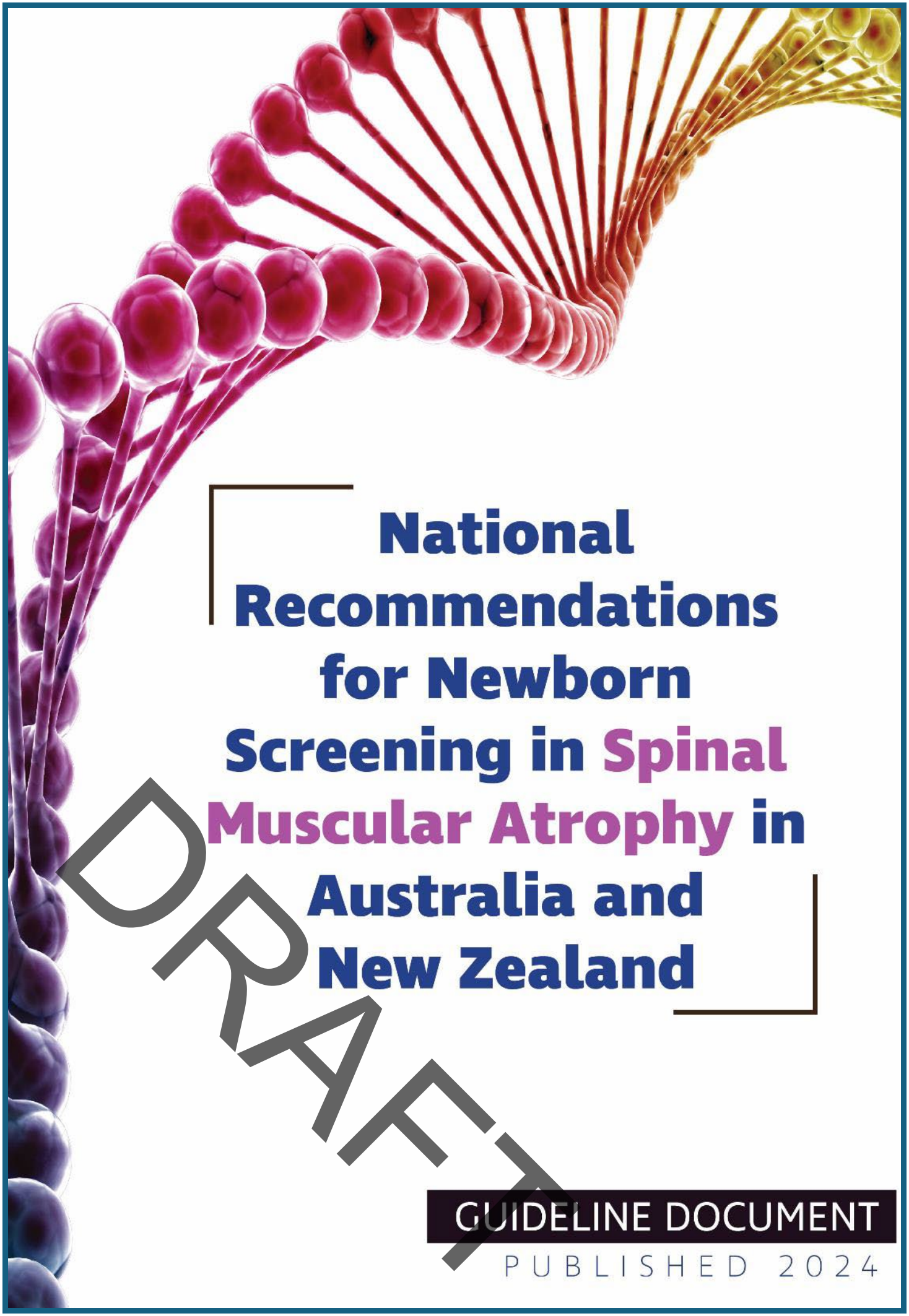

National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand

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

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Glossary of terms

Accuracy

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

Allele

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

Analyte

component represented in the name of a measurable quantity.

Assay

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

Carrier screening

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

Clinical evaluation

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

Clinical sensitivity

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

Clinical validity

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

Confirmatory test

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

Copy number variant

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

Diagnostic accuracy

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

Diagnostic test

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

Digital polymerase chain reaction

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

Discrepant result (also discordant result)

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

Dried blood spot

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

Ethylene diamine tetraacetic acid (EDTA)

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

Exon

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

False-negative screening result

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

False-positive screening result

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

First-tier screen

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

Follow-up

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

Gene

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

Gene sequencing

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

Genetic counselling

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

Genetic variant

a DNA sequence that varies from a reference DNA sequence.

Genotype

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

Genotype phenotype correlation

the association between the presence of a certain mutation or mutations (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 mutation on both alleles of a specific gene. However, when both alleles of a gene harbour mutations, but the mutations are different, these mutations are called compound heterozygous. This is important, for example, in recessive diseases in which each allele carries a different mutation, 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.

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 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 child-hood 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 used to be 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 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 New Zealand may give rise to regional differences in newborn screening programs, which has the potential to create inequity in the access to diagnosis, treatment, care, and potential outcomes of affected children.(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)

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

The Guideline has been formulated using a validated methodology for searching, appraising and grading evidence.(18-25) Recommendations have been developed using systematic evidence synthesis in combination with expertise and evidence from an Australian and 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 medical professionals (neurologists, paediatricians, general practitioners, geneticists, nurses, allied health workers) 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 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 changes (pathogenic variants) in 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) 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 nearby related gene 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.(26) 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 federal governments of Australia and New Zealand respectively, agreed that SMA should be part of routine national newborn screening programs i.e. be offered to all babies.(12, 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.(12, 29)

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

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

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

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

As SMA can progress quickly, it is important that all healthcare practitioners communicate and work together to make sure that the screen positive newborn has a molecular genetic diagnosis confirmed accurately and quickly, and that treatment plans are considered early. Healthcare practitioners should be competent and provide high quality services that are safe and supportive. They should collect, use, and share information in ways that are helpful,

respectful, and accessible. Families of screen positive newborns should be referred to supports when needed and desired at any point of the newborn screening for SMA pathway.

Guideline purpose, scope, population and setting

Purpose

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

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

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

Scope

The Guideline takes the view of the healthcare journey for the newborn and family from screening for SMA, through to confirmation of a diagnosis, and clinical care and support after the diagnostic period.

The 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

(24) and internationally developed Standards of Care for SMA. (25, 26) It is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across Australia and New Zealand. Developed to support equitable implementation of newborn screening across Australia and New Zealand, 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)(8-10, 27) (ref), technical aspects of screening (as covered by the Clinical & Laboratory Standards Institute Guideline for Newborn Screening for SMA) and diagnostic methodologies and ongoing management of individuals with SMA beyond the initial post-diagnostic period (as covered by international standards of care guidelines) will not be covered in this 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.

Population

Whilst developing and writing 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 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

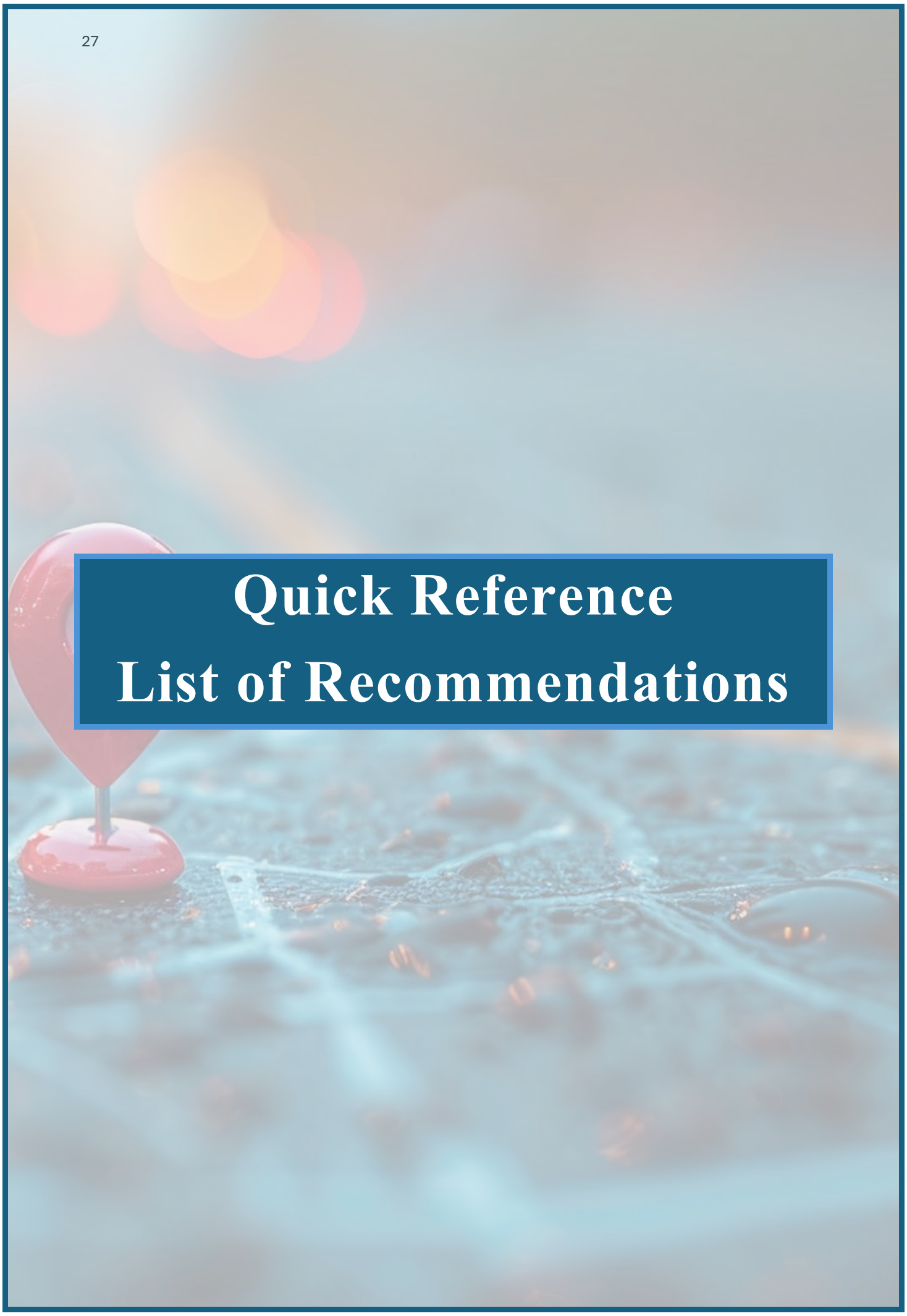
The Guideline applies to the public health care setting (including primary, secondary and tertiary/specialist care) and clinical areas including hospitals and community health care services. The guideline also applies to screening, diagnosis, assessment and treatment clinical stages.

Target end users

Targeted primary end users of the Guideline include Australian and 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 (neurologists, paediatricians, general practitioners, geneticists, nurses, allied health workers) 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 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 New Zealand training providers including peak bodies and institutions that may use the Guideline to streamline educational and clinical resources.
3. Australian and New Zealand families of children undergoing and screening positive for SMA through NBS programs.



Quick Reference List of Recommendations

List of recommendations

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

Each recommendation includes a 'grade of Recommendation.' All Recommendations within the Guideline represent good practice and should be implemented. For evidence-based recommendations we provide a grade of A to D as defined by the quality and consistency of available evidence, generalisability, impact and applicability to the Australasian healthcare context of the evidence base available to support the recommendation. The grade of recommendations (strong, conditional) for consensus-based recommendations is intended to support users in considering a range of factors when implementing a given Recommendation, such as the benefits and harms, resources needed, and the acceptability to individuals, families, and practitioners. Here, where a Recommendation is strong, it is written as '*we recommend*' and when a 'conditional' Recommendation has been made, it indicates that there are factors to consider during implementation and is written in the format of '*we suggest'*. This approach to providing grades is consistent with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) framework.(19, 24) Further information about this approach is provided in the Administrative and Technical Report (https://www.unsw.to/nbs-sma).

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

Recommendation 1.1

Evidence based recommendation

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

Grade of recommendation B

Recommendation 1.2

Evidence based recommendation

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

Grade of recommendation Grade B

Recommendation 1.3

Consensus based recommendation

We recommend that the screening method selected by the screening program should have a sensitivity of ≥ 95% for the detection of S*MN1* exon 7 homozygous deletion.

Grade of recommendation Strong, Grade 1C

Recommendation 1.4

Consensus based recommendation

We recommend that the screening test for SMA should determine the S*MN1* exon 7 absence, using suitably validated quantitative or qualitative assays.

Grade of recommendation Strong, Grade 1B

Recommendation 1.5.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 1.6.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 1.7.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 1.8.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1B

Recommendation 1.9.

Consensus based recommendation

We suggest that newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, low (weight < 2500g) or very low birthweight (< 1500g) newborns should proceed using the same screening protocols as for term newborns and those weighing > 2500g.

Grade of recommendation Conditional, Grade 2B

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

Recommendation 2.1.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Recommendation 2.2

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 2.3.

Consensus based recommendation

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).

Grade of recommendation Strong, Grade 1C

Recommendation 2.4.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 2.5.

Consensus based recommendation

We recommend that irrespective of *SMN2* incorporation into newborn screening for SMA, *SMN2* copy number determination should be included in diagnostic testing during follow-up care.

Grade of recommendation Strong, Grade 1B

Recommendation 2.6.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 2.7.

Consensus based recommendation

We recommend that the newborn screening 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.

Grade of recommendation Strong, Grade 1C

Recommendation 2.8.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

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

Recommendation 3.1

Evidence based recommendation

We recommend that diagnostic testing should include confirmation homozygous deletion of exon 7 on *SMN1*.

Grade of recommendation Strong, Grade B

Recommendation 3.2

Consensus based recommendation

We recommend that diagnostic testing should also include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making.

Grade of recommendation Strong, Grade 1B

Recommendation 3.3

Consensus based recommendation

We recommend that validated *SMN1* and *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.

Grade of recommendation Strong, Grade 1B

Recommendation 3.4

Consensus based recommendation

We suggest that diagnostic *SMN1* testing is conducted using a different methodology to the newborn screening assay.

Grade of recommendation Conditional, Grade 2C

Recommendation 3.5

Consensus based recommendation

We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means), should ideally occur so that stakeholders understand when a diagnostic sample will be collected, delivered to diagnostic laboratories and expectant timelines for diagnostic analysis and receipt of results.

Grade of recommendation Conditional, Grade 2B

Recommendation 3.6

Consensus based recommendation

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.

