recommendations on screening for *SMN2* copy number as part of (newborn) screening in SMA

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### Recommendation 2.1.

#### Consensus based recommendation

We suggest that *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes but the result should not delay notification of the absence of exon 7 on *SMN1*.

Grade of recommendation Conditional, Grade 2B

### Recommendation 2.2

#### Consensus based recommendation

We recommend that *SMN2* copy number should be completed on suitably validated quantitative *SMN2* assays when completed as part of newborn screening.

Grade of recommendation Strong, Grade 1C

### Recommendation 2.3.

#### Consensus based recommendation

We recommend that when *SMN2* copy number is known to be  $> 4$  at the time of initial newborn screen identification i.e. in the absence of exon 7 on *SMN1*, this is **not** designated as a screen positive result.

Grade of recommendation Strong, Grade 1C

#### Recommendation 2.4.

Consensus based recommendation

We recommend that the (in)availability of *SMN2* copy number should not delay clinical notification of a screen positive result based on absence of exon 7 on *SMN1*.

Grade of recommendation Strong, Grade 1C

#### Recommendation 2.5.

Consensus based recommendation

We recommend that if screening for *SMN2* is not incorporated into the newborn screening process, diagnostic testing for *SMN2* copy number should occur during follow-up care.

Grade of recommendation Strong, Grade 1B

#### Recommendation 2.6.

Consensus based recommendation

We suggest that for the purposes of the screening program, unvalidated prognostic biomarkers outside of *SMN2* copy number (including *SMN2* splicing modifier variants and modifiers outside of the *SMN2* gene) will not be incorporated into screening algorithms.

Grade of recommendation Conditional, Grade 2C

#### Recommendation 2.7.

Consensus based recommendation

We recommend that the newborn screening program for SMA program should establish a clinical referral pathway for screen positive newborns. A positive newborn screening result should be verbally relayed to a designated paediatric neurologist.

Grade of recommendation Strong, Grade 1C

### Recommendation 2.8.

#### Consensus based recommendation

We suggest that written notification of a screen positive SMA result should be issued to the individual(s) listed in Recommendation 2.7. within 24 hours of the verbal notification of a screen positive result.

Grade of recommendation Conditional, Grade 2C

## Section 3. The process of confirming a diagnosis of SMA in screen positive newborns

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### Recommendation 3.1

Evidence based recommendation

We recommend that diagnostic testing should include confirmation of an absence of exon 7 on *SMN1* (i.e. zero copies of *SMN1*).

Grade of recommendation Strong, Grade B

### Recommendation 3.2

Consensus based recommendation

We recommend that diagnostic testing should also include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making. Diagnostic testing for *SMN2* copy number should occur from whole blood samples or repeat dried blood spot from a recalled newborn.

Grade of recommendation Strong, Grade 1B

### Recommendation 3.3

Consensus based recommendation

We recommend that validated quantitative *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.

Grade of recommendation Strong, Grade 1B

### Recommendation 3.4

Consensus based recommendation

We suggest that diagnostic *SMNI* testing is conducted using a different methodology to the newborn screening assay.

Grade of recommendation Conditional, Grade 2C

### Recommendation 3.5

Consensus based recommendation

We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means) should occur upon identification of a screen positive result, so that stakeholders understand when a diagnostic sample will be collected and delivered to diagnostic laboratories to proactively prioritise timelines and avoid delays.

Grade of recommendation Conditional, Grade 2B

### Recommendation 3.6

Consensus based recommendation

We recommend that diagnostic results for *SMNI* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory, to enable timely treatment.

Grade of recommendation Strong, Grade 1C

### Recommendation 3.7

Consensus based recommendation

We suggest that for the purposes of diagnostic testing for SMA (within the newborn screening context), genetic modifiers outside of *SMN2* copy number will not routinely be tested.

Grade of recommendation Conditional, Grade 2B

### Recommendation 3.8.

Consensus based recommendation

We recommend that a diagnosis of SMA (including *SMN1* and *SMN2* copy number) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment.

Grade of recommendation

Strong, Grade 1B

### Recommendation 3.9

Consensus based recommendation

We suggest that diagnostic reports should detail the methodology used for analysis and the precise *SMN2* copy number (avoiding reports such as  $SMN2 \geq 4$ ) where possible.

Grade of recommendation Conditional, Grade 2B



## Section 4. Managing uncertain, false positive and false negative newborn screening results

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### Recommendation 4.1

Consensus based recommendation

We suggest that for newborns with a false positive **or** uncertain screening result, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and explained to parents.

Grade of recommendation Conditional, Grade 2C

### Recommendation 4.2

Consensus based recommendation

We suggest that families of newborns with false positive or uncertain results should be given the option of returning to discuss the implications of results with members of the neurology/neuromuscular multidisciplinary team\*.

Grade of recommendation Conditional, Grade 2C.

### Recommendation 4.3

Consensus based recommendation

We recommend that if there is a difference in *SMNI* results between screening and diagnostic assays, retesting for *SMNI* with another method/laboratory. A further sample from the newborn may be required for repeat screening and/or diagnostic testing if resolution of *SMNI* genotype does not occur.

Grade of recommendation Strong, Grade 1C.

#### Recommendation 4.4

Consensus based recommendation

We recommend that if there is a difference in *SMN2* results between screening and diagnostic assays, retesting for *SMN2* copy number with another method/laboratory. A repeat sample from the newborn may be required for further diagnostic testing if resolution of *SMN2* copy number variation does not occur.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.5

Consensus based recommendation

We recommend that if there is uncertainty as to the diagnosis of SMA the child should be clinically followed up by a paediatric neurologist until diagnostic certainty is reached.

Grade of recommendation Strong Grade 1C

#### Recommendation 4.6.

Consensus based recommendation

We recommend that if there is uncertainty as to the diagnosis of SMA, families should be provided with clear instructions on red flags for signs and clinical symptoms that warrant medical attention (Recommendation 5.9).

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.7.

Consensus based recommendation

We recommend that for newborns with a false negative result, (diagnostically confirmed to have SMA after a negative newborn screen result), a case review with communication and

collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of this result.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.8.

Consensus based recommendation

We recommend that families who receive a false negative or uncertain screening result should be provided psychosocial support by relevant members within the multidisciplinary team.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.9.

Consensus based recommendation

We recommend that open disclosure between appropriate healthcare practitioners and families should occur with any false positive, uncertain or false negative screening results.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.10.

Consensus based recommendation

We recommend that healthcare practitioners conducting health check-ups for infants should be aware of the existence of false-negative SMA cases and the typical symptoms of SMA, for expedient referral to paediatric neurology services (due to current newborn screening assays only detecting absence of exon 7 on *SMN1*).

Grade of recommendation Strong, Grade 1C

## Section 5. Communicating a SMA screen positive result to families

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### Recommendation 5.1

Consensus based recommendation

We suggest that a screen positive result should be ideally disclosed to the family within  $\leq 2$  working days (of notification to healthcare services).

Grade of recommendation Conditional, Grade 2B

### Recommendation 5.2

Consensus based recommendation

We recommend that the paediatric neurologist, receiving the screen positive SMA result, should coordinate with relevant healthcare practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process.

Grade of recommendation Strong, Grade 1C

### Recommendation 5.3

Consensus based recommendation

We suggest that it is acceptable for a designated healthcare practitioner with support from a paediatric neurologist to disclose a screen positive result to a family.

Grade of recommendation Conditional, Grade 2C

#### Recommendation 5.4

We recommend that healthcare practitioners disclosing results to families from culturally and linguistically diverse backgrounds should be aware of particular issues arising from this disclosure. If the healthcare practitioner is not bilingual, a professional interpreter should be used.

Grade of recommendation Strong, Grade 1C

#### Recommendation 5.5.

Consensus based recommendation

We recommend that healthcare practitioners disclosing screen positive results for SMA to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori, or other First Nation backgrounds should be aware of culturally sensitive issues arising from this disclosure. The healthcare practitioner may seek advice from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) in how to best support families who receive a screen positive result.

Grade of recommendation Strong, Grade 1C

#### Recommendation 5.6

Consensus based recommendation

We suggest that key points in the (screen positive disclosure) call to the family should include:

The screen positive status of the newborn.

The name of the condition.

Time frame and place for clinical review of the screen positive newborn.

General discussion of SMA as a condition that can be treated.

Named healthcare practitioner as a point of contact for the family.

Clinical questions on the newborn's current status including feeding, movement and breathing and/or clinical concerns from families.

Grade of recommendation Conditional, Grade 2C

#### Recommendation 5.7

Consensus based recommendation

We recommend that screen positive newborns should be offered a clinical review within paediatric neurology/neuromuscular services, if they are able to travel safely and promptly to these centres.

Grade of recommendation Strong, Grade 1C

#### Recommendation 5.8

Consensus based recommendation

We recommend that a clinical review within local paediatric services, with clinical involvement through telehealth from a paediatric neurologist should be offered to screen positive newborns where access to specialist (neurology) services is limited and may cause delay in diagnostic evaluation.

Grade of recommendation Strong, Grade 1C

#### Recommendation 5.9.

Consensus based recommendation

We suggest that from time of disclosure, a screen positive newborn should be reviewed at a clinical service for diagnostic evaluation as soon as possible and ideally within  $\leq 2$  working days, from time of screen positive disclosure.

Grade of recommendation Conditional, Grade 2B

### Recommendation 5.10.

#### Consensus based recommendation

We recommend that healthcare practitioners should instruct families to contact them immediately to facilitate urgent clinical review at any time following screen positive disclosure if the following are noted in the newborn/infant.

Change in movement, feeding, or breathing pattern.

Change in voice or weak cry.

Increased fatigue without increased activity, decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability.

Abdominal breathing and/or failure to thrive.

In case of an acute event that requires hospitalisation

Grade of recommendation Strong, Grade 1C

## Section 6. Assessments required at the diagnostic evaluation of the newborn

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### Recommendation 6.1

#### Consensus based recommendation

We recommend that the following assessments are completed immediately as part of the diagnostic and clinical evaluation of the newborn, who screens positive for SMA.

Neurological examination.

Venous sampling for quantification of *SMN1* on whole blood.

Venous sampling for determination of *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number.

Grade of recommendation Strong, Grade 1C



## Section 7. Information provision to families during diagnostic evaluation and after confirming the diagnosis of SMA in the (screen positive) newborn

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### Recommendation 7.1

Consensus based recommendation

We recommend that in order to optimise knowledge and support, families of newborns who screen positive for SMA should be provided with information that is compassionate, accurate and tailored to the information needs and preferences of the family, and this should be provided by clinical services.

Grade of recommendation Strong, Grade 1C

### Recommendation 7.2

Consensus based recommendation

We suggest that the number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a paediatric neurologist or paediatrician), and ideally support from a healthcare practitioner which may include clinical geneticists and/or genetic counsellors, nurse specialists and/or medical social work and/or psychological services.

Grade of recommendation Conditional, Grade 2C

### Recommendation 7.3

Consensus based recommendation

We recommend that healthcare practitioners providing information to, and discussing diagnosis with, families of newborns from culturally and linguistically diverse backgrounds should be aware of particular issues arising from information provision and diagnostic

evaluation. If the healthcare practitioner is not bilingual, a professional interpreter should be used.

Grade of recommendation Strong, Grade 1C

#### Recommendation 7.4

Consensus based recommendation

We recommend that healthcare practitioners providing information to, and discussing diagnosis with, families of newborns from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other First Nations backgrounds should be aware of particular issues arising from information provision and diagnostic evaluation. The healthcare practitioner may elicit the advice of Indigenous Health Liaison professionals in how to best conduct these evaluations and offer families the support of Indigenous Health Liaison services at the time of diagnosis.

Grade of recommendation Strong, Grade 1C

#### Recommendation 7.5

Consensus based recommendation

We recommend that all families receiving a diagnosis of SMA for their newborn, through a newborn screening program should be offered the opportunity of support through referral to a counselling service, and/or medical social services and/or psychological services, and/or SMA advocacy services as appropriate.

Grade of recommendation Strong, Grade 1C

#### Recommendation 7.6

Consensus based recommendation

We recommend that families receiving a diagnosis of SMA for their newborn, through a newborn screening program, should be directed to high quality and reliable educational

resources that support information provision on the implications of the diagnosis and potential treatments for their newborn.

Grade of recommendation Strong, Grade 1B

*Educational resources provided should reflect the contemporary treatment and care landscape and be nationally consistent.*

### Recommendation 7.7

Consensus based recommendation

We recommend that all families receiving a diagnosis of SMA for their newborn, through a newborn screening program should be provided with the contact details of a dedicated healthcare practitioner who can direct a response to their queries.

Grade of recommendation Strong, Grade 1C

## Section 8. Supporting families as they receive the diagnosis of SMA

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### Recommendation 8.1

Consensus based recommendation

We recommend that the process of disclosing a diagnosis of SMA to families should occur when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result, to avoid delays in treatment planning.

Grade of recommendation Strong, Grade 1C

### Recommendation 8.2.

Consensus based recommendation

We recommend that diagnostic results should be disclosed to families by a paediatric neurologist.

Grade of recommendation Strong, Grade 1C

### Recommendation 8.3.

Consensus based recommendation

We recommend that if circumstances dictate, it is acceptable for a designated healthcare practitioner (such as a paediatrician, general practitioner, specialist nurse, clinical geneticist or genetic counsellor) with involvement through telehealth from a paediatric neurologist, to disclose a diagnostic result to a family.

Grade of recommendation Strong, Grade 1C

#### Recommendation 8.4

Consensus based recommendation

We suggest that diagnostic results should be disclosed to families face to face.

Grade of recommendation Conditional, Grade 2C

#### Recommendation 8.5

Consensus based recommendation

We suggest that if circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for diagnostic disclosure to occur through telephone or Telehealth.

Grade of recommendation Conditional, Grade 2C

## Section 9. Immediate post diagnosis care for newborns and infants receiving a diagnosis of SMA through a newborn screening program

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### Recommendation 9.1

Consensus based recommendation

We recommend that all newborns diagnostically confirmed with SMA through a newborn screening program should be reviewed by a paediatric neurologist.

Strength of recommendation Strong, Grade 1C

### Recommendation 9.2

Consensus based recommendation

We recommend that at the time of diagnosis, all newborns confirmed with SMA should initially be managed within a paediatric neurology service.

Strength of recommendation Strong, Grade 1C

### Recommendation 9.3.

Consensus based recommendation

We recommend that all newborns should have a neurological and neonatal examination including cardiac, respiratory and gastrointestinal systems to assess their clinical status.

Strength of recommendation Strong, Grade 1C

#### Recommendation 9.4

##### Consensus based recommendation

We suggest that all children diagnosed with SMA through newborn screening should have a shared model of care between local community (general practitioners and allied health therapists), secondary (paediatric services) and specialist (paediatric neurology) services, to facilitate post diagnosis care, which is personalised according to the biopsychosocial characteristics of the child and family.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 9.5

##### Consensus based recommendation

We recommend that families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to clinical genetics service).

Strength of recommendation Strong, Grade 1C

#### Recommendation 9.6

##### Consensus based recommendation

We suggest that the sibling(s) of a newborn diagnosed with SMA through newborn screening could be offered a clinical review within paediatric neurology services, at an appropriate time.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.7

#### Consensus based recommendation

We suggest that for sibling(s) of affected children who live in remote regions, a review for signs and symptoms of SMA may be offered and conducted by a designated healthcare practitioner, such as a paediatrician or general practitioner, with support from a paediatric neurologist.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.8.

#### Consensus based recommendation

We suggest that the symptomatic status of the child should be defined by healthcare practitioners primarily by the presence of signs and symptoms of SMA on neurological and neonatal examination.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.9.

#### Consensus based recommendation

We suggest that newborns undergo neurophysiological assessments within a reasonable time of diagnosis, including collation of compound muscle action potential (CMAP) +/- electromyography (EMG), to obtain predictive information on disease course.

Strength of recommendation Conditional, Grade 2C



## Section 10. Therapeutic planning and treatment initiation for newborns and infants diagnosed with SMA through newborn screening programs

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### Recommendation 10.1

Consensus based recommendation

We suggest that treatment planning should commence as soon as the *SMN1* diagnostic result is received.

Strength of recommendation Conditional, Grade 2C

### Recommendation 10.2

Consensus based recommendation

We recommend that for screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset), options for immediate treatment with SMN augmenting treatments should be discussed with the family, independent of *SMN2* copy number.

Strength of recommendation Strong, Grade 1A

### Recommendation 10.3

Consensus based recommendation

We suggest that for newborns who demonstrate signs and symptoms of SMA (consistent with disease onset) with 1 *SMN2* copy, therapeutic decision making is dependent on the newborn/infant's clinical status and open discussions with families regarding treatment options or referral for supportive care alone.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 10.4.

Consensus based recommendation

We recommend that for newborns with diagnostic confirmation of SMA and 1, 2 or 3 *SMN2* copies and who are presymptomatic, options for immediate SMN augmenting treatments should be discussed with the family.

Strength of recommendation Strong, Grade 1B

#### Recommendation 10.5

Consensus based recommendation

We recommend that in the absence of comparative data, currently single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended.

Strength of recommendation Strong, Grade 1C

#### Recommendation 10.6

Consensus based recommendation

We recommend that families should be informed as part of the therapeutic decision-making process that expedient therapeutic intervention may change motor and developmental trajectories and respiratory and feeding outcomes for symptomatic newborns/infants and those presymptomatic newborns/infants with 1, 2 or 3 *SMN2* copies.

Strength of recommendation Strong, Grade 1C

#### Recommendation 10.7

Consensus based recommendation

We recommend that healthcare practitioners should explain to families and document the potential benefits, risks, uncertainties, of SMN augmenting treatments and need for long term surveillance.

Strength of recommendation Strong, Grade 1C

#### Recommendation 10.8

Consensus based recommendation

We recommend that therapeutic care planning should take into consideration disease status (presymptomatic/symptomatic), genotype (including *SMN2* copy number), current motor function, disease duration, and individualised factors including social and family circumstances, goals of care and preferences.

Strength of recommendation Strong, Grade 1C

#### Recommendation 10.9

Consensus based recommendation

We suggest that parents may require support with therapeutic decision making and resources may be made available to them (including as appropriate referral to medical social work, clinical geneticists and genetic counsellors, psychology, and/or patient advocacy groups) to facilitate this process.

Strength of recommendation Conditional, Grade 2B

#### Recommendation 10.10

Consensus based recommendation

We suggest that the administration of SMN augmenting treatments should occur in a paediatric neurology treatment/care service within a multidisciplinary team.

Strength of recommendation Conditional, Grade 2A

### Recommendation 10.11

Consensus based recommendation

We suggest that where appropriate, SMN augmenting treatments may be planned to be initiated from a non-specialist treatment centre/service, with paediatric neurology support.

Strength of recommendation Conditional, Grade 2C

### Recommendation 10.12

Consensus based recommendation

We suggest that post treatment monitoring for newborns who access SMN augmenting treatments may be shared between paediatric neurology centres, secondary paediatric services and community (general practitioner) services (with support from the specialist centres) as child and family factors dictate.

Strength of recommendation Conditional, Grade 2C

### Recommendation 10.13

Consensus based recommendation

We recommend that newborns with diagnostic confirmation of SMA who are unable to access approved and reimbursed treatments immediately should be managed by a paediatric neurologist specialist.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.14

#### Consensus based recommendation

We suggest that newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.

Strength of recommendation Conditional, Grade 2C

### Recommendation 10.15

#### Consensus based recommendation

We recommend that for all newborns diagnosed with SMA through newborn screening, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), best practice care includes the following assessments, conducted at each visit

Comprehensive history taking including changes in movement, breathing and feeding.

Growth parameters including length, weight and head circumference

Neurological examination.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.16

#### Consensus based recommendation

We suggest that for all newborns diagnosed with SMA, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments as part of best practice care may include motor assessments that should be adapted to the objectives set for the newborn/infant and considers function, SMA type, age, comorbidities and clinical status. The timing and frequency of assessments may vary between children and will be dependent on therapeutic goals, clinical questions raised, and child and family factors.

Strength of recommendation Conditional, Grade 2C

### Recommendation 10.17

Consensus based recommendations

We recommend that evaluators must meet the standards for training for the administration of each examination or assessment.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.18

Consensus based recommendation

We recommend that all children diagnosed with SMA should be referred for multidisciplinary allied therapy interventions aligning with international standards of care (Consensus Statement of Standards for Care of Spinal Muscular Atrophy).(35, 36)

Strength of recommendation Strong, Grade 1C

## Section 11. Post diagnosis care for newborns, infants and children with SMA and $\geq 4$ *SMN2* copies, who are not initially treated with SMN augmenting therapies

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### Recommendation 11.1.

Consensus based recommendation

We suggest that for newborns with  $\geq 4$  *SMN2* copies not initially treated with SMN augmenting therapies (due to a shared decision by family and the healthcare practitioner or for newborns who cannot access treatment), clinical follow-up should occur with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.

Strength of recommendation Conditional, Grade 2C

### Recommendation 11.2

Consensus based recommendation

We suggest that redetermination of *SMN2* copy number in a different laboratory or using a different method, may be considered in all newborns with  $\geq 4$  *SMN2* copies due to methodological imprecision arising from *SMN2* copy number methodologies that can impact therapeutic decision making.

Strength of recommendation Conditional, Grade 2C

### Recommendation 11.3

Consensus based recommendations

We suggest that neurophysiological techniques (including CMAP +/- EMG +/- motor unit number estimation methods) may be incorporated in the clinical follow-up for newborns with  $\geq 4$  *SMN2* copies who cannot access immediate treatment, to screen for disease onset as the basis to initiate therapeutic intervention.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 11.4

Consensus based recommendation

We suggest that families of children who are presymptomatic and with  $\geq 4$  *SMN2* copies should be educated on the necessity of ongoing clinical surveillance and supported by the multidisciplinary team through this process (including referral to psychological and medical social work services) as appropriate.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 11.5

Consensus based recommendation

We suggest that national clinical paediatric neurology centres should coordinate and establish databases to collect outcome data for newborns who have  $\geq 4$  *SMN2* copies and are under clinical surveillance, to establish an evidence-base to guide therapeutic and policy decision making.

Strength of recommendation Conditional, Grade 2C





# The Guideline Development Process

## Step 1

### Defining the need for a Guideline and criteria for its development

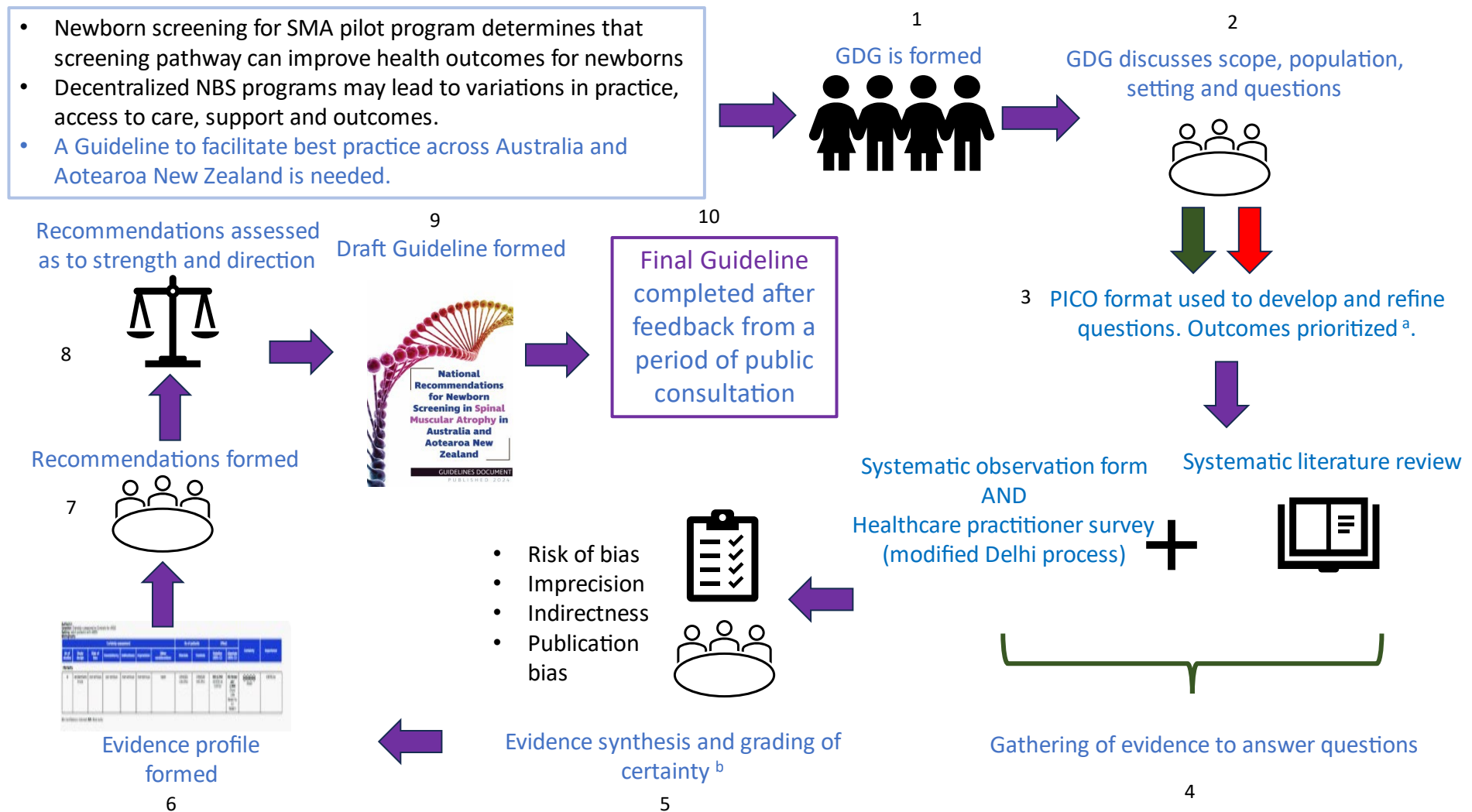
During the pilot newborn screening for SMA program (that ran across New South Wales and the Australian Capital Territory from 2018-2022), clinical researchers and healthcare practitioners across Australia and Aotearoa New Zealand identified the necessity for a coordinated clinical strategy to optimise access to, equity and timing of diagnosis for SMA through newborn screening (12) (Figure 1). Understanding and developing recommendations to establish predetermined roles and responsibilities amongst screening, diagnostic and clinical services was considered essential to enable an efficient and smooth transition of the newborn and their family through the healthcare journey.(12) This would ultimately lead to improved health outcomes for newborns and support and care for their families. Consequently, an evidence-based guideline for Australia and Aotearoa New Zealand was proposed.

The development of the Guideline was in accordance with the Procedures and Requirements for meeting the National Health and Medical Research Council (NHMRC) standards for guidelines,(40) and adhered to nine standards.

- Standard 1 – Be relevant and useful for decision making.
- Standard 2 - Be transparent.
- Standard 3 - Be overseen by a guideline development group.
- Standard 4 - Identify and manage conflicts of interest.
- Standard 5 - Be focused on health and related outcomes.
- Standard 6 - Be evidence informed.
- Standard 7 - Make actionable recommendations.
- Standard 8 - Be up to date.
- Standard 9 - Be accessible.

Due to SMA being within a rare disease field, the methodology also aligned with the National Strategic Action Plan for Rare Diseases (NSAPRD)(15) with an emphasis on developing

guidelines that accounted for the paucity of high-level evidence in the rare disease field but remained highly relevant to the care and support of affected children and their families



**Figure 1. The Guideline development process.** A Guideline Development Group (GDG) was formed (1) and met to discuss scope, population applicable settings and broad questions for the Guideline (2). A Population, Intervention, Comparator, Outcome (PICO) format was used to develop,

refine questions and prioritise outcomes (3). An evidence base was formed through systematic literature review and stakeholder consultation processes (4). The evidence was synthesised and graded as to certainty (5,6) to form and grade the strength of evidence-based recommendations (7,8). The scholarly literature combined with results from a modified Delphi process and systematic observation forms were synthesised to form consensus-based recommendations (7), which were also graded for direction and strength (8). Draft Guideline was formed (9) and submitted for a period of public consultation, with feedback incorporated where appropriate before submission of the final Guideline (10).

## Step 2

### Forming the Guideline Development Group and governance structure

The Guideline Development Group (GDG) was formed for the purpose of leading the research. The objectives of the GDG were to devise evidence and consensus-based recommendations for the standardised implementation of newborn screening for SMA in Australia and Aotearoa New Zealand. The GDG collated evidence, provided expert opinion where evidence was lacking, and used the evidence to formulate then grade the strength of recommendations using an evidence to decision process. The GDG also provided oversight for of the public consultation and international peer review process, revising the Guideline and associated documents according to feedback, and endorsing the finalised Guideline for dissemination.

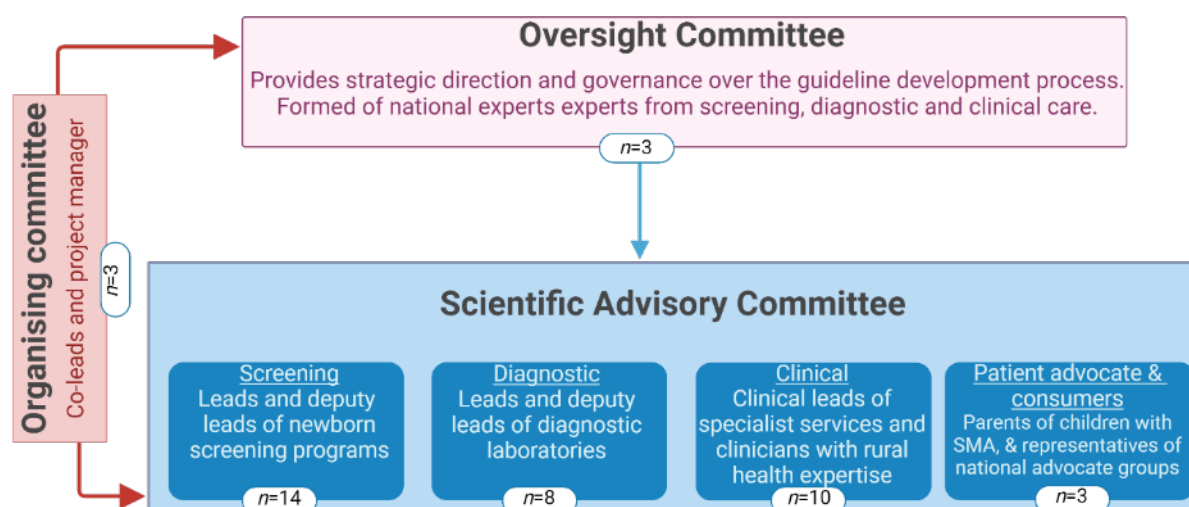
The GDG was formed with an Organising Committee, Scientific Advisory Committee (SAC) and Oversight Committee (Figure 2.). Oversight Committee members were invited by the Co-leads to provide expert advice on the methodology and strategy used to develop the Guideline.

SAC members had diverse and key perspectives and eligibility was determined by experience, knowledge, skills and/or lived experiences related to NBS and/or SMA in Australia or Aotearoa New Zealand (Table 1). Individuals were purposively approached by the Organising Committee to be a SAC member if they fulfilled one or more of the following criteria:

1. Leads and Deputy leads of state and territory based (Australia) or national (Aotearoa New Zealand) newborn screening programs.
2. Leads and Deputy leads of SMA state and territory based (Australia) or national (Aotearoa New Zealand) SMA diagnostic laboratories.
3. Clinical Leads of specialist (paediatric) neurology services within each state and territory (Australia) and Aotearoa New Zealand, with expertise in managing children with SMA.

4. Healthcare practitioners with expertise in regional/rural health systems, and healthcare provision within culturally diverse populations.
5. Parents of children with SMA.
6. Chief Executive Officers of national patient advocate groups.

Processes were put in place to declare and manage any potential conflicts of interest, consistent with the NHMRC guidance (Administrative and Technical Report).(40, 41)



**Figure 2. The Guideline Development Group and its governance structure.** The oversight committee ( $n=3$ ) was comprised of representatives with national expertise in the areas of screening, diagnosis and clinical care. The Scientific Advisory Committee (SAC) contained leaders within their relevant areas of expertise, including screening ( $n=14$ ), diagnostic ( $n=8$ ), clinical ( $n=10$ ), and patient advocate and consumer representation ( $n=3$ ). The organising committee was comprised of two co-leads and a project manager ( $n=3$ ). The co-leads of the project were also part of the SAC. The Oversight Committee was formed of national experts who provided strategic direction on the Guideline development process.

