UK National Screening Committee

# Newborn screening for spinal muscular atrophy (SMA)

## An evidence map to outline the volume and type of evidence related to PCR-based newborn screening for S M A for the UK National Screening Committee

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Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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# Summary

This document discusses the findings of the evidence map on newborn screening for spinal muscular atrophy (SMA).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, further work on newborn screening for SMA should be commissioned in line with the UK NSC evidence review process.

It is recommended that full systematic reviews of newborn screening for SMA, as well as presymptomatic treatment of SMA, should be undertaken in this area.

# Abbreviations

The following abbreviations are used in this report:

| | |
|---|---|
| CDSR | Cochrane Database of Systematic Reviews |
| DBS | Dried blood spot |
| ddPCR | Digital droplet PCR |
| DNA | Deoxyribonucleic acid |
| FN | False negative |
| FP | False positive |
| IQWiG | Institute for Quality and Efficiency in Health Care (Germany) |
| MLPA | Multiplex ligation-dependent probe amplification |
| NBS | Newborn blood spot screening |
| NICE | National Institute for Health and Care Excellence |
| NPV | Negative predictive value |
| NR | Not reported |
| PCR | Polymerase chain reaction |
| PPV | Positive predictive value |
| qPCR | Quantitative PCR |
| qRT-PCR | Quantitative real-time PCR |
| RCT | Randomised controlled trial |
| RFLP-PCR | Restriction fragment length polymorphism PCR |
| RT-PCR | Real-time PCR |
| SCID | Severe combined immunodeficiency |
| SMA | Spinal muscular atrophy |
| SMC | Scottish Medicines Consortium |
| SMN | Survival motor neuron |
| SR | Systematic review |
| TN | True negative |
| TP | True positive |
| UK | United Kingdom |
| UK NSC | UK National Screening Committee |
| US | United States |

# Introduction and approach

## Background and objectives

Overview of evidence review process

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Newborn screening for spinal muscular atrophy (SMA) is a topic currently due for an update external review.

Overview of spinal muscular atrophy (SMA)

SMA is an autosomal recessive disease. It involves degeneration of the alpha motor neurons in the spinal cord, leading to symmetrical muscle weakness, atrophy and paralysis in late-stage disease of the most severe types. The impact upon the muscles used to support breathing can have lethal consequences. SMA is traditionally categorised into five different types, from type 0 (the most severe) to type 4 (stable and mild disease). Type 1, also referred to as Werdnig-Hoffman disease, is the most common, accounting for approximately 50% of cases of SMA. In spite of this categorisation system, there remains a large degree of overlap between the types.

Most cases of SMA are caused by mutations in survival motor neuron *(SMN)* genes, which code for the SMN protein. The *SMN1* gene is in the chromosome region 5q, and people with two faulty copies of the *SMN1* gene have 5q SMA. The vast majority of cases (95%) are due to a homozygous deletion of both alleles of the *SMN1* gene in exon 7 (and exon 8 in the majority of cases). Other causes include mutations in the *SMN1* gene, or "compound heterozygotes" where one copy of *SMN1* is deleted and the other has a mutation leading to loss of function. Overall, these genetic changes lead to a decrease in functional SMN protein and ultimately lead to patients developing SMA. A person with one faulty copy of the *SMN1* gene will not have SMA but is a carrier for the condition.

The related *SMN2* gene can also make SMN protein but due to a genetic difference in the gene, only around 10% of the SMN protein from the *SMN2* gene is functional. Therefore, *SMN2* can partially compensate for deletions or mutations in *SMN1*. People can have multiple copies of the *SMN2* gene, with a higher number of *SMN2* copies generally correlating with reduced disease severity. However, it is not currently possible to accurately predict severity from genetic information alone.

Treatments for SMA

In the UK, there are three main treatments available for SMA as follows.

Nusinersen (Spinraza, Biogen Idec) is an antisense oligonucleotide designed to modify the product of the *SMN2* gene to produce more functional SMN protein.

- Nusinersen was recommended by the National Institute for Health and Care Excellence (NICE) in 2019 for treatment of 5q SMA, including SMA types 1, 2 or 3, **or** presymptomatic SMA, subject to a managed access agreement (TA588).

- Nusinersen was also recommended by the Scottish Medicines Consortium (SMC) for treatment of symptomatic type 1 5q SMA, and also for types 2 and 3 SMA (the latter from July 2019 for up to 3 years while further evidence is generated).

Risdiplam (Evrysdi, Roche) is a small molecule drug that targets the *SMN2* gene to produce more SMN protein.

- Risdiplam was recommended by NICE in 2021 for treatment of 5q SMA in people aged 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3, **or** presymptomatic SMA and 1 to 4 *SMN2* copies, subject to a managed access agreement (TA755).
- Risdiplam is also recommended by the SMC in Scotland for treatment of 5q SMA in patients aged 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3, **or** with 1 to 4 *SMN2* copies.

Onasemnogene abeparvovec (Zolgensma; Novartis Gene Therapies) is a gene therapy product which expresses the SMN protein.

- Onasemnogene abeparvovec was recommended by NICE in 2021 for treatment of 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies aged 6 months or younger (or aged 7 to 12 months if their treatment is agreed by the national multidisciplinary team), if permanent ventilation for more than 16 hours per day or a tracheostomy is not needed, and subject to a commercial arrangement. It was also recommended for presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies, subject to a managed access agreement (HST15).
- Subsequently, onasemnogene abeparvovec was recommended by NICE in 2023 as an option for treatment of presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under, subject to a commercial arrangement (HST24).
- Onasemnogene abeparvovec is also recommended by the SMC in Scotland for treatment of 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, **or** presymptomatic 5q SMA patients with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene (where patients are expected to develop SMA type 1).

Newborn screening for SMA

Newborn screening for SMA aims to identify babies with SMA via the screening of all newborns. Newborn screening for SMA often uses real-time quantitative polymerase chain reaction (qRT-PCR) techniques to assess the patient's *SMN* genes, using DNA isolated from dried blood spots (DBS) collected soon after birth. Most newborn screening for SMA screens for 5q SMA with homozygous deletion of the *SMN1* gene, but will not identify the approximately 5% of patients who have point mutations, or who are "compound heterozygotes" with a deletion and a point mutation.

## Previous review on screening for spinal muscular atrophy

The UK NSC currently recommends against screening for SMA. The Committee based this recommendation on the evidence provided by the 2018 review carried out by Costello Medical on behalf of the UK NSC [1]. The 2018 review of screening for SMA followed the methodology for an evidence review. The 2018 review assessed three types of screening for 5q SMA:

newborn screening, carrier screening and antenatal screening. The 2018 review also sought evidence on the effectiveness of pharmacological treatment for SMA.

In terms of screening, the 2018 review did not identify any prospective studies relating to carrier or antenatal screening; these are not the focus of the current review and are not discussed further. In terms of newborn screening, the 2018 review identified four publications reporting on five studies. Three were case-control studies, which may not be reflective of a general screening population (Ar Rochmah et al., 2017; Er et al., 2012 and Liu et al., 2016). Two were cohort studies, one in Taiwan which screened 120,000 newborns (Chien et al., 2017), and one in China which screened 2,000 stored DBS samples rather than a live population (Liu et al., 2016). The review concluded that it was not yet possible to robustly quantify the accuracy of newborn screening methods [1].

In terms of treatment, five randomised controlled trials (RCTs) were found by the 2018 review to report outcomes of treatment for SMA [1]. All related to treatment of symptomatic patients. Two RCTs suggested that nusinersen is effective compared to sham control in improving outcomes for patients with symptomatic SMA. In addition, olesoxime, valproic acid and somatropin were investigated in one RCT each, but were not found to be effective treatments for SMA. The review concluded that there was still insufficient evidence that presymptomatic treatment is more beneficial than usual care, and there was also a lack of long-term efficacy and safety data [1].

## Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on screening for SMA should be commissioned in 2023 and to evaluate the volume and type of evidence on key issues related to newborn screening for SMA.

The aim was to address the following questions:

1. **Question 1:** What is the volume and type of evidence available on PCR-based testing for newborn screening for SMA?
2. **Question 2:** What is the volume and type of evidence on the effectiveness of pharmacological treatment for presymptomatic SMA?

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on newborn screening for SMA in 2023. The aim of this document is to present the information necessary for the UK NSC to decide this.

# Search methods and results

The searches were conducted in December 2022 on three databases: Medline, Embase and the Cochrane Library. The Medline search strategies are available in Appendix 1. In addition, recent reviews and relevant studies identified in the search were checked, and experts were consulted, for additional relevant studies.

For Objective 2 Question 1 (newborn screening for SMA), thesaurus and free-text terms for SMA were combined with terms for newborn screening. No further limits or search filters were applied.

For Objective 2 Question 2 (treatment of presymptomatic SMA), thesaurus and free-text terms for SMA were combined with methodological search filters selected from the ISSG Search Filter Resource to identify the study types of interest (systematic reviews, RCTs, and observational studies). The search was not restricted to specific treatments. The search for Q2 was limited to studies published since the searches for the previous UK NSC review, i.e. January 2018 to December 2022.

The inclusion criteria for the two questions are available in Appendix 1. In brief, Q1 sought evidence (UK and international) on PCR-based testing using DBS for newborn screening of 5q SMA. The review sought studies reporting test accuracy outcomes and logistic/feasibility outcomes. Includable study designs included RCTs, cohort studies, case-control (two gate) studies, and systematic reviews of the above. Where sufficient randomly assigned or consecutively enrolled studies were available, other study designs such as case-control studies were listed but not extracted. The review primarily sought studies published in English since January 2018; however, since only a small number of relevant studies were published before January 2018, studies of all dates were included for completeness.

For Q2, evidence (UK and international) was sought relating to the effectiveness of pharmacological treatment for presymptomatic SMA. Includable study designs included RCTs, cohort studies, prospective comparative and non-comparative observational studies, and systematic reviews of the above. Studies published in English since January 2018 were included.

The search for Q1 (screening) returned 533 results. After automatic and manual de-duplication, 372 unique references were sifted for relevance to the question; 89 full-text papers were examined; and 56 references relating to 57 studies were included in the final evidence map.

The search for Q2 (treatment) returned 2993 results. After automatic and manual de-duplication, 1972 unique references were sifted for relevance to the question; 137 full-text papers were examined; and 38 references relating to 32 studies were included in the final evidence map.

A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

One reviewer sifted all titles and abstracts. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2.

**Figure 1A: PRISMA flow diagram for Objective 2 Question 1 (newborn screening)**

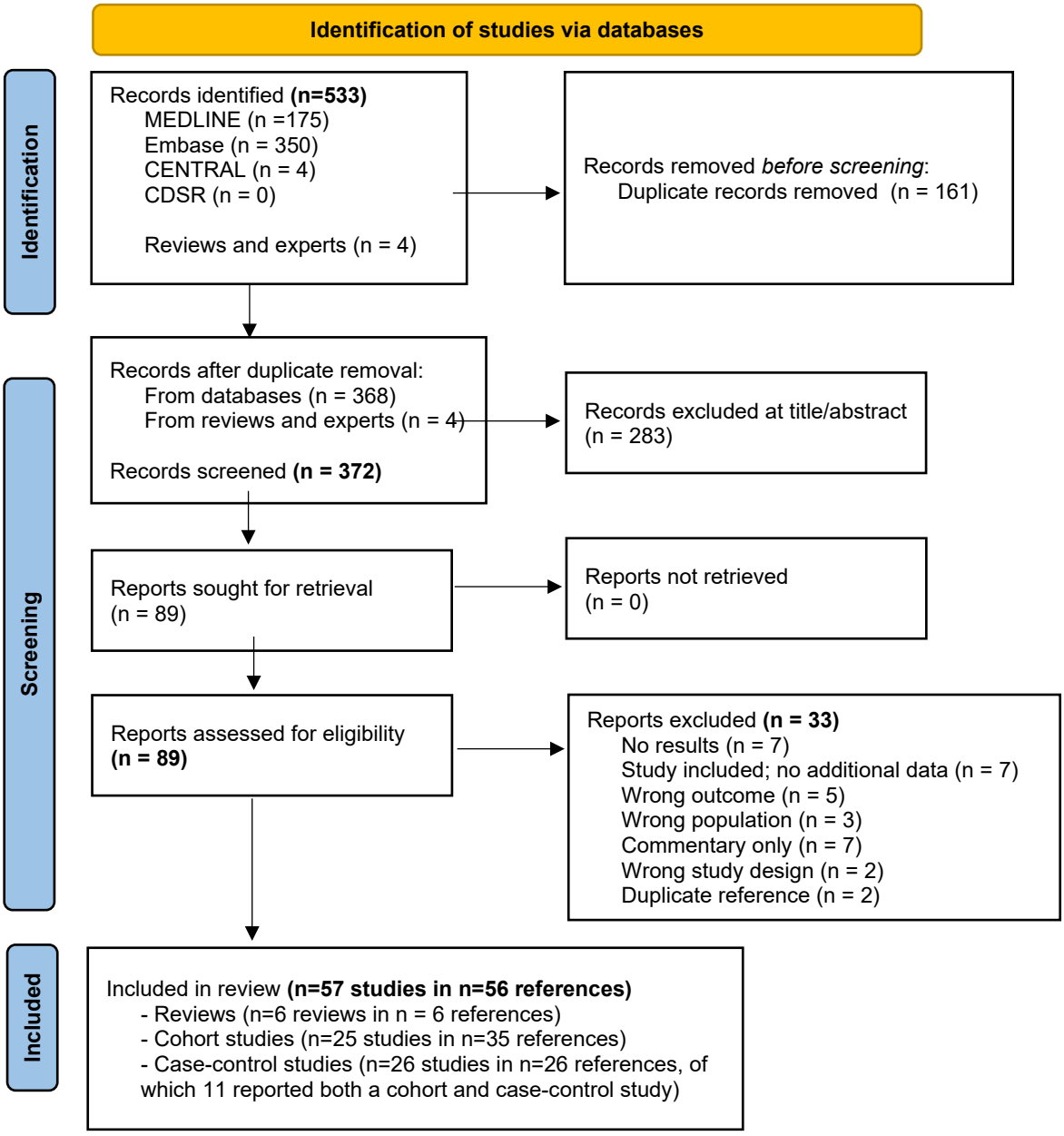
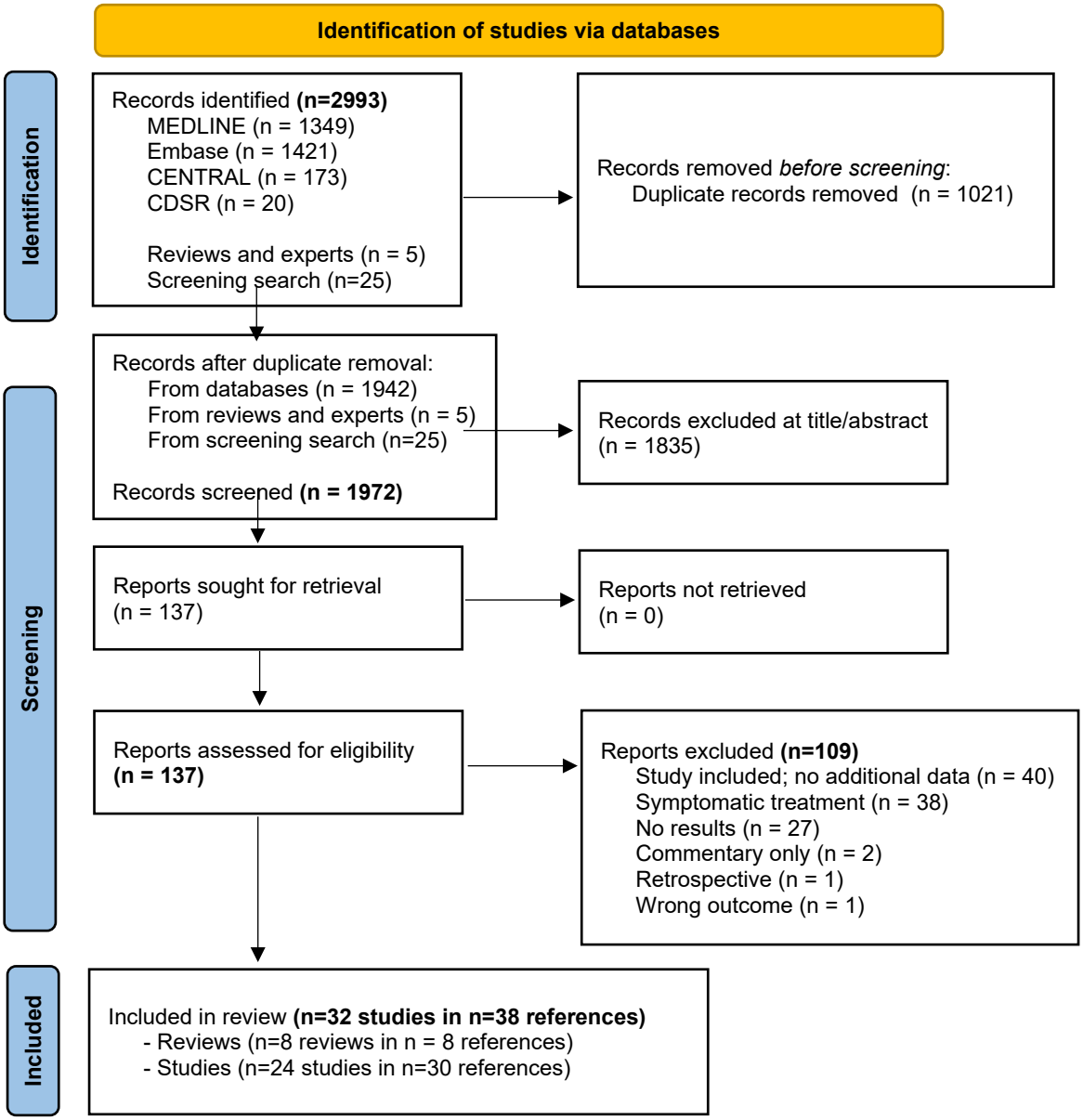


**Figure 1B: PRISMA flow diagram for Objective 2 Question 2 (presymptomatic treatment)**



# Summary of findings

## Question 1: What is the volume and type of evidence available on PCR-based testing for newborn screening for SMA?

**Summary of evidence on newborn screening**

Relating to newborn screening for SMA, 6 reviews [1–6], 25 cohort studies [7–41] and 26 case-control studies [11,13,14,22–25,29,30,35,38,42–56] were identified. No RCTs or comparative studies of screening versus no screening were identified. The inclusion and exclusion criteria are summarised in Appendix 1. Further information about the references is provided in the abstract reporting tables in Appendix 2.

