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

ADMINISTRATIVE AND TECHNICAL REPORT

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Table of contents

Executive Summary

Spinal muscular atrophy (SMA) is a group of rare inherited genetic conditions, affecting around 1 in 10,000 individuals.(1) Considered as a predominantly childhood onset condition, SMA is caused by progressive loss of lower motor neurons from the spinal cord and brain stem.(2) 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.(3)

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.(4-7)

Newborn screening (NBS) 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, 8-10)

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.(11) This was followed in 2023 by Te Whatu Ora (Health New Zealand) endorsing routine inclusion of SMA onto routine newborn screening panels.(12)

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.(13, 14) To address this barrier, a best practice Guideline that is founded in evidence and that aligns with an Australasian healthcare landscape is essential. (15)

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.

The Guideline has been formulated using a validated methodology for searching, appraising and grading evidence.(16-23) 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.

Purpose, population, scope and settings

Purpose

The Guideline has been developed to provide a set of recommendations that align with the evidence base, which can be used to inform the processes of screening, diagnostic and immediate post-diagnostic clinical management for all newborns/infants undertaking newborn screening for SMA in Australia and 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. The Guideline has been developed to support equitable implementation of newborn screening across Australia and New Zealand and as such 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), technical aspects of screening (as covered by the Clinical & Laboratory Standards Institute Guideline for Newborn Screening, (28) 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 deficiency 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 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.

Funding Statement

This was an investigator led process. Funding for Co-Lead Didu Kariyawasam for the development of the Guideline was provided by the National Health & Medical Research Council (NHMRC) Investigator Grant 2024 (2026317). The publication of the Guideline will be funded through a component of Didu Kariyawasam's Investigator Grant. The funding bodies for individual participants in the SAC and oversight committee did not play any role in the development (writing, editing or review) of the Guideline.

Process for ensuring editorial independence from funders

Although this is a NHMRC aligned Guideline, the Granting body is a separate affiliate to the Guideline Development Group. The former did not play any role in the development (writing, editing or review) of the Guideline.

The Guideline Development Process

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 (Figure 1).(10) 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.(10) 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, (29) 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.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used in the Guideline development. This is a systematic and transparent approach for assessing the certainty (or quality) of a body of evidence in systematic reviews and other evidence syntheses such as clinical practice guidelines, and for developing and

determining the strength of clinical practice recommendations.(16, 17, 30, 31) GRADE provides a framework for identifying health care questions, selecting outcomes of interest and rating their importance, assessing the available evidence, and collating the evidence with considerations of values and preferences of people with lived experience and society to generate recommendations. Figure 1 shows the steps in the Guideline development process.

Due to SMA being within a rare disease field, the methodology also aligned with the National Strategic Action Plan for Rare Diseases (NSAPRD)(13) 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.

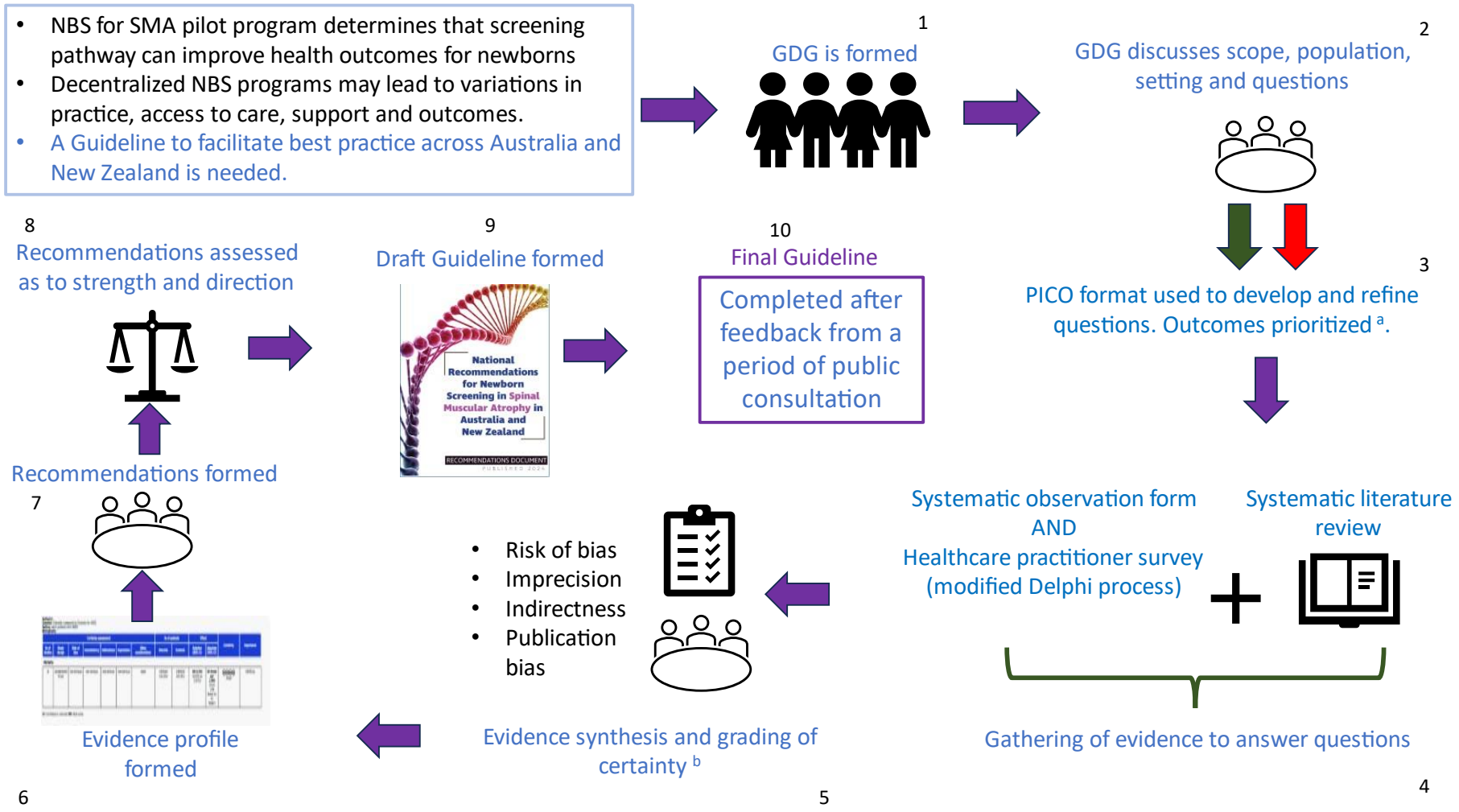

Figure 1. The Guideline development process. A Guideline Development Group (GDG) was formed (1) and met to discuss scope, population applicable settings and broad questions for the Guideline (2). A Population, Intervention, Comparator, Outcome (PICO) format was used to develop, refine questions and prioritise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

Forming the Guideline Development Group

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.

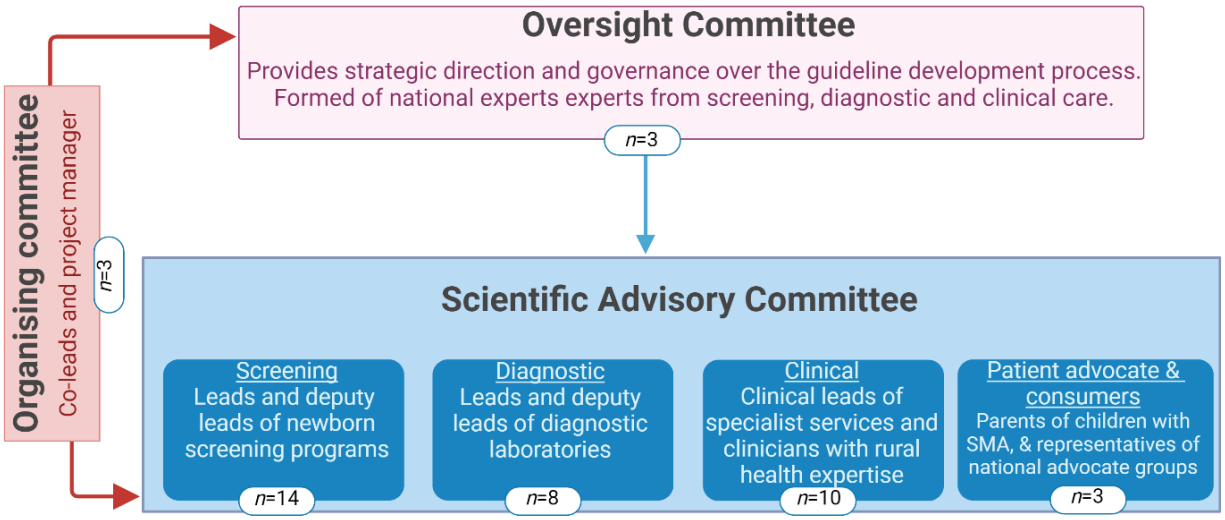

Figure 2. The Guideline Development Group and its governance structure. The oversight committee (*n*=3) was comprised of representatives with national expertise in the areas of screening, diagnosis and clinical care who provided strategic direction on the Guideline development process. The Scientific 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.

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.

Table 1. Members of the Guideline Development Group

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

Simon Carrivick	Endocrinologist	PathWest Laboratory Medicine WA	WA	SAC
Alexandra Kay	Pathology	SA Pathology	SA	SAC
Carol Siu	Genetic Pathologist	Women's and Children's Hospital, Adelaide	SA	SAC
Dianne Webster	Clinical scientist	Auckland City Hospital	NZ	SAC
Enzo Ranieri	Newborn Screening Lead	Sydney Children's Hospitals Network	NSW	SAC
Francesca Moore	Clinical Biochemistry	Pathwest Laboratory Medicine WA	WA	SAC
Gabrielle Crisp	Newborn Screening	Queensland Health	QLD	SAC
James Pitt	Newborn Screening	Victorian Clinical Genetics Services	VIC	SAC
Lawrence Greed	Pathology / Genetics	University of Western Australia	WA	SAC
Mark De Hora	Biochemical Genetics	Auckland City Hospital	NZ	SAC
Ronda Greaves	Biochemical Genetics	Murdoch Children's Research Institute	VIC	SAC
Tiffany Wotton	Newborn Screening	Sydney Children's Hospitals Network	NSW	SAC
Urs Wilgen	Genetic Pathologist	Queensland Health	QLD	SAC
Veronica Wiley	Paediatric biochemist	Sydney Children's Hospitals Network	NSW	SAC
Anita Cairns	Paediatric Neurologist	Children's Hospital Queensland	QLD	SAC
Damian Clark	Neurologist	Women's and Children's Hospital	SA	SAC
Eppie Yiu	Paediatric Neurologist	Royal Children's Hospital, Melbourne	VIC	SAC
Gina O'Grady	Paediatric Neurologist	Auckland City Hospital	NZ	SAC
Maina Kava	Paediatric Neurologist	Perth Children's Hospital	WA	SAC
Tyson Ware	Paediatric Neurologist	Royal Hobart Hospital	Tasmania	SAC
Corin Miller	Rural Generalist - Paediatrics	Southeast Regional Hospital Bega and Djing.gii. Gudjaagalali (Children Stars) Eden	NSW	SAC
Fiona Tolich	Patient Advocate	Not applicable	NZ	SAC
Chauntel Wedlake	Patient Advocate	Not applicable	NZ	SAC

NSW = New South Wales; NZ = New Zealand, QLD = Queensland; SA = South Australia;

SAC = Scientific Advisory Committee; VIC = Victoria; WA = Western Australia

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

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.

Conflict of Interests

Processes were put in place to declare and manage any potential conflicts of interest, consistent with NHMRC guidance (Table 2).(32) All members of the GDG whose names appeared as contributors to the Guideline provided full written disclosure of any real or perceived conflict of interest prior to participating in the working party (Table 2). Conflicts of interest were reviewed by the Co-leads to determine if any would affect the guideline development process. Each person was obliged to report any real or perceived conflict of interest (should it have arisen) during the guideline development process. A range of perceived and actual conflicts of interest were reported but none were deemed to affect the Guideline development process.

Table 2. Conflicts of Interest declarations for the Guideline Development Group

Name	Conflict of Interest(s)
Didu Kariyawasam	Has received honoraria and travel grants from Biogen, Novartis and Roche (Industry sponsors of disease modifying treatments). Expert Panel Advisory Member for Biogen. Grants: National Health & Medical Research Council (NHMRC) Investigator Grant 2024 (2026317) and MRFF grant
Michelle Farrar	Has received honoraria and travel grants from Biogen, Novartis and Roche (Industry sponsors of disease modifying treatments). Expert Panel Advisory Member for Biogen and Novartis. Principal investigator in SMA clinical trials sponsored by Biogen, Novartis Gene Therapies and Roche, with payments received by the institution for research activities and no personal payments made. Medical Director and Board Member of Muscular Dystrophy NSW (pro bono)
Christian Meagher	No conflicts of interest.
Natasha Heather	Held an unpaid position as Newborn Screening Committee Chair for Human Genetics Society of Australasia.
Kaustav Bhattacharya	No conflict of interest.
Hugo Sampaio	No conflicts of interest.
Julie Cini	No conflict of interest.
Chiyan Lau	Receives salary from Pathology Queensland (QLD health). Member on a Genetics Advisory Committee for the Royal College of Pathologist of Australasia.
Emilie Mas	No conflicts of interest
Linda Burrows	Receives salary through SA Pathology (April 2023-present) for role as Senior Scientist in Newborn Screening.
Mark Greenslade	No conflict of interest.
Raoul Heller	No conflict of interest.
Richard Allcock	No conflict of interest disclosed
Sandra Divanisova	No conflict of interest.
Simon Carrivick	No conflict of interest disclosed
Alexandra Kay	No conflicts of interest.
Carol Siu	Receives salary from SA Pathology as primary employer.
Dianne Webster	Has received salary through Health New Zealand.
Enzo Ranieri	No conflict of interest disclosed
Francesca Moore	Has received salary contributions from PathWest Laboratory Medicine for role in WA Newborn Bloodspot Screening Program.
Gabrielle Crisp	No conflict of interest.

James Pitt	No conflict of interest.
Lawrence Greed	Has received salary contributions from PathWest Laboratory Medicine for role in WA Newborn Bloodspot Screening Program. Unpaid member of Newborn Bloodspot screening Program Management Committee and unpaid member of Human Genetics Society of Australasia Newborn Screening Committee.
Mark De Hora	No conflict of interest.
Ronda Greaves	Has received salary contributions from Victorian Clinical Genetics Services, Murdoch Children's Research Institute. Has received consulting fees, funding of travel, accommodation from Degruyter Publishing House as a journal associate editor for Clinical Chemistry and Laboratory Medicine. Paid speaking feed by Roche Diagnostic Asia Pacific for a Mass Spectrometry talk (unrelated to SMA). Has also received funding of travel and accommodation from the International Federation of Clinical Chemistry and Laboratory Medicine as an IFCC officer (unrelated to SMA).
Tiffany Wotton	No conflict of interest
Urs Wilgen	No conflict of interest.
Veronica Wiley	Has held leadership role in professional society-Australasian Society for Inborn Errors of Metabolism. Has social relationship with PerkinElmer.
Anita Cairns	Has received speaking fee, professional development, and indirect hospitality from Novartis for Managing SM. Also received speaking fee, travel and accommodation, professional development, and hospitality from Biogen for both the SMA forum and NMD forum. Has held a board member role at the Australasian Neuromuscular Network.
Damian Clark	No conflict of interest.
Eppie Yiu	Has received consulting payment for Biogen and Roche advisory board honoraria. Has received funding via Biogen for one night accommodation and interstate flights to attend NeuYou neuromuscular forum. Requested no honoraria from Biogen for steering committee role at interstate education meeting. Held an unpaid role as treasurer for the Australasian neuromuscular network.
Gina O'Grady	Has received a consulting fee and speaking fee for Biogen (2023), and travel and accommodation costs to a Biogen forum (2022).
Maina Kava	Receives salary from Perth Children's Hospital. Has attended meetings as Scientific Advisory board member for Biogen, Roche, and Novartis.
Tyson Ware	No conflict of interest.
Corin Miller	Has received a speaking fee and accommodation for attending the NSW Rural Doctors Network. Has performed unpaid work for Child Unlimited as part of PhD. Has received support payment for outreach clinical work via the NSW Rural Doctors Network, research assistance payment via Sydney Child Health Program, payment to attend Executive Committee Meeting of the NSW Agency for Clinical Innovation, PhD scholarship/stipend via UNSW, and payments for shifts worked via NSW Health.

Fiona Tolich	Maintains unpaid position as Head of SMA New Zealand. Completed tenure as founding Trustee of Patient Voice Aotearoa on 31-03-2024.
Chauntel Wedlake	No conflict of interest

Defining the scope and content of 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. Broad questions to inform Guideline development included:

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

13. For newborns diagnosed with SMA through newborn screening programs, what is the best way of organising services in terms of integration of care, patient and family centred care, multidisciplinary assessment, and care management?
14. How do we consider equity of access to the NBS for SMA pathway, independent of health literacy, regional/remote location, gender, and cultural and language background of the family?

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 and Pacific Islander and Māori communities was to create specific questions related to these groups and conduct 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 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), (31, 33). During this phase, outcomes were selected and prioritised into those that were critical, important, and not important to include, by the GDG. Outcomes that were deemed critical and important were used to form the systematic literature review.

Consumer Consultation

Consumer consultation was considered by the GDG to fundamental to the Guideline development process. To enable this, the SAC consisted of a patient advocacy representative (current Chief Executive Officer of Advocacy without Borders, Asia-Pacific) and two consumer representatives (Table 1). These individuals were involved in all aspects of the development of the Guideline including determination of key topics, priorities, clinical questions and formulation of consensus-based recommendations. Evidence was also gathered during the systematic review process which encompassed parent and carer perspectives, and where appropriate incorporated this body of evidence to form and grade recommendations (*Systematic review of the evidence*). Consumer input was also sought from key consumer and stakeholder organisations during the public consultation process (*Revising the Guideline*). All comments received were considered in the final editing stage of the guidelines.

Rationale and approach for processes used in the evidence gathering stage

Prior to initiating this study, systematic reviews of the scholarly literature pertaining to newborn screening for SMA had not been conducted. The quantitative data generated through the systematic reviews of the scholarly literature undertaken in this project was considered by the GDG as insufficient to answer several of the questions that the SAC considered relevant to include in the Guideline. 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 outcomes 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).(29) For this same reason, the recommendations included in the Guideline were a mixture of evidence-based and consensus-based recommendations.

Gathering the Evidence

The Guideline was intended to be evidence-based, adhering to an evidence-based practice framework that combined best available evidence.(16, 17) 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).

Systematic review of the evidence

Aim

The aim of the 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).(34)

Search Strategy and sources

A series of 14 systematic literature reviews were performed from 18 October to 27 November 2023 across three databases including Scopus (Ovid), Embase (Ovid), and PubMed, using both keywords and MESH terms. A professional database consultant (Helen Jones, University of New South Wales) reviewed and refined each search strategy. The search was updated on 1st May 2024. The search included all peer-reviewed publications and was limited to the paediatric population (up to 18 years of age). Although non-English databases were not searched, studies identified in languages other than English were captured by the three databases and were transcribed into English using the Google translate function. Each search strategy was repeated with and without filters for Aboriginal, Torres Strait Islander, Pacific Islander and Māori peoples for the population of interest.

The 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 3). Where systematic reviews existed, these were used preferentially to individual studies.

Table 3. *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.

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 Department 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).

Search Terms for Systematic Reviews

Population and Intervention apply to all systematic review questions. The Outcomes category change as determined by the research question. All systematic reviews were run with and without filters for CALD, Aboriginal, Torres and Pacific Strait Islander, Māori, First nations.

Systematic review 1:

What are the most appropriate methods to identify newborns/infants at risk of SMA through newborn screening?	
Population:	All newborns and infants
Intervention:	Newborn screening for SMA
Outcomes:	Impact on detection of children with SMA
	Accuracy of screening test (sensitivity, specificity)
	Reliability of screening test
	Time to screen result
	Resources required
	Equity of access to a result

Population

A. Pubmed

1. Title/Abstracts = "spinal muscular atroph*" or "SMA" or "5qSMA" or "5q-SMA" or "Survival Motor Neuron*" or "Hereditary Motor Neuronopath*" or "Werdnig-

Hoffmann Disease" or "Werdnig Hoffman" or "Kugelberg Welander Syndrome" or "Kugelberg–Welander disease" or "Infantile Muscular Atroph*" or "Anterior horn cell disease" or "Ventral horn cell*" or "Motor neuron disease*" or "Dubowitz" or "MND"

2. MESH terms = Muscular Atrophy, Spinal or Anterior Horn Cells or SMN complex proteins

B. Embase

3. (“spinal muscular atrophy*” or “SMA” or “5qSMA” or “5q-SMA” or “Survival Motor Neuron*” or “Hereditary Motor Neuronopath*” or “Werdnig-Hoffmann Disease” or ”Werdnig Hoffman” or “Kugelberg Welander Syndrome” or “Kugelberg–Welander disease” or “Infantile Muscular Atroph*” or “Anterior horn cell disease” or “Ventral horn cell*” or “Motor neuron disease*” or “Dubowitz” or “MND”).ti,ab,kw.

4. spinal muscular atrophy/ or spinal muscular atrophy type 2/ or spinal muscular atrophy type 4/ or hereditary spinal muscular atrophy/ or anterior horn cell/ or anterior horn cell disease/ or survival motor neuron protein/ or survival motor neuron protein 1/ or survival motor neuron protein 2/

C. Scopus

5. TITLE-ABS-KEY (“spinal muscular atrophy*” or “SMA” or “5qSMA” or “5q-SMA” or “Survival Motor Neuron*” or “Hereditary Motor Neuronopath*” or “Werdnig-Hoffmann Disease” or “Werdnig Hoffman” or “Kugelberg Welander Syndrome” or “Kugelberg–Welander disease” or “Infantile Muscular Atroph*” or “Anterior horn cell disease” or “Ventral horn cell*” or “Motor neuron disease*” or “Dubowitz” or “MND”)

Intervention

A. Pubmed

6. Title / abstracts = "neonatal screening*" or "newborn Screening*" or "newborn Infant Screening*" or "newborn bloodspot screening" or "NBS" or "Dried Blood Spot*" or "Guthrie*" or "newborn blood spot*" or "screening panel*" or "blood spot screen*" or "screening test*" or "Universal screening" or "Screening program*" or "Population screening*" or "screening panel*" or "genomic newborn screening*" or "newborn genetic screening*" or "newborn and carrier screening*" or "Newborn sequencing" or

"Genomic sequencing" or "next generation sequencing" or "heelprick" or "heelstick" or "heel prick" or "heel stick" or "expanded screening"

7. MESH terms = neonatal screening or dried blood spot testing

B. Embase

8. (“neonatal screening*” or “newborn Screening*” or “newborn Infant Screening*” or “newborn bloodspot screening” or “NBS” or “Dried Blood Spot*” or “Guthrie*” or “newborn blood spot*” or “screening panel*” or “blood spot screen*” or “screening test*” or “Universal screening” or “Screening program*” or “Population screening*” or “screening panel*” or “genomic newborn screening*” or “newborn genetic screening*” or “newborn and carrier screening*” or “Newborn sequencing” or “Genomic sequencing” or “next generation sequencing” or “heelprick” or “heelstick” or “heel prick” or “heel stick” or “expanded screening”).ti,ab,kw.

9. Newborn screening/ or dried blood spot testing/ or prenatal screening/

C. Scopus

10. TITLE-ABS-KEY (“neonatal screening*” or “newborn Screening*” or “newborn Infant Screening*” or “newborn bloodspot screening” or “NBS” or “Dried Blood Spot*” or “Guthrie*” or “newborn blood spot*” or “screening panel*” or “blood spot screen*” or “screening test*” or “Universal screening” or “Screening program*” or “Population screening*” or “screening panel*” or “genomic newborn screening*” or “newborn genetic screening*” or “newborn and carrier screening*” or “Newborn sequencing” or “Genomic sequencing” or “next generation sequencing” or “heelprick” or “heelstick” or “heel prick” or “heel stick” or “expanded screening” and carrier screening*” or “Newborn sequencing” or “Genomic sequencing” or “next generation sequencing”)

Outcomes

A. Pubmed

11. Title / abstracts ="Sensitivity" or "Specificity" or "positive predictive value" or ‘discord*” or "accuracy" or "negative predictive value" or "reliability" or "clinical validity" or "analytical validity" or "clinical utility" or "clinical usefulness" or "False positive*" or "false-positive*" or "Genotype*" or "Heterozygote" or "Homozyg*" or

"Phenotype*" or "Sequence Deletion" or "Risk factor*" or "prognostic" or "Disease Progression" or "Time Factor*" or "laboratory method*" or "Reproducibility" or "Genetic Testing" or "allele-specific PCR" or "allele specific PCR" or "national policy" or "exon 7" or "Analyte" or "screening method*" or "quantitative assay*" or "false negative" or "false-negative" or "notif*" or "result*" or " homozygous deletion" or "validated assay*" or "risks" or "benefits" or "gestational age" or "preterm" or "pre-term" or "compound heterozyg*" or "test performance") AND ("survival motor neuron 1" or "SMN1" or "survival motor neuron-1" or "first tier" or "first-tier" or "SMN 1" or "tier 1" or "multiplex*"

12. MESH terms = "Sensitivity" or "Specificity" or "Risk factors" or "Survival analysis" or "Genotype" or "Polymerase Chain Reaction" or "Preventive health services" or "Specimen Handling" or "Genetic testing" or "Workflow" or "Reproducibility of Results" or "Phenotype" or "Sequence Deletion" or "Disease Progression" or "Time Factors" or "Health Information Exchange" or "evidence gaps" or "benchmarking" or "guidelines as Topic" or "health care evaluation mechanisms" or "quality indicators, Health care" or "standards of care" or "public health practice" or "Clinical Studies as Topic" or "Multicenter Studies as Topic" or "Health Impact Assessment" or "Negative Results" or "Clinical Decision-Making" or "Delayed Diagnosis" or "Diagnostic Errors" or "Clinical Laboratory Techniques" or "Diagnostic Techniques, Neurological" or "Diagnostic Tests, Routine" or "Treatment Outcome" or "Data Accuracy"

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. "Sensitivity" or "Specificity" or "positive predictive value" or "accuracy" or "negative predictive value" or 'discord' or "reliability" or "clinical validity" or "analytical validity" or "clinical utility" or "clinical usefulness" or "False positive*" or "false-positive*" or "Genotype*" or "Heterozygote" or "Homozyg*" or "Phenotype*" or "Sequence Deletion" or "Risk factor*" or "prognostic" or "Disease Progression" or "Time Factor*" or "laboratory method*" or "Reproducibility" or "Genetic Testing" or "allele-specific PCR" or "allele specific PCR" or "national policy" or "exon 7" or "Analyte" or "screening method*" or "quantitative assay*" or "false negative" or "false-negative" or "notif*" or "result*" or " homozygous deletion" or "validated assay*" or "risks" or "benefits" or "gestational age" or "preterm" or "pre-term" or

"compound heterozyg*" or "test performance" or "survival motor neuron 1" or "SMN1" or "survival motor neuron-1" or "first tier" or "first-tier" or "SMN 1" or "tier 1" or "multiplex*").ti,ab,kw.

14. newborn monitoring/ or sensitivity and specificity/ or good laboratory practice/or allele/ or phenotype/ or genotype/ or Preventive health services/ or laboratory/ or blood sampling/ or workflow/ or evaluation study/ or reproducibility/ or newborn disease/ or gene deletion/ or disease exacerbation/ or Time Factor/ or medical information system/ or benchmarking/ or practice guideline/ or clinical handover/ or clinical pathway/ or good clinical practice/ or clinical competence/ or health care organization/ or multicenter study / or health impact assessment/ or performance measurement system/ or clinical decision making/ or medical decision making/ or diagnostic test/ or laboratory test/ or data accuracy/ or measurement accuracy/ or clinical outcome/ or outcome assessment/ or risk factor/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("Sensitivity" or "Specificity" or "positive predictive value" or "accuracy" or "negative predictive value" or "reliability" or "clinical validity" or "analytical validity" or "clinical utility" or "clinical usefulness" or "False positive*" or "false-positive*" or "Genotype*" or "Heterozygote" or "Homozyg*" or "Phenotype*" or "Sequence Deletion" or "Risk factor*" or "prognostic" or "Disease Progression" or "Time Factor*" or "laboratory method*" or "Reproducibility" or "Genetic Testing" or "allele-specific PCR" or "allele specific PCR" or "national policy" or "exon 7" or "Analyte" or "screening method*" or "quantitative assay*" or "false negative" or "false-negative" or "notif*" or "result*" or " homozygous deletion" or "validated assay*" or "risks" or "benefits" or "gestational age" or "preterm" or "pre-term" or "compound heterozyg*" or "test performance") AND ("survival motor neuron 1" or "SMN1" or "survival motor neuron-1" or "first tier" or "first-tier" or "SMN 1" or "tier 1" or "multiplex*")

(5) AND (10) AND (15)

Systematic review 2:

What is the clinical utility and the most appropriate methods to provide prognostic information on disease severity in newborns/infants at risk of SMA through newborn screening?	
Population:	All newborns and infants
Intervention:	Newborn screening for SMA
Outcomes:	Accuracy of *SMN2* screening test (sensitivity, specificity)
	Reliability of *SMN2* screening test
	Time to *SMN2* screen result
	Resources required
	Impact on care sought/received
	Impact on time to diagnosis and treatment
	Impact on health outcomes for newborns/infants
	Impact on decision making (for families, for clinicians)
	Equity of access to a result

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts =(“Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “clinical useful*” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Risk factor*” or “Genetic Predisposition*” or “disease severity” or “prognostic” or “Disease Progression” or “laten*” or “time frame” or “time line*” or “therapeutic window” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analyte” or “screening method*” or “quantitative assay*” or “copy number” or “upper limit” or “documentation” or “report” or “notif*” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “SMN” or “predict” or “biomarker” or “quantitative assay*” or “quantitative method*” or “validation” or “feasibil*” or “second tier” or “second-tier” or “proficiency” or “SMN2” or “survival motor neuron 2” or “SMN 2” or “SMN-2”) AND (“SMN2” or “SMN 2” or “SMN-2” or “survival motor neuron 2”)

12. MESH terms = “Sensitivity” or “Specificity” or “Risk factors” or “Survival analysis” or “Genotype” or "Polymerase Chain Reaction" or “Preventive health services” or “Genetic testing” or “Workflow” or “Evaluation Studies as Topic” or “Reproducibility of Results” or “Infant, Newborn, Diseases” or “Parents” or “Phenotype” or “Sequence Deletion” or “Genetic Predisposition to Disease” or “Disease Progression” or “Time Factors” or "Health Information Exchange" or "Quality Improvement” or "evidence gaps" or "benchmarking" or "guidelines as Topic" or "clinical competence" or "health care evaluation mechanisms" or "quality indicators, Health care" or "standards of care” or “Epidemiologic Factors” or “public health practice” or “epidemiology” or "Clinical Studies as Topic" or "Multicenter Studies as Topic” or "Health Impact Assessment" or "Negative Results" or "Clinical Decision-Making" or "Delayed Diagnosis" or "Diagnostic Errors" or "Clinical Laboratory Techniques" or "Diagnostic Techniques, Neurological" or "Diagnostic Tests, Routine" or "Treatment Outcome" or “Data Accuracy”

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (“Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “clinical useful*” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Risk factor*” or “Genetic Predisposition*” or “disease severity” or “prognostic” or “Disease Progression” or “laten*” or “time frame” or “time line*” or “therapeutic window” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analyte” or “screening method*” or “quantitative assay*” or “copy number” or “upper limit” or “documentation” or “report” or “notif*” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “SMN” or “predict” or “biomarker” or “quantitative assay*” or “quantitative method*” or “validation” or “feasibil*” or “second tier” or “second-tier” or “proficiency” or “SMN2” or “survival motor neuron 2” or “SMN 2” or “SMN-2”).mp. and (“SMN2” or “SMN 2” or “SMN-2” or “survival motor neuron 2”).ti,ab,kw.

14. early diagnosis/ or time factor/ or missed diagnosis/ or sensitivity and specificity/ or good laboratory practice/ or allele/ or phenotype/ or genotype/ or polymerase chain reaction/ or clinical laboratory/ or hospital laboratory/ or genetic screening/ or blood sampling/ or workflow/ or evaluation study/ or reproducibility/ or gene deletion/ or disease exacerbation/ or information gap/ or practice guideline/ or clinical handover/ or clinical pathway/ or consensus development/ or clinical competence/ or multicenter study / or health impact assessment/ or performance measurement system/ or medical decision making/ or diagnostic test/ or delayed diagnosis/ or laboratory test/ or data accuracy/ or measurement accuracy/ or clinical outcome/ or outcome assessment/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “clinical useful*” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Risk factor*” or “Genetic Predisposition*” or “disease severity” or “prognostic” or “Disease Progression” or “laten*” or “time frame” or “time line*” or “therapeutic window” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analyte” or “screening method*” or “quantitative assay*” or “copy number” or “upper limit” or “documentation” or “report” or “notif*” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “SMN” or “predict” or “biomarker” or “quantitative assay*” or “quantitative method*” or “validation” or “feasibil*” or “second tier” or “second-tier” or “proficiency” or “SMN2” or “survival motor neuron 2” or “SMN 2” or “SMN-2”) AND (“SMN2” or “SMN 2” or “SMN-2” or “survival motor neuron 2”)

(5) AND (10) AND (15)

Systematic review 3:

What are the most appropriate processes to resolve uncertain, false positive or false negative screening results?
Population: All newborns and infants
Intervention: Newborn screening for SMA
Outcomes: Impact of diagnostic uncertainty on families (well-being,

financial, social, resources)

Impact on diagnostic uncertainty for clinicians

Accuracy of screening result

Accuracy of the diagnosis

Acceptability (of NBS for SMA) to the public, to families

Harms/risks to newborns of a false screen result

Impact on health outcomes (for newborns)

Impact on decision making (for families, for clinicians)

Impact on public confidence (in NBS for SMA)

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts =(“Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analy*” or “screening method*” or “sequenc*” or “next generation” or “next-generation” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “PCR” or “validation” or “variant*” or (“misdiagnosis*” or “diagnos*” or “prevention” or “health information” or "Quality Improvement” or “QI” or “sensitiv*” or “specificity” or “false positive*” or “error*” or “reproducibil*” or “immunoassay” or “assay” or “reactive” or “non-reactive” or “explan*” or “detect*” or “non-detection” or “test performance” or “discordant” or “discrepanc*” or “analyte” or “detectable” or “non-detectable” or “conflict*” or “Exome Sequencing” or "communication” or “pathway*” or “resolution*” or “resolve*” or “disparit*” or “genotype–phenotype correlation” or “biomarkers” or “genetic variation” or “Prognosis” or “standard*” or “legislation” or “jurisprudence” or “legal” or “second tier” or “second-tier” or “first tier” or “first-tier” or "genotype-phenotype” or "variation*” or "noncongenital” or "policy” or “best practice” or “method validation” or “data analys*” or "MLPA” Or "qPCR” or "ddPCR” or "quantitative polymerase chain reaction” or "multiplex ligation probe

amplification” or "droplet digital PCR” or "high-resolution melting” or "HRM” or "PCR/CE” or “polymerase chain reaction-capillary electrophoresis” or “validity” or “Copy number analy*” or “reliability” or “validity” or “Test-retest” or "SMN2*” or "next-generation sequencing” or "Copy Number Variation*” or "workflow” or “repeat” or “Quality assurance”) or “mutation*” or “feasibil*” or “validation” or “exome” or “third tier” or “third-tier” or “three-tier” or “high throughput” or “DNA sequencing” or “Sanger”) AND (“third tier” or “third-tier” or “three-tier” or “high throughput” or “DNA sequencing” or “Sanger”)

12. MESH terms = “Sensitivity” or “Specificity” or “Risk factors” or “Survival analysis” or “Genotype” or "Polymerase Chain Reaction" or “Preventive health services” or “Genetic testing” or “Evaluation Studies as Topic” or “Reproducibility of Results” or “Infant, Newborn, Diseases” or “Parents” or “Phenotype” or “Sequence Deletion” or “Genetic Predisposition to Disease” or “Disease Progression” or “Time Factors” or "Quality Improvement” or "evidence gaps" or "guidelines as Topic” or "health care evaluation mechanisms" or "quality indicators, Health care" or "Clinical Studies as Topic" or "Multicenter Studies as Topic” or "Health Impact Assessment" or "Negative Results" or "Clinical Decision-Making" or "Delayed Diagnosis" or "Diagnostic Errors" or "Clinical Laboratory Techniques" or "Diagnostic Techniques, Neurological" or "Diagnostic Tests, Routine" or "Treatment Outcome" or “Data Accuracy” “Reproducibility of Results”[MeSH Terms] or "Diagnostic Errors/prevention and control*”[MeSH Terms] "Missed Diagnosis"[MeSH Terms] or "Diagnosis"[MeSH Terms:noexp] or "Health Information Exchange/standards*”[MeSH Terms] or "Quality Improvement”[MeSH Terms] or “Sensitivity and Specificity”[MeSH Terms] or “Polymerase Chain Reaction/methods*”[MeSH Terms] or “Delivery of health care”[MeSH Terms] or “False positive Reactions”[MeSH Terms] or “Neonatal Screening/methods”[MeSH Terms] or “Sensitivity and Specificity”[MeSH Terms] or “Diagnostic Errors”[MeSH Terms] or “Blotting, Western”[MeSH Terms] or “Genomics”[MeSH Terms] or “Exome Sequencing”[MeSH Terms] or “biomarkers”[MeSH Terms] or “genetic variation”[MeSH Terms] or “Prognosis”[MeSH Terms] or “biological assay”[MeSH Terms] or “Laboratory Proficiency Testing”[MeSH Terms] or “False Positive Reactions”[MeSH Terms] or “DNA Copy Number Variations*”[MeSH Terms] or “Sequence Deletion”[MeSH Terms] or “Exons”[MeSH Terms] or “Multiplex Polymerase Chain Reaction”[MeSH Terms] or “Time Factors”[MeSH Terms] or “Survival analysis”[MeSH Terms] or “Diagnostic

Services”[MeSH Terms] or “Blood Specimen Collection*”[MeSH Terms] or “Laboratories”[MeSH Terms] or “Predictive Value of Tests”[MeSH Terms] or “Workflow”[MeSH Terms] or “Dried Blood Spot Testing”[MeSH Terms] or “Health Priorities”[MeSH Terms:noexp] or "Health Care Evaluation Mechanisms"[MeSH Terms:noexp] or "Quality Indicators, Health Care”[MeSH Terms]

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. “Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analy*” or “screening method*” or “sequenc*” or “next generation” or “next-generation” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “PCR” or “validation” or “variant*” or “mutation*” or “feasibil*” or “validation” or “exome”. (“misdiagnosis*” or “diagnos*” or “prevention” or “health information” or "Quality Improvement” or “QI” or “sensitiv*” or “specificity” or “false positive*” or “error*” or “reproducibil*” or “immunoassay” or “assay” or “reactive” or “non-reactive” or “explan*” or “detect*” or “non-detection” or “test performance” or “discordant” or “discrepanc*” or “analyte” or “detectable” or “non-detectable” or “conflict*” or “Exome Sequencing” or "communication” or “pathway*” or “resolution*” or “resolve*” or “disparit*” or “genotype–phenotype correlation” or “biomarkers” or “genetic variation” or “Prognosis” or “standard*” or “legislation” or “jurisprudence” or “legal” or “second tier” or “second-tier” or “first tier” or “first-tier” or "genotype-phenotype” or "variation*” or "noncongenital” or "policy” or “best practice” or “method validation” or “data analys*” or "MLPA” Or "qPCR” or "ddPCR” or "quantitative polymerase chain reaction” or "multiplex ligation probe amplification” or "droplet digital PCR” or "high-resolution melting” or "HRM” or "PCR/CE” or “polymerase chain reaction-capillary electrophoresis” or “validity” or “Copy number analy*” or “reliability” or “validity” or “Test-retest” or "SMN2*” or "next-generation sequencing” or "Copy Number Variation*” or "workflow” or “repeat” or “Quality assurance”).ti,ab,kw.

14. exp diagnostic error/ or "prevention and control"/ or diagnosis/ or total quality management/ or "sensitivity and specificity"/ or polymerase chain reaction/ or health care delivery/ or false positive result/ or genotype/ or (heterozygote/ or heterozygosity/) or (homozygosity/ or homozygote/) or gene deletion/ or early diagnosis/ or real time polymerase chain reaction/ or multiplex polymerase chain reaction/ or risk factor/ or disease exacerbation/ or time factor/ or preventive health service/ or clinical laboratory service/ or blood sampling/ or laboratory/ or clinical laboratory/ or hospital laboratory/ or laboratory technique/ or laboratory diagnosis/ or predictive value/ or workflow/ or reproducibility/ or molecular diagnosis/ or genetic association study/ or copy number variation/ or multiplex ligation dependent probe amplification/ or whole exome sequencing/ or exon/ or high throughput sequencing/ or follow up/ or dna sequencing/ or genetic polymorphism/ or genetic linkage/ or (restriction fragment length polymorphism/ or polymerase chain reaction restriction fragment length polymorphism/) professional standard/ or clinical competence/ or health care quality/ or health care planning/ or clinical decision support system/ or clinical decision making/ or evaluation study/ or reproducibility/ or information gap/ or practice guideline/ or health impact assessment/ or performance measurement system/ or medical decision making/ or diagnostic test/ or laboratory test/ or data accuracy/ or measurement accuracy/ or clinical outcome/ or outcome assessment/ or high throughput sequencing/ or high throughput analysis/ or targeted resequencing/ or feasibility study/ or sanger sequencing/ ti,ab,kw.

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“Sensitivity” or “Specificity” or “positive predictive value” or “accuracy” or “negative predictive value” or “reliability” or “clinical validity” or “analytical validity” or “clinical utility” or “Polymerase Chain Reaction*” or “Genotype*” or “Phenotype*” or “Sequence Deletion” or “Workflow” or “Reproducibility” or "Genetic Testing” or "allele-specific PCR” or “allele specific PCR” or “national policy” or “Analy*” or “screening method*” or “sequenc*” or “next generation” or “next-generation” or “clinical useful*” or “validated assay*” or “risks” or “benefits” or “PCR” or “validation” or “variant*” or “mutation*” or “feasibil*” or “validation” or “exome” or “third tier” or “third-tier” or “three-tier” or “high throughput” or “DNA sequencing” or “Sanger”) AND (“third tier” or “third-tier” or

"three-tier" or "high throughput" or "DNA sequencing" or "Sanger"or "misdiagnosis*" or "diagnos*" or "prevention" or "health information" or "Quality Improvement" or "QI" or "sensitiv*" or "specificity" or "false positive*" or "error*" or "reproducibil*" or "immunoassay" or "assay" or "reactive" or "non-reactive" or "explan*" or "detect*" or "non-detection" or "test performance" or "discordant" or "discrepanc*" or "analyte" or "detectable" or "non-detectable" or "conflict*" or "Exome Sequencing" or "communication" or "pathway*" or "resolution*" or "resolve*" or "disparit*" or "genotype–phenotype correlation" or "biomarkers" or "genetic variation" or "Prognosis" or "standard*" or "legislation" or "jurisprudence" or "legal" or "second tier" or "second-tier" or "first tier" or "first-tier" or "genotype-phenotype" or "variation*" or "noncongenital" or "policy" or "best practice" or "method validation" or "data analys*" or "MLPA" Or "qPCR" or "ddPCR" or "quantitative polymerase chain reaction" or "multiplex ligation probe amplification" or "droplet digital PCR" or "high-resolution melting" or "HRM" or "PCR/CE" or "polymerase chain reaction-capillary electrophoresis" or "validity" or "Copy number analy*" or "reliability" or "validity" or "Test-retest" or "SMN2*" or "next-generation sequencing" or "Copy Number Variation*" or "workflow" or "repeat" or "Quality assurance")

(5) AND (10) AND (15)

Systematic review 4:

What are the most appropriate supports and information for families undertaking newborn screening for SMA?	
Population:	All families of newborns
Intervention:	Newborn screening for SMA
Outcomes:	Impact on knowledge and understanding
	Satisfaction with healthcare
	Informed consent
	Impact on well-being of family
	Impact on health outcomes for newborns
	Impact on wellbeing and quality of life for newborns
	Acceptability of educational resources
	Equity of access to information and support
	Culturally and linguistically competent information provision

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts =“Parent*” or “Delivery of health care” or “Public Health” or “Early diagnosis” or “Education*” or “support*” or “Advise” or “information” or “recommendation*” or “health planning” or “Integrated Health Care System*” or “Best Practice*” or “Psychosocial” or “Preventive Health Services” or “Communication” or “Health Knowledge” or “Health Attitude*” or “Patient Acceptance of Health Care” or "Mother*" or “Father*” or "Parent Satisfaction" or “Caregiver*" or "Choice Behav*" or "Pamphlet*” or “Complementary Therap*” or “Patient Care” or “Self Care” or “Self-care” or “Psychological Technique*” or “Decision Support*” or “Decision-Making” or “Decision Making” or “Attitude to Health” or “Culturally Competent Care” or “Health Priorit*” or “Needs Assessment*” or "Value Based Health Care" or “Quality of Health Care” or “standards of care” or “informed consent” or “expectation*” or “self-report*” or “self report*” or “attitude*” or “opinion*” or “knowledge” or “decision making” or “deliberation” or “family function*” or “empower” or “health care decision*” or “values” or “moral*” or “ethic*” or “accountability” or “counselling” or “psychometric” or “benefit*” or “distress” or “acceptab*” or “survey*” or “opting” or “comprehension” or “Indigenous” or “First nations” or “Torres” or “Aborigin*” or “culturally diverse” or “linguistically diverse” or “minorit*” or “ethnic*” or “language barrier*” or “equity” or “resource*” or “CALD” or “co-develop*” or “codevelopment” or “stakeholder*”
12. MESH terms = “Quality Indicators, Health Care" or "Clinical Competence" or "Guideline Adherence" or "Outcome and Process Assessment, Health Care" or "Guidelines as Topic" or "Standard of Care" or “Health Care Quality, Access, and Evaluation” or "Consumer Health Information" or "Health Promotion" or "Patient Education as Topic" or “social support” or “health planning” or “health communication” or “Attitude to health” or "Educational Status" or "Early Intervention, Educational" or "Choice Behaviour" or "Pamphlets” or “Complementary Therapies” or "Perinatal Care" or “Patient Care Bundles” or “Psychological Techniques” or “Decision Support Techniques” or “Clinical Decision-Making” or “Attitude to Health” or “Health Priorities” or “needs Assessment” or “Psychosocial Intervention” or “Preventive Health

Services” or “Patient care planning” or “Interdisciplinary communication” or “Early diagnosis” or “Time Factors” or “Health communication” or ”Parents” or “Health Care Economics and Organizations” or “Caregivers” or "Health Services, Indigenous" or "Australian Aboriginal and Torres Strait Islander Peoples" or “Culturally Competent Care”

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (”Parent*” or “Delivery of health care” or “Public Health” or “Early diagnosis” or “Education*” or “support*” or “Advise” or “information” or “recommendation*” or “health planning” or “Integrated Health Care System*” or “Best Practice*” or “Psychosocial” or “Preventive Health Services” or “Communication” or “Health Knowledge” or “Health Attitude*” or “Patient Acceptance of Health Care” or "Mother*" or “Father*” or "Parent Satisfaction" or “Caregiver*" or "Choice Behav*" or "Pamphlet*” or “Complementary Therap*” or “Patient Care” or “Self Care” or “Self-care” or “Psychological Technique*” or “Decision Support*” or “Decision-Making” or “Decision Making” or “Attitude to Health” or “Culturally Competent Care” or “Health Priorit*” or “Needs Assessment*” or "Value Based Health Care" or "Quality of Health Care” or “standards of care” or “informed consent” or “expectation*” or “self-report*” or “self report*” or “attitude*” or “opinion*” or “knowledge” or “decision making” or “deliberation” or “family function*” or “empower” or “health care decision*” or “values” or “moral*” or “ethic*” or “accountability” or “counselling” or “psychometric” or “benefit*” or “distress” or “acceptab*” or “survey*” or “opting” or “comprehension” or “Indigenous” or “First nations” or “Torres” or “Aborigin*” or “culturally diverse” or “linguistically diverse” or “minorit*” or “ethnic*” or “language barrier*” or “equity” or “resource*” or “CALD” or “co-develop*” or “codevelopment” or “stakeholder*”).ti,ab,kw.