## Involving and acknowledging Aboriginal, Torres Strait Islander, Pacific Islander and Māori Peoples and culturally and linguistically diverse communities

Of particular note, barriers to health access for Aboriginal, Torres Strait Islander, Pacific Islander and/or Māori communities prevent health equity and access to therapeutics. Factors include but are not limited to lack of transport, waiting times, and lack of culturally appropriate health information and materials.<sup>(42)</sup> Therefore, specific consideration should be given to create a more equitable system for First Nations peoples. Although representation was sought early in the guideline development process from representatives of Aboriginal, Torres Strait Islander, Pacific Islander and/or Māori communities, we were unable to have formal representation as part of the GDG. However, representation and co-development of the guidelines was facilitated through Dr Corin Miller, a clinician with expertise in rural and regional health and issues relevant to peoples of Aboriginal and Torres Strait Islander descent who formed part of the GDG. Specific areas of evidence as pertaining to Aboriginal, Torres Strait Islander and Māori Peoples and culturally and linguistically diverse communities were developed, to inform the development of targeted and relevant recommendations. During the public consultation process, health and organisational bodies with specific expertise and knowledge of First Nation populations were specifically invited to provide feedback.

### Step 3

## Defining the scope and content for the Guideline

To ensure Guideline relevance and usefulness, the SAC collaboratively identified key domains, the scope, population, settings, and end users, through a series of videoconferences. The GDG iteratively developed a set of broad questions within each domain of (newborn) screening, diagnosis and clinical care and advocacy. It was considered that the Guideline would apply to all newborns/infants undergoing newborn screening for SMA, and their families. The population was inclusive of Aboriginal, Torres Strait and Pacific Islander, Māori and other peoples from First Nation communities, and culturally and linguistically diverse (CALD) peoples.



Within each domain specific questions were presented, discussed and refined by a working group comprised of SAC members with relevant expertise. Each working group was run over three 1-hour meetings through videoconference and chaired by Co-leads of the GDG.

Potential factors relevant to CALD and Aboriginal/Torres Strait, Pacific Islander and Māori groups, included creation of specific questions related to these groups and conducting systematic reviews of the evidence as pertinent to these questions. Issues identified fit under two broad categories; information and support provided to families, and equity of care for newborns undergoing the screening process for SMA.

The compiled list of potential questions from which to base recommendations were presented and refined and at a meeting with the entire SAC and through email contact. At each stage, questions were developed using a PICO format (P= population of interest, I= intervention, C= comparison or alternative to the intervention, O=outcome of interest), as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.(43, 44) At this juncture, potential outcomes were selected and prioritised. This framework is a systematic and transparent approach for rating the certainty of evidence in systematic reviews and clinical practice guidelines, and for developing and determining the strength of clinical practice recommendations.

## Step 4

### Rationale and approach for processes used in the evidence gathering stage

Prior to this study, systematic reviews of the scholarly literature pertaining to newborn screening for SMA had not been conducted. The quantitative data generated through a systematic review of the scholarly literature using a PICO format (Step 5) was considered by the GDG as insufficient to answer several of the questions that the SAC considered relevant to include in the Guideline as these varied in methodological quality, clarity of outcome data, the nature and delivery of the defined intervention and how the outcomes were assessed. Additional evidence generated through systematic and qualitative methods of collecting consensus from a group of experts that included the preferences and values of stakeholders was also considered relevant to development of the evidence base. Consequently, the GDG

prioritised development of questions relevant to everyday best practice. This was consistent with NHMRC Standard 1 (to be relevant and useful for decision making) and Standard 7 (to make actionable recommendations). For this same reason, the recommendations included in the Guideline were a mixture of evidence-based and consensus-based recommendations.

## Step 5

### Gathering the evidence

The purpose of gathering evidence was to facilitate the formulation of recommendations in a systematic manner, consistent with GRADE, and reflecting multiple converging sources of evidence. The Guideline was intended to be evidence-based, adhering to an evidence-based practice framework that combined best available evidence.(20, 45) The sources of data gathered for the purpose of Guideline development included:

1. Systematic review of the evidence found in the scholarly literature
2. An online survey to generate expert evidence (systematic observation) for stakeholders.
3. A healthcare practitioner survey to generate expert opinion (in the form of a modified Delphi process)

#### 1. Systematic review of the evidence

##### Aim

The aim of this systematic review was to identify, explore and evaluate the scholarly literature relating to the processes of newborn screening for SMA from screening, through to diagnosis, and post diagnostic clinical care of the newborn. The views, preferences and perspectives of families on information provision, support needs and communication were also evaluated.

## Research question

For each domain the research question was what are the processes and their associated outcomes?

## Study Design

A systematic review of the scholarly literature was selected as the most appropriate method for addressing the research aim and questions. The review was conducted in accordance with the procedures outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis guideline (PRISMA).(46) A series of 14 systematic literature reviews were performed from 18 October to 27 November 2023 across three databases of Scopus (Ovid), Embase (Ovid), and PubMed, using both keywords and MESH terms. A professional database consultant (Helen Jones, University of New South Wales) reviewed and refined each search strategy. The search was updated on 1<sup>st</sup> May 2024. The search included all peer-reviewed publications and was limited to the paediatric population (up to 18 years of age). Although non-English databases were not searched, studies identified in languages other than English were captured by the three databases and were transcribed into English using the Google translate function. Each search strategy was repeated with and without filters for Aboriginal, Torres Strait Islander, Pacific Islander and Māori peoples for the population of interest. The systematic literature reviews and search strategies are described in the Administration and Technical report.

The methodology formulated for the search strategy included the following processes:

1. Broad searches were formed to facilitate the inclusion a breadth of medical literature.
2. A combination of subject heading and keyword searches were used for each question.
3. Where possible, identical search strategies were utilised across databases.
4. A single search strategy was run across the three chosen databases, to reduce duplication of citations.
5. Searches were limited to individuals < 18 years i.e. paediatric age groups.
6. Searches were not limited by year i.e. all years available within each database were included.

## Eligibility criteria for studies

The inclusion and exclusion criteria for studies included in the systematic literature searches were formed using a **Population, Intervention, Comparator, Outcome(s)** framework (Table 2). Where systematic reviews existed, these were used preferentially to individual studies.

Table 2. *Population, Intervention, Comparator, Outcome(s) framework and eligibility criteria for studies included in the systematic reviews.*

Clinical Question	Population(s)	Intervention or Exposure	Comparator	Outcome	Study Design
<b>Inclusion</b>	Newborns, infants and children with SMA. Birth up to 18 years. Any cultural or ethnic background OR families of newborns, infants and children with SMA.	Newborn screening for SMA.	Children diagnosed with SMA through (non) newborn screening pathways including through prenatal screening, clinical referral of symptoms.	Change in outcomes related to the relevant question.	Any study design. ** Peer reviewed. Publication date not limited. Any language or geographic location.
<b>Exclusion</b>	Adults (> 18 years with SMA)*	Prenatal or carrier screening programs.	-	-	Conference abstracts, abstracts without full manuscript editorials, and unpublished data.

\*For publications that combined adult and paediatric participants, only studies where the outcomes for children could be separately identified were included.

\*\* This included systematic reviews of randomised control trials (RCTs), RCTs, Comparative non-randomised (observational) studies including prospective and retrospective cohort studies, case series, cross-sectional studies and case reports.

## Study Selection

### Screening

The review process was managed by importing the identified citations into COVIDENCE ([www.covidence.org](http://www.covidence.org)). A two-pass selection process was used to identify relevant citations and was conducted in duplicate by two independent reviewers (Didu Kariyawasam and Christian Meagher).

*First Pass (Title and Abstract Screening):* The retrieved citations were reviewed against the clinical question and eligibility criteria based on information contained in the title, abstract and description (including MeSH headings), and coded (Table 3.). The studies identified for inclusion in the first pass were compared and if discarded, were tagged with a reason for exclusion. If there was disagreement between reviewers, an additional independent reviewer was consulted to enable consensus to be reached. Where eligibility was unclear, the study was reviewed at second pass.

*Second Pass (Full text screening):* Full text articles of studies included in the first pass were obtained and assessed against the clinical question and eligibility criteria by Didu Kariyawasam and a second code was assigned (INC2). Author names, study titles, locations and dates were used to identify multiple reports arising from the same study. Studies identified for inclusion in the second pass were compared and discarded articles were tagged with a reason for exclusion. If there was uncertainty as to inclusion, an additional independent reviewer (Michelle Farrar) was consulted to enable consensus to be reached. A second reviewer (Christian Meagher) also re-reviewed nearly 30% of excluded full text articles to ensure that they met (exclusion) criteria. Studies remaining after the second pass went on to data extraction and evidence grading.

Table 3. Coding frame for citation and full text screening

Code	Definition
INC1	Include in first pass.
INC2	Include in second pass.
DUP	Duplicate study.
NS	Not an included study design.
NP	Not a population.

<b>NI</b>	No intervention.
<b>NO</b>	Not an outcome.
<b>NSPD</b>	No split paediatric data.

## Data Extraction

Two reviewers (Didu Kariyawasam and Christian Meagher) completed data extraction templates independently prior to comparison.

The following information was extracted from included papers:

- Affiliations and funding source.
- Study location and setting.
- Study design: (Systematic review, RCT, observational study).
- Population characteristics: sample size, interventions, exclusion/inclusion, outcomes.
- Country/region.
- Analysis methods.
- Reported results/outcomes.
- Author's conclusions.
- Comments from extractor.

No attempts were made to obtain or clarify data from published peer-reviewed studies. There was also no attempt made to obtain additional data from eligible primary studies not published in English, ongoing trials and studies published as conference abstracts.

## Identifying other sources of literature

In addition to the systematic searches as above, simple text searches using search terms as relevant to the appropriate questions were conducted to identify other non-commercial and non-peer reviewed literature (that could inform the current guideline). Searches were conducted across the following databases/websites.

1. Guideline databases (Guidelines International Network).

2. Websites of relevant international and national agencies including the World Health Organisation (WHO), National Institute for Health and Care Excellence (NICE), State and Commonwealth Departments of Health.
3. Literature searches were supplemented by the hand searching of bibliographies of identified studies for additional relevant studies.
4. Grey literature in the form of government reports/policies, public health monitoring or surveillance data, and data from clinical trials registries.
5. Systematic review databases (PROSPERO and Cochrane Database of Systematic reviews).

## Data Analysis

The evidence generated through the series of systematic reviews were collated and appraised by two reviewers Christian Meagher and Didu Kariyawasam using a GRADE framework to assess the certainty of evidence (Step 6).

## 2. Systematic observation forms to collect expert evidence

The systematic synthesis of expert evidence is valued in rare disease research, where a shortage of consistent scholarly literature is a common challenge.(15) Direct observation methods can collate the healthcare practices and opinions from experts. This corresponds to expert evidence defined as the observations or experiences of a person who is knowledgeable or skilled in a defined area.(26) Of relevance, collating expert evidence in a systematic and structured manner is integral to minimising interpretation of the extent to which the evidence supports (or does not support) recommendations.

### Aim

To collate expert evidence in a systematic and structured manner relating to the processes of newborn screening for SMA from the following domains: screening, diagnosis, post diagnostic clinical care of the newborn and offering information and support to families.

### Research question

For each domain, the research questions were, what is the magnitude of benefit and harm for each intervention and outcome, as evidenced by your practice and knowledge?

### Study Design and participants

This was mixed methods study to collate expert evidence. All members of the SAC were eligible and invited to participate in this part of the evidence gathering process.

### Methods

SAC members completed an online survey, specifically designed to collect direct experiences and observations. For each defined intervention, an estimate of the magnitude of effect for an outcome was measured using 5-point Likert scale (“Large benefit”, “Small benefit”, “Unsure”, “Small harm”, “Large Harm”). SAC members also provided their opinions and experiences through free responses. The emphasis was to collect direct experiential data useful for judgement, rather than “second hand” expert opinions based on low quality publications or common practice.(23, 26)



## Data analysis

The results of the systematic observation were analysed using a convergent parallel design.(47) Here quantitative and qualitative data were concurrently collected, analyzed and synthesised. Quantitative data was analysed using descriptive statistics in the Statistical Package for the Social Sciences version 12 (SPSS) and percentages and proportions were used to describe results. Qualitative items were collated non-thematically and compared to the quantitative data to provide contextual information. Results were presented to the GDG through email, as part of the evidence base to be used for informing recommendations.

### 3. Healthcare practitioner survey (modified Delphi process)

In questions where a lack of evidence (meta-analyses, randomized control trial or high-quality observational studies) was identified, a modified Delphi methodology was used to gather expert consensus.

#### Aim

The aim was to detail consensus agreement amongst healthcare practitioners on what was considered best practice in the processes of newborn screening for SMA across screening, diagnosis, clinical care and offering information and support to families.

#### Research question

The research question was what is considered best practice within the Australian and Aotearoa New Zealand healthcare context.

#### Study Design and Participants

A sequential modified Delphi methodology was used to gather evidence. All members of the SAC and Oversight Committee were eligible and invited to participate in this part of the evidence gathering process.

#### Methods

A modified Delphi process was employed, using two rounds of iterative online surveys (Qualtrics XM platform software, Provo, UT, 2024).

The items for the first round of the Delphi process were iteratively developed by three smaller working groups within the SAC, each based on their area of knowledge and expertise. The first survey was divided into 15 sections and accompanied by a narrative summary of available evidence from the systematic review process and the results of the systematic observation forms where available.

Members of the SAC anonymously answered survey questions that related to their area of expertise/scope of practice only, therefore not all questions were answered by all participants. They chose a response to each statement using a Likert scale (1 = “strongly disagree”, 3 = “disagree”, 5 = “do not agree/disagree”, 7 = “agree”, 9 = “strongly agree”). Survey answers were confidential and de-identified.

Following the first survey, results were collated and shared with SAC members. At a virtual meeting, SAC members discussed the data gathered and this informed modification of items categorised as near or no consensus for the second round of the Delphi process. A second survey was developed by the Organising Committee, consisting of 16 items linked to near consensus statements and no consensus statements (if deemed to have important relevance for practice and high priority) from the first round of the Delphi process.

### Data analysis

Descriptive statistics (means and 95% confidence intervals) were calculated for each answer using IBM SPSS Statistics (Version 27). Consensus, near consensus and no consensus to each statement was categorised according to the mean score and number of outliers: Items achieving consensus-were defined as a mean score of  $\geq 7.00$  AND no more than one outlier (the latter defined as any rating  $> 1$  Likert point away from the mean). Items meeting near consensus were defined as a mean score of  $\geq 6.5$  AND-no more than two outliers (the latter defined as any rating  $> 1$  Likert point away from the mean). No consensus was defined as statements that did not meet the threshold for consensus or near consensus.

## Step 6

### Synthesis of the evidence and assessment of certainty

The heterogeneity of the questions formed and evidence generated through the systematic review precluded statistical (meta-analysis) synthesis methods and alternative, non-statistical methods were used to describe and explore the evidence base in a structured and systematic manner.(43) A narrative synthesis of the available evidence from the scholarly literature was

considered as the most appropriate way of analysing the data from the systematic reviews, allowing for the description, comparison and ability to combine quantitative results with qualitative data.(48, 49) Here, the focus was on the interpretive synthesis of the narrative findings of the research. To facilitate this synthesis process, the following steps as defined by Popay et al. were followed.(50)

1. **Theory development** – this was the first stage of the process and included the theoretical basis that (newborn screening) interventions would improve health outcomes for newborns.
2. The literature identified in the systematic searches were **assessed and appraised** by two reviewers, Christian Meagher and Didu Kariyawasam. The preliminary synthesis consisted of collating descriptive characteristics of the studies in a table (study design, level of evidence, quality assessment of the study, outcome measures and other results). This process facilitated a descriptive synthesis of data, allowing the reviewers to consider and compare results between studies. Additionally, differences in study populations, methods of data collection and data analysis were easier to identify during this process. Textual descriptions (short descriptive summaries) from the studies were added and where possible, studies were grouped into those with similar outcomes or study designs, to aid comparisons.
3. **Exploration of relationships** within and between studies. This enabled an assessment of the impact of an intervention, or explanations of how or why a component had a particular impact. These narrative methods were considered important to investigate the aetiology of outcome heterogeneity across studies, dependent on the components of the intervention or other theoretical variables.

### Assessing the certainty of the body of evidence to form evidence-based recommendations

Outcomes were assessed as to their certainty using the GRADE framework. The quality of the body of evidence was assessed against domains of inconsistency, indirectness, imprecision, risk of bias and publication bias. The quality of the outcomes were then categorised as to a grade of evidence from high (very confident that the true effect lies close an estimate of effect), moderate (true effect is likely to be close to the estimate of effect but may be substantially different), low (true effect may be substantially different from estimate of effect) to very low (the true effect is likely to be substantially different from the estimate

of effect. Of note, observational studies started at a low certainty of evidence. An overall summary of findings table regarding all relevant aspects of the evidence base was formulated which also included characteristics of the defined outcome including clinical usefulness (acceptability to end users and implementability in Australia and Aotearoa New Zealand (Administrative and Technical Report)).

## Step 7

### Forming recommendations from the evidence

The taxonomy and framework used to formulate recommendations in the Guideline adhered to the definitions and standards as below (Table 4.).<sup>(51)</sup> Evidence-based recommendations were formed if an actionable statement could be derived using the systematic review of evidence, generated through questions within a PICO format.

Evidence generated through the systematic review (that did not adhere to the methodology required to form evidence-based recommendations), the systematic observation forms and the healthcare practitioner (modified Delphi) survey were combined to form the evidence base for consensus-based recommendations. The supporting evidence from these three data gathering streams were presented in an evidence summary for each recommendation (Technical and Administrative report). These statements aligned with relevant clinical practice, were considered impactful to the community and formed where there was a lack of empirical evidence alone to make evidence-based judgements.

If questions were outside the scope of the systematic review and not necessarily linked to evidence but were important to address and yielding large net positive downstream consequences for the population in question, a *good practice statement* was developed. This statement was used to contextualise an associated Recommendation i.e. for a specific clinical population, under specific circumstances or how it should be conducted in practice.

Table 4. Taxonomy and framework for Recommendations used in the Guideline.

Grade of Recommendation	Description
Evidence based recommendation	Is an actionable recommendation that is evidence based, derived from systematic literature review of the evidence. Supported by systematic reviews or health technology assessments.
Consensus based recommendation	Is an actionable recommendation based on clinical expertise, expert opinion and available evidence, and formulated using a modified
Good Practice statement	A recommendation based on indirect evidence that defines the population and intervention and is clear and actionable. This may possibly be linked to evidence. Cannot be rated by certainty of evidence or strength of recommendation.
Implementation consideration, tool, tips	Describes the how, who, where, what and when related to implementing a recommendation and may not have a clear link to evidence.

The Organising Committee used an iterative process, using evidence to decision (EtD) framework to move from evidence to forming evidence and consensus-based recommendations. (25, 45) .

The Organising Committee checked these statements for any misalignment or conflict against the following sources

- Evidence emerging from the systematic review.
- Other relevant research (standards of care guidelines for SMA;(35, 36) CLSI terminology databases;(1) National Newborn Screening Framework; (34) US Health Resources and Services Administration, Advisory Committee on Heritable Disorders in Newborns and Children).(52)
- Conceptual and ethical frameworks (e.g., AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research, 2020;(53) International Classification of Functioning, Disability and Health;(54) World Health Organisation Screening Guidelines).(55)
- Conventions (e.g., United Nations Convention on the Rights of the Child, 1989).(56)

Refinements to wording occurred and if required, addition of context was made by the Organising Committee and subsequently discussed and refined at a SAC meeting prior to the formation of the preliminary recommendations. Feedback from this meeting facilitated the revision of wording of practice statements into a set of preliminary recommendations, supported by evidence tables.

Implicit in this process was the fact that not all evidence collected during the research activities converged in such a way as to warrant a recommendation or good practice point. The language used to form Recommendations were in plain English, clear, had consistent terminology and were accessible to all stakeholders. The wording described a specific action within the Recommendation and aligned with the evidence base.

## Step 8

### Grading the direction and strength of recommendations

#### Evidence base recommendations

The GDG made decisions based on the Evidence to decision framework, balancing the undesirable and desirable consequences of the intervention. Evidence strength was graded according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.(57, 58)

The framework, as detailed below, consists of seven domains including priority of the problem, benefits and harms of the proposed intervention, certainty of the body of evidence (as assessed in Step 7), values and preferences to end users, resource and cost effectiveness implications and health equity, acceptability and feasibility factors. (59) The evidence and justification provided in each domain were considered by the SAC and used to structure their decisions on how to convey the direction of the recommendation (for or against) and the strength through wording and grading through a considered judgement form. Letters of (A to D) were assigned to the recommendation and indicative of the strength of the body of evidence that underpinned the recommendation (Table 5).(60)

Table 5. Grading the strength of evidence-based recommendations within the Guideline

Grade of recommendation	Description and body of evidence matrix
A	<p>Body of evidence can be trusted to guide practice.</p> <p>One or more level I or several level II studies with low risk of bias and all studies consistent, or inconsistencies can be explained.</p> <p>The clinical impact is very large.</p> <p>The populations studied in the body of evidence are the same as the target population for the guideline.</p> <p>The studies are directly applicable to the Australasian health care context.</p>
B	<p>Body of evidence can be trusted to guide practice in most situations.</p> <p>One or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias with most studies consistent, or inconsistencies can be explained.</p> <p>Clinical impact is substantial.</p> <p>Population studied in the body of evidence is similar to the guideline population. Applicable to Australasian health care context with few caveats.</p>
C	<p>Body of evidence provides some support for recommendation(s) but care should be taken in its application.</p> <p>One or two level III studies with low risk of bias or level I or II studies with a moderate risk of bias. Some inconsistency reflecting some uncertainty.</p> <p>Clinical impact is moderate.</p> <p>Population studied in the body of evidence differs from the guideline population, but it is sensible to apply it to target population. Applicable to Australasian health care context with some caveats.</p>
D	<p>Body of evidence is weak, and recommendation must be applied with caution.</p> <p>Level IV studies or level I to II studies/systematic reviews with a high risk of bias. Evidence is inconsistent. The clinical impact is slight. Population studies in the body of evidence differ to target population and hard to judge whether it is sensible to apply it to the target population.</p>
Consensus based evidence required	<p>Formulation of recommendation through discussion, Delphi process and assignment of agreement by individual participants.</p>



## Consensus-based recommendations

The *strength* of each consensus-based recommendation was evaluated using a modified approach (Table 6.) based on the NHMRC grading technique and used in prior paediatric consensus-based guidelines (40), which incorporated the seven domain of the GRADE process. This included evidence base consistency, clinical impact (benefits and risks), resource implications, equity factors, acceptability and values of stakeholders, generalisability and applicability of the evidence base

This adapted approach amalgamated and systematically graded a range of data sources including evidence from the systematic review process, the systematic observation form data and Delphi survey results.

Co-Chair Didu Kariyawasam and Christian Meagher independently rated each consensus-based recommendation according to a set of descriptors developed for use in prior clinical guidelines based on NHMRC terminology.(61)

The descriptors included

1. Consistency which was assigned for each recommendation a category of ‘fully’, ‘mostly’, ‘somewhat’ or ‘not’.
2. Generalisability which was assigned for each recommendation a category of ‘fully’, ‘mostly’, ‘somewhat’ or ‘not’.
3. ‘Impact’ which was assigned for each recommendation a category a grading of ‘large’ ‘substantial’ ‘moderate’ and ‘slight’.
4. ‘Evidence sources’, which was assigned for each recommendation a category of ‘numerous’, ‘number’, ‘limited’ or ‘lacking’ could be assigned.
5. ‘Support from experts’, which was assigned for each recommendation a category of ‘excellent’, ‘good’, ‘satisfactory’ or ‘poor’ was assigned.

Table 6. Descriptors and definitions for GRADING the strength of consensus-based recommendations.

The GRADE of recommendations aligns with NHMRC Guidelines that take into consideration a need for transparency in how all recommendations are formulated and assessed for strength.

<sup>a</sup> The direction of impact is not stipulated (positive or negative effect). Impact could be on different levels including for newborns, families, healthcare practitioners and health systems

Descriptor	Source(s) of evidence	Definition
Consistency	Scholarly literature generated through systematic review	<p><b>Fully:</b> Studies have fully consistent population, study design intervention and/or outcomes</p> <p><b>Mostly:</b> Scholarly literature mostly consistent with some variation as to population, study design, intervention/and or outcomes</p> <p><b>Somewhat:</b> Scholarly literature inconsistent with multiple domains affected</p> <p><b>Not:</b> Scholarly literature not consistent across population, study design, intervention/and or outcomes</p>
Generalisability	Scholarly literature generated through systematic review AND/OR Systematic observation form AND/OR Delphi survey	<p><b>Fully</b> generalisable to target population</p> <p><b>Mostly</b> generalisable to target population with some caveats (may be dependent on jurisdictional resources, potential to increase inequities in population)</p> <p><b>Somewhat</b> generalisable to target population with multiple caveats</p> <p><b>Not</b> generalisable to target population</p>
<sup>a</sup> Impact	Scholarly literature generated through systematic review AND/OR Systematic observation form AND/OR Delphi survey	<p><b>Large impact</b></p> <p><b>Substantial impact</b></p> <p><b>Moderate Impact</b></p> <p><b>Slight Impact</b></p>

Evidence Sources	Scholarly literature generated through systematic review AND/OR Systematic observation form AND/OR Delphi survey	<p><b>Numerous:</b> Scholarly literature, Delphi survey and systematic observation forms.</p> <p><b>Number:</b> Scholarly literature and Delphi survey.</p> <p><b>Number:</b> Scholarly literature and systematic observation forms.</p> <p><b>Limited:</b> Delphi survey and systematic observation forms.</p>
Support from experts	Delphi survey	<p><b>Excellent</b> = Strong consensus, 0 outlier</p> <p><b>Good</b>= Strong consensus, 1 outlier</p> <p><b>Satisfactory</b>= Near consensus</p> <p><b>Poor</b>= No consensus from experts</p>

The ratings were compared, with 84% agreement achieved on descriptor ratings. Discussion subsequently led to an agreed rating for each descriptor for all consensus-based recommendations, resulting in 100% agreement on the strength of recommendations assigned.

A consensus-based recommendation grade was assigned considering these components with 1A (highest) to 2C (lowest). Here, the recommendations were defined as 1A: strong recommendation, high-quality evidence; 1B: strong recommendation, moderate-quality evidence; 1C: strong recommendation, low- or very low-quality evidence (categorised as strong recommendations); 2A: conditional recommendation, high-quality evidence; 2B: conditional recommendation, moderate-quality evidence; 2C: conditional recommendation, low- or very low-quality evidence (categorised as conditional recommendations). For the purposes of the Guideline, conditional recommendations indicated uncertainty around the acceptability to and values/preferences of stakeholders, a potential to increase health inequity and/or a potential barrier to feasibility to implement the Recommendation. As such the grade given to each Recommendation aligned with the judgements of the GDG, based on the available evidence and other relevant considerations. The complete set of judgements is provided in the Technical and Administrative Report (Supporting Evidence).

Consensus-based recommendations were initially graded for the first draft of the Guideline, and the grading process was repeated prior to submitting the draft for external review to ensure grades reflected new or revised recommendations following feedback processes.

## Step 9

### Finalising the draft Guideline and the process of public consultation

The first version of the draft guidelines including evidence and consensus-based recommendations and practice points, with their certainty (for evidence-based recommendations) and strength (for consensus-based recommendations) were compiled by the Organising Committee and disseminated to the SAC and Oversight Committee on 3<sup>rd</sup> July 2024 by email, with written feedback expected over a two-week period. A videoconference for all SAC members and members of the Oversight Committee was convened on the 7<sup>th</sup>

August 2024 to review the draft Guideline and address additional feedback as appropriate. A second draft of the Guideline was formulated based on the discussions of this meeting and using (written) email feedback from the SAC. This updated draft was disseminated to members of the SAC, oversight committee and organising committee and uploaded onto a dedicated portal for public consultation and feedback. The GDG simultaneously prepared the draft Guideline and supporting documents (Supporting Evidence, Administration and Technical report and Plain Language Summary) for public consultation, which opened on 12<sup>th</sup> August 2024 and closed on 23<sup>rd</sup> September 2024 (six weeks).

Ahead of this phase, a webpage was developed through the University of New South Wales, to house all relevant documents and to collate feedback through a link to an online survey and feedback portal (<https://www.unsw.to/nbs-sma>). Documents could be viewed online or downloaded as required. The opening and closing dates of the public consultation period were announced through a University of New South Wales promotion, through email dissemination and through social media. Key professional and consumer organisations were identified through GDG networks and formally invited to provide feedback, with a letter of invitation sent out prior to the opening of the public consultation period (Table 7). This letter of invite to provide feedback was sent to the Office of the Director General, Chief Executive or Secretary of each state, territory, and Commonwealth Health Department to prepare those offices for the publication of the draft Guideline. These officers were then directly emailed the draft Guideline, when it was released. Consumer organisations representing the needs of Aboriginal, Torres Strait and Pacific Islander, and Māori communities were specifically and formally invited to participate in providing feedback of the draft Guideline during the period of public consultation.

Public consultation feedback was collected through a feedback form on the dedicated webpage, through email or letter directly to members of the Organising Committee. Feedback could be provided on individual sections, individual recommendations or practice points, and/or general feedback about the Guideline. Feedback could be on an individual basis or on behalf of an organisation. Respondents were able to choose whether they wanted their feedback to be published anonymously in the final Guideline.

Aligning with NHMRC Guidelines for Guidelines, the GDG nominated national and international clinical researchers with expertise in newborn screening for SMA to

independently review the draft Guideline. The NHMRC organised for experts to independently review the draft Guideline using a standard form supplied by NHMRC. These reviewers focused on the extent to which the draft updated Guideline aligned with its identified scope and clinical questions, whether the Recommendations adequately consider the risks and potential harms of clinical practice, and whether there are relevant international guidelines on the same topic that conflict with the Recommendations made. The NHMRC also arranged for methodological review of the draft Guideline, focusing on the extent to it complied with the NHMRC Standards for Guidelines.(40)

**Table 7. A list of organisations contacted to provide feedback for the Guideline.**

Organisation name
The Royal Australian College of Physicians
Australian and New Zealand Child Neurology Society
SMA Australia
Rare Voices Australia
Human Genetics Society of Australia
New Zealand Paediatric Society / The Paediatric Society of New Zealand
Commonwealth Department of Health Australia
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Australian Genomics
Syndromes Without a Name
Rare Disorders NZ
Rare Disease Foundation Australia
Australasian Association of Clinical Geneticists
Australasian Society of Diagnostic Genomics
Australasian Society of Genetic Counselling

Rural Doctors Association of Australia
Australian College of Children and Young People's Nurses
Australian College of Rural and Remote Medicine
Australian Primary Health Care Nurses Association
Secretaries of Health in all States and Territories of Australia
Neurology Clinical Network of the Paediatric Society of New Zealand Te Kāhui Mātai Arotamariki o Aotearoa
Ministry of Health – Manatū Hauora

## Step 10

### Revising the Guideline

The feedback collated through the period of public consultation was considered and used to facilitate revisions to the draft guideline. The feedback was reviewed systematically by the Organising Committee. Initially all feedback was exported from the online portal to a data spreadsheet, in deidentified format. Feedback for specific domains or recommendations/practice points were collated for the GDG to review and respond to formally. General feedback was utilised, but there was no specific published response to this section from the GDG. Here, feedback was defined as either (a) requiring no change to the Guideline, (b) requiring a possible change to the Guideline, or (c) requiring broader consultation with the GDG to address the feedback.

The definitions applied to each part of the feedback were independently reviewed by members of the Oversight Committee at a meeting convened on 23<sup>rd</sup> September 2023. Here, representatives could (a) agree with the initial response, or (b) propose an amendment to the initial response. The members of the Oversight Committee reviewed each piece of feedback and proposed change to the Guideline before final approvals were given.

Final changes were incorporated into the Guideline, supporting evidence, the plain language summary and Administrative and Technical reports as appropriate. The finalised Guideline

was disseminated to the entire SAC for review. The compiled feedback and final responses to reviewer comments alongside the location of any change that had been made were provided in the Public Consultation Summary and International Reviewer Comment Summary alongside the final Guideline.

## Step 11 Endorsement of the Guideline

Relevant stakeholders were approached to endorse the Guideline.