**Cohort studies of newborn screening**

Number and setting

Cohort studies relating to newborn screening programmes for SMA were identified from 11 countries: Belgium [9–11], Germany [14,33,34,39,40], Italy [7,12], Latvia [17], Australia [15,19], Canada (Ontario) [21,32], Japan [22,37,38], Taiwan [13,41], China [29,30,35], Russia [23] and USA. The USA screening programmes were reported for 8 US states (California [31], Georgia [16], Kentucky [27], Massachusetts [18,26], New York State [20,24,28], North Carolina [25], Ohio [36], Wisconsin [8]). All studies reported prospective screening programmes of newborns either as part of a pilot programme or routine screening, except for three studies which screened a cohort of anonymised DBS samples (one in Ohio [36] and two in China [30,35]).

Methods of screening

Most studies aimed to screen for homozygous deletion of *SMN1* exon 7, with many studies acknowledging that screening would not detect SMA caused by compound heterozygotes (*SMN1* deletion on one allele and point mutation on the other), which are estimated as 2-5% of 5q SMA cases.

Most studies only undertook confirmatory testing on positive cases. Therefore, false negative (FN) cases (those missed by screening) were generally only identified if they presented with symptoms, and therefore numbers of FN cases may have been underestimated, particularly milder cases of SMA which may not be clinically apparent in early life.

In terms of methods, the majority of studies (24 of 25) used real-time quantitative PCR (qRT-PCR) as a first-tier screening method (the remaining study did not report the method [27]). Screen-positive cases generally underwent a second-tier confirmatory test for *SMN1* deletion. A variety of methods were reported for this, including multiplex ligation-dependent probe amplification (MLPA; 8 studies), qPCR (4 studies), MLPA and qPCR (2 studies) and restriction fragment length polymorphism PCR (RFLP-PCR; 1 study); the remaining studies did not report this clearly. Screen-positive cases also generally underwent testing for *SMN2* copy number. Again a variety of methods were reported for this, including MLPA (6 studies), digital droplet PCR (ddPCR; 2 studies), ddPCR and qPCR (2 studies), qPCR (1 study), qPCR and MLPA (1 study), and ddPCR and MLPA (1 study); the remaining studies did not report this clearly. One study reported a three-tier testing system (Massachusetts [18]).

Test accuracy outcomes from cohort studies

Most cohort studies reported the total number of newborns screened, the number testing positive, and the number of true positives (TP) and false positives (FP), where true positives are those confirmed via a second-tier test as having *SMN1* homozygous deletion, and false positives are those who test positive initially but are found via a second-tier test to not have SMA. Some studies reported the number of FN cases, but this was generally based on patients not identified via testing who later presented with symptoms, so some FN cases may have been missed; many studies did not mention FN cases at all so it was unclear whether information on missed cases had been sought. Most studies did not directly report test accuracy outcomes such as positive and negative predictive value, sensitivity and specificity. These could be calculated from the reported data but some assumptions were necessary, as outlined below.

Prevalence: The total number of newborns screened per study (not including the three studies using anonymised DBS samples) ranged from 3,826 to nearly 650,000. The total number of screen-positive cases from the initial screen ranged from n=0 to n=50 cases. Of these, the number of false positives ranged from n=0 to n=8 (except within two studies with n=22 and n=24 false positives, in China [30] and USA, Georgia State [16]). Based on these data, most studies reported the observed prevalence of SMA (TP/N screened), which ranged from 1 in 3,826 to 1 in 27,960.

Positive predictive value: It was generally possible to calculate the positive predictive value (TP/[TP+FP]), bearing in mind this was generally based on small numbers of cases as described above. Where the positive predictive value could be calculated, it was 100% in 13 studies, and in the remainder was 4%, 38%, 47%, 50%, 69%, 90%, 92% and 95%. It should be noted that these data apply to the first-tier test. If the second-tier test was included as part of the testing system, it was generally implied that there would be no remaining false positives by the end of the diagnostic process, therefore the positive predictive value would be 100%.

Negative predictive value: The negative predictive value (TN/[TN+FN]) could generally be calculated, but may be overestimated due to underestimation of FN cases as described above. Where negative predictive value could be calculated, it was 100% in all studies (to the nearest whole percentage point). This was the case even where a study reported some false negatives, due to the low prevalence of SMA.

Sensitivity: It was generally possibly to calculate sensitivity (TP/[TP+FN]), but again this may be overestimated due to underestimation of FN cases as described above. Sensitivity may be calculated for homozygous deletions of *SMN1*, which is what most screening programmes aimed to detect. Where sensitivity for homozygous deletions could be calculated, it was 100% in 17 studies and 91% and 94% in two further studies with 2 and 1 false negative cases respectively [15,16]. A few studies noted that compound heterozygotes (around 2-5% of cases) would not be detected by most screening methods; therefore the sensitivity for all 5q SMA cases (including compound heterozygotes) would be a maximum of 95-98%. Three studies each identified one compound heterozygous case (identified via symptoms and classed as false negative); the sensitivity for these studies, calculated for all SMA cases rather than just homozygous deletions, was 90%, 95% and 98% [10,34,41].

Specificity: It was also generally possible to calculate the specificity (TN/[TN+FP]), because the number of FP cases was generally reported. Where specificity could be calculated, it was 100% in all studies (to the nearest whole percentage point). This was the case even where a study reported some false positives, due to the low prevalence of SMA.

Logistic, feasibility and clinical outcomes from cohort studies

Timings: Several studies noted timings of the testing process. These were usually reported as time from birth to: initial results, confirmatory results; specialist visit; and start of treatment (actual timings have not been extracted for this evidence map).

Initial incomplete results: Some studies mentioned initial incomplete results. One study (Italy [7]) noted some failed tests in the first months of the study; these were reduced by avoiding heparin-coated capillaries for blood sampling. One study (Latvia [17]) reported that 40 cases required repeat sampling due to poor DNA quality due to either quality of blood punch or manual mistakes during DNA isolation. One study (California [31]) noted that 5 newborns required a repeat DBS (2 due to inconclusive result; no reason reported for the other 3) but all eventually tested negative. The New York State pilot study [24] reported that 3% of cases were retested due to suboptimal DNA quality or quantity and all later classed as negative; in addition, 33 cases (0.9%) 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/carriers (n=2) while 1 case was found to carry a rare heterozygous sequence variant of uncertain significance (discussed below). One study in North Carolina [25] noted that 2 cases were not tested due to insufficient quantity, while 36 were re-tested due to the first test being above the cut-off; on retesting 34 were considered screen-negative and 2 screen-positive. A study in Ohio [36] reported that 7 speciments (0.02%) required repeat extraction from the original DBS and all gave a robust result on re-testing. A study in Taiwan [13] stated that 50 samples gave unsatisfactory results; a repeat DNA extraction re-test classified all as negative. The study in Georgia State [16] reports that 147 patients had inconclusive results, and that of these 126 were also inconclusive for severe combined immunodeficiency (SCID) screening; it is not reported whether these patients were followed up further. The Massachusetts study [18] notes that more NICU babies required a tier 2 and/or tier 3 screen; the authors speculate that this may involve a PCR inhibitor, though the mechanism for this is not explained.

Incidental findings: A range of incidental findings were reported. Three studies reported screen-detected SMA patients with 4 copies of *SMN2*, where siblings were then tested and also found to have SMA (Belgium [10], Germany [40] and Italy [7]). In the Massachusetts study [18], 10 newborns were found to be *SMN1* hybrids with an exon 7 variant; these patients were assumed to have normal function and were observed but not referred, and the first six were followed up at 6 months and all considered healthy with no concerns. In the New York State pilot study [24], 1 patient testing in the equivocal range was found to carry a rare heterozygous sequence variant of uncertain significance; this patient was classed as screen-negative, as in vitro studies have shown that this variant does not affect function; however the clinical significance is unknown. The study in North Carolina [25] identified 1 false positive who was later found to have an unrelated blood disorder. Finally, while most screening programmes aimed to identify homozygous deletions of *SMN1*, some studies also identified heterozygous carriers, including the New York State pilot study [24], a study in Russia [23] and a study in China using anonymised DBS samples [35]; in New York State [24], parents of heterozygous carriers were offered genetic testing to determine whether both parents were carriers, for future family planning.

Organisational considerations: A conference abstract reported on organisational, ethical and regulatory considerations based on screening experience in Belgium and UK [9]. A report of a nationwide screening programme in Germany reports on the process of converting from pilot to nationwide screening, e.g. selection of specialist centres, criteria for follow-up care, and developing information for laboratories, clinics and parents [34]. The study in Latvia reports on the number of samples analysed per month at the start and end of the programme [17]. The

Australian study also reports on implementation effectiveness [15]. The Canadian study also reports recommendations for diagnosis and treatment of children with SMA identified via newborn screening [21]. The Californian study also reports treatment barriers and delays [31].

Compliance: Three studies reported on compliance of families with SMA newborn screening; this was reported as 70% in Latvia [17], 91% in Italy [7] and 93% in the New York State pilot [24].

### Reviews of newborn screening

Reviews of newborn screening are summarised in Appendix 2. Two systematic reviews [2,4] and a narrative review [5], as well as the previous NSC evidence summary [1], reported search dates between 2018 and 2021, reported studies of newborn screening programmes for SMA in up to 9 countries. One review noted that first-tier screening is real-time qPCR in most programmes, while second-tier screening is usually MLPA or (in USA and Italy) qPCR [2].

Two narrative reviews of SMA newborn screening in the USA [3,6] reported that 34 US states had implemented newborn screening for SMA (not including pilot projects) as of June 2021, and 38 states as of Quarter 3, 2021. The majority of programmes (n=25) had multiplexed SMA screening with SCID screening. All programmes used real-time qPCR as first-tier screening, while as second-tier, some states use qPCR while others use ddPCR [3]. More than 276 infants with SMA had been identified via newborn screening. Of 44 infants included in the Cure SMA registry, the median diagnosis age was 7 days and the median time to treatment after diagnosis was 19 days [6].

### Case-control studies of newborn screening

In total, 26 case-control studies of newborn screening for SMA were identified. The aim of these studies is generally to validate a screening method under test conditions, using a set of known positive cases and a set of known negative controls. Because case-control studies tend to overestimate test accuracy parameters, and due to the availability of several cohort studies, case-control studies were not extracted, but are listed for information in Appendix 2.

### Summary of current state of evidence for newborn screening

In summary, substantial evidence for PCR-based newborn screening for SMA has been published since the previous NSC review in 2018. Based on the findings of this evidence map, a full systematic review of newborn screening for SMA may be considered.

# Question 2: What is the volume and type of evidence on the effectiveness of pharmacological treatment for presymptomatic SMA?

**Summary of evidence on presymptomatic treatment**

Relating to presymptomatic treatment for SMA, 24 studies [10,16,18,19,25,28,31,37,40,41,57–76] and 8 reviews [1,4,5,77–81] were identified. The inclusion and exclusion criteria are summarised in Appendix 1. Further information about the references is provided in the abstract reporting tables in Appendix 2.

**Studies on presymptomatic treatment**

Number and type of studies

No RCTs of presymptomatic treatment were identified. The 24 studies included 3 single-arm interventional studies of presymptomatic treatment: the NURTURE study of nusinersen [61,66,68], the SPR1NT study of onasemnogene abeparvovec [74,75] and the RAINBOWFISH study of risdiplam [72].

There was 1 retrospective comparative study of presymptomatic vs. early symptomatic nusinersen [4,57], as well as 1 analysis of early vs. late symptomatic nusinersen [4,64].

In addition, the review identified 10 prospective follow-up cohorts within newborn screening studies [10,16,18,19,25,28,31,40,41,58,69], and 9 additional observational studies [59,60,62,63,65,67,69–71,73,76].

Outcomes from single-arm trials

The NURTURE study of nusinersen [61,66,68] is a phase 2, multicentre, open-label, single-arm trial which enrolled 25 babies with presymptomatic SMA (15 with two SMN2 copies and 10 with three SMN2 copies), who received nusinersen starting aged ≤6 weeks, with a planned treatment duration of 5 years. At the interim analysis with a median follow-up of 2.9 years [61], all were alive and none required tracheostomy or permanent ventilation. Among patients with two SMN2 copies, all could sit without support, 13/15 achieved walking with assistance, 12/15 achieved walking independently; however 10/15 had symptoms of SMA at age 13 months and 7/15 at age 24 months. Patients with three SMN2 copies had slightly better outcomes; all could sit without support, all could walk independently; and only 2/10 had symptoms of SMA at age 13 months and 0/10 at age 24 months.

The SPR1NT study of onasemnogene abeparvovec [74,75] is a phase 3, multicentre, open-label, single-arm trial which enrolled 29 babies with presymptomatic SMA (14 with two SMN2 copies and 15 with three SMN2 copies), who received onasemnogene abeparvovec starting aged ≤6 weeks, with a follow-up duration of 18 months for the two-copy cohort and 2 years for the three-copy cohort. Data for the two-copy and three-copy cohorts were reported in separate papers. All survived without permanent ventilation at 14 months as per protocol. Among patients with two SMN2 copies, all sat independently, 11/14 stood independently, and 10/14 walked independently. Patients with three SMN2 copies had slightly better outcomes; all stood independently and 14/15 walked independently.

The RAINBOWFISH study of risdiplam is a multicentre, open-label, single-arm trial. It is still ongoing, with limited preliminary data available in conference abstracts. The planned treatment

duration is 2 years with a further 3 years follow-up. In a preliminary analysis of 7 patients who had received risdiplam for ≥12 months [72], all were alive without permanent ventilation, and all maintained swallowing and feeding abilities and had not required hospitalisation.

Outcomes from other trial analyses of treatment timing

A systematic review by IQWiG 2020 [4] cites a manufacturer study [57] which undertook a retrospective comparison of presymptomatic nusinersen (NURTURE single-arm study) vs. early symptomatic treatment (nusinersen arm of ENDEAR RCT [64]) in patients with two SMN2 copies. This analysis found large effects in favour of a presymptomatic treatment start over early symptomatic treatment start (disease duration ≤ 12 weeks).

In addition, the IQWiG 2020 review [4] cites an analysis of the ENDEAR RCT [64] of nusinersen vs. sham in early symptomatic SMA patients. This analysis compared subgroups with early symptomatic vs. late symptomatic treatment start, and found greater benefit with early treatment for time to death or permanent ventilation and for motor milestone achievement.