14. health care quality/ or health equity/ or professional standard/ or program evaluation/ or social validity/ or clinical competence/ or protocol compliance/ or consensus development/ or good clinical practice/ or professional standard/ or health care quality/ or consumer health information/ or health promotion/ or public health campaign/ or health education/ or childbirth education/ or parenting education/ or social support/ or

community support/ or emotional support/ or family support/ or health care planning/ or medical information/ or attitude to health/ or early childhood intervention/ or decision making/ or family decision making/ or patient decision making/ or perinatal care/ or decision support system/ or clinical decision support system/ or clinical decision making/ or needs assessment/ or psychosocial intervention/ or preventive health service/ or patient care planning/ or interdisciplinary communication/ or early diagnosis/ or time factor/ or expectant parent/ or expectant father/ or expectant mother/ or caregiver/ or indigenous people/ or first nation/ or indigenous australian/ or communication barrier/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY "Parent*" or "Delivery of health care" or "Public Health" or "Early diagnosis" or "Education*" or "support*" or "Advise" or "information" or "recommendation*" or "health planning" or "Integrated Health Care System*" or "Best Practice*" or "Psychosocial" or "Preventive Health Services" or "Communication" or "Health Knowledge" or "Health Attitude*" or "Patient Acceptance of Health Care" or "Mother*" or "Father*" or "Parent Satisfaction" or "Caregiver*" or "Choice Behav*" or "Pamphlet*" or "Complementary Therap*" or "Patient Care" or "Self Care" or "Self-care" or "Psychological Technique*" or "Decision Support*" or "Decision-Making" or "Decision Making" or "Attitude to Health" or "Culturally Competent Care" or "Health Priorit*" or "Needs Assessment*" or "Value Based Health Care" or "Quality of Health Care" or "standards of care" or "informed consent" or "expectation*" or "self-report*" or "self report*" or "attitude*" or "opinion*" or "knowledge" or "decision making" or "deliberation" or "family function*" or "empower" or "health care decision*" or "values" or "moral*" or "ethic*" or "accountability" or "counselling" or "psychometric" or "benefit*" or "distress" or "acceptab*" or "survey*" or "opting" or "comprehension" or "Indigenous" or "First nations" or "Torres" or "Aborigin*" or "culturally diverse" or "linguistically diverse" or "minorit*" or "ethnic*" or "language barrier*" or "equity" or "resource*" or "CALD" or "co-develop*" or "codevelopment" or "stakeholder*"

(5) AND (10) AND (15)

Systematic review 5:

What are the most appropriate methods to confirm a diagnosis of SMA, for a screen positive newborn/infant?

Population: All newborns

Intervention: Newborn screening for SMA

Outcomes: Impact on health outcomes (for children)

Accuracy of diagnostic test (sensitivity, specificity)

Reliability of diagnostic test

Time to diagnosis

Resources required

Equity of access to diagnosis

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts ==“copy number*” or “analytical valid*” or “genomics” or “next generation DNA sequencing” or “next generation sequencing” or “molecular technique*” or “molecular analysis” or “confirmatory” or “confirmation” or “follow-up test*” or “procedures” or “process*” or “MLPA” or “Multiplex ligation-dependent probe amplification” or “validation” or “diagnos*” or “standard operating procedures” or “standard operating protocol*” or “genetic*” or “long read sequencing” or “copy number variation*” or “analysis” or “deletion” or “molecular basis” or “positive predictive value” or “negative predictive value” or “test performance” or “sensitive*” or “specific*” or “prognosis” or “laboratory” or “best practice” or “primer” or “PCR” or “polymerase chain reaction” or “DDPCR” or “digital droplet polymerase chain reaction” or “SMN mutations” or “intragenic” or “genetic variation*” or “SMN1 deletion” or “exon 7” or “deletion” or “best practice” or “guidelines” or “multiple ligation dependent probe amplification” or “accura*” or “technical standards” or “approaches” or “false positive” or “false negative” or “true positive” or “true negative” or “qPCR” or “quantitative polymerase chain reaction” or “melting curve” or “melt curve” or “time*” or “turnaround” or “assay”

12. MESH terms = “diagnosis”[Mesh:NoExp] or "Diagnostic Errors"[MeSH Terms] or "Early Diagnosis"[MeSH Terms] or "Diagnostic Techniques and Procedures"[MeSH:noexp] or “clinical laboratory techniques”[MeSH Terms] or “Diagnostic Techniques, Neurological”[MeSH Terms] or "Quality of Health Care"[MeSH:noexp] or “Data Collection”[MeSH Terms] or “evaluation studies as topic”[Mesh:noexp] or “data collection”[MeSH Terms] or “quality improvement”[MeSH Terms] or “sensitivity and specificity”[MeSH Terms]—or "Polymerase Chain Reaction"[MeSH Terms] or "Genotype"[MeSH Terms] or "Mutation"[MeSH Terms] or "Disease Progression"[MeSH Terms] or "Time Factors"[MeSH Terms] or "Laboratories"[MeSH Terms] or "Workflow"[MeSH Terms] or "Genetic Association Studies"[MeSH Terms] or "Inheritance Patterns"[MeSH Terms] or "Molecular Sequence Data"[MeSH Terms] or "Exons"[MeSH Terms] or "Sequence Analysis"[MeSH Terms]

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (“copy number*” or “analytical valid*” or “genomics” or “next generation DNA sequencing” or “next generation sequencing” or “molecular technique*” or “molecular analysis” or “confirmatory” or “confirmation” or “follow-up test*” or “procedures” or “process*” or “MLPA” or “Multiplex ligation-dependent probe amplification” or “validation” or “diagnos*” or “standard operating procedures” or “standard operating protocol*” or “genetic*” or “long read sequencing” or “copy number variation*” or “analysis” or “deletion” or “molecular basis” or “positive predictive value” or “negative predictive value” or “test performance” or “sensitive*” or “specific*” or “prognosis” or “laboratory” or “best practice” or “primer” or “PCR” or “polymerase chain reaction” or “DDPCR” or “digital droplet polymerase chain reaction” or “SMN mutations” or “intragenic” or “genetic variation*” or “SMN1 deletion” or “exon 7” or “deletion” or “best practice” or “guidelines” or “multiple ligation dependent probe amplification” or “accura*” or “technical standards” or “approaches” or “false positive” or “false negative” or “true positive” or “true negative” or “qPCR” or “quantitative polymerase chain reaction” or “melting curve” or “melt curve” or “time*” or “turnaround” or “assay”).ti,ab,kw.

14. exp diagnostic error/ or "prevention and control"/ or diagnosis/ or "sensitivity and specificity"/ or polymerase chain reaction/ or health care delivery/ or false positive

result/ or-genotype/ or (heterozygote/ or heterozygosity/) or (homozygosity/ or homozygote/) or gene deletion/ or early diagnosis/ or real time polymerase chain reaction/ or multiplex polymerase chain reaction/ or risk factor/ or disease exacerbation/ or time factor/ or preventive health service/ or clinical laboratory service/ or blood sampling/ or laboratory/ or clinical laboratory/ or hospital laboratory/ or laboratory technique/ or laboratory diagnosis/ or predictive value/ or workflow/ or reproducibility/ or molecular diagnosis/ or mutation/ or copy number variation/ or multiplex ligation dependent probe amplification/ or molecular genetics/ or recessive gene/ or whole exome sequencing/ or prognosis/ or exon/ or high throughput sequencing/ or follow up/ or dna sequencing/ or genetic polymorphism/ or genetic linkage/ or dna mutational analysis/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY = (“copy number*” or “analytical valid*” or “genomics” or “next generation DNA sequencing” or “next generation sequencing” or “molecular technique*” or “molecular analysis” or “confirmatory” or “confirmation” or “follow-up test*” or “procedures” or “process*” or “MLPA” or “Multiplex ligation-dependent probe amplification” or “validation” or “diagnos*” or “standard operating procedures” or “standard operating protocol*” or “genetic*” or “long read sequencing” or “copy number variation*” or “analysis” or “deletion” or “molecular basis” or “positive predictive value” or “negative predictive value” or “test performance” or “sensitive*” or “specific*” or “prognosis” or “laboratory” or “best practice” or “primer” or “PCR” or “polymerase chain reaction” or “DDPCR” or “digital droplet polymerase chain reaction” or “SMN mutations” or “intragenic” or “genetic variation*” or “SMN1 deletion” or “exon 7” or “deletion” or “best practice” or “guidelines” or “multiple ligation dependent probe amplification” or “accura*” or “technical standards” or “approaches” or “false positive” or “false negative” or “true positive” or “true negative” or “qPCR” or “quantitative polymerase chain reaction” or “melting curve” or “melt curve” or “time*” or “turnaround” or “assay”)

(5) AND (10) AND (15)

Systematic review 6:

What is the clinical utility and the most appropriate methods to confirm prognostic (*SMN2* copy number) for a screen positive newborn/infant?	
Population:	All newborns
Intervention:	Newborn screening for SMA
Outcomes:	Accuracy of diagnostic test (sensitivity, specificity)
	Reliability of diagnostic test
	Resources required
	Equity of access to prognostic information
	Impact on care sought/received
	Impact on time to diagnosis and treatment
	Impact on health outcomes for newborns/infants
	Impact on decision making (for families, for clinicians)

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("severity" or "Confirmation" or "modifier*" or "cycle" or "copy number*" or "analytical valid*" or "genomics" or "next generation DNA sequencing" or "next generation sequencing" or "molecular technique*" or "molecular analysis" or "confirmatory" or "confirmation" or "follow-up test*" or "procedures" or "process*" or "MLPA" or "Multiplex ligation-dependent probe amplification" or "validation" or "diagnos*" or "standard operating procedures" or "standard operating protocol*" or "long read sequencing" or "copy number variation*" or "analysis" or "deletion" or "variant spectrum" or "mutation spectrum" or "molecular basis" or "positive predictive value" or "negative predictive value" or "test performance" or "sensitive*" or "specific*" or "prognosis" or "laboratory" or "best practice" or "primer" or "PCR" or "polymerase chain reaction" or "DDPCR" or "digital droplet polymerase chain reaction" or "SMN mutations" or "intragenic" or "genetic variation*" or "SMN1 deletion" or "exon 7" or "deletion" or "best practice" or "guidelines" or "data" or "multiple ligation dependent probe amplification" or "accura*" or "technical standards" or "approaches" or "characterization" or "false positive" or "false negative" or "true

positive” or “true negative” or “qPCR” or “quantitative polymerase chain reaction” or “melting curve” or “melt curve” or “time*” or “turnaround” or “assay” or “repeat” or “recall*” or “severity” or “repeat”)

12. MESH terms = =“diagnosis”[Mesh:NoExp] or "Diagnostic Errors"[MeSH Terms] or "Early Diagnosis"[MeSH Terms] or "Diagnostic Techniques and Procedures"[MeSH:noexp] or “clinical laboratory techniques”[MeSH Terms] or “Diagnostic Techniques, Neurological”[MeSH Terms] or "Prognosis"[MeSH Terms] or "prevention and control"[MeSH Subheading] or "Health Information Management"[MeSH Terms] or "Quality of Health Care"[MeSH:noexp] or “Data Collection”[MeSH Terms] or “evaluation studies as topic”[Mesh:noexp] or “data collection”[MeSH Terms] or “quality improvement”[MeSH Terms] or “sensitivity and specificity”[MeSH Terms] or “follow-up studies”[MeSH Terms] or “risk-factors”[MeSH Terms] or "Polymerase Chain Reaction"[MeSH Terms] or "Genotype"[MeSH Terms] or "Mutation"[MeSH Terms] or "Disease Progression"[MeSH Terms] or "Time Factors"[MeSH Terms] or "Laboratories"[MeSH Terms] or "Workflow"[MeSH Terms] or "Genetic Association Studies"[MeSH Terms] or "Inheritance Patterns"[MeSH Terms] or "Molecular Sequence Data"[MeSH Terms] or "Exons"[MeSH Terms] or "Sequence Analysis"[MeSH Terms] or “Genetic Linkage”[MeSH Terms]

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (”severity” or “Confirmation” or “modifier*” or “cycle” or “copy number*” or “analytical valid*” or “genomics” or “next generation DNA sequencing” or “next generation sequencing” or “molecular technique*” or “molecular analysis” or “confirmatory” or “confirmation” or “follow-up test*” or “procedures” or “process*” or “MLPA” or “Multiplex ligation-dependent probe amplification” or “validation” or “diagnos*” or “standard operating procedures” or “standard operating protocol*” or “long read sequencing” or “copy number variation*” or “analysis” or “deletion” or “variant spectrum” or “mutation spectrum” or “molecular basis” or “positive predictive value” or “negative predictive value” or “test performance” or “sensitive*” or “specific*” or “prognosis” or “laboratory” or “best practice” or “primer” or “PCR” or “polymerase chain reaction” or “DDPCR” or “digital droplet polymerase chain reaction” or “SMN mutations” or “intragenic” or “genetic variation*” or “SMN1

deletion” or “exon 7” or “deletion” or “best practice” or “guidelines” or “data” or “multiple ligation dependent probe amplification” or “accura*” or “technical standards” or “approaches” or “characterization” or “false positive” or “false negative” or “true positive” or “true negative” or “qPCR” or “quantitative polymerase chain reaction” or “melting curve” or “melt curve” or “time*” or “turnaround” or “assay” or “repeat” or “recall*” or “severity” or “repeat”).ti,ab,kw.

14. "prevention and control"/ or diagnosis/ or total quality management/ or "sensitivity and specificity"/ or health care delivery/ or genotype/ or (heterozygote/ or heterozygosity/) or (homozygosity/ or homozygote/) or gene deletion/ or early diagnosis/ or risk factor/ or disease exacerbation/ or time factor/ or preventive health service/ or clinical laboratory service/ or blood sampling/ or laboratory/ or clinical laboratory/ or hospital laboratory/ or laboratory technique/ or laboratory diagnosis/ or predictive value/ or workflow/ or reproducibility/ or molecular diagnosis/ or mutation/ or copy number variation/ or multiplex ligation dependent probe amplification/ or molecular genetics/ or recessive gene/ or whole exome sequencing/ or prognosis/ or exon/ or high throughput sequencing/ or follow up/ or dna sequencing/ or genetic polymorphism/ or genetic linkage/ or dna mutational analysis/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“severity” or “Confirmation” or “modifier*” or “cycle” or “copy number*” or “analytical valid*” or “genomics” or “next generation DNA sequencing” or “next generation sequencing” or “molecular technique*” or “molecular analysis” or “confirmatory” or “confirmation” or “follow-up test*” or “procedures” or “process*” or “MLPA” or “Multiplex ligation-dependent probe amplification” or “validation” or “diagnos*” or “standard operating procedures” or “standard operating protocol*” or “long read sequencing” or “copy number variation*” or “analysis” or “deletion” or “variant spectrum” or “mutation spectrum” or “molecular basis” or “positive predictive value” or “negative predictive value” or “test performance” or “sensitive*” or “specific*” or “prognosis” or “laboratory” or “best practice” or “primer” or “PCR” or “polymerase chain reaction” or “DDPCR” or “digital droplet polymerase chain reaction” or “SMN mutations” or “intragenic” or “genetic variation*” or “SMN1 deletion” or “exon 7” or “deletion” or “best practice” or “guidelines” or “data” or

"multiple ligation dependent probe amplification" or "accura*" or "technical standards" or "approaches" or "characterization" or "false positive" or "false negative" or "true positive" or "true negative" or "qPCR" or "quantitative polymerase chain reaction" or "melting curve" or "melt curve" or "time*" or "turnaround" or "assay" or "repeat" or "recall*" or "severity" or "repeat")

(5) AND (10) AND (15)

Systematic review 7:

What are the most appropriate methods to disclose screen positive SMA results to families?	
Population:	All newborns/infants and their families
Intervention:	Newborn screening for SMA
Outcomes:	Impact on family (well-being, quality of life)
	Impact on knowledge, understanding
	Informed consent
	Resources required
	Equity of access to information and support
	Impact on care sought/received
	Impact on time to diagnosis and treatment
	Impact on health outcomes for newborns/infants
	Impact on newborn (wellbeing, quality of life)
	Impact on decision making (for families)
	Impact on satisfaction with care
	Acceptability to families

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("disclos*" or "inform*" or "notif*" or "screen-positive" or "screen positive" or "support" or "result*" or "management" or "education" or "health information" or "adverse outcome*" or "referral*" or "parent*" or "caregiver*" or "follow up" or "mother*" or "Father*" or "follow-up" or "surveillance" or "psych*" or "clinical review*" or "available resource*" or "sharing information" or "deteriorat*" or

"disease onset" or "disease-onset" or "urgency" or "medical delay*" or "barriers" or "implementation" or "healthcare systems" or "integration" or "challenges" or "presymptomatic" or "pre-symptomatic" or "health literac*" or "care" or "informed consent" or "Attitude to Health" or "health planning" or "Acceptance" or "Time*" or "Education" or "distress" or "co-ordinat*" or "coordinat*" or "flagged" or "turnaround" or "duty to warn" or "recommendation*" or "relative*" or "implementation" or "ethic*" or "Policy" or "regulat*" or "framework" or "Guideline*" or "Family*" or "communicat*" or "Point-of-care" or "implementation" or "initial" or "HCP" or "personnel" or "social implication*" or "Healthcare professional" or "best practice" or "specialist review" or "medical review" or "clinical review" or "neuromuscular services" or "tertiary service*" or "rural" or "sociodemographic*" or "tele*" or "video* *" or "multidisciplinary team" or "urgency" or "expedi*" or "emergency" or "travel" or "gold standard*" or "gold-standard" or "risk" or "harm" or "bad news" or "trauma*" or "guidance" or "grief" or "advoca*" or "transparen*" or "perspective*" or "experience*" or "Indigenous" or "First nations" or "Torres" or "Aborigin*" or "culturally diverse" or "linguistically diverse" or "minorit*" or "ethnic*" or "language barrier*" or "equity" or "resource*" or "CALD" or "interpreter" or "guidance" or "instruction*" or "local" or "regional")

12. MESH terms = "Disclosure" or "access to information" or "communication barriers" or "Health communication" or "information dissemination" or "information literacy" or "preventive health services" or "Education, Medical" or "Parental notification" or "confidentiality" or "social support" or "community support" or "Cultural Diversity" or "counselling" or "referral and consultation" or "genetic counselling" or "Delivery of Health Care" or "attitude to health" or "Knowledge of Results, Psychological" or "public health surveillance" or "health education" or "medical history taking" or "information sources" or "Health Information Exchange" or "Professional-Patient Relations" or "Interdisciplinary communication" or "Time-to-Treatment" or "health planning" or "holistic health" or "practice guidelines as topic" or "time factors" or "Clinical Decision-Making" or "Evidence-Based Practice" or "patient care team" or "Early diagnosis" or "comprehensive health care" or "Health Services, Indigenous" or "Australian Aboriginal and Torres Strait Islander Peoples" or "Culturally Competent Care"

B. Embase

13. (“disclos*” or “inform*” or “notif*” or “screen-positive” or “screen positive” or “support” or “result*” or “management” or “education” or “health information” or “adverse outcome*” or “referral*” or “parent*” or “caregiver*” or “follow up” or “mother*” or “Father*” or “follow-up” or “surveillance” or “psych*” or “clinical review*” or “available resource*” or “sharing information” or “deteriorat*” or “disease onset” or “disease-onset” or “urgency” or “medical delay*” or “barriers” or “implementation” or “healthcare systems” or “integration” or “challenges” or “presymptomatic” or “pre-symptomatic” or “health literac*” or “care” or “informed consent” or “Attitude to Health” or “health planning” or “Acceptance” or “Time*” or “Education" or “distress” or “co-ordinat*” or “coordinat*” or “flagged” or “turnaround” or “duty to warn" or "recommendation*" or "relative*" or “implementation" or “ethic*” or “Policy” or “regulat*” or “framework” or “Guideline*” or “Family*” or “communicat*” or “Point-of-care” or “implementation” or “initial” or “HCP” or “personnel” or “social implication*” or “Healthcare professional” or “best practice” or “specialist review” or “medical review” or “clinical review” or “neuromuscular services” or “tertiary service*” or “rural” or “sociodemographic*” or “tele*”or “video* *” or “multidisciplinary team” or “urgency” or “expedi*” or “emergency” or “travel” or “gold standard*” or “gold-standard” or “risk” or “harm” or “bad news” or “trauma*” or “guidance” or “grief” or “advoca*” or “transparen*” or “perspective*” or “experience*” or “Indigenous” or “First nations” or “Torres” or “Aborigin*” or “culturally diverse” or “linguistically diverse” or “minorit*” or “ethnic*” or “language barrier*” or “equity” or “resource*” or “CALD” or “interpreter” or “guidance” or “instruction*” or “local” or “regional”).ti,ab,kw.

14. interpersonal communication/ or access to information/ or digital divide/ or information asymmetry/ or internet access/ or communication barrier/ or limited english proficiency/ or medical information/ or information dissemination/ or information gap/ or information literacy/ or preventive health service/ Or medical education/ or clinical education/ or parental notification/ or confidentiality/ or patient right/ or confidential information/ or cultural diversity/ or "diversity, equity and inclusion"/ or cultural identity/ or genetic counseling/ or genetic service/ or health care delivery/ or aftercare/ or age specific care/ or care bundle/ or community care/ or health care access/ or home care/ or hospital care/ or integrated health care system/ or patient triage/ or primary health care/ or secondary health care/ or self care/ or telehealth/ or tertiary health care/

or value-based care/ or public health surveillance/ or epidemiological surveillance/ or anamnesis/ or information source/ or counseling/ or anticipatory guidance/ or bereavement counseling/ or directive counseling/ or e-counseling/ or family counseling/ or genetic counseling/ or parent counseling/ or medical information system/ or health care management/ or interdisciplinary communication/ or interdisciplinary education/ or interdisciplinary research/ or time to treatment/ or health care personnel/ or health care planning/ or health care policy/ or health care practice/ or health care quality/ or practice guideline/ or disease management/ or health care quality/ or clinical handover/ or clinical pathway/ or clinical protocol/ or consensus development/ or good clinical practice/ or prescribing guideline/ or refusal to participate/ or time factor/ or clinical decision making/ or clinical decision support system/ or health care quality/ or health care concepts/ or benchmarking/ or health equity/ or practice guideline/ or value-based care/ or evidence based practice/ or patient care planning/ or patient care team/ or collaborative care team/ or early diagnosis/ or social support/ or social care/ or emotional support/ or family support/ or social support index/ or indigenous people/ or first nation/ or indigenous australian/ or communication barrier/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“disclos*” or “inform*” or “notif*” or “screen-positive” or “screen positive” or “support” or “result*” or “management” or “education” or “health information” or “adverse outcome*” or “referral*” or “parent*” or “caregiver*” or “follow up” or “mother*” or “Father*” or “follow-up” or “surveillance” or “psych*” or “clinical review*” or “available resource*” or “sharing information” or “deteriorat*” or “disease onset” or “disease-onset” or “urgency” or “medical delay*” or “barriers” or “implementation” or “healthcare systems” or “integration” or “challenges” or “presymptomatic” or “pre-symptomatic” or “health literac*” or “care” or “informed consent” or “Attitude to Health” or “health planning” or “Acceptance” or “Time*” or “Education” or “distress” or “co-ordinat*” or “coordinat*” or “flagged” or “turnaround” or “duty to warn" or "recommendation*" or "relative*" or “implementation" or “ethic*” or “Policy” or “regulat*” or “framework” or “Guideline*” or “Family*” or “communicat*” or “Point-of-care” or “implementation” or “initial” or “HCP” or “personnel” or “social implication*” or “Healthcare

professional" or "best practice" or "specialist review" or "medical review" or "clinical review" or "neuromuscular services" or "tertiary service*" or "rural" or "sociodemographic*" or "tele*" or "video* *" or "multidisciplinary team" or "urgency" or "expedi*" or "emergency" or "travel" or "gold standard*" or "gold-standard" or "risk" or "harm" or "bad news" or "trauma*" or "guidance" or "grief" or "advoca*" or "transparen*" or "perspective*" or "experience*" or "Indigenous" or "First nations" or "Torres" or "Aborigin*" or "culturally diverse" or "linguistically diverse" or "minorit*" or "ethnic*" or "language barrier*" or "equity" or "resource*" or "CALD" or "interpreter" or "guidance" or "instruction*" or "local" or "regional")

(5) AND (10) AND (15)

Systematic review 8:

What are the most appropriate clinical assessments (as part of the diagnostic evaluation) of a newborn who has screened positive for SMA?	
Population:	All newborns/infants
Intervention:	Newborn screening for SMA
Outcomes:	Impact on health outcomes (newborns, infants)
	Impact on time to diagnosis and treatment
	Impact on time to access, availability and
	quality of support and care (for newborn, for families)
	Resources required
	Equity of access to diagnosis and treatment
	Impact on decision making (for families, for clinicians)
	Acceptability to families

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("symptom*" or "assessment*" or "clinical" or "evaluation" or "examination" or "review" or "diagnos*" or "testing" or "confirmation" or "referral" or "care" or "neurophysiology" or "electrophysiology" or "time" or "timing" or "timeline*" or "benefits" or "follow-up" or "recommendations" or "testing" or "management" or "information" or "phenoty*" or "feeding" or "respiratory" or

"Breathing" or "quality of life" or "burden" or "detection" or "function*" or "therapy" or "surveillance" or "disease modifying" or "bulbar" or "motor" or "therapeutic window" or "molecular" or "protocols" or "standard*" or "practice" or "guideline*" or "report*" or "genetic*" or "prognosis" or "treatment" or "confirm" or "course" or "option*" or "neurological" or "CHOP*" or "Hammersmith" or "neurophysiological" or "blood" or "feeding" or "delivery" or "risk assessment" or "decision making" or "decision-making" or "clinician" or "referral" or "judgement" or "expertise" or "outcome*" or "framework*" or "consensus" or "recommendation*" or "responsibility*" or "administration" or "priority" or "procedure*" or "initiation" or "management" or "biomarkers")

12. MESH terms = "Symptom Assessment" or "Health Impact Assessment" or "Nutrition assessment" or "Time-to-treatment" or "Therapeutics" or "Health status" or "diagnosis" or "precision medicine" or "referral and consultation" or "consensus" or "Time" or "genetic counselling" or "severity of illness index" or "disease management" or "early medical intervention" or "electromyography" or "motor skills" or "guidelines" or "genetic therapy" or "neurologic examination" or "muscle strength" or "molecular diagnostic techniques" or "genetic association studies" or "genetic testing" or "referral and consultation" or "pediatricians*" or "Signs and Symptoms, Respiratory" or "Infant Nutritional Physiological Phenomena" or "Neurophysiology" or "Pathological Conditions, Signs and Symptoms" or "attitude of health personnel" or "disease progression" or "biomarkers" or "Physical Examination" or "Health Services Accessibility" or "evidence gaps" or "benchmarking" or "clinical competence" or "health care evaluation mechanisms" or "quality indicators, Health care" or "standard of care"

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. ("symptom*" or "assessment*" or "clinical" or "evaluation" or "examination" or "review" or "diagnos*" or "testing" or "confirmation" or "referral" or "care" or "neurophysiology" or "electrophysiology" or "time" or "timing" or "timeline*" or "benefits" or "follow-up" or "recommendations" or "testing" or "management" or "information" or "phenoty*" or "feeding" or "respiratory" or "Breathing" or "quality of life" or "burden" or "detection" or "function*" or "therapy" or "surveillance" or

"disease modifying" or "bulbar" or "motor" or "therapeutic window" or "molecular" or "protocols" or "standard*" or "practice" or "guideline*" or "report*" or "genetic*" or "prognosis" or "treatment" or "confirm" or "course" or "option*" or "neurological" or "CHOP*" or "Hammersmith" or "neurophysiological" or "blood" or "feeding" or "delivery" or "risk assessment" or "decision making" or "decision-making" or "clinician" or "referral" or "judgement" or "expertise" or "outcome*" or "framework*" or "consensus" or "recommendation*" or "responsibility*" or "administration" or "priority" or "procedure*" or "initiation" or "management" or "biomarkers").ti,ab,kw

14. symptom assessment/ or health impact assessment/ or nutritional assessment/ or "evaluation and follow up"/ or therapy/ or health status/ or physical mobility/ or health status indicator/ or diagnosis/ or diagnostic procedure/ or genotype phenotype correlation/ or phenotype/ or early childhood intervention/ or consensus/ or genetic counseling/ or "severity of illness index"/ or disease management/ or managed care/ or practice guideline/ or treatment outcome/ or early intervention/ or aftercare/ or electromyography/ or motor performance/ or physical performance/ or motor reaction time/ or practice guideline/ or clinical handover/ or clinical pathway/ or clinical protocol/ or good clinical practice/ or gene therapy/ or neurologic examination/ or molecular diagnosis/ or patient referral/ or consultation/ or respiratory care/ or infant nutrition/ or physiological process/ or neurophysiological monitoring/ or neurophysiology/ or disease exacerbation/ or biological marker/ or physical examination/ or health care access/ or primary care access/ or right to health/ or unmet medical need/ or clinical competence/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("symptom*" or "assessment*" or "clinical" or "evaluation" or "examination" or "review" or "diagnos*" or "testing" or "confirmation" or "referral" or "care" or "neurophysiology" or "electrophysiology" or "time" or "timing" or "timeline*" or "benefits" or "follow-up" or "recommendations" or "testing" or "management" or "information" or "phenoty*" or "feeding" or "respiratory" or "Breathing" or "quality of life" or "burden" or "detection" or "function*" or "therapy" or "surveillance" or "disease modifying" or "bulbar" or "motor" or "therapeutic window" or "molecular" or "protocols" or "standard*" or "practice" or "guideline*" or

"report*" or "genetic*" or "prognosis" or "treatment" or "confirm" or "course" or "option*" or "neurological" or "CHOP*" or "Hammersmith" or "neurophysiological" or "blood" or "feeding" or "delivery" or "risk assessment" or "decision making" or "decision-making" or "clinician" or "referral" or "judgement" or "expertise" or "outcome*" or "framework*" or "consensus" or "recommendation*" or "responsibility*" or "administration" or "priority" or "procedure*" or "initiation" or "management" or "biomarkers")

(5) AND (10) AND (15)

Systematic review 9:

What are the most appropriate educational materials/information a family should receive at time of diagnosis of a screen positive newborn	
Population:	All newborns/infants
Intervention:	Newborn screening for SMA
Outcomes:	Impact on family (well-being, quality of life)
	Impact on knowledge, understanding
	Informed consent
	Resources required
	Equity of access to information
	Impact on care sought/received
	Impact on time to diagnosis and treatment
	Impact on health outcomes for newborns/infants
	Impact on newborn (wellbeing, quality of life)
	Impact on decision making (for families)
	Impact on satisfaction with care
	Acceptability to families
	Culturally and linguistically competent information provision

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("educat*" or "psychoeducation*" or "support" or "advise" or "advice" or "advocac*" or "inform*" or "counsel*" or "knowledge" or "psychosocial"

or “quality of life” or “communication” or “resource*” or “CALD” or “cultural*” or “diverse” or “language barriers” or “health literacy” or “communication” or “translation” or “interpreter” or “indigenous” or “torres” or “aboriginal” or “first nation*)

12. MESH terms = “social support” “Early Intervention, Educational” or “referral and consultation” or “consensus” or “Time” or “genetic counselling” or “severity of illness index” or “disease management” or “early medical intervention” or “referral and consultation” or “health knowledge, attitudes, practice” or “Parents” or “disease progression” or “Health Services Accessibility” or "quality indicators, Health care" or "standards of care" or “Process Assessment, Health Care” or “communication barriers” or “Health communication” or “information dissemination” or “information literacy” or “confidentiality” or “social support” or “community support” or “Cultural Diversity” or “information sources” or “Health Information Exchange” or “Professional-Patient Relations” “health planning” or “holistic health” or “practice guidelines as topic” or “patient care team” or “comprehensive health care” or "Health Services, Indigenous" or "Australian Aboriginal and Torres Strait Islander Peoples" or “Culturally Competent Care”

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (“educat*” or “psychoeducation*” or “support” or “advise” or “advice” or “advocac*” or “inform*” or “counsel*” or “knowledge” or “psychosocial” or “quality of life” or “communication” or “resource*” or “CALD” or “cultural*” or “diverse” or “language barriers” or “health literacy” or “communication” or “translation” or “interpreter” or “indigenous” or “torres” or “aboriginal” or “first nation*”).ti,ab,kw.

14. indigenous people/ or first nation/ or indigenous australian/ or communication barrier/ or interpersonal communication/ or access to information/ or communication barrier/ or limited english proficiency/ or information dissemination/ or information literacy/ or preventive health service/ Or medical education/ or parental notification/ or confidentiality/ or patient right/ or confidential information/ or cultural diversity/ or "diversity, equity and inclusion"/ or cultural identity/ or self care/ or value-based care/ or attitude to health/ or attitude to illness/ or counseling/ or anticipatory guidance/ or parent counselling/ or psychological counseling/ or medical information system/ or

health care management/ or health care planning/ or health care practice/ or clinical pathway/ or education/ or education program/ or health education/ or clinical education/ or self care education/ or parenting education/ or patient education/ or medical education/ or health literacy/ or psychoeducation/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("educat*" or "psychoeducation*" or "support" or "advise" or "advice" or "advocac*" or "inform*" or "counsel*" or "knowledge" or "psychosocial" or "quality of life" or "communication" or "resource*" or "CALD" or "cultural*" or "diverse" or "language barriers" or "health literacy" or "communication" or "translation" or "interpreter" or "indigenous" or "torres" or "aboriginal" or "first nation*)

(5) AND (10) AND (15)

Systematic review 10:

What are the most appropriate methods to support families as their newborns undergo diagnostic evaluation of SMA (including CALD, Aboriginal, Torres Strait, Pacific Islander and Māori communities?

Population: All newborns/infants

Intervention: Newborn screening for SMA

Outcomes: Impact on family (well-being, quality of life)

Impact on knowledge, understanding

Informed consent

Resources required

Equity of access to support

Impact on care sought/received

Impact on time to diagnosis and treatment

Impact on health outcomes for newborns/infants

Impact on newborn (wellbeing, quality of life)

Impact on decision making (for families)

Impact on satisfaction with care

Acceptability to families

Impact on reproductive choices (for families)

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("Famil*" or "caregiver*" or "parent" or "mental health" or "mental well-being" or "mental well being" or "psychosocial" or "psychological" or "support" or "social work*" or "advoca*" or "peer-support" or "support" or "CALD" or "cultural*" or "diverse" or "language barriers" or "health literacy" or "communication" or "translation" or "interpreter" or "indigenous" or "torres" or "aboriginal" or "first nation*" or "evaluation" or "clinical" or "education*" or "information*" or "refer*" or "ethic*" or "evaluation" or "examination" or "review" or "surveillance" or "evaluation" or "pamphlet")

12. MESH terms = "Disclosure" or "access to information" or "communication barriers" or "Health communication" or "information dissemination" or "information literacy" or "preventive health services" or "Education, Medical" or "Parental notification" or "confidentiality" or "social support" or "community support" or "Cultural Diversity" or "counselling" or "referral and consultation" or "genetic counselling" or "models, educational" or "Delivery of Health Care" or "attitude to health" or "Knowledge of Results, Psychological" or "public health surveillance" or "health education" or "information sources" or "Health Information Exchange" or "Professional-Patient Relations" or "Interdisciplinary communication" or "Time-to-Treatment" or "health planning" or "holistic health" or "practice guidelines as topic" or "time factors" or "Clinical Decision-Making" or "Evidence-Based Practice" or "patient care team" or "comprehensive health care" or "Health Services, Indigenous" or "Australian Aboriginal and Torres Strait Islander Peoples" or "Culturally Competent Care"

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. ("Disclosure" or "access to information" or "communication barriers" or "Health communication" or "information dissemination" or "information literacy" or "preventive health services" or "Education, Medical" or "Parental notification" or "confidentiality" or "social support" or "community support" or "Cultural Diversity" or

"counselling" or "referral and consultation" or "genetic counselling" or "models, education" or "Delivery of Health Care" or "attitude to health" or "Knowledge of Results, Psychological" or "public health surveillance" or "health education" or "information sources" or "Health Information Exchange" or "Professional-Patient Relations" or "Interdisciplinary communication" or "Time-to-Treatment" or "health planning" or "holistic health" or "practice guidelines as topic" or "time factors" or "Clinical Decision-Making" or "Evidence-Based Practice" or "patient care team" or "comprehensive health care" or "Health Services, Indigenous" or "Australian Aboriginal and Torres Strait Islander Peoples" or "Culturally Competent Care").ti,ab,kw.

14. health equity/ or professional standard/ or social validity/ or clinical competence/ or protocol compliance/ or good clinical practice/ or consumer health information/ or health promotion/ or public health campaign/ or health education/ or childbirth education/ or parenting education/ or social support/ or community support/ or emotional support/ or family support/ or health care planning/ or medical information/ or attitude to health/ or early childhood intervention/ or decision making/ or family decision making/ or decision support system/ or clinical decision support system/ or clinical decision making/ or needs assessment/ or psychosocial intervention/ or preventive health service/ or patient care planning/ or time factor/ or caregiver/ or indigenous people/ or first nation/ or indigenous australian/ or communication barrier/ or interpersonal communication/ or access to information/ or communication barrier/ or limited english proficiency/ or information dissemination/ or information literacy/ or preventive health service/ Or medical education/ or parental notification/ or confidentiality/ or patient right/ or confidential information/ or cultural diversity/ or "diversity, equity and inclusion"/ or cultural identity/ or self care/ or value-based care/ or attitude to health/ or attitude to illness/ or counseling/ or anticipatory guidance/ or parent counselling/ or psychological counseling/ or medical information system/ or health care management/ or health care planning/ or health care practice/ or clinical pathway/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("Famil*" or "caregiver*" or "parent" or "mental health" or "mental well-being" or "mental well being" or "psychosocial" or "psychological" or "support" or "social work*" or "advoca*" or "peer-support" or "support" or "CALD" or "cultural*" or "diverse" or "language barriers" or "health literacy" or "communication" or "translation" or "interpreter" or "indigenous" or "torres" or "aboriginal" or "first nation*" or "evaluation" or "clinical" or "education*" or "information*" or "refer*" or "ethic*" or "evaluation" or "examination" or "review" or "surveillance" or "evaluation" or "pamphlet")

(5) AND (10) AND (15)

Systematic review 11:

What is the most appropriate post diagnostic assessments for a newborn/infant diagnosed with SMA through a newborn screening program?
Population: All newborns/infants
Intervention: Newborn screening for SMA
Outcomes: Resources required
Equity of access (to assessment, to treatment)
Impact on care sought/received
Impact on time to treatment
Impact on health outcomes for newborns/infants
Impact on newborn (wellbeing, quality of life)
Impact on decision making (for families, for clinicians)
Impact on satisfaction with care (for families)
Acceptability to families

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("communicat*" or "diagnos*" or "physician-patient relationship" or "physician patient relationship" or "care" or "well-being" or "well being" or "decision*" or "continuity" or "decision-making" or "famil*" or "parent*" or "mother*" or "father*" or "sibling*" or "caregiver*" or "teleconsult*" or "telehealth" or "teleconference" or "support*" or "psychosocial" or "discussion*" or "inform*" or

"consent" or "time" or "confirmation" or "holistic" or "disclosure" or "clinical assessment" or "therapeutic" or "education*" or "paediatric" or "pediatric" or "neurological exam*" or "local health" or "multidisciplinary" or "multi-disciplinary" or "interdisciplinary" or "specialist review" or "tertiary review" or "clinical review" or "clinical evaluation" or "respiratory" or "feeding" or "motor" or "treatment*" or "pre-symptomatic" or "presymptomatic" or "pre symptomatic" or "priority" or "surveillance" or "genetic*" or "case review" or "procedure*" or "quality improvement" or "QI" or "early discharge" or "health outcome*" or "variant" or "onset" or "clinical follow-up" or "clinical followup" or "clinical surveillance" or "health planning" or "interdisciplinary" or "referral" or "watchful waiting" "outcome assessment" or "neurogenetic*" or "urgency" or "delay" or "guideline*" or "asymptomatic" or "initiation" or "HINE" or "efficacy" or "equity" or "inequity" or "standard of care" or "SOC" or "prognostic" or "untreated" or "predictive" or "baseline motor" or "silent carrier" or "prognosis" or "CHOP-INTEND" or "CHOP" or "Hammersmith" or "EMG" or "electromyography" or "model of care" or "nerve conduction" or "neurophysiology" or "electrophysiology" or "CMAP" or "compound muscle action potential" or "quality of life" or "QOL" or "early intervention" or "genetic counsel*" or "cascade screen*")

12. MESH terms = "Evidence-Based Medicine" or "health plan implementation" or "Primary health care" or-"minority groups" or "Benchmarking" or "Caregivers" or "Family" or "Genetic counselling" or "Genetic markers" or "Molecular diagnostic techniques" or "inheritance patterns" or "Genetic testing" or "neurologic examination" or "Referral and consultation" or "Prognosis" or "Treatment outcome" or "Workflow" or "Symptom Assessment" or "Health Impact Assessment" or "Time-to-treatment" or "social support" or "precision medicine" or "Early Intervention, Educational" or "referral and consultation" or "genetic therapy" or "Signs and Symptoms, Respiratory" or "health knowledge, attitudes, practice" or "Parents" or "Physical Examination" or "Health Services Accessibility" or "health care evaluation mechanisms" or "Informed Consent" or "Disclosure" or "Health Communication" or "Telemedicine" or "Neurologic Examination" or "Decision Support Systems, Clinical" or "Clinical Decision-Making" or "Decision Making" or "Health Priorities" or "Watchful Waiting" or "Siblings" or "Health Resources" or "Health Services Administration" or "Health Information Management" or "Interdisciplinary Communication" or "Secondary Care

Centers" or "Tertiary Care Centers" or "Congenital, Hereditary, and Neonatal Diseases and Abnormalities" or "Signs and Symptoms, Respiratory" or "Infant Nutritional Physiological Phenomena" or "Quality-Adjusted Life Years"

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. ("communicat*" or "diagnos*" or "physician-patient relationship" or "physician patient relationship" or "care" or "well-being" or "well being" or "decision*" or "continuity" or "decision-making" or "famil*" or "parent*" or "mother*" or "father*" or "sibling*" or "caregiver*" or "teleconsult*" or "telehealth" or "teleconference" or "support*" or "psychosocial" or "discussion*" or "inform*" or "consent" or "time" or "confirmation" or "holistic" or "disclosure" or "clinical assessment" or "therapeutic" or "education*" or "paediatric" or "pediatric" or "neurological exam*" or "local health" or "multidisciplinary" or "multi-disciplinary" or "interdisciplinary" or "specialist review" or "tertiary review" or "clinical review" or "clinical evaluation" or "respiratory" or "feeding" or "motor" or "treatment*" or "pre-symptomatic" or "presymptomatic" or "pre symptomatic" or "priority" or "surveillance" or "genetic*" or "case review" or "procedure*" or "quality improvement" or "QI" or "early discharge" or "health outcome*" or "variant" or "onset" or "clinical follow-up" or "clinical followup" or "clinical surveillance" or "health planning" or "interdisciplinary" or "referral" or "watchful waiting" "outcome assessment" or "neurogenetic*" or "urgency" or "delay" or "guideline*" or "asymptomatic" or "initiation" or "HINE" or "efficacy" or "equity" or "inequity" or "standard of care" or "SOC" or "prognostic" or "untreated" or "predictive" or "baseline motor" or "silent carrier" or "prognosis" or "CHOP-INTEND" or "CHOP" or "Hammersmith" or "EMG" or "electromyography" or "model of care" or "nerve conduction" or "neurophysiology" or "electrophysiology" or "CMAP" or "compound muscle action potential" or "quality of life" or "QOL" or "early intervention" or "genetic counsel*" or "cascade screen*").ti,ab,kw.

14. symptom assessment/ or health equity/ or health impact assessment/ or nutritional assessment/ or "evaluation and follow up"/ or time to treatment/ or therapy/ or health services research/ or health status/ or physical mobility/ or health status indicator/ or diagnosis/ or diagnostic procedure/ or genotype phenotype correlation/ or phenotype/ or social support/ or community support/ or emotional support/ or family support/ or

personalized medicine/ or early childhood intervention/ or consensus/ or time factor/ or genetic counseling/ or "severity of illness index"/ or disease management/ or managed care/ or practice guideline/ or "quality of life"/ or treatment outcome/ or early intervention/ or aftercare/ or motor performance/ or physical performance/ or motor reaction time/ or practice guideline/ or clinical handover/ or clinical pathway/ or clinical protocol/ or good clinical practice/ or neurologic examination/ or molecular diagnosis/ or genetic association study/ or genetic screening/ or patient referral/ or consultation/ or pediatrician/ or delayed diagnosis/ or respiratory care/ or infant nutrition/ or physiological process/ or neurophysiological monitoring/ or neurophysiology/ or attitude to health/ or parent/ or father/ or mother/ or disease exacerbation/ or disease course/ or physical examination /or health care access/ or eligibility/ or mental health care access/ or primary care access/ or right to health/ or unmet medical need/ or benchmarking/ or clinical competence/ or health care quality/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“communicat*” or “diagnos*” or “physician-patient relationship” or “physician patient relationship” or “care” or “well-being” or “well being” or “decision*” or “continuity” or “decision-making” or “famil*” or “parent*” or “mother*” or “father*” or “sibling*” or “caregiver*” or “teleconsult*” or “telehealth” or “teleconference” or “support*” or “psychosocial” or “discussion*” or “inform*” or “consent” or “time” or “confirmation” or “holistic” or “disclosure” or “clinical assessment” or “therapeutic” or “education*” or “paediatric” or “pediatric” or “neurological exam*” or “local health” or “multidisciplinary” or “multi-disciplinary” or “interdisciplinary” or “specialist review” or “tertiary review” or “clinical review” or “clinical evaluation” or “respiratory” or “feeding” or “motor” or “treatment*” or “pre-symptomatic” or “presymptomatic” or “pre symptomatic” or “priority” or “surveillance” or “genetic*” or “case review” or “procedure*” or “quality improvement” or “QI” or “early discharge” or “health outcome*” or “variant” or “onset” or “clinical follow-up” or “clinical followup” or “clinical surveillance” or “health planning” or “interdisciplinary” or “referral” or “watchful waiting” “outcome assessment” or “neurogenetic*” or “urgency” or “delay” or “guideline*” or “asymptomatic” or “initiation” or “HINE” or “efficacy” or “equity” or “inequity” or

"standard of care" or "SOC" or "prognostic" or "untreated" or "predictive" or "baseline motor" or "silent carrier" or "prognosis" or "CHOP-INTEND" or "CHOP" or "Hammersmith" or "EMG" or "electromyography" or "model of care" or "nerve conduction" or "neurophysiology" or "electrophysiology" or "CMAP" or "compound muscle action potential" or "quality of life" or "QOL" or "early intervention" or "genetic counsel*" or "cascade screen*")

(5) AND (10) AND (15)

Systematic review 12:

What are the most appropriate treatments for children diagnosed with SMA through newborn screening programs?	
Population:	All newborns/infants
Intervention:	Newborn screening for SMA
Outcomes:	Resources required
	Equity of access (to treatment and post treatment care)
	Impact on care sought/received
	Impact on time to treatment
	Impact on modality of treatment
	Impact on health outcomes for newborns/infants
	Impact on newborn (wellbeing, quality of life)
	Impact on decision making (for families, for clinicians)
	Impact on satisfaction with care (for families, for clinicians)
	Acceptability to families
	Impact on harms/risks to newborns/infants

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = ("Parent*" or "Education*" or "support*" or "Advise" or "information" or "recommendation*" or "health planning" or "Preventive Health Services" or "Communication" or "Health Knowledge" or "Mother*" or "Father*" or "Caregiver*" or "Choice Behav*" or "Pamphlet*" or "Decision-Making" or "Decision Making" or "Culturally Competent Care" or "Health Priorit*" or "Needs Assessment*"

or "Value Based Health Care" or “empower” or “health care decision*” or “values” or “moral*” or “ethic*” or “diagnos*” or “degenerative” or “cultur*” or “continuity” or “famil*” or “teleconsult*” or “telehealth” or “teleconference” or “psychosocial” or “discussion*” or “inform*” or “consent” or “time” or “confirmation” or “holistic” or “disclosure” or “clinical assessment” or “therapeutic” or “paediatric” or “pediatric” or “neurology*” or “local health” or “multidisciplinary” or “multi-disciplinary” or “interdisciplinary” or “co-ordinat*” or “coordinat*” or “clinical review” or “motor” or “treatment*” or “pre-symptomatic” or “presymptomatic” or “pre symptomatic” or “priority” or “surveillance” or “genetic*” or “case review” or “procedure*” or “quality improvement” or “QI” or “follow-up” or “follow up” or “detection error” or “health outcome*” or “first tier” or “second tier” or “first-tier” or “second-tier” or “variant” or “onset” or “clinical validity” or “interdisciplinary” or “referral” or “Evidence informed” or “outcome assessment” or “neurogenetic*” or “urgency” or “delay” or “Nusinersen” or “Onasemnogene” or “Risdiplam” or “gene therapy” or “asymptomatic” or “initiation” or “efficacy” or “equity” or “inequity” or “standard of care” or “SOC” or “prognostic” or “predictive” or “milestone*” or “DMT” or “disease-modifying” or “disease modifying” or “baseline motor” or “disease duration” or “genetic therap*” or “antisense oligo*” or “Zolgensma” or “risdiplam” or “nusinersen” or “advanced therap*” or “prognosis” or “Early diagnosis” or “Time Factor*” “Integrated Health Care System*” or “Best Practice*” or “Complementary Therap*” or “Patient Care” or “Psychological Technique*” or “Quality of Health Care” or “standards of care” or “informed consent” or “expectation” or “attitude*” or “opinion*” or “deliberation” or “accountability” or “benefit*” or “distress” or “acceptab*” or “survey*” or “opting” or “comprehension” or “risk*” or “long term” or “long-term”)

12. MESH terms = “Quality Indicators, Health Care" or "Clinical Competence” or "Outcome and Process Assessment, Health Care" or "Guidelines as Topic" or "Standard of Care" or “Health Care Quality, Access, and Evaluation” or "Consumer Health Information" or "Health Promotion" or "Patient Education as Topic" or “social support” or “health planning” or “health communication” or "Educational Status" or "Early Intervention, Educational" or "Choice Behaviour" or “Complementary Therapies” or “Patient Care Bundles” or “Decision Support Techniques” or “Clinical Decision-Making” or “Health Priorities” or “needs Assessment” or “Psychosocial Intervention” or “Preventive Health Services” or “Patient care planning” or “Interdisciplinary communication” or “Early diagnosis” or “Time Factors” or “Health communication” or

”Parents” or “Caregivers” **or** “Evidence-Based Medicine” or “health plan implementation” or “Primary health care” or “minority groups” or “Benchmarking” or “Family” or “Genetic counselling” or “Molecular diagnostic techniques” or “Genetic testing” or “neurologic examination” or “Referral and consultation” or “Prognosis” or “Treatment outcome” or “Workflow” or “Symptom Assessment” or “Health Impact Assessment” or “Time-to-treatment” or “social support” or “precision medicine” or “Early Intervention, Educational” or “referral and consultation” or “genetic therapy” or “Signs and Symptoms, Respiratory” or “health knowledge, attitudes, practice” or “Physical Examination” or “Health Services Accessibility” or “health care evaluation mechanisms” or “Informed Consent” or “Disclosure” or “Health Communication” or “Telemedicine” or “Neurologic Examination” or “Decision Support Systems, Clinical” or “Clinical Decision-Making” or “Decision Making” or “Health Priorities” or “Watchful Waiting” or “Health Resources” or “Secondary Care Centers” or “Tertiary Care Centers” or “Immunologic Surveillance” or “Congenital, Hereditary, and Neonatal Diseases and Abnormalities” or “Infant Nutritional Physiological Phenomena” or “Pathological Conditions, Signs and Symptoms”

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. (”Parent*” or “Education*” or “support*” or “Advise” or “information” or “recommendation*” or “health planning” or “Preventive Health Services” or “Communication” or “Health Knowledge” or "Mother*" or “Father*” or “Caregiver*" or "Choice Behav*" or "Pamphlet*” or “Decision-Making” or “Decision Making” or “Culturally Competent Care” or “Health Priorit*” or “Needs Assessment*” or "Value Based Health Care" or “empower” or “health care decision*” or “values” or “moral*” or “ethic*” or “diagnos*” or “degenerative” or “cultur*” or “continuity” or “famil*” or “teleconsult*” or “telehealth” or “teleconference” or “psychosocial” or “discussion*” or “inform*” or “consent” or “time” or “confirmation” or “holistic” or “disclosure” or “clinical assessment” or “therapeutic” or “paediatric” or “pediatric” or “neurology*” or “local health” or “multidisciplinary” or “multi-disciplinary” or “interdisciplinary” or “co-ordinat*” or “coordinat*” or “clinical review” or “motor” or “treatment*” or “pre-symptomatic” or “presymptomatic” or “pre symptomatic” or “priority” or “surveillance” or “genetic*” or “case review” or “procedure*” or “quality improvement” or “QI” or “follow-up” or “follow up” or “detection error” or “health

outcome*" or "first tier" or "second tier" or "first-tier" or "second-tier" or "variant" or "onset" or "clinical validity" or "interdisciplinary" or "referral" or "Evidence informed" or "outcome assessment" or "neurogenetic*" or "urgency" or "delay" or "Nusinersen" or "Onasemnogene" or "Risdiplam" or "gene therapy" or "asymptomatic" or "initiation" or "efficacy" or "equity" or "inequity" or "standard of care" or "SOC" or "prognostic" or "predictive" or "milestone*" or "DMT" or "disease-modifying" or "disease modifying" or "baseline motor" or "disease duration" or "genetic therap*" or "antisense oligo*" or "Zolgensma" or "risdiplam" or "nusinersen" or "advanced therap*" or "prognosis" or "Early diagnosis" or "Time Factor*" "Integrated Health Care System*" or "Best Practice*" or "Complementary Therap*" or "Patient Care" or "Psychological Technique*" or "Quality of Health Care" or "standards of care" or "informed consent" or "expectation" or "attitude*" or "opinion*" or "deliberation" or "accountability" or "benefit*" or "distress" or "acceptab*" or "survey*" or "opting" or "comprehension" or "risk*" or "long term" or "long-term").ti,ab,kw.