Organisation name
The Royal Australian College of Physicians
Australian and New Zealand Child Neurology Society
SMA Australia
Rare Voices Australia
Human Genetics Society of Australia
New Zealand Paediatric Society / The Paediatric Society of New Zealand
Commonwealth Department of Health Australia
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Australian Genomics
Syndromes Without a Name
Rare Disorders NZ
Rare Disease Foundation Australia



Australasian Association of Clinical Geneticists
Australasian Society of Diagnostic Genomics
Australasian Society of Genetic Counselling
Rural Doctors Association of Australia
Australian College of Children and Young People's Nurses
Australian College of Rural and Remote Medicine
Australian Primary Health Care Nurses Association
Secretaries of Health in all States and Territories of Australia
Neurology Clinical Network of the Paediatric Society of New Zealand Te Kāhui Mātai Arotamariki o Aotearoa
Ministry of Health – Manatū Hauora

A magnifying glass with a silver frame is positioned over an open book. The book's pages are visible, and the magnifying glass is held at an angle, focusing on the text. The background is a soft, out-of-focus light blue.

## Reading the Guideline

## Reading the Guideline

The GDG purposely adopted several approaches when considering and writing about the implementation of newborn screening for SMA across Australia and Aotearoa New Zealand. To make the best use of the Guideline, it is recommended that end users read all the sections therein as relates to the healthcare journey of the newborn/infant as they undertake the newborn screening pathway for SMA. The recommendations are best considered as a whole, rather than in isolation, however the GDG acknowledges that stakeholders may want to familiarise themselves with their areas of expertise first and foremost. Hence, the Guideline is deliberately divided into screening, diagnostic and clinical care and advocacy domains (Figure 3).

The Guideline is designed to complement and not replace key national and international policy documents including the Newborn Bloodspot Screening National Policy Framework, (34) standards of care for spinal muscular atrophy (35, 36) and technical protocols for screening and diagnostics within SMA such as Clinical & Laboratory Standards Institute (CLSI) Guideline for newborn screening in SMA (in the process of public consultation July 2024).(62)

The Guideline is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across Australia and Aotearoa New Zealand. As such it does not include recommendations for medicines or services that are unavailable or restricted in these jurisdictions.

## Who may benefit from reading the Guideline

It is envisaged that adopting best practice methods for the screening, diagnosis and management of newborns with SMA, will streamline these processes, improve health outcomes for affected individuals across Australia and Aotearoa New Zealand and provide informed guidance for Australian and Aotearoa New Zealand healthcare practitioners, defined for the purpose of the Guideline as professionals working in the (newborn) screening and diagnosis process (including scientists and laboratory staff) and medical practitioners (doctors; paediatric neurologists, paediatricians, general practitioners, clinical geneticists, nurses, allied health therapists) involved in the care and management of individuals with SMA and their families as identified through an newborn screening for SMA process.

We anticipate that the Guideline will also inform Australian and Aotearoa New Zealand health system planners including public funding bodies, managers and administrators whose organisations provide services for population screening, diagnosis and care of individuals with SMA and their families. Additionally, Australian and Aotearoa New Zealand training providers including peak bodies and institutions may use the Guideline to streamline educational and clinical resources. Lastly but most importantly, we envisage that the Guideline will be useful to Australian and Aotearoa New Zealand families of children undergoing and screening positive for SMA through newborn screening programs.

### What is not covered by the Guideline

It has been decided *a priori* that the risk-benefits of newborn screening for SMA, technical aspects of screening (including the determination of analytical validity of specific tests, validation of laboratory methods, the implementation of pilot studies and transitioning to routine newborn screening for SMA) will not be covered by the Guideline. Furthermore, the validation of diagnostic tests and ongoing management of individuals with SMA beyond the initial post-diagnostic period (the latter covered by international standards of care guidelines (35, 36) will not be covered in the guidance. It has been decided *a priori* that the Guideline will provide recommendations for newborn screening for SMA related to lack of survival motor neuron (SMN) protein (synonymous with 5q SMA or classic SMA) and thus SMA related to other causes will fall outside its scope. It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and Aotearoa New Zealand. As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address reimbursement pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded health services or treatments.

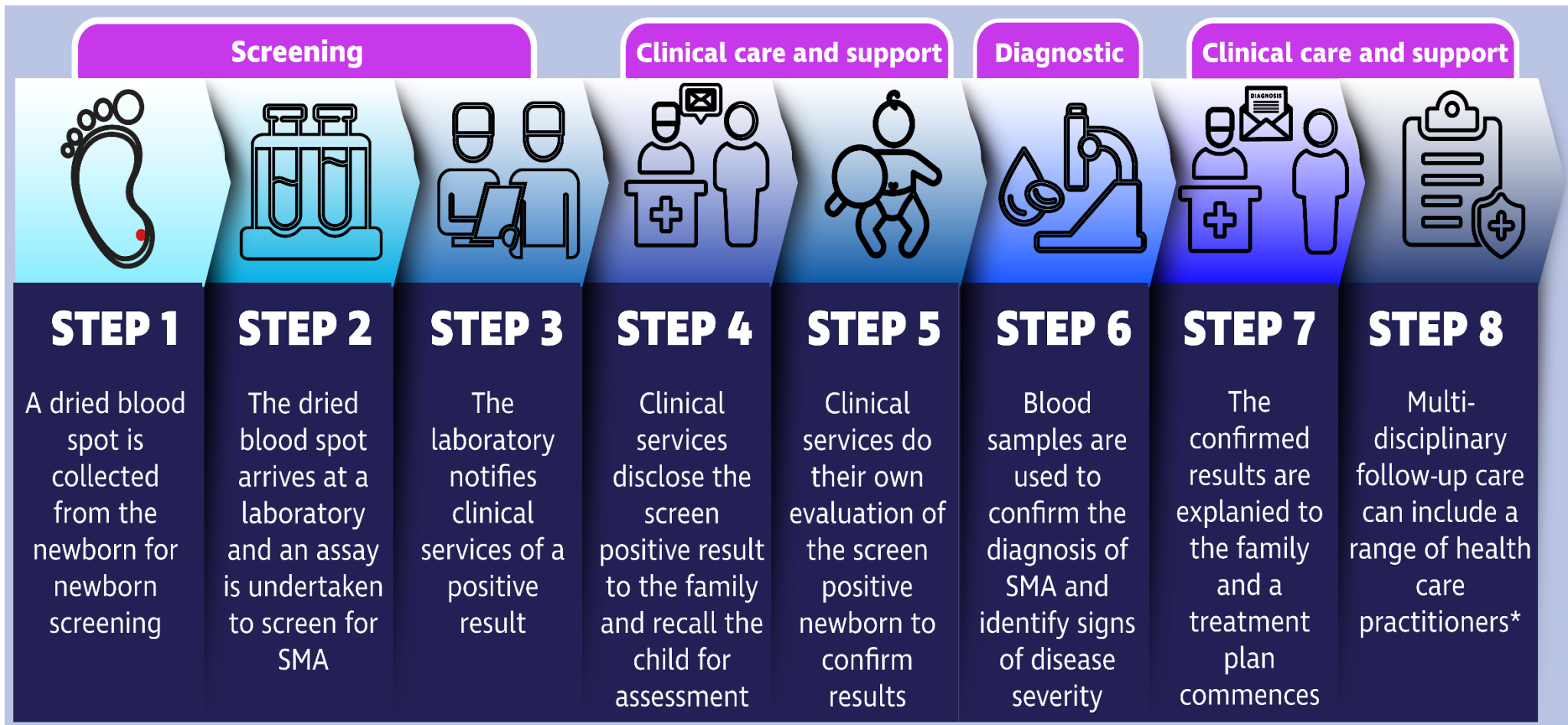


Figure 3. The newborn screening pathway for spinal muscular atrophy as encompassed by the Guideline. The domains in the Guideline pertain to screening, diagnostic, clinical care and support. \* Healthcare practitioners that work within the multidisciplinary team vary dependent on jurisdiction and may include paediatric neurologists, paediatricians, general practitioners, clinical geneticists and genetic counsellors, specialist nurses, psychologists, social workers and allied health therapists.

## The definition of newborn screening in SMA

Historically, guidelines that encompass newborn screening practices have been heavily focussed on the technological aspects of (newborn) screening for the named condition(s). The GDG however considered the newborn screening program for SMA as a program of activities that encompassed screening, diagnostic confirmation and clinical care of the newborn/infant undertaking the pathway. Accordingly, the Guideline for the program is defined within these domains, with acknowledgement that coordination and communication are required between services to provide effective and efficient care to affected children and their families. The GDG considered newborn screening from the perspective of the population of *all* children born with the most common form of SMA i.e. those with a biallelic deletion of exon 7 on *SMN1* **and** those with biallelic pathogenic sequence variants (including children with a compound heterozygous genotype i.e. one allelic deletion of exon 7 on *SMN1* and a pathogenic sequence variant on exon 7 *SMN1* on the second allele, *or* homozygous sequence variants on each allele). There are other forms of SMA that are not related to SMN protein deficiency, and these are considered outside the scope of this Guideline.

## The definition of newborns, infants and children with SMA

Whilst developing and writing the Guideline, the GDG acknowledged that whilst newborns ( $\leq 28$  days of age) generally undertook newborn screening for SMA within the first 2-3 days of life, in some jurisdictions and within some families, processes could occur after this defined period. Hence, newborn screening for SMA could technically also occur in infants i.e. children 29 days of age to 12 months. Where newborns and infants were considered together, the GDG defined these two cohorts as synonymous with ‘children’.

## The definition of healthcare practitioners

The term ‘healthcare practitioners’ were used within the Guideline to refer to medical, nursing, allied health therapists, advocacy and laboratory and scientific professionals undertaking screening, diagnostic and clinical care and advocacy activities for children undergoing newborn screening for SMA. Medical practitioners were considered synonymous with clinicians. Specialist medical practitioners were considered as paediatric neurologists with training, experience and expertise in managing children with neurological and/or

neuromuscular conditions in Australia and Aotearoa New Zealand. The GDG acknowledged in the development of the Guideline that some states and territories had shared access to screening, diagnosis and specialist medical (paediatric neurology and neuromuscular services), which required interstate coordination of services and referral pathways.

### The definition of families

The GDG recognised through the development of the Guideline that families across Australia and Aotearoa New Zealand are formed in ways that are often culturally bound and equally relevant. Families within the Guideline included but were not limited to parent(s), partners, siblings, and caregivers (related to or not related to the newborn/infant). The Guideline lists best practice recommendations, however the recommendations are to be considered within the ethos of shared decision making with families, where informed consent from a parent or legal guardian is obtained and respected. This is deemed particularly relevant for recommendations within the clinical care domain. Thus, each Recommendation and Good Practice Point are to be considered and implemented that respect each family's perspectives, preferences, and consent.

### The definition of advocacy services

The GDG recognised that a variety of international, national, and jurisdictional support services exist for children with SMA and their families. For the purposes of this Guideline, these have been grouped under the terminology of advocacy services. We leave it to the discretion of relevant healthcare practitioners to direct families to the most appropriate services based on the individual needs and preferences of the family.

# Background on Newborn Screening in Spinal Muscular Atrophy



## Introduction

### Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare genetic condition with an incidence of around 1 in 10000 individuals.(63) Based on birth statistics, an estimated 30 new families are affected by the condition across Australia every year and an estimated 5 families affected in Aotearoa New Zealand per annum.(64, 65) Although frequencies vary between ethnicities, SMA affects all populations and overall carrier frequency is around 1 in 50 and SMA prevalence is estimated to be 1-2 per 100,000 individuals.(2)

SMA is characterised by progressive degeneration of lower motor neurons (the anterior horn cells) of the spinal cord and the brainstem nuclei.(66) The ramifications of this neurodegenerative condition are muscle wasting, predominantly of the proximal muscles of the legs and arms, leading to skeletal and respiratory muscle weakness and atrophy, appendicular and truncal hypotonia, decreased or absent reflexes, and impaired motor function.(66) The pattern of weakness is usually symmetrical and length dependent, affecting legs before arms.(67) Associated consequences of the condition include respiratory and feeding difficulties, progressive neurodisability, and high medical and supportive care needs.(68) SMA has a spectrum of severity and a predominant childhood onset.(69)

Individuals living with SMA have a varied presentation (Table 8.). The majority (around 60%) present with a severe infantile onset form, starting before the age of six months,(2) where the ability to independently sit is never achieved without treatment, with this phenotype synonymous with SMA phenotype I or historically named as Werdnig Hoffmann disease. SMA in its severe, untreated form was considered the leading genetic cause of infant mortality, with only 10% of children surviving past their second birthday.(69, 70)

Untreated children who have disease onset before the age of 18 months may sit but never walk (SMA type II). Children who have a milder, later onset presentation (> age of 18 months) may walk but can have deterioration in their ambulation skills over time (the latter defined as SMA type III or Kugelberg Welander disease).(71) Rarely (in 5%) of presentations, prenatal (SMA type 0) or adult onset (SMA type IV) is noted. In the former, newborns present with florid signs and symptoms of SMA including joint contractures,

respiratory distress requiring early breathing support, challenges with maintaining temperature, heart and respiratory rates (dysautonomia) and congenital organ malformations,(2, 67, 72) whilst in the latter, individuals generally retain ambulation skills but may find higher motor tasks challenging and/or fatiguing.(73)

Table 8. The historical phenotypic classification of spinal muscular atrophy.

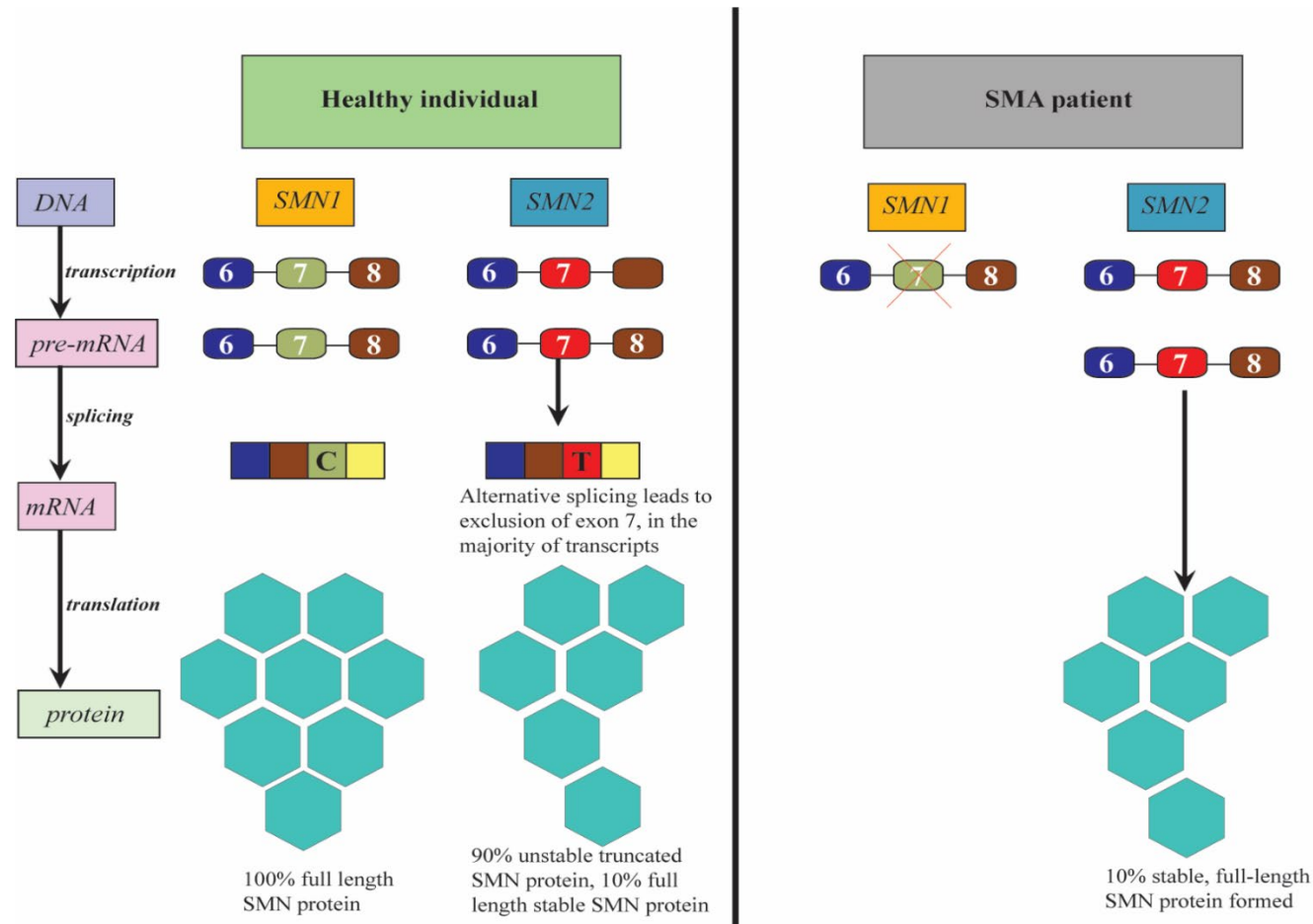
Type	Age of Onset	Clinical features and survival
<b>SMA TYPE 0</b> <i>(Congenital, Prenatal SMA)</i>	Prenatal (30-36 weeks)	Decreased foetal movements in utero, issues with asphyxia, severe weakness at birth.  Without treatment most children do not survive beyond 6 months.
<b>SMA Type I</b> <i>(Severe infantile acute; Werdnig-Hoffmann disease)</i>	Birth to six months	Cannot sit independently, difficulty breathing.  Without treatment 90% of children do not survive beyond 2 years of age.
<b>SMA Type II</b> <i>(Infantile chronic)</i>	Six to 18 months	Sit independently but cannot stand or walk.  Without treatment, survival rate is variable, with 98.5% of children reaching the age of 5 years, and 68.5% reaching the age of 25 years.
<b>SMA Type III</b> <i>(Juvenile, Kugelberg-Welander disease)</i>	After 18 months	May stand or walk, but with progressive weakness. Wheelchair assistance usually needed in later life.  Normal life expectancy.
<b>SMA Type IV</b> <i>(Adult-onset)</i>	20-30 years	Mild to moderate muscle weakness, tremor twitching in proximal muscles  Normal life expectancy

## The genetic basis of spinal muscular atrophy

SMA is caused in 95% of children by biallelic (homozygous) deletion of exon 7 of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.13.2 and as such is inherited in an autosomal recessive manner (Figure 4).(74) Other condition-causing variants account for the remainder of genetic changes leading to SMA in (< 5%) of cases, and these are not detected by current newborn screening methods.(75)

*SMN1* encodes for full length survival motor neuron protein, which is present in all cells of the body but appears particularly essential for lower motor neuron development, maturation, connection, and survival. A coding region within *SMN1*, known as the exon 7 region, appears particularly vital for SMN protein folding and interaction with other cell proteins, and also prevents degradation of protein complex.(75, 76)

A duplication within chromosome 5 gives rise to a paralogous gene called survival motor neuron 2 (*SMN2*), which has the same coding sequences as *SMN1*, however a single base pair nucleotide change in exon 7 alters splicing recognition.(75) The majority of transcripts produce a truncated, unstable protein leaving it vulnerable to degradation.(77, 78) *SMN2* copy numbers vary in humans from 0 to 8. Higher *SMN2* copy numbers generally ameliorate the clinical presentation, by producing greater amounts of functional SMN protein, but does not fully compensate for the lack of SMN protein secondary to absence of exon 7 on *SMN1*.(30, 79-86) *SMN2* copy number is generally considered the best predictor of age of onset and severity of the condition.



**Figure 4. The genetics of spinal muscular atrophy.** In individuals without SMA, *SMN1* produces 100% of full-length SMN protein. In *SMN2* the exchange of one nucleotide allows for splicing out of exon 7 in *SMN2* resulting in a shortened pre-mRNA transcript that produces mostly shortened form of SMN protein which is rapidly degraded. *SMN2* copy number can change phenotype in a dose dependent manner but the correlation is not absolute.

## The introduction of SMN augmenting treatments in SMA

From being considered an untreatable condition, where supportive and often palliative care strategies were considered the primary goals of management, genetic advances have facilitated the introduction of approved and reimbursed treatments for SMA, which have modified the disease course and changed outcomes for affected individuals (Figure 5.). Treatments have concentrated on SMN repletion or augmentation through inclusion of exon 7 in *SMN2* through splice modification (to more reliably produce full-length pre-mRNA transcripts), leading to increase in stable SMN protein (nusinersen and risdiplam) or introducing *SMN* transgene into all cells within a viral vector (onasemnogene abeparvovec-xioi). As such these treatments sit under the umbrella term of SMN augmenting or disease modifying therapies. For the purposes of the Guideline, the former definition is used in forming the recommendations. Whilst these treatments can help to support surviving lower motor neurons and the muscle fibres that they innervate (together known as a motor unit), they cannot replace irreversibly damaged motor units.(87)

Clinical trials, managed access programs and real-world evidence have shown that the greatest magnitude of benefit in terms of increased survival, reduction in comorbidities and clinically meaningful gains in motor function, occur when affected children are treated prior to the onset of signs and symptoms of SMA i.e. in the presymptomatic phase of the condition, independent of modality of intervention chosen.(6-9)

	<b>NUSINERSEN</b> ( <i>Spinraza</i> )	<b>RISDIPLAM</b> ( <i>Evrysdi</i> )	<b>ONASEMNOGENE ABEPARVOVEC</b> ( <i>Zolgensma</i> )
<b>MODE OF ACTION</b>	Antisense oligonucleotide. Binds to an <i>SMN2</i> gene sequence to increase SMN protein production.	<i>SMN2</i> mRNA splicing modifier. Increases SMN protein levels produced by <i>SMN2</i> by shifting balance from exon 7 exclusion to exon 7 inclusion.	A fully functional <i>SMN</i> transgene is delivered through adeno-associated viral vector 9 (AAV9).
<b>ROUTE AND FREQUENCY</b>	<ul style="list-style-type: none"> <li>▶ Intrathecal.</li> <li>▶ One dose on days 0, 14, 28 and 58. Maintenance dose 3 times per year.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Oral.</li> <li>▶ Once daily.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Intravenous.</li> <li>▶ Single dose.</li> </ul>
<b>POTENTIAL SIDE EFFECTS</b>	<ul style="list-style-type: none"> <li>▶ Mostly related to lumbar puncture, including:               <ul style="list-style-type: none"> <li>(Low pressure) headache.</li> <li>Localised pain.</li> <li>Anxiety.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▶ No significant side effects reported in humans.</li> <li>▶ Retinal degeneration seen in animal models.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Derangement of liver enzymes (in rare cases, acute liver injury).</li> <li>▶ Thrombocytopenia. Concurrent administration of oral corticosteroid reduces side effects.</li> <li>▶ Thrombotic microangiopathy.</li> </ul>

**Figure 5. Approved SMN augmenting treatments for spinal muscular atrophy across Australasia.** Approvals and reimbursements vary across Australasia and are dependent on age, *SMN2* copy number and clinical status (symptomatic or presymptomatic status). The potential side effects listed are not exhaustive and accompanying product information should be adhered to for a wider discussion on potential risks. For families taking part in therapeutic decision making, risk-benefits of treatment should be discussed with a specialist, incorporating up to date knowledge.

## The rationale for newborn screening in SMA

*Newborn screening as a public health program aims to identify children at risk of serious and treatable conditions, providing timely access to diagnosis, medical interventions and care that can improve health outcomes for the affected child as a primary aim.(88)*

The imperative and rationale for newborn screening in SMA is thereby founded on three central concepts (Figure 6.). Firstly, prior to the consideration of newborn screening in SMA, children have been diagnosed with the condition based on recognition of clinical signs and symptoms, initially by the family and then by healthcare professionals, leading to substantial diagnostic delays. Average diagnostic delays internationally have been noted of 3.8 months for children with SMA type 1 and 12.4 and 11.3 months respectively for children with SMA types II and III.(89) The Australian evidence base mirrors this global trend with a median of 5 months (range 0.5-7.2 months) delay between onset of symptoms and diagnostic confirmation for the infantile onset form of the condition, underpinned by irreversible and relentless lower motor neuron loss.(12)

Motor neuron loss appears precipitous without early treatment across all forms of the condition, however within the severest affected, infantile form, 90% of motor units are lost by six months of age (80, 90). Presymptomatic treatment is essential to replete SMN protein within a therapeutic window where there will be the greatest chance of clinical benefit.

Newborn screening programs to date have mainly leveraged biochemical analysis techniques such as tandem mass spectrometry to screen for a variety of conditions, using dried blood spots. Genetic screening has been incorporated into newborn screening practices, namely as second (tier) tests for conditions such as cystic fibrosis (CF) i.e. first test on the dried blood spot confirms elevation of an enzyme, immunoreactive trypsinogen above a threshold and the second process on the same dried blood spot screens for a panel of genetic variants that are known to cause CF.(91) However, the inclusion of SMA into routine newborn screening processes is the first-time genetic screening has been used as a first-tier methodology to identify children at risk of a rare (neurological) condition, on a population level. SMA lends

itself to accurate and sensitive newborn screening due to the presence of the same pathogenic variant causing the condition i.e. biallelic loss of exon 7 on *SMN1* in 95% of the affected population. Based on advances in genetic capabilities, genetic screening for SMA on a whole population level has become feasible and cost effective, with pilot programs initiated in Taiwan and New York, USA leading the methodologies for optimising the sensitivity, specificity and feasibility of incorporating genetic screening into newborn screening programs.(29, 92)

In recognition of this foundation of evidence, SMA as a condition is now able to meet the screening principles set out by *Wilson and Jungner*,(55) which have been used as international standards of practice when delineating conditions to be part of effective routine screening panels. This includes the fact that SMA is an important health problem, the natural history is well characterised, a presymptomatic and early symptomatic phase in which to intervene is defined, a population screening test and treatments are available, and there is evidence that that cost of case finding is balanced financially against possible expenditure on medical care.



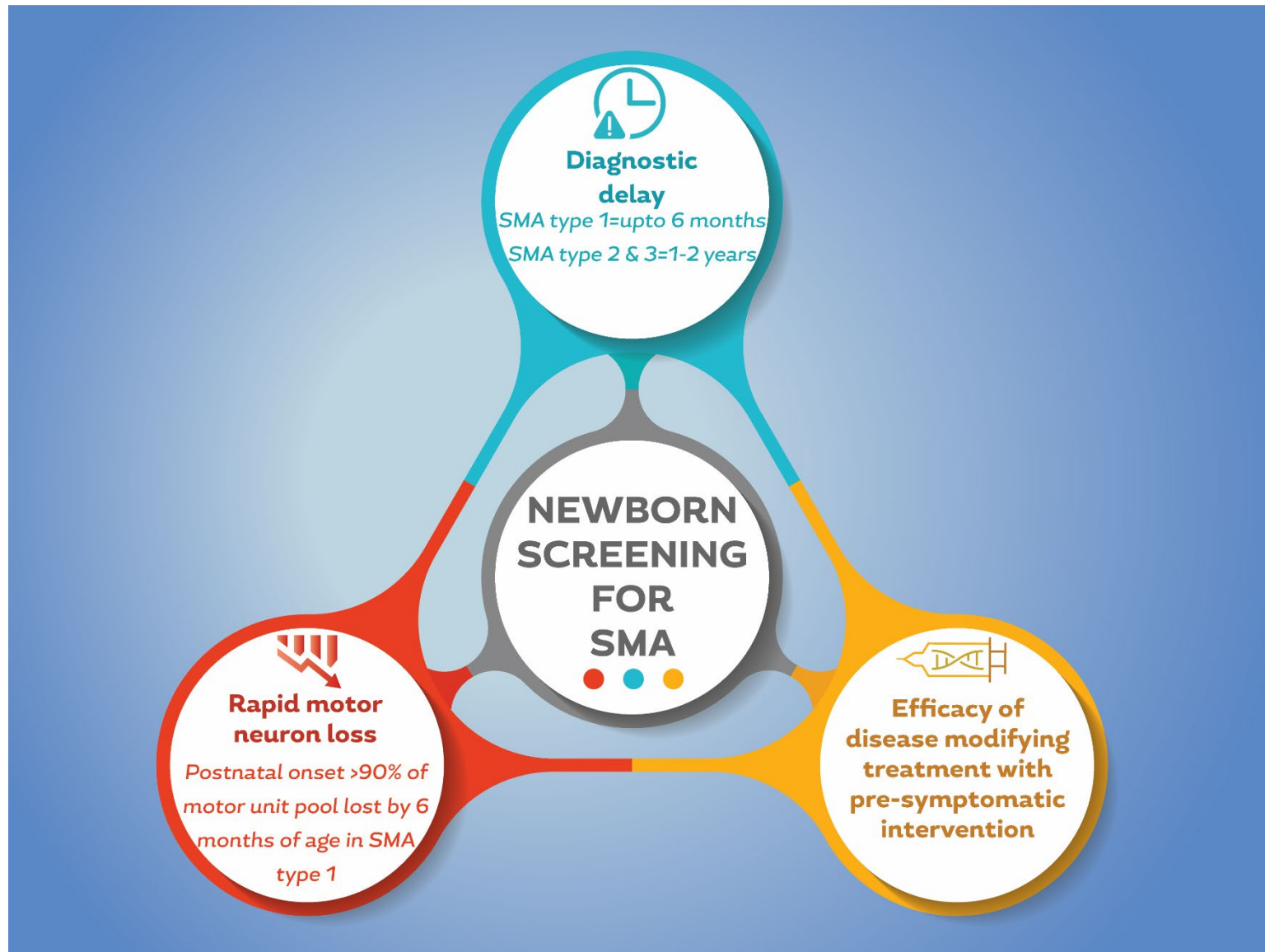


Figure 6. The rationale for newborn screening for spinal muscular atrophy

## The global perspective of newborn screening in SMA and where Australasia and Aotearoa New Zealand sit within the international context

In 2018, the United States of America (USA) endorsed the addition of SMA onto the Recommended Uniform Screening Panel (RUSP).(93) Across the international landscape, as of 2024 the following jurisdictions were conducting newborn screening for SMA routinely, and many more health jurisdictions were performing pilot studies. All 50 USA states are screening for SMA and in Canada, the majority of provinces have adopted similar programs.(94) In Europe, around 65% of newborn babies are screened for SMA in the newborn period,(95) while screening for SMA within the Asia-Pacific region is currently implemented in Japan, Taiwan, Australia and endorsed by Aotearoa New Zealand. In the Middle East and North Africa newborn screening programs are variably established and none screen routinely for SMA except for Qatar.(33, 96)

In Australia and Aotearoa New Zealand, newborn screening has high participation rates (around 99% and 97.9% respectively)(34, 97) reflecting high public confidence, with families opting in to have the screening test performed on their newborn within the first 2-3 days of life. In Australia, a pilot or scoping newborn screening program for SMA was commenced on 1<sup>st</sup> August 2018, covering the states of New South Wales and Australian Capital Territory. Through this program the feasibility and accuracy of newborn screening for SMA from a laboratory perspective was established, and the public acceptability, cost effectiveness, challenges and opportunities of implementing the program was noted. (10, 12, 37, 38, 98) The evidence base for the benefits of newborn screening for SMA within the Australian context was established and was thus considered *a priori* outside the scope of the current Guideline.

In 2022, the Commonwealth Department of Health and Aged Care recommended SMA for national incorporation into Australian NBS programs, (99), and one year later, Te Whatu Ora (Health New Zealand) endorsed the same for its national newborn screening program (on 14<sup>th</sup> September 2023).(14) In Australia, newborn screening programs are implemented according to the Newborn Bloodspot Screening National Policy Framework (34) with each state and

territory responsible for implementing and funding the screening, diagnostic and clinical care aspects of the pathway.(100, 101)

## Newborn bloodspot screening organisation and coordination in Australia and Aotearoa New Zealand

In Australia, the organisation and implementation of newborn screening programs aligns with the national federated system of government, with eight jurisdictional governments (representing 6 States and 10 Territories) and a national Commonwealth government.(102) Here, newborn screening for the nation is coordinated out of five established (screening) reference centres. In Aotearoa New Zealand, the newborn screening program is centralised and under the implementational governance of the national Newborn and Metabolic Screening Programme.