Grade of recommendation Conditional, Grade 2B

Recommendation 3.7

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Recommendation 3.8

Consensus based recommendation

We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth.

Grade of recommendation Conditional, Grade 2B

Recommendation 3.9

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

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

Recommendation 4.1

Consensus based recommendation

We suggest that for newborns with a false positive or uncertain screening result i.e. for those diagnostically not confirmed to have SMA despite a screen positive result on newborn screening for SMA, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and openly explained to parents.

Grade of recommendation Conditional, Grade 2C

Recommendation 4.2

Consensus based recommendation

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*.

*Multidisciplinary team members may vary dependent on health jurisdiction and include but are not limited to paediatric neurologists, genetic counsellors, geneticists, social worker, psychologist, allied therapists, specialist nurses.

Grade of recommendation Conditional, Grade 2C.

Recommendation 4.3

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C.

Recommendation 4.4

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.5

Consensus based recommendation

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

Grade of recommendation Strong Grade 1C

Recommendation 4.6.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.7.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.8.

Consensus based recommendation

We recommend that 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.

Grade of recommendation Strong, Grade 1C

Recommendation 4.9.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.10.

Consensus based recommendation

We recommend that healthcare professionals 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 specialist neurology services (due to current newborn screening assays only detecting exon 7 homozygous deletion of *SMN1*).

Grade of recommendation Strong, Grade 1C

Section 5. Communicating a SMA screen positive result to families

Recommendation 5.1

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Recommendation 5.2

Consensus based recommendation

We recommend that the designated paediatric neurologist, receiving the screen positive SMA result (recommendation 2.10), should coordinate with relevant healthcare practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process.

Grade of recommendation Strong, Grade 1C

Recommendation 5.3

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 5.4

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

Grade of recommendation Strong, Grade 1C

Recommendation 5.5.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 5.6

Consensus based recommendation

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

The screen positive status of the newborn.

The name of the condition.

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

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

Named health professional as a point of contact for the family.

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

Grade of recommendation Conditional, Grade 2C

Recommendation 5.7

Consensus based recommendation

We suggest that screen positive newborns should ideally be offered a clinical review within paediatric neurology/neuromuscular services.

Grade of recommendation Conditional, Grade 2C

Recommendation 5.8

Consensus based recommendation

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.

Grade of recommendation Conditional, Grade 2C

Recommendation 5.9.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 5.10.

Consensus based recommendation

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

Change in movement, feeding, or breathing pattern.

Change in voice or weak cry.

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

Abdominal breathing and/or failure to thrive.

Grade of recommendation Strong, Grade 1C

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

Recommendation 6.1

Consensus based recommendation

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

Neurological examination.

Venous sampling for *SMN1* on whole blood (for the purposes of diagnostic testing).

Venous sampling for *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number (for the purposes of diagnostic testing).

Grade of recommendation Strong, Grade 1C

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

Recommendation 7.1

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.2

Consensus based recommendation

We suggest that the number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a medical practitioner), and ideally support from representatives of the clinical genetics service and/or medical social/psychological services.

Grade of recommendation Conditional, Grade 2C

Recommendation 7.3

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.4

Consensus based recommendation

We recommend that 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.

Grade of recommendation Strong, Grade 1C

Recommendation 7.5

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1B

Recommendation 7.6

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.7

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

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

Recommendation 8.1

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 8.2.

Consensus based recommendation

We suggest that ideally, diagnostic results should be disclosed to families by a specialist medical practitioner such as a paediatric neurologist.

Grade of recommendation Conditional, Grade 2C

Recommendation 8.3.

Consensus based recommendation

We suggest that if circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for a responsible medical practitioner with support from a specialist medical practitioner to disclose a diagnostic result to a family.

Grade of recommendation Conditional, Grade 2C

Recommendation 8.4

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 8.5

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

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

Recommendation 9.1

Consensus based recommendation

We suggest that all newborns diagnostically confirmed with SMA through a newborn screening program should be reviewed by a specialist medical practitioner such as a paediatric neurologist.

Strength of recommendation Conditional, Grade 2C

Recommendation 9.2

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.3.

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 9.4

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.5

Consensus based recommendation

We suggest that families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review at a clinical genetics service for genetic counselling and cascade screening.

Strength of recommendation Conditional, Grade 2C

Recommendation 9.6

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 9.7

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.8.

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.9.

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

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

Recommendation 10.1

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.2

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1A

Recommendation 10.3

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.4.

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1B

Recommendation 10.5

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.6

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.7

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.8

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.9

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2B

Recommendation 10.10

Consensus based recommendation

We recommend that the administration of SMN augmenting treatments should occur in a specialist (paediatric neurology) care centre/service.

Strength of recommendation Strong, Grade 1C

Recommendation 10.11

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.12

Consensus based recommendation

We suggest that post treatment monitoring for newborns who access SMN augmenting treatments may be shared between specialist centres and regional (non-specialist) care centres/services (with support from the specialist centre) as child and family factors dictate.

Strength of recommendation Conditional, Grade 2C

Recommendation 10.13

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.15

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.15

Consensus based recommendation

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

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

Growth parameters including length, weight and head circumference

Neurological examination.

Strength of recommendation Strong, Grade 1C

Recommendation 10.17

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.17

Consensus based recommendations

We recommend that evaluators should have adequate training for the application of each examination or assessment.

Strength of recommendation Strong, Grade 1C

Recommendation 10.18

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

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

Recommendation 11.1

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.2

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.3

Consensus based recommendations

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.4

Consensus based recommendation

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

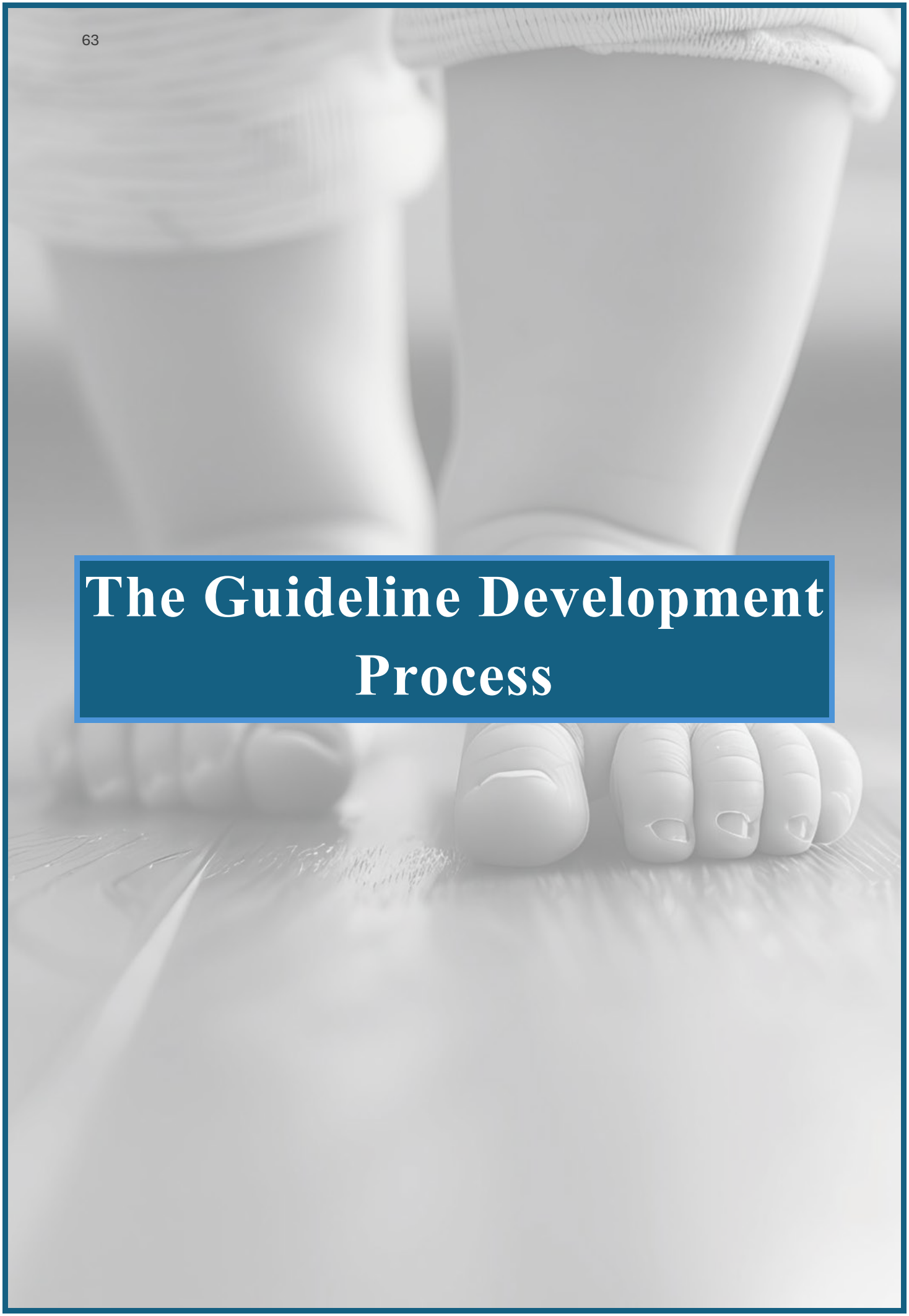
Strength of recommendation Conditional, Grade 2C

Recommendation 11.5

Consensus based recommendation

We suggest that national clinical paediatric neurology centres/services 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.

Strength of recommendation Conditional, Grade 2C



The Guideline Development Process

Step 1: Defining the need for a Guideline and criteria for its development

During the pilot newborn screening for SMA program (that ran across New South Wales and the Australian Capital Territory from 2018-2022), clinical researchers and healthcare practitioners across Australia and 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 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,(34) and adhered to nine standards.

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

Due to SMA being within a rare disease field, the methodology also aligned with the National Strategic Action Plan for Rare Diseases (NSAPRD)(15) with an emphasis on developing guidelines that accounted for the paucity of high-level evidence in the rare disease field but remained highly relevant to the care and support of affected children and their families.

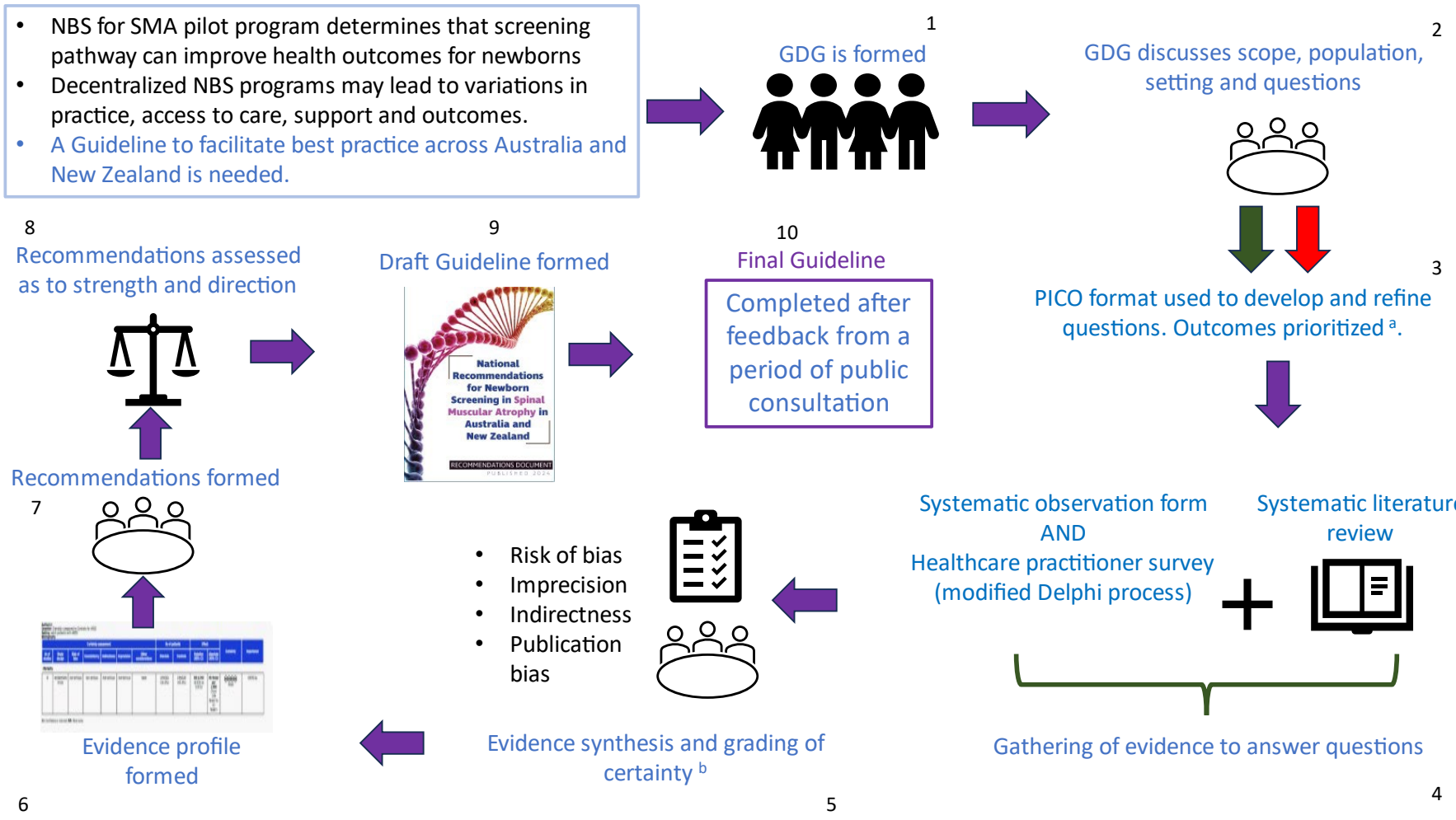


Figure 1. The Guideline Development Process. A Guideline Development Group (GDG) was formed (1) and met to discuss scope, population applicable settings and broad questions for the Guideline (2). A Population, Intervention, Comparator, Outcome (PICO) format was used

to develop, refine questions and prioritise outcomes (3). An evidence base was formed through systematic literature review and stakeholder consultation processes (4). The evidence was synthesised and graded as to certainty (5,6) to form and grade the strength of evidence-based recommendations (7,8). The scholarly literature combined with results from a modified Delphi process and systematic observation forms were synthesised to form consensus-based recommendations (7), which were also graded for direction and strength (8). Draft Guideline was formed (9) and submitted for a period of public consultation, with feedback incorporated where appropriate before submission of the final Guideline (10). . 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 New Zealand. 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 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 (New Zealand) newborn screening programs.
2. Leads and Deputy leads of SMA state and territory based (Australia) or national (New Zealand) SMA diagnostic laboratories.
3. Clinical Leads of specialist (paediatric) neurology services within each state and territory (Australia) and New Zealand, with expertise in managing children with SMA.
4. Medical 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).(35)