These two studies did not technically meet the inclusion criteria for this review, due to the first being retrospective and the second not relating to presymptomatic treatment. However, they are included here as they relate to timing of treatment.

Prospective follow-up within newborn screening studies

The searches identified 10 prospective follow-up cohorts within newborn screening studies in 10 countries or states [10,16,18,19,25,28,31,40,41,58,69]. These studies mainly reported on small numbers of patients with differing numbers of *SMN2* copies, treated presymptomatically or after symptom onset, with different treatments, and with varying levels of follow-up and outcome reporting. It was therefore difficult to draw conclusions about presymptomatic treatment within any one patient group. Further details are provided in Appendix 2.

Other observational studies

The searches also identified studies 9 additional observational studies, mostly including small numbers of SMA patients [59,60,62,63,65,67,69–71,73,76]. Some of these reported one set of results across patients receiving symptomatic and presymptomatic treatment, while others compared cohorts with symptomatic versus presymptomatic treatment. Further details are provided in Appendix 2.

### Reviews of presymptomatic treatment

Eight systematic or narrative reviews covering presymptomatic treatment were identified [1,4,5,77–81]. The main evidence cited by these reviews consisted of the three single-arm trials of presymptomatic treatment (NURTURE, SPR1NT and RAINBOWFISH).

### Summary of current state of evidence for presymptomatic treatment

In summary, some relevant evidence for presymptomatic treatment of SMA has been published since the previous NSC review in 2018. Based on the findings of this evidence map, a full systematic review of presymptomatic treatment of SMA may be considered.

# Conclusions

Substantial evidence has been published since the previous NSC review in 2018, relating to both newborn screening for SMA and presymptomatic treatment of SMA.

## Recommendations

Based on the findings of this evidence map, it is recommended that full systematic reviews of newborn screening for SMA, as well as presymptomatic treatment of SMA, should be undertaken.

# Appendix 1 — Search strategy for the evidence map

## Databases and platforms searched

Medline, Embase and Cochrane Library

## Search dates

Objective 2 Question 1 (newborn screening for SMA): Database inception to December 2022

Objective 2 Question 2 (presymptomatic treatment): January 2018 to December 2022

## Search strategies

**Medline search strategy: Objective 2, Question 1 (newborn screening)**

1. "Spinal Muscular Atrophies of Childhood"/
2. Muscular Atrophy, Spinal/
3. werdnig-hoffman.tw.
4. wohlfart-kugelberg-welander.tw.
5. Spinal muscular atroph*.tw.
6. or/1-5
7. Neonatal Screening/
8. ((neonat* or newborn?) adj2 (screen* or detect* or diagnos* or test*)).ti,ab.
9. 7 or 8
10. 6 and 9

**Medline search strategy: Objective 2, Question 2 (presymptomatic treatment)**

1. "Spinal Muscular Atrophies of Childhood"/
2. Muscular Atrophy, Spinal/
3. werdnig-hoffman.tw.
4. wohlfart-kugelberg-welander.tw.
5. Spinal muscular atroph*.tw.
6. or/1-5
7. randomized controlled trial.pt. or randomized.mp. or placebo.mp.
8. 6 and 7
9. limit 8 to yr="2018 -Current"
10. Epidemiologic studies/
11. exp case control studies/
12. exp cohort studies/
13. Case control.tw.

14. (cohort adj (study or studies)).tw.
15. Cohort analy$.tw.
16. (Follow up adj (study or studies)).tw.
17. (observational adj (study or studies)).tw.
18. Longitudinal.tw.
19. Retrospective.tw.
20. Cross sectional.tw.
21. Cross-sectional studies/
22. or/10-21
23. 6 and 22
24. limit 23 to yr="2018 -Current"
25. meta analysis.mp,pt. or review.pt. or search:.tw.
26. 6 and 25
27. limit 26 to yr="2018 -Current"
28. 9 or 24 or 27

## Numbers of results for each database and question if applicable

**Objective 2 Question 1 (newborn screening for SMA):**

Medline: n=175

Embase: n=350

Cochrane CENTRAL: n=4

Cochrane Database of Systematic Reviews (CDSR): n=0

Reviews and experts: n=4

**Objective 2 Question 2 (presymptomatic treatment):**

Medline: n=1349

Embase: n=1421

Cochrane CENTRAL: n=173

Cochrane Database of Systematic Reviews (CDSR): n=20

Reviews and experts: n=5

Screening search: n=25

## Inclusions and exclusions

**Objective 2 Question 1 (newborn screening for SMA)**

The inclusion criteria were as follows:

**Question:** What is the volume and type of evidence available on PCR based testing for newborn screening for spinal muscular atrophy (SMA)?

**Sub-questions:** This question should provide information on UK and international studies reporting:

- Test accuracy outcomes
- Logistic / feasibility outcomes

**Population:** Neonatal

**Target condition:** 5q spinal muscular atrophy

**Index test:** PCR-based newborn screening using dried blood spots (DBS)

**Comparator:** Any of the following:

- Any alternative approach to newborn screening using DBS
- Any alternative PCR method e.g. two-tier vs single tier
- None

**Reference standard:** Any of the following:

- For screen positives: confirmatory genetic testing e.g. multiplex ligation-dependent probe amplification (MLPA)
- For screen negatives: clinical reporting / follow up or none
- Or any other specific “gold standard,” as determined by the study itself

**Outcomes:** Any of the following:

Test accuracy outcomes:

- Sensitivity
- Specificity
- False positive rate
- False negative rate
- Positive predictive values (PPV)
- Negative predictive values (NPV)
- Likelihood ratios
- Area under the curve

Logistic, feasibility and clinical outcomes

- E.g. time to diagnosis, time to treatment, laboratory or clinic workload, by product / incidental findings including variants of uncertain significance

**Study design:** Any of the following:

- Randomised controlled trials (RCTs)
- Cohort studies
- Case-control (two gate) studies

- Systematic reviews (SRs) of the above [comprehensive narrative reviews were also included]

A hierarchical approach was taken; studies in randomly assigned or consecutively enrolled populations and systematic reviews of these were prioritised. If sufficient studies of these designs were found, other study designs, for example case-control studies, were listed but not extracted. Prospective studies with nested cases were included.

**Setting:** UK and international

**Language:** English language

**Date limits:** Published since January 2018 [no date limits were placed on the search for this question, and since few relevant studies were published before January 2018, studies of all dates were included for completeness]

**UK NSC criteria:** Criterion 4. There should be a simple, safe, precise and validated screening test.

**Objective 2 Question 2 (presymptomatic treatment):**

The inclusion criteria were as follows:

**Question:** What is the volume and type of evidence on the effectiveness of pharmacological treatment for Spinal Muscular Atrophy in presymptomatic SMA?

**Sub-questions:** Papers addressing the following will be particularly sought:

- Is the pharmacological treatment for Spinal Muscular Atrophy equally effective for all Spinal Muscular Atrophy types?
- Are pharmacological treatments for SMA more effective if administered in presymptomatic SMA?

**Population:** Individuals with SMA

**Intervention:** Pharmacological treatment administered presymptomatically

**Comparator:** Any of the following:

- Usual care
- Pharmacological treatment (same as Intervention above) administered following symptomatic presentation
- Pharmacological treatment (different to Intervention above) administered presymptomatically
- None

**Outcomes:** Any of the following:

- Quality of life
- Improved mobility (preventing joint stiffness, and improving flexibility and range of movement)
- Improved breathing
- Nutrition and feeding (avoiding problems such as dehydration and ensure healthy development)
- Decrease in respiratory complications (fatal breathing problems caused by a weakening of the respiratory muscles and respiratory tract infections)

- Increased life expectancy

**Study design:** Any of the following:

- Randomised controlled trials (RCTs)
- Prospective comparative and non-comparative observational studies
- Systematic reviews (SRs) of the above [comprehensive narrative reviews were also included]

If available, RCTs were prioritised for reporting. Otherwise, other study designs were summarised.

**Setting:** UK and international

**Language:** English language

**Date limits:** Published since January 2018

**UK NSC criteria:** The following criteria were applicable to this question:

Criterion 9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

Criterion 10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

# Appendix 2 – Abstract reporting

## Question 1: What is the volume and type of evidence available on PCR-based testing for newborn screening for SMA?

## Cohort studies of newborn screening

The following section summarises cohort studies of newborn screening.

### Study 1: Belgium

#### Citations

Boemer 2021 [10] (3yr data); Boemer 2019 [11] (methods); Betts 2022 [9] (logistics)

#### Study type

Cohort study

#### Objectives

To evaluate newborn screening for SMA

#### Components of the study

**Setting:** Southern Belgium

**Population:** Newborns

**Duration:** 3 years (March 2018 to February 2021)

**Index test:** Real-time qPCR of DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion via MLPA from second blood sample. Test for *SMN2* copy number via MLPA using original DBS

[Full text checked]

#### Outcomes reported

Outcomes reported (at 3 years; Boemer 2021):

- N screened: 136,339
- N testing positive: 9
- True positives: 9
- False positives: 0

- False negatives: 1 known of (identified via symptoms; heterozygous for *SMN1* deletion and point mutation); no homozygous *SMN1* deletions missed, to the authors' knowledge
- True negatives: NR [assumed 136,329]
- Prevalence: 10 of 136,339 (or 1 in 13,634) for SMA; 9 of 136,339 (or 1 in 15,149) for SMA with homozygous *SMN1* deletion
- Positive predictive value [calculated]: 9/9 (100%), i.e. all 9 tested positive on confirmatory testing
- Negative predictive value [calculated]: 136,329/136,330 = 100%
- Sensitivity [calculated]: 9/9 = 100% for homozygous deletion; 9/10 = 90% including compound heterozygote. States sensitivity for SMA NBS estimated at 95-98% as will not detect compound heterozygotes
- Specificity [calculated]: 136,329/136,329 = 100%
- Initial incomplete results: None mentioned
- Time from: receipt of DBS sample to validation of result (turnaround time; first consultation to treatment; birth to treatment
- Incidental findings: One patient with 4 copies of *SMN2* had siblings who were also found to have homozygous deletion of *SMN1* exon 7 and 4 copies of *SMN2*
- Organisational, ethical and regulatory considerations for Belgium and UK [Betts 2002 abstract]

[Full text checked]

### Conclusions

The authors concluded that the pilot program has now successfully transitioned into the official neonatal screening program in Southern Belgium.

## Study 2: Germany [pilot]

### Citations

Vill 2021 [40] (2yr data); Czibere 2020 [14] (18mo data); Muller-Felber 2020 [33] (clinical); Vill 2019 [39] (1yr data); Muller-Felber 2023 [34] (pilot + nationwide)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Germany (two states: Bavaria and North Rhine-Westphalia)

**Population:** Newborns

**Duration:** 2 years (January 2018 to January 2020)

**Index test:** qPCR of DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion and *SMN2* copy number by PCR (MLPA) from new whole blood sample

[Full text checked]

## Outcomes reported

Outcomes reported (at 2 years of pilot; Vill 2021):

- N screened: 297,163
- N testing positive: 43
- True positives: 43
- False positives: 0
- False negatives: Authors state none reported so far
- True negatives: NR [assumed 297,120]
- Prevalence: 43 of 297,163 (or 1 in 6,910)
- Positive predictive value [calculated]: 43/43 (100%), i.e. all 43 tested positive on confirmatory testing
- Negative predictive value [calculated]: 297,120/297,120 = 100%
- Sensitivity [calculated]: 43/43 = 100%
- Specificity [calculated]: 297,120/297,120 = 100%
- Accuracy for *SMN2* copy number determination: 3/43 (7%) gave incorrect results, discovered by repeated analysis with improved kit
- Time from birth to: positive result; second blood sample; confirmatory test result; specialist visit; start of treatment
- Incidental findings: Two patients with 4 copies of *SMN2* had affected siblings with SMA type 3, diagnosed after detection of the index patient via screening

[Full text checked]

## Conclusions

The authors concluded that identification of newborns with infantile SMA and prompt SMA-specific treatment substantially improves neurodevelopmental outcomes.

## Study 3: Germany (nationwide screening)

### Citations

Muller-Felber 2023 [34] (6mo data)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Germany (whole country)

**Population:** Newborns

**Duration:** 6 months (October 2021 to March 2022)

**Index test:** qPCR of DBS to screen for homozygous deletion of *SMN1* exon 7 [assumed same methods as for pilot]

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion and *SMN2* copy number by PCR (MLPA) from new whole blood sample [assumed same methods as for pilot]

[Full text checked]

### Outcomes reported

Outcomes reported (at 6 months nationwide; Muller-Felber 2023):

- N screened: NR
- N testing positive: 50
- True positives: 46
- False positives: 4 (1 had two normal copies of *SMN1*; 2 had heterozygous deletion of *SMN1*; 1 had inconsistent results using different parts of DBS; final result unclear. All in first 2 months, after which screening process was modified)
- False negatives: 1 (heterozygous deletion and point mutation, identified via symptoms); none known of with homozygous *SMN1* deletion
- True negatives: NR
- Prevalence: NR [incidence reported as 1 in 8,554]
- Positive predictive value [calculated]: 46/50 (92%), i.e. 46 of 50 positive for homozygous deletion on confirmatory testing
- Negative predictive value: Not calculable
- Sensitivity [calculated and reported]: 46/46 = 100% for homozygous deletion; 46/47 (98%) including compound heterozygote

- Specificity: Not calculable
- Time from birth to: positive result (to clinicians and to parents); confirmatory test result; specialist visit; start of treatment
- Also reports on process of converting from pilot to nationwide screening, e.g. selection of specialist centres, criteria for follow-up care, developing information for laboratories, clinics and parents

[Full text checked]

### Conclusions

The authors concluded that it is possible to expand genetic newborn screening from a small, well defined pilot group to nationwide implementation with no loss of speed and quality.

## Study 4: Italy (Lazio and Tuscany)

### Citations

Abiusi 2022 [7] (2yr data)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Italy (Lazio and Tuscany regions)

**Population:** Newborns

**Duration:** 2 years (September 2019 to September 2021)

**Index test:** Real-time qPCR of DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion on new sample from initial DBS, then on a new blood sample using RFLP-PCR, *SMN2* copy number by semi-quantitative qPCR, and identification of *SMN1* exon 7 splicing-modifier variants

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 90,885
- N testing positive: 15

- True positives: 15
- False positives: None reported
- False negatives: Authors state none known so far
- True negatives: NR [assumed 90,840]
- Prevalence: 15 of 90,885 (or 1 in 6,059)
- Positive predictive value [calculated]: 15/15 (100%), i.e. all 15 tested positive on confirmatory testing
- Negative predictive value [calculated]: 90,840/90,840 = 100%
- Sensitivity [calculated]: 15/15 = 100%
- Specificity [calculated]: 90,840/90,840 = 100%
- Initial incomplete results: Some failed tests in first months of study; reduced when avoided heparin-coated capillaries for blood sampling; failed samples required manual DNA extraction but all were successfully screened with no re-sampling required.
- Time from birth to: diagnosis, confirmatory results, start of treatment
- Compliance of families to screening: 91%
- Also reports full screening programme following pilot in same two regions: during first 8 months, 3/49,887 (1 in 16,629) diagnosed with SMA, but no detail on false positives, false negatives etc
- Incidental findings: One patient with 4 copies of *SMN2* had sibling who was also found to have homozygous deletion of *SMN1* exon 7 [during 8 months of full screening programme]

[Full text checked]

### Conclusions

The authors concluded that the molecular diagnosis of SMA needs to adapt to the new era of the disease with specific guidelines and standard operating procedures.

## Study 5: Italy (Ligura)

### Citations

Bruno 2022 [12] (abstract; 1yr data)

### Study type

Cohort study

## Objectives

To evaluate simultaneous newborn screening for SMA and SCID

## Components of the study

**Setting:** Italy (Ligura region)

**Population:** Newborns

**Duration:** 1 year (dates NR)

**Index test:** Real-time PCR of DBS to screen for homozygous deletion of *SMN1* exon 7 to 8

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion using MLPA

[Reported as abstract only]

## Outcomes reported

Outcomes reported:

- N screened: 8,434
- N testing positive: NR
- True positives: 2
- False positives: NR
- False negatives: NR
- True negatives: NR
- Prevalence: 2 of 8,434 (or 1 in 4,217)
- Positive predictive value: Not calculable
- Negative predictive value: Not calculable
- Sensitivity: Not calculable
- Specificity: Not calculable
- Time from birth to: confirmatory results

[Reported as abstract only]

## Conclusions

The authors concluded that combined screening of SMA and SCID allows identification in early phases of infants with severe and potentially treatable diseases.

