A Guideline for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand

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Endorsements

The following organisations have endorsed the Guideline for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand (found in alphabetical order).

Advocacy Beyond Borders

Australia and New Zealand Child Neurology Service

Human Genetics Society of Australasia

New Zealand Child & Youth Clinical Network

Rare Disorders New Zealand

Patient Voice Aotearoa

Royal Australasian College of Physicians

Spinal Muscular Atrophy Australia

Spinal Muscular Atrophy New Zealand

The Paediatric Society of New Zealand

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Table of Contents

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

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. In the SMA context, this may occur

secondary to the sensitivity of the assays employed or the fact that the screening test does not screen for the 5% of the SMA population with genetic variants outside biallelic deletion of exon 7 on *SMN1*

False-positive screening result

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. In the SMA context, this may occur when diagnostic confirmation does not identify homozygous deletion of exon 7 on *SMN1*, in a screen positive newborn.

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 (≈ 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 partly 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 children with SMA from Australia and Aotearoa New Zealand, equitable access to an expedient diagnosis of SMA and evidence-based best care. It is envisaged that the recommendations therein will serve to improve health and psychosocial outcomes for affected children, and to support their families through the healthcare journey .

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.

Companion documents including information for consumers can be found in Appendix A.

Purpose, scope, population and settings

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 newborn screening for SMA in a manner that is equitable, feasible and sustainable across Australia and Aotearoa New Zealand. 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 does 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 (≤ 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 diagnostics 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. Questions to inform Guideline development are as below.

Topic	Question
Screening	What biological sample should be used for SMA newborn screening?
Screening	What should the target analyte be in newborn screening for SMA?

Screening	Should the screening assay have a minimum sensitivity and specificity? What should this be?
Screening	Should *SMN2* copy number be part of newborn screening for SMA?
Screening	How (when, where and who) should notify clinical services of a screen positive result?
Screening	How (when, where and who) who should notify families of a screen positive SMA result?
Screening	Should there be specific processes to manage false positive results?
Screening	Should there be specific processes to manage false negative or uncertain results?
Diagnosis	How should a screen positive child be diagnosed with SMA?
Diagnosis	Should diagnosis of SMA include SMN2 copy number?
Diagnosis	What assessments should be completed in a child that is diagnosed with SMA? • Should diagnosis of SMA include a clinical exam? • Should diagnosis of SMA include electrophysiological tests? • Should diagnosis of SMA include motor assessments? • Assessments to prepare for treatment • Other
Clinical	How should a screen positive infant be managed within clinical services? • When should the screening result be available to clinical services? • When should the diagnostic result be available to clinical services? • When should a screen positive newborn be first reviewed by clinical services (after screen positive result disclosure)? • Who should conduct the review of the screen positive newborn • Where should screen positive newborns be reviewed?
Clinical	How should treatment decisions be made in children diagnosed with SMA? • When should treatment be started for a presymptomatic child with SMA (diagnosed through newborn screening)? • When should treatment be started for a symptomatic child with SMA (diagnosed through newborn screening)? • Should a specific treatment be used to treat a child with SMA (diagnosed through newborn screening)? • How should children without access to immediate treatment be managed?
Clinical	Should families of children diagnosed with SMA through newborn screening be referred for genetic counselling?
Care and support	Should specific care or support be provided at the time of screen positive or diagnostic disclosure for families of First nations descent and/or culturally and linguistically diverse families?
Care and support	Should specific information be given to families of screen positive or diagnosed children with SMA?
Care and support	Should specific psychological support be given to families of screen positive children?

Summary of Recommendations

The following are a reference list of Evidence based and Consensus 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. Practice standards and implementation guidance are found further on within the Guideline within the relevant sections.

All Recommendations within the Guideline represent good practice and should be implemented. For evidence-based recommendations are defined as either strong or conditional. In summary, the principle for the strength of recommendations is:

1. The strength is strong when most or all individuals will be best served by the recommended course of action
2. The strength is conditional when not all individuals will be best served by the recommended course of action and there is a need to consider the individual patient's circumstances, preferences, and values.

The grade of recommendations (strong, conditional) for evidence-based recommendations is intended to support users in considering a range of factors when implementing a given Recommendation, such as the benefits and harms, including priority of the problem, feasibility, benefits and harms of the proposed intervention, certainty of the body of evidence, values and preferences to end users, resource and cost effectiveness implications and health equity, acceptability and feasibility factors.

Where a Recommendation is strong, it is written as '*it is recommended*' 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 '*it is suggested'*. 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.

Consensus recommendations have been formed using data generated where there is no or low certainty evidence, based on expert opinion (through a modified Delphi process and systematic observation form collection of expert practice).

Section 1: 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 with absence of exon 7 on *SMN1* as the target analyte.

Grade of recommendation Strong, for

Recommendation 1.2

Consensus recommendation

The screening method selected by the screening program should have a sensitivity of ≥ 95% for the detection of S*MN1* exon 7 absence (0 *SMN1* copies) using suitably validated quantitative and qualitative assays

Recommendation 1.3.

Consensus recommendation

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).

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

Recommendation 2.1.

Consensus recommendation

SMN2 copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*.

Recommendation 2.2.

Consensus recommendation

Newborn screening programs should establish a clinical referral pathway that includes simultaneous notification of a screen positive result to a paediatric neurology specialist and a local healthcare practitioner.

Section 3: Confirming a diagnosis of SMA in screen positive newborns

Recommendation 3.1

Evidence based recommendation

Diagnostic testing should include confirmation of an absence of exon 7 on *SMN1 (*i.e. zero copies of *SMN1)*.

Grade of recommendation: Strong, for

Recommendation 3.2

Consensus recommendation

Diagnostic testing using suitably validated assays, from whole blood samples or repeat dried blood spot from a recalled infant should include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making.

Recommendation 3.3

Consensus recommendation

Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory.

Recommendation 3.4

Consensus recommendation

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

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

Recommendation 4.1

Consensus recommendation

For newborns with a false positive, false negative **or** uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families.

Recommendation 4.2

Consensus recommendation

If there is a difference in *SMN1* and/or *SMN2* copy number results between screening and diagnostic assays, retesting for *SMN1* and/or *SMN2* copy number with another method/laboratory should be considered.

Recommendation 4.3

Consensus recommendation

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.

Section 5: Communicating a SMA screen positive result to families

Recommendation 5.1

Consensus recommendation

Screen positive result should be disclosed to the family within ≤ 2 working days (of notification to healthcare services).

Recommendation 5.2

Consensus recommendation

Screen positive newborns should be offered a clinical review within paediatric neurology/neuromuscular services within ≤ 2 working days, from the time of screen positive disclosure.

Recommendation 5.3

Consensus recommendation

Culturally safe care is required by healthcare practitioners when disclosing screening results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.

Section 6: Assessments required at diagnostic evaluation of the newborn

Recommendation 6.1

Consensus recommendation

The following assessments should be 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* exon 7 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.

Section 7: Provision of information and support for families after confirming the diagnosis of SMA in the (screen positive) newborn

Recommendation 7.1

Consensus recommendation

The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result.

Recommendation 7.2

Consensus recommendation

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 reflect the contemporary care landscape and are nationally consistent.

Recommendation 7.3

Consensus recommendation

Culturally safe care is required by healthcare practitioners when disclosing diagnostic results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.

Section 8: Immediate post diagnostic care for newborns and infants receiving a diagnosis of SMA through a newborn screening program

Recommendation 8.1

Consensus recommendation

For screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset i.e. clinically manifest), a paediatric neurologist should discuss options for immediate treatment with SMN augmenting treatments, with the family.

Recommendation 8.2.

Consensus recommendation

For newborns with diagnostic confirmation of SMA and 1, 2 or 3 *SMN2* copies and who are presymptomatic (i.e. clinically silent), a paediatric neurologist should discuss options for immediate SMN augmenting treatments, with the family.

Recommendation 8.3

Consensus recommendation

In the absence of comparative data, single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended, started within paediatric neurology treatment centre.

Recommendation 8.4.

Consensus recommendation

Newborns with diagnostic confirmation of SMA who are unable to access approved and reimbursed treatments or chose not to be treated 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.

Recommendation 8.5.

Consensus recommendation

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 services).

The Guideline Development Process

Step 1
Defining the need for a Guideline and the 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 67 National Guideline for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand (2024). 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.

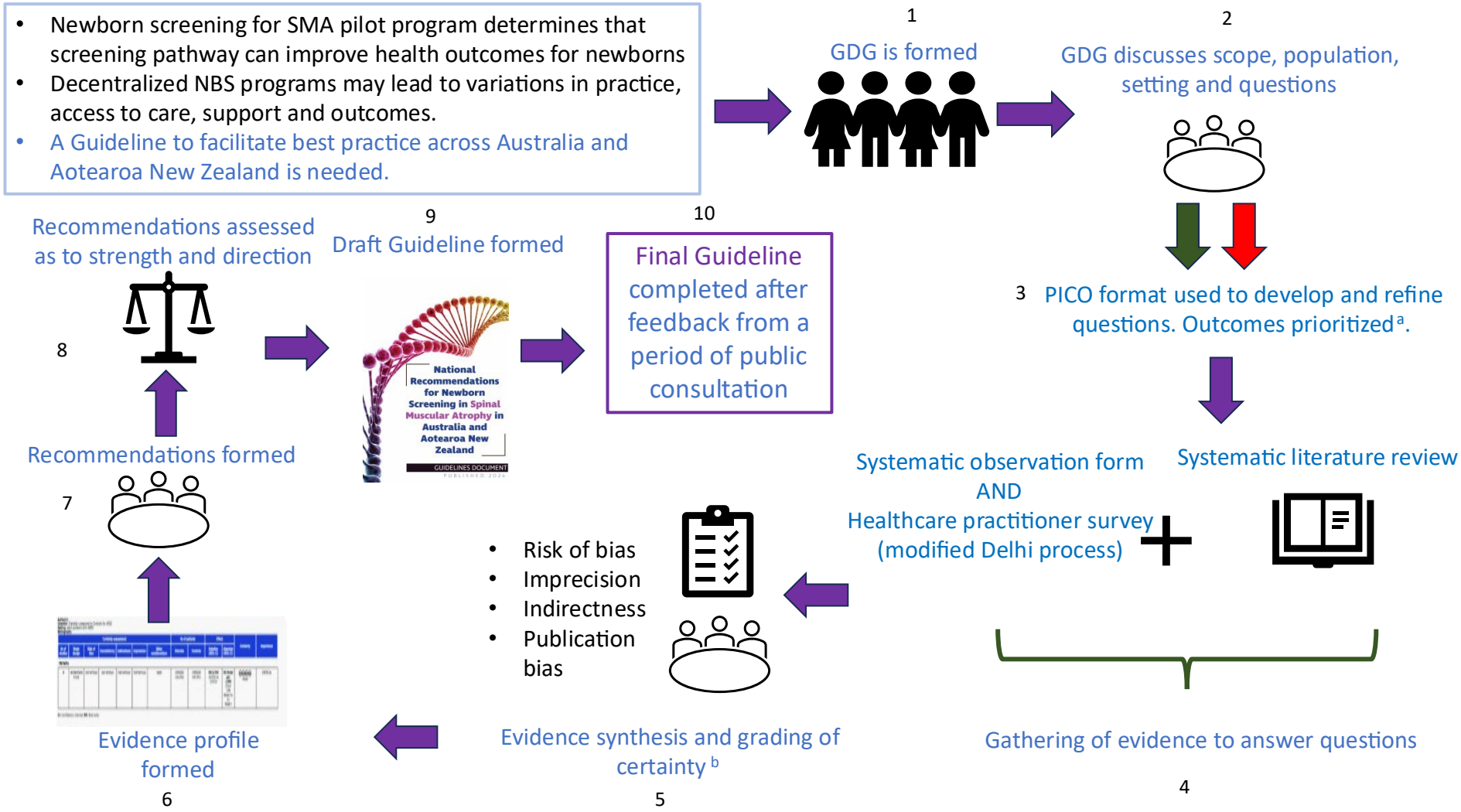


Figure 1. The Guideline development process. A Guideline Development Group (GDG) was formed (1) and met to discuss scope, population applicable settings and broad questions for the Guideline (2). A Population, Intervention, Comparator, Outcome (PICO) format was used to develop, refine questions and prioritise 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 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), accessed through (https://www.unsw.to/nbs-sma). (40, 41)

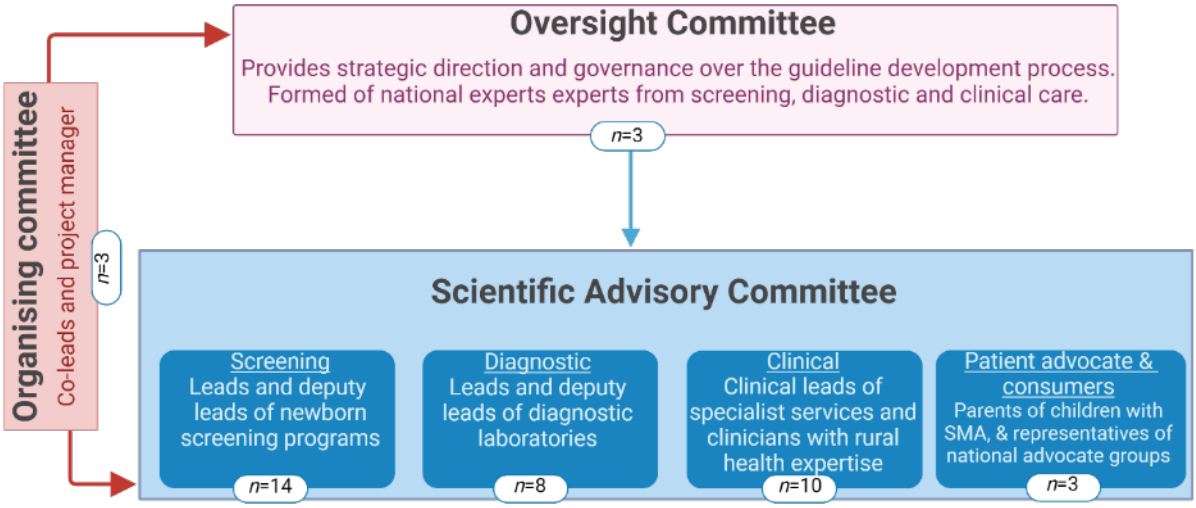


Figure 2. The Guideline Development Group and its governance structure. The oversight committee (*n*=3) was comprised of representatives with national expertise in the areas of screening, diagnosis and clinical care. The Scientific Advisory Committee (SAC) contained leaders within their relevant areas 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.

Table 1. Members of the Guideline Development Group

Name	Discipline/Area of expertise	Affiliation	State/ territory/ country	Role
Didu Kariyawasam	Paediatric Neurologist	Sydney Children's Hospital, Randwick and University of New South Wales	NSW	Co-Lead of Guideline Development Group Organising Committee
Michelle Farrar	Paediatric Neurologist	Sydney Children's Hospital, Randwick and University of New South Wales	NSW	Co-Lead of Guideline Development Group Organising Committee
Christian Meagher	Research Assistant	University of New South Wales	NSW	Organising Committee Project Manager
Natasha Heather	Paediatric Endocrinologist	Auckland City Hospital	NZ	Chair of Oversight Committee and SAC
Kaustav Bhattacharya	Metabolic clinician	Sydney Children's Hospitals Network	NSW	Oversight Committee
Hugo Sampaio	Paediatric Neurologist	Sydney Children's Hospital, Randwick and University of New South Wales	NSW	Oversight Committee
Julie Cini	Patient advocate	Advocacy Beyond Borders	VIC	SAC
Chiyan Lau	Genetic Pathologist	University of Queensland	QLD	SAC
Emilie Mas	Genetics and Molecular Pathology	University of Adelaide	SA	SAC
Linda Burrows	Genetics and Molecular Pathology	SA Pathology	SA	SAC
Mark Greenslade	Clinical Scientist	Auckland City Hospital	NZ	SAC
Raoul Heller	Clinical Geneticist	Auckland City Hospital	NZ	SAC

Richard Allcock	Geneticist	University of Western Australia	WA	SAC
Sandra Divanisova	Chemical Pathology	Auckland District Health Board	NZ	SAC
Simon Carrivick	Endocrinologist	Path West Laboratory Medicine WA	WA	SAC
Alexandra Kay	Pathology	SA Pathology	SA	SAC
Carol Siu	Genetic Pathologist	Women's and Children's Hospital, Adelaide	SA	SAC
Dianne Webster	Clinical scientist	Auckland City Hospital	NZ	SAC
Enzo Ranieri	Newborn Screening Lead	Sydney Children's Hospitals Network	NSW	SAC
Francesca Moore	Clinical Biochemistry	Path west Laboratory Medicine WA	WA	SAC
Gabrielle Crisp	Newborn Screening	Queensland Health	QLD	SAC
James Pitt	Newborn Screening	Victorian Clinical Genetics Services	VIC	SAC
Lawrence Greed	Clinical Scientist newborn screening	Path West Laboratory Medicine WA	WA	SAC
Mark De Hora	Biochemical Genetics	Auckland City Hospital	NZ	SAC
Ronda Greaves	Biochemical Genetics	Murdoch Children's Research Institute	VIC	SAC
Tiffany Wotton	Newborn Screening	Sydney Children's Hospitals Network	NSW	SAC
Urs Wilgen	Genetic Pathologist	Queensland Health	QLD	SAC
Veronica Wiley	Paediatric biochemist	Sydney Children's Hospitals Network	NSW	SAC
Anita Cairns	Paediatric Neurologist	Children's Hospital Queensland	QLD	SAC
Damian Clark	Neurologist	Women's and Children's Hospital	SA	SAC
Eppie Yiu	Paediatric Neurologist	Royal Children's Hospital, Melbourne	VIC	SAC
Gina O'Grady	Paediatric Neurologist	Auckland City Hospital	NZ	SAC

Maina Kava	Paediatric Neurologist	Perth Children's Hospital	WA	SAC
Tyson Ware	Paediatric Neurologist	Royal Hobart Hospital	Tasmania	SAC
Corin Miller	Rural Generalist-Paediatrics	Southeast Regional Hospital Bega and Djing.gii Gudjaagalali (Child Stars) Eden	NSW	SAC
Fiona Tolich	Patient Advocate	Not applicable	NZ	SAC
Chauntel Wedlake	Patient Advocate	Not applicable	NZ	SAC

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

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

The recommendations apply to all newborns / infants undergoing newborn screening for SMA and their families. This is inclusive of Aboriginal, Torres Strait and Pacific Islander, Māori and other First Nation peoples, and culturally and linguistically diverse (CALD) communities. However, the Guideline Development Group have noted barriers to health access for these communities prevent health equity. Factors include but are not limited to lack of transport, waiting times, and lack of culturally appropriate health information and materials. (42) Therefore, specific consideration should be given to create a more equitable system for First Nations and CALD 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 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 1st 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 **P**opulation, **I**ntervention, **C**omparator, **O**utcome(s) framework (Table 2). Where systematic reviews existed, these were used preferentially to individual studies.

Table 2. *P*opulation, *I*ntervention, *C*omparator, *O*utcome(s) framework and eligibility criteria for studies included in the systematic reviews.

Clinical Question	Population(s)	Intervention or Exposure	Comparator	Outcome	Study Design
Inclusion	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.

Exclusion	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). 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.
NI	No intervention.
NO	Not an outcome.
NSPD	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 ≥ 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 ≥ 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.

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. The Newcastle-Ottawa Quality Assessment tool for cohort studies and case control studies was used to determine the risk of bias and quality of individual (predominantly nonrandomised)

studies across the domains of selection, comparability and outcome. (51) Two researchers independently scored 60% of the studies and concordance of overall quality rating was observed in 100% of studies.

2. **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. (20, 45, 52) 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.). (53) 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 practice standard 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. Implementation guidance was formulated to describe the how, who, where, what and when an intervention or recommendation should occur and was not directly linked to evidence.

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 recommendation	Is an actionable recommendation based on clinical expertise, expert opinion and available evidence, and formulated using the PICO format.
Practice standard	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 Guidance	Describes the how, who, where, what and when related to implementing a recommendation and may not have a clear link to evidence.
Research Guidance	Given when there is insufficient evidence to determine if an intervention is either beneficial or harmful. When an "only in research" recommendation is given, the panel recommends that the intervention should only be considered within clinical research settings within randomised clinical trial or observational study with appropriate ethical approval. In any other circumstance, the intervention is not recommended.

The Organising Committee used an iterative process, using evidence to decision (EtD) framework to move from evidence to forming evidence and consensus 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). (54)
- Conceptual and ethical frameworks (e.g., AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research, 2020; (55) International Classification of Functioning, Disability and Health; (56) World Health Organisation Screening Guidelines). (57)
- Conventions (e.g., United Nations Convention on the Rights of the Child, 1989). (58)

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. (59, 60)

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. (Table 5.) (61, 62)

Table 5. Grading the strength of evidence-based recommendations within the Guideline (46)

Grade and direction of recommendation	Description and body of evidence matrix
Strong for (orange)	Moderate to high certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it.
Strong against (red)	Moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
Conditional for (grey)	Low certainty evidence suggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.
Conditional against (black)	Low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications

Consensus recommendations

Evidence generated through the systematic review (scholarly literature that could not generate answers to the research questions using a PICO format, was absent or of insufficient certainty), the systematic observation forms and the healthcare practitioner (modified Delphi) survey were combined to form consensus recommendations (characterised in blue). The supporting evidence from these three data gathering streams were presented in an evidence summary for each recommendation and the GDG considered areas fulfilling aspects of consistency, generalisability, impact and support from experts. The priority of the consensus recommendation (high, moderate or low) was based on domains of evidence consistency, impact, acceptability, values and preferences, equity implications, feasibility, cost effectiveness and resources.

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 3rd 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 7th 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 12th August 2024 and closed on 23rd 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) A version of the public consultation submission summary with submission deidentified is found in Appendix B

Table 6. 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
The National Aboriginal Community Control Health Organisation
Queensland Aboriginal and Islander Health Council

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 23rd 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 and endorsed the Guideline (Table 7).

Table 7. Organisations and peak bodies endorsing the Guideline

Organisation name
Australian and New Zealand Child Neurology Society
SMA Australia
SMA New Zealand
Advocacy Beyond Borders
Patient Voice Aotearoa
Human Genetics Society of Australasia
The Paediatric Society of New Zealand
Paediatric Neurology Clinical Network of the Paediatric Society of New Zealand
Rare Disorders New Zealand
Royal Australasian College of Physicians

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). (63)

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.

Understanding how the recommendations were developed

Each recommendation includes a brief description of benefits and risks, certainty of evidence and other issues related to consumer preferences (Evidence to Decision), how these factors were weighed up (Rationale), practical information regarding the Recommendation and specific considerations encompassing (Practical Information, Future directions or Strategies to Promote Implementation of the Recommendation) and references for the Recommendation (References).

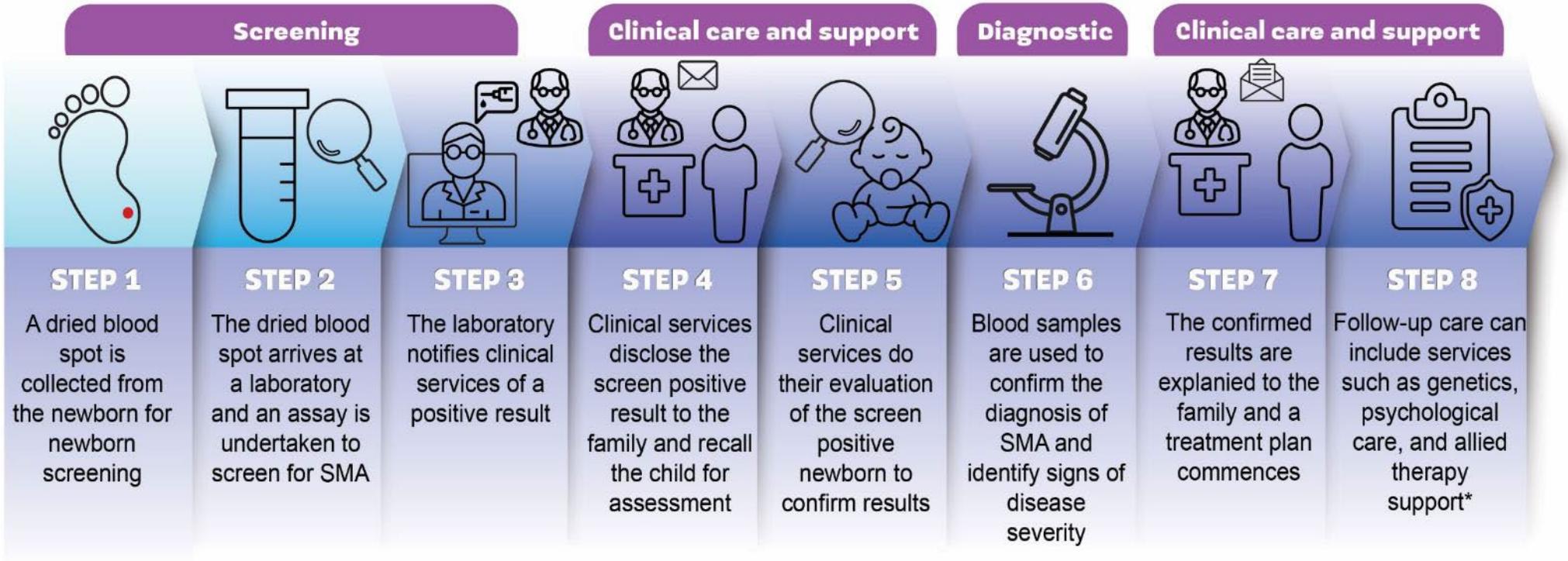


Figure 3. The newborn screening pathway for spinal muscular atrophy as encompassed by the Guideline. The domains in the Guideline pertain to screening, diagnostic, clinical care and support. * Healthcare practitioners that work within the multidisciplinary team vary dependent on jurisdiction and may 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 (≤ 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.

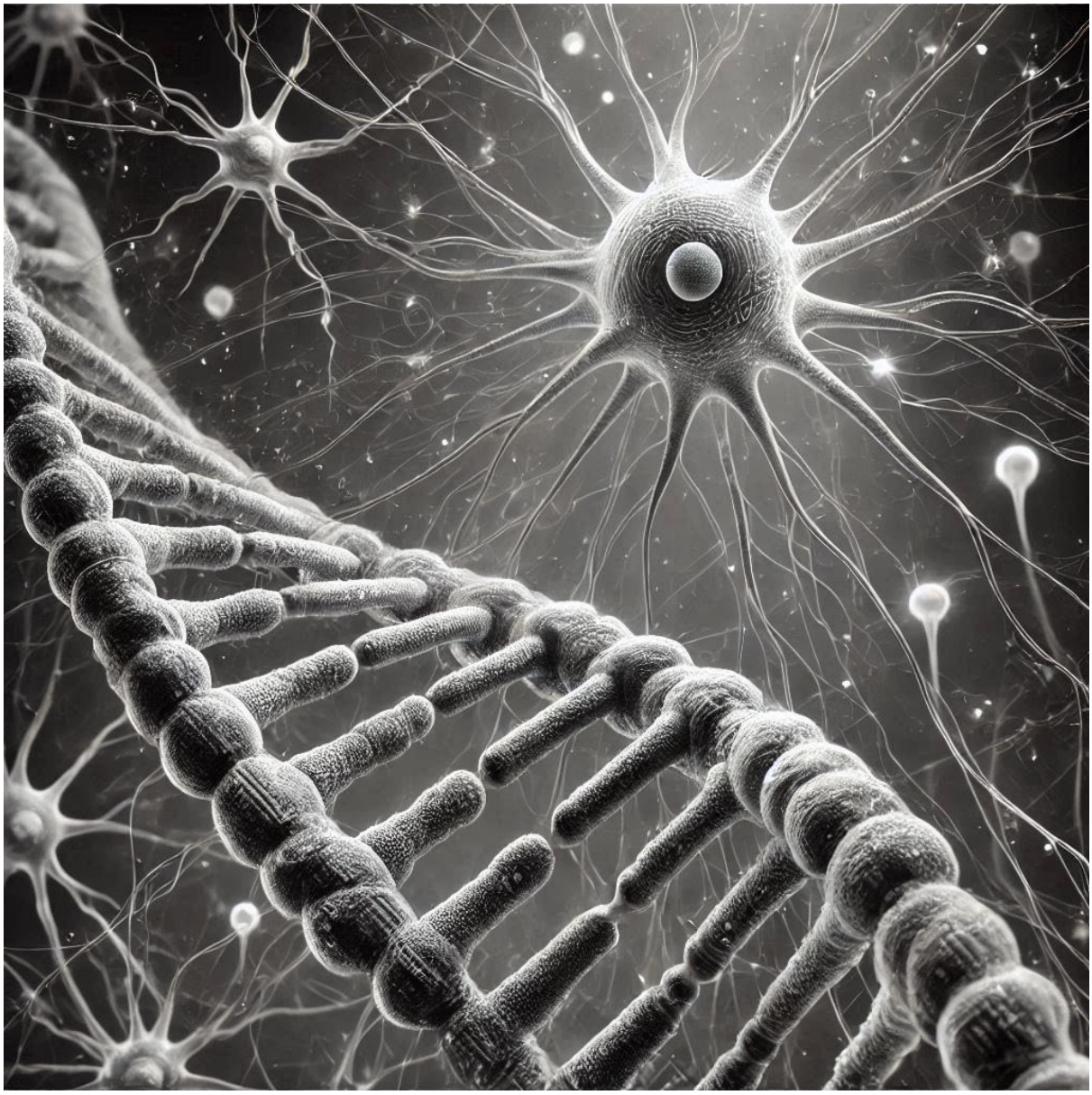
The definition of families

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. (64) 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. (65, 66) 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. (67) 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. (67) The pattern of weakness is usually symmetrical and length dependent, affecting legs before arms. (68) Associated consequences of the condition include respiratory and feeding difficulties, progressive neurodisability, and high medical and supportive care needs. (69) SMA has a spectrum of severity and a predominant childhood onset. (70)

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. (70, 71)

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). (72) 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, 68, 73) whilst in the latter, individuals generally retain ambulation skills but may find higher motor tasks challenging and/or fatiguing. (74)

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

Type	Age of Onset	Clinical features and survival
SMA TYPE 0 *(Congenital, Prenatal SMA)*	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.
SMA Type I *(Severe infantile acute; Werdnig-Hoffmann disease)*	Birth to six months	Cannot sit independently, difficulty breathing. Without treatment 9 0% of children do not survive beyond 2 years of age.
SMA Type II *(Infantile chronic)*	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.
SMA Type III *(Juvenile, Kugelberg-Welander disease)*	After 18 months	May stand or walk, but with progressive weakness. Wheelchair assistance usually needed in later life. Normal life expectancy.
SMA Type IV *(Adult-onset)*	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.). (75) 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. (76)

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. (76, 77)

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. (76) The majority of transcripts produce a truncated, unstable protein leaving it vulnerable to degradation. (78, 79) *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, 80-87) *SMN2* copy number is generally considered the best predictor of age of onset and severity of the condition.

