

Technical and Administrative Report

Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand

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Table of contents

Title page.....	1
Executive Summary	4
Purpose, population, scope and settings.....	6
The Guideline Development Process	10
Systematic review of the evidence	22
Stakeholder consultation activities.....	85
Systematic observation form evidence	85
Healthcare practitioner survey (modified Delphi process)	87
Finalising the draft Guideline and the process of public consultation	91
Revising the Guideline	93
Publication of the finalised Guideline and endorsement	94
Risk Assessment	95
Dissemination, Implementation and Evaluation	97
Supporting Evidence	101
Evidence-based recommendations	101
Consensus-based recommendations	134
Evidence to decision tables.....	135
Evidence summaries of individual studies	156
Consensus-based recommendations	156
Systematic observation form results	196
Healthcare Practitioner Survey (modified Delphi Process) results.....	209
Glossary of terms	235
Abbreviations.....	243
References	245
Appendix A. Members of the Guideline Development Group.....	255
Appendix B. Professional and consumer organisations invited to provide feedback	258
Appendix C. Conflicts of Interest declarations for the Guideline Development Group	259
Appendix D. List of priority questions to be included in the systematic literature search.....	262
Appendix E: Assessment tool for cohort and case control studies.....	264
Appendix F: Components of first survey in modified Delphi	268
Appendix G: Endorsement letter	277
Appendix H. Assessment of Guideline by independent reviewers using AGREE II scale.....	279
Appendix I. List of organisations and peak bodies endorsing the Guideline	288

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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. (4-8)

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. (6, 9-11)

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. (12) This was followed in 2023 by Te Whatu Ora (Health New Zealand) endorsing routine inclusion of SMA onto routine newborn screening panels. (13)

Decentralisation of newborn screening in Australia and a separate centralised system in Aotearoa New Zealand may give rise to regional differences in newborn screening programs, which has the potential to create inequity in the access to diagnosis, treatment, care, and potential outcomes of affected children. (14, 15) To address this barrier, a best practice Guideline that is founded in evidence and that aligns with an Australasian healthcare landscape is essential. (15, 16)

Of note, access to multidisciplinary care services for children and families with rare diseases such as SMA, can be challenging, particularly in outer regional, remote, and very remote parts of Australia and Aotearoa New Zealand, generating a potential for inequity for all Australasians. This is perpetuated by specialist services, clinical genetics and genomics that centre on urban areas with limited investment in regional and rural areas. (17, 18) These factors have the potential to create inequity in the access to diagnosis, treatment, care, and potential outcomes of affected children.

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, clinical geneticists and genetic counsellors, nurses, allied health therapists) involved in the management of individuals with SMA and their families as identified through a newborn screening for SMA process (collectively defined for the purpose of the Guideline as healthcare practitioners). Targeted secondary end users included health system planners, managers and administrators whose organisations provided services for population screening and care of individuals with SMA and their families. It is recommended that the Guideline be reviewed and updated at a maximum of every five years.

The Guideline has been formulated using a validated methodology for searching, appraising and grading evidence. (19-25) Recommendations have been developed using systematic evidence synthesis in combination with expertise and evidence from an Australian and Aotearoa New Zealand multidisciplinary national committee, with state and territory representation across (newborn) screening, diagnostics, clinical care, advocacy and lived experiences from consumer domains.

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 Aotearoa New Zealand (collectively defined as Australasia for the purpose of the Guideline).

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

To provide specific, child and family focussed recommendations on the screening, diagnosis, post diagnostic clinical care, information provision and support of children (and their families) undertaking newborn screening for spinal muscular atrophy.

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 not replace, clinical reasoning or acumen. It is linked with and thus do not replace the National Screening Policy Framework (26) and internationally developed Standards of Care for SMA (27, 28). It is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across Australia and Aotearoa New Zealand. As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address access to healthcare and treatment pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded healthcare. Furthermore, it does not include recommendations for medicines or services that are unavailable or restricted in these jurisdictions.

It has been decided *a priori* that the risk-benefits of NBS for SMA (which have been predetermined through a pilot study), (9) technical aspects of screening (as covered by the Clinical & Laboratory Standards Institute Guideline for Newborn Screening, (5, 8, 29, 30) and diagnostic methodologies and ongoing management of individuals with SMA beyond the initial post-diagnostic period (as covered by international standards of care guidelines (27, 28) 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.

The scope of the Guideline was established after discussion with the Scientific Advisory Group and endorsed by the Oversight Committee.

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 Aotearoa New Zealand; however, it may be used as a template in other health jurisdictions.

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

Healthcare settings and clinical stage

The Guideline applies to the public health care setting and clinical areas including hospitals and community health care services. The guideline also applies to screening, diagnosis, assessment, and treatment clinical stages.

Target end users

Targeted primary end users of the Guideline include Australian and Aotearoa New Zealand healthcare practitioners, defined for the purpose of the Guideline as professionals working in the (newborn) screening and diagnosis process (including scientists and laboratory staff) and

medical practitioners (neurologists, paediatricians, general practitioners, clinical geneticists and genetic counsellors, nurses, allied health therapists) involved in the care and management of individuals with SMA and their families as identified through an NBS for SMA process.

Targeted secondary end users include:

1. Australian and Aotearoa New Zealand health system planners including public funding bodies, managers, and administrators whose organisations provide services for population screening, diagnosis and care of individuals with SMA and their families.
2. Australian and Aotearoa New Zealand training providers including peak bodies and institutions that may use the Guideline to streamline educational and clinical resources.
3. Australian and Aotearoa New Zealand families of children undergoing and screening positive for SMA through NBS programs. To this end, an accompanying illustrative fact package, tailored to families, has been purpose made and available at....

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). An allocation of 20% of the NHMRC Grant is assigned to this project (valued at \$132308). 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

This report outlines the processes and methods taken to develop the Guideline.

Defining the need for a Guideline and criteria for its development

During the pilot newborn screening for SMA program (that ran across New South Wales and the Australian Capital Territory from 2018-2022), clinical researchers and healthcare practitioners across Australia and Aotearoa New Zealand identified the necessity for a coordinated clinical strategy to optimise access to, equity and timing of diagnosis for SMA through newborn screening. (11) 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. (11) This would ultimately lead to improved health outcomes for newborns and support and care for their families. Consequently, an evidence-based guideline for Australia and Aotearoa New Zealand was proposed.

The development of the Guideline was in accordance with the Procedures and Requirements for meeting the National Health and Medical Research Council (NHMRC) standards for guidelines, (31) 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. (19, 32-34) 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) (14) 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.

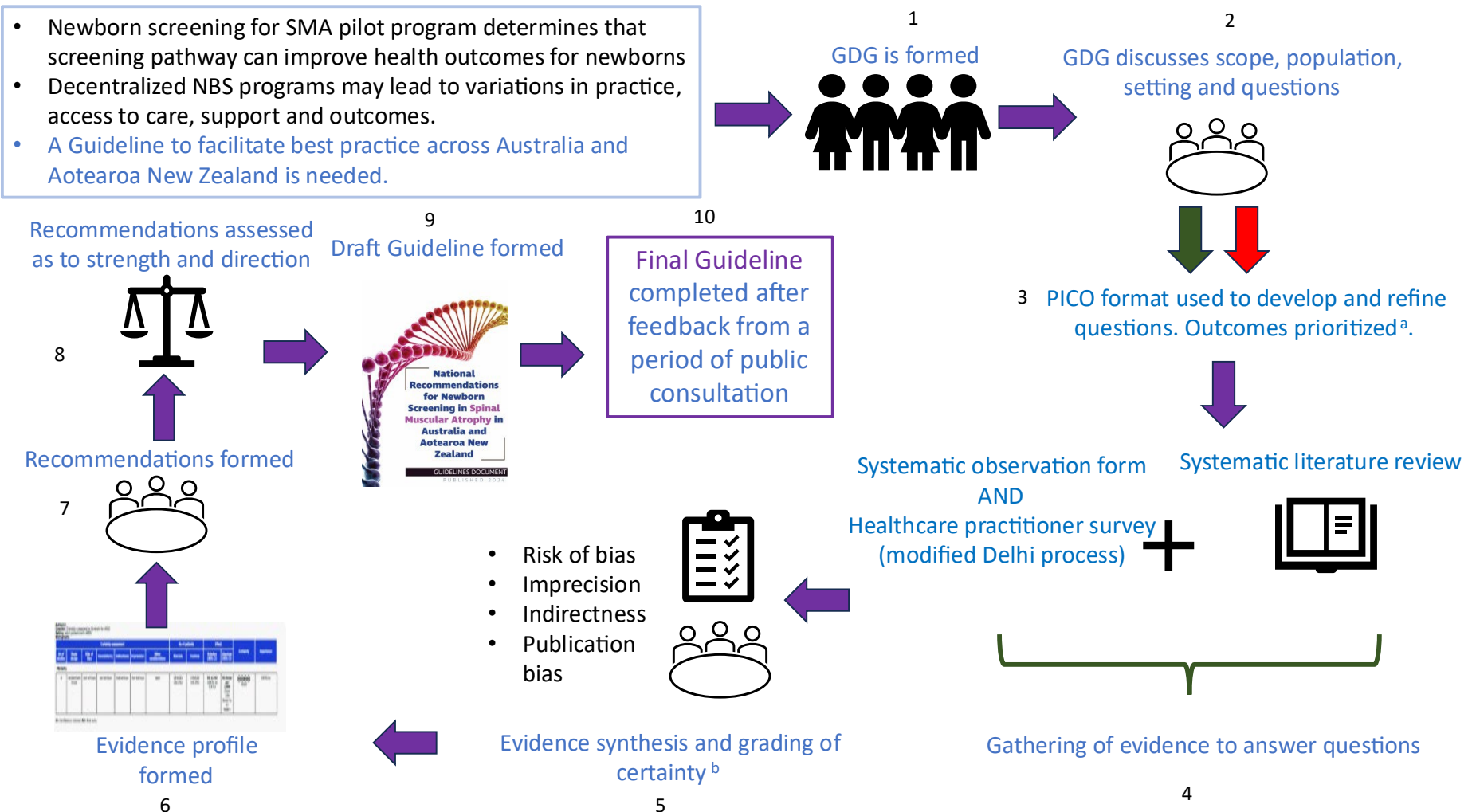


Figure 1. The Guideline development process. A Guideline Development Group (GDG) was formed (1) and met to discuss scope, population applicable settings and broad questions for the Guideline (2). A Population, Intervention, Comparator, Outcome (PICO) format was used to

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 and Consumer Involvement

The Guideline Development Group (GDG) was formed for the purpose of leading the research. The objectives of the GDG were to devise evidence and consensus-based recommendations for the standardised implementation of newborn screening for SMA in Australia and Aotearoa New Zealand. The GDG 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. Consumer involvement was considered to be key to Guideline development. Representatives with lived experiences of SMA and patient advocates from Australia and New Zealand, who would provide a consumer perspective were purposively invited to join the GDG.

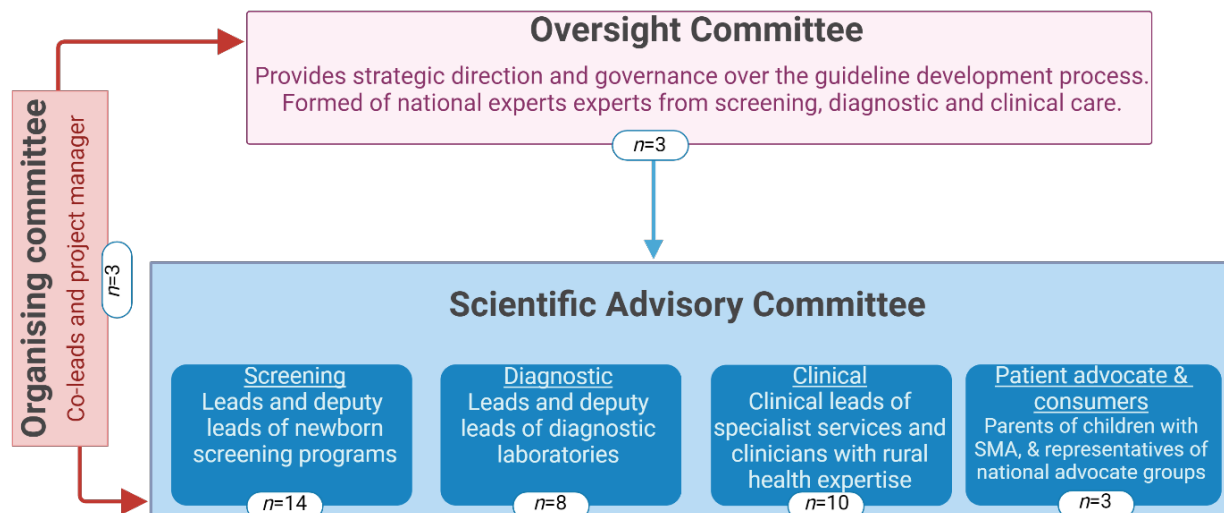


Figure 2. The Guideline Development Group and its governance structure. The oversight committee ($n=3$) was comprised of representatives with national expertise in the areas of screening, diagnosis and clinical care who provided strategic direction on the Guideline development process. The Scientific 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 Aotearoa New Zealand ([Appendix A](#)). Individuals were purposively approached by the Organising Committee to be a SAC member if they fulfilled one or more of the following criteria:

1. Leads and Deputy leads of state and territory based (Australia) or national (Aotearoa New Zealand) newborn screening programs.
2. Leads and Deputy leads of SMA state and territory based (Australia) or national (Aotearoa New Zealand) SMA diagnostic laboratories.
3. Clinical Leads of specialist (paediatric) neurology services within each state and territory (Australia) and Aotearoa New Zealand, with expertise in managing children with SMA.
4. Healthcare practitioners with expertise in regional/rural health systems, and healthcare provision within culturally diverse populations.
5. Parents and caregivers of children with SMA.
6. Chief Executive Officers of national patient advocate groups.

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

The recommendations within the Guideline apply to all Australasians including children and families from Aboriginal, Torres Strait, Pacific Islander and Māori peoples and culturally and linguistically diverse communities.

Although representation was sought early in the Guideline development process from representatives of Aboriginal, Torres Strait Islander, Pacific Islander and/or Māori communities, we were unable to have formal representation as part of the GDG. However, representation and co-development of the guidelines was facilitated through Dr Corin Miller, a clinician with expertise in rural and regional health and issues relevant to peoples of Aboriginal and Torres Strait Islander descent who formed part of the GDG. Systematic searches have been designed and conducted to include all population groups (i.e. no limitations made on searches in terms of population). Specific clinical questions pertaining to Aboriginal, Torres Strait Islander and Māori Peoples and culturally and linguistically diverse communities were developed, to inform the development of targeted and relevant recommendations. During the public consultation process, health and organisational bodies with expertise and knowledge of First Nation populations were specifically invited to provide feedback. Endorsement for the Guideline was sought from these organisations.

Consumer Consultation

Consumer consultation was considered by the GDG to be 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 ([Appendix A](#)). 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*).

([Appendix B](#)). All comments received were considered in the final editing stage of the guidelines.

Conflict of Interests

Processes were put in place to declare and manage any potential conflicts of interest, consistent with NHMRC guidance. 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 ([Appendix C](#)). 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.

Defining the clinical questions 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 clinical questions within each domain of (newborn) screening, diagnosis and clinical care and advocacy. Broad clinical questions were formed and prioritised based on three factors

1. Question was high priority for stakeholders (especially children and their families)
2. Currently not enough relevant or robust evidence to support strong recommendations i.e. best clinical practice is unclear based on the level of uncertainty in the evidence base.
3. There is a reasonable potential for new evidence to be developed in the future.

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. Questions were prioritised and refined based on the likely impact on child and family outcomes, the extent of variability in current practice and the potential for new evidence to emerge to inform decisions.

The compiled list of high priority potential questions from which to base recommendations were presented and refined at a meeting with the entire SAC and through email contact. Outcomes that were deemed critical and important were used to form the systematic literature review. The detailed list of questions is detailed in [Appendix D](#).

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). (35) 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. (19, 34) 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). (36)

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

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

Table 1. Population, Intervention, Comparator, Outcome(s) framework and eligibility criteria for studies included in the systematic reviews.

Clinical Question	Population(s)	Intervention or Exposure	Comparator	Outcome	Study Design
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 should the target analyte be in newborn screening for SMA?

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 Welanders 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

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"

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:

Should SMN2 copy number be part of newborn screening for SMA?

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:

Should screening assays (for SMN1) have a minimum sensitivity and specificity and what should this be?

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” or “Reproducibility of Results”[MeSH Terms] or “Diagnostic Errors/prevention and control*”[MeSH Terms] or “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 “explain*” 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*”) AND (“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”)

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:

Should specific psychological interventions be provided to families of screen positive children?

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:

How should a screen positive child be diagnosed with SMA?

Population: All newborns with screen positive (SMA) result

Intervention: Diagnostic tests 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

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:

Should diagnosis of SMA include SMN2 copy number determination?

Population: All newborns with a SMA screen positive result

Intervention: Diagnosis of 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)

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:

How (when, where and who) who should notify families of a screen positive SMA result?

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 assessments should be completed in a child that is diagnosed with 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:

Should specific information be given to families of screen positive children?

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:

Should specific care or support be provided at the time of screen positive or diagnostic disclosure for families of First Nations descent or culturally and/or linguistically diverse populations?

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 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:

How should a screen positive infant be managed within clinical services?

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” or “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:

How should treatment decisions be made in children diagnosed with SMA?

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*" or "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:

Should there be specific processes to manage (false positive),(false negative) and/or uncertain 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 2.). 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 2. 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, (37) and presented in evidence summary tables (*Evidence summaries of individual studies page*).

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.

The Newcastle-Ottawa Quality Assessment tool for cohort studies and case control studies was used to determine the risk of bias and quality of individual (predominantly nonrandomised) studies across the domains of selection, comparability and outcome.([See Appendix E](#)) Two researchers independently scored 60% of the studies and concordance of quality rating was observed in 100% of studies.

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.

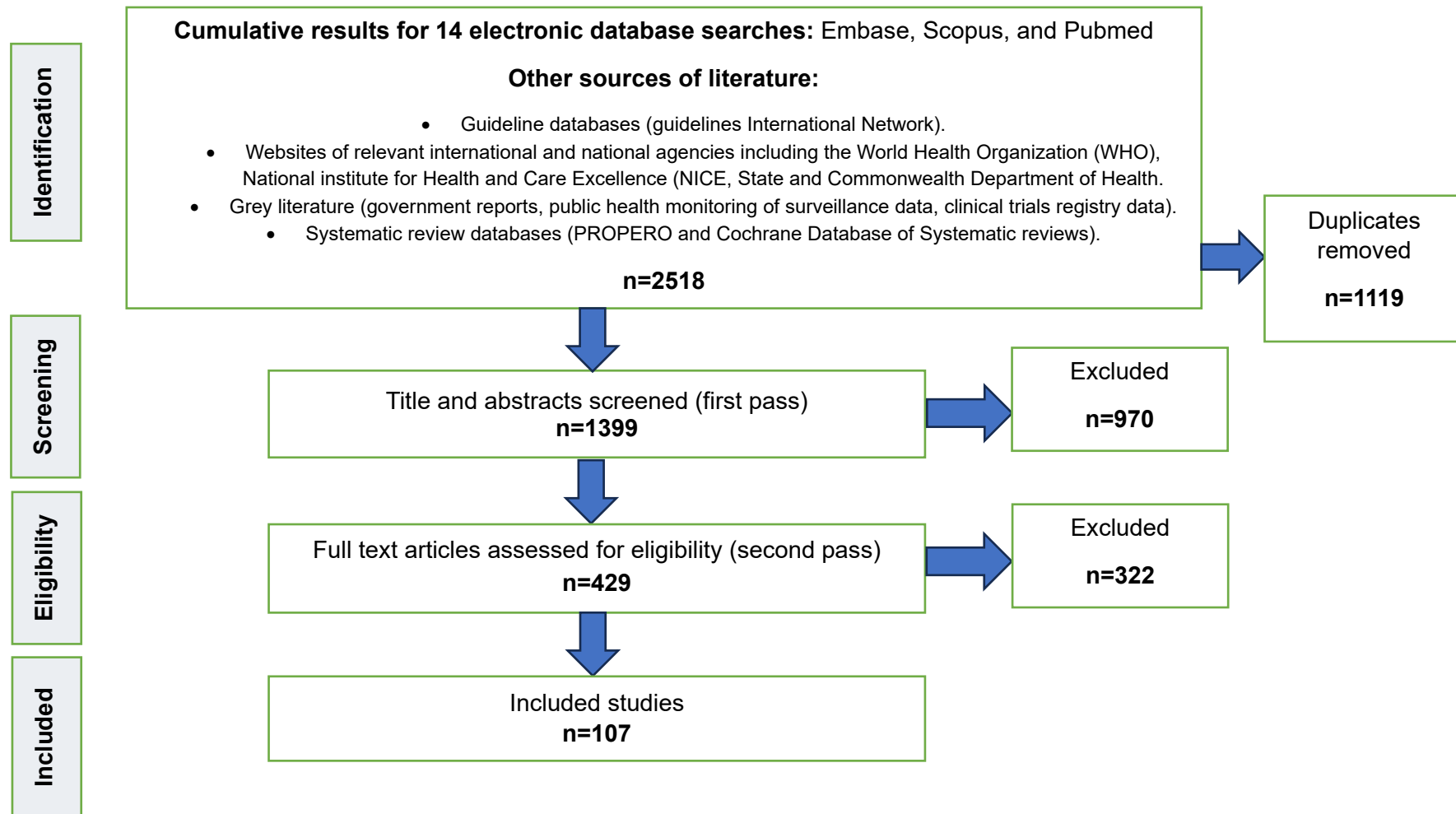


Figure 3. A Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram to depict the screening process for the systematic literature review

Formulating recommendations based on the GRADE method

The Guideline was developed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology which provides a structured framework for specifying clinical questions, choosing relevant outcomes, rating their importance, evaluating the evidence and combining the evidence base with values and preferences of affected individuals and societal factors to form evidence-based recommendations. The steps within the GRADE method included framing the health question, selecting and rating importance of outcomes, summarising the evidence, assessing certainty and converting the evidence to recommendations.