14. health care quality/ or health equity/ or clinical competence/ or protocol compliance/ or good clinical practice/ or professional standard/ or "scope of practice"/ or consumer health information/ or health promotion/ or health education/ or parenting education/ or social support/ or community support/ or family support/ or health care planning/ or medical information/ or early childhood intervention/ or decision making/ or family decision making/ or patient decision making/ or perinatal care/ or decision support system/ or clinical decision support system/ or clinical decision making/ or needs assessment/ or psychosocial intervention/ or preventive health service/ or patient care planning/ or interdisciplinary communication/ or early diagnosis/ or time factor/ or caregiver/ or evidence based medicine/ or health care personnel/ or resource limited setting/ or primary health care/ or primary medical care/ or minority group/ or indigenous people/ or indigenous australian/ or Benchmarking/ or family/ or parenthood/ or genetic counseling/ or genetic service/ or molecular diagnosis/ or severity of illness index/ or disease severity assessment/ or health status indicator/ or neurologic examination/ or neuromonitoring/ or neuropsychological assessment/ or patient referral/ or prognosis/ or "prediction and forecasting"/ or treatment outcome/ or clinical outcome/ or clinical significance/ or critical care outcome/ or disease worsening with drug treatment/ or workflow/ or Symptom Assessment/ or Health Impact Assessment/ or time to treatment/ or emotional support/ or personalized medicine/ or

patient referral/ or consultation/ or teleconsultation/ or telemedicine/ or gene therapy/ or respiratory care/ or respiratory care practice/ or parent/ or father/ or mother/ or Physical Examination/ or health care access/ or primary care access/ or unmet medical need/ or clinical effectiveness/ or clinical indicator/ or Informed Consent/ or ethical decision making/ or medical decision making/ or Watchful Waiting/ or secondary care center/ or secondary health care/ or Tertiary Care Center/ or Immunologic Surveillance/ or infant nutrition/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY (“Parent*” or “Education*” or “support*” or “Advise” or “information” or “recommendation*” or “health planning” or “Preventive Health Services” or “Communication” or “Health Knowledge” or "Mother*" or “Father*” or “Caregiver*" or "Choice Behav*" or "Pamphlet*” or “Decision-Making” or “Decision Making” or “Culturally Competent Care” or “Health Priorit*” or “Needs Assessment*” or "Value Based Health Care" or “empower” or “health care decision*” or “values” or “moral*” or “ethic*” or “diagnos*” or “degenerative” or “cultur*” or “continuity” or “famil*” or “teleconsult*” or “telehealth” or “teleconference” or “psychosocial” or “discussion*” or “inform*” or “consent” or “time” or “confirmation” or “holistic” or “disclosure” or “clinical assessment” or “therapeutic” or “paediatric” or “pediatric” or “neurology*” or “local health” or “multidisciplinary” or “multi-disciplinary” or “interdisciplinary” or “co-ordinat*” or “coordinat*” or “clinical review” or “motor” or “treatment*” or “pre-symptomatic” or “presymptomatic” or “pre symptomatic” or “priority” or “surveillance” or “genetic*” or “case review” or “procedure*” or “quality improvement” or “QI” or “follow-up” or “follow up” or “detection error” or “health outcome*” or “first tier” or “second tier” or “first-tier” or “second-tier” or “variant” or “onset” or “clinical validity” or “interdisciplinary” or “referral” or “Evidence informed” or “outcome assessment” or “neurogenetic*” or “urgency” or “delay” or “Nusinersen” or “Onasemnogene” or “Risdiplam” or “gene therapy” or “asymptomatic” or “initiation” or “efficacy” or “equity” or “inequity” or “standard of care” or “SOC” or “prognostic” or “predictive” or “milestone*” or “DMT” or “disease-modifying” or “disease modifying” or “baseline motor” or “disease duration” or “genetic therap*” or “antisense oligo*” or “Zolgensma” or “risdiplam” or “nusinersen”

or “advanced therap*” or “prognosis” or “Early diagnosis” or “Time Factor*” “Integrated Health Care System*” or “Best Practice*” or “Complementary Therap*” or “Patient Care” or “Psychological Technique*” or “Quality of Health Care” or “standards of care” or “informed consent” or “expectation” or “attitude*” or “opinion*” or “deliberation” or “accountability” or “benefit*” or “distress” or “acceptab*” or “survey*” or “opting” or “comprehension” or “risk*” or “long term” or “long-term”)

(5) AND (10) AND (15)

Systematic review 13:

What are the most appropriate methods of managing uncertain, false positive or false negative screening results?	
Population:	All newborns/infants and their families
Intervention:	Newborn screening for SMA
Outcomes:	Resources required
	Accuracy of tests
	Equity of access (to diagnosis, to support, to information)
	Impact on care sought/received
	Impact on time to treatment
	Impact on health outcomes for newborns/infants
	Impact on well-being and quality of life (for newborn, for families)
	Impact on decision making (for families)
	Impact on satisfaction with care (for families)
	Acceptability to families
	Impact on knowledge (for families)

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = (“communicat*” or “diagnos*” or “false positive” or “diagnostic*” or “famil*” or “parent*” or “caregiver*” or “implication” or “discussion” or “certain*” or “uncertain*” or “review” or “support*” or “inform*” or “disclosure” or “clinical assessment” or “therapeutic” or “education*” or “paediatric” or “pediatric” or “multidisciplin*” or “interdisciplinary” or “referral” or “geneticist” or “undetected” or

"neurologist" or "false positive" or "error" or "standard of care" or "SOC" or "prognosis")

12. MESH terms = "Evidence-Based Medicine" or "Primary health care" or "Caregivers" or "Family" or "Genetic counselling" or "Genetic markers" or "Molecular diagnostic techniques" or "Referral and consultation" or "Prognosis" or "Workflow" or "Health Impact Assessment" or "social support" or "referral and consultation" or "health knowledge, attitudes, practice" or "Parents" or "Physical Examination" or "health care evaluation mechanisms" or "Disclosure" or "Health Communication" or "Clinical Decision-Making" or "Decision Making" or "Watchful Waiting" or "Interdisciplinary Communication" or "Pathological Conditions, Signs and Symptoms"

B. Embase

13. ("communicat*" or "diagnos*" or "false positive" or "diagnostic*" or "famil*" or "parent*" or "caregiver*" or "implication" or "discussion" or "certain*" or "uncertain*" or "review" or "support*" or "inform*" or "disclosure" or "clinical assessment" or "therapeutic" or "education*" or "paediatric" or "pediatric" or "multidisciplin*" or "interdisciplinary" or "referral" or "geneticist" or "undetected" or "neurologist" or "false positive" or "error" or "standard of care" or "SOC" or "prognosis").ti,ab,kw.

14. evidence based medicine/ or health care personnel/ or health care planning/ or Benchmarking/ or family/ or family decision making/ or family service/ or parenthood/ or caregiver/ or genetic counseling/ or genetic service/ or genetic marker/ or health status indicator/ or patient referral/ or prognosis/ or "prediction and forecasting"/ or clinical significance/ or workflow/ or Symptom Assessment/ or Health Impact Assessment/ or emotional support/ or family support/ or patient referral/ or consultation/ or parent/ or father/ or mother/ or health care access/ or clinical effectiveness/ or clinical indicator/ or health equity/ or medical decision making/ or health care planning/ or Watchful Waiting/ or Interdisciplinary Communication/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("communicat*" or "diagnos*" or "false positive" or "diagnostic*" or "famil*" or "parent*" or "caregiver*" or "implication" or "discussion" or "certain*"

or “uncertain*” or “review” or “support*” or “inform*” or “disclosure” or “clinical assessment” or “therapeutic” or “education*” or “paediatric” or “pediatric” or “multidisciplin*” or “interdisciplinary” or “referral” or “geneticist” or “undetected” or “neurologist” or “false positive” or “error” or “standard of care” or “SOC” or “prognosis”**)**

(5) AND (10) AND (15)

Systematic review 14:

For newborns diagnosed with SMA through newborn screening programs, what is the appropriate way of organising services to provide child and family centred, multidisciplinary assessment and management?
Population: All newborns/infants and their families
Intervention: Newborn screening for SMA
Outcomes: Resources required
Equity of access (to diagnosis, to support, to information)
for (newborns, for families)
Impact on care sought/received
Impact on time to treatment
Impact on health outcomes for newborns/infants
Impact on well-being and quality of life (for newborn, for families)
Impact on decision making (for families, for clinicians)
Impact on satisfaction with care (for families, for clinicians)
Acceptability to families
Impact on knowledge (for families)
Health system coordination

Population and Intervention the same as Systematic review 1

Outcomes

A. Pubmed

11. Title / abstracts = (“integrat*” or “famil*” or “parent*” or “multidisciplinary” or “care management” or “agreement” or “co-ordinat*” or “coordinat*” or “diagnosis” or “service provider*” or “contact” or “protocol*” or “transpot*” or “AAV-9” or “titres” or “gene therapy” or “jurisdiction*” or “communication” or “review*” or “referral*” or

"standard of care" or "SOC" or "holistic" or "planning" or "diagnosed" or "referral" or "treatment" or "polic*" or "procedure*" or "access")

12. MESH terms = "Evidence-Based Medicine" or "Primary health care" or "Caregivers" or "Family" or "Referral and consultation" or "Prognosis" or "Workflow" or "Health Impact Assessment" or "referral and consultation" or "health knowledge, attitudes, practice" or "Parents" or "Physical Examination" or "health care evaluation mechanisms" or "Disclosure" or "Health Communication" or "Clinical Decision-Making" or "Decision Making" or "Watchful Waiting" or "Interdisciplinary Communication" or "Pathological Conditions, Signs and Symptoms"

(1 OR 2) AND (6 OR 7) AND (11 OR 12)

B. Embase

13. ("integrat*" or "famil*" or "parent*" or "multidisciplinary" or "care management" or "agreement" or "co-ordinator" or "diagnosis" or "service provider*" or "contact" or "protocol" or "transpot*" or "AAV-9" or "titres" or "gene therapy" or "jurisdiction*" or "communication" or "review" or "referral" or "standard of care" or "SOC" or "holistic" or "polic*" or "procedure*" or "access").ti,ab,kw.

14. evidence based medicine/ or health care personnel/ or health care planning/ or Benchmarking/ or family/ or family decision making/ or family service/ or parenthood/ or caregiver/ or genetic counseling/ or genetic service/ or health status indicator/ or patient referral/ or prognosis/ or "prediction and forecasting"/ or clinical significance/ or workflow/ or Symptom Assessment/ or Health Impact Assessment/ or emotional support/ or family support/ or patient referral/ or consultation/ or parent/ or father/ or mother/ or health care access/ or clinical effectiveness/ or clinical indicator/ or health equity/ or medical decision making/ or health care planning/ or Watchful Waiting/ or Interdisciplinary Communication/

(3 OR 4) AND (8 OR 9) AND (13 or 14)

C. Scopus

15. TITLE-ABS-KEY ("integrat*" or "famil*" or "parent*" or "multidisciplinary" or "care management" or "agreement" or "co-ordinat*" or "coordinat*" or "diagnosis" or "service provider*" or "contact" or "protocol*" or "transpot*" or "AAV-9" or "titres"

or “gene therapy” or “jurisdiction*” or “communication” or “review*” or “referral*” or “standard of care” or “SOC” or “holistic” or “planning” or “diagnosed” or “referral” or “treatment” or “polic*” or “procedure*” or “access”

(5) AND (10) AND (15)

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 (DK, CM).

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 4.). 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 reviewed 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 (MF) was consulted to enable consensus to be reached. A second reviewer (CM) 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 4. 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 (DK and CM) 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.

Data analysis and synthesis

The heterogeneity of the other questions formed and evidence generated precluded statistical (meta-analysis) synthesis methods and alternative, non-statistical methods were used to describe and explore the evidence base generated by the systematic review process in a structured and systematic manner.(30, 34) 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. (35) 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. 2006 were followed,(35) and presented in evidence summary tables (*Evidence summaries of individual studies page 188*).

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.

Assessment and appraisal - The literature identified in the systematic searches were read and evaluated by two reviewers (CM and DK). The preliminary synthesis consisted of collating descriptive characteristics of the studies in a table (study design, level of evidence, quality assessment of the study (i.e. consideration of factors of relevance of outcomes to the research question, appropriateness of study design to the research question, study methodology and if these addressed important sources of bias, study being performed to original protocol, study hypothesis stated, statistical analyses performed correctly, data sufficient to justify conclusions and presence of conflicts of interests). This process facilitated a descriptive synthesis of data, allowing the reviewer 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.

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.

Results of the Systematic Reviews

This search strategy yielded 2518 articles, theses and reports, with 1119 duplicates found across databases, resulting in 1119 articles once duplications were removed (Figure 3). In total 107 articles met all eligibility criteria, passing the first and second rounds of data extraction and were available for analysis.

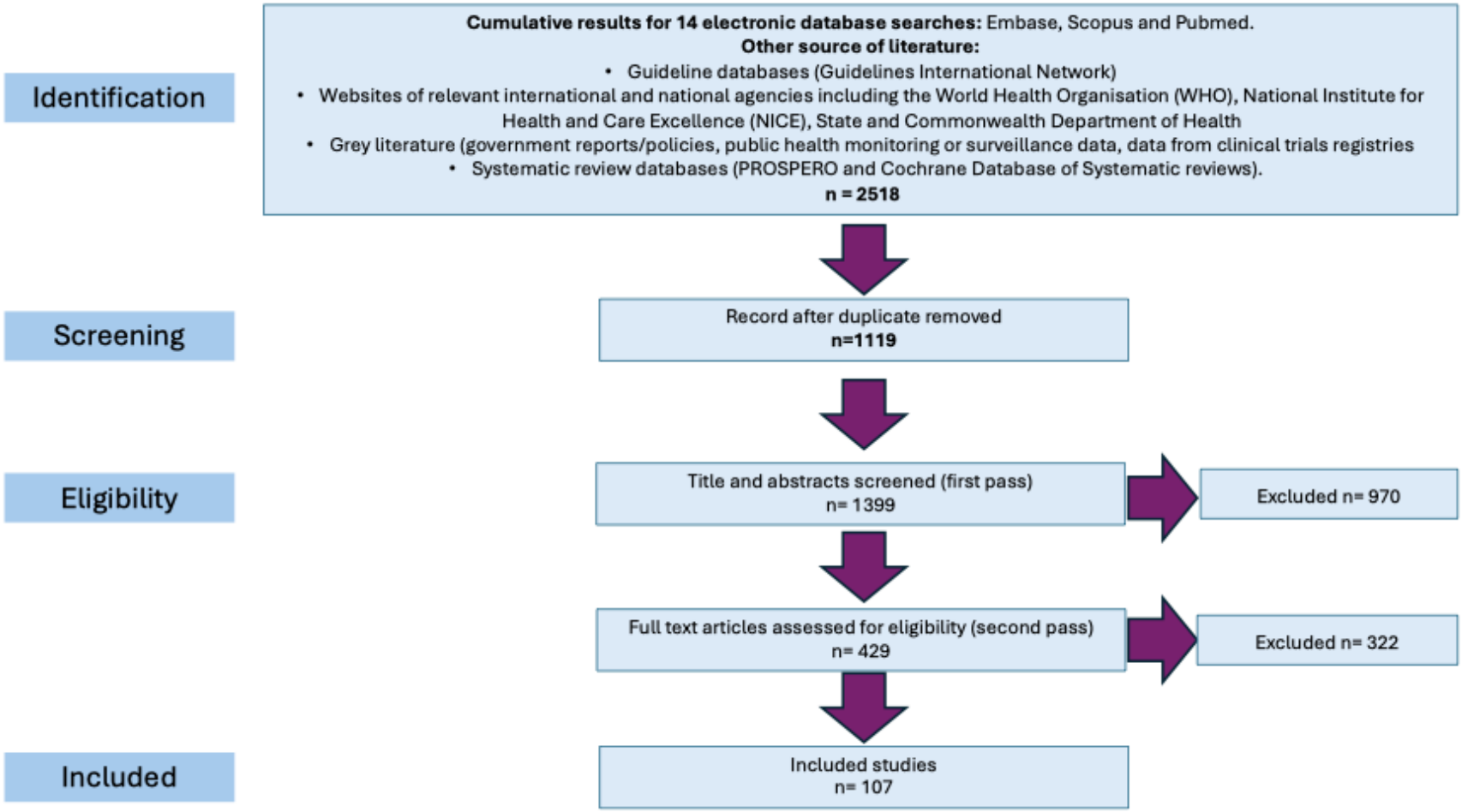

Figure 3. A Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram to depict the screening process for the systematic literature review

Assessment of the certainty of evidence

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. A summary of evidence table was presented for each of the outcomes. 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. Of note, when using GRADE for observational studies, studies start at low certainty of evidence.(30) Due to the selection and prioritisation of outcomes for the Guideline, no studies from the systematic review determined diagnostic test accuracy or prognostic factors (these studies start with a high grade of certainty aligned with GRADE).

Forming evidence-based recommendations

The taxonomy and framework used to formulate recommendations in the Guideline adhered to the definitions and standards as per GRADE.(16, 17, 22, 36) Evidence-based recommendations, were formed if an actionable statement could be derived using the systematic review of evidence, generated through questions within the above methodology.

The Organising Committee used an iterative process, using evidence to decision (EtD) framework to move from evidence to forming recommendations (16, 20). The Organising Committee checked preliminary evidence-based recommendations for any misalignment or conflict against the following sources:

- Evidence emerging from the systematic review.
- Other relevant research (standards of care guidelines for SMA, Clinical and Laboratory Standards Institute (CLSI) terminology databases, National Newborn Screening Framework, U.S Health Resources and Services Administration,

Advisory Committee on Heritable Disorders in Newborns and Children.(24, 28, 37, 38)

- 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).(39-41)
- Conventions (e.g., United Nations Convention on the Rights of the Child, 1989).(42)

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 finalisation of the preliminary evidence-based recommendations.

Implicit in this process was the fact that not all evidence collected during the research activities converged in such a way as to warrant an evidence-based recommendation. 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.

Grading the direction and strength of **evidence-based** recommendations

The GDG considered factors that influenced the strength of an evidence-based recommendation, balancing the undesirable and desirable consequences of the intervention across seven domains, including priority of the problem, benefits and harms of the proposed intervention, certainty of the body of evidence, values and preferences to end users, resource and cost effectiveness implications and health equity, acceptability and feasibility factors. (38) These were summarised in Evidence to Decision tables for each evidence-based Recommendation (*Supporting evidence: Evidence to Decision Tables p144*).

The evidence and justification provided in each domain were considered by the SAC through a summary of decision judgement. Letters (A to D) were assigned to the recommendation and indicative of the strength of the body of evidence that underpinned the Recommendation (Table 5.).(43)

Table 5. Grading the strength of evidence-based recommendations within the Guideline(43)

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.

Stakeholder consultation activities: the rationale for gathering more data

Whilst the gathering of evidence through the systematic review process was essential to form and grade evidence-based recommendations, the GDG also identified outcomes aligned with relevant clinical practice, which were considered impactful to the community, but precluded evidence-based judgments due to a lack of empirical evidence.

Here, consensus-based recommendations i.e. actionable statements drawing on evidence from the research literature, combined with evidence collected through a process of stakeholder consultation (*Systematic observation form and Delphi process evidence*) were formulated (Table 6.).

Consensus and evidence-based recommendations were defined as key elements of practice to be followed to deliver evidence-based supports.(19, 22, 36) 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 6. Taxonomy and framework for Recommendations used in the Guideline aligning with GRADE.(16, 17, 22, 36)

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.

Stakeholder consultation activities

Systematic observation form evidence

The systematic synthesis of expert evidence is valued in rare disease research, where a shortage of consistent scholarly literature is a common challenge. (10) 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.(13) Of relevance, collating expert evidence in a systematic and structured manner is integral to minimising interpretation of the extent to which the evidence supports (or does not support) recommendations.

Aim

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

Research question

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

Study Design and participants

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

Methods

SAC members completed an online survey, specifically designed to collect direct experiences and observations. For each defined intervention, an estimate of the magnitude of effect for an outcome was measured using 5-point Likert scale (“Large benefit”, “Small benefit”,

"Unsure", "Small harm", "Large Harm"). SAC members also provided their opinions and experiences through free responses. The emphasis was to collect direct experiential data useful for judgement, rather than "second hand" expert opinions based on low quality publications or common practice.(19, 21)

Data analysis

The results of the systematic observation were analysed using a convergent parallel design.(44) 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

The results are denoted in tabular format *(Systematic observation form results, p228)*. The results of this study were presented to the GDG through email, as part of the evidence base to form consensus-based recommendations.

Stakeholder consultation activities

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 and form consensus-based recommendations.

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 (Appendix 2) 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 and 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.

Results

The first Delphi round consisted of 151 items. 114 items met consensus, 11 items were defined as near consensus and refined and reworded after discussion with the GDG, for inclusion in the second Delphi round. Six no consensus items were considered important outcomes within a clinical context and were reworded for inclusion in the second Delphi round. The second Delphi round consisted of 19 items (17 near and no consensus items from the first round which were reworded and two items that reached first round consensus but was discussed by the GDG and wording refined. Of these, 13 items met consensus, and 2 items met near consensus. The latter were considered of clinical relevance by the Co-Leads

and Oversight Committee and included as Good Practice Points after rewording for jurisdictional variations in implementational feasibility.

Evidence synthesis and forming consensus-based recommendations

Evidence generated through the systematic review (scholarly literature that could not generate answers to the research questions using a PICO format) 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 (*Supporting Evidence: Consensus-based recommendations. P. 126*). Here, an iterative process built around the Evidence to Decision Framework was again utilised to form recommendations from the evidence base. (16, 17, 20, 45)

Grading the direction and strength of **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 (46) which incorporated the seven domain of the GRADE process including 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 scholarly literature from the systematic review process, the systematic observation form data and Delphi survey results, with findings presented in Evidence to decision tables for each recommendation (*Supporting evidence, consensus-based recommendations p 131*).

Co-Lead 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 (Table 7).

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.

These 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.

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.

Table 7. Descriptors and definitions for GRADING the strength of consensus-based recommendations. 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).
The strength of recommendations was defined by the confidence in the balance of benefits to harms. 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 and was not intended to guide the prioritisation of implementation. As such the grade given to each Recommendation aligned with the judgements of the GDG, based on the available evidence and other relevant considerations.

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
Impact	Scholarly literature generated through systematic review AND/OR Systematic observation form AND/OR Delphi survey	**Large impact** **Substantial impact** **Moderate Impact** **Slight Impact** The direction of impact is not stipulated (positive or negative effect). Impact could be on different levels including for newborns, families, healthcare practitioners and health systems
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

Finalising the draft Guideline and the process of public consultation

The first version of the draft guidelines including evidence and consensus-based recommendations and practice points, with their certainty (for evidence-based recommendations) and strength (for consensus-based recommendations) were compiled by the Organising Committee and disseminated to the SAC and Oversight Committee on 3rd July 2024 by email, with written feedback expected over a two-week period. A videoconference for all SAC members and members of the Oversight Committee was convened on the 7th August 2024 to review the draft Guideline and address additional feedback as appropriate. A second draft of the Guideline was formulated based on the discussions of this meeting and using (written) email feedback from the SAC. This updated draft was disseminated to members of the SAC, oversight committee and organising committee and uploaded onto a dedicated portal for public consultation and feedback.

The GDG simultaneously prepared the draft Guideline and supporting documents (Supporting Evidence, Administration and Technical report and Plain Language Summary) for public consultation, which opened on 12th August 2024 and closed on 23rd September 2024 (six weeks).

Ahead of this phase, a webpage was developed through the University of New South Wales, to house all relevant documents and to collate feedback through a link to an online survey and feedback portal (https://www.unsw.to/nbs-sma).

Documents could be viewed online or downloaded as required. The opening and closing dates of the public consultation period were announced through a University of New South Wales promotion, through email dissemination and through social media. Key professional and consumer organisations were identified through GDG networks and formally invited to provide feedback, with a letter of invitation sent out prior to the opening of the public consultation period (Table 8.)

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.

Table 8. Professional and consumer organisations invited to provide feedback for the Guideline.

Organisation	Contacts Role
The Royal Australian College of Physicians	Administrative officer
Australian and New Zealand Child Neurology Society	President
SMA Australia	Administrative officer
Rare Voices Australia	CEO Education and advocacy manager
Human Genetics Society of Australia	Administrative officer
New Zealand Paediatric Society / The Paediatric Society of New Zealand	President
Commonwealth Department of Health	Director, NBS condition assessment Medical Advisor
The Royal Australian and New Zealand College of Obstetricians and Gynaecologists	via Executive & Advocacy Office
The Royal Australian College of General Practitioners	Quality care team
Australian Genomics	Managing director
Syndromes Without a Name	Administrative officer
Rare Disorders NZ	Chief Executive CEO
Rare Disease Foundation Australia	Operations manager
Australasian Association of Clinical Geneticists	Administrative officer
Human Genetics Society of Australasia	Administrative officer
Australasian Society of Diagnostic Genomics	Via HGSA
Australasian Society of Genetic Counselling	Via HGSA
Australian College of Rural and Remote Medicine	Senior policy and development officer
Director General or Secretaries of Departments of Health for ACT, VIC, SA, TAS, WA, NT	Administrative officers

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.

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. An initial response and/or proposed change to the Guideline was drafted, where possible. 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 18th September 2024. Here, representatives could (a) agreed with the initial response, or (b) proposed 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.

Publication of the finalised Guideline and endorsement

The list of organisations contacted for feedback during the period of public consultation were also approached to endorse the Guideline (Table 8). This section will be updated once the Guideline has been finalised, following public consultation.

Risk Assessment

The potential risks and benefit profile of recommendations within the Guideline were considered as a whole, as the paucity of evidence precluded the ability to always assign risk and benefit for individual (especially consensus-based) recommendations.

Overall, the risks of implementing the NBS for SMA pathway as detailed in the Guideline were considered low, with the intention of providing equitable access to timely diagnosis and specialist management for children with this neurodegenerative disease, whilst concurrently providing individualistic child and family centred care, information and support throughout the screening, diagnosis and clinical care journey. Although screening occurs through invasive means i.e. a heel prick to the newborn generally, the risk of NBS for SMA was mitigated as screening would occur on routine dried blood spots collected for (newborn) screening of other conditions. Other considerations included

- The financial feasibility of adding SMA onto routine NBS panels, with public funding requiring adjustments to provide screening, diagnostic and clinical care services. The GDG acknowledged that for some jurisdictions, the implementation of recommendations within the Guideline could lead to changes in service delivery and the need for personnel with expertise in genetic screening and equipment to perform these tests on a population scale, and also the coordination of clinical care services to review screen positive newborns in an expedient manner. The extent of changes to services and organisations would vary by sector and organisation. To mitigate this, the GDG were committed to recommendations that were founded in evidence but were also flexible and practical, and applicable to the Australasian health context.

- The risk of widening health inequities across Australia - to address this specific barrier, targeted recommendations were formulated that could optimise access to health care services. These included the incorporation of telehealth (videoconferencing) and local medical practitioner review (with support from specialist practitioners) as an acceptable process to enable access to medical care for newborns and their families living in regional/remote regions.

- The risk of widening health inequities across Australia - consideration of optimising processes for specific populations including culturally and linguistically diverse and Aboriginal, Torres Strait and Pacific Islander and Māori communities were incorporated into the Guideline development process.

Dissemination, Implementation and Evaluation

Dissemination and Implementation plan

The Newborn Screening Program of each state and territory of Australia is responsible for the implementation of the Guideline. This includes the screening, diagnostic and clinical (paediatric neurology, paediatric and community) services that form a network for the newborn screened as part of this process.

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. The latter will house the Guideline and associated documents. 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.

Guideline Evaluation

To ensure the relevance of the Guideline and to support its effective implementation, the recommendations therein should continue to be evaluated. 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 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.(24)

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 plan and initiation alongside the longitudinal evaluation of the short- and long-term clinical outcomes for children screening positive for SMA.

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

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

4. 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.

Supporting Evidence

Evidence-based recommendations

Evidence Tables

Question: How should you screen for SMA in the newborn period?

Certainty assessment							No. children		Effect		Certainty	Importance
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	No intervention	Relative	Absolute		
46	Cohort	Not Serious[a]	Not Serious[b]	Serious[c]	Serious[d]	Serious[e]	3,114,909	-	-	-	⬤⬤◯◯ Low	Critical

NBS for SMA should be conducted on the dried blood spot taken from the newborn

[a]Limitations related to study design that increase risk of selection bias, however the GDG upgraded rating due to the cumulative number of children being screened sensitively and specifically for SMA using this intervention.

[b]Consistent across most of the literature.

[c]Outcome applies to population in question, however potential for indirectness for the intervention as no head-to-head comparisons of using other substrates for NBS for SMA

[d]Narrative synthesis conducted and estimates are not precise.

[e]Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review

Question: How should you screen for SMA in the newborn period?

The target analyte of newborn screening for SMA is homozygous deletion of exon 7 on *SMN1*.

Certainty Assessment							No of children		Effect		Certainty	Importance
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	No intervention	Relative	Absolute		
46	Cohort	Serious[a]	Not Serious	Serious[b]	Serious[c]	Serious[d]	3,155,446	-	-	-	⬤⬤◯◯ Low	Critical

[a] Limitations related to study design, that increase risk of selection bias.

[b] Outcome applies to population in question, however potential for indirectness for the intervention as no head to head comparisons of using other target analytes for SMA

[c] Narrative synthesis conducted and estimates are not precise.

[d] Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review

Question: What should the diagnostic process be for screen positive newborns?

Inclusion of homozygous deletion of exon 7 on *SMN1* on blood samples from a recalled newborn

Certainty Assessment							No of children		Effect		Certainty	Importance
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Publication bias[c]	Relative	Absolute		Critical
18	Cohort	Serious[a]	Not serious	Not Serious	Serious[b]	Serious[c]	286	Serious	-	-	 Low	Critical

[a] Limitations related to study design, that increase risk of selection bias.

[b] Narrative synthesis conducted and estimates are not precise.

[c] Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review

Summary of findings table

Outcome	Certainty of evidence[1]	Number of participants (studies)	Clinical usefulness: Acceptability[2]	Clinical usefulness: Implementability[3]	Clinical usefulness: Impact[4]	Narrative summary
NBS for SMA conducted on dried blood spots	●●○○ Low	3,114,909 (79)	High	High	High	In 79 studies, screening for SMA was conducted on dried blood spots (DBS),. One study used fresh blood for first tier (newborn screening for SMA) analysis.(47) One case series utilised DNA extracted from dried saliva spots.(48) No studies used cord blood for the purpose of newborn screening for SMA The DBS lent itself to a range of screening tests used in NBS for SMA
Target analyte of newborn screening for SMA	Low ●●○○	3,155,446 (79)	High	High	High	All studies use homozygous deletion of exon 7 on *SMN1* as the target analyte in newborn screening
Diagnostic testing includes tests for homozygous deletion of exon 7 from *SMN1*	Low ●●○○	286(18)	High	High	High	Diagnostic confirmation of SMA is beneficial, using assays that detect homozygous deletion of exon 7 on *SMN1*

[1] Certainty assessed within risk of bias, study design, imprecision, indirectness and inconsistency domains.

[2] Acceptability based on the overall judgement of the SAC and pertaining to acceptability to healthcare practitioners and affected children and their families.

[3] Implementability based on the overall judgement of the SAC and pertaining to the ability to implement the recommendation by health systems across Australia and New Zealand.

[4] Clinical impact based on the overall judgement of the SAC and pertaining to clinical impact on affected children and their families.

Evidence to decision tables

1. Should newborn screening for SMA be conducted on the dried blood spot taken from the newborn/infant?

	Criteria	Judgements	Research evidence	Additional considerations
Priority of problem	Is the intervention a priority	Yes	SMA is a serious and life threatening condition affecting 1 in 10000 children. Early identification of at-risk infants through established NBS programs (which use DBS) leads to early diagnosis and intervention which is known to improve survival, motor function, quality of life and reduce comorbidities	DBS is already used in established NBS programs in Australia and New Zealand.
Benefits and harms	How substantial are the desirable effects of the intervention How substantial are the undesired effects Does the balance between desirable and undesirable effects favour the option	Large effects Trivial effects Favours the option	In studies using DBS, screening is 98% sensitive and 100% specific. Using DBS but collecting blood indirectly from newborn i.e. through heparinised lines etc can increase false positive rate. DBS storage conditions may affect screening assays	
Certainty of evidence	What is the certainty of overall evidence	Low Serious risk of bias, imprecision and indirectness	3,155,446 newborns screened using this target analyte across 46 studies. Narrative summary therefore serious imprecision.	DBS lends itself to a range of screening tests used to identify children at risk of SMA through NBS.
Values and preferences	Is there uncertainty about or variability in how much people value the outcome	Probably no important uncertainty of variability	No direct evidence that using a DBS is preferred or valued by families or healthcare professionals however as NBS programs that use DBS are already in place, no additional collection of biosamples is required and therefore	

			considered to be preferred to families and health systems.	
Resources and cost effectiveness	What is the certainty of evidence resource requirements	Very low	Adding NBS for SMA onto routine DBS estimated USD 1 to the cost of the NBS assay	Not all estimates as to costs of adding this screen onto routine panels identified i.e. cost of training, personnel, equipment. NBS for SMA can be done on same DBS as assays for biochemical analysis.
Cost effectiveness	Does cost effectiveness favour the intervention	Favours the option	Indirect evidence where NBS for SMA using DBS is coupled with treatment initiation. Several cost effectiveness studies in Australia:(27, 49) More than three quarters of simulated ICERs by probability sensitivity analyses showed NBS (and gene therapy) would be dominant or less than $50 000/QALY, compared with no screening and late nusinersen treatment Internationally After detection of SMA by NBS in 17 patients, the number of quality-adjusted life-years gained per annual birth cohort was estimated at 320 with NBS (using DBS) followed by treatment compared with treatment after clinical SMA diagnosis. Total healthcare costs, including screening, diagnostics, treatment, and other healthcare resource use, were estimated to be €12 014 949 lower for patients identified by NBS.(50)	

Equity	What would the impact be on health equity?	Probably increased	Indirect evidence however two studies using an implementation study design showed that NBS for SMA (using DBS) improves health equity across Australia.(9, 10)	
Acceptability	Is the intervention acceptable to stakeholders	Probably Yes	Indirect evidence: Mixed methods study showing acceptability of intervention to healthcare professionals and families.(8)	
Feasibility	Is the intervention feasible to implement	Probably yes	Feasibility of implementation in an Australasian healthcare context shown in Kariyawasam et al. 2020(10) where time to achieving a screen positive result, using DBS and low false positive rate.(10)	The panel consider this as probably feasible within state and territory (Australia) and national (New Zealand) NBS programs
References: Boemer et al. 2021 (51), Singh et al. 2023 (52), Groulx-Boivin et al. 2024 (53), Boemer et al. 2019 (54), Tesorero et al. 2023 (55), Shinohara et al. 2019 (56), Olkhovych et al .2023 (57), Wallace et al. 2023 (58), Fonseca et al. 2024 (59), Kimizu et al. 2023 (60), Kernohan et al. 2022 (61), Oliveira-Netto et al. 2023 (62), Lakhotia et al. 2022 (63), Kumar et al. 2021 (64), Wong et al. 2024 (65), Tavares et al. 2021 (66), Sonehara et al. 2023 (67), Kraszewski et al. 2018 (68), ArRochmah et al. 2017 (69), Gailite et al. 2022 (70), Elkins et al. 20222 (71), Mikhalchuk et al. 2023 (72), Kucera et al. 2021(73), Kato et al. 2015 (74), Niba et al. 2019 (75), Czibere et al 2020. (76) Wijaya et al. 2019 (77), Dobrowolski et al. 2012 (78), Vill et al. 2019 (79), Vill et al. 2021 (80), Er et al. 2012 (81), Kariyawasam et al. 2020 (10), Noguchi et al. 2022 (82), Hale et al. 2021 (83), Kay et al. 2020 (84), Pyatt et al. 2007 (85), Gutierrez-Mateo et al. 2019 (86), Vidal-Folch et al. 2018 (87), Kiselev et al. 2024 (88), Liu et al. 2016 (89), Hashimoto et al. 2023 (90), Lin et al. 2019 (91), Adams et al. 2021 (92), Abiusi et al. 2023 (93), Niri et al. 2023 (94), Baker et al. 2022 (95), Kubar et al. 2023 (96), Shum et al. 2023 (97), Sawada et al. 2022 (98), Kato et al. 2015 (74), Chien et al. 2017 (99), McMillan et al. 2020 (100), Muller-Felber et al. 2023 (101), Lee et al. 2022 (102), Abiusi et al. 2024 (103), Kernohan et al. 2022 (61), Kemper et al. 2018 (104), Matteson et al. 2022 (105), Prior et al. 2010 (106) .					

Summary of decisions

Balance of consequences	Undesirable consequences clearly outweigh desirable consequences in most settings	Undesirable consequences probably outweigh desirable consequences in most settings	Balance between desirable and undesirable consequence is closely balanced or uncertain	Desirable consequences probably outweigh desirable consequences in most settings	Desirable consequences clearly outweigh desirable consequences in most settings
				X	

Type of evidence-based recommendation: direction	We recommend not offering the intervention		We recommend offering the intervention X	
Type of evidence-based recommendation: strength	A Conclusion is supported by good evidence	B Conclusion is supported by fair evidence	C Conclusion is supported by limited evidence	D Conclusion is not possible or extremely limited because the evidence is unavailable/very low certainty
		X		
Recommendation, Grade B We recommend that newborn screening for SMA should be performed on the routine newborn dried blood spot.				
Justification There is low certainty of evidence for this intervention. Benefits are likely to outweigh risks. The intervention is probably cost effective and is feasible within an Australian healthcare context. This intervention is thought probably likely to increase health equity and is probably acceptable to stakeholders.				

2. Should the target analyte for newborn screening for SMA be homozygous deletion of exon 7 on *SMN1?*

	Criteria	Judgements	Research evidence	Additional considerations
Priority of problem	Is the intervention a priority	Yes	SMA is a condition affecting 1 in 10000 children. 95% of children have homozygous deletion of exon 7 on SMN1 and so the majority of children with SMA will be screened for using this target analyte.	5% of children with genetic variations other than homozygous deletion of exon 7 will not be screened for using this target.
Benefits and harms	How substantial are the desirable effects of the intervention How substantial are the undesired effects Does the balance between desirable and undesirable effects favour the option	Large effects Small effects Favours the option	No direct evidence	Down stream consequences of using this target analyte is the potential to diagnose 95% of the population with SMA, and consider early treatment. Combined, this leads to greater survival, improvement in motor skills and reduction in comorbidities.
Certainty of evidence	What is the certainty of overall evidence	Low Serious risk of bias, imprecision and indirectness	3,155,446 newborns screened using this target analyte across 46 studies. Narrative summary therefore very serious imprecision.	
Values and preferences	Is there uncertainty about or variability in how much people value the outcome	Probably no important uncertainty of variability	Some mixed methods studies show people placing high value on newborn screening for SMA (where target analyte is homozygous deletion of exon 7 on SMN1)(8)	
Resources	What is the certainty of evidence resource requirements	Very low	Adding NBS for SMA where target analyte is homozygous deletion of exon 7 on SMN1 adds an estimated USD 1 to the cost of the NBS assay	Not all estimates as to costs of adding this screen onto routine panels identified i.e. cost of training, personnel, equipment
Cost effectiveness	Does cost effectiveness favour the intervention	Favours the option	Several cost effectiveness studies in Australia (27, 49):	

			More than three quarters of simulated ICERs by probability sensitivity analyses showed NBS and gene therapy would be dominant or less than $50 000/QALY, compared with no screening and late nusinersen treatment Internationally After detection of SMA by NBS in 17 patients, the number of quality-adjusted life-years gained per annual birth cohort was estimated at 320 with NBS followed by treatment compared with treatment after clinical SMA diagnosis. Total healthcare costs, including screening, diagnostics, treatment, and other healthcare resource use, were estimated to be €12 014 949 lower for patients identified by NBS (50)	
Equity	What would the impact be on health equity?	Probably increased	Two studies using a implementation study design showed that NBS for SMA using target analyte improves health equity across Australia (9, 10)	Equity pertaining to families of Aboriginal, Torres Strait and Pacific islander and Māori descent not reflected in literature.
Acceptability	Is the intervention acceptable to stakeholders	Probably Yes	Mixed methods study showing acceptability of intervention to healthcare professionals and families.(8)	Within these studies, no false negative cases arose and the acceptability of targeting exon 7 on SMN1 in these populations is unknown.
Feasibility	Is the intervention feasible to implement	Probably yes	Feasibility of implementation in an Australasian healthcare context shown in Kariyawasam et al. 2020(10) where time to	The panel consider this as probably feasible within state and territory (Australia) and

			achieving a screen positive result, using this target analyte was 8 days of life (range 5-18 days).(10)	national (New Zealand) NBS programs
Boemer et al. 2021 (51), Singh et al. 2023 (52), Groulx-Boivin et al. 2024 (53), Boemer et al. 2019 (54), Tesorero et al. 2023 (55), Shinohara et al. 2019 (56), Olkhovych et al .2023 (57), Wallace et al. 2023 (58), Fonseca et al. 2024 (59), Kimizu et al. 2023 (60), Kernohan et al. 2022 (61), Oliveira-Netto et al. 2023 (62), Lakhotia et al. 2022 (63), Kumar et al. 2021 (64), Wong et al. 2024 (65), Tavares et al. 2021 (66), Sonehara et al. 2023 (67), Kraszewski et al. 2018 (68), ArRochmah et al. 2017 (69), Gailite et al. 2022 (70), Elkins et al. 20222 (71), Mikhalchuk et al. 2023 (72), Kucera et al. 2021(73), Kato et al. 2015 (74), Niba et al. 2019 (75), Czibere et al 2020. (76) Wijaya et al. 2019 (77), Dobrowolski et al. 2012 (78), Vill et al. 2019 (79), Vill et al. 2021 (80), Er et al. 2012 (81), Kariyawasam et al. 2020 (10), Noguchi et al. 2022 (82), Hale et al. 2021 (83), Kay et al. 2020 (84), Pyatt et al. 2007 (85), Gutierrez-Mateo et al. 2019 (86), Vidal-Folch et al. 2018 (87), Kiselev et al. 2024 (88), Liu et al. 2016 (89), Hashimoto et al. 2023 (90), Lin et al. 2019 (91), Adams et al. 2021 (92), Abiusi et al. 2023 (93), Niri et al. 2023 (94), Baker et al. 2022 (95), Kubar et al. 2023 (96), Shum et al. 2023 (97), Sawada et al. 2022 (98), Kato et al. 2015 (74), Chien et al. 2017 (99), McMillan et al. 2021 (100), Muller-Felber et al. 2023 (101), Lee et al. 2022 (102), Kernohan et al. 2022 (61), Kemper et al. 2018 (104), Matteson et al. 2022 (105), Prior et al. 2010 (106) .				

Summary of decisions

Balance of consequences	Undesirable consequences clearly outweigh desirable consequences in most settings	Undesirable consequences probably outweigh desirable consequences in most settings	Balance between desirable and undesirable consequence is closely balanced or uncertain	Desirable consequences probably outweigh desirable consequences in most settings	Desirable consequences clearly outweigh desirable consequences in most settings
				X	

Type of evidence-based recommendation: direction	We recommend not offering the intervention		We recommend offering the intervention X	
Type of evidence-based recommendation: strength	A Conclusion is supported by good evidence	B Conclusion is supported by fair evidence	C Conclusion is supported by limited evidence	D Conclusion is not possible or extremely limited because the evidence is unavailable/very low certainty
		X		
Recommendation, Grade B We suggest that the target analyte of newborn screening for SMA is homozygous deletion of exon 7 on *SMN1*				
Justification				

There is low certainty of evidence for this intervention, but a high value placed on the intervention. Benefits are likely to outweigh risks. The intervention is cost effective and feasible within an Australian healthcare context. This intervention is thought probably likely to increase health equity and is probably acceptable to stakeholders
Subgroup considerations This intervention will not identify 5% of children with genetic variants other than homozygous deletion of exon 7 on *SMN1*.

3. Should diagnostic tests for screen positive newborns include homozygous deletion of exon 7 on *SMN1?*

	Criteria	Judgements	Research evidence	Additional considerations
Priority of problem	Is the intervention a priority	Yes	The screening test is 95% sensitive and 100% specific for SMA, however false positive results are noted in the research. The screening result requires confirmation through diagnostic assays.	
Benefits and harms	How substantial are the desirable effects of the intervention How substantial are the undesired effects Does the balance between desirable and undesirable effects favour the option	Large effects Trivial effects Favours the option	Benefits include confirming the diagnosis. Across 11 studies, 71 false positive results were noted.	Diagnostic confirmation of homozygous deletion of exon 7 on *SMN1* is required to access treatments on the Pharmaceutical Benefit Scheme.
Certainty of evidence	What is the certainty of overall evidence	Low Serious risk of bias, imprecision and indirectness	218 newborns screened confirmed with SMA using diagnostic assays for SMN1. Narrative summary therefore very serious imprecision.	
Values and preferences	Is there uncertainty about or variability in how much people value the outcome	Probably no important uncertainty of variability	Some mixed methods studies show people placing high value on confirming a diagnosis of SMA as a gateway to unlocking therapeutic options and care but also reducing feelings of uncertainty associated with a screen positive result (8)	
Resources	What is the certainty of evidence resource requirements	Very low	Varieties of methodologies used to confirm a diagnosis in SMA therefore precludes effective resourcing and cost effectiveness analysis.	Resources required to conduct accurate diagnostic assays will vary across Australia and New Zealand. i.e. cost of training, personnel, equipment.