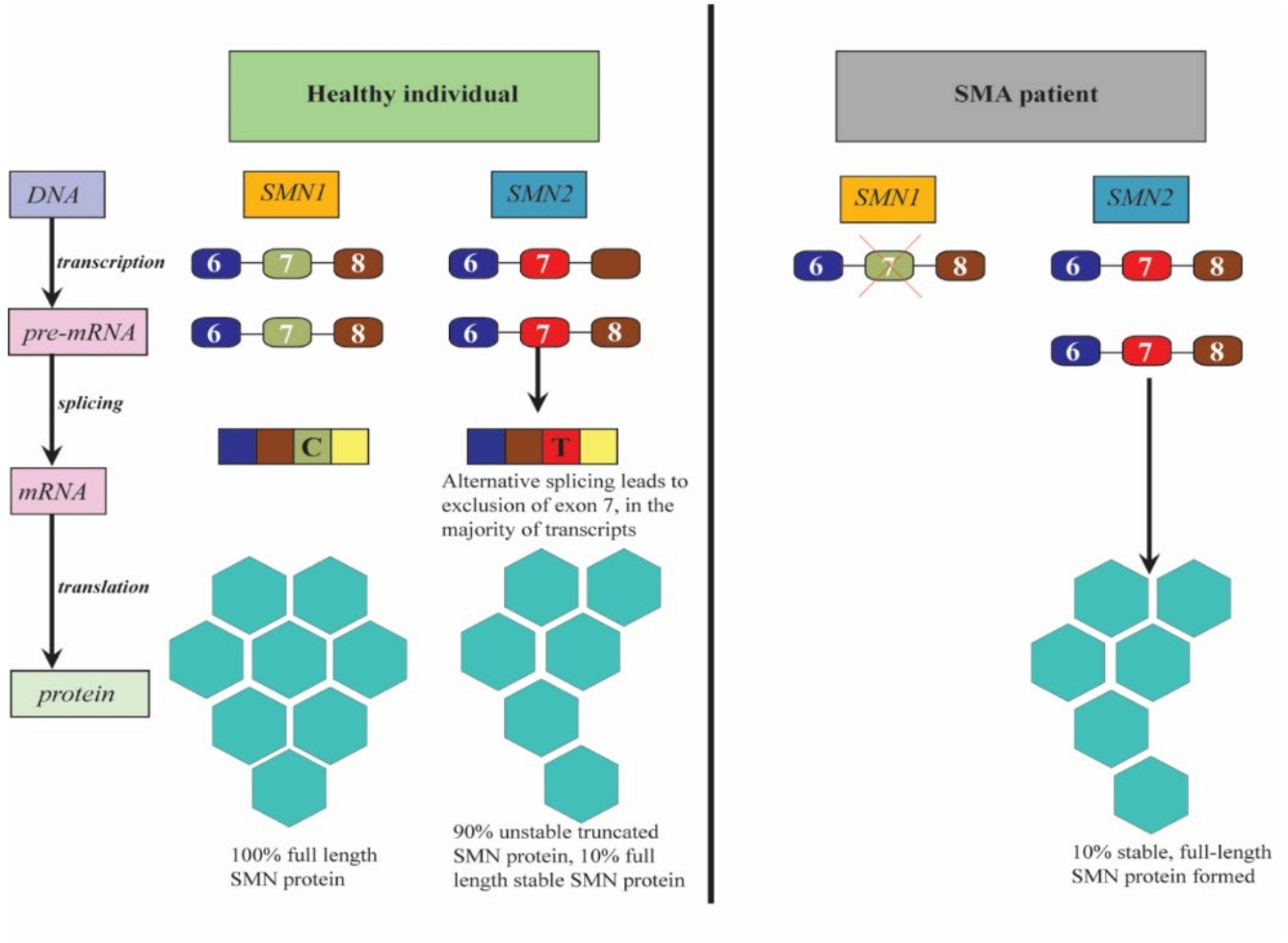


Figure 4. The genetics of spinal muscular atrophy. In individuals without SMA, *SMN1* produces 100% of full-length SMN protein. In *SMN2* the exchange of one nucleotide allows for splicing out of exon 7 in *SMN2* resulting in a shortened pre-mRNA transcript that produces mostly shortened form of SMN 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. (88)

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)

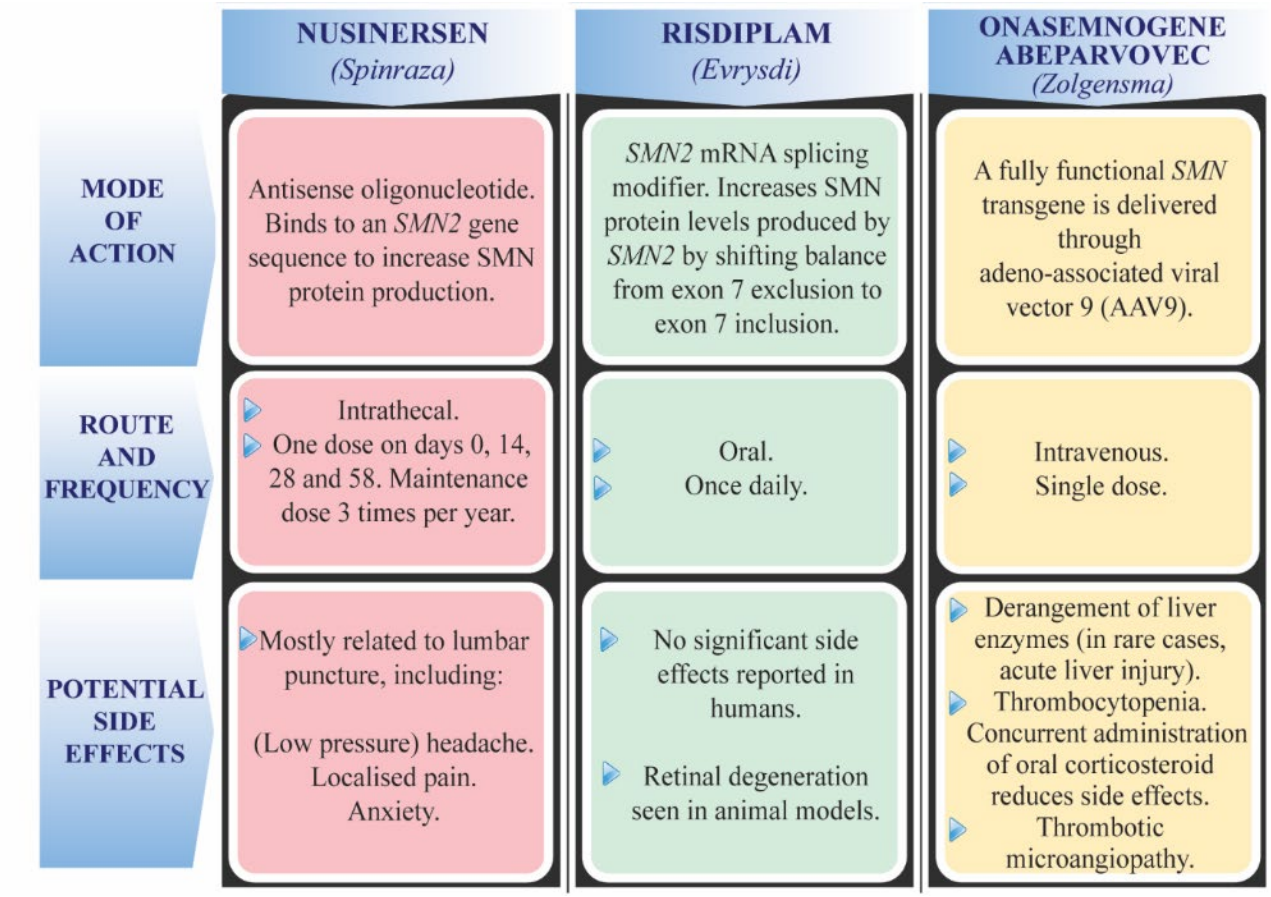


Figure 5. Approved SMN augmenting treatments for spinal muscular atrophy across Australasia. Approvals and reimbursements vary across Australasia and are dependent on age, *SMN2* copy number and clinical status (symptomatic or presymptomatic status). The potential side effects listed are not exhaustive 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. (89)

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. (90) 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. (81, 91) 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. (92) 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, 93)

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*, (57) 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.

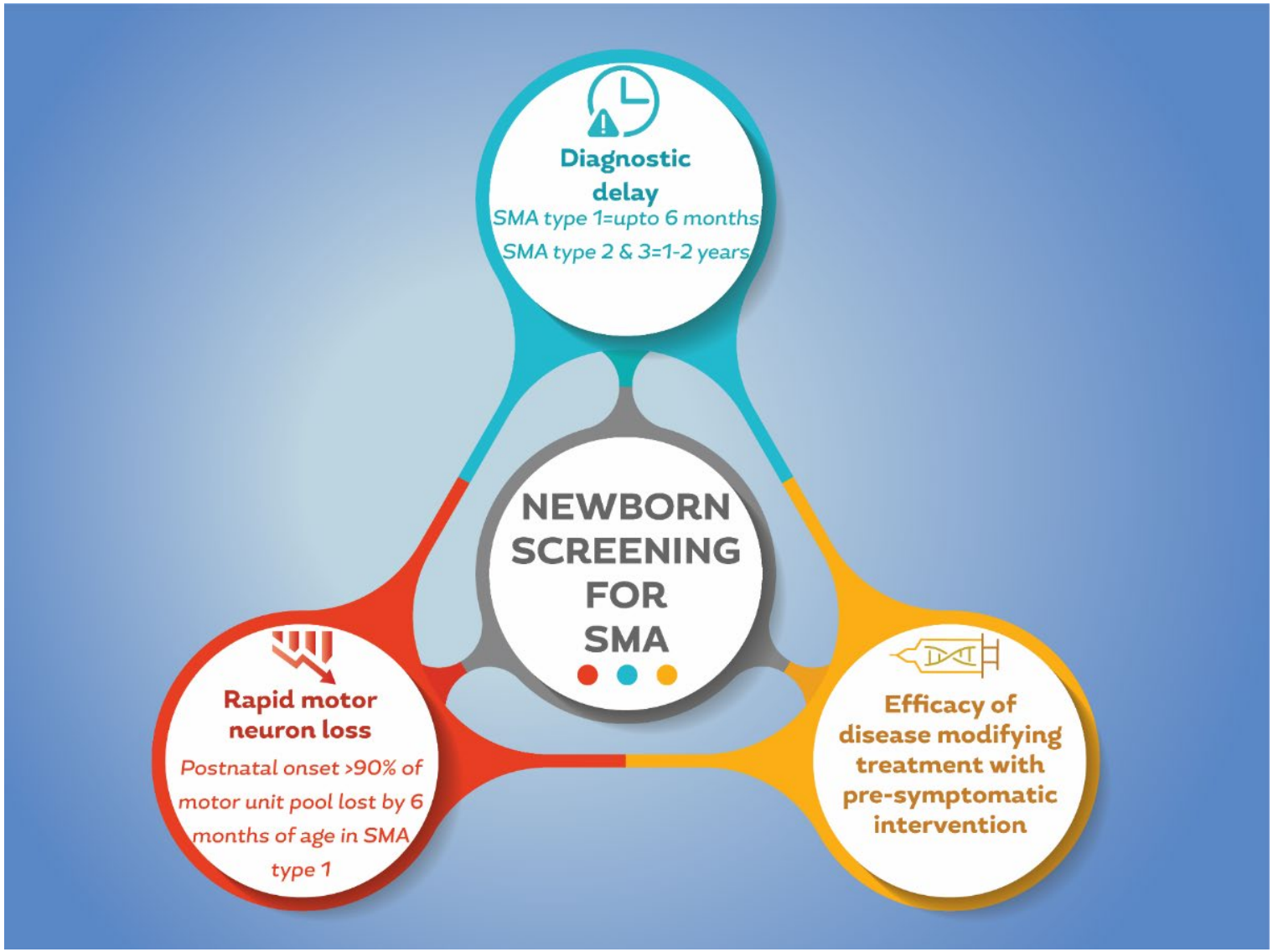


Figure 6. The rationale for newborn screening for spinal muscular atrophy.

The global perspective of newborn screening in SMA and where Australia 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). (94) 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. (95) In Europe, around 65% of newborn babies are screened for SMA in the newborn period, (96) 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, 97)

In Australia and Aotearoa New Zealand, newborn screening has high participation rates (around 99% and 97.9% respectively) (34, 98) 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 1st 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, 99) 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, (100), and one year later, Te Whatu Ora (Health New Zealand) endorsed the same for its national newborn screening program (on 14th 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. (101, 102)

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. (103) 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. (104) 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. (105)

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, 105) 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. (106) 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^2) with wide diversity in health literacy, socioeconomic circumstances, language, and cultural perspectives. (107) 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. (103)

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. (108) 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

Section 1

Screening for *SMN1* as part of (newborn) screening in SMA

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. (109) Population-based screening for SMA is considered feasible, fast and cost effective, using high throughput nucleic acid-based methods to detect *SMN1* exon 7 absence. (110, 111) Whilst pathogenic variants in exon 1, 3 and 6 of *SMN1* are noted in individuals with SMA, leveraging the fact that 95% of individuals with SMA have an absence of exon 7, *SMN1* assays have generally targeted this genetic change, with rare studies targeting exon 7 ***and*** exon 8 loss within *SMN1*. (112) Accordingly, these methods do not screen for newborns with *SMN1* exon 7 deletion in one allele and a pathogenic sequence variant in exon 7 of the other *SMN1* 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. (113) Further, DNA extracted from dried saliva spots, (114) as the substrate for *SMN1* 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 *SMN1* i.e. homozygous deletion of exon 7 on *SMN1*.

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 *SMN1*. The incidence of SMA has been ascertained as between 1 in 6059 to 1 in 28,137. (115, 116) 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 *SMN1* 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, 117) Other methodologies include but are not limited to restriction fragment length polymorphism analysis (RFLP), (118) high resolution melting analysis, (119, 120) multiplex ligation probe amplification, (121) DNA tandem mass spectrometry, (122) modified competitive oligonucleotide priming PCR (mCOP-PCR) (123) and DNA sequencing. (124). 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. (125) Accordingly, the GDG acknowledges that health jurisdictions in Australia and Aotearoa New Zealand may utilise varying (*SMN1*) assays for SMA newborn screening purposes.

Some screening programs for SMA leverage multi-tiered processes to further test for the absence of *SMN1* 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 *SMN1* deletion using a range of methodologies from ddPCR (126-128) through to MLPA (129) and RFLP-PCR (120, 123, 130). Rarely, established newborn screening programs use three tiers of screening for *SMN1* to look for exon 7 variants caused by hybrid genes in screen positive children and then sequencing *SMN1* to reconcile differences between first and second tier assays. (131)

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 *SMN1* (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 *SMN1* is 100% across the available literature. From a whole of population level, the sensitivity of *SMN1* screening assays are predicted to be 95-98% due to the presence of newborns with a compound heterozygous *SMN1* genotype or biallelic pathogenic variants in exon 7 on *SMN1* (132). 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, 95, 122, 124, 133, 134) 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), (135) sickle cell disease, (136) and sensorineural hearing loss. (112) 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. (93, 137) 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, 138) 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. (130)

Recommendation 1.1

Evidence based: strong recommendation for

We recommend that newborn screening for SMA should be performed on the routine newborn dried blood spot with absence of exon 7 on *SMN1* as the target analyte.

ADDITIONAL INFORMATION

This recommendation is developed with an evidence-based framework. This is a high priority recommendation based on substantial benefits for the affected population. Benefits outweigh harms for almost all affected children. All or nearly all affected children and their families would likely want this option. Screening assays may vary but all should target the absence of exon 7 on *SMN1* which is the genotype for 95% of individuals with SMA.

RESEARCH EVIDENCE

Population: Newborns, infants and children with SMA. Birth up to 18 years.

Intervention: Newborn screening for SMA using exon 7 on *SMN1* as the target analyte.

Comparator: Children diagnosed with SMA through (non) newborn screening pathways including through prenatal screening, clinical referral of symptoms.

Outcome(s): Identifying children at risk of SMA

Summary

Exon 7 on *SMN1* is used as the target analyte on dried blood spots to screen for children with SMA.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Clinical (non-NBS) diagnosis of SMA	Newborn Screening	**Certainty of the evidence** (Quality of evidence)	**Summary**
Identifying children at risk of SMA[1]	Based on data from 3155450 participants in 46 studies			**Very low** Due to very serious risk of bias, serious risk of imprecision and publication bias, and very serious inconsistency[2]	We are uncertain whether newborn screening where exon 7 on the dried blood spot is the target analyte increases or decreases true screen positive results for SMA.

Certainty of evidence

Step 1: Are the studies you took randomized?

Study type: Observational (non-randomized)

Step 2: Factors that might cause rating down certainty

Risk of Bias: very serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Inconsistency: very serious.** Results variable across studies with 8 studies and 32 children having false positive or false negative results; **Indirectness: no serious.** generalisable to the population in question; **Imprecision: serious.** Large number of patients across multiple studies however narrative summary conducted and estimates not precise; **Publication bias: serious.** Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review.

Step 3: Factors that might cause rating up certainty

None

Step 4: Certainty level: Confidence in estimates reflecting the true values of target population?

Certainty level GRADE: Very low

Short summary of assessments: Due to very serious risk of bias, serious risk of imprecision and publication bias, and very serious inconsistency

Graphical representation

Results favour the comparator	Results favour the intervention
Children diagnosed with SMA through (non) newborn screening pathways including through prenatal screening, clinical referral of symptoms.	Newborn screening for SMA using exon 7 on SMN1 as the target analyte

Expected results with the intervention

Newborn screening for SMA using absence of exon 7 on SMN1 as the target analyte on dried blood spot	High uncertainty	Very low 

Summary

Evidence for this recommendation come from 46 observational (non-randomised) studies of 3155450 children undergoing (newborn) screening for SMA using exon 7 as the target analyte on dried blood spots. Of these, 330 children have been identified with SMA with 295 children confirmed to have the condition.

EVIDENCE TO DESCISION

Priority of problem:

SMA is a serious and life-threatening condition affecting 1 in 10000 children. Early identification of at-risk infants through established newborn screening programs leads to early diagnosis and intervention which is known to improve survival, motor function, quality of life and reduce comorbidities.

Benefits and harms: Substantial net benefits

Large potential for benefit due to development of a newborn screening process that will identify all children with homozygous deletion of exon 7 (occurring in 95% of population with SMA) with a newborn period. There is a risk of 5% of children *not* being identified by these screening methods and research studies.

Certainty of evidence:

For key outcome measures of identifying children at risk of SMA, the GDG considers the evidence to be of very low certainty (please see Research evidence)

References:

Boemer et al. 2021, (139) Singh et al. 2023, (140) Groulx-Boivin et al. 2024, (121) Boemer et al. 2019, (141) Tesorero et al. 2023, (136) Shinohara et al. 2019, (123) Olkhovych et al .2023, (142) Wallace et al. 2023, (143) Fonseca et al. 2024, (144) Kimizu et al. 2023, (145) Kernohan et al. 2022, (129) Oliveira-Netto et al. 2023, (146) Lakhotia et al. 2022, (147) Kumar et al. 2021, (148) Wong et al. 2024, (149) Tavares et al. 2021, (125) Sonehara et al. 2023, (130) Kraszewski et al. 2018, (93) ArRochmah et al. 2017, (150) Gailite et al. 2022, (151) Elkins et al. 20222, (152) Mikhalchuk et al. 2023, (120) Kucera et al. 2021, (153) Kato et al. 2015, (154) Niba et al. 2019, (118) Czibere et al 2020, (110) Wijaya et al. 2019, (155) Dobrowolski et al. 2012, (156) Vill et al. 2019, (157) Vill et al. 2021, (158) Er et al. 2012, (119) Kariyawasam et al. 2020, (12) Noguchi et al. 2022, (159) Hale et al. 2021, (131) Kay et al. 2020, (115) Pyatt et al. 2007, (160) Gutierrez-Mateo et al. 2019, (135) Vidal-Folch et al. 2018, (117) Kiselev et al. 2024, (137) Liu

et al. 2016, (161) Hashimoto et al. 2023, (162) Lin et al. 2019, (122) Adams et al. 2021, (163) Abiusi et al. 2023, (116) Niri et al. 2023 (95), Baker et al. 2022, (127) Kubar et al. 2023, (164) Shum et al. 2023, (124) Sawada et al. 2022, (165) Chien et al. 2017, (29) McMillan et al. 2021, (112) Muller-Felber et al. 2023, (133) Lee et al. 2022, (138) Kemper et al. 2018, (94) Matteson et al. 2022, (126) Prior et al. 2010. (109)

Values and preferences: No variability in value or preference expected.

The GDG believed that all stakeholders would agree with this recommendation. One study has shown that consumers place a high value on newborn screening for SMA (where target analyte is homozygous deletion of exon 7 on SMN1)

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of specific assays however, adding NBS for SMA where target analyte is homozygous deletion of exon 7 on *SMN1* adds an estimated USD 1 to the cost of the NBS assay. (166)

Equity: Important issues, or potential issues not identified.

There are no equity issues identified. Two studies using an implementation study design showed that newborn screening for SMA using target analyte improves health equity across Australia. (10, 12)

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. One study determines that this screening process is acceptable to healthcare professionals and consumers. (11)

Feasibility: Some important issues identified

The GDG acknowledges that feasibility issues may arise including the need for specific screening equipment, processes and personnel to conduct screening assays. However, the GDG agree that within the Australasian context, it is feasible to implement population wide screening for SMA using exon 7 as the target analyte as determined in scoping programs run within the two countries.

JUSTIFICATION

When moving from evidence to the strong recommendation for identifying children at risk of SMA using the target analyte of exon absence on *SMN1* on dried blood spot, the GDG considered several factors. The GDG acknowledged the uncertainty of evidence and other potential contextual barriers to implementation including issues of feasibility and costs and the potential risks of 5% of the (affected) population not being able to be identified through this methodology. Ultimately, the GDG thought that the theoretical benefit targeted to identifying the majority of affected children outweighed risks and the uncertainty of evidence, alongside other contextual factors including the potential to improve equity of access to diagnosis of a rare genetic condition, the likelihood that this Recommendation would be acceptable to nearly all consumers, and in line with their preferences and values.

Specific considerations: This Recommendation applies to all children in Australasia including from culturally and linguistically diverse backgrounds and those who identify as First Nations peoples (i.e. Aboriginal, Torres and Pacific Islander, Māori peoples). The GDG encourage research to clarify uncertainties especially in jurisdictions where there are barriers to feasibility and also ongoing efforts to enable the identification of all children at risk of SMA (beyond those with the commonest *SMN1* genotype).

Recommendation 1.2

Consensus recommendation

The screening method selected by the screening program should have a sensitivity of ≥ 95% for the detection of S*MN1* exon 7 absence (0 *SMN1* copies) using suitably validated quantitative and qualitative assays.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on substantial benefits for the affected population.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit due to development of a newborn screening process that will identify all children with homozygous deletion of exon 7 (occurring in 95% of population with SMA).

There is a risk of 5% of children *not* being identified by these screening methods. Given the seriousness of harm from a false positive and false negative result, the GDG agreed that assays should have a minimum of 95% sensitivity and 100% specificity.

Certainty of evidence:

Six cohort studies identified with variability in sensitivity of assays and a range of qualitative and quantitative methods used. However, the sensitivity of most methods (qPCR, ddPCR) employed for NBS for SMA are 100% for exon 7 absence on *SMN1*, however compound heterozygotes with SMA will not be identified through this methodology so sensitivity changes to 95%.

References: Lin et al. 2019, (122) Niri et al. 2023, (95) Shum et al. 2023, (124) Muller-Felber et al. 2023, (133) Zhi et al. 2023, (134) Kariyawasam et al. 2020. (12)

Range of qualitative and quantitative *SMN1* assays used to screen for SMA on dried blood spots, including but not limited to restriction fragment length polymorphism analysis (RFLP), high resolution melting analysis, multiplex ligation dependent probe amplification, luminex genotyping, DNA sequencing, quantitative real time PCR (qPCR), with no head-to-head comparative studies to evaluate one methodology over another.

References: Boemer et al. 2021, (139) Tesorero et al. 2023, (136) Kernohan et. 2022, (129) Kraszewski et al. 2018, (93) Chien et al 2017, (29) Sawada et al. 2022. (165)

Values and preferences: No variability in value or preference expected.

The GDG believed that in line with expert consensus, all stakeholders would agree with this recommendation to optimise the accuracy of screening assays.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of specific assays although there is cost benefit analysis of NBS for SMA (linked to treatment) as a program of activities (Shih et al.) Further, the GDG acknowledges that there are no head-to-head comparisons on the cost effectiveness of different methodological assays used for screening.

Equity: Important issues, or potential issues not investigated.

There are no equity issues identified. Health equity may be improved by the screening test with this recommended sensitivity (Kariyawasam et al 2020). (12)

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders.

Feasibility: Some important issues identified

The GDG acknowledges that feasibility issues may arise including the need for specific screening equipment, processes and personnel to conduct screening assays. However, defining a minimum sensitivity whilst considering a range of methods (quantitative and qualitative) will allow flexibility of assays whilst maintaining accuracy, to increase the feasibility of this Recommendation across health jurisdictions.

RATIONALE

There are substantial benefits for implementing this recommendation with consensus from experts and evidence from the literature pertaining to minimum sensitivities for validated assays. Providing a recommendation that allows for adaptability in quantitative and qualitative assays utilised is important to optimise feasibility across health jurisdictions. Current methods cannot identify children with SMA not related to absence of exon 7 on *SMN1* and this recommendation may need to be revised based on evolving screening technologies.

Specific considerations (Future directions): 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. This Recommendation will need to be reviewed and refined according to the changing screening landscape.

Practice standard 1.2.1

As part of newborn screening processes, **s**creen positive samples (0 *SMN1* copies) should immediately be repeated on the same dried blood spot.

Recommendation 1.3.

Consensus recommendation

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).

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on substantial benefits for the affected population in reducing the time to diagnosis and treatment.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit due to expediting access to diagnosis and treatment that is known to maximise clinical benefits for the child.

Certainty of evidence:

No studies were identified that addressed this recommendation.

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

There are no equity issues identified.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders.

Feasibility: No important issues identified

There are likely no important issues identified.

RATIONALE

There are substantial benefits for implementing this recommendation. SMA is considered a neurogenetic emergency for many children (especially those with 2 *SMN2* copies where disease onset and progress can be fulminant, with 40% of children presenting with signs and symptoms of SMA at the time of referral to clinical services). Expedient *SMN1* communication to clinical services unlocks next steps in pathway for diagnostic confirmation and timely therapeutic decision making.

Implementation Guidance

1.3.1. 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.

1.3.2. 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.

1.3.3. If blood transfusion in the neonate is considered, the dried blood spot should be taken prior to transfusion aligning with processes with the National Policy Framework for Newborn Screening.

1.3.4. 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.

Section 2

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 clinical onset. (27, 87, 167) 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 this knowledge 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). (168)

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. (169, 170) 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. (170-173), 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 the magnitude of benefit to support instigation of SMN augmenting treatments but is being undertaken in some studies. (138) 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, compared with initiating this as part of the diagnostic process.

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). (138, 139, 158, 174). 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. (158)

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. (81, 93, 99) This helps to minimise treatment delays to reduce the exponential rate of motor unit loss, (81, 175) 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. (81, 99)

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. (168) *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. (168, 176-178) *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. (116) 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. (89, 131)

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.* (131) 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. (93, 131) 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, 179)

When *SMN2* copy number 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. (131)

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* copy number. (180) Methodologically, *SMN2* copy number can vary dependent on the methodology (digital droplet PCR, MLPA or qPCR) used in up to 50% of cases. (179, 181) 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* ≤ 4 due to inherent technological challenges in maintaining accuracy in *SMN2* copy number estimation with *SMN2* copy numbers > 4. (32)

Within Australasia, the newborn screening process may differ with some jurisdictions concurrently analysing *SMN1* and *SMN2* number on the dried blood spot (reporting only those with *SMN2* copies < 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.

Recommendation 2.1.

Consensus recommendation

SMN2 copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a moderate priority recommendation based on substantial benefits for the affected population informing the necessity, pace and modality of therapeutic intervention required, and as such will be updated when new evidence becomes available that is likely to impact its strength.

EVIDENCE TO DECISION

Benefits and harms: Moderate net benefits

Moderate potential for benefit due to expediting access to treatment, to optimise clinical benefits. *SMN2* copy number is the leading prognosticator of SMA disease severity. Whilst incorporating *SMN2* copy number testing on the same dried blood spot as *SMN1* testing, is not required to identify newborns screening positive for SMA, it 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 in Australasia). Harms include the fact that *SMN2* assays are imprecise beyond a certain copy number i.e. *SMN2* copy number > 3 and basing treatment decisions prior to diagnostic confirmation may cause harms to the child.

Certainty of evidence: 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*. 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. This variability in practice is replicated across the international landscape, with the majority of programs incorporating *SMN2* copy number into newborn screening activities where 44 observational studies incorporated *SMN2* as second tier screening for all newborns with absence of *SMN1* on first tier analysis. In 11 studies, *SMN2* copy number identification was part of the confirmatory (diagnostic) process.

References: Abiusi et al 2024, (32) Hale et al. 2021. (131)

Values and preferences: Variability in value or preference expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, for families and many healthcare professionals providing post diagnostic care, the GDG acknowledges that *SMN2* copy number is important for shared decision making in terms of how quickly to treat.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

Equity issues include the fact that some jurisdictions will incorporate *SMN2* copy number into screening algorithms whilst others will depend on the diagnostic process. This may lead to variabilities in health outcomes for children within Australasia.

Acceptability: Some important issues identified

The recommendation is likely to have varied acceptability. For many NBS laboratories, this prognostic information will be considered outside of the true scope of screening which is to identify children with increased risk of the condition.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that not all jurisdictions will have the capacity or resources to perform *SMN2* copy number as part of screening from an equipment, personnel and process standpoint. 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.