# Study 6: Latvia

## Citations

Gailite 2022 [17]

## Study type

Cohort study

## Objectives

To evaluate newborn screening for SMA

## Components of the study

**Setting:** Latvia

**Population:** Newborns

**Duration:** 10 months (February 2021 to November 2021)

**Index test:** qPCR of DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion on original sample, then on new blood sample using both qPCR (for fast validation) and MLPA (for *SMN1* validation and *SMN2* copy number)

[Full text checked]

## Outcomes reported

Outcomes reported:

- N screened: 10,411
- N testing positive: 2
- True positives: 2
- False positives: 0
- False negatives: Authors state none known so far
- True negatives: NR [assumed 10,409]
- Prevalence: 2 of 10,411 (or 1 in 5,205)
- Positive predictive value [calculated]: 2/2 (100%), i.e. all 2 tested positive on confirmatory testing
- Negative predictive value [calculated]: 10,409/10,409 = 100%
- Sensitivity [calculated]: 2/2 = 100%
- Specificity [calculated]: 10,409/10,409 = 100%
- Initial incomplete results: 40 cases required repeat sampling due to poor DNA quality due to either quality of blood punch or manual mistakes during DNA isolation
- Time from birth to results, time from DBS to results
- Workload: 83 samples analysed in first month, 1,054 in final month
- Consent rate approx. 70% for SMA testing (compared with national NBS)

[Full text checked]

### Conclusions

The authors concluded that expansion of the screening procedure to the whole country is feasible and would facilitate early diagnosis and result in more effective treatment.

## Study 7: Australia

### Citations

D'Silva 2022 [15] (2.5yr data); Kariyawasam 2020 [19] (1yr data + methods)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Australia (New South Wales and Australian Capital Territory)

**Population:** Newborns

**Duration:** 2.5 years (August 2018 to January 2021)

**Index test:** Real-time PCR 4-plex assay using DBS to screen for homozygous deletion of *SMN1* exon 7. Kariyawasam 2020 states that patients were considered screen-positive if homozygous deletion of *SMN1* and <4 copies of *SMN2*; however, D'Silva 2022 states that *SMN2* copy number did not determine screen positivity

**Reference standard:** Screen-positives: Tested for *SMN2* copy number using ddPCR. Second DBS; MLPA to confirm deletion of *SMN1* and qPCR to confirm *SMN2* copy number detection

[Full text checked]

### Outcomes reported

Outcomes reported (at 2.5 years; D'Silva 2022):

- N screened: 252,081
- N testing positive: 22
- True positives: 21
- False positives: 1 (homozygous for rare sequence variant in *SMN1* or *SMN2*; possibly related to parental consanguinity)
- False negatives: 2 (1 where *SMN1* not analysed due to system errors during establishment of pilot; and 1 where laboratory did not receive a sample; neither relate to

screening test accuracy; both presented due to clinical symptoms). Note: paper records this as 0 false negatives

- True negatives: NR [assumed 252,057]
- Prevalence: 22 of 252,081 (or 1 in 11,458)
- Positive predictive value [calculated]: 21/22 (95%), i.e. 21 of 22 tested positive on confirmatory testing
- Negative predictive value [calculated]: 252,057/252,059 = 100%
- Sensitivity [calculated]: 21/23 = 91%. Reported as 21/21 = 100% as due to system errors not test accuracy.
- Specificity [calculated]: 252,057/252,058 = 100%. Reported as 252,058/252,059 = >99.9%
- Time from birth to: screen-positive result; diagnostic confirmation; start of treatment
- Logistics: Reports implementation effectiveness

[Full text checked]

### Conclusions

The authors concluded that newborn screening is essential for early identification of infants at risk of SMA and can be effectively translated into clinical practice.

## Study 8: Canada (Ontario)

### Citations

Kernohan 2022 [21] (1yr data); McMillan 2021 [32] (methods)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Canada (Ontario)

**Population:** Newborns

**Duration:** 1 year (pilot from Jan 2020; permanent from July 2020)

**Index test:** PCR (MassARRAY) test on DBS to screen for homozygous deletion or conversion of *SMN1* exon 7. Considered positive if homozygous deletion or conversion of *SMN1* and up to 4 copies of *SMN2*

**Reference standard:** Screen-positives: Confirmation of *SMN1* deletion and *SMN2* copy number detection via MLPA on original DBS. Further confirmatory testing of positives on new blood sample

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 139,800
- N testing positive: 5
- True positives: 5
- False positives: 0
- False negatives: Authors state none identified so far
- True negatives: NR [assumed 139,795]
- Prevalence: 5 of 139,800 (or 1 in 27,960)
- Positive predictive value [calculated]: 5/5 (100%), i.e. all 5 tested positive on confirmatory testing
- Negative predictive value [calculated]: 139,795/139,795 = 100%
- Sensitivity [calculated]: 5/5 = 100%
- Specificity [calculated]: 139,795/139,795 = 100%
- Time from birth to: blood sampling, sample receipt, initial result, confirmatory result, referral, specialist visit, start of treatment
- McMillan 2021 also reports recommendations for diagnosis and treatment of children with SMA identified via newborn screening

[Full text checked]

### Conclusions

The authors concluded that expansion of the screening procedure to the whole country is feasible and would facilitate early diagnosis and result in more effective treatment.

## Study 9: USA (California)

### Citations

Matteson 2022 [31]

### Study type

Cohort study

## Objectives

To evaluate newborn screening for SMA

## Components of the study

**Setting:** USA (California)

**Population:** Newborns

**Duration:** 18 months (June 2020 to December 2021)

**Index test:** Multiplex real-time PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positive and incomplete specimens: retested in triplicate on three fresh DBS punches. Also ddPCR from original DBS to determine *SMN1* and *SMN2* copy numbers. Second multiplex PCR on new blood specimen to confirm deletion of *SMN1* and to determine *SMN2* copy number

[Full text checked]

## Outcomes reported

Outcomes reported:

- N screened: 628,791
- N testing positive: 34
- True positives: 34
- False positives: 0 (but 5 initial incomplete results; see below)
- False negatives: States none reported so far
- True negatives: NR [assumed 628,757]
- Prevalence: 34 of 628,791 (or 1 in 18,494)
- Positive predictive value [calculated]: 34/34 (100%), i.e. all 34 tested positive on confirmatory testing
- Negative predictive value [calculated]: 628,757/628,757 = 100%
- Sensitivity [calculated]: 34/34 = 100%
- Specificity [calculated]: 628,757/628,757 = 100%
- Initial incomplete results: 5 newborns required a repeat DBS; 2 were inconclusive (slightly above cut-off) on initial and repeat samples; not reported why other 3 required repeat; all 5 eventually tested negative
- Time from birth to: test results; referral; diagnosis; starting treatment
- Reports treatment barriers and delays

[Full text checked]

### Conclusions

The authors concluded that SMA newborn screening is a highly sensitive and specific test which identifies infants with SMA early when treatment is most effective.

## Study 10: USA (Georgia state)

### Citations

Elkins 2022 [16]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (Georgia state)

**Population:** Newborns

**Duration:** 2 years (February 2019 to February 2021) (1yr pilot; 1yr standard)

**Index test:** Multiplex real-time PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmatory testing to confirm deletion of *SMN1* and to determine *SMN2* copy number (method NR)

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 301,418
- N testing positive: 39
- True positives: 15
- False positives: 24 (13 in pilot year; reasons NR; 9 were sick and in hospital at sample collection and 3 of these were born premature)
- False negatives: 1 (detected by assay but not reported due to human error during first month of pilot, presented after symptom onset). Not aware of any other FNs
- True negatives: NR [assumed 301,378]
- Prevalence: 16 of 301,418 (or 1 in 18,839)

- Positive predictive value [calculated]: 15/39 (38%), i.e. 15 of 39 tested positive on confirmatory testing
- Negative predictive value [calculated]: 301,378/301,379 = 100%
- Sensitivity [calculated]: 15/16 = 94%
- Specificity [calculated]: 301,378/301,402 = 100%
- Inconclusive results: 147 (not reported what happened to these; 126 were also inconclusive for SCID screening)
- Time from birth to: results; confirmatory testing; specialist visit; starting treatment; time from screening result to confirmatory testing

[Full text checked]

### Conclusions

The authors concluded that the implementation of newborn screening for SMA will continue to identify pre-symptomatic individuals who are most likely to experience long-term benefits of early intervention.

## Study 11: USA (Kentucky)

### Citations

Lakhotia 2022 [27] (abstract)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (Kentucky)

**Population:** Newborns

**Duration:** 2 years (2019 to 2021; months NR)

**Index test:** NR

**Reference standard:** NR

[Reported as abstract only]

### Outcomes reported

Outcomes reported:

- N screened: 108,511
- N testing positive: 16
- True positives: 11
- False positives: 5 (reasons NR; 4/5 also had false positive SCID screen)
- False negatives: NR
- True negatives: NR [assumed 108,495]
- Prevalence: 11 of 108,511 (or 1 in 9,865)
- Positive predictive value [calculated]: 11/16 (69%), i.e. 11 of 16 tested positive on confirmatory testing
- Negative predictive value [calculated]: 108,495/108,495 = 100%
- Sensitivity [calculated]: 11/11 = 100%
- Specificity [calculated]: 108,495/108,500 = 100%
- Time from birth to: screening, specialist visit, confirmatory testing, starting treatment

[Reported as abstract only]

### Conclusions

The authors concluded that SMA diagnosis and confirmation were quick but there were treatment delays due to other factors.

## Study 12: USA (Massachusetts)

### Citations

Hale 2021 [18] (3yr data); Kumar 2021 [26] (methods)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (Massachusetts)

**Population:** Newborns

**Duration:** 3 years (January 2018 to January 2021)

**Index test:** Multiplex real-time qPCR from DBS to screen for homozygous deletion of *SMN1* exon 7. Three-tier test:

- Tier 1: for homozygous deletion of *SMN1* exon 7

- Tiers 2 and 3 described under Reference Standard

**Reference standard:** Three-tier test:

- Tier 1 described under Index Test

- Tier 2 (screen-positives): checks for *SMN1* hybrids with an Exon 7 variant (these count as screen-negative)

- Tier 3 (inconclusive on Tier 1+2): sequencing for presence of C nucleotide at position 840, to confirm deletion of *SMN1* exon 7 and assess *SMN2* copy number

- Also assess *SMN2* copy number at specialist referral

- Repeat screening by specialist noted in relation to the one false positive case

[Full text checked]

## Outcomes reported

Outcomes reported (at 3 years; Hale 2021):

- N screened: 179,467
- N testing positive: 10
- True positives: 9
- False positives: 1 (during first months of screening; sample may have contained inhibitor). States that use of a single Tier 1 assay would have generated many more false positives, some due to SMN1 hybrids which were classed as negative at Tier 2, and others classed as negative at Tier 3
- False negatives: States none observed
- True negatives: NR [assumed 179,457]
- Prevalence: 9 of 179,467 (or 1 in 19,941)
- Positive predictive value [calculated]: 9/10 (90%), i.e. 9 of 10 tested positive on confirmatory testing
- Negative predictive value [calculated and reported]: 179,457/179,457 = 100%
- Sensitivity [calculated and reported]: 9/9 = 100%
- Specificity [calculated and reported]: 179,457/179,458 = 100%
- Time from birth to: test results; specialist referral, starting treatment
- Incidental findings: *SMN1* hybrids with an Exon 7 variant: 10 (these were assumed to have normal function and were observed but not referred; the first six were followed up at 6 months and all considered healthy with no concerns)
- Time from birth to: test results; specialist referral, starting treatment
- Initial incomplete results: More NICU babies required Tier 2/3 screen; authors speculate this may involve a PCR inhibitor (unclear how)

[Full text checked]

### Conclusions

The authors concluded that SMA newborn screeing is feasible, can be implemented on a population basis, and helps engage infants for early treatment.

## Study 13: USA (New York State routine screening)

### Citations

Lee 2022 [28] (3yr data); Kay 2020 [20] (1yr data)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (New York State routine screening)

**Population:** Newborns

**Duration:** 3 years (October 2018 to September 2021)

**Index test:** Multiplex real-time qPCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Second qPCR on new blood specimen to confirm deletion of *SMN1*. Also qPCR and droplet digital PCR to determine *SMN2* copy number

[Full text checked]

### Outcomes reported

Outcomes reported (at 3 years; Lee 2022):

- N screened: Nearly 650,000
- N testing positive: 34
- True positives: 34
- False positives: 0
- False negatives: Not mentioned
- True negatives: NR [assumed 649,966]
- Prevalence: 34 of 650,000 (or 1 in 19,118) [may be lower than expected due to better awareness of genetic transmission, and carrier screening]

- Positive predictive value [calculated]: 34/34 (100%), i.e. all 34 tested positive on confirmatory testing
- Negative predictive value [calculated]: 649,966/649,966 = 100%
- Sensitivity [calculated]: 34/34 = 100%
- Specificity [calculated]: 649,966/649,966 = 100%
- Time from birth to: test results; specialist visit; start of treatment
- Reports delays and barriers to treatment

[Full text checked]

### Conclusions

The authors concluded that the findings of this screening programme were consistent with other reports of improved outcomes from early diagnosis and treatment.

## Study 14: USA (New York State pilot study)

### Citations

Kraszewski 2018 [24]

### Study type

Cohort study

### Objectives

Pilot study to evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (New York State pilot; three hospitals in New York City)

**Population:** Newborns

**Duration:** 1 year (January 2016 to January 2017)

**Index test:** Multiplex real-time qPCR (TaqMan) from DBS to screen for homozygotes and heterozygotes (carriers) for deletion of *SMN1* exon 7. Assays run in triplicate

**Reference standard:** Screen-positives (homozygous or heterozygous deletion) and specimens not meeting quality criteria: rerun for confirmation using DNA extracted from a fresh DBS punch

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 3,826
- N testing positive: 1
- True positives (homozygous *SMN1* deletion): 1
- Carrier frequency (heterozygous): 59/3,826 (1.5% or 1 in 65)
- False positives: 0
- False negatives: None identified so far
- True negatives: NR [assumed 3,825]
- Prevalence: 1 in 3,826
- Positive predictive value [calculated]: 1/1 (100%), i.e. 1 positive tested positive on confirmatory testing
- Negative predictive value [calculated]: 3,825/3,825 = 100%
- Sensitivity [calculated]: 1/1 = 100%
- Specificity [calculated]: 3,825/3,825 = 100%
- Initial incomplete results:
    - First assay failure/rejection: 3% (all suboptimal DNA quality or quantity; all classified as screen-negative or carriers upon retest)
    - Initial test in equivocal range: 33 (0.9%); upon retesting using a fresh DNA sample, all but one resolved as screen negative (N = 30) or heterozygous deletions/carriers (N = 2)
    - Of the above, 1 retested in equivocal range; upon sequencing, it was found to carry a rare heterozygous sequence variant of uncertain significance; classed as screen-negative; in vitro studies have shown does not affect function; do not know clinical significance
- Time from birth to: test results; starting treatment
- Consent rate 93%
- Incidental findings: Also screened for heterozygous carriers of *SMN1* exon 7 deletion. Parents offered genetic testing to determine whether both parents were carriers, for future family planning. Also 1 newborn with variant of unknow significance as described above

[Full text checked]

## Conclusions

The authors concluded that this pilot study demonstrates the feasibility, acceptance by families, and benefit of newborn screening for SMA

## Study 15: USA (North Carolina)

### Citations

Kucera 2021 [25]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA (pilot study “Early Check”)

### Components of the study

**Setting:** USA (North Carolina)

**Population:** Newborns

**Duration:** 26 months (October 2018 to December 2020)

**Index test:** Real-time qPCR (TaqMan) from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Re-testing *SMN1* in duplicate from initial DBS for specimens above the initial cut-off. Confirmatory testing [method NR] on new whole blood sample for *SMN1* and *SMN2* copy number

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 12,065
- N testing positive: 2
- True positives: 1
- False positives: 1 (likely due to unrelated blood disorder associated with a low white blood cell count)
- False negatives: None mentioned
- True negatives: NR [assumed 12,063]
- Prevalence: 1 in 12,065
- Positive predictive value [calculated]: 1/2 (50%), i.e. 1 of 2 tested positive on confirmatory testing
- Negative predictive value [calculated]: 12,063/12,063 = 100%
- Sensitivity [calculated]: 1/1 = 100%
- Specificity [calculated]: 12,063/12,064 = 100%

- Initial incomplete results:
- Not tested due to insufficient quantity: 2 (considered unsatisfactory results)
- First test above cut-off: 36; upon retesting, 2 were above cut-off and considered screen-positive, while 34 considered normal
- Time from birth to: test results; specialist visit; confirmatory test; start of treatment
- Incidental findings: 1 unrelated blood disorder as described above

[Full text checked]

### Conclusions

The authors concluded that the pilot project provided important information about SMA screening in anticipation of forthcoming statewide expansion as part of regular newborn screening.