The implementation of newborn screening programs is the responsibility of the state and territory governments and as such five Australian newborn screening reference centres exist.(103) These are located in Adelaide, Brisbane, Melbourne, Perth, and Sydney providing coordination of these public health programs. These laboratories screen dried blood spots collected onto filter paper, taken from the newborn's heel ideally 48-72 h from birth, and population wide screening encompasses around 300,000 newborns annually.(13) Each dried blood spot contains three unique patient identifiers and a named medical practitioner (usually a general practitioner, paediatrician, obstetrician or neonatologist) for contact. In Aotearoa New Zealand, one national program, the Newborn Metabolic Screening Program (NMSP) coordinates the screening of around 60,000 newborns every year, with results returned to midwifery/maternity services.(104)

The consent process for the collection of the dried blood spot typically includes a verbal description of the test and its benefits postnatally, a pamphlet, and, in some jurisdictions, a guide to a web-based resource (developed and maintained by the reference screening centres). The Australian and Aotearoa New Zealand newborn screening program is not mandatory, and parents can opt out of the screening test, with a small proportion of parents

declining screening for their newborns.(13, 104) All newborn screening programs in Australia and Aotearoa New Zealand, are publicly funded with no out-of-pocket costs for the screened individual.

Funding for clinical follow-up of screen positive newborns in Australia is derived from a mix of public and private sources, with the majority (70.6%) of healthcare funded by the government through the Medicare rebate program, for eligible citizens and residents.(105) Similarly, in Aotearoa New Zealand, children who are citizens of the country are eligible for care and treatment in the public healthcare system. Access to clinical care for screen-positive newborns can be highly variable depending on familial knowledge of and access to public and/or private health services, possibly driven by the relatively small population (25.7 million) spread across a large geographical area (7.7 million km<sup>2</sup>) with wide diversity in health literacy, socioeconomic circumstances, language, and cultural perspectives.(106) More frequently, challenges with accessing appropriate care are apparent in referral pathways for newborns and children diagnosed with rare conditions, as specialist services required for care tend to be in a limited number of major metropolitan hubs.(102)

### Newborn screening for SMA as part of a proactive paradigm of population screening

As a public health initiative, screening for rare and degenerative conditions such as SMA are ideally conducted on multiple levels, including options of screening prior to conception (reproductive genetic carrier screening) to inform reproductive decision-making for those at risk. Accordingly, on 1st November 2023, reproductive genetic carrier testing for SMA, alongside fragile X syndrome (FXS) and cystic fibrosis has been fully reimbursed through the medical rebate system in Australia, making these technologies accessible to the wider Australian population, independent of the probability of having these conditions.(107) The test is covered once in an individual's lifetime. The newborn screening program for SMA thus augments and complements the program for reproductive genetic carrier testing in Australia.



## **Recommendations and their Evidence Base**

## Sections 1 and 2: Screening



## Background

Due to the paucity of high-quality scholarly literature to provide evidence-based recommendations, the majority of recommendations in this domain were founded on consensus, which was based on systematic collation and review of the existing literature. One recommendation was evidence-based. A narrative summary of findings is presented on which consensus-based recommendations were formed. A more detailed view is encompassed in the Administrative and Technical Report.

## What encompasses newborn screening for SMA

For the purposes of the Guideline and the recommendations therein, the screening domain was defined as processes and activities starting from the collection of a biological specimen from the newborn for screening purposes, through to laboratory processes for screening for SMA to the point of notification of a screen positive result for SMA to clinical services. As SMA is embedded into established national newborn screening programs, the scope of the recommendations excluded recommendations to guide the consent process for newborn screening in general.

## Screening for SMA in the newborn period, evidence from the literature

Identifying SMA in the newborn period is only possible with DNA (genetic) testing since there are no validated biochemical markers associated with the condition.(108) Population-based screening for SMA is considered feasible, fast and cost effective, using high throughput nucleic acid-based methods to detect *SMNI* exon 7 absence.(109, 110) Whilst pathogenic variants in exon 1, 3 and 6 of *SMNI* are noted in individuals with SMA, leveraging the fact that 95% of individuals with SMA have an absence of exon 7, *SMNI* assays have generally targeted this genetic change, with rare studies targeting exon 7 **and** exon 8 loss within *SMNI*.(111) Accordingly, these methods do not screen for newborns with *SMNI* exon 7 deletion in one allele and a pathogenic sequence variant in exon 7 of the other *SMNI* allele i.e. children with a compound heterozygote genotype, those with biallelic pathogenic sequence variants, or children with other forms of SMA not related to SMN protein deficiency.

Newborn screening for SMA is in the majority conducted using dried blood spots (DBS), usually taken from the heel of the newborn within the first 2-3 days of life. Fresh blood on dried blood spots collected through venepuncture (i.e. a blood test directly from the child) for (newborn) screening for SMA purposes have also been rarely utilised, with high sensitivity and specificity.(112) Further, DNA extracted from dried saliva spots,(113) as the substrate for *SMNI* analysis have been evaluated, however no studies have shown evidence for the use of dried saliva spots at a population level for newborn screening in SMA. No studies have used cord blood for the purpose of newborn screening for SMA. In all studies screen positivity in newborn screening for SMA has been defined as an absence of the target sequence within exon 7 *SMNI* i.e. homozygous deletion of exon 7 on *SMNI*.

Cumulatively, to date (2024), 3,155,446 newborns have undergone newborn screening for SMA using methodologies where the target sequence is absence of exon 7 in *SMNI*. The incidence of SMA has been ascertained as between 1 in 6059 to 1 in 28,137.(114, 115) The incidence of SMA through newborn screening in 2022 was 1 in 11458 in an Australian study.(10)

In terms of methodology, a spectrum of qualitative and quantitative *SMNI* assays have been used to screen for SMA on dried blood spots.(33) Predominantly, quantitative real-time polymerase chain reaction (qPCR) and digital droplet polymerase chain reaction (ddPCR) methodologies have been utilised for this purpose.(29, 116) Other methodologies include but are not limited to restriction fragment length polymorphism analysis (RFLP),(117) high resolution melting analysis,(118, 119) multiplex ligation probe amplification,(120) DNA tandem mass spectrometry,(121) modified competitive oligonucleotide priming PCR (mCOP-PCR)(122) and DNA sequencing.(123). One study evaluating methodological accuracies between the most commonly used assays for newborn screening in SMA have determined that real-time PCR assays are generally robust, accurate, cost effective and have the potential to be used on an automated level required for population wide screening.(124) Accordingly, the GDG acknowledges that health jurisdictions in Australia and Aotearoa New Zealand may utilise varying (*SMNI*) assays for SMA newborn screening purposes.



Some screening programs for SMA leverage multi-tiered processes to further test for the absence of *SMNI* on the same dried blood spot (defined for the purposes of the Guideline as second and third tier testing). Second tier testing may include repetition of the same assay on the dried blood spot, or use of alternative screening methods (including to confirm first tier results. The evidence has shown that a minority of screening programs perform further tests on the same dried blood spot for ascertainment of *SMNI* deletion using a range of methodologies from ddPCR(125-127) through to MLPA(128) and RFLP-PCR (119, 122, 129). Rarely, established newborn screening programs use three tiers of screening for *SMNI* to look for exon 7 variants caused by hybrid genes in screen positive children and then sequencing *SMNI* to reconcile differences between first and second tier assays.(130)

Sensitivity can be considered in two ways for the purposes of newborn screening in SMA, i.e. for detecting homozygous deletion of exon 7 on *SMNI* (the target of the most commonly used assays) or for detecting all cases of SMA in a population (including genotypes other than the target sequence). The sensitivity of detecting biallelic deletion of exon 7 on *SMNI* is 100% across the available literature. From a whole of population level, the sensitivity of *SMNI* screening assays are predicted to be 95-98% due to the presence of newborns with a compound heterozygous *SMNI* genotype or biallelic pathogenic variants in exon 7 on *SMNI* (131). Accordingly, six studies have defined a sensitivity of 91 – 98% based on the presence of false negatives, generally secondary to compound heterozygous genotype in the newborn.(12, 94, 121, 123, 132, 133) The sensitivity of screening to identify all children with SMA in the population may decline over time, as false-negative cases present with clinical symptoms in the future. Where reported, the specificity of screening assays for SMA are 100%, even with the occurrence of false positive cases in some studies, secondary to the low population prevalence of SMA.

Screening assays for SMA are frequently and effectively combined with screening for severe combined immunodeficiency (SCID) in a single assay in around 40% of population newborn screening programs (including in Australia)(12), and less commonly multiplexed with newborn screening for X-linked agammaglobulinemia (XLA),(134) sickle cell disease,(135) and sensorineural hearing loss.(111) In all programs screen negative cases are not followed further.

Carrier status (presence of 1 *SMN1* copy) is generally not reported in population wide newborn screening programs.(92, 136) Although no studies denote methodologies specifically used for newborns with special circumstances studies have provided indirect evidence for the accurate screening of newborn with gestational age < 37 weeks.(10, 137) Of note, a high false positive rate has been identified in studies of unwell neonates, thought to be due to the use and screening of heparinised blood collected from central lines used in sick and premature babies instead of collection of a blood spot directly from the newborn.(129)

**Section 1:**  
**Recommendations on screening for *SMN1* as  
part of (newborn) screening in SMA**

### Recommendation 1.1

#### Evidence based recommendation

We recommend that newborn screening for SMA should be performed on the routine newborn dried blood spot (DBS).

Grade of recommendation, Grade B

#### Good Practice point 1.1.1

Newborn screening for SMA for newborns who are unwell at birth and require neonatal care should proceed using the same screening protocols as for the well neonate. The dried blood spot should be taken directly from the neonate onto the provided filter paper. Samples collected from capillary tubes, umbilical lines and other sources where there is potential for contamination with heparinised products, should be avoided, to prevent uncertain or false screening results.

#### Good Practice point 1.1.2

We recommend that information sources including written and multimedia resources that detail newborn screening processes, and the conditions included, should be updated with the addition of SMA, to facilitate informed consent of parents opting in for newborn screening.

### Recommendation 1.2

#### Evidence based recommendation

We recommend that the target analyte of newborn screening for SMA is absence of exon 7 on *SMN1*.

Grade of recommendation B

### Recommendation 1.3

#### Consensus based recommendation

We recommend that the screening method selected by the screening program should have a sensitivity of  $\geq 95\%$  for the detection of *SMNI* exon 7 absence (0 *SMNI* copies).

Grade of recommendation Strong, Grade 1C

### Recommendation 1.4

#### Consensus based recommendation

We recommend that the screening test for SMA should determine the absence of *SMNI* exon 7 (0 *SMNI* copies) using suitably validated quantitative or qualitative assays.

Grade of recommendation Strong, Grade 1B

### Recommendation 1.5.

#### Consensus based recommendation

We suggest that screen positive samples (0 *SMNI* copies) should immediately be repeated on the same dried blood spot.

Grade of recommendation Conditional, Grade 2C

### Recommendation 1.6.

#### Consensus based recommendation

We recommend that the newborn screening process for SMA should not identify carrier status.

Grade of recommendation Strong, Grade 1C

### Recommendation 1.7.

Consensus based recommendation

We recommend that a screen positive result should be communicated to clinical services when the *SMN1* screening result is available (independent of the availability of *SMN2* copy number on screening assays), to reduce timelines to diagnosis and treatment.

Grade of recommendation Strong, Grade 1C

### Recommendation 1.8.

Consensus based recommendation

We recommend that if blood transfusion is considered, the dried blood spot (for purposes of screening for SMA) should be taken prior to transfusion of blood products.

Grade of recommendation Strong, Grade 1B

### Recommendation 1.9.

Consensus based recommendation

We suggest that newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, and low or very low birthweight newborns should proceed using the same screening protocols as for term newborns.

Grade of recommendation Conditional, Grade 2B

*Evidence summary of individual studies for recommendations 1.1-1.9 located in technical report on page 127-131.*

## Rationale and impact section on screening for *SMNI* as part of newborn screening for SMA

The evidence showed that there were gaps in current practice in the screening processes for *SMNI* and the GDG agreed that there should be a standardised process for first tier testing. The GDG agreed that diagnostic test accuracy for *SMNI* testing was out of scope of the Guideline, however, did consider the fact that any assay used should have high sensitivity and specificity. The evidence showed that newborn screening for SMA could be conducted on the dried blood spot taken as part of established newborn screening programs in Australasia and that there was consistent evidence to show that the target analyte should be absence of exon 7 of *SMNI*. The GDG acknowledged that this screening target would miss the 5% of children with compound heterozygosity or biallelic pathogenic variants in *SMNI*. However, given the seriousness of harms from a false positive and false negative result (section 4), the GDG agreed that assays should have a minimum of 95% sensitivity and 100% specificity. The GDG recognised that although there were resource implications to adding genetic testing to newborn screening programs, the health impact of early identification of SMA, leading to options for treatment would have a large health impact on the target population. The GDG strongly considered the need for coordination of care and communication between services, with consideration to shorten the time to notification of a screening result to clinical services (independent of the availability of prognostic information). The incorporation of reporting carrier status through a newborn screening program was discussed iteratively by the GDG and whilst members acknowledged the utility of this, it was felt that this was outside the scope of present programs and would be unfeasible across Australasia from a health system perspective.

## How the recommendations might affect practice

The recommendations reflect aspects of current practice however the GDG agreed that there were resource implications for jurisdictions starting to implement newborn screening for SMA in terms of personnel with relevant expertise to conduct and report (genetic) assays, equipment and reagent and coordination of services for timely notification between services.

**Section 2:**  
**Recommendations on screening for *SMN2* copy number as part of (newborn) screening in SMA**



### *SMN2* copy number as relates to newborn screening for SMA processes

*SMN2* copy number is the leading prognosticator of SMA disease severity, with higher copy numbers generally modifying phenotype to confer a milder phenotype and later onset clinical course.(27, 86, 138) As such incorporating *SMN2* copy number testing on the same dried blood spot as *SMN1* testing, is not required to identify newborns screening positive for SMA, however is clinically useful for determining disease severity, planning the pace and type of treatment (where approved and reimbursed access for presymptomatic individuals is dependent on *SMN2* copy number) and to stratify newborns into clinical trials.(139)

Namely, current international clinical guidelines for infants with SMA identified through newborn screening programs recommend immediate treatment of presymptomatic infants with 2–3 *SMN2* copies.(140, 141) Treatment recommendations for infants with 4 *SMN2* copies are evolving, with some guidelines advocating immediate treatment whilst others are in favour of a surveillance approach for symptom onset.(141-144), with access to SMN augmenting therapies in these individuals varying between countries. The treatment of presymptomatic infants with > 4 *SMN2* has less clear evidence in terms of efficacy to support instigation of SMN augmenting treatments but is being undertaken in some studies.(137) Therefore, obtaining *SMN2* copy number information as part of the screening result can help to start the shared decision-making process between parents and clinicians over treatment necessity, timing and eligibility and to guide the pace of initiating treatment based on local approvals and reimbursement policies.

Risk stratification of infants at the highest risk of earlier clinical symptom onset is particularly facilitated by incorporating *SMN2* copy number screening into newborn screening processes. Infants with 2 *SMN2* copies show higher risk of clinically manifesting disease in the newborn/early infancy period (with denervation potentially starting in utero, and the active disease process progressing into the peri and early postnatal period).(137, 145-147). For newborns screening positive for SMA up to 47% of with those with 2 *SMN2* copies, clinically display signs and symptoms of SMA onset within the first month of life. (146)

*SMN2* copy number availability from newborn screening informs medical practitioners on the probable optimal therapeutic window available for the infant and facilitates the instigation of therapeutic planning whilst genotypic (diagnostic) confirmation is underway. (80, 92, 98) This helps to minimise treatment delays to reduce the exponential rate of motor unit loss,(80, 148) especially in infants with 2 *SMN2* copies, which in turn significantly improve long term outcomes as relates to motor function, independent feeding and breathing at two years of age.(80, 98)

However, *SMN2* copy number is a prognostic marker which is not absolute, and whilst it can act as a guide to management, discordant genotype-phenotype cases (i.e. where the genetic presentation does not match the predicted clinical presentation), are noted in both presymptomatic and symptomatic infants.(139) *SMN2* copy number can be considered as the ‘tip of the iceberg’ with rare *SMN2* variants, hybrid structures and other single nucleotide variants leading to functional differences in *SMN2*, which go beyond gene dosage.(139, 149-151) *SMN2* analysis outside of newborn screening algorithms i.e. during follow-up care may therefore be more appropriate than incorporating *SMN2* screening into newborn for SMA programs.(115) Furthermore, the incorporation of *SMN2* into newborn screening programs potentially falls outside the defined scope of these public health programs i.e. to identify those at risk of SMA, but not to facilitate predication or prognostication of disease onset and severity.(88, 130)

Reflecting this, there is variability in international practice as regards to *SMN2* number incorporation in screening programs. Across the USA, 10 out of 37 states incorporate screening for *SMN2* into newborn screening programs, completed on the same dried blood spot and following detection of absence of exon 7 on *SMN1*.(130) However, other states determine *SMN2* copy number as part of clinical follow-up through dried blood spot testing on a recalled infant or through diagnostic testing.(92, 130) This variability in practice is replicated across the international landscape, with the majority of programs incorporating *SMN2* copy number into newborn screening activities or as expeditiously as possible in the diagnostic period.(32, 152)

When *SMN2* is incorporated into newborn screening process, quantitative methods are used, using a variety of methods including real time quantitative PCR, digital droplet PCR methods, multiplex ligation PCR amplification (MLPA) and reverse transcriptase PCR.(130)

The methodology for determining the *SMN2* copy number accurately can be complex with ongoing efforts to improve both the reliability of the process (between screening and diagnostic assays) and the ability to better determine the *SMN2* count.(153)

Methodologically, *SMN2* copy number can vary dependent on the methodology (digital droplet PCR, MLPA or qPCR) used in up to 50% of cases.(152, 154) A consensus statement issued on the topic of *SMN2* copy number determination within newborn screening programs notes that the use of validated technology is important to allow for the exact determination of *SMN2* copy number.(32) The majority of (newborn screening) studies delineate copy number of *SMN2*  $\leq 4$  due to inherent technological challenges in maintaining accuracy in *SMN2* copy number estimation with *SMN2* copy numbers  $> 4$ .(32)

### Recommendation 2.1.

Consensus based recommendation

We suggest that *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes but not delay notification of absence of exon 7 on *SMN1*.

Grade of recommendation Conditional, Grade 2B

### Recommendation 2.2

Consensus based recommendation

We recommend that *SMN2* copy number should be completed on suitably validated quantitative *SMN2* assays when identified as part of newborn screening.

Grade of recommendation Strong, Grade 1C

### Recommendation 2.3.

Consensus based recommendation

We recommend that when *SMN2* copy number is known to be > 4 at the time of initial newborn screen identification i.e. in the absence of exon 7 on *SMN1*, this is **not** designated as a screen positive result.

Grade of recommendation Strong, Grade 1C

### Recommendation 2.4.

Consensus based recommendation

We recommend that the (in)availability of *SMN2* copy number should not delay clinical notification of a screen positive result based on absence of exon 7 on *SMN1*.

Grade of recommendation Strong, Grade 1C

### Recommendation 2.5.

#### Consensus based recommendation

We recommend that if screening for *SMN2* is not incorporated into the newborn screening process, diagnostic testing for *SMN2* should occur during follow-up care.

Grade of recommendation Strong, Grade 1B

### Recommendation 2.6.

#### Consensus based recommendation

We suggest that for the purposes of the screening program, unvalidated prognostic biomarkers outside of *SMN2* copy number (including *SMN2* splicing modifier variants and modifiers outside of the *SMN2* gene) will not be incorporated into screening algorithms.

Grade of recommendation Conditional, Grade 2C

### Recommendation 2.7.

#### Consensus based recommendation

We recommend that the newborn screening program for SMA should establish a clinical referral pathway for screen positive newborns. A positive newborn screening result should be verbally relayed to a designated paediatric neurologist.

Grade of recommendation Strong, Grade 1C

### Implementation point 2.7.1.

In many health jurisdictions, newborn screening programs have an established notification strategy that involves notifying a healthcare practitioner (usually general practitioner, obstetrician, maternity nurse or paediatrician) on the child's dried blood spot demographics. Due to the imperative to have access to expedient diagnosis and treatment, newborn

screening programs should establish a clinical referral pathway that includes simultaneous, early notification of a screen positive result to a paediatric neurology specialist.

#### Good Practice point 2.7.1.

We suggest that the newborn screening for SMA program will establish a clinical referral pathway for newborns who screen positive for SMA. A positive newborn screening result may also be verbally relayed to a relevant listed healthcare practitioner (that is or has been involved in the care and management of the child such as a general practitioner or paediatrician).

#### Recommendation 2.8.

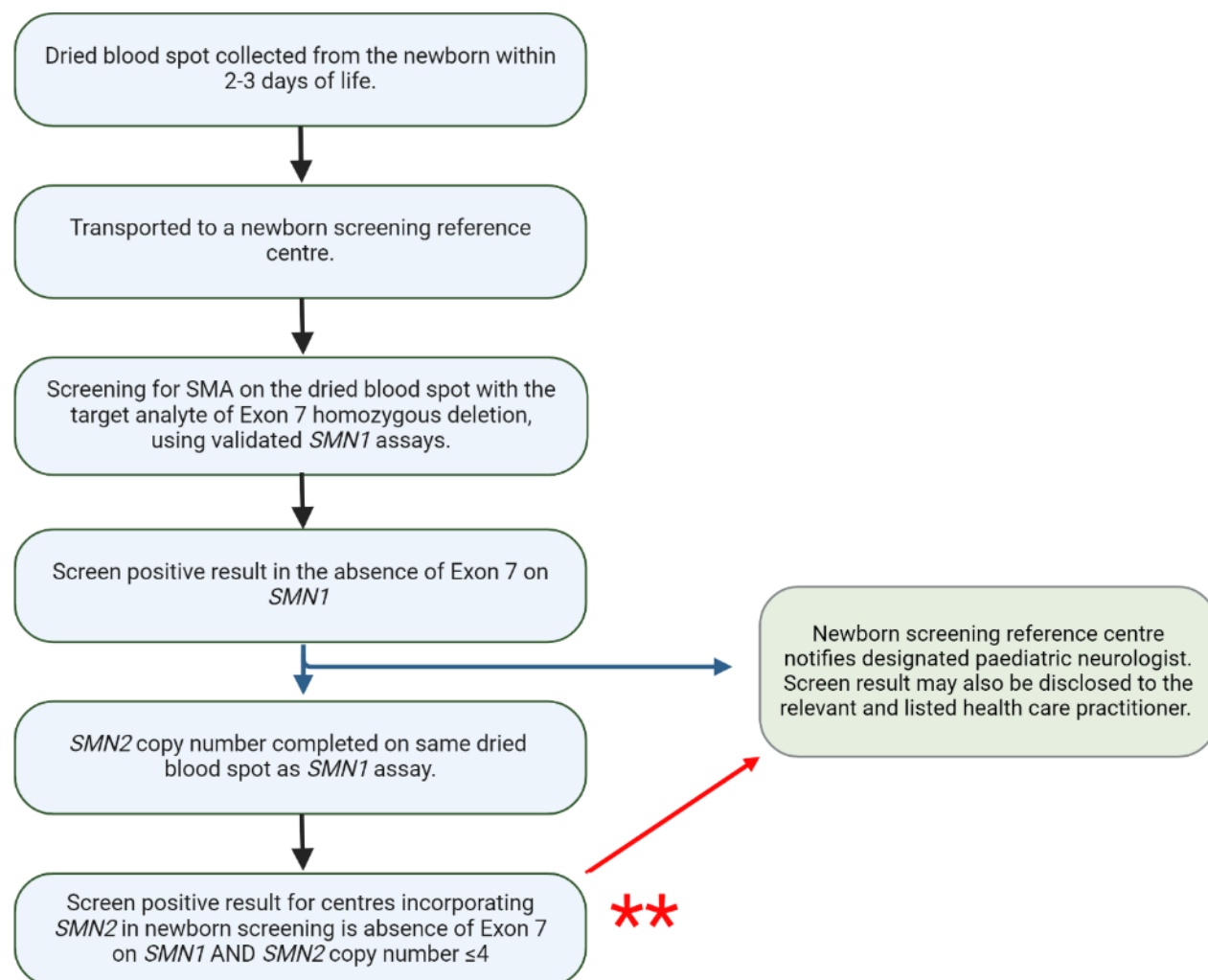
##### Consensus based recommendation

We suggest that written notification of a screen positive SMA result should be issued to the individual(s) listed in 2.7. within 24 hours of the verbal notification of a screen positive result.

Grade of recommendation Conditional, Grade 2C

*As such, the recommendations encompassed in section 1 and 2 form an (evidence and consensus based) pathway as follows (Figure 7)*

*Evidence summary of individual studies for recommendations 2.1-2.8 located in technical report on page 132-137.*



**Figure 7.** The proposed flow of screening activities based on recommendations within the Guideline. \*\**SMN2* as part of newborn screening may be considered to provide additional information but should not delay notification of the screen positive result i.e. exon 7 absence on *SMN1*. Relevant designated healthcare practitioner is dependent on healthcare jurisdiction and can include the general practitioner, obstetrician, neonatologist, maternity nurse or paediatrician listed on the child’s dried blood spot card.

## Rationale and impact section on screening for *SMN2* as part of newborn screening for SMA

The evidence showed inconsistencies in whether *SMN2* should be incorporated as part of newborn screening for SMA or as a component of the post diagnostic pathway, leading to potential variations in practice. The GDG agreed that *SMN2* as the best prognostic indicator of disease severity and onset was essential to inform treatment planning, however considered that a flexibility of approach was required to be feasible for implementation across all health jurisdictions. Thus, it was considered ideal for *SMN2* to be part of newborn screening but not mandatory. The GDG were unanimous in their agreement that the central outcome was diagnostic confirmation of SMA through *SMN1* testing, which should not be delayed due to inavailability of *SMN2*, to reduce time to treatment and thus the health impact of screening on newborns. Whilst the GDG understood that across the evidence, *SMN2* copy numbers > 4 were reported within newborn screening programs, it was considered that within Australasia where access to *SMN* augmenting treatments and options of surveillance were established for (symptomatic children or presymptomatic newborns < 4 copies) and symptomatic children with (4 *SMN2* copies) respectively, higher copy numbers would not be reported when known. This was also considered important due to methodological imprecision with assays detecting *SMN2* copy number > 4. The GDG agreed that due to the precipitous clinical course in SMA, screening results would be relayed verbally and through written means to clinical experts (usually neurology specialists) pre-identified within each healthcare jurisdiction, to reduce time to appropriate treatment, care and support which would have substantial impacts on health and wellbeing for newborns and families.

## How the recommendations might affect practice

The recommendations reflect aspects of current practice for some jurisdictions however the GDG agreed that there were resource implications for jurisdictions starting to implement newborn screening for SMA in terms of personnel with relevant expertise to conduct and report *SMN2* screening assays, procurement of equipment and reagents, and coordination of services for timely notification between services. The GDG acknowledged that in particular, if *SMN2* copy number was part of the diagnostic process, reference laboratories would need to establish processes to prioritise and streamline results, to enable timely therapeutic decision making.



**Section 3:**  
**Confirming the diagnosis of spinal muscular atrophy**



## Background

Due to the paucity of high-quality scholarly literature to provide evidence-based recommendations, the majority of recommendations in this section were founded on consensus, which was based on systematic collation and review of the existing literature. A narrative summary of findings is presented on which consensus-based recommendations were formed. A more detailed view is encompassed in the Supporting Evidence Summary document.

### What encompasses diagnostic confirmation of SMA after a screen positive result

For the purposes of the Guideline and the recommendations therein, the diagnostic domain was defined as processes and activities performed within the diagnostic laboratories for confirmation of genetic diagnosis of SMA. Unlike the designated reference centres for newborn screening, publicly funded diagnostic capabilities vary across Australia and Aotearoa New Zealand, with laboratories having variable capacity and capability to process *SMN1* and/or *SMN2* copy number results and using a spectrum of methods. Thus, recommendations of methodology for *SMN1* and *SMN2* diagnostic confirmation were considered outside the scope of the Guideline.

### The pathway to diagnosing SMA after a screen positive result, evidence from the literature

Screening assays used for SMA are highly sensitive and specific with low false positive and false negative rates. However, diagnostic confirmation of SMA is required in all screen positive newborns, to overcome inaccuracies due to sampling errors and misidentification of screening samples which can occur in rare circumstances during the processes of whole of population screening.<sup>(155)</sup> The process of diagnostic confirmation requires recalling a newborn for diagnostic purposes, consent and the collection of fresh blood samples or repeat dried blood spots to confirm the biallelic deletion of exon 7 on *SMN1* on molecular assays (section 4). There are no comparative studies to detail the optimal method(s) for diagnostic analysis of *SMN1*, however most commonly used methods include MLPA,<sup>(10, 94, 123, 146, 147, 156-</sup>

158), ddPCR(156, 159), qPCR(108, 136, 157), sequencing(119, 160), or restriction fragment length polymorphism PCR(32, 115), +/- analysis of splicing variants.(32, 115)

*SMN2* diagnostic testing is considered clinically useful to determine prognosis and long-term outcomes. Therefore, there is a clinical imperative for *SMN2* quantification which should be completed as soon as possible within the diagnostic process (if not done within newborn screening) and/or confirmed during this process (if incorporated within newborn screening programs).(32) However, *SMN2* copy number confirmation can be challenging, with *SMN2* copy number discrepancies arising in 45% (9/20) of children with known SMA, retested on different methodological platforms(161) and with modernised technologies,(146) underlining the necessity of using validated and up to date methods for denoting *SMN2* copy number.(146) In these studies, discrepant *SMN2* results are secondary to sensitivity to contamination of probes and reagents, variability in definition of exact cut off values for interpretation, quality and quantity of nucleic acid used, and the availability and usage of appropriate controls.(32)

Whilst there are currently no comparative studies for *SMN2* copy number determination, as *SMN2* copy number is one of the main stop-or-go tools for initiating the treatment of children, especially if identified in the context of newborn screening programs, an inaccurate diagnostic result may be very harmful to patient health. As a mitigator, the development of standard operating procedures for *SMN2* analysis using validated assays and completed in accredited and centralised diagnostic centres is thought to be appropriate and relevant for greater diagnostic accuracy, in line with national pathology standards.(152)

Beyond *SMN2* copy number, additional genetic modifiers may influence variability of transcription, translation and stability of *SMN2* transcripts and disease course and severity. For example, the *SMN2* c.859G>C, (p.Gly287Arg) (NM\_000344.4) variant in exon 7, in which a greater proportion of *SMN2* mRNA transcripts contain exon 7, can produce a milder clinical course in individuals with this genotype.(151) The implications of *SMN2* modifier variants and hybrid genes for treatment are not currently understood and these may be interrogated on a case-by-case basis if there is discordance in genotype and phenotype.(162)

The timelines appropriate for completion of all diagnostic tests for SMA (including *SMN1* and *SMN2* copy number) should be as short as possible, without compromising the accuracy of the process. This is emphasised by the fact that children diagnosed and started on SMN augmenting treatment by 6 weeks of life have a higher probability of following motor development trajectories of typically developing children, independent of *SMN2* copy number.<sup>(163)</sup> Therefore, time to diagnosis and subsequent treatment appears to be a substantial modifier of health outcomes for these children.

### Recommendation 3.1

#### Evidence based recommendation

We recommend that diagnostic testing should include confirmation of homozygous absence of exon 7 on *SMN1* (0 copies of *SMN1*).

Grade of recommendation B

#### Implementation point 3.1.1

Assays for diagnostic confirmation can be conducted on whole blood samples or repeat dried blood spots from the recalled newborn, dependent on processes within local diagnostic services. Relevant healthcare practitioners should provide diagnostic laboratories with the optimal sample collected from the recalled newborn, for diagnostic purposes.

### Recommendation 3.2

#### Consensus based recommendation

We recommend that diagnostic testing should also include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making. Diagnostic testing for *SMN2* copy number should occur from freshly obtained whole blood samples or repeat dried blood spot from a recalled newborn.

Grade of recommendation Strong, Grade 1B

### Recommendation 3.3

#### Consensus based recommendation

We recommend that validated quantitative *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.

Grade of recommendation Strong, Grade 1B

### Recommendation 3.4

Consensus based recommendation

We suggest that diagnostic *SMNI* testing is conducted using a different methodology to the newborn screening assay.

Grade of recommendation Conditional, Grade 2C

### Recommendation 3.5

Consensus based recommendation

We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means) should occur upon identification of a screen positive result, so that stakeholders understand when a diagnostic sample will be collected and delivered to diagnostic laboratories to proactively prioritise timelines and avoid delays.

Grade of recommendation Conditional, Grade 2B

#### Implementation point 3.5.1.

Clinical and diagnostic services should have pre-established protocols and pathways in place that lead to rapid collection, authorisation of diagnostic tests and result notification.

### Recommendation 3.6

Consensus based recommendation

We recommend that diagnostic results for *SMNI* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory, to enable timely treatment.