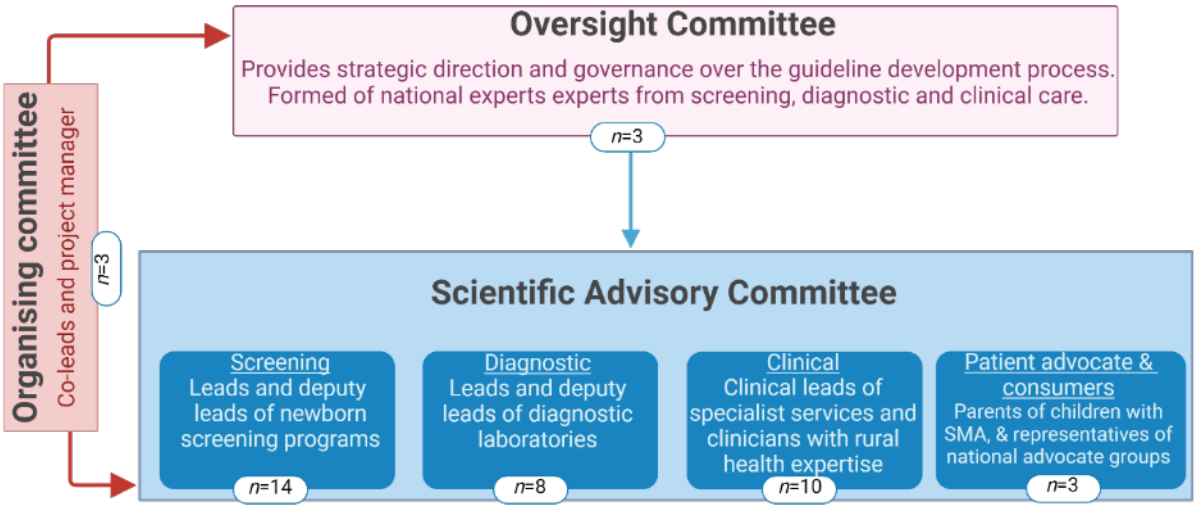


Figure 2. The Guideline Development Group and its governance structure. The oversight committee (*n*=3) was comprised of representatives with national expertise in the areas of screening, diagnosis and clinical care. The Scientific Advisory Committee (SAC) contained leaders within their relevant areas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

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

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.

The GDG collated evidence, provided expert opinion where evidence was lacking, and used the evidence to formulate then grade the strength of recommendations using an evidence to decision process. The GDG also provided oversight for of the public consultation process, revising the Guideline and associated documents according to feedback, and endorsing the finalised Guideline for dissemination.

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.(18, 36) At this juncture, potential outcomes were selected and prioritised. This framework is a systematic and transparent approach for rating the certainty of evidence in systematic reviews and clinical practice guidelines, and for developing and determining the strength of clinical practice recommendations.

Step 4: Rationale and approach for processes used in the evidence gathering stage

Prior to this study, systematic reviews of the scholarly literature pertaining to newborn screening for SMA had not been conducted. The quantitative data generated through a systematic review of the scholarly literature using a PICO format (Step 5) was considered by the GDG as insufficient to answer several of the questions that the SAC considered relevant to include in the Guideline as these varied in methodological quality, clarity of outcome data, the nature and delivery of the defined intervention and how the outcomes were assessed. Additional evidence generated through systematic and qualitative methods of collecting consensus from a group of experts that included the preferences and values of stakeholders was also considered relevant to development of the evidence base. Consequently, the GDG prioritised development of questions relevant to everyday best practice. This was consistent with NHMRC Standard 1 (to be relevant and useful for decision making) and Standard 7 (to make actionable recommendations). For this same reason, the recommendations included in the Guideline were a mixture of evidence-based and consensus-based recommendations.

Step 5: Gathering the evidence

The purpose of gathering evidence was to facilitate the formulation of recommendations in a systematic manner, consistent with GRADE, and reflecting multiple converging sources of evidence. The Guideline was intended to be evidence-based, adhering to an evidence-based practice framework that combined best available evidence.(19, 37) 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).(38) 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 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.(25) 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 knowledge 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.(22, 25)

Data analysis

The results of the systematic observation were analysed using a convergent parallel design.(39) 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 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.(36) 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. (40) 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.(41)

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

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

Outcomes were assessed as to their certainty using the GRADE framework. The quality of the body of evidence was assessed against domains of inconsistency, indirectness, imprecision, risk of bias and publication bias. The quality of the outcomes were then categorised as to a grade of evidence from high (very confident that the true effect lies close an estimate of effect), moderate (true effect is likely to be close to the estimate of effect but may be substantially different), low (true effect may be substantially different from estimate of effect) to very low (the true effect is likely to be substantially different from the estimate of effect. Of note, observational studies started at a low certainty of evidence. An overall summary of findings table regarding all relevant aspects of the evidence base was formulated which also included characteristics of the defined outcome including clinical usefulness (acceptability to end users and implementability in Australia and 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.).(42) Evidence-based recommendations were formed if an actionable statement could be derived using the systematic review of evidence, generated through questions within a PICO format.

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

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

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

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

The Organising Committee used an iterative process, using evidence to decision (EtD) framework to move from evidence to forming evidence and consensus-based recommendations. (24, 37) .

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, CLSI terminology databases, National Newborn Screening Framework, US Health Resources and Services Administration, Advisory Committee on Heritable Disorders in Newborns and Children.).
- Conceptual and ethical frameworks (e.g., AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research, 2020; International Classification of Functioning, Disability and Health, World Health Organisation Screening Guidelines).
- Conventions (e.g., United Nations Convention on the Rights of the Child, 1989).

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.(43, 44) 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.

(45) The evidence and justification provided in each domain were considered by the SAC and used to structure their decisions on how to convey the direction of the recommendation (for or against) and the strength through wording and grading through a considered judgement form. Letters of (A to D) were assigned to the recommendation and indicative of the strength of the body of evidence that underpinned the recommendation (Table 5.).(46)

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

Grade of recommendation	Description and body of evidence matrix
A	Body of evidence can be trusted to guide practice. One or more level I or several level II studies with low risk of bias and all studies consistent, or inconsistencies can be explained. The clinical impact is very large. The populations studied in the body of evidence are the same as the target population for the guideline. The studies are directly applicable to the Australasian health care context.
B	Body of evidence can be trusted to guide practice in most situations. One or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias with most studies consistent, or inconsistencies can be explained. Clinical impact is substantial. Population studied in the body of evidence is similar to the guideline population. Applicable to Australasian health care context with few caveats.
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application. One or two level III studies with low risk of bias or level I or II studies with a moderate risk of bias. Some inconsistency reflecting some uncertainty. Clinical impact is moderate. Population studied in the body of evidence differs from the guideline population, but it is sensible to apply it to target population. Applicable to Australasian health care context with some caveats.

D	Body of evidence is weak, and recommendation must be applied with caution. Level IV studies or level I to II studies/systematic reviews with a high risk of bias. Evidence is inconsistent. The clinical impact is slight. Population studies in the body of evidence differ to target population and hard to judge whether it is sensible to apply it to the target population.
Consensus based evidence required	Formulation of recommendation through discussion, Delphi process and assignment of agreement by individual participants.

Consensus-based recommendations

The *strength* of each consensus-based recommendation was evaluated using a modified approach based on the NHMRC grading technique and used in prior paediatric consensus based guidelines (47), which incorporated the seven domain of the GRADE process. This included evidence base consistency, clinical impact (benefits and risks), resource implications, equity factors, acceptability and values of stakeholders, generalisability and applicability of the evidence base

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

Co-Chair Didu Kariyawasam and Christian Meagher independently rated each consensus-based recommendation according to a set of descriptors developed for use in prior clinical guidelines based on NHMRC terminology.(48)

The descriptors included

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

5. ‘Support from experts’, which was assigned for each recommendation a category of ‘excellent’, ‘good’, ‘satisfactory’ or ‘poor’ was assigned.

Table 6. Descriptors and definitions for GRADING the strength of consensus-based recommendations. The GRADE of recommendations aligns with NHMRC Guidelines that take into consideration a need for transparency in how all recommendations are formulated and assessed for strength.

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

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

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

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

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

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

Step 9: Finalising the draft Guideline and the process of public consultation

The first version of the draft guidelines including evidence and consensus-based recommendations and practice points, with their certainty (for evidence-based recommendations) and strength (for consensus-based recommendations) were compiled by the Organising Committee and disseminated to the SAC and Oversight Committee on 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. 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.

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.

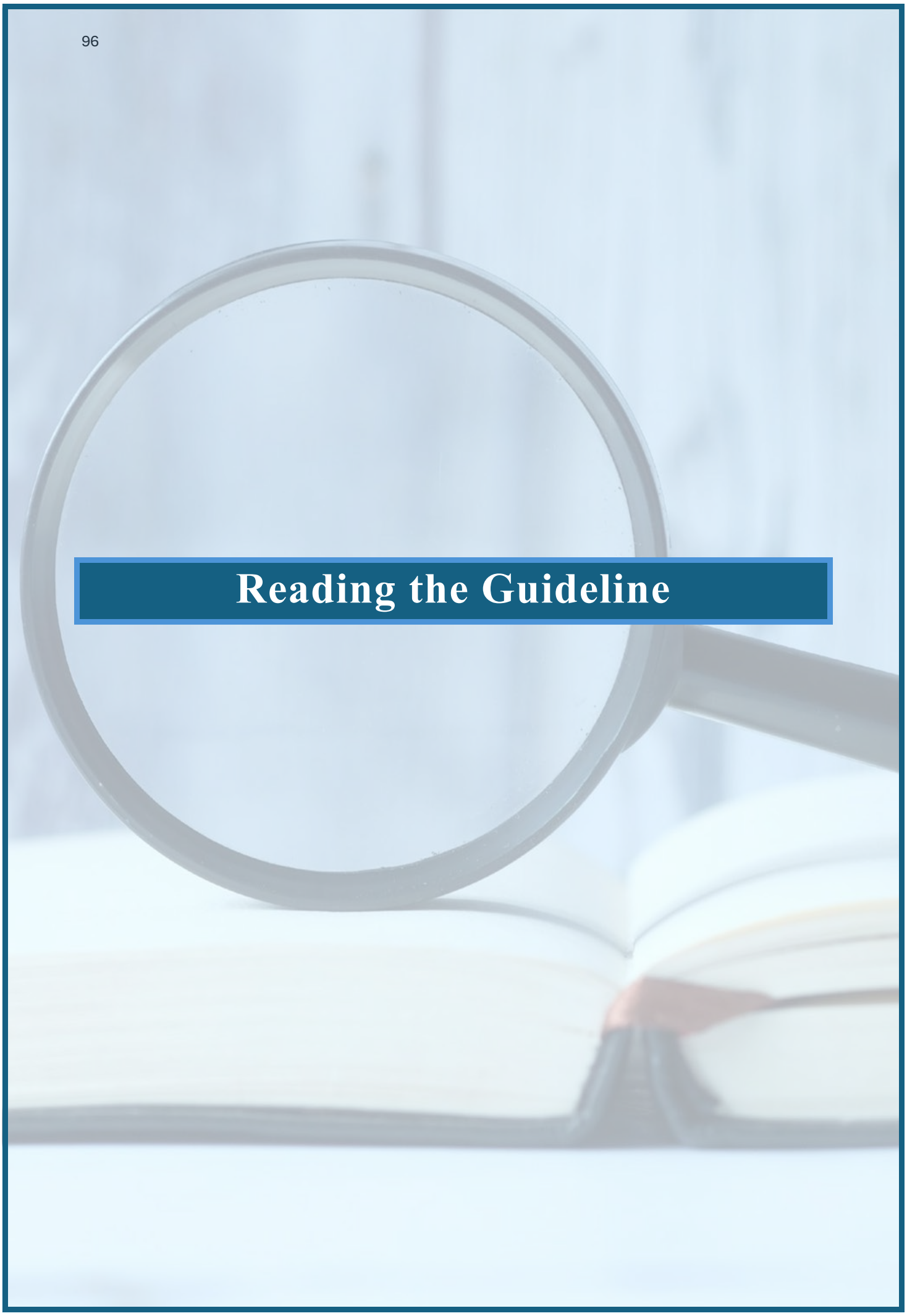
Final changes were incorporated into the Guideline, supporting evidence, the plain language summary and Administrative and Technical reports as appropriate. The finalised Guideline was disseminated to the entire SAC for review. The compiled feedback and final responses alongside the location of any change that had been made were provided in the Public Consultation summary alongside the final Guideline.

Step 11: Endorsement of the Guideline

The following list of organisations were contacted to endorse the Guideline.

Organisation name
The Royal Australian College of Physicians
Australian and New Zealand Child Neurology Society
SMA Australia
Rare Voices Australia
Human Genetics Society of Australia
New Zealand Paediatric Society / The Paediatric Society of New Zealand
Commonwealth Department of Health
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
The Royal Australian College of General Practitioners
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 the states and territories of Australia and in New Zealand



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 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,(49, 50) standards of care for spinal muscular atrophy (49, 50) 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).

The Guideline is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across Australia and 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 New Zealand and provide informed guidance for Australian and 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; neurologists, paediatricians, general practitioners, geneticists, nurses, allied health workers) 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 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 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 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) 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.