## Study 16: USA (Ohio)

### Citations

Prior 2010 [36]

### Study type

Retrospective cohort study (used anonymised DBS samples, not part of screening programme)

### Objectives

To evaluate methods for newborn screening for SMA

### Components of the study

**Setting:** USA (Ohio)

**Population:** Newborns

**Duration:** Used anonymised DBS samples, not part of screening programme

**Index test:** PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation using competitive PCR, and *SMN2* copy numbers determined

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 40,103

- N testing positive: 4
- True positives: 4
- False positives: 0
- False negatives: Not mentioned; possibly not sought
- True negatives: NR [assumed 40,099]
- Prevalence: 4 of 40,103 (1 in 10,026)
- Positive predictive value [calculated]: 4/4 (100%), i.e. all 4 tested positive on confirmatory testing
- Negative predictive value [calculated]: 40,099/40,099 = 100%
- Sensitivity: not calculable. Notes that sensitivity of SMA NBS expected to be 95-98% as would not identify compound heterozygotes
- Specificity [calculated]: 40,099/40,099 = 100%
- Initial incomplete results: Specimens requiring repeat re-extraction from original DBS: 7/40,103 (0.02%). On re-testing, all 7 gave robust result
- Workload: demonstrated that the assay has a high throughput and can handle a large number of samples

[Full text checked]

### Conclusions

The authors concluded that their research demonstrated an effective technology exists for SMA newborn screening.

## Study 17: USA (Wisconsin)

### Citations

Baker 2022 [8]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** USA (Wisconsin)

**Population:** Newborns

**Duration:** 1 year (October 2019 to October 2020)

**Index test:** Multiplex real-time PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: ddPCR for *SMN2* copy number determination. Confirmatory testing via ddPCR on new DBS for *SMN1* and *SMN2* copy number

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 60,984
- N testing positive: 6
- True positives: 6
- False positives: 0
- False negatives: None mentioned
- True negatives: NR [assumed 60,978]
- Prevalence: 6 of 60,984 (1 in 10,164)
- Positive predictive value [calculated and reported]: 6/6 (100%), i.e. all 6 tested positive on confirmatory testing
- Negative predictive value [calculated]: 60,978/60,978 = 100%
- Sensitivity [calculated]: 6/6 = 100%. Notes that sensitivity of SMA NBS expected to be approx. 96% as would not identify compound heterozygotes
- Specificity [calculated]: 60,978/60,978 = 100%
- Time from birth to: test results; confirmatory test; start of treatment

[Full text checked]

### Conclusions

The authors concluded that this approach facilitated timely clinical follow-up, family counseling, and treatment planning.

## Study 18: Japan (Kumamoto)

### Citations

Sawada 2022 [37]

### Study type

Cohort study

## Objectives

To evaluate newborn screening for SMA

## Components of the study

**Setting:** Japan (Kumamoto prefecture)

**Population:** Newborns

**Duration:** 1 year (February 2021 to January 2022)

**Index test:** Real-time PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Second qPCR to confirm deletion of *SMN1*. Also MLPA to determine *SMN1* and *SMN2* copy number

[Full text checked]

## Outcomes reported

Outcomes reported:

- N screened: 13,587
- N testing positive: 1
- True positives: 1
- False positives: 0
- False negatives: None identified so far
- True negatives: NR [assumed 13,586]
- Prevalence: 1 in 13,587
- Positive predictive value [calculated]: 1/1 (100%), i.e. the 1 patient tested positive on confirmatory testing
- Negative predictive value [calculated]: 13,586/13,586 = 100%
- Sensitivity [calculated]: 1/1 = 100%
- Specificity [calculated]: 13,586/13,586 = 100%
- Time from birth to: test results; diagnosis; start of treatment

[Full text checked]

## Conclusions

The authors concluded that we should acquire a better screening and treatment system that enables individuals with SMA to undergo treatment within the appropriate time window.

## Study 19: Japan (Osaka)

### Citations

Kimizu 2021 [22]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Japan (Osaka prefecture)

**Population:** Newborns

**Duration:** 3 months (February 2021 to May 2021)

**Index test:** Real-time PCR from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** NR

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: more than 10,000
- N testing positive: 0
- True positives: 0
- False positives: 0
- False negatives: Not mentioned
- True negatives: NR
- Prevalence: Not calculable
- Positive predictive value: Not calculable
- Negative predictive value: Not calculable
- Sensitivity: Not calculable
- Specificity: Not calculable

[Full text checked]

### Conclusions

The authors concluded with their hope that SMA newborn screening programs will soon be implemented in all prefectures in Japan.

## Study 20: Japan (all)

### Citations

Shinohara 2019 [38]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Japan (49 hospitals in 23 of 47 prefectures in Japan)

**Population:** Newborns

**Duration:** 15 months (January 2018 to April 2019)

**Index test:** Pre-amplification of *SMN* genes by conventional PCR, then gene-specific amplification of *SMN1* and *SMN2* exon 7 by real-time modified competitive oligonucleotide priming-PCR (mCOP-PCR), to detect homozygous deletion of *SMN1* exon 7 from DBS

**Reference standard:** NR

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 4,157
- N testing positive: 0
- True positives: 0
- False positives: 0
- False negatives: None identified so far
- True negatives: NR
- Prevalence: Not calculable
- Positive predictive value: Not calculable

- Negative predictive value: Not calculable
- Sensitivity: Not calculable [reported separately for case-control study]
- Specificity: Not calculable [reported separately for case-control study]

[Full text checked]

### Conclusions

The authors concluded that their method can be reliably used in SMA newborn screening.

## Study 21: Taiwan

### Citations

Weng 2021 [41]; Chien 2017 [13]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Taiwan

**Population:** Newborns

**Duration:** Weng 2021: 5 years (November 2014 to December 2019). Chien 2017: 22 months (November 2014 to September 2016)

**Index test:** Real-time PCR (TaqMan) from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: ddPCR on original DBS and MLPA on a new whole blood sample, for confirmation of *SMN2* copy number and exon 7 c.840C>T mutation

[Full text checked]

### Outcomes reported

Outcomes reported (extracted two papers separately as both have gaps in data):

Weng 2021:

- N screened: 364,000
- N testing positive: NR

- True positives: 20
- False positives: NR [Weng 2021 notes primers later modified to avoid false positives]
- False negatives: 1 (*SMN1* heterozygous for deletion and point mutation)
- True negatives: NR
- Prevalence: 21 of 364,000 (or approx. 1 in 17,000)
- Positive predictive value: Not calculable
- Negative predictive value: Not calculable
- Sensitivity [calculated]: 20/20 = 100% for homozygous deletion; 20/21 = 95% including compound heterozygote
- Specificity: Not calculable

Chien 2017:

- N screened: 120,267
- N testing positive: 15
- True positives: 7
- False positives: 8 (all 8 had 1 copy of *SMN1*; 5 caused by intragenic recombination between *SMN1* and *SMN2*)
- False negatives: None identified so far
- True negatives: NR [assumed 120,252]
- Prevalence: 7 of 120,267 (or 1 in 17,181)
- Positive predictive value [calculated and reported]: 7/15 (47%), i.e. 7 of 15 tested positive on confirmatory testing. When including second-tier ddPCR, positive predictive value = 7/7 = 100%
- Negative predictive value [calculated]: 120,252/120,252 = 100%
- Sensitivity [calculated]: 7/7 = 100%. Notes that sensitivity of SMA NBS expected to be approx. 95% as would not identify compound heterozygotes [also reported separately for case-control study]
- Specificity [calculated and reported]: 120,252/120,260 = 100%
- Initial incomplete results: 50 samples gave unsatisfactory results; a repeat DNA extraction and RT-PCR excluded SMA [also reported separately for case-control study]

[Full text checked]

## Conclusions

The authors concluded that newborn screening can detect patients affected by SMA before symptom onset and enable early therapeutic intervention

## Study 22: China (Hunan)

### Citations

Pan 2021 [35]

### Study type

Cohort study (used anonymised DBS samples, not part of screening programme)

### Objectives

To evaluate methods for newborn screening for SMA

### Components of the study

**Setting:** China (Hunan province)

**Population:** Newborns

**Duration:** Used randomly selected stored DBS samples, not part of screening programme

**Index test:** Duplexed real-time PCR from DBS to amplify *SMN1*

**Reference standard:** Screen-positives: Confirmation using MLPA [unclear whether for screening study or only for case-control study]

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 753
- N testing positive: 0 homozygous *SMN1* deletions (15 heterozygous carriers)
- True positives: 0 (15 carriers)
- False positives: Not mentioned
- False negatives: Not mentioned; possibly not sought
- True negatives: NR
- Prevalence: Not calculable
- Positive predictive value: Not calculable
- Negative predictive value: Not calculable
- Sensitivity: Not calculable [reported separately for case-control study]
- Specificity: Not calculable [reported separately for case-control study]

[Full text checked]

### Conclusions

The authors concluded that their approach could be applied to newborn screening.

## Study 23: China (six hospitals)

### Citations

Lin 2019 [29]

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** China (six hospitals)

**Population:** Newborns

**Duration:** 4 months (March 2018 to June 2018)

**Index test:** DNA mass spectrometry (Agena iPLEX assay; target-specific PCR followed by single-base extension) from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmatory MLPA to determine *SMN1* and *SMN2* copy number

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 29,364
- N testing positive: 3
- True positives: 3
- False positives: 0
- False negatives: Not mentioned
- True negatives: NR [assumed 29,361]
- Prevalence: 3 of 29,364 (or 1 in 9,788)
- Positive predictive value [calculated]: 3/3 (100%), i.e. all 3 tested positive on confirmatory testing

- Negative predictive value [calculated]: 29,361/29,361 = 100%
- Sensitivity [calculated]: 3/3 = 100% [also reported separately for case-control study]
- Specificity [calculated]: 29,361/29,361 = 100% [also reported separately for case-control study]

[Full text checked]

### Conclusions

The authors concluded that this study showed that large-scale implementation of population-based newborn screening for SMA is feasible.

## Study 24: China (Southwest)

### Citations

Liu 2016 [30]

### Study type

Cohort study (used anonymised DBS samples, not part of screening programme)

### Objectives

To evaluate methods for newborn screening for SMA

### Components of the study

**Setting:** China (Southwest)

**Population:** Newborns

**Duration:** Used randomly selected stored DBS samples, not part of screening programme

**Index test:** Multiplex real-time PCR

**Reference standard:** Screen-positives: Confirmatory DNA sequencing

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 2,000
- N testing positive: 23
- True positives (homozygous *SMN1* deletion): 1
- False positives: 22
- False negatives: Not mentioned; possibly not sought

- True negatives: NR [assumed 1,977]
- Prevalence: Not calculable
- Positive predictive value [calculated]: 1/23 (4%), i.e. 1 of 23 tested positive on confirmatory testing
- Negative predictive value [calculated]: 1,977/1,977 = 100%
- Sensitivity: Not calculable
- Specificity: 1,977/1,977 = 100%

[Full text checked]

### Conclusions

The authors concluded that their work demonstrates potential usage in newborn screening for early diagnosis of SMA

## Study 25: Russia

### Citations

Kiselev 2023 [23] (preprint; not peer reviewed)

### Study type

Cohort study

### Objectives

To evaluate newborn screening for SMA

### Components of the study

**Setting:** Russia (Saint Petersburg, 21 hospitals)

**Population:** Newborns

**Duration:** 11 months (January 202 to November 2022)

**Index test:** Real-time PCR (GenomeX) from DBS to screen for homozygous deletion of *SMN1* exon 7

**Reference standard:** Screen-positives: Confirmation using different real-time PCR system and MLPA, and *SMN2* copy numbers determined

[Full text checked]

### Outcomes reported

Outcomes reported:

- N screened: 36,140
- N testing positive (homozygous SMN1 deletion): 4
- Heterozygous carriers: 772 (carrier frequency 1 in 47)
- True positives: 4
- False positives for homozygous SMN1 deletion: 0 (2 false positives for heterozygous carriers)
- False negatives: Not mentioned
- True negatives: NR [assumed 36,136]
- Prevalence: 4 of 36,140 (or 1 in 9,035)
- Positive predictive value [calculated]: 4/4 (100%), i.e. all 4 tested positive on confirmatory testing
- Negative predictive value [calculated]: 36,136/36,136 = 100%
- Sensitivity [calculated]: 4/4 = 100%
- Specificity [calculated]: 36,136/36,136 = 100%
- Time from: sample receipt to analysis
- Consent rate 99.8%

[Full text checked]

### Conclusions

The authors concluded that providing timely SMN1 information and SMN2 copy number as part of SMA newborn screening can improve clinical follow-up, family members testing, and SMA patients' treatment.

## Reviews of newborn screening

The following section summarises reviews of newborn screening.

## Review 1

### Citation

Dangouloff 2021 [2]

### Study type

Systematic review

### Objectives

Systematic review of newborn screening for SMA and other neuromuscular diseases

### Components of the study

Methods: Search of PubMed to May 2021

### Findings reported

Summarises 9 newborn screening programmes for SMA:

- Belgium, Germany, Italy, Australia, Canada (Ontario), USA (New York State), Taiwan, Japan, Russia
- In most programmes, first-tier screening is real-time qPCR. Second-tier screening usually MLPA, or (in USA and Italy) qPCR
- Recent survey found several countries intend to initiate a newborn screening programme soon

[Full text checked]

### Conclusions

The authors concluded that the future of newborn screening for neuromuscular disorders will pass through a global technological switch, from a biochemical to a genetic-based approach.

## Review 2

### Citation

IQWiG 2020 [4]

### Study type

Systematic review

### Objectives

Systematic review of newborn screening and treatment for SMA

### Components of the study

Methods: Search of Medline, Embase, Cochrane, and HTA Database to October 2019

### Findings reported

Summarises 4 newborn screening programmes for SMA:

- Germany, Australia, USA (New York State), Taiwan
- No comparative interventional studies of the screening chain were identified

[Full text checked]

### Conclusions

The authors concluded that the examined test methods are suitable for newborn screening for 5q-linked SMA, though it remains unclear how many affected children were missed by the testing.

## Review 3

### Citation

Jedrzejowska 2020 [5]

### Study type

Narrative review

### Objectives

Narrative review of newborn screening and treatment for SMA

### Components of the study

Methods: Does not report search dates/method

### Findings reported

Narrative review of newborn screening for SMA:

- States that many countries have started national or pilot newborn screening programmes for SMA, including Belgium, Germany, Australia, USA, Taiwan

[Full text checked]

### Conclusions

The authors concluded that early treatment of SMA seems to be crucial for maximizing therapeutic effects and, at present, the best solution may be to screen all newborns for SMA.

## Review 4

### Citation

UK NSC (Costello Medical) 2018 [1]

### Study type

Evidence summary

### Objectives

Evidence summary of screening and treatment for SMA

### Components of the study

Methods: Search of Medline, Embase, Cochrane to August 2017; update search in February 2018

### Findings reported

Identified 4 publications reporting on 5 studies of newborn screening for SMA:

- 3 case-control studies
- 2 cohort studies (Taiwan, China)

[Full text checked]

### Conclusions

The authors concluded that it was not yet possible to robustly quantify the accuracy of newborn screening methods.

## Review 5

### Citation

Hale 2021 [3]

### Study type

Narrative review

### Objectives

Narrative review of newborn screening for SMA in the USA

### Components of the study

Methods: Does not report search dates/method

### Findings reported

Summarises newborn screening programmes for SMA in USA:

- 3 case-control studies
- 2 cohort studies (Taiwan, China)

[Full text checked]

### Conclusions

The authors concluded that it was not yet possible to robustly quantify the accuracy of newborn screening methods.

## Review 6

### Citation

Schroth 2022 [6] (abstract)

### Study type

Narrative review

### Objectives

Narrative review of newborn screening for SMA in the USA

### Components of the study

Methods: Does not report search dates/method

### Findings reported

Summarises newborn screening programmes for SMA in USA:

- SMA was approved by the US recommended uniform screening panel (RUSP) in July 2018
- As of Quarter 3 2021, 38 states had implemented SMA NBS, representing 85% of infants born in US
- More than 276 infants had been identified by SMA NBS, with 30 states reporting data
- Of 44 infants included in the Cure SMA registry: median diagnosis age was 7 days; median time to treatment after diagnosis was 19 days

[Full text checked]

### Conclusions

The authors concluded that widespread newborn screening is critical toward ensuring SMA infants receive prompt diagnosis and treatment.