Specific considerations (Strategies to promote implementation of the Recommendation): The systematic evidence shows the technical challenges in determining *SMN2* copy number, especially for children with *SMN2* copy number ≥ 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. 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 will be essential to implement *SMN2* copy number accurately within newborn screening programs across Australasia.

RATIONALE

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, with scope to perform this within the diagnostic framework. This Recommendation was therefore considered a moderate priority.

Implementation Guidance

Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.

Recommendation 2.2.

Consensus recommendation

Newborn screening programs should establish a clinical referral pathway that includes simultaneous early notification of a screen positive result to a paediatric neurology specialist and local healthcare practitioner.

ADDITIONAL INFORMATION:

Newborn screening programs have an established notification strategy that involves verbally notifying a nominated healthcare practitioner (usually general practitioner, obstetrician, neonatologist, maternity nurse or paediatrician) on the child's dried blood spot demographics. This recommendation is high priority and seeks to form a coordinated plan to also notify the nominated healthcare practitioner and a designated neurology specialist of the screen positive

result. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit due to expediting access to diagnosis and treatment that is known to maximise clinical benefits for the child. Notifying the paediatric neurologist is important as the treatment landscape is fast evolving and families need to understand and be able to make decisions based on current available evidence. The notification of a paediatric neurologist also allows for children to be managed expediently within a specialist centre, which is a pre-requisite for accessing approved and reimbursed treatments in Australasia.

Certainty of evidence: 5 observational studies showed that there was variability in who receives the screening result between jurisdictions, but in the majority, the person of contact is a designated paediatric neurologist working in a specialist referral centre.

References: Kariyawasam et al. 2020, (12) D'Silva et al 2022, (10) Boemer et al. 2019, (141) Muller-Felber et al. 2023. (133)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, one observational study did reflect on parents' experiences of NBS for SMA and the value of expedient communication and access to specialists with the knowledge to counsel on the ramifications of a screen positive diagnosis, answer questions as to next steps and therapeutic plans (Kariyawasam et al. 2020). (12)

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Some important issues, or potential issues.

Equity of access to expert knowledge through specialist input is considered important for the coordination, management, care and support of children with rare conditions such as SMA.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. As symptoms can rapidly emerge and progress in some newborn with SMA, screening results relayed verbally and through

written means to clinical experts (usually neurology specialists) pre-identified within each healthcare jurisdiction, reduce time to appropriate treatment, care and support which has been valued in families undertaking newborn screening for SMA.

Feasibility: Some important issues identified

This would require each specialist centre to assign medical practitioner(s) responsible for receiving the screen positive result. Whilst this is feasible in major centres, other smaller specialist centres with reduced numbers of specialists may find this challenging. NBS programs within each healthcare jurisdiction will need to develop appropriate communication processes to support this recommendation.

RATIONALE

There are substantial benefits for implementing this recommendation. Early notification of paediatric neurologists allows for a streamlined and coordinated approach to next steps for diagnostic confirmation and treatment planning, which is essential to reduce the time to treatment for the child, to magnify their future health outcomes. Early access to specialists, at the point of screen positive notification also allows families to ask and receive expert informed evidence for decision making.

Implementation Guidance

2.2.1 Written notification of a screen positive result should be issued to the paediatric neurologist within 24 hours of the verbal notification of a screen positive result.

2.2.2. 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.

A screening flow chart encompassing Recommendations in Sections 1 and 2 is proposed (Figure 7).

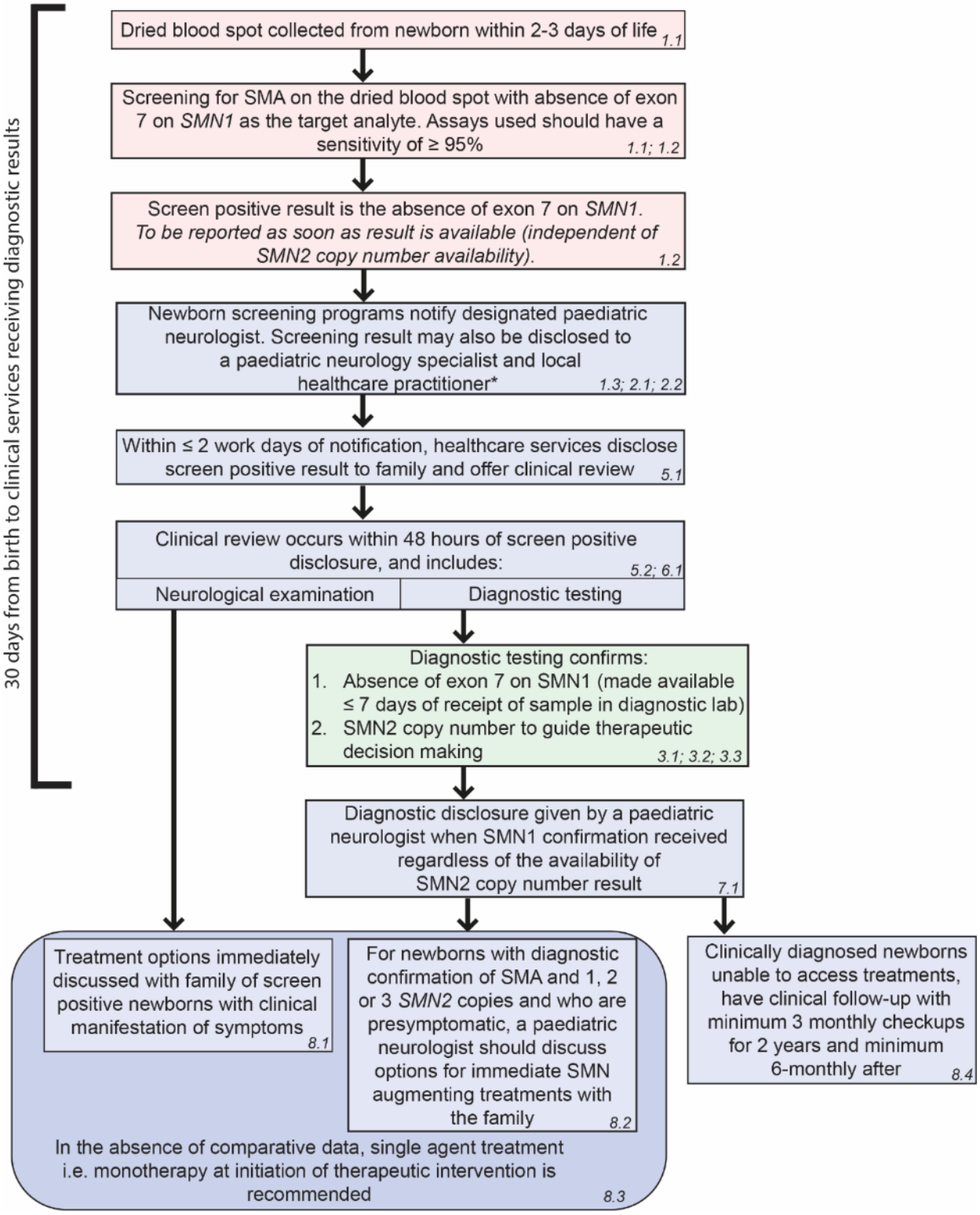


Figure 7. A flowchart to represent key recommendations within screening (red), diagnostic (green) and clinical care (blue) services for newborn screening in spinal muscular atrophy.

*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.

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. (182) 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, (10, 95, 124, 139, 145, 153, 158, 165), ddPCR (153, 159), qPCR (109, 137, 165), sequencing (120, 161), or restriction fragment length polymorphism PCR (32, 116), +/- analysis of splicing variants. (32, 116)

SMN2 copy number diagnostic testing is considered clinically useful to determine prognosis and long-term outcomes. Therefore, there is a clinical imperative for *SMN2* copy number 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 (183) and with modernised technologies, (158) underlining the necessity of using validated and up to date methods for denoting *SMN2 c*opy number. (158) 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)

In a presymptomatic individual with SMA, SMN2 copy number is the determinant of therapeutic decision making; thus an inaccurate diagnosis can cause considerable harm. 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. (179)

Beyond *SMN2* copy number, additional genetic modifiers may influence variability of transcription, translation and stability of *SMN2* transcripts, 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. (178) 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. (184)

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 presymptomatic 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.

(185) Therefore, time to diagnosis and subsequent treatment appears to be a substantial modifier of health outcomes for these children.

Recommendation 3.1

Evidence based: strong recommendation for

Diagnostic testing should include confirmation of an absence of exon 7 on *SMN1* (i.e. zero copies of *SMN1)*.

ADDITIONAL INFORMATION

This recommendation is developed with an evidence-based framework. This is a high priority recommendation based on substantial benefits for the affected population. Benefits outweigh harms for almost all affected children. All or nearly all affected children and their families would likely want this option. Diagnostic assays may vary but all should target the absence of exon 7 on *SMN1*.

RESEARCH EVIDENCE

Population: Newborns, infants and children with SMA. Birth up to 18 years.

Intervention: Newborn screening for SMA using exon 7 on *SMN1* as the target analyte.

Comparator: Children diagnosed with SMA through (non) newborn screening pathways including through prenatal screening, clinical referral of symptoms.

Outcome(s): Confirming the diagnosis of SMA

Summary

Evidence for this recommendation come from 19 observational (non-randomised) studies of 286 screen positive children with SMA where using absence of exon 7 on *SMN1* (with a variety of assays) to confirm the diagnosis was achieved in 262 individuals.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Clinical (non-NBS) diagnosis of SMA	Newborn Screening	**Certainty of the evidence** (Quality of evidence)	**Summary**
Confirming the diagnosis of SMA	Based on data from 218 participants in 19 studies			**Very low** Due to very serious risk of bias, serious risk of imprecision and publication bias, and very serious inconsistency	We are uncertain whether using an absence of exon 7 on *SMN*1 should be used to diagnose within newborn screening programs

Certainty of evidence

Step 1: Are the studies randomized?

Study type: Observational (non-randomized)

Step 2: Factors that might cause rating down certainty

Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: very serious.** Narrative synthesis conducted and estimates are not precise. **Indirectness: not serious**; **Imprecision: serious.** Low number of patients across a relatively small number of studies. **Publication bias: serious.** Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review.

Step 3: Factors that might cause rating up certainty

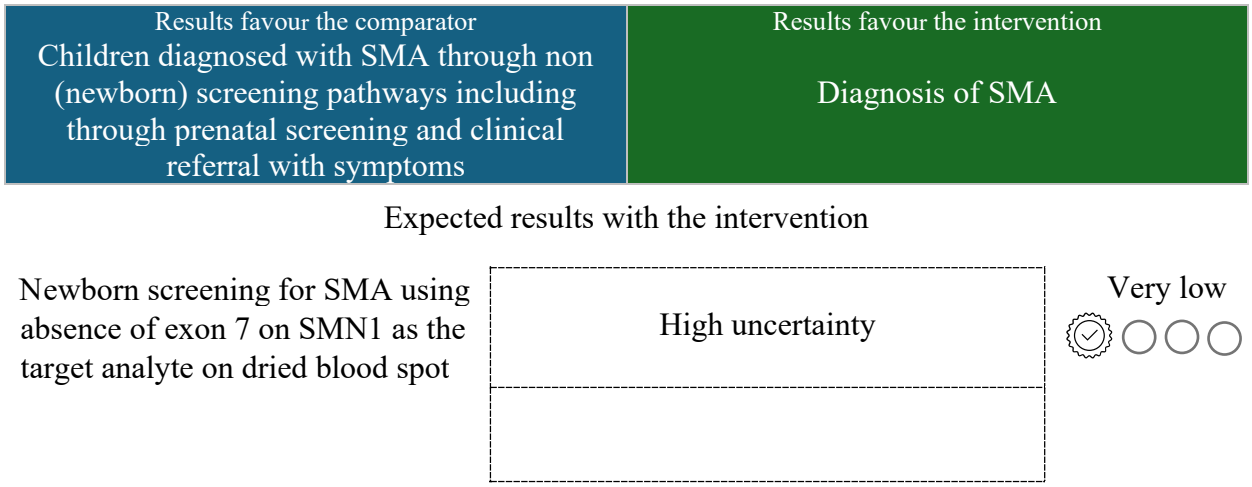
None

Step 4: Certainty level: Confidence in estimates reflecting the true values of target population?

Certainty level GRADE: Very low

Short summary of assessments: Due to very serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias, Due to very serious inconsistency.

Graphical representation



EVIDENCE TO DESCISION

Priority of problem

This a high priority Recommendation as the (newborn) screening test, though accurate can still have associated false negative and positive results. The screening result requires confirmation through diagnostic assays.

Benefits and harms: Substantial net benefits

Large potential for benefit due to the confirmation of a diagnosis of SMA, which in Australasia is the basis of access to treatment. No definite risks identified.

Certainty of evidence:

For key outcome measures of confirming the diagnosis of SMA in (screen positive) children the GDG considers the evidence to be of very low certainty (please see Research evidence).

References: Groulx-Boivin et al. 2024 (121), Prior et al. 2010 (109), Liu et al. 2016 (161), Kiselev et al. 2024 (137), Mikhalchuk et al. 2023 (120), Lin et al. 219 (122), Chien et al. 2017 (29), Kimizu et al. 2023 (145), Sawada et al . 2022 (165), Oliviera-Netto et al. 2023 (146), Kuchera et al. 2021, Niri et al. 2023 (95), D'Silva et al. 2022 (10), Gailite et al. 2022 (151), Vill et al. 2021 (158), Boemer et al. 2021 (139), Wang et al. 2020 (186), Strunk et al. 2019 (187)

Values and preferences: No variability in value or preference expected.

The GDG believed that all stakeholders would agree with this recommendation. One study has shown that consumers place a high value on confirming a diagnosis of SMA for screen positive children as a gateway to unlocking therapeutic options and multidisciplinary team management

and also to reduce the potential feelings of uncertainty with a screening result. The consumer representatives on the GDG highlight the highly desirable value of this Recommendation.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this Recommendation. Diagnosis of SMA is implemented across all healthcare jurisdictions in Australasia and bringing forward the time of diagnosis to the newborn period may have costing implications that have not been currently identified.

Equity: Important issues, or potential issues not identified.

There are no equity issues identified and there is an absence of systematically collected data. However, the GDG recognise the potential of this Recommendation to improve equity of access to a genetic diagnosis of a rare condition across Australasia, independent of sociodemographic status of affected children.

Acceptability: No important issues identified

The recommendation is likely to be highly acceptable to all stakeholders, and this has been emphasised by the consumer representatives on the GDG.

Feasibility: Some important issues identified

The GDG acknowledges that feasibility issues may arise including the need for specific screening equipment, processes and personnel to conduct diagnostic assays. However, the GDG agree that within the Australasian context, it is feasible to implement this Recommendation as jurisdictions already have access to diagnostic laboratories. Close coordination between screening, clinical and diagnostic services are mandatory to ensure the feasibility of this Recommendation and promote efficiency of confirming a diagnosis of SMA.

JUSTIFICATION

When moving from evidence to the strong recommendation for confirming the diagnosis of SMA in screen positive children (using absence of exon 7 on SMN1), the GDG considered several factors. The GDG acknowledged the uncertainty of evidence Ultimately, the GDG thought that the theoretical benefit targeted to confirm the diagnosis of SMA as a road towards accessing treatment and care outweighed the uncertainty of evidence, alongside other contextual factors including the potential to improve equity of access to diagnosis of a rare genetic

condition, the likelihood that this Recommendation would be acceptable to nearly all consumers, and in line with their preferences and values.

Specific considerations: This Recommendation applies to all children in Australasia including from culturally and linguistically diverse backgrounds and those who identify as First Nations peoples (i.e. Aboriginal, Torres and Pacific Islander, Māori peoples). The GDG encourage research to clarify uncertainties especially in jurisdictions where there are barriers to feasibility and also ongoing efforts to understand the resourcing issues for diagnostic confirmation within defined jurisdictions.

Implementation Guidance

3.1.1 Diagnostic *SMN1* testing conducted using a different methodology to the newborn screening assay should be considered.

Recommendation 3.2

Consensus recommendation

Diagnostic testing using suitably validated assays, from whole blood samples or repeat dried blood spot from a recalled infant should include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on substantial benefits for the affected population informing the necessity, pace and modality of therapeutic intervention required.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

High potential for benefit due to expediting access to treatment, to optimise clinical benefits. *SMN2* copy number is the leading prognosticator of SMA disease severity and diagnostic confirmation of the copy number is essential to access approved and reimbursed treatments in Australasia, particularly for children who do not have signs and symptoms of SMA. *SMN2* copy number is clinically essential for shared decision making between clinicians and families, as it

helps to determine disease severity and informs the pace of treatment. As such it should be part of the diagnostic workflow for children screening positive through newborn screening programs.

Certainty of evidence: Across the observational studies through the systematic literature review, all incorporated *SMN2* copy number identification as part of the diagnostic process (independent of if *SMN2* copy number was available during the screening process).

References: Abiusi et al 2024, (32) Hale et al. 2021. (131)

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG in its deliberations acknowledges that *SMN2* copy number as part of the diagnostic workflow was mandatory to guide treatment planning and initiation.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

SMN2 copy number determination can be challenging and as such should be performed in expert reference centres. Equity issues include the fact that not all jurisdictions will have intrastate capacity to conduct *SMN2* copy number, therefore processes and pathways need to be established for accurate and expedient interstate *SMN2* copy number identification.

Acceptability: No important issues identified

The recommendation is likely to have consistent acceptability.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that not all jurisdictions will have the capacity or resources to perform *SMN2* copy number as part of the diagnostic process from an equipment, personnel and process standpoint. The GDG acknowledged that in particular reference laboratories would need to establish processes to prioritise and streamline results, to enable timely therapeutic decision making.

RATIONALE

The GDG agreed that *SMN2* as the best prognostic indicator of disease severity and onset was essential to inform treatment planning and should be an integral part of the post screening pathway. This Recommendation was therefore considered as a high priority.

Practice Standards

3.2.1. 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.

Implementation Guidance

3.2.1. *SMN2* copy number identification should be conducted in approved expert reference centres.

3.2.2. Redetermination of *SMN2* copy number in a different laboratory or using a different method may be considered in newborns with ≥ 4 *SMN2* copies, due to imprecision arising from *SMN2* copy number methodologies that can impact therapeutic decision making.

Recommendation 3.3

Consensus recommendation

Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on substantial clinical benefits for the affected population.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

High potential for benefit due to expediting access to treatment, to optimise clinical benefits.

Certainty of evidence: There is a high certainty of evidence that the time to treatment should be as short as possible to magnify clinical benefits, (99) and as such all steps within the process including time to diagnostic result availability should be as short as possible. Whilst there is no direct evidence or defined time for diagnostic result availability internationally, Australian pilot data determines that *SMN1* result can be available by a median of 6 days from point of first clinical review with median time for completion of screening to diagnosis 13.5 days of age of the infant (Kariyawasam et al. 2020).

References: Kariyawasam et al. 2020, (12) McMillan et al. 2021. (112)

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG acknowledges that a defined time interval (which is feasible but clinically beneficial) is probably valued by families as discussed with the patient advocates within the GDG.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding equity for this Recommendation, however providing a standardises time interval for diagnostic results will improve equity of access to a diagnosis and appropriate treatment and care, which is founded on the *SMN1* diagnostic result. This may lead to reduction in variabilities in health outcomes for children within Australasia.

Acceptability: Some important issues identified

The recommendation is likely to have varied acceptability. For some diagnostic laboratories, this time interval will challenge workflow processes and require reconfiguration and prioritisation of samples.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that for some jurisdictions, the capacity or resources to deliver *SMN1* results within this timeframe may be challenging. The pilot program data, generated within a defined area of Australia may not be generalisable in terms of feasibility to other healthcare jurisdictions. (12)

Specific considerations (Strategies to promote implementation of the Recommendation): The GDG acknowledged the need for pre-established pathways between clinical and diagnostic services to ensure the timeline within this Recommendation were met. Stakeholders within states/territories that had a vast geographical expanse or took clinical referrals across multiple states suggested implementation of courier services for transportation of diagnostic samples to laboratories, written and verbal communication to laboratories of an expected sample and prioritisation of diagnostic samples within the laboratory.

RATIONALE

Whilst the feasibility of this Recommendation identified some important issues, the GDG acknowledged throughout the deliberation process that the impact on clinical outcomes, and mitigation of inequities in practice outweighed feasibility factors. Jurisdictions were encouraged to establish processes that could deliver results for this time critical condition within the recommended time frame. This Recommendation was therefore considered a high priority.

Recommendation 3.4

Consensus recommendation

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

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on substantial clinical benefits for the affected population.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

High potential for benefit due to expediting access to diagnosis and treatment, to optimise clinical benefits.

Certainty of evidence: There is a high certainty of evidence that the time to treatment should be as short as possible to magnify clinical benefits (Kariyawasam et al. 2023), and as such all steps within the process including time to diagnostic result availability should be as short as possible. Whilst there is no direct evidence or defined time for diagnostic result availability internationally, Australian pilot data determines that the diagnostic process can be completed within the first 28 days of birth. (12) Evidence has been noted that health outcomes are significantly reduced (motor and odds of requiring ventilatory and feeding support) when treatment is initiated after 6 weeks of age.

References: Kariyawasam et al. 2020, (12) Aragon-Gawinska et al. 2023. (188)

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG acknowledges that a defined time interval for diagnosis is likely to be valued by families, as emphasised by the patient advocates within the group.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding equity for this Recommendation, however providing a standardised time interval for diagnostic results will improve equity of access to a diagnosis and appropriate treatment and care. This may lead to reduction in variabilities in health outcomes for children within Australasia.

Acceptability: Some important issues identified

The recommendation is likely to have varied acceptability. For some diagnostic laboratories, this time interval will challenge workflow processes and require reconfiguration and prioritisation of samples.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that for some jurisdictions, clinical and diagnostic processes are complex with families sometimes travelling great distances to confirm and diagnosis and multiple laboratories providing results, all increasing the time interval till diagnosis is confirmed. Thus, the capacity or resources to deliver *SMN1* and *SMN2* results within this defined timeframe may be challenging. The pilot program results that allowed diagnostic processes to be completed within 28 days of birth were conducted within a defined area of Australia (NSW and ACT) which may not be generalisable to other healthcare jurisdictions. (12)

RATIONALE

Whilst the feasibility of this Recommendation identifies some important issues, the GDG acknowledged throughout the deliberation process that the impact on clinical outcomes, and mitigation of inequities in practice outweighed feasibility factors. Jurisdictions were encouraged to establish processes that could streamline the screening to diagnostic pathway to deliver results for this time critical condition within the recommended time frame. This Recommendation was therefore considered a high priority. It was noted that as the evidence base changed in the future, the timelines set out in the Guideline would potentially reduce.

Information Box

The timings included in Recommendations 3.3 and 3.4 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.

Implementation Guidance

3.4.1 Clinical and diagnostic services should have pre-established protocols and pathways in place (upon receiving a screen positive result) that lead to rapid collection, authorisation of diagnostic tests and result notification.

3.4.2. Diagnostic reports should detail the methodology used for analysis and preferably the precise *SMN2* copy number (avoiding reports such as *SMN2* ≥4), where possible.

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

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.

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, 189) DNA quality and/or quantity of the dried blood spot samples, (125, 153) and instrument performance in detecting *SMN1* gene deletion. (125) 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 (152). False positive results have been noted with a concurrent false positive SCID screen, (147) 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, 133, 139, 152). 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. (190)

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, (116) the presence of PCR inhibitors (seen predominantly in blood collected from newborns in intensive care units) (131), poor DNA quality/quantity or system errors. (95)

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. (162) 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. (162)

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, 162) 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. (191, 192) Furthermore, segregation analyses and a precise understanding regarding *SMN1* and *SMN2* copy numbers are imperative to identify the aetiology of false negative results. (193)

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)

Information Box

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.

False negative results are defined by individuals with a negative screening result but who are later confirmed to have SMA through 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. *(194)*

Recommendation 4.1

Consensus recommendation

For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families.

Information Box

Information regarding the implications of results may be provided by a paediatric neurologist and/or clinical geneticists and/or genetic counsellors.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

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. High potential for benefit due to identifying the correct diagnosis in the child which has substantial implications for interventions, care, support and outcomes. Identifying the correct diagnosis for a child is important to facilitate the wellbeing of affected families and promote their confidence in newborn screening as a population program. Risks include the time, expertise and technology from relevant healthcare practitioners required to identify and understand the aetiology of false positive, false negative or uncertain result.

Certainty of evidence: There is no direct evidence for this Recommendation.

References: None

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG acknowledges that this recommendation is likely to be acceptable to stakeholders as it improves the quality of healthcare for the child and family. This is emphasised by the patient advocates within the GDG.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Important issues, or potential issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding equity for this Recommendation however this Recommendation is unlikely to create equity issues.

Acceptability: No important issues identified

The recommendation is likely to have acceptability.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that for some jurisdictions, there are limitations in time, expertise and technology required to identify the aetiology of false positive, false negative and uncertain results. Feasibility is improved with access to a multidisciplinary team (including national and international experts) for discussion.

RATIONALE

It was agreed by the GDG that the Recommendation 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. Whilst the expertise to understand the aetiology of results may

not be feasible within all healthcare jurisdictions, the GDG acknowledge the presence of national and international experts that can be contacted to facilitate this process.

Recommendation 4.2

Consensus recommendation

If there is a difference in *SMN1* and/or *SMN2* copy number results between screening and diagnostic assays, retesting for *SMN1* and/or *SMN2* copy number with another method/laboratory should be considered.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a moderate priority recommendation based on substantial clinical benefits for the affected population and its strength and direction will be updated as the evidence base grows.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

High potential for benefit due to providing an accurate diagnostic (*SMN1*) and/or prognostic (*SMN2* copy number) result for the affected child so that therapeutic decision making is founded on the correct genetic information. Reduces the risk of harm caused by providing invasive treatments in children who do not have SMA or are unlikely to develop a childhood onset form of the condition. Obtaining an accurate genotype is likely to have a large impact on families in terms of wellbeing and satisfaction with care.

Certainty of evidence: There is a low certainty of evidence which is based on one case report and a case series. The case report showed the aetiology of aetiology of a false positive result after blood was retaken from a recalled infant and *SMN1* analysed using different assays to the first diagnostic method. Issues surrounded the probe binding site on the initial screening test. The case series showed two intron 6 variants leading to a wrong diagnosis of SMA due to variants lying within the primer or probe target sequences. The recommendation from this study was for combined molecular assays to improve diagnostic accuracy in uncertain or discordant cases.

References: Qu et al 2024, (189) D'Silva et al 2022. (10)

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG acknowledges that there is unlikely to be substantial variation in acceptability.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Some important issues identified.

The GDG acknowledges that in some healthcare jurisdictions, there is little or no provisions or capacity to (re)test samples using different methods.

Acceptability: No important issues identified

Whilst there is no systematically collected information regarding the acceptability of this recommendation, the GDG acknowledges that there is unlikely to be substantial variation in acceptability.

Feasibility: Some important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that for some jurisdictions, there may not be capacity or process to retest *SMN1* and/or *SMN2* in a different laboratory or with a different method.

RATIONALE

The feasibility and equity considerations of this Recommendation identifies some important issues, however the GDG acknowledged throughout the deliberation process that the impact on clinical outcomes, and mitigation of harms outweighed these factors. Therefore, the GDG formed a consensus as to the direction of the Recommendation but deemed this as moderate priority to reflect feasibility considerations.

Implementation Guidance

4.2.1. A further blood sample from the newborn may be required for repeat screening and/or diagnostic testing if resolution of *SMN1* and/or *SMN2* genotype does not occur.

4.2.2. Blood samples from parents for *SMN1* quantification purposes should be considered to understand the aetiology of a false positive or uncertain result for the newborn.

4.2.3. 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 issues and errors can be identified as part of quality improvement.

Recommendation 4.3

Consensus recommendation

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.

ADDITIONAL INFORMATION

This recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation based on the potential to change the outcomes for the child.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

The benefits of this recommendation include the potential for children without a confirmed diagnosis to access specialist review, so that care planning can be based on expert knowledge and assessment. This has the added potential for positively impacting the psychological wellbeing of families as they wait for elucidation of their child's genetic status. The risks include the need for children and families to travel to specialist centres to access expert care when they may not have a diagnosis of SMA, conferring on them a surveillance burden.

Certainty of evidence: There is no direct evidence for this Recommendation.

References: None

Values and preferences: Variability in value or preference not expected.

Whilst there is no systematically collected information regarding the preferences and values of stakeholders aligning with this recommendation, the GDG acknowledges that this

recommendation is likely to be acceptable to stakeholders as it improves the quality of healthcare for the child and family. This is emphasised by the patient advocates within the GDG.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: Potential issues expected.

The GDG acknowledges that there is no systematically collected evidence regarding equity for this Recommendation however for families travelling from rural/regional areas of Australasia to access expert care, this may confer substantial logistical and opportunity costs on them. The use of telehealth technologies provides the opportunity to mitigate this by working with local healthcare practitioners and the preferences of the family.

Acceptability: No important issues identified

The recommendation is likely to have acceptability.

Feasibility: No important issues identified

Although there is no systematically identified evidence as to feasibility, the GDG acknowledges that the number of expected false positive, false negative and uncertain results will continue to be low, and that clinical review within specialist services will be feasible.

RATIONALE

It was agreed by the GDG that the Recommendation would enable standardisation of practice across the population and lead to access to best practice for children with discordant screening and diagnostic results. The clinical experience and expertise of the GDG informed the need for a paediatric neurologist to provide expert guidance and this was deemed to be feasible across Australasia. The benefits of clinical assessment to guide treatment for those with a clinical phenotype of SMA, at the earliest opportunity is considered by the GDG to outweigh potential risks for children in rural and regional communities.

4.3.1. 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. These include 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.

4.3.2. Families who receive a false negative, false positive or uncertain screening result should be provided psychosocial support by relevant members within the multidisciplinary team.

Information Box

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.

4.3.3. 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.

Section 5

Communicating a SMA 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. (166) 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. (81)

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%-40% of newborns/infants are symptomatic at the time of first clinical review. (194) 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. (133)

The designation of healthcare practitioners tasked with notifying the family of screen positive results vary internationally, dependent on jurisdiction-specific SMA workflow processes. (133) 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. (133).

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. (112) Screening results are generally disclosed over the telephone where the child and family are directed to the closest paediatric hospital for clinical review. (112) 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. (112, 121)

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. (195). 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. (195)

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, 195)

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. (133) 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. (133)

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. (169) 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 recommendation

Screen positive result should be disclosed to the family within ≤ 2 working days (of notification to healthcare services)

ADDITIONAL INFORMATION:

The time to treatment is a significant factor in future health outcomes due to the rapid and progressive neurodegeneration of the motor unit pool in SMA, therefore the time to screen positive disclosure should be as short as possible. Although there is no direct evidence for this time interval, the GDG acknowledges that disclosure is feasible across Australasia within 48 hours of screen positive results. This recommendation is therefore a high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit due to expediting access to diagnosis and treatment that is known to maximise clinical benefits for the child. No risks have been identified by the GDG.