Cost effectiveness	Does cost effectiveness favour the intervention	Favours the option	Varieties of methodologies used to confirm a diagnosis in SMA therefore precludes effective	
Equity	What would the impact be on health equity?	Probably increased	Achieving a diagnosis of SMA improves health equity across Australia.(9, 107)	Equity of Aboriginal, Torres Strait and Pacific islander and Māori families not reflected in literature.
Acceptability	Is the intervention acceptable to stakeholders	Probably Yes	Mixed methods study showing acceptability of intervention to healthcare professionals and families.(8)	
Feasibility	Is the intervention feasible to implement	Probably yes	Feasibility of implementation in an Australasian healthcare context shown in Kariyawasam et al. 2020(10) where time to achieving a diagnosis through reference laboratory was 12.5 days of life (range 8-23 days).	The panel consider this as probably feasible within state and territory (Australia) and national (New Zealand) NBS programs
References: Groulx-Boivin et al. 2024 (53), Prior et al. 2010 (106), Liu et al. 2016 (89), Kiselev et al. 2024 (88), Mikhalchuk et al. 2023 (72), Lin et al. 219 (91), Chien et al. 2017 (99), Kimizu et al. 2023 (60), Sawada et al . 2022 (98), Oliviera-Netto et al. 2023 (62), Kuchera et al. 2021, Niri et al. 2023 (94), D'Silva et al. 2022(9), Gailite et al. 2022 (70), Vill et al. 2021 (80), Boemer et al. 2021 (51), Wang et al. 2020 (108), Strunk et al. 2019(109) .				

Summary of decisions

Balance of consequences	Undesirable consequences clearly outweigh desirable consequences in most settings	Undesirable consequences probably outweigh desirable consequences in most settings	Balance between desirable and undesirable consequence is closely balanced or uncertain	Desirable consequences probably outweigh desirable consequences in most settings	Desirable consequences clearly outweigh desirable consequences in most settings
				X	

Type of evidence-based recommendation: direction	We recommend not offering the intervention		We recommend offering the intervention X	
Type of evidence-based recommendation: strength	A	B	C	D

	Conclusion is supported by good evidence	Conclusion is supported by fair evidence	Conclusion is supported by limited evidence	Conclusion is not possible or extremely limited because the evidence is unavailable/very low certainty
		X		
Recommendation, Grade B We recommend that diagnostic testing should include confirmation of homozygous deletion of exon 7 on *SMN1*.				
Justification There is low certainty of evidence for this intervention, but a high value placed on the intervention. Benefits are likely to outweigh risks. The intervention is considered to increase health equity by providing a diagnosis for children with SMA so that they can access treatment and care. The intervention is likely to be acceptable to stakeholders and feasible to implement.				
Subgroup considerations None				

Supporting Evidence

Consensus-based recommendations

Evidence to decision tables

Descriptor	Definition
Consistency	**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	**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
Impact	**Large impact** **Substantial impact** **Moderate Impact** **Slight Impact** The direction of impact is not stipulated (positive or negative effect). Impact could be on different levels including for newborns, families, healthcare practitioners and health systems
Evidence Sources	**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	**Excellent** = Strong consensus, 0 outlier **Good**= Strong consensus, 1 outlier **Satisfactory**= Near consensus **Poor**= No consensus from experts

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

Evidence Table	
Recommendation	1.3 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.
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across the scholarly literature with minimal 95% sensitivity of test but study quality limited to observational studies, with risk of bias due to study design. • Fully generalisable to current population. • Large impact due to development of a newborn screening process that will identify all children with homozygous deletion of exon 7 (occurring in 95% of population with SMA). Other factors for evidence to decision making. • Undesirable effects include the fact that 5% of population with SMA (compound heterozygotes) will not be identified through this test. Balance of benefits outweigh harms. • Intervention is feasible with adequate resourcing for equipment and personnel. • Health equity improved by screening test (identifying those at risk across geographic and sociodemographic lines. (Kariyawasam et al. 2020)(10) • Unclear if this specific recommendation is acceptable to stakeholders as 5% of population will not be identified through this method.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms
Research literature	Analytical sensitivity of most methods (qPCR, ddPCR) employed for NBS for SMA are 100% for exon 7 biallelic deletion on *SMN1*, however compound heterozygotes with SMA will not be identified through this methodology so sensitivity changes to 95%.
Support from experts	Excellent: 1st round Delphi: respondents 21, mean 8.71, no outliers.
References	Lin et al. 2019,(91) Niri et al. 2023,(94) Shum et al. 2023,(97) Muller-Felber et al. 2023,(101) Zhi et al. 2023,(110), Kariyawasam et al. 2020.(10)

Evidence Table	
Recommendation	1.4. We recommend that the screening test for SMA should determine the S*MN1* exon 7 absence, using suitably validated quantitative or qualitative assays.
Category/grade	Strong, Grade 1B.
Rationale	• Mostly consistent across the scholarly literature with variety of methods being used for screening in SMA in the newborn period with high sensitivity and specificity. These approaches use quantitative and qualitative assays. (some studies as per design using unvalidated methods for *SMN1* exon 7 deletion identification). Mainly consisting of observational studies. • Fully generalisable to current population. • Large impact due to development of a newborn screening process that are accurate (sensitive and specific with high positive predictive value). • The overall certainty of effects is moderate. Other factors for evidence to decision making. • Methodological processes do vary across jurisdictions depending on workflow. Highly feasible due to flexibility in approach of tests being used.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms
Research literature	Range of qualitative and quantitative *SMN1* assays used to screen for SMA on dried blood spots, including but not limited to restriction fragment length polymorphism analysis (RFLP), high resolution melting analysis, multiplex ligation dependent probe amplification, luminex genotyping, DNA sequencing, quantitative real time PCR (qPCR), with no head-to-head comparative studies to evaluate one methodology over another.
Support from experts	Excellent: 1st round Delphi: respondents 21, mean 8.81, no outliers.
References	Boemer et al. 2021,(51) Tesorero et al. 2023,(55) Kernohan et. 2021,(51) Kraszewski et al. 2018,(68) Chien et al 2017,(111) Sawada et al. 2018,(68) Sawada et al. 2022.(98)

Evidence Table	
Recommendation	1.5. We suggest that screen positive samples (0 *SMN1* copies) should immediately be repeated on the same dried blood spot.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence across the scholarly literature. • Mostly generalisable to Australasia. • Large impact due to increasing the certainty of a screen positive test for SMA prior to disclosure to families. • Benefits of repeating the test on the same dried blood spot to ensure screen positive result may outweigh challenges in terms of feasibility. Other factors for evidence to decision making. • Variability in feasibility to repeat dried blood spots within workflow processes across the health jurisdictions, dependent on resourcing.
Evidence source	Limited: Delphi survey and systematic observation forms.

Research literature	Not applicable.
Support from experts	Good: 1st round: 21 respondents, mean 8.43, 1 outlier.
References	Not applicable.

Evidence Table	
Recommendation	1.6. We recommend that the screening process performed by newborn screening for SMA programs should **not** identify carrier status.
Category/grade	Strong, Grade 1C.
Rationale	• Some consistency across the scholarly literature. • Fully generalisable to Australasia. • Large impact on health system resources to diagnose and manage individuals and families with a screening (carrier status) result e.g. genetic counselling, further genetic analysis of families AND increasing emotional distress for families. • Improves future reproductive decision making for identified individuals but does not benefit the newborn identified with carrier status within the newborn/infancy period as carriers are asymptomatic and not treated. Other factors for evidence to decision making. • Outside the scope of NBS for SMA.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms
Research literature	3 studies reporting carrier status as part of NBS for SMA.
Support from experts	Good. 1st round Delphi: 21 respondents, mean 7.86, 1 outlier. Systematic observation form results: Large harm (7/13;54%): Increasing demands on health system resources to diagnose and manage individuals and families with a screening (carrier status) result e.g. genetic counselling, further genetic analysis of families AND Increasing emotional distress for families. 9/13; 69% Increasing uncertainty and misunderstanding of genetic diagnosis in children who cannot understand the implications of a genetic result.
References	Kiselev et al 2024,(88) Kraszewski et al 2018.(68)

Evidence Table	
Recommendation	1.7. 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.
Category/grade	Strong, Grade 1C.
Rationale	• No direct evidence within the scholarly literature, however efficiency of all steps in the NBS for SMA pathway considered as key to produce net benefits.

	• Fully generalisable to Australasia. • Large impact on expediting access to diagnosis and treatment/care that will increase magnitude of health benefit to newborns. Other factors for evidence to decision making. • SMA is considered a neurogenetic emergency for many children (especially those with 2 *SMN2* copies and with clinical signs and symptoms of SMA). Expedient *SMN1* communication to clinical services unlocks next steps in pathway for diagnostic confirmation and timely therapeutic decision making. • Feasible within Australasian health landscape.
Evidence source	Limited: Delphi survey and systematic observation-forms
Research literature	Not applicable.
Support from experts	Excellent: 1st round Delphi 21 respondents, mean 8.52, 0 outliers.
References	Not applicable.

Evidence Table	
Recommendation	1.8. 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.
Category/grade	Strong, Grade 1B.
Rationale	• Some consistency across scholarly literature. • Fully generalisable to Australasia. • Large impact on standardising workflow processes to reduce false or uncertain screening results.
Evidence source	Limited: Delphi survey.
Research literature	In line with National NBS Screening policy framework and aligning with scholarly literature and consensus. Blood samples should be collected after 3 months for patients with whole blood transfusions. For newborns who are scheduled to undergo bone marrow transplantation or stem cell transplantation, blood samples should be collected before treatment (Zhi et al 2023).(110) Risk of DNA contamination is possible and in the ideal situation, DBS for SMA should be collected before transfusion. If collected after transfusion of red blood cell concentrates, test may be performed but should be repeated after 2 months since transfusion. Abiusi et al 2024.(103)
Support from experts	Good: 1st round Delphi: No consensus: reworded. 2nd round Delphi: 21 respondents, mean 8.52, 1 outlier.
References	Zhi et al 2023,(110) Abiusi et al 2024.(103)

Evidence Table	
Recommendation	1.9. We suggest that newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, and low or very low birth weight newborns should proceed using the same protocols as for term newborns.
Category/grade	Conditional, Grade 2B.
Rationale	• Some consistency across scholarly literature, but only three studies • Fully generalisable to Australasian population. • High impact to identify all newborns at risk of SMA, independent of clinical circumstances at birth.
Evidence source	Limited: Delphi survey and systematic observation-forms
Research literature	Although no studies denoted methodologies specifically for newborns with special circumstances in three studies, preterm newborns (gestational age < 37 weeks were accurately screened for SMA using methods used in term infants.
Support from experts	Excellent:1st round Delphi: 21 respondents, mean 8.62, outliers 0.
References	D Silva et al. 2022,(9) Nigro et al. 2023,(112) and Lee et al. 2022.(102)

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

Evidence Table	
Recommendation	2.1. We suggest that *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes but not delay notification of absence of exon 7 on *SMN1*
Category/grade	Conditional, Grade 2B.
Rationale	• No consistency across scholarly literature of observational studies. • Some generalisable to Australasian population. • Moderate Impact. Other factors for consideration: • *SMN2* copy number is the leading prognosticator of SMA disease severity. Incorporating *SMN2* copy number testing on the same dried blood spot as *SMN1* testing, is not required to identify newborns screening positive for SMA, but 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). *SMN2* copy number guides the pace of initiating treatment. • *Feasibility:* Not all jurisdictions will have the capacity to perform *SMN2* copy number as part of screening. There is variability in the systematic literature on programs that perform *SMN2* as part of NBS and those that incorporate this into a diagnostic algorithm. This recommendation has thus been made on a conditional basis acknowledging the inconsistencies in data and challenges to feasibility across Australasia.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	44 studies incorporated *SMN2* as second tier screening for all newborns with absence of *SMN1* on first tier analysis. In 11 studies, *SMN2* copy number identification was part of the confirmatory (diagnostic) process. Across the USA, 10 out of 37 states incorporate screening for *SMN2* into newborn screening programs, completed on the same dried blood spot and following detection of absence of exon 7 on *SMN1*. However, other states determine *SMN2* copy number as part of clinical follow-up through dried blood spot testing on a recalled infant or through diagnostic testing. This variability in practice is replicated across the international landscape, with the majority of programs incorporating *SMN2* copy number into newborn screening activities or as expeditiously as possible in the diagnostic period.
Support from experts	Excellent 1st round Delphi: no consensus reached, respondents 21, mean 7.19, outliers 5. 2nd round Delphi with rewording: meets consensus, respondents 22, mean 8.36, no outliers.
References	Abiusi et al 2024,(103) Hale et al. 2021.(83)

Evidence Table	
Recommendation	2.2.

	We recommend that *SMN2* copy number should be completed on suitably validated quantitative *SMN2* assay when identified as part of newborn screening.
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across the scholarly literature. • Fully generalisable to current population. • Large impact on having standardised approaches to increase screening accuracy. • The overall certainty of effects is high. Other factors for evidence to decision making. • Methodological processes do vary across jurisdictions depending on workflow. Highly feasible due to flexibility in approach of tests being used.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms
Research literature	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.
Support from experts	Excellent: 1st round Delphi: respondents 21, mean 8.62, no outliers.
References	Hale et al. 2021,(83)Kraszewski et al. 2018,(68) Abiusi et al. 2024,(103) Schorling et al. 2019 (113)

Evidence Table	
Recommendation	2.3. We recommend that the definition of screen positivity for the Australian and New Zealand newborn screening for SMA program is homozygous deletion of exon 7 on *SMN1* and *SMN2* copy number ≤ 4. (where *SMN2* copy number is conducted as part of newborn screening).
Category/grade	Strong, Grade 1C.
Rationale	• Somewhat consistent across the scholarly literature. • Fully generalisable to current population. • Large impact on having standardised approaches to the definition of a screen positive result. • The overall certainty of effects is high. Other factors for evidence to decision making: • Delineation of copy number of *SMN2* > 4 is technologically challenging • In Australia, there is no current access to treatment for (presymptomatic) newborns with copies ≥ 4 *SMN2* copies and therefore the delineation of individuals with higher copy numbers will not afford a large benefit as they have no recourse and need for intervention.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Of the studies incorporating *SMN2* as part of newborn screening, (n=26) studies described notification of 0,1,2,3,4 *SMN2* copy numbers whilst 14 reported ≥ 4 *SMN2* copies (with some screening methods unable to delineate more precisely *SMN2* copy numbers ≥ 4. 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.

	SMN2 copy number can vary dependent on the methodology (digital droplet PCR, MLPA or qPCR) used in up to 50% of cases. 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.
Support from experts	Excellent:1st round Delphi: respondents 21, mean 7, no outliers.
References	Schorling et al. 2019,(113) Dangouloff et al. 2020,(114) Alias et al. 2011,(115) Abiusi et al 2024,(103) Kemper et al. 2018.(116)

Evidence Table	
Recommendation	2.4. 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.
Category/grade	Strong, Grade 1C.
Rationale	• No evidence across the scholarly literature. • Fully generalisable to current population. • Large impact on reducing time to diagnostic confirmation, and by default intervention and care.
Evidence source	Limited: Delphi survey and systematic observation form.
Research literature	Not applicable.
Support from experts:	Good. 1st Round Delphi Respondents 21, mean 8.14, 1 outlier. Systematic observation form: Large benefit in reducing time to diagnosis (10/13; 77%), clinical care (10/13; 77%) and treatment (7/13; 54%) for newborn, with no effect on placing demands on health system (6/12; 50%)
References	Not applicable

Evidence Table	
Recommendation	2.5. We recommend that if screening for *SMN2* is not incorporated into the newborn screening process, (diagnostic) testing for *SMN2* should occur during follow-up care.
Category/grade	Strong, Grade 1B.
Rationale	• Fully consistent across the scholarly literature. • Fully generalisable to current population. • Large impact on providing early prognostic information to guide therapeutic decision making, set expectations and goals of care with families and stratify newborns into surveillance pathways. • The overall certainty of effects is high. Other factors for evidence to decision making: • Flexibility of approach means that the benefits of having *SMN2* copy number available early in decision making process is balanced against local capacity to undertake *SMN2* testing.

	• Health equity optimised as all newborns should receive *SMN2* copy number within a relevant therapeutic window.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Across the USA, 8 out of 37 states incorporated second tier screening for *SMN2* into clinical programs whilst the others determined *SMN2* copy number as part of clinical follow-up on confirmatory testing for all individuals who have a lack the target sequence of exon 7 on *SMN1* on first tier screening. In one study the lack of the target sequence of exon 7 on *SMN1* was first determined and then the copy number of *SMN2* was determined concurrently alongside confirmatory tests (but as part of a newborn screening algorithm). 44 studies incorporated *SMN2* as second tier screening for all newborns with absence of *SMN1* on first tier analysis whilst in 11 studies, *SMN2* copy number identification was part of the confirmatory (diagnostic) process.
Support from experts:	Good: 1st round Delphi Respondents 21, mean 8.33, 1 outlier.
References	Hale et al. 2021,(83) Kraszewski et al 2018,(68)

Evidence Table	
Recommendation	2.6. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Mostly consistent across the scholarly literature. • Fully generalisable to current population. • Small impact on providing prognostic information outside that of *SMN2* to guide family discussions on expected phenotype, however this will not guide therapeutic decision making. • The overall certainty of effects is high. Other factors for evidence to decision making. • Incorporating unvalidated biomarkers as part of screening for SMA on a population level considered to be challenging for Australasian healthcare systems whilst not adding clinical benefit on a whole of population scale. Evidence in the literature scant for this and based on expert opinion only.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	International consensus aligns with incorporating *SMN2* splicing modifiers as part of screening, however the majority of NBS for SMA programs do not incorporate prognostic biomarkers in SMA.
Support of experts	Good Delphi 1st round: no consensus 21 respondents, mean 7.48, outliers 4. Delphi 2nd round meets consensus. 21 respondents, mean 8.14, outliers 1. Systematic observation form: small benefit for incorporating unvalidated biomarkers outside of *SMN2* copy number including prediction of phenotype (5/10; 50%), no

	benefit in improving therapeutic decision-making processes (4/10; 40%) or care of newborn (4/10; 40%).
References	Abiusi et al 2024.(103)

Evidence Table	
Recommendation	2.7. 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.
Category/grade	Strong, Grade 1C.
Rationale	• Somewhat inconsistent evidence across the scholarly literature. • Fully generalisable to current population. • Substantial impact. • The overall certainty of effects is high. Other factors for evidence to decision making. • Feasible as each NBS for SMA program is within a health jurisdiction that has access to a specialist in child neurology. • Improves health equity as all children identified with this result have a coordinated plan, instigated by an expert for clinical review and diagnostic confirmation. • Early specialist contact highly valued by families Kariyawasam et al. 2020.(10)
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Variability in who receives the screening result between jurisdictions, but in the majority, the person of contact is a designated paediatric neurologist working in an expert referral centre.
Support from experts	Good: 1st round Delphi Respondents 21, mean 7.95, outliers 1.
References	Kariyawasam et al. 2020,(10) D'Silva et al 2022,(9) Boemer et al. 2019,(54) Muller-Felber et al. 2023.(101)

Evidence Table	
Recommendation	2.8. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence across the scholarly literature. • Some generalisability across Australasia. • Moderate impact: screen positive disclosure can occur without a formal report, however this is not best practice. It is optimal to ensure rigorous communication between services of a screen positive result through written means. • The overall certainty of effects is high. Other factors for evidence to decision making:

	• SMA is added to currently established NBS for SMA programs, which may not be able to issue screening reports within this timeline, depending on existing workflow practices.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Satisfactory: Delphi 1st round: 21 respondents, mean 8.14, outliers 2 Good: Delphi 2nd round: 21 respondents, mean 8.14, 1 outlier.
References	Not applicable.

Section 3: Confirming the diagnosis of spinal muscular atrophy

Evidence Table	
Recommendation	3.2. We recommend that diagnostic testing should also include *SMN2* copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making. Diagnostic testing for *SMN2* should occur from freshly obtained whole blood samples or repeat dried blood spot from a recalled newborn.
Category/grade	Strong, Grade 1B.
Rationale	• Fully consistent across the scholarly literature. • Fully generalisability across Australasian population. • Substantial impact. • The overall certainty of effects is high. Other factors for evidence to decision making: • Health jurisdictions are developing the capacity to undertake *SMN2* diagnostic testing so that treatment decisions including approvals and reimbursement structures for treatments can be made.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	*SMN2* diagnostic testing considered clinically useful to determine prognosis, aid therapeutic and decision making (Crawford et al. 2023)(4). A consensus statement by Abiusi et al.2024(103) stated that *SMN2* copy number determination could be challenging and should be conducted in expert reference centres with standard workflows. All studies complete *SMN2* testing as part of a diagnostic work up in a screen positive child.
Support from experts	Good: Delphi survey respondents 12, mean 8.50, outlier 1.
References	Muller-Felber et al. 2023,(101) Strunk et al. 2019,(109) Vill et al. 2019.(79) Crawford et al. 2023)(4), Abiusi et al.2024.(103)

Evidence Table	
Recommendation	3.3. We recommend that validated quantitative *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.
Category/grade	Strong, Grade 1B.
Rationale	• Fully consistent across the scholarly literature. • Fully generalisable across Australasian population. • Substantial impact. • The overall certainty of effects is high. Other factors for evidence to decision making. • Health jurisdictions are developing the capacity to undertake *SMN2* diagnostic testing so that treatment decisions including approvals and reimbursement structures for treatments can be made. • *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 NBS programs.

	Therefore, an inaccurate determination (outside of expertise developed by reference centres) may be very harmful to patient health.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Discrepant *SMN2* results could be secondary to sensitivity to contamination of probes and reagents, variability in definition of exact cut off values for interpretation, quality and quantity of DNA used, and availability and usage of appropriate controls. Development of standard operating procedures for *SMN2* analysis using validated assays and completed in centralised diagnostic centres is considered appropriate for greater diagnostic accuracy There were no comparative studies to detail the optimal method for diagnostic analysis of *SMN2,* however all methods require quantitative approaches such as MLPA, ddPCR, PCR methods and next generation sequencing,
Support from experts	Excellent respondents 12, mean 8.67, 0 outliers.
References	Schorling et al. 2019,(113) Abiusi et al 2024.(103)

Evidence Table	
Recommendation	3.4. We suggest that diagnostic *SMN1* testing is conducted using a different methodology to the newborn screening assay.
Category/grade	Conditional, Grade 2C.
Rationale	• Limited consistency of evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • Moderate impact. • Moderate certainty of effect. Other factors for evidence to decision making: • Feasibility: Within finite resourcing structures, health jurisdictions may not be able to use testing assays that are different to diagnostic methods employed.
Evidence source	Limited: Delphi survey.
Research literature	One study makes direct reference to the potential to reduce false positive rate by using *SMN1* assays with different *SMN1* primers.
Support from experts	Excellent respondents 12, mean 8.67, 0 outliers.
References	D'Silva et al 2022.(9)

Evidence Table	
Recommendation	3.5. We suggest that discussions between clinical and diagnostic services (either through verbal and/or written means), should ideally occur so that stakeholders understand when a diagnostic sample will be collected, delivered to diagnostic laboratories and expectant timelines for diagnostic analysis and receipt of results.
Category/grade	Conditional, Grade 2B.
Rationale	• Limited evidence across the scholarly literature. • Somewhat generalisable across Australasian population.

	• High impact on improving efficiency of healthcare journey for newborn, to reduce time to diagnosis, intervention and care and thus to optimise outcomes. • High certainty of effect.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	One study makes direct reference to the need for an integrated system that allows for expedient diagnostic confirmation of a screen positive infant but does not expand on how this can be done.
Support from experts	Excellent respondents 12, mean 8.17, 0 outliers.
References	D'Silva et al 2022.(9)

Evidence Table	
Recommendation	3.6. We suggest that to enable timely treatment, diagnostic results for *SMN1* should be available within 7-10 days of receipt of the sample by the diagnostic laboratory.
Category/grade	Conditional, Grade 2B.
Rationale	• Somewhat consistent evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • High impact on improving efficiency of healthcare journey for newborn, to reduce time to diagnosis, intervention and care and thus to optimise outcomes. • High certainty of positive effect. Other factors for evidence to decision making. • Feasibility of meeting this turn around time dependent on jurisdictional workflow processes. • Having a standardised time for diagnostic confirmation improves health equity and timings of access to care and support across Australasia.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	No defined time for diagnostic result availability (varies internationally). Australian pilot data determines that *SMN1* result can be available by a median of 6 days from point of first clinical review with median time for completion of screening to diagnosis 13.5 days.
Support from experts	Good: Delphi survey respondents 12, mean 7.67, 1 outlier. Systematic observation forms: Reducing time to diagnosis for the newborn (large benefit 8/10; 80%), Reducing time to treatment Large benefit (8/10; 80%), improving health outcomes for newborns Large benefit (8/9; 89%), reducing distress for families Large benefit (7/10; 70%), small harm of increasing demand on health systems (7/10; 70%).
References	Kariyawasam et al. 2020,(10) McMillan et al. 2021.(100)

Evidence Table	
Recommendation	3.7.

	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.
Category/grade	Conditional, Grade 2B.
Rationale	• Some inconsistency of evidence across the scholarly literature. • Fully generalisable across Australasian population. • Large impact on resourcing with little positive effect on health outcomes.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Beyond *SMN2* copy number, additional genetic modifiers may influence variability of transcription, translation and stability of *SMN2* transcripts and disease course and severity. These may be interrogated on a case-by-case basis if there is discordance in genotype and phenotype. Expert opinion is that *SMN2* modifier variants (c.859G>C and c.835-44A>G) should be routinely tested and reported by diagnostic laboratories (experts from non-Australasian healthcare areas).
Support from experts	Good: respondents 12, mean 7.67, 1 outlier.
References	Blasco-Perez et al. 2021,(117) Abiusi et al 2024.(103)

Evidence Table	
Recommendation	3.8. We suggest that diagnostic test results (including *SMN1* **and** *SMN2* copy number) should be available to clinical services within 30 days of birth.
Category/grade	Conditional, Grade 2B
Rationale	• No consistent evidence across the scholarly literature for exact timelines to complete diagnostic process. • Somewhat generalisable across Australasian population. • High impact to improve health outcomes by confirming diagnosis to unlock treatment and management pathway within a defined time. • High certainty of effect. Other considerations: • Feasibility of completing diagnostic testing dependent on workflow processes within each jurisdiction. Timeline is dependent on several prior steps including time of DBS collection, transport to screening lab, screening result provision etc, which may change time of availability of diagnostic result. • High impact on equity of healthcare to have standardised times for diagnostic result disclosure. • Should not impact the accuracy of the diagnostic process. • Families value certainty of diagnosis to reduce psychological distress and unlock pathways for care and support (Kariyawasam et al 2021).(8)
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Indirect evidence: Newborns treated within 6 weeks of age had highest magnitude of benefit in terms of the probability of normal motor development. Time to diagnostic confirmation (including SMN2) therefore should be as short as possible.

Support from experts	Good: respondents 12, mean 8.00, 1 outlier.
References	Aragon-Gawinska et al. 2023,(118) Kariyawasam et al 2021.(8)

Evidence Table	
Recommendation	3.9. We suggest that diagnostic reports should detail the methodology used for analysis and the precise *SMN2* copy number (avoiding reports such as *SMN2* ≥4).
Category/grade	Conditional, Grade 2B.
Rationale	• Some inconsistent evidence across the scholarly literature. • Somewhat generalisable across Australasian population. Other considerations: • Dependent on diagnostic technology used, it may not be feasible to delineate higher copy numbers for reporting purposes.
Evidence source	Limited: Delphi survey.
Research literature	Expert report states that technology used and the exact *SMN2* copy number should be issued in diagnostic reports to reduce ambiguity.
Support from experts	Excellent respondents 12, mean 8.50, 0 outliers.
References	Abiusi et al 2024.(103)

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

Evidence Table	
Recommendation	4.1. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No direct evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • Substantial impact on health outcomes for newborns to ascertain diagnosis and access to treatment. Substantial impact on wellbeing of families and satisfaction with care. Substantial impact on quality improvement of screening and diagnostic services. Other considerations: • Feasibility dependent on communication and coordination of care between health domains.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Excellent: Delphi survey respondents 26, mean 8.41. 1 outlier.
References	Not applicable.

Evidence Table	
Recommendation	4.2. We suggest that families of newborns with false positive results should be given the option of returning to discuss the implications of results with members of the neurology/neuromuscular multidisciplinary team*.
Category/grade	Conditional, Grade 2C.
Rationale	• No direct evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • Substantial impact on wellbeing of families and satisfaction with care. Other considerations: • Feasibility dependent on jurisdictional health resources.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Satisfactory: 1st round Delphi survey respondents 26, mean 7.92 outliers 2. Good: 2nd round with rewording: respondents 19, mean 8.16, outlier 1.

References	Not applicable.

Evidence Table	
Recommendation	4.3. 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.
Category/grade	Strong, Grade 1C.
Rationale	Consistency between limited observational studies. Fully generalisable to the population. Large impact of determining accuracy of diagnostic results on health outcomes of newborn determined by access to management (including treatment options). Large impact of families in terms of wellbeing and satisfaction with care. Enables therapeutic decision making for clinicians. Enables improvement of quality within screening and diagnostic domains. Other considerations: Implementability dependent on establishing collaborative links between screening and diagnostic services, which may be jurisdictionally dependent.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	Indirect evidence only. One case within an implementation study showed the aetiology of a false positive result after blood as retaken from a recalled infant and SMN1 analysed using different assays to first diagnostic method. Showed issues with probe binding site on screening test. Case series showed` two intron 6 variants led to a wrong diagnosis of SMA due to variants lying within the primer or probe target sequences. Recommends combined molecular assays to improve diagnostic accuracy in uncertain or discordant cases.
Support from experts	Good: respondents 26, mean 8.31, outlier 1.
References	Qu et al 2024,(119) and D'Silva et al 2022).(9)

Evidence Table	
Recommendation	4.4. 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.
Category/grade	Strong, Grade 1C.
Rationale	Substantial inconsistency in limited observational studies as to when to retest *SMN2* copy number, however a number of studies agree in challenges of precisely identifying coy number. Fully generalisable to the population

	Large impact of determining accuracy of results on health outcomes of newborn determined by access to management (including treatment options). Large impact of families in terms of wellbeing and satisfaction with care. Enables therapeutic decision making for clinicians. Enables improvement of quality within screening and diagnostic domains. Substantial risks to outcomes of newborns if *SMN2* copy number is not correctly identified, but also asks for a repeat (invasive test) for the newborn. GDG consider benefits outweigh risks. Other considerations: Implementability dependent on establishing collaborative links between screening and diagnostic services, which may be jurisdictionally dependent.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	Known discordance between laboratories (up to 40%) in determining *SMN2* copy number (Schorling et al. 2019).(113) In discordant genotype-phenotype situations, recommends retesting for *SMN2* copy number on different lab/method and/or with new sample for presymptomatic children with 1 or ≥4 *SMN2* copies. In symptomatic discordant situations, recommendations are for retesting *SMN2* copy number with different lab/ method initially and/or with a repeat patient sample (Cusco et al. 2020).(120) Repeat testing also suggested by Abiusi et al. 2024(103) with an expert panel providing narrative summary that for the management of worse- or better-than-expected cases, retesting the sample by a different method and/or in another laboratory is recommended; if the result is still uncertain, resampling is suggested. No clear evidence to denote how to resolve discrepancies between screening and diagnostic SMN2 copy number results.
Support from experts	Good: respondents 26, mean 8, outlier 1.
References	Schorling et al. 2019,(113) Cusco et al. 2020,(120), Abiusi et al. 2024.(103)

Evidence Table	
Recommendation	4.5. 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.
Category/grade	Strong, Grade 1C.
Rationale	No literature found. Fully generalisable to the population. **Large impact** on health outcomes of newborn which is determined by access to management (including treatment options). Large impact of families in terms of wellbeing and satisfaction with care. Enables therapeutic decision making for clinicians. Substantial risks to outcomes of newborns if treatment delayed due to a lack of a certain diagnosis and clinical surveillance. GDG consider benefits outweigh risks.
Evidence source	Limited: Delphi survey and systematic observation forms.
Research literature	Not applicable.

Support from experts	Good: respondents 27, mean 8.48, outlier 1.
References	Not applicable

Evidence Table	
Recommendation	4.6. 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.
Category/grade	Strong, Grade 1C.
Rationale	No direct scholarly literature noted. **Large impact** on maintaining safety and promoting health outcomes of newborn, determined by expedient access to management and treatment, noting that time to treatment is a substantial modifier of outcomes. Large impact of families in terms of wellbeing and satisfaction with care. Enables therapeutic decision making for clinicians. Substantial risks to health outcomes of newborns if treatment delayed due to a lack of information provision to families. Other considerations: Low resource needs to impart information but families may require additional (non-verbal) educational resources to refer to which may require a plan of implementation done on a jurisdictional level.
Evidence source	Limited: Delphi survey and systematic observation forms.
Research literature	Not applicable.
Support from experts	Good: respondents 27, mean 8.26, respondent 1.
References	Not applicable.

Evidence Table	
Recommendation	4.7. 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.
Category/grade	Strong, Grade 1C.
Rationale	No direct evidence across the literature. Fully generalisable across the population. Substantial benefit in improving the quality of screening, diagnostic and clinical care processes. May improve family knowledge, acceptability of the NBS for SMA program, wellbeing, engagement and satisfaction with care.

Evidence source	Limited: Delphi survey and systematic observation forms.
Research literature	Not applicable.
Support from experts	Excellent respondents 27, mean 8.78, outlier 0.
References	Not applicable.

Evidence Table	
Recommendation	4.8. We recommend that parents should be supported by the multidisciplinary team, including referral to medical social services and psychology as appropriate, during the process of managing false positive, uncertain or false negative results for their newborn/infant.
Category/grade	Strong, Grade 1C.
Rationale	No direct evidence across the literature on this specific subpopulation although families in general going through the NBS for SMA process value and prefer support and care. Fully generalisable across the population. Substantial benefit in improving family knowledge, acceptability of the NBS for SMA program, wellbeing, engagement and satisfaction with care. Other consideration: Barrier to implementation and feasibility of this recommendation is the availability of resources which may be jurisdictionally dependent.
Evidence source	Limited: Delphi survey and systematic observation forms.
Research literature	Not applicable.
Support from experts	Excellent respondents 27, mean 8.33, outlier 0.
References	Not applicable.

Evidence Table	
Recommendation	4.9. We recommend that open disclosure between appropriate health care practitioners and parents should occur with any false positive, uncertain or false negative screening results.
Category/grade	Strong, Grade 1C.
Rationale	No direct evidence across the literature. Fully generalisable across the population. Substantial benefit in improving family knowledge, acceptability of the NBS for SMA program, wellbeing, engagement and satisfaction with care.

	Other considerations: No additional resources required to implement this recommendation.
Evidence source	Limited: Delphi survey and systematic observation forms.
Research literature	Not applicable.
Support from experts	Satisfactory: 1st Delphi survey respondents 27, mean 8.41, outlier 2 Excellent: 2nd Delphi : respondent 20, mean 8, outlier 0.
References	Not applicable.

Evidence Table	
Recommendation	4.10. 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*).
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across available scholarly literature • Substantial health benefit in identifying symptomatic infants efficiently for referral to diagnostic and appropriate clinical care services as it is known that disease duration is a significant modifier of health outcomes (Finkel et al. 2017).(121) • Fully generalisable across health jurisdictions. • Other considerations: barrier to implementation may be education and training required of medical practitioners to detect signs and symptoms of SMA especially as number of cases reduce in the community due to NBS and carrier screening.
Evidence source	Numerous: Scholarly literature, Delhi survey and systematic observation forms.
Research literature	Indirect evidence for this recommendation however false negative cases identified in the literature secondary to genotypes other than biallelic deletion of exon 7 from *SMN1 (*Hashimoto et al. 2023,(90) Muller-Felber et al. Indirect evidence for this recommendation however false negative cases identified in the literature secondary to genotypes other than biallelic deletion of exon 7 from *SMN1 (*Hashimoto et al. 2023,(90) Muller-Felber et al. 2023,(101) Boemer et al.2021.)Indirect evidence for this recommendation however false negative cases identified in the literature secondary to genotypes other than biallelic deletion of exon 7 from *SMN1 (*Hashimoto et al. 2023,(90) Muller-Felber et al. 2023,(101) Boemer et al.2021.(51)
Support from experts	Good: Delphi survey respondents 27, mean 8.48, outlier 1. Systematic observation form.
References	Hashimoto et al. 2023,(90) Muller-Felber et al. 2023,(101) Boemer et al.2021,(51) Finkel et al. 2017.(121)

Section 5. Disclosing a screen positive result to families

Evidence Table	
Recommendation	5.1. We suggest that a screen positive result should be ideally disclosed to the family within ≤ 2 working days (of notification to healthcare services).
Category/grade	Conditional, Grade 2B.
Rationale	• Inconsistent evidence across the scholarly literature on exact timelines but consistency across studies that time to disclosure should be as short as possible. • Somewhat generalisable across Australasian population. • Substantial impact on health outcomes to reduce timeline to diagnosis and treatment. Other considerations: • Feasibility dependent on clinical processes within health jurisdictions.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Variability in time to disclosure to families but generally within 1-2 days of screen positive result. Time to notify families of a screen positive result should be as short as possible. Within the Australian pilot newborn screening for SMA program 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).
Support from experts	Excellent: Delphi survey respondents 13, mean 8.54 outliers 0.
References	Kariyawasam et al. 2020,(10) Muller-Felber et al. 2023,(101) Boemer et al. 2019.(54)

Evidence Table	
Recommendation	5.2. 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.
Category/grade	Strong, Grade 1C.
Rationale	• Some inconsistency across the scholarly literature. • Fully generalisable across Australasian population. • Substantial impact on provision of information provision to fit the needs of families. Other considerations: • Feasible across Australia. • No additional costs involved. • Increases satisfaction in healthcare for families and aims to increase health equity, based on the circumstances of the family.
Evidence source	Limited: Delphi survey.
Research literature	Designation of healthcare practitioners tasked with notifying the family of screen positive results vary internationally, dependent on jurisdiction-specific SMA workflow processes. In the majority, parents are notified by a paediatric neurologist working in a

	specialist neuromuscular centre, by the hospital where the child is born, and less commonly by the screening laboratory or a designated paediatrician. Dependant on health expertise and confidence in disclosing sensitive results to families, other programs leverage the experience of trained genetic counsellors or nurses. Screening results are generally disclosed over the telephone where the child and family are directed to the closest paediatric hospital for clinical review. 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. Close coordination noted as an implementation point in a knowledge to action study to support disclosure strategy.
Support from experts	Satisfactory: 1st Delphi survey respondents 13, mean 7.31. Outliers 2. Good: 2nd Delhi survey with rewording: respondents 16, mean 8.38, outlier 1.
References	Muller-Felber et al. 2023,(101) Kariyawasam et al. 2020,(10) McMillan et al. 2021,(100) Groulx-Boivin et al. 2024,(53) Kolbel et al. 2022.(122)

Evidence Table	
Recommendation	5.3. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No direct evidence across the scholarly literature. • Fully generalisable across Australasian population. • Substantial impact on quality of information provided dependent on expertise and knowledge of practitioner Other considerations: • May be feasible and appropriate for families living remotely/regionally. • Possible impact on satisfaction of healthcare and confidence in the process for families. • Families value direct contact with medical practitioners with knowledge of the condition and its sequalae.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable directly however in studies, a spectrum of medical practitioners disclose results. The effects and satisfaction with care from a family perspective dependent on disclosure modality and expertise of the information provider not evaluated.
Support from experts	Satisfactory: 1st Delphi survey respondents 13, mean 7.31, outliers 2. Good: 2nd Delhi survey with rewording: respondents 16, mean 8.38, outlier 1.
References	Not applicable.

Evidence Table	
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.
Category/grade	Strong, Grade 1C.
Rationale	• Limited generalisability across Australasian population. • Substantial impact on familial satisfaction with care, understanding and engagement. • Other factors to consider. • Feasibility varies across Australia although most specialist centres have recourse to interpreter services. • May have additional costs involved. • Increases satisfaction in healthcare for families and aims to increase health equity. • Decreases uncertainty and psychosocial consequences on families. • Families value accurate and understandable information.
Evidence source	Limited: Delphi survey.
Research literature	One study directly identifies the use of interpreter services for information provision across the NBS for SMA healthcare journey as an enabler of effective and high-quality implementation of the program.
Support from experts	Excellent: Respondents 12, mean 8.67, outliers 0.
References	Kariyawasam et al. 2020.

Evidence Table	
Recommendation	5.5. We recommend that healthcare practitioners disclosing screen positive results for SMA to families from Aboriginal, Māori or Torres Strait Islander 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 inform families of a screen positive result.
Category/grade	Strong, Grade 1C.
Rationale	• No direct evidence across the scholarly literature. • Not generalisable across Australasian population. • **However,** substantial impact on the quality of information provision to fit the individual and specific needs of these families. Other considerations: • Dependent on resources that will determine feasibility and access to support services across Australia. • May have additional costs involved. • Potential to increase engagement and satisfaction in healthcare for families and aims to increase health equity. • Families value culturally competent and accurate and understandable information.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Good: Respondents 13, mean 7.92, 1 outlier.

References	Kariyawasam et al. 2020.

Evidence Table	
Recommendation	5.6. 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 current status including feeding, movement and breathing and/or clinical concerns from parents. **AND** 5.10. 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.
Category/grade	Strong, Grade 2C.
Rationale	• Limited consistency of evidence across the scholarly literature of observational studies. • Fully generalisable across Australasian population. • **S**ubstantial impact on health outcomes for newborns and psychological consequences of screen positive disclosure on families. Other factors to consider: • Ensures equity of information provided to families. • Families value open and clear disclosure to increase trust in healthcare system, and reduce distress.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Information provided at the time of screen positive disclosure varies between health jurisdictions and between medical practitioners. 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. International recommendations underline the need to update families of the signs and symptoms of SMA (at any point in healthcare journey) that can be used at home to monitor for 'red flag' signs and symptoms of clinical deterioration that would trigger immediate clinical (re) review. Including, 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.
Support from experts	Excellent: Respondents 13, all with mean > 7.5 and 0-1 outlier.
References	Kariyawasam et al.2018,(123) Meyer et al. 2024,(124) Kariyawasam et al. 2020(10) and Muller-Felber et al.2023.(101)

Evidence Table	
Recommendation	5.7. We suggest that screen positive newborns should ideally be offered a clinical review within paediatric neurology/neuromuscular services.
Category/grade	Conditional, Grade 2C.
Rationale	• Limited consistency of evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • Moderate impact on health outcomes for newborns. Other factors to consider: • Geographical and logistical barriers for specialist review for some families with a screen positive child across Australasia. • Time to diagnosis is key, independent of health setting where review takes place. • Families value expedient access to specialist review. (Kariyawasam et al. 2021)
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	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. Consideration has been given to the need for flexibility for 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 (McMillan et al, 2021).(100) Programs generally refer children to neuromuscular centres for the first clinical review (Kariyawasam et al 2020, Muller-Felber et al. 2023)
Support from experts	Excellent: Respondents 13, mean 9, outlier 0.
References	Kariyawasam et al. 2021,(8) Meyer et al 2024,(124) Muller-Felber et al. 2023,(101) McMillan et al. 2021(100) and Groulx-Boivin et a. 2024.(53)

Evidence Table	
Recommendation	5.8. 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.
Category/grade	Conditional, Grade 2C.

Rationale	• No direct evidence from the scholarly literature. • Mostly generalisable across Australasian population. • Substantial impact on health outcomes for newborns from remote/regional areas in expediting route to diagnosis. Other factors to consider: • Geographical and logistical barriers for specialist review for some families with a screen positive child across Australasia. • Time to diagnosis is key, independent of health setting where review takes place. • Resources needed to educate and upskill (non-specialist) medical practitioners to evaluate for signs and symptoms of SMA in newborns.
Evidence source	Limited: Delphi survey.
Research literature	None.
Support from experts	Good: Respondents 13, mean 8.33, 1 outlier.
References	Not applicable

Evidence Table	
Recommendation	5.9. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat consistent across the scholarly literature. • Mostly generalisable across Australasian population. • Substantial impact on health outcomes for newborns. Other factors to consider: • Geographical and logistical barriers for review for some families within 2 days dependent on family factors. • Impact on health system resources to facilitate urgent review, which may feasibility of this recommendation.
Evidence source	Limited: Delphi survey.
Research literature	Studies describe clinical review between 1-4 days of screen positive result disclosure.
Support from experts	Good: Respondents 13, mean 8.33, 1 outlier.
References	Kariyawasam et al. 2020,(10) Muller-Felber et al. 2023.(101)

Evidence Table	
Recommendation	6.1. 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. Venous sampling for diagnostic bloods with *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number.
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across the scholarly literature of observational studies. • Fully generalisable across Australasian population. • Large impact on health outcomes for newborns to confirm diagnosis and clinical status by reducing time to diagnosis, treatment and therapeutic decision making. Other factors. • Feasible to implement if local protocols are established for diagnostic confirmation.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation forms.
Research literature	Specific clinical assessments include a systematic and structured neurological examination in addition to a non-SMA specific validated 'floppy child module', to increase the potential to detect subtle signs of SMA disease onset in newborns. All studies that describe pathway include diagnostic SMN1 and SMN2 bloods collected at this point.
Support from experts	Excellent: Delphi survey results. Neuro exam, respondents 13, mean 9, 0 outliers. SMN1 venous sample respondents 13, mean 8.69 0 outliers. SMN2 venous sample respondents 13, mean 8.69, 0 outliers. Systematic observation forms: (Appendix 3)
References	Kariyawasam et al. 2022,(125) Kariyawasam et al. 2020,(10) Muller-Felber et al.2023,(101) McMillan et al. 2021,(100) Abiusi et al. 2024,(103) Elkins et al. (100) Tizzano et al. 2019,(126) Castalleno et al. (127)

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

Evidence Table	
Recommendation	7.1. 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.
Category/grade	Strong, Grade 1C
Rationale	• Fully consistent across the scholarly literature made up of observational studies. • Fully generalisable across Australasian population. • Large impact on familial satisfaction with care, understanding and engagement. Other factors to consider: • Impact on resources required to train and educate medical practitioners on new advances in SMA so that accurate information can be delivered. • Families place value and prefer compassionate and individualised information provision.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Dominant themes on information provision from the parent perspective included having a child and family centred approach to the timing and content of information given at diagnosis, emphasising a paced approach to information provision (Kariyawasam et al. 2021).(8) Families valued a compassionate approach at this first clinic visit and appreciated providers taking time to explain aspects of their' child's diagnosis (Meyer et al. 2024).(124)
Support from experts	Excellent: Respondents 13, mean 9.00, 0 outliers.
References	Kariyawasam et al. 2021,(8) Meyer et al. 2024.(124)

Evidence Table	
Recommendation	7.2. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• One study (mixed methods) with outcomes centred on family preferences for information disclosure at diagnostic evaluation. • Fully generalisable across Australasian population. • Large impact on familial satisfaction with care, understanding and engagement. Other factors to consider.

	• Families place value and prefer compassionate and individualised information provision.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Family perspectives explored and preferences established (mixed methods).
Support from experts	Excellent: Respondents 13, mean 8.54, 0 outliers.
References	Meyer et al. 2024(124)

Evidence Table	
Recommendation	7.3. 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.
Category/grade	Strong, Grade 1C.
Rationale	• One study (mixed methods) with outcomes centred on family preferences from CALD communities for information disclosure at diagnostic evaluation. • Limited generalisability across Australasian population. • Large impact on familial satisfaction with care, understanding and engagement. Other factors to consider: • Feasibility varies across Australia although most specialist centres have recourse to interpreter services. • May have additional costs involved. • Increases satisfaction in healthcare for families and aims to increase health equity. • Decreases uncertainty and psychosocial consequences on families. • Families value accurate and understandable information.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-form
Research literature	One study directly identifies the use of interpreter services for information provision across the NBS for SMA healthcare journey as an enabler of effective and high-quality implementation of the program.
Support from experts	Excellent: Delphi survey Respondents 12, mean 8.83, 0 outliers. Systematic observation form Large benefit on improving psychological well-being of families (100%;7/7), knowledge of families (6/7; 86%), quality of life for families (100%;7/7), therapeutic decision making (86%;6/7), providing equal opportunity (86%;6/7), improving quality of life for newborn (5/7;71%) and small harm in increasing resources.
References	Kariyawasam et al. 2020.(10)

Evidence Table	
Recommendation	7.4. 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 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 also offer families the support of Indigenous Health Liaison services at the time of diagnosis.
Category/grade	Strong, Grade 1C.
Rationale	• No direct evidence across the scholarly literature. • Not generalisable across Australasian population. • **However,** substantial impact on the quality of information provision to fit the individual and specific needs of these families. Other considerations: • Dependent on resources that will determine feasibility and access to support services across Australia. • May have additional costs involved. • Potential to increase engagement and satisfaction in healthcare for families and aims to increase health equity. • Families value culturally competent and accurate and understandable information.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	None.
Support from experts	Poor: 1st Delphi round respondents 12, mean 6.67, outliers 5. Excellent 2nd round, respondents 12, mean 8.5, outliers 0. Systematic observation forms: Large benefit on improving psychological well-being of families (100%;6/6), knowledge of families (5/6; 83%), quality of life for families (100%;6/6), therapeutic decision making (83%;5/6), providing equal opportunity (67%;6/7), improving quality of life for newborn (3/5;60%) and small harm in increasing resources.
References	Not applicable.