Grade of recommendation Strong, Grade 1C

*The timings included in the Recommendation define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.*

### Recommendation 3.7

Consensus based recommendation

We suggest that for the purposes of diagnostic testing for SMA (within the newborn screening context), genetic modifiers outside of *SMN2* copy number will not routinely be tested.

Grade of recommendation Conditional, Grade 2B

### Recommendation 3.8

Consensus based recommendation

We recommend that a diagnosis of SMA (including *SMN1* and *SMN2* copy number) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment.

Grade of recommendation Strong, Grade 1B

*This Recommendation defines the **maximum** time for the completion of the screening and diagnostic process, in keeping with pathways that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to completion of the screening and diagnostic cycle (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.*

### Recommendation 3.9

#### Consensus based recommendation

We suggest that diagnostic reports should detail the methodology used for analysis and the precise *SMN2* copy number (avoiding reports such as  $SMN2 \geq 4$ ), where possible.

Grade of recommendation Conditional, Grade 2B

#### Implementation point 3.9.1.

To facilitate ongoing quality assessment and improvement activities, processes should be in place to notify newborn screening programs of all diagnostic SMA results.

*Evidence summary of individual studies for recommendations 3.1-3.9 located in technical report on page 138-142*



## Rationale and impact section on diagnostic processes with newborn screening for SMA

The GDG agreed that there was consistent and generalisable evidence to support diagnostic confirmation of *SMN1* and expert consensus for the utility of diagnostic testing for *SMN2* copy number on a recalled screen positive newborn. There was consistent evidence in the literature and through expert consensus that a genetic confirmation of SMA was essential as a gateway to treatment, care and support and was also considered valuable from a family perspective in reducing feelings of uncertainty and increasing wellbeing. The GDG discussed that whilst it was preferable for diagnostic tests for *SMN1* to be conducted on different methodological platforms to the screening assay to improve diagnostic accuracy, this would not always be feasible across health jurisdictions. As newborn screening programs are implemented across Australia and Aotearoa New Zealand, it was felt that diagnostic capacity might reasonably expand in line with increased need. However, the GDG considered that considerable harm to children and their families could occur with inaccurate *SMN1* and *SMN2* copy number identification, and diagnostic assays should be conducted in expert reference centres to mitigate these risks. Whilst timelines for diagnostic results varied across the evidence, the GDG considered the need to define optimal timings for diagnostic result availability in the Guideline to mitigate inequities based on time to diagnosis, treatment and care, which was felt to be the basis for increasing the magnitude of benefit from treatments across the affected population.

## How the recommendations might affect practice

The use of diagnostic (genetic) testing for SMA may vary. The recommendations clarify what tests should be conducted, and how quickly results should be made available. This will reduce variation in clinical practice and enable diagnostic (*SMN1*) and prognostic (*SMN2*) information to be available to inform treatment planning. Diagnostic services may have to increase capacity and change workflow processes to expedite results, which may affect allocation of resources.

**Section 4:**  
**Managing uncertain, false positive and false  
negative screening results**



## Background

Due to the paucity of high-quality scholarly literature to provide evidence-based recommendations, the majority of recommendations in this section were founded on consensus, which was based on systematic collation and review of the existing literature. A narrative summary of findings is presented on which consensus-based recommendations were formed. A more detailed view is encompassed in the Supporting Evidence Summary document.

### The definition of false positive, false negative and uncertain results within newborn screening for SMA

A false positive screening result applies to a test that incorrectly indicates the increased risk of the presence of a condition. In the SMA context, a false positive screening result may occur after diagnostic confirmation does not identify homozygous deletion of exon 7 on *SMN1*, in a screen positive newborn. In contrast true positive screening results are defined by diagnostic confirmation of SMA in a screen positive newborn. A false negative screening result occurs when the newborn screen does not indicate the presence of the condition when it is present. In the SMA newborn screening context, a false negative screening result may occur secondary to the sensitivity of the assays employed or the fact that the recommended screening test (Recommendation 1.2.) does not screen for the 5% of the SMA population with genetic variants outside biallelic deletion of exon 7 on *SMN1*. These children may present with signs and symptoms of SMA and be referred to clinical services accordingly.

### Managing false positive, false negative and uncertain results within newborn screening for SMA, evidence from the literature

The literature shows that in the majority, screening studies report no false positives. Across the literature, in 11 studies, 71 false positive cases have been reported. For those described, the aetiology of false-positive results may be divided broadly into three groups: genetic variation of *SMN1*, including the presence of heterozygous carriers of exon 7 *SMN1* deletion, *SMN* hybrids and genetic variants in probe binding sites,(29, 164) DNA quality and/or quantity of the dried blood spot samples,(124, 156) and instrument performance in

detecting *SMN1* gene deletion.(124) A high false positive rate (10 false positives in a screening sample of 8336) has been accounted for by use of diluted or heparinised blood for screening purposes, collected from the umbilical lines of sick neonates.(159) and further false positive screening results have occurred in premature neonates for uncertain reasons (165). False positive results have been noted with a concurrent false positive SCID screen,(166) with no clear cause described for this association.

There are few (six) reports describing false-negative results within newborn screening for SMA population studies and the aetiologies of these results noted across five studies range from human/systems errors, to children who have pathogenic genetic variants other than biallelic exon 7 deletion of *SMN1* (which will not be detected through proposed screening assays).(10, 29, 132, 147, 165). From a methodological standpoint, when using the widely used qPCR techniques for screening for the absence of *SMN1*, cross signals from homologous *SMN2* can occur. Accordingly, high specificity and targeted probes are required to discriminate the *SMN2* sequences to avoid false negative results.(167)

Uncertain results on initial screening assays have also been described and are resolved through second and third tier screening processes i.e. testing for *SMN1* either through repeating the same assay or by deploying different methodologies on the same dried blood spot. The aetiology of uncertain results mirrors that of false positives and been thought to be secondary to contamination with heparin,(115) the presence of PCR inhibitors (seen predominantly in blood collected from newborns in intensive care units)(130), poor DNA quality/quantity or system errors.(94)

False-negative screening results caused by a *SMN2* hybrid (*SMN1* homozygous deletion in the presence of a *SMN2* hybrid) also can occur, although the risk is negligible compared with the 5% false-negative results caused by single nucleotide pathogenic variants, which cannot be detected by commonly employed current screening methods.(168) This implies that false-negative cases are likely to become apparent over time as children with SMA who screen negative through newborn screening programs due to compound heterozygous pathogenic variants may later present with SMA-related symptoms to clinical services. Therefore, it is important for general paediatricians and physical examiners conducting

health checkups for infants to be aware of the limitations of current SMA newborn screening tests, existence of false-negative SMA cases and the typical symptoms of SMA.(168)

For newborns/infants with false negative results, complete sequencing of *SMN1* (coding and regulatory regions of *SMN1*) may be required to better understand the aetiology of the screening results.(29, 168) Due to the high degree of homology between *SMN1* and *SMN2*, both genes are sequenced simultaneously using standard Sanger sequencing from genomic DNA, making an unequivocal assignment impossible. Various, more laborious techniques have been developed including but not limited to long read sequencing techniques.(169, 170) Furthermore, segregation analyses and a precise understanding regarding *SMN1* and *SMN2* copy numbers are imperative to identify the aetiology of false negative results.(171)

The psychological impact of uncertain, false positive and false negative results within SMA newborn screening programs are well understood, with the psychological challenges faced by families and clinicians of uncertain/equivocal screening results emphasised, overcome by standardised and streamlined pathways to specialist review of the result (with coordination between screening, diagnostic, neurology and genetic services to understand the result),(10) and access to support and care for families who receive uncertain, false positive and false negative results.(11)

### Recommendation 4.1

Consensus based recommendation

We suggest that for newborns with a false positive **or** uncertain screening result, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and explained to parents.

Grade of recommendation Conditional, Grade 2C

*False positive results are defined by individuals with a screen positive result through newborn screening who have been confirmed **not** to have SMA on diagnostic testing.*

*Uncertain results are defined by individuals with an uncertain result on newborn screening assays, who then have definitive results on further testing of the initial dried blood spot.*

*These are not classed as false positives as issues resolve through further testing of the initial dried blood spot, which is considered as part of the index test process.(172)*

### Recommendation 4.2

Consensus based recommendation

We suggest that families of newborns with false positive or uncertain results should be given the option of returning to discuss the implications with members of the neurology/neuromuscular multidisciplinary team\*.

Grade of recommendation Conditional, Grade 2C

*\*Multidisciplinary team members may vary dependent on health jurisdiction. Information may be provided by paediatric neurologists or paediatricians with support from genetic counsellors and/or clinical geneticists.*

### Recommendation 4.3

#### Consensus based recommendation

We recommend that if there is a difference in *SMN1* results between screening and diagnostic assays, retesting for *SMN1* with another method/laboratory is recommended. A further sample from the newborn may be required for repeat screening and/or diagnostic testing if resolution of *SMN1* genotype does not occur.

Grade of recommendation Strong, Grade 1C

#### Good practice point 4.3.1.

Venous samples from parents for *SMN1* quantification purposes may be required to understand the aetiology of a false positive or uncertain result for the newborn.

### Recommendation 4.4

#### Consensus based recommendation

We recommend that if there is a difference in *SMN2* results between screening and diagnostic assays, retesting for *SMN2* copy number with another method/laboratory is recommended. A repeat sample from the newborn may be required for further diagnostic testing if resolution of *SMN2* copy number variation does not occur.

Grade of recommendation Strong, Grade 1C

### Recommendation 4.5

#### Consensus based recommendation

We recommend that if there is uncertainty as to the diagnosis of SMA the child should be clinically followed up by a paediatric neurologist till diagnostic certainty is reached.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.6.

Consensus based recommendation

We recommend that if there is uncertainty as to the diagnosis of SMA, families should be provided with clear instructions on red flags for signs and clinical symptoms that warrant medical attention (Recommendation 5.9).

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.7.

Consensus based recommendation

We recommend that for newborns with a false negative result, (diagnostically confirmed to have SMA after a negative newborn screen result), a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of this result.

Grade of recommendation Strong, Grade 1C

##### Implementation point 4.7.1.

We suggest that lessons or insights derived from the case review of false positive/false negative or uncertain results should be shared across Australasian Newborn Bloodspot services so that common issues and errors can be identified.

#### Recommendation 4.8.

Consensus based recommendation

We recommend that families who receive a false negative or uncertain screening result should be provided psychosocial support by relevant members within the multidisciplinary team\*.

Grade of recommendation Strong, Grade 1C



*\*Multidisciplinary team members may vary dependent on health jurisdiction. Support may be provided by paediatric neurologists or paediatricians, genetic counsellors and/or clinical geneticists, social workers, psychologists, allied therapists and/or specialist nurses.*

#### Recommendation 4.9.

Consensus based recommendation

We recommend that open disclosure between appropriate healthcare practitioners and families should occur with any false positive, uncertain or false negative screening results.

Grade of recommendation Strong, Grade 1C

#### Recommendation 4.10.

Consensus based recommendation

We recommend that healthcare practitioners conducting health checkups for infants should be aware of the existence of false-negative SMA cases and the typical symptoms of SMA, for expedient referral to specialist neurology services (due to current newborn screening assays only detecting absence of exon 7 on *SMN1*).

Grade of recommendation Strong, Grade 1C

*Evidence summary of individual studies for recommendations 4.1-4.10 located in technical report on page 143-148.*

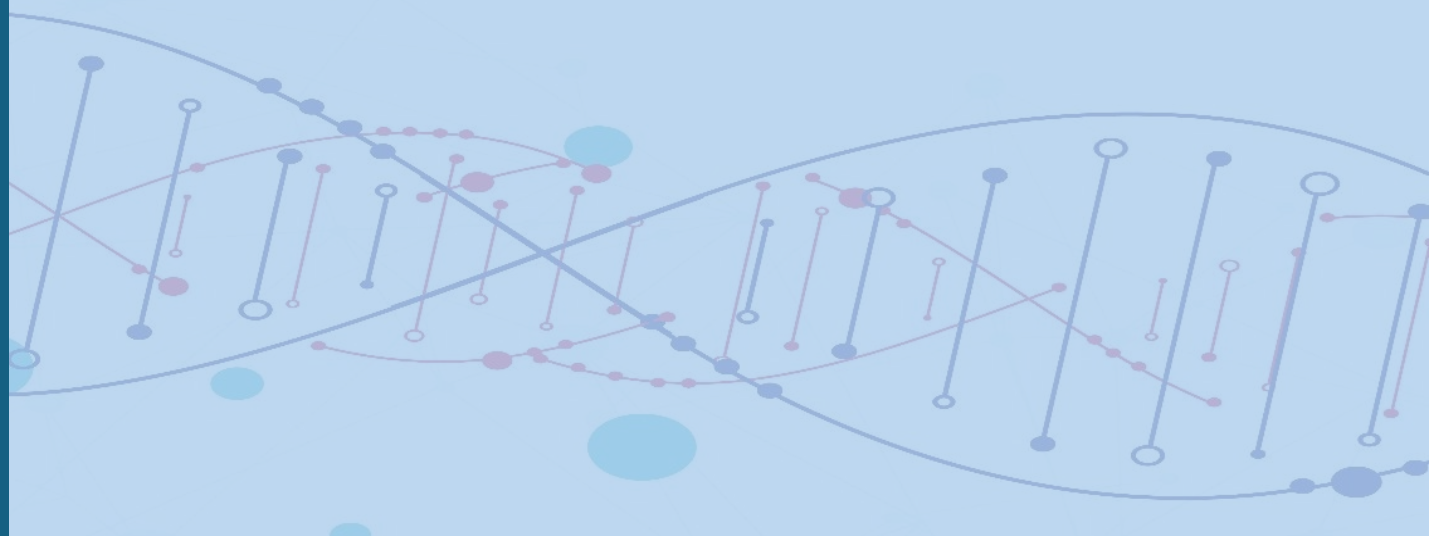
## Rationale and impact section on managing false screening results within newborn screening for SMA

The evidence identified a small number of false positives and rare false negatives through newborn screening, but the GDG agreed that there were evidence gaps as to the management and resolution of these results, that could lead to several serious harms on a number of levels. Harms to the newborn included either unnecessary treatment (with false-positive screening results) or children remaining undiagnosed and untreated (with false negative screening results) and the psychological distress caused to families, potential dissatisfaction with care and an erosion of public trust in newborn screening as a population health initiative. It was agreed by the GDG that recommendations would enable standardisation of practice across the population and lead to resolution of discordant screening and diagnostic results in a timely and accurate manner. The clinical experience and expertise of the GDG informed the need for a case-by case systematic ‘root cause analysis’ of the aetiology of the false positive/false negative or uncertain result with close communication between screening, diagnostic and clinical services. The GDG acknowledged that families receiving these results were vulnerable to substantial psychological distress, mitigated to an extent by referral to appropriate social, advocacy or psychological services. The GDG highlighted the need to undertake knowledge exchange activities across Australasia of the limitations of newborn screening for SMA, to emphasise the necessity for prompt referral to clinical services for symptomatic children due to the potential for false negative cases (due to the inherent limitations of the target assay, human/system error or probe binding issues).

### How the recommendations might affect practice

The recommendations will standardise best practice across Australasia to ensure that children identified as at risk of SMA through newborn screening programs have their diagnosis accurately diagnosed and that children who may not be identified with SMA through these programs are clinically detected and referred for intervention as expediently as possible. The recommendations will form the basis for quality improvement across the newborn screening program in each jurisdiction.

**Section 5:**  
**Disclosing a screen positive result to families**



## Background

### Disclosing screen positive SMA results to families: the start of the healthcare journey

Notifying families of a newborn screen positive result can be challenging for both healthcare practitioners designated to this task, and for families receiving the results. Providing information in a compassionate, family centred, and accurate manner is considered important to facilitate understanding for families, reduce psychological distress and uncertainty and to instil confidence in the healthcare journey for the child and family. The recommendations in this section are consensus based for best practice, however the GDG acknowledges the need for flexibility in approach to communicating a screen positive result to families.

Clinical and preclinical data indicate that early treatment is critical to modulate the rapid and progressive degeneration seen in SMA.(173) There is robust evidence that the irreversible loss of motor neurons in humans with the early and infantile onset form (especially SMA type 1) begins early in the perinatal period, with severe denervation in the first three months and loss of more than 90% of motor units within six months.(80)

Therefore, the time to notify families of a screen positive result should be as short as possible.(12) Within the Australian pilot newborn screening for SMA program it has been noted that screen positive results can feasibly be communicated to families by 10.5 days of life (range 5-18 days), after screening result availability at 8 days of life (range 5-18 days).(12) Newborn screening programs globally have refined and adapted their processes in real-time to ensure efficiency at the point of screen positive disclosure and clinical evaluation for diagnosis, after noting that 27% of newborns/infants are symptomatic at the time of first clinical review. Facilitators for a streamlined process include instigating clinical referral pathways directly to specialist centres for clinical care and treatment initiation.(11)

Inconsistent information provision at the point of screen positive disclosure may lead to increased parental uncertainty and can increase feelings of hope and expectation of a false positive screening result.(132)

The designation of healthcare practitioners tasked with notifying the family of screen positive results vary internationally, dependent on jurisdiction-specific SMA workflow processes.(132) In the majority, parents are notified by a paediatric neurologist working in a specialist neuromuscular centre,(12) by the hospital where the child is born, and less commonly by the screening laboratory or a designated paediatrician.(132).

With their role expanding in a new therapeutic era, genetic counsellors can now provide information not only on the genetics of a condition but work in conjunction with neurology specialists to facilitate understanding of treatment timing, delivery and follow-up. Dependant on health expertise and confidence in disclosing sensitive results to families, other programs have leveraged the experience of trained genetic counsellors or nurses, particularly in regional and remote areas.(111) Screening results are generally disclosed over the telephone where the child and family are directed to the closest paediatric hospital for clinical review.(111) Consideration has been given to the need for flexibility when communicating a screen positive result to families, with provision of expedient access to diagnosis for children who live a distance from specialist or children's hospitals. For these individuals, families have been directed to complete diagnostic tests at a regional diagnostic centre prior to meeting with the paediatric neuromuscular specialist.(111, 120)

### Providing child and family centred care at the point of notification of a screen positive result

A standardised modality and content of information provision at the point of screen positive disclosure aligns with the needs and values of families receiving this information.

Parents often do not understand the implications of the SMA diagnosis, at the point of screen positive disclosure, with only 42% perceiving that the information provision at this point facilitates their understanding of the diagnosis, contrasted with 28% of parents feeling empowered to understand the next steps for their child at this juncture.(174). This variability may be secondary to the designation (and thus experience and expertise) of the person identified for disclosure which can range from paediatricians, neurologists to midwives and obstetricians.(174)

Parents who are well informed about symptoms of SMA, treatment availability, and details of treatment options report an improved understanding of their child's screening result, diagnosis, and next steps required for their child's medical care, which increases trust and confidence in the healthcare team.(11)

Families perceive value in having direct contact with specialists with expertise in neurological conditions at the point of screen positive disclosure and/or closely thereafter, citing the clarity of information and the depth of expertise to answer questions as mitigating factors to a period of high psychological distress and uncertainty.(11, 174)

### The content of information provision when notifying families of a screen positive SMA result

Australian and Aotearoa New Zealand families of newborns with a screen positive SMA disclosure come from a broad range of sociodemographic backgrounds including culturally and linguistically diverse communities and regional areas.(10) Thus, there is a necessity to tailor information (including at the time of screen positive notification of families) to fit a variety of needs amongst these families and to focus on family centred care, by establishing a dedicated team and communication strategy to facilitate effective screen positive disclosure.

To facilitate implementation of integrated services, close liaison between newborn screening services, local healthcare professionals and paediatric neurology specialists appear mandatory to identify the most appropriate setting for screen positive disclosure. Options include immediate referral to the neurology/neuromuscular team or, for those with difficulties travelling long distances, with the local paediatrician, genetic counsellor, clinical geneticists nurse specialists or general practitioner and specialist support using videoconferencing (telehealth) systems.

Information provided at the time of screen positive disclosure is variable between health jurisdictions and between medical practitioners.(132) Information provided generally

includes the name of the condition (provided to families in 95% of instances), symptoms of untreated SMA, the existence of treatments (detailed for 57% of families) and more in-depth discussion on treatment options (40% of families). Defining the plan for timely follow-up care for the newborn at the time of screen positive disclosure, helps to reduce the psychological stress and uncertainty on the family.(132)

International recommendations underline the need to update families of the signs and symptoms of SMA, so that caregivers have access to information (educational materials or a written checklist) that can be used at home to monitor for ‘red flag’ signs and symptoms of clinical deterioration that would trigger immediate clinical (re) review.(140) These include a change in the child’s movement, increased fatigue without increased activity, trouble feeding, decline or loss in function in previously attained motor ability or change in breathing patterns including a change in voice/weak cry. The presence of abdominal breathing and failure to thrive are also deemed important but later onset signs of SMA.

Families often describe a period of information seeking between screen positive disclosure and diagnosis, associated with feelings of distress and confusion. Well curated and reliable sources of information at screen positive disclosure are considered vital to bridge the information gap and provide accurate counsel.(11) .

### Recommendation 5.1

Consensus based recommendation

We suggest that a screen positive result should be ideally disclosed to the family within  $\leq 2$  working days (of notification to healthcare services).

Grade of recommendation Conditional, Grade 2B

### Recommendation 5.2

Consensus based recommendation

We recommend that the designated paediatric neurologist, receiving the screen positive SMA result, should coordinate with other relevant healthcare practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process.

Grade of recommendation Strong, Grade 1C

#### Good Practice point 5.2.1.

The process for communication of a screen positive result to families may be conducted through a telephone call or a telehealth consultation, and considers (if known), the families' comfort, convenience, privacy as well as practical considerations such as location and in the case of telehealth, access to appropriate and reliable equipment and connectivity.

### Recommendation 5.3

Consensus based recommendation

We suggest that it is acceptable for a designated healthcare practitioner with support from a paediatric neurologist to disclose a screen positive result to a family\*.

Grade of recommendation Conditional, Grade 2C



*\*The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians, specialist nurses and/or genetic counsellors. These individuals should have training and expertise in disclosing screen positive SMA results to families.*

*Support as defined in this recommendation can range from exchange of advice, information (verbal and/or written) or a formal offer to be part of the screen positive disclosure, alongside the designated healthcare practitioner.*

#### Good Practice point 5.3.1.

The healthcare practitioner disclosing the result should be honest and respectful and use an individualised approach when communicating the screen positive result to the family.

#### Recommendation 5.4

We recommend that healthcare practitioners disclosing results to families from culturally and linguistically diverse backgrounds should be aware of particular issues arising from this disclosure. If the healthcare practitioner is not bilingual, a professional interpreter should be used.

Grade of recommendation Strong, Grade 1C

#### Recommendation 5.5.

Consensus based recommendation

We recommend that healthcare practitioners disclosing screen positive results for SMA to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other First Nations backgrounds should be aware of culturally sensitive issues arising from this disclosure. The healthcare practitioner may seek advice from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) in how to best inform families who receive a screen positive result.

Grade of recommendation Strong, Grade 1C

### Recommendation 5.6

Consensus based recommendation

We suggest that the key points in the (screen positive disclosure) call to the family should include:

The screen positive status of the newborn.

The name of the condition.

Time frame and place for clinical review of the screen positive newborn.

General discussion of SMA as a condition that can be treated.

Named healthcare practitioner as a point of contact for the family.

Clinical questions on the newborn's current status including feeding, movement and breathing and/or clinical concerns from parents.

Grade of recommendation Conditional, Grade 2C

### Recommendation 5.7

Consensus based recommendation

We recommend that screen positive newborns should be offered a clinical review within paediatric neurology/neuromuscular services, if they are able to safely and promptly travel to these centres.

Grade of recommendation Strong, Grade 1C

### Recommendation 5.8

Consensus based recommendation

We recommend that a clinical review within local paediatric services, with clinical involvement through telehealth from a paediatric neurologist should be provided to screen positive newborns where access to specialist (neurology) services is limited and may cause delay in diagnostic evaluation.

Grade of recommendation Strong, Grade 1C

*The local healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians and/or specialist nurses. These individuals should have training and expertise in the clinical evaluation of screen positive children with SMA.*

#### Recommendation 5.9.

Consensus based recommendation

We suggest that from time of disclosure, a screen positive newborn should be reviewed at a clinical service for diagnostic evaluation as soon as possible and ideally within  $\leq 2$  working days, from the time of screen positive disclosure.

Grade of recommendation Conditional, Grade 2B

#### Good Practice point 5.9.1.

Dependent on child and family factors including geographical location, it is acceptable for a screen positive newborn to be reviewed within a clinical service for diagnostic evaluation within  $\leq 3$  working days, from time of screen positive disclosure.

#### Recommendation 5.10.

Consensus based recommendation

We recommend that healthcare practitioners should instruct families to contact them immediately to facilitate urgent clinical review at any time following screen positive disclosure if the following are noted in the newborn/infant.

Change in movement, feeding, or breathing pattern.

Change in voice or weak cry.

Increased fatigue without increased activity, decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability.

Abdominal breathing and/or failure to thrive.

In case of an acute event that requires hospitalisation

Grade of recommendation Strong, Grade 1C

#### Implementation point 5.10.1

We suggest that written information is provided to families either as a stand-alone document or by referral to a website so that families can access reliable and well curated information at the point of screen positive disclosure, inclusive of red flag signs and symptoms that necessitate immediate clinical review. This information should be in an accessible format and made available in a range of languages,

*Evidence summary of individual studies for recommendations 5.1-5.10 located in technical report on page 148-155.*

## Rationale and impact section on disclosing screen positive results to families

There was some evidence for the preference of families for early specialist input in disclosure of results, and the potential for feelings of uncertainty, distress and confusion due to a lack of standardisation of this process. The evidence reported that some families felt that the information given at this juncture set the tone of the healthcare journey and could challenge family perception, engagement and trust in care thereafter. The GDG considered that disclosure of screen positive results to families was nuanced, based on family preference, cultural, information and linguistic needs, but should encompass key themes derived from clinical consensus and the evidence. The GDG agreed that a tailored mode of information provision should be provided to families to enable them to understand and assimilate the information, augmented by rapid referral for face-to-face review. It was considered the responsibility of the specialist (usually a paediatric neurologist) to communicate with other healthcare providers to understand who was best placed to conduct the disclosure. Dependent on healthcare jurisdictions, designated healthcare practitioners such as genetic counsellors, paediatricians and specialist nurses with training in SMA result disclosure, were also deemed important information providers at this juncture. Whilst there was a lack of evidence into the specific needs and preferences of CALD and Aboriginal, Torres Strait and Pacific Islander and Māori communities, consumer members of the GDG highlighted the need to offer specific supports within these communities at screen positive disclosure if practicable. The GDG highlighted the need to standardise information provision (through verbal and written means) and highlight signs and symptoms of clinical deterioration, to mitigate clinical risks to the child.

## How the recommendations might affect practice

The recommendations will balance the standardisation of the process of result disclosure with the needs and preferences of the family. The recommendations should not require additional resources, but may challenge the workflow of clinical services, due to the need to disclose results and arrange urgent follow-up in an expedient manner. Non-specialist medical practitioners who may reasonably be expected to perform result disclosure where appropriate may require a process of training and education on SMA and implications of a screen positive result for optimal information provision. This may include education and training for

Indigenous Health Liaison professionals, and other professionals in the indigenous health workforce. Advocacy and support websites may require updating with specific resources for information provision targeted at families receiving screen positive and diagnostic results.

**Section 6:**  
**Assessments required at the diagnostic  
evaluation of the screen positive newborn**



## Background

Whilst Section 4 encompasses laboratory activities for the diagnosis of screen positive newborns with SMA, Section 6 aligns with activities completed within the clinical domain, to facilitate the confirmation of an SMA diagnosis, in a recalled screen positive newborn.

The GDG acknowledges variations in access to clinical services, expertise and skills across the Australian and Aotearoa New Zealand healthcare landscape and have formed consensus-based guidelines that aim to be effective and concurrently equitable across this landscape.

The focus of the first clinical review in a screen positive newborn is multifold i.e. to provide information and support to the family, expanding on the knowledge exchange instigated at the time of screen positive disclosure, to confirm the diagnosis of SMA in the newborn (including assessment of clinical status and safety) and to start the process of therapeutic planning. This changes the conventional order of management for children screening positive for other conditions, whereby treatment planning is started after a diagnostic confirmation of the condition is reached and speaks to the neurogenetic emergency of SMA as a quickly progressive neurodegenerative condition in some infants.

Specific clinical assessments for newborns with a screen positive SMA result, include a systematic and structured neurological examination, to increase the potential to detect subtle signs of SMA disease onset in newborns.(175) In a proportion of newborns with a screen positive SMA result, 44% are symptomatic within the neonatal period, presenting with early and subtle signs of truncal hypotonia (floppiness), poor or deteriorating head control and weakness of hip flexion, underscoring the need for careful neurological examination of the newborn.(12)

The utility of undertaking neurophysiology assessments (collection of compound muscle action potential and electromyographic evidence of denervation) in the clinical evaluation of a screen positive newborn with SMA is less well ascertained, with utility being described



instead for ongoing monitoring of disease or treatment response, beyond the period of diagnostic evaluation.(10)

Therapeutic decision making starts within the newborn screen for SMA pathway, as determined by the evidence of benefits of early treatment,(144) before irreversible loss of motor neurons can occur.(11, 80) Recommendations to prepare newborns expediently for treatment are recognised in the literature, with specific and early evaluation recommended for underlying medical conditions including severe or symptomatic liver disease, thrombocytopenia, or other serious underlying conditions that may heighten the risk of therapeutic intervention.(176) The timing of these assessments however are not defined and may precede or be part of post diagnostic care for the newborn.

There has been considerable emphasis on the challenges and facilitators of preparation for treatment for children with SMA, which should be started early in the care pathway. For example, for effective and safe use of intravenous onasemnogene abeparvovec-xioi, antibody titres for adeno-associated virus (AAV) serotype 9, the vector for gene therapy, are required.(176) Whilst testing capacity is now being developed in Australasia, currently, transport of samples to international laboratories for AAV-9 antibody titre testing requires significant coordination and challenging timelines.(177) Expedient collection of AAV-9 antibody titres is proposed as a facilitator of timely access to treatment; however, the defined timing of this within the clinical care pathway is less well established, with some programs that have recourse to gene therapy advocating early collection of blood for AAV-9 antibody testing.(176, 178)

## Recommendation 6.1

### Consensus based recommendation

We recommend that the following assessments are completed immediately as part of the diagnostic and clinical evaluation of the newborn, who screens positive for SMA.

Neurological examination.

Venous sampling for quantification of *SMN1* on whole blood.

Venous sampling for determination of *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number.

Grade of recommendation Strong, Grade 1C

*Genetic (whole) bloods are usually collected in an ethylenediaminetetraacetic acid (EDTA) vial, however healthcare practitioners should adhere to processes for blood collection for genetic confirmation of SMA as defined by the relevant diagnostic laboratories servicing the specified health jurisdiction.*

### Good Practice point 6.1.1

We suggest that the following assessments are completed as part of the diagnostic and clinical evaluation of the newborn, who screens positive for SMA to facilitate future therapeutic decision making. However, dependant on clinical, child and family factors these assessments and interventions may be deferred till diagnostic confirmation of SMA is achieved.

Neonatal examination including cardiac, respiratory gastrointestinal systems and growth parameters.

Bloods for full blood count, renal function tests, liver function tests, coagulation studies to determine suitability for treatment(s).

Blood for adeno-associated virus (AAV-9) antibody titres to determine suitability for (onasemnogene abeparvovec-xioi, Zolgensma™) gene therapy.