## Case-control studies of newborn screening

The following section lists case-control studies of newborn screening. Because case-control studies tend to overestimate test accuracy parameters, and due to the availability of several cohort studies, case-control studies were not extracted, but are listed here for information.

**Case-control studies:**

Adams 2021 [42]: UK

Boemer 2019 [11]: Belgium

Czibere 2020 [14]: Germany

Gutierrez-Mateo 2019 [47]: Denmark

Strunk 2019 [51]: Netherlands

Cavdarli 2020 [44]: Turkey

Kraszewski 2018 [24]: USA (New York State)

Pyatt 2007 [48]: USA (Ohio)

Pyatt 2006 [49]: USA (Ohio)

Kucera 2021 [25]: USA (North Carolina)

Taylor 2015 [52]: USA (North Carolina)

Vidal-Folch 2018 [53]: USA

Romanelli Tavares 2021 [50]: Brazil

Ar Rochmah 2017 [43]: Japan

Kimizu 2021 [22]: Japan

Shinohara 2019 [38]: Japan

Wijaya 2021 [56]: Japan (DBS)

Wijaya 2021 [55]: Japan (saliva rather than DBS; doesn't technically meet inclusion criteria)

Chien 2017 [13]: Taiwan

Er 2012 [45]: Taiwan

Wang 2021 [54]: Taiwan

Lin 2019 [29]: China

Liu 2016 [30]: China

Pan 2021 [35]: China

Kiselev 2023 [23]: Russia

Guo 2021 [46]: Location unclear (abstract only)

# Question 2: What is the volume and type of evidence on the effectiveness of pharmacological treatment for presymptomatic SMA?

## Studies of presymptomatic treatment

The following section summarises studies of presymptomatic treatment.

## Study 1: NURTURE study of nusinersen

### Citations

De Vivo 2019 [61] (full paper); Kirschner 2022 [66] (abstract, QoL); Sansone 2021 [68] (abstract, swallowing function)

### Study type

Phase 2, multicentre, open-label, single-arm trial

### Objectives

To evaluate nusinersen in presymptomatic SMA

### Components of the study

**Setting:** 15 sites in 7 countries

**Population:** Babies with presymptomatic SMA (total n=25); two *SMN2* copies (n=15) or three *SMN2* copies (n=10); likely to develop SMA type I or II; ≤6 weeks old at first dose

**Intervention:** Nusinersen for 5 years (as 12 mg intrathecal injections by lumbar puncture; four loading doses on days 1, 15, 29, and 64, then maintenance dose every 119 days)

**Follow-up duration:**

Planned: 5-year treatment then post-treatment follow-up

De Vivo 2019 interim analysis: median follow-up 2.9 years (35 months), median age 2.9 years (35 months); data cut March 2019)

Kirschner 2022 analysis (QoL): median follow-up 2.4 and 3.1 years for different QoL tools (data cut February 2021)

Sansone 2021 analysis (swallowing function): median age 3.8 years (data cut February 2020)

[Full text checked]

### Outcomes reported

De Vivo 2019 interim analysis:

Outcomes (efficacy):

- Median age 34.8mo and past age of symptoms for SMA types I and II
- All (25/25, 100%) were alive
- None required tracheostomy or permanent ventilation
- Four (16%) with two SMN2 copies used respiratory support for ≥6 h/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. No others received respiratory intervention
- All (25/25, 100%) achieved ability to sit without support
- 23/25 (92%) achieved walking with assistance (13/15 with two SMN2 copies and 10/10 with three SMN2 copies)
- 22/25 (88%) achieved walking independently (12/15 with two SMN2 copies and 10/10 with three SMN2 copies)
- Mean CHOP INTEND motor function total scores rose steadily to Day 183 then remained stable; mean score at last visit was 62.1 (two SMN2 copies) and 63.4 (three SMN2 copies); 10/15 (67%) with two SMN2 copies and 10/10 (100%) with three SMN2 copies achieved a maximum score of 64
- HINE-2 motor milestone total scores: increased from 2.7 to 23.9 (two SMN2 copies) and from 3.2 to 26.0 (three SMN2 copies)
- HINE-1 neurological assessment: 22/25 (12/15 with two SMN2 copies, 10/10 with three SMN2 copies) achieved the maximum score of 3 (good sucking and swallowing) while 3 had score of 1 (poor sucking and swallowing) and had gastrostomy tubes placed
- Proportions with protocol-defined symptoms of SMA: two SMN2 copies: 10/15 at age 13 months and 7/15 at age 24 months; three SMN2 copies: 2/10 at age 13 months and 0/10 at age 24 months; the 7 who developed symptoms all continued to grow and achieve motor milestones inconsistent with type I SMA or with their siblings
- Exploratory endpoints (change in pNF-H and CMAP) and predictors of future motor function: not extracted

Outcomes (safety):

- 25/25 (100%) had AEs. Of these, 8/25 (32%) had adverse events considered possibly related to nusinersen; all resolved despite continued treatment, other than 1 case of proteinuria and 1 case of clonus
- 12/25 (48%) had SAEs. Of these, none considered to be related to nusinersen

[Full text checked]

Kirschner 2022 analysis (QoL):

Outcomes:

- Overall pattern of increases in ACEND mean scores among caregivers of participants (with two and three SMN2 copies) from first assessment in NURTURE to Day 1440 in the physical impact subdomains: feeding/grooming/dressing, transfer, and mobility
- Near-maximum ACEND mean scores (signifying reduced caregiver impact) were observed at first assessment and maintained over time to Day 1440 for the sitting/play physical impact subdomain, regardless of SMN2 copy number

- ACEND mean scores in all seven domains were generally higher among caregivers of participants who had three versus two SMN2 copies at both timepoints
- PedsQL-GCS and -NM mean scores were higher among caregivers of participants who had three versus two SMN2 copies at first assessment and at Day 1440
- Although small decreases were observed over time, PedsQL-GCS mean scores observed at first assessment and at Day 1440 remained high, especially among caregivers of participants with three SMN2 copies
- Mean (SD) scores of the PedsQL-GCS among caregivers of participants with three SMN2 copies at both first assessment: 93.7 (5.9) and at Day 1440: 88.3 (10.8) were comparable to those reported by caregivers in healthy toddlers aged 2-4: 87.4 (12.5) as reported in a validation study by Varni et al 2003

[This citation is an abstract only]

Sansone 2021 analysis (swallowing function):

Outcomes (swallowing function assessed via Parent Assessment of Swallowing Ability (PASA) questionnaire):

- At last assessment (Day 778), 84% were not tube fed (11/15 with two SMN2 copies, all with three SMN2 copies)
- Of the 4 tube fed participants, 2 participants' parents answered "always" and 2 answered "often" to being tube fed in the previous 7 days
- 91% never gagged or choked on liquid food, 87% never gagged or choked on solid food; 88% (21/24) and 96% (23/24) of parents disagreed/strongly disagreed with being concerned over their child choking and aspirating on their food while eating

[This citation is an abstract only]

### Conclusions

De Vivo 2019: The authors concluded that these results emphasize the importance of proactive treatment with nusinersen immediately after establishing the genetic diagnosis of SMA in presymptomatic infants and emerging newborn screening efforts

Kirschner 2022: The authors concluded that nusinersen was associated with sustained reduced impact on caregiver experience and high levels of HRQoL over time among caregivers of participants with presymptomatic SMA who had been treated for several years

Sansone 2021: The authors concluded that swallowing ability was maintained in most patients with two SMN2 copies and all patients with three SMN2 copies with nusinersen

## Study 2: SPR1NT study of onasemnogene abeparvovec

### Citations

Strauss 2022 [74] (full paper; three copies *SMN2*); Strauss 2022 [75] (full paper; two copies *SMN2*)

## Study type

Phase 3, multicentre, open-label, single-arm trial

## Objectives

To evaluate onasemnogene abeparvovec in presymptomatic SMA (three *SMN2* copies in one paper; two copies in other paper)

## Components of the study

**Setting:** 16 sites in 6 countries

**Population:** Babies with presymptomatic SMA, ≤6 weeks old at treatment:

a) Three SMN2 copies (n=15); likely to develop SMA type II; 13/15 were diagnosed via newborn screening

b) Two SMN2 copies (n=14); likely to develop SMA type I; 5/14 (36%) diagnosed via prenatal screening and 9/14 (64%) via newborn screening

**Intervention:** Onasemnogene abeparvovec (Zolgensma) via infusion at median age of 32 days (three-copy cohort) and 21 days (two-copy cohort)

**Comparator:** No comparator within the study; however efficacy was compared with a matched Pediatric Neuromuscular Clinical Research natural-history cohort (n = 81 for three-copy cohort; N=23 for two-copy cohort)

**Follow-up duration:**

Three-copy cohort: Total follow-up 24 months (2 years)

Two-copy cohort: Total follow-up 18 months (1.5 years)

[Full text checked]

## Outcomes reported

Three copies *SMN2* (Strauss 2022):

Outcomes (efficacy):

- All (15/15, 100%) survived without permanent ventilation at 14 months
- All (15/15, 100%) stood independently before 24 months; 14 within normal developmental window (24% in PNCR natural history cohort; p< 0.0001)
- 14/15 (93%) walked independently; 11 within normal developmental window (21% in PNCR natural history cohort; p< 0.0001)
- 10/15 (67%) maintained body weight (≥3rd WHO percentile) without feeding support through 24 months
- None required nutritional or respiratory support
- Bayley Scales of Infant and Toddler Development (BSID) motor endpoints: Not extracted

Outcomes (safety):

- To attenuate the inflammatory response, all 15 commenced oral prednisolone 1 day before infusion and completed a median of 63 days of therapy
- All had treatment-emergent AEs; 8/15 (53%) had AEs considered to be related to treatment
- 3/15 (20%) had SAEs. Of these, none considered to be related to treatment

Two copies *SMN2* (Strauss 2022):

Outcomes (efficacy):

- All (14/14, 100%) survived without permanent ventilation at 14 months as per protocol (26% in PNCR natural history cohort; p<0.0001)
- All (14/14, 100%) sat independently for ≥30 seconds at any visit ≤18 months (Bayley-III item #26; 11 within the normal developmental window (0% in PNCR natural history cohort; p < 0.0001)
- 11/14 (79%) stood independently; 7 within the developmental window
- 9/14 (64%) walked independently by BSID criteria and 10/14 (71%) by WHO-MGRS criteria
- 13/14 (93%) maintained body weight (≥3rd WHO percentile) through 18 months
- None required nutritional or respiratory support

Outcomes (safety):

- To attenuate the inflammatory response, all 14 commenced oral prednisolone 1 day before infusion and completed a median of 60 days of therapy
- All had treatment-emergent AEs; 10/14 (71%) had AEs considered to be related to treatment
- 5/14 (36%) had SAEs. Of these, none considered to be related to treatment

[Full text checked]

### Conclusions

Three-copy cohort: The authors concluded that onasemnogene abeparvovec was effective and well-tolerated for presymptomatic infants at risk of SMA type 2, underscoring the urgency of early identification and intervention

Two-copy cohort: The authors concluded that onasemnogene abeparvovec was effective and well-tolerated for children expected to develop SMA type 1, highlighting the urgency for universal newborn screening

## Study 3: RAINBOWFISH study of risdiplam

### Citations

RAINBOWFISH study: Servais 2022 [72] (abstract)

### Study type

Multicentre, open-label, single-arm trial

### Objectives

To evaluate risdiplam in presymptomatic SMA

### Components of the study

**Setting:** Global (NR sites and countries)

**Population:** Babies with presymptomatic SMA (n=18); results presented are for n=7 with ≥12 months treatment (4 with two *SMN2* copies; 3 with >2 *SMN2* copies); ≤6 weeks old at first dose

**Intervention:** Risdiplam once daily for 24 months (median age at first dose 26.5 days)

**Follow-up duration:** Planned: 24 months treatment then at least 36 months further follow-up. This interim analysis: follow-up ≥12 months for analysed patients (n=7); data cut July 2021

[Full text checked]

### Outcomes reported

Outcomes (efficacy, for n=7 receiving risdiplam for ≥12 months):

- Most infants reached near maximum scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale by 4-5 months of age and achieved motor milestones
- All 7 were alive without permanent ventilation
- All maintained swallowing and feeding abilities and had not required hospitalisation

Outcomes (safety, for n=7 receiving risdiplam for ≥12 months):

- No treatment-related SAEs

[Full text checked]

### Conclusions

The authors concluded that RAINBOWFISH will provide valuable information about outcomes following presymptomatic administration of risdiplam and will help determine the dose for infants <2 months of age

## Study 4

### Citations

NURTURE vs. ENDEAR: Biogen 2019 [57] (data taken from IQWiG 2020 review)

## Study type

Retrospective comparative study of presymptomatic nusinersen (NURTURE single-arm study) vs. early symptomatic treatment (nusinersen arm of ENDEAR RCT)

## Objectives

To compare presymptomatic nusinersen vs. early symptomatic treatment

## Components of the study

**Setting:** Various

**Population:** SMA (two SMN2 copies): a) Early symptomatic group: ENDEAR nusinersen arm, early treatment subgroup (n=34). B) Presymptomatic group: NURTURE, subset with two SMN2 copies (n=15)

**Intervention:** Nusinersen arm from each study

**Follow-up duration:** NR

[Full text checked]

## Outcomes reported

Outcomes for comparison of presymptomatic versus early symptomatic treatment start (taken from IQWiG 2020 review):

- For motor milestone achievement, large effects were found in favour of a presymptomatic treatment start over early symptomatic treatment start (disease duration ≤ 12 weeks); these effects were not explicable solely by bias (dramatic effect)
- For serious AEs and severe AEs, statistically significant differences were found in favour of a presymptomatic treatment start over early treatment start. These observed differences were assessed as small enough to be explicable solely by the effect of confounders
- For overall survival, permanent ventilation, treatment discontinuation due to AEs, and back pain, no statistically significant differences were found. The criteria of a dramatic effect were not met

[Full text checked]

## Conclusions

(No summary as information taken from existing review)

# Study 5

## Citations

ENDEAR study: Finkel 2017 [64] (data taken from IQWiG 2020 review)

(Not met inclusion criteria but may be of interest due to comparison of treatment timings)

### Study type

Comparison of early vs. late symptomatic treatment start, based on stratified subgroups of ENDEAR multicentre RCT

### Objectives

To compare early vs. late symptomatic nusinersen treatment start

### Components of the study

**Setting:** Various

**Population:** Symptomatic early-onset SMA (two SMN2 copies) (n=121): comparison of early (n=52) vs. late (n=69) symptomatic treatment start

**Intervention:** Nusinersen vs. sham; compared subgroups with early vs. late symptomatic treatment start

**Follow-up duration:** Mean follow-up at final data cut: 40 weeks

[Full text checked]

### Outcomes reported

Outcomes for comparison of early versus late symptomatic treatment start (disease duration ≤ 12 weeks vs. disease duration > 12 weeks):

- For time to death or permanent ventilation, and for motor milestone achievement, subgroup analyses revealed that children with an early symptomatic treatment start benefit more than children with a later treatment start
- There was no effect difference between early and late subgroups for serious AEs, severe AEs, and treatment discontinuation due to AEs

[Full text checked]

### Conclusions

(No summary as information taken from existing review)

## Study 6

### Citations

Boemer 2021 [10]

### Study type

Newborn screening study

## Objectives

Clinical follow-up of SMA cases

## Components of the study

**Setting:** Belgium

**Population:** N=10 (5 presymptomatic with three or four SMN2 copies; 5 early symptomatic with 2 SMN2 copies); 9 identified via screening, 1 via symptoms

**Intervention:** Nusinersen (n=7); onasemnogene abeparvovec (n=2); risdiplam (n=1)

**Follow-up duration:** Various

[Full text checked]

## Outcomes reported

Outcomes:

Two SMN2 copies (n=5):

- All 5 symptomatic; 4 had nusinersen, 1 onasemnogene abeparvovec
- Treated at age 29 to 54 days (except 1 patient identified symptomatically at age of 4 months)
- All had developmental delays despite treatment
- Nusinersen: 3/4 sat independently; 1/4 walked with help and 3/4 could not walk
- Onasemnogene abeparvovec; 1/1 sat independently; could stand but not walk

Three SMN2 copies (n=3):