Evidence Table	
Recommendation	7.5. 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.
Category/grade	Strong, Grade 1B.
Rationale	• Mostly consistent across the limited scholarly literature. • Fully generalisable across Australasian population. • Large impact on improving family well-being, acceptance and engagement with healthcare services. Other considerations:

	• Dependent on resources that will determine feasibility and access to support services across Australia. • May have additional costs involved. • Potential to increase engagement and satisfaction in healthcare for families and aims to increase health equity. • Families value and have strong preferences for being offered psychological support and care.
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	45 parents of newborns diagnosed with SMA through NBS. Assessments included three questionnaires including QoL survey, family burden questionnaire and work productivity assessment. High scores of personal strain and worry for future in all families, higher in families where infant was treated (however these infants were those with lower *SMN2* copy numbers). High social burden noted (p = 0.016). Work productivity assessment showed significant negative effects on daily activities of parents. Evidence to inform support through access to psychology, social services and advocacy groups (Kolbel et al. 2022).(122) The paediatric neuromuscular model of care in D'Silva et al. 2022(9) includes dedicated psychosocial input for families at a time of significant psychosocial stress at point of diagnostic disclosure. Mixed methods study of 50 parents with perspectives of NBS for SMA pathway show a theme of valuing embedded psychosocial support within NBS for SMA pathways (Meyer et. al.2024).(124)
Support from experts	Good: 1st Delphi round, respondents 13, mean 8.54, 1 outlier. Systematic observation forms: Large benefit on improving psychological well-being of families (5/6; 83%), knowledge of families (5/6; 83%), quality of life for families (5/6; 83%), therapeutic decision making (6/6; 100%), providing equal opportunity (4/6; 67%), improving quality of life for newborn (5/6; 83%) and small harm in increasing resources.
References	Meyer et al. 2024,(124) D'Silva et al. 2022,(9) Kolbel et al. 2022.(122)

Evidence Table	
Recommendation	7.6. 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.
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across the limited scholarly literature. • Fully generalisable across Australasian population. • Large impact on improving family well-being, acceptance and engagement with healthcare services. Other considerations: • Feasibility dependant on resources to revise currently available educational materials or develop and disseminate new materials. • May have additional costs involved. • Potential to increase engagement and satisfaction in healthcare for families, improve decision making and knowledge transfer. • Families value and have strong preferences for being offered educational materials to augment verbal diagnostic disclosure.

	• Coordination required to understand who within the healthcare system should be responsible for educational content and how to standardise this across jurisdictions.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Mixed methods study of 50 parents with a screen positive NBS result. Themes identified included difficulty in processing information due to complexity and emotional state with enablers of information provision inclusive of standardising information at diagnosis through written means (Meyer et al. 2024).(124) Written information also valued by parents in a separate mixed methods study to aid understanding of diagnosis and treatment options (Kariyawasam et al. 2021).(8)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.69, 0 outliers.
References	Meyer et al. 2024,(124) Kariyawasam et al. 2021.(8)

Evidence Table	
Recommendation	7.7. 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.
Category/grade	Strong, Grade 1C.
Rationale	• Fully consistent across the limited scholarly literature. • Fully generalisable across Australasian population. • Large impact on improving family well-being, acceptance and engagement with healthcare services. Other considerations: • Feasibility dependant on resources to revise currently available educational materials or develop and disseminate new materials. • May have additional costs involved. • Potential to increase engagement and satisfaction in healthcare for families, improve decision making and knowledge transfer. • Families value and have strong preferences for being offered educational materials to augment verbal diagnostic disclosure • Coordination required to understand who within the healthcare system should be responsible for educational content and how to standardise this across jurisdictions.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Mixed methods study of 50 parents with a screen positive NBS result. Themes identified included difficulty in processing information due to complexity and emotional state with enablers of information provision inclusive of standardising information at diagnosis through written means (Meyer et al. 2024).(124) Written information also valued by parents in a separate mixed methods study to aid understanding of diagnosis and treatment options (Kariyawasam et al. 2021).(8)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.69, 0 outliers.
References	Meyer et al. 2024,(124) Kariyawasam et al. 202.1(8)

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

Evidence Table	
Recommendation	8.1. 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.
Category/grade	Strong, Grade 1C.
Rationale	• No direct evidence across the literature. • Fully generalisable across Australasian population. • **Large** impact on improving time to treatment and subsequent health outcomes of newborns. Other considerations: • Feasible across Australasia. • No additional costs involved.
Evidence source	Limited: Delphi survey.
Research literature	Time to treatment is a significant modifier of health outcomes for newborns (Swoboda et al. 2005,(128) Kariyawasam et al. 2023(107) and Aragon-Gawinska et al. 2023 (118), therefore indirect evidence that diagnostic disclosure to families to start the process of treatment planning may reduce time to treatment and modify health outcomes for affected children.
Support from experts	Good: 1st Delphi round, respondents 13, mean 8.08, 1 outlier.
References	Swoboda et al. 2005,(128) Kariyawasam et al. 2023,(107) and Aragon-Gawinska et al. 2023 (118),

Evidence Table	
Recommendation	8.2. We suggest that ideally, diagnostic results should be disclosed to families by a specialist medical practitioner such as a paediatric neurologist.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat consistent evidence across the literature. • Somewhat generalisable across Australasian population. • Large impact on improving time to treatment, health outcomes for newborn, satisfaction with care for families, well-being and quality of life for families, for newborns. Other considerations: • May not be feasible across Australasia, dependent of health service set up and child and family factors. • Additional training may be required to support medical practitioners with appropriate disclosure strategies.
Evidence source	Number: Delphi survey, limited scholarly literature, systematic observation form.

Research literature	Implementation action identified as the need to provide a clinical team that is aware of circumstances to provide targeted but personalised management plan including psychosocial support. Options included immediate referral to the neuromuscular team or, for those with difficulties travelling long distances, with the local paediatrician and specialist telehealth support. Process identified was to establish a standard operating procedure to provide family centred care (D'Silva et al. 2022).(9) Implementational aspects for the effective translation of NBS for SMA included the ability to access specialist support/expertise by regional HCPs and need to develop expertise outside of specialist centres so that care could be shared between local and specialist centres. However, parents prefer and value early contact with paediatric neurologists as a means to manage psychological sequalae of a diagnostic result (Kariyawasam et al. 2021).(8) Other studies describe disclosure model of care (predominantly through paediatric neurologists) but do not interrogate family preferences, values. (Muller-Felber et al. 2023)(101)
Support from experts	Excellent: Delphi and systematic observation form. Good: 1st Delphi round, respondents 13, mean 8.08, 1 outlier. Systematic observation form: Large benefit for increasing knowledge for families (7/7; 100%), Reducing time to treatment (6/7; 86%), Improving therapeutic decision making for clinicians' Large benefit (6/7; 86%), Reducing psychological distress for families Large benefit (6/7; 86%), Promoting health equity for rural and remote families Large benefit (5/7;71%). Improving planned care for the newborn Large benefit (6/7; 86%). Increasing equity of access to specialist care for screen positive SMA newborns Small benefit (1/7; 14%).
References	D'Silva et al. 2022,(9) Kariyawasam et al. 2021(8), and Muller-Felber et al. 2023).(101)

Evidence Table	
Recommendation	8.3. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Limited evidence across the literature. • Somewhat generalisable across Australasian population. • **Large** impact on improving time to treatment, health outcomes for newborn, satisfaction with care for families, well-being and quality of life for families, for newborns and equity of access to care and support. Other considerations: • Additional training may be required to support medical practitioners with appropriate disclosure strategies. • Additional resources may be required to support telehealth services across Australasia (for conjoint specialist and local health practitioner disclosure strategies).
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Implementation action identified as the need to provide a clinical team that is aware of circumstances to provide targeted but personalised management plan including psychosocial support. Options included immediate referral to the neuromuscular team or, for those with difficulties travelling long distances, with the local

	paediatrician and specialist telehealth support. Process identified was to establish a standard operating procedure to provide family centred care (D'Silva et al. 2022).(9)
Support from experts	Good: 1st Delphi round, respondents 13, mean 7.92 1 outlier.
References	D'Silva et al. 2022.(9)

Evidence Table	
Recommendation	8.4. We suggest that ideally, diagnostic results should be disclosed to families face to face.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence across the literature. • Mostly generalisable across Australasian population. • **Large** impact on improving time to treatment, health outcomes for newborn, satisfaction with care for families, well-being and quality of life for families, for newborns, provision of appropriate multidisciplinary support. Other considerations: • May not be feasible for all families dependent on family and child centred factors.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.54 0 outliers.
References	Not applicable.

Evidence Table	
Recommendation	8.5. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence across the literature. • Mostly generalisable across Australasian population. • **Large** impact on time to treatment, health outcomes for newborn, satisfaction with care for families, well-being and quality of life for families, for newborns, provision of appropriate multidisciplinary support. Other considerations: • Potential to improve equity of access to diagnostic information and care planning, especially for families where it is not feasible to travel for a face to face appointment. • Providing child and family centred care as appropriate.

Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 7.62, 0 outliers.
References	Not applicable.

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

Evidence Table	
Recommendation	9.1. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat consistent across the literature, with variability dependent on availability of experts and jurisdictional healthcare referral pathways. • Fully generalisable across Australasian population. • **Large** impact on ability to determine clinical status accurately and reduce time to treatment, health outcomes for newborn, satisfaction with care for families, well-being and quality of life for families, for newborns, provision of appropriate multidisciplinary support. Other considerations: • Potential to improve equity of access to expert care and support. • Somewhat feasible across Australia and New Zealand as health jurisdictions linked with specialist neurology services. • Specialist review valued by families (Kariyawasam et al. 2021)(8), however flexibility needed dependent on family circumstances e.g. families travelling from regional/remote areas.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Review by paediatric neurologist recommended in some (observational studies) Muller-Felber et al. 2023,(101) McMillan et al. 2021.(100) Paediatric neurology expertise important in defining clinical status of the child to guide therapeutic decision making (Kariyawasam et al. 2020,(10) Finkel et al 2022,(129) and Aragon-Gawinska et al. 2023(118)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 9.00, outliers 0.
References	Kariyawasam et al. 2020.(10) Finkel et al. 2022(129), Aragon-Gawinska et al. 2023,(118) Muller-Felber et al. 2023,(118) McMillan et al 2021,(100) Kariyawasam et al. 2021).(8)

Evidence Table	
Recommendation	9.2.

	We suggest that all newborns confirmed with SMA should initially be managed within a paediatric neurology service.
Category/grade	Conditional, Grade 2C.
Rationale	• Consistent across the limited (observational studies) literature. • Fully generalisable across Australasian population. • **Large** impact on ability access to MDT care to support improvement of health outcomes for newborns. Also to access correct treatment efficiently, monitor for side effects of treatments to improve safety for newborn. Other considerations: • Potential to improve equity of access to expert care and support. • Somewhat feasible across Australia and New Zealand as health jurisdictions linked with specialist neurology services. • Management in a paediatric neurology centre with access to MDT support high valued by families (Kariyawasam et al. 2021).(8)
Evidence source	Numerous: Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	Review by paediatric neurologist recommended in some (observational studies) Muller-Felber et al. 2023,(101) McMillan et al. 2021.(100) Paediatric neurology expertise important in defining clinical status of the child to guide therapeutic decision making (Kariyawasam et al. 2020(10) and Aragon-Gawinska et al. 2023).(118) Being managed within a specialist MDT, with access to allied therapy, genetic counselling, psychological support and medical expertise highly valued by families (Kariyawasam et al. 2021).(8)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 9.00, outliers 0. Systematic observation form: Large benefit Reducing time to treatment (5/7; 71%, provision of early interventions to improve health outcomes (6/7; 86%), improving therapeutic decision making for clinicians (6/7; 86%) and families (6/7; 86%), forming a management plan for newborn (6/7; 86%), equity of access to care and support (6/7; 86%).
References	Kariyawasam et al. 2020(10) and Aragon-Gawinska et al. 2023,(118) Muller-Felber et al. 2023,(101) McMillan et al 2021,(100) Kariyawasam et al. 2021.(8)

Evidence Table	
Recommendation	9.3. 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.
Category/grade	Strong, Grade 1C.
Rationale	• Consistent across observational studies. • Fully generalisable across Australasian population. • **Large** impact on determination of clinical status, ensuring safety of child and pace of therapeutic decision making, to facilitate improved outcomes. Other considerations: • Feasible across Australia and New Zealand as health jurisdictions linked with specialist neurology services. • Medical practitioners may require knowledge and training to optimise clinical acumen o detect subtle features of SMA disease onset in the newborn.

Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	The multisystemic nature of SMA and its effects may precede motor involvement with dysautonomia and cardiac anomalies detailed as part of the clinical manifestation, detected through a comprehensive neonatal examination (Tizzano et al. 2017).(130) Comprehensive neurological examination important to identify subtle signs and symptoms of disease onset (Elkins et al. 2022).(71)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 9.00, outliers 0.
References	Kariyawasam et al. 2020(10)- and Aragon-Gawinska et al. 2023,(118) Muller-Felber et al. 2023,(118) Tizzano et al. 2017(130) Elkins et al. 2022.(71)

Evidence Table	
Recommendation	9.4. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat generalisable across Australasian population. • **Large** impact on newborn and family well-being and satisfaction with care. Other considerations: • Coordination required to ensure model of care is transparent and roles and responsibilities are defined. • Medical practitioners outside of specialist centres may require knowledge and training to optimise clinical acumen o detect subtle features of SMA disease onset in the newborn. • Potential for parents to value clinical care closer to home as well as access to specialist expertise as required. • Reconfiguration of healthcare resources may be required to develop this model of care.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Narrative summary that identifies wider resources required to access treatments including issues of equity, especially for families living regionally or with varying resources to attend specialist clinics. Solutions identified include building a hub and spoke model of care for post treatment monitoring where follow-up is shared or supported between specialist and regional centres (Gaviglio et al. 2023).(131)
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.38, outliers 0.
References	D'Silva et al. 2022(9), Gaviglio et al. 2023(131):

Evidence Table	
Recommendation	9.5. 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.

Category/grade	Conditional, Grade 2C.
Rationale	• Genetic complexity of SMN region means that genetic counselling is essential within an NBS program (Rouzier et al. (132) D'Amico et al.2020,(132) D'Amico et al. 2011).(133) Part of post diagnostic care is access to genetic counselling for families, which is valued by parents (Kariyawasam et al. 2020 and 2021. D'Amico et al. 2011).(133) Part of post diagnostic care is access to genetic counselling for families, which is valued by parents (Kariyawasam et al. 2020 and 2021).(8, 10) • Somewhat generalisable across Australasian population • **Large** impact on reproductive decision making for families and may be part of the aetiology for a changing incidence in the condition (Kay et al. 2020).(84) Other considerations: • Somewhat feasible: barriers include capacity of genetic services to provide cascade counselling and screening. • Education and training may be required within genetics and genetic counselling to optimise knowledge on available treatments (Zettler et al. 2022).(134) • Potential high resource needs require to implement this recommendation.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	As above.
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.69, outliers 0.
References	Rouzier et al. 2020,(132) Kay et al. 2020,(84) Zettler et al. 2022,(134) D'Amico et al. 2011(133) , Kay et al. 2020,(84)

Evidence Table	
Recommendation	9.6. We recommend 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.
Category/grade	Strong, Grade 1C.
Rationale	• Genetic complexity of SMN region means that genetic counselling is essential within an NBS program (Rouzier et al. (132) D'Amico et al.2020,(132) D'Amico et al. 2011).(133) Part of post diagnostic care is access to genetic counselling for families, which is valued by parents Kariyawasam et al. 2020 and 2021.(8, 10), D'Amico et al. 2011).(133) Part of post diagnostic care is access to genetic counselling for families, which is valued by parents (Kariyawasam et al. 2020 and 2021).(8, 10) • Somewhat generalisable across Australasian population. • **Large** impact on reproductive decision making for families and may be part of the aetiology for a changing incidence in the condition (Kay et al. 2020).(84) Other considerations: • Somewhat feasible: barriers include capacity of genetic services to provide cascade counselling and screening. • Education and training may be required within genetics and genetic counselling to optimise knowledge on available treatments (Zettler et al. 2022).(134)

	• Potential high resource needs require to implement this recommendation.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	As above.
Support from experts	Excellent: 1st Delphi round, respondents 13, mean 8.69, outliers 0.
References	Rouzier et al. 2020,(132) Kay et al. 2020,(84) Zettler et al. 2020,(132) D'Amico et al. 2011(133), Kariyawasam et al.2020,(132) Kay et al. 2020,(84) Zettler et al. 2022,(134) D'Amico et al. 2011(133)

Evidence Table	
Recommendation	9.7. We suggest that 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence within the literature. • Somewhat generalisable across Australasian population. • **Large** impact on access to care and support for siblings. Other considerations: • Somewhat feasible: barriers include capacity of clinical and genetic. services to provide clinical review and access to genetic testing. • Potential high resource needs require to implement this recommendation.
Evidence source	Limited: Delphi survey.
Research literature	No applicable.
Support from experts	Satisfactory: 1st Delphi round, respondents 13, mean 7.31, outliers 2. Good: 2nd round with rewording: respondents 13, mean 7.93, outliers 1.
References	Not applicable.

Evidence Table	
Recommendation	9.7. We recommend 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.
Category/grade	Conditional, Grade 2C.
Rationale	• No evidence within the literature. • Fully generalisable across Australasian population. • **Large** impact on access to care and support for siblings. Other considerations: • Somewhat feasible: barriers include capacity of clinical and genetic services to provide clinical review and access to genetic testing. • Potential high resource needs require to implement this recommendation, with requirements for education and training for medical practitioners.

Evidence source	Limited: Delphi survey.
Research literature	No applicable.
Support from experts	Satisfactory: 1st Delphi round, respondents 13, mean 7.46, outliers 2. Excellent: 2nd round with rewording: respondents 13, mean 7.62, outliers 0.
References	Not applicable.

Evidence Table	
Recommendation	9.8. We suggest that symptomatic status of the newborn should be defined by medical practitioners primarily by the presence of signs and symptoms of SMA on neurological and neonatal examination.
Category/grade	Conditional, Grade 2C.
Rationale	• Not fully consistent outcomes amongst observational studies. • Fully generalisable across Australasian population. • **Large** impact on time to treatment and health outcomes for newborns (Kariyawasam et al. 2023).(107) • Risk is the inability to detect subtle signs and symptoms of disease onset on clinical exam alone (Kariyawasam et al. 2020,(10) Finkel et al 2022.(129) Other considerations: • Fully feasible across the population, especially in health jurisdictions that do not have access to adjunctive assessments. • Potential resource needs require to implement this recommendation, with requirements for education and training for medical practitioners to understand subtle onset of disease in SMA.
Evidence source	Limited: Delphi survey.
Research literature	Clinical examination is the mainstay of post diagnostic assessment and can determine disease onset.
Support from experts	Good. 1st Delphi round, respondents 13, mean 7.92, outliers 1.
References	Kariyawasam et al. 2023, (107), Kariyawasam et al. 2020,(10) Finkel et al 2022.(129)

Evidence Table	
Recommendation	9.9. 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.
Category/grade	Conditional, Grade 2C.

Rationale	• Not consistent outcomes amongst observational studies. • Not fully generalisable across Australasian population. • Moderate impact on time to treatment and health outcomes for newborns (Kariyawasam et al. 2023).(107) • Risk is the inability to detect subtle signs and symptoms of disease onset on clinical exam alone. Kariyawasam et al. 2020,(10) Finkel et al 2020(129) • Benefit: Neurophysiological techniques can be an adjunctive measure to determine disease onset. Other considerations: • Somewhat feasible across the population. Barriers to implementation include health jurisdictions that do not have access to the expertise and equipment to perform these assessments. • Potential resource needs require to implement this recommendation, with requirements for education and training for medical practitioners to develop neurophysiological skills in newborns and infants.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	D'Silva et al. 2022(9) use a knowledge to action framework to generate real-world outcomes to inform changes in clinical practice. Authors conclude that neurophysiology assessments are a useful adjunct to clinical exam to identify disease onset (which may be within period of first clinical review). Weng et al. 2021(135) CMAP at baseline in 12 newborns (cohort study) may predict motor response. Serial CMAP showing decline denote disease onset even in absence of clinical symptoms. Kariyawasam et al. 2020(10) Disease onset identified in one newborn prior to evolution of clinical signs and symptoms of SMA in a screen positive newborn. McMillan et al. 2021(100) For newborn with 2 or 3 *SMN2* copies, recommendation for immediate treatment. Neurophysiology not recommended for this treatment group as it does not change management. Surveillance includes motor assessments but not neurophysiology.
Support from experts	Good. 1st Delphi round, respondents 12, mean 8.33, outliers 1.
References	Kariyawasam et al. 2023(107), Kariyawasam et al. 2020,(10) Finkel et al 2022.(129), Weng et al. 2021(135), McMillan et al.2021(100) D'Silva et al. 2022.(9)

Section 10. Treatment planning in children diagnosed with SMA through NBS

Evidence Table	
Recommendation	10.1. We suggest that treatment planning should commence as soon as the *SMN1* diagnostic result is received.
Category/grade	Conditional, Grade 2C.
Rationale	• No direct evidence base from the scholarly literature. However, indirect evidence shows health outcomes are founded on rapid treatment of infants diagnosed with SMA, especially for those with 2 *SMN2* copies (Lee et al. 2021 (102)) who have higher probability of improvements in motor outcomes and reduction in comorbidities with reduced time to treatment. • Mostly generalisable across the population. • Large impact on time to treatment, and therefore health outcomes of the newborn. Other factors for evidence to decision making: • Feasibility of implementing this recommendation may be based on access to centres with expertise for treatment planning. • Treatment access also founded on *SMN2* copy number and therefore diagnostic confirmation of this prognostic biomarker may change therapeutic decision making. • Values and preferences of families show an inclination to expedient access to treatment. • No evidence to determine if this specific recommendation is acceptable to ALL stakeholders.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Good. Delphi survey 13 respondents, mean 8.08, outlier 1.
References	Lee et al. 2021 (102)

Evidence Table	
Recommendation	10.2 We recommend that for newborns who demonstrate signs and symptoms of SMA, options for immediate treatment with SMN augmenting treatments should be discussed with the family and started without delay.
Category/grade	Strong, Grade 1A
Rationale	• Fully consistent across scholarly literature. • Somewhat generalisable to current population. • Large impact on time to treatment and reduction in disease duration which is a known modifier of long-term health outcomes. • The overall certainty of effects is high. Other factors for evidence to decision making: • Feasibility of implementation of this recommendation is based on access to treatment centres with expertise and knowledge in initiation of treatments, which is jurisdictionally dependent. • Health equity may be improved by ensuring time to treatment is as short as possible. • Values and preferences of families show an inclination to expedient access to treatment.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Randomised control trials of SMN augmenting treatments in symptomatic children with SMA show improved survival, motor outcomes, and reduction of comorbidities with shorter disease duration. (Finkel et al. 2017)(121) Systematic review using outcomes from 153 newborns (combined symptomatic and presymptomatic) across clinical trials in real world studies show a high probability of normal motor development if treated before the age of 6 weeks. (Aragon-Gawinska et al. 2023).(118) Time to treatment for symptomatic children changed final HINE scores for children with SMA (Kariyawasam et al. 2023).(107) Expert evidence of panel of 5 members determines urgency to treat infants and young children to minimise loss of motor neurons (Ramos Platt et al. 2022).(136)
Support from experts	Good. Delphi survey passes consensus respondents 13, mean 8.54, outlier 1.
References	(Finkel et al. 2017)(121) (Aragon-Gawinska et al. 2023).(118) (Kariyawasam et al. 2023).(107) (Ramos Platt et al. 2022).(136)

Evidence Table	
Recommendation	10.3. We suggest that for newborns who demonstrate signs and symptoms of SMA (consistent with disease onset) with 1 *SMN2* copy, therapeutic decision making is dependent on the newborn/infant's clinical status and open discussions with families regarding treatment options or referral for supportive care alone.
Category/grade	Conditional, Grade 2C
Rationale	• Mostly consistent across scholarly literature. • Fully generalisable to current population. • Large impact on newborn quality of life and well-being and potential to have impact on health services managing children with long-term needs. Other factors for evidence to decision making: • Family values and preferences will determine management pathways. • Training and education for medical practitioners supporting these conversations may be required. • Health system resources to ensure supportive care and palliative services are in place may be jurisdictionally dependent, which may influence the feasibility of implementation for the recommendation.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Paucity of data on which to inform decision making for newborns diagnosed with SMA with 1 *SMN2* copy with no clinical trials including children with this genotype. (Carvalho et al. 2023),(137) however children are generally significantly symptomatic at birth (Tizzano et al.2017)(130) In a systematic review looking at outcomes from 3/153 newborns with 1 *SMN2* copies, 2 died without treatment, and 1 who was treated at 2.5 months was invasively ventilated, supplementally fed, with minimal motor improvements at 6 months (Aragon -Gawinska et al. 2023).(118) For newborns with 1 *SMN2* copy, the treatment is at the discretion of clinical expert and based on the clinical status of the child. (Glascock et al. 2018)(123)
Support from experts	Good. Delphi survey passes consensus 13 respondents, mean 8.08, outlier 1.
References	(Carvalho et al. 2023),(137) (Tizzano et al.2017)(130) (Aragon -Gawinska et al. 2023).(118) (Glascock et al. 2018)(123)

Evidence Table	
Recommendation	10.4 We recommend that for newborns with diagnostic confirmation of SMA and 1,2, or 3 *SMN2* copies who are presymptomatic, options for immediate SMN augmenting treatments should be discussed with the family and started without delay.
Category/grade	Strong, Grade 1B.
Rationale	• Mostly consistent across scholarly literature. • Somewhat generalisable to SMA population but subpopulations may have differing outcomes. • Large impact on time to treatment and therefore long-term health outcomes for newborns. Other factors for evidence to decision making: • Feasibility of implementation of this recommendation is based on access to treatment centres with expertise and knowledge in initiation of treatments, which is jurisdictionally dependent. • Health equity may be improved by ensuring time to treatment is as short as possible across all diagnosed newborns. • Values and preferences of families show an inclination to expedient access to treatment.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Immediate treatment for presymptomatic children is founded on biological plausibility with precipitous degeneration of motor neurons noted in the neonatal period which is apparent across on SMN2 copies numbers but is especially precipitous in children with 2 *SMN2* copies (Swoboda et al).(138) Systematic review of the evidence in 22/36 children treated presymptomatically no delays in motor development were noted at mean age of 15 months (range of 1-28 months). In 13/36 subjects clear motor delay was reported. (Aragon-Gawinska et al. 2023)(118) Outcomes for children treated presymptomatically are dependent on copy number with reduction in disease duration inversely correlated with a greater magnitude of benefit noted consistently for children with 2 *SMN2* copies, Australian PBAC notes the magnitude of benefit for children who are presymptomatic and who have 3 *SMN2* copies is less clear from the clinical data available,and consider the incremental benefit of presymptomatic treatment with one of the SMN augmenting treatments (gene therapy) compared to symptomatic treatment for children with this genotype would be less than 4 patients with 1-2 *SMN2* copies. (139-141) There is remaining uncertainty regarding the cost-effectiveness of presymptomatic treatment for all presymptomatic children with SMA due to uncertain magnitude of incremental benefits compared to symptomatic treatment. However, acceptability for families to await treatment could be low due increasing anxiety and hypervigilance in waiting for symptoms to develop. (139-141)
Support from experts	Excellent. Delphi survey passes consensus 13 respondents, mean 8.54, outlier 0.
References	(Swoboda et al).(138) (Aragon-Gawinska et al. 2023)(118), The Pharmaceutical Benefits Advisory Committee (139-141)

Evidence Table	
Recommendation	10.5 We recommend that in the absence of comparative data, single agent treatment should be initiated.
Category/grade	Strong, Grade 1C.
Rationale	• No head-to-head comparative trials between SMN augmenting treatments. • Fully generalisable to current population. • Unknown risk-benefit profile of initiating combination or sequential SMN treatments and evidence gap on if and who would most benefit from regimens other than single agent interventions. • Feasibility of implementation of this recommendation is based on access to treatment centres with expertise and knowledge in safe initiation of treatments, which is jurisdictionally dependent. • High cost therapeutics and therefore starting treatments in combination without delineation of magnitude of benefit may not be cost effective or sustainable to health systems.
Evidence source	Limited: Delphi survey
Research literature	Not applicable
Support from experts	Good. Delphi survey passes consensus 12 respondents, mean 8.17, outlier 1.
References	Not applicable

Evidence Table	
Recommendation	10.6 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.
Category/grade	Strong, Grade 1C
Rationale	• Somewhat consistent evidence across scholarly literature • Fully generalisable to the population • Large impact on reducing time to treatment and therefore changing the magnitude of health benefits for newborns. Empowers families to become engaged and informed on therapeutic choices and rationale and is a low risk recommendation Other considerations • Recommendation is already part of best practice and does not incur resource adjustments • Families value informed decision making
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Kichula et al. 2021(142) International panel of seven experts produced a narrative summary determining that clinicians should discuss timing of treatment and be informed of the urgency for children with 2 SMN2 copies, to prevent irreversible

	loss of motor unit pool within 2 months of age. Goals of care to be based on the clinical context and genotype and shared with families.
Support from experts	Excellent: 1st round Delphi, respondents 21, mean 8.67, outlier 0
References	Kichula et al. 2021 (142)

Evidence Table	
Recommendation	10.7 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.
Category/grade	Strong, Grade 1C
Rationale	• No direct evidence across scholarly literature • Fully generalisable to the population • Large impact on information exchange on uncertainties, risks and benefits of treatments. Empowers families to become engaged and informed on therapeutic choices and rationale and is a low-risk recommendation. Other considerations • Recommendation is already part of best practice and does not incur resource adjustments • Families value informed decision making
Evidence source	Limited: Delphi survey
Research literature	Not applicable
Support from experts	Excellent: 1st round Delphi: respondents 13, mean 8.69, outlier 0
References	Not applicable

Evidence Table	
Recommendation	10.8. 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.
Category/grade	Strong, Grade 1C
Rationale	• Fully consistent evidence across scholarly literature, for incorporating the above factors into therapeutic decision making • Fully generalisable to the population • Large impact on optimising benefits and mitigating harms to newborn, tailored to biopsychosocial factors. • Families value tailored and shared therapeutic decision making.
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Discrete choice experiment of 1113 stakeholders (HCPS, parents and general population) showed that treatments that improved function and mobility were highly

	valued and those with higher costs, invasive delivery and risks of adverse events were less acceptable (within a symptomatic SMA population) (Carey et al. 2022)(143) *SMN2* copy number, current motor function and disease duration and clinical status are variables that can all change health outcomes and should be incorporated in therapeutic decisions and setting of goals of care (Kariyawasam et al. 2023)(107)
Support from experts	Good: 1st round Delphi: respondents 13, mean 8.54, outlier 1
References	(Carey et al. 2022)(143) , (Kariyawasam et al. 2023)(107)

Evidence Table	
Recommendation	10.9 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.
Category/grade	Conditional, Grade 2B
Rationale	• Fully consistent evidence across scholarly literature • Fully generalisable to the population • Large impact on optimising information provision, support and care to facilitate family understanding, sense of well-being and engagement with healthcare services. Minimal risks from this recommendation. • Families value ongoing information and support as their feelings and perspectives evolve during the SMA healthcare journey Other considerations • Feasibility of implementing this recommendation dependent of jurisdictional healthcare resources. • May increase health inequities for families who cannot access support services due to sociodemographic factors e.g. families from remote or regional areas or secondary to limitations on the capacity of available support services within a health jurisdiction.
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Significantly decreased quality of life, reduced work productivity and increased social burden of care noted in parents of children undertaking treatments for SMA compared to parents not undertaking treatments for their children (Kolbel et al 2022), with conclusions drawn that therapeutic decision making and embarking on treatments is psychologically challenging for families. Families value psychological support and information as they make decisions for their children (Meyer et al. 2024 (124) and Kariyawasam et al. 2021(8)) Rigorous Delphi methodology leading to consensus statements from SMA experts has recommended that therapeutic decisions be made within multidisciplinary teams (Pitarch Castellano et al. 2022)(127)
Support from experts	Excellent: 1st round Delphi respondents 13, mean 8.69, outlier 0
References	Meyer et al. 2024 (124), Kariyawasam et al. 2021(8), Pitarch Castellano et al. 2022(127)

Evidence Table	
Recommendation	10.10 We recommend that the administration of SMN augmenting treatments should occur in a specialist (paediatric neurology) care centre.
Category/grade	Grade 1C
Rationale	• Mostly consistent across scholarly literature as nearly all studies refer to treatment being started in paediatric neurology centres • Mostly generalisable to the population • Large impact on ensuring risks of treatment are mitigated with access to standardised processes for storage of agents (including biological agents), administration and post administration surveillance. Access to expert care to mitigate adverse events. • Other considerations • May increase health inequities for families who cannot access specialist services due to sociodemographic factors e.g. families from remote or regional areas, safety concerns of travelling with a symptomatic child or due to the capacity of jurisdictional services to provide centralised services for SMA treatment. • May not be appropriate for all treatments such as oral splicing modifiers that can be started in the community.
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Studies of newborn screening programs internationally show implementation of centralised services to facilitate treatment of children with SMA diagnosed through newborn screening. Rigorous Delphi process conducted with SMA experts show consensus to start treatment for SMA in specialist centres to improve safety for children receiving interventions (Pitarch Castellano et al 2022)(127)
Support from experts	Excellent: 1st round Delphi: respondents 12, mean 8.67, outlier 0
References	(Pitarch Castellano et al 2022)(127)

Evidence Table	
Recommendation	10.11 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.
Category/grade	Grade 2C
Rationale	• Somewhat consistent evidence across the limited scholarly literature • Somewhat generalisable to the population • Large impact on allowing for the preferences of the family for example in being treated close to home. Considerations include clinical status of child, modality of SMN augmenting treatment being considered, the capacity and capability of local services to facilitate treatment and surveillance, a robust and coordinated plan to evaluate efficacy and safety. • Other considerations

	• May reduce health inequities for families who cannot access specialist services due to sociodemographic factors e.g. families from remote or regional areas or due to the capacity of jurisdictional services to provide centralised services for SMA treatment. • May not be appropriate for all treatments such as gene therapies that require standardised approvals for access, storage and administration due to their biological status.
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Narrative review that suggests that resources are required to provide equity of access to SMA treatments and surveillance of effects for families living regionally or without resources to travel and attend specialist clinics (missed work and family days, costs of travel, impact on siblings), with a potential solution to implement a hub and spoke model of shared care between tertiary, secondary and community services (Gaviglio et al. 2023)(131)
Support from experts	Good 1st round Delphi: 11 respondents, mean 6.27, outlier 6 2nd round Delphi (with rewording) 13 respondents, mean 8.08, 1 outlier
References	(Gaviglio et al. 2023)(131)

Evidence Table	
Recommendation	10.12 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.
Category/grade	Conditional, Grade 2C
Rationale	• No evidence across scholarly literature • Somewhat generalisable to the population • Large impact on allowing for the preferences and values of the family. Considerations include clinical status of child, modality of SMN augmenting treatment being considered, the capacity and capability of local services to facilitate surveillance, a robust and coordinated plan to evaluate efficacy and safety. May improve family wellbeing and satisfaction with care. • Other considerations • May reduce health inequities for families who cannot access specialist services due to sociodemographic factors e.g. families from remote or regional areas or due to the capacity of jurisdictional services to provide centralised services for ongoing (frequent) monitoring of treatment effects. • Families may prefer and value in being managed closer to home, especially if clinical course post treatment is stable. • May change workload of services across the health system, improving capacity in some domains and increasing resourcing burdens on others.
Evidence source	Limited: Delphi survey
Research literature	None
Support from experts	Excellent. 1st round Delphi: 12 respondents, mean 7.82, outlier 0

References	Not applicable

Evidence Table	
Recommendation	10.13 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.
Category/grade	Strong, Grade 1C
Rationale	• Somewhat consistent evidence across the limited scholarly literature. • Somewhat generalisable to the population. • Large impact on health outcomes for children to clinically determine a therapeutic window for intervention, which may be optimised through expert clinical review and adjunctive assessments. Risks of over-surveillance for some children noted however benefits (to detect disease onset at the earliest juncture) outweigh risks. • Other considerations • May reduce health inequities for families of newborns who cannot access treatments immediately due to Australasian approval and reimbursement structures.
Evidence source	Limited: Delphi survey
Research literature	Delphi methodology of international experts determines that a neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function, which would improve time to treatment and health outcomes for this subpopulation (Glascock et al. 2018).(123)
Support from experts	Excellent. 1st round Delphi 13 respondents, mean 8.54, outlier 0
References	(Glascock et al. 2018).(123)

Evidence Table	
Recommendation	10.14 We suggest that newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.
Category/grade	Conditional, Grade 2C
Rationale	• Somewhat consistent across scholarly literature. • Somewhat generalisable to the population. • Large impact on health outcomes for children to clinically determine a therapeutic window for intervention, which may be optimised through regular expert clinical review and adjunctive assessments. Benefits are to facilitate the detection of disease onset at the earliest juncture for intervention to optimise outcomes and risks include potential of over surveillance to the newborn and an increased logistical and psychological

	burden to families to engage in serial assessments throughout this period of time Other considerations • May help to reduce the health inequities for families of newborns who cannot access treatments immediately due to Australasian approval and reimbursement structures
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	International expert consensus established using a Delphi methodology determines that frequent assessments within the first 2 years of life are required as children with disease onset at this time are more likely to have the severe or intermediate forms of SMA, with a rapid decline in function (Glascock et al 2018).(123) Once the child reaches two years of age having achieved motor milestones, an early severe form of SMA can be considered excluded and the follow-up frequency can be reduced, as less severe forms of disease are known to have later onset and slower functional decline.
Support from experts	Excellent. 1st round Delphi 13 respondents, mean 8.23, outlier 0.
References	(Glascock et al 2018).(123)

Evidence Table	
Recommendation	10.15 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
Category/grade	Strong, Grade 1C
Rationale	• No direct evidence base • Fully generalisable to the population • Large impact in optimising health outcomes by facilitating assessment of changes in clinical status, signs and symptoms of deterioration or unmet clinical needs necessitating escalation or change in management. Large impact in evaluating effects (benefits and risks) of interventions. Minimal risk to child and family. Other considerations • Currently part of best practice care and therefore no additional resource implications expected.
Evidence source	Limited: Delphi survey
Research literature	Not applicable
Support from experts	Excellent. 1st round Delphi: 13 respondents, mean 8.03-9.00, 0 outliers

References	Not applicable
Evidence Table	
Recommendation	10.16 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 take into account 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
Category/grade	Conditional, Grade 2C
Rationale	• No direct evidence as to which motor assessments should be utilised, however motor assessments can augment clinical examination to increase sensitivity to detect changes that may overly disease onset/progression • Fully generalisable to the population • Large impact on optimising health outcomes by facilitating assessment for changes in clinical status, signs and symptoms of deterioration or unmet clinical needs necessitating escalation or change in management. Large impact in evaluating effects (benefits and risks) of interventions. Minimal risk to child and family. • Non-invasive assessments therefore minimal risk to the child Other considerations • The expertise and training required to conduct assessments may be jurisdictionally dependent and preclude the feasibility of implementation of this recommendation.
Evidence source	Number: Scholarly literature and Delphi survey
Research literature	Not applicable
Support from experts	Excellent. 1st round Delphi 12 respondents, mean 8.05, 0 outliers
References	Not applicable

Evidence Table	
Recommendation	10.17 We recommend that evaluators must meet the standards for training for the administration of each examination or assessment.
Category/grade	Strong, Grade 1C
Rationale	• No direct scholarly evidence • Fully generalisable across target population • Large impact in standardising assessments to minimise intra and interobserver variabilities, so that decision making is informed by accurate data. Other considerations • Training, education, peer review and mentorship may be required for evaluators to gain skills, competence and confidence in performing assessments. • Training and education of evaluators may impact on health resources

Evidence source	Limited: Delphi survey
Research literature	Not applicable
Support from experts	Excellent. 1st round Delphi respondents 12, mean 8.67, outlier 0.
References	Not applicable

Evidence Table	
Recommendation	10.18 We recommend that all children diagnosed with SMA through newborn screening should be referred for multidisciplinary allied therapy interventions.
Category/grade	Strong, Grade 1C
Rationale	• Scholarly evidence determines that access to treatments across Australasia are prefaced on children with SMA being managed within a multidisciplinary setting (PBAC) (139-141), however there is no direct scholarly evidence for the impact of access to MDT care for children receiving a diagnosis through NBS. The clinical benefit of managing children who continue to have a normal developmental trajectory (i.e. those treated presymptomatically and/or with 3 *SMN2* copies) is uncertain. • Fully generalisable to target population • Large impact in optimising health outcomes, proactively identifying and planning for future health challenges, and reducing risks of comorbidities. Large impact on well-being of affected children and their families, especially if psychological support and counselling are part of the MDT model. Large impact on satisfaction and engagement with care. Other considerations: • Resources for multidisciplinary model of care are jurisdictionally dependent but as all children with SMA should be managed in a setting aligned with international standards of care, and this should augment current best practice recommendations.
Evidence source	Number: Delphi survey
Research literature	Not applicable
Support from experts	Excellent 1st round Delphi: 13 respondents, mean 8.69, outlier 0.
References	The Pharmaceutical Benefits Advisory Committee (139-141)

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

Evidence table	
Recommendation	11.1. 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 may occur with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat inconsistent outcomes, amongst observational studies and data indirectly informs recommendation. • Somewhat generalisable across Australasian population. • Large impact on time to treatment and health outcomes for newborns with this genotype. • Risk is of burdening families with serial assessments. • Impact (benefit) outweighs risk as considered by the GDG. Other considerations: • Somewhat feasible across the population, however regular surveillance may require additional resources to implement this recommendation, due to need frequent follow-up. • Value and preference of families with newborn with ≥ 4 *SMN2* genotype is unknown. • Potential resource needs require to implement this recommendation, with requirements for education and training for medical practitioners to develop neurophysiological skills in newborns and infants.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Recommendations that a higher frequency of clinical visits are required early on for those who do not access treatment and are ≥ 4 *SMN2* copies. Diminishing frequency of visits recommended as less severe forms of disease have later onset, so that burden of clinical visits can be balanced with minimising treatment related risks with less severe SMA (Glascock et al. 2018).(123) However, in Vill et al. 2021(80) 43 screen positive newborns identified with 4 *SMN2* copies and no phenoconversion to symptomatic status noted in first 12 months of follow-up. Vill et al 2024:(144) Median disease onset for 268 screen positive newborns is 3y (range 1 month-6.4y). Ricci et al. 2023,(145) of 4 presymptomatic children with this genotype (diagnosed through NBS and through family history), none showed symptoms by at 2.5 +/- 1 year. Muller Felber et al. 2020.(146) One child in cohort series of 15 children with ≥ 4 *SMN2* copies developed symptoms by 8 months age. Heterogeneity of timing of disease onset makes it difficult to ascertain surveillance regimen for children with ≥ 4 *SMN2* copies.
Support from experts	Excellent 1st Delphi round, respondents 11, mean 8.09 outlier 0.
References	Vill et al. 2021 and 2024,(80, 144) Glascock et al. 2018,(123) Muller-Felber et al. 2020(146), Ricci et al. 2023.(145)

Evidence table	
Recommendation	11.2. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Somewhat consistent outcomes across the limited data amongst observational studies and data indirectly informs recommendation. • Somewhat generalisable across Australasian population. • Large impact on access to treatment, therapeutic decision making and prognostication of health outcomes for newborns with this genotype. • Impact (benefit) outweighs other consideration as considered by the GDG. Other considerations: • Somewhat feasible across the population, however additional resources may be required to implement this recommendation: may affect workflow of diagnostic services however as children with 4 *SMN2* copy number make up only 10% of the population, cases for repeat *SMN2* copy confirmation will not be high. • Psychological impact on parents of changing prognostic information not well explored or understood.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Muller-Felber et al. 2020(146) 38 screen positive newborns with 40% ≥ 4 *SMN2* copies. copies. Due to methodological imprecision in identifying SMN2 copy number accurately, Determination of *SMN2* copy number with up-to-date methodologies and in different laboratories advised. Blaschek et al. 2022;(147) 3/21 patients had redetermination of genotype.
Support from experts	Excellent, 1st Delphi round, respondents 11, mean 8.09 outlier 0.
References	Muller-Felber et al. 2020,(146) Blaschek et al. 2022.(147)

Evidence table	
Recommendation	11.3. We suggest incorporating assessments 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 screen for disease onset as the basis to initiate therapeutic intervention.
Category/grade	Conditional, Grade 2C.

Rationale	• Somewhat inconsistent outcomes across the limited data amongst observational studies and data indirectly informs recommendation. • Somewhat generalisable across Australasian population. • Large impact on access and timing of treatment, therapeutic decision making and ultimately health outcomes for newborns with this genotype. • Impact (benefit) outweighs other consideration as considered by the GDG. • Risk is the challenges in tolerating serial assessments within the newborn period and subsequent potential ramifications on family well-being, engagement with monitoring and satisfaction with care received. • Benefit: Neurophysiological techniques can be an adjunctive measure to determine disease onset, to target a therapeutic window. • • Other considerations: • Somewhat feasible across the population: Barriers to implementation include health jurisdictions that do not have access to the expertise and equipment to perform these assessments. • Potential resource needs require to implement this recommendation, with requirements for education and training for assessors.
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Surveillance can include clinical exam, motor function scores, muscle ultrasound and neurophysiology. EMG can detect neurogenic process in patients, but this is not well tolerated on repeated attempts. CMAP can be normal in patient with SMA type III despite underlying motor neuron loss and is not a sensitive biomarker for disease onset in those with chronic denervation Muller-Felber et al. 2020.(146) Expert consensus (Glascock et al. 2018)(123) determined that CMAP and EMG assessments has potential value in defining disease onset.
Support from experts	Excellent: 1st Delphi round, respondents 11, mean 8.09 outlier 0.
References	Muller-Felber et al. 2020(146) and Glascock et al 2018.(123)

Evidence table	
Recommendation	11.4. 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.
Category/grade	Conditional, Grade 2C.
Rationale	• Fully consistent outcomes across the limited data amongst observational studies and data indirectly informs recommendation. • Somewhat generalisable across Australasian population. • Large impact on time to treatment, and ultimately health outcomes for newborns with this genotype. Large impact on family wellbeing and satisfaction with care. • Impact (benefit) outweighs other consideration as considered by the GDG. Other considerations: • Somewhat feasible across the population: Barriers to implementation include health jurisdictions that do not have access to the resources to implement this recommendation. • Families value ongoing care and support through MDT services independent of their access to treatments (Kariyawasam et al. 2021).(8).
Evidence source	Number: Scholarly literature and Delphi survey.
Research literature	Blaschek et al. 2022.(147) 3/21 patients diagnosed with SMA through NBS with 4 *SMN2* copies lost to follow-up suggesting a compliance issue with clinical surveillance strategy.
Support from experts	Excellent 1st Delphi round, respondents 12, mean 8.67 outlier 0.
References	Blaschek et al. 2022.(147)

Evidence table	
Recommendation	11.5. 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.
Category/grade	Conditional, Grade 2C
Rationale	• No scholarly literature. • Large impact on understanding the outcomes for children with 4 *SMN2* copies and addressing the evidence gap on when it is best to treat these children. • Potential to narrow therapeutic benefit vs risk of over surveillance or over treatment. • Impact (benefit) of implementing this recommendation outweighs other consideration as considered by the GDG. Other considerations: • Fully feasible across the population with coordination between specialist centres to collate standardised data.
Evidence source	Limited: Delphi survey.
Research literature	Not applicable.
Support from experts	Excellent 1st Delphi round, respondents 11, mean 8.45 outlier 0.
References	Not applicable.

Evidence Summaries of Individual Studies

Narrative synthesis

The output from the systematic literature review was heterogenous in terms of study quality, endpoints, population and settings. It was considered that meta-analysis of the evidence base was not the appropriate strategy for data synthesis. A narrative synthesis was considered appropriate as has been used in other clinical practice guidelines for rare conditions (ref). Evidence summaries of individual studies were formulated and used by the GDG to grade the quality of evidence and form recommendations.