Framing high priority questions and selecting and rating the importance of outcomes:

Questions were developed using a PICO format (P= population of interest, I= intervention i.e. newborn screening for SMA C= comparison or alternative to the intervention, O=outcome of interest). During this phase, outcomes were selected and prioritised into those that were critical, important, and not important to include by iterative discussion by the GDG, consistent with GRADE methodology, with important or critical outcomes (for the newborn or their family) for which no evidence existed, still included. Judgements about the balance between benefits and risks on health outcomes were based on a summary of findings table or evidence profile derived from the high-quality systematic review of the effects of the intervention of interest. Where available, evidence about the value that stakeholders placed on key outcomes could also guide the panel's deliberations on these judgements.

Summarising the evidence

A summary of evidence was included with an estimate of effect for each outcome, a rating of certainty of evidence for that outcome and a narrative summary for the evidence and its findings.

Assessment of the certainty of the evidence

Outcomes were assessed as to their certainty using the GRADE framework. The quality of the body of evidence was assessed against domains of study design limitations, 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 Aotearoa New Zealand. Of note, when using GRADE for observational studies, studies start at low certainty of evidence. (32) 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).

Certainty of evidence assessments are defined according to the GRADE approach and MagicApp portal was used to populate the certainty of evidence:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Forming evidence-based recommendations from the evidence

The taxonomy and framework used to formulate recommendations in the Guideline adhered to the definitions and standards as per GRADE. (19, 24, 34, 38) 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 (22, 34). 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, (27, 28) Clinical and Laboratory Standards Institute (CLSI) terminology databases, (39) National Newborn Screening Framework, (26) U.S Health Resources and Services Administration, (40) Advisory Committee on Heritable Disorders in Newborns and Children.
- Conceptual and ethical frameworks (e.g., AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research, 2020; International Classification of Functioning, Disability and Health, World Health Organisation Screening Guidelines). (41-43)
- Conventions (e.g., United Nations Convention on the Rights of the Child, 1989). (44)

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, feasibility, benefits and harms of the proposed intervention, certainty of the body of evidence, values and preferences to end users, resource and cost effectiveness implications and health equity, acceptability and

feasibility factors. (45) These were summarised in Evidence to Decision tables for each evidence-based Recommendation.

Based on the aforementioned factors, GRADE rates evidence-based recommendations as either strong or conditional (for or against). The evidence and justification provided in each domain were considered by the SAC through a summary of decision judgement assigned to the recommendation and indicative of the strength of the body of evidence that underpinned the Recommendation (Table 3.). (46) In summary, the principle for the strength of recommendations is:

1. The strength is strong when most or all individuals will be best served by the recommended course of action and the GDG is certain that the evidence supports a clear balance towards either benefits or risks.
2. The strength is conditional when not all individuals will be best served by the recommended course of action and there is a need to consider the individual patient's circumstances, preferences, and values, or the GDG is uncertain of the balance between benefits and risks.
3. The GDG could not form a recommendation if the confidence in the effect estimate was so low that they felt that it was too speculative, risks and benefits were balanced, values and preferences not understood or too variable or the intervention would have a range of effects and values/preferences were likely to be too variable to consider.

Table 3. Grading the strength of evidence-based recommendations within the Guideline (46)

Grade of recommendation	Description and body of evidence matrix
Strong for	Moderate to high certainty evidence suggests that benefits in critical 9 outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it
Strong against	Moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
Conditional for	Moderate to high certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so

	Low certainty evidence suggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.
Conditional against	Moderate to high certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications; low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications
Consensus based evidence required	Formulation of recommendation through discussion, Delphi process, systematic observation form 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 4.).

Consensus and evidence-based recommendations were defined as key elements of practice to be followed to deliver evidence-based supports. (21, 24, 38) If questions were outside the scope of the systematic review and not necessarily linked to evidence but were important to address and yielding large net positive downstream consequences for the population in question, a *practice standard* was developed. This statement was used to contextualise an associated Recommendation i.e. for a specific clinical population, under specific circumstances or how it should be conducted in practice.

Table 4. Taxonomy and framework for Recommendations used in the Guideline aligning with GRADE. (19, 24, 34, 38)

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
Practice standards	A normative statement of standards of professional conduct, responsibilities, ideals, or standards, based on accepted formal or informal norms and/or standards in a specific healthcare context.
Implementation guidance	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. (14) 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. (14) 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. (21, 23)

Data analysis

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

Results

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 Aotearoa New Zealand healthcare context.

Study Design and Participants

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

Methods

A modified Delphi process was employed, using two rounds of iterative online surveys (Qualtrics XM platform software, Provo, UT, 2024). The items for the first round of the Delphi process were iteratively developed by three smaller working groups within the SAC, each based on their area of knowledge and expertise. The first survey was divided into 15 sections ([Appendix F](#)) 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 recommendations

Evidence generated through the systematic review (scholarly literature that could not generate answers to the research questions using a PICO format, was absent or of insufficient certainty), the systematic observation forms and the healthcare practitioner (modified Delphi) survey were combined to form consensus recommendations if these were considered as high priority to stakeholders or had the potential to have variation in practice.

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 ([Appendix G](#)).

This letter of invite to provide feedback was sent to the Office of the Director General, Chief Executive or Secretary of each state, territory, and Commonwealth Health Department to

prepare those offices for the publication of the draft Guideline. These officers were then directly emailed the draft Guideline when it was released. Consumer organisations representing the needs of Aboriginal, Torres Strait and Pacific Islander, and Māori communities were specifically and formally invited to participate in providing feedback of the draft Guideline during the period of public consultation.

Public consultation feedback was collected through a feedback form on the dedicated webpage, through email or letter directly to members of the Organising Committee. Feedback could be provided on individual sections, individual recommendations, or practice points, and/ or general feedback about the Guideline. Feedback could be on an individual basis or on behalf of an organisation. Respondents were able to choose whether they wanted their feedback to be published anonymously in the final Guideline. Anonymised feedback has been made available as a separate document at <https://www.unsw.to/nbs-sma>.

Aligning with NHMRC Guidelines for Guidelines, (31) 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 international 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) agree 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.

The Guideline was assessed by two independent reviewers using AGREE II scale ([Appendix H](#)).

Publication of the finalised Guideline and endorsement

Peak bodies and stakeholder organisations identified through GDG networks and through the process of consumer consultation and feedback were approached to endorse the Guideline. A list of organisations endorsing the Guideline is shown in [Appendix I](#).

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 introduction of genetic testing to NBS programs may lead to disengagement with the overall program, which currently has high public confidence and uptake. This may be particularly relevant for First Nations communities where concerns surrounding data sovereignty and custodianship need to be proactively addressed and managed. The GDG took the view of actively formulating recommendations that would involve the curation and delivery of appropriate and tailored information to all families of screen positive newborns, to mitigate information seeking and public mistrust in NBS.
- 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 Australasia - 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 Australasia - 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.

The GDG used several measures to identify high priority clinical questions and therefore all recommendations within the Guideline can be considered as key recommendations and should be implemented by health jurisdictions in Australia and Aotearoa New Zealand.

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 Aotearoa 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 impact and implementation of the Guideline may be evaluated using the following strategies.

1. Mixed qualitative and quantitative methods to assess awareness, understanding, value use and outcomes of the Guideline. This may include

Outcome measures

- 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. (49)
- Evaluation of the model of care within each jurisdiction. This may include assessment of the temporal processes such as time to screen positive result, diagnostic evaluation, confirmation of diagnosis and time to treatment plan and initiation alongside the longitudinal evaluation of the short- and long-term clinical outcomes for children screening positive for SMA.
- 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.

2. Measuring awareness of the Guideline

- Website traffic.
- Traditional and social media mentions.
- Number of organisational and individual members of the GDG engaged in work aligned with the Guideline.

3. Acceptance and adoption measures including

- Endorsement/adoption of recommendations by clinical bodies, jurisdictional groups.
- Approval of guidelines by NHMRC.
- Use/explicit consideration of recommendations or guidelines in development and/or revision of jurisdictional or health service protocols.

Guideline Revisions

The Guideline should be reviewed and updated (at maximum) in 5 years (that is on or before the 1st of April 2030) or sooner if the screening, diagnostic or clinical landscape changes in the interim.

The Guideline will be updated to reflect and respond to new evidence from research, clinical practice and changes in community needs, values and preferences. We aim to add new recommendations to address emerging high-priority clinical questions. Publication frequency varies depending on whether changes are needed to the Guideline. Where there is one or more new or updated recommendations, we will publish a ‘major’ version. Where evidence is updated but there is no change to the strength and/or direction of recommendations, or text is revised within the evidence summary, evidence to decision or remark sections, we will publish a ‘minor’ version of the Guideline. Revisions and new recommendations will be reviewed and endorsed by the Oversight Committee and revisions will be highlighted in preexisting Guideline documents. The new or revised recommendations will be distributed to each of the representatives of the GDG for dissemination, and through traditional and social media avenues.

The methodology employed for the update should identify and prioritise topics required for the identification of a new evidence base published since the search period for the existing Guideline. A future revised Guideline should advise on the scope and clinical questions for the evaluation and methods to identify and evaluate relevant evidence, continue to be systematic and align with the recommendations and approvals required by the National Health and Medical Research Council.

Supporting Evidence

Evidence-based recommendations

Evidence statement forms

Clinical Question: What should the target analyte be in newborn screening for SMA?

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

Intervention: Newborn screening for SMA

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

Outcome(s): Identifying children at risk of SMA

Literature review and search results

Searches were conducted in the databases listed below to identify relevant studies, using search terms listed in [Systematic review 1](#).

A total of 46 (nonrandomised) studies were retrieved that met eligibility criteria (after duplicate removal). The search did not identify any RCTS or systematic reviews.

Database	Dates Searched	Period Covered	Citations retrieved
Embase	01/05/2024 (updated search)	1975-2024	1085
Scopus	01/05/2024 (updated search)	1975-2024	460 (335 duplicates removed)
Pubmed	01/05/2024 (updated search)	1975-30/05/2024	353 (306 duplicates removed)

Total = 1283

Evidence summary

Across 46 studies including 33516 participants, where absence of exon 7 on SMN1 was the target analyte, 295 children were identified and genetically diagnosed with SMA. Studies came from across Europe, North and South America, Asia-Pacific and Australasia. Studies included a

variety of SMN1 assay techniques, and all used dried blood spots as the biological medium. For (n=35) studies, there were no children that had false positive or false negative results.

In (n=11) studies 71 children were falsely diagnosed and in 4 studies, 6 children were diagnosed after clinical referral of symptoms i.e. were not detected with this target analyte. This target will not identify (=5%) of children with an alternative i.e. compound heterozygous genotype.

Summary of studies included in systematic review

Author, year	Level of Evidence	Study description	Narrative summary	Quality Appraisal ¹
Boemer et al. 2021 (55)	IV	Observational: 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. Methodology for first tier testing validated with 53 SMA patients and heterozygous carriers, and with a pre-pilot of 1000 NBS samples	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Singh et al. 2023 (56)	IV	Scoping 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	Quality appraisal not relevant.
Groulx-boivin et al 2024 (57)	IV	Observational: Cross-sectional survey	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 <i>SMN1</i> deletion status and <i>SMN2</i> copy number. Differences exist in what constitutes a positive screening test among Canadian provinces. The Saskatchewan NBS program reports all biallelic <i>SMN1</i> deletions, whereas Alberta, Manitoba, Ontario, and more recently BC only report newborns with biallelic <i>SMN1</i>	Selection = 3 Comparability = 0 Exposure = 2 Overall = Poor quality

			deletions who also have ≤ 4 copies of <i>SMN2</i> . 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	
Boemer et al. 2019 (58)	IV	Observational: Prospective cohort study	qPCR assay of <i>SMN1</i> 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. Small population size to validate test method, leading to potential for selection bias. Assumption that <i>SMN2</i> copy number does not affect assay.	Selection = 1 Comparability = 0 Exposure = 3 Overall = Poor quality
Tesorero et al. 2023 (59)	IV	Observational: 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).	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Shinohara et al 2019(60)	IV	Observational: Case-control and prospective cohort	Assay process consists of two steps: (1) targeted pre-amplification of <i>SMN</i> genes by direct polymerase chain reaction (PCR) and (2) detection of <i>SMN1</i> 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.	Selection = 3 Comparability = 2 Exposure = 2 Overall = Good quality
Olkhovych et al 2023(61)	IV	Observational:	65880 newborns screened and 11 screen positive No description given of how program was implemented or	Selection = 3 Comparability = 0

		Prospective cohort	details on first and second tier screening methods/processes.	Exposure = 2 Overall = Poor quality
Wallace et al 2023(62)	IV	Observational: Prospective cohort	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 preclude applicability and feasibility in Australian context.	Selection = 1 Comparability = 0 Exposure = 2 Overall = Poor quality
Fonseca et al 2024(63)	IV	Observational: 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. Narrative summary of processes. Risk of bias reduced due to consecutive sampling methods used within a screening program.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kimizu et al. 2023(64)	IV cohort	Observational: Prospective cohort	22951 newborns screened using real time quantitative PCR as part of pilot and all screen negative	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kerhohan et al. 2021 (65)	NA	Protocol or consensus	Proposed qPCR multiplexed with assays for SCID and genetic sensorineuronal hearing loss. Target analyte is exon 7 single nucleotide variant.	Quality appraisal not relevant.
Oliveira-Netto et al. 2023(66)	IV	Observational: Prospective 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	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality

Lakhotia et al 2022 (67)	IV	Observational: 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.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kumar et al. 2021 (68)	IV	Observational: 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)	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Wong et al. 2024(69)	IV	Observational: Prospective cohort study	239,844 infants were screened. 13 babies screened positive and were confirmed to have SMA. One false positive	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Tavares et al. 2021 (70)	IV	Observational: Prospective cohort	129 blood samples: 54 samples had <i>SMN1</i> and <i>SMN2</i> 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.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Sonehara et al. 2023(71)	IV	Observational: Prospective cohort study	16,000 DBS, 3 true screen positives, 14 false positives, SMN1 exon 7 deletion on <i>SMN1</i> assay using real-time PCR	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality

Kraszewski et al. 2018(72)	IV	Observational: 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	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
ArRochmah et al. 2017(73)	IV	Observational: 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 <i>SMN1</i> and <i>SMN2</i> Exon 7. <i>SMN1</i> assay Sensitivity = 1 (CI 0.87, 1) Specificity = 1 (CI 0.9, 1). <i>SMN2</i> assay Sensitivity = 1 (CI 0.4, 1), Specificity for <i>SMN2</i> = 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.	Selection = 3 Comparability = 1 Exposure = 2 Overall = Good quality
Gailite et al. 2022 (74)	IV	Observational: Prospective cohort study	10,411 neonate cohort. DBS used. Target analyte exon 7 <i>SMN1</i> . Q-PCR for <i>SMN1</i> . 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.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Elkins et al. 2022 (75)	IV	Observational: Prospective cohort study	301,418 newborn cohort. RT-PCR methodology (qualitative assay). Exon 7 <i>SMN1</i> target analyte. Multiplexed with SCID. 15 true positives, and 24 false positive cases.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality

Mikhalchuk et al. 2023 (76)	IV	Observational: Prospective cohort study	Melt assay from DBS. PCR RFLP as a second tier to test exon 7 deletion.	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality
Kucera et al. 2021 (77)	IV	Observational: 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 <i>SMN1</i> . Two borderline/false positive results: one in a child with a bone marrow disorder (found to be a carrier on ddPCR of <i>SMN1</i>). Used a conservative <i>SMN1</i> cut off which may also have led to false positive result. 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.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kato et al. 2015 (78)	IV	Observational: Case-control	50 DNA samples from DBS. 29 = SMA. 21 = controls. Using competitive oligonucleotide priming PCR to distinguish between <i>SMN1</i> and <i>SMN2</i> 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.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Good quality
Niba et al. 2019 (79)	IV	Observational: Case control	3 individuals (2 controls; 1 SMA). DBS. Using competitive oligonucleotide priming PCR to distinguish between <i>SMN1</i> and <i>SMN2</i> Exon 7. Method 100% concordant with SMA genotype established by other PCR methods.	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality

Czibere et al. 2020 (80)	IV	Observational: Prospective cohort study	QPCR on DBS. 213,279 neonates, target analyte exon 7 absence of SMN1. 30 true positive. No false positive or false negative. sensitivity 1 (95% CI 0.88) and specificity 1 (95% CI 1).	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Wijaya et al. 2019 (81)	IV	Observational: Prospective Cohort study	6 DNA samples from SMA positive individuals. Using competitive oligonucleotide priming PCR to distinguish between <i>SMN1</i> and <i>SMN2</i> Exon 7. Method 100% concordant with SMA genotype established by other PCR methods.	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality
Dobrowolski et al. 2012 (82)	IV	Observational: Prospective Cohort study	Post PCR high resolution melt profiling to establish <i>SMN1</i> and <i>SMN2</i> genotype. 1000 purified DNA samples. 100 self-created DBS. 1200 DBS from NBS. 100% sensitivity for homozygous deletions of <i>SMN1</i> .	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality
Vill et al. 2019 (83)	IV	Observational: Prospective Cohort study	Target analyte Exon 7 <i>SMN1</i> . From DBS. QPCR. 165,525 newborns. 22 children screen positive; no false positives.	Selection = 3 Comparability = 0 Exposure = 2 Overall = Poor quality
Vill et al. 2021 (84)	IV	Observational: Prospective cohort study	43 SMA patients identified via quantitative PCR of <i>SMN1</i> gene from DBS; screening for homozygous deletion of exon 7. 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.	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality

Er et al. 2012 (85)	IV	Observational: Case control	DBS. 60 individuals. High resolution melting analysis. Authors aim to develop a method for identifying the substitution of single nucleotide in <i>SMN1</i> 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.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Good quality
Kariyawasam et al. 2020 (11)	IV	Observational: Prospective Cohort study	103, 903 screened. Target analyte exon 7. Multiplexed with SCID. 10 screen positives. 1 false positive, no false negatives. 100% sensitivity, specificity, and precision.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Noguchi et al. 2022 (86)	IV	Observational: Prospective Cohort study	First-tier: DBS. Real-time qPCR assay with fluorescent hybridizing probes to detect presence/absence of <i>SMN1</i> 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.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Hale et al. 2021 (87)	IV	Observational: Prospective Cohort study	Real time qPCR to detect absence of <i>SMN1</i> Exon 7. Multiplexed tiered testing system. Tier 1=single assay targeting <i>SMN1</i> Exon 7 and RNaseP (assay A) with thermoprofiles set to push the assay to its limits. Tier 2= Two assays. An additional assay targeting <i>SMN1</i> Exon 7, <i>SMN1</i> 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 <i>SMN1</i> Exon 8, and preliminary data on <i>SMN2</i> 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	Selection = 2 Comparability = 1 Exposure = 3 Overall = Fair quality

			90%. 314 samples went to second-tier. 10 of these showed presence of Exon 7 with absence of Intron 7 (<i>SMN1</i> hybrid genes). 294 had present Exon 7. 9 confirmed with SMA.	
Kay et al. 2020 (88)	IV	Observational: Prospective Cohort study	DNA extracted from DBS with multiplex real-time qPCR assay targeting <i>SMN1</i> exon 7 deletion. 225,093 infants tested. 8 screen positives.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Pyatt et al. 2007 (89)	IV	Observational: Case control	Real-time PCR. Multiplex assay to detect homozygous deletion in <i>SMN1</i> Exon 7; validated using 266 samples (84 carriers and 32 individuals affected with SMA, 150 controls) with defined <i>SMN1</i> and <i>SMN2</i> 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.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Good quality
Gutierrez-Mateo et al. 2019 (90)	IV	Observational: 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 known <i>SMN1</i> and 4 newborn DBS samples confirmed with SMA added.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Good quality

			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 (91)	IV	Observational: Case control	Multiplex ddPCR to detect <i>SMN1</i> deletion and <i>SMN2</i> CN variation in single DBS. 1,530 DBS's and 12 SMA patients. 100% sensitivity and specificity.	Selection = 3 Comparability = 1 Exposure = 2 Overall = Fair quality
Kiselev et al, 2024 (92)	IV	Observational: 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.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Liu et al. 2016 (93)	IV	Observational: 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.	Selection = 2 Comparability = 1 Exposure = 3 Overall = Fair quality
Hashimoto et al. 2023 (94)	IV	Observational: Case report	Case report of one child with a false negative result on NBS.	Quality appraisal not completed
Lin et al. 2019 (95)	IV	Observational: Prospective Cohort study	SMA assay based on matrix assisted laser desorption/ionization mass spectrometry for <i>SMN1</i> . 29,364 individuals screened and 3 neonates true positive. Target analyte exon 7 SMN1	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality

Adams et al. 2021 (96)	IV	Observational: Prospective Cohort study	real-time PCR assay to simultaneously detect <i>SMN1</i> exon 7 and control gene RPP30, using DNA from a DBS. 4810 normal/leftover DBS + 43 known SMA positive DBS. <i>SMN1</i> amplification detected in all 4810 normal samples. 42/43 SMA positive samples showed complete absence of <i>SMN1</i> amplification.	Selection = 2 Comparability = 1 Exposure = 3 Overall = Fair quality
Abiusi et al. 2023 (97)	IV	Observational: Prospective Cohort study	In-house qPCR assay coamplifies and differentiates <i>SMN1</i> and <i>SMN2</i> by the C-T transition in exon 7.90,885 samples. 15 individuals with homozygous deletion of <i>SMN1</i> 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.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Niri et al. 2023 (98)	IV	Observational: 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 <i>SMN1</i> . Analytical sensitivity of this screening multiplex assay remained at 100% and the analytical specificity was determined to be 99.999%.	Selection = 2 Comparability = 1 Exposure = 3 Overall = Fair quality
Baker et al. 2022 (99)	IV	Observational: Prospective Cohort study	DNA isolated from routine NBS DBS. multiplex real-time PCR assay to identify newborns with homozygous <i>SMN1</i> exon 7 deletion. 60,984 newborns were screened for spinal muscular atrophy. Six newborns screened	Selection = 2 Comparability = 1

			positive for and were confirmed to have spinal muscular atrophy. An independent dried blood spot specimen was collected and tested to confirm the initial screening results for <i>SMN1</i> and <i>SMN2</i> .	Exposure = 3 Overall = Fair quality
Kubar et al. 2023 (100)	IV	Observational: 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 <i>SMN1</i> gene. 580 DBS newborn samples and air dried 50 DBS from whole blood including 20 samples for homozygous deletion of the <i>SMN1</i> gene detected earlier with MLPA.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Shum et al. 2023 (101)	IV	Observational: 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%. NGS may be an alternative tech for NBS programs to consider.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Sawada et al 2022 (102)	IV	Observational: Prospective Cohort study	13,587 newborns (96% of all births). DBS taken 4-6 days after birth. Target analyte exon 7 <i>SMN1</i> deletion by real-time PCR 1 true screen positive. No false positive or negatives.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
Kato et al 2015 (78)	IV	Observational: 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 <i>SMN1</i> –deletion detection and <i>SMN2</i> presence.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Good quality
Chien et al. 2017(103)	IV	Observational:	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	Selection = 2 Comparability = 1

		Prospective Cohort study	.15 screen positive on first tier: ddPCR on same DBS for exon 7 <i>SMN1</i> excluded 8 false positives and 7 individuals confirmed to have SMA by MLPA. False positives due to hybrids of <i>SMN1/SMN2</i> . 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.	Exposure = 3 Overall = Fair quality
McMillan et al. 2020 (104)	IV	Observational: Prospective Cohort study	First tier Mass Array test for <i>SMN1</i> (alongside 22 other variants for hearing loss and SCID). Assesses for the presence of an <i>SMN1</i> exon 7 single-nucleotide variant (SNV), and of exon 8 <i>SMN1</i> and <i>SMN2</i> SNVs. No results of cohort provided apart from implementation descriptions.	Selection = 1 Comparability = 0 Exposure = 2 Overall = Poor quality
Müller-Felber et al. 2023 (105)	IV	Observational: 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.	Selection = 1 Comparability = 0 Exposure = 2 Overall = Poor quality
Lee et al. 2022 (106)	IV	Observational:	qPCR for <i>SMN1</i> exon 7 deletion multiplexed with assay for SCID. 650,000 neonates screened. 32 screen positive.	Selection = 3

		Prospective Cohort study	Large pilot study which reduces selection bias. No false positives or negatives. Lower incidence than predicted.	Comparability = 0 Exposure = 3 Overall = Poor quality
Abiusi et al. 2024 (107)	NA	Consensus /expert opinion	Meeting of experts and expert opinion. Non-systematic (narrative) evidence base provided to augment recommendations.	Quality appraisal not relevant
Kernohan et al. 2022 (65)	IV	Observational: 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 <i>SMN1</i> assay should be $\geq 95\%$, and the positive predictive value should be $\geq 90\%$. Real world NBS for SMA cohort study. MassARRAY for presence <i>SMN1</i> and MLPA for <i>SMN1</i> and <i>SMN2</i> . 5 screen positive newborns. No false negatives	Selection = 1 Comparability = 0 Exposure = 1 Overall = Poor quality
Kemper et al. 2018 (108)	II	Literature review and report	First tier testing involves qPCR (qualitative) for most states in US which reduces inconclusive results due to absence of <i>SMN1</i> exon 7 on both alleles. 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.	Quality appraisal not relevant
Matteson et al. 2022 (109)	IV	Observational: Prospective Cohort study	628,791 infants screened using multiplex RT-PCR to detect deletions in exon 7 of <i>SMN1</i> . 34 screen positive	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality

Prior et al. 2010 (110)	IV	Observational: Prospective Cohort study	Liquid bead microarray NBS assay performed on DBS. 40103 DBS analysed and 7 required repeat extraction of DNA from DBS due to ambiguity of screening result. Assay repeated on re-extracted DNA and ambiguity resolved. Four screen positive newborns identified.	Selection = 2 Comparability = 0 Exposure = 3 Overall = Poor quality
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¹ Quality Appraisal using the Newcastle-Ottawa Quality Assessment Scale. Thresholds for converting the Newcastle-Ottawa scales to Agency for Healthcare and Research Quality standards (good, fair, and poor): Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Evidence Statement

Evidence Statement	GRADE Quality	Related Recommendation
High uncertainty for the effects of using exon 7 on <i>SMN1</i> as the target analyte for identifying children at risk of SMA within newborn screening	Very Low	1.1. EBR

EBR; Evidence based recommendation

GRADE Evidence Profile

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

Certainty of evidence

Step 1: Are the studies you took randomized?

Study type: Observational (non-randomized)

Step 2: Factors that might cause rating down certainty

Risk of Bias: very serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias;

Inconsistency: very serious. Results variable across studies with 8 studies and 32 children having false positive or false negative results;

Indirectness: no serious. generalisable to the population in question; **Imprecision: serious.** Large number of patients across multiple studies

however narrative summary conducted and estimates not precise; **Publication bias: serious.** Risk of publication bias as only studies with significant findings likely to be published and studies limited to those in English for purpose of systematic review.

Step 3: Factors that might cause rating up certainty

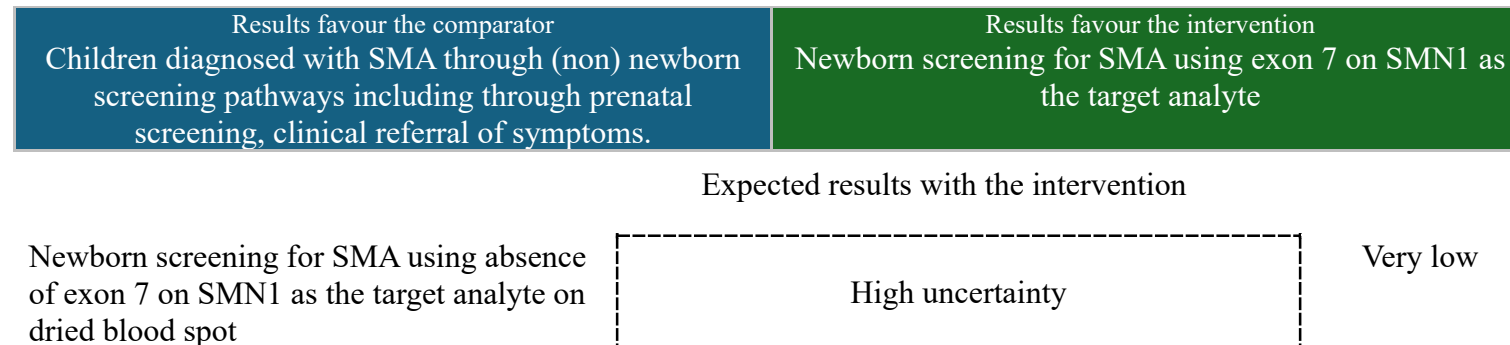
None

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

Certainty level GRADE: Very low

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

Graphical representation



Evidence to decision tables

Strong recommendation (for)

The target analyte of newborn screening for SMA should be an absence 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.	
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		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. Risk of 5% of the population not being identified with SMA with this target analyte.
Certainty of evidence	What is the certainty of overall evidence	Very Low Very Serious risk of bias, very serious inconsistency, extremely serious risk of imprecision and serious risk of publication bias	3,155,446 newborns screened using this target analyte across 46 studies.	
Values and preferences	Is there uncertainty about or variability in how much people value the outcome	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) (9)	The patient advocates and representatives on the panel with lived experience highlight the fact that this intervention is likely to be highly valued and preferred across the community.
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	Not all estimates as to costs of adding this screen onto routine panels identified i.e. cost of training, personnel, equipment

			adds an estimated USD 1 to the cost of the NBS assay	
Cost effectiveness	Does cost effectiveness favour the intervention	Favours the option	Several cost effectiveness studies in Australia (52, 53): 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 (54)	
Equity	What would the impact be on health equity?	Probably increased	Two studies using an implementation study design showed that NBS for SMA using target analyte improves health equity across Australia (10, 11)	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. (9)	Within these studies, no false negative cases arose and therefore the full acceptability of targeting exon 7 on SMN1 in these populations is unknown.

				However the patient advocates on the panel and consumers with lived experience highlight that this recommendation will likely be highly desired by most of the population.
Feasibility	Is the intervention feasible to implement	Probably yes	Feasibility of implementation in an Australasian healthcare context shown in Kariyawasam et al. 2020 (11) where time to achieving a screen positive result, using this target analyte was 8 days of life (range 5-18 days). (11)	The panel consider this as feasible within state and territory (Australia) and national (Aotearoa New Zealand) NBS programs
Boemer et al. 2021 (55), Singh et al. 2023 (56), Groulx-Boivin et al. 2024 (57), Boemer et al. 2019 (58), Tesorero et al. 2023 (59), Shinohara et al. 2019 (60), Olkhovych et al. 2023 (61), Wallace et al. 2023 (62), Fonseca et al. 2024 (63), Kimizu et al. 2023 (64), Kernohan et al. 2022 (65), Oliveira-Netto et al. 2023 (66), Lakhotia et al. 2022 (67), Kumar et al. 2021 (68), Wong et al. 2024 (69), Tavares et al. 2021 (70), Sonehara et al. 2023 (71), Kraszewski et al. 2018 (72), ArRochmah et al. 2017 (73), Gailite et al. 2022 (74), Elkins et al. 2022 (75), Mikhalchuk et al. 2023 (76), Kucera et al. 2021 (77), Kato et al. 2015 (78), Niba et al. 2019 (79), Czibere et al. 2020. (80) Wijaya et al. 2019 (81), Dobrowolski et al. 2012 (82), Vill et al. 2019 (83), Vill et al. 2021 (84), Er et al. 2012 (85), Kariyawasam et al. 2020 (11), Noguchi et al. 2022 (86), Hale et al. 2021 (87), Kay et al. 2020 (88), Pyatt et al. 2007 (89), Gutierrez-Mateo et al. 2019 (90), Vidal-Folch et al. 2018 (91), Kiselev et al. 2024 (92), Liu et al. 2016 (93), Hashimoto et al. 2023 (94), Lin et al. 2019 (95), Adams et al. 2021 (96), Abiusi et al. 2023 (97), Niri et al. 2023 (98), Baker et al. 2022 (99), Kubar et al. 2023 (100), Shum et al. 2023 (101), Sawada et al. 2022 (102), Chien et al. 2017 (103), McMillan et al. 2021 (104), Muller-Felber et al. 2023 (105), Lee et al. 2022 (106), Kemper et al. 2018 (108), Matteson et al. 2022 (109), Prior et al. 2010 (110).				

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
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Type of evidence-based recommendation: strength	Conditional against	Strong against	Conditional for	Strong for
				X
Recommendation, The target analyte of newborn screening for SMA should be homozygous deletion of exon 7 on <i>SMN1</i>				
Justification There is low certainty of evidence for this intervention, but a high value and acceptability 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 likely to increase health equity and be acceptable to all stakeholders. Of note a strong recommendation can be made even if the certainty of evidence is low if consumers are highly likely to desire it. Currently there are no screening methods or target analytes that can be used within a population level to identify all children with SMA.				
Subgroup considerations None identified in the literature.				

Recommendation 3.1

Strong recommendation (for)

Clinical question: How should a screen positive child (identified through newborn screening) be diagnosed with SMA?

Population: Screen positive newborns with SMA

Intervention: Diagnostic tests for SMA

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

Outcome(s): Confirming the diagnosis of SMA

Literature review and search results

Searches were conducted in the databases listed below to identify relevant studies, using search terms listed in [Systematic review 5](#).

A total of 19 (nonrandomised) studies were retrieved that met eligibility criteria (after duplicate removal). The search did not identify any RCTS or systematic reviews.

Database	Dates Searched	Period Covered	Citations retrieved
Pubmed	01/05/2024 (updated search)	1975-30/05/2024	608
Scopus	01/05/2024 (updated search)	1975-2024	460 (279 duplicates)
Embase	01/05/2024 (updated search)	1975-2024	1228 (585 duplicates)

Total = 1432

Evidence summary

Across 19 studies including 286 participants, 262 children had a confirmed diagnosis of SMA using diagnostic testing for absence of exon 7 on SMN1.

Summary of studies included in systematic review

Author, year	Level of Evidence	Study description	Narrative summary	Quality Appraisal ¹
Abiusi et al. 2024 (107)	N/A	Consensus statement	Representative of European Molecular Quality Network presented data from 92 out of 99 laboratories using PCR based methods to ascertain <i>SMN1</i> and <i>SMN2</i> gene dosage. MLPA most commonly used technique. Seven laboratories reported eight critical <i>SMN1</i> genotyping errors. Important to reassess <i>SMN1</i> testing protocols including used of validated positive and negative controls isolated through the same method as patient DNA samples.	Consensus statement and quality appraisal not relevant
Strunk et al. 2019 (113)	IV	Observational: Prospective Cohort study	Confirmation of <i>SMN1</i> available by day 14 of life (mean 15.6+/- 5.9 days) for 63 screen positive newborns, confirming 43 children with SMA.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Wang et al. 2020 (112)	IV	Observational: Prospective Cohort study	Whole blood collection and digital PCR vs HRM analysis used to determine <i>SMN1</i> 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 <i>SMN1</i> / <i>SMN2</i> ratio. Digital PCR methodology provides absolute quantification for copy number variation and rare mutation detection.	Selection = 3 Comparability = 2 Exposure = 3 Overall = Good quality
Boemer et al 2021 (55)	IV	Observational: Prospective Cohort study	Whole blood collection from recalled screen positive newborn and MLPA performed to confirm <i>SMN1</i> diagnosis. Process of implementation focuses on rapid turnaround time of all screening and diagnostic processes	Selection = 3 Comparability = 0 Exposure = 2 Overall = Poor quality

Vill et al.2021 (84)	IV	Observational: Prospective Cohort study	Confirmation of homozygous deletion of exon 7 on <i>SMN1</i> confirmed by MLPA on whole blood sample from recalled screen positive infants.	Selection = 3 Comparability = 0 Exposure = 2 Overall = Poor quality
Gailite et al 2022 (74)	IV	Observational: Prospective Cohort study	Confirmation of homozygous deletion of exon 7 on <i>SMN1</i> confirmed by MLPA on whole blood sample from recalled screen positive infants.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
D'Silva et al 2022 (10)	IV	Observational: Prospective Cohort study	Diagnostic confirmation contingent on corroboration of <i>SMN1</i> deletion in a freshly collected blood sample using assays with different primers to screening assays. Turn around time for diagnostic results important due to the urgency of treatment for some – triage of <i>SMN1</i> copy number may be informed by <i>SMN2</i> copy number on screening assay (overtime for 2 <i>SMN2</i> copies or urgent within hours run for 3 <i>SMN2</i> copies)	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Niri et al 2023 (98)	IV	Observational: Prospective Cohort study	Blood collected on screen positive newborns and confirmation of diagnosis of <i>SMN1</i> copy number with MLPA.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kucera et al.2021 (77)	IV	Observational: Prospective Cohort study	ddPCR used to confirm diagnosis and detected a single intact <i>SMN1</i> 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	Selection = 2 Comparability = 0 Exposure = 2 Overall = Poor quality

Oliveira-Netto et al. 2023 (66)	IV	Narrative review	MPLA considered gold standard for confirmation of exon 7 <i>SMN1</i> deletion, but RFLP may also be considered to expedite results. Non-systematic review of current literature with up to date references	Non-systematic review and therefore quality appraisal not relevant.
Sawada et al 2022 (102)	IV	Observational: Prospective Cohort study	MLPA used to confirm copy numbers of exon 7 and 8 in <i>SMN1</i> and <i>SMN2</i> genes on freshly obtained whole blood samples.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Kimizu et al. 2023 (64)	IV	Observational: Prospective Cohort study	MLPA for <i>SMN1</i> for diagnostic testing	Selection = 3 Comparability = 0 Exposure = 2 Overall = Poor quality
Chien et al. 2017 (103)	IV	Observational: Prospective Cohort study	Positive screening results confirmed by ddPCR assay using original DBS and MLPA using whole blood from recalled newborn.	Selection = 3 Comparability = 1 Exposure = 3 Overall = Fair quality
Lin et al.2019 (95)	IV	Observational: Prospective Cohort study	MLPA analysis confirms <i>SMN1</i> and <i>SMN2</i> copy number in two patients identified through a MassARRAY based genotyping screening assay.	Selection = 1 Comparability = 0 Exposure = 1 Overall = Poor quality
Mikhalchuk et al. 2023 (76)	IV	Observational: Prospective Cohort study	Fresh whole blood sample collected from recalled newborn. Use of RFLP to confirm diagnosis of exon 7 homozygous deletion in <i>SMN1</i> and the MLPA completed for <i>SMN1</i> and <i>SMN2</i>	Selection = 3 Comparability = 0 Exposure = 3

				Overall = Poor quality
Kiselev et al. 2024 (92)	IV	Observational: Prospective Cohort study	MLPA performed on whole blood samples for <i>SMN1</i> and <i>SMN2</i> (results available within 1-2 days of receipt at diagnostic lab)	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
Liu et al 2016 (93)	IV	Observational: Retrospective and Prospective Cohort study	Accuracy of real-time PCR to detect pathogenic deletions in exon 7 <i>SMN1</i> was at least 98.8% compared with DNA sanger sequencing and MLPA, but faster and less DNA required. Also cheaper than dPCR.	Selection = 3 Comparability = 0 Exposure = 3 Overall = Poor quality
² Groulx-Boivin et al 2024 (57)	IV	Observational: Cross sectional survey	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.	Selection = 2 Comparability = 0 Exposure = 1 Overall = Poor quality

¹ Quality Appraisal using the Newcastle-Ottawa Quality Assessment Scale. Thresholds for converting the Newcastle-Ottawa scales to Agency for Healthcare and Research Quality standards (good, fair, and poor): Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Evidence Statement

Evidence Statement	GRADE Quality	Related Recommendation
High uncertainty for the effects of diagnosing SMA (following a positive screening test) using exon 7 on SMN1	Very Low	3.1. EBR

EBR; Evidence based recommendations

GRADE Evidence Profile

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Clinical (non- NBS) diagnosis of SMA	Newborn Screening		
Confirming the diagnosis of SMA	Based on data from 218 participants in 19 studies			Very low Due to very serious risk of bias, serious risk of imprecision and publication bias, and very serious inconsistency	We are uncertain whether using an absence of exon 7 on <i>SMN1</i> should be used to diagnose within newborn screening programs

Certainty of evidence

Step 1: Are the studies randomized?