Certainty of evidence: Low certainty of evidence.

The observational studies denote variability in timelines for screen positive disclosure however where notes, these are between 1-2 days. Within the Australian pilot newborn screening for SMA program screen positive results were communicated to families by 10.5 days of life of the newborn (range 5-18 days), after screening result availability at 8 days of life (range 5-18 days).

References: Kariyawasam et al. 2020, (12) Muller-Felber et al. 2023, (133) Boemer et al. 2019. (141)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, the GDG acknowledges that families value a streamlined pathway to access diagnosis and treatment, and the first step for this is screen positive disclosure.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No equity issues identified.

Equity of access to a screen positive result within a standardised time may mitigate healthcare inequities across Australasia.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. Due to the precipitous clinical course in SMA, screening results relayed within a standardised, narrow time interval is likely to be highly acceptable to stakeholders.

Feasibility: Some important issues identified

This would require each specialist centre to assign medical practitioner(s) responsible for receiving the screen positive result and disclosing this to families or delegating the notification responsibility as appropriate. Whilst this is feasible in major centres, other smaller specialist centres with reduced numbers of specialists may find this challenging. NBS programs within each healthcare jurisdiction will need to develop appropriate communication processes to support this recommendation.

RATIONALE

There are substantial benefits for implementing this recommendation. Timely notification of families allows for a streamlined and coordinated approach to next steps for diagnostic confirmation and treatment planning, which is essential to reduce the time to treatment for the child, to magnify their future health outcomes. Benefits to health outcomes, equity considerations and preferences outweigh potential feasibility issues.

Practice Standards

5.1.1. 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.

Information Box

Dependent on child and family circumstances, it may be appropriate for a designated healthcare practitioner with support from the paediatric neurologist through telehealth to disclose a screen positive result to the family. The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians, neonatologists, specialist nurses and/or genetic counsellors.

5.1.2 Key points in the (screen positive disclosure) call to the family 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.

5.1.3. 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 5.2

Consensus recommendation

Screen positive newborns should be offered a clinical review within paediatric neurology/neuromuscular services within ≤ 2 working days, from the time of screen positive disclosure.

ADDITIONAL INFORMATION:

This is a moderate priority recommendation which will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation. The recommendation is not developed with an evidence-based framework but formed through consensus.

Benefits and harms: Substantial net benefits

Large potential for benefit due to expediting access to diagnosis and therapeutic planning that is known to maximise clinical benefits for the child. There may be a safety risk for parents who travel with a symptomatic child to seek specialist care.

Certainty of evidence: Low certainty of evidence.

The observational studies denote variability in timelines for clinical review once a family is notified of the screening result. Within the Australian pilot newborn screening for SMA program screen positive results were communicated to families by 10.5 days of life and the child reviewed in a specialist clinic by 12.5 days of life (8-23) days.

References: Kariyawasam et al. 2020, (12) Muller-Felber et al. 2023. (133)

Values and preferences: Some variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, the GDG acknowledges that whilst many families value early access specialist review within a defined interval from screen positive disclosure, for some families, review for diagnosis and care planning is preferred closer to home, dependent on geographical and child and family factors.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No equity issues identified.

Equity of access to a clinical review conducted by a specialist and within a standardised time may mitigate healthcare inequities across Australasia.

Acceptability: Some important issues identified

The recommendation is likely to be acceptable to most stakeholders, however, for some families within regional/rural communities, travelling long distances with a newborn is not acceptable and may confer risks if safe travel is not an option. This has been emphasised by the patient advocates, medical practitioners and specialists in rural medicine within the GDG. However, there is no systematically collected evidence regarding acceptability.

Feasibility: Some important issues identified

This Recommendation would require each specialist centre to reconfigure workflow processes to ensure that the screen positive child is seen as an emergency within 2 days of screen positive disclosure and for some specialist services, this may challenge already finite resources and require coordination of personnel to optimise feasibility. NBS programs within each healthcare jurisdiction will need to develop appropriate communication processes to enforce this recommendation. The clinical service would have to be configured to cover leave and holiday periods throughout the year to facilitate this Recommendation.

Specific considerations (Strategies to promote implementation of the Recommendation): A broader and deeper evidence base needs to be established which includes an evaluation of the perspective, enablers and barriers for families seeking to access diagnosis and treatment for SMA from rural and remote regions, for effective implementation of this Recommendation. This will serve as a first step to codesigning and codeveloping pathways that meet the needs of consumers from geographically remote areas, to overcomes obstacles to expedient diagnosis and best care.

RATIONALE

The time to treatment is a significant factor in future health outcomes due to the rapid and progressive neurodegeneration of the motor unit pool in SMA, therefore the time to clinical review and diagnostic processes (as a gateway to treatment) should be as short as possible. For children with 2 *SMN2* copies in particular, symptom onset is within the first weeks of life in 80% and for these children there is an imperative for immediate treatment (once a diagnosis is confirmed) as every day without treatment leads to increasing chance of long-term comorbidities and motor delays. Benefits outweigh harms, but not for everyone within the population with some children and families unable to access specialist review within this defined time frame.

Practice Standards

5.2.1. Some screen positives newborns and families are unable to travel to paediatric neurology/neuromuscular services safely or promptly. For these newborns, clinical review, and diagnostic evaluation within local paediatric services with telehealth support from a paediatric neurologist, should be undertaken within ≤ 2 working days of screen positive disclosure.

5.2.2. Healthcare practitioners should instruct families and provide them with written information as to when immediate contact is required to facilitate urgent clinical review for their screen positive newborn/infant. Circumstances include

- 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

Recommendation 5.3.

Consensus recommendation

Culturally safe care is required by healthcare practitioners when disclosing screening results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Providing supported and high quality culturally relevant information has a large potential for benefit in improving the wellbeing, reducing psychological risks and satisfaction and engagement in care for families of screen positive children. Families are able to make informed and shared decisions in care planning and treatment for their child, which also has the potential to optimise the child's own future health and psychosocial outcomes.

Certainty of evidence: Low certainty of evidence. Two mixed method studies identified the need for interpreter services for non-English speaking families to understand the complexities of the screen positive SMA result and for informed therapeutic decision making.

References: Kariyawasam et al. 2021, (11) Meyer 2024. (195)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, it is likely that this Recommendation would be acceptable to families as emphasised by the patient advocate and specialists in First Nation healthcare within the GDG.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No important issues, or potential issues.

Equity of access to culturally sensitive and linguistically appropriate information is expected to reduce health inequities secondary to variations in the sociodemographic and health literacy profile of families. The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. The GDG acknowledges that there is no systematically collected evidence regarding acceptability factors of this recommendation.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Most healthcare systems have professional interpreter services; however, these require coordination at the time of diagnostic disclosure. Indigenous Health resourcing is variable across Australasia and education and training is required for professionals within this area so that families can be appropriately supported through the healthcare journey.

Specific considerations (Strategies to promote implementation of the Recommendation):
Non-specialist medical practitioners who may reasonably be expected to support result disclosure where appropriate may require a process of training and education on SMA and implications of a screening result for optimal information provision. This may include specific

education and training for Indigenous Health Liaison professionals, and other professionals in the indigenous health workforce.

RATIONALE

There are substantial benefits for implementing this recommendation for children and their families, where information provision is considered the foundation for informed decision making, satisfaction and engagement in ongoing care and reduction is psychological distress for families. This recommendation also services to mitigate potential healthcare inequities secondary to the sociodemographic status of families, so that all children with a diagnosis of SMA through newborn screening can receive high quality health provision.

Section 6

Assessments required at diagnostic evaluation of the newborn

Background

This section 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. (196) In a proportion of newborns with a screen positive SMA result, 40% 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 positive for SMA, as determined by the evidence of benefits of early treatment, (173) before irreversible loss of motor neurons can occur. (11, 81) 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, thrombocytopaenia, or other serious underlying conditions that may heighten the risk of therapeutic intervention. (197) 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. (197) 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. (198) 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. (197, 199)

Recommendation 6.1

Consensus recommendation

The following assessments should be 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* exon 7 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.

Information Box

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.

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit. Diagnostic confirmation of absence of *SMN1* exon 7 and quantifying the copy number of *SMN2* is mandatory to access treatment in Australasia, in presymptomatic individuals. A neurological examination of the child to ascertain symptomatic status is essential to identify the pace of intervention required. The evidence suggested that a substantial proportion (40%) of children screening positive for SMA would display signs and symptoms of disease onset within four weeks of life. Symptomatic children are at higher risk of future motor, feeding and respiratory comorbidities and stratifying those who require urgent treatment has the potential to improve their health outcomes. Identifying the disease status of the child through a structured neurological examination also allows for therapeutic expectations to be shared with parents. The GDG acknowledges that neurological examination in a newborn can be challenging and dependent on disease stage, illness and physiological status of child (due to feeds and sleep

needs). Risks of invasive blood collection for confirmation of genotype are outweighed by the benefits.

Certainty of evidence: Low certainty of evidence. 7 observational studies implemented a structured neurological examination alongside blood for *SMN1* and *SMN2* diagnostic testing from a recalled (screen positive) child as part of the diagnostic process.

References: Kariyawasam et al. 2022, (174) Kariyawasam et al. 2023, (99) Muller-Felber et al.2023, (133) McMillan et al. 2021, (112) Abiusi et al. 2023, (116) Elkins et al 2022, (152) Tizzano et al. 2019, (200)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, there is a high likelihood that this Recommendation will be valued by all stakeholders.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No important issues, or potential issues.

There is no systematically collected information regarding equity considerations for this Recommendation. However, there is a high likelihood that this Recommendation will optimise equity of access to a diagnosis of SMA across Australasia, aligning with National Rare Disease directives. (201)

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. However, there is no systematically collected information regarding equity considerations for this Recommendation.

Feasibility: No important issues identified

The confirmation of a diagnosis of SMA with a neurological examination and diagnostic bloods for *SMN1* exon 7 and *SMN2* copy number are undertaken in routine clinical practice for children with signs and symptoms of the condition (diagnosed outside of newborn screening pathways). Therefore, this Recommendation should be feasible to implement as part of current working practices and best care. Education and training for healthcare practitioners outside of specialist centres in the correct blood samples to be taken and requested and signs and symptoms of SMA in the neonatal period will be required to optimise the feasibility of this recommendation.

Specific considerations (Strategies to promote implementation): For implementation of this recommendation, knowledge exchange, training and upskilling of healthcare practitioners is mandatory, through formation of clinical networks that facilitate knowledge exchange and mentoring between specialist neurology services, secondary healthcare systems and local healthcare communities. A formal program of education on the signs and symptoms of SMA in the newborn period and need for expedient diagnostic evaluation will be essential to facilitate the effective implement this recommendation across Australasia.

RATIONALE

There are substantial benefits for implementing this recommendation, namely, to confirm a diagnosis of SMA which is the only route to access approved and reimbursed treatment in Australasia. Ascertaining disease status is important to set the pace of therapeutic intervention (which will modify future health outcomes for affected children) and set therapeutic expectations with families.

Practice Standard

6.1.1. The following assessments may be 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 received.

- 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.

Section 7

Provision of information and support for families after confirming the diagnosis of spinal muscular atrophy

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. (195)

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. (195)

Recommendation 7.1

Consensus recommendation

The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result.

ADDITIONAL INFORMATION:

Benefits of this Recommendation are substantial to expedite access to diagnosis and shorten the time to treatment, which has significant implications on health outcomes for affected children. The recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority recommendation.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit due to expediting access to diagnosis and treatment that is known to maximise clinical benefits for the child. *SMN2* copy number is important to set the pace of treatment planning, but its availability can be delayed dependent on jurisdictional diagnostic capacity. Its availability does not preclude diagnostic disclosure and planning with parents for next steps. Risks of starting therapeutic planning for a child with a confirmed genotype of ≥ 4 *SMN2* copies is small, however these children will not be able to access treatment in the current therapeutic landscape and they will require clinical surveillance.

Certainty of evidence: No direct evidence across the literature.

References: None

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, one study does identify that families value expedient confirmation of diagnosis to help to start to plan next steps for the child. The GDG agrees that all consumers who value expedient diagnostic disclosure.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No important issues, or potential issues.

There are no systematically collected information regarding this domain however, the GDG agree that there are no specific or potential equity issues arising from this Recommendation.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. Due to the precipitous clinical course in SMA, diagnostic disclosure dependent on *SMN1* results in streamlined therapeutic planning, care and support which is likely to be acceptable to stakeholders.

Feasibility: No important issues identified

The recommendation is likely to be feasible across all jurisdictions.

RATIONALE

Time to treatment is a significant modifier of health outcomes for newborns, therefore there is likely to be substantial clinical benefit from early diagnostic disclosure to families to start the process of treatment planning which may reduce time to treatment and modify health outcomes for affected children. There are no specific equity, acceptability or feasibility issues that would preclude the direction or strength of this Recommendation.

Implementation Guidance

7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis.

Information Box

The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor.

Recommendation 7.2

Consensus recommendation

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 reflect the contemporary care landscape and are nationally consistent.

ADDITIONAL INFORMATION:

Benefits of this Recommendation to families of affected children are substantial to set therapeutic expectations and facilitate shared and informed decision making between families and healthcare practitioners. The recommendation is not developed with an evidence-based framework but formed through consensus. This is a high priority Recommendation.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Large potential for benefit. Information provision is considered by families as a means of empowering them to make the appropriate decisions for their children. Information provision has also been found to reduce psychological distress in families receiving a diagnosis of SMA, promoting satisfaction and engagement in the healthcare journey. Risks of misinformation and the psychological distress caused by a period of information seeking would be mitigated by this Recommendation

Certainty of evidence: Two mixed methods studies both denote the importance and preferences of well curated information resources for families receiving a diagnosis of SMA through newborn screening. Mixed methods study of 50 parents with a screen positive NBS result identified a period of difficulty in processing information post diagnostic disclosure due to complexity and emotional state with enablers of information provision inclusive of standardising information at diagnosis through written means. Written information as also valued by parents in a separate mixed methods study to aid understanding of diagnosis and treatment options.

References: Meyer et al. 2024, (195) Kariyawasam et al. 2021. (11)

Values and preferences: No variability in value or preference expected.

As aligns with the above evidence base, consumers are likely to value the implementation of this Recommendation.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No important issues, or potential issues.

There are no systematically collected information regarding equity considerations aligning with this Recommendation. However, provision of high quality and well curated information is considered by the GDG to reduce health inequities secondary to variations in health literacy within the population.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders with families valuing and having strong preferences for being offered educational materials to augment verbal diagnostic disclosure.

Feasibility: Some important issues identified

Feasibility of this recommendation may be dependent on resources to revise currently available educational materials or develop and disseminate new materials, which has the potential to incur additional costs involved.

Specific considerations (strategies to promote implementation of the Recommendation):
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 will be essential to support knowledge translation in a way that meets the needs and values of affected families. The implementation of this Recommendation may be augmented by linking with consumer groups, treatment sponsors and clinical services to delegate roles and responsibilities for the update or establishment of educational resources for families.

RATIONALE

Information provision in a fast changing clinical and treatment landscape is essential for families receiving a diagnosis of SMA with substantial net benefits incurred and potential to mitigate health inequities secondary to variations in health literacy within the community. This is also highly valued and acceptable to families as noted in the few studies that evaluate stakeholders' perspectives. Whilst there are feasibility factors, these can be overcome by updating existing information resources.

Practice standards

7.2.1. Clinical services should provide families with information that is compassionate, accurate and tailored to their information needs and preferences. Information provided may include information on the (genetic) cause and clinical implications of SMA, next steps and approximate timelines to confirm a diagnosis, information on psychosocial supports (including referral to social work services), and/or psychology and/or advocacy services.

7.2.2. 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.

7.2.3. Families should be invited to bring support person(s) at the time of diagnostic disclosure.

7.2.4. 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.

Information Box

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.

Recommendation 7.3

Consensus recommendation

Culturally safe care is required by healthcare practitioners when disclosing diagnostic results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison

professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Providing supported and high quality culturally relevant information has a large potential for benefit in improving the wellbeing, reducing psychological risks and satisfaction and engagement in care for families of screen positive children. Families can make informed and shared decisions in care planning and treatment for their child, which also has the potential to optimise the child's own future health and psychosocial outcomes.

Certainty of evidence: Low certainty of evidence. Two mixed method studies identified the need for interpreter services for non-English speaking families to understand the complexities of the genetic diagnosis of SMA and for informed therapeutic decision making.

References: Kariyawasam et al.2021, (11) Meyer 2024. (195)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation for First Nation families. However, it is likely that this Recommendation would be acceptable to families as emphasised by the patient advocate and specialists in First Nation healthcare within the GDG.

Resources: Important issues not investigated.

The GDG acknowledges that there is no systematically collected evidence regarding cost-benefit of this recommendation.

Equity: No important issues, or potential issues.

Equity of access to culturally sensitive and linguistically appropriate support and information may reduce health inequities secondary to variations in the sociodemographic and health literacy profile of families. The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. The GDG acknowledges that there is no systematically collected evidence regarding acceptability factors of this recommendation.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Most healthcare systems have professional interpreter services; however, these require coordination at the time of diagnostic disclosure. Indigenous Health resourcing is variable across Australasia and education and training is required for professionals within this area so that families can be appropriately supported through the healthcare journey.

Specific considerations (Strategies to promote implementation of the Recommendation):
Non-specialist medical practitioners who may reasonably be expected to support result disclosure where appropriate may require a process of training and education on SMA and implications of a diagnostic result for optimal information provision. This may include specific education and training for Indigenous Health Liaison professionals, and other professionals in the indigenous health workforce.

RATIONALE

There are substantial benefits for implementing this recommendation for children and their families, where information provision is considered the foundation for informed decision making, satisfaction and engagement in ongoing care and reduction is psychological distress for families. This recommendation also services to mitigate potential healthcare inequities secondary to the sociodemographic status of families, so that all children with a diagnosis of SMA through newborn screening can receive high quality health provision.

Section 8

Immediate post diagnostic care for newborn 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 neuromuscular condition. 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. (202)

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. (167, 199, 203-207) 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 is 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. (81) 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 ≥ 2 *SMN2* copies AND those who are presymptomatic with 1,2, or 3 *SMN2* copies should have immediate access to treatment. (169) There is a lack of evidence on the outcomes for symptomatic 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, (169) offering supportive care as a valid pathway in the first instance. (208)

A higher probability of motor function attainment is observed when therapeutic intervention (of any modality) is administered < 6 weeks of age, (188) 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. (99) 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 whilst presymptomatic, there is study and consensus evidence for clinical surveillance at defined intervals within a neuromuscular centre. (10, 170, 198) 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, 128, 169, 198, 209)

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. (210) Thus, therapeutic decision making is ideally commenced in a paediatric neurology centre with

expertise in the management of children with SMA. (211) Long term surveillance of efficacy and safety is required to effectively manage children receiving these therapeutics. (212) 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. (213) Potential mitigators of these psychosocial outcomes include access to psychological support through referrals to appropriate health care services or advocacy groups, (214) alongside targeted information. 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). (215) 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. (216) 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. (81, 216) 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. (216) 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, 202) 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, 217) 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. (211, 218)

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 if dysautonomia and cardiac anomalies may become apparent as detected through a comprehensive neonatal examination. (218)

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. (219) 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. (220) 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. (221) This will help to define the thresholds to determine clinical (presymptomatic or symptomatic) status, which are currently not fully understood. (196) 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 (222) within the heterogenous clinical presentations found within a newborn screening for SMA cohort. (223)

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. (202) 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 onset, progress and augment the often clinically challenging assessment of the newborn with SMA. (10, 12)

Recommendation 8.1.

Consensus recommendation

For screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset i.e. clinically manifest), a paediatric neurologist should discuss options for immediate treatment with SMN augmenting treatments with the family.

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Substantial net benefits noted. SMA is a progressive condition where motor neuron loss starts prenatally with the majority of the motor unit pool lost by 3 months of age in children with severest infantile onset form of the condition (generally with a 2 *SMN2* copy number genotype). Intervention with SMN augmenting treatments at the earliest opportunity provides an ability to salvage the remaining motor unit pool and confers a clinical benefit. The paediatric neurologist is aware of the dynamic treatment landscape and can help set therapeutic goals and set out treatment options for the family.

Certainty of evidence: High certainty of evidence. Three randomised control trials of SMN augmenting treatments in symptomatic children with SMA show significantly improved survival, motor outcomes, and reduction of comorbidities in symptomatic children with shorter disease durations. This is complemented by a real-world study that shows that in symptomatic children, longitudinal increase in motor unit number correlates inversely with disease duration and later functional motor outcomes. A systematic review using outcomes from 153 newborns (combined symptomatic and presymptomatic) across clinical trials in real world studies show a high probability of normal motor development if children are treated before the age of 6 weeks. Time to treatment for symptomatic children changed final HINE scores for children with SMA in one study. Expert evidence of panel of 5 members determines urgency to treat symptomatic infants and young children to minimise loss of motor neuron loss.

References: Aragon-Gawinska et al. 2023, (188) Kariyawasam et al. 2023, (99) Ramos Platt et al. 2022. (224) Day et al. 2021, (203), Finkel et al. 2019, (225) Servais et al. 2021, (226) Kariyawasam et al. 2020, (88), Finkel et al. 2017, (167)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, it is likely that this Recommendation would be acceptable to families as emphasised by the patient advocates within the GDG.

Resources: Important issues not investigated.

There is no systematically evaluated evidence for the cost benefit of treating children (diagnosed through newborn screening for SMA) who have signs and symptoms of the condition.

Equity: No important issues, or potential issues.

The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation however the GDG agree that access to treatment at the earliest opportunity is likely to mitigate health inequities across Australasia.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. The GDG acknowledges that there is no systematically collected evidence regarding acceptability factors of this recommendation.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Children diagnosed with SMA through newborn screening will in the majority be reviewed and managed in specialist centres, with experience in the screening for, administering and post administration surveillance of SMN augmenting treatments. However, for some families where travel is not possible for access to treatments, a flexibility in approach will be required as to where the treatment is initiated, however discussions with the family for the immediacy of treatment is still required.

Specific considerations (Strategies to promote implementation of the Recommendation):
Non-specialist medical practitioners who may reasonably be expected to participate in therapeutic decision making and support treatment initiation may require a process of training and education on the immediate need for SMA treatment, how to initiate this and post treatment monitoring. The use of telehealth to establish close links between specialists and non-specialist healthcare practitioners is required to exchange knowledge and offer support and guidance when treatment decision making occurs and is implemented outside of specialist centres.

RATIONALE

There are substantial benefits for implementing this recommendation for children, with the potential to magnify health gains, promote future functional independence and reduce comorbidities by reducing time to treatment. This recommendation also services to mitigate potential healthcare inequities secondary to the sociodemographic status of families or geographical location, so that all children with a diagnosis of SMA through newborn screening can receive access to treatment and be guided by specialists in treatment decision making.

Practice Standard

When newborns demonstrate signs and symptoms of SMA i.e. are clinically manifest (symptomatic) and have 1 *SMN2* copy, therapeutic decision making is dependent on the child's clinical status. Shared decision making between healthcare practitioners (guided by a paediatric neurologist) and families, to access treatment or proceed with supportive care alone should be discussed.

Recommendation 8.2

Consensus recommendation

For newborns with diagnostic confirmation of SMA and 1, 2 or 3 *SMN2* copies and who are presymptomatic (i.e. clinically silent), a paediatric neurologist should discuss options for immediate SMN augmenting treatments, with the family.

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Substantial net benefits noted. Immediate treatment for presymptomatic children is founded on biological plausibility with precipitous degeneration of motor neurons noted in the neonatal period which is apparent across all genotypes but is especially precipitous in children with 2 *SMN2* copies. Presymptomatic treatment confers the highest health benefits for affected children.

Certainty of evidence: High certainty of evidence. Three randomised control trials of SMN augmenting treatments in presymptomatic children with SMA show significantly improved survival, motor outcomes, and reduction of comorbidities with the majority of children with 3 SMN2 copies following a normal developmental trajectory and those with 2 *SMN2* copies gaining skills over time. Systematic review of the evidence showed that in 22/36 children treated presymptomatically no delays in motor development were noted at mean age of 15 months (range of 1-28 months). Outcomes for children treated presymptomatically are dependent on copy number with reduction in disease duration inversely correlated with a greater magnitude of benefit in children with 2 *SMN2* copies. Australian PBAC notes the magnitude of benefit for children who are presymptomatic and who have 3 *SMN2* copies is less clear from the clinical data available and consider the incremental benefit of presymptomatic treatment with onasemnogene abeparvovec compared to symptomatic treatment for children with this genotype would be less than 4 patients with 1-2 *SMN2* copies.

References: Swoboda et al.2010, (175) Aragon-Gawinska et al. 2023, (188) The Pharmaceutical Benefits Advisory Committee, (227-229) Strauss et al. 2022, (9) Strauss et al. 2022, (8) De Vivo et al. 2019, (7) Crawford et al. 2023, (6)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, it is likely that this Recommendation would be acceptable to families as emphasised by the patient advocates within the GDG.

Resources: Important issues not investigated.

One study shows that by treating one presymptomatic SMA infant with nusinersen or gene therapy, an additional 9.93 QALYs were gained over 60 years compared with late treatment in clinically diagnosed SMA. The societal cost was $9.8 million for early nusinersen treatment, $4.4 million for early gene therapy and $4.8 million for late nusinersen treatment. (37, 38)

Equity: No important issues, or potential issues.

The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation however the GDG agree that access to treatment at the earliest opportunity is likely to mitigate health inequities in terms of access to treatment across Australasia.

Acceptability: No important issues identified

The recommendation is likely to be acceptable to all stakeholders. The GDG acknowledges that there is no systematically collected evidence regarding acceptability factors of this recommendation.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Children diagnosed with SMA through newborn screening will in the majority be reviewed and managed in specialist centres, with experience in the screening for, administering and post administration surveillance of SMN augmenting treatments. However, for some families where travel is not possible for access to treatments, a flexibility in approach will be required as to where the treatment is initiated, however discussions with the family for the immediacy of treatment is still required. Studies outside of Australasia have noted that resources are required to provide equity of access to SMA treatments and surveillance of effects for families living regionally or without resources to travel and attend specialist clinics (missed work and family days, costs of travel, impact on siblings), with feasibility dependent on forming a hub and spoke model of shared care between tertiary, secondary and community services. (230)

Specific considerations (Strategies to promote implementation of the Recommendation):

Non-specialist medical practitioners who may reasonably be expected to participate in therapeutic decision making and support treatment initiation may require a process of training and education on the immediate need for SMA treatment, especially in children with 2 SMN2 copies, with training on how to initiate this and continue post treatment monitoring. The use of telehealth to establish close links between specialists and non-specialist healthcare practitioners is required to exchange knowledge and offer support and guidance for efficient and effective treatment decision making to aide implementation outside of specialist centres.

RATIONALE

There are substantial benefits for implementing this recommendation for children, with the potential to magnify health gains, promote future functional independence and reduce comorbidities by reducing time to treatment. For many children, especially with a 3 SMN2 copy genotype, normal development trajectories can be expected if treatment is started within this narrow therapeutic window. This recommendation also services to mitigate potential healthcare inequities secondary to the sociodemographic status of families or geographical location, so that all children with a diagnosis of SMA through newborn screening can receive access to treatment and be guided by specialists in treatment decision making.

Practice Standard

8.2.1. 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 8.3

Consensus recommendation

In the absence of comparative data, single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended, started within paediatric neurology treatment centre.

Implementation Guidance

8.3.1. 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.

8.3.2. Dependent on the needs and preferences of the child and family, SMN augmenting treatments may be planned to be initiated from a non-specialist treatment centre/service, with paediatric neurology support and guidance.

Information Box

Onasemnogene abeparvovec-xioi can only be administered in designated and approved paediatric treatment centres in Australasia.

Practice standards

8.3.1. 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.

8.3.2. Healthcare practitioners should explain to families and document the potential benefits, risks, uncertainties, of SMN augmenting treatments and need for long term surveillance.

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

8.3.4. Families 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. Written information as a standalone document or direction to a well-curated, reliable and up to date website should be 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 8.4

Consensus recommendation

Newborns with diagnostic confirmation of SMA who are unable to access approved and reimbursed treatments or chose not to be treated 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.

ADDITIONAL INFORMATION:

This recommendation is moderate priority and as such its strength will be updated when new evidence becomes available. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Substantial net benefits noted. Large impact on health outcomes for children by facilitating the detection of disease onset at the earliest juncture so that treatment can be initiated within a therapeutic window. Risks include the potential of over surveillance of the newborn and an increased logistical and psychological burden to families to engage in serial assessments throughout this period of time. Surveillance is required with increased frequency in the first two years from diagnosis as this is when the majority of children > 3 *SMN2* copies become symptomatic.

Certainty of evidence: Low certainty of evidence. International expert consensus established using a Delphi methodology determines that frequent assessments within the first 2 years of life are required as children with disease onset at this time are more likely to have the severe or intermediate forms of SMA, with a rapid decline in function. Once the child reaches two years of age having achieved motor milestones, an early severe form of SMA can be considered excluded and the follow-up frequency can be reduced, as less severe forms of disease are known to have later onset and slower functional decline. This will reduce the burden of clinical visits which can be balanced with minimising treatment related risks with less severe SMA. However, the heterogeneity of timing of disease onset for children unable to access treatment in Australasia (generally presymptomatic and > 3 *SMN2* copies) makes it challenging to determine the correct surveillance regime. For example, in 43 screen positive newborns identified with 4 *SMN2* copies there was no phenoconversion to symptomatic status noted in first 12 months of follow-up. Median disease onset for 268 screen positive newborns is 3y (range 1 month-6.4y). Of 4 presymptomatic children with this genotype (diagnosed through NBS and through family history), none showed symptoms by at 2.5 +/- 1 year. One child in a cohort series of 15 children with ≥ 4 *SMN2* copies developed symptoms by 8 months age.

References: Glascock et al. 2018. (169) Vill et al. 2021 and 2024, (158, 231) Muller-Felber et al. 2020, (172) Ricci et al. 2023. (183)

Values and preferences: Some variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, there is a potential for some variability in preferences for families as serial assessment every 3 months may confer on them a high logistical, financial (travel time, lost opportunity) and psychological burden.