Evidence summary table for the evaluation of first tier and second tier newborn screening processes for SMA

Author, year	Level of Evidence	Study description	First tier (*SMN1*) screening	Second tier (*SMN2*) screening	Comments/Appraisal
Boemer et al. 2021 (51)	IV	Prospective cohort study	136,339 neonates screened. DBS used. Target analyte exon 7 deletion using RT-PCR. 9 screen positive cases. No false negative or false positive. 1 compound heterozygote neonate with clinical symptoms at 4 months.	*SMN2* completed on DBS using MLPA.	Selection bias minimised by prospective consecutive sampling of the population and a large sample size. Methodology for first tier testing validated with 53 SMA patients and heterozygous carriers, and with a pre-pilot of 1000 NBS samples.
Singh et al. 2023 (52)	IV	Review	DBS cards used and DNA extracted using PCR. Screening multiplexed with assays for SCID with pace of implementation for NBS across USA fastest for SMA when compared to SCID, X-ALD and Pompe disease		Limited narrative on the variability of screening assays used for NBS for SMA
Groulx-boivin et al 2024 (53)	IV	Qualitative cohort study	Numerous techniques used for NBS for SMA including quantitative polymerase chain reaction (qPCR), multiplex ligation-dependent probe amplification (MLPA), MassArray, and droplet digital polymerase chain reaction (ddPCR), all of which can potentially be used to determine *SMN1* deletion status and *SMN2* copy number. Differences exist in what constitutes a positive screening test among Canadian provinces. The Saskatchewan NBS program reports all biallelic *SMN1* deletions, whereas Alberta, Manitoba, Ontario, and more recently BC only report newborns with		Small number of respondents and not all states conducting NBS for SMA at time of study. Survey administered to all 8 screening labs in Canada. 4 labs conducting NBS for SMA at the time of study with 11 respondents

			biallelic *SMN1* deletions who also have ≤4 copies of *SMN2*.		
Boemer et al. 2019 (54)	IV	Prospective cohort study	qPCR assay of *SMN1* gene on DNA extracted from DBS. Target analyte homozygous exon 7 deletion. 53 known children with SMA and 93 carrier screened, and also 1000 DBS cards. 100% sensitivity and specificity.	*SMN2* assay not conducted.	Small population size to validate test method, leading to potential for selection bias. Assumption that *SMN2* copy number does not affect assay.
Tesorero et al. 2023 (55)	IV	Prospective cohort study	96, 694 Neonates screened. DBS used. Target analyte exon 7 deletion targeting C.840C>T single nucleotide variant. qPCR assay. 14 screen positive cases, no false negatives or false positives. Multiplexed with assays for SCID and haemoglobinopathy (Sickle cell).		Bias minimised by consecutive sampling of the population and a large population size. Data includes 3-month pilot and 6-month screening program.
Shinohara et al 2019(56)	IV	Case-control	Assay process consists of two steps: (1) targeted pre-amplification of *SMN* genes by direct polymerase chain reaction (PCR) and (2) detection of *SMN1* deletion by real-time modified competitive oligonucleotide priming-PCR (mCOP-PCR) using the pre-amplified products. Compared with PCR analysis results of freshly collected blood samples, system had sensitivity of 1.00 (95% confidence interval [CI] 0.96-1.00) and specificity of 1.00 (95% CI 0.96-1.00). Assay applied to NBS for SMA from 4157 newborns. All DBS tested negative, and no screening failures.	Not described	Well conducted study with a diagnostic accuracy phase and then implementation on a population level. Methodology answers research question but may not be sensitive to detect intragenic pathogenic variants (not part of case-control series).

Olkhovych et al 2023(57)	IV	Prospective cohort	65880 newborns screened and 11 screen positive	Not described	No description given of how program was implemented or details on first and second tier screening methods/processes.
Wallace et al 2023 (148)	IV	Prospective cohort	1st tier test is a quantitative PCR analysis of exon 7 in the *SMN1* gene multiplexed with the SCID biomarker TREC. Samples with two exon 7 deletions are analyzed with 2nd tier droplet PCR to confirm the diagnosis and quantify *SMN2* copy number. Copy numbers of *SMN1* and *SMN*2 further verified by whole genome sequencing. In samples with a heterozygous deletion, analysis for a specific point mutation seen in approximately five percent of Norwegian patients with SMA is also performed. 10 screen positive		Narrative summary of processes. Risk of bias reduced due to consecutive sampling methods used within a screening program. Multiple tiers to screening assay that may be preclude applicability and feasibility in Australian context.
Fonseca et al 2024(59)	IV	Prospective cohort	25,000 newborns screened for SMA using qualitative detection of exon 7 of the SMN1 gene. The assay was performed using a commercially available real-time PCR, multiplexed with SCID assay. Two screen positive and confirmed to have SMA	*SMN2* copy number determined during diagnostic phase.	Narrative summary of processes. Risk of bias reduced due to consecutive sampling methods used within a screening program.
Kimizu et al. 2023(60)	IV cohort	Prospective cohort	22951 newborns screened using real time quantitative PCR as part of pilot and all screen negative	Not described	Opt in study and therefore risk of selection bias.
Wijaya et al. 2021 (48)	IV	Case-control study	Dried saliva spots used. Case control 2:1 (40 SMA patients, 20 controls). Competitive oligonucleotide priming-polymerase chain reaction and melting peak analysis distinguished samples with and without *SMN1*.		Small sample size. Variability of DNA quality and quantity from saliva. PCR inhibitors may confound results leading to assay failure of 1.6%, limiting generalisability to population screening.
Kerhohan et al. 2021 (61)	NA	Protocol or consensus	Proposed qPCR multiplexed with assays for SCID and genetic sensorineuronal hearing loss. Target analyte is exon 7 single nucleotide variant.	Second tier on DBS (for those with first tier exon 7 deletion) includes: 1. MLPA for *SMN1* & *SMN2* 2. Screen positivity classified as *SMN1* absence and ≤ 4 *SMN2*	No results available due to the study design.

Oliveira-Netto et al. 2023(62)	IV	Cohort	46, 289 DBS samples with 35,000 DBS samples with sufficient material for testing. Real-time PCR and then second tier MLPA on same DBS for diagnostic confirmation		One false positive No false negative
Lakhotia et al 2022 (149)	IV	Prospective cohort study	108,511 neonates screened for SMA on Kentucky NBS. 16 neonates screened positive, of which 11 (68.75%) were confirmed to have SMA. 4/5 neonates with false positive SMA screen, had an accompanying false positive SCID screen.	Not described	Brief narrative summary of findings with no clear aetiology of false positive results noted.
Kumar et al. 2021 (64)	IV	Prospective cohort study	Two tier assay: First to detect absence of exon 7 on SMN1 and second to detect if this is due to a hybrid gene that carries a variant in the region used to prime the amplification of Exon 7 in Assay A. Third tier used when assay A and B are not reconciled (DNA sequencing)	Modification of DNA sequencing assay used to identify SMN2 copy number on DBS. Tested against nine known patients with SMA and this assay matched their SMN2 diagnostic copy number results in 6 cases.	
Wong et al. 2024(65)	IV	Prospective cohort study	239,844 infants were screened. 13 babies screened positive and were confirmed to have SMA. One false positive	Not described	Narrative summary of processes. Risk of bias reduced due to consecutive sampling methods used within a screening program
Tavares et al. 2021 (66)	IV	Prospective cohort	129 blood samples: 54 samples had *SMN1* and *SMN2* genotype confirmed by MLPA(retrospective cohort).75 samples included blood from SMA and non SMA patients (prospective cohort). 26 patients from this combined cohort had bloods collected onto filter paper.	100% concordance of real-time PCR assay with known results from retrospective cohort. Using 26 DBS and the same assay, 20 true negatives, 6 true positives and no false negatives/positives noted.	Estimated costs for assay included but may not be applicable to a Australasian healthcare landscape. Non-automated methodology therefore applicability to a whole of population process uncertain.
Sonehara et al. 2023(67)	IV	Prospective cohort study	16,000 DBS 3 true screen positives, 14 false positives SMN1 exon 7 deletion on *SMN1* assay using realtime PCR		

Kraszewski et al. 2018(68)	IV	Prospective cohort study	DBS used. Exon 7 target analyte. RT-QPCR assay, with sequencing around the primer binding sites instigated for those with screen positivity to eliminate potential for false positives due to polymorphisms in these binding sites. 7,3826 neonates screened. 98.43% (95 % CI=97.99-98.78%) normal screening result. Carrier status reported (59 carriers). 1 screen positive. No false positives or negatives.	Second tier screening not part of the study and *SMN2* determined through diagnostic methods.	Small sample size. Risk of selection bias potentially due to enrolment of 93% of the population (opt out option). Assays done in triplicate which may limit generalisability in implementation. First-pass assay failure rate 3.0%, attributed to suboptimal DNA quality and quantity; all classified as screen negative or carriers upon retest. An additional 33 specimens (0.86%) initially tested in the equivocal range. Upon retesting using a fresh DNA sample, all but one resolved as screen negative ($N = 30$) or heterozygous deletions ($N = 2$). One specimen retested in the equivocal range. Upon sequencing, the specimen was found to carry a rare heterozygous sequence variant of uncertain significance.
ArRochmah et al. 2017(69)	IV	Case control	88 individuals (37 SMA patients, 12 carriers, 39 controls). Analyzed on DBS. Real time mCOP-PCR with pre-amplified PCR products performed for gene specific amplification of *SMN1* and *SMN2* Exon 7. *SMN1* assay Sensitivity = 1 (CI 0.87, 1) Specificity = 1 (CI 0.9,1). *SMN2* assay Sensitivity = 1 (CI 0.4, 1), Specificity for *SMN2* =1 (CI 0.94, 1). This system developed to accommodate poor quantity or quality DBS DNA, because of presence of a pre amplification step prior to the MCOP PCR.		Pre amplification may be inappropriate for determination of *SMN1* copy number or *SMN2* copy number, as primary purpose of SMA screening is to determine presence or absence of *SMN1*. Confounders not included were storage conditions, and DBS sampling techniques.

Gailite et al. 2022 (70)	IV	Prospective cohort study	10,411 neonate cohort. DBS used. Target analyte exon 7 *SMN1*. Q-PCR for *SMN1*. 40 DBS need to be repeated due to unsuccessful DNA isolation resulting in PCR failure or inconclusive results. Two screen positives. No false positives or false negatives.	Second tier screening not part of the study and *SMN2* determined through diagnostic methods.	Fairly high assay failure rate with no explanation given. 30% of potential participants not recruited into cohort, but potential for selection bias mitigated by consecutive recruitment from population.
Elkins et al. 2022 (71)	IV	Prospective cohort study	301,418 newborn cohort. RT-PCR methodology (qualitative assay). Exon 7 *SMN1* target analyte. Multiplexed with SCID. 15 true positives, and 24 false positive cases.	Second tier screening not part of the study and *SMN2* determined through diagnostic methods.	Potential reasons for high false positive and inconclusive results were not well defined, attributed to 9 children being sick; small DBS size used for assay (1.5 mm DBS card); and/or environmental degradation of DNA due to temperature and weather conditions and/or conservative threshold for defining first tier positivity.
Mikhalchuk et al. 2023 (72)	IV	Diagnostic test accuracy	Melt assay from DBS. PCR RFLP as a second tier to test exon 7 deletion.		
Kucera et al. 2021 (73)	IV	Prospective cohort study	Validation study then population study for 12,065 neonates. 1 true positive. 2 unsatisfactory results/false positive (borderline). qPCR assay used to detect presence or absence of exon 7 on *SMN1*. Two borderline/false positive results: one in a child with a bone marrow disorder (found to be a carrier on ddPCR of *SMN1*). Used a	Second tier screening not part of the study and *SMN2* determined through diagnostic methods.	Validation studies yielded comparable precision for affected and carrier samples, with assay performance being stable for 18 months. Opt in study therefore variability in timing of DBS collection. Analysis and result reporting not performed daily so difficult to generalise to a NBS program.

			conservative *SMN1* cut off which may also have led to false positive result.		
Kato et al. 2015 (74)	IV	Case-control	50 DNA samples from DBS. 29 = SMA. 21 = controls. Using competitive oligonucleotide priming PCR to distinguish between *SMN1* and *SMN2* Exon 7. Method 100% concordant with SMA genotype established by other PCR methods.		No enzyme digestion step needed for COP methodology; therefore more timely results may be achieved.
Niba et al. 2019 (75)	IV	Case control	3 individuals (2 controls; 1 SMA). DBS. Using competitive oligonucleotide priming PCR to distinguish between *SMN1* and *SMN2* Exon 7. Method 100% concordant with SMA genotype established by other PCR methods.		Very low sample size with high risk of bias as no mention of blinding to cohort, which increases the risk of experimenter bias. More proof of concept study.
Czibere et al. 2020 (76)	IV	Prospective cohort study	QPCR on DBS. 213,279 neonates. 30 true positive. No false positive or false negative. sensitivity 1 (95% CI 0.88) and specificity 1 (95% CI 1).		
Wijaya et al. 2019 (77)	IV	Prospective Cohort study	6 DNA samples from SMA positive individuals. Using competitive oligonucleotide priming PCR to distinguish between *SMN1* and *SMN2* Exon 7. Method 100% concordant with SMA genotype established by other PCR methods.		Very low sample size with high risk of bias as investigators not blinded to cohort conditions.
Dobrowolski et al. 2012 (78)	IV	Prospective Cohort study	Post PCR high resolution melt profiling to establish *SMN1* and *SMN2* genotype. 1000 purified DNA samples. 100 self-created DBS. 1200 DBS from NBS. 100% sensitivity for homozygous deletions of *SMN1*.		

Vill et al. 2019 (79)	IV	Prospective Cohort study	Target analyte Exon 7 *SMN1*. From DBS. QPCR. 165,525 newborns. 22 children screen positive; no false positives.	*SMN2* not done.	Selection bias minimised by consecutive sampling of the population and a large population size.
Vill et al. 2021 (80)	IV	Prospective cohort study	43 SMA patients identified via quantitative PCR of *SMN1* gene from DBS; screening for homozygous deletion of exon 7.	Confirmation of homozygous deletion of exon 7 of the *SMN1* gene and determination of *SMN2* copy number by MLPA performed using new, whole blood sample in a collaborative laboratory for human genetics.	Misanalysis found in one patient, leading to a modernized MLPA kit being used and re-testing of all individuals. Descriptive study; not randomized case-control study Relatively small sample size Short follow up period.
Er et al. 2012 (81)	IV	Case control	DBS. 60 individuals. High resolution melting analysis. Authors aim to develop a method for identifying the substitution of single nucleotide in *SMN1* exon 7 (c.840 C > T) by HRM analysis. Genomic DNA was extracted from peripheral blood samples and dried blood spots obtained from 30 patients with SMA and 30 normal individuals. All results were previously confirmed by DHPLC.		Appears to be a highly efficient methodology but the study is limited by sample size, leading to selection bias.
Kariyawasam et al. 2020 (10)	IV	Prospective Cohort study	103, 903 screened. Target analyte exon 7. Multiplexed with SCID. 10 screen positives.	Second tier is ddPCR for *SMN2*. Screen positivity is *SMN1* deletion and less than four copies of *SMN2*.	Large population size and consecutive recruitment of newborns to minimise selection bias. Generalisable to the Australian health context.

			1 false positive, no false negatives. 100% sensitivity, specificity, and precision.		
Noguchi et al. 2022 (82)	IV	Prospective Cohort study	First-tier: DBS. Real-time qPCR assay with fluorescent hybridizing proves to detect presence/absence of *SMN1* exon 7 (did not detect one allelic deletion). Second tier: Whole blood (QIAamp DNA Blood Mini Kit) used for gene analysis. 8,336 newborns screened. 10-false positives (.012%). 12 screen positives.	MLPA and ddPCR analysis of freshly collected blood. MLPA assay excluded ten false positives and identified two patients.	Interim report for ongoing pilot study. False-positive detection rate decreased following instructions not to use heparinised blood when preparing NBS samples, however this was still done and caused more false positives.
Hale et al. 2021 (83)	IV	Prospective Cohort study	Real time qPCR to detect absence of *SMN1* Exon 7. Multiplexed tiered testing system. Tier 1=single assay targeting *SMN1* Exon 7 and RNaseP (assay A) with thermoprofiles set to push the assay to its limits. Tier 2= Two assays. An additional assay targeting *SMN1* Exon 7, *SMN1* Intron 7, and RNaseP (Assay B) as well as a retest of Assay A used in Tier 1. Tier 2 assays performed in triplicate. Tier 3 sanger sequencing assay to confirm *SMN1* Exon 8, and preliminary data on *SMN2* copy number. 179,467 neonates screened. 9 confirmed with SMA. No false-negative. 100% sensitivity and specificity of 99.9%, and positive prediction value of 90%. 314 samples went to second-tier. 10 of these showed presence of Exon 7 with absence of		*SMN1* hybrids observed in 1 in 17,947 (95CI 1/11080-1/47202). Low disease incidence secondary to limited population sampling, reproductive choice or combination of factors is unclear.

			Intron 7 (*SMN1* hybrid genes). 294 had present Exon 7. 9 confirmed with SMA.		
Kay et al. 2020 (84)	IV	Prospective Cohort study	DNA extracted from DBS with multiplex real-time qPCR assay targeting *SMN1* exon 7 deletion. 225,093 infants tested. 8 screen positives.		
Pyatt et al. 2007 (85)	IV	Case control	Real-time PCR. Multiplex assay to detect homozygous deletion in *SMN1* Exon 7; validated using 266 samples (84 carriers and 32 individuals affected with SMA, 150 controls) with defined *SMN1* and *SMN2* copy number. DNA extracted from whole blood using salting-out procedure. 153 (39 carriers, 56 normal individuals, and 58 affected individuals) additional independent samples analysed to examine sensitivity and specificity. The correct identification of all 57 affected samples gives this technology an analytic sensitivity of 100%, and the correct exclusion of the 39 carrier and 56 normal samples also gives this strategy an analytic specificity of 100% for this blood spot series.	*SMN2* copy number conducted using the same competitive PCR and DNA extraction method.	
Gutierrez-Mateo et al. 2019 (86)	IV	Case control	Four-plex, real-time PCR assay to screen for SCID, XLA, and SMA in DNA extracted from a single DBS. 3,036 newborn DBS samples (leftovers). Specificity was evaluated testing a set of 28 reference DBS samples for SMA, with	*SMN2* copy numbers determined by digital PCR. This set included five SMA carriers and 23 SMA positive samples homozygous for the exon 7 deletion and *SMN2* copy numbers ranging from one to four copies.	

			known *SMN1* and 4 newborn DBS samples confirmed with SMA added. 26/27 SMA positive samples detected (23 reference samples and 3 confirmed samples; one false negative from a previously confirmed SMA case).		
Vidal-Folch et al. 2018 (87)	IV	Case control	Multiplex ddPCR to detect *SMN1* deletion and *SMN2* CN variation in single DBS. 1,530 DBS's and 12 SMA patients. 100% sensitivity and specificity.		MLPA performed to assess ddPCR accuracy. SMA positive cases collected between 12 and 77 days of age.
Kiselev et al, 2024 (88)	IV	Prospective Cohort study	Real-time PCR assay with DBS. 36,140 screened newborns. Homozygous deletion (4) heterozygous carriers (722), wild-type individuals (35,364). The sensitivity and specificity of the test were determined, which were 99.74% and 100%, respectively.		
Liu et al. 2016 (89)	IV	Retrospective and Prospective cohort study	Realtime PCR performed on 2000 randomly selected DBS samples (trace-DNA samples). 23 positive detections, reconfirmed by real time PCR and then DNA sequenced. 22 of them were false-positive. The other samples was the only true positive sample from the 2000.		
Hashimoto et al. 2023 (90)	IV	Case report	Case report of one child with a false negative result on NBS.		Reported as a false negative case but child had compound heterozygous genotype and therefore would not have been detected through a screening program established to detect exon 7 *SMN1* deletion.

Lin et al. 2019 (91)	IV	Prospective Cohort study	SMA assay based on matric assisted laser desorption/ionization mass spectrometry for *SMN1*. 29,364 individuals screened and 3 neonates true positive.	SMA assay based on mass spectrometry for *SMN2*.	100% specificity and sensitivity assay in validation phase, dropping to 95% sensitivity in larger cohort phase. Double blinded validation study so reduces observer bias.
Adams et al. 2021 (92)	IV	Prospective Cohort study	real-time PCR assay to simultaneously detect *SMN1* exon 7 and control gene RPP30, using DNA from a DBS 4810 normal/leftover DBS + 43 known SMA positive DBS. *SMN1* amplification detected in all 4810 normal samples. 42/43 SMA positive samples showed complete absence of *SMN1* amplification.	No measure of *SMN2* taken.	The remaining one sample turned out to be from a carrier which the kit did not detect.
Abiusi et al. 2023 (93)	IV	Prospective Cohort study	In-house qPCR assay coamplifies and differentiates *SMN1* and *SMN2* by the C-T transition in exon 7. 90,885 samples. 15 individuals with homozygous deletion of *SMN1* correctly detected. No false negatives.		Global failure rate of assay 2.1%. Assay failures concentrated in first months of the study and were substantially reduced after an alert was sent to birth centres to avoid the use of heparin-coated capillaries for blood sampling. Subsequently, the failure dropped to 0.5% (479 samples) that required manual DNA extraction. All samples were successfully screened, and no resampling was required.
Niri et al. 2023 (94)	IV	Prospective Cohort study	multiplex qPCR assay. 47,005 screened, with 6 samples testing positive for SMA. Each positive sample was repeated in duplicate, and all confirmed the initial test results. Additional blood samples were collected from the infants for confirmatory testing. Five of the six screen positive samples were confirmed to have SMA. The diagnostic test, which was performed using		

			an MLPA kit, confirmed the homozygous absence of exon 7 of *SMN1*. Analytical sensitivity of this screening multiplex assay remained at 100% and the analytical specificity was determined to be 99.999%.		
Baker et al. 2022 (95)	IV	Prospective Cohort study	DNA isolated from routine NBS DBS. multiplex real-time PCR assay to identify newborns with homozygous *SMN1* exon 7 deletion. 60,984 newborns were screened for spinal muscular atrophy. Six newborns screened positive for and were confirmed to have spinal muscular atrophy.	ddPCR assay for *SMN2* copy number assessment.	An independent dried blood spot specimen was collected and tested to confirm the initial screening results for *SMN1* and *SMN2*.
Kubar et al. 2023 (96)	IV	Prospective Cohort study	Real time PCR test procedure without nucleic acid extraction in dried blood spots (DBS) to screen for homozygous deletion of exon 7 of the *SMN1* gene. 580 DBS newborn samples and air dried 50 DBS from whole blood including 20 samples for homozygous deletion of the *SMN1* gene detected earlier with MLPA.		
Shum et al. 2023 (97)	IV	Prospective Cohort study	NGS assay on over 2500 newborns. Technical feasibility study. 12 positive and 4 negative control DBS samples also included in the analysis. Sensitivity = 100%. Specificity = 100%. Failure rate = 0%.	*SMN2* copy number calculation beyond scope of validation study.	NGS may be an alternative tech for NBS programs to consider.

Sawada et al 2022 (98)	IV	Prospective Cohort study	13,587 newborns (96% of all births). DBS taken 4-6 days after birth. Target analyte exon 7 *SMN1* deletion by real-time PCR 1 true screen positive. No false positive or negatives.	*SMN2* copy number not part of screening process.	Large population size reduces chance of sampling bias.
Kato et al 2015 (74)	IV	Case-control	50 individuals assayed. 28 SMA and 22 controls using DNA extracted from DBS and using COP-PCR methods that is able to differentiate between *SMN1* –deletion detection and *SMN2* presence.		Small sample size as befits a validation study. No blinding, increasing possibility of observer bias.
Chien et al. 2017 (111)	IV	Prospective Cohort study	Pre-pilot validation on 2937 deidentified samples and 9 DNA samples with known genotype and SMA carriers. Cohort study of 120,267 newborns. 50 samples needed repeat DNA extraction. Real time PCR assay for first tier . 15 screen positive on first tier: ddPCR on same DBS for exon 7 *SMN1* excluded 8 false positives and 7 individuals confirmed to have SMA by MLPA. False positives due to hybrids of *SMN1/SMN2.* No false negatives.		Only 35-37% of population opt in for screening however consecutive sampling and large sample size may limit selection bias. Two assay screening process may not be generalisable to current NBS laboratories. Specificity of RT-PCR assay alone was 99.9% and positive prediction rate 47%. Adding ddPCR gave a 100% positive predictive value.
McMillan et al. 2020 (100)	IV	Prospective Cohort study	First tier Mass Array test for *SMN1* (alongside 22 other variants for hearing loss and SCID). Assesses for the presence of an *SMN1* exon 7 single-nucleotide variant	MLPA for *SMN1* and *SMN2* from same DBS. Screen positivity defined as *SMN1* null and *SMN2* ≤ 4. Lab analysed inconclusive results (exon 8 null, exon 7 *SMN1* present) by	No results of cohort provided apart from implementation descriptions.

			(SNV), and of exon 8 *SMN1* and *SMN2* SNVs.	MLPA weekly (thought to be due to high *SMN2 copy* number).	
Müller-Felber et al. 2023 (101)	IV	Prospective Cohort study	117 screen positive cases over 4 years. 92% confirmed to have SMA. Four false positives. One case with compound heterozygous genotype presenting with symptoms at day 68 of life (not considered a false negative as not able to be screened for by the current assay). Sensitivity of the assay for SMA was 98%.		False positives occurred in first two months due to the process being decentralised from one screening lab. Study does not give the number of newborns screened therefore test performance difficult to elicit. No methodology for first tier screening mentioned.
Lee et al. 2022 (102)	IV	Prospective Cohort study	qPCR for *SMN1* exon 7 deletion multiplexed with assay for SCID. 650,000 neonates screened. 32 screen positive.	*SMN2* copy number second tier testing with qPCR targeting exon 7 in *SMN2* and ddPCR.	Large pilot study which reduces selection bias. No false positives or negatives. Lower incidence than predicted.
Abiusi et al. 2024 (103)	NA	Prospective Cohort study		*SMN2* copy assessment should be performed on Dried Blood Spot (DBS) DNA only on purified samples and if quantity and quality are adequate for quantitative approaches. Control samples should be extracted through the same approach as DBS-DNA. Use of validated technology that allows determination of the exact *SMN2* number is recommended. *SMN2* modifier variants (c.859G>C and c.835-44A>G) should be	Meeting of experts and expert opinion. Non-systematic (narrative) evidence base provided to augment recommendations.

				routinely tested and reported (also in NBS).	
Kernohan et al. 2022 (61)	IV	Prospective Cohort study	Screening institutions should select appropriate methods to carry out screening based on national regulatory requirements, industry technical specifications and the actual conditions of their own laboratories. The detection sensitivity for an *SMN1* assay should be ≥95%, and the positive predictive value should be ≥90%. Real world NBS for SMA cohort study. MassARRAY for presence *SMN1* and MLPA for *SMN1* and *SMN2*. 5 screen positive newborns.	*SMN2* gene copy number is an important modifier of SMA but is not required for screening testing and may increase screening costs. Therefore, clinical newborn screening for SMA may not include quantitative detection of *SMN2* gene copy number. *SMN2* gene copy number has important guiding value for the subsequent clinical treatment of newborns diagnosed with SMA. Therefore, the diagnostic test of newborns with positive screening should include *SMN2* gene copy number information. NBS programs reports only report < 4 *SMN2*.	No false negatives
Kemper et al. 2018 (116)	II	Systematic literature review and report	First tier testing involves qPCR (qualitative) for most states in US which reduces inconclusive results due to absence of *SMN1* exon 7 on both alleles.	Some states assess *SMN2* copy number as part of a second-tier newborn screen test or confirmatory testing to facilitate timely information for short-term follow up with the clinicians.	Studies updated from 2017-2020. Wide number of databases searched and detailed search terms, inclusion/exclusions and search strategies identified. Focus is on clinical impact, care of NBS for SMA and barriers to implementation.
Matteson et al. 2022 (105)	IV	Prospective Cohort study	628,791 infants screened using multiplex RT-PCR to detect deletions in exon 7 of *SMN*1. 34 screen positive		
Prior et al. 2010 (106)	IV	Prospective Cohort study	Liquid bead microarray NBS assay performed on DBS. 40103 DBS analysed and 7 required repeat extraction of DNA	Not described	

			from DBS due to ambiguity of screening result. Assay repeated on re-extracted DNA and ambiguity resolved. Four screen positive newborns identified.		

Evidence summary table for the evaluation of newborn screening processes for SMA where blood transfusion is required

Author, year	Level of Evidence	Study description	Study outcome/findings	Comments/Appraisal
Zhi et al. 2023(110)	NA	Consensus statement	Blood samples should be collected after 3 months for patients with whole blood transfusions. For newborns who are scheduled to undergo bone marrow transplantation or stem cell transplantation, blood samples should be collected before treatment.	
Abiusi et al. 2024 (103)	NA	Consensus statement	Risk of DNA contamination is possible and in the ideal situation, DBS for SMA should be collected before transfusion. If collected after transfusion of red blood cell concentrates, test may be performed but should be repeated after 2 months since transfusion.	Meeting of experts and expert opinion. Non-systematic (narrative) evidence base provided to augment recommendations.

Evidence summary table for the processes required for NBS for SMA with premature, low birthweight of very low birthweight babies

Author, year	Level of Evidence	Study description	Study outcome/findings	Comments/Appraisal
Lee et al. 2022 (102)	IV	Prospective Cohort study	2 cases identified through NBS for SMA with gestational age of 34 + 6-weeks and another of 34 + 1 weeks.	No deviation in process for NBS for SMA identified for preterm infants.
D'Silva et al. 2022 (9)	IV	Cohort and implementation	NBS for SMA identified a preterm infant.	No deviation in process for NBS for SMA identified for preterm infants.
Nigro et al. 2023 (112)	IV	Case report	NBS for SMA identified a 32-week-old infant.	No deviation in process for NBS for SMA identified in case report.

Evidence summary table for the processes required for diagnostic confirmation of SMA and its severity for screen positive newborns

Author	Level of evidence	Study description	Findings	Comments/appraisal
Abiusi et al. 2024 (103)	N/A	Consensus statement	*SMN2* copy number one of key determinants of treatment. *SMN2* copy number determination can be difficult and requires standard workflow and processes within expert reference centres. Representative of European Molecular Quality Network presented data from 92 out of 99 laboratories using PCR based methods to ascertain *SMN1* and *SMN2* gene dosage. MLPA most commonly used technique. Five genotyping errors noted from 5 laboratories for *SMN2* and seven laboratories reported eight critical *SMN1* genotyping errors.	Important to reassess *SMN1/SMN2* testing protocols including used of validated positive and negative controls isolated through the same method as patient DNA samples.
Crawford et al. 2023 (4)	II	Long term follow up study of infants with 2 and 3 *SMN2* copies initiating treatment presymptomatically	10 infants with 3 *SMN2* copies, who had comparably the best baseline values in WHO, CHOP INTEND, and HINE-2 scores and in CMAP (Compound Motor Action Potentials), showed physiologic motor developmental milestones. This is compared to 15 infants with 2 *SMN2* copies with lower functional motor performances: 7/15 (46 %) showed some motor delay and 4/15 (26 %) needed respiratory intervention.	*SMN2* copy number is a useful predictor of longer term functional motor outcomes and is a key guide to clinical severity for presymptomatic children, receiving treatment.
Muller-Felber et al. 2023 (101)	IV	Prospective Cohort study	Time to confirmation of diagnosis including estimation of *SMN2* copy number is median 13 days of life for 117 children with a screen positive SMA result.	Range not given for time to diagnostic confirmation.
Strunk et al. 2019 (109)	IV	Prospective Cohort study	Confirmation of *SMN1* available by day 14 of life (mean 15.6+/- 5.9 days) for 63 screen positive newborns, confirming 43 children with SMA. *SMN2* copy number varied between DBS and diagnostic assay for 3 of 43 true screen positive samples.	

Schorling et al. 2019 (113)	IV	Prospective Cohort study	*SMN2* copy number discordance of up to 40% reported between initial and repeat tests using MPLA methodology.	Small population size may increase risk of sampling bias. One methodology for *SMN2* analysis (MLPA) investigated.
Ricci et al. 2023 (145)	IV	Prospective Cohort study	Retrospective study comparing retested *SMN2* copy number with prior results *SMN2* copy number discordant in 20/189 (11%) of cases with known SMA, when retested with new MLPA assessment.	Postulation as to why discrepant results arose, including poor quality of DNA and choice of controls in semiquantitative assays.
Vill et al 2021 (80)	IV	Prospective Cohort study	*SMN2* copy number variance in 3/47 neonates confirmed as having SMA through NBS. Occurred with copy number ≥ 3.	
Wang et al. 2020 (108)	IV	Prospective Cohort study	Whole blood collection and digital PCR vs HRM analysis used to determine *SMN1* and *SMN2* copy number rapidly and can be used for rapid diagnosis in screen positive children.	Quantitative PCR-based method may cause controversial results in unaffected individuals and SMA carriers due to the similar SMN1/SMN2 ratio. Digital PCR methodology provides absolute quantification for copy number variation and rare mutation detection.
Boemer et al 2021(51)	IV	Prospective Cohort study	Whole blood collection from recalled screen positive newborn and MLPA performed to confirm *SMN1* diagnosis. *SMN2* gene sequenced to look for presence of two intragenic modifier variants - *SMN2* specific primers used to achieve specificity to *SMN2.* Process of implementation focuses on rapid turn around time of all screening and diagnostic processes	
Vill et al.2021(80)	IV	Prospective Cohort study	Confirmation of homozygous deletion of exon 7 on *SMN1* and *SMN2* copy number confirmed by MLPA on whole blood sample from recalled screen positive infants.	

Gailite et al 2022 (70)	IV	Prospective Cohort study	Confirmation of homozygous deletion of exon 7 on *SMN1* and *SMN2* copy number confirmed by MLPA and qPCR on whole blood sample from recalled screen positive infants.	
D'Silva et al 2022 (9)	IV	Prospective Cohort study	Diagnostic confirmation contingent on corroboration of *SMN1* deletion in a freshly collected blood sample using assays with different primers to screening assays, Establishing capacity to facilitate *SMN2* copy number confirmation overcomes barriers to delays in initiating treatment. Turn around time for diagnostic results important due to the urgency of treatment for some – triage of *SMN1* copy number may be informed by *SMN2* copy number on screening assay (overtime for 2 *SMN2* copies or urgent within hours run for 3 *SMN2* copies)	
Blasco-Perez et al 2021 (117)	IV	Cohort study	Intragenic *SMN2* variants may change amount of complete SMN transcripts and full-length SMN protein. Complete sequencing of the SMN2 gene based on long-range polymerase chain reaction and next-generation sequencing validated by analyzing samples from 53 SMA patients who lack *SMN1*. *Study was able to* characterize paralogous, rare variants, and single-nucleotide polymorphisms of *SMN2* as well as *SMN2-SMN1* hybrid genes.	The method identifies partial deletions and can be adapted to determine rare pathogenic variants in patients with at least one *SMN1* copy
Niri et al 2023(94)	IV	Prospective Cohort study	Blood collected on screen positive newborns and confirmation of diagnosis of *SMN1* and *SMN2* copy number with MLPA.	
Kucera et al.2021 (73)	IV	Prospective Cohort study	ddPCR used to confirm diagnosis and detected a single intact *SMN1* gene in a screen positive newborn who had blood collected whilst in NICU, leading to a false positive result.	Opt in study therefore risk of selection bias. Processes and timelines for automated diagnostic confirmation may not be generalisable to a whole of population NBS program
Oliveira-Netto et al. 2023(62)	IV	Narrative review	MPLA considered gold standard for confirmation of exon 7 *SMN1* deletion, but RFLP may also be considered to expedite results. RFLP cannot identify *SMN2* copy numbers and MLPA may still be useful here. However, distinguishing between copy	Non systematic review of current literature with up to date references

			numbers may be challenging with MLPA and labs now moving to digital PCR to overcome barriers of imprecision.	
Sawada et al 2022(98)	IV	Prospective Cohort study	MLPA used to confirm copy numbers of exon 7 and 8 in *SMN1* and *SMN2* genes on freshly obtained whole blood samples.	
Kimizu et al. 2023(60)	IV	Prospective Cohort study	MLPA for *SMN1 f*or diagnostic testing	
Noguchi et al. 2022(82)	N/A	Narrative summary	Definitive diagnosis: MLPA and ddPCR on freshly collected blood	
Chien et al. 2017(111)	IV	Prospective Cohort study	Positive screening results confirmed by ddPCR assay using original DBS and MLPA using whole blood from recalled newborn.	
Lin et al.2019(91)	IV	Prospective Cohort study	MLPA analysis confirms *SMN1* and *SMN2* copy number in two patients identified through a MassARRAY based genotyping screening assay.	
Mikhalchuk et al. 2023(72)	IV	Prospective Cohort study	Fresh whole blood sample collected from recalled newborn. Use of RFLP to confirm diagnosis of exon 7 homozygous deletion in *SMN1* and the MLPA completed for *SMN1* and *SMN2*	
Kiselev et al. 2024(88)	IV	Prospective Cohort study	MLPA performed on whole blood samples for *SMN1* and *SMN2* (results available within 1-2 days of receipt at diagnostic lab)	
Liu et al 2016(89)	IV	Retrospective and Prospective Cohort study	Accuracy of real-time PCR to detect pathogenic deletions in exon 7 *SMN1* was at least 98.8% compared with DNA sanger sequencing and MLPA, but faster and less DNA required. Also cheaper than dPCR.	
Prior et al. 2010(106)	IV	Prospective Cohort study	Four screen positive newborns confirmed to have SMA though competitive PCR analysis and *SMN2* copies determined in diagnostic pathway.	

Groulx-Boivin et al 2024 (53)	IV	Qualitative cohort study	In some jurisdictions, positive NBS screen result is sufficient to access disease modifying treatment, while others require confirmatory genetic tests, leading to 1-2 week delays in treatment initiation.	

Evidence summary table for the evaluation of management of newborns with false positives, false negatives, and uncertain screening results for SMA

Author, year	**Level of evidence**	**Study description**	**Findings**	**Comments/Appraisal**
Noguchi et al. 2022 (82)	IV	Cohort	Conducted experiments to understand aetiology of high false positive rate by testing effect of low white cell count, gene sequence and heparin on PCR amplification efficiency.	DBS samples that are poor in white blood cells would be unable to obtain the required amount of PCR products for SMA-NBS. Amplification efficiency of *SMN* is lower than that of other gene target such as cystic fibrosis transmembrane regulator, suggesting that *SMN* may be difficult to amplify under some conditions. PCR product amounts of *SMN* decreased in the presence of heparin. The decrease in PCR product amounts may occur in a dose-dependent manner. This suggests that heparin in the DBS sample may hamper PCR amplification in SMA-NBS.
Boemer et al. (51)	IV	Prospective cohort	1 false negative from 136,339 screened	Compound heterozygote
Sonehara et al. 2023 (67)	IV	Cohort	14 false positives from 16037 DBS	All false positive cases came from hospital with NICU where heparinised blood taken to prepare samples. No infant identified as false positive after this practice ended.
Chien et al. 2017 (111)	IV	Cohort	Added ddPCR of *SMN1* to reduce false positive rate. 8 false positives using only RT-PCR assay. *SMN1* specific sequences amplified from all false positives. In 2/8 (25%), a nucleotide variant (c.888+102A>C) stopped annealing of	ddPCR can differentiate false positive results caused by hybrid genes. 8 reported single nucleotide polymorphisms flanking the probe binding site are known and can cause false-positive screening results when using a c.840 RT-PCR assay.

			the assay primer to the sequence, causing false positive results. 5 patients had gene hybrid events which stopped primers annealing.	
D'Silva et al. 2021 (9)	IV	Cohort and implementation study	One false positive case identified after sequencing of *SMN1* exon 7 showing a single nucleotide variation which changed the way that the NBS *SMN1* probe annealed to the DNA. Two false negatives secondary to system error and sample not being received by screening lab.	*SMN1* exon 7 sequencing led to resolution and aetiology of the false positive NBS for SMA result.
Tavares et al. 2021 (66)	IV	Cohort	One false positive due to low DNA quantity, not interfering with internal control.	
Kucera et al. 2021 (73)	IV	Cohort	One false positive result likely caused by an unrelated blood disorder.	Both *SMN1* and internal control threshold cutoff values were close to the cut-off, indicating lower qPCR efficiency and suggesting that a higher *SMN1* cut-off might be appropriate to increase the specificity of the assay used in this study.
Hashimoto et al. 2023 (90)	IV	Case report	False negative case described.	MLPA for *SMN1* and *SMN2* first conducted after clinical exam showed signs and symptoms of SMA and then sequencing was performed. The latter showed 3 copies of exons 1, 7, and 8 but only two copies each of exons 2a, 2b, 3, and 4 Structural similarities made it difficult to distinguish between the two genes, and thus, two possible scenarios could be inferred from available results: a) heterozygous deletion of *SMN1* exons 1-8 and the heterozygous deletion of *SMN2* exons 2a-4; or b) the heterozygous deletion of *SMN1* exons 1-8 and the heterozygous deletion of *SMN1* exons 2a-4. In the first scenario, one copy of normal *SMN1* without mutation would be present, while in the latter, compound heterozygous deletions of *SMN1* exons 2a-4 would be present, which could lead to the development of SMA. The infant was given the latter genotype.

Elkins et al. 2022 (71)	IV	Prospective cohort	301418 newborns screened 1 false negative due to human error, 13 false positives from sick neonates and 147 uncertain results ? Aetiology with the majority also having inconclusive SCID screen	
Lakhotia et al.2022 (149)	IV	Prospective cohort	5 false positives with 4/5 also having false positive SCID screen of unclear aetiology	
Cusco et al. 2020 (120)	N/A	Guideline	In discordant genotype-phenotype situations, recommends retesting for *SMN2* copy number on different lab/method and/or with new sample for presymptomatic children with 1 or ≥4 *SMN2* copies and also testing for genetic modifiers outside of *SMN2* in those with 2 and 3 *SMN2*. In symptomatic discordant situations, recommendations are for retesting *SMN2* copy number with different lab/ method initially and/or with a repeat patient sample.	Based on meta-analysis of SMA genotype-phenotype correlations in pretreat and pre NBS era and experience. Guidelines based on data in a different paradigm of diagnosis and intervention and no indication as to whether other evidence sources were considered when making guidelines. No methodology as to the collation of clinical experience to guide recommendations.
Qu et al. 2024 (119)	IV	Case series	Two intron 6 variants led to a wrong diagnosis of SMA due to variants lying within the primer or probe target sequences.	Small cohort with inherent risk of sample bias due to their discordant phenotype. Recommends combined molecular assays to improve diagnostic accuracy in uncertain or discordant cases.
Mikhalchuk et al. 2023 (72)	IV	Prospective cohort	36140 DBS samples with 219 DBS showing equivocal results and resolved with second tier testing. Postulated secondary to 1 *SMN1* and multiple *SMN2* copies.	
Ricci et al. 2023 (145)	IV	Cohort, retrospective study	*SMN2* copy number discordant in 20/189 (11%) of cases with known	Postulation as to why discrepant results arose, including poor quality of DNA and choice of controls in semiquantitative assays.

		comparing retested *SMN2* copy number with prior results	SMA, when retested with new MLPA assessment.	
Muller-Felber et al.2023 (101)	IV	Prospective cohort	1 false negative, 4 false positives	False negative had compound heterozygous genotype For four false positives, 2 heterozygous carriers, 1 had two normal *SMN1* copies and 1 uncertain result, resolved through tiers of testing.
Abiusi et al. 2023(93)	IV	Cohort	Test failure due to possible heparin contamination and failed samples require manual DNA extraction-processes rectified.	
Gailite et al. 2022(70)	IV	Prospective cohort	Significant number of samples required repeat sampling due to poor DNA quality ? Secondary to travel and storage conditions.	
Niri et al.2023 (94)	IV	Prospective cohort	1 false positive for heterozygous carrier and 1 uncertain result due to missing sample that was tested after a time interval and found to be screen negative	
Matteson et al. 2022(105)	IV	Prospective cohort	5 samples required repeating DBS out of 628791 samples, with resolution between of results between samples. All tests screen negative.	Unclear aetiology described as to uncertain results.
Kumar et al.2021(64)	IV	Prospective cohort	1 false positive from 179,467 screened	Reduction in false positive rate due to tiered assays. NICU newborns had more inconclusive results on first tier screening? Secondary to PCR inhibitors.
Wong et al.2024(65)	IV	Prospective cohort	1 false positive	
Oliveira Netto et al.2023 (62)	IV	Prospective cohort	1 false positive due to heterozygous carrier genotype.	High rate of sample failure due to insufficient DNA for testing on initial screen

Kimizu et al.2023(60)	IV	Prospective cohort	1.1% of samples have insufficient material to use for screening	

Evidence summary table for the optimal method of communicating an SMA screen positive result to parents

Author and year	Level of Evidence	Study description	Findings	Comments/appraisal
Muller-Felber et al. 2023 (101)	IV	Cohort	Process considered for 117 screen positive newborns. Screening laboratory informed sender of the DBS of the suspicion of SMA after a mean of 7.7 days after birth (median 7, range 4–15). In 1 case delayed mailing of the screening card was responsible for a delay until day 15. During population screening 44.5% cases the parents were informed by the nearest neuromuscular centre, in 32% by the hospital where the child was born, in 10% by the screening laboratory and in 4% by the practicing paediatrician. Information provided included the name of the diagnosis for 95% (*n*=40), symptoms of SMA for 60% (*n*=25), existence of treatments for 57% (*n*=24), and details of treatment options for 40% (*n*=17).	Variability in the designation of healthcare professional who discloses screen positive result with no indication of which option parents valued.
Abiusi et al. 2024 (103)	N/A	Consensus statement	In case of positive screening results, a consultation with the family should be carried out ideally within three working days.	Consensus statement from US and European experts.
Kariyawasam et al. 2021 (8)	IV	Mixed methods cohort study	17/29 (58%) parents value a healthcare professional with expert knowledge of SMA disclosing the screen positive result and or expedient access to specialist services. Median time from receiving screen positive result to disclosure was 1 day. Dominant was transparent and supported dissemination of information at all contact points with healthcare services, with use of interpreters if required.	Small sample size but included all parents of newborns with a screen positive disclosure.
Kariyawasam et al. 2020 (10)	IV	Cohort	Median time to screen positive disclosure was 10.5 days of life (range: 5–18 days), after having received result on 8 days of life (range: 5–18 days). Communication and delegation of roles between the paediatrician and neurology specialist prior to disclosure, with family contacted by the assigned clinician and advised (over the telephone) of a screen-positive result for a neuromuscular disorder.	Data derived from first year of pilot program, with a view to improve processes and timelines for timely diagnosis and intervention over the course of the program. Prospective collected data reduces potential for recall bias.

Muller-Felber et al. 2023 (101)	N/A	Review	With an NBS for SMA screen positive disclosure, the person who sends the DBS is notified by the screening laboratory, informs the family and establishes contact with the nearest muscle centre. In order to keep the psychological stress on the family as low as possible, a consultation appointment should be made at a qualified muscle centre within one to two working days of the telephone call in which the family was informed of the suspicion of a possible illness.	Opinion of author, not augmented by evidence base and timelines vague.
Glascock et al. 2018 (123)	N/A	Consensus	Guideline 5. derived from non-systematic review of evidence base and consensus by SMA experts that parents should be appraised of and asked to seek medical intervention at any point in the healthcare journey of significant change in child's movement, feeding, or breathing pattern including: 1. Change in voice/weak cry. 2. Increased fatigue without increased activity. 3. Trouble feeding in young children or infants. 4. Decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability. 5. Abdominal breathing. 6. Failure to thrive.	Consensus made with non-systematic evidence to inform the reader of decision-making process. These characteristics were used as they traditionally indicated a severe SMA phenotype (in the pretreatment era).
Zhi et al. 2023(110)	N/A	Consensus	Consensus agreement on following screen positive disclosure aspects: Communication content should include (1) disease-related information, screening results and their significance; (2) limitations of screening technology and various possibilities of current results; (3) immediate consultation.	Consensus made on basis of expert opinion with little evidence provided to inform the reader of decision-making process.
D'Silva et al. 2022 (9)	IV	Hybrid cohort study with implementation effectiveness design	Identified real-world challenges and processes for effective implementation of NBS for SMA including: 1. Dedicated (specialist) team for screen positive disclosure. 2. Provision of information to families to identify symptoms of SMA while treatment plan being formulated. 3. Standard operating procedure to coordinate urgent and personalized clinic appointment. 4. Identified heterogeneity of NBS population with varying needs and identified need for family centred provision of care and information. 5. Options included immediate referral to the neuromuscular team or, for those with difficulties travelling long distances, with the local paediatrician and specialist telehealth support.	Knowledge to action framework used to facilitate implementation of NBS for SMA.

Meyer et al. 2024 (124)	IV	Prospective mixed methods cohort study	For 50 parents receiving screen positive results through NBS (63% of total cohort) paediatricians most commonly disclosed the positive NBS result (71%, *n*=30) neurologists (12%, *n*=5), genetics providers (12%, *n*=5) or obstetric medical practitioners (5%, *n*=2). Information provided in the disclosures included the name of the diagnosis for 95% (*n*=40), symptoms of SMA for 60% (*n*=25), existence of treatments for 57% (*n*=24), and details of treatment options for 40% (*n*=17). Disclosing provider (paediatrician vs non-paediatrician) did not impact the inclusion of diagnosis name (*p*=.49), symptoms of SMA (*p*=.55), existence of treatment (*p*=.92) or details of treatments (*p*=.43) in the NBS result call. Provider type did not impact parents' understanding of the results (*p*=.09), diagnosis (*p*=.31) or next steps (*p*=.49). The majority of parents (88%) were anxious following the disclosure, regardless of amount of information provided (*p*=.16) or disclosing provider (*p*=.30).	Response rate only 23% may increase selection bias. No thematic saturation sought for qualitative component. Exclusion criteria not defined. No indication of how long after screening this data was collected, increasing risk of recall bias.
Elkins et al. 2022 (71)	IV	Cohort	301,418 newborns screened. 15 true positives, 24 false positives. 4 patients died and all had 1 or 2 *SMN2* copies and were symptomatic at time of first clinical review at median age of 55 days (range 10-686 days). Non-neurologist health care providers (designation not specified), advised to contact family although modality of contact not defined. Unclear narrative as to process of screen positive disclosure.	Several reasons we identified that may have contributed to delays in care and treatment in Georgia. Including initially using same approach to short-term follow-up for SMA as for other disorders NBS panel. This included multiple steps to have diagnostic specimens collected locally and sent to our follow-up program, including an evaluation in the genetics clinic with a medical geneticist and genetic counsellor prior to referral to paediatric neurology, Study adapted the protocol to improve timelines by referring all children with abnormal SMA results, excluding inconclusive results, directly to paediatric neurology for collection of diagnostic specimens, clinical evaluation of the child, genetic counselling, and education for the family.