Study type: Observational (non-randomized)

Step 2: Factors that might cause rating down certainty

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

Step 3: Factors that might cause rating up certainty

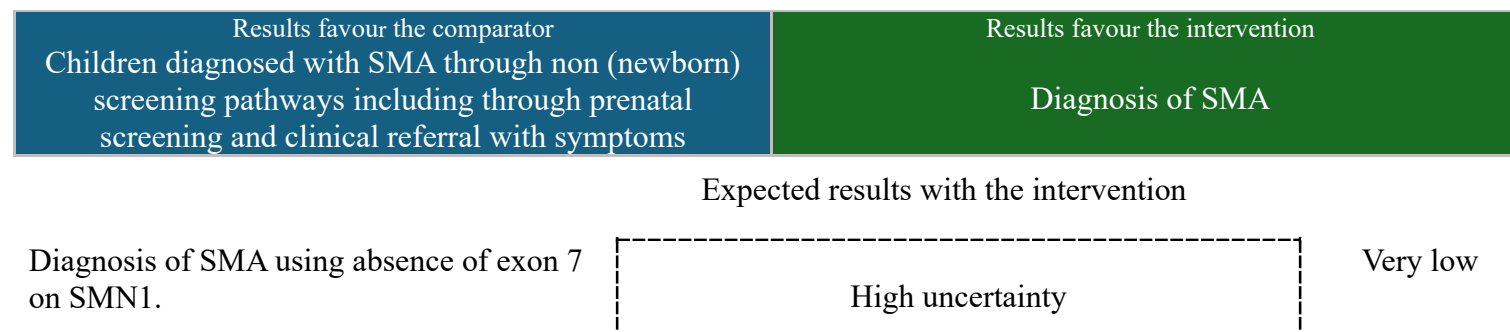
None

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

Certainty level GRADE: Very low

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

Graphical representation



Evidence to Decision

	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 <i>SMN1</i> is required to access treatments on the Pharmaceutical Benefit Scheme.
Certainty of evidence	What is the certainty of overall evidence			
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 (9)	Patient advocates on the panel and consumers with lived experience highlight that this recommendation will likely be highly desired by the families of affected children.
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 Aotearoa 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 analysis of cost effectiveness	
Equity	What would the impact be on health equity?	Probably increased	Achieving a diagnosis of SMA improves health equity across Australia. (10, 111)	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. (9)	Patient advocates on the panel and consumers with lived experience highlight that this recommendation will likely be acceptable to the community.
Feasibility	Is the intervention feasible to implement	Probably yes	Feasibility of implementation in an Australasian healthcare context shown in Kariyawasam et al. 2020 (11) 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 (Aotearoa New Zealand) NBS programs
References: Groulx-Boivin et al. 2024 (57), Prior et al. 2010 (110), Liu et al. 2016 (93), Kiselev et al. 2024 (92), Mikhalechuk et al. 2023 (76), Lin et al. 219 (95), Chien et al. 2017 (103), Kimizu et al. 2023 (64), Sawada et al. 2022 (102), Oliviera-Netto et al. 2023 (66), Kuchera et al. 2021, Niri et al. 2023 (98), D'Silva et al. 2022 (10), Gailite et al. 2022 (74), Vill et al. 2021 (84), Boemer et al. 2021 (55), Wang et al. 2020 (112), Strunk et al. 2019 (113) .				

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	
Type of evidence-based recommendation: strength	Conditional against	Strong against	Conditional for	Strong for

				X
Recommendation				
Diagnostic testing should include confirmation of an absence of exon 7 on <i>SMNI</i> (i.e. zero copies of <i>SMNI</i>)				
Justification				
There is very 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 all stakeholders and feasible to implement. Of note a strong recommendation can be made even if the certainty of evidence is low if consumers are highly likely to desire it.				
Subgroup considerations				
None				

Supporting Evidence

Consensus-based recommendations

Evidence to decision tables

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

Clinical question: Should the screening assay have a minimum sensitivity and specificity?
What should this be?

Literature review ([Systematic review 3](#))

Evidence Table	
Recommendation	1.2 The screening method selected by the screening program should have a sensitivity of $\geq 95\%$ for the detection of <i>SMNI</i> exon 7 absence (0 <i>SMNI</i> copies) using suitably validated quantitative and qualitative assays
Rationale	• Very low certainty of studies that do not assess sensitivity/specificity between assays and GDG agree to form a consensus recommendation. • 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). • 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) (11) • Uncertain if this specific recommendation is acceptable to stakeholders as 5% of population will not be identified through this method.
Evidence sources	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 <i>SMNI</i> , however compound heterozygotes with SMA will not be identified through this methodology so sensitivity changes to 95%. Range of qualitative and quantitative <i>SMNI</i> 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: 1 st round Delphi: respondents 21, mean 8.71, no outliers.
References	Lin et al. 2019, (95) Niri et al. 2023, (98) Shum et al. 2023, (101) Muller-Felber et al. 2023, (105) Zhi et al. 2023, (114), Kariyawasam et al. 2020. (11)

Clinical question: When should a screen positive result be communicated to clinical services?

Literature review ([Systematic review 11](#))

Evidence Table	
Recommendation	1.3. A screen positive result should be communicated to clinical services when the <i>SMN1</i> screening result is available (independent of the availability of <i>SMN2</i> copy number on screening assays).
Rationale	• No direct evidence within the systematic literature review, however efficiency of all steps in the NBS for SMA pathway considered as key to reduce time to diagnosis and treatment and magnify health benefits. SMA is considered a neurogenetic emergency for many children (especially those with 2 <i>SMN2</i> copies and with clinical signs and symptoms of SMA). Expedient <i>SMN1</i> communication to clinical services unlocks next steps in pathway for diagnostic confirmation and timely therapeutic decision making. GDG agree that should this be a consensus based recommendation. • Fully generalisable to Australasia. • Large impact on expediting access to diagnosis and treatment/care that will increase magnitude of health benefit to newborns. • No systematically collected evidence of preferences, values or cost benefit. • No equity issues identified. • Feasible within Australasian health landscape.
Evidence source	Delphi survey and systematic observation-forms
Research literature	None.
Support from experts	Excellent: 1 st round Delphi 21 respondents, mean 8.52, 0 outliers.
References	Not applicable.

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

Clinical question: Should *SMN2* copy number be part of newborn screening for SMA?

Literature review ([Systematic review 2](#))

Evidence Table	
Recommendation	2.1. <i>SMN2</i> copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on <i>SMN1</i>.
Rationale	• No direct evidence from the systematic literature review. • <i>SMN2</i> copy number is the leading prognosticator of SMA disease severity. Incorporating <i>SMN2</i> copy number testing on the same dried blood spot as <i>SMN1</i> 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 <i>SMN2</i> copy number). <i>SMN2</i> copy number guides the pace of initiating treatment, therefore likely to have a moderate benefit. • No consistency across observational studies. • Somewhat generalisable to Australasian population. • No systematically collected information regarding preferences and values of stakeholders aligning with this recommendation, for families and many healthcare professionals providing post diagnostic care, the GDG acknowledges that <i>SMN2</i> copy number is important for shared decision making in terms of how quickly to treat. • Equity issues include the fact that some jurisdictions will incorporate <i>SMN2</i> copy number into screening algorithms whilst others will depend on the diagnostic process. This may lead to variabilities in health outcomes for children within Australasia. • Feasibility: Not all jurisdictions will have the capacity to perform <i>SMN2</i> copy number as part of screening. There is variability in the systematic literature on programs that perform <i>SMN2</i> as part of NBS and those that incorporate this into a diagnostic algorithm.
Evidence source	Scholarly literature and Delphi survey.
Research literature	44 studies incorporated <i>SMN2</i> as second tier screening for all newborns with absence of <i>SMN1</i> on first tier analysis. In 11 studies, <i>SMN2</i> copy number identification was part of the confirmatory (diagnostic) process. Across the USA, 10 out of 37 states incorporate screening for <i>SMN2</i> into newborn screening programs, completed on the same dried blood spot and following detection of absence of exon 7 on <i>SMN1</i>. However, other states determine <i>SMN2</i> 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 <i>SMN2</i> 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;

	2 nd round Delphi with rewording: meets consensus, respondents 22, mean 8.36, no outliers.
References	Abiusi et al 2024, (107) Hale et al. 2021. (87)

Clinical question: How should a screen positive result be communicated to clinical services?

Literature review ([Systematic review 11](#))

Evidence Table	
Recommendation	2.2. Newborn screening programs should establish a clinical referral pathway that includes simultaneous early notification of a screen positive result to a paediatric neurology specialist and local healthcare practitioner.
Rationale	• Large impact on having standardised approaches to increase screening accuracy. Notification of paediatric neurologist important to make informed decision making in fast moving therapeutic landscape. Notification of a paediatric neurologist allows for children to be managed expediently within a specialist centre, which is a pre-requisite for accessing approved and reimbursed treatments in Australasia. • Methodological processes do vary across jurisdictions depending on workflow. Highly feasible due to flexibility in approach of tests being used. • Values and preferences of consumers aligned with this recommendation showing that they value expedient access to specialist services. • Equity of access to specialist knowledge important to manage children with rare conditions such as SMA. • Feasibility may be an issue (especially for health jurisdictions with smaller tertiary centres).
Evidence source	Scholarly literature, Delphi survey and systematic observation-forms
Research literature	5 observational studies showed that there was variability in who receives the screening result between jurisdictions, but in the majority, the person of contact is a designated paediatric neurologist working in a specialist referral centre. Fully generalisable to current population.
Support from experts	Excellent: 1 st round Delphi: respondents 21, mean 8.62, no outliers.
References	Hale et al. 2021, (87) Kraszewski et al. 2018, (72) Abiusi et al. 2024, (107) Schorling et al. 2019 (116)

Section 3: Confirming the diagnosis of spinal muscular atrophy

Clinical question: Should diagnosis of SMA include *SMN2* copy number?

Literature review ([Systematic review 6](#))

Evidence Table	
Recommendation	3.2. Diagnostic testing using suitably validated assays, from whole blood samples or repeat dried blood spot from a recalled infant should include <i>SMN2</i> copy number as a guide to prediction of clinical severity and to facilitate therapeutic decision making.
Rationale	- Fully consistent across the scholarly literature. - Fully generalisability across Australasian population. - Substantial impact. <i>SMN2</i> copy number determination can be challenging and should be performed in expert reference centres. Equity issues include the fact that not all jurisdictions will have intrastate capacity to conduct <i>SMN2</i> copy number, therefore processes and pathways need to be established for accurate and expedient interstate <i>SMN2</i> copy number identification. <i>SMN2</i> copy number as part of the diagnostic workflow is in all likelihood valued and generally acceptable to healthcare practitioners and consumers to guide therapeutic decision making. - Health jurisdictions may need to develop the capacity to undertake <i>SMN2</i> diagnostic testing so that treatment decisions including approvals and reimbursement structures for treatments can be made, to ensure the feasibility of the recommendation.
Evidence source	Scholarly literature and Delphi survey.
Research literature	<i>SMN2</i> diagnostic testing considered clinically useful to determine prognosis, aid therapeutic and decision making. (4) A consensus statement by Abiusi et al.2024 (107) stated that <i>SMN2</i> copy number determination could be challenging and should be conducted in expert reference centres with standard workflows. All studies complete <i>SMN2</i> 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, (105) Strunk et al. 2019, (113) Vill et al. 2019. (83) Crawford et al. 2023) (4), Abiusi et al.2024. (107)

Clinical question: When should the screening to diagnostic process be completed

Literature review ([Systematic review 11](#))

Evidence Table	
Recommendation	3.3. Diagnostic results for <i>SMN1</i> should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory.
Rationale	High impact on improving efficiency of healthcare journey for newborn, to reduce time to diagnosis, intervention and care and thus to optimise outcomes

	• One study within Australasia notes that SMN1 diagnostic result can be made available by 13.5 days of life (of newborn) and within 6 days of clinical review. • A defined time interval likely to be valued and acceptable to consumers and healthcare practitioners and this is likely to standardise timings to mitigate inequities to accessing diagnosis and treatment in Australasia. • Feasibility of meeting this turn around time dependent on jurisdictional workflow processes, however all screening laboratory representatives considered this an acceptable turn around time for diagnostic results.
Evidence source	Scholarly literature and Delphi survey.
Research literature	No defined time for diagnostic result availability (varies internationally). Australian pilot data determines that <i>SMN1</i> 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 (11)

Clinical question: When should the screening to diagnostic process be completed

Literature review ([Systematic review 11](#))

Evidence Table	
Recommendation	3.4. A diagnosis of SMA (including <i>SMN1</i> and <i>SMN2</i> copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment.
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. • 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. (9)
Evidence source	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 <i>SMN2</i>) therefore should be as short as possible. Australian pilot

	data determines that the diagnostic process can be completed within the first 28 days of birth (Kariyawasam et al. 2020).
Support from experts	Good: respondents 12, mean 8.00, 1 outlier.
References	Aragon-Gawinska et al. 2023, (120) Kariyawasam et al 2021. (9)

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

Clinical question: Should there be specific processes to manage false positive results? Should there be specific processes to manage uncertain and false negative results?

Literature review ([Systematic review 13](#))

Evidence Table	
Recommendation	4.1. For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families.
Rationale	• No direct evidence across the scholarly literature. • Somewhat generalisable across Australasian population. • Small number of false positives and rare false negatives through newborn screening in the systematic literature. • Several serious harms can be incurred without this recommendation including; harms to the newborn included either unnecessary treatment (with false-positive screening results) or children remaining undiagnosed and untreated (with false negative screening results) and the psychological distress caused to families, potential dissatisfaction with care and an erosion of public trust in newborn screening as a population health initiative. High potential for benefit due to identifying the correct diagnosis in the child which has substantial implications for interventions, care, support and outcomes. Identifying the correct diagnosis for a child is important to facilitate the wellbeing of affected families and promote their confidence in newborn screening as a population program. • Feasibility challenged by the time, expertise and technology from relevant healthcare practitioners required to identify and understand the aetiology of false positive, false negative or uncertain result. Feasibility also dependent on communication and coordination of care between health domains. • This recommendation is likely to be highly valued and acceptable to all consumers.
Evidence source	Delphi survey.
Research literature	Not applicable.
Support from experts	Excellent: Delphi survey respondents 26, mean 8.41. 1 outlier.
References	Not applicable.

Clinical question: Should there be specific processes to manage false positive results? Should there be specific processes to manage uncertain and false negative results?

Literature review ([Systematic review 13](#))

Evidence Table	
Recommendation	4.2.

	If there is a difference in <i>SMN1</i> and/or <i>SMN2</i> copy number results between screening and diagnostic assays, retesting for <i>SMN1</i> and/or <i>SMN2</i> copy number with another method/laboratory should be considered.
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. • Feasibility dependent on establishing collaborative links between screening and diagnostic services, which may be jurisdictionally dependent.
Evidence source	Scholarly literature, Delphi survey and systematic observation-forms.
Research literature	SMN1: 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 <i>SMN1</i> 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. SMN2: Substantial inconsistency in limited observational studies as to when to retest <i>SMN2</i> copy number, however a number of studies agree in challenges of precisely identifying copy 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 <i>SMN2</i> 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.
Support from experts	Good: respondents 26, mean 8.31, outlier 1 (<i>SMN1</i>) Good: respondents 26, mean 8, outlier 1. (<i>SMN2</i>)
References	Qu et al 2024, (121) and D'Silva et al 2022, (10) Schorling et al. 2019, (116) Cusco et al. 2020, (122), Abiusi et al. 2024. (107)

Clinical question: Should there be specific processes to manage false positive results? Should there be specific processes to manage uncertain and false negative results?

Literature review ([Systematic review 13](#))

Evidence Table	
Recommendation	4.3. 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.

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. • Recommendation is likely to be valued and acceptable to stakeholders as it improves the quality of healthcare for the child and family. • Equity considerations include for families travelling from rural/regional areas of Australasia to access expert care, this may confer substantial logistical and opportunity costs on them. The use of telehealth technologies provides the opportunity to mitigate this by working with local healthcare practitioners and the preferences of the family. • Likely to be feasible due to likely small number of false and uncertain cases.
Evidence source	Delphi survey and systematic observation forms.
Research literature	Not applicable.
Support from experts	Good: respondents 27, mean 8.48, outlier 1.
References	Not applicable

Section 5. Disclosing a screen positive result to families

Clinical question: When should a screen positive newborn be communicated to families?

Literature review ([Systematic review 7](#))

Evidence Table	
Recommendation	5.1. Screen positive result should be disclosed to the family within ≤ 2 working days (of notification to healthcare services)
Rationale	• Inconsistent evidence across the scholarly literature on exact timelines but consistency across studies that time to disclosure should be as short as possible. • Time to treatment is a significant factor in future health outcomes due to the rapid and progressive neurodegeneration of the motor unit pool in SMA, therefore the time to screen positive disclosure should be as short as possible. Therefore substantial impact on health outcomes to reduce timeline to diagnosis and treatment. • Recommendation likely to be valued and acceptable to consumers and healthcare practitioners. • Equity of access to a screen positive result within a standardised time may mitigate healthcare inequities across Australasia. • Although there is no direct evidence for this time interval, the GDG acknowledges that disclosure is feasible across Australasia within 48 hours of screen positive results. 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, (11) Muller-Felber et al. 2023, (105) Boemer et al. 2019. (58)

Clinical question: When should a screen positive newborn be first reviewed by clinical services?

Literature review ([Systematic review 11](#))

Evidence Table	
Recommendation	5.2. Screen positive newborns should be offered a clinical review within paediatric neurology/neuromuscular services within ≤ 2 working days, from the time of screen positive disclosure.
Rationale	• Large potential for benefit due to expediting access to diagnosis and therapeutic planning that is known to maximise clinical benefits for the child.