Resources: Important issues not investigated.

There is no systematically collected information regarding the cost benefit of this Recommendation

Equity: No important issues, or potential issues.

The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation however the GDG agree that the Recommendation may help to reduce the health inequities for families of newborns who cannot access treatments immediately due to Australasian approval and reimbursement structures and provide a pathway of follow-up for families that have a risk of disengaging from healthcare services due to lack of access to treatment.

Acceptability: Some important issues identified

The recommendation is likely to have variable acceptance by stakeholders, with some families being unwilling or unable due to child and family circumstances to travel to specialist centres for surveillance and healthcare systems unable to maintain a sustainable surveillance strategy. The GDG acknowledges that there is no systematically collected evidence regarding acceptability factors of this recommendation.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Health system readiness for frequent surveillance is required for children not accessing SMN augmenting treatments.

Specific considerations (Strategies to promote implementation of the Recommendation):

Care coordination is required for children who are unable to access SMN augmenting treatments immediately, preferably overseen by designated clinical coordinators who will set out the timing of clinical visits. Surveillance may be shared between local and specialist centres dependent on child and family factors and preferences to support the frequency of assessment, whilst mitigating the surveillance burden on children and families.

RATIONALE

There are substantial benefits for implementing this recommendation for children, with the potential to magnify health gains, promote future functional independence and reduce comorbidities by reducing time to treatment, despite the fact that there is a low certainty of evidence on the therapeutic window for children who cannot access treatment in Australasia (generally those with > 3 *SMN2* copies) This recommendation also services to mitigate potential healthcare inequities caused by inability to access immediate treatment based on genotype.

However, it is considered as a moderate priority recommendation as the values, preferences and acceptability to all families is unknown and has the potential to be variable.

Practice standards

8.4.1. All children diagnosed with SMA through newborn screening should continue to have access to multidisciplinary standards of care, (35, 36) guided by the expertise of a paediatric neurology centre. Surveillance, intervention and care may be shared between local community (general practitioners and allied health therapists), secondary (paediatric) services and specialist (paediatric neurology) services, which is personalised according to the clinical status, needs and preferences of the child and family.

8.4.2. Newborns diagnosed with SMA may have additional motor assessments conducted as part of best practice care. These 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.

8.4.3. Newborns diagnosed with SMA may have additional neurophysiological assessments conducted including 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.

8.4.4. 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.

Information Box

The type of motor and neurophysiological assessments will vary dependent on jurisdictional capacity including training and expertise of the assessors conducting these assessments.

Recommendation 8.5

Consensus recommendation

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 services).

ADDITIONAL INFORMATION:

This recommendation is high priority. The recommendation is not developed with an evidence-based framework but formed through consensus.

EVIDENCE TO DECISION

Benefits and harms: Substantial net benefits

Substantial net benefits noted. The genetic complexity of the SMN region means that genetic counselling is essential within an NBS program and can inform and restore reproductive confidence for families of diagnosed children.

Certainty of evidence: Low certainty of evidence. Narrative review where the options for genetic cascade testing have been highlighted for families of children diagnosed with SMA through newborn screening programs. A further study with an implementation science framework highlighted the need for genetic counsellors to be part of the MDT to offer clarification of genetic implications for parents and the wider family.

References Rouzier et al.2020, (232) D'Silva et al.2022 (10)

Values and preferences: No variability in value or preference expected.

There is no systematically collected information regarding the preferences and values of stakeholders aligning with this Recommendation. However, the GDG agree that all families would value the opportunity to decide if they would like to seek further genetic clarification due to the substantial implications on future pregnancies within the family.

Resources: Important issues not investigated.

There is no systematically collected information regarding the cost benefit of this Recommendation

Equity: No important issues, or potential issues.

The GDG acknowledges that there is no systematically collected evidence regarding equity factors of this recommendation however the GDG agree that the Recommendation is not likely to have potential associated equity issues.

Acceptability: Some important issues identified

The recommendation is likely to have acceptance for all stakeholders. The First Nations representative on the GDG acknowledged that some families may not want to take up the opportunity to clarify the genetic status of the wider family, however agreed that this should still be offered to all families as best practice.

Feasibility: Some important issues identified

The implementation of this Recommendation is resource dependent. Across Australasia, genetic services are in demand with some health jurisdictions having long waiting lists. Feasibility is also based on resource allocation and personnel with appropriate training and expertise in this area, and a knowledge of reproductive options for families.

Specific considerations (Strategies to promote implementation of the Recommendation):

Training of the genetic workforce (including counsellors, clinical geneticists) will be important for implementation of this Recommendation. Focus should be placed on training the regional and rural genetic counsellor workforce so that families have timely access to genetic information to facilitate reproductive decision making. For specialist centres, the development of conjoint neurogenetic clinics may help streamline access to genetic counselling and cascade screening for affected families.

RATIONALE

There are substantial benefits for implementing this recommendation for families with the potential to restore reproductive choice and confidence. There are no potential equity, value/preference or acceptability issues however feasibility of implementation requires consideration and workforce training and planning.

Implementation Guidance

8.5.1. Sibling(s) (who have not previously had a newborn screen for SMA result through a state-based screening program) should be offered a clinical review within paediatric neurology services, at an appropriate time.

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

Research guidance

National clinical paediatric neurology centres should coordinate and establish databases to collect outcome data for newborns who have ≥ 4 *SMN2* copies and are under clinical surveillance, to establish an evidence-base to guide therapeutic and policy decision making.

Dissemination, implementation and evaluation of the Guideline

Dissemination and implementation of the Guideline

Overview

This Guideline provides a set of Evidence and Consensus 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. To ensure this is carried out equitably and efficiently, the dissemination and implementation of the Guideline is a necessary step to inform policy and practice and evaluating its usefulness and impact.

The Guideline should be reviewed and updated (at maximum) in 5 years (that is on or before the 1st of April 2030) or sooner if the screening, diagnostic or clinical landscape changes in the interim. The Guideline should be 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 identify and prioritise topics required for the identification of a new evidence base published since the search period for the existing Guideline. A future revised Guideline should advise on the scope and clinical questions for the evaluation and methods to identify and evaluate relevant evidence. continue to be systematic and align with the recommendations and approvals required by the National Health and Medical Research Council.

Dissemination

Pursuant to the publication of the Guideline, dissemination will be facilitated primarily through the Organising Committee, and further facilitated through a range of activities, conducted in close liaison with relevant professional colleges, societies and consumer representative organisations (Table 1). It is planned that 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 within the teaching hospitals across Australasia. 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.

Furthermore, emails will be delivered 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.

Table 1. Professional and consumer organisations invited to distribute the Guideline

Organisation	Audience
All state and federal health departments	Policy makers/ jurisdictional responsibility
Australian and New Zealand Child Neurology Society	Clinical decision making
Australian Genomics	Clinical decision making
Australian College of Rural and Remote Medicine	Clinical decision making
Australasian Association of Clinical Geneticists	Clinical decision making
Australasian Society of Diagnostic Genomics	Clinical decision making
Human Genetics Society of Australasia	Clinical decision making
Ministry of Health – Manatū Hauora	Policy makers/ jurisdictional responsibility
New Zealand Paediatric Society / The Paediatric Society of New Zealand	Clinical decision making
Queensland Aboriginal and Islander Health Council	Policy representatives, and advocates for Aboriginal health
Rare Disease Foundation Australia	Advocacy groups and families of children screened positive for SMA
Rare Disorders NZ	Advocacy groups and families of children screened positive for SMA
Rare Voices Australia	Advocacy groups and families of children screened positive for SMA
SMA Australia	Advocacy groups and families of children screened positive for SMA
Syndromes Without a Name	Advocacy groups
The National Aboriginal Community Control Health Organisation	Policy representatives, and advocates for Aboriginal health
The Royal Australian College of Physicians	Clinical decision making
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists	Clinical decision making

The Royal Australian College of General Practitioners	Clinical decision making

The methods of dissemination and purpose for each consumer group (healthcare practitioners, general public, consumer representatives, researchers, government sector) are discussed below (Table 2)

Table 2. Dissemination methods for stakeholder type

Audience	Purpose	Method
Healthcare practitioners	Increase awareness and adaptation of Guideline Improve best standards of care Ensure equitable and timely delivery of services	GDG to circulate with peers. Conference presentations. (e.g. ANZCNS congress, RACP congress, HGSA annual scientific meeting) Forwarded via organisations contacted (Table 1) Published in International Guidelines Network Publications in journals Incorporation into student teaching
Researchers	Increase awareness of Guideline Contribute to international best practice standards around newborn screening and SMA.	Conference presentations (e.g. ANZCNS congress, RACP congress, HGSA annual scientific meeting) Publications in journals Published in International Guidelines Network GDG to circulate to peers
Consumer representatives	Increase awareness of Guideline. Ensure advocacy is in line with best practice expectations.	Personalised emails to relevant representatives with links to documents. SCHN/UNSW media launch and external media engagement
Government sector	Increase awareness of Guideline Jurisdictional responsibility for ensuring standards are met.	Personalised emails to relevant representatives with links to documents.
General public	Increase awareness of Guideline	Newsletters and social media SCHN/UNSW media launch and external media engagement

Abbreviations: GDG, Guideline Development Group; ANZCNS, Australia and New Zealand Child Neurology Society; RACP, Royal Australasian College of Physicians; HGSA, Human Genetics Society of Australasia; SCHN, Sydney Children's Hospital Network; UNSW, University of New South Wales.

Evaluating the effectiveness of dissemination

The evaluation of the dissemination phase will be considered from the perspectives of healthcare practitioners, jurisdictional bodies, consumers and consumer representatives, and the general public. Continual evaluation of the effectiveness of dissemination will be enabled through a dedicated section on the website for ongoing feedback and impact of the Guideline.

Table 3. Evaluation methods and metrics

Evaluation tool	Details	Proposed Metrics
Downloads	Total download number for each document via UNSW website	150 downloads within first 12 months
Website traffic	Total views for each document via UNSW website	1000 views within first 12 months
Conference presentations	Total number of presentations to target audiences	Guideline presented at 4 national conferences within 12 months and 2 international conferences within 12 months
Consumer surveys	General awareness of documents (in particular family fact sheets) for parents who have received an SMA positive result for their child	Metrics to be established by consumer advisory group (high level of awareness expected)
Healthcare surveys	General awareness of documents for relevant professionals.	Metrics to be established by consumer advisory group (high level of awareness expected)
Endorsements	Total number of organisations	Endorsements by 12 organisations, including primary targeted organisations (SMA advocacy groups, ANZCNS, HGSA).
Jurisdictional incorporation	Total number of health jurisdictions utilising the Guideline	All government bodies representing states, territories, and regions.
Social media	Total number of posts	12 posts by relevant organisations
Traditional media	Total number of articles	2 articles published
Scientific articles	Impact of journal article	Citations

Implementation

The overall goal of the Guideline is to standardise newborn screening for SMA to diagnose children and improve access to management for children with this condition, and to optimise their health and psychological benefits. The implementation of recommendations in the Guideline are the responsibility of each state and territory in Australia (which has a non-federated system) and of Aotearoa New Zealand. The implementation of the Guideline is facilitated by the fact that newborn screening programs are well established across Australasia and screening for SMA will be incorporated into routine screening panels. Scoping programs have been conducted in several jurisdictions to establish the barriers, facilitators of implementation and best practice standards. (10, 12)

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 facilitate implementation 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.

Whilst all recommendations in the Guideline are considered as **key recommendations** and as such should be implemented, consensus recommendations have associated prioritisation categories which are meant to help healthcare jurisdictions implement recommendations in a staged manner based on their priority level. However, the Guideline and the recommendations therein are an adjunct to and do not replace healthcare practitioner judgement in each case. More details on the barriers to implementation and the methods with which they may be mitigated are discussed in Table 4.

Table 4: Potential barriers/risks and mitigating strategies to facilitate implementation

Barriers/risks	Contextual factors	Mitigating strategies
Challenges in accessing healthcare practitioners to conduct post diagnosis activities, treatment planning, care and support in a timely manner.	Health care workforce capacity limited in some jurisdictions and typically located in specific (metropolitan) hubs.	Leveraging existing Australasian healthcare infrastructure that includes well established specialist (paediatric neurology), children's (paediatric) and multidisciplinary services. These networks are used to managing children within and between states and territories and accepting and prioritising referrals for children with emergency and complex needs. The Recommendations within the Guideline have been formed from an Australasian perspective with specific consideration regarding the need to work collaboratively within networks and prioritise children with a positive screening result.
Inability to identify all children at risk of SMA with current target analytes and assays	Current screening assays identify the 95% of children with absence of *SMN1* due to biallelic deletion on exon 7.	Ongoing national/international research into new technologies that can identify the 5% of the population with an alternative genotype and future review of the Guideline to align with the changing landscape of genomic technologies.
Increased demand for reproductive counselling, cascade testing and preimplantation genetic testing	Altering the diagnostic pathway, shifting it from a clinical diagnosis triggered by clinical signs to a newborn screening triggered diagnosis.	Expansion of neurogenetic services and adopting the MDT style of care (with access to genetic and neurology services in one location). Members of the wider multidisciplinary team could augment roles as information and support providers dependent on jurisdictional resources and capacity. Updating educational resources to provide tailored and accurate information regarding the processes and implications of reproductive genetic testing.
Lack of speciality knowledge, and access to those with specialist knowledge.	Particularly noticeable for rural regions where specialists are less accessible.	Utilisation of telehealth services to enable a hub and spoke model of care where paediatric neurology services guide and support local healthcare practitioners in post diagnostic care and treatment surveillance. Education program development with implementation strategies to be codesigned with relevant stakeholders to disseminate knowledge of the condition, treatment options and best practice considerations.

Different organisational demands and infrastructure between health jurisdictions	Laboratories may use different technology and protocols. Varying catchment areas for laboratories and hospitals may lead to different processing times.	Recommendations are assay agnostic and therefore there is flexibility for each jurisdiction to utilise technology and services available to them.
Widening of health inequities	Introduction of genetic testing to the newborn screening program may lead to disengagement and reduce the uptake for the overall program. Data sovereignty and potential for genetic discrimination may be particularly important concepts for indigenous families and those within CALD populations.	Public dissemination of information as to the benefits and risks of newborn (genetic) screening for SMA and educational resources that are codeveloped by these groups and address their specific needs and concerns.
Missing awareness about this Guideline and why it is necessary, by healthcare practitioners and advocacy groups.	Newborn Screening for SMA is a recent development and not all states and territories currently administer these pathways.	The Guideline will be disseminated across the spectrum of stakeholders through relevant channels (Table 1).
Missing awareness about this Guideline by families/ general public.	SMA is a rare disease and relatively unknown within the broader community. Best standards of care are similarly unknown.	Co-design and co-development of educational resources for families and advocacy groups guided by the formation of a National Consumer Advisory Group (CAG). The CAG will contribute to equitable access to information and support across Australasia, enabling the successful translation of the Guideline. This group will seek specific input from Culturally and Linguistically Diverse groups and Aboriginal, Torres Strait and Pacific Islander, and Māori people, and will be tasked with the responsibility of ensuring relevant platforms provide the necessary education nationally (including the production and dissemination of multimedia resources), while aligning with this Guideline. (Recommendations: 5.3,7.2, 7.3)

Inequitable access and delivery of healthcare arising from sociodemographic factors including cultural and linguistic barriers	Contributing factors include health literacy, socio-economic differences, geographical location of communities in relation to health services.	The CAG will seek specific input from Culturally and Linguistically Diverse groups including Aboriginal, Torres Strait and Pacific Islander, and Māori people to develop resources that are informed by and meet the needs of the community. Financial and travel support for families with financial difficulties to enable access to best care and treatment. Education and training for the Indigenous healthcare workforce on the aspects of newborn screening for SMA that can facilitate support for families (Recommendations 5.3. 7.3.)
Consistent application of the Guideline over time	Interest may peak at the initial implementation but peter out as activities lessen.	Screening and diagnostic laboratory annual reports will be part of quality assurance, auditing activities. Clinical services will be encouraged to audit post diagnosis activities, pathways and outcomes as part of quality improvement studies. The Guideline will be reviewed at maximum within 5 years to ensure it adequately meets best practice standards and those standards are being met. Auditing of screening and diagnostic services, along with clinical referrals and time of diagnosis, will reveal whether outcomes are consistent, and what alterations are necessary.
Challenges satisfying the timelines within the recommendations	Costs associated with personnel and staff time to expedite diagnostic assays and reporting Geographical challenges in specimen collection and distribution to diagnostic laboratories and access to specialist services for families for regional and rural communities. Timely access to necessary services	Where possible, recommendations take advantage of existing structures and processes within the Australasian healthcare system. Auditing of screening and diagnostic services and timelines will indicate where changes are necessary. (Newborn) screening laboratories have pre-established annual audits of implementation timelines, and accuracy of assays which will be leveraged to facilitate streamlined processes and maintain the quality of newborn screening for SMA. Utilisation of technology to streamline processes and overcome geographical distances including telehealth., empowering to local healthcare practitioners to facilitate care and intervention (with paediatric neurologists supporting this process).

		Jurisdictions will be encouraged to establish a workflow that involves coordination and communication between screening, diagnostic and clinical care stakeholders to meet the timelines within the Guideline.
Costs of implementation	Healthcare resourcing is finite within Australasia with complex funding streams for screening, diagnosis and clinical care services.	Economic analysis shows that newborn screening for SMA coupled with treatment reduces long term costs and associated demands on healthcare services.

Evaluating the impact and implementation of the Guideline.

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 implementation and 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. The members of the organising committee have expertise in clinical research and implementation science and are well placed to evaluate the awareness, understanding and impact of the Guideline. As such, it is envisaged that the impact and implementation of the Guideline may be evaluated using the following strategies.

Table 5: Mixed qualitative and quantitative methods to assess awareness, understanding, and impact of the Guideline.

Evaluation strategy	Details
Longitudinal data collection of outcomes for newborns diagnosed with SMA	This will consider health indicators for newborns diagnosed with SMA with newborn screening. In particular, improvement in quality of life, attainment of motor milestones, and time to diagnosis within and between health jurisdictions. Particular attention will be given to comparisons of health outcomes between areas of high and low Guideline uptake.
Screening laboratory annual reports	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. (Recommendations: 1.1, 1.2, 1.3, 2.1, 2.2, 3.2, 4.1, 4.2, 5.1)
Evaluation of model of care across health jurisdiction	This may include assessment of the temporal processes such as time to screen positive result, diagnostic evaluation, confirmation of diagnosis and time to treatment plan and initiation alongside the longitudinal evaluation of the short- and long-term clinical outcomes for children screening positive for SMA. (Recommendations: 1.2, 1.3, 2.1, 2.2, 3.3, 3.4, 5.1, 5.2, 61, 8.4)
Consumer surveys for general public	The public acceptability of the newborn screening for SMA program as guided by the recommendations within the Guideline, and the barriers, facilitators and impact of implementation from a consumer perspective. (Recommendations 4.1, 5.3, 7.2, 8.5). These surveys will also seek to evaluate consumer understanding and knowledge of newborn screening for SMA.
Consumer surveys for CALD, Aboriginal, Torres Strait, Pacific Islander, & Māori peoples.	To ensure equitable delivery of healthcare to all Australians and New Zealanders, these surveys will be conducted to ensure accessibility, awareness, understanding, and use is felt and delivered equally to these communities, when compared with the general public. (Recommendations 5.3, 7.3)
Healthcare professional surveys	These surveys will evaluate whether the Guideline has changed clinical practice and the magnitude and direction of this change. This survey will seek to evaluate challenges arising for healthcare practitioners in screening, diagnostic, clinical care, and advocacy domains. Surveys will also be utilised during a maintenance phase to understand challenges that may arise if initial interest and awareness in the Guideline changes. Particular attention will be given to understanding why Guideline uptake may differ between regions and what can be done about this.
Sustainability and economic analysis	To determine capacity restraints, human resource availability, intervention costs, staff recruitment and turnover, and local context adaptation. This will be vital to the Guideline review process.

Abbreviations: CALD, Culturally and Linguistically Diverse

References


SMA
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Index

Appendix A: Consumer guide

INTRODUCTION

Thank you for taking the time to access this Guideline. We include a summary of its purpose, steps we took to form the Guideline and a summary of the recommendations for Newborn Bloodspot Screening (NBS) for Spinal Muscular Atrophy (SMA).

On the following pages you will find:

- What is SMA?
- What is NBS for SMA?
- Why are these guidelines needed?
- The process of the project.
- Newborn screening timeline.
- Overview of guidelines.

If you would like a more detailed version of the Guideline please access the full report located on the home page.

WHAT IS SMA?

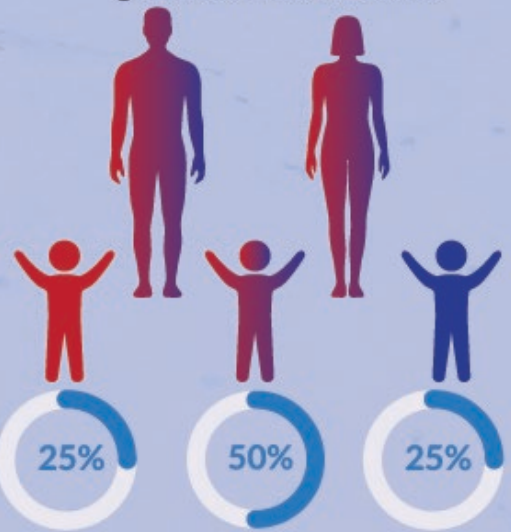
SMA is caused by genetic variations in the survival motor neuron 1 (*SMN1*) gene. This creates a lack of survival motor neuron (SMN) protein. A lack of SMN protein leads to a loss of motor nerves from the spinal cord and brainstem.

This leads to muscle wasting, weakness and can cause difficulties with movement, breathing and feeding.

All of us have a related gene called survival motor neuron gene 2 (*SMN2*) that can produce some SMN protein to make up for the loss of the *SMN1* gene. The number of copies of *SMN2* is different between people and changes the severity of SMA.

Generally people who have more copy numbers of *SMN2* have a milder form of SMA.

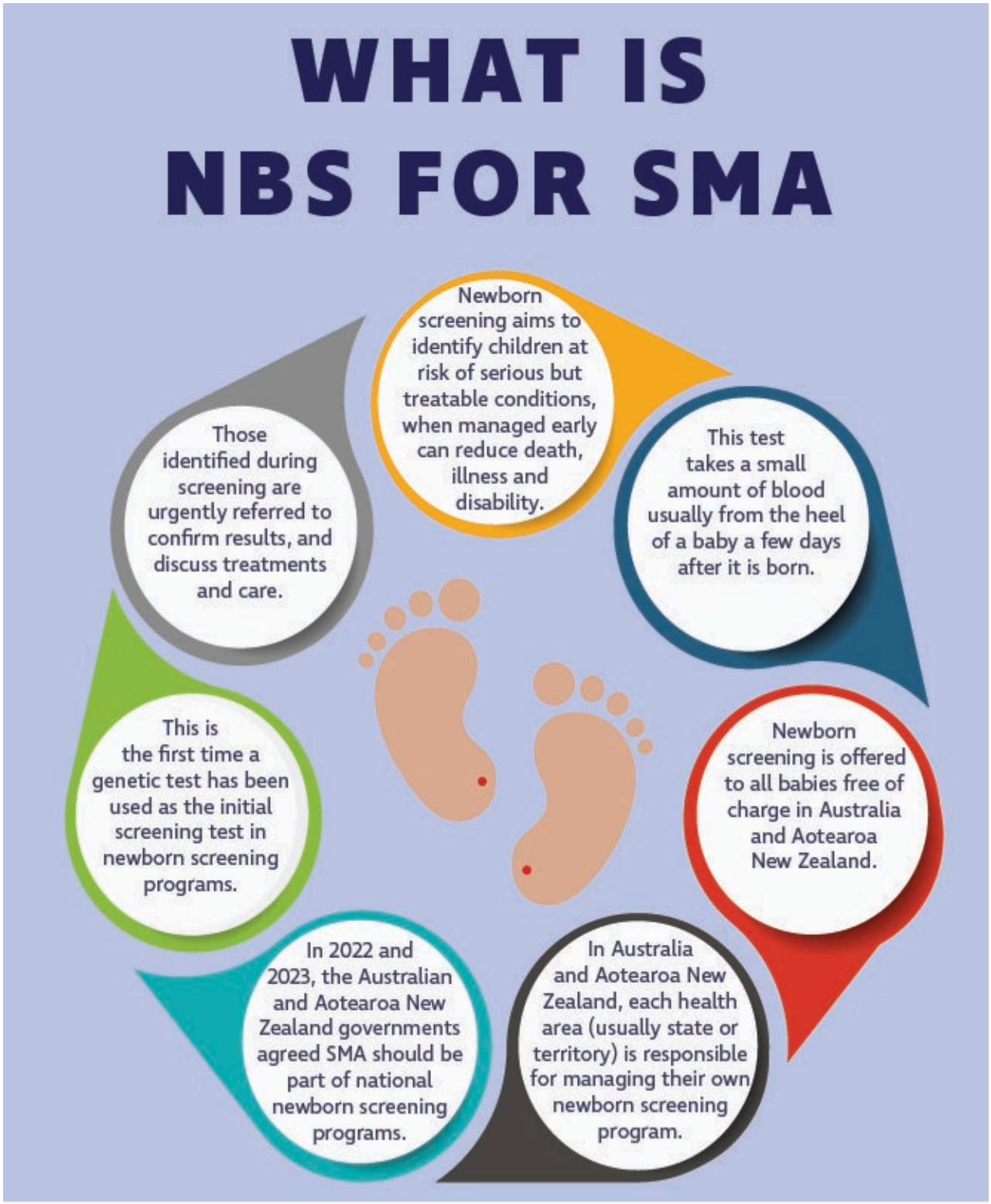
How SMA is typically inherited:
If both parents carry the genetic variant in *SMN1*



Child will not have SMA.

Child will be a carrier.

Child will have SMA.


WHAT IS
NBS FOR SMA
Newborn screening aims to identify children at risk of serious but treatable conditions, when managed early can reduce death, illness and disability.
This test takes a small amount of blood usually from the heel of a baby a few days after it is born.
Newborn screening is offered to all babies free of charge in Australia and Aotearoa New Zealand.
In Australia and Aotearoa New Zealand, each health area (usually state or territory) is responsible for managing their own newborn screening program.
In 2022 and 2023, the Australian and Aotearoa New Zealand governments agreed SMA should be part of national newborn screening programs.
This is the first time a genetic test has been used as the initial screening test in newborn screening programs.
Those identified during screening are urgently referred to confirm results, and discuss treatments and care.

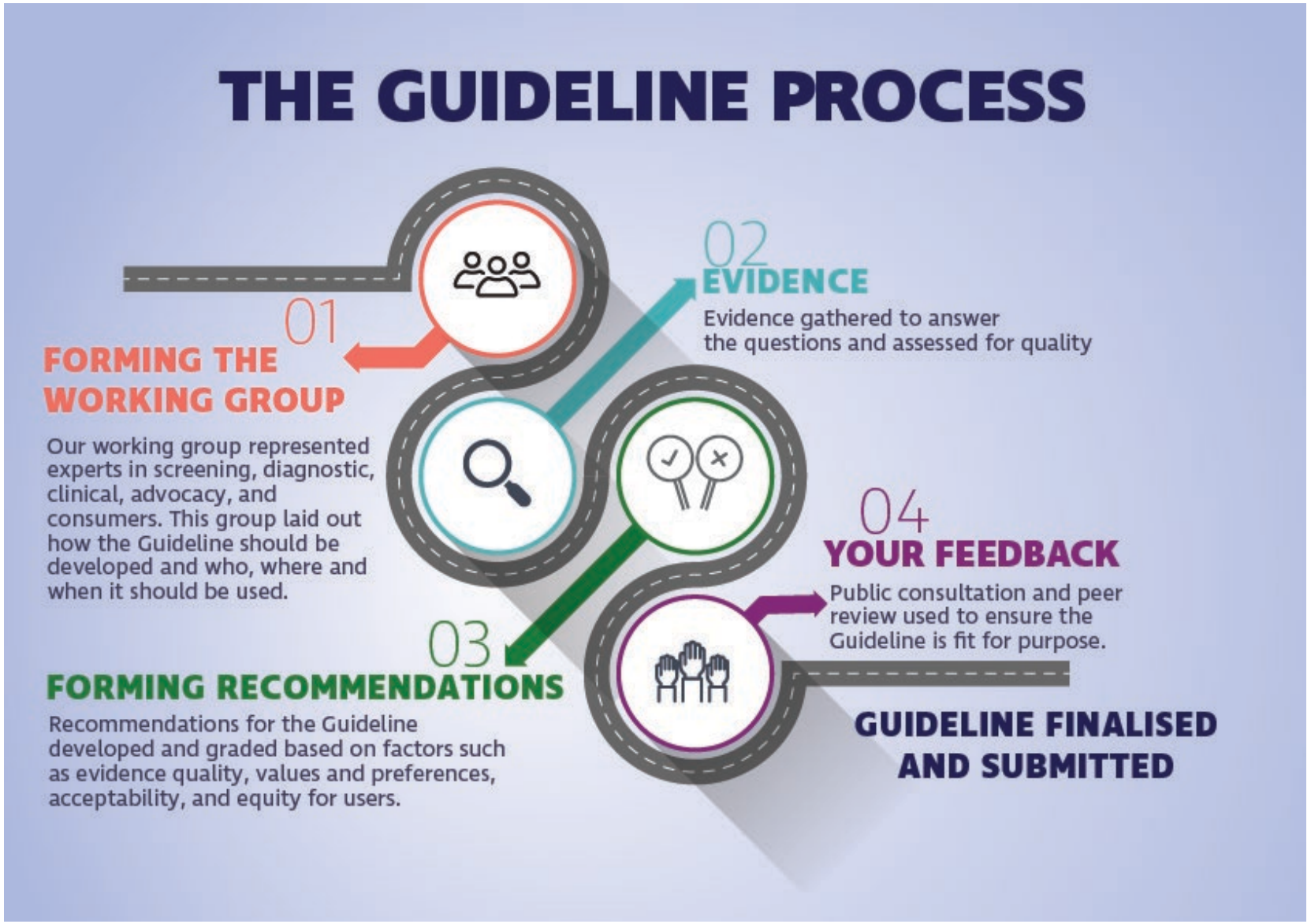
WHY WE NEED A GUIDELINE?

This Guideline aims to provide recommendations that improve the care of newborns based on the best available evidence.