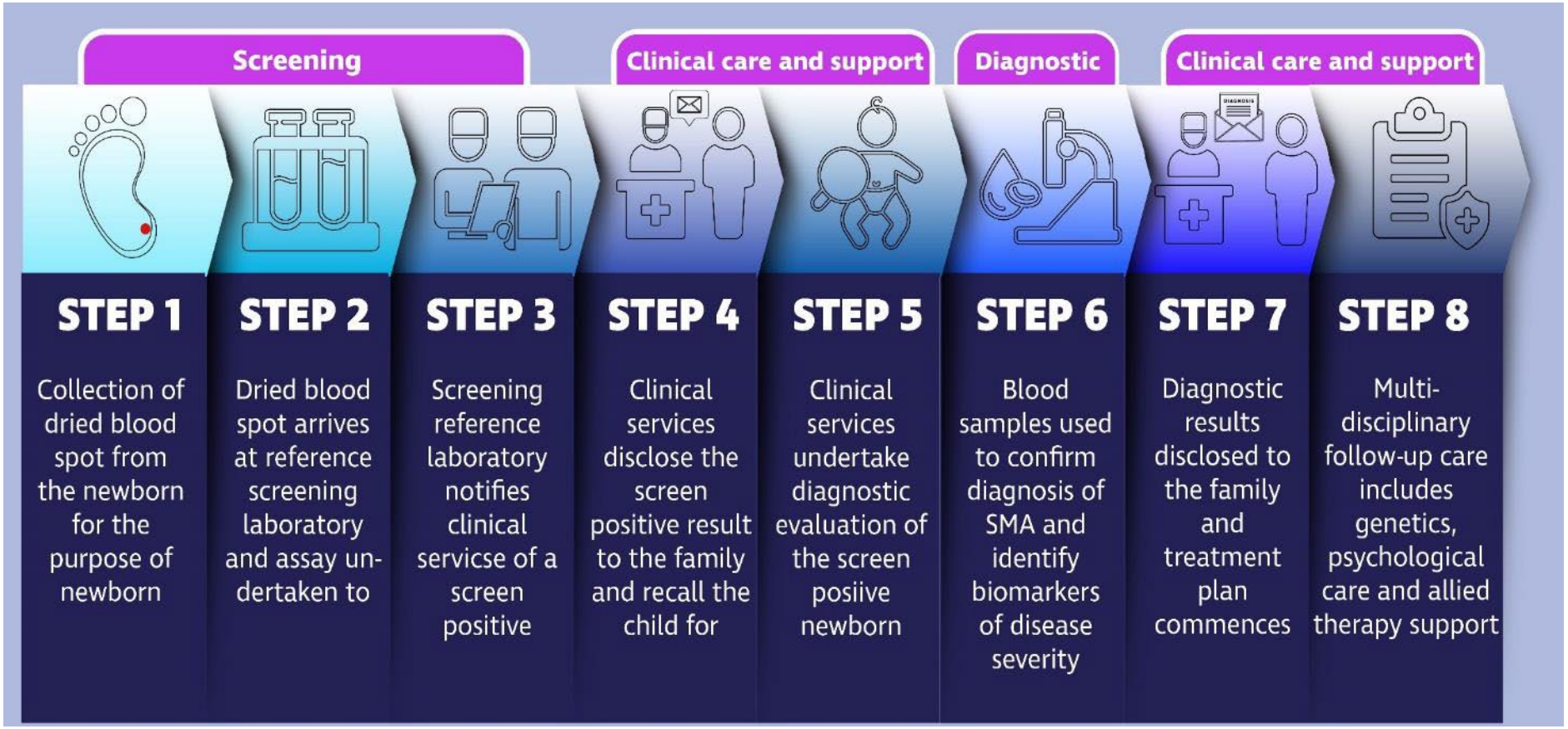


Figure 3. The newborn screening pathway for spinal muscular atrophy as encomapssed by the Guideline.

The domains in the Guideline pertain to screening, diagnostic, clinical care and support

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’.

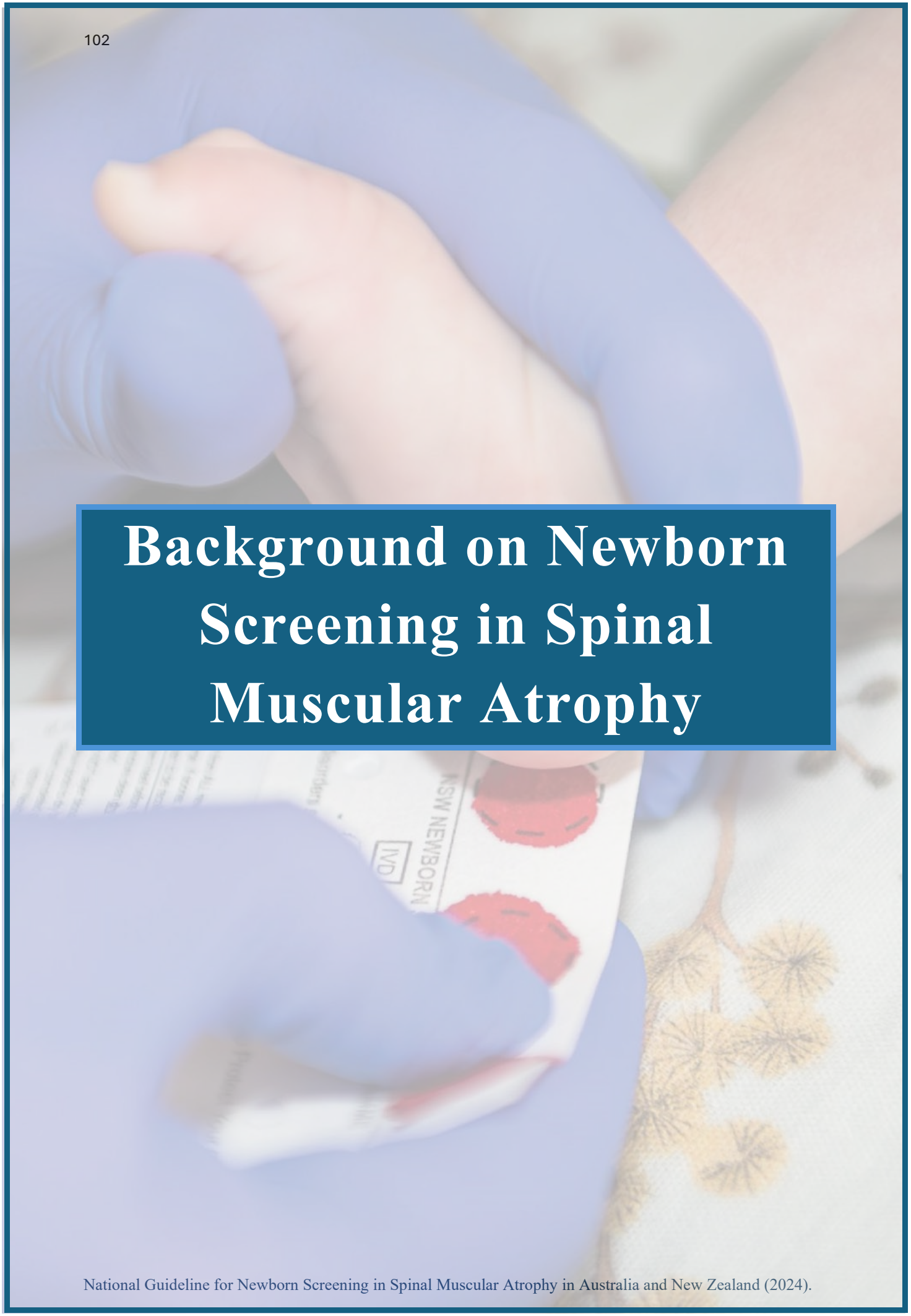
The definition of healthcare practitioners

The term ‘healthcare practitioners’ were used within the Guideline to refer to medical, nursing, allied health, 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 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 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.



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.(51) Amongst the autosomal recessively inherited conditions, it is second only in birth prevalence to cystic fibrosis, with an estimated 30 new families affected by the condition across Australia every year and an estimated 5 families affected in New Zealand per annum.(52) Although frequencies vary between ethnicities, 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. (53) 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.(53) The pattern of weakness is usually symmetrical and length dependent, affecting legs before arms.(54) Associated consequences of the condition include respiratory and feeding difficulties, progressive neurodisability, and high medical and supportive care needs.(55-60) SMA has a spectrum of severity and a predominant childhood onset.(61)

Individuals living with SMA have a varied presentation (Table 6.). 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 Hoffman 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.(61, 62)

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).(63, 64) 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, 54, 65) whilst in the latter, individuals generally retain ambulation skills, but may find higher motor tasks challenging and/or fatiguing.(60)

Table 6. 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-Hoffman 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 and/or 8 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.).(27) Hybrid (rearranged) genes (5%) and other condition-causing variants (other deletions and pathogenic sequence variants) (< 5%) account for the remainder of genetic changes leading to SMA.(27, 66)

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.(66, 67)

A duplication within chromosome 5 gives rise to a homologous gene called survival motor neuron 2 (*SMN2*), which has the same coding areas as *SMN1* apart from a single base pair nucleotide change in exon 7.(27) This change removes exon 7 in the majority (90%) of SMN mRNA transcripts and produces a short length protein that cannot self-associate, attach and function with other proteins, leaving it vulnerable to degradation.(27, 68, 69) *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, 70-77) *SMN2* copy number is generally considered the best predictor of age of onset and severity of the condition.

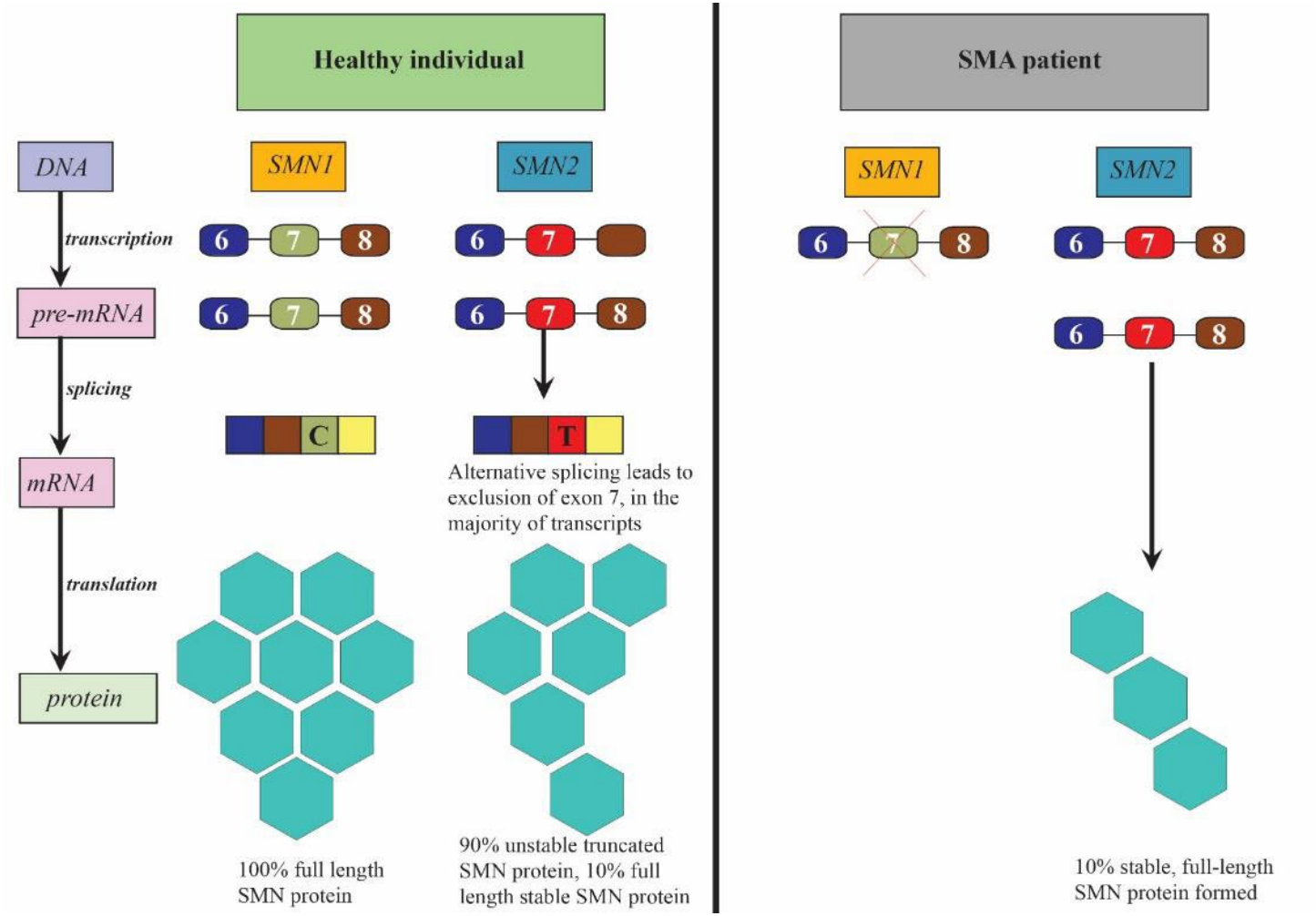


Figure 4. The genetics of spinal muscular atrophy. In healthy individuals, *SMN1* produces 100% of full-length SMN protein. In *SMN2* the exchange of one nucleotide allows for splicing out of exon 7 in *SMN2* resulting in a shortened pre-mRNA transcript that produces mostly shortened form of SMN protein which is rapidly degraded. SMN2 copy number can change phenotype in a dose dependent manner but the correlation is not absolute.

National Guideline for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand (2024).

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.(78)

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, 27, 35, 79-84)

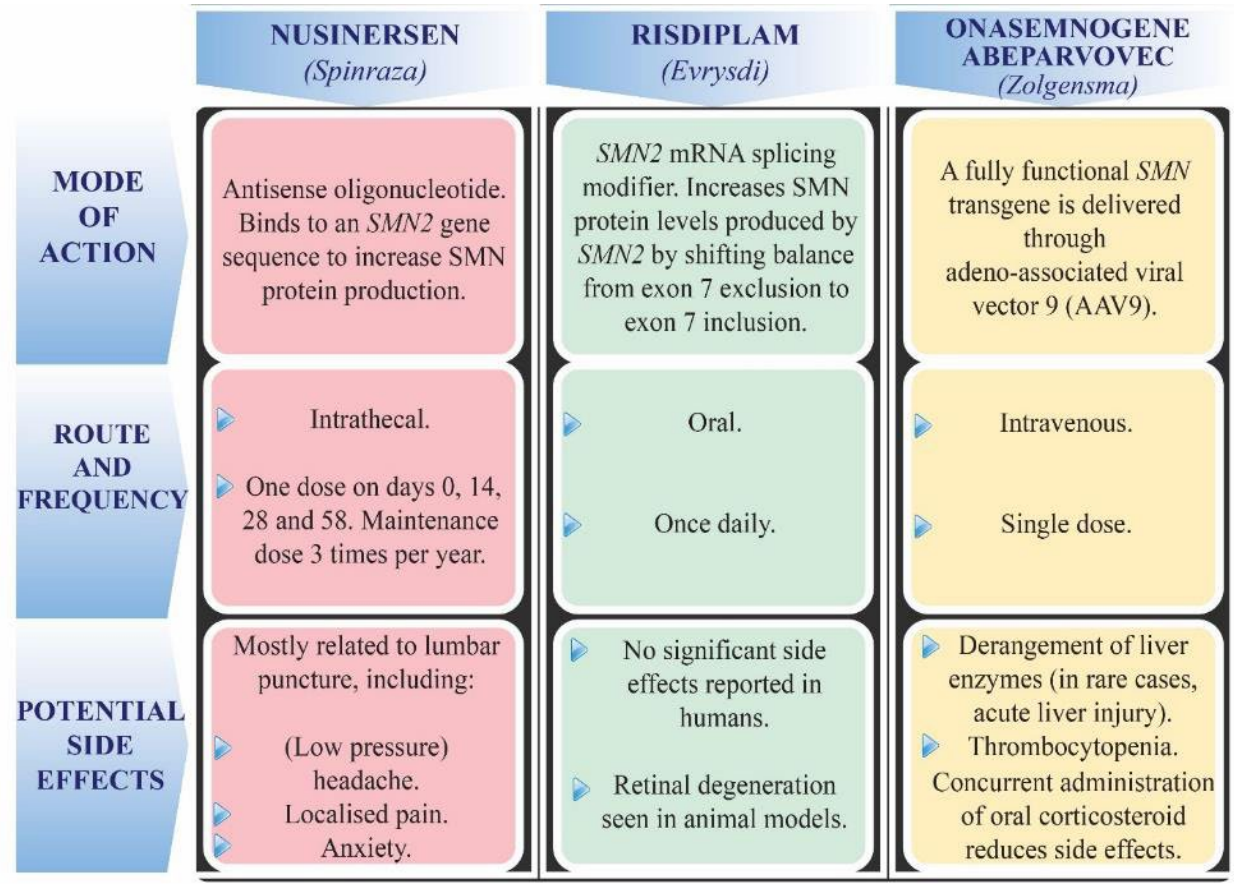


Figure 5. Approved SMN augmenting treatments for spinal muscular atrophy across Australasia. Approvals and reimbursements vary across the two health jurisdictions and are dependent on age, *SMN2* copy number and clinical status (symptomatic or presymptomatic status).