McMillan et al. 2021 (100)	IV	Cohort	Disclosure of screen positive result delegated to a trained genetic counsellor or nurse, and results were disclosed by telephone. At this notification, the infant and family were directed to the closest paediatric hospital for clinical review or were directed to have confirmatory genetic testing performed at a regional diagnostic centre prior to meeting with the paediatric neuromuscular specialist.	No results as to timelines for this process or analysis on if these processes were effective and acceptable.

Evidence summary table for the type(s) of assessments required at first clinic review to aid in diagnostic and clinical evaluation, and to facilitate treatment readiness of the screen positive newborn.

Author, year	Level of evidence	Study description	Findings	Comments/Appraisal
Pane et al. 2022 (150)	Level III	Cohort study identifying the utility of Hammersmith Neonatal Neurological Examination (structured neonatal examination for neonates) and module designed specifically for floppy newborns.	N=17 9/17 infants (53%) had completely normal assessments. The remaining 47% had some abnormal findings in the first days, ranging from minimal clinical signs to the obvious severely abnormal signs. Each assessment helped to better document the clinical signs HNNE, designed as a general neurological assessment for newborns, was able to detect all cases with obvious or minimal clinical signs, the floppy module provided a more qualitative assessment providing the opportunity to subdivide patients according to the presence or absence of SMA specific signs including paradoxical breathing pattern and the presence of the typical SMA distribution of weakness with predominant involvement of lower limbs and proximal muscles.	Structured neurological examination using the 34 items grouped in six categories (posture and tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behaviour) can detect subtle signs of disease onset. Additional module for floppy infants includes section on neurological aspects, one on physical examination and one on additional information such as antenatal history that can help to identify signs suggestive of neuromuscular disorders. The use of this module allows to recognize the signs that are specific of 1 SMA, i.e., the typical posture with intrarotated arms, the pattern of weakness and hypotonia (lower limb > upper limb, proximal > distal), the diaphragmatic breathing pattern, together with absent reflexes and fasciculations. Small sample size so effect requires validation in larger cohorts. No power calculation noted.
Castellano et al. 2022 (127)	N/A	Consensus statement	Presymptomatic patients diagnosed by screening should be assessed at first clinic visit with at least one motor scale for SMA (CHOP INTEND) **and** with the developmental milestones of the WHO or the HINE2.	Rigorous Delphi methodology using expertise form a wide range of specialist only professionals. Patients, advocated and non-specialists not part of process, which may reduce translation of recommendations nationally.
Elkins et al. 2022 (71)	Level IV	Cohort	Clinical examination included components of muscle tone, head lag, extremity anti-gravity strength, presence or absence of tongue fasciculations, and tendon reflexes. Neonatal reflexes including suck, rooting, Moro's and Gallant were elicited, to understand clinical status of child and set goals for timing of treatment.	Part retrospective study, increasing risk of selection bias and observer bias. The utility of SMA validated motor assessments to understand motor function in a presymptomatic cohort, is not well defined.

			Newborns assessed with baseline and serial motor assessments such as CHOP-INTEND.	Authors commented that data from ancillary tests could be helpful in identifying patients who may be already showing more subtle symptoms and need treatment more urgently and/or providing objective data to families who may not understand need for urgent treatment in a normal appearing child.
Kariyawasam et al. 2020 (10)	Level IV	Cohort	10 newborns screened positive, 9 confirmed to have SMA. 4/9 (44%) showed evidence of disease onset which was detected through neurological exam (loss in truncal strength and tone very early on) and supported by denervated EMG in 3/3 (100%) individuals having this procedure and a low CMAP in 2/4 (50%).	Assessments to understand disease onset included low/falling CMAP and EMG conducted serially, but no minimum interval defined and timing of first point of data collection unclear i.e. it may not have been done at first clinic visit. Definition of low CMAP not apparent in paper. Small population within cohort, may preclude generalisability to larger populations, where availability and expertise in conducting nerve conduction assessments is more variable.
Tizzano et al. 2019 (126)	Level IV	Non-systematic narrative summary	Described need of systematic examination of the neonate including complete neonatal (systems) examination, with focus on neurology, cardiac, respiratory, musculoskeletal and endocrine systems, to identify disease onset.	Non-systematic review and evidence limited to highlight once case where neonatal examination identified disease onset.
D'Silva et al. 2022 (9)	Level IV	Cohort	21 screen-positive infants with 6/21 (29%) showing clinical signs and symptoms of SMA disease onset in < 4 weeks of life. Significant differences in CMAPs at time of diagnosis, between infants with different SMA genotypes (two *SMN2* copies, mean tibialis anterior 2.5±1.2mV, range 0.2–4.4; three *SMN2* copies, mean tibialis anterior 4.3±1.5mV, range 3.2–7.2; p=0.02. Serial assessments in 3 presymptomatic infants with two *SMN2* copies, over 7 -14 days, showed rapid reductions in amplitude (mean baseline 2.9±1.0mV, mean follow-up 1.2±1.2mV; p=0.07 associated with symptom onset in one neonate.	Knowledge to action framework used to generate real-world outcomes to inform changes in clinical practice. Authors conclude that neurophysiology assessments are a useful adjunct to clinical exam to identify disease onset (which may be within period of first clinical review).
Vill et al. 2021 (80)	Level IV	Cohort	43 screen positive newborns.	Relatively large cohort for a rare disease, despite 87% opt in rate for NBS for SMA.

			Ulnar CMAP conducted at baseline and showed values of < 1 mV which were considered directly symptomatic. All other children found to be early symptomatic by clinical parameters also had ulnar CMAP amplitudes < 1.5 mV. After treatment, CMAPs increased in the early symptomatic group but did not reach the level of the asymptomatic children.	Subtle reduction of muscular strength or low ulnar CMAPs can be a feature of disease onset. Defines utility of conducting baseline CMAP (at first clinic visit, or shortly thereafter), to define clinical status.

Evidence summary table for on optimal ways to provide information to families at the first clinic visit (after screen positive disclosure).

Author	Level of evidence	Study description	Findings	Comments/Appraisal
Kariyawasam et al. 2021 (8)	IV	Mixed methods study of 44 clinicians and parents going through the NBS for SMA pilot program.	Dominant themes on information provision from the parent perspective included having a child and family centred approach to the timing and content of information given at diagnosis. Parents and healthcare professionals had a dominant theme of access to (multimedia/written resources) to augment verbal information provision.	Small sample size but thematic saturation reached. Purposive sampling framework ensured that a range of sociodemographics, was captured.
Meyer et al. 2024 (124)	IV	Mixed methods study of 50 parents with perspectives of NBS for SMA pathway.	Dominant qualitative themes emerged of: 1. Inaccuracies in information disclosure can lead to parental disbelief of diagnostic results. 2. First clinic appointment was overwhelming for families and authors advocated reduced numbers of professionals in room. Parents who were well informed on SMA symptoms, treatments reported better understanding of NBS result, diagnosis and care. Parents receiving information in more than one category had better understanding of NBS result and diagnosis ($p< 0.05$). Verbal communication was preferred but 40-58% felt visual formats would be helpful. Mixed methods allow for gathering breadth of data and for more granular information.	Low response rate (23%) and mainly mothers, with higher education and of Caucasian ethnicity. Sample size with homogenous characteristics may increase risk of sample bias.

Evidence summary table on optimal way of communicating screen positive results to families

Author	Level of evidence	Description	Findings	Comments/Appraisal
Kolbel et al. 2022 (122)	IV	Cohort	45 parents of newborns diagnosed with SMA through NBS. Assessments included three questionnaires including QoL survey, family burden questionnaire and work productivity assessment. High scores of personal strain and worry for future in all families, higher in families where infant was treated (however these infants were those with lower *SMN2* copy numbers). High social burden noted (p = 0.016). Work productivity assessment showed significant negative effects on daily activities of parents.	Evidence to inform support through access to psychology, social services and advocacy groups. Small cohort and children predominantly with low *SMN2* copies numbers, thereby introducing risk of bias for families of children expected to have a more severe course. Study not powered for in depth statistical analysis of effects of copy number, treatment type or clinical status on findings.
D'Silva et al. 2022 (9)	IV	Implementation study	Knowledge to action framework used. NBS for SMA diagnosed children of families in remote areas, culturally and linguistically diverse backgrounds.	Implementation action identified as the need to provide a clinical team that is aware of circumstances to provide targeted but personalised management plan including psychosocial support. Options included immediate referral to the neuromuscular team or, for those with difficulties travelling long distances, with the local paediatrician and specialist telehealth support Process identified was to establish a standard operating procedure to provide family centred care. The paediatric neuromuscular model of care included capability in clinical genetics to lead the investigation of unusual results, provide genetic counselling, and facilitate family cascade testing, supported by dedicated psychosocial input for families at a time of significant psychosocial stress.
Kariyawasam et al. 2021 (8)	IV	Mixed methods cohort study	Providing equitable diagnosis and access to health resources noted as an opportunity of NBS for SMA by health care professionals. Implementational aspects for the effective translation of NBS for SMA included the ability to access specialist support/expertise by regional HCPs and need to develop expertise outside of specialist centres so that	Small parent cohort increases risk of sample bias but captured a broad range of families with heterogenous characteristics. Thematic saturation reached. Higher response rate 81% with at least one family member from consecutive newborns screened through the NBS program captured which may reduce bias. Sample too small to understand whether demographics have an effect on qualitative outcomes.

			care could be shared between local and specialist centres. Theme of supported information provision established including access to interpreter services if required and written information to augment verbal diagnostic disclosure.	Healthcare professionals mainly aligned or working within specialist services. Remote and regionally working professionals not included, increasing risk of sampling bias.
Castellano et al. 2022 (127)	N/A	Consensus	Recommended management of all newborns diagnosed with SMA through NBS to occur in a specialist centre due to complexities of therapeutic decision making and monitoring (minimum accredited level 5 SMA patients)	National Delphi process with three rounds and high consensus cut-offs.
Meyer et al. 2024 (124)	IV	Mixed methods	Mixed methods study of 50 parents with perspectives of NBS for SMA pathway.	Themes identified included difficulty in processing information due to complexity and emotional state. Authors recommended standardising information at diagnosis, providing written information and offering psychological resources to families.

Evidence summary table for the type(s) of assessments for the newborn required at the time of diagnosis of SMA.

Author	Level of evidence	Study description	Study findings	Comments/appraisal
Finkel et al. 2022 (129)	N/A	Narrative summary/ expert opinion	Subtle clinical findings (neurological) denoting period of transition from presymptomatic to clinically manifest.	Recommends against incorporating neurophysiology outcomes into clinical definition of SMA disease stage, due to lack of age-appropriate normative data, but notes prognostic value of CMAP in denoting earlier onset of symptoms if below normative values.
Tizzano et al. 2017 (130)	N/A	Narrative summary	Clinical status of newborn challenging to define. Requires careful neurological exam and well as a system approach to detect signs such as vascular dysautonomia and cardiac anomalies.	Non-systematic review and evidence limited to highlight once case where neonatal examination identified disease onset.
De Vivo et al. 2019 (6)	III	Open-label single arm cohort	Nusinersen in presymptomatic newborns Inclusion for presymptomatic status was: • Ulnar CMAP ≥ 1 mV • Absence of hypoxemia • No clinical signs and symptoms of SMA Assessments completed at baseline include WHO criteria, HINE-2 and CHOP-INTEND and ulnar CMAP.	Interpretation of signs and symptoms of SMA dependent on clinician expertise.
Strauss et al. 2021 (2 *SMN2* (7) and 3 *SMN2* copies) (151)	III	Open label single arm	Onasemnogene aberparvovec in presymptomatic newborns. Presymptomatic infants had CHOP-INTEND median 49 (28-57), CMAP 3.9mV (2.1-6.1mV) and normal feeding and breathing.	Inclusion criteria for presymptomatic status not defined by current evidence base.

Kolb et al. 2017 (152)	IV	Cohort	Cohort study of 26 infants with SMA and 27 controls. Ulnar CMAP in children with symptomatic SMA was 1.4 mV ± 2.2mV compared to controls of 5.5 ± 2 mV. CHOP-INTEND SMA cohort, 21.4 (SD = 9.6, *n* = 23, range = 10–52) significantly lower than the control cohort, 50.1 (SD = 10.2, *n* = 14, ranged 32–62, *P* < 0.01).	Median age of enrolment into study was 3.7 ± 1.7 months that limits generalisability of data to children outside a NBS population. Small data set increases risk of sample bias.
Servais et al. 2021(153)	III	Open label single arm	Risdiplam in presymptomatic newborns For newborns with 2 *SMN2* copies, ulnar CMAP ≥ 1.5 mV required for categorisation of presymptomatic status.	
Alves et al. 2021 (154)	III	Case-Control	Healthy controls (n=13), untreated SMA infants (n =68) and SMA infants receiving treatment (n=22). 4 infants presented with typical signs and symptoms of SMA < 6 weeks of age, and all had ulnar CMAP of ≤ 1.0mV (normal ≥ 5mV).	Large cohort included a proportion of neonates but predominantly outcomes pertaining to infants > 6 weeks of age.
Pane et al. 2022 (125)	III	Cohort	Prospective study to investigate the utility of Hammersmith Neonatal Neurological Examination (structured neonatal examination for neonates) and module designed specifically for floppy newborns. N=17. 9/17 infants (53%) had completely normal assessments. The remaining 47% had some abnormal findings in the first days, ranging from minimal clinical signs to the obvious severely abnormal signs. Each assessment helped to better document the clinical signs HNNE, designed as a general neurological assessment for newborns, was able to detect all cases with obvious or minimal clinical signs, the floppy module provided a more qualitative assessment providing the opportunity to subdivide patients according to	Structured neurological examination using the 34 items grouped in six categories (posture and tone, tone patterns, reflexes, movements, abnormal signs/patterns, and orientation and behaviour) can detect subtle signs of disease onset. Additional module for floppy infants includes section on neurological aspects, one on physical examination and one on additional information such as antenatal history that can help to identify signs suggestive of neuromuscular disorders. The use of this module allows to recognize the signs that are specific of 1 SMA, i.e., the typical posture with intrarotated arms, the pattern of weakness and hypotonia (lower limb > upper limb, proximal > distal), the diaphragmatic breathing pattern, together with absent reflexes and fasciculations. Small sample size so effect requires validation in larger cohorts. No power calculation noted.

			the presence or absence of SMA specific signs including paradoxical breathing pattern and the presence of the typical SMA distribution of weakness with predominant involvement of lower limbs and proximal muscles.	
Castalleno et al. 2022 (127)	N/A	Consensus statement	Presymptomatic patients diagnosed by screening should be assessed at first clinic visit with at least one motor scale for SMA (CHOP INTEND) **and** with the developmental milestones of the WHO or the HINE2.	Rigorous Delphi methodology using expertise form a wide range of specialist only professionals. Patients, advocates and non-specialists not part of process, which may reduce translation of recommendations nationally.
Elkins et al. 2022 (71)	Level IV	Cohort	Clinical examination included components of muscle tone, head lag, extremity anti-gravity strength, presence or absence of tongue fasciculations, and tendon reflexes. Neonatal reflexes including suck, rooting, Moro's and Gallant were elicited, to understand clinical status of child and set goals for timing of treatment. Newborns assessed with baseline and serial motor assessments such as CHOP-INTEND.	Part retrospective study, increasing risk of selection bias and observer bias. The utility of SMA validated motor assessments to understand motor function in a presymptomatic cohort, is not well defined. Authors commented that data from ancillary tests could be helpful in identifying patients who may be already showing more subtle symptoms and need treatment more urgently and/or providing objective data to families who may not understand need for urgent treatment in a normal appearing child.
Kariyawasam et al. 2020 (10)	Level IV	Cohort	10 newborns screened positive, 9 confirmed to have SMA. 4/9 (44%) showed evidence of disease onset which was detected through neurological exam (loss in truncal strength and tone very early on) and supported by denervated EMG in 3/3 (100%) individuals having this procedure and a low CMAP in 2/4 (50%).	Assessments to understand disease onset included low/falling CMAP and EMG conducted serially, but no minimum interval defined and timing of first point of data collection unclear i.e. it may not have been done at first clinic visit. Definition of low CMAP not apparent in paper. Small population within cohort, may preclude generalisability to larger populations, where availability and expertise in conducting nerve conduction assessments is more variable.
D'Silva et al. 2022 (9)	Level IV	Cohort	21 screen-positive infants with 6/21 (29%) showing clinical signs and symptoms of SMA disease onset in < 4 weeks of life. Significant differences in CMAPs at time of diagnosis, between infants with different SMA genotypes	Knowledge to action framework used to generate real-world outcomes to inform changes in clinical practice.

			(two *SMN2* copies, mean tibialis anterior 2.5±1.2mV, range 0.2–4.4; three *SMN2* copies, mean tibialis anterior 4.3±1.5mV, range 3.2–7.2; *p*=0.02. Serial assessments in 3 presymptomatic infants with two *SMN2* copies, over 7 -14 days, showed rapid reductions in amplitude (mean baseline 2.9±1.0mV, mean follow-up 1.2±1.2mV; *p*=0.07 associated with symptom onset in one neonate.	Authors conclude that neurophysiology assessments are a useful adjunct to clinical exam to obtain a baseline on which to compare longitudinal measurements to identify disease onset.
Vill et al. 2021 (80)	Level IV	Cohort	43 screen positive newborns. Ulnar CMAP conducted at baseline and showed values of < 1 mV which were considered directly symptomatic. All other children found to be early symptomatic by clinical parameters also had ulnar CMAP amplitudes < 1.5 mV (when assessed within 6-14 days of life). After treatment, CMAPs increased in the early symptomatic group but did not reach the level of the presymptomatic children. Children with normal muscle tone, a CHOP INTEND score of > 35 points, and no deterioration in their first 4 weeks of life were considered pre-symptomatic.	Relatively large cohort for a rare disease, despite 87% opt in rate for NBS for SMA. Subtle reduction of muscular strength or low ulnar CMAPs can be a feature of disease onset. Defines utility of conducting baseline CMAP (at first clinic visit, or at diagnosis), to define clinical status. No evidence provided for defining presymptomatic children with CHOP-INTEND < 35.
Mc Millan et al. 2021 (100)	N/A	Protocol	Baseline functional assessments (CHOP-INTEND, HINE) would be performed by a trained physiotherapist or clinical evaluator at time of diagnosis.	No indication as to the evidence base for defining clinical status by cross-sectional analysis of functional assessment.

Evidence summary table on the processes for therapeutic decision making for newborns/infants receiving a diagnosis of SMA through the newborn screening for SMA program.

Author	Level of evidence	Study description	Findings	Comments/Appraisal
Finkel et al. 2017 (121)	Level II	Randomized, sham-controlled clinical trial with nusinersen as the investigational product (2:1 randomisation)	121 subjects with infantile-onset SMA and 2 *SMN2 copies* diagnosed < 6 months of age and who were less than 7 months old at time of first dose. 51% of patients treated with nusinersen achieved improvement in motor milestones, whereas none of the control subjects did (p<0.001). 32% of infants with disease duration >12 weeks responded positively on the Hammersmith Infant Neurological Examination (HINE) motor milestone, compared to 75% of infants with disease duration of < 12 weeks.	Timing of intervention for 2 *SMN2* copy infants, who are within a symptomatic phase predicts future motor outcomes. Outcomes relate to children older than those expected in a screening cohort.
Finkel et al. 2019 (155)	Level III	Open label study	Long term outcomes followed for children treated symptomatically with nusinersen. 22 children <5.42 months of age at the time of first injection improved CHOP INTEND scores by median 19.4 (14.8 to 23.9) at 1058 days post first treatment, whereas the 19 who were between 5.42 months and 7.96 months of age at the time of their first injection improved by 13.8 points (9.2 to 18.4). Unsupported sitting position attained 240 days after modified maintenance dosing regimen was achieved in 18 of 30 (60%) of children treated before 5.42 months but in only 8 of 21 (38%) of those treated later. Three of the 30 (10%) treated before 5.42 months were able to walk with assistance, but none of those treated later were able to walk with assistance.	Long term improvements with motor function noted in children who have an early (infantile) onset phenotype and who are treated early. This population is not comparable to a newborn screening cohort in clinical characteristics but does imply that early intervention for early onset SMA is required.

Pharmaceutical Benefits Advisory Committee (139-141)	NA	Public summary document	Gene therapy recommended for treatment of SMA in children < 9 m with type 1 SMA or presymptomatic with 1-2 copies of *SMN2*. The incremental benefit of presymptomatic treatment for children with 3 SMN2 with DMTs, compared to symptomatic treatment remains unaddressed. *SMN2* copy number variation offers some prognostic value, it was more reliable for infants with ≤2 copies of *SMN2* compared to ≥3 copies of *SMN2*. The PBAC noted that on average patients with 3 copies of *SMN2* would have less severe disease than patients with 1-2 copies.	Summary document of studies presented to PBAC for evaluation of whether children with 3 SMN2 copies have access to immediate and (presymptomatic treatment). Overall, there is uncertainty of the incremental benefit of intervention within the presymptomatic period for those with this genotype, although PBAC acknowledge consumer feedback relating to improved outcomes for children treated prior to symptom onset.
De Vivo et al. 2019 (6)	Level III	Open label single arm phase 3 trial Interim results as of May 2018	25 presymptomatic newborns with 2 (n=15) or 3 (n=10) *SMN2* copies included and received treatment with nusinersen < 6 weeks and whilst clinically presymptomatic. Median (range) age at last visit 26.0 (14.0–34.3) months. All children alive, and none needed permanent ventilation. All (100%) reached sitting position, 22 of 25 (88%) could walk with assistance, and 17 of 22 patients aged more than 18 months (77%) could walk independently.	Newborns diagnosed with SMA with 2,3 *SMN2* copies and who are presymptomatic at time of treatment have improved survival, reduction in comorbidities and motor attainment.
Day et al. 2021 (156)	Level III	Open-label, single-arm, single-dose, phase 3 trial	22 symptomatic children with 1 or 2 *SMN2* copies with SMA phenotype of infantile onset SMA receiving onasemnogene abeparvovec. 13/22 (59%, 97·5% CI 36-100) achieved independent sitting >30 s at the 18 month of age study visit (vs 0 of 23 patients in the untreated control cohort; p<0·0001). 20 patients (91%, 79-100]) survived free from permanent ventilation at age 14 months (vs 6 [26%], 8-44; p<0·0001 in the untreated control cohort).	Multicentre trial. Single arm trial as placebo unethical due to availability of other disease modifying treatments. To minimise bias, a historical cohort was taken as a control population, which differed from the demographics of the investigational group. Precluding direct comparisons of outcomes. Outcomes relate to children older than those expected in a screening cohort and therefore findings may not be fully extrapolated to a NBS and symptomatic population.
Strauss et al. 2021 (2 *SMN2* (7) and 3 *SMN2* copies) (151)	Level III	Open label, single arm, phase 3 clinical trial	30 presymptomatic newborns with 2 or 3 *SMN2* copies, treated with onasemnogene aberparvovec. 14 children with 2 *SMN2* copies. All 14 (100%, 97.5% confidence interval (CI): 77–100%) children in the treated population achieved independent sitting for > 30 seconds up to 18 months compared with none of 23 untreated patients with SMA type 1 in a historical	Newborns diagnosed with SMA with 2 or 3 *SMN*2 copies and who are presymptomatic at time of treatment have improved survival, reduction in comorbidities and motor attainment.

			(non-treated) cohort ($P < 0.0001$). 11 of 14 (79%) achieved sitting motor milestone within the World Health Organization (WHO) normal developmental time window of ≤279 days of age. All 14 (100%) children in the 2 *SMN2* cohort were alive and free of permanent ventilation at 14 months of age and at end of study (first secondary endpoint), compared with 6 of 23 (26%) patients in the historical cohort ($P < 0.0001$). 15 children with 3 *SMN2* copies treated before symptom onset, all stood independently before 24 months ($P < 0.0001$; 14 within normal developmental window), and 14 walked independently ($P < 0.0001$; 11 within normal developmental window). All survived without permanent ventilation at 14 months; ten (67%) maintained body weight (≥3rd WHO percentile) without feeding support through 24 months; and none required nutritional or respiratory support.	Narrow inclusion/exclusion criteria led to 14 exclusions from study, precluding ability to extrapolate findings fully to a real-world cohort.
Carvalho et al. 2023 (137)	N/A	Narrative summary and expert opinion	Paucity of data for treatment of newborns with 1 SMN2 copy, diagnosed through NBS. Expert opinion is to discuss palliation first.	Acknowledges the paucity of evidence on which to found decision making for newborns diagnosed with SMA through NBS with 1 *SMN2* copy.
Aragon-Gawinska et al. 2023 (118)	Level 1	Systematic review evaluating the outcomes of treatment on newborns identified with SMA through NBS.	13 articles with outcomes from 153 newborns (clinical trials and real-world studies). Treatment administered at median of 23 and 52 days for those with 2 and 3 *SMN2* copies. For those treated < 42 days of age (28/38) all but one had normal motor development. Three patients had 1 *SMN2* copies and all had severe symptoms at birth. 2 died without treatment and one treated at 2.5 months was alone at 6 months and invasively ventilated, supplementally fed with minimal movement.	Risk of bias minimised by comprehensive literature, search using multiple databases with well-defined inclusion and exclusion criteria and two reviewers to extract data. Data searches were conducted twice, to include most contemporary data. Treatment < 6 weeks of age, correlates with higher probability of normal motor development.
Kichula et al. 2021 (142)	NA	Expert recommendation and non-systematic narrative review	International panel of seven experts all having role in clinical trials for onasemnogene aberparvovec Recommendations are: 1. Clinicians to discuss timing of treatment with families and highlight urgency of motor neuron degeneration, especially with 2 postnatal months. 2. Clinicians to highlight benefits of early treatment. 3. Treatment for presymptomatic infants guided by clinical context and *SMN2* copy number.	Small expert panel, however with international perspective. Methodology for gaining consensus appears to be through virtual meetings, and no criteria for evidence review. A formal consensus methodology process not employed.

			4. To inform parents of goals of treatment based on clinical context and need for long term multidisciplinary care.	
Kernohan et al. 2022 (61)	IV	Cohort	139,800 infants screened. Pathway adapted to decrease time to treatment to 16-30 days of life. Modifications include diagnostic laboratory open on weekend, reduction in transport time to diagnostic lab, reduction in time for diagnostic analysis and submission of prelim paper work for DMT approval.	
Sawada et al. 2023 (157)	IV	Case series	Describes two infants with different *SMN2* copies and outcomes with early and later treatment. Notes normal motor attainment for 3 *SMN2* copy baby, treated < 42 days of age.	Authors hypothesise that timing of treatment as well as copy number influences motor trajectory, study underpowered to show a clear association. High number of confounders present.
Castalleno et al. 2022(127)	N/A	Consensus statement	Recommendations from process included: 1. Treatment and follow-up of patients with SMA should be carried out in centres that offer multidisciplinary care, with specialists trained in neuromuscular diseases. Experience (follow-up of at least 5 patients with SMA) and minimum accredited training is recommended in those centres in which the treatment and evaluation of the response to treatment of patients with SMA is carried out. 2. Therapeutic decision-making is recommended in multidisciplinary teams. 3. Parents/guardians, prior to the initiation of treatment with drugs that modify the course of the disease, must be informed of the available options, the benefit/risk ratio of each drug, as well as the treatment monitoring conditions (initiation and interruption criteria). 4. It is recommended to agree on therapeutic decisions with patients and/or parents/guardians and obtain their informed consent. 5. Also described factors important in therapeutic goal setting.	Rigorous Delphi methodology using expertise form a wide range of specialist only professionals. Patients advocated and non-specialists not part of process, which may reduce translation of recommendations nationally.
Vill et al. 2021 (80)	IV	Cohort	8/15 children with 2 *SMN2* copies who were treated presymptomatically remain presymptomatic and making normal developmental progress, however symptomatic infants had slower	The extent of motor deterioration not defined in this study.

			developmental progress defined by CHOP-INTEND and HINE scores. 6 newborns treated at 20-29 days of life were asymptomatic at median follow up of 13.2 months (range 5-24 months) 2 untreated children with 2 *SMN2* copies died within one year of diagnosis. 4 infants with 3 *SMN2* copies who were untreated all had motor deterioration.	
Glascock et al. 2018 (123)	N/A	Consensus	For all newborns confirmed with SMA through NBS and with 2 and 3 *SMN2* copies, treatment should be immediately planned. For newborns with 1 *SMN2* copy, treatment is at discretion of clinician and/or if truly presymptomatic. For newborns not treated immediately, management should be through a specialist neuromuscular centre and 3-6 monthly surveillance for first two years and 12 monthly thereafter.	15 international experts, using modified Delphi to generate consensus. Iterative process to gain consensus, based on expert opinion.
Kariyawasam et al. 2023 (107)	Level III	Non-randomised cohort	33 children consecutively recruited. 15 in NBS group and 18 in comparator (referred with clinical symptoms) In NBS group, age at which intervention was administered changed motor outcomes at 2y Early treatment in the screening group was strongly and significantly associated with a positive change in motor function (HINE-2 score, r=0·74, p=0·009; WHO motor milestones, r=0·67, p=0·02). Age of treatment particularly influential, with newborn screening and symptomatic children showing smaller gains in motor function with delays in therapeutic intervention, even over a matter of days, than children in the newborn screening and pre-symptomatic group. Statistical differences in HINE-2 score are noted between groups: newborn screening and symptomatic mean HINE-2 score, 17·0 (SD 3·7) versus newborn screening and pre-symptomatic mean HINE-2 score, 21·7 (SD 1·9); p=0·020	
Oskoui et al. 2022 (158)	Level IV	Cross sectional survey	21 SMA experts across one health jurisdiction, with view to look at international consensus guidelines for treatment of children with SMA with onasemnogene aberparvovec within a local context.	60% response rate may increase sampling bias.

			Recommendations as follows: 1. Administration of gene therapy and follow-up to be carried out by specialized experienced centres. 2. Trained and experienced physical therapists are needed at these sites to perform standardized motor outcome measures specifically validated in this population. 3. The earlier any disease-modifying therapy in SMA is introduced, before any clinically apparent, irreversible motor neuron loss occurs, the better the outcome. 4. Treatment should not be delayed, especially in infants who have a more rapidly degenerative course. If gene therapy is considered and is predicted to be delayed beyond 2 weeks, another disease-modifying therapy should be initiated to maintain motoneurons before gene therapy can be administered.	NBS not implemented across whole of health jurisdiction at time of survey. 9/21 (43%) had a financial conflict of interest with study sponsor. Although thresholds for reaching consensus were established in methods, descriptive statistics of survey results were not presented on which recommendations were based.
Ramos Platt et al. 2022 (136)	N/A	Expert evidence	Recommendations included: 1. Urgency to treat infants and younger children as soon as possible following a diagnosis of SMA to minimize the loss of motor neurons and, therefore, motor function, therefore bridging treatments may be considered if there are delays with first choice disease modifying intervention. 2. Clinicians should present all treatment options in a comprehensive, fair, and balanced manner, explaining the known attributes and potential differentiating features of each therapy.	Small panel (< 5 members). Not based on clinical evidence and narrative description of expertise in this field, severely limiting evidence generated. Limitations acknowledged by authors and included biases' with all experts coming from clinical research centres, challenges extrapolating findings to other health jurisdictions.
Deng et al. 2022 (159)	Level IV	Mixed methods study of parental views on therapeutic decision making	18 parents of children diagnosed with SMA through NBS. 83.3% of parents felt that physician counselling on treatment options impacted decision making. Treatment frequency, potential of long-term side effects and methods of delivery considered important factors for therapeutic decision making.	Small sample size increases risk of selection bias. Confounders may include *SMN2* copy number, and timing of when parent' completed survey (data not collected). Recruitment through an advocacy group also gives a self -sampled population.

D'Silva et al 2022 (160)	Level IV	Cohort and Implementation study	Study of 21 patients accessing onasemnogene aberparvovec as part of the managed access program in Australia. Challenges identified by study are the complex geographical location of patients, with implementation action relying on close collaboration with interstate neurologists and rural/regional health services, using telehealth as required to increase equity of access and streamline timelines to therapeutic intervention.	Implementation aspect of study does not have a clear methodology/framework, which may reduce rigour of recommendations.
Pechmann et al. 2019 (161)	N/A	Protocol	Clinical surveillance as recommended by the data registry includes: 1. Respiratory and nutritional status including growth parameters at each visit. 2. Orthopaedic symptoms including experience of pain and fatigue. 3. Adverse events and the subjective impression of the patient or caregiver. 4. Clinical examination including assessment of contractures and the current motor function using HINE-2 used plus SMA validated scales such as Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) in children under 2 years of age and in patients without ability to sit independently. The Hammersmith Functional Motor Scale Expanded (HFMSE) in children older > 2 years of age with ability to sit and in patients with a CHOP INTEND score > 50. Revised Upper Limb Module (RULM) in patients older than 2 years of age with the ability to sit in a wheelchair. Additionally, in ambulant patients older >3 years of age, the 6-Minute-Walk Test (6MWT) was utilised.	No outcomes defined in this protocol for the SMARTCare registry. Multicentre cohort (registry) study.
D'Silva et al. 2022 (9)	IV	Cohort	21 screen-positive infants with 6/21 (29%) showing clinical signs and symptoms of SMA disease onset in < 4 weeks of life. Significant differences in CMAPs at time of diagnosis, between infants with different SMA genotypes (two *SMN2* copies, mean tibialis anterior 2.5±1.2mV, range 0.2–4.4; three *SMN2* copies, mean tibialis anterior 4.3±1.5mV, range 3.2–7.2; p=0.02. Serial assessments in 3 presymptomatic infants with two *SMN2* copies,	Knowledge to action framework used to generate real-world outcomes to inform changes in clinical practice. Authors conclude that neurophysiology assessments are a useful adjunct to clinical exam

			over 7 -14 days, showed rapid reductions in amplitude (mean baseline 2.9±1.0mV, mean follow-up 1.2±1.2mV; *p*=0.07 associated with symptom onset in one neonate.	to identify disease onset (which may be within period of first clinical review).
Weng et al. 2021 (135)	IV	Cohort – cross sectional and longitudinal	Measuring ulnar CMAP pre and post treatment in 21 newborns with SMA confirmed through a NBS program. 12 newborns within cohort. Initial CMAP amplitudes lower in infants with 2 *SMN2* copies (1.39 ± 0.79 mV) vs 3 *SMN2* copies (3.70 ± 0.59 mV). CMAP amplitude decreased rapidly in all SMA1 infants, with those with 3 *SMN2* copies dropping significantly when the muscle power of their upper extremities was normal. CMAP data from six infants who were treated with nusinersen were available. The pretreatment CMAP amplitudes were 0.89 ± 0.76 mV and 2.36 ± 1.71 mV in 2 and 3 *SMN2* copies, respectively, compared with 1.33 ± 0.22 mV and 3.69 ± 2.84 mV 6 months after treatment. In those with a pretreatment CMAP amplitude ≥2 mV, CMAP increased significantly after treatment, accompanied by normal motor development. In those with a pretreatment CMAP amplitude <2 mV, the increase in CMAP after treatment was small and slow, although still accompanied by functional improvements. The only outlier was patient 7 (with two *SMN2* copies) whose pretreatment CMAP amplitude was <1 mV and who showed significant improvements in CMAP after treatment. He had mild motor developmental delay, while he could sit independently at the age of 9 months and walk holding on at the age of 15 months.	Small cohort increases risk of sampling bias. Assessors not blinded to clinical or genetic status of infant, increasing risk of observer bias. CMAP at baseline may predict motor response. Serial CMAP showing decline denote disease onset even in absence of clinical symptoms.
Gaviglio et al. 2023 (131)	N/A	Narrative review	Authors identify wider resources required to access treatments including issues of equity, especially for families living regionally or with varying resources to attend specialist clinics. Solutions identified include building a hub and spoke model of care for post treatment monitoring where follow-up is shared or supported between specialist and regional centres.	Narrative summary with little evidence base provided for recommendations or access considerations.
McMillan et al. 2021 (100)	N/A	Consensus	For newborn with 2 or 3 *SMN2* copies, recommendation for immediate treatment. Neurophysiology not recommended for this	No documentation on the number, designation, affiliation, or experience of experts used for panel.

			treatment group as it does not change management. Surveillance includes motor assessments but not neurophysiology. For children with 4 *SMN2* copies (not accessing treatment unless clinically symptomatic or neurophysiology showed denervation or CMAP < 80% lower limit for age), 3 monthly surveillance for 12 months and then 'regular' assessment thereafter.	No explanation of evidence reviewed by panel to come to recommendations.
Kolbel et al. 2022 (122)	IV	Cohort	45 parents of newborns diagnosed with SMA through NBS. Assessments included three questionnaires including QoL survey, family burden questionnaire and work productivity assessment. Significantly higher scores for Family Burden Questionnaire (domains of social burden, personal strain, and worry) in parents of treated children vs. parents of untreated children and also significant loss in work productivity for fathers of treated vs untreated children.	Treatment confined to nusinersen only as other treatments unavailable at the time of the study, perhaps precluding generalisability of findings to current therapeutic landscape where three interventions are available. Sample size too small to account for confounders related to phenotype i.e. untreated children more likely to have higher *SMN2* copy numbers and a milder phenotype, which may confound findings.
Carey et al. 2022 (143)	IV	Cohort	Discrete choice experiment of 1113 parents of children with SMA, healthcare professionals and general population. Treatment rationale based on several factors including potential to improve function and mobility and invasive (more acceptable) compared to treatments with invasive delivery and risks of adverse events.	Large respondent pool. Did not capture parents of children going through NBS for SMA.

Evidence summary table for the management of newborns with≥ 4 *SMN2* copies not initially treated with disease modifying treatments.

Author	Level of evidence	Study type	Study findings	Comment/appraisal
Vill et al. 2021 (80)	IV	Cohort	43 screen positive cases, with confirmation of SMA on diagnostic testing.14/45 (32.5%) had 4 *SMN2* copies. Median follow-up 12.2 months (1.5-26 months). One parent opted for treatment. No symptoms noted by end of follow-up period however three siblings had developed symptoms and were treated in early childhood.	Comparatively large number of children with 4 *SMN2* copies and predominantly untreated. Short follow-up time may preclude longer-term evidence of disease onset and progression in childhood. Presentation of siblings with SMA type III in childhood shows some evidence that clinical course may not be later in onset but this is a biased population, from known index cases. Small sample size limits in depth statistical analyses and data collection not uniform. Timing of therapeutic intervention unclear based on current evidence but authors If surveillance strategy is chosen, *SMN2* copy number should be redetermined (due to chances of discrepancies between methods). Findings reduce ascertainment bias of individuals presenting with SMA with 4 *SMN2* copies in pretreatment era.
Vill et al. 2024 (144)	IV	Cohort (registry study)	Prospective data. 90% of registry participants have undergone *SMN2* copy number with 23.2% having 4 *SMN2* copies. 268 patients included in sub cohort analysis. Disease onset median 3y, mean 6.4 years (1 month to 47 years). 55% had disease onset within 36 months of age. 15.7% did not obtain ability to walk. Of 226 patients achieving ambulation, 33% lost ability over median 21.2 years.	Large population with multi-centre collection of data. Analysed only outcomes from those > 18 months age. Presymptomatic newborns excluded which may bias population outcomes. Limitations include under representation of minimally symptomatic or presymptomatic individuals in registry, biasing towards more severe cases.

Calucho et al. 2018 (162)	IV	Cohort	167 symptomatic patients clinically defined with type III SMA. Of this cohort, 51/167 (31%) had 4 *SMN2* copies. No patient with 4 *SMN2* copies had type I or II SMA.	Large cohort. Ascertainment bias due to outcomes from a prevalent and symptomatic population. Does not account for presymptomatic or mildly symptomatic individuals.
Glascock et al. 2018 (123)	N/A	Consensus	Recommendations that a higher frequency of clinical visits are required early on for those who do not access treatment and are ≥ 4 *SMN2* copies. Diminishing frequency of visits recommended as less severe forms of disease have later onset, so that burden of clinical visits can be balanced with minimising treatment related risks with less severe SMA.	Consensus group acknowledged that neurological exam, motor assessments and myometry were important to define disease onset, however had reduced sensitivity in defining phenoconversion for presymptomatic individuals. Recommended neurophysiology (CMAP and EMG) had potential value in defining disease onset early on (also acknowledging variabilities in availability, expertise in conducting assessments and patient related factors such as age, tolerability).
Glascock et al. 2020 (163)	N/A	Consensus	Consensus reached for immediate access to treatment for those with 4 *SMN2* copies.	Although consensus reached as to treatment of those with 4 *SMN2* copies, differing opinions noted within the expert group. Evidence for 4 *SMN2* copy management extrapolated from data from presymptomatic 3 *SMN2* copies, which may not be translatable across genotypes. Experts came from jurisdictions with access to treatment across 4 *SMN2* copies, and one reason for recommendation was that approved treatments could now be given and were safer when given in younger individuals, which may also bias consensus recommendations towards access to therapeutic interventions.
Deng et al. 2022 (159)	N/A	Letter	Data for 4 *SMN2* copy presymptomatic infants missing across all clinical trials and therefore outcomes with treatment unknown.	Short letter which is more of an opinion piece than grounded in evidence.
Ricci et al. 2023 (145)	IV	Cross-sectional cohort	169 patients with 4 *SMN2* copies. For 4 children diagnosed through NBS for SMA and 2 with family history, only 1/3 of families opted to proceed with treatment. All infants had no symptoms and achieved expected motor function age at 2.5 +/- 1 year. For symptomatic patients, 5% type II, 90% type III and 5%	Large mixed (paediatric and adult) cohort, however study within a pretreatment era and in the majority not within an NBS for SMA paradigm. Evidence of progression and higher number of patients with childhood onset disease considered additional data to help with therapeutic decision making for those with *4 SMN2* copies. Cross-sectional functional data only and progression of disease with loss of functional skills not determined through prospective analysis but with functional

			type IV. 74% of type III individuals had onset > 3y of age and 47% >9 years of age. 1 in 4 of those with type III and IV disease lost ambulation with time, despite having a supposedly milder and later onset of disease.	score against age, which may bias interpretation of disease progression in a given individual.
Muller-Felber et al. 2020 (146)	IV	Case series	38 screen positive newborns. 15/37 (40%) had 4 *SMN2* copies. Six cases presented with one child developing signs of SMA at 8 months of age. Risk lack of compliance with clinical surveillance defined in two cases (due to psychological and sociodemographic factors.) Surveillance included clinical exam, motor function scores, muscle ultrasound and neurophysiology. EMG can detect neurogenic process in patients, but this is not well tolerated on repeated attempts. CMAP can be normal in patient with SMA type III despite underlying motor neuron loss and is not a sensitive biomarker for disease onset in those with chronic denervation.	Incidence of SMA in cohort 1: 7350m identical to that found in symptomatic population in pretreatment therefore conclusions drawn that all children diagnosed with SMA through NBS would become symptomatic regardless of *SMN2* copy number (over diagnosis of 4 *SMN2* copies through NBS for SMA refuted). High percentage of 4 *SMN2* copies compared to other European rates, however, concordant with a metanalysis of all SMA patients which shows 38% population having 4 *SMN2* copies. Determination of *SMN2* copy number with up-to-date methodologies and in different laboratories advised. Case series small and highlights some of the potential pitfalls of a surveillance approach but the characteristics of the rest of the 4 *SMN2* copy cohort is not well defined which may lead to reporting biases. t
Blaschek et al. 2022 (147)	IV	Cohort	21 patients diagnosed with SMA through NBS with 4 *SMN2* copies . 3 patients had to have *SMN2* copy number corrected and 3 lost to follow-up suggesting a compliance issue with clinical surveillance strategy.	Small cohort, increasing potential for sample bias. Potential for ascertainment bias, with outcomes defined from a prevalent symptomatic population with 4 *SMN2* copies. This precludes the availability of data from whole of population studies which may include mildly symptomatic or presymptomatic individuals who have not been brought to the attention of health services and/or deceased individuals with a severe onset phenotype.

			6/15 patients who were treated remained presymptomatic at follow-up. 7/15 had clinical surveillance of which 5/7 showed clinical or electrophysiological disease onset between 1.5-4y.	

Systematic observation form results

Systematic observation form tables

NBS reports detailing carrier status (1 *SMN1* copy) will not be issued by Australian and New Zealand NBS for SMA programs

Reporting carrier status in NBS for SMA		**Outcomes**					
		Facilitating future reproductive decisions of individuals with genetic screening results and their families	Increasing emotional distress for families	No immediate health benefit to the newborn	Increasing the potential for discrimination of individuals with genetic screening results (social, financial, insurance)	Increasing uncertainty and misunderstanding of genetic diagnosis in children who cannot understand the implications of a genetic result.	Increasing demands on health system resources to diagnose and manage individuals and families with a screening (carrier status) result e.g. genetic counselling, further genetic analysis of families etc.
Intervention	Reporting newborns with 0 and 1 *SMN1* copies (i.e. reporting carrier status)	Small benefit (7/13; 54%)	Large harm (7/13; 54%)	No effect (6/13; 54%)	Small/large harm (11/13; 92%)	Large harm (9/13; 69%)	Large harm (7/13; 54%)

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

Screening for genetic modifiers as part of NBS for SMA		**Outcome**				
		Improving prediction of phenotype for the newborn	Improving therapeutic decision making for clinicians	Improving therapeutic decision making for families	Improving care planning for newborns	Increasing demands on health system resources to provide this intervention
Intervention	Screening for genetic modifiers outside of *SMN2*	Small benefit (5/10; 50%)	No effect (4/10; 40%)	No effect (4/10; 40%)	Small benefit (4/10; 40%)	Small harm (2/11; 18%)

Screen positive disclosure should occur when the *SMN1* screening result is available (independent of the availability of *SMN2* copy number on the screening test), to reduce timelines to diagnosis and treatment

Defining screen positivity for NBS for SMA		**Outcome**						
		Reducing time to diagnosis for the newborn	Reducing time to treatment for the newborn	Reducing time to clinical care for the newborn	Improving health outcomes to the newborn	Improving therapeutic decision making for families	Improving therapeutic decision making for clinicians	Increasing demands on health system (screening) resources to provide this intervention
Intervention	Referring a screen positive SMA newborn result to a clinical service as soon as the *SMN1* screening result is available	Large benefit (10/13; 77%)	Large benefit (7/13; 54%)	Large benefit (10/13; 77%)	Small benefit (6/11; 55%)	Small benefit (3/12; 25%)	No effect (4/13; 31%)	No effect (6/12; 50%)

The NBS 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 the named medical practitioner on the dried blood spot care AND a designated paediatric neurologist. Ideally, a formal screening report should be issued to these individuals within 24 hours of this verbal communication.

Referring screen positive newborns to clinical services after a screen positive result		**Outcome**				
		Reducing time to diagnosis for the newborn	Strengthening health care communication and coordination between stakeholders	Reducing time to treatment for the newborn	Reducing time to clinical care for the newborn	Increasing demands on health system resources to provide this intervention
Intervention	Referring a screen positive SMA newborn result to a clinical service by verbal means (e.g. with a phone call)	Large benefit (10/13; 77%)	Large benefit (11/13; 85%)	Large benefit (9/13; 69%)	Large benefit (10/13; 77%)	Small harm (8/13; 62%)

The process to manage newborns with false positive screening results.

Process to manage newborns with false positive screening results		**Outcome**							
		Increasing emotional wellbeing for families	Reducing diagnostic uncertainty for clinicians	Reducing diagnostic uncertainty for families	Increasing knowledge for families	Improving procedural accountability and improvement of the NBS for SMA program	Improving health outcomes for newborns with a false positive result	Maintaining public confidence in NBS for SMA	Increasing equity of access to care and support for all newborns undergoing NBS for SMA
Intervention	Coordinated plan to establish aetiology of false positive result with communication between screening, diagnostic and clinical services	Large benefit (9/12;75%)	Large benefit (11/12; 92%)	Large benefit (9/12;75%)	Large benefit (7/12; 58%)	Large benefit (9/12;75%)	Small benefit (3/12; 25%)	Large benefit (9/12;75%)	Small benefit (3/12; 25%)
	Disclosure of the false positive result given or supported by a paediatric neurologist	Large benefit (9/12;75%)	Large benefit (7/12; 58%)	Large benefit (7/12; 58%)	Large benefit (8/12; 67%)	Small benefit (4/12;33%)	Small benefit (5/12; 42%)	Small benefit (5/12; 42%)	No effect (6/11; 55%)
	Implications of a false positive for the newborn and family explained to the family	Large benefit	Small benefit / no	Large benefit (7/12; 58%)	Large benefit (10/12; 83%)	Large benefit (7/12; 58%)	Small benefit (4/11;36%)	Large benefit (8/11; 73%)	Small benefit (4/10; 30%)

		(11/12; 92%)	effect (8/12; 67%)						
	Families referred to appropriate (psychological/social) services for support and care	Large benefit (10/12; 83%)	No effect (8/12; 67%)	Small benefit (4/12;33%)	Large/small benefit (11/12 92%)	Small benefit (3/12; 25%)	Large benefit (7/12; 58%)	Small benefit (4/11;36%)	No effect (6/12; 50%)
	Families given the option to return to clinical services for further discussions on the implications of a false positive result	Large benefit (9/12;75%)	Small benefit / No effect (8/12; 67%)	Large/Small benefit (10/12; 83%)	Large benefit / Small benefit (9/12; 75%)	Small benefit (6/12; 50%)	Small benefit (2/12;17%)	Small benefit (5/12; 42%)	No effect (6/12; 50%)
	Newborn/infant followed by clinical service (through access to a dedicated paediatric neurology service or with support from a paediatric neurology service, until diagnostic certainty is reached	Large benefit (9/12;75%)	Large benefit (8/12; 67%)	Large benefit (8/12; 67%)	Large benefit (9/12;75%)	Small benefit (5/12; 42%)	Large/small benefit (10/12; 83%)	Small benefit (5/12; 42%)	Small benefit (3/12; 25%)

The process to manage newborns with false negative screening results.