	There may be a safety risk for parents who travel with a symptomatic child to seek specialist care. Time to diagnosis is key, independent of health setting where review takes place. • Eight observational studies denote variability in timelines for clinical review once a family is notified of the screening result. • 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. (104) Programs generally refer children to neuromuscular centres for the first clinical review. (11, 105) • Families value expedient access to specialist review. (9)
Evidence source	Scholarly literature and Delphi survey
Research literature	Within the Australian pilot newborn screening for SMA program screen positive results were communicated to families by 10.5 days of life and the child reviewed in a specialist clinic by 12.5 days of life (8-23) days.
Support from experts	Excellent: Respondents 13, mean 9, outlier 0.
References	Kariyawasam et al. 2021, (9) Meyer et al 2024, (126) Muller-Felber et al. 2023, (105) McMillan et al. 2021 (104) and Groulx-Boivin et al. 2024. (57)

Clinical question: Should specific care or support be provided to families at the time of results disclosure to families of First Nations descent and/or culturally and linguistically diverse families?

Literature review ([Systematic review 10](#))

Evidence Table	
Recommendation	5.3. Culturally safe care is required by healthcare practitioners when disclosing results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.
Rationale	• Substantial impact on the quality of information provision to fit the individual and specific needs of these families. Potential to increase engagement and satisfaction in healthcare for families • Two mixed method studies identified the need for interpreter services for non-English speaking families to understand the complexities of the screen positive SMA result and for informed therapeutic decision making. • May have additional costs involved. • Has the potential to reduce health inequities related to sociodemographic factors. • Families value culturally competent and accurate and understandable information.

	Feasibility dependent of trained personnel and availability of services to provide cultural competent and safe care.
Evidence source	Scholarly literature and Delphi survey
Research literature	Not applicable
Support from experts	Good: Respondents 13, mean 7.92, 1 outlier.
References	Kariyawasam et al. 2021, (9)

Section 6. Assessments required at diagnostic evaluation of the newborn

Clinical question: What assessments should be completed in a child diagnosed with SMA through newborn screening?

Literature review ([Systematic review 8](#))

Evidence Table	
Recommendation	6.1. The following assessments should be completed immediately as part of the diagnostic and clinical evaluation of the newborn, who screens positive for SMA. • Neurological examination. • Venous sampling for quantification of <i>SMN1</i> exon 7 on whole blood. • Venous sampling for determination of <i>SMN2</i> copy number on whole blood OR repeat dried blood spot for confirmation of <i>SMN2</i> copy number
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 <i>SMN1</i> and <i>SMN2</i> bloods collected at this point.
Support from experts	Excellent: Delphi survey results. Neuro exam, respondents 13, mean 9, 0 outliers. <i>SMN1</i> venous sample respondents 13, mean 8.69 0 outliers. <i>SMN2</i> venous sample respondents 13, mean 8.69, 0 outliers.
References	Kariyawasam et al. 2022, (127) Kariyawasam et al. 2020, (11) Muller-Felber et al. 2023, (105) McMillan et al. 2021, (104) Abiusi et al. 2024, (107) Elkins et al. (104) Tizzano et al. 2019, (128) Castalleno et al. (129)

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

Clinical question: What assessments should be completed in a child diagnosed with SMA through newborn screening?

Literature review ([Systematic review 8](#))

Evidence Table	
Recommendation	7.1. The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when <i>SMN1</i> (diagnostic) confirmation is received, regardless of the availability of <i>SMN2</i> copy number result.
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. - 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	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. (9) Families valued a compassionate approach at this first clinic visit and appreciated providers taking time to explain aspects of their' child's diagnosis. (126)
Support from experts	Excellent: Respondents 13, mean 9.00, 0 outliers.
References	Kariyawasam et al. 2021, (9) Meyer et al. 2024. (126)

Clinical question: Should specific information be given to families of diagnosed children with SMA

Literature review ([Systematic review 9](#))

Evidence Table	
Recommendation	7.2. Families receiving a diagnosis of SMA for their newborn through a newborn screening program, should be directed to high quality and reliable educational resources that reflect the contemporary care landscape and are nationally consistent.
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. • 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. (126) Written information also valued by parents in a separate mixed methods study to aid understanding of diagnosis and treatment options. (9)
Support from experts	Excellent: 1 st Delphi round, respondents 13, mean 8.69, 0 outliers.
References	Meyer et al. 2024, (126) Kariyawasam et al. 2021. (9)

Clinical question: Should specific care or support be provided at the time of diagnosis for families of First Nations descent and/or culturally and linguistically diverse families?

Literature review ([Systematic review 10](#))

Evidence Table	
Recommendation	7.3. Culturally safe care is required by healthcare practitioners when disclosing diagnostic results to families from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other culturally and linguistically diverse backgrounds. If the healthcare practitioner is not bilingual, a professional interpreter should be used and advice and support sought from Indigenous Health Liaison professionals (which may include a First Nations nurse, midwife or healthcare practitioner) where relevant and appropriate.
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. • 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. (11)

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

Clinical question: When should treatment(s) be started for a symptomatic child with SMA?

Literature review ([Systematic review 12](#))

Evidence Table	
Recommendation	8.1. For screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset i.e. clinically manifest), a paediatric neurologist should discuss options for immediate treatment with SMN augmenting treatments, with the family.
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. - 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. (123) 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. (120) Time to treatment for symptomatic children changed final HINE scores for children with SMA. (111) Expert evidence of panel of 5 members determines urgency to treat infants and young children to minimise loss of motor neurons. (138)
Support from experts	Good. Delphi survey passes consensus respondents 13, mean 8.54, outlier 1.
References	Finkel et al. 2017, (123) Aragon-Gawinska et al. 2023, (120) Kariyawasam et al. 2023, (111) Ramos Platt et al. 2022. (138)

Clinical question: When should treatment(s) be started for a presymptomatic child with SMA?

Literature review ([Systematic review 12](#))

Evidence Table	
Recommendation	8.2. For newborns with diagnostic confirmation of SMA and 1, 2 or 3 <i>SMN2</i> copies and who are presymptomatic (i.e. clinically silent), a paediatric neurologist should discuss options for immediate SMN augmenting treatments, with the family.
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. • 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 <i>SMN2</i> copies numbers but is especially precipitous in children with 2 <i>SMN2</i> copies. (140) 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. (120) 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 <i>SMN2</i> copies, Australian PBAC notes the magnitude of benefit for children who are presymptomatic and who have 3 <i>SMN2</i> 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 <i>SMN2</i> copies. (141-143) 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. (141-143)
Support from experts	Excellent. Delphi survey passes consensus 13 respondents, mean 8.54, outlier 0.
References	Swoboda et al,2010. (140) Aragon-Gawinska et al. 2023, (120) The Pharmaceutical Benefits Advisory Committee (141-143)

Clinical question: What treatment(s) should be started for a child with SMA?

Literature review ([Systematic review 12](#))

Evidence Table	
Recommendation	8.3 In the absence of comparative data, single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended, started within paediatric neurology treatment centre.
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

Clinical question: When should treatment(s) be started for a presymptomatic child with SMA who cannot access treatments?

Literature review ([Systematic review 12](#))

Evidence Table	
Recommendation	8.4. Newborns with diagnostic confirmation of SMA who are unable to access approved and reimbursed treatments or chose not to be treated immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter.
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. (125) 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. 1 st round Delphi 13 respondents, mean 8.23, outlier 0.
References	Glascocock et al. 2018. (125)

Clinical question: 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?

Literature review ([Systematic review 14](#))

Evidence Table	
Recommendation	8.5. Families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to clinical genetics services).
Rationale	- Genetic complexity of SMN region means that genetic counselling is essential within an NBS program (134, 135) Rouzier et al.2020, (134). Part of post diagnostic care is access to genetic counselling for families, which is valued by parents. (9, 11, 135) Part of post diagnostic care is access to genetic counselling for families, which is valued by parents. (9, 11) - 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. (88) 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. (136) - 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, (134) Kay et al. 2020, (88) Zettler et al. 2022, (136) D'Amico et al. 2011, (135) Kay et al. 2020, (88)

Evidence summaries of individual studies

Consensus-based recommendations

Clinical question: Should *SMN2* copy number be part of newborn screening for SMA?

Encompassing recommendation 2.1.

Author, year	Level of Evidence	Study description	Second tier (<i>SMN2</i>) screening	Comments/Appraisal
Boemer et al. 2021 (55)	IV	Prospective cohort study	<i>SMN2</i> 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.
Boemer et al. 2019 (58)	IV	Prospective cohort study	<i>SMN2</i> assay not conducted as part of NBS	Small population size to validate test method, leading to potential for selection bias. Assumption that <i>SMN2</i> copy number does not affect assay.
Tesorero et al. 2023 (59)	IV	Prospective cohort study	<i>SMN2</i> copy number not conducted as part of screening in this multiplexed assay.	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(60)	IV	Case-control	<i>SMN2</i> copy number not conducted as part of screening	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(61)	IV	Prospective cohort	<i>SMN2</i> copy number not conducted as part of screening	No description given of how program was implemented or details on first and second tier screening methods/processes.
Wallace et al 2023(62)	IV	Prospective cohort	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(63)	IV	Prospective cohort	<i>SMN2</i> copy number determined during diagnostic phase.	Narrative summary of processes. Risk of bias reduced due to consecutive sampling methods used within a screening program.
Kerhohan et al. 2021 (65)	NA	Protocol or consensus	Second tier on DBS (for those with first tier exon 7 deletion) includes:	No results available due to the study design.

			1. MLPA for <i>SMN1</i> & <i>SMN2</i> 2. Screen positivity classified as <i>SMN1</i> absence and ≤ 4 <i>SMN2</i>	
Kumar et al. 2021 (68)	IV	Prospective cohort study	Modification of DNA sequencing assay used to identify <i>SMN2</i> copy number on DBS. Tested against nine known patients with SMA and this assay matched their <i>SMN2</i> diagnostic copy number results in 6 cases.	Methodology ineffective for more than 4 <i>SMN2</i> copies, and only approximate in nature rather than an absolute ratio (e.g. 3.25 rather than 3)
Tavares et al. 2021 (70)	IV	Prospective cohort	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 processes uncertain.
Sonehara et al. 2023(71)	IV	Prospective cohort study	Infants diagnosed through clinical symptoms retroactively compared with NBS identification using real-time qPCR assay with hybridization probes for <i>SMN1</i> detection, diagnostically confirmed with MLPA	Small sample size and short study duration. No data on possible false negatives. 14 of 17 cases were false positive: Heparinised blood used to prepare samples, suggested to account for significant numbers of false positives. Authors document a fall in false positives once removing the use of heparinised blood.
Kraszewski et al. 2018(72)	IV	Prospective cohort study	Second tier screening not part of the study and <i>SMN2</i> 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(73)	IV	Case control		Pre amplification may be inappropriate for determination of <i>SMN1</i> copy number or <i>SMN2</i> copy number, as primary purpose of SMA screening is to determine presence or absence of <i>SMN1</i> . Confounders not included were storage conditions, and DBS sampling techniques.
Gailite et al. 2022 (74)	IV	Prospective cohort study	Second tier screening not part of the study and <i>SMN2</i> 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 (75)	IV	Prospective cohort study	Second tier screening not part of the study and <i>SMN2</i> 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 (76)	IV	Prospective cohort study	23405 newborns screened. <i>SMN2</i> not done as part of NBS but as part of confirmatory blood tests.	<i>SMN2</i> copy number confirmed by diagnostic testing on 7-12 days of life of the newborn.
Kucera et al. 2021 (77)	IV	Prospective cohort study	Second tier screening not part of the study and <i>SMN2</i> 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.

Vill et al. 2019 (83)	IV	Prospective Cohort study	<i>SMN2</i> not done.	Selection bias minimised by consecutive sampling of the population and a large population size.
Vill et al. 2021 (84)	IV	Prospective cohort study	Confirmation of homozygous deletion of exon 7 of the <i>SMN1</i> gene and determination of <i>SMN2</i> 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.
Kariyawasam et al. 2020 (11)	IV	Prospective Cohort study	Second tier is ddPCR for <i>SMN2</i> . Screen positivity is <i>SMN1</i> deletion and less than four copies of <i>SMN2</i> .	Large population size and consecutive recruitment of newborns to minimise selection bias. Generalisable to the Australian health context.
Noguchi et al. 2022 (86)	IV	Prospective Cohort study	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.
Pyatt et al. 2007 (89)	IV	Case control	<i>SMN2</i> copy number conducted using the same competitive PCR and DNA extraction method as <i>SMN1</i> .	<i>SMN2</i> copy number determined as part of confirmatory blood tests and not part of the NBS program.
Gutierrez-Mateo et al. 2019 (90)	IV	Case control	<i>SMN2</i> copy numbers determined by digital PCR. This set included five SMA carriers and 23 SMA positive samples homozygous for the exon 7 deletion and <i>SMN2</i> copy numbers ranging from one to four copies.	
Kiselev et al, 2024 (92)	IV	Prospective Cohort study	<i>SMN2</i> copy number determined using MLPA analysis.	Aims of this pilot study was primarily <i>SMN1</i> screening process determination and accuracy, alongside carrier screening. MLPA analysis was used to determine <i>SMN2</i> however little detail is given beyond stating all positive

				screening assays had confirmation of SMN2 genotype (4 cases of 36,140 screened).
Lin et al. 2019 (95)	IV	Prospective Cohort study	SMA assay based on mass spectrometry for <i>SMN2</i> .	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 (96)	IV	Prospective Cohort study	No measure of <i>SMN2</i> taken.	The remaining one sample turned out to be from a carrier which the kit did not detect.
Baker et al. 2022 (99)	IV	Prospective Cohort study	ddPCR assay for <i>SMN2</i> copy number assessment.	An independent dried blood spot specimen was collected and tested to confirm the initial screening results for <i>SMN1</i> and <i>SMN2</i> .
Shum et al. 2023 (101)	IV	Prospective Cohort study	<i>SMN2</i> copy number calculation beyond scope of validation study.	NGS may be an alternative tech for NBS programs to consider.
Sawada et al 2022 (102)	IV	Prospective Cohort study	<i>SMN2</i> copy number not part of screening process.	Large population size reduces chance of sampling bias.
Kato et al 2015 (78)	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 <i>SMN1</i> –deletion detection and <i>SMN2</i> presence.	Small sample size as befits a validation study. No blinding, increasing possibility of observer bias. Four samples showing no COP-PCR amplification (false positive) were excluded following further tests indicating degradation of DNA sample
Chien et al. 2017(103)	IV	Prospective Cohort study	ddPCR used to identify <i>SMN2</i> copy number on the original screening DBS, and confirmed using MLPA on recalled whole blood samples.	Only 35-37% of population opt in for screening however consecutive sampling and large sample size may limit selection bias. NBS for SMA which includes <i>SMN2</i> copy number on screening panels facilitates early therapeutic intervention.

McMillan et al. 2020 (104)	IV	Prospective Cohort study	MLPA for <i>SMN1</i> and <i>SMN2</i> from same DBS. Screen positivity defined as <i>SMN1</i> null and <i>SMN2</i> ≤ 4 . Lab analysed inconclusive results (exon 8 null, exon 7 <i>SMN1</i> present) by MLPA weekly (thought to be due to high <i>SMN2</i> copy number).	No results of cohort provided apart from implementation descriptions.
Müller-Felber et al. 2023 (105)	IV	Prospective Cohort study	<i>SMN2</i> methodology/screening assay not documented	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 second tier (<i>SMN2</i> copy number) screening provided.
Lee et al. 2022 (106)	IV	Prospective Cohort study	<i>SMN2</i> copy number second tier testing with qPCR targeting exon 7 in <i>SMN2</i> and ddPCR on confirmatory testing	Large pilot study which reduces selection bias. No false positives or negatives.
Abiusi et al. 2024 (107)	NA	Prospective Cohort study	<i>SMN2</i> 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 <i>SMN2</i> number is recommended. <i>SMN2</i> modifier variants (c.859G>C and c.835-44A>G) should be routinely tested and reported (also in NBS).	Meeting of experts and expert opinion. Non-systematic (narrative) evidence base provided to augment recommendations.
Kernohan et al. 2022 (65)	IV	Prospective Cohort study	Second tier MLPA for <i>SMN1</i> and <i>SMN2</i> copy number. is an important modifier of SMA but is not required for screening testing and may increase	<i>SMN2</i> gene copy number has important guiding value for the subsequent clinical treatment of newborns diagnosed with SMA

			screening costs. Therefore, clinical newborn screening for SMA may not include quantitative detection of <i>SMN2</i> gene copy number. It was recommended that screen-positive infants undergo confirmatory molecular genetic testing and, in the case of children with 2 or 3 copies of <i>SMN2</i>, begin treatment within 16–30 days. Children with four copies of <i>SMN2</i> are closely monitored for symptoms with treatment initiated at the first sign of disease. NBS programs reports only report < 4 <i>SMN2</i>.	
Kemper et al. 2018 (108)	II	Systematic literature review and report	Some states assess <i>SMN2</i> 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.
Prior et al. 2010 (110)	IV	Prospective Cohort study	<i>SMN2</i> copy number completed on diagnostic testing only	

Clinical question: Should the diagnosis of SMA include *SMN2* copy number?

Encompassing recommendation 3.2

Author	Level of evidence	Study description	Findings	Comments/appraisal
Abiusi et al. 2024 (107)	N/A	Consensus statement	<i>SMN2</i> copy number one of key determinants of treatment. <i>SMN2</i> 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 <i>SMN1</i> and <i>SMN2</i> gene dosage. MLPA most commonly used technique. Five genotyping errors noted from 5 laboratories for <i>SMN2</i> and seven laboratories reported eight critical <i>SMN1</i> genotyping errors.	Important to reassess <i>SMN1/SMN2</i> 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 <i>SMN2</i> copies initiating treatment presymptomatically	10 infants with 3 <i>SMN2</i> 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 <i>SMN2</i> copies with lower functional motor performances: 7/15 (46 %) showed some motor delay and 4/15 (26 %) needed respiratory intervention.	<i>SMN2</i> 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 (105)	IV	Prospective Cohort study	Time to confirmation of diagnosis including estimation of <i>SMN2</i> 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.	<i>SMN2</i> copy number important to guide access to treatment.
Strunk et al. 2019 (113)	IV	Prospective Cohort study	Confirmation of <i>SMN1</i> available by day 14 of life (mean 15.6+/- 5.9 days) for 63 screen positive newborns, confirming 43 children with SMA. Independent confirmation of <i>SMN2</i> was done using MLPA. 47 of 422 samples lacked <i>SMN1</i> exon 7, with MLPA matching melt curve analysis in 100% <i>SMN2</i> copy number varied between DBS and diagnostic assay for 3 of 43 true screen positive samples.	<i>SMN2</i> data was not available for 4/47 previously confirmed SMA patients Re-analysis is pending for 2 of the 3 true screen positive samples with varied <i>SMN2</i> copy number

Schorling et al. 2019 (116)	IV	Prospective Cohort study	<i>SMN2</i> 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 <i>SMN2</i> analysis (MLPA) investigated.
Ricci et al. 2023 (147)	IV	Prospective Cohort study	Retrospective study comparing retested <i>SMN2</i> copy number with prior results <i>SMN2</i> 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 (84)	IV	Prospective Cohort study	Diagnostic confirmation performed on new whole blood samples using MLPA <i>SMN2</i> copy number variance in 3/47 neonates confirmed as having SMA through NBS. Occurred with copy number ≥ 3	Small sample size Modernised version of MLPA kit used following the discovery of a misanalysis
Wang et al. 2020 (112)	IV	Prospective Cohort study	Whole blood collection and digital PCR vs HRM analysis used to determine <i>SMN1</i> and <i>SMN2</i> 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 <i>SMN1</i> / <i>SMN2</i> ratio. Digital PCR methodology provides absolute quantification for copy number variation and rare mutation detection.
Boemer et al 2021(55)	IV	Prospective Cohort study	Whole blood collection from recalled screen positive newborn and MLPA performed to confirm <i>SMN1</i> diagnosis. <i>SMN2</i> gene sequenced to look for presence of two intragenic modifier variants - <i>SMN2</i> specific primers used to achieve specificity to <i>SMN2</i> . Process of implementation focuses on rapid turnaround time of all screening and diagnostic processes	HINE scores and clinical symptoms correlated with <i>SMN2</i> copy number. Patients exhibiting developmental delays after treatment were those with lower copy numbers of <i>SMN2</i> , indicating the utility of <i>SMN2</i> as a diagnostic and prognostic tool.
Gailite et al 2022 (74)	IV	Prospective Cohort study	Confirmation of homozygous deletion of exon 7 on <i>SMN1</i> and <i>SMN2</i> copy number confirmed by MLPA and qPCR on whole blood sample from recalled screen positive infants.	Awaiting long term health outcomes, with treatments only initiated 6 months prior to study publication.