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.(85)

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.(86) 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 (71, 87). Presymptomatic treatment is essential to replete SMN protein within a therapeutic window where they 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. 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.(88, 89)

In recognition of this foundation of evidence, SMA as a condition is now able to meet the screening principles set out by *Wilson and Junger*,(90) 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.

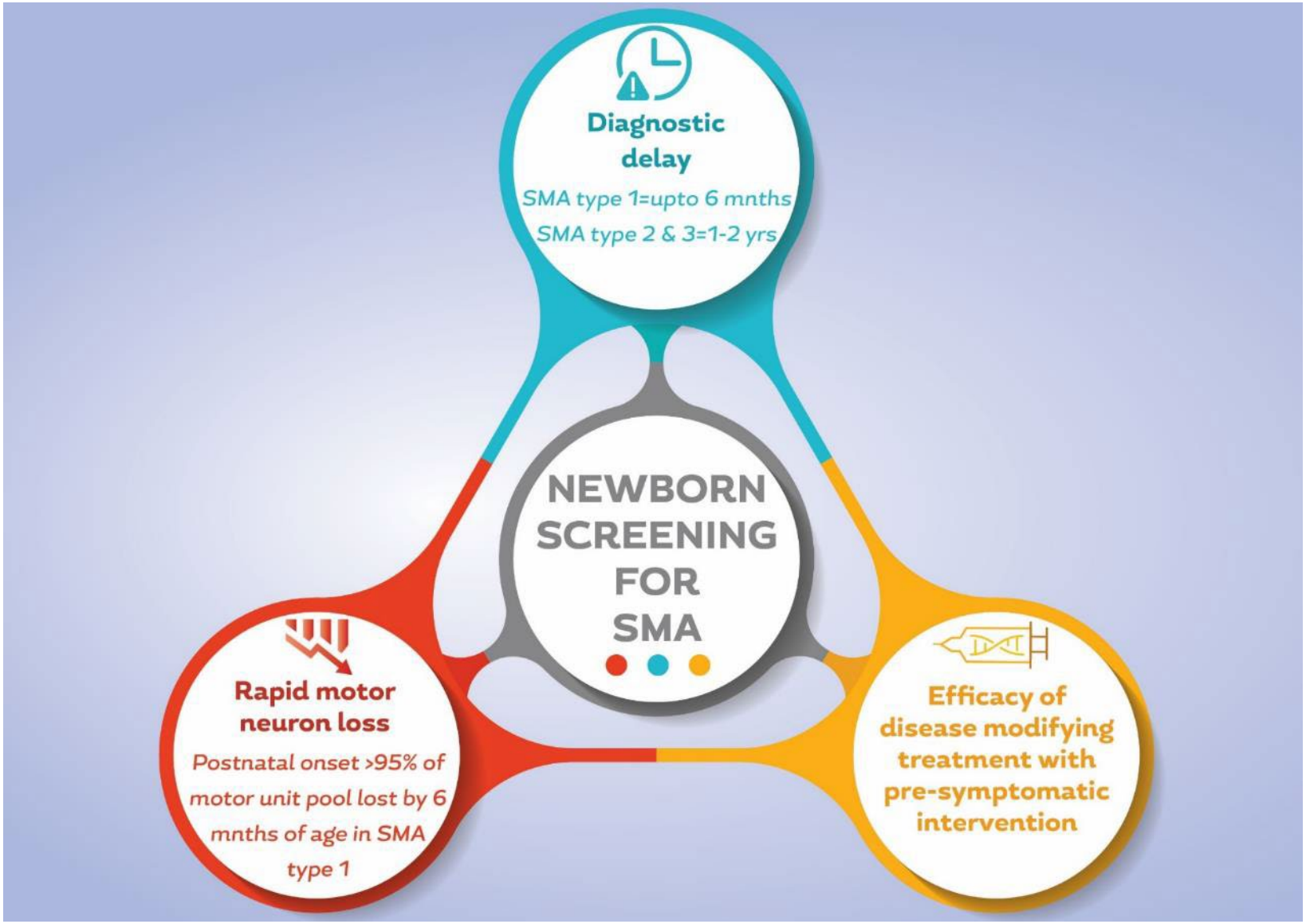


Figure 6. The rationale for newborn screening for spinal muscular atrophy

National Guideline for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand (2024).

The global perspective of newborn screening in SMA and where Australasia and 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).(91) 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.(92, 93) In Europe, around 65% of newborn babies are screened for SMA in the newborn period,(94) while screening for SMA within the Asia-Pacific region is currently implemented in Japan, Taiwan, Australia and endorsed by New Zealand. In the Middle East and North Africa newborn screening programs are variably established and none screen routinely for SMA except for Qatar. (95)

In Australia and New Zealand, newborn screening has high participation rates (around 99.9 and 99.5% respectively) (96, 97) reflecting high public confidence, with families opting in to have the screening test performed on their newborn within the first 2-3 days of life. In Australia, a pilot or scoping newborn screening program for SMA was commenced on 1st August 2018, covering the states of New South Wales and Australian Capital Territory.(10) 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, 78, 81, 83, 84, 98-101) 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 July 2022, the Commonwealth Department of Health and Aged Care recommended SMA for national incorporation into Australian NBS programs(102), and one year later, Te Whatu Ora (Health New Zealand) endorsed the same for its national newborn screening program.(103) In Australia, newborn screening programs are implemented according to the Newborn Bloodspot Screening National Policy Framework with each state and territory responsible for implementing and funding the screening, diagnostic and clinical care aspects of the pathway.(104) In the Australian context newborn screening for the nation is coordinated out of five established (screening) reference centres. In New Zealand, one

national program, the Newborn Metabolic Screening Program (NMSP) coordinates the screening of around 60,000 newborns every year. On 23rd September 2023, screening for SMA was recommended to be added to the NMSP.(28)

Newborn bloodspot screening organisation and coordination in Australia and 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.(105)

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.(106) 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.

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 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.(104) All newborn screening programs in Australia and 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.(107) In New Zealand, children 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 their 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.(108) More frequently, though, 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.(105)

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 (genetic carrier screening) to inform reproductive decision-making for those at risk. Accordingly, on 1st November 2023, genetic carrier screening for SMA, alongside fragile X syndrome (FXS) and cystic fibrosis has been fully reimbursed through the medical rebate system in Australia, making genetic carrier screening accessible to the wider Australian population, independent of the probability of having these conditions. The test is covered once in an individual's lifetime. The newborn screening program for SMA thus augments and complements the program for genetic carrier screening in Australia.

Recommendations and their Evidence Base

Sections 1 and 2:
Screening

Background

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

What encompasses newborn screening for SMA

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

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

Identifying SMA in the newborn period is only possible with DNA (genetic) testing since there are no validated biochemical markers associated with the condition.(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 deletions.(110, 111) Leveraging the fact that 95% of individuals with SMA have a homozygous absence of exon 7, *SMN1* assays have generally targeted this genetic change, with rare studies targeting exon 7 ***and*** exon 8 deletion 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, 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.(11)

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.(27) Other methodologies include but are not limited to restriction fragment length polymorphism analysis (RFLP)( ), high resolution melting analysis,(117, 118) multiplex ligation probe amplification,(119) DNA tandem mass spectrometry,(120) modified competitive oligonucleotide priming PCR (mCOP-PCR)(121) and DNA sequencing.(122). 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 a automated level required for population wide screening.(123) Accordingly, the GDG acknowledges that health jurisdictions in Australia and 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(124-126) through to MLPA(127) and RFLP-PCR (118, 121, 128). Rarely, established newborn screening programs use three tiers of screening for *SMN1* to look for f exon 7 variants caused by hybrid genes in screen positive children and then sequencing *SMN1* to reconcile differences between first and second tier assays.(129)

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* (130). Accordingly, five studies have defined a sensitivity of 91 – 98% based on the presence of false negatives, generally secondary to compound heterozygous genotype in the newborn.(11, 131, 132) 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),(133) sickle cell disease,(134) 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.(89, 135) 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.(11, 136) 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.(128)

Section 1:

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

Recommendation 1.1

Evidence based recommendation

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

Grade of recommendation, Grade B

Good Practice point 1.1.1

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

Good Practice point 1.1.2

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

Recommendation 1.2

Evidence based recommendation

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

Grade of recommendation B

Recommendation 1.3

Consensus based recommendation

We recommend that the screening method selected by the screening programme should have a sensitivity of ≥ 95% for the detection of S*MN1* exon 7 homozygous deletion.

Grade of recommendation Strong, Grade 1C

Recommendation 1.4

Consensus based recommendation

We recommend that the screening test for SMA should determine the S*MN1* exon 7 absence, using suitably validated quantitative or qualitative assays.

Grade of recommendation Strong, Grade 1B

Recommendation 1.5.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 1.6.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 1.7.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 1.8.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1B

Recommendation 1.9.

Consensus based recommendation

We suggest that newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, low (weight < 2500g) or very low birthweight (< 1500g) newborns should proceed using the same screening protocols as for term and newborns weighing > 2500g.

Grade of recommendation Conditional, Grade 2B

Rationale and impact section on screening for *SMN1* as part of newborn screening for SMA

The evidence showed that there were gaps in current practice in the screening processes for *SMN1* and the GDG agreed that there should be a standardised process for first tier testing. The GDG agreed that diagnostic test accuracy for *SMN1* testing was out of scope of the Guideline, however, did consider the fact that any assay used should have high sensitivity and specificity. The evidence showed that newborn screening for SMA could be conducted on the dried blood spot taken as part of established newborn screening programs in Australasia and that there was consistent evidence to show that the target analyte should be absence of exon 7 of *SMN1*. The GDG acknowledged that this screening target would miss the 5% of children with compound heterozygosity or biallelic pathogenic variants in *SMN1*. However, given the seriousness of harms from a false positive and false negative result (section 4), the GDG agreed that assays should have a minimum of 95% sensitivity and 100% specificity. The GDG recognised that although there were resource implications to adding genetic testing to newborn screening programs, the health impact of early identification of SMA, leading to options for treatment would have a large health impact on the target population. The GDG strongly considered the need for coordination of care and communication between services, with consideration to shorten the time to notification of a screening result to clinical services (independent of the availability of prognostic information). The incorporation of reporting carrier status through a newborn screening program was discussed iteratively by the GDG and whilst members acknowledged the utility of this, it was felt that this was outside the scope of present programs and would be unfeasible across Australasia from a health system perspective.

How the recommendations might affect practice

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

Section 2:

Recommendations on screening for *SMN2* copy number as part of (newborn) screening in SM

SMN2 copy number as relates to newborn screening for SMA processes

SMN2 copy number is the leading prognosticator of SMA disease severity, with higher copy numbers generally modifying phenotype to confer a milder phenotype and later onset clinical course.(77, 137, 138) As such incorporating *SMN2* copy number testing on the same dried blood spot as *SMN1* testing, is not required to identify newborns screening positive for SMA, however is clinically useful for determining disease severity, planning the pace and type of treatment (where approved and reimbursed access for presymptomatic individuals is dependent on *SMN2* copy number) and to stratify newborns into clinical trials.(139)

Namely, current international clinical guidelines for infants with SMA identified through newborn screening programs recommend immediate treatment of presymptomatic infants with 2–3 *SMN2* copies.(140, 141) Treatment recommendations for infants with 4 *SMN2* copies are evolving, with some guidelines advocating immediate treatment whilst others are in favour of a surveillance approach for symptom onset.(132, 141-143) Similarly, access to SMN augmenting therapies in these individuals vary between countries and changing. The treatment of presymptomatic infants with > 4 *SMN2* has less clear evidence in terms of efficacy to support instigation of SMN augmenting treatments but is being undertaken in some studies.(136) Therefore, obtaining *SMN2* copy number information as part of the screening result can help to start the shared decision-making process between parents and clinicians over treatment necessity, timing and eligibility and to guide the pace of initiating treatment based on local approvals and reimbursement policies.

Risk stratification of infants at the highest risk of earlier clinical symptom onset is particularly facilitated by incorporating *SMN2* copy number screening into newborn screening processes. Infants with 2 *SMN2* copies show higher risk of clinically manifesting disease in the newborn/early infancy period (with denervation potentially starting in utero, and the active disease process progressing into the peri and early postnatal period).(101, 131, 136, 144). 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. (71, 89, 144)

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. (100) This helps to minimise treatment delays to reduce the exponential rate of motor unit loss,(71, 145) especially in infants with 2 *SMN2* copies,(71) which in turn significantly improve long term outcomes as relates to motor function, independent feeding and breathing at two years of age.(100)

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 frequently noted in both presymptomatic and symptomatic infants.(139) *SMN2* copy number can be considered as the 'tip of the iceberg' with rare *SMN2* variants, hybrid structures and other single nucleotide variants leading to functional differences in *SMN2*, which go beyond gene dosage.(139, 146-148) *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.(85, 90)

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*.(129) 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.(89, 129) 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, 149)

When *SMN2* is incorporated into newborn screening process, quantitative methods are used, using a variety of methods including real time quantitative PCR, digital droplet PCR methods, multiplex ligation PCR amplification (MLPA) and reverse transcriptase PCR.(129)

The methodology for determining the *SMN2* copy number accurately can be complex with ongoing efforts to improve both the reliability of the process (between screening and diagnostic assays) and the ability to better determine the *SMN2* count.(150) Methodologically, *SMN2* copy number can vary dependent on the methodology (digital droplet PCR, MLPA or qPCR) used in up to 50% of cases.(149, 151) 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.(152)

Recommendation 2.1.