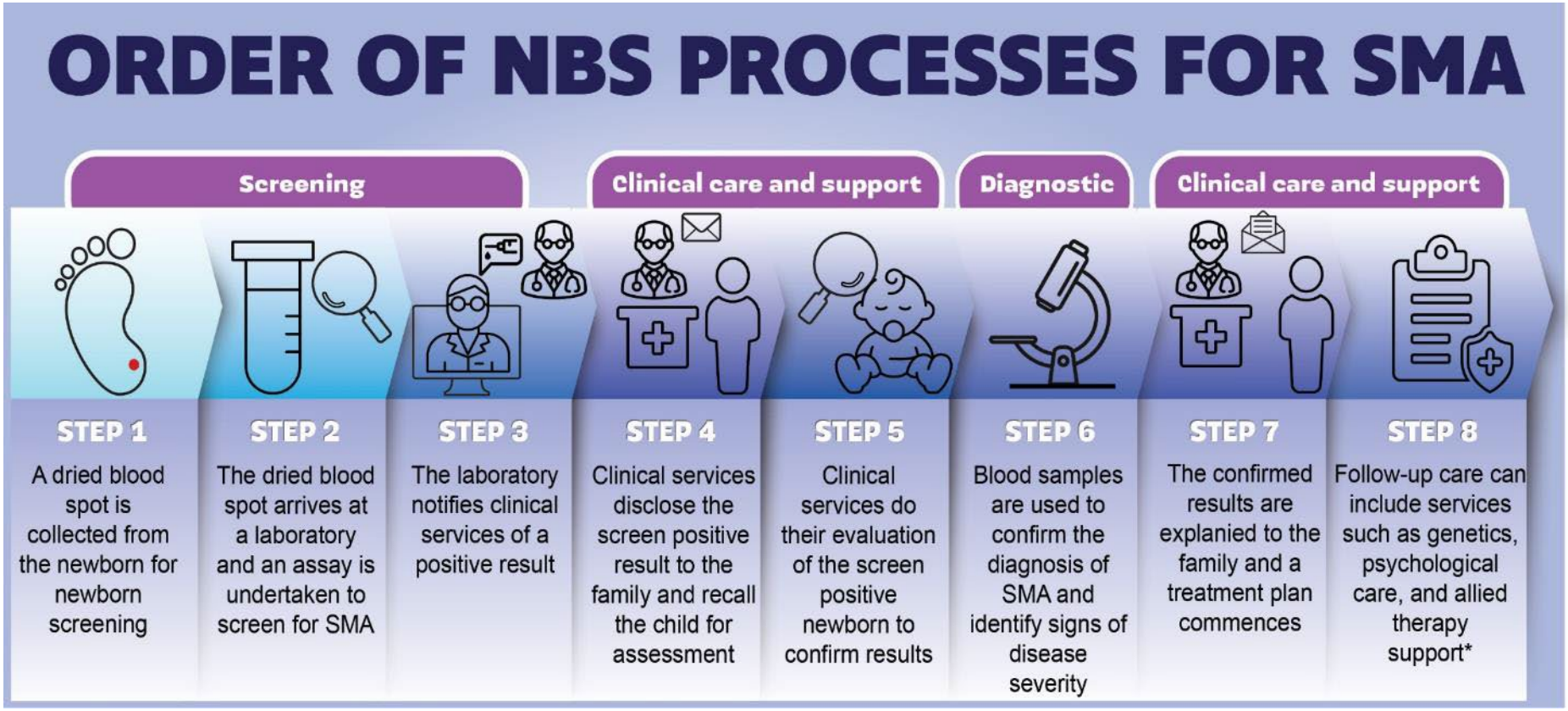
Its important whoever you are or where you live in Australia and Aotearoa New Zealand, that you and your baby will have access to the best care and support available.

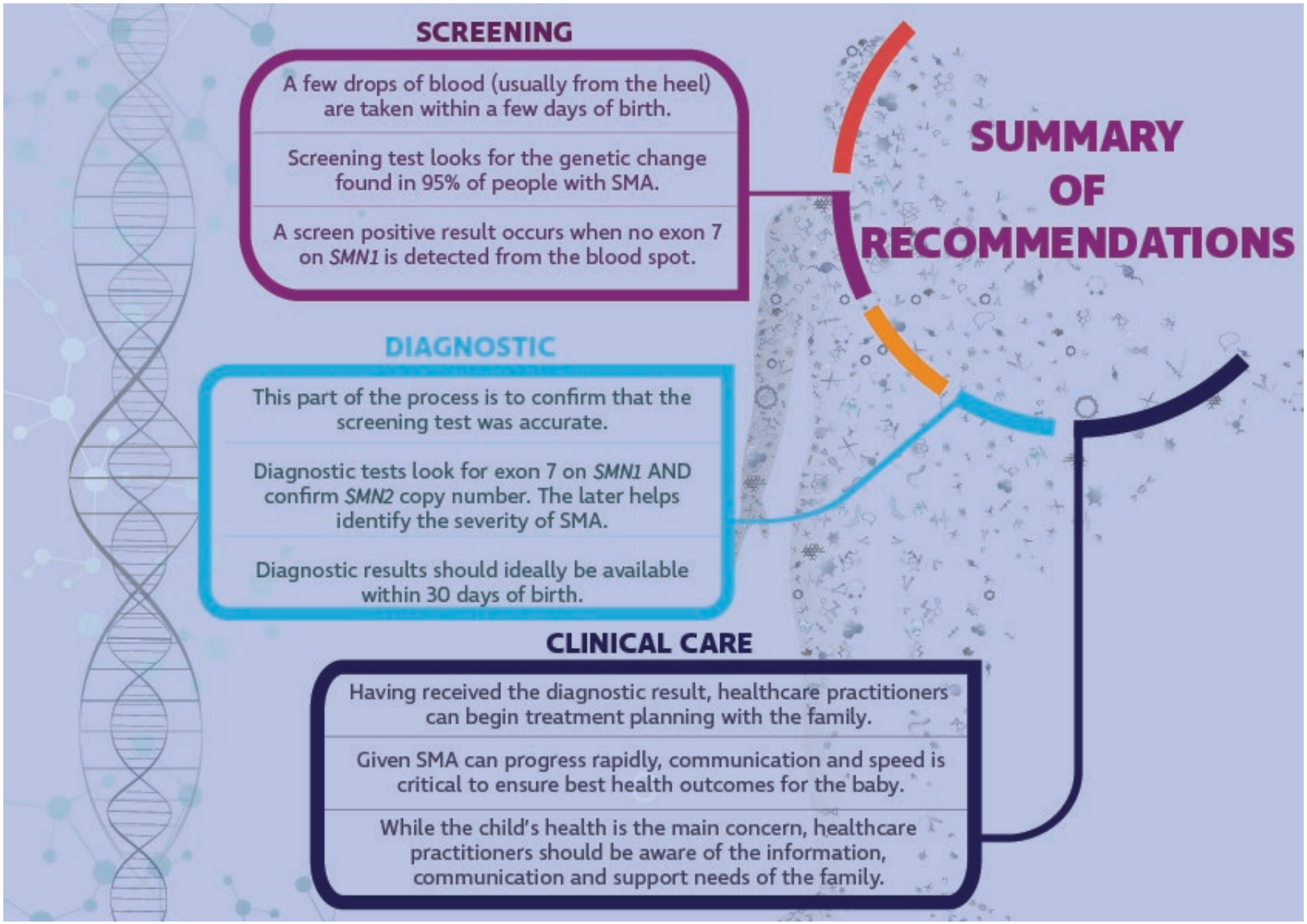
The Guideline has been developed so that babies and their families living in remote areas can access diagnosis, treatment and care quickly and effectively.

The Guideline provides recommendations on how we can provide best care that is tailored to the needs, values, and prefences of families.


THE GUIDELINE PROCESS
01
FORMING THE WORKING GROUP
Our working group represented experts in screening, diagnostic, clinical, advocacy, and consumers. This group laid out how the Guideline should be developed and who, where and when it should be used.
02
EVIDENCE
Evidence gathered to answer the questions and assessed for quality
03
FORMING RECOMMENDATIONS
Recommendations for the Guideline developed and graded based on factors such as evidence quality, values and preferences, acceptability, and equity for users.
04
YOUR FEEDBACK
Public consultation and peer review used to ensure the Guideline is fit for purpose.
GUIDELINE FINALISED AND SUBMITTED

ORDER OF NBS PROCESSES FOR SMA




SUMMARY OF RECOMMENDATIONS
SCREENING
A few drops of blood (usually from the heel) are taken within a few days of birth.
Screening test looks for the genetic change found in 95% of people with SMA.
A screen positive result occurs when no exon 7 on SMN1 is detected from the blood spot.
DIAGNOSTIC
This part of the process is to confirm that the screening test was accurate.
Diagnostic tests look for exon 7 on SMN1 AND confirm SMN2 copy number. The later helps identify the severity of SMA.
Diagnostic results should ideally be available within 30 days of birth.
CLINICAL CARE
Having received the diagnostic result, healthcare practitioners can begin treatment planning with the family.
Given SMA can progress rapidly, communication and speed is critical to ensure best health outcomes for the baby.
While the child's health is the main concern, healthcare practitioners should be aware of the information, communication and support needs of the family.

Appendix B: Public Consultation and Feedback

Public consultation summary document

Organisation /Individual	Feedback	Changes made	Oversight Committee review
[*redacted*]	The report appears very comprehensive. One area that could be bolstered is the role of clinical genetics in SMA and other genomic newborn screening. If this is not adequately included then the genetic support for genomic newborn screening will be diminished at the expense of the direct and indirect family. We are somewhat biased at [*redacted*] given our model mostly means that a genetic counsellor usually joins the paediatric neurologist at the first appointment. I think it would be useful to have a genetic counsellor as a member of the working group to contribute to this component of the pathway. I don't think the genetics aspects of newborn screening are being adequately considered. Many of the psychosocial supporting clinicians provided by the MDT do not feel confident addressing the genetic questions that families inevitably have (reproductive carrier testing,	 The GDG has already been formed and therefore this feedback cannot retrospectively be actioned. The role of clinical genetics services and genetic counsellors have been expanded in the background of section 5 which now reads "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-	 Agree Agree

	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). A genetic counsellor can provide support and provide detailed knowledge around the genetic aspects of an SMA diagnosis. These questions are usually raised at the same time of the diagnosis disclosure and access to a genetic counsellor (F2F or via telehealth) is an essential component of care to support the family through a very stressful time.	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. “ 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).(214) 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 5.1.1. 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. **Information Box** Dependent on child and family circumstances, it may be appropriate for a designated healthcare practitioner with support from the paediatric neurologist through telehealth to disclose a screen positive result to the family. The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians, neonatologists, specialist nurses and/or genetic counsellors. 7.2.2. 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	

	I can see that referral recommendations to clinical genetic services are present but they appear optional or something that can be addressed later issue which is not our experience.	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. The recommendation has been revised and is a high priority Recommendation 8.5 Consensus recommendation 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 services).	
[*redacted*]	Congratulations on this, it's a great draft. I do however have two concerns: **Genetic Counsellors (GCs) should be mentioned as specific health care practitioners in the guideline** o Families value the education and psychosocial support routinely provided by after a NBS screening diagnosis per our pathway here at [*redacted*]. [*redacted*] is a Genetic Counsellor who did a study comparing our SMA NBS cohort with the Metabolic NBS cohort from [*redacted*]who do not receive genetic counselling. The results demonstrated the benefit of genetic counselling after a NBS diagnosis. [*redacted*] o There are numerous GCs in Regional Settings available to support local Medical	The role of genetic counsellors has been further highlighted through the Guideline in view of the feedback in the following sections. Background section 5: 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. The role of genetic counsellors and clinical geneticists have been reinforced throughout the recommendations Practice Standards 5.1.1. 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. **/nformation Box** Dependent on child and family circumstances, it may be appropriate for a designated healthcare practitioner with support from the	Agree

	Practitioners when disclosing the diagnostic results. This has not been mentioned in this document and I feel that it needs to be. A regional GC is the ideal person to provide follow up support and education for the family, as well organising cascade testing and advice for future pregnancies. This would be done by a GC rather than a Clinical Geneticist, as is the case in our pathway.	paediatric neurologist through telehealth to disclose a screen positive result to the family. The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians, neonatologists, specialist nurses and/or genetic counsellors. 7.2.2. 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. 7.2.4. 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. **Information Box** 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. Recommendation 8.5 Consensus recommendation 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 services).	Agree

	Aside from these points, I think it is a very exciting to see this come together. Congratulations again on a wonderful document! **At least one GC should be present on the Guideline Development Group** Given the importance of the role, the Guideline Development group would benefit from a GC's detailed subject-specific knowledge in the area.	The GDG has already been formed and therefore this feedback cannot retrospectively be actioned. However, the public feedback system has targeted a number of genetic peak bodies for feedback.	
[*redacted*]	The feedback from one colleague was to please replace "New Zealand" with "Aotearoa New Zealand" in all documents P25 of the Guideline "… internationally developed SoC for SMA.." - References 25 and 26 are quoted. I wondered whether specifically for SMA the reference 50 and PMID: 29305137 (which is not listed as a reference at all) would be more appropriate. P59 of the Guideline - there are two recommendations 10.15 and two recommendations 10.17 – 1 of each should be 10.14 and 10.16, respectively. Page 106 Fig 4 – SMN2 produces 6 hexagons worth of full length SMN protein in a healthy individual but only 3 in a SMA patient – not sure what this is meant to indicate?	Aotearoa has been added All references are now aligned These recommendations have been reconfigured and realigned The Figure has been redesigned to be representative	Agree Agree Agree

	Again, my respect and congratulations for your amazing work!		
[*redacted*]	[*redacted*] in the Newborn Bloodspot Screening (NBS) decision-making pathway, which ensures national consistency in partnership with states and territories 2. Spinal Muscular Atrophy (SMA) is a condition listed for screening as part of the NBS program 3. Children born in [*redacted*] with SMA would be cared for in partnership with sub-specialists based at institutions such as [*redacted*].	No changes required	Agree
[*redacted*]	Health and Social Policy Branch has reviewed the draft Guideline and do not have any specific feedback. [*redacted*] is committed to participation in the national process underway to achieve national consistency for NBS, and I commend you and your team on your work to support these principles. I look forward to reading the final version of the guideline when published.	No changes required	Agree
[*redacted*]	Upon review of both the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand Guideline Document, as well as the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand Administrative and	As per NHMRC guidance, grading process is preferable in both documents	

	Technical Report, there were noted areas of repetition that may be truncated or condensed to enhance accessibility and readability. Specifically, but not exhaustively: 1.Grading the direction and strength of evidence-based recommendations Page 85 Page 84 While not a word-for word repetition, suggest limiting to one document 2.Stakeholder consultation activities – systematic observation form evidence on page 89 Systematic observation forms to collect expert evidence on page 77 Text repeated word for-word 3.Healthcare practitioner survey (modified Delphi process) Page 91 Page 79 Text repeated word for-word		
[*redacted*]	[*redacted*] supports the implementation of the National Recommendations for Newborn Screening in Spinal Muscular Atrophy guideline.	No changes required	Agree
[*redacted*]	• P21 whilst I agree that 'back up gene' is not an ideal term for SMN2, to me the phrase 'nearby related gene' is a bit confusing, so I wonder if it would be clearer to say 'related gene… located near SMN1'? • P25 Population – I know it is mentioned further on, but I wonder whether it would be good to mention early in the document that	This has been corrected and now reads related gene, located near SMN1. This has been incorporated and now reads Guideline purpose, scope, population and settings: Whilst incidence and prevalence varies between groups, SMA affects all ethnic populations.	

	SMA affects all populations/ethnic groups (albeit at varying frequencies)
	• I note that you have varyingly referred to absence/loss of SMN1 as 'deletion' throughout the document
	  • I suggest that you are consistent
	  • In most places throughout the document I think it is most correct to avoid the term deletion – as this implies mechanism for the loss of SMN1, whereas the testing that we do is just quantitative and only tells us whether SMN1 is present, not how it was lost. I understand that a significant proportion of patients are thought to have lost their SMN1 through gene conversion rather than deletion per se
	  • Suggest using loss, absence, deficiency.
	  • Suggest adding 'clinical' to geneticist throughout the document (where that Is what you mean!) – including the diagram
	  • P39 I think it would be useful to add that sometimes testing of parents is suggested to try to work out why there is a false positive or uninterpretable result
	  • P42 – I think the term 'responsible medical practitioner' is ambiguous – I
		Whilst the screening assays are targeted at biallelic deletion of exon 7 in SMN1 and have thus remained the same, where appropriate, absence of exon 7 on SMN1 has been added.
		
		This has been changed
		
		The word clinical has been incorporated throughout the document.
		
		This has now been added as a good practice point which reads Implementation Guidance
		4.2.2. Blood samples from parents for *SMN1* quantification purposes should be considered to understand the aetiology of a false positive or uncertain result for the newborn.
		
		This has now been changed to designated healthcare practitioner throughout the document.
			Agree to all feedback

	presume you mean responsible for the patient rather than someone not irresponsible! P46 – there are a few places where you say 'venous sampling for SMN1' – I don't think this makes sense? Should be it venous sampling for quantification of SMN1? – and then similarly, venous sampling for determination of SMN2 copy number? • P100 – in 1st paragraph – you mention the scenario of two sequence variants – but they need not necessarily be homozygous – is more correct to say 'biallelic sequence variants' (could be homozygous or compound heterozygous). • P114 I think the more correct term is 'reproductive genetic carrier screening' (but noting that the MBS uses 'testing' not screening)	Now changed and reads Recommendation 6.1 Consensus recommendation The following assessments should be 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* exon 7 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. This has now been altered. This has now been changed to reproductive carrier testing.	

	• P117 last paragraph & p119 – I don't think the sequence variant needs to be in exon 7 – there are recurrent variants in exons 1,3 & 6 in particular P161 you mention the phrase 'done incorrectly' - I am not sure that this is a binary thing - right or wrong – I suspect it is better to reword this in a way that says we want to deliver this devastating news in the most constructive/least traumatic way possible rather than correct vs incorrect • I note the use of the term 'allied therapist' in several places throughout the document – I am more familiar with - 'allied health therapist/specialist/professional'? • I wasn't sure whether I was looking in the right place for ref 24, 25 and 26 below – which don't appear to match the numbered ones at the end of the document	Please see ICER comments This has been changed and now reads in the background of Section 5: *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 term has now been rewritten as allied health therapist throughout the document. The references have been realigned	
[*redacted*]	Section 5: Disclosing a screen positive result to families [*redacted*] recommends that written information, either as a standalone document or by referral to a website, is provided to parents immediately following the disclosure phone call. This information should be available in an accessible format and in different languages. The 2021 Census shows that a language other	Additions have been made to reflect the feedback. 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. This now reads Practice standard	

	than English is used in 28% of households in [*redacted*] (Cultural diversity: Census, 2021 | Australian Bureau of Statistics (abs.gov.au)). We suggest the written information provided to families includes plain language information for recommendation	8.3.4. Families 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. Written information as a standalone document or direction to a well-curated, reliable and up to date website should be 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.	
	5.10 advising families to contact the medical practitioner 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. It is unlikely that parents will be able to remember or assess clinical signs without written resources and accessible support from a health professional. Alternatively, this recommendation may need to be simplified to alerting a health professional if parents have any concerns about their newborn rather than listing the clinical signs which may be too burdensome for newborn parents who have received a positive screening result.	Practice standard 5.2.2. Healthcare practitioners should instruct families **and provide them with written information** as to when immediate contact is required to facilitate urgent clinical review for their screen positive newborn/infant. Circumstances include • 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	

	Section 3: Confirming the diagnosis of spinal muscular atrophy. We recommend the timeline for diagnostic results is clearly stated in the guidelines. For example, results are required such that treatment can begin by 6 weeks of life, if this is consistent with the evidence provided below in Section 3. 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 normal motor development trajectories, independent of SMN2 copy number. Therefore, time to diagnosis and subsequent treatment appears to be a substantial modifier of health outcomes for these children. Section 4: Managing uncertain, false positive and false negative screening results We suggest that lessons or insights derived from the 'root cause analyses' of false positive/false negative or uncertain results are shared between Australasian Newborn Bloodspot services so that common issues and errors can be identified. This would be in addition to the knowledge exchange activities described below in Section 4. The Guideline Development Group (GDG) highlighted the need to undertake knowledge	Recommendations 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. Recommendations 3.4. A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 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. Implementation Guidance 4.2.3. 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 issues and errors can be identified as part of quality improvement.	

	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).		
	Section 7: Information provision to families during the diagnostic evaluation of a screen positive newborn and after confirming the diagnosis of SMA We recommend nationally consistent and up to date information is available to all families who receive a screen positive newborn result and a diagnostic positive result based on the evidence below from Section 7. 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.	Section 7 background: 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. Recommendation 7.2 Consensus recommendation 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 reflect the contemporary care landscape and are nationally consistent.	
	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. We recommend there is a smooth process to transition the	Recommendation 7.2 Consensus recommendation 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 reflect the contemporary care landscape and are nationally consistent.	

	newborn from screening, diagnosis and post diagnosis across clinical care, with information and resources and psychosocial support throughout. The process should 3 Guideline Feedback recognise each family will be at different stages of understanding the information and be tailored to each families' unique needs based on the information below from Section 7. 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. Section 8: Delivering the diagnosis and supporting families as they receive the diagnosis of SMA Consistent with Section 7 and recognising the intent of the GDG in addressing the psychological and support needs of families, we recommend all families either have a psychosocial support healthcare professional present at the appointment or receive a phone call offering psychosocial support to the family after the results disclosure.	Practice standard 7.2.1. Clinical services should provide families with information that is compassionate, accurate and tailored to their information needs and preferences. Information provided may include information on the (genetic) cause and clinical implications of SMA, next steps and approximate timelines to confirm a diagnosis, information on psychosocial supports (including referral to social work services), and/or psychology and/or advocacy services. Practice standard 8.3.4. Families 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. Written information as a standalone document or direction to a well-curated, reliable and up to date website should be provided to families that will inform them on the potential benefits, risks, uncertainties of SMN augmenting	

	Section 10: Treatment planning and initiation for newborns and infants diagnosed with SMA through newborn screening programs We suggest that written information or website information is provided with Recommendation 10.9 where medical practitioners will explain to families and document the potential benefits, risks, uncertainties of SMN augmenting treatments and need for long term surveillance. This information must be available in accessible format and in different languages. The recommendations 10.15 onwards refer to the newborn diagnosed with SMA "through newborn screening" where this terminology has not been used in the other recommendations. It is unclear whether the clinical recommendations apply to newborns diagnosed with SMA regardless of whether it is through newborn screening or clinically following a negative newborn screen. Guideline impact For [*redacted*], and likely other jurisdictions, the guideline will alter the diagnostic pathway, shifting it from a clinical diagnosis triggered by clinical signs to a newborn screening triggered diagnosis. The implementation of additional newborn and reproductive screening will increase the demand for both reproductive counselling and pre-implant genetic testing.	treatments and the need for long term surveillance. The information should be in an accessible format and ideally provided in different languages. This is now acknowledged in the dissemination and implementation plan These barriers and facilitators have been added in the implementation and dissemination sections	

	Barriers and facilitators of implementation recommendations Barrier to implementation: Lack of appropriate resources for patients/families. For example, the Australian SMA advocacy and support group website will need resources specific for families when a positive screening result and diagnostic result is received. Spinal Muscular Atrophy: Causes, Symptoms, & Treatment (smaaustralia.org.au). Facilitator of implementation: Jurisdictional consistency in implementation is preferable, and identification of a mechanism for key stakeholders in each jurisdiction to coordinate and provide consistent communications will support successful implementation of the recommendations across screening, diagnostic and post diagnosis care. Overall feedback The title of the guideline does not reflect the breadth of the content. Suggest the title includes reference to 'diagnosis' and 'post diagnosis' in addition to screening to ensure it captures the attention of the appropriate stakeholders beyond the newborn bloodspot screening laboratories. This will align with the Executive Summary, 'to span the entire healthcare journey of the newborn'. Technical report No feedback Family fact sheet No feedback Additional feedback	Title unchanged on recommendation of the SAC, Reworded and now states The Guideline should be reviewed 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	

	The draft guidelines recommend five yearly review and update. We suggest adding an option to review the guideline should new practice changing evidence become available.	research, clinical practice and changes in community needs, values and preferences.	
[*redacted*]	<u>Guideline document</u> Really good. Obviously very thoroughly researched, proof read and edited. Few notes. On page 20, states: "Decentralisation of newborn screening in Australia and New Zealand may give rise to regional differences in newborn screening programs"New Zealand has a centralised NBS programme. Not sure if they are trying to say it that it's not centralised across the two countries? May be better to say: "Decentralisation of newborn screening in Australia and a separate system in New Zealand may give rise to regional differences in newborn screening programs" On page 21: "In 2022 and 2023, the federal governments of Australia and New Zealand respectively…"Federal government is not a term used in NZ. Would suggest deleting the word federal to just say: "In 2022 and 2023, the governments of Australia and New Zealand respectively" On page 25: "It is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across	 This has now been amended and reads Decentralisation of newborn screening in Australia and a separate system in New Zealand may give rise to regional differences in newborn screening programs This has been deleted and reworded as per suggestion This has been deleted and reworded as per suggestion	Agree Agree Agree

	Australia and New Zealand."Would suggest: "It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and New Zealand. On Page 54: "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 " [*redacted*] Technical report • Previous comments about the executive summary in the other document regarding inclusive language [*redacted*] is all true in this one too. • Under Risk Assessment pg 103: A further risk not mentioned that could be consider that's no specifically mentioned is that the introduction of genetic testing to the NBS programme may lead to disengagement with the overall NBS programme, particularly for	The variability of access to equipment and personnel to complete these assessments has been acknowledged in the Guideline and no change required This has been addressed in the implementation plan (barriers and risks to implementation)	

	indigenous populations who may have additional concerns around data sovereignty of genetic information and implications [*redacted*]. This could be considered in the context of point 3 "the risk of widening health inequalities across Australia". Also both point 2 and 3 should be "… across Australasia". • Under Dissemination and Implementation plan pg 105: No mention of implementation in NZ. Add a sentence "In New Zealand this is overseen by the national Newborn Metabolic Screen Programme". Otherwise all good.	This has been added Sentence added	

[*redacted*]	<u>General feedback</u> Clinical services have already absorbed 3 SMA treatments, increased patient numbers due to survival, increased complexity in treated symptomatic patients, coordination of care, coordination of treatment programs and support and managing the care. NBS programs have also increased demand for clinical services, critically urgent review and initiation of treatment & the intense monitoring post treatment. There has been no additional resourcing of services to support the increased clinical workloads. It remains challenging to provide SOC to patients with NM	-Resourcing has been addressed in the implementation protocol. 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 reimbursement pathways for children with SMA	

	disorders. To implement the SOC for NBS screening programs, clinical services need additional funding to build capacity, workforce, succession planning. <u>Screening feedback</u> Health literacy ... non English speaking backgrounds, cultural considerations, Temporary Visa status - NBS offered to all infants, regardless of Medicare status and eligibility, however access to care and PBS funded treatments is restricted. Families may not be able to afford access to care or genetic testing, genetic counselling etc. How is this managed in other NBS programs? <u>Diagnostic feedback</u> Variability between in states for Tier 2 testing SMN1 & SMN2 confirmatory testing timeframes. [*redacted*] for 2nd tier .. - 7-10 days turn around. Much quicker for other states - [*redacted*] [*redacted*]- logistics with timely access to care and confirmatory testing - will likely cause delays - maybe outside of the recommended timeframe of 7-10 days. <u>Clinical feedback</u> Our local experience has shown that whilst NBS is done on most patients, however not all have Medicare. 50% of NBS this year.	(diagnosed through newborn screening) who are not eligible for subsidised or publicly funded health services or treatments. While the SAC recognises the geographical differences between states, this Guideline has been developed as a best practice protocol for NBS for SMA. Addressed in Scope: The Guideline is intended to inform and guide, but 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	

	Immigration /Visa status impacts access to clinical care and treatment options. Hospital systems, service demand/capacity restraints. Impact on clinical services .. demand, survival, critical timeframes , clinical services struggle to juggle and absorb workload to provide diagnostic, treatment and ongoing clinical care. Clinical services need additional resourcing / staff to deliver services. SMA care has changed dramatically in the last decade, however clinical resourcing & funding of service has not responded to this demand. <u>Guideline potential implications</u> Improved awareness and understanding. Consumer expectations ... logistical and systematic barriers which impact the delivery of clinical services. Recognition for the importance of SMA care, timely access to treatment. Hopefully - appropriate resourcing of services, additional funding, capacity building, succession planning <u>Barriers and facilitators</u> Inequity in care still exist - Treatment eligibility - no Medicare - can't access PBS funded treatments, can't access NDIS supports to meet SOC recommendations.	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.	

	Insurance status - variability ... SMA treatments are high cost, they won't necessarily be covered by insurance. Family who have NO private health insurance and no Medicare. Challenges - NBS positive, confirmatory genetic testing, unable to access treatments; family with no insurance to cover treatment or care. Will State based health systems absorb the cost, how do we advocate for compassionate access to treatments ?		

[*redacted*]	<u>General feedback</u> Slide - What is NBS for SMA Blue circle Please correct 2 spelling errors "manging" to managing and "screeing" to screening	-Changes made according to feedback	

[*redacted*]	<u>General feedback</u> fantastic, well thought out <u>Clinical feedback</u> Recommendation 9.5 (referral to genetic counselling) does not seem to incorporate an understanding that some areas of mainstreaming genetic counselling is growing and it may not necessarily be a 'clinical genetics unit' that provides this counselling. There	Recommendation 8.5 Consensus recommendation 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 services).	

	may be genetic counsellors within the neuromuscular multi-D team who will provide this. Would it be easier to say refer for genetic counselling and cascade testing (which may include referral to a clinical genetics unit)???		
[*redacted*]	General feedback • On review, the guideline appears comprehensive and aligns with the work by policy makers in states and territories and the Commonwealth. • Keen to understand how these guidelines when finalised will be disseminated, promoted and used to support SMA integration into newborn bloodspot screening (NBS) – noting it is already part of NBS programs across the country. Assume this will be via s/t and hospital networks to reach clinicians, consumers etc?	An implementation and dissemination document has been provided as a separate file and is also incorporated into the Guideline document	
[*redacted*]	General feedback We have sought expert clinical feedback on the guideline. The advice is, while the recommendations are reasonable, they are mostly not of direct relevance to GPs.	-no change needed [*redacted*]	
[*redacted*]	General feedback The consensus-based recommendation grading system detailed on pg 90 (i.e., 1A-2C) would be useful to		

	include in the 'list of recommendations' on pg 28 to help understand the grading for these recommendations, and minimise confusion with the evidence-based recommendation grading system. <u>Screening feedback</u> A few recommendations are a little redundant and/or may overlap with other guidance already available/applicable to all NBS conditions, e.g., Recommendation 1.1 is national policy in Australia that has already occurred through an alternative recommendation pathway and has already been implemented, and Recommendation 1.8 – does this duplicate existing guidance on taking bloodspots prior to transfusions? Also, if this recommendation is targeted at sample collection staff it differs from almost all of the other recommendations and it is not clear that this is a key audience for the guidelines. The use of the term "screen positive" is used differently in different parts of the guidelines and wording may need to be clarified – Recommendation 1.7 refers to the "screen positive" result being communicated as just the SMN1 result, which does not align with the definition in Recommendation 2.3 being both the SMN1 and SMN2 results defining a "screen positive".	The grading system has been removed to reduce confusion and a prioritisation system (high, moderate and low priority) has been assigned to consensus recommendations based on GDG review and evidence. Whilst recommendation 1.1. is true, the SAC felt that it was still important to keep within the Guideline as other jurisdictions (outside of Australasia) continue to assess saliva and whole blood to implement NBS for SMA. Recommendation 1.8. is now a practice standard 1.3.3. If blood transfusion in the neonate is considered, the dried blood spot should be taken prior to transfusion aligning with processes with the National Policy Framework for Newborn Screening. The wording has been corrected accordingly. Recommendation 1.3. Consensus recommendation 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.	