D'Silva et al 2022 (10)	IV	Prospective Cohort study	Diagnostic confirmation contingent on corroboration of <i>SMN1</i> deletion in a freshly collected blood sample using assays with different primers to screening assays, Establishing capacity to facilitate <i>SMN2</i> 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 <i>SMN1</i> copy number may be informed by <i>SMN2</i> copy number on screening assay (overtime for 2 <i>SMN2</i> copies or urgent within hours run for 3 <i>SMN2</i> copies)	Significant differences in CMAP corresponding to <i>SMN2</i> copy number, indicating its usefulness in diagnosis and prognosis.
Blasco-Perez et al 2021 (119)	IV	Cohort study	Intragenic <i>SMN2</i> variants may change amount of complete SMN transcripts and full-length SMN protein. Complete sequencing of the <i>SMN2</i> gene based on long-range polymerase chain reaction and next-generation sequencing validated by analyzing samples from 53 SMA patients who lack <i>SMN1</i> . <i>Study was able to</i> characterize paralogous, rare variants, and single-nucleotide polymorphisms of <i>SMN2</i> as well as <i>SMN2-SMN1</i> hybrid genes.	The method identifies partial deletions and can be adapted to determine rare pathogenic variants in patients with at least one <i>SMN1</i> copy
Niri et al 2023(98)	IV	Prospective Cohort study	Blood collected on screen positive newborns and confirmation of diagnosis of <i>SMN1</i> and <i>SMN2</i> copy number with MLPA.	Relatively small number of screen positive cases, all with 3 copies of <i>SMN2</i> . While not inconsistent with literature, further clarification on population composition would be beneficial
Kucera et al.2021 (77)	IV	Prospective Cohort study	ddPCR used to confirm diagnosis and detected a single intact <i>SMN1</i> 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(66)	IV	Narrative review	MPLA considered gold standard for confirmation of exon 7 <i>SMN1</i> deletion, but RFLP may also be considered to expedite results. RFLP cannot identify <i>SMN2</i> copy numbers and MLPA may still be useful here. However, distinguishing between copy numbers may be challenging with MLPA and labs now moving to digital PCR to overcome barriers of imprecision.	Non-systematic review of current literature with up to date references
Sawada et al 2022(102)	IV	Prospective Cohort study	MLPA used to confirm copy numbers of exon 7 and 8 in <i>SMN1</i> and <i>SMN2</i> genes on freshly obtained whole blood samples.	Only one case screen positive.

Kimizu et al. 2023(64)	IV	Prospective Cohort study	MLPA for <i>SMN1</i> for diagnostic testing	
Noguchi et al. 2022(86)	IV	Observational: Prospective Cohort study	Diagnostic tests included MLPA and ddPCR of freshly collected blood. Diagnostic confirmation was consistent on both tests for the two cases. 2 SMA cases of 8336 screened. 1 case (SMA type 1-A) showed respiratory symptoms at birth and diagnosed with MAS, so SMA would have likely been overlooked and the therapeutic window closed if not for screening and diagnostic results.	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.
Chien et al. 2017(103)	IV	Prospective Cohort study	Positive screening results confirmed by ddPCR assay using original DBS and MLPA using whole blood from recalled newborn.	8 of 15 screen positives were excluded as false-positives following ddPCR assay.
Lin et al. 2019(95)	IV	Retrospective study Prospective Cohort study	MassArray validated through double blinded testing of 167 previously genotyped DBS samples with accurate identification of the 1 SMA sample. For NBS, MLPA analysis confirms <i>SMN1</i> and <i>SMN2</i> copy number in two patients identified through a MassARRAY based genotyping screening assay.	Double blinded validation study so reduces observer bias. Efforts made to adequately power their statistical analysis of pilot study results.
Mikhalechuk et al. 2023(76)	IV	Prospective Cohort study	Fresh whole blood sample collected from recalled newborn. Use of RFLP to confirm diagnosis of exon 7 homozygous deletion in <i>SMN1</i> and the MLPA completed for <i>SMN1</i> and <i>SMN2</i> 23,405 neonates screened with MLPA analysis confirming 3 cases of SMA.	Authors allude to human error involved in the handling of samples leading to potential inconsistencies. 219 of 23,405 samples were interpreted as 'ambiguous' because of signals in the temperature range corresponding to exon 7 of the <i>SMN1</i> gene.
Kiselev et al. 2024(92)	IV	Retrospective study	4 screen positives of 36,140 neonates screened.	Pilot study funded by Novartis, with onasemnogene abeparvovec the

		Prospective Cohort study	Diagnostic confirmation: MLPA performed on whole blood samples for <i>SMN1</i> and <i>SMN2</i> (results available within 1-2 days of receipt at diagnostic lab). <i>SMN2</i> copy number important to guide treatment decisions.	treatment offered to screen positive newborns.
Liu et al 2016(93)	IV	Retrospective and Prospective Cohort study	Accuracy of real-time PCR to detect pathogenic deletions in exon 7 <i>SMN1</i> 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(110)	IV	Prospective Cohort study	Four screen positive newborns confirmed to have SMA though competitive PCR analysis and <i>SMN2</i> copies determined in diagnostic pathway. 4 of 40,103 blood spots screened positive.	Authors allude to competitive PCR being used to determine <i>SMN2</i> copy number, however detailed descriptions are not given
Groulx-Boivin et al 2024 (57)	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.	Author makes several inferences about the likely outcome for health districts where time will impact health outcomes, rather than referencing actual data.

Clinical Question: Should there be specific processes to manage false positive, false negative and uncertain (screening) results?

Encompassing consensus recommendation 4.2.

Author, year	Level of evidence	Study description	Findings	Comments/Appraisal
Noguchi et al. 2022 (86)	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 <i>SMN</i> is lower than that of other gene target such as cystic fibrosis transmembrane regulator, suggesting that

				<i>SMN</i> may be difficult to amplify under some conditions, leading to the potential for false negative screening results. PCR product amounts of <i>SMN</i> 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, leading to uncertain or false screening results
Boemer et al. (55)	IV	Prospective cohort	1 false negative from 136,339 screened	False negative explained by Compound heterozygote genotype.
Sonehara et al. 2023 (71)	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 (103)	IV	Cohort	Added ddPCR of <i>SMN1</i> to reduce false positive rate. 8 false positives using only RT-PCR assay. <i>SMN1</i> specific sequences amplified from all false positives. In 2/8 (25%), a nucleotide variant (c.888+102A>C) stopped annealing of the assay primer to the sequence, causing false positive results. 5 patients had gene hybrid events which stopped primers annealing.	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.
D'Silva et al. 2021 (10)	IV	Cohort and implementation study	One false positive case identified after sequencing of <i>SMN1</i> exon 7 showing a single nucleotide variation which changed the way that the NBS <i>SMN1</i> probe annealed to the DNA. Two false negatives secondary to system error and sample not being received by screening lab.	<i>SMN1</i> exon 7 sequencing led to resolution and aetiology of the false positive NBS for SMA result.

Tavares et al. 2021 (70)	IV	Prospective cohort	129 blood samples. One false positive due to low DNA quantity, not interfering with internal control (prospective cohort)	Small participant numbers for both prospective and retrospective cohorts.
Kucera et al. 2021 (77)	IV	Cohort	One false positive result likely caused by an unrelated blood disorder.	Both <i>SMN1</i> and internal control threshold cutoff values were close to the cut-off, indicating lower qPCR efficiency and suggesting that a higher <i>SMN1</i> cut-off might be appropriate to increase the specificity of the assay used in this study.
Hashimoto et al. 2023 (94)	IV	Case report	False negative case described.	MLPA for <i>SMN1</i> and <i>SMN2</i> 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 <i>SMN1</i> exons 1-8 and the heterozygous deletion of <i>SMN2</i> exons 2a-4; or b) the heterozygous deletion of <i>SMN1</i> exons 1-8 and the heterozygous deletion of <i>SMN1</i> exons 2a-4. In the first scenario, one copy of normal <i>SMN1</i> without mutation would be present, while in the latter, compound heterozygous deletions of <i>SMN1</i> 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 (75)	IV	Prospective cohort	301418 newborns screened. 24 of 39 screen positives were false positives Initial pilot year: 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	Screening assay specifically designed to amplify <i>SMN1</i> and not <i>SMN2</i> , to ideally increase specificity for the <i>SMN1</i> gene while avoiding false negatives brought on by <i>SMN2</i> signals. Second tier screening not part of the study and <i>SMN2</i> determined through diagnostic methods. Confirmatory results for 2 false positives not known Uncertain results are not fully understood or explained.
Lakhotia et al. 2022 (67)	IV	Prospective cohort	5 false positives with 4/5 also having false positive SCID screen of unclear aetiology	

Cusco et al. 2020 (122)	N/A	Guideline	In discordant genotype-phenotype situations, recommends retesting for <i>SMN2</i> copy number on different lab/method and/or with new sample for presymptomatic children with 1 or ≥ 4 <i>SMN2</i> copies and also testing for genetic modifiers outside of <i>SMN2</i> in those with 2 and 3 <i>SMN2</i>. In symptomatic discordant situations, recommendations are for retesting <i>SMN2</i> 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 (121)	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 (76)	IV	Prospective cohort	23405 DBS samples with 219 DBS showing equivocal results and resolved with second tier testing. Postulated secondary to 1 <i>SMN1</i> and multiple <i>SMN2</i> copies.	219 of 23,405 samples were interpreted as 'ambiguous' because of signals in the temperature range corresponding to exon 7 of the <i>SMN1</i> gene. Authors state they should be interpreted as false positives since they confirmed the abnormal peak ratios were brought on by multifold prevalence of <i>SMN2</i> copies over <i>SMN1</i> in the relevant samples.
Ricci et al. 2023 (147)	IV	Cohort, retrospective study comparing retested <i>SMN2</i> copy number with prior results	<i>SMN2</i> 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.
Muller-Felber et al. 2023 (105)	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 <i>SMN1</i> copies and 1 uncertain result, resolved through tiers of testing.
Abiusi et al. 2023 (97)	IV	Cohort	15/90885 neonates screened positive. Fresh blood samples collected and a	Test failure due to possible heparin contamination and failed samples require manual DNA extraction- processes rectified.

			separate molecular prognosis conducted for diagnostic purposes. Screening test showed 100% specificity except for one case which the authors described as due to a mosaic deletion of <i>SMN1</i>. While prevalence of this is unknown in the wider literature, it raises the possibility of screening false positives.	Case of mosaic deletion lost to follow-up.
Gailite et al. 2022 (74)	IV	Prospective cohort	Significant number of samples required repeat sampling due to poor DNA quality. Secondary to travel and storage conditions.	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.
Niri et al.2023 (98)	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	Following a travel logistics error, a second sample was collected for one sample. The second sample returned negative, while the initial sample arrived later and was positive. A third collection was negative, and diagnostic tests confirmed carrier for <i>SMN1</i> deletion with 3 copies of <i>SMN2</i> . Authors did not investigate initial lack of <i>SMN1</i> amplification.
Matteson et al. 2022 (109)	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 (68)	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 (69)	IV	Prospective cohort	14 screen positive from 239,844 screened neonates. 1 false positive	False positive thought to be due to poor sample quality after repeat tests showed normal <i>SMN1</i> amplification. 5 years since initial screening implementation means any false negative cases would have more than likely arisen (excluding type 3 or 4 SMA cases).

Oliveira Netto et al.2023 (66)	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 (64)	IV	Prospective cohort	22,951 neonates screened (from 23,799 samples collected) over 8 months. 1.1% of samples have insufficient material to use for screening	Small sample size and testing time (8 months) means little can be deduced about false negative.

Clinical question: How (when, where and who) who should notify families of a screen positive SMA result?

Encompassing recommendations 5.1, 5.2, 5.3

Author and year	Level of Evidence	Study description	Findings	Comments/appraisal
Muller-Felber et al. 2023 (105)	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 (107)	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 (9)	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 (11)	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	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

			clinician and advised (over the telephone) of a screen-positive result for a neuromuscular disorder.	collected data reduces potential for recall bias.
Muller-Felber et al. 2023 (105)	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 neuromuscular centre. To keep the psychological stress on the family as low as possible, a consultation appointment should be made at a qualified neuromuscular 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 (125)	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 (114)	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 (10)	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.	Knowledge to action framework used to facilitate implementation of NBS for SMA.

			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.	
Meyer et al. 2024 (126)	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 (75)	IV	Cohort	301,418 newborns screened. 15 true positives, 24 false positives. 4 patients died and all had 1 or 2 <i>SMN2</i> 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 (104)	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.

Clinical question: Should specific psychological support be given to families of screen positive children? Should specific care or support be provided at the time of screen positive or diagnostic disclosure for families of First nations descent and/or culturally and linguistically diverse families?

Encompassing recommendations 5.3, 7.2

Author	Level of evidence	Description	Findings	Comments/Appraisal
Kolbel et al. 2022 (124)	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 <i>SMN2</i> 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 <i>SMN2</i> 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 (10)	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 (9)	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 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.	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. Healthcare professionals mainly aligned or working within specialist services. Remote and regionally working professionals not included, increasing risk of sampling bias.
Meyer et al. 2024 (126)	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 offering psychological resources to families.

Clinical question: What assessments should be completed in a child that is diagnosed with SMA?

- Should diagnosis of SMA include a clinical exam?
- Should diagnosis of SMA include electrophysiological tests?
- Should diagnosis of SMA include motor assessments?
- Assessments to prepare for treatment
- Other

Encompassing recommendation 6.1.

Author, year	Level of evidence	Study description	Findings	Comments/Appraisal
Pane et al. 2022 (152)	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 (129)	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 (75)	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 (11)	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 (128)	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 (10)	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 <i>SMN2</i> copies, mean tibialis anterior 2.5±1.2mV, range 0.2–4.4; three <i>SMN2</i> copies, mean tibialis anterior 4.3±1.5mV, range 3.2–7.2; $p=0.02$. Serial assessments in 3 presymptomatic infants with two <i>SMN2</i> 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).
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Author	Level of evidence	Study description	Study findings	Comments/appraisal
Finkel et al. 2022 (131)	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.
De Vivo et al. 2019 (7)	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.
Kolb et al. 2017 (153)	IV	Cohort	Cohort study of 26 infants with SMA and 27 controls. Ulnar CMAP in children with symptomatic SMA was $1.4 \text{ mV} \pm 2.2 \text{ mV}$ compared to controls of $5.5 \pm 2 \text{ mV}$. CHOP-INTEND SMA cohort, 21.4 (SD = 9.6, $n = 23$, range = 10–52) significantly lower than the	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.

			control cohort, 50.1 (SD = 10.2, $n = 14$, ranged 32–62, $P < 0.01$).	
Alves et al. 2021 (155)	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 $\leq 1.0\text{mV}$ (normal $\geq 5\text{mV}$).	Large cohort included a proportion of neonates but predominantly outcomes pertaining to infants > 6 weeks of age.
Castalleno et al. 2022 (129)	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 from 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 (75)	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.
Vill et al. 2021 (84)	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	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.

			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.	
Mc Millan et al. 2021 (104)	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.

Clinical question: Should specific information be given to families of screen positive or diagnosed children with SMA?

Encompassing recommendations 7.2, 7.3.

Author	Level of evidence	Study description	Findings	Comments/Appraisal
Kariyawasam et al. 2021 (9)	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 (126)	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.

Clinical question: How should treatment decisions be made in children diagnosed with SMA?

- When should treatment be started for a presymptomatic child with SMA (diagnosed through newborn screening)?
- When should treatment be started for a symptomatic child with SMA (diagnosed through newborn screening)?
- Should a specific treatment be used to treat a child with SMA (diagnosed through newborn screening)?
- How should children without access to immediate treatment be managed?

Encompassing recommendations 8.1, 8.2, 8.3, 8.4, 8.5

Author	Level of evidence	Study description	Findings	Comments/Appraisal
Finkel et al. 2017 (123)	Level II	Randomized, sham-controlled clinical trial with nusinersen as the investigational product (2:1 randomisation)	121 subjects with infantile-onset SMA and 2 <i>SMN2</i> 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 <i>SMN2</i> copy infants, who are within a symptomatic phase predicts future motor outcomes. Outcomes relate to children older than those expected in a screening cohort.
Castellano et al. 2022 (129)	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.

Finkel et al. 2019 (156)	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 (141-143)	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 <i>SMN2</i> . The incremental benefit of presymptomatic treatment for children with 3 <i>SMN2</i> with DMTs, compared to symptomatic treatment remains unaddressed. <i>SMN2</i> copy number variation offers some prognostic value, it was more reliable for infants with ≤ 2 copies of <i>SMN2</i> compared to ≥ 3 copies of <i>SMN2</i> . The PBAC noted that on average patients with 3 copies of <i>SMN2</i> 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 <i>SMN2</i> 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 (7)	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) <i>SMN2</i> 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 <i>SMN2</i> copies and who are presymptomatic at time of treatment have improved survival, reduction in comorbidities and motor attainment.

Day et al. 2021 (157)	Level III	Open-label, single-arm, single-dose, phase 3 trial	22 symptomatic children with 1 or 2 <i>SMN2</i> 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 <i>SMN2</i> (8) and 3 <i>SMN2</i> copies) (5)	Level III	Open label, single arm, phase 3 clinical trial	30 presymptomatic newborns with 2 or 3 <i>SMN2</i> copies, treated with onasemnogene aberparvovec. 14 children with 2 <i>SMN2</i> 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 (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 <i>SMN2</i> 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 <i>SMN2</i> 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 (≥ 3 rd WHO percentile) without feeding support through 24 months; and none required nutritional or respiratory support.	Newborns diagnosed with SMA with 2 or 3 <i>SMN2</i> copies and who are presymptomatic at time of treatment have improved survival, reduction in comorbidities and motor attainment. 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 (139)	N/A	Narrative summary and expert opinion	Paucity of data for treatment of newborns with 1 <i>SMN2</i> 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 <i>SMN2</i> copy.

Aragon-Gawinska et al. 2023 (120)	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 <i>SMN2</i> copies. For those treated < 42 days of age (28/38) all but one had normal motor development. Three patients had 1 <i>SMN2</i> 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 (144)	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 <i>SMN2</i> copy number. 4. To inform parents of goals of treatment based on clinical context and need for long term multidisciplinary care.	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.
Kernohan et al. 2022 (65)	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 (158)	IV	Case series	Describes two infants with different <i>SMN2</i> copies and outcomes with early and later treatment. Notes normal motor attainment for 3 <i>SMN2</i> 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 (129)	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	Rigorous Delphi methodology using expertise from a wide range of specialist only professionals. Patients advocated and non-specialists not part of

			(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. - Therapeutic decision-making is recommended in multidisciplinary teams. - 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). - It is recommended to agree on therapeutic decisions with patients and/or parents/guardians and obtain their informed consent. - Also described factors important in therapeutic goal setting.	process, which may reduce translation of recommendations nationally.
Vill et al. 2021 (84)	IV	Cohort	8/15 children with 2 <i>SMN2</i> copies who were treated presymptotically remain presymptomatic and making normal developmental progress, however symptomatic infants had slower 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 <i>SMN2</i> copies died within one year of diagnosis. 4 infants with 3 <i>SMN2</i> copies who were untreated all had motor deterioration.	The extent of motor deterioration not defined in this study.
Glascocock et al. 2018 (125)	N/A	Consensus	For all newborns confirmed with SMA through NBS and with 2 and 3 <i>SMN2</i> copies, treatment should be immediately planned. For newborns with 1 <i>SMN2</i> 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 (111)	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 (159)	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. 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.	60% response rate may increase sampling bias. 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 (138)	N/A	Expert evidence	Recommendations included:	Small panel (< 5 members).