Consensus based recommendation

We suggest that S*MN2* 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.

Grade of recommendation Conditional, Grade 2B

Recommendation 2.2

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 2.3.

Consensus based recommendation

We recommend that 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 where *SMN2* copy number is conducted as part of newborn screening) an *SMN2* copy number ≤ 4.

Grade of recommendation Strong, Grade 1C

Recommendation 2.4.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 2.5.

Consensus based recommendation

We recommend that irrespective of *SMN2* incorporation into newborn screening for SMA, *SMN2* copy number determination should be included in diagnostic testing during follow-up care.

Grade of recommendation Strong, Grade 1B

Recommendation 2.6.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 2.7.

Consensus based recommendation

We recommend that the newborn screening 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.

Grade of recommendation Strong, Grade 1C

Implementation point 2.7.1.

In many health jurisdictions, newborn screening programs have an established notification strategy that involves notifying the medical practitioner (usually general practitioner, obstetrician or paediatrician) on the child's dried blood spot demographics. Due to the imperative to have access to expedient diagnosis and treatment, newborn screening programs should establish a clinical referral pathway that includes early notification of a screen positive result to a neurology specialist.

Good Practice point 2.7.1.

We suggest that the newborn screening for SMA program will establish a clinical referral pathway for newborns who screen positive for SMA. A positive newborn screening result may also be verbally relayed to a relevant listed medical practitioner.

Recommendation 2.8.

Consensus based recommendation

We suggest that ideally, written notification of a screen positive SMA result should be issued to the individuals listed in 2.10 and/or 2.11. within 24 hours of the verbal notification of a screen positive result.

Grade of recommendation Conditional, Grade 2C

As such, the recommendations encompassed in section 1 and 2 form an (evidence and consensus based) pathway as follows (Figure 4)

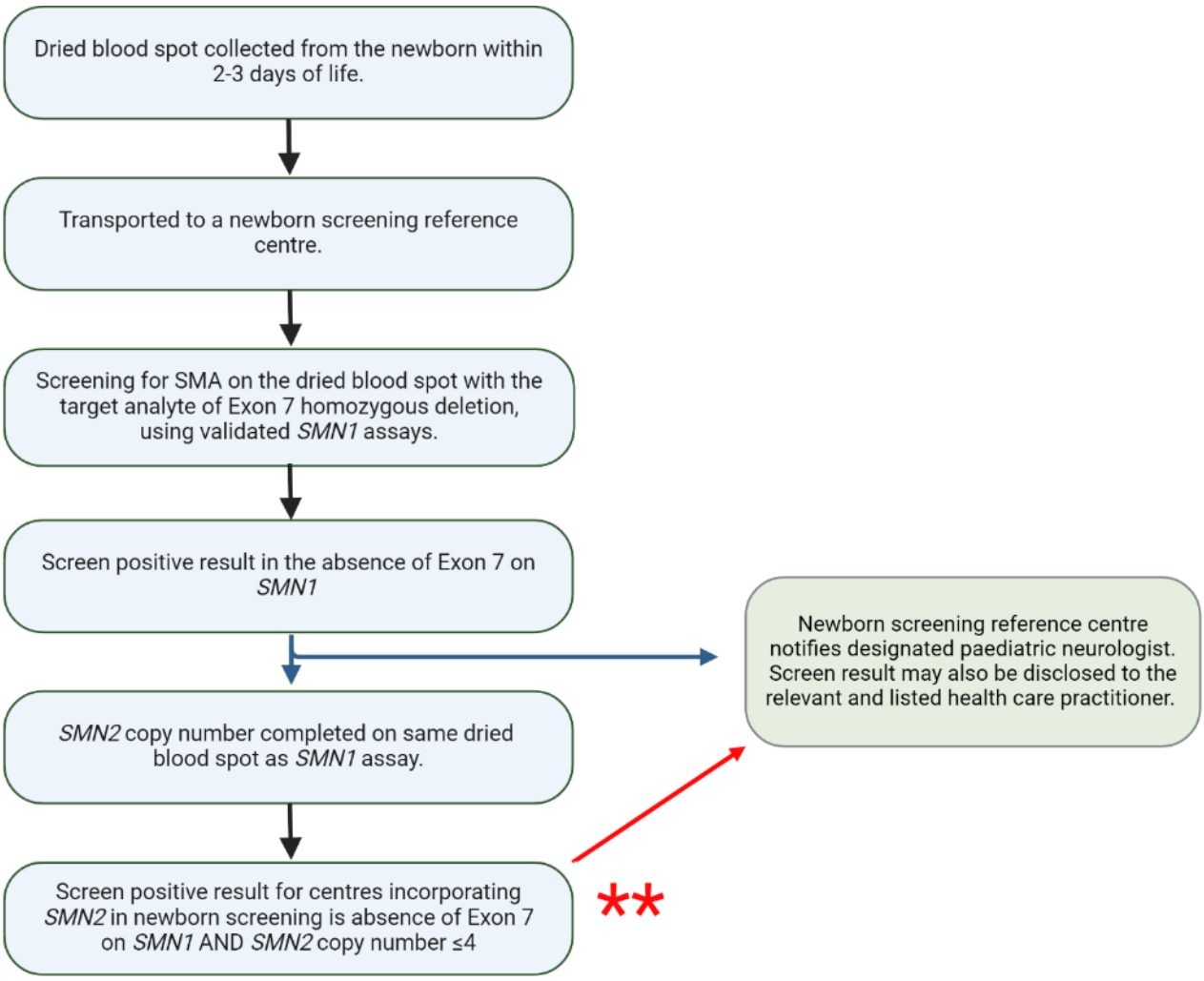


Figure 4. The proposed flow of screening activities based on recommendations within the Guideline.

******SMN2* as part of newborn screening may be considered to provide additional prognostic information but should not delay notification of the screen positive result i.e. biallelic exon 7 deletion on *SMN1*.

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

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

How the recommendations might affect practice

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

Section 3:
Confirming the diagnosis of spinal muscular atrophy

Background

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

What encompasses diagnostic confirmation of SMA after a screen positive result

For the purposes of the Guideline and the recommendations therein, the diagnostic domain was defined as processes and activities performed within the diagnostic laboratories for confirmation of genetic diagnosis of SMA. Unlike the designated reference centres for newborn screening, publicly funded diagnostic capabilities vary across Australia and 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.(153)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,(11, 93, 122, 131, 144, 154-

156), ddPCR(154, 157), PCR(109, 135, 155), sequencing(118, 158), restriction fragment length polymorphism PCR(32, 116) or analysis of splicing variants.(32, 116)

SMN2 diagnostic testing is considered clinically useful to determine prognosis and long-term outcomes. Therefore, there is a clinical imperative for *SMN2* quantification which should be completed as soon as possible within the diagnostic process (if not done within newborn screening) and/or confirmed during this process (if incorporated within newborn screening programs).(6, 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(159) and with modernised technologies,(144) underlining the necessity of using validated and up to date methods for denoting *SMN2 c*opy number.(144) In these studies, discrepant *SMN2* results are secondary to sensitivity to contamination of probes and reagents, variability in definition of exact cut off values for interpretation, quality and quantity of nucleic acid used, and the availability and usage of appropriate controls.(32)

Whilst there are currently no comparative studies for *SMN2* copy number determination, as *SMN2* copy number is one of the main stop-or-go tools for initiating the treatment of children, especially if identified in the context of newborn screening programs, an inaccurate diagnostic result may be very harmful to patient health. As a mitigator, the development of standard operating procedures for *SMN2* analysis using validated assays and completed in centralised diagnostic centres is thought to be appropriate and relevant for greater diagnostic accuracy.(149)

Beyond *SMN2* copy number, additional genetic modifiers may influence variability of transcription, translation and stability of *SMN2* transcripts and disease course and severity. For example, the *SMN2* c.859G>C, (p.Gly287Arg) (NM_000344.4) variant in exon 7, in which a greater proportion of *SMN2* mRNA transcripts contain exon 7, can produce a milder clinical course in individuals with this genotype.(160)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.(161)

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

Recommendation 3.1

Evidence based recommendation

We recommend that diagnostic testing should include confirmation of homozygous deletion of exon 7 on *SMN1*.

Grade of recommendation B

Recommendation 3.2

Consensus based recommendation

We recommend that diagnostic testing should also include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making.

Grade of recommendation Strong, Grade 1B

Implementation point 3.2.1

Assays for diagnostic confirmation (of *SMN1* and *SMN2* copy number) can be conducted on whole blood samples or repeat dried blood spots from the recalled newborn, dependent on processes within local diagnostic services. Diagnostic laboratories should provide the relevant healthcare practitioners with the optimal sample to be collected from the recalled newborn, for diagnostic purposes.

Recommendation 3.3

Consensus based recommendation

We recommend that validated *SMN1* and *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.

Grade of recommendation Strong, Grade 1B

Recommendation 3.4

Consensus based recommendation

We suggest that diagnostic *SMN1* testing is conducted using a different methodology to the newborn screening assay.

Grade of recommendation Conditional, Grade 2C

Recommendation 3.5

Consensus based recommendation

We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means), should ideally occur so that stakeholders understand when a diagnostic sample will be collected, delivered to diagnostic laboratories and expectant timelines for diagnostic analysis and receipt of results.

Grade of recommendation Conditional, Grade 2B

Implementation point 3.5.1.

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

Recommendation 3.6

Consensus based recommendation

We 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.

Grade of recommendation Conditional, Grade 2B

Recommendation 3.7

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Recommendation 3.8

Consensus based recommendation

We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth.

Grade of recommendation Conditional, Grade 2B

Recommendation 3.9

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Implementation point 3.9.1.

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

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

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

How the recommendations might affect practice

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

Section 4:

Managing uncertain, false positive and false negative screening results

Background

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

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

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

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

The literature shows that in the majority, screening studies report no false positives. Across the literature, in 11 studies, 71 false positive cases have been reported. For those described, the aetiology of false-positive results may be divided broadly into three groups: genetic variation of *SMN1,* including the presence of heterozygous carriers of exon 7 *SMN1* deletion, *SMN* hybrids and genetic variants in probe binding sites,(88, 163) DNA quality and/or quantity of the dried blood spot samples,(123, 154) and instrument performance in detecting *SMN1* gene deletion.(123) 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.(157) and further false positive screening results have occurred in premature neonates for uncertain reasons (164). False positive results have been noted with a concurrent false positive SCID screen ,(165) 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 bialleleic exon 7 deletion of *SMN1* (which will not be detected through proposed screening assays).(11, 131, 164, 166, 167). 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.(168)

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)(129), poor DNA quality/quantity or system errors.(93)

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.(169) 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.(169)

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.(88, 169) 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.(170, 171) In addition, segregation analyses and exact knowledge about *SMN1* and *SMN2* copy numbers are helpful to identify the aetiology of false negative results.(160)

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),(11) and access to support and care for families who receive uncertain, false positive and false negative results.(10)

Recommendation 4.1

Consensus based recommendation

We suggest that for newborns with a false positive or uncertain screening result i.e. diagnostically not confirmed to have SMA despite a screen positive result on newborn screening for SMA, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and openly explained to parents.

Grade of recommendation Conditional, Grade 2C

Recommendation 4.2

Consensus based recommendation

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

*Multidisciplinary team members may vary dependent on health jurisdiction and include but are not limited to paediatric neurologists, genetic counsellors, geneticists, social worker, psychologist, allied therapists, specialist nurses.

Grade of recommendation Conditional, Grade 2C

Recommendation 4.3

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.4

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.5

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.6.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.7.

Consensus based recommendation

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

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.8.

Consensus based recommendation

We recommend that 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.

Grade of recommendation Strong, Grade 1C

Recommendation 4.9.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 4.10.

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

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

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

How the recommendations might affect practice

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

Section 5:
Disclosing a screen positive result to families

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.(172) 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.(71)

Therefore, the time to notify families of a screen positive result should be as short as possible.(12) Within the Australian pilot newborn screening for SMA program it has been noted that screen positive results can feasibly be communicated to families by 10.5 days of life (range 5-18 days), after screening result availability at 8 days of life (range 5-18 days).(12) Newborn screening programs globally have refined and adapted their processes in real-time to ensure efficiency at the point of screen positive disclosure and clinical evaluation for diagnosis, after noting that 27% of newborns/infants are symptomatic at the time of first clinical review. Facilitators for a streamlined process include instigating clinical referral pathways directly to specialist centres for clinical care and treatment initiation.(10)

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.(166)

The designation of healthcare practitioners tasked with notifying the family of screen positive results vary internationally, dependent on jurisdiction-specific SMA workflow processes.(166) 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.(166). Dependant on health expertise and confidence in disclosing sensitive results to families, other programs have leveraged the experience of trained genetic counsellors or nurses.(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, 119)

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.(173). 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.(173)

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.(10)

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.(10, 173)

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

Australian and 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.(11) 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 health care professionals and paediatric neurology specialists appear mandatory to identify the most appropriate setting for screen positive disclosure. Options include immediate referral to the neuromuscular team or, for those with difficulties travelling long distances, with the local paediatrician 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.(166) 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.(166)

International recommendations underline the need to update families of the signs and symptoms of SMA, so that caregivers have access to information (educational materials or a written checklist) that can be used at home to monitor for ‘red flag’ signs and symptoms of clinical deterioration that would trigger immediate clinical (re) review.(140) These include a change in the child’s movement, feeding, 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.

Recommendation 5.1

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Recommendation 5.2

Consensus based recommendation

We recommend that the designated paediatric neurologist, receiving the screen positive SMA result (recommendation 2.10), should coordinate with relevant health practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process.

Grade of recommendation Strong, Grade 1C

Good Practice point 5.2.1

Many newborn screening programs use a family notification strategy that includes the disclosure of a screen positive result to a specialty clinic and/or a primary healthcare practitioner for direct family communication. It is the responsibility of these healthcare practitioners to decide who is best placed to contact the family for screen positive disclosure.

Good Practice point 5.2.2.

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

Recommendation 5.3

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Support can range from exchange of advice, information (verbal and/or written) or formal offer to be part of the screen positive disclosure, alongside the responsible medical practitioner.