*Evidence summary of individual studies for recommendations 6.1 located in technical report on page 155-156*

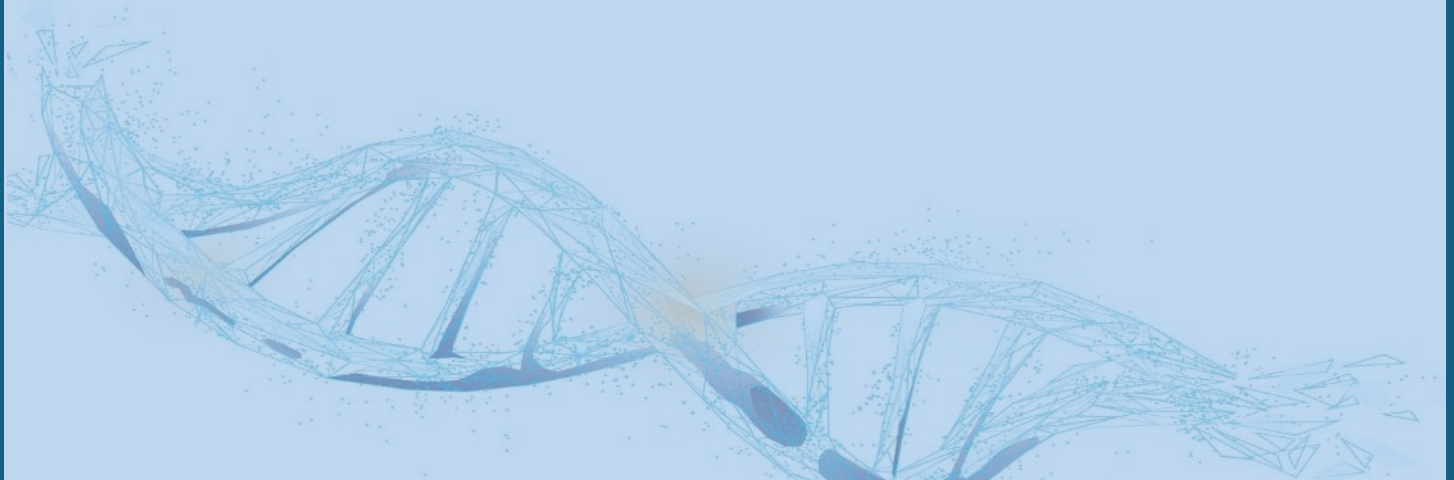
### Rationale and impact section on post diagnostic assessment processes

In assessing the evidence for individual assessments required after the diagnosis of SMA, the GDG agreed that from experience and consensus, a neurological examination of the newborn was mandatory to ascertain the clinical status of the child, which would impact the pace and mode of treatment. The evidence suggested that a substantial proportion of children screening positive for SMA would display signs and symptoms of disease onset at this early stage, and that a systematic neurological examination would improve therapeutic decision making. However, the GDG acknowledged that neurological examination in a newborn could be challenging and dependent on disease stage, illness and physiological stage of child (due to feeds and sleep needs). However, it was determined that a baseline assessment post diagnosis could provide the foundation for understanding a change in disease progress on serial assessment. Diagnostic blood tests to confirm the diagnosis and provide prognostic information were also mandatory. There was insufficient evidence and a lack of complete consensus on other investigations that would be helpful during the post diagnosis phase. To enable treatment readiness, it was considered good practice to consider additional blood tests to ascertain safety for SMN augmenting treatments and in particular AAV-9 antibody testing if gene therapy was a consideration (due to inherent delays in having these results available for treatment planning).

### How the recommendations might affect practice

The recommendations aim to standardise the post diagnostic period and provide all newborns with a determination of their clinical status that can affect how quickly a treatment plan is instigated and which therapeutic options are available. The detection of subtle signs and symptoms of disease onset may require additional resources to train and educate specialist and non-specialist medical practitioners in the nuances of a neurological examination in the newborn and infancy period.

**Section 7:**  
**Information provision to families during the  
diagnostic evaluation of a screen positive  
newborn and after confirming the diagnosis of  
SMA**



## Background

Information provision and support both during the period of diagnostic evaluation and on disclosing the confirmation of a diagnosis of SMA to families, should aim to answer the family's questions and may be helpful in identifying the need for other referrals, assessments, and supports as part of ongoing clinical care. Information provision is best conducted within a multidisciplinary model of care, where there is access to genetic counselling, psychosocial support and clinical evaluation. It is the responsibility of the medical practitioner/s in charge of information provision to facilitate knowledge exchange such that the family are informed of the outcomes of the diagnostic evaluation, key timelines and next steps within the process. Information is best relayed through verbal means and could and should be augmented through referral to other high quality and reliable (multimedia) resources, as available within the health jurisdiction and nationally.

Enabling timely disclosure is crucial to meeting treatment timelines. Utilisation of telehealth services facilitates an efficient process and ensures access to specialist expertise and input, whilst also empowering local healthcare practitioners to manage children in a local context, which is valued by families.

Information provision from the family perspective includes having a child and family centred approach to the timing and content of information given at diagnosis, and a paced approach to information provision, despite the need to intervene expediently in achieving the diagnosis and offering treatment.(11)

Families have also described optimal ways of receiving the diagnosis of SMA in a screen positive newborn. Parents perceive that receiving information verbally is most useful for understanding of disease, testing, genetics, and treatment, but the majority perceive that written or visual information would also be helpful and adjunctive including information on well curated educational resources for families receiving a screen positive result.(174)

Aligning with the distress caused by receiving a diagnosis in a seemingly healthy newborn/infant, families also express difficulty in understanding information provided at the first clinic visit. Facilitators to assimilating information include limiting the number of healthcare practitioners to those most pertinent to the initial visit, providing written and visual summary information for families to take home, and providing recommendations for parents to bring a support person to this first appointment to help with processing information and asking appropriate questions. Families value a compassionate approach at this first clinic visit and appreciate providers taking the time to explain aspects of their child's diagnosis.(174)

Section 7 and 8 are recommended to run concurrently to provide information, care and support to families, that is embedded within the care pathway.

### Recommendation 7.1

Consensus based recommendation

We recommend that to optimise knowledge and support, families of newborns who screen positive for SMA should be provided with information that is compassionate, accurate and tailored to the information needs and preferences of the family, and this should be provided by clinical services.

Grade of recommendation Strong, Grade 1C

### Recommendation 7.2

Consensus based recommendation

We suggest that the number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a paediatric neurologist or paediatrician), and ideally support from a healthcare practitioner which may include clinical geneticists and/or genetic counsellors, nurse specialists and/or medical social work and/or psychological services.

Grade of recommendation Conditional, Grade 2C

#### Good Practice point 7.2.1

We recommend that the following information should be provided to families during the diagnostic evaluation stage (at the first clinic visit) and documented in the medical records

Information on the (genetic) cause and clinical implications of SMA.

Information on next steps to confirm a diagnosis.

Information on psychosocial supports (including referral to social work services), and/or psychology services.

Information on SMA advocacy services.

Information on where and how to access high quality and reliable educational resources for families receiving a screen positive result of SMA.

### Recommendation 7.3

Consensus based recommendation

We recommend that healthcare practitioners providing information to, and discussing diagnosis with, families of newborns from culturally and linguistically diverse backgrounds should be aware of particular issues arising from information provision and diagnostic evaluation. If the healthcare practitioner is not bilingual, a professional interpreter should be used.

Grade of recommendation Strong, Grade 1C

### Recommendation 7.4

Consensus based recommendation

We recommend that healthcare practitioners providing information to, and discussing diagnosis with, families of newborns from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other First Nations backgrounds should be aware of particular issues arising from information provision and diagnostic evaluation. The healthcare practitioner may elicit the advice of Indigenous Health Liaison professionals in how to best conduct these evaluations and also offer families the support of Indigenous Health Liaison services at the time of diagnosis.

Grade of recommendation Strong, Grade 1C

### Recommendation 7.5

Consensus based recommendation

We recommend that all families receiving a diagnosis of SMA for their newborn, through a newborn screening program should be offered the opportunity of support through referral to a



counselling service, and/or medical social services and/or psychological services, and/or SMA advocacy services as appropriate.

Grade of recommendation Strong, Grade 1C

### Recommendation 7.6

Consensus based recommendation

We recommend that families receiving a diagnosis of SMA for their newborn, through a newborn screening program, should be directed to high quality and reliable educational resources that support information provision on the implications of the diagnosis and potential treatments for their newborn.

Grade of recommendation Strong, Grade 1B

*Educational resources provided should reflect the contemporary treatment and care landscape and be nationally consistent.*

### Recommendation 7.7

Consensus based recommendation

We recommend that all families receiving a diagnosis of SMA for their newborn, through a newborn screening program should be provided with the contact details of a designated healthcare practitioner who can direct a response to their queries.

Grade of recommendation Strong, Grade 1C

*The designated healthcare practitioner will vary between health jurisdictions and may include but are not limited to paediatric neurologists, paediatricians, clinical geneticists, genetic counsellors or specialist nurses.*

*Evidence summary of individual studies for recommendations 7.1-7.7 located in technical report on page 157-161*

## Rationale and impact section on information provision to families

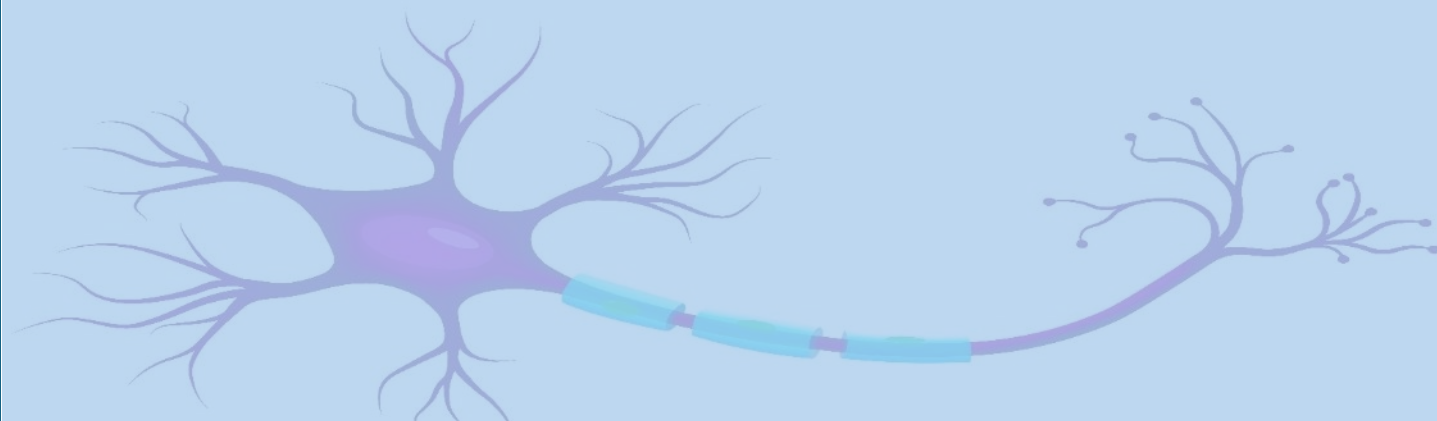
The evidence showed that there are gaps in current practice in communication, information and support available to families. Benefits of high quality, accurate and tailored information provision were considered by the GDG to encompass many levels including improving therapeutic decision making for families and clinicians, improving access to appropriate support, increasing family wellbeing and satisfaction with care and empowering families to be active participants and engage in the healthcare process for their child. The GDG considered their clinical experience and emphasised the multidisciplinary model of care as an important source of support for families. GDG members also acknowledged limited capacity in social care and psychological services to support these recommendations, and consumers highlighted the role of patient organisations to fill this potential gap in resources. The evidence showed that families struggled to find sources of information other than their doctor and the GDG acknowledged that clinics could leverage local and national support groups to augment information provision. The GDG highlighted through clinical experience and consensus that a tailored program of information provision was required, paced and adjusted according to the preferences and circumstances of the family. They acknowledged that information exchange was a dynamic, ongoing two-way process, necessitating a reliable point of contact for this purpose. The GDG understood that the designated contact person for support and information would vary jurisdictionally but acknowledged that nurse specialists, social workers and genetic counsellors played a substantial role in augmenting clinician-based information.

## How the recommendations might affect practice

The recommendations complement current practice, that encourages family centred care for families within a multidisciplinary team setting, so the GDG agreed that for some jurisdictions there would be no substantial resource impact. However, with the alteration of the diagnostic pathway through newborn screening, the demand for reproductive counselling and preimplantation genetic counselling would increase in certain health jurisdictions. The GDG acknowledged that members of the wider multidisciplinary team (extending to patient organisations) could augment roles as information and support providers dependent on

jurisdictional resources and capacity, and that their websites could be leveraged to provide targeted and reliable information for families receiving a diagnostic result.

**Section 8:**  
**Delivering the diagnosis and supporting families  
as they receive the diagnosis of SMA**



### Recommendation 8.1

Consensus based recommendation

We recommend that the process of disclosing a diagnosis of SMA to families should occur when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number results, to avoid delays in treatment planning.

Grade of recommendation Strong, Grade 1C

### Good Practice point 8.1.2

Consensus based recommendation

We recommend that families should be invited to bring a support person(s) at the point of diagnostic disclosure.

### Recommendation 8.2.

Consensus based recommendation

We recommend that diagnostic results should be disclosed to families by a paediatric neurologist.

Grade of recommendation Strong, Grade 1C

### Recommendation 8.3.

Consensus based recommendation

We recommend that if circumstances dictate and dependent on child and family factors, it is acceptable for a designated healthcare practitioner (such as a paediatrician, general practitioner, specialist nurse, clinical geneticist or genetic counsellor) with involvement through telehealth with a paediatric neurologist, to disclose a diagnostic result to a family.

Grade of recommendation Strong, Grade 1C

*The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians and specialist nurses. These individuals should have training and expertise in the process of diagnostic disclosure for children with SMA.*

*Child and family factors include but are not limited to geographical location, safety of travel for the child (relevant in a child with signs and symptoms of SMA) and need for cultural or linguistic support to facilitate disclosure of the diagnosis*

#### Recommendation 8.4

Consensus based recommendation

We suggest that diagnostic results should be disclosed to families face to face.

Grade of recommendation Conditional, Grade 2C

#### Recommendation 8.5

Consensus based recommendation

We suggest that if circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for diagnostic disclosure to occur through telephone or telehealth.\*

Grade of recommendation Conditional, Grade 2C

*\*Child and family factors include but are not limited to geographical location, safety of travel for the child (relevant in a child with signs and symptoms of SMA), need for cultural or linguistic support to facilitate disclosure of the diagnosis and the availability of technology and connectivity for the use of telehealth.*

*Evidence summary of individual studies for recommendations 8.1-8.5 located in technical report on page 162-165*

## Rationale and impact section on delivering the diagnosis and supporting families.

The evidence showed a variability in practice on how families were provided with the diagnosis of SMA and supported through this process. The evidence also showed the lasting impact of diagnostic disclosure on families, and the imperative to provide holistic care to families as they embarked on the next stage of therapeutic planning and management. The GDG emphasised the importance of tailored support to align with the needs and preferences of families. Extra support and time in consultations was considered important to help families understand the often-complex genetics of SMA and the rationale for treatment where appropriate and indicated. The GDG recognised that families receiving the diagnosis would experience a range of feelings, which could change over time, which was born out in the evidence. They agreed that care that embedded psychological support was important for families, to improve wellbeing and engagement with healthcare services. The GDG expressed particular concern in addressing the psychological and support needs of families with variable health literacy, those with socioeconomic disadvantage and CALD communities. The GDG also noted the value in delivering culturally competent care and leveraging appropriate hospital support services for families identifying as of Aboriginal, Torres Strait and Pacific Islander or Māori descent if families considered this as appropriate. There was a unanimous consensus that the preference was for result disclosure to be the responsibility of specialist medical practitioners (usually paediatric neurologists) with expertise and knowledge in the condition and next steps to expedite treatment, aligning with the evidence of parents valuing early specialist input. However, the GDG agreed that processes for result disclosures were jurisdictionally dependent, and that medical practitioners such as genetic counsellors, nurse specialists and non-specialist medical practitioners could also be well placed to disclose and counsel on the results. For these professionals, the evidence showed that access to and advice from specialist services, enabled a streamlined and effective disclosure process.

## How the recommendations might affect practice

The recommendations complement current practice, that encourages family centred information provision and support for families within a multidisciplinary team setting. The GDG agreed that not all jurisdictions would have capacity or easy access to multidisciplinary support services. The use of a shared model of care between specialist and local health

services was considered optimal, to provide tailored, family centred diagnostic disclosure and support.



**Section 9:**  
**Immediate post diagnosis care for newborns and infants receiving a diagnosis of SMA through a newborn screening program**



## Background

The post diagnostic care pathway for children with SMA, identified through newborn screening programs is both similar and different to post diagnostic care for children referred through conventional pathways i.e. seen within clinical services after signs and symptoms of SMA raise concern for a lower motor neuron pathology. Similarities arise in the need for care and support for families receiving the diagnosis, however differences arise in the imperative for accurate identification of the clinical status (presence or absence of symptoms) of the newborn/infant diagnosed with SMA through a newborn screening program. Careful characterisation of the disease phase is vital to delineate the pace required for therapeutic decision making and the eligibility for and modality of therapeutic interventions.(179)

Care, support and targeted information is imperative within the post diagnostic stage for families. Genetic counsellors fulfil a vital role in providing support and addressing the genetic questions that families inevitably have as pertains to a diagnosis of SMA (i.e. on reproductive carrier testing, pattern of inheritance, implications to other siblings and the wider family, complexities around and facilitating carrier testing and implications to future offspring and reproductive testing).(180) Whilst many jurisdictions have conjoined clinical genetics and neurology services to facilitate genetic support at the time of diagnosis, for families living in jurisdictions without these shared services, early referral to clinical genetics centres for review is deemed important.(11)

Notably, clinical assessments can be challenging in newborns who have variability in their neurology dependent on gestational maturity, sleep or feed state and illness, alongside disease related factors.(181) This is compounded by the fact that a presymptomatic child (who has no overt symptoms, normal neurological appearance and motor exam) does not equate to a child who has no underlying neurodegenerative pathology, as the loss of motor neurons is subclinical until a significant amount of the motor neuron pool is lost.(80, 181) In fact, the transition of a newborn from one who is clinically silent to clinically manifest of disease may progress through a ‘prodromal’ phase where there are only very subtle symptoms, with findings on examination that are not definitive but consistent with a

rapidly evolving disease.(181) As such a standardised and comprehensive approach to post diagnostic assessments are imperative.

Clinical examination including systematic neurological examination, preferably by a specialist trained within this domain is important to classify the clinical status of the newborn after a diagnosis of SMA is confirmed.(12, 179) This is particularly vital to characterise the subtle signs and symptoms of disease occurring in up to 44% of newborns with 2 copies of *SMN2*, before 6 weeks of age.(12, 182) Symptoms of SMA in the newborn/infant may be variable and include for example hyperreflexia (increased briskness of reflexes) prior to the loss of reflexes, varying patterns of weakness of the limbs, truncal and neck weakness. Feeding and breathing changes may precede motor manifestations.(183, 184)

The multisystemic nature of SMA is also understood (with SMN protein present in all cells within the body) and multi-organ manifestations of SMN deficiency may precede or accompany motor involvement. Here, difficulties in regulating blood pressure, heart rate, respiratory rate and temperature i.e. features of dysautonomia and cardiac anomalies may become apparent as detected through a comprehensive neonatal examination.(183)

Motor assessments within the post diagnostic assessment phase can augment the clinical exam although there is a broad range of scales that may be utilised, all with inherent benefits and limitations. The WHO Multicentre Growth Reference Study (WHO-MRGS) scale is an observational assessment, evaluating a typical developmental hierarchy which assesses the quality of progression of motor skills.(185) The lowest attainable item is sitting without support and the highest attainable item is walking alone. Whilst it can be utilised longitudinally to assess gains across the functional spectrum, it has no utility in defining disease onset in the newborn/infant diagnosed with SMA as part of immediate post diagnostic evaluation. Similarly, the Children's Hospital of Philadelphia Infant Test of Neuromuscular disorders (CHOP-INTEND), was developed specifically for symptomatic infants (< 2 y) to understand the changes in motor function over time.(186) Recent findings have suggested that this scale may be used before the age of 3 months, with results being

interpreted with caution and consideration as to the developmentally most appropriate items at the time of testing.(187) This will help to define the thresholds to determine clinical (presymptomatic or symptomatic) status, which are currently not fully understood.(175) The Hammersmith Infant Neurological Examination-2 is a neonatal specific developmental scale that is being more widely utilised in this population to help denote clinical status (188) within the heterogenous clinical presentations found within a newborn screening for SMA cohort.(189)

The inclusion of neurophysiology assessments (collation of compound muscle action potential and electromyographic studies) to aid in definition of clinical status within the immediate post diagnostic stage is also less certain, with expertise and training, specialised equipment and standard procedures required to conduct these assessments with rigor.(179) Baseline compound muscle action potential (a summation of voltage output from a group of simultaneous action potential from several muscle fibres in a defined area, after stimulation of the innervating peripheral nerve) and electromyographic evidence of the muscle response or electrical activity in response to a nerve's stimulation of the muscle have been used on sequential monitoring to determine disease progress and augment the often clinically challenging assessment of the newborn with SMA.(10, 12)

### Recommendation 9.1

Consensus based recommendation

We recommend that all newborns diagnostically confirmed with SMA through a newborn screening program should be reviewed by a paediatric neurologist.

Strength of recommendation Strong, Grade 1C

### Recommendation 9.2

Consensus based recommendation

We recommend that at the time of diagnosis, all newborns confirmed with SMA should initially be managed within a paediatric neurology service.

Strength of recommendation Strong, Grade 1C

### Recommendation 9.3.

Consensus based recommendation

We recommend that all newborns should have a neurological and neonatal examination including cardiac, respiratory and gastrointestinal systems to assess their clinical status.

Strength of recommendation Strong, Grade 1C

### Recommendation 9.4

Consensus based recommendation

We suggest that all children diagnosed with SMA through newborn screening should have a shared model of care between local community (general practitioners and allied health therapists), secondary (paediatric) services and specialist (paediatric neurology) services, to facilitate post diagnosis care, which is personalised according to the biopsychosocial characteristics of the child and family.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.5

Consensus based recommendation

We recommend that families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to a clinical genetics service).

Strength of recommendation Strong, Grade 1C

#### Implementation point 9.5.1.

Whilst it is ideal that families have support and genetic information from clinical geneticists and genetic counsellors at the time of diagnosis (as part of the multidisciplinary care team), healthcare jurisdictions have variations in access to clinical genetic services. Therefore, clinical referral should occur within appropriate local pathways.

### Recommendation 9.6.

Consensus based recommendation

We suggest that the sibling(s) of a newborn diagnosed with SMA through newborn screening should be offered a clinical review within paediatric neurology services, at an appropriate time.\*

Strength of recommendation Conditional, Grade 2C

*\*The Recommendation applies to siblings who have **not** previously had a newborn screen for SMA result through a state-based screening program.*

### Recommendation 9.7

Consensus based recommendation

We suggest that for sibling(s) of affected children who live in regional or remote jurisdictions, a review for signs and symptoms of SMA may be offered and conducted by a designated healthcare practitioner, with support from a paediatric neurologist.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.8.

Consensus based recommendation

We suggest that symptomatic status should be defined by healthcare practitioners primarily by the presence of signs and symptoms of SMA on neurological and neonatal examination.

Strength of recommendation Conditional, Grade 2C

### Recommendation 9.9.

Consensus based recommendation

We suggest that newborns may undergo neurophysiological assessments within a reasonable time of diagnosis, including collation of compound muscle action potential (CMAP) +/- electromyography (EMG), to obtain predictive information on disease course.

Strength of recommendation Conditional, 2C

*\*The use of neurophysiological assessments will vary dependent on jurisdictional capacity including training and expertise of the assessors conducting these assessments. It has been noted by the GDG that the Pharmaceutical Benefit Scheme (PBS) that provides approval for treatments in Australia, does include information derived from neurophysiology studies to denote disease onset and facilitate access to SMN augmenting treatments. However, the GDG acknowledged variations in the availability and experience of healthcare practitioners in the conduct and interpretation of neurophysiological assessments and proposes the conditional strength of this Recommendation based on feasibility for implementation across Australasia.*

### Good Practice point 9.9.1

We suggest that newborns should undergo motor assessments to assess functional baseline which may include the Hammersmith Infant Neurological Examination (HINE), and/or the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and/or World Health Organisation Multicentre Growth Reference Scale (WHO-MGRS), within a reasonable time of diagnostic confirmation of SMA.

The use of the scales will vary dependent on jurisdictional capacity including the training and expertise of assessors administering these assessments.

*Evidence summary of individual studies for recommendations 9.1-9.9 located in technical report on page 165-170*



## Rationale and impact section on delivering the diagnosis and supporting families.

There was a lack of evidence on the range of assessments required for the newborn in the post diagnostic phase of care. However, the GDG based on their experience and consensus, and leveraging the international standards of care guidelines agreed that optimal outcomes for children diagnosed with SMA would require early referral for assessment and review in specialist (tertiary) centre under the care of paediatric neurologists. Due to the multisystemic nature of SMA, the GDG agreed that children diagnosed with SMA through newborn screening programs would benefit from a multidisciplinary model of care, often provided by tertiary services that would lead to improved health outcomes, reductions in comorbidities, improvements in wellbeing and functional independence over the longer term, through a program of proactive early intervention. The GDG agreed that whilst clinical examination was the mainstay of assessment of the newborn, the evidence shows that signs and symptoms of SMA were often subtle and could be augmented by motor, development and neurophysiological assessments. There was no evidence to inform decisions on the optimal motor assessments to be used within the newborn and infancy period, and the GDG agreed that further research was required to codevelop assessment scales that were applicable and standardised within a newborn population. However, the GDG agreed that recommendations for post diagnostic assessment should reflect variability in availability and experience of assessors across healthcare jurisdictions that could increase health care inequities. Therefore, recommendations were framed to support local context.

## How the recommendations might affect practice

The recommendations have been developed to provide equity of access to specialist assessment and to embed care of children with a diagnosis of SMA through newborn screening within a multidisciplinary model of care. The recommendations have been developed to reflect variable resources in terms of education and access to expertise across Australia, required to conduct post diagnostic assessments to an acceptable and robust standard. To implement and sustain assessment(s) including motor assessments and neurophysiological techniques, practitioners may require education and training.

**Section 10:**  
**Treatment planning and initiation for newborns  
and infants diagnosed with SMA through  
newborn screening programs**



## Background

Across the range of available (SMN augmenting) treatments, symptomatic children with 2 and 3 *SMN2* copies benefit from access to treatment, with a greater chance of survival, reduction in comorbidities and motor stability or gains noted in these cohorts.(138, 178, 190-194) Here the magnitude of benefit appears to be inversely correlated on disease duration and associated with motor function at time of treatment and SMA phenotype .

Early treatment appears to be an important modifier of longer-term outcomes. The magnitude of benefit increases with interventions before children develop symptoms, but even within this cohort there is a heterogeneity of outcomes. In presymptomatic newborns, with 3 *SMN2* copies, a normal neurodevelopmental trajectory can be observed in most at 2 years, whilst with those with 2 *SMN2* copies follow a more variable disease course, gaining motor skills progressively, albeit at a potentially delayed pace and/or having plateau in skills over time.(7-9)

There have been no published head-to-head trials of efficacy of SMN augmenting interventions. Instead, clinical and electrophysiological studies have consistently demonstrated the existence of a narrow therapeutic window and the benefits of early treatment initiation in SMA, before irreversible loss of motor neurons, occurs. Expedient treatment is especially vital for those with 2 *SMN2* copies where a precipitous decline of motor units within 3 months of postnatal age occurs, leaving 90% of an irreversible denervated motor neuron pool by 6 months of age.(80) In this group a presymptomatic clinical status does not correspond with an absence of pathology.

Aligning with this evidence base, international consensus recommendations denote that all newborns with signs and symptoms of SMA (consistent with disease onset) with  $\geq 2$  *SMN2* copies AND those who are presymptomatic with 1,2, or 3 *SMN2* copies should have immediate access to treatment.(140) There is a lack of evidence on the outcomes for newborns with 1 *SMN2* copy, and thus expert opinion is to take a pragmatic approach and base therapeutic decision making on the clinical status of the child and professional opinion

of outcomes,(140) offering supportive care as a valid pathway in the first instance.(195) A higher probability of motor function attainment is observed when therapeutic intervention (of any modality) is administered < 6 weeks of age,(196) whilst a significantly higher magnitude of motor function attainment at 2 years of age is seen with decreasing time to intervention, even over a matter of days in a newborn screening for SMA cohort.(98) There are no currently published head-to-head comparative studies of therapeutic efficacy and safety for combined or sequential treatments. All therapeutic decisions should be made within a model of multidisciplinary care that aligns with international best practice guideline for the care and management of children with SMA.(35, 36)

For children without access to treatment, there is study and consensus evidence for clinical surveillance at defined intervals within a neuromuscular centre.(10, 141, 177) The use of motor myometry and neurophysiology assessments, to augment clinical examination has been defined in the literature for the follow-up of infants being diagnosed with SMA through newborn screening programs.(10, 127, 140, 177, 197)

Therapeutic planning and decision making requires expert consideration in not only the benefits and risks of individual treatments, but also family preferences, the therapeutic burden for the child and the uncertainties of long-term outcomes and access to treatment.(198) Thus, therapeutic decision making is ideally commenced in a paediatric neurology centre with expertise in the management of children with SMA.(184) Long term surveillance of efficacy and safety is required to effectively manage children receiving these therapeutics.(199) Whilst treatments have changed the trajectory of outcomes for children, the process of therapeutic planning and administration can increase familial burdens and negatively impact caregiver productivity and quality of life.(200) Potential mitigators of these psychosocial outcomes include access to psychological support through referrals to appropriate health care services or advocacy groups.(201)

### Recommendation 10.1

Consensus based recommendation

We suggest that treatment planning should commence as soon as the *SMN1* diagnostic result is received.

Strength of recommendation Conditional, Grade 2C

#### Implementation point 10.1.1

When children do not have access to publicly funded treatments and healthcare in Australasia, healthcare practitioners will be proactive in providing care and support for the child and family.

### Recommendation 10.2

Consensus-based recommendation

We recommend that for screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset), options for immediate treatment with SMN augmenting treatments should be discussed with the family, independent of *SMN2* copy number.

Strength of recommendation Strong, Grade 1A

### Recommendation 10.3

Consensus based recommendation

We suggest that for newborns who demonstrate signs and symptoms of SMA (consistent with disease onset) with 1 *SMN2* copy, therapeutic decision making is dependent on the newborn/infant's clinical status and open discussions with families regarding treatment options or referral for supportive care alone.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 10.4.

Consensus based recommendation

We recommend that for newborns with diagnostic confirmation of SMA and 1, 2 or 3 *SMN2* copy numbers and who are presymptomatic, options for immediate SMN augmenting treatments should be discussed with the family.

Strength of recommendation Strong, Grade 1B

#### Recommendation 10.5

Consensus based recommendation

We recommend that in the absence of comparative data, currently single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended.

Strength of recommendation Strong, Grade 1C

#### Good practice point 10.5.1

In the absence of comparative data for efficacy, the optimal SMN augmenting treatment is the one which can be expediently accessed within the health jurisdiction.

#### Recommendation 10.6

Consensus based recommendation

We recommend that families should be informed as part of the therapeutic decision-making process that expedient therapeutic intervention may change motor and developmental trajectories and respiratory and feeding outcomes for symptomatic newborns/infants and those presymptomatic newborns/infants with 1, 2 or 3 *SMN2* copies.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.7

Consensus based recommendation

We recommend that healthcare practitioners should explain to families and document the potential benefits, risks, uncertainties, of SMN augmenting treatments and need for long term surveillance.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.8

Consensus based recommendation

We recommend that therapeutic care planning should take into consideration disease status (presymptomatic/symptomatic), genotype (including *SMN2* copy number), current motor function, disease duration, and individualised factors including social and family circumstances, goals of care and preferences.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.9

Consensus based recommendation

We suggest that parents may require support with therapeutic decision making and resources may be made available to them (including as appropriate referral to medical specialists, social work, clinical geneticists and genetic counsellors, psychology, and/or patient advocacy groups) to facilitate this process.

Strength of recommendation Conditional, Grade 2B

### Good practice point 10.9.1

We suggest that written information as a standalone document or direction to a well-curated, reliable and up to date website is provided to families that will inform them on the potential

benefits, risks, uncertainties of SMN augmenting treatments and the need for long term surveillance. The information should be in an accessible format and ideally provided in different languages.

#### Recommendation 10.10

Consensus based recommendation

We suggest that the administration of SMN augmenting treatments should occur in a paediatric neurology treatment/care service within a multidisciplinary team.

Strength of recommendation Conditional, Grade 2A

#### Recommendation 10.11

Consensus based recommendation

We suggest that for some newborns, SMN augmenting treatments may be planned to be initiated from a non-specialist treatment centre, with paediatric neurology support. \*

Strength of recommendation Conditional, Grade 2C

*\*This recommendation may be appropriate for children living in regional and rural areas where travel to paediatric neurology treatment centres is logistically or clinically challenging.*

#### Recommendation 10.12

Consensus based recommendation

We suggest that post treatment monitoring for newborns who access SMN augmenting treatments may be shared between paediatric neurology centres, secondary paediatric services and community (general practitioner) services (with support from the specialist centres) as child and family factors dictate.