			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.	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 (160)	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 <i>SMN2</i> 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 (161)	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 (162)	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	No outcomes defined in this protocol for the SMARTCare registry. Multicentre cohort (registry) study.

			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.	
D'Silva et al. 2022 (10)	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 <i>SMN2</i> copies, mean tibialis anterior 2.5±1.2mV, range 0.2–4.4; three <i>SMN2</i> copies, mean tibialis anterior 4.3±1.5mV, range 3.2–7.2; $p=0.02$. Serial assessments in 3 presymptomatic infants with two <i>SMN2</i> 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).
Weng et al. 2021 (137)	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 <i>SMN2</i> copies (1.39 ± 0.79 mV) vs 3 <i>SMN2</i> copies (3.70 ± 0.59 mV). CMAP amplitude decreased rapidly in all SMA1 infants, with those with 3 <i>SMN2</i> 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 <i>SMN2</i> 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	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.

			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 <i>SMN2</i> 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.	
Gaviglio et al. 2023 (133)	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 (104)	N/A	Consensus	For newborn with 2 or 3 <i>SMN2</i> 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. For children with 4 <i>SMN2</i> 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 documentation on the number, designation, affiliation, or experience of experts used for panel. No explanation of evidence reviewed by panel to come to recommendations.
Kolbel et al. 2022 (124)	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 <i>SMN2</i> copy numbers and a milder phenotype, which may confound findings.
Carey et al. 2022 (145)	IV	Cohort	Discrete choice experiment of 1113 parents of children with SMA, healthcare professionals and general population.	Large respondent pool.

			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.	Did not capture parents of children going through NBS for SMA.
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Systematic observation form results

Systematic observation form tables

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

<i>Reporting carrier status in NBS for SMA</i>		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 <i>SMN1</i> 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%)

Table 2. 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 <i>SMN2</i>	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%)

Table 3. 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 <i>SMN1</i> 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%)

Table 4. 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.

<i>Referring screen positive newborns to clinical services after a screen positive result</i>		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%)

Table 5. The process to manage newborns with false positive screening results.

<i>Process to manage newborns with false positive screening results</i>		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%)

Table 6. The process to manage newborns with false negative screening results.

<i>Process to manage newborns with false negative screening results</i>		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%)

Table 7. The process to resolve discordant *SMNI* results.

<i>Resolving discordant SMNI (screening and diagnostic) results</i>		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 <i>SMN1</i>	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 <i>SMN1</i> 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%)

Table 8. The process to resolve discordant *SMN2* results.

<i>Resolving discordant SMN2 (screening and diagnostic) results</i>		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 <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN1</i> 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%)

Table 9. Communicating a screen positive result to families

<i>Communicating a screen positive result to families.</i>		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%)

Table 10: Conducting the first clinical review

<i>Conducting the first clinical review (for diagnostic evaluation) after a screen positive result disclosure</i>		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%)

Table 11. The assessments undertaken at first clinical review of a screen positive newborn/infant.

<i>Assessments undertaken at the first clinical review (for diagnostic evaluation) after a screen positive result disclosure.</i>		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 <i>SMN1</i> 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 <i>SMN2</i> copy number on whole blood EDTA OR repeat dried blood spot for <i>SMN2</i> 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%)

Table 12. Communication of a diagnostic result by a paediatric neurologist to families of newborns who are screen positive for SMA.

<i>Communicating a diagnostic result to families of newborns who are screen positive for SMA</i>		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%)

Table 13. Provision of information to families receiving a diagnostic SMA result

<i>Information provision to families receiving a diagnostic result of SMA</i>		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, Māori 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)								
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Table 14. Conducting a clinical review after a diagnosis of SMA

<i>Conducting a clinical review after a diagnosis of SMA</i>		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%)
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Healthcare Practitioner Survey (modified Delphi Process) results

Table 14. 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. Rows shaded in green meet consensus, yellow (near consensus and may be modified and entered into second Delphi round and red do not meet consensus.

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 <i>SMN1</i> 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 $\geq 95\%$ for the detection of homozygous deletion of exon 7 of the <i>SMN1</i> 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 <i>SMN1</i> , 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 <i>SMN1</i> 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 <i>SMN1</i> screening result is available (independent of the availability of <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN2</i> copy number should be completed on suitably validated quantitative <i>SMN2</i> assays.	21	8.62	0.81	0.35	0	Meets consensus
2.3. <i>SMN2</i> 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 Aotearoa New Zealand NBS for SMA program is homozygous deletion of exon 7 on dried blood spot (and where <i>SMN2</i> copy number is conducted as a second-tier assay) an <i>SMN2</i> copy number ≤ 4 .	21	7.00	1.67	0.73	0	Meets consensus
2.6. The (in)availability of <i>SMN2</i> copy number should not delay clinical notification of a screen positive result based on absence of <i>SMN1</i> on first tier screening.	21	8.14	1.20	0.52	1	Meets consensus
2.7. If second tier screening for <i>SMN2</i> is not incorporated into the newborn screening process, (diagnostic) testing for <i>SMN2</i> 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 <i>SMN2</i> copy number (including <i>SMN2</i> splicing modifier variants and modifiers outside of the <i>SMN2</i> 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 <i>SMN2</i> copies (avoiding formulas like <i>SMN2</i> ≥ 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 <i>SMN1</i> , which should occur from whole blood samples from the recalled newborn.	12	8.83	0.58	0.33	0	Meets consensus

Validated <i>SMN1</i> assays should be used for diagnostic testing and conducted in expert reference centres.						
3.2. Diagnostic testing should also include <i>SMN2</i> copy number as a guide to clinical severity and to facilitate therapeutic decision making. Diagnostic testing for <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN1</i> 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 <i>SMN2</i> copy number will not routinely be tested.	12	7.67	1.30	0.75	1	Meets consensus
3.8. Diagnostic test results (including <i>SMN1</i> and <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN1</i> results between screening and diagnostic assays, retesting for <i>SMN1</i> with another method/laboratory is recommended. A repeat sample from the newborn may be required for further diagnostic testing if resolution of <i>SMN1</i> 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 <i>SMN1</i> gene dosage.	25	7.40	1.73	0.69	5	No consensus
4.5. If there is a difference in <i>SMN2</i> results between screening and diagnostic assays, retesting for <i>SMN2</i> copy number with another method/laboratory is recommended. A repeat sample from the newborn may be required for further diagnostic testing if resolution of <i>SMN2</i> 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 <i>SMN2</i> copy number.	26	7.23	1.63	0.64	5	No consensus

4.7. Identification and retesting of <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN1</i> (diagnostic) confirmation is received, regardless of the (availability of) <i>SMN2</i> 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. presymptomatic 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). (27, 28)	13	8.69	0.75	0.42	0	Meets consensus
11.1. For newborns with ≥ 4 <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN2</i> copy number in a different laboratory or using a different method, may be considered in all newborns with 4 <i>SMN2</i> copies due to methodological imprecision arising from <i>SMN2</i> 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 <i>SMN2</i> 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 <i>SMN2</i> 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

Table 15. 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. <i>SMN2</i> copy number should be performed expeditiously, ideally as part of newborn screening but not delay notification of absence of exon 7 on <i>SMN1</i> , 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 <i>SMN2</i> copy number (including <i>SMN2</i> splicing modifier variants and modifiers outside of the <i>SMN2</i> 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 2 Parents of newborns with false positive results should be given the option of returning to discuss the implications with members of the neurology/neuromuscular multidisciplinary team* *Multidisciplinary team members may vary dependent on health jurisdiction and include but are not limited to paediatric neurologists, genetic counsellors, geneticists, social worker, psychologist, allied therapists, specialist nurses.	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 non diseased subjects or between two or more clinical states.

Diagnostic test

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

Digital polymerase chain reaction

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

Discrepant result (also discordant result)

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

Dried blood spot

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

Ethylene diamine tetraacetic acid (EDTA)

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

Exon

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

False-negative screening result

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

False-positive screening result

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

First-tier screen

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

Follow-up

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

Gene

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

Gene sequencing

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

Genetic counselling

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

Genetic variant

a DNA sequence that varies from a reference DNA sequence.

Genotype

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

Genotype phenotype correlation

the association between the presence of a certain mutation or mutations (genotype) and the resulting pattern of abnormalities (phenotype).

Gestational age

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

Gold standard

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

Homozygous deletion

the deletion of two alleles at corresponding loci on homologous chromosomes identical for one or more loci.

A homozygous mutation is the presence of the identical mutation on both alleles of a specific gene. However, when both alleles of a gene harbour mutations, but the mutations are different, these mutations are called compound heterozygous. This is important, for example, in recessive diseases in which each allele carries a different mutation, one from each parent.

Intervention

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

Jurisdiction

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

Multiplex

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

Multiplex assay

the simultaneous quantitative or qualitative analysis of multiple analytes.

Newborn dried blood spot screening

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

Newborn screening program

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

Next-generation sequencing

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

Phenotype

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

Polymerase chain reaction

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

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

Protocol

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

Quality-adjusted life years

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

Quantitative

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

Repeat screening (requested)

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

Repeat screening (routine)

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

Retest

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

Screening

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

Screen inconclusive

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

Screen negative

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

Screen positive

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

Second-tier screen

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

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

Appendix B. 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
Ministry of Health – Manatū Hauora	Administrative officers
The National Aboriginal Community Control Health Organisation	CEO
Queensland Aboriginal and Islander Health Council	CEO

Appendix C. 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

Appendix D. List of priority questions to be included in the systematic literature search

Topic	Question
Screening	What biological sample should be used for SMA newborn screening?
Screening	What should the target analyte be in newborn screening for SMA?
Screening	Should the screening assay have a minimum sensitivity and specificity? What should this be?
Screening	Should <i>SMN2</i> copy number be part of newborn screening for SMA?
Screening	How (when, where and who) should notify clinical services of a screen positive result?
Screening	How (when, where and who) who should notify families of a screen positive SMA result?
Screening	Should there be specific processes to manage false positive results?
Screening	Should there be specific processes to manage false negative or uncertain results?
Diagnosis	How should a screen positive child be diagnosed with SMA?
Diagnosis	Should diagnosis of SMA include <i>SMN2</i> copy number?
Diagnosis	What assessments should be completed in a child that is diagnosed with SMA? • Should diagnosis of SMA include a clinical exam? • Should diagnosis of SMA include electrophysiological tests? • Should diagnosis of SMA include motor assessments? • Assessments to prepare for treatment • Other
Clinical	How should a screen positive infant be managed within clinical services? • When should the screening result be available to clinical services? • When should the diagnostic result be available to clinical services? • When should a screen positive newborn be first reviewed by clinical services (after screen positive result disclosure)? • Who should conduct the review of the screen positive newborn? • Where should screen positive newborns be reviewed?
Clinical	How should treatment decisions be made in children diagnosed with SMA? • When should treatment be started for a presymptomatic child with SMA (diagnosed through newborn screening)?

	• When should treatment be started for a symptomatic child with SMA (diagnosed through newborn screening)? • Should a specific treatment be used to treat a child with SMA (diagnosed through newborn screening)? • How should children without access to immediate treatment be managed?
Clinical	Should families of children diagnosed with SMA through newborn screening be referred for genetic counselling?
Care and support	Should specific care or support be provided at the time of screen positive or diagnostic disclosure for families of First nations descent and/or culturally and linguistically diverse families?
Care and support	Should specific information be given to families of screen positive or diagnosed children with SMA?
Care and support	Should specific psychological support be given to families of screen positive children?
OBJ	

Appendix E: Assessment tool for cohort and case control studies

Newcastle-Ottawa Quality Assessment tool for cohort studies and case control studies (164).

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1. Is the Case Definition Adequate?
 - a. Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) ☆
 - b. Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record
 - c. No description
2. Representativeness of the Cases
 - a. All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample) ☆
 - b. Not satisfying requirements in part (a), or not stated.
3. Selection of Controls
 - a. This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.
 - b. Community controls (i.e. same community as cases and would be cases if had outcome) ☆
 - c. Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
 - d. No description
4. Definition of Controls
 - a. If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. ☆
 - b. No mention of history of outcome

COMPARABILITY

1. Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = ☆ , Other controlled factors = ☆

EXPOSURE

1. Ascertainment of Exposure

Allocation of stars as per rating sheet

2. Non-Response Rate

Allocation of stars as per rating sheet

CODING MANUAL FOR COHORT STUDIES

SELECTION

1. Representativeness of the Exposed Cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users.

While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen).

Allocation of stars as per rating sheet

2. Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3. Ascertainment of Exposure

Allocation of stars as per rating sheet

4. Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1. Comparability of Cohorts on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = ☆, Other controlled factors = ☆

OUTCOME

1. Assessment of Outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

- a. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.) ☆
- b. record linkage (e.g. identified through ICD codes on database records) ☆
- c. Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)

d. No description.

2. Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3. Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

Appendix F: Components of first survey in modified Delphi

Screening	
1. What is the analytical and clinical validity of newborn screening approaches for spinal muscular atrophy	
1.	Newborn screening for SMA should be performed on the routine newborn dried blood spot (DBS), taken from the heel of the newborn as recommended by the NBS National Policy Framework. EBR
2.	If blood transfusion is considered, the DBS should be taken prior to, and 3 months after, transfusion of blood products as per standard protocol. EBR
3.	Newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants should proceed using the same protocols as for term newborns. EBR
4.	Newborn screening for SMA should be performed on the routine newborn dried blood spot (DBS), taken from the heel of the newborn as recommended by the NBS National Policy Framework. EBR
5.	Newborn screening for SMA should be performed on the routine newborn dried blood spot (DBS), taken from the heel of the newborn as recommended by the NBS National Policy Framework. EBR
6.	If blood transfusion is considered, the DBS should be taken prior to, and 3 months after, transfusion of blood products as per standard protocol. EBR
7.	Newborn screening for SMA in infants < 37 weeks gestational age i.e. preterm infants should proceed using the same protocols as for term newborns. EBR
8.	The target analyte of NBS for SMA is homozygous deletion of exon 7 of the <i>SMN1</i> gene
9.	The screening method selected by the screening institution should have a sensitivity of $\geq 99\%$ for the detection of homozygous deletion of exon 7 of the <i>SMN1</i> gene. EBR
10.	The first-tier screening test for SMA should determine the absence of exon 7 of <i>SMN1</i> , using suitably validated quantitative assays. EBR
11.	First-tier screen positive samples (0 <i>SMN1</i> copies) should immediately be repeated on the same dried blood spot. Consensus
12.	NBS reports detailing carrier status (1 <i>SMN1</i> copy) will not be issued by Australian and New Zealand NBS for SMA programs. Consensus
2. Are there any screening methods that can inform or predict the age of onset or clinical severity of SMA. What is the analytical and clinical validity and clinical utility of incorporating these methods (if any) as second tier testing in newborn screening approaches for spinal muscular atrophy	

1. Ideally, second tier screening with identification of <i>SMN2</i> copy number is performed on the first dried blood spot (as a guide to expected clinical severity). EBR
2. <i>SMN2</i> copy number should be completed on suitably validated quantitative <i>SMN2</i> assays. EBR
3. If <i>SMN2</i> quantification is included as a second-tier screening test, the upper limit for a positive screen and referral is ≤ 4 <i>SMN2</i> copies. EBR
3.What is the analytical and clinical validity of incorporating third tier testing (SMN1 sequencing) for newborn screening approaches for spinal muscular atrophy
4. For families what type of information and support is beneficial prior to undertaking NBS for SMA
1. The state NBS program should update educational resources provided to parents/caregivers considering participating in NBS to include spinal muscular atrophy (SMA) as a condition. CBR
2. Educational resources aimed at providing information and support to parents/caregivers at the time of screen positive notification should be developed by: • The newborn screening program. • Clinical (healthcare) services. • Patient advocacy groups. • Co-developed by national stakeholders within screening, diagnostic, clinical and consumer domains. • Do not agree with statement. CBR
3. Consultation with culturally and linguistically diverse (CALD) community representatives who have appropriate knowledge and skills should occur in the development, implementation and review of any educational materials developed on NBS for SMA. Appropriate CALD representation should be sought on an ongoing basis to ensure relevant consultation and appropriate support is provided. CBR
4. Consultation with Indigenous community representatives and the local Indigenous medical service should occur in the development, implementation and review of any educational materials developed for NBS for SMA. Appropriate First nations representation should be sought on an ongoing basis to ensure relevant consultation and appropriate support is provided. CBR
5. If language or culture is a barrier to accessing or understanding NBS for SMA healthcare professionals should provide families with: • information in the preferred language and in an accessible format • professional interpreters CBR or EBR (look at National Policy)

Diagnostic

5. What methods are available to confirm the diagnosis of SMA after a screen positive result is received.
1. Diagnostic tests include confirmation of homozygous deletion of exon 7 on <i>SMN1</i> from whole blood sampling obtained from the recalled newborn EBR
2. It is preferable that quantitative analysis techniques for diagnostic tests for <i>SMN1</i> are different in methodology or assay to the (newborn) screening test. CR
3. To enable timely treatment, <i>SMN1</i> diagnostic results should be available within 7-10 days of receipt of the sample by the diagnostic laboratory. CR or PP
6. What diagnostic methods are available to predict or inform the age of onset or clinical severity of SMA
1. Diagnostic tests include confirmation of <i>SMN2</i> copy number as a guide to clinical severity from whole blood sampling or on a repeat dried blood spot obtained from the recalled newborn EBR
2. For the purposes of NBS for SMA programs, genetic modifiers of phenotype outside <i>SMN2</i> copy number will not be analysed CBR
3. The cycle from birth to completion of all diagnostic testing (including <i>SMN2</i> copy number) should be within 30 days of birth. CBR or PP
7. If there are differences in screening and diagnostic test results for a newborn identified as screen positive for SMA through newborn screening programs, how should these be resolved.
1. One tube of whole blood (EDTA, 3 ml) or a repeat DBS will be collected from the screen positive infant and sent to the Newborn Screening Service for quality assurance purposes and rapid resolution of any discordant results (i.e., between the original screening results, diagnostic lab results, and second sample results at the Newborn Screening Service). CBR or PP
2. Where discrepancies arise between <i>SMN2</i> copy number on screening and diagnostic results, <i>SMN2</i> copy number should be retested with another method/laboratory. PP
3. Digital droplet PCR is the gold standard for resolving discrepancies (if and when they arise) between <i>SMN2</i> copy number on screening and diagnostic testing. EBR
4. <i>SMN1</i> DNA sequencing methodologies can be useful for resolving discrepancies (if and when they arise) between <i>SMN1</i> on screening and diagnostic testing EBR

<u>Clinical</u>
8. How should a screen positive result for SMA be communicated to families
1. Clinicians should develop a coordinated local system so that an NBS screen positive result can be flagged by the Newborn Screening services to the responsible clinician as designated on the dried blood spot card AND a healthcare professional within a manned clinical neurology service (including on public holidays and leave days). CBR

2. A screen positive result should be communicated verbally to the family through a Telehealth consult or by telephone. CBR
3. A screen positive result should be ideally disclosed to the family within (time after screen positive result is available to the designated medical practitioner). CBR • ≤ 2 working days • ≤ 5 working days • ≤ 7 working days • 7 working days • Do not agree with this statement.
4. The screen positive result should ideally be disclosed to the family by a child neurologist CBR
5. 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.
6. Screen positive disclosure should occur when the <i>SMN1</i> screening result is available (independent of the availability of <i>SMN2</i> copy number on the screening test) CBR
7. The medical practitioner should be honest and respectful and use an individualised approach when communicating the screen positive result to the family.
8. 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 must be used. EBR (low)
9. Medical practitioners disclosing screen positive results for SMA to families from Indigenous or Torres Strait Islander backgrounds should be aware of particular 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. CBR or PP
10. Key points in the (screen positive disclosure) call to the family should include: The screen positive status of the newborn Time frame and place for clinical review of the screen positive newborn General information about the availability of treatment options Named health professional as 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
11. Screen positive newborns should ideally be offered a clinical review within tertiary neurology/neuromuscular services CBR or PP

12. A clinical review within local paediatric services, with clinical support from paediatric neurologists should be offered to screen positive newborns where access to tertiary services is limited and may cause delay in diagnostic evaluation CBR or PP
13. From time of disclosure, ideally a screen positive newborn should be reviewed at a clinical service for diagnostic evaluation within the following (working) days. CBR or PP • ≤ 2 days • ≤ 5 days • ≤ 7 days • > 7 days • Do not agree with this statement.
14. 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) EBR • Change in movement, feeding, or breathing pattern • Change in voice/weak cry • Increased fatigue without increased activity • Trouble feeding in young children or infants • Decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability • Abdominal breathing • Failure to thrive
9. What assessments are required as part of the diagnostic evaluation of a newborn who has screened positive for SMA through the newborn screening program. EBR and PP
• a neurological examination • neonatal examination including review of cardiac, respiratory and gastrointestinal systems • clinical feeding assessment including recording of growth parameters • functional (motor) assessment including SMA validated scores (i.e., CHOP-INTEND) and Hammersmith Infant Neurological Scale examination by a trained allied health therapist or clinician trained in administering these scales. • neurophysiological assessment including nerve conduction studies +/- EMG. • venous sampling for diagnostic bloods with <i>SMN1</i> on whole blood EDTA. • venous sampling for diagnostic bloods with <i>SMN2</i> copy number on whole blood EDTA sample or repeat dried blood spot. • Bloods for FBC, EUC, LFTs, Calcium, Coagulation

• 1-2ml of blood should be collected in a specialist red top container (available from the testing laboratory) for testing of AAV-9 titres to determine suitability of gene therapy treatment.
10. What information and educational materials should the family receive (if any) at diagnostic evaluation of the screen positive newborn with SMA (all CBR or PP)
• Information of the implications of the screen positive result • Information on how the diagnosis will be confirmed • Information on SMA including the clinical implications of condition progression in untreated forms • Information on psychosocial supports • Information on the genetics of SMA including the role of SMN2 copy number as a guide to severity • Potential for treatment options
11. How can health care services support families as their newborns undergo the diagnostic evaluation for SMA
4. Medical practitioners should be aware that people all families including those where caregivers have a history of depression and/or self-harm may be at risk of mental health issues following a screen positive result of SMA for their newborn. For families the following should be provided • Information on psychosocial supports including referral to social work services • Information on SMA Advocacy services • Information on peer-support groups
5. Medical practitioners undertaking diagnostic evaluation of newborns from culturally and linguistically diverse backgrounds should be aware of particular issues arising from diagnostic genetic testing. If the medical practitioner is not bilingual, a professional interpreter must be used. EBR (low)
6. Medical practitioners undertaking diagnostic evaluation of newborns families of Indigenous or Torres Strait Islander backgrounds should be aware of particular issues arising from diagnostic genetic testing. 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 diagnostic evaluation . CBR or PP
7. Clinical services should consider the development of educational materials that inform families on the above points.
12. For newborns diagnosed with SMA, what follow-up protocols modify health outcomes and quality of life for the newborn/infant and their families CBR and PP
1. Disclosure of a diagnosis should occur when <i>SMN1</i> diagnostic confirmation is received, regardless of (availability of) <i>SMN2</i> copy number.