Good Practice point 5.3.1.

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

Recommendation 5.4

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

Grade of recommendation Strong, Grade 1C

Recommendation 5.5

Consensus based recommendation

We recommend that medical practitioners disclosing screen positive results for SMA to families from Aboriginal or Torres Strait Islander backgrounds should be aware of culturally sensitive issues arising from this disclosure. The medical practitioner may seek advice from

Indigenous Health Liaison professionals in how to best inform families of a screen positive result.

Grade of recommendation Strong, Grade 1C

Recommendation 5.6

Consensus based recommendation

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

The screen positive status of the newborn.

The name of the condition.

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

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

Named health professional as a point of contact for the family.

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

Grade of recommendation Conditional, Grade 2C

Recommendation 5.7

Consensus based recommendation

We suggest that screen positive newborns should ideally be offered a clinical review within paediatric neurology/neuromuscular services.

Grade of recommendation Conditional, Grade 2C

Recommendation 5.8

Consensus based recommendation

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.

Grade of recommendation Conditional, Grade 2C

Recommendation 5.9.

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2B

Good Practice point 5.9.1.

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

Recommendation 5.10.

Consensus based recommendation

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

Change in movement, feeding, or breathing pattern.

Change in voice or weak cry.

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

Abdominal breathing and/or failure to thrive.

Grade of recommendation Strong, Grade 1C

Rationale and impact section on disclosing screen positive results to families

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

How the recommendations might affect practice

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

Section 6:

Assessments required at the diagnostic evaluation of the screen positive newborn

Background

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

The GDG acknowledges variations in access to clinical services, expertise and skills across the Australian and 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.(174) In a proportion of newborns with a screen positive SMA result, 44% are symptomatic within the neonatal period, presenting with early and subtle signs of truncal hypotonia (floppiness), poor or deteriorating head control and weakness of hip flexion, underscoring the need for careful neurological examination of the newborn.(12)

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

instead for ongoing monitoring of disease or treatment response, beyond the period of diagnostic evaluation.(11)

Therapeutic decision making starts within the newborn screen for SMA pathway, as determined by the evidence of benefits of early treatment,(143) before irreversible loss of motor neurons can occur.(10, 71) 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.(175) 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.(175) 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.(81) 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.(82, 175, 176)

Recommendation 6.1

Consensus based recommendation

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

Neurological examination.

Venous sampling for *SMN1* on whole blood (for the purposes of diagnostic testing).

Venous sampling for *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number (for the purposes of diagnostic testing).

Grade of recommendation Strong, Grade 1C

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

Good Practice point 6.1.1

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

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

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

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

Rationale and impact section on post diagnostic assessment processes

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

How the recommendations might affect practice

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

Section 7:

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

Background

Information provision 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. 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.

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.(10)

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.(173)

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.(173)

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

Recommendation 7.1

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.2

Consensus based recommendation

We suggest that the number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a medical practitioner), and ideally support from representatives of the clinical genetics service and/or medical social/psychological services.

Grade of recommendation Conditional, Grade 2C

Good Practice point 7.2.1

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

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

Information on next steps to confirm a diagnosis.

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

Information on SMA advocacy services.

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

Recommendation 7.3

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.4

Consensus based recommendation

We recommend that medical practitioners providing information to, and discussing diagnosis with, families of newborns from Aboriginal, Torres Strait Islander or Māori backgrounds should be aware of 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 also offer families the support of Indigenous Health Liaison services at the time of diagnosis.

Grade of recommendation Strong

Recommendation 7.5

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Recommendation 7.6

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1B

Recommendation 7.7

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Rationale and impact section on information provision to families

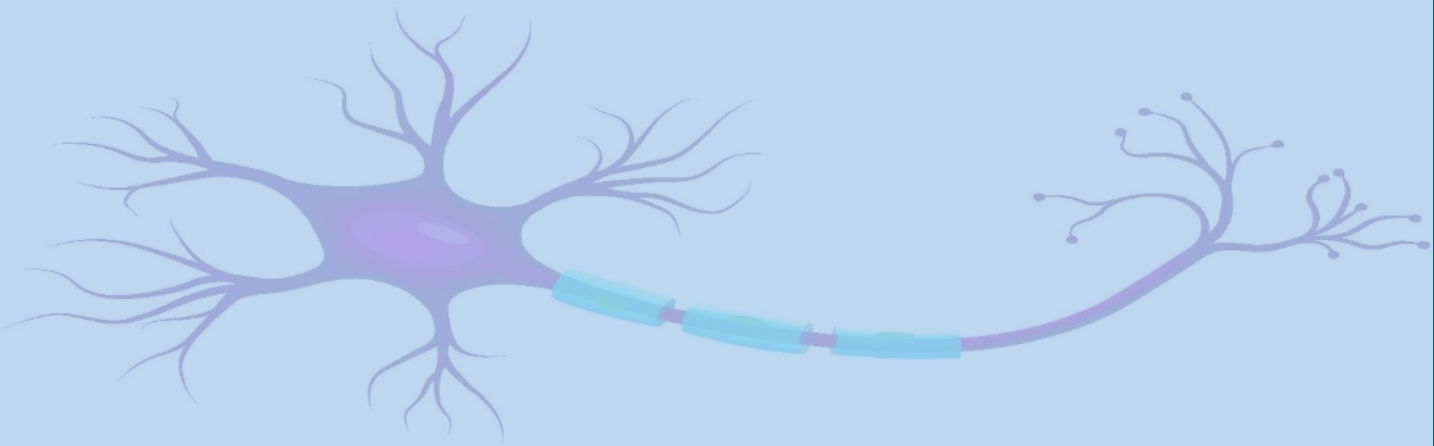
The evidence showed that there are gaps in current practice in communication, information and support available to families. Benefits of high quality, accurate and tailored information provision were considered by the GDG to encompass many levels including improving therapeutic decision making for families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

How the recommendations might affect practice

The recommendations complement current practice, that encourages family centred care for families within a multidisciplinary team setting, so the GDG agreed that there should be no substantial resource impact. The GDG acknowledged that members of the wider multidisciplinary team (extending to patient organisations) could augment roles as information and support providers dependent on jurisdictional resources and capacity.

Section 8:

Delivering the diagnosis and supporting families as they receive the diagnosis of SMA



Recommendation 8.1

Consensus based recommendation

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

Grade of recommendation Strong, Grade 1C

Good Practice point 8.1.2

Consensus based recommendation

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

Recommendation 8.2.

Consensus based recommendation

We suggest that ideally, diagnostic results should be disclosed to families by a specialist medical practitioner such as a paediatric neurologist.

Grade of recommendation Conditional, Grade 2C

Recommendation 8.3.

Consensus based recommendation

We suggest that if circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for a responsible medical practitioner with support from a specialist medical practitioner to disclose a diagnostic result to a family.

Grade of recommendation Conditional, Grade 2C

Recommendation 8.4

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

Recommendation 8.5

Consensus based recommendation

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

Grade of recommendation Conditional, Grade 2C

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

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

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

How the recommendations might affect practice

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

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

Section 9:

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

Background

The post diagnostic care pathway for children with SMA, identified through newborn screening programs is both similar and different to post diagnostic care for children referred through conventional pathways i.e. seen within clinical services after signs and symptoms of SMA raise concern for a lower motor neuron pathology. Similarities arise in the need for care and support for families receiving the diagnosis, however differences arise in the imperative for accurate identification of the clinical status (presence or absence of symptoms) of the newborn/infant diagnosed with SMA through a newborn screening program. Careful characterisation of the disease phase is vital to delineate the pace required for therapeutic decision making and the eligibility for and modality of therapeutic interventions.(177)

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.(178) 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 appears to continue without treatment until a significant amount of the motor neuron pool is lost.(71, 178) In fact, the transition of a newborn from one who one who is 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.(178) 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, 177) This is particularly vital to characterise the subtle signs and symptoms of disease occurring in up to 44% of newborns, before 6 weeks of age.(84) 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.(179, 180)

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.(179)

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.(181) The lowest attainable item is (1) sitting without support and the highest attainable item is walking alone.(6) 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.(182) Recent findings have suggested that this scale may be used before the age of 3 months, with results being interpreted with caution with consideration as to the developmentally most appropriate items at the time of testing.(183) This will help to define the thresholds to determine clinical (presymptomatic or symptomatic) status, which are currently not fully understood.(174) The Hammersmith Infant Neurological Examination-2 (HINE-2) is a neonatal specific developmental scale that is being more widely utilised in this population to help denote clinical status (184) within the heterogenous clinical presentations found within a newborn screening for SMA cohort.(185)

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.(177) Baseline compound muscle action potential (a summation of voltage output from a group of simultaneous action potential from several muscle fibres in a defined area, after stimulation of the innervating peripheral nerve) and electromyographic evidence of the muscle response or electrical activity in response to a nerve's stimulation of the muscle have been used on sequential monitoring to determine disease progress and augment the often clinically challenging assessment of the newborn with SMA.(12, 81)

Recommendation 9.1

Consensus based recommendation

We suggest that all newborns diagnostically confirmed with SMA through a newborn screening program should be reviewed by a specialist medical practitioner such as a paediatric neurologist.

Strength of recommendation Conditional, Grade 2C

Recommendation 9.2

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.3.

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 9.4

Consensus based recommendation

We suggest that all children diagnosed with SMA through newborn screening should have a shared model of care between local community (general practitioners and allied therapists), paediatric services and specialist paediatric neurology services, to facilitate post diagnosis

care, which is personalised according to the biopsychosocial characteristics of the child and family.

Strength of recommendation Conditional, Grade 2C

Recommendation 9.5

Consensus based recommendation

We suggest that families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review at a clinical genetics service for genetic counselling and cascade screening.

Strength of recommendation Conditional, Grade 2C

Recommendation 9.6.

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 1C

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

Recommendation 9.7

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.8.

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 9.9.

Consensus based recommendation

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

Strength of recommendation Conditional, 2C

*The use of neurophysiological assessments will vary dependent on jurisdictional capacity including training and expertise of the assessors conducting these assessments. It has been noted by the GDG that the Pharmaceutical Benefit Scheme (PBS) that provides approval for treatments in Australia, does include information derived from neurophysiology studies to denote disease onset and facilitate access to SMN augmenting treatments.(186) However, the GDG acknowledged variations in the availability and experience of healthcare practitioners

in the conduct and interpretation of neurophysiological assessments and proposes the conditional strength of this Recommendation based on feasibility for implementation across Australasia.

Good Practice point 9.9.1

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

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

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

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

How the recommendations might affect practice

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

Section 10:

Treatment planning and initiation for newborns and infants diagnosed with SMA through newborn screening programs

Background

Across the range of available (SMN augmenting) treatments, symptomatic children with 2 and 3 *SMN2* copies benefit from access to treatment, with a greater chance of survival, reduction in comorbidities and motor stability or gains noted in these cohorts.(176, 187-192) 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 (i.e. non-sitter, sitter or walker).

Early treatment appears to be an important modifier of longer-term outcomes. The magnitude of benefit increases with interventions before children develop symptoms, but even within this cohort there is a heterogeneity of outcomes. In presymptomatic newborns, with 3 *SMN2* copies, a normal neurodevelopmental trajectory can be observed 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.(71) 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, 3 *SMN2* copies should have immediate access to treatment.(140) There is a lack of evidence on the outcomes for newborns with 1 *SMN2* copy, however it is considered that there is a high probability of neurodisability, dependent on the severity of the clinical presentation and disease duration. Thus, expert

opinion is to take a pragmatic approach and base therapeutic decision making on the clinical status of the child and professional opinion of outcomes,(140) offering supportive care as a valid pathway in the first instance.(193) A higher probability of motor function attainment is observed when therapeutic intervention (of any modality) is administered < 6 weeks of age,(194) 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.(100) There are currently no 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.(49, 50)

For children without access to treatment, there is study and consensus evidence for clinical surveillance at defined intervals within a neuromuscular centre.(11, 81, 141) 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.(11, 81, 126, 140, 195)

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.(196) Thus, therapeutic decision making is ideally commenced in a paediatric neurology centre with expertise in the management of children with SMA.(180) Long term surveillance of efficacy and safety is required to effectively manage children receiving these therapeutics.(82) 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.(197) Potential mitigators of these psychosocial outcomes include access to psychological support through referrals to appropriate health care services or advocacy groups.(198, 199)

Recommendation 10.1

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.2

Consensus-based recommendation

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

Strength of recommendation Strong, Grade 1A

Recommendation 10.3

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.4.

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1B

Recommendation 10.5

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.6

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.7

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.8

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.9

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2B

Recommendation 10.10

Consensus based recommendation

We recommend that the administration of SMN augmenting treatments should occur in a specialist (paediatric neurology) care centre.

Strength of recommendation Strong, Grade 1C

Recommendation 10.11

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.12

Consensus based recommendation

We suggest that post treatment monitoring for newborns who access SMN augmenting treatments may be shared between specialist centres and regional centres (with support from the specialist centre) as child and family factors dictate.

Strength of recommendation Conditional, Grade 2C

Recommendation 10.13

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Recommendation 10.14

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 10.15

Consensus based recommendation

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

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

Growth parameters including length, weight and head circumference

Neurological examination.

Strength of recommendation Strong, Grade 1C

Recommendation 10.16

Consensus based recommendation

We suggest that for all newborns diagnosed with SMA through newborn screening, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments as part of best practice care may include motor assessments that should be adapted to the objectives set for the newborn/infant and considers function, SMA type, age, comorbidities, clinical status. The timing and frequency of assessments may vary

between children and will be dependent on therapeutic goals, clinical questions raised, and child and family factors.

Strength of recommendation Conditional, Grade 2C

Good Practice point 10.16.1

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

Recommendation 10.17

Consensus based recommendation

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

Strength of recommendation Strong. Grade 1C

Recommendation 10.18

Consensus based recommendation

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

Strength of recommendation Strong, Grade 1C

Rationale and impact section on treatment planning and decision making

The evidence showed that for children with SMA, there was a biological imperative to prevent precipitous and early motor unit loss, through expedient intervention with SMN augmenting treatments. The evidence showed that this was particularly the case for children predicted to have an early onset and severe form of SMA, based on their genotype i.e. those with 2 *SMN2* copies. The greatest magnitude of benefit across all SMN augmenting therapies (where outcomes included survival, reduction in comorbidities and gains in motor function) were observed in children who were treated prior to clinical manifestation of signs and symptoms of SMA disease (i.e. within the presymptomatic phase). Based on this evidence, the GDG agreed that processes for immediate access to treatments should be streamlined especially for those with signs and symptoms of the condition and presymptomatic children with 2 *SMN2* copy numbers. For presymptomatic children with 3 *SMN2* copies, the GDG came to a consensus that there was sufficient evidence and clinical experience to determine that this subgroup would also benefit from immediate access to treatments on diagnostic confirmation of SMA, noting that many could achieve a normal developmental trajectory if treated prior to symptom onset.