- All 3 presymptomatic; 2 had nusinersen, 1 onasemnogene abeparvovec
- Treated at age 30 to 41 days
- All 3 reached hit motor developmental milestones at the usual ages (sat independently, walked independently)

Four SMN2 copies (n=2):

- All presymptomatic; 1 had nusinersen, 1 risdiplam
- Treated at age 39 to 49 days
- All 2 reached hit motor developmental milestones at the usual ages (sat independently, walked independently)

Other information:

- Also reports CHOP-INTEND and HINE-2 scores per patient

- Nusinersen was routinely available, but 3 patients receiving onasemnogene abeparvovec and risdiplam had this via trials (SPR1NT, STRIVE-EU, RAINBOWFISH) so some overlap with trial data

[Full text checked]

### Conclusions

The authors concluded that the pilot program has now successfully transitioned into the official neonatal screening program in Southern Belgium

## Study 7

### Citations

Vill 2021 [40]; Blaschek 2022 [58]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** Germany

**Population:** N=43 (17 with 2 SMN2 copies; 10 with 3 copies; 14 with 4 copies; 2 with 5 copies); identified via screening

**Intervention:** Nusinersen (n=22); untreated (n=21)

**Follow-up duration:** Median follow-up 13 months

[Full text checked]

### Outcomes reported

Outcomes:

Vill 2021:

Two SMN2 copies (n=17):

- 15 received nusinersen at age 14-39 days
- 8 presymptomatic with nusinersen; remained symptom-free and achieved normal motor milestones
- 7 symptomatic with nusinersen; CHOP-INTEND and HINE-2 scores improved under therapy but motor milestones were delayed

- All 15 treated patients had no respiratory involvement, orthopaedic complications, or tube feeding
- 2 patients not treated (1 parent decision; 1 without German citizenship); both died at 5.5 months due to respiratory failure

Three SMN2 copies (n=10):

- 6 presymptomatic, had nusinersen (at age 20-29 days); 5/6 remained symptom-free with normal motor milestones and no respiratory issues (median follow-up 13 months); 1/6 had minimal delay of motor milestones
- 4 patients not treated (3 parent decision; 1 misdiagnosed as four SMN2 copies); 3 developed proximal weakness (1 at 8 months, 2 at 11 months) and 1 developed motor deterioration at 6 months

Four SMN2 copies (n=14) and five copies (n=2):

- 1 presymptomatic (four SMN2 copies) received nusinersen at age 6 months; remained asymptomatic (median follow-up 13.2 months)
- 15 untreated; all remained asymptomatic (median follow-up 13.2 months)

Siblings:

- Two families with newborns with four SMN2 copies reported motor symptoms in a sibling (5 and 6 years old)
- Both diagnosed with SMA type 3 and treatment initiated (NR type)

Blaschek 2022:

Four SMN2 copies (n=15):

- 8 presymptomatic, treated (at 3-36 months of age), no symptoms at follow-up
- 7 presymptomatic, untreated, 5 showed clinical or electrophysiological disease onset (at 1.5 to 4 years of age); in 2, complete recovery was not achieved despite immediate initiation of treatment after symptom onset

[Full text checked]

## Conclusions

The authors concluded that identification of newborns with infantile SMA and prompt SMA-specific treatment substantially improves neurodevelopmental outcome.

## Study 8

### Citations

Kariyawasam 2020 [19]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** Australia

**Population:** N=9 (6 with 2 SMN2 copies; 3 with 3 copies); did not include those with 4+ copies in this analysis; identified via screening

**Intervention:** Nusinersen (n=4); onasemnogene abeparvovec or risdiplam (n=4); untreated (n=1)

**Follow-up duration:** Follow-up 6 weeks to 12 months

[Full text checked]

### Outcomes reported

Outcomes:

Two SMN2 copies (n=6):

- 3 presymptomatic, all in clinical trial (SPR1NT or RAINBOWFISH)
    - no results presented
- 2 symptomatic, treated with nusinersen:
    - 1 improving motor function
    - 1 deteriorating motor function, noninvasive ventilation, tube feeding
- 1 symptomatic + comorbidities, no treatment (palliation)
    - no results presented

Three SMN2 copies (n=3):

- 2 presymptomatic at treatment
    - 1 received nusinersen; improving motor function
    - 1 in clinical trial (SPR1NT or RAINBOWFISH); no results presented
- 1 symptomatic
    - received nusinersen; improving motor function

Other information:

- Median time to care plan or treatment: 26.5 days from birth (16-37 days)

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 9

### Citations

Matteson 2022 [31]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** USA (California)

**Population:** N=34 (16 with 2 SMN2 copies; 12 with 3 copies; 6 with ≥4 copies); identified via screening

**Intervention:** Onasemnogene abeparvovec (n=29); nusinersen (n=3); both (n=1); untreated (n=1)

**Follow-up duration:** Follow-up of at least 1 year form birth in 22/34 patients

[Full text checked]

### Outcomes reported

Outcomes:

- 34 patients (16 with two SMN2 copies, 12 with three copies, 6 with ≥4 copies)
- Infants were referred, diagnosed, and treated at a median of 8, 12, and 33 days of life. Treatment at median 30 days (2 or 3 copies SMN2) or median 57 days (≥4 copies SMN2)
- Of 34 patients, 33 treated, 1 died prior to treatment (had two SMN2 copies and congenital heart defect)
- Of 33 treated: 29 onasemnogene abeparvovec, 3 nusinersen, 1 both

- 21 (62%) received presymptomatic treatment
- Of 34 infants, long-term follow-up data for 22 (at least 1 year old at time of report); all had treatment:
    - 8 with 2 SMN2 copies: 6 had symptoms (3 initially asymptomatic); 3 symptomatic children had delays or barriers to treatment
    - 7 with 3 SMN2 copies: None with symptoms
    - 1 with ≥4 SMN2 copies: No symptoms

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 10

### Citations

Elkins 2022 [16]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** USA (Georgia State)

**Population:** N=16 (2 with 1 SMN2 copy; 5 with 2 SMN2 copies; 7 with 3 copies; 2 with 4+ copies); identified via screening (n=15) or symptoms (n=1)

**Intervention:** Onasemnogene abeparvovec (n=9); nusinersen (n=1); untreated (n=6)

**Follow-up duration:** Various

[Full text checked]

### Outcomes reported

Outcomes:

One SMN2 copy (n=2):

- 2 symptomatic; both died at 10 days and 22 months

Two SMN2 copies (n=5):

- 2 presymptomatic; both received onasemnogene abeparvovec at 1 and 2 months; 1 had follow-up data though unclear how severe
- 3 symptomatic; 2 died at 44 and 66 days; 1 received onasemnogene abeparvovec at age 1.5 months (no follow-up data)

Three SMN2 copies (n=7):

- 6 presymptomatic; all 6 received onasemnogene abeparvovec at age 3-6 months; 3 had no follow-up data, 1 had some symptoms and 2 had normal exam at follow-up
- 1 symptomatic (identified via symptoms); received nusinersen at 20 months; progression of symptoms by 22 months

Four+ SMN2 copies (n=2):

- 2 presymptomatic; 1 lost to follow-up, 1 untreated and normal exam at 1.5 months of age

Other information:

- Median age at first clinic visit 33 days; median age of treatment with onasemnogene abeparvovec 106 days

[Full text checked]

### Conclusions

The authors concluded that trends for treated patients show improved or stable motor function, and that long-term follow-up will help determine the durability of treatment.

## Study 11

### Citations

Hale 2021 [18]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** USA (Massachusetts)

**Population:** N=9 (7 with 2 SMN2 copies; 2 with 4 copies); identified via screening

**Intervention:** Nusinersen (n=2); onasemnogene abeparvovec (OA) (n=5); nusineren+OA (n=1); nusinersen+OA+risdiplam (n=1)

**Follow-up duration:** Various

[Full text checked]

### Outcomes reported

Outcomes:

Two SMN2 copies (n=7):

- 5 presymptomatic:
  - 1 had nusinersen, 1 onasemnogene abeparvovec (OA), 1 nusineren+OA, 1 nusinersen+OA+risdiplam; 2 had normal exam at follow-up and 2 mostly normal
  - 1 had OA and had symptoms at follow-up
- 2 symptomatic; 2 had onasemnogene abeparvovec, both mild/moderate motor delays at follow-up

Four SMN2 copies (n=2):

- 2 presymptomatic; 1 had onasemnogene abeparvovec, 1 had nusinersen, both normal exam at follow-up

Other information:

- Mean and median age of 9 and 7 days for age at first clinic visit. Mean and median days of age at first treatment was 36 and 18 days

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 12

### Citations

Lee 2022 [28]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

## Components of the study

**Setting:** USA (New York State)

**Population:** N=34 (1 with 1 SMN2 copy; 18 with 2 SMN2 copies; 11 with 3 copies; 4 with ≥4 copies); identified via screening

**Intervention:** Onasemnogene abeparvovec (OA) (n=23); nusinersen (n=1); risdiplam (n=1); nusineren+OA (n=5); risdiplam+OA (n=2); untreated (n=2)

**Follow-up duration:** Various

[Full text checked]

## Outcomes reported

Outcomes:

One SMN2 copy (n=1):

- 1 severely symptomatic, had risdiplam, severe symptoms at follow-up

Two SMN2 copies (n=18):

- 10 presymptomatic, all treated (at median age 34 days), 4/10 had symptoms at follow-up but achieved motor milestones; 6/10 no symptoms at follow-up
- 8 symptomatic; all treated (at median age 34 days), all 8 had symptoms at follow-up

Three SMN2 copies (n=11):

- All 11 presymptomatic, all treated (at median age 34 days), all asymptomatic at follow-up

Four SMN2 copies (n=2) and five SMN2 copies (n=2):

- 2 presymptomatic, treated with onasemnogene; both asymptomatic at follow-up
- 2 presymptomatic, untreated; both asymptomatic at follow-up

[Full text checked]

## Conclusions

The authors concluded that the findings from the New York State cohort of newborn screen-identified infants are consistent with other reports of improved outcomes from early diagnosis and treatment.

## Study 13

### Citations

Kucera 2021 [25]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** USA (North Carolina)

**Population:** N=1 (1 with 2 SMN2 copies); identified via screening

**Intervention:** Nusinersen (n=1)

**Follow-up duration:** Follow-up 12 weeks

[Full text checked]

### Outcomes reported

Outcomes:
Two SMN2 copies (n=1):

- 1 symptomatic, had nusinersen (at day 30), symptoms initially worsened but then improved by 12 weeks

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 14

### Citations

Sawada 2022 [37]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** Japan (Kumamoto)

**Population:** N=1 (1 with 3 SMN2 copies); identified via screening

**Intervention:** Onasemnogene abeparvovec (n=1)

**Follow-up duration:** Follow-up 11 months

[Full text checked]

### Outcomes reported

Outcomes:
Three SMN2 copies (n=1):

- 1 presymptomatic, had onasemnogene abeparvovec (at day 42), normal motor development at 11 months

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 15

### Citations

Weng 2021 [41]

### Study type

Newborn screening study

### Objectives

Clinical follow-up of SMA cases

### Components of the study

**Setting:** Taiwan

**Population:** N=21 (9 with 2 SMN2 copies; 6 with 3 copies; 6 with 4 copies); identified via screening (n=20) or symptoms (n=1)

**Intervention:** Nusinersen (n=9); onasemnogene abeparvovec (n=2); untreated (n=5); not reported (n=5)

**Follow-up duration:** Various

[Full text checked]

### Outcomes reported

Outcomes:

Two SMN2 copies (n=9, followed up 8):

- 5 symptomatic (before age of 1 month), all developed SMA type 1, treated with nusinersen or onasemnogene abeparvovec, 3 had some symptoms at follow-up, 2 not followed up
- 3 symptomatic (SMA type 1), untreated, died

Three SMN2 copies (n=6):

- 5 symptomatic (before age of 1 year); 4 had nusinersen after symptom onset and 1 untreated; 4 developed SMA type 1, and 1 SMA type 2a
- 1 treated presymptomatically (no follow-up)

Four SMN2 copies (n=6, followed up 4):

- 4 followed without treatment, 1 became symptomatic at 37 months

Other information:

- CMAP amplitudes of 12 newborns were available, including 6 who were subsequently treated with nusinersen. Found that a rapid decrease of CMAP amplitude was an early predictor of symptom onset. Pretreatment CMAP and rapid increment of post-treatment CMAP could predict better treatment outcome

[Full text checked]

### Conclusions

Conclusions not specific to presymptomatic treatment.

## Study 16

### Citations

Chiang 2022 [59] (abstract)

### Study type

Case series of 4 screened patients

### Objectives

To report on sleep disordered breathing in infants with SMA identified via screening

### Components of the study

**Setting:** Canada (Ontario)

**Population:** N=4 SMA patients from screening (2 with 2 SMN2 copies, 2 with 3 SMN2 copies)

**Intervention:** Nusinersen, onasemnogene abeparvovec

**Follow-up duration:** NR

[Full text checked]

### Outcomes reported

Outcomes:

- 4 infants diagnosed with significant sleep disordered breathing on polysomnography while receiving treatment with nusinersen and onasemnogene abeparvovec. Reporting on the first cases of sleep disordered breathing in infants with SMA identified via a newborn screening program

[Full text checked]

### Conclusions

The authors concluded that this case series highlights the importance of formal respiratory evaluations and ongoing monitoring of pre-symptomatic infants identified by newborn screening treated with nusinersen and/or onasemnogene abeparvovec

## Study 17

### Citations

Dangouloff 2022 [60]

### Study type

Data from two prospective studies

### Objectives

To assess financial costs and quality of life of SMA patients identified via screening or via symptoms (only QoL data extracted here)

## Components of the study

**Setting:** Belgium, France, Germany, Poland

**Population:** N=149 SMA patients:

a) 93 untreated symptomatic (NatHis-SMA study and Liege NMRC cohort)

b) 42 treated after presenting with symptoms (Liege NMRC cohort)

c) 14 treated after early diagnosis (Belgium screening or diagnosed via sibling)

**Intervention:** 56 treated patients had: nusinersen (n=38), risdiplam (n=13), onasemnogene abeparvovec (OA) (n=5); risdiplam and OA were within trials

**Follow-up duration:** NR

[Full text checked]

## Outcomes reported

Outcomes for QoL:

Patients not identified by symptoms (diagnosed via screening or sibling):

- Health-related QoL and utility scores were much higher in patients not identified by symptoms than in the other groups; some patients not identified by symptoms reached full health as measured on the HUI scale. The range of values were also much narrower in patients not identified by symptoms. However, on the PedsQL Family Impact scale, patients not identified by symptoms were as impacted as untreated and treated symptomatic patients

Untreated vs. treated symptomatic patients:

- Difference not significant on PedsQL Family Impact or EQ-5D Visual Analogue Scale. Very similar QOL values on HUI

SMN2 copies:

- QoL and utility values for the different groups as a function of the number of SMN2 copies: not extracted

[Full text checked]

## Conclusions

(Conclusions relate to costs not QoL)

# Study 18

## Citations

D'Silva 2022 [62]

## Study type

Prospective cohort study

## Objectives

To provide data on tolerability, safety and clinical outcomes of onasemnogene abeparvovec in real-world practice

## Components of the study

**Setting:** Australia

**Population:** Children with SMA (n=21), via newborn screening (n=11) or symptoms (n=10), some presymptomatic (n=NR). Treated at Sydney Children's Hospital Network (2019-2021)

**Intervention:** Onasemnogene abeparvovec (n=21); of these, 19 had previous nusinersen

**Follow-up duration:** NR

[Full text checked]

## Outcomes reported

Outcomes:

- Safety: Transient treatment-related side effects occurred in all children; vomiting (100%), transaminitis (57%) and thrombocytopaenia (33%). Duration of prednisolone following treatment was prolonged (mean 87.5 days, range 57–274 days). Incidence of moderate/severe transaminitis was significantly greater in infants weighing ≥8 kg compared with <8 kg ($p < 0.05$).
- Efficacy: 16/21 (76%) children gained at least one WHO motor milestone. Stabilisation orimprovement in bulbar or respiratory function was observed in 20/21 (95.2%)
- Implementation: Implementation challenges were mitigated by developing standard operating procedures and facilitating exchange of knowledge

[Outcome data taken from abstract]

## Conclusions

The authors concluded that this study provides real-world evidence to inform treatment decisions and guide therapeutic expectations for onasemnogene abeparvovec and combination therapy

# Study 19

## Citations

Kariyawasam 2023 [65]