2. Diagnostic results should be <i>ideally</i> disclosed by a paediatric neurologist
3. If circumstances dictate, it is acceptable for a responsible medical practitioner with support from a paediatric neurologist to disclose a diagnostic result to a family.
4. If circumstances dictate, it is acceptable for the diagnostic disclosure to occur through telephone or Telehealth
5. All newborns diagnostically confirmed with SMA should be reviewed by a paediatric neurologist
6. All newborns diagnostically confirmed with SMA should be managed within a multidisciplinary neurological or neuromuscular service
7. All newborns should have the following components completed at the first clinical review after diagnostic confirmation of SMA: • Neurological examination • Neonatal examination including assessment of cardiac, respiratory, growth and gastrointestinal systems • Assessment of respiratory function • Assessment of feeding status
8. All newborns should undergo the following within a reasonable time of diagnostic confirmation • functional (motor) assessment including SMA validated scores (i.e., CHOP-INTEND) and Hammersmith Infant Neurological Scale examination by a trained allied health therapist or clinician trained in administering these scales. • neurophysiological assessment include nerve conduction studies +/- EMG if this has not been completed previously
9. All children diagnosed with SMA through newborn screening should be managed in a multidisciplinary care setting.
10. All children diagnosed with SMA through newborn screening should have shared model of care between local community, paediatric services and specialist paediatric neurology services.
11. Families should be offered a review by a genetics counsellor/clinical geneticist regarding carrier status for <i>SMN1</i> .
12. Siblings of the affected child should be invited to be reviewed for signs and symptoms of SMA.
13. For siblings of affected children, who live in remote regions, a review for signs and symptoms may be offered and conducted by a local medical practitioner.
13. 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. For these treatments, are there any risks that need to be managed. EBR

1. For newborns with SMA who are already demonstrating symptoms consistent with disease onset, regardless of <i>SMN2</i> copy number, options for disease modifying treatments should be discussed immediately with the family.
2. For newborns with diagnostic confirmation of SMA with 2 or 3 <i>SMN2</i> copy numbers and who are presymptomatic, options for disease modifying treatments should be discussed with the family.
3. For all disease modifying treatments, the potential benefits, risks, uncertainties, need for long term surveillance should be explained to families.
4. Educational materials for families should be developed by healthcare services to help with information sharing on disease modifying treatments
5. Therapeutic care planning should be done in partnership with families and should take into consideration disease status, genotype, and individualised factors including social and family circumstances, goals of care and preferences.
6. In the absence of additional evidence for best treatment pathways, the priority is initiation of disease modifying treatment without delay.
7. Where appropriate, disease modifying therapy may be planned to be delivered from a non-tertiary care centre with specialist (neuromuscular) support for risdiplam and nusinersen.
8. For newborns with diagnostic confirmation of SMA and ≥ 4 <i>SMN2</i> copy numbers and without symptoms of disease, management options for 3-6 monthly clinical surveillance for the first two years of age and every 6-12 months thereafter, should be provided to the family.
9. Neurophysiological assessment including nerve conduction studies +/- EMG may be a useful assessment for newborns/infants with diagnostic confirmation of SMA and ≥ 4 <i>SMN2</i> copies, to define disease onset, to trigger therapeutic intervention.
14. What protocols are available to manage newborns with false positive and false negative SMA screening results CBR
1. For newborns with a false positive screening result (diagnostically not confirmed to have SMA) - the reasons for this should be explored with screening and diagnostic (including clinical genetic) services and explained to parents. - Parents should be supported by the multidisciplinary team. - Parents should be given the option of returning to the neurology services for further discussions on the implications of a false positive result - 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

2. A case review should be conducted for any child who present with signs and symptoms of SMA but were not detected by newborn screening.
15. 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 directed care, multidisciplinary assessment and care management. CBR
1. Screening, diagnostic, healthcare services should coordinate and integrate, referral, transitions and communication across all sectors involved in the assessment, treatment, support and care of newborns going through newborn screening for SMA and their families, including jointly agreeing on written policies and procedures.
2. Health system planners should ensure that families of newborns diagnosed with SMA through newborn screening programs should have access to a care coordinator who can work with them from the time of diagnosis.
3. Healthcare services should agree on one provider as the family's main contact, who is responsible for coordinating care for the newborn across services at whatever intensity is required.
4. Clinical services should develop a protocol for collecting and transporting AAV-9 titres in anticipation of instigating gene therapy treatment in jurisdictions where gene therapy is available.

Appendix G: Endorsement letter

[REDACTED]



Dear [REDACTED],

We are writing with regard to the National Guideline for Newborn Screening in Spinal Muscular Atrophy (SMA) in Australia and Aotearoa New Zealand, which was developed according to the National Health and Medical Research Council (NHMRC) and its standards for guidelines. While research was carried out primarily through the University of New South Wales, the work done represents the Guideline Development Group comprising a broad range of 37 experts in screening, diagnostics, clinical care, advocacy, and patient representation, across Australia and New Zealand.

We are writing to request formal review and endorsement of the National Guideline by the

[REDACTED] [REDACTED] We attach the full National Guideline and Technical Report. A summary of feedback gathered during the public consultation phase and an infographic family fact sheet can also be found at the following: [NBS for SMA | School of Clinical Medicine - UNSW Sydney](#). These documents are currently under review, and we will contact you if any substantial revisions are made.

About the National Guideline for Newborn Screening in Spinal Muscular Atrophy.

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

The aim of the National Guideline is to outline how health professionals in Australia and New Zealand can provide a child and family focussed approach to newborn screening for SMA. It is intended to span the entire healthcare journey of the newborn, from screening, through to diagnosis and immediate post-diagnosis assessment and care for the newborn and their family. The Guideline was considered essential to give all Australian and Aotearoa New Zealand children with SMA, equitable access to an expedient diagnosis of SMA and best care, based on evidence.

Due to the small (but growing) evidence base, a modified Delphi survey and a systematic gathering of professional opinions was used in conjunction with systematic review of evidence and grading according to the GRADE methodology. The draft Guidelines were put to public consultation between August and September 2024. Feedback was also provided through the NHMRC methodological review process. Several illustrative quotes from the consultation period are listed below.

"As a general comment, the technical and administrative report was very useful, particularly the evidence tables for each section, for each respective recommendation."

This will be a valuable resource for future revisions of the guidelines as the evidence base changes"

"We strongly support the proposal for guidelines to be flexible which aligns with existing guidelines including the National Screening Framework and internationally developed Standards of Care for SMA. This is particularly relevant giving the likely ongoing

advancements in treatment for SMA. We also support the proposed strategies for Guideline evaluation including the need for update of guidelines in a rapidly evolving landscapes, further investigation of barriers and enablers to implementation and acknowledgment of jurisdictional differences in adoption of the guidelines"

" Thank you for such a comprehensive guideline and for thinking so deeply about the experience of patients and families."

Endorsement

We are approaching the Australian College of Rural and Remote Medicine in the hopes that your organisation will provide endorsement by January 17th 2025. We would be grateful if you could reply to this letter to either confirm potential endorsement (after review by your organisation) or clarify alternative processes through which we can seek your endorsement.

Please do not hesitate to contact us if you require any further information. We look forward to hearing from you soon.

With best regards,

Dr Didu Kariyawasam

BA, MA (Cantab), MBBS, MRCPCH, CCST (UK), FRACP, PhD

Paediatric Neurologist

Lecturer UNSW

Medical Lead, Kids Neuro Trials Randwick

School of Clinical Medicine, UNSW Medicine & Health

Randwick Clinical Campus

Discipline of Paediatrics and Child Health

Bright Alliance Building

UNSW SYDNEY

Email: Didu.Kariyawasam@health.nsw.gov.au

Appendix H. Assessment of Guideline by independent reviewers using AGREE II scale

Appraiser:
 Date: 13 January 2025
 Email: m.mandarakas@unsw.edu.au
 URL of this appraisal: <https://www.agreetrust.org/appraisal/113439>
 Guideline URL: <https://www.unsw.to/nbs-sma>
 Dr Melissa Mandarakas

Overall Assessment

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

Overall quality of this guideline: 7/7

Guideline recommended for use? Yes.

Notes:

Kariyawasam, et al present a high quality guideline for newborn screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand. The rigour of development was outstanding. Further, the scope and purpose, stakeholder involvement, clarity of presentation and editorial independence were of high quality. Whilst some minor, additional detail could enhance applicability, I would recommend this guideline for use without modification. Rating summary Domain 1: 100% Domain 2: 94% Domain 3: 98% Domain 4: 100% Domain 5: 71% Domain 6: 100%

Domain Total

1. Scope and Purpose 21
2. Stakeholder Involvement 20
3. Rigour of Development 55
4. Clarity of Presentation 21
5. Applicability 21
6. Editorial Independence 14

1. Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.

Rating: 7

Intent: 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 (Guidelines p.25) Expected outcome: 1. Streamline and standardise these processes across Australasia to ensure efficiency of access to diagnosis, treatment and care for affected children; 2. Optimise access to information, care and support for families going through the healthcare journey with their children; 3. adoption of high-quality care which will improve the health and psychosocial outcomes of affected children and the wellbeing of their

families (Guidelines p.25) Targets users: Primary: Australian and Aotearoa New Zealand healthcare practitioners and medical practitioners involved in the care and management of individuals with SMA and their families as identified through an NBS for SMA process. Secondary: health system planners, training providers and families of children undergoing and screening positive for SMA through newborn screening programs (Guidelines p.27-28)

2. The health question(s) covered by the guideline is (are) specifically described.

Rating: 7

Thirteen questions specifically listed in PICO format to inform Guideline development (Guidelines p.28-29, 44)

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Rating: 7

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 (Guidelines p.27). Further clarification on the population is provided on (Guidelines p.69-70).

2. Stakeholder Involvement

4. The guideline development group includes individuals from all relevant professional groups.

Rating: 7

Names, speciality, affiliation, location and roles clearly detailed in Table 1 (Guidelines p.40-42). Wide range of members relevant to scope of guidelines (clinicians, researchers, patient advocates, industry). Librarian and methodologist acknowledged for their input and guidance in the development of the project (Guidelines p.5).

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Rating: 6

Thorough public consultation process implemented to obtain views and feedback, however no evidence of a literature review of values and preferences. Methods of consultation process clearly detailed in guidelines and technical report. Appendix B (Guidelines document) details the outcomes of the process and actions taken to form guidelines based on feedback.

6. The target users of the guideline are clearly defined.

Rating: 7

Clearly defined in guidelines and appropriate for the scope (Guidelines p.27-28).

3. Rigour of Development

7. Systematic methods were used to search for evidence.

Rating: 7

Detailed systematic methods provided using questions in the PICO format (Guidelines p.46-47). Electronic databases named (Scopus (Ovid), Embase (Ovid), and PubMed, time of search specified clearly. Search terms and strategy for each question provided in Technical Report to enable replication of the literature search.

8. The criteria for selecting the evidence are clearly described.

Rating: 7

Inclusion and exclusion criteria clearly specified and explained where necessary (Technical Report p.23-25). Criteria clearly aligned with the health questions and no reason to believe that all relevant literature may not have been sourced.

9. The strengths and limitations of the body of evidence are clearly described.

Rating: 7

GRADE used to evaluate evidence. Evidence to decision (EtD) framework implemented to move from evidence to forming recommendations - detailed in EtD tables showing strength and direction. Descriptions were appropriate, neutral, unbiased and complete (Technical Report p. 104-110).

10. The methods for formulating the recommendations are clearly described.

Rating: 7

Sequential modified Delphi technique implemented to formulate recommendations. Outcomes of rounds clearly detailed in results of Technical Report (p.244-269), along with how consensus (or non consensus) influenced recommendations.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Rating: 7

Development group 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, feasibility, benefits and harms of the proposed intervention, certainty of the body of evidence, values and preferences to end users, resource and cost effectiveness implications and health equity, acceptability and feasibility factors (Technical report p.81-82). Evidence to Decision tables demonstrate that the group considered benefits and harms equally.

12. There is an explicit link between the recommendations and the supporting evidence.

Rating: 7

Supporting evidence for evidence-based and consensus-based recommendations provided,

demonstrating a clear link between evidence and recommendations (Technical Report p.102-230, Guidelines p. 83-145). For recommendations formed predominantly by consensus, this was clearly specified in the Evidence-to-Decision tables.

13. The guideline has been externally reviewed by experts prior to its publication.

Rating: 6

External review sought by experts in the field and intended users of the guidelines. Public consultation feedback was collected through a feedback form, through email or letter (Guidelines p.59-60). It was unclear what the feedback form entailed, or what type of questions were included. However, there was a clear report of findings and description of how recommendations from the review were implemented (Guidelines Appendix B). The external reviewers were relevant and appropriate to the scope of the guideline.

14. A procedure for updating the guideline is provided.

Rating: 7

Details regarding the proposed time frame, criteria and methodology to update the guidelines provided (Guidelines p. 182). Sufficient information was provided to know when an update will occur or what criteria would trigger an update.

4. Clarity of Presentation

15. The recommendations are specific and unambiguous.

Rating: 7

Recommendations are concrete, descriptive and specific, identifying the recommended action, intent/purpose, relevant population and any caveats.

16. The different options for management of the condition or health issue are clearly presented.

Rating: 7

Options are provided and clearly presented, particularly in the \"Specific considerations\" listed for each of the recommendations.

17. Key recommendations are easily identifiable.

Rating: 7

Recommendations are easily identifiable, highlighted using formatted headings and grouped in one section. They are placed alongside summaries of the key evidence.

5. Applicability

18. The guideline describes facilitators and barriers to its application.

Rating: 4

Facilitators for the application of guidelines not clearly defined, focussed more on the evaluation of implementation in clinical practice. A brief description of possible barriers is

provided. No specific suggestions of how to overcome the barriers is provided (Technical Report p.98-100).

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Rating: 5

A clear implementation section is provided in the Guidelines document (p.183-184), including a link to resources available for dissemination (Guideline documents, Family fact sheet, brief summary). No evidence of pilot testing provided, or links to 'how to' manuals.

20. The potential resource implications of applying the recommendations have been considered.

Rating: 6

Evidence-to-decision tables detail evidence on the costs/resources associated with each recommendation. No evidence of additional experts (e.g. health economists) involved to source or evaluate cost information.

21. The guideline presents monitoring and/or auditing criteria.

Rating: 6

Monitoring guidelines use is described in the Implementation Plan (Guidelines p. 186-187). The guideline will be evaluated using mixed qualitative and quantitative methods to assess awareness, understanding, value use and outcomes of the Guideline; measuring awareness of the Guideline and evaluating acceptance and adoption measures. No advice on the frequency and interval of measurement was found.

6. Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.

Rating: 7

Funding statement provided in the Guidelines (p.6). Whilst there is not a specific statement that the funding body did not influence the content of the guideline included, it is evident from the grant type from the public source listed that there would be negligible influence from the funding body.

23. Competing interests of guideline development group members have been recorded and addressed.

Rating: 7

A critical appraisal of: National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and Aotearoa New Zealand using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.
No endorsement of the content of this document by the AGREE Research Trust should be implied.

Appraiser: Dr Kristi Jones

Date: 14 January 2025

Email: kristi.jones@health.nsw.gov.au

Guideline URL: <https://www.unsw.to/nbs-sma>

Overall Assessment

APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II INSTRUMENT

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

Overall quality of this guideline: 7/7

Guideline recommended for use? Yes.

Notes:

Rating summary Domain 1: 100% Domain 2: 100% Domain 3: 100% Domain 4:

100% Domain 5: 100% Domain 6: 100%

Domain Total

1. Scope and Purpose 21

2. Stakeholder Involvement 21

3. Rigour of Development 56

4. Clarity of Presentation 21

5. Applicability 21

6. Editorial Independence 14

1. Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.

Rating: 7

2. The health question(s) covered by the guideline is (are) specifically described.

Rating: 7

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Rating: 7

2. Stakeholder Involvement

4. The guideline development group includes individuals from all relevant professional groups.

Rating: 7

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Rating: 7

6. The target users of the guideline are clearly defined.

Rating: 7

3. Rigour of Development

7. Systematic methods were used to search for evidence.

Rating: 7

8. The criteria for selecting the evidence are clearly described.

Rating: 7

9. The strengths and limitations of the body of evidence are clearly described.

Rating: 7

10. The methods for formulating the recommendations are clearly described.

Rating: 7

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Rating: 7

12. There is an explicit link between the recommendations and the supporting evidence.

Rating: 7

13. The guideline has been externally reviewed by experts prior to its publication.

Rating: 7

14. A procedure for updating the guideline is provided.

Rating: 7

4. Clarity of Presentation

15. The recommendations are specific and unambiguous.

Rating: 7

16. The different options for management of the condition or health issue are clearly presented.

Rating: 7

17. Key recommendations are easily identifiable.

Rating: 7

5. Applicability

18. The guideline describes facilitators and barriers to its application.

Rating: 7

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Rating: 7

20. The potential resource implications of applying the recommendations have been considered.

Rating: 7

21. The guideline presents monitoring and/or auditing criteria.

Rating: 7

6. Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.

Rating: 7

23. Competing interests of guideline development group members have been recorded and addressed.

Rating: 7

Created online at www.agreetrust.org 14 January 2025

Appendix I. List of organisations and peak bodies endorsing the Guideline

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