The GDG agreed that the complexity of treatment planning, administration of treatments and at least short-term surveillance of side effects, necessitated treatments to be initiated in specialist centres where possible. Balanced against this was the potential to increase health inequities in terms of therapeutic access for families who could not travel to specialist centres readily, due to disease related or logistical factors. It was determined that in individual cases, it was appropriate for treatments such as oral splicing modifiers (risdiplam) to be initiated outside of specialist centres, with clear delegation of roles and responsibilities as to the follow-up of the child to determine efficacy and safety. Similarly, the GDG agreed on the value of managing children close to home and reflecting their clinical experience, recommended that long-term monitoring of safety signals and treatment response, could be shared between specialist and non-specialist services.

The GDG was unanimous in their consensus that children with SMA should be managed within a multidisciplinary team for optimisation of health outcomes, and that SMN

augmenting treatments amplified but did not replace standards of care. The GDG agreed that detecting the signs and symptoms of SMA disease onset could be challenging within the newborn/early infancy period. Whilst there was evidence of benefit in augmenting serial clinical examinations with motor assessments and neurophysiological studies, the GDG agreed that the expertise required to undertake these assessments varied across Australasia and that these assessments should be undertaken to answer specific clinical questions, based on the needs of the child, and not mandated across recommendations.

How the recommendations might affect practice

The GDG agreed that the process of newborn screening for SMA, diagnostic confirmation and treatment planning were a continuum which was geared towards providing an accurate and efficient timeline to diagnosis and therapeutic intervention, to optimise the health outcomes of affected children. The GDG agreed that SMA, particularly in children with symptoms and those with 2 *SMN2* copies could be considered as a neurogenetic emergency. The GDG agreed that workflow processes within screening, diagnostic laboratories and clinical services could be challenged when prioritising these children and that a flexibility of approach (using a shared-care or hub and spoke model) could be used to manage children living in regional or remote areas. Education and training would be required to equip practitioners across the community in managing children accessing SMN augmenting treatments, and resources would need to be considered to upskill the workforce to conduct motor and neurophysiological assessments, to aide in therapeutic decision making. As all children with SMA should be managed within a multidisciplinary model of care (a predeterminant to access SMN augmenting treatments and adherent to international standards of care), the GDG agreed that these recommendations would also reinforce aspects of best practice.

Section 11:

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

Background

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

The therapeutic landscape in Australasia in 2024 is such that newborns identified through newborn screening for SMA, who are presymptomatic and have ≥4 *SMN2* copies, do not have access to approved and reimbursed treatments.(186, 200, 201) These high-cost therapeutics cannot usually be self-funded and thus this section takes consideration of the current therapeutic landscape. Alongside limitations in access, there is a global variation in how to manage children with SMA and ≥4 *SMN2* copies. Even in jurisdictions where there is access to SMN augmenting treatment for presymptomatic infants with 4 *SMN2* copies (identified through newborn screening), there has been variability in the uptake, with the timing of therapeutic intervention remaining unclear.(202) This is partly due to data gaps that preclude a comprehensive understanding of the natural history of disease onset and progression for those with ≥ 4 *SMN2* copies, the heterogeneity of disease progression,(137) and the variability in phenotype for those untreated with 4 *SMN2* copies. There is ongoing uncertainty regarding accurate prediction of phenotype, long term outcomes and safety profile for individuals with this genotype.(203) These knowledge gaps are compounded by a current lack of clinical trial data for the efficacy, durability and safety of SMN augmenting treatments in those with ≥ 4 *SMN2* copies.

Balanced against these uncertainties are the potential benefits of early intervention and the possibility of preserving a motor pool from irreversible deterioration, defined in those children with 4 *SMN2* copies, who do not receive immediate treatment. Clinical manifestation of SMA have been noted as early as within the infancy period (132) but predominantly within early childhood,(204) and in 22-55% of untreated children with 4 *SMN2* copies before the age of three years.(159) By 18 years of age 95% of children with 4 *SMN2* copies display signs and symptoms of SMA.(202) Children may develop only subtle signs and symptoms of disease between 1.5 and 4 years of age, however, a minority of them experience significant motor deterioration with time.(142)

This clinical evidence base has led to the suggestion that SMN production in those with 4 *SMN2* copies is insufficient to support the motor neuron pool and that early initiation of treatment at a time when high SMN levels are required would prevent motor neuron degeneration. For newborns with 4 *SMN2* copies not initially treated, the focus is on monitoring for disease onset, to initiate treatment at the earliest possible opportunity.(140) International consensus recommendations define high frequency visits within the first two years of life, where there is greatest risk of identifying a severe SMA phenotype, balanced against a more measured approach to reduce the risk of over assessment and increase flexibility for caregivers thereafter.(140) The added risk of undertaking a clinical surveillance strategy alone is the potential to be lost to follow-up, which may be mitigated by information and support around the benefits of follow-up for the newborn/infant.(132, 142)

Neurological and motor assessment, myometry and neurophysiological studies (including CMAP and EMG data) are considered valuable tools to screen for disease onset in presymptomatic newborns with 4 *SMN2* copies who cannot access immediate SMN augmenting treatment.(140) There is acknowledgement that the availability and expertise to conduct these assessments is varied across health jurisdictions (140) and that the tolerability of assessments varies between children.(132)

Recommendation 11.1

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.2

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.3

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.4

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

Recommendation 11.5

Consensus based recommendation

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

Strength of recommendation Conditional, Grade 2C

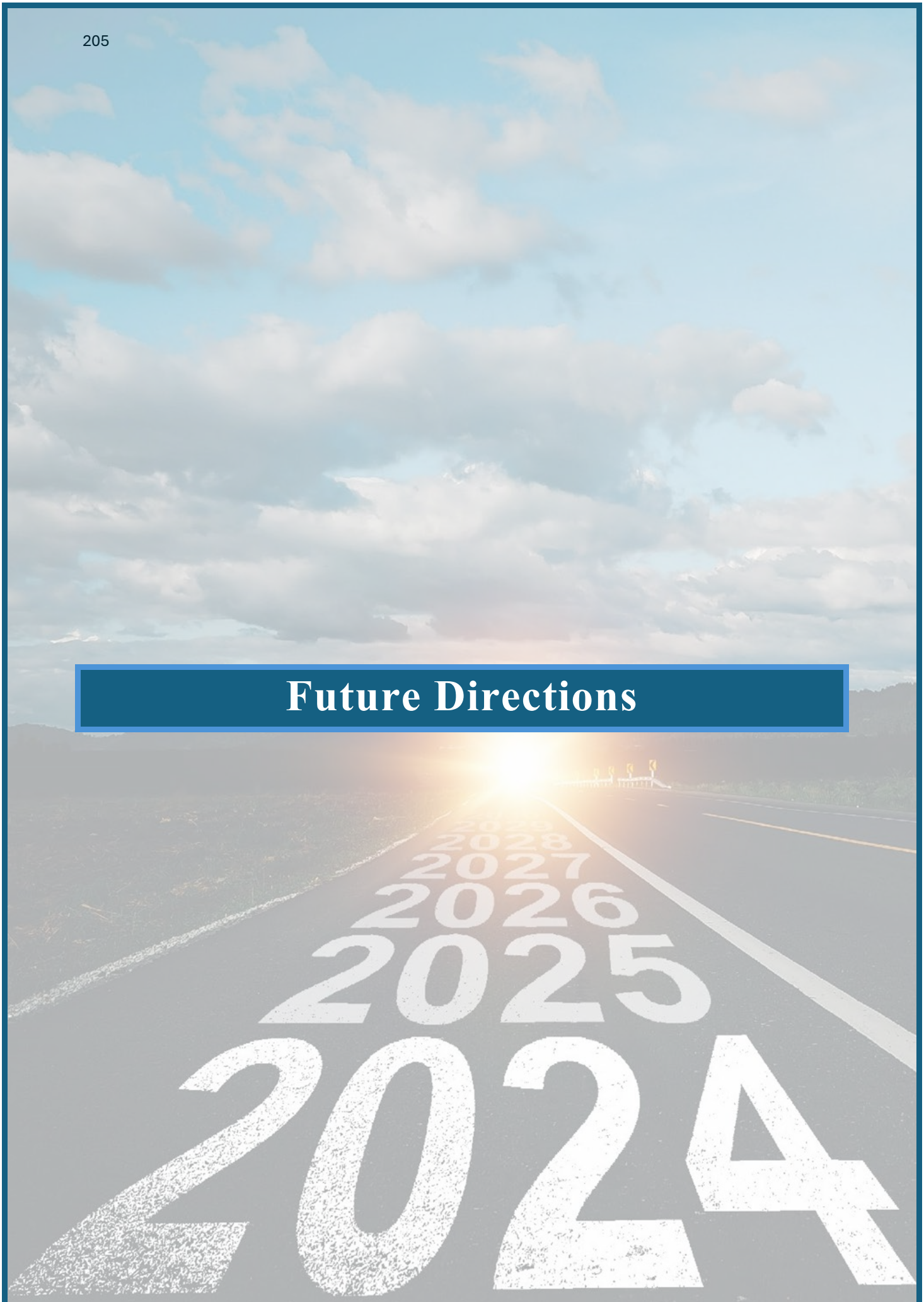
Rationale and impact section on managing children with ≥ 4 *SMN2* copies

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

How the recommendations might affect practice

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

Future Directions



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

Dissemination and Implementation of recommendations within the Guideline

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

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

Future directions

Future directions include evaluation of the utility and impact of the Guideline for newborn screening for SMA across the Australasian continent, updating the Guideline in keeping with the pace of change within the domains of SMA (newborn) screening, diagnosis and clinical

care and setting a coordinated pan-national research agenda to fill the evidence gaps that are emerging within this rapidly evolving landscape. It remains imperative to determine the impacts, enablers, and barriers of translating newborn screening for SMA into healthcare systems within Australia and New Zealand, to support its effective implementation and ensure that in the future, the Guideline can be updated based on co-developed and systematically collected real-world evidence, alongside other scholarly outputs.

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

1. Screening laboratory annual reports that determine the timing and process of newborn screening for SMA. These assessments are conducted as part of formal quality assurance and audit activities that evaluate newborn screening programs as a whole.(104)

2. Evaluation of the model of care within each jurisdiction, to aid the improvement of processes to meet the needs of the communities that they serve. This may include assessment of the temporal processes such as time to screen positive result, diagnostic evaluation, confirmation of diagnosis and time to treatment initiation, alongside the longitudinal evaluation of the short- and long-term clinical outcomes for children screening positive for SMA.

3. The public acceptability of the newborn screening for SMA program as guided by the recommendations within the Guideline, and the barriers and facilitators of implementation from a consumer and healthcare practitioner perspective within individual healthcare jurisdictions.

4. Measuring changes in knowledge about the Guideline recommendations amongst end users.

5. Auditing compliance with Guideline recommendations in a range of service settings.

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

Evidence gaps and future directions for stakeholders

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

Within newborn screening

1. **The evolution of genomic capabilities in newborn screening.** Genomic platforms that have the potential to identify a spectrum of genetic conditions, are being considered within a newborn screening scope of practice. These include gene panels, whole exome and whole genome sequencing. The future role of current assays for SMA within this evolving landscape will be important to ascertain, especially as next generation sequencing may increase the sensitivity of screening processes and better identify children with a compound heterozygous SMA genotype.

2. **Improving the precision of *SMN2* copy number determination.** The systematic evidence shows the technical challenges in determining *SMN2* copy number both within a screening and diagnostic process, especially for children with *SMN2* copy number ≥ 4. Errors in *SMN2* quantification are numerous within the literature and can lead to substantial harms based on preclusion from access to treatments and challenges with predicting phenotype for affected children and establishing goals of

care with their families. Future work will involve collaborative global engagement of scientists, clinical researchers and companies that produce molecular assays for this purpose, to provide updated and standardised processes for the improved determination of *SMN2* copy number within newborn screening programs.

Within clinical practice

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

4. **The management of newborns with SMA and ≥ 4 *SMN2* copies.** The available literature does not provide a robust evidence base for presymptomatic therapeutic intervention for newborns/infants with this genotype, with potential risks and benefits of early treatment being postulated internationally, namely due to the heterogeneity of (untreated) clinical outcomes within this subgroup. Addressing this evidence gap will be imperative and a multicentre pan-national prospective collection of clinical, neurophysiological, biomarker and functional data from newborns with ≥ 4 *SMN2* copies is imperative to evaluate their optimal therapeutic window, to guide the timing of treatment.

5. **Evaluating and refining the model of care.** The systematic literature is starting to define the significant psychological effects on families of receiving a diagnosis of a serious condition such as SMA within the newborn period, and the ongoing psychosocial sequalae of caring for and managing an affected child, even for those

who have recourse to therapeutic intervention. Future work may further define the values and preferences of families in how they are supported through this process and focus on evaluating the benefits and resources required to provide a seamless and integrated model of psychological care at screen result disclosure, diagnosis and throughout the clinical care journey.

6. **Development of a holistic toolkit for the evaluation of outcomes from newborn screening for SMA programs.** The systematic evidence reviews to inform the development of the Guideline showed the heterogeneity and variability of assessment scales used to assess newborns/infants with SMA at diagnosis and longitudinally. The development of assessments that can be utilised specifically in the newborn period remains essentially to help augment decision making based on the clinical status of the child.

   Beyond the scope of the current Guideline, but relevant to health outcomes for affected children is the need to expand the evaluation of the condition beyond a motor-centric assessment. Additionally, the co-design and development (with input from a range of stakeholders, including children and their families), of assessment scales will be important, as a basis to understand the evolving clinical trajectory of children diagnosed and treated within newborn screening for SMA programs. These assessment tools will target outcomes that are meaningful to affected children and their families and will also encompass the multisystemic nature of SMA, broadening the scope of assessment to the realms of cognition, behaviour, functional independence and neurodevelopment.

Within education and training

7. **Mitigating inequities in healthcare and providing culturally affirming practices.** Across the literature review, there was a paucity of evidence to understand how newborn screening for genetic conditions such as SMA is conceptualised and discussed in culturally diverse populations, including within Aboriginal, Torres Strait Islander, Pacific Islander, Māori and other First Nation populations. It is vital to include these communities in further research opportunities, to ensure culturally competent practices, that may change the relevant Consensus based recommendations and Practice Points. Furthermore, it is important that a broader and deeper evidence

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

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

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

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