[*redacted*]	General feedback Thank you for such a comprehensive guideline and for thinking so deeply about the experience of patients and families. The only feedback I would like to give and have considered is the inclusion of referring or at least making families aware of the existence of SMA Australia, and other support organisations like Genetic Support Network of Victoria and Genetic Alliance Australia. We have learnt that unless this is explicit it is often overlooked. Section 9 I believe is where this would be most relevant.	The SAC has discussed this feedback and felt it is not prudent to incorporate specific advocacy group names. We have titled these within an umbrella term of support organisations, with the clinician role to identify the most appropriate in terms of the family's needs and preferences. This has been added into the definition section of the Guideline under the title 'The definition of advocacy services' and states the GDG recognised that a variety of international, national and jurisdictional services exist for children with SMA and their families. For the purpose of the 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 individual needs and preferences.	

[*redacted*] GUIDELINE -See next box for Tech report	Screening feedback • **The definition of newborns, infants and children with SMA (pg 25, 100).** The Reading the Guideline the Population sections of the guideline outline that NBS for SMA could occur after the defined period for newborns (<= 28 days), expanding the NBS testing period out to 12 months of age. We note that the Guideline Development Group (GDG) defined the cohorts of newborns and infants with children. Although this seems to contrast with recommendation 3.8, regarding diagnostic *SMN1* results being delivered within 30 days of birth, we recognize, as outlined in the Guideline, that in some	No changes required.	

	circumstances this timeframe may not be logistically practical. • Recommendation 1.2 As outlined in the guidelines, recommendation 1.2 reflects that 95% of newborns with SMA is due to homozygous deletion of exon 7. The other 5% is made up of a compound heterozygote genotype, biallelic pathogenic sequence variants or SMA not due to SMN protein deficiency. This approach is consistent with other countries including Canada (Groulx-Boivin et al., 2024). As outlined in the guidelines, patients affected by SMA not picked up by newborn screening would follow the normal clinical pathway. We anticipate future review of the guidelines would include a consideration of ways to incorporate this 5% group into newborn screening, particularly as testing technologies advance. • Recommendation 2.4 (pg 33,130) We recognize the complex question regarding timing of result disclosure of an *SMN1* positive screening result in relation to the result of determination of *SMN2* copy number. The reasons outlined in the guidelines for this decoupling reflect that *SMN2* copy number determination is not a confirmatory test; as a prognostic marker is not absolute and can vary depending on the methodology used. Clinical presentation is the absolute measure of disease severity. The approach adopted by the guidelines is balanced regarding the timing of the *SMN1* screening	We have added this change No changes required.	

	result which still incorporates guidelines on the utility of *SMN2* copy number as a prognostic marker (recommendation 2.1, 2.2, 2.3, 2.4, 2.5, 2.6). <u>Diagnostic feedback</u> **General comment on technique of screening.** As noted in Mercuri et al., (2018), the gold standard of SMA genetic testing is a quantitative analysis of both *SMN1* and *SMN2* using multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS). The guideline summarized a study by Tavares et al., (2023) that concluded real-time PCR methodologies are accurate and cost effective. This study used MLPA as the confirmatory second test. In a systematic review of NBS programmes for SMA, Cooper et al., (2024) found that most programmes used RT-PCR or RT-qPCR as the index test method, with most programmes using MLPA as the confirmatory test. We agree with the need for flexibility in the guidelines including of the technique employed – to allow for the possibility of advances in technology associated with testing.	No changes required. No changes required.	

	As mentioned in the guidelines, the accreditation for tests will be governed by the usual regulations for diagnostic laboratory clinical testing accreditation. • Recommendation 3.4 (pg 35, 140) We strongly agree with the need of orthogonal validation utilizing a different methodology for diagnostic testing. This will aid in the robustness of the test overall and decrease the chance of false positives. This was evident in the systematic review of newborn screening programmes by Cooper et al., (2024) with in most programmes, the index test method being RT-PCR and the confirmatory test MLPA (refer to Table 1, Cooper et al., 2024). • Recommendation 3.8 We strongly agree with the need for timely screening and diagnostic results, given the implications for clinical care. Newborn screening directly addresses issues relating to delayed diagnosis in the absence of screening (Nishio et al., 2023 review; Lin et al., 2015). The recommended turnaround time of the diagnostic tests should be regularly reviewed with new advances in methodology. Our understanding is that 30 days is feasible in terms of current timelines – approximately 2 weeks for	No changes required. No changes required. This has been reinforced by the addition of a statement which now reads The Guideline should be reviewed 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. This is particularly pertinent as evolving screening, and diagnostic assays change the time to confirmation of SMA.	

	SMN1 NBS and 8-10 days for *SMN2* copy number determination. • Recommendation 3.9 We agree with this statement, particularly in relation to accurately detailing the method for copy number determination. Additionally, the number of repeats >4 is important for informing phenotype severity (Prior et al, 2020). The information regarding methodology is also important in terms of false positives and negatives. We encourage these conventions to be incorporated into internal diagnostic laboratory policies regarding SMA testing and reporting. <u>Clinical feedback</u> • Recommendation 5.3 / 8.2 / 9.7 / 10.10 / In the guidelines and literature there is a strong emphasis on the need for a multidisciplinary approach to the management of SMA patients. Part of this relates to access to specialised neurology services and clinical genetics services when SMA patients are referred for further genetic testing. We note the access to such services can be challenging in outer regional, remote and very remote parts of Australia which creates issues of equity of access for all Australians including Aboriginal and Torres Strait Islander patients in remote areas. For example, Best et al., (2021) identified barriers of access to clinical genetics	No change required	

	and genomics, including current service model designs which centre on urban areas, and limited investment in rural areas. Workforce capacity and capability were also raised including the lack of capacity to engage with genetics specialists. A study by Baazeem et al., (2023) found most tertiary hospitals in Australian cities were in major centres (72% in Sydney for NSW; 82% in Melbourne for VIC; 57% in Brisbane for QLD). We encourage investigation of Telehealth as one possible solution for access to specialist neurology services (as indicated in Recommendation 5.3 and Recommendation 8.2 where travel is not feasible. A recent study (Marne et al., 2023) evaluated a neurology outreach programme to aid in paediatrician training in neurology via video-conferencing and was found to be both accepted and effective. In relation to health access for Aboriginal and Torres Strait Islanders, there are general barriers that contribute to health inequities, including lack of transport, waiting times and a lack of culturally appropriate health information and materials (Australian Institute of Health and Welfare 2024). We note in the recent Health Technology Assessment Policy and Methods Review Recommendation 1: Creating a more equitable system for First Nations peoples and Recommendation 2: Providing equitable access to medicines for paediatric patients.	We thank the reviewer for these insights and have incorporated these barriers to equity in the dissemination and implementation plan.	

	• Recommendation 9.5 [*redacted*] supports this recommendation and that referral occurs in a timely fashion. This is consistent with current practice, where referral to a specialist genetics service can provide families with expert advice regarding cascade screening testing and recurrence risk. Involvement of genetic counselling at the time of SMA diagnosis is consistent with the 2017 International Standards of Care for SMA (Mercuri et al., 2018). It should be noted that the role of genetic counsellors in SMA has adapted in the new therapeutic era (Serra-Juhe et al., 2019). Clinical geneticists and genetic counsellors will play important roles in collaboration with neurology specialists in terms of providing information around treatment options and timing, how treatment will be delivered and follow-up of patients. Additionally, at the appropriate time, information and advice surrounding future reproductive options can be discussed. • Recommendation 11.11 – comment on treatment options for infants with 4 SMN2 copies As outlined on pg 200 of the Guidelines document, at the time of writing, pre-symptomatic children with 4 or more *SMN2* copies do not have access to approved and reimbursed treatments. This contrasts with an international consensus treatment algorithm (Glascock et al., 2020) which was inclusive of such infants. We note pt 4 of the 'Evidence gaps and future directions'	These excellent points have been incorporated into the Guideline on the expanding role of genetic counsellors. This now reads: 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. No changes required.	

	relates to the management of newborns with SMA and 4 or more *SMN2* copies and the need for an increased evidence base for informed decisions regarding the risks and benefits of early treatment. <u>Potential Guideline Impact</u> • Comment on likelihood of workforce issues for neurologists, GPs, genetic counsellors, laboratory diagnostic staff. In Queensland, an SMA newborn screening program has been in operation since May 2023 and it is anticipated that 6 individuals a year would be identified by the program, on average. Based on 2022 figures (D'Silva et al., 2022) and 300,000 births per year in Australia, one would expect 26-30 individuals per year affected by SMA. Given the complex nature of a multidisciplinary approach, workforce issues could be a barrier to successful implementation (as outlined on pg 198 of the National Guidelines). To mitigate such barriers, education of diagnostic laboratory workforce in terms of importance of turn-around-times for *SMN1* confirmation and *SMN2* copy number determination will be important. Regarding training, page 161 notes: "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	A sentence has been added to incorporate Indigenous Health professionals within an education and training model, within the future	

	information provision". This may include Indigenous **Health Liaison Professionals** (IHLPs) but potentially other professionals in the Indigenous health workforce. <u>Overall feedback</u> We strongly support the proposal for guidelines to be **flexible** (pg 24, pg 25) which aligns with existing guidelines including the National Screening Framework and internationally developed Standards of Care for SMA. This is particularly relevant giving the likely ongoing advancements in treatment for SMA. We also support the proposed strategies for Guideline evaluation (pg 206/207) including the need for update of guidelines in a rapidly evolving landscapes, further investigation of barriers and enablers to implementation and acknowledgment of jurisdictional differences in adoption of the guidelines. In terms of the length of time for review – five years is suggested. This timeline seems appropriate; however, we envisage that any major changes in treatment or diagnostic methods may warrant an out-of-session review. As these are the first implementation of the guidelines, a 1-year 'fit-for-purpose' review could be of benefit. This would allow for adjustments based on any feedback from those stakeholders who are utilising the guideline or identify any key gaps that might have only been highlighted once the guideline was used in the practical sense. We	directions section; education and training for relevant medical practitioners in rural and regional areas. The need for a flexible approach to review of document is noted in the Future directions section which now reads: 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.	

	note that the 2016 NHMRC standards for guidelines state in section 6.1: Be informed by well conducted systematic reviews, however a timeframe is not given. <u>Broader feedback on relationship between NBS and RCS.</u> Pg 114 of the guidelines references the inclusion of SMA1 (and fragile X and cystic fibrosis) as a condition screened via reproductive carrier screening (RCS) (Medicare item number 73451). This will allow couples more information regarding their reproductive decision making in the context of SMA. The guideline document indicates the complementation of the two programs – this may warrant further comment and linking to guidelines for reproductive carrier screening as they become available. Potential bi-directional impacts of reproductive and newborn screening programs for certain conditions may include cost effectiveness, and awareness and education of the different health practitioners, including the strengths and limitations of screening programs in identifying conditions like SMA. <u>Possibility of generally streamlining Guidelines.</u> Due to the structured nature of their development there is some overlap between specific guidelines and the opportunity of streamlining. As an example, recommendation 8.4 and 8.5 concerning diagnostic	Whilst the SAC felt that comment on reproductive genetic testing was outside the scope of the current Guideline, the existence of guidelines for other screening methods for SMA was delineated in the Scope, population and setting section: 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 We have streamlined the recommendations accordingly.	

	results disclosure. We suggest such streamlining could be incorporated into future reviews. <u>Recommendation 11.5</u> We are very supportive of Recommendation 11.5 and the collection of real-world evidence by neurology services after identification and management of children identified as screen positive Post implementation evaluation metrics will be important to inform future refinement of the guidelines / screening practice. <u>Aboriginal and Torres Strait Islander, Pacific Islander and/or Māori representation on the GDG.</u> It was indicated that there was no formal representation of Indigenous populations on the GDG. We suggest invitation of consultation by respective groups such as Queensland Aboriginal and Islander Health Council (QAIHC), National Aboriginal Community Controlled Health Organisation (NACCHO), Te Aka Whai Ora (Māori Health Authority). This also relates to Recommendation 7.4 (pg 48). With no formal involvement, there was no clear messaging or guidance on how the lack of representation would be addressed within the framework. The guidelines lay the responsibility for supporting families whose child has been diagnosed with SMA with the **Indigenous Health Liaison Professionals** to provide advice and be involved in how the clinical test is communicated to the family.	We agree with the stakeholder perspectives that these communities should be represented in future work. We have incorporated the advice for a Consumer Group with purposive sampling from Indigenous Stakeholders to support future work in this domain.	

	This puts pressure on these roles/people and there are no clear recommendations for appropriate training that the IHLPs could be supported to undertake. Pg 210 refers to continued involvement of Aboriginal and Torres Strait Islander peoples in the evolving SMA research but no clear pathways identified for how this can be or should be achieved. In their current form the guidelines do not identify culturally appropriate pathways or best practice approaches to supporting Aboriginal and Torres Strait Islander families whose child has been diagnosed with SMA. We encourage the development of an Indigenous Governance Advisory Group to support ongoing guideline work.		

[*redacted*] Tech and family fact sheet	<u>Technical report General comment</u> As a general comment, the technical and administrative report was very useful, particularly the evidence tables for each section, for each respective recommendation. This will be a valuable resource for future revisions of the guidelines as the evidence base changes (for example relevant literature). <u>Family fact sheet comments</u> • The family fact sheet is an important communications tool and so Australian Genomics' community engagement team provide specific feedback to this section. This includes brief background on SMA, the guidelines process, a summary of screening, diagnostic and clinical care steps and a summary of recommendations. We	No change needed This title has been added.	

	suggest a further heading in slide 7 such as "Summary of screening and clinical pathway". • We also suggest mention (and link) to the Family fact sheet in the main Guidelines Document. <u>What is SMA</u> • Formatting of question mark at top and bottom • Instead of numbering each of the points, it may be better to use icons here that represent the content (e.g. a picture of someone walking/moving for point 2) • The gradient background could make it difficult for people who are vision impaired • More detail on inheritance may be warranted, for example, the sliders depicting percentage is a bit difficult to understand could use a pie chart or similar • Great explainer of the cause of SMA but there is a new term "higher copy number" introduced at the end and not explained <u>What is NBS for SMA</u> • suggest changing the order of the circles – leading with what NBS is: 1. NBS aims to identify children at risk	Family fact sheet now incorporated into main documents via link in the targeted secondary end users section. This has been changed Icons have been added Backgrounds have been placed in monotone for readability Changed sliders to pie charts. Added sentence "If both parents carry the gene mutation" to make clearer the linkage with % likelihood that child develops SMA The wording has been changed and now reads, 'more copy numbers of SMN2' Order of circles changed according to feedback	

	2. This test takes a small amount of blood 3. NBS is offered to all babies 4. In Australia and NZ each health area 5. In 2022 and 2023 6. this is the first times genetic 7. Those identified during screening • Rather than "confirmatory testing" suggest " …urgently referred to confirm the results." • Formatting: Breaking up the heading at the top and bottom of the page make it difficult to read. <u>Why we need a guideline</u> • Content: The opening sentence "the intent of these guidelines…" is quite formal. Could reword to something like "These guidelines aim to provide recommendations that improve the care of newborns based on the best available evidence." • Formatting: Suggest placing text in boxes around the graphic <u>Steps page</u> • Content: 1. Steps could be reworded to the active voice e.g. Step 1 could be reworded to 'A dried blood spot is collected from the newborn for newborn screening'. 2. Step 2: Suggest "laboratory" rather than "reference screening"	Words changed to match suggestion Heading from bottom brought under heading at top Words changed to match suggestion The SAC felt that this formatting change did not improve readability. Words changed to match suggestion	

	3. Step 3: suggest removing “reference screening” and use laboratory. Spelling error: services. Could removing “screen” and replace with “positive result” 4. Step 5: Suggest simpler explanation of “diagnostic evaluation”. Spelling error: positive 5. Step 6: Suggest changing biomarkers to markers/signs. 6. Step 7: Reword ‘The family is told the results and treatment plan starts’ 7. Step 8: suggest rewording • Formatting: Icons are difficult to see. Would also make the outline of icons bolder	Bold added to icons to ensure they are visible	
	<u>Summary page</u> • Screening box: Is there a need to mention exon 7? This has not been introduced previously. • Consider rewording of some of the Recommendations boxes, as some appear more to be explanations, rather than a summary of key recommendations. • gradient background will make it difficult for people who are vision impaired	Co-leads feel Exon 7 is important in this context. The wording has been changed to make this style more in reflection of recommendations, linked in part to explanations to provide context. Gradient changed to single colour background	
	<u>Further general comments</u>		

	[*redacted*] endorses the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand. Specific points of consideration: • Further engagement with Indigenous Health representatives and peak bodies across Australia and New Zealand. As stated previously, we suggest development of an appropriate Indigenous Governance Advisory Group to support this work. • Commend recommendations that address the **potential health inequity of access** to specialist neurology services and multi-disciplinary teams in outer regional, remote and very remote areas of Australia and New Zealand. • We commend the need for **flexibility** in the guidelines given potential advancements in treatment and potentially developments in diagnostic technology. We suggest the possibility of out-of-session updates aside from the scheduled 5 years schedule for any major disruptive changes in treatment or diagnosis relating to SMA and newborn screening.	We have reached out to the peak bodies for further consultation and have added the need for an Indigenous Advisory Group to inform further research. This now reads: 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. No change required. We have updated the need for a minimum 5 year review as above.	

	• We agree with the section on pg 8 regarding **evidence gaps and future directions for stakeholders**. In relation to point 1- the evolution of genomics capabilities in newborn screening, we encourage further work in this area in benchmarking various platforms including exome and whole genome sequencing. Point 2 is also a very important consideration given the challenges in determining *SMN2* copy number and variables in linking copy number to disease prediction.	No changes required.	
	• **Relationship and potential overlap between Guidelines and Implementation.** We note that there is considerable reference to downstream clinical management associated healthcare support that are very specific, given these are guidelines. It is not clear if a separate implementation document is planned at a separate stage.	An implementation document has been provided as a separate file and is located on the website, with a link provided in the Guideline document under the section of future directions; dissemination and implementation of recommendations within the Guideline.	
	• **Although not directly addressed in the guidelines, individuals residing in Australia who are not eligible for Medicare do not have the same access to newborn screening or potential treatments.** We understand reimbursement of treatment in this scenario would be reviewed on a case-by-case basis	This has been a point considered across the feedback. In response, the SAC agrees to add an implementation point in 10.1.1 that states: in Australia and Aotearoa New Zealand treatments for SMA are subsided by the publicly funded healthcare system for children who meet eligibility criteria. Reimbursement strudtures and options for treatment vary across the two countries. For children who are not eligible to access	

	on compassionate grounds which exacerbates inequities and widens the health gap. • There are a few differences between the Australian and New Zealand health systems relevant to SMA which may impact the guidelines – for example New Zealand currently funds Nusinersen as a treatment option, from January 2023 via Pharmac, New Zealand's pharmaceutical management agency (Pharmac 2022). Risdiplam was available from May 2023. • **we reinforce the potential need for revisions of the guidelines,** given most of the evidence was consensus based. This may be particularly relevant for SMA given the rapid recent advancements in treatment and technologies relating to methodology.	subsided treatments on the basis of their residency status or other factors, treatment pathways require interrogation on a case-by-case basis. The variations in practice and access to treatments have been added to the implementation point 10.1.1 which now reads In Australia and Aotearoa New Zealand treatments for SMA are subsidised by the publicly funded healthcare system for children who meet eligibility criteria. Reimbursement structures and options for treatment vary across the two countries. For children who are not eligible to access subsidised treatments, on the basis of residency status or other factors, treatment pathways require interrogation on a case-by-case basis. -No change needed	

[*redacted*]	• Equity / rural and remote context Stakeholders uniformly highlighted that timely access to treatment services and teams may not be achievable in context of the timeframes recommended. The geographical size of [*redacted*] can present challenges for families in a rural or remote setting; their ability to access services and/or receive care in a timely manner	These barriers to implementation have been discussed within each recommendation (in terms of resourcing required, feasibility) and have also been explored in the implementation plan.	

	is likely to be extremely challenging when considering the recommendations. Medicare eligibility of diagnosed infants can impact the ability to access specialist services. Confirmation testing of SMA is only available [*redacted*], and presents significant risk and delay to diagnosis and care of [*redacted*] infants. For rural and remote infants and their families, several stakeholders proposed that an adjustment to recommendations should be made to promote the increase of utilisation telehealth and local clinicians in an effort to reduce the impact on the centralised service and improve equity of access and support. • Workforce [*redacted*] noted that specialised allied health services were identified as a need, however, additional capacity in nursing and medical may be required to maintain or increase service provision based on the recommendations. Particularly, specialist neuromuscular clinicians are indicated to have key roles within the recommendations, however, the availability to resource this is not realistic in terms of clinical workforce availability and funding to resource services to the levels indicated in the recommendations	After discussion with the GDG it was considered essential to maintain maximal timelines for completion of screening and diagnostic pathway, to facilitate best outcomes for children with SMA. The use of telehealth services has been incorporated throughout the Guideline recommendations. These barriers to implementation have been discussed within each recommendation (in terms of resourcing required, feasibility) and have also been explored in the implementation plan. The GDG acknowledged challenges to resourcing however felt the benefit of implementing the recommendations in the Guideline were in line with international standards, requiring reconfiguration of healthcare services	

	• Service funding Funding for pre-screening and post-screening services does not specifically exist for newborn bloodspot screening. For post-screening services this especially presents a challenge when considering implementing the recommendations as essentially more services are being required without additional funding and resourcing to support them. • Service capacity Clinical and genetic services are currently operating at or over service capacity. If implemented, some of the recommendations will result in additional service delivery challenges to meet increased testing, family support, treatment, education, travel, and other needs. • First Nations [*redacted*] stakeholders emphasised that implementation of recommendations should include ensuring culturally appropriate and safe support for First Nations families with infants diagnosed with SMA. • Education Clinical education was highlighted as an essential component when considering implementation of the recommendations. Contemporary education for clinicians involved in pre and post-natal conversations, diagnosis, treatment and care of infants	We have addressed this in the relevant recommendations and implementation plan. We have addressed this in the relevant recommendations and dissemination and implementation plan.	

	with SMA will strengthen their ability to provide safe, informed care.		

[*redacted*]	In principle agree with all recommendations; they are mostly consistent with the model-of-care in the neuromuscular service in [*redacted*]. However, in order to continue to meet the recommendations there are some hurdles. • Equity a. [*redacted*]provides NBS for [*redacted*] – timely access to services and teams, may not be able to meet the timeframes recommended. [*redacted*]can offer telehealth for the initial conversation; however, these infants need some specific genetic and investigative blood sampling – this would be messy across health systems – challenging enough in [*redacted*]. Also, they need clinical examination by a Neurologist and physiotherapist who are specialists in SMA. The family would need to travel to [*redacted*], on short notice, within 1-2 days after NBS positive. Consideration for post-partum mothers and families is relevant given the geography of [*redacted*].		

	Tier 2 genetic testing – In [*redacted*], confirmatory genetic testing needs to be sent interstate – [*redacted*] for SMN1 & SMN2 testing. Most states can offer this testing locally with a quicker turnaround time. At best these test results take 7-10 days for [*redacted*]families. This testing is essential to determine eligibility for PBS funded SMA medications. Testing and results is time critical. c. Medicare Eligibility – 50% of our patients diagnosed through NBS in [*redacted*]in 2024 have not had Medicare …. this impacts their ability to self-fund/access specialist NM services, allied health teams, and PBS funded treatments. They're also ineligible for NDIS. One family did not have private health insurance, which impacts delivering on Standards of Care (SOC) recommendations. The family does not have capacity to fund the appropriate standard of care. d. Delivering care to SMA patients has impacted the NM service significantly with no additional resourcing. There are less appointments • Specialist nursing support a. Allied health teams were noted. Clinical nurse consultants/ nurse specialists weren't specifically mentioned, however have a vital role in supporting families from screen	Whilst the SAC acknowledged the timelines for screening and diagnostic results could vary across health jurisdictions, due to the neurogenetic emergency of SMA, it was considered on the whole feasible to implement these timelines. Specific recommendations have been developed to help promote equity of access to best care for children in remote and rural areas. These include the use of telehealth systems to support screen positive disclosure, diagnosis and clinical surveillance and treatment for children and families unable to travel to tertiary centres. This is considered outside of the scope of the Guideline and has been set out in the Scope. The SAC acknowledges this point but felt it was outside the scope of the Guideline to address. This was added as a point in Scope, which now reads "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." The barriers outlined in this comment are considered in the implementation plan. 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.	

	positive, through to coordination of care, clinical advice and ongoing specialist • Resourcing / funding of NM services / access to timely care a. NBS laboratory received funding to build capacity and capability of their service, however clinical services have not had additional funding to support care and management. b. Psychological support for NBS positive – none at [*redacted*]. Our service has access to a Social Worker (SW) only, and we link all families with SW, however they also have other workloads and competing clinical commitments with other teams/inpatients etc. There is also a high turnover in the SW service for Neurology, so I would advocate for a consistent team that can develop specialised knowledge in this area. The SW do an excellent job; however, the turnover of staff is less than ideal. It's difficult for them to provide psychological support if they're only in the role for a few months. c. Sustainability of services – Some states were successful in securing additional government funding. Unfortunately, our department, has absorbed the NBS workload and treatments for SMA, however this has been challenging and workloads have increased significantly. Previously, palliation was the only option for many infants born with SMA, however they are now surviving, require high-cost PBS funded	The barriers to implementation as discussed (b-e) have been discussed within relevant recommendations (in terms of resourcing required, feasibility, education and training) and have also been explored in the implementation plan. The GDG acknowledged challenges to resourcing however felt the benefit of implementing the recommendations in the Guideline were in line with international standards, requiring reconfiguration of healthcare services	

	medications and intensive monitoring and coordination of care. We have had a 320% increase in SMA1 since 2018 when treatments became available. This means, higher number of patients, increased complexity and acuity. If we are to consistently deliver on the SOC recommendations it will be a challenge, without impacting other aspects of the service delivery in the Neuromuscular service and patients with other neuromuscular conditions. We are a very small team, resourcing and succession planning needs to be addressed. Services need to be reviewed and resourced accordingly. We already have long wait times for CAT 2 and review appointments. Timely access to ongoing care is a challenge, clinics are overbooked, and if a patient FTAs or cancels it's a 9 month wait for a review appointment. Currently all NBS SMA and SMA treatment monitoring are done over and above other workload. Appointments are booked adhoc and overbooked. This is not a sustainable system for patients or staff. Services cannot deliver the SOC recommendations without reviewing resourcing. d. SMN2 4 copies – impact on clinical services... frequency of reviews to monitor for disease progression, puts more demand on existing appointment availability. We know firsthand as we are one of the few states with an SMN2 4 copy patient. This patient became symptomatic … and was then eligible for PBS funded treatment. So close monitoring is very important to ensure timely		

	initiation of treatment which can change long term health outcomes. e. Workforce for NM clinics – our service is significantly oversubscribed for appointments; we've had a reduction in medical FTE attached to the service and do not have capacity to absorb the workloads. Patients diagnosed with SMA need to be seen in a specialist NM service, however managing the demand and capacity is at a tipping point. We have done extensive work to ensure optimisation of services over the last few years, yet still struggle to see patients in clinically recommended time frames.		
[*redacted*]	1. Consensus based recommendation 7.4 on page 48 of the National Recommendations for Newborn Screening in SMA states "We recommend that medical 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 medical 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." When considering appropriate support for First Nations families, consideration should be given to providing additional cultural support and sensitivity. We suggest a First Nations Nurse, Midwife or a Health Worker practitioner with a sound understanding of the Newborn Screening process be	- The suggested professionals have been incorporated into the relevant recommendations	

	included in conversations with these families where possible. 2. Consideration should be given to providing some detail about potential sensitivities for First Nations patients. This is not to remove the need for an Indigenous Health Liaison Officer or a First Nations health professional, but to provide better guidance for the clinician's discussions and to benefit the pursuit of cultural safety in the long-term with better understanding of this issues.	-Currently there is a paucity of evidence for potential sensitivities for First Nations peoples within the remits of NBS for SMA, as considered by a targeted systematic literature review. We have aligned our implementation plan to incorporate the need for research to address these data gaps.	
[*redacted*]	1. Supportive of the DRAFT Guideline supplied. 2. Makes perfect sense that the NBS recommendations align with current evidence base given treatment advancements for SMA. 3. The biggest factor for the midwifery cohort will not be the resources in terms of education and access to expertise for post diagnostic assessments but more so the educational requirements for having discussions with parents postnatally while gaining informed consent for NBS (with SMA screening included). 4. With the addition of SMA in the NBS will there be communication and educational update provided to maternity clinicians working with families at the point of NBS screening?	No change required. See implementation plan linked to the Guideline See implementation plan linked to the Guideline	
[*redacted*]	1. Agree with the draft documents rationale for including SMA testing, as described, in the routine NBS paradigm.	No change required	

	2. Recommendation 1.6 is important (not reporting heterozygous state) – reporting of carrier state would have significant implications for genetics services given the population carrier frequency for SMA. 3. Important to emphasise that inclusion of SMA on newborn screening will increase demands on neurology and clinical genetics services. Consequently, recommendations should also be made that Hospital and Health Services should ensure these clinical teams are appropriately resourced to meet the assessment / counselling demands that will result. 4. While those with clinical SMA would have been seen eventually by these services anyway, there is likely to be a false positive load that will increase work for both services. Given the nature of the condition, these families are still likely to need robust and timely counselling	No change required Resourcing issues are considered in the implementation plan and where relevant in the justification of each recommendation. Recommendation 4.1 Consensus recommendation For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families. Information Box Information can be provided by paediatric neurologists and/or clinical geneticists and/or genetic counsellors. Practice Standard 4.3.2. Families who receive a false negative, false positive or uncertain screening result should be provided information and psychosocial support by relevant members within the multidisciplinary team.	
[*redacted*]	• Consensus feedback		

	1. The document is comprehensive however at over 200 pages it may impact readability. 2. There are many repetitive statements, with the formatting impacting on the ease of reading the document. 3. The suggested requirement for the availability of a paediatric neurologist as the point of contact and the person for initial screening mentioned throughout may be impractical, especially in [*redacted*]. For reference, there is one paediatric neurologist in [*redacted*], but otherwise no others outside the [*redacted*]. Relying on the sole practitioner for a very large area to be available may be a quite cumbersome and risk delays in diagnoses. Currently, [*redacted*]has an effective system for following up abnormal results, involving the appropriate teams from Metabolic, Immunology or Neurology, in which the results then defer to the local delivery/paediatric centre. This works well for metabolic conditions which require very rapid management. The [*redacted*]suggests utilising the already well-established system, along with a co-referral to the paediatric neurologist as a consideration. – a query for [*redacted*]is, will the neurologist at [*redacted*] be deemed the link person for the state? 4. Page 104 – there is a spelling error, foetal should be corrected to- fetal.	The Guideline has been reduced and streamlined to avoid repetition whilst maintaining a solid evidence base for recommendations. The emergency nature of SMA warrants specialist input and therefore the SAC maintains that a paediatric neurologist should be contacted for the screen positive result. The QLD medical team were part of the consultation process and have agreed to this recommendation. We acknowledge that work flow will vary between health jurisdictions and this has been accounted for in a slight rewording of these recommendations as follows: Recommendation 2.2. Consensus recommendation Newborn screening programs should establish a clinical referral pathway that includes simultaneous early notification of a screen positive result to a paediatric neurology specialist and local healthcare practitioner. This is the English/Australia spelling of foetal and therefore has been retained.	