Process to manage newborns with false negative screening results		**Outcome**							
		Increasing emotional wellbeing for families	Decreasing time to treatment	Increasing access to management of SMA for newborns	Increasing knowledge for families	Improving procedural accountability and improvement of the NBS for SMA program	Improving health outcomes for newborns with a false negative result	Maintaining public confidence in NBS for SMA	Increasing equity of access to care and support for all newborns undergoing NBS for SMA
Intervention	Immediate referral to a paediatric neurology service	Large benefit (9/12;75%)	Large benefit (10/12; 83%)	Large benefit (10/12; 83%)	Large benefit (9/11;82%)	Large benefit (7/12; 58%)	Large benefit (10/12; 83%)	Large benefit (7/11; 64%)	Large benefit (6/11; 55%)
	Disclosure of the false negative result given or supported by a paediatric neurologist	Large benefit (9/12;75%)	Large benefit (8/12; 67%)	Large benefit (7/12; 58%)	Large benefit (9/12;75%)	Large benefit (8/12; 67%)	Large benefit (7/12; 58%)	Large benefit (6/12; 50%)	Small benefit (4/11; 36%)

	Implications of a false negative for the newborn and family explained to the family	Large benefit (7/12; 58%)	Large benefit (8/12; 67%)	Large benefit (7/11; 64%)	Large benefit (10/12; 83%)	Large benefit (8/12; 67%)	Large benefit (8/12; 67%)	Large benefit (8/12; 67%)	Small benefit (4/11; 36%)
	Management for the newborn instigated within or supported by a neurology /neuromuscular service	Large benefit (7/12; 58%)	Large benefit (11/12;92%)	Large benefit (11/12;92%)	Large benefit (9/12;75%)	Large/small benefit (8/12; 67%)	Large benefit (11/12;92%)	Small benefit (4/12;33%)	Large benefit (7/12; 58%)
	Coordinated plan to establish aetiology of false positive result with communication between screening, diagnostic and clinical services	Large benefit (8/12; 67%)	Small benefit / No effect (7/12; 58%)	Small benefit (0/12; 0%)	Large / small benefit (9/12;75%)	Large benefit (12/12; 100%)	Large/ small benefit (9/12;75%)	Large benefit (10/12; 83%)	Large benefit (7/12; 58%)
	Families referred to appropriate (psychological/social) services for support and care	Large benefit (11/12;92%)	Small benefit (3/12; 25%)	Small benefit (2/11; 18%)	Large benefit (7/12; 58%)	Small benefit / No effect (7/12; 58%)	Large/small benefit (9/12; 75%)	Small benefit (4/11; 36%)	Small benefit (2/12; 17%)

The process to resolve discordant *SMN1* results.

Resolving discordant SMN1 (screening and diagnostic) results		**Outcome**						
		Ensuring correct diagnosis	Improving therapeutic decision making for clinicians	Improving therapeutic decision making for families	Improving care planning for the newborn	Reducing emotional distress of families	Increasing diagnostic burden on newborn	Increasing health system resourcing to undertake the above interventions
Intervention	Coordination between screening, diagnostic and clinical services to ascertain aetiology of discordant results	Large benefit (11/11; 100%)	Large benefit (9/11; 82%)	Large benefit (9/11; 82%)	Large benefit (8/11; 73%)	Large benefit (6/11; 55%)	No effect (6/10; 60%)	Small harm (7/11; 64%)
	Re-test on same dried blood spot using different screening assay (including different lab)	Large benefit (6/11; 55%)	Large benefit (6/11; 55%)	Small benefit (2/11; 18%)	*Small benefit (4/10; 40%)	Small benefit (4/11; 36%)	No effect (8/11; 73%)	Small harm (7/11; 64%)
	Recollect another dried blood spot from the newborn and rerun the same screening assay	Small benefit (3/11; 27%)	Small benefit (2/11; 18%)	Small benefit (1/11; 9%)	Small benefit (4/11; 36%)	No effect (4/11; 36%)	Small harm (5/11; 45%)	Small harm (6/11; 55%)
	Recollect another dried blood spot sample from the newborn and run this on a different screening assay	Large benefit (6/11; 55%)	Small benefit (3/11; 27%)	Small benefit (2/11; 18%)	Small benefit (4/11; 36%)	No effect (4/11; 36%)	Small harm (5/11; 45%)	Small harm (7/11; 64%)
	Re-test same diagnostic sample using a different diagnostic assay	Large benefit (9/11; 82%)	Large benefit (9/11; 82%)	Large benefit (8/11; 73%)	Large benefit (7/10; 70%)	Small harm (3/11; 27%)	No effect (7/11; 64%)	Small harm (8/11; 73%)

	Recollect a second diagnostic sample from the newborn and rerun the same diagnostic assay	Large benefit (6/11; 55%)	Large benefit (6/11; 55%)	Large benefit (6/10; 60%)	Small benefit (5/11; 45%)	No effect (3/11; 27%)	Small harm (6/11; 55%)	Small harm (7/11; 64%)
	Recollect second diagnostic sample from newborn and run on different diagnostic assay	Large benefit (10/11; 91%)	Large benefit (8/11; 73%)	Large benefit (7/10; 70%)	Large benefit (8/11; 73%)	No effect (3/11; 27%)	Small harm (8/11; 73%)	Small harm (7/11; 64%)
	Refer diagnostic blood sample for genetic sequencing of *SMN1*	Large benefit (9/11; 82%)	Large benefit (7/11; 64%)	Large benefit (7/11; 64%)	Large benefit (6/11; 55%)	Small benefit (2/10; 20%)	No effect (3/10; 30%)	Small harm (7/10; 70%)
	Clinical review of newborn/infant clinically till genetic diagnosis can be ascertained, by or supported by a paediatric neurologist	Large benefit (9/10; 90%)	Large benefit (9/10; 90%)	Large benefit (9/10; 90%)	Large benefit (8/10; 80%)	Large benefit (7/11; 64%)	No effect (4/10; 40%)	Small harm (5/10; 50%)
	Provide families with open and clear communication on uncertainties of diagnosis, until a genetic diagnosis can be ascertained	Large benefit (7/11; 64%)	Large benefit (7/11; 64%)	Large benefit (8/11; 73%)	Large benefit (6/11; 55%)	Large benefit (8/11; 73%)	No effect (7/10; 70%)	Small harm (3/11; 27%)
	Refer families who receive discordant *SMN1* results to appropriate psychological and social services for care and support	No effect (7/11; 64%)	No effect (7/11; 64%)	Large benefit (6/11; 55%)	Small benefit (6/11; 55%)	Large benefit (6/10; 60%)	No effect (7/9;78%)	Small harm (7/10; 70%)

The process to resolve discordant *SMN2* results.

Resolving discordant SMN2 (screening and diagnostic) results		**Outcome**						
		Ensuring correct prognostic information is available	Improving therapeutic decision making for clinicians	Improving therapeutic decision making for families	Improving care planning for the newborn	Reducing emotional distress of families	Increasing diagnostic burden on newborn	Increasing health system resourcing to undertake the above interventions
Intervention	Coordination between screening, diagnostic and clinical services to ascertain aetiology of discordant results	Large benefit (6/8; 75%)	Large benefit (5/8; 63%)	Large benefit (5/8; 63%)	Large/small benefit (7/8; 88%)	Large benefit (5/8; 63%)	No effect (3/8; 38%)	Small harm (3/8; 38%
	Re-test *SMN2* on the same dried blood spot using a different screening assay (including different laboratory)	Large benefit (5/8; 63%)	Large/small benefit (7/8; 88%)	Small benefit (4/8; 50%)	Small benefit (5/8; 63%)	Small benefit 3/8; 38%)	No effect (4/8; 50%)	Small harm (3/8; 38%)
	Recollect another dried blood spot from the newborn and rerun the same *SMN2* screening assay	Large benefit (4/7; 57%)	Small benefit (2/7; 29%)	Small benefit (3/7; 43%)	Small benefit (4/7; 57%)	No effect / small harm (4/8; 50%)	Small harm (5/8; 63%)	Small harm (3/8; 38%)

	Recollect another dried blood spot sample from the newborn and run this on a different *SMN2* screening assay	Large /small benefit (7/8; 88%)	Small benefit (4/8; 50%)	Small benefit (4/8; 50%)	Small benefit (5/8; 63%)	No effect (0/8; 0%)	Small harm (5/8; 63%)	Small harm (3/8; 38%
	Re-test same diagnostic sample using add PCR diagnostic assay	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Small benefit (1/7; 14%)	No effect (3/7; 43%)	Small harm (2/7; 29%)
	Clinical review of newborn/infant clinically till genetic diagnosis can be ascertained, by or supported by a paediatric neurologist	Large benefit (6/8; 75%)	Large/small benefit (7/8; 88%)	Large/small benefit (7/8; 88%)	Large benefit (6/8; 75%)	Large benefit (5/8; 63%)	Small harm (3/7; 43%)	Small harm (2/7; 29%)
	Provide families with open and clear communication on the uncertainties of diagnosis, till a genetic diagnosis can be ascertained	Large benefit (5/8; 63%)	Large benefit (5/8; 63%)	Large benefit (5/8; 63%)	Large / small benefit (6/8; 75%)	Large benefit (6/8; 75%)	No effect (4/7; 57%)	No effect / small harm (3/8; 38%)
	Refer families who receive discordant *SMN1* results to appropriate psychological and social services for care and support	No effect (5/8; 63%)	No effect (4/8; 50%)	Small benefit (2/8; 25%)	Small benefit / no effect (4/8; 50%)	Large benefit (6/8; 75%)	No effect (4/8; 50%)	Small harm (2/7; 29%)

Communicating a screen positive result to families

Communicating a screen positive result to families.		**Outcome**					
		Increasing knowledge for families	Reducing to time diagnosis for newborns	Reducing time to treatment for newborns	Reducing psychological distress for families	Increasing demand on health system resources to manage clinical workflow	Increasing equity of access to specialist care for all SMA screen positives
Intervention	Child neurologist /neuromuscular physician disclosing screen positive result	Large benefit (4/7; 57%)	No effect (4/7; 57%)	Small benefit (2/7; 29%)	Large benefit (4/7; 57%)	Small harm (5/7; 71%)	Small benefit (2/7; 29

Conducting the first clinical review

Conducting the first clinical review (for diagnostic evaluation) after a screen positive result disclosure		**Outcome**					
		Increasing knowledge for families	Reducing to time diagnosis for newborns	Reducing time to treatment for newborns	Supporting family's well-being and psychological stress	Promoting health equity for rural and remote families	Resourcing clinical services to provide a timely review
Intervention	First clinical review conducted and/or clinically supported by paediatric neurology services.	Large benefit (7/7; 100%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Large benefit (6/7; 86%)	Large benefit (4/7; 57%)	Small harm (3/7; 43%)

The assessments undertaken at first clinical review of a screen positive newborn/infant.

Assessments undertaken at the first clinical review (for diagnostic evaluation) after a screen positive result disclosure.		**Outcome**					
		Reducing time to diagnosis	Reducing time to treatment	Provision of early interventions to improve health outcomes for the newborn	Improving health outcomes of newborns by confirming clinical status	Improving therapeutic decision making for families	Demand on health system resources required to conduct the above interventions
Intervention	Neurological examination to establish if symptomatic to diagnosis	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Small harm (4/7; 57%)
	Neonatal exam including cardiac, respiratory and gastrointestinal systems to assess clinical status of newborn	No effect (5/7; 71%)	No effect (4/7; 57%)	Small benefit (3/7; 43%)	Small benefit (3/7; 43%)	Small benefit (4/7; 57%)	Small harm (3/7; 43%)
	SMA validated motor assessments to assess functional baseline	No effect (4/7; 57%)	Small benefit (2/7; 29%)	Small benefit (1/7; 14%)	Small benefit (2/7; 29%)	Small benefit (5/7; 71%)	Small harm (4/6; 67%)
	Nerve conduction studies +/- EMG to assess for active disease onset	No effect (4/6; 67%)	Small benefit / no effect (4/6; 67%)	Small benefit (2/6; 33%)	Large/small benefit (5/6; 83%)	Large/small benefit 4/6; 67%)	Large harm (3/5; 60%)

	Venous sampling for *SMN1* on whole blood EDTA (diagnostic bloods)	Large benefit (5/5; 100%)	Large benefit (5/5; 100%)	Large benefit (4/5; 80%)	Large benefit (4/5; 80%)	Large benefit (5/5; 100%)	No effect / Small harm (3/4; 75%)
	Venous sampling for diagnostic bloods with *SMN2* copy number on whole blood EDTA OR repeat dried blood spot for *SMN2* diagnosis	Large benefit (4/5; 80%)	Large benefit (5/5; 100%)	Large benefit (5/5; 100%)	Large benefit (4/5; 80%)	Large benefit (5/5; 100%)	Small harm (2/4; 50%)
	Bloods for FBC, EUC, LDT, Calcium, Coagulation to determine suitability for treatment(s)	No effect (5/6; 83%)	Large benefit (4/6; 67%)	Small benefit (1/5; 20%)	Small benefit / No effect (5/6; 83%)	Small benefit (3/6; 50%)	Small harm (3/5; 60%)

Communication of a diagnostic result by a paediatric neurologist to families of newborns who are screen positive for SMA.

Communicating a diagnostic result to families of newborns who are screen positive for SMA		**Outcome**							
		Increasing knowledge for families	Reducing time to treatment	Improving therapeutic decision making for clinicians	Reducing psychological distress for families	Promoting health equity for rural and remote families	Improving planned care for the newborn	Increasing equity of access to specialist care for screen positive SMA newborns	Increasing demand on health system resources to manage clinical workflow
Intervention	Child neurologist disclosing result to families	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (5/7;71%)	Large benefit (6/7; 86%)	Small benefit (1/7; 14%)	Small harm (4/7; 57%)

Provision of information to families receiving a diagnostic SMA result

Information provision to families receiving a diagnostic result of SMA		**Outcome**								
		Improving psychological well-being of families	Improving knowledge of families	Improving quality of life for families	Improving equity of access to care	Improving families therapeutic decision-making	Improving equal opportunities for families	Improving health outcomes for newborn through family support	Improving quality of life for newborn through family support	Increasing resources required to conduct the interventions
Intervention	Information on SMA	Large benefit (6/7; 86%)	Large benefit (7/7; 100%)	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Large benefit (6/7; 86%)	Large/small benefit (5/6; 83%)	Large benefit (4/7; 57%)	Large benefit (4/7; 57%)	Small harm (5/7; 71%)
	Information on options for treatment	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Large benefit (7/7; 100%)	Large benefit (4/7; 57%)	Large benefit (4/7; 57%)	Large benefit (4/7; 57%)	Small harm (4/7; 57%)
	Information on multidisciplinary care	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Small harm (4/7; 57%)
	Information on timing of clinical reviews	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Small benefit (2/7; 29%)	Small benefit (2/7; 29%)	Small benefit (3/7; 43%)	Small benefit (2/7; 29%)	Small benefit (4/7; 57%)	Small benefit (3/7; 43%)	Small harm (3/7; 43%)
	Information on red flag signs /symptoms prompting further clinical review	Large benefit (5/7; 71%)	Large benefit (7/7; 100%)	Large benefit (4/7; 57%)	Small benefit (4/7; 57%)	Large benefit (4/7; 57%)	Small benefit (2/7; 29%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Small harm (4/7; 57%)
	Information on point of contact for questions	Large benefit (7/7; 100%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Small benefit (3/7; 43%)	Large benefit (4/7; 57%)	Large benefit (5/7; 71%)	Large benefit (4/7; 57%)	Small harm (5/7; 71%)
	Information on psychosocial supports (incl. referrals)	Large benefit (5/6; 83%)	Large/small benefit (5/6; 83%)	Large benefit (5/6; 83%)	Large benefit (6/6; 100%)	Large/small benefit (4/6; 67%)	Large benefit (6/6; 100%)	Large benefit (5/6; 83%)	Large benefit (5/6; 83%)	Small harm (4/6; 67%)
	Provision of interpreter services for culturally and linguistically diverse populations	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Small harm (4/7; 57%)
	Provision of Indigenous Health Liaison support for First Nations, Maori or Torres	Large benefit (6/6; 100%)	Large benefit (5/6; 83%)	Large benefit (6/6; 100%)	Large benefit (5/6; 83%)	Large benefit (5/6; 83%)	Large benefit (4/6; 67%)	Large benefit (4/5; 80%)	Large benefit (3/5; 60%)	Small benefit (4/6; 67%)

	Strait Islander background(s)									

Conducting a clinical review after a diagnosis of SMA

Conducting a clinical review after a diagnosis of SMA		**Outcome**							
		Reducing time to treatment	Provision of early interventions to improve health outcomes for the newborn	Improving therapeutic decision making for clinicians	Improving therapeutic decision making for families	Improving ability to form a management care plan for the newborn	Improving equity of access to care and support	Increasing health system resources required to conduct the above interventions	Restoring reproductive confidence
Intervention	Clinical review conducted or supported by a paediatric neurologist	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (5/6; 83%)	Large benefit (6/7; 86%)	Small harm (4/7; 57%)	Small benefit (3/6; 50%)
	Clinical review in a multidisciplinary care setting	Large benefit (5/7; 71%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Small benefit (2/7; 29%)	Small benefit (3/6; 50%)
	Neurological Examination to determine symptomatic SMA	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Small harm (4/7; 57%)	No effect (6/6; 100%)
	Neonatal exam including cardiac, respiratory and gastrointestinal systems	Large benefit (4/6; 67%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Small benefit (3/7; 43%)	No effect (6/6; 100%)
	Assessment of feeding status including weight, height, feeding behaviours	Large benefit (4/6; 67%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Small harm (4/7; 57%)	No effect (6/6; 100%)
	Assessment of respiratory status (breathing rate /pattern, abdominal breathing & saturation monitoring)	Large benefit (5/7; 71%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (7/7; 100%)	Large benefit (5/7; 71%)	Small harm (2/7; 29%)	No effect (6/6; 100%)
	Motor assessments including validated SMA scales	Large benefit (4/7; 57%)	Large benefit (5/7; 71%)	Large benefit (6/7; 86%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Large benefit (5/7; 71%)	Small benefit (3/7; 43%)	No effect (6/6; 100%)
	Neurophysiological assessment including nerve conduction studies +/- EMG	Small benefit (5/6; 83%)	Small benefit (5/6; 83%)	Small benefit (5/6; 83%)	Small benefit (5/6; 83%)	Small benefit (4/6; 67%)	Small benefit (4/6; 67%)	Small harm / Large harm (5/6; 83%)	No effect (6/6; 100%)
	Clinical genetics referral (within a reasonable post diagnostic period) to determine parent SMA carrier status	No effect (6/7; 86%)	No effect (5/7; 71%)	No effect (5/7; 71%)	No effect (4/7; 57%)	No effect (6/7; 86%)	Small benefit (2/7; 29%)	Small harm (3/6; 50%)	Large benefit (5/7; 71%)

	Clinical review of siblings (within a reasonable post diagnostic period)	No effect (4/7; 57%)	No effect (5/7; 71%)	No effect (3/7; 43%)	Small benefit (3/7; 43%)	No effect (5/7; 71%)	Small benefit (2/7; 29%)	Small harm (4/7; 57%)	Large benefit (5/7; 71%)

Healthcare Practitioner Survey (modified Delphi Process) results

Summary of findings from the first round of the Delphi process including recommendations meeting consensus (green), near consensus (yellow), and no consensus (red).

Near and no consensus statements were reviewed by the GDG at a virtual meeting and reworded if members considered outcomes important to be included in the Guideline, to form the basis for the second round of the Delphi process .

Recommendation	Number of participants	Mean	Standard Deviation	Confidence intervals	Outlier number	Comments
1.1. Newborn screening for SMA should be performed on the routine newborn dried blood spot (DBS).	21	8.81	0.60	0.26	1	Meets consensus
1.2. The target analyte of NBS for SMA is homozygous deletion of exon 7 of the *SMN1* gene.	21	8.90	0.44	0.19	0	Meets consensus
1.3. The screening method selected by the screening institution should have a sensitivity of ≥ 95% for the detection of homozygous deletion of exon 7 of the *SMN1* gene.	21	8.71	0.72	0.31	0	Meets consensus
1.4. The first-tier screening test for SMA should determine the absence of exon 7 of *SMN1*, using suitably validated quantitative or qualitative assays.	21	8.81	0.60	0.26	0	Meets consensus
1.5. First-tier screen positive samples (0 *SMN1* copies) should immediately be repeated on the same dried blood spot.	21	8.43	1.12	0.49	1	Meets consensus
1.6 The methodology selected by NBS for SMA programs should not detect carrier status	21	8.05	1.36	0.59	2	Near consensus
1.7.	21	8.52	0.87	0.38	0	Meets consensus

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.						
1.8. If blood transfusion is considered, the DBS should be taken prior to, and 3 months after, transfusion of blood products.	21	6.71	2.36	1.03	15	No consensus SAC offers rewording
1.9. Newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants, low or very low birthweight newborns should proceed using the same (first tier) screening protocols as for term newborns.	21	8.62	0.81	0.35	0	Meets consensus
1.10. 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 from the heel of the neonate directly 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.	21	7.67	1.59	0.69	4	No consensus Practice point
2.1. Ideally, second tier screening with identification of *SMN2* copy should be performed as part of newborn screening for SMA as a guide to disease severity and to help guide timely planning of treatment.	21	7.19	2.31	1.01	5	No consensus SAC offers rewording
2.2 *SMN2* copy number should be completed on suitably validated quantitative *SMN2* assays.	21	8.62	0.81	0.35	0	Meets consensus
2.3. *SMN2* copy number assessment should be performed on dried blood spot DNA only on purified samples and if the quantity and quality are adequate for quantitative approaches.	21	7.00	1.67	0.73	7	No consensus
2.4. The assay should be carried out using the SMA DNA extraction procedures as for testing samples and controls.	21	7.19	2.18	0.95	6	No consensus

2.5. The definition of screen positivity for the Australian and New Zealand NBS for SMA program is homozygous deletion of exon 7 on dried blood spot (and where *SMN2* copy number is conducted as a second-tier assay) an *SMN2* copy number ≤ 4.	21	7.00	1.67	0.73	0	Meets consensus
2.6. The (in)availability of *SMN2* copy number should not delay clinical notification of a screen positive result based on absence of *SMN1* on first tier screening.	21	8.14	1.20	0.52	1	Meets consensus
2.7. If second tier screening for *SMN2* is not incorporated into the newborn screening process, (diagnostic) testing for *SMN2* should occur during follow-up care.	21	8.33	1.16	0.50	1	Meets consensus
2.8. For the purposes of the NBS for SMA program, prognostic biomarkers outside *SMN2* copy number (including *SMN2* splicing modifier variants and modifiers outside of the *SMN2* gene) will not be incorporated into screening algorithms.	21	7.48	1.54	0.67	4	No consensus SAC offers rewording
2.9. Screening reports should state the technology used and the exact number of *SMN2* copies (avoiding formulas like *SMN2* ≥4).	21	6.81	2.52	1.10	11	No consensus SAC offer a second round
2.11. The NBS for SMA program will establish a clinical referral pathway for newborns who screen positive for SMA. A positive newborn screening result must be verbally relayed to a designated paediatric neurologist.	21	7.95	1.86	0.81	1	Meets Consensus SAC suggests rewording
Following on from 2.11 Ideally, written notification of the NBS for SMA result report should be issued to these individuals within 24 hours of this verbal communication.	21	8.14	1.35	0.59	2	Near consensus
3.1. Diagnostic testing should include confirmation of homozygous deletion of exon 7 on *SMN1*, which should occur from whole blood samples from the recalled newborn.	12	8.83	0.58	0.33	0	Meets consensus

Validated *SMN1* assays should be used for diagnostic testing and conducted in expert reference centres.						
3.2. Diagnostic testing should also include *SMN2* copy number as a guide to clinical severity and to facilitate therapeutic decision making. Diagnostic testing for *SMN2* should be occur on whole blood samples or repeat dried blood spot from a recalled newborn.	12	8.50	1.24	0.72	1	Meets consensus
3.3 Validated quantitative *SMN2* assays should be used for diagnostic testing and conducted in expert reference centres.	12	8.67	0.78	0.45	0	Meets consensus
3.4. It is preferable that diagnostic testing is conducted using a different methodology to the newborn screening assay.	12	7.50	1.24	0.72	1	Meets consensus
3.5. 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.	12	8.17	1.03	0.59	0	Meets consensus
3.6. To enable timely treatment, diagnostic results for *SMN1* should be available within 7-10 days of receipt of the sample by the diagnostic laboratory.	12	7.67	1.78	1.02	1	Meets consensus
3.7. For the purposes of diagnostic testing within NBS for SMA programs, genetic modifiers outside of *SMN2* copy number will not routinely be tested.	12	7.67	1.30	0.75	1	Meets consensus
3.8. Diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth.	12	8.00	1.81	1.04	1	Meets consensus
3.9.	12	8.50	0.91	0.52	0	Meets consensus

Diagnostic reports should detail the methodology used for analysis and the precise *SMN2* copy number.						
4.1. For newborns with a false positive or uncertain screening result i.e. diagnostically not confirmed to have SMA despite a screen positive result on NBS for SMA, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and openly explained to parents.	27	8.41	1.08	0.42	1	Meets consensus
4.2. Parents should be given the option of returning to the genetics and/or neurology services for further discussions on the implications of a false positive result.	26	7.92	1.29	0.51	2	Near consensus
4.3. 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.	26	8.31	1.12	0.44	1	Meets consensus
4.4. Diagnostic testing using SMN next generation sequencing may be considered in cases where there continues to be diagnostic uncertainty as to *SMN1* gene dosage.	25	7.40	1.73	0.69	5	No consensus
4.5. 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.	26	8.00	1.17	0.46	1	Meets consensus
4.6. Diagnostic testing using digital droplet polymerase chain reaction (PCR) or next generation sequencing (NGS) may be used in cases where there continues to be diagnostic uncertainty as to *SMN2* copy number.	26	7.23	1.63	0.64	5	No consensus

4.7. Identification and retesting of *SMN2* copy numbers with up-to-date methods (preferably using a different methodology or laboratory) should be considered in all children who have a true screen positive result for SMA and go onto have a discordant genotype-phenotype. If the *SMN2* result is still uncertain, a further sample from the child should be collected for testing. Diagnostic testing using digital droplet PCR (ddPCR) or NGS may be used to resolve *SMN2* copy number variations in complex cases.	25	7.00	1.73	0.69	9	No consensus
4.8. 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.	27	8.48	1.05	0.40	1	Meets consensus
4.9. If there is uncertainty as to the diagnosis of SMA, parents should be provided with clear instructions on red flags for signs and symptoms of clinical deterioration that warrant medical attention (section 1.1).	27	8.26	1.13	0.43	1	Meets consensus
4.10. For newborns with a false negative result, (diagnostically confirmed to have SMA after a negative NBS 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.	27	8.78	0.64	0.25	0	Meets consensus
4.11. 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.	27	8.33	0.96	0.37	0	Meets consensus
4.12. Open disclosure between clinicians or genetics services and parents should occur with any false positive, uncertain or false negative screening results.	27	8.41	1.22	0.47	2	Near consensus
4.13. It is important for all healthcare professionals conducting health checkups for infants to be aware of the existence of false-negative SMA cases and the typical symptoms of	27	8.48	1.05	0.40	1	Meets consensus

SMA, for expedient referral to specialist neurology services (due to current newborn screening assays only detecting exon 7 homozygous deletion of SMN1).						
5.1. A screen positive result should be ideally disclosed to the family within (time after screen positive result is available to the designated medical practitioner). - ≤ 2 working days.	13	8.54	0.88	0.49	0	Meets consensus
5.2. The screen positive result should ideally be disclosed to the family by a child neurologist.	13	7.31	2.14	1.19	2	Near consensus SAC offers rewording
5.3. If circumstances dictate, it is acceptable for a responsible medical practitioner with support from a paediatric neurologist to disclose a screen positive result to a family.	13	8.08	1.04	0.58	0	Meets consensus
5.4. The medical practitioner should be honest and respectful and use an individualised approach when communicating the screen positive result to the family.	13	8.85	0.56	0.31	0	Meets consensus
5.5. 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.	12	8.67	0.78	0.45	0	Meets consensus
5.6. Medical practitioners disclosing screen positive results for SMA to families from Indigenous 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.	13	7.92	1.32	0.73	1	Meets consensus
5.7. Key points in the (screen positive disclosure) call to the family should include: - The screen positive status of the newborn.	13	8.54	1.66	0.92	1	Meets consensus
5.7.	13	8.08	1.94	1.07	1	Meets consensus

Key points in the (screen positive disclosure) call to the family should include: - The name of the condition.						
5.7. Key points in the (screen positive disclosure) call to the family should include: - Time frame and place for clinical review of the screen positive newborn.	13	8.85	0.56	0.31	0	Meets consensus
5.7. Key points in the (screen positive disclosure) call to the family should include: - General information about the availability of treatment options.	13	7.62	1.90	1.05	2	Near consensus No need for rewording from the SAC
5.7. Key points in the (screen positive disclosure) call to the family should include: - Named health professional as a point of contact for the family.	13	8.69	1.11	0.62	1	Meets consensus
5.7. Key points in the (screen positive disclosure) call to the family should include: - Clinical questions on the newborn's current status including feeding, movement and breathing and/or clinical concerns from parents.	13	8.54	0.88	0.49	0	Meets consensus
5.8. Screen positive newborns should ideally be offered a clinical review within paediatric neurology/neuromuscular services.	13	9.00	0.00	0.00	0	Meets consensus
5.9. 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.	12	8.33	1.30	0.75	1	Meets consensus
5.10. From time of disclosure, ideally a screen positive newborn should be reviewed at a clinical service for diagnostic evaluation within the following (working) days - ≤ 2 days.	13	8.08	1.04	0.58	0	Meets consensus
5.10. From time of disclosure, ideally a screen positive newborn should be reviewed at a clinical service for diagnostic evaluation within the following (working) days - ≤ 3 days.	13	7.46	2.18	1.21	1	Meets consensus

5.11. 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.	13	9.00	0.00	0.00	0	Meets consensus
5.11. 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 voice/weak cry.	13	8.54	1.20	0.66	1	Meets consensus
5.11. 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) - Increased fatigue without increased activity.	13	8.08	1.32	0.73	1	Meets consensus
5.11. 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) - Trouble feeding in young children or infants.	13	8.54	1.20	0.66	1	Meets consensus
5.11. 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) - Decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability.	13	8.85	0.56	0.31	0	Meets consensus
5.11. 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) - Abdominal breathing.	13	8.69	0.75	0.42	0	Meets consensus
5.11.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) - Failure to thrive.	13	8.54	0.88	0.49	0	Meets consensus

6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - a. Neurological examination to establish if symptomatic of SMA, to guide timing of treatment.	13	9.00	0.00	0.00	0	Meets consensus
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - b. Neonatal examination including cardiac, respiratory and gastrointestinal systems to assess clinical status of newborn.	13	8.69	0.75	0.42	0	Meets consensus
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - c. 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.	13	6.23	1.74	0.96	3	No consensus SAC feel this is better as part of a practice point
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - d. Nerve conduction studies including collation of compound muscle action potential (CMAP) +/- electromyography (EMG) to assess for active disease onset.	13	5.77	2.39	1.32	7	No consensus SAC feel this is better as part of a practice point
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - e. Venous sampling for SMN1 on whole blood EDTA (diagnostic bloods).	13	8.69	0.75	0.42	0	Meets consensus

6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - f. Venous sampling for diagnostic bloods with SMN2 copy number on whole blood EDTA OR repeat dried blood spot for SMN2 diagnosis.	13	8.69	0.75	0.42	0	Meets consensus
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - g. Bloods for full blood count, renal function tests, liver function tests, coagulation studies to determine suitability for treatment(s).	13	8.08	1.32	0.73	1	Meets consensus
6.1. Assessments that are required as part of the immediate diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program i.e. at the first clinic visit include - h. Blood for AAV-9 titres to determine suitability for gene therapy.	13	7.77	1.74	0.96	1	Meets consensus
7.1. To optimise knowledge and support, families attending the first clinic visit with their newborn (after screen positive disclosure) should be provided with information that is compassionate, accurate and tailored to the information needs of the family.	13	9.00	0.00	0.00	0	Meets consensus
7.2. The number of healthcare professionals at the first clinic visit 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.	13	8.54	0.88	0.49	0	Meets consensus
7.3. The following information should be provided to families at this visit - a. Information on the cause and clinical implications of SMA.	13	8.85	0.56	0.31	0	Meets consensus
7.3.	13	9.00	0.00	0.00	0	Meets consensus

The following information should be provided to families at this visit - b. Information on next steps to confirm a diagnosis.						
7.3. The following information should be provided to families at this visit - c. Information on the options and timing of treatment if a diagnosis of SMA is confirmed.	13	8.69	1.11	0.62	1	Meets consensus
7.3. The following information should be provided to families at this visit - d. Information on the options for supportive care through the multidisciplinary team if a diagnosis of SMA is confirmed.	13	8.38	1.26	0.70	1	Meets consensus
7.3. The following information should be provided to families at this visit - e. Information on the timing of clinical reviews/follow-up.	13	8.54	0.88	0.49	0	Meets consensus
7.3. The following information should be provided to families at this visit - f. Information on the red flag signs/symptoms prompting further clinical review.	13	9.00	0.00	0.00	0	Meets consensus
7.3. The following information should be provided to families at this visit - g. Information on a point of contact for questions.	13	9.00	0.00	0.00	0	Meets consensus
7.3. The following information should be provided to families at this visit - h. Information on psychosocial supports (including referral to social work services), and/or psychology services.	13	8.38	0.96	0.53	0	Meets consensus
7.3. The following information should be provided to families at this visit - i. Information on SMA advocacy services.	13	8.08	1.32	0.73	1	Meets consensus
7.3.	13	8.69	0.75	0.42	0	Meets consensus

The following information should be provided to families at this visit - j. Information on well curated educational resources for families receiving a screen positive result of SMA.						
7.4. Medical practitioners providing information to families' of newborns from culturally and linguistically diverse backgrounds at the first clinic visit 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.	12	8.83	0.58	0.33	0	Meets consensus
7.5. Medical practitioners providing information to families' of newborns from Indigenous or Torres Strait Islander backgrounds at the first clinic visit 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 also offer families the support of Indigenous Health Liaison services at the time of diagnosis.	12	8.50	0.91	0.52	0	Meets consensus
8.1. 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.	13	8.08	1.32	0.73	1	Meets consensus
8.2. Medical practitioners undertaking diagnostic disclosure for families from culturally and linguistically diverse backgrounds should assess the need for formal interpreter services to facilitate this process.	12	8.50	0.91	0.52	0	Meets consensus
8.3. Medical practitioners undertaking diagnostic disclosure with Indigenous or Torres Strait Islander backgrounds may elicit the advice of Indigenous Health Liaison professionals in how best to conduct this process and also offer families the support of Indigenous Health liaison services.	12	6.67	2.06	1.19	5	No consensus SAC advised on rewording

8.4. Families should be invited to bring a support person(s) at the point of diagnostic disclosure.	13	7.92	1.32	0.73	1	Meets consensus
8.5. Ideally, diagnostic results should be disclosed to families by a paediatric neurologist.	13	8.08	1.32	0.73	1	Meets consensus
8.6. If circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for a responsible medical practitioner with support from a paediatric neurologist to disclose a diagnostic result to a family.	13	7.92	1.32	0.73	1	Meets consensus
8.7. Ideally, diagnostic results should be disclosed to families face to face.	13	8.54	0.88	0.49	0	Meets consensus
8.8. If circumstances dictate and dependent on individual (family and child related) factors, it is acceptable for diagnostic disclosure to occur through telephone or Telehealth.	13	7.62	1.71	0.95	1	Meets consensus
8.9. All families receiving a diagnosis of SMA 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.	13	8.54	1.20	0.66	1	Meets consensus
8.10. Families should be directed to educational resources that support information provision on the diagnosis and potential treatments for their newborn.	13	8.69	0.75	0.42	0	Meets consensus
8.11. Families should be provided with the contact details of a designated professional who can direct their queries after a diagnosis of SMA has been received.	13	8.85	0.56	0.31	0	Meets consensus
9.1. All newborns diagnostically confirmed with SMA should be reviewed by a paediatric neurologist.	13	9.00	0.00	0.00	0	Meets consensus
9.2.	13	8.69	0.75	0.42	0	Meets consensus

At the time of diagnosis, all newborns confirmed with SMA should initially be managed within a paediatric neurology service.						
9.3. All newborns should have the following components completed at the first clinical review after diagnostic confirmation of SMA - Neurological examination to establish if symptomatic of SMA, to guide timing of treatment.	13	9.00	0.00	0.00	0	Meets consensus
9.3. All newborns should have the following components completed at the first clinical review after diagnostic confirmation of SMA - Neonatal examination including cardiac, respiratory and gastrointestinal systems to assess the clinical status of newborn.	13	8.54	0.88	0.49	0	Meets consensus
9.4. All newborns should undergo the following within a reasonable time of diagnostic confirmation - 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.	12	8.50	0.91	0.52	0	Meets consensus
9.4. All newborns should ideally undergo the following within a reasonable time of diagnostic confirmation - Neurophysiological assessments including collation of compound muscle action potential (CMAP) +/- electromyography (EMG) to assess for denervation, if this has not been completed previously.	13	7.31	1.80	1.00	2	Near consensus
9.5. 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, which is personalised according to the biopsychosocial characteristics of the child and family.	13	8.38	0.96	0.53	0	Meets consensus
9.6.	13	8.69	0.75	0.42	0	Meets consensus

Families should be offered referral and review to a clinical genetics service for genetic counselling and cascade screening.						
9.7. The siblings of a newborn diagnosed with SMA through newborn screening should be offered a clinical review within paediatric neurology services, at an appropriate time.	13	7.31	1.80	1.00	2	Near consensus Rewording required
9.8. For siblings 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.	13	7.46	1.45	0.80	2	Near consensus Rewording not required
9.9. The clinical status of the newborn diagnosed through NBS i.e. presymptomaic or symptomatic is important to define as it sets the pace of therapeutic care planning and implementation, however it can be challenging to define clinical status in the newborn period. Symptomatic status may be defined primarily by the presence of signs and symptoms of SMA on neurological and neonatal examination.	13	7.92	1.75	0.97	1	Meets consensus
9.10. To help define symptomatic status, additional assessments (that increase the sensitivity of the clinical review) include - Neurophysiological assessment obtained by recording from the abductor digiti minimi muscle, after ulnar nerve stimulation of the wrist, which includes a CMAP one standard deviation below the mean age for typically developing infants and/or ulnar CMAP < 1.5 mV and/or evidence of denervation on EMG.	12	8.33	1.30	0.75	1	Meets consensus
9.10. To help define symptomatic status, additional assessments (that increase the sensitivity of the clinical review) include - Motor assessments including CHOP-INTEND score <35.	12	7.83	1.99	1.15	2	Near consensus
10.1. Treatment planning should commence as soon as the SMN1 diagnostic result is received.	13	8.08	1.32	0.73	1	Meets consensus
10.2.	13	8.54	1.20	0.66	1	Meets consensus

For newborns who demonstrate signs and symptoms of SMA (consistent with disease onset), options for immediate treatment with disease modifying treatments should be discussed with the family, independent of SMN2 copy number.						
10.3. For newborns who demonstrate signs and symptoms of SMA (consistent with disease onset) with 1 SMN2 copy, therapeutic decision making is dependent on the newborn/infant's clinical status and open discussions with families regarding treatment options or referral for supportive care alone.	13	8.08	1.75	0.97	1	Meets consensus
10.4. For newborns with diagnostic confirmation of SMA and 1, 2 or 3 SMN2 copy numbers and who are presymptomatic, options for immediate disease modifying treatments should be discussed with the family.	13	8.54	0.88	0.49	0	Meets consensus
10.5. In the absence of additional evidence for best treatment pathways, the priority for children with either signs and symptoms of SMA (symptomatic SMA) or 1, 2 or 3 SMN2 copies without signs and symptoms of SMA (presymptomatic SMA), is the initiation of disease modifying treatment without delay.	13	7.92	1.75	0.97	1	Meets consensus
10.6. In the absence of comparative data, currently single agent treatment at initiation of therapeutic intervention is recommended.	12	8.17	1.34	0.77	1	Meets consensus
10.7. 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.	12	8.67	0.78	0.45	0	Meets consensus
10.8. For all disease modifying treatments, the potential benefits, risks, uncertainties, and need for long term surveillance should be explained to families and documented.	13	8.69	0.75	0.42	0	Meets consensus

10.9. Therapeutic care planning should be done in partnership with families and should take into consideration disease status (presymptomatic/symptomatic), genotype, current function, disease duration, and individualised factors including social and family circumstances, goals of care and preferences.	13	8.54	1.20	0.66	1	Meets consensus
10.10. Parents may require support with therapeutic decision making and resources should be 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.	13	8.69	0.75	0.42	0	Meets consensus
10.11. Compassionate access to disease modifying treatments may be considered by the managing medical practitioner for newborns diagnosed with SMA through newborn screening, who do not have access to reimbursed (pharmaceutical benefits scheme or private health insurance) therapeutic interventions.	13	7.77	1.74	0.96	3	No consensus
10.12. It is preferable to plan for administering disease modifying treatments in a specialist (neurology) care centre.	12	8.67	0.78	0.45	0	Meets consensus
10.13. Where appropriate, disease modifying treatments may be planned to be delivered from a non-specialist neurology care centre, with specialist support.	11	6.27	2.41	1.45	6	No consensus SAC offers rewording
10.14. Post treatment monitoring for newborns who access disease modifying treatments may be shared between specialist centres and regional centres (with support from the specialist centre) as child and family factors dictate.	12	7.83	1.03	0.59	0	Meets consensus
10.15. Newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately should be managed by a (neurology) specialist.	13	8.54	0.88	0.49	0	Meets consensus

10.16. 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.	13	8.23	1.01	0.56	0	Meets consensus
10.17. For all newborns diagnosed with SMA through NBS, (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.	12	9.00	0.00	0.00	0	Meets consensus
10.17. For all newborns diagnosed with SMA through NBS, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), best practice care includes the following assessments conducted at each visit - Growth parameters.	12	8.83	0.58	0.33	0	Meets consensus
10.17. For all newborns diagnosed with SMA through NBS, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), best practice care includes the following assessments conducted at each visit - Neurological examination.	12	9.00	0.00	0.00	0	Meets consensus
10.18. For all newborns diagnosed with SMA through NBS, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments as part of best practice care include - Motor assessments that should be adapted to the objectives set for the newborn/infant and take into account 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.	12	8.50	0.91	0.52	0	Meets consensus
10.18.	11	7.18	1.89	1.14	2	Near consensus

For all newborns diagnosed with SMA through NBS, (independent of initiation of prompt SMN augmenting treatment, phenotype or genotype), additional assessments as part of best practice care include - Neurophysiological studies including nerve conduction studies with acquisition of compound muscle action potential from the abductor digiti minimi stimulating the ulnar nerve at the wrist (with/without) electromyography. 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.						
10.19. Evaluators must have adequate training for the application of each examination or assessment.	12	8.67	0.78	0.45	0	Meets consensus
10.20. All children diagnosed with SMA through NBS should be referred for multidisciplinary allied therapy interventions aligning with international standards of care (Consensus Statement of Standards for Care of Spinal Muscular Atrophy).	13	8.69	0.75	0.42	0	Meets consensus
11.1. For newborns with ≥ 4 *SMN2* copies not initially treated (shared decision or cannot access), clinical follow-up should occur with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.	11	8.09	1.04	0.63	0	Meets consensus
11.2. For newborns with 4 *SMN2* copies, clinical follow-up can be coordinated between a paediatric neurology centre and local paediatric services.	11	6.45	2.38	1.44	6	No consensus
11.3. 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.	11	8.09	1.04	0.63	0	Meets consensus
11.4.	11	8.09	1.04	0.63	0	Meets consensus

Neurophysiological techniques (including CMAP +/- EMG +/- motor unit number estimation methods) have a high sensitivity towards early changes in presymptomatic children. As such, there is value in incorporating these assessments 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.						
11.5. Parents 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).	12	8.67	0.78	0.45	0	Meets consensus
11.6. 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.	11	8.45	0.93	0.56	0	Meets consensus

Summary of findings from the second round of the Delphi process with refinement of recommendations meeting consensus (green), near consensus (yellow) and no consensus (red).

Outcomes that reached consensus in this round were used to formulate recommendations. Outcomes that reached (near consensus) were reviewed by the Co-leads and discussed with the members of the Oversight Committee to determine if they included important outcomes to be incorporated into the Guideline.

Recommendation	Number of participants	Mean	Standard Deviation	Confidence intervals	Outlier number	Comments
1.6. The screening process performed by NBS for SMA programs should not identify carrier status.	21	7.86	1.85	.79	1	Consensus
1.8: Option 1 of 2 If blood transfusion is considered, the DBS should be taken prior to transfusion of blood products.	21	8.52	1.08	.46	1	Consensus
1.8: Option 2 of 2 If blood transfusion is considered, the dried blood spot (for purposes of screening for SMA) should be taken prior to, and after, transfusion of blood products.	19	5.11	2.45	1.10	12	No consensus
2.1. *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening but not delay notification of absence of exon 7 on *SMN1*, as per recommendation 2.6	22	8.36	.92	.38	0	Consensus
2.8. 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.	21	8.05	1.36	.58	1	Consensus
2.11: Option 1 of 2	21	7.86	1.62	.69	1	Consensus

The NBS for SMA program will establish a clinical referral pathway for newborns who screen positive for SMA. A positive newborn screening result should be verbally relayed to a designated paediatric neurologist.						
2.11: Option 2 of 2 The NBS 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 health care practitioner.	20	7.2	1.70	.75	4	No consensus
2.12: Option 1 of 2 Ideally, written notification of a screen positive SMA result should be issued to the individuals listed in 2.11. within 24 hours of verbal notification of a screen positive result.	18	7.67	2.06	.95	3	No consensus
2.12: Option 2 of 2 Written notification of a screen positive SMA result (as defined in section), should be issued to the individuals listed in 2.11. within 24 hours of verbal notification of a screen positive result.	21	8.14	1.20	.51	1	Consensus
4.2: Option 1 of 2 Parents should be given the option of returning to genetics and/or paediatric neurology services for further discussions on the implications of a false positive result.	19	8.16	1.21	.54	1	Consensus
4.2: Option 2 of 2Parents 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.	20	8.00	1.03	.45	0	Consensus
4.12: Option 1 of 2	19	7.84	1.68	.76	2	Near consensus

Open disclosure between appropriate health care professionals and parents should occur with any false positive, uncertain or false negative screening results.						
4.12: Option 2 of 2 Open disclosure between members of the neurology/neuromuscular multidisciplinary team* and parents should occur with any false positive, uncertain or false negative screening results. *Multidisciplinary team members may vary dependent on health jurisdiction and include but are not limited to paediatric neurology, genetic counsellors, geneticist, social worker, psychologist, allied therapists, specialist nurses	20	8.00	1.03	.45	0	Consensus
5.2. The paediatric neurologist 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.	16	8.38	1.20	.59	1	Consensus
9.4. Newborns may undergo neurophysiological assessments within reasonable time of diagnosis, including collation of compound muscle action potential (CMAP) +/- electromyography (EMG), to obtain predictive information on disease course.	12	7.50	1.24	.70	1	Consensus
9.7. The siblings of a newborn diagnosed with SMA through newborn screening should be offered a clinical review within paediatric neurology services, at an appropriate time	15	7.93	1.28	.65	1	Consensus
9.8. For siblings 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.	13	7.62	.96	.52	0	Consensus
9.10	10	7.00	1.63	1.01	3	No consensus

To help define symptomatic status, additional assessments may include motor assessments including CHOP-INTEND or HINE-2.						
10.18 a. For newborns diagnosed with SMA through NBS, (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 monitoring disease course and/or treatment response.	11	7.36	1.50	.89	2	Near consensus Oversight Committee feels this is an important practice point [a]
10.18 b. 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.	10	7.40	1.58	.98	2	Near consensus. Important practice point

[a] Outliers consider that whilst neurophysiology studies can improve outcomes for some newborns, not all newborns will benefit from serial assessment. Jurisdictional variations in expertise to conduct and interpret assessments may preclude implementation of this recommendation across Australia. Statement reworded as a practice point to account for the lack of robust evidence base, and the need to mitigate health inequities due to a lack of resourcing.

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 nondiseased 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 mutation is the presence of the identical mutation on both alleles of a specific gene. However, when both alleles of a gene harbor 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.

Third-tier screen

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

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 adapted from the Clinical and Laboratory Standards Institute (CLSI) Harmonzied Newborn Screening Database.

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

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

HCP: Health Care 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: 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

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

SMN1: Survival Motor Neuron-1 gene

SMN2: Survival Motor Neuron-2 gene

SMN: Survival motor neuron

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