Strength of recommendation Conditional, Grade 2C



### Recommendation 10.13

Consensus based recommendation

We recommend that newborns with diagnostic confirmation of SMA who are unable to access approved and reimbursed treatments immediately should be managed by a paediatric neurologist specialist.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.14

Consensus based recommendation

We suggest that newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.

Strength of recommendation Conditional, Grade 2C

*Children who have 2 and 3 SMN2 copies who do not access treatments immediately may require more frequent surveillance, as part of an informed management plan between families and healthcare practitioners. The frequency of surveillance will be dependent on the child's individual biopsychosocial characteristics and should be made with consideration of their healthcare needs and family preferences.*

### Recommendation 10.15

Consensus based recommendation

We recommend that for all newborns diagnosed with SMA, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), best practice care includes the following assessments conducted at each visit

Comprehensive history taking including changes in movement, breathing and feeding.

Growth parameters including length, weight and head circumference

Neurological examination.

Strength of recommendation Strong, Grade 1C

### Recommendation 10.16

Consensus based recommendation

We suggest that for all newborns diagnosed with SMA, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments as part of best practice care may include motor assessments that should be adapted to the objectives set for the newborn/infant and considers function, SMA type, age, comorbidities, clinical status. The timing and frequency of assessments may vary between children and will be dependent on therapeutic goals, clinical questions raised, and child and family factors.

Strength of recommendation Conditional, Grade 2C

#### Good Practice point 10.16.1

For newborns diagnosed with SMA, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments may include neurophysiological studies with acquisition of compound muscle action potential (with/without) electromyography to assist in diagnosis and monitoring disease course and/or treatment response. The timing and frequency of neurophysiological assessments may vary between children and will be dependent on therapeutic goals, clinical questions raised, and child and family factors. Evaluators should have training and expertise for the application and interpretation of this assessment.

### Recommendation 10.17

Consensus based recommendation

We recommend that evaluators must meet the standards for training for the administration of each examination or assessment.

Strength of recommendation Strong. Grade 1C

#### Recommendation 10.18

Consensus based recommendation

We recommend that all children diagnosed with SMA should be referred for multidisciplinary allied therapy interventions aligning with international standards of care (Consensus Statement of Standards for Care of Spinal Muscular Atrophy). (35, 36)

Strength of recommendation Strong, Grade 1C

*Evidence summary of individual studies for recommendations 10.1-10.18 located in technical report on page 171-183*

## Rationale and impact section on delivering the diagnosis and supporting families.

There is evidence that the initiation of SMN augmenting treatment in the presymptomatic stage of SMA positively affects the prognosis for neonates with 2 or 3 copies of *SMN2*. There is also evidence that the latent period can be brief in these individuals. The GDG agreed that a newborn diagnosed with SMA and 2 or 3 copies of *SMN2* is an emergency, and the most appropriate response is expedient initiation of SMN augmenting therapy for optimal outcomes. Consequently, the GDG developed recommendations for treatment planning of screen positive newborns that are proactive, concurrent with the diagnostic process, founded on family centred care, and involve a paediatric neurology centre with expertise in SMA management. The GDG acknowledged the key role of local healthcare services for families in regional and remote areas and agreed that use of telehealth was important to enable equitable and timely access to specialist services. While already part of clinical practice, to support best practice the GDG developed recommendations to inform families about the risks, benefits and uncertainties of proposed treatments, alongside providing additional information resources.

There is evidence that some SMA screen positive newborns can manifest signs of SMA in the first weeks of life. This can range from minimal features, ‘pauci-symptomatic’, to marked respiratory impairment and minimal movement in newborns. The GDG agreed that identifying clinical features of SMA are relevant to therapeutic decision making and prognosis and developed recommendations for treatment planning and initiation accordingly. There is limited evidence regarding treatment response in symptomatic newborns with 1 copy of *SMN2*, who are likely to have a severe phenotype. For these individuals, the GDG agreed with a pragmatic approach, basing therapeutic decision making on the clinical status of the neonate, and offering supportive care alone as a valid pathway.

The GDG recognised that the availability of SMN augmenting therapies for presymptomatic people with SMA and 4 copies of *SMN2* is limited in Australasia. Clinical trial evidence has not included or reported outcomes beyond 12 months for such individuals and retrospective studies characterise a heterogeneous phenotype. In one study, 11% of individuals with four copies of *SMN2* would be expected to present with SMA type 2 and 1% with SMA type 1.(27) To standardise care, identification of phenoconversion and treatment initiation, the

GDG developed recommendations for the clinical monitoring of newborns diagnosed with SMA and 4 copies of *SMN2*.

The 2018 international standards of care recommendations for the diagnosis and management of SMA do not incorporate newborn screening or SMN augmenting therapies.(35, 36) To support contemporary best practice care the GDG developed recommendations for assessments, to assist with diagnosis and monitoring, and the provision of multidisciplinary care. There is no evidence of the therapeutic efficacy and safety for combined SMN augmenting treatments, such that GDG did not recommend concurrent combination therapy.

### How the recommendations might affect practice

The recommendations are aimed to achieve expedient planning and initiation of SMN augmenting therapy for optimal outcomes. The GDG recognised that paediatric neurologists will need to respond promptly to a screen positive SMA and complete *ad hoc* urgent consultations. This has implications for the planning duty rosters and availability, noting that children with a possible presentation of SMA are currently prioritised for assessment and management in paediatric neurology centres.

Multidisciplinary neuromuscular clinics currently practice family centred care and can support treatment planning and initiation for newborns diagnosed with SMA through NBS programmes. Practitioners may require education and training to implement and utilise motor assessments and neurophysiological techniques for monitoring.

In the absence of comparative data for efficacy, the choice of SMN augmenting therapy will depend on patient safety and suitability, family preferences for administration and medication availability. As expeditious treatment initiation is a priority, the latter may influence treatment choices when a longer timeframe for supply is anticipated.

## **Section 11:**

**Post diagnosis care for newborns, infants and children with SMA and  $\geq 4$  *SMN2* copies, who are not initially treated with SMN augmenting therapies**

## Background

In 2018, an international consensus treatment algorithm recommended immediate access to SMN augmenting treatment for infants with 3 or fewer *SMN2* copies.(140) Their position was subsequently updated to be inclusive of infants with 4 *SMN2* copies.(141)

Within Australasia, the newborn screening process will differ, with some jurisdictions concurrently analysing *SMN1* and *SMN2* number on the dried blood spot (reporting only those with *SMN2* copies  $\leq 4$ ) whilst others complete *SMN2* quantification as part of diagnostic care. Thus, in some jurisdictions it is conceivable that children with copy  $> 4$  *SMN2* copies will be diagnosed through newborn screening programs.

The therapeutic landscape in Australasia in 2024 is such that newborns identified through newborn screening for SMA, who are presymptomatic and have  $\geq 4$  *SMN2* copies, do not have access to approved and reimbursed treatments.(202-204) These high-cost therapeutics cannot usually be self-funded and thus this section takes consideration of the current therapeutic landscape. Alongside limitations in access, there is a global variation in how to manage children with SMA and  $\geq 4$  *SMN2* copies. Even in jurisdictions where there is access to SMN augmenting treatment for presymptomatic infants with 4 *SMN2* copies (identified through newborn screening), there has been variability in the uptake, with the timing of therapeutic intervention remaining unclear.(205) This is partly due to data gaps that preclude a comprehensive understanding of the natural history of disease onset and progression for those with  $\geq 4$  *SMN2* copies, the heterogeneity of disease progression,(27) and the variability in phenotype for those untreated with 4 *SMN2* copies. There is ongoing uncertainty regarding accurate prediction of phenotype, long term outcomes and safety profile for individuals with this genotype.(32) These knowledge gaps are compounded by a current lack of clinical trial data for the efficacy, durability and safety of SMN augmenting treatments in those with  $\geq 4$  *SMN2* copies.

Balanced against these uncertainties are the potential benefits of early intervention and the possibility of preserving a motor pool from irreversible deterioration, defined in those children with 4 *SMN2* copies, who do not receive immediate treatment. Clinical manifestations of SMA have been noted as early as within the infancy period (132, 143) but predominantly within early childhood,(32) and in 22-55% of untreated children with 4 *SMN2*

copies before the age of three years.(161, 205) By 18 years of age 95% of children with 4 *SMN2* copies display signs and symptoms of SMA.(205) Children may develop only subtle signs and symptoms of disease between 1.5 and 4 years of age, however, a minority of them experience significant motor deterioration with time.(142)

This clinical evidence base has led to the suggestion that SMN production in those with 4 *SMN2* copies is insufficient to support the motor neuron pool and that early initiation of treatment at a time when high SMN levels are required would prevent motor neuron degeneration. For newborns with  $\geq 4$  *SMN2* copies not initially treated, the focus is on monitoring for disease onset, to initiate treatment at the earliest possible opportunity.(140) International consensus recommendations define high frequency visits within the first two years of life, where there is greatest risk of identifying a severe SMA phenotype, balanced against a more measured approach to reduce the risk of over assessment and increase flexibility for caregivers thereafter.(140) The added risk of undertaking a clinical surveillance strategy alone is the potential to be lost to follow-up, which may be mitigated by information and support around the benefits of follow-up for the newborn/infant.(142, 143)

Neurological and motor assessment, myometry and neurophysiological studies (including CMAP and EMG data) are considered valuable tools to screen for disease onset in presymptomatic newborns with 4 *SMN2* copies who cannot access immediate SMN augmenting treatment.(140) There is acknowledgement that the availability and expertise to conduct these assessments is varied across health jurisdictions (140) and that the tolerability of assessments varies between children.(143)



### Recommendation 11.1

#### Consensus based recommendation

We suggest that for newborns with  $\geq 4$  *SMN2* copies not initially treated with SMN augmenting therapies (due to a shared decision by family and the healthcare practitioner or for newborns who cannot access treatment), clinical follow-up should occur with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.

Strength of recommendation Conditional, Grade 2C

### Recommendation 11.2

#### Consensus based recommendation

We suggest that redetermination of *SMN2* copy number in a different laboratory or using a different method, may be considered in all newborns with  $\geq 4$  *SMN2* copies due to methodological imprecision arising from *SMN2* copy number methodologies that can impact therapeutic decision making.

Strength of recommendation Conditional, Grade 2C

### Recommendation 11.3

#### Consensus based recommendation

We suggest that neurophysiological techniques (including CMAP +/- EMG +/- motor unit number estimation methods) may be incorporated in the clinical follow-up for newborns with  $\geq 4$  *SMN2* copies who cannot access immediate treatment, to screen for disease onset as the basis to initiate therapeutic intervention.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 11.4

Consensus based recommendation

We suggest that families of children who are presymptomatic and with  $\geq 4$  *SMN2* copies should be educated on the necessity of ongoing clinical surveillance and supported by the multidisciplinary team through this process (including referral to psychological and medical social work services) as appropriate.

Strength of recommendation Conditional, Grade 2C

#### Recommendation 11.5

Consensus based recommendation

We suggest that national clinical paediatric neurology centres should coordinate and establish databases to collect outcome data for newborns who have  $\geq 4$  *SMN2* copies and are under clinical surveillance, to establish an evidence-base to guide therapeutic and policy decision making.

Strength of recommendation Conditional, Grade 2C

*Evidence summary of individual studies for recommendations 11.1-11.5 located in technical report on page 184-188*

## Rationale and impact section on managing children with $\geq 4$ *SMN2* copies

The GDG agreed that the evidence for the management of presymptomatic children with  $\geq 4$  *SMN2* copies was heterogenous. The GDG also acknowledged the lack of access to treatments within the reimbursement and regulatory domain for children with this genotype across Australasia. With the lack of evidence, the GDG reflected on their clinical experience and determined that specialist clinical review, on a frequent basis within the first two years post diagnosis had the potential to detect children who were transitioning from a clinically silent (presymptomatic) to clinically manifest (symptomatic state), and who were more likely to present with early and severe onset forms of SMA. The GDG agreed that the benefits of defining disease onset at the earliest possible point; to enable access to treatments and thus improve long term outcomes outweighed the potential risks of over surveillance, and the logistical burdens imposed on families to travel to specialist centres for review. The GDG agreed that whilst neurophysiological assessments could aid the characterisation of disease onset in this subgroup, health inequities across Australasia could widen due to differences in expertise required to conduct and interpret these assessments, if presented as a strong recommendation. Due to methodological imprecision for determination of *SMN2* copy number, the GDG agreed that children showing discordant phenotype, including children with  $\geq 4$  *SMN2* copies and presenting with an early and severe onset form of SMA, should have repeat *SMN2* copy number identification using a different methodology. The GDG determined that the lack of evidence on the optimal strategies for management for children with  $\geq 4$  *SMN2*, necessitated a multicentre approach to collection of real-world outcome data for this subgroup across Australasian clinical and research networks.

## How the recommendations might affect practice

The recommendations should not change current practice but will reinforce current best practice.

## Future Directions

This Guideline provides a set of Evidence and Consensus based recommendations for newborn screening for SMA across Australia and Aotearoa New Zealand. As such it is relevant to all health jurisdictions undertaking newborn screening programs for SMA across Australasia. Future directions will include amongst other steps, disseminating the Guideline to inform policy and practice and evaluating its usefulness and impact.

### Dissemination and Implementation of recommendations within the Guideline

Pursuant to the publication of the Guideline, the Organising Committee will participate proactively in dissemination of the Guideline. It is planned that dissemination activities will include dissemination through the International Guideline Portal and the University of New South Wales who will house the Guideline and associated documents on a dedicated website (<https://www.unsw.to/nbs-sma>). Dissemination of the Guideline will also be in the form of promotion within newsletters, social media, websites, and utilisation in student teaching. To date, systematic reviews of available literature spanning the entire newborn screening for SMA journey are not part of the scholarly literature and thus it is envisaged that manuscripts will be developed pertaining to the systematic literature review that formed the evidence base for the recommendations and published in a peer review journal.

Additionally, dissemination of the Guideline will be facilitated through a range of activities, conducted in close liaison with relevant professional colleges, societies and consumer representative organisations. These include dissemination of the Guideline by email to organisations that have endorsed the Guideline, to members of the GDG for distribution to relevant stakeholders, to individuals or organisations providing feedback during the public consultation process and through national and international presentations to the scientific, clinical and SMA advocacy/consumer communities.

### Implementation plan

The overall goal of the Guideline was to standardise newborn screening for SMA to diagnose children and improve access to management for children with this condition, to optimise their health and psychological benefits.

The GDG acknowledge that workforce capacity varies across health jurisdictions and that implementation of the recommendations in the Guideline will require appropriate healthcare planning and resourcing to ensure implementation of the Guideline and sustainability of services. These include health policy decisions on appropriate resourcing for screening and diagnostic purposes alongside allocation of provisions for meeting Guideline requirements within paediatric (specialist and non-specialist) services, genetic testing and counselling domains, and multidisciplinary healthcare services. Recommendations for the implementation have also been provided in the '*Implementation and dissemination plan*', found at a dedicated website (<https://www.unsw.to/nbs-sma>).

## Future directions

Future directions include evaluation of the utility and impact of the Guideline for newborn screening for SMA across the Australasian continent, updating the Guideline in keeping with the pace of change within the domains of SMA (newborn) screening, diagnosis and clinical care and setting a coordinated pan-national research agenda to fill the evidence gaps that are emerging within this rapidly evolving landscape. It remains imperative to determine the impacts, enablers, and barriers of translating newborn screening for SMA into healthcare systems within Australia and Aotearoa New Zealand, to support its effective implementation and ensure that in the future, the Guideline can be updated based on co-developed and systematically collected real-world evidence, alongside other scholarly outputs.

Given the unique challenges facing rural and remote regions, it remains a priority to incorporate representative voices of this population into any future co-developed evidence. Furthermore, the information gap at the point of screening, diagnosis, and therapeutic decision making for families can only be filled through co-design of targeted and relevant educational resources, with the child and family perspective to remain central.

Key considerations will include but are not limited to, jurisdictionally dependent feasibility and sustainability of implementing the recommendations, effects on equity of access to diagnosis and care, effects on clinical practice and health system readiness for a change in workflow with the addition of SMA into routine newborn screening, and the short and long term clinical and psychosocial outcomes for children and their families. Systematic evaluation of the impact of the recommendations will thus facilitate wide stakeholder engagement to build resources, infrastructure and logistical capabilities to sustain an effective program of newborn screening for SMA into the future. As such, it is envisaged that the Guideline may be evaluated using the following strategies.

1. Screening laboratory annual reports that determine the timing and process of newborn screening for SMA. These assessments are conducted as part of formal quality assurance and audit activities that evaluate newborn screening programs as a whole.(206)
2. Evaluation of the model of care within each jurisdiction, to aid the improvement of processes to meet the needs of the communities that they serve. This may include

assessment of the temporal processes such as time to screen positive result, diagnostic evaluation, confirmation of diagnosis and time to treatment initiation, alongside the longitudinal evaluation of the short- and long-term clinical outcomes for children screening positive for SMA.

3. The public acceptability of the newborn screening for SMA program as guided by the recommendations within the Guideline, and the barriers and facilitators of implementation from a consumer and healthcare practitioner perspective within individual healthcare jurisdictions.
4. Measuring changes in knowledge about the Guideline recommendations amongst end users.
5. Auditing compliance with Guideline recommendations in a range of service settings.

The Guideline should be reviewed (at maximum) in 5 years of publications or sooner if the screening, diagnostic or clinical landscape changes in the interim, updated to reflect and respond to new evidence from research, clinical practice and changes in community needs, values and preferences. The methodology employed for the update should continue to be systematic and align with the recommendations and approvals required by the National Health and Medical Research Council.

## Evidence gaps and future directions for stakeholders

Over the course of Guideline development, key evidence gaps have been recognised and these lay the foundation for future research. The following evidence gaps have been highlighted throughout the Guideline development process. These include the following:

### Within newborn screening

1. **The evolution of genomic capabilities in newborn screening.** Genomic platforms that have the potential to identify a spectrum of genetic conditions, are being considered within a newborn screening scope of practice. These include gene panels,



whole exome and whole genome sequencing. The future role of current assays for SMA within this evolving landscape will be important to ascertain, especially as next generation sequencing may increase the sensitivity of screening processes and better identify children with a compound heterozygous SMA genotype. This is particularly important for the 5% of children who would not be identified through current newborn screening for SMA practices. Timelines as defined within this Guideline will require review and potential revisions as processes become implemented and streamlined in the future.

- 2. Improving the precision of *SMN2* copy number determination.** The systematic evidence shows the technical challenges in determining *SMN2* copy number both within a screening and diagnostic process, especially for children with *SMN2* copy number  $\geq 4$ . Errors in *SMN2* quantification are numerous within the literature and can lead to substantial harms based on preclusion from access to treatments and challenges with predicting phenotype for affected children and establishing goals of care with their families. Future work will involve collaborative global engagement of scientists, clinical researchers and companies that produce molecular assays for this purpose, to provide updated and standardised processes for the improved determination of *SMN2* copy number within newborn screening programs.

### Within clinical practice

- 3. Understanding and managing the emergence of children with new SMA phenotypes.** Children diagnosed with SMA and treated within the newborn/infancy period are emerging with new phenotypes, variable clinical trajectories and heterogenic clinical responses to treatment. Future work will involve forming clinical-research networks across Australasia and globally to collate standardised clinical, genetic, functional and biomarker data from this population to inform the evidence gaps. Due to the multisystemic nature of SMN depletion, it will be imperative for future outcomes to include and evaluate non-motor domains including communication, language, cognition and behaviour, quality of life, patient and family reported measures and functional independence scales alongside conventional endpoints. Understanding the changing clinical presentations for children diagnosed

and treated early in their disease course is the foundation to assessing unmet needs in this population and defining areas for early intervention and support.

4. **The management of newborns with SMA and  $\geq 4$  *SMN2* copies.** The available literature does not provide a robust evidence base for presymptomatic therapeutic intervention for newborns/infants with this genotype, with potential risks and benefits of early treatment being postulated internationally, namely due to the heterogeneity of (untreated) clinical outcomes within this subgroup. Addressing this evidence gap will be imperative and a multicentre pan-national prospective collection of clinical, neurophysiological, biomarker and functional data from newborns with  $\geq 4$  *SMN2* copies is imperative to evaluate their optimal therapeutic window, to guide the timing of treatment.
5. **Evaluating and refining the model of care.** The systematic literature is starting to define the significant psychological effects on families of receiving a diagnosis of a serious condition such as SMA within the newborn period, and the ongoing psychosocial sequelae of caring for and managing an affected child, even for those who have recourse to therapeutic intervention. Future work may further define the values and preferences of families in how they are supported through this process and focus on evaluating the benefits and resources required to provide a seamless and integrated model of psychological care at screen result disclosure, diagnosis and throughout the clinical care journey.
6. **Development of a holistic toolkit for the evaluation of outcomes from newborn screening for SMA programs.** The systematic evidence review to inform the development of the Guideline showed the heterogeneity and variability of assessment scales used to assess newborns/infants with SMA at diagnosis and longitudinally. The development of assessments that can be utilised specifically in the newborn period remains essential to help augment decision making based on the clinical status of the child.

Beyond the scope of the current Guideline, but relevant to health outcomes for affected children is the need to expand the evaluation of the condition beyond a motor-centric assessment. Additionally, the co-design and development (with input

from a range of stakeholders, including children and their families), of assessment scales will be important, as a basis to understand the evolving clinical trajectory of children diagnosed and treated within newborn screening for SMA programs. These assessment tools will target outcomes that are meaningful to affected children and their families and will also encompass the multisystemic nature of SMA, broadening the scope of assessment to the realms of cognition, behaviour, language, functional independence and neurodevelopment.

### Within education and training

#### 7. **Mitigating inequities in healthcare and providing culturally affirming practices.**

Across the literature review, there was a paucity of evidence to understand how newborn screening for genetic conditions such as SMA is conceptualised and discussed in culturally diverse populations, including within Aboriginal, Torres Strait Islander, Pacific Islander, Māori and other First Nation populations. It is vital to include these communities in further research opportunities, to ensure culturally competent practices, that may change the relevant Consensus based recommendations and Practice Points. This is particularly relevant to maintain high public trust in newborn screening programs as a whole, in the context of concerns around data sovereignty of genetic information by First Nations peoples and a fundamental principle of genealogy or ‘whakapapa’ in Māori communities. The establishment of an Indigenous Advisory Group to inform future revisions and implementation of the Guideline will be a necessary future step towards equitable delivery of best care for all children with SMA across the diverse communities of Australasia.

Furthermore, it is important that a broader and deeper evidence base is created of the perspective and challenges for families seeking to access diagnosis and treatment for SMA from rural and remote regions, as a first step to developing solutions to improve access. Whilst this is a SMA centred approach, learning from the outcomes of these future research directions will directly inform clinical practices for children with other rare conditions, and their families, across Australia and Aotearoa New Zealand.

#### 8. **Education and training for relevant medical practitioners in rural and regional areas.** It is important that medical practitioners undertake the relevant training to

ensure that they have appropriate knowledge and expertise to implement the Guideline within their service. This will mean close liaison and coordination between specialist neurology services to facilitate knowledge exchange with secondary and local healthcare communities, and the development of expedient referral services between screening, diagnostic and clinical care domains. This may involve individualising the available resources to meet the needs of the local community and type of service and will help ensure ongoing capacity within all communities (including regional and remote communities). This will also entail the upskilling of Indigenous Health Liaison professionals to provide culturally appropriate care. Additionally, the formation of clinical networks to promote knowledge exchange and peer-peer support and mentoring for (neurology) specialists is vital. This is especially important as the clinical presentation or phenotype of children being diagnosed with SMA and treated as part of newborn screening programs are changing, thus challenging historical perceptions and strategies employed in their clinical care.

9. **Co-design of educational resources for families.** The co-design of educational resources is important so that families are provided with meaningful, clear, accurate and relatable information on SMA and the consequences of being diagnosed in the newborn/infancy period. Involving consumers with lived experiences in the development of multimedia resources remains essential to support knowledge translation in a way that meets the needs and values of affected families.

# References

1. The Clinical and Laboratory Standards Institute. Harmonized Terminology Database. Last updated 2023. Available online at <https://htd.clsi.org/listallterms.asp>. [Accessed online 01/02/2024]
2. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis*. 2017;12(1):124.
3. Aponte Ribero V, Marti Y, Batson S, Mitchell S, Gorni K, Gusset N, et al. Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures. *Neurology*. 2023;101(21):e2103-e13.
4. Miniño AM, Xu J, Kochanek KD. Deaths: preliminary data for 2008. *Natl Vital Stat Rep*. 2010;59(2):1-52.
5. Sumner CJ, Crawford TO. Early treatment is a lifeline for infants with SMA. *Nat Med*. 2022;28(7):1348-9.
6. Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. *Muscle Nerve*. 2023;68(2):157-70.
7. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29(11):842-56.
8. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparovvec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med*. 2022;28(7):1390-7.
9. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparovvec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nat Med*. 2022;28(7):1381-9.
10. D'Silva AM, Kariyawasam DST, Best S, Wiley V, Farrar MA, Group NSNS. Integrating newborn screening for spinal muscular atrophy into health care systems: an Australian pilot programme. *Dev Med Child Neurol*. 2022;64(5):625-32.
11. Kariyawasam DST, D'Silva AM, Vetsch J, Wakefield CE, Wiley V, Farrar MA. "We needed this": perspectives of parents and healthcare professionals involved in a pilot newborn screening program for spinal muscular atrophy. *EClinicalMedicine*. 2021;33:100742.
12. Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. *Genet Med*. 2020;22(3):557-65.
13. Australian Government. Department of Health and Aged Care. About Newborn Bloodspot Screening. 2022 [updated 27 June 2023. Available from: <https://www.health.gov.au/our-work/newborn-bloodspot-screening/about-newborn-bloodspot-screening> [Accessed online 27/06/2024]
14. Te Whatu Ora; New Zealand Health. Media release. Available online at <https://www.tewhatauora.govt.nz/corporate-information/news-and-updates/new-screening-for-spinal-muscular-atrophy-sma-to-help-babies-access-life-saving-treatments-earlier>. [Accessed online 27/06/2024]
15. Government. A. *National Strategic Action Plan for Rare Disease*. 2020. [Available from: <https://www.health.gov.au/sites/default/files/documents/2020/03/national-strategic-action-plan-for-rare-diseases.pdf> . [Accessed online 02/02/2024]

16. Cloete E, Gentles TL, Dixon LA, Webster DR, Agnew JD, Davidkova S, et al. Feasibility study assessing equitable delivery of newborn pulse oximetry screening in New Zealand's midwifery-led maternity setting. *BMJ Open*. 2019;9(8):e030506.
17. Rare Disease Awareness E, Support and Training (RAREST) Project. . National Recommendations for Rare Disease Health Care. 2024 [Available from: <https://www.rarevoices.org.au/national-recommendations>. [Accessed online 03/02/2024]
18. Best S, Long JC, Gaff C, Braithwaite J, Taylor N. Investigating the Adoption of Clinical Genomics in Australia. An Implementation Science Case Study. *Genes (Basel)*. 2021;12(2).
19. Baazeem M, Kruger E, Tennant M. Strategic threat health response in Australia capital cities: Predicting the optimum locations for field hospitals through geospatial analysis. *Public Health Challenges*. 2024;3(2):e177.
20. Alonso-Coello P, Schunemann HJ, Moher J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016.
21. Cuello CA, Morgan RL, Brozek J, Verbeek J, Thayer K, Ansari MT, et al. Case studies to explore the optimal use of randomized and nonrandomized studies in evidence syntheses that use GRADE. *J Clin Epidemiol*. 2022;152:56-69.
22. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. *J Clin Epidemiol*. 2017;87:4-13.
23. Mustafa RA, Garcia CAC, Bhatt M, Riva JJ, Vesely S, Wiercioch W, et al. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. *J Clin Epidemiol*. 2021;137:231-5.
24. Schunemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol*. 2019;111:105-14.
25. Schunemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.
26. Schunemann HJ, Zhang Y, Oxman AD, Expert Evidence in Guidelines G. Distinguishing opinion from evidence in guidelines. *BMJ*. 2019;366:l4606.
27. Calucho M, Bernal S, Alias L, March F, Vencesla A, Rodriguez-Alvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord*. 2018;28(3):208-15.
28. Australian Government. The Department of Health and Aged Care. 2020. Life-saving Spinal Muscular Atrophy medicine to be made available to Australian babies. Available online at <https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/life-saving-spinal-muscular-atrophy-medicine-to-be-made-available-to-australian-babies?language=und> [Accessed online 04/04/2024]
29. Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening. *J Pediatr*. 2017;190:124-9 e1.
30. Lefebvre S, Burlet P, Liu Q, Bertrand S, Clermont O, Munnich A, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet*. 1997;16(3):265-9.

31. Prior TW, Swoboda KJ, Scott HD, Hejmanowski AQ. Homozygous SMN1 deletions in unaffected family members and modification of the phenotype by SMN2. *Am J Med Genet A*. 2004;130A(3):307-10.
32. Abiusi E, Costa-Roger M, Bertini ES, Tiziano FD, Tizzano EF, group SMNS, et al. 270th ENMC International Workshop: Consensus for SMN2 genetic analysis in SMA patients 10-12 March, 2023, Hoofddorp, the Netherlands. *Neuromuscul Disord*. 2024;34:114-22.
33. Dangouloff T, Burghes A, Tizzano EF, Servais L, Group NSS. 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofddorp, The Netherlands. *Neuromuscul Disord*. 2020;30(1):93-103.
34. Australian Government, Department of Health. Newborn Blood Spot Screening- National Policy Framework. (2018) Available online at: <https://www.health.gov.au/sites/default/files/documents/2020/10/newborn-bloodspot-screening-national-policy-framework.pdf> [Accessed online 03/02/2024.]
35. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*. 2018;28(3):197-207.
36. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28(2):103-15.
37. Shih ST, Farrar MA, Wiley V, Chambers G. Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis. *J Neurol Neurosurg Psychiatry*. 2021;92(12):1296-304.
38. Shih STF, Keller E, Wiley V, Farrar MA, Wong M, Chambers GM. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. *Int J Neonatal Screen*. 2022;8(3).
39. Hendrickson BC, Donohoe C, Akmaev VR, Sugarman EA, Labrousse P, Boguslavskiy L, et al. Differences in SMN1 allele frequencies among ethnic groups within North America. *J Med Genet*. 2009;46(9):641-4.
40. National Health and Medical Research Council. *Procedures and requirements for meeting the NHMRC standards for clinical practice guidelines*. Melbourne: National Health and Medical Research Council; 2020
41. NHMRC. Guidelines for Guidelines: Identifying and managing conflicts of interest. <https://www.nhmrc.gov.au/guidelinesforguidelines/plan/identifying-and-managing-conflicts-interest>. Last published 22/11/2018. [Accessed online 03/02/2024]
42. Australian Institute of Health and Welfare. (2024). Determinants of health for First Nations people. AIHW, Australian Government. Accessible on <https://www.aihw.gov.au/reports/australias-health/social-determinants-and-indigenous-health> [Accessed online 05/01/2024]
43. Langer G, Meerpohl JJ, Perleth M, Gartlehner G, Kaminski-Hartenthaler A, Schunemann H. [GRADE guidelines: 2. Framing the question and deciding on important outcomes]. *Z Evid Fortbild Qual Gesundhwes*. 2012;106(5):369-76.
44. Granholm A, Alhazzani W, Moller MH. Use of the GRADE approach in systematic reviews and guidelines. *Br J Anaesth*. 2019;123(5):554-9.



45. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016;353:i2089.
46. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
47. Creswell JW, Clark VLP. *Designing and conducting mixed methods research*: Sage publications; 2017.
48. Murad MH, Mustafa RA, Schunemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22(3):85-7.
49. McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. *Cochrane handbook for systematic reviews of interventions*. 2019:321-47.
50. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006;1(1):b92.
51. Lotfi T, Hajizadeh A, Moja L, Akl EA, Piggott T, Kredo T, et al. A taxonomy and framework for identifying and developing actionable statements in guidelines suggests avoiding informal recommendations. *J Clin Epidemiol*. 2022;141:161-71.
52. U.S Department of Health and Human Services. Health Resources and Services Administration. Advisory Committee on Heritable Disorders in Newborns and Children. Accessible online at <https://www.hrsa.gov/advisory-committees/heritable-disorders> [Accessed online 22/02/2024]
53. Australian Institute of Aboriginal and Torres Strait Islander Studies (AIATSIS). AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research. 2020 [Available from: <https://aiatsis.gov.au/research/ethical-research/code-ethics>. [Accessed online 16/02/2024]
54. World Health Organization. International Classification of Functioning, Disability and Health (ICF). 2018. Available from: <https://www.who.int/classifications/icf/en/> [Accessed online 11/02/2024]
55. Wilson JMG, Jungner G. *Principles and practice of screening for disease* Geneva: WHO; 1968. Available from: <http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf> [Accessed online 03/02/2024]
56. Assembly UNG, Directorate CHR. *Convention on the Rights of the Child*: Human Rights Directorate; 1991.
57. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-6.
58. Schunemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol*. 2017;81:101-10.
59. Hillier S, Grimmer-Somers K, Merlin T, Middleton P, Salisbury J, Tooher R, et al. FORM: an Australian method for formulating and grading recommendations in evidence-based clinical guidelines. *BMC Med Res Methodol*. 2011;11:23.
60. Coleman K, Norris S, Weston A. National Health and Medical Research Council. *NHMRC Additional Levels of Evidence and Grades for Recommendations for Developers of Guidelines: Stage 2 Consultation; Early 2008–End Jun 2009*. 2009.

61. Trembath D, Varcin K, Waddington H, et al. National guideline for supporting the learning, participation, and wellbeing of autistic children and their families in Australia. Autism CRC, 2022.
62. The Clinical and Laboratory Standards Institute (CLSI). CLSI Projects in Progress. Accessible at <https://clsi.org/standards-development/projects-in-progress/> [Accessed online 05/01/2024]
63. Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlf EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* 2012;20(1):27-32.
64. Australian Bureau of Statistics (ABS). Births, Australia. Available at: <https://www.abs.gov.au/statistics/people/population/births-australia/latest-release> [Accessed online 05/06/2024.]
65. Stats NZ Tauranga Aotearoa. (2023). Births and deaths. Available at: <https://www.stats.govt.nz/information-releases/births-and-deaths-year-ended-december-2023-including-abridged-period-life-table/> [Accessed online 05/06/2024.]
66. Farrar MA, Vucic S, Johnston HM, du Sart D, Kiernan MC. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. *J Pediatr.* 2013;162(1):155-9.
67. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. *Neurol Clin.* 2015;33(4):831-46.
68. Wan HWY, Carey KA, D'Silva A, Vucic S, Kiernan MC, Kasparian NA, et al. Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. *Orphanet J Rare Dis.* 2020;15(1):70.
69. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017;82(6):883-91.
70. Smith M, Calabro V, Chong B, Gardiner N, Cowie S, du Sart D. Population screening and cascade testing for carriers of SMA. *Eur J Hum Genet.* 2007;15(7):759-66.
71. Salort-Campana E, Quijano-Roy S. Clinical features of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander disease). *Arch Pediatr.* 2020;27(7S):7S23-7S8.
72. Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. *Eur J Paediatr Neurol.* 1999;3(2):49-51.
73. Finkel R, Bertini E, Muntoni F, Mercuri E, Group ESWS. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord.* 2015;25(7):593-602.
74. Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, et al. Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. *Nature.* 1990;344(6266):540-1.
75. Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci U S A.* 1999;96(11):6307-11.
76. Monani UR, Lorson CL, Parsons DW, Prior TW, Androphy EJ, Burghes AH, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. *Hum Mol Genet.* 1999;8(7):1177-83.
77. Cartegni L, Hastings ML, Calarco JA, de Stanchina E, Krainer AR. Determinants of exon 7 splicing in the spinal muscular atrophy genes, SMN1 and SMN2. *Am J Hum Genet.* 2006;78(1):63-77.

78. Parsons DW, McAndrew PE, Monani UR, Mendell JR, Burghes AH, Prior TW. An 11 base pair duplication in exon 6 of the SMN gene produces a type I spinal muscular atrophy (SMA) phenotype: further evidence for SMN as the primary SMA-determining gene. *Hum Mol Genet.* 1996;5(11):1727-32.
79. Butchbach MER. Genomic Variability in the Survival Motor Neuron Genes (SMN1 and SMN2): Implications for Spinal Muscular Atrophy Phenotype and Therapeutics Development. *Int J Mol Sci.* 2021;22(15).
80. Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol.* 2005;57(5):704-12.
81. Lefebvre S, Burglen L, Reboullet S, Clermont O, Bulet P, Villet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995;80(1):155-65.
82. Coovert DD, Le TT, McAndrew PE, Strasswimmer J, Crawford TO, Mendell JR, et al. The survival motor neuron protein in spinal muscular atrophy. *Hum Mol Genet.* 1997;6(8):1205-14.
83. Crawford TO, Paushkin SV, Kobayashi DT, Forrest SJ, Joyce CL, Finkel RS, et al. Evaluation of SMN protein, transcript, and copy number in the biomarkers for spinal muscular atrophy (BforSMA) clinical study. *PLoS One.* 2012;7(4):e33572.
84. Wirth B, Brichta L, Schrank B, Lochmuller H, Blick S, Baasner A, et al. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. *Hum Genet.* 2006;119(4):422-8.
85. Mailman MD, Heinz JW, Papp AC, Snyder PJ, Sedra MS, Wirth B, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. *Genet Med.* 2002;4(1):20-6.
86. Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet.* 2002;70(2):358-68.
87. Kariyawasam D, D'Silva A, Howells J, Herbert K, Geelan-Small P, Lin CS, et al. Motor unit changes in children with symptomatic spinal muscular atrophy treated with nusinersen. *J Neurol Neurosurg Psychiatry.* 2020;92(1):78-85.
88. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ.* 2008;86(4):317-9.
89. Lin CW, Kalb SJ, Yeh WS. Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. *Pediatr Neurol.* 2015;53(4):293-300.
90. Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *Appl Clin Genet.* 2021;14:11-25.
91. Rehani MR, Marcus MS, Harris AB, Farrell PM, Ren CL. Variation in cystic fibrosis newborn screening algorithms in the United States. *Pediatr Pulmonol.* 2023;58(3):927-33.
92. Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genet Med.* 2018;20(6):608-13.
93. Kemper AR, Ream MA, Lam KK. Review of newborn screening implementation for spinal muscular atrophy final report. The Health Resources and Services Administration (HRSA). 2018 Mar;13.

94. Niri F, Nicholls J, Baptista Wyatt K, Walker C, Price T, Kelln R, et al. Alberta Spinal Muscular Atrophy Newborn Screening-Results from Year 1 Pilot Project. *Int J Neonatal Screen*. 2023;9(3).
95. The European Alliance for Newborn Screening in Spinal Muscular Atrophy. Screening for SMA status map. Updated 2024. Available online at <https://www.sma-screening-alliance.org/about-us> [Accessed online 27/06/2024.]
96. Map – SMA Newborn Screening Alliance. (2024). <https://www.sma-screening-alliance.org/map>. [Accessed online 27/06/2024 ]
97. Antenatal and Childhood Screening. 2024. Newborn Metabolic Screening Programme: Annual Report 2022. Wellington: Health New Zealand.
98. Kariyawasam DS, D'Silva AM, Sampaio H, Briggs N, Herbert K, Wiley V, et al. Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. *Lancet Child Adolesc Health*. 2023;7(3):159-70.
99. DOHA. (2024). Australian Government. Newborn Bloodspot Screening Expansion. Readiness Assessment Executive Summary. Accessible online at [https://www.health.gov.au/sites/default/files/2024-06/newborn-bloodspot-screening-expansion-readiness-assessment-executive-summary\\_0.pdf](https://www.health.gov.au/sites/default/files/2024-06/newborn-bloodspot-screening-expansion-readiness-assessment-executive-summary_0.pdf) [Accessed online 27/05/2024.]
100. Australian Institute of Health and Welfare. (2018). Australian Government. Australia's Health. How does Australia's health system work?. Available online at <https://www.aihw.gov.au/getmedia/63fe0895-b306-4375-95ff-162149ffc34b/aihw-aus-221-chapter-2-1.pdf.aspx> [Accessed online 29/06/2024]
101. DOHA. (2023). Australian Government. Delivering newborn bloodspot screening programs. Available online at <https://www.health.gov.au/our-work/newborn-bloodspot-screening/delivering-programs#state-and-territory-nbs-programs> [Accessed online 07/07/2024.]
102. Charli J, Michelle AF, Sarah N, Kaustuv B, Bruce B, Ainsley JN, et al. The Australian landscape of newborn screening in the genomics era. *Rare Disease and Orphan Drugs Journal*. 2023;2(4):26.
103. Arah OA, Klazinga NS, Delnoij DM, ten Asbroek AH, Custers T. Conceptual frameworks for health systems performance: a quest for effectiveness, quality, and improvement. *Int J Qual Health Care*. 2003;15(5):377-98.
104. National Screening Unit. 2023. Newborn Metabolic Screening Programme: Annual Report 2021. Wellington: National Screening Unit. Accessible at [nsu.govt.nz](http://nsu.govt.nz)
105. Australian Institute of Health and Welfare. Health expenditure report for 2020-2021, updated on 2023. Available online at <https://www.aihw.gov.au/getmedia/931a083a-e2a1-4f0d-9a09-140d55682711/health-expenditure-australia-2020-21.pdf?v=20221104125902&inline=true> [Accessed online 06/06/2024.]
106. Cao M, Notini L, Ayres S, Vears DF. Australian healthcare professionals' perspectives on the ethical and practical issues associated with genomic newborn screening. *J Genet Couns*. 2023;32(2):376-86.
107. Australian Government. Department of Health and Aged Care. \$148 million in new Medicare rebates for genetic testing. Accessible at [health.gov.au/ministers/the-hon-mark-butler-mp/media/148-million-in-new-medicare-rebates-for-genetic-testing?language=en](http://health.gov.au/ministers/the-hon-mark-butler-mp/media/148-million-in-new-medicare-rebates-for-genetic-testing?language=en)
108. Prior TW, Snyder PJ, Rink BD, Pearl DK, Pyatt RE, Mihal DC, et al. Newborn and carrier screening for spinal muscular atrophy. *Am J Med Genet A*. 2010;152A(7):1608-16.

109. Czibere L, Burggraf S, Fleige T, Gluck B, Keitel LM, Landt O, et al. High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. *Eur J Hum Genet.* 2020;28(1):23-30.
110. Pyatt RE, Prior TW. A feasibility study for the newborn screening of spinal muscular atrophy. *Genet Med.* 2006;8(7):428-37.
111. McMillan HJ, Kernohan KD, Yeh E, Amburgey K, Boyd J, Campbell C, et al. Newborn Screening for Spinal Muscular Atrophy: Ontario Testing and Follow-up Recommendations. *Can J Neurol Sci.* 2021;48(4):504-11.
112. Niba ETE, Ar Rochmah M, Harahap NIF, Awano H, Morioka I, Iijima K, et al. SMA Diagnosis: Detection of SMN1 Deletion with Real-Time mCOP-PCR System Using Fresh Blood DNA. *Kobe J Med Sci.* 2017;63(3):E80-E3.
113. Wijaya YOS, Nishio H, Niba ETE, Okamoto K, Shintaku H, Takeshima Y, et al. Detection of Spinal Muscular Atrophy Patients Using Dried Saliva Spots. *Genes (Basel).* 2021;12(10).
114. Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA, Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. *Genet Med.* 2020;22(8):1296-302.
115. Abiusi E, Vaisfeld A, Fiori S, Novelli A, Spartano S, Faggiano MV, et al. Experience of a 2-year spinal muscular atrophy NBS pilot study in Italy: towards specific guidelines and standard operating procedures for the molecular diagnosis. *J Med Genet.* 2023;60(7):697-705.
116. Vidal-Folch N, Gavrilov D, Raymond K, Rinaldo P, Tortorelli S, Matern D, et al. Multiplex Droplet Digital PCR Method Applicable to Newborn Screening, Carrier Status, and Assessment of Spinal Muscular Atrophy. *Clin Chem.* 2018;64(12):1753-61.
117. Niba ETE, Rochmah MA, Harahap NIF, Awano H, Morioka I, Iijima K, et al. Spinal Muscular Atrophy: Advanced Version of Screening System with Real-Time mCOP-PCR and PCR-RFLP for SMN1 Deletion. *Kobe J Med Sci.* 2019;65(2):E49-E53.
118. Er TK, Chang JG. High-resolution melting: applications in genetic disorders. *Clin Chim Acta.* 2012;414:197-201.
119. Mikhalchuk K, Shchagina O, Chukhrova A, Zabnenkova V, Chausova P, Ryadninskaya N, et al. Pilot Program of Newborn Screening for 5q Spinal Muscular Atrophy in the Russian Federation. *Int J Neonatal Screen.* 2023;9(2).
120. Groulx-Boivin E, Osman H, Chakraborty P, Lintern S, Oskoui M, Selby K, et al. Variability in Newborn Screening Across Canada: Spinal Muscular Atrophy and Beyond. *Can J Neurol Sci.* 2024;51(2):203-9.
121. Lin Y, Lin CH, Yin X, Zhu L, Yang J, Shen Y, et al. Newborn Screening for Spinal Muscular Atrophy in China Using DNA Mass Spectrometry. *Front Genet.* 2019;10:1255.
122. Shinohara M, Niba ETE, Wijaya YOS, Takayama I, Mitsuishi C, Kumasaka S, et al. A Novel System for Spinal Muscular Atrophy Screening in Newborns: Japanese Pilot Study. *Int J Neonatal Screen.* 2019;5(4):41.
123. Shum BOV, Henner I, Cairns A, Pretorius C, Wilgen U, Barahona P, et al. Technical feasibility of newborn screening for spinal muscular atrophy by next-generation DNA sequencing. *Front Genet.* 2023;14:1095600.
124. Romanelli Tavares VL, Monfardini F, Lourenco NCV, da Rocha KM, Weinmann K, Pavanello R, et al. Newborn Screening for 5q Spinal Muscular Atrophy: Comparisons between Real-Time PCR Methodologies and Cost Estimations for Future Implementation Programs. *Int J Neonatal Screen.* 2021;7(3).

125. Matteson J, Wu CH, Mathur D, Tang H, Sciortino S, Feuchtbaum L, et al. California's experience with SMA newborn screening: A successful path to early intervention. *J Neuromuscul Dis.* 2022;9(6):777-85.
126. Baker MW, Mochal ST, Dawe SJ, Wiberley-Bradford AE, Cogley MF, Zeitler BR, et al. Newborn screening for spinal muscular atrophy: The Wisconsin first year experience. *Neuromuscul Disord.* 2022;32(2):135-41.
127. Weng WC, Hsu YK, Chang FM, Lin CY, Hwu WL, Lee WT, et al. CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening. *Genet Med.* 2021;23(2):415-20.
128. Kernohan KD, McMillan HJ, Yeh E, Lacaria M, Kowalski M, Campbell C, et al. Ontario Newborn Screening for Spinal Muscular Atrophy: The First Year. *Can J Neurol Sci.* 2022;49(6):821-3.
129. Sonehara S, Bo R, Nambu Y, Iketani K, Lee T, Shimomura H, et al. Newborn Screening for Spinal Muscular Atrophy: A 2.5-Year Experience in Hyogo Prefecture, Japan. *Genes (Basel).* 2023;14(12).
130. Hale K, Ojodu J, Singh S. Landscape of Spinal Muscular Atrophy Newborn Screening in the United States: 2018-2021. *Int J Neonatal Screen.* 2021;7(3).
131. Wirth B. An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). *Hum Mutat.* 2000;15(3):228-37.
132. Muller-Felber W, Blaschek A, Schwartz O, Glaser D, Nennstiel U, Brockow I, et al. Newborn screening SMA - From Pilot Project to Nationwide Screening in Germany. *J Neuromuscul Dis.* 2023;10(1):55-65.
133. Society for N, Neurology CRHA, Dedicated Fund for Neuromuscular Disorders MoDBDFoC. [Expert consensus on newborn screening for spinal muscular atrophy (2023 edition)]. *Zhonghua Yi Xue Za Zhi.* 2023;103(27):2075-81.
134. Gutierrez-Mateo C, Timonen A, Vaahtera K, Jaakkola M, Hougaard DM, Bybjerg-Grauholm J, et al. Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA. *Int J Neonatal Screen.* 2019;5(4):39.
135. Tesorero R, Janda J, Horster F, Feyh P, Mutze U, Hauke J, et al. A high-throughput newborn screening approach for SCID, SMA, and SCD combining multiplex qPCR and tandem mass spectrometry. *PLoS One.* 2023;18(3):e0283024.
136. Kiselev A, Maretina M, Shtykalova S, Al-Hilal H, Maslyanyuk N, Plokhiih M, et al. Establishment of a Pilot Newborn Screening Program for Spinal Muscular Atrophy in Saint Petersburg. *Int J Neonatal Screen.* 2024;10(1).
137. Lee BH, Deng S, Chiriboga CA, Kay DM, Irumudomon O, Laureta E, et al. Newborn Screening for Spinal Muscular Atrophy in New York State: Clinical Outcomes From the First 3 Years. *Neurology.* 2022;99(14):e1527-e37.
138. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2017;377(18):1723-32.
139. Cusco I, Bernal S, Blasco-Perez L, Calucho M, Alias L, Fuentes-Prior P, et al. Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. *Neurol Genet.* 2020;6(6):e530.
140. Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *J Neuromuscul Dis.* 2018;5(2):145-58.

141. Glascock J, Sampson J, Connolly AM, Darras BT, Day JW, Finkel R, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. *J Neuromuscul Dis.* 2020;7(2):97-100.
142. Blaschek A, Kolbel H, Schwartz O, Kohler C, Glaser D, Eggermann K, et al. Newborn Screening for SMA - Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies? *J Neuromuscul Dis.* 2022;9(5):597-605.
143. Muller-Felber W, Vill K, Schwartz O, Glaser D, Nennstiel U, Wirth B, et al. Infants Diagnosed with Spinal Muscular Atrophy and 4 SMN2 Copies through Newborn Screening - Opportunity or Burden? *J Neuromuscul Dis.* 2020;7(2):109-17.
144. Dangouloff T, Servais L. Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives. *Ther Clin Risk Manag.* 2019;15:1153-61.
145. Kariyawasam DST, D'Silva AM, Herbert K, Howells J, Carey K, Kandula T, et al. Axonal excitability changes in children with spinal muscular atrophy treated with nusinersen. *J Physiol.* 2022;600(1):95-109.
146. Vill K, Schwartz O, Blaschek A, Glaser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. *Orphanet J Rare Dis.* 2021;16(1):153.
147. Boemer F, Caberg JH, Beckers P, Dideberg V, di Fiore S, Bours V, et al. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. *Sci Rep.* 2021;11(1):19922.
148. Swoboda KJ. Seize the day: Newborn screening for SMA. *Am J Med Genet A.* 2010;152A(7):1605-7.
149. Bernal S, Alias L, Barcelo MJ, Also-Rallo E, Martinez-Hernandez R, Gamez J, et al. The c.859G>C variant in the SMN2 gene is associated with types II and III SMA and originates from a common ancestor. *J Med Genet.* 2010;47(9):640-2.
150. Wu X, Wang SH, Sun J, Krainer AR, Hua Y, Prior TW. A-44G transition in SMN2 intron 6 protects patients with spinal muscular atrophy. *Hum Mol Genet.* 2017;26(14):2768-80.
151. Prior TW, Krainer AR, Hua Y, Swoboda KJ, Snyder PC, Bridgeman SJ, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. *Am J Hum Genet.* 2009;85(3):408-13.
152. Schorling DC, Becker J, Pechmann A, Langer T, Wirth B, Kirschner J. Discrepancy in redetermination of SMN2 copy numbers in children with SMA. *Neurology.* 2019;93(6):267-9.
153. Dangouloff T, Boemer F, Dideberg V, Caberg JH, Servais L. Reader response: Discrepancy in redetermination of SMN2 copy numbers in children with SMA. *Neurology.* 2020;95(3):144-5.
154. Alias L, Bernal S, Barcelo MJ, Also-Rallo E, Martinez-Hernandez R, Rodriguez-Alvarez FJ, et al. Accuracy of marker analysis, quantitative real-time polymerase chain reaction, and multiple ligation-dependent probe amplification to determine SMN2 copy number in patients with spinal muscular atrophy. *Genet Test Mol Biomarkers.* 2011;15(9):587-94.
155. McCabe ERB. Newborn screening system: Safety, technology, advocacy. *Mol Genet Metab.* 2021;134(1-2):3-7.
156. Kucera KS, Taylor JL, Robles VR, Clinard K, Migliore B, Boyea BL, et al. A Voluntary Statewide Newborn Screening Pilot for Spinal Muscular Atrophy: Results from Early Check. *Int J Neonatal Screen.* 2021;7(1).
157. Sawada T, Kido J, Sugawara K, Yoshida S, Ozasa S, Nomura K, et al. Newborn screening for spinal muscular atrophy in Japan: One year of experience. *Mol Genet Metab Rep.* 2022;32:100908.

158. Kimizu T, Ida S, Oki K, Shima M, Nishimoto S, Nakajima K, et al. Newborn screening for spinal muscular atrophy in Osaka -challenges in a Japanese pilot study. *Brain Dev.* 2023;45(7):363-71.
159. Noguchi Y, Bo R, Nishio H, Matsumoto H, Matsui K, Yano Y, et al. PCR-Based Screening of Spinal Muscular Atrophy for Newborn Infants in Hyogo Prefecture, Japan. *Genes (Basel).* 2022;13(11).
160. Liu Z, Zhang P, He X, Liu S, Tang S, Zhang R, et al. New multiplex real-time PCR approach to detect gene mutations for spinal muscular atrophy. *BMC Neurol.* 2016;16(1):141.
161. Ricci M, Cicala G, Capasso A, Coratti G, Fiori S, Cutrona C, et al. Clinical Phenotype of Pediatric and Adult Patients With Spinal Muscular Atrophy With Four SMN2 Copies: Are They Really All Stable? *Ann Neurol.* 2023;94(6):1126-35.
162. Blasco-Perez L, Paramonov I, Leno J, Bernal S, Alias L, Fuentes-Prior P, et al. Beyond copy number: A new, rapid, and versatile method for sequencing the entire SMN2 gene in SMA patients. *Hum Mutat.* 2021;42(6):787-95.
163. Aragon-Gawinska K, Mouraux C, Dangouloff T, Servais L. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening-A Systematic Review. *Genes (Basel).* 2023;14(7).
164. Qu Y, Bai J, Jiao H, Qi H, Huang W, OuYang S, et al. Variants located in intron 6 of SMN1 lead to misdiagnosis in genetic detection and screening for SMA. *Heliyon.* 2024;10(6):e28015.
165. Elkins K, Wittenauer A, Hagar AF, Logan R, Sekul E, Xiang Y, et al. Georgia state spinal muscular atrophy newborn screening experience: Screening assay performance and early clinical outcomes. *Am J Med Genet C Semin Med Genet.* 2022;190(2):187-96.
166. Lakhota, A.; Toupin, D.; Thamann, A.; Jackson, K.; Sevier, D.; Crutcher, A.; Wei, S.; Arora, V.; Asamoah, A.; Robertson, W. Demographic and Clinical Profiles of Neonates Diagnosed with Spinal Muscular Atrophy (SMA) via the Kentucky Newborn Screening (NBS) Program: A Two-Year Experience. In *Proceedings of the 74th Annual Meeting of the American Academy of Neurology, AAN, Seattle, WA, USA, 2–7 April 2022; Volume 98.*
167. Pan J, Zhang C, Teng Y, Zeng S, Chen S, Liang D, et al. Detection of Spinal Muscular Atrophy Using a Duplexed Real-Time PCR Approach With Locked Nucleic Acid-Modified Primers. *Ann Lab Med.* 2021;41(1):101-7.
168. Hashimoto K, Yokokawa M, Yamashita D, Yuge K, Otsubo Y. Spinal Muscular Atrophy Type I With False Negative in Newborn Screening: A Case Report. *Cureus.* 2023;15(7):e42382.
169. Chen X, Harting J, Farrow E, Thiffault I, Kasperaviciute D, Genomics England Research C, et al. Comprehensive SMN1 and SMN2 profiling for spinal muscular atrophy analysis using long-read PacBio HiFi sequencing. *Am J Hum Genet.* 2023;110(2):240-50.
170. Bai J, Qu Y, Huang W, Meng W, Zhan J, Wang H, et al. A high-fidelity long-read sequencing-based approach enables accurate and effective genetic diagnosis of spinal muscular atrophy. *Clin Chim Acta.* 2024;553:117743.
171. Eggermann K, Gläser D, Abicht A, Wirth B. Spinal muscular atrophy (5qSMA): best practice of diagnostics, newborn screening and therapy. *Medizinische Genetik.* 2020;32(3):263-72.
172. Cooper K, Nalbant G, Sutton A, Harnan S, Thokala P, Chilcott J, et al. Systematic Review of Newborn Screening Programmes for Spinal Muscular Atrophy. *Int J Neonatal Screen.* 2024;10(3).
173. Phan HC, Taylor JL, Hannon H, Howell R. Newborn screening for spinal muscular atrophy: Anticipating an imminent need. *Semin Perinatol.* 2015;39(3):217-29.



174. Meyer AP, Connolly AM, Vannatta K, Hacker N, Hatfield A, Decipeda A, et al. Parental Experiences with Newborn Screening and Gene Replacement Therapy for Spinal Muscular Atrophy. *J Neuromuscul Dis.* 2024;11(1):129-42.
175. Pane M, Donati MA, Cutrona C, De Sanctis R, Pirinu M, Coratti G, et al. Neurological assessment of newborns with spinal muscular atrophy identified through neonatal screening. *Eur J Pediatr.* 2022;181(7):2821-9.
176. Kichula EA, Proud CM, Farrar MA, Kwon JM, Saito K, Desguerre I, et al. Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. *Muscle Nerve.* 2021;64(4):413-27.
177. D'Silva AM, Holland S, Kariyawasam D, Herbert K, Barclay P, Cairns A, et al. Onasemnogene abeparvovec in spinal muscular atrophy: an Australian experience of safety and efficacy. *Ann Clin Transl Neurol.* 2022;9(3):339-50.
178. Day JW, Finkel RS, Mercuri E, Swoboda KJ, Menier M, van Olden R, et al. Adeno-associated virus serotype 9 antibodies in patients screened for treatment with onasemnogene abeparvovec. *Mol Ther Methods Clin Dev.* 2021;21:76-82.
179. Finkel RS, Benatar M. Pre-symptomatic spinal muscular atrophy: a proposed nosology. *Brain.* 2022;145(7):2247-9.
180. Rovira-Moreno E, Abulí A, Muñoz-Cabello P, Codina-Solà M, Baillès E, de Lemus M, et al. The diagnosis communication process in spinal muscular atrophy: A cross-cutting view of the new challenges facing the therapeutic era. *Genetics in Medicine Open.* 2023;1(1):100825.
181. Farrar MA, Kiernan MC, Kariyawasam DS. Presymptomatic spinal muscular atrophy: a cautionary approach to the proposed new terminology. *Brain.* 2023;146(9):e65-e6.
182. Kariyawasam D, Carey KA, Jones KJ, Farrar MA. New and developing therapies in spinal muscular atrophy. *Paediatr Respir Rev.* 2018;28:3-10.
183. Tizzano EF, Finkel RS. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. *Neuromuscul Disord.* 2017;27(10):883-9.
184. Balaji L, Farrar MA, D'Silva AM, Kariyawasam DS. Decision-making and challenges within the evolving treatment algorithm in spinal muscular atrophy: a clinical perspective. *Expert Rev Neurother.* 2023;23(7):571-86.
185. de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull.* 2004;25(1 Suppl):S15-26.
186. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord.* 2010;20(3):155-61.
187. Cutrona C, de Sanctis R, Coratti G, Capasso A, Ricci M, Stanca G, et al. Can the CHOP-INTEND be used as An Outcome Measure in the First Months of Age? Implications for Clinical Trials and Real World Data. *J Neuromuscul Dis.* 2024;11(1):85-90.
188. Bishop KM, Montes J, Finkel RS. Motor milestone assessment of infants with spinal muscular atrophy using the hammersmith infant neurological Exam-Part 2: Experience from a nusinersen clinical study. *Muscle Nerve.* 2018;57(1):142-6.
189. Pane M, Coratti G, Pera MC, Sansone VA, Messina S, d'Amico A, et al. Nusinersen efficacy data for 24-month in type 2 and 3 spinal muscular atrophy. *Ann Clin Transl Neurol.* 2022;9(3):404-9.
190. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular

atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol.* 2021;20(4):284-93.

191. Michelson D, Ciafaloni E, Ashwal S, Lewis E, Narayanaswami P, Oskoui M, et al. Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;91(20):923-33.

192. Pechmann A, Behrens M, Dornbrack K, Tassoni A, Wenzel F, Stein S, et al. Improvements in Walking Distance during Nusinersen Treatment - A Prospective 3-year SMARtCARE Registry Study. *J Neuromuscul Dis.* 2023;10(1):29-40.

193. Pechmann A, Behrens M, Dornbrack K, Tassoni A, Wenzel F, Stein S, et al. Improved upper limb function in non-ambulant children with SMA type 2 and 3 during nusinersen treatment: a prospective 3-years SMARtCARE registry study. *Orphanet J Rare Dis.* 2022;17(1):384.

194. Pechmann A, Behrens M, Dornbrack K, Tassoni A, Stein S, Vogt S, et al. Effect of nusinersen on motor, respiratory and bulbar function in early-onset spinal muscular atrophy. *Brain.* 2023;146(2):668-77.

195. De Siqueira Carvalho AA, Tychon C, Servais L. Newborn screening for spinal muscular atrophy - what have we learned? *Expert Rev Neurother.* 2023;23(11):1005-12.

196. Aragon-Gawinska K, Mouraux C, Dangouloff T, Servais L. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening—A Systematic Review. *Genes.* 2023;14(7):1377.

197. Pechmann A, König K, Bernert G, Schachtrup K, Schara U, Schorling D, et al. SMARtCARE - A platform to collect real-life outcome data of patients with spinal muscular atrophy. *Orphanet J Rare Dis.* 2019;14(1):18.

198. Farrar MA, Carey KA, Paguinto SG, Kasparian NA, De Abreu Lourenco R. "The Whole Game is Changing and You've Got Hope": Australian Perspectives on Treatment Decision Making in Spinal Muscular Atrophy. *Patient.* 2020;13(4):389-400.

199. Farrar MA, Calotes-Castillo L, De Silva R, Barclay P, Attwood L, Cini J, et al. Gene therapy-based strategies for spinal muscular atrophy-an Asia-Pacific perspective. *Mol Cell Pediatr.* 2023;10(1):17.

200. Kolbel H, Modler L, Blaschek A, Schara-Schmidt U, Vill K, Schwartz O, et al. Parental Burden and Quality of Life in 5q-SMA Diagnosed by Newborn Screening. *Children (Basel).* 2022;9(12).

201. Nguyen CQ, Alba-Concepcion K, Palmer EE, Scully JL, Millis N, Farrar MA. The involvement of rare disease patient organisations in therapeutic innovation across rare paediatric neurological conditions: a narrative review. *Orphanet J Rare Dis.* 2022;17(1):167.

202. The Pharmaceutical Benefits Advisory Committee. PBAC Public Summary Documents for risdiplam; 2023. Accessible online at <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/risdiplam-psd-03-2023.pdf> [Accessed online 01/02/2024.]

203. The Pharmaceutical Benefits Advisory Committee. PBAC Public Summary Documents for onasemnogene abeparvovec; 2023. Available from: <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2023-07/onasemnogene-abeparvovec-Zolgensma-PSD-July-2023> [Accessed online 01/02/2024.]

204. The Pharmaceutical Benefits Advisory Committee. PBAC Public Summary Documents for Nusinersen; 2022. Available from: <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/nusinersen-psd-march-2022.pdf> [Accessed online 01/02/2024]
205. Vill K, Tacke M, Konig A, Baumann M, Baumgartner M, Steinbach M, et al. 5qSMA: standardised retrospective natural history assessment in 268 patients with four copies of SMN2. *J Neurol.* 2024;271(5):2787-97.
206. Australian Commission on Safety and Quality in Health Care. The National Clinical Trials Governance Framework and user guide for health service organisations conducting clinical trials. Sydney: ACSQHC; 2022 [Available from: [https://www.safetyandquality.gov.au/sites/default/files/2022-05/final\\_design\\_-\\_national\\_clinical\\_trials\\_governance\\_framework\\_and\\_user\\_guide\\_-\\_30\\_may\\_2022.pdf](https://www.safetyandquality.gov.au/sites/default/files/2022-05/final_design_-_national_clinical_trials_governance_framework_and_user_guide_-_30_may_2022.pdf). [Accessed online 05/05/2024.]