	• Additional late feedback 1. Page 33 Recommendation 2.7 – Formatting error – needs a space inserted between the first two sentences, highlighted in yellow, for readability - We recommend 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 should be verbally relayed to a designated paediatric neurologist. 2. I agree group, the pathway including the handling of false positive results, should follow that already established for NBS. 3. Page 42 Recommendation 5.3 – this wording could be changed to 'responsible healthcare practitioner' instead of medical. For example, a specialist neurology nurse practitioner or genetic counsellor with support from a paediatric neurologist would be a suitable person to disclose a screen positive result, the latter not typically falling under the descriptor of 'medical' which could be taken to mean doctors only, or doctors/nurses but would typically not be used as a descriptor of allied health including genetic counsellors, who are arguably well placed to perform this role. This would also make this recommendation congruent with the following recommendation 5.4, which does reference healthcare practitioners.	Extra space entered between sentences This has been changed to read designated healthcare practitioner. This has been added to the recommendation	

	4. Page 48 Recommendation 7.5 – should include clinical geneticist or genetic counsellor or genetic service. 5. Page 106 – the use of the term 'healthy individual' is not in line with best practice around the language used in disability, as it's a value laden term that many parents of children with a disability find distressing. Alternative terminology has been recommended. Equally, 'SMA patient' is better stated as Individual with SMA or Neonate with SMA or Child with SMA or Person with SMA. Recommend "person without SMA" and "person with SMA" for this section.	Changed 'healthy individuals' to 'individuals without SMA'. -All mentions of 'patient' are in the context of definitions by CLSI, or 'patient organisation' etc.	
[*redacted*]	1. There should be more consideration/emphasis for patients and families who live in more rural/remote regions of the country (e.g. rural QLD and WA, the NT) who are already at a disadvantage from receiving high quality healthcare. Most families from rural QLD and WA, as well as the NT are often more than a couple hours away from their local tertiary paediatric hospital. a. Travel with a young infant, especially when they are initially diagnosed can often be challenging. b. The utilisation of telehealth and local medical resources might be an avenue to emphasise and consider.	The SAC agrees with these comments and have accounted for this in the recommendations as follows, with wording changed to incorporate the wider role of general practitioners. Several recommendations include the use of telehealth systems to support result (screen positive and diagnostic) disclosure and post treatment surveillance (done with support and guidance of specilaists),	Some adjustments made to account for the feedback but the recommendations are across the board centred on equity of access in

	c. For example, at the initial consultation/on initial diagnosis, patient and family can be with the local paediatrician, and the paediatric neurologist can provide the initial consult via telehealth. Additionally, this method can be used to support the local paediatric team during subsequent reviews. 2. Should there be more involvement of a general paediatrician in the holistic care of these children, especially ones who live in rural/remote regions of the country, where access to a specialist multidisciplinary clinic might be challenging to access. a. Involvement of a local general paediatrician, especially at the time of diagnosis, gives these patients a local contact person, but also someone who can coordinate the patient's overall care (e.g. growth, development etc). 3. The guidelines should strongly encourage the development of a state based neuromuscular clinic (which I suspect is likely to be available in all tertiary paediatric hospitals across the country), where there can be multidisciplinary review of these patients. Additionally, these clinics should also closely liaise to regional teams (including various allied health teams) to empower them to help provide care to these patients in rural and remote regions.	This is considered in the implementation plan	regional and rural areas.
[*redacted*]	It's great to see in the evidence gaps and future directions for stakeholders' section of the Guidelines, there is reference made to broadening and deepening the evidence base of perspectives and challenges for	In the future directions section we have incorporated specific mention of rural populations and their role in future co-design. "Given the unique challenges facing rural and remote regions, it remains a priority to incorporate representative voices of this population into any future co-	

	families from rural and remote regions. We would recommend that rural and remote families are prioritised for co-design of educational resources for families.	developed evidence. Furthermore, the information gap at the point of screening, diagnosis and therapeutic decision making for families can only be filled through codesign of targeted and relevant educational resources with the child and family perspective to remain central.	
[*redacted*]	1. [*redacted*]has no comment. The guideline appears comprehensive on the topic. Recommendations noted for inclusion in the [*redacted*]g guideline (in development). 2. Note also that SMA forms part of the reproductive genetic carrier screening recommendations as per the [*redacted*]: Preconception and prenatal genetic screening clinical guideline.	-No change required. This has been addressed within the Scope section which now reads: 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.	

International Peer review (via NHMRC) summary document

Reviewer One (USA)	NHMRC Comment	Developer Response
In the Plain Language Summary, it is not clearly stated that both copies of *SMN1* have exon 7 deletions in the majority of those with SMA. Also, recommend stating that approximately 4% of SMA is caused by other mutations in the *SMN1* gene and thus will be missed by the newborn screen. Being missed on the screen for those rare genotypes could also be stated when it is discussed on page 100.	Please consider this suggestion.	Suggestion has been incorporated into plain language summary which reads: Plain language summary; Background (p22) 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. This has also been clarified in the section (p123) on the genetic basis of spinal muscular atrophy which reads 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
Recommendation 2.3 does not make sense to me; those with *SMN2* copy number >4 also have SMA and should be seen by a neuromuscular specialist.	Please consider this suggestion.	This recommendation has been reviewed and removed due to the confusion caused. Recommendations now read Recommendation 1.3. Consensus recommendation 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.

		Recommendation 2.1. Consensus recommendation *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*. Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.
Recommendation 3.6 and 3.8 – these two time windows seem long, especially for infants with two copies of SMN2 – unless there are logistical hurdles that cannot be overcome would recommend a shorter turnaround.	Please consider adding text to clarify these recommendations.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances that incur logistical barriers between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most

		feasible as pertains to the entire national landscape. Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. Recommendation 3.4 Consensus recommendation A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 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
Pg. 103 and Table 6: Spelling of Hoffmann.	Please amend typographical error.	This typographical error has bene rectified in p105 and the table 6
Figure 5: suggest adding concern for impact on male fertility and GI upset to risdiplam side effects. For OA: thrombotic microangiopathy.	Please consider this suggestion.	The potential risk of thrombotic microangiopathy for OA has been added to the Figure. There is limited information on male fertility for risdiplam and this suggestion has not been incorporated.

		However, the legend for Figure 5 has been revised to accommodate changes in knowledge and now reads 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.
Page 110 and Figure 6 do not match re. % of motor neurons lost at 6 months (90 vs. 95) – consistently 90 for the rest of the document.	Please consider this suggestion or add a reference to support.	The percentage is now consistent (90%) over all figures and in the document.
Page 199: extra "f" in the second to last line of the first paragraph.	Please amend typographical error.	This has been removed
Section 2 title is missing "A" in "SMA".	Please amend typographical error.	This has been changed on P 129
Pg 127: Sentence "Similarly, access to SMN augmenting therapies…" isn't clear.	Please consider rewording this for clarity.	This has been changed and now reads 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.(138, 146-148), with access to SMN augmenting therapies in these individuals varying between countries
Pg. 128 – disagree that phenotype/genotype correlation violation is "frequently" noted, it is rare but does occur.	Please consider this suggestion or add a reference to support.	The word frequently has been removed.
Pg 155 – feeding mentioned twice.	Please amend typographical error.	The first feeding has been removed.
Pg 180 – paragraph 2 "one who" is repeated.	Please amend typographical error.	This has been changed
Pg 204 – first word "The" not "There".	Please amend typographical error.	This has been changed
Reviewer Two (UK)		

Recommendation 2.1 “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, as per recommendation 2.4.” I tend to agree with this. There is a balance between seeing parents as soon as possible and having a fully informed discussion. If SMN2 copy numbers are assessed on the NBS sample, while the results may not be available at the timing of phoning to arrange an appointment, they may be available when the family are actually seen. One way to cut down delay, might be to initiate the SMN2 assay once the initial SMN1 result is known to be abnormal, rather than await confirmation of the repeat test on the NBS.	Please note this comment.	Comment is noted
Recommendation 2.3 is "We recommend that the definition of screen positivity for the Australian and New Zealand newborn screening for SMA program is homozygous deletion of exon 7 on SMN1 and SMN2 copy number ≤ 4 (where SMN2 copy number is conducted as part of newborn screening)." On page 127 it is stated that "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,...." My understanding is that reporting from the bloodspot sample will be on the basis of the SMN1 assay, irrespective of whether SMN2 copies have been ascertained or their number. If this is correct, a simpler more consistent definition would be “homozygous deletion of exon 7”. If SMN2 copy numbers are performed on NBS, but the result is only available after the baby has been referred, would the child be re-designated if there were >4 SMN2 copies?	Please consider this comment or add a reference.	The feedback has been taken and the consensus recommendations changed in terms of wording: Recommendation 1.3. Consensus recommendation 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. Recommendation 2.1. Consensus recommendation *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*.

		Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.
Recommendation 3.6 states "We suggest that … diagnostic results for SMN1 should be available within 7-10 days of receipt of the sample by the diagnostic laboratory." My understanding is that the available technology would allow a turn around time of 3-4 days allowing for the test to be repeated. Bearing in mind the urgency of initiating treatment, do you think this recommendation might be strengthened. One could replace "suggest" with "recommend" and/or change "7-10 days" to "3-4 working days".	Consider wording change.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances that incur logistical barriers between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape. A commentary has been added below each recommendation to explain this Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. **Information Box**

		The timings included in Recommendations 3.3 and 3.4 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 3.8 states that "We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth." For the same reasons as above, might "suggest" be changed to "recommend" and change "30 days" to "21 days". While there may be special instances where these recommendations could not be met, for the overwhelming number of cases, it should be possible. The results of the Australian pilot (page 152) shows what can be done.	Consider wording change.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings (which were not seen in the NSW/ACT pilot). These include long distances for travel between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape, and align with barriers suggested through the public consultation process. A commentary

		has been added below each recommendation to explain this. Recommendation 3.4 Consensus recommendation A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 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 5.8 states "We suggest that a clinical review within local paediatric services, with clinical support from paediatric neurologists should be offered to screen positive newborns where access to specialist services is limited and may cause delay in diagnostic evaluation." As is emphasised, parents, quite rightly, expect to talk to someone who knows about the disease *and its treatment* and can answer their questions. If they can't, there is a real danger that they will 'surf the net' and come across inaccurate information. In the interests of time, it may not be possible to arrange an in-person consultation with a paediatric neurologist. If that is not	Please consider this suggestion.	The feedback has been considered and several recommendations changed in line with this Recommendation 7.1 Consensus recommendation The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1*

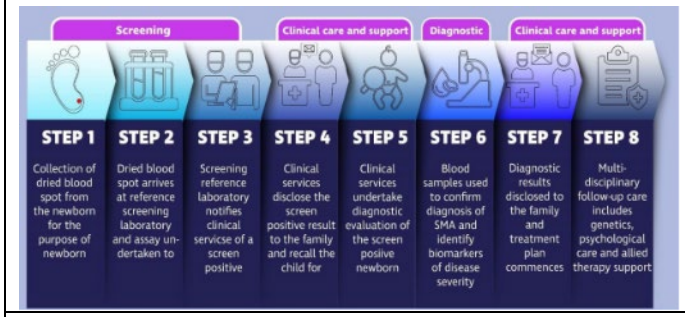
possible, the consultation might be with local paediatric services to examine the child and take blood, with the specialist present at the same time, but remotely, to answer questions and explain the next stages. Perhaps this could be suggested as the wording could be interpreted to mean that the specialist briefs the local services, which would be a very much less satisfactory option.		(diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result. Implementation Guidance 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor.
Recommendation 8.2 states "We suggest that ideally, diagnostic results should be disclosed to families by a specialist medical practitioner such as a paediatric neurologist." This seems a bit permissive. This is the consultation at which the treatment options will be confirmed and the parents will want to go into the practicalities. I would suggest it is essential that the parents talk to a specialist, albeit virtually. I would suggest rephrasing as "We recommend diagnostic results …."	Please consider this comment or add a reference.	We acknowledge the reviewer comment and have changed this as a priority recommendation which now reads Recommendation 7.1. . The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result.
For the reasons stated above, I would suggest that "recommend" replaces suggest in Recommendation 9.1 and Recommendation 9.2. This could be virtual in co-operation with local paediatric services.	Please consider this comment or add a reference.	The grading system for consensus recommendations have changed to reflect the feedback, the GDG have placed a high priority on these recommendations

		Recommendation 7.1 Consensus recommendation The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result. Implementation Guidance 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor.
On page 134, it is stated that copy numbers >4 would not be reported. I assume that this applies where they are measured on NBS, as they would have to be reported as part of the diagnostic process. If they are not to be reported on NBS, if families are referred on the basis of the SMN1 result, but SMN2 is measured on NBS and becomes available after referral, this would have to be disclosed, would it not?	Please consider this comment.	The reviewer is correct and the differences in jurisdictional screen positive results has now been clarified in p 134 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 < 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.
Recommendation 10.14 "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." This worries me considerably. If this applies to those with SMN2 copy numbers >4, I can understand, but otherwise, can it be ethical to screen for a condition when the family will not be able to get treatment?	Please consider this comment or add a reference.	We acknowledge the reviewer's ethical concerns however, as its stands Federal policy is to screen for all children with routine NBS panels (even if they are not eligible for reimbursed treatment in Australasia). The scope of this issue falls outside the Guideline and as it stands the target population is all children in Australasia. Some of these children do have access to care under private health insurance policies. The consideration for screening for newborns with 4 SMN2 copies and surveying them closely is that they are eligible for treatment as soon as symptoms appear. This was the state of play across most jurisdictions as per Glascock et al. before urgent treatment was recommended. As per the evidence base, there are still limitations to knowledge on the therapeutic window for newborns with 4 SMN2 copies. The

		recommendations have therefore not changed.
Reviewer Three (UK)		
For recommendation 3.6, the timeline for the diagnostic results for *SMN1* should be shortened to 2-3 days of receipt of the sample to ensure more timely treatment.	Please consider this suggestion.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances for travel between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape. A commentary has been added below each recommendation to explain this. 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 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.

For recommendation 5.10, to the second paragraph: change in movement, feeding or breathing 'or in case of any acute event (e.g. respiratory difficulties) that requires hospitalization'.	Please consider this suggestion.	This recommendation has been modified and the sentence added as per reviewer recommendation.
Reviewer Four (AUS)		
P21 whilst I agree that 'back up gene' is not an ideal term for SMN2, to me the phrase 'nearby related gene' is a bit confusing, so I wonder if it would be clearer to say 'related gene… located near SMN1'?	Please consider this suggestion.	This has been changed P 23.
P25 Population – I know it is mentioned further on, but I wonder whether it would be good to mention early in the document that SMA affects all populations/ethnic groups (albeit at varying frequencies)	Please consider this suggestion.	This has been changed p29
I note that you have varyingly referred to absence/loss of SMN1 as 'deletion' throughout the document o I suggest that you are consistent o In most places throughout the document I think it is most correct to avoid the term deletion – as this implies mechanism for the loss of SMN1, whereas the testing that we do is just quantitative and only tells us whether SMN1 is present, not how it was lost. I understand that a significant proportion of patients are thought to have lost their SMN1 through gene conversion rather than deletion per se o Suggest using loss, absence, deficiency.	Please consider suggestion and use consistent language throughout documents.	This has been changed throughout the document where appropriate and we have kept the terminology consistent with 'absence of SMN1). However we have kept the terminology as 'deletion' when necessary to be consistent with terminology used in the literature to date.
Suggest adding 'clinical' to geneticist throughout the document (where that Is what you mean) – including the diagram	Consider suggestion about clinical role titles.	This has been changed throughout the document.
P39 I think it would be useful to add that sometimes testing of parents is suggested to try to work out why there is a false positive or uninterpretable result	Please consider this suggestion.	This has been revised Implementation Guidance Blood samples from parents for *SMN1* quantification purposes should be considered to understand the aetiology of a false positive or uncertain result for the newborn.
P42 – I think the term 'responsible medical practitioner' is ambiguous – I presume you mean responsible for the patient rather than someone not irresponsible!	Please consider this suggestion.	This has been changed to designated medical practitioner.

P46 – there are a few places where you say 'venous sampling for SMN1' – I don't think this makes sense? Should be it venous sampling for quantification of SMN1? – and then similarly, venous sampling for determination of SMN2 copy number?	Please consider this suggestion and edit for clarity.	This has been changed
I know you can't put everything in this quick guide, but I wonder if it would be sensible to include the words 'paediatric neurologist/paediatrician' as they are really central to the whole process? - given that you include all the multidisciplinary teams (should say clinical genetics) 	Please consider change to the quick guide.	This Figure has been changed and the legend incorporates the members of the MDT team.
P100 – in 1st paragraph – you mention the scenario of two sequence variants – but they need not necessarily be homozygous – is more correct to say 'biallelic sequence variants' (could be homozygous or compound heterozygous).	Please consider this suggestion.	This now reads 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).
P114 I think the more correct term is 'reproductive genetic carrier screening' (but noting that the MBS uses 'testing' not screening)	Please consider this suggestion.	This has been changed

P117 last paragraph & p119 – I don't think the sequence variant needs to be in exon 7 – there are recurrent variants in exons 1,3 & 6 in particular		Please consider this suggestion, if correct, please edit.	We acknowledge the reviewer comment but as per the literature, the target exon for most NBS programs is exon 7. We have contextualised this by adding the following: Whilst variants in exon 1, 3 and 6 of *SMN1* are noted in individuals with SMA, leveraging the fact that 95% of individuals with SMA have an absence of exon 7, *SMN1* assays have generally targeted this genetic change, with rare studies targeting exon 7 ***and*** exon 8 loss within *SMN1*
Reviewer Five (Taiwan)			
Recommendation 2.3. We recommend that the definition of screen positivity for the Australian and New Zealand newborn screening for SMA program is homozygous deletion of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 (where *SMN2* copy number is conducted as part of newborn screening).	Not sure if SMN2 copy number should be included here as a criteria. How about a baby with no SMN1 but 5 SMN2 copies? It may have some confusion especially not every screening program has SMN2 information. Such recommendation may be violated to recommendation 2.4.	Please consider this suggestion.	The wording of several recommendations have been changed in line with this feedback Recommendation 2.1. *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*. AND Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.

Recommendation 3.5 We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means), should ideally occur so that stakeholders understand…..	I suggest to add something like "should ideally occur *upon screening positive"* to better emphasize the urgency of screening positive to the further management.	Please consider this suggestion, if correct, please edit.	The language has been revised to reflect the feedback and now reads 3.4.1 Clinical and diagnostic services should have pre-established protocols and pathways in place upon receipt of a screen positive result that lead to rapid collection, authorisation of diagnostic tests and result notification.
Recommendation 3.6 We suggest that to enable timely treatment, diagnostic results for *SMN1* should be available within *7-10 days of receipt* of the sample by the diagnostic laboratory	If in the real-world setting that a diagnostic result comes back after 10 days, other procedures need to be taken especially for the babies with 2 SMN2 copies. Otherwise, they are getting the diagnosis at age 14(or longer) days, and may only get treatment probably after symptoms onset.	Please consider this suggestion, if correct, please edit.	This has been revised Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. **Information Box** The timings included in Recommendations 3.3 and 3.4 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 3.8 We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to	The timeline is too long especially for a baby with 2 SMN2 copies. Such limitations should be addressed properly.	Please consider this suggestion, if correct, please edit.	Feedback through the process of public consultation shows that some states and territories will find even these timelines challenging to meet.

clinical services within 30 days of birth.			A qualification statement has been added for the purposes of the recommendations and timelines defined. Recommendation 3.4. A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 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 4.1 …and openly explained to parents.	Not sure if openly to the public as well as the NBS governance is a proper suggestion. If yes, that will enhance the screening method and understanding of SMA.	Please note this comment.	Due to the rarity of the condition, disclosure of false positive, false negative and uncertain cases to the public are likely to be highly identifiable. This statement has therefore not been changed but a standard to improve the quality of the program has been added. Implementation Guidance

			4.2.3. 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 issues and errors can be identified as part of quality improvement.
Recommendation 4.2 We suggest that families of newborns with false positive results should be given the option of returning to discuss the implications of results with members of the neurology/neuromuscular multidisciplinary team.	False positive cases should be properly counselling by clinical geneticists (or genetic counsellors), or paediatric neurologists who understand the tests well. It may not be a proper suggestion to consult a team member such as social worker about the false positive results.	Please consider this suggestion.	Recommendation 4.1. For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families. Information Box Information may be provided by a paediatric neurologist and/or clinical geneticists and/or genetic counsellors.
Recommendation 4.8. We recommend that parents should be supported by the multidisciplinary team, including referral to medical social services and psychology as appropriate, during the process of managing false positive, uncertain or false negative results for their newborn/infant.	It should include babies who are screening positives. (as Recommendation 10.18) Similarly, referring babies with false positives to social worker may not be necessary. (as suggestion in recommendation 4.2)	Please consider this suggestion.	The recommendation has been in part modified and now reads as a practice standard 4.3.2. Families who receive a false negative, false positive or uncertain screening result should be provided psychosocial support by relevant members within the multidisciplinary team. Information box. 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.
Section 4	False positives may be only confirmed after the diagnostic test. Therefore, who are not confirmed by the diagnostic test should be referred as uncertain results.	Please note this comment.	We have now clarified the definition of false positive and of uncertain results 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 openly explained to parents. 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
Recommendation 8.2. diagnostic results should be disclosed to families by a specialist medical	Suggest to revise as "such as a paediatric neurologist *or clinical geneticist*".	Please consider suggestion.	In keeping with challenges for clinical genetics services to facilitate diagnostic results and treatment planning at this first point of contact in Australia we

practitioner such as a paediatric neurologist.			have maintained recommendation 7.1 as is but have added implementation guidance to enhance the role and capability of clinical geneticists 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor. .
Recommendation 10.2 We recommend that for newborns who demonstrate signs and symptoms of SMA (consistent with disease onset),	Please consider to specify newborns here is classified by only "diagnosis" or including newborns with "screening positive". For planning, probably screening positive should also trigger that discussion.	Please consider this suggestion and if you agree edit.	Recommendation modified and now reads Recommendation 8.1. Consensus recommendation For screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset i.e. clinically manifest), a paediatric neurologist should discuss options for immediate treatment with SMN augmenting treatments with the family

Recommendation 10.10 …should occur in a specialist (paediatric neurology) care centre/service.	should occur in a specialist (paediatric neurology) care centre/service *with a multidisciplinary team*.	Please consider this suggestion and if you agree edit.	Modified to align with addition. Of 'within a multidisciplinary team'
Recommendation 10.15 .. should have clinical follow-up with a minimum of 3 monthly assessments for the first two years	The suggestion needs to take SMN2 copies into consideration. For babies with 2 or 3 copies, 3 monthly assessments may be too late to capture symptoms. The current version may be only good for babies with 4 SMN2 copies.(as Recommendation 11.1)	Please consider this suggestion and if you agree edit.	This recommendation has been modified to reflect this point and now reads: 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. Practice standard 8.4.3. 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 11.2 .. all newborns with 4 *SMN2* copies…	Consider revise as ≥ 4 *SMN2* copies	Please consider this suggestion and if you agree edit.	This has been revised and reads Implementation Guidance 3.2.2. Redetermination of *SMN2* copy number in a different laboratory or using a different method may be considered in newborns with ≥ 4 *SMN2* copies, due to

		imprecision arising from *SMN2* copy number methodologies that can impact therapeutic decision making.
Reviewer Six (AUS)		
Pg 13 - Glossary – Loci not described	Please consider adding to glossary.	This has been added
Pg 15 – Glossary – definition of variant to replace mutation	Please consider adding to glossary.	This has been replaced
Pg 25 – Are the guidelines only to be used where there is availability of SMA treatments i.e. that would only be applicable in the developing world?	Please consider adding text to clarify.	As per the Scope, the Guideline is for use in Australia and New Zealand, although other countries may find it useful to refer to.
Pg 29 – Difference between B and 1B grading of recommendations?	Please consider adding text to clarify.	We have now removed this grading system for consensus recommendations to avoid confusion.
Pg 33 – last paragraph, space missing between SMA. A positive…	Please amend typographical error.	This has been changed.
Pg 35 – Recommendation 3.4 – should it include an orthogonal assay type?	Please consider suggestion.	The SAC agrees not to depict the name of assays used as these will vary on capabilities across jurisdictions and may also evolve over time.
Pg 37 – Recommendation 3.9 This is probably a NPAAC requirements though these don't apply to NZ. Perhaps in the introduction there should be reference to laboratory accreditation standards.	Please consider suggestion.	This has been added to the introduction section for section 3 which now reads (as is referenced accordingly). *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*

Pg 39 – Recommendation 4.3 Should there be a recommendation for a review/repeat of the NBS testing to ensure that another child is not positive for SMA. That is specimen mix-up in NBS. Is this covered in 4.1?	Please consider suggestion.	This suggestion has been considered and added to the implementation guidance which now reads Implementation Guidance 4.2.1. A further blood sample from the newborn may be required for repeat screening and/or diagnostic testing if resolution of *SMN1* and/or *SMN2* genotype does not occur.
Pg 40 - Recommendation 4.7 This would be part of a laboratory quality system review. It should lead to recommendation that minimise the potential for this to occur again.	Please consider suggestion.	This suggestion has been considered and added to the implementation guidance which now reads 4.2.3. 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 issues and errors can be identified as part of quality improvement.
Pg 46 – Recommendation 6.1 The implication is that these should be separate collections. A single diagnostic collection could suffice for both SMN1 and SMN2 testing.	Please note this comment.	This recommendation has not been changed as in some jurisdictions two different samples are required as the specimens for SMN1 and SMN2 go to separate labs and has been qualified by an information box statement *…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.*

Pg 56 – Recommendation 10.5 Is single agent treatment gene therapy?	Please consider comment and add text for clarity.	The text has been clarified and reads Recommendation 8.3. We recommend that in the absence of comparative data, currently single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended.
Pg 58 - do 10.10 and 10.11 contradict? is 10.10 the preferred option? Is 10.11 a fallback position? These are recommendations and not "musts".	Please consider comment and if you agree, edit.	The feedback has been used to clarify the recommendations which now read Recommendation 8.3 Consensus recommendation In the absence of comparative data, single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended, started within paediatric neurology treatment centre. Implementation Guidance 8.3.2. Dependent on the needs and preferences of the child and family, SMN augmenting treatments may be planned to be initiated from a non-specialist treatment centre/service, with paediatric neurology support and guidance. **Information Box** Onasemnogene abeparvovec-xioi can only be administered in designated and approved paediatric treatment centres in Australasia.

Recommendation 10.13 Is this where the guidelines comment on patients without access to funded therapy. If funded therapy is not available should these newborns be screened for SMA?	Please consider comment and if you agree, edit.	This is an ethical consideration for the NBS program as a whole. Currently, children without recourse to treatment are screened in Australasia for all conditions on the NBS panel. This has now been addressed in Practice Standard 8.2.1. 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.
Pg 58 – is 10.14 missing?	Please amend numbering of recommendations.	This has been rectified
Recommendation 10.16 missing	Please amend numbering of recommendations.	This has been rectified.
There are two 10.17 listed in recommendations	Please amend numbering of recommendations.	This has been changed.
Pg 66 – this paragraph is duplicated	Please amend typographical error.	This has been changed.
Pg 95 - The Royal College of Pathologist Australasia was not asked to endorse the Guidelines?	Please clarify RCPA position.	The RCPA will be approached for endorsement of the Guideline.
Pg 95 - The HGSA and several of its special interest groups are asked to endorse the guidelines. Should this be done under the single banner of the HGSA? It would be awkward for the HGSA if there were differing opinions?	Please consider suggestion and add text to clarify if you agree.	Suggestion taken on board and the HGSA as a single entity will be approached for endorsement of the finalised Guideline.
Pg 112 - Do NBS have high public confidence or low antagonistic views? Is awareness of NBS high?	Please consider adding text to into this section about public opinion.	Several studies from Australia show high public trust in this system and therefore the wording has not been changed.
Pg 117 - Should there be guidelines for the broader consenting process for NBS. I can understand it being out of scope for these guidelines.	Please consider comment and clarify.	This is considered outside the scope of the Guideline and has been added to the Scope section.

Pg 118 – typo a automated level required	Please amend typographical error.	Typographical error changed
Pg 119 – typo for f exon 7 variants	Please amend typographical error.	Typographical error changed