## Study type

Controlled cohort study

## Objectives

To compare outcomes in children with SMA diagnosed via screening vs. symptoms

## Components of the study

**Setting:** Australia

**Population:** Children with SMA (n=33) at Sydney Children's Hospital Network diagnosed via: a) newborn screening (n=15); b) clinical referral (n=18). Excluded compound heterozygotes and trial patients

**Intervention:** Screening group: nusinersen (n=8), onasemnogene abeparvovec (n=5), none (n=2). Clinical referral group: nusinersen (n=16), none (n=2)

**Follow-up duration:** 2 years after diagnosis

[Full text checked]

## Outcomes reported

Outcomes:

- 2-year survival rate was 14/15 (93%) in screening group and 16/18 (89%) in comparator group
- Among survivors, 11/14 (79%) walked independently or with assistance in screening group vs. 1/16 (6%) in comparator group (p<0·0001)
- Significantly greater change in motor function observed in screening group vs. comparator group over 2 years (HINE-2 score group difference, 12·32; p<0·0001)
- Requirement for non-intensive ventilation or feeding support at follow-up was higher in comparator group vs. screening group (odds ratio 7·1; 95% CI 0·7–70·2)
- Significant predictors of functional motor outcomes as determined by HINE-2 score at 2 years post diagnosis were HINE-2 score (p=0·0022), CHOP-INTEND (p=0·0001), compound muscle action potential (CMAP; p=0·0006), and disease status (p=0·023) at diagnosis

[Full text checked]

## Conclusions

The authors concluded that newborn screening for SMA, coupled with early access to disease-modifying therapies, effectively ameliorates the functional burden and associated comorbidities for affected children

## Study 20

### Citations

Ngawa 2021 [67] (abstract)

### Study type

Longitudinal study

### Objectives

To assess the developmental trajectory of treated SMA type 1 and presymptomatic patients

### Components of the study

**Setting:** NR

**Population:** Children with SMA (n=15); SMA type 1 (n=10) and presymptomatic patients (n=5)

**Intervention:** All treated with an approved drug (NR which)

**Follow-up duration:** NR

[This reference is an abstract only]

### Outcomes reported

Outcomes for patients treated pre- and post-symptom development:

- Assessed in all three BSID-III domains (cognitive, motor skills, language) (2018-2021)
- Motor scale: All patients treated presymptomatically obtained scores higher than those treated post-symptomatically
- Cognitive scores: 4/5 patients treated presymptomatically were average; 1 patient was in the low average. 6/10 treated post-symptomatically scored low or abnormal
- Communication scores: 3/5 pre-symptomatic treated patients obtained an average score, 1 obtained a low average score, 1 is below the norm. 7/10 treated post-symptomatically scored below averagex

[This reference is an abstract only]

### Conclusions

The authors concluded that this study indicates that cognitive development assessments should be considered as part of the standard of care in patients with SMA1

# Study 21

## Citations

Schwartz 2022 [69]

## Study type

Prospective cohort study

## Objectives

To describe neurological status at time of screening and reversibility of neurological deficits in patients with two SMN2 copies

## Components of the study

**Setting:** Germany

**Population:** SMA patients (n=21) identified via screening; all with two SMN2 copies

**Intervention:** All treated at ≤6 weeks of age

**Follow-up duration:** Follow-up to at least 9 months of age

[Full text checked]

## Outcomes reported

Outcomes:

- 12/21 (57%) developed completely normally, reaching motor milestones in time and having no bulbar or respiratory problems
- 3/21 (14.5%) caught up after initial delay in motor development
- 6/21 (29%) developed proximal weakness despite early treatment; 3 of them (14.5%) achieved the ability to walk with assistance and the other three (14.5%) showed an SMA type 2 phenotype at the age of 16–30 months
- 1/21 (4.8%) had respiratory problems
- 3/21 (14.5%) had mild chewing problems and 2/21 (9.5%) needed feeding via gastrotube

[Full text checked]

## Conclusions

The authors concluded that more than 70% of SMA patients with two SMN2 copies achieved independent ambulation with immediate initiation of therapy

## Study 22

### Citations

Stettner 2023 [73]

### Study type

Prospective case series

### Objectives

To describe real-world experience with onasemnogene abeparvovec

### Components of the study

**Setting:** Switzerland

**Population:** SMA patients (n=9) from Swiss Registry; SMA type 1 (n=6), type 2 (n=1), presymptomatic diagnosed via family history (n=2)

**Intervention:** Onasemnogene abeparvovec (n=9)

**Follow-up duration:** Median 383 days (1 year)

[Full text checked]

### Outcomes reported

Outcomes for n=9 SMA patients, n=2 pre-symptomatic treatment:

- In SMA type 1, CHOP Intend score increased by 28.1 from a mean score of 20.5±7.6 at baseline. At end of follow-up, 50% of SMA type 1 patients required nutritional support and 17% night-time ventilation; 67% developed scoliosis
- The n=1 SMA type 2 patient and the n=2 pre-symptomatically treated individuals reached maximum CHOP Intend scores
- No patient required adaptation of the concomitant prednisolone treatment, although transient decrease of platelet count and increase of transaminases were observed in all patients. Troponin-T was elevated prior to OA treatment in 100% and showed fluctuations in 57% thereafter

[Full text checked]

### Conclusions

The authors concluded that onasemnogene abeparvovec is a potent treatment for SMA leading to significant motor function improvements

## Study 23

### Citations

Waldrop 2020 [76]

### Study type

Cohort study

### Objectives

To report key safety and early outcome data from the first 21 children treated with onasemnogene abeparvovec in Ohio

### Components of the study

**Setting:** USA (Ohio)

**Population:** SMA patients (n=21) via screening (presymptomatic; n=5) or symptoms (n=16)

**Intervention:** Onasemnogene abeparvovec (n=21)

**Follow-up duration:** NR

[Full text checked]

### Outcomes reported

Outcomes for n=21 SMA patients, n=5 pre-symptomatic treatment:

- In children ≤6 months, gene transfer was well tolerated. In this young group, serum transaminase elevations were modest and not associated with gamma glutamyl transpeptidase elevations. Initial prednisolone administration matched that given in the clinical trials
- In older children, elevations in aspartate aminotransferase, alanine aminotransferase and gamma glutamyl transpeptidase were more common and required a higher dose of prednisolone, but all were without clinical symptoms
- 19/21 (90%) children experienced an asymptomatic drop in platelets in the first week after treatment that recovered without intervention
- Of the 19 children with repeated outcome assessments, 2/19 (11%) experienced stabilization and 17/19 (89%) experienced improvement in motor function

[Full text checked]

### Conclusions

The authors concluded that in this population, with thorough screening and careful post–gene transfer management, replacement therapy with onasemnogene abeparvovec is safe and shows promise for early efficacy

## Study 24

### Citations

Finkel 2020 [63]; Servais 2022 [70] (abstract); Servais 2021 [71] (abstract)

### Study type

RESTORE SMA registry; analysis of screened vs. symptomatic patients

### Objectives

To better understand outcomes in US children with SMA identified by newborn/ prenatal screening versus diagnosed clinically

### Components of the study

**Setting:** Global registry; US data for this analysis

**Population:**

Servais 2022:

SMA patients (n=55) with ≤2 SMN2 copies and ≥16 months follow-up, stratified into two diagnosis groups:

a) clinical via symptoms (n=42);

b) via newborn/ prenatal screening (n=13; 2 with 1 SMN2 copy and 11 with 2 copies)

Servais 2021:

SMA patients (n=84) with ≤2 SMN2 copies or clinical diagnosis of SMA type 1, stratified into two diagnosis groups:

a) clinical via symptoms (n=56);

b) via newborn/ prenatal screening (n=28)

**Intervention:** Various

**Follow-up duration:**

Servais 2022: ≥16 months follow-up; data cut-off May 2021

Servais 2021: Follow-up NR; data cut-off December 2020

[Abstracts only]

### Outcomes reported

Servais 2022:

Outcomes for clinically diagnosed patients compared with screened patients:

- Mean age at diagnosis was 3.2 versus 0.8 months (p<0.0001)

- Age at first treatment was 4.9 versus 1.7 months (p<0.0001)
- Time from diagnosis to initial treatment was 1.3 versus 1.2 months (p=0.8099 [non-significant])
- A significantly greater percentage of clinically diagnosed patients received >1 SMA therapy compared with NBS patients (90.5% [n=38/42] vs. 53.9% [n=7/13], respectively; p=0.0118)
- CHOP INTEND increases of ≥4 points were observed for 75.0% (n=15/20) of clinically diagnosed patients and 83.3% (n=5/6) of patients identified by NBS
- Patients identified via NBS consistently achieved motor milestones at younger ages compared with clinically diagnosed patients

Servais 2021:

Outcomes for screened/prenatally identified vs. clinically diagnosed patients:

- Mean (95% CI) age at diagnosis was 0.8 vs. 3.5 months (P<0.0001)
- Mean age at first treatment was 1.7 vs. 4.4 months (P<0.0001)
- Mean time from diagnosis to first treatment was 0.9 vs. 0.9 months (P=0.7092; non-significant)

[Abstracts only]

### Conclusions

Servais 2022: The authors concluded that NBS for SMA is associated with significantly earlier diagnosis and intervention, and NBS-identified patients achieved motor milestones at earlier ages and more consistently achieved CHOP INTEND increases of ≥4 points

Servais 2021: The authors concluded that newborn screening for SMA is associated with significantly earlier diagnosis and intervention

# Reviews of presymptomatic treatment

The following section summarises reviews of presymptomatic treatment.

## Review 1

### Citation

Albrechtsen 2020 [77]

### Study type

Systematic review

### Objectives

Systematic review of nusinersen for SMA

### Components of the study

Methods: Search of Medline, Embase, Cochrane CENTRAL, Web of Science to November 2019

### Findings reported

Summarises the following studies relevant to presymptomatic treatment:

- NURTURE: single-arm study of presymptomatic nusinersen
- Vill 2019: German screening study with data on 6 treated patients

[Full text checked]

### Conclusions

The authors concluded that better outcomes were seen in young children with a short disease duration, particularly in children receiving nusinersen before symptom onset.

## Review 2

### Citation

Chiriboga 2022 [78]

### Study type

Narrative review

### Objectives

Narrative review of pharmacotherapy for SMA

### Components of the study

Methods: Search methods and date not reported

### Findings reported

Summarises Summarises the following studies relevant to presymptomatic treatment

- NURTURE: single-arm study of presymptomatic nusinersen
- SPR1NT: single-arm study of presymptomatic onasemnogene abeparvovec
- RAINBOWFISH: single-arm study of presymptomatic risdiplam

[Full text checked]

### Conclusions

The authors concluded that in infant-onset SMA, the benefits of early treatment clearly justify any potential risks from onasemnogene abeparvovec treatment.

## Review 3

### Citation

Dangouloff 2019 [79]

### Study type

Narrative review

### Objectives

Narrative review of evidence for early treatment in SMA

### Components of the study

Methods: Search methods and date not reported

### Findings reported

Summarises the following studies relevant to presymptomatic treatment

- NURTURE: single-arm study of presymptomatic nusinersen
- SPR1NT: single-arm study of presymptomatic onasemnogene abeparvovec

[Full text checked]

### Conclusions

The authors concluded that emerging data suggest that the treatments discussed here have better efficacies when patients are treated pre-symptomatically or soon after symptoms are observed rather than months after symptom onset.

## Review 4

### Citation

IQWiG 2020 [4]

### Study type

Systematic review

### Objectives

Systematic review of newborn screening and treatment for SMA

### Components of the study

Methods: Search of Medline, Embase, Cochrane, and HTA Database to October 2019

### Findings reported

Summarises the following studies relevant to presymptomatic treatment or timing of treatment:

- Retrospective comparative study of presymptomatic nusinersen (NURTURE single-arm study) vs. early symptomatic treatment (nusinersen arm of ENDEAR RCT), cited as Biogen 2019
- ENDEAR study of nusinersen vs. sham; comparison of subgroups with early vs. late symptomatic treatment start (doesn't meet our inclusion criteria but may be of interest)

[Full text checked]

### Conclusions

The authors concluded that the studies indicate that an earlier treatment start is associated with better treatment results for symptomatic patients. However, the available data do not facilitate conclusions as to whether children identified by screening to have late onset SMA (e.g. those with ≥4 SMN2 copies) would benefit from a presymptomatic treatment start.

## Review 5

### Citation

Jedrzejowska 2020 [5]

### Study type

Narrative review

### Objectives

Narrative review of newborn screening and treatment for SMA

### Components of the study

Methods: Does not report search dates/method

### Findings reported

Summarises the following studies relevant to presymptomatic treatment or timing of treatment:

- NURTURE: single-arm study of presymptomatic nusinersen

- SPR1NT: single-arm study of presymptomatic onasemnogene abeparvovec
- ENDEAR study of nusinersen vs. sham; comparison of subgroups with early vs. late symptomatic treatment start (doesn't meet our inclusion criteria but may be of interest)

[Full text checked]

### Conclusions

The authors concluded that early treatment of SMA seems to be crucial for maximizing therapeutic effects and, at present, the best solution may be to screen all newborns for SMA

## Review 6

### Citation

Markati 2022 [80]

### Study type

Narrative review

### Objectives

Narrative review of risdiplam for SMA

### Components of the study

Methods: Search of PubMed/ Medline and Embase for last 10 years (search date not reported)

### Findings reported

Summarises the following studies relevant to presymptomatic treatment:

- RAINBOWFISH: single-arm study of presymptomatic risdiplam

[Full text checked]

### Conclusions

The authors concluded that risdiplam has proved its efficacy in pivotal trials for SMA Types 1, 2, and 3 with a satisfactory safety profile

## Review 7

### Citation

UK NSC (Costello Medical) 2018 [1]

### Study type

Evidence summary

### Objectives

Evidence summary of screening and treatment for SMA

### Components of the study

Methods: Search of Medline, Embase, Cochrane to August 2017; update search in February 2018

### Findings reported

Did not identify any studies of treatment of presymptomatic SMA
[Full text checked]

### Conclusions

The authors concluded that that there was still insufficient evidence that presymptomatic treatment is more beneficial than usual care, and there was also a lack of long-term efficacy and safety data.

## Review 8

### Citation

Yang 2022 [81]

### Study type

Systematic review

### Objectives

Systematic review of treatment for SMA (symptomatic and presymptomatic)

### Components of the study

Methods: Search of Medline, Embase, Cochrane CENTRAL, EconLit, conference proceedings, HTA databases, and trial registries to November 2020

## Findings reported

Summarises the following studies relevant to presymptomatic treatment:

- NURTURE: single-arm study of presymptomatic nusinersen
- SPR1NT: single-arm study of presymptomatic onasemnogene abeparvovec

[Full text checked]

## Conclusions

(Conclusions relate mainly to studies in symptomatic patients)

# References


1 UK National Screening Committee (UK NSC) (Costello Medical). Screening for spinal muscular atrophy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2018. https://view-health-screening-recommendations.service.gov.uk/sma/

2 Dangouloff T, Boemer F, Servais L. Newborn screening of neuromuscular diseases. *Neuromuscular Disorders* 2021;**31**:1070–80. doi:10.1016/j.nmd.2021.07.008

3 Hale K, Ojodu J, Singh S. Landscape of Spinal Muscular Atrophy Newborn Screening in the United States: 2018-2021. *International Journal of Neonatal Screening* 2021;**7**:24. doi:10.3390/ijns7030033

4 Institute for Q, Efficiency in Health C. Newborn screening for 5q-linked spinal muscular atrophy IQWiG Reports - Commission No. S18-02. *Institute for Quality and Efficiency in Health Care* 2020;**04**:22.

5 Jedrzejowska M. Advances in Newborn Screening and Presymptomatic Diagnosis of Spinal Muscular Atrophy. *Degenerative Neurological & Neuromuscular Disease* 2020;**10**:39–47. doi:10.2147/DNND.S246907

6 Schroth M, Friesz M, Belter L, *et al.* Implementation of Spinal Muscular Atrophy Newborn Screening acrossthe US. *Neurology Conference: 74th Annual Meeting of the American Academy of Neurology, AAN* 2022;**98**.https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=638416362

7 Abiusi E, Vaisfeld A, Fiori S, *et al.* Experience of a 2-year spinal muscular atrophy NBS pilot study in Italy: towards specific guidelines and standard operating procedures for the molecular diagnosis. *Journal of Medical Genetics* 2022;**22**:22. doi:10.1136/jmg-2022-108873

8 Baker MW, Mochal ST, Dawe SJ, *et al.* Newborn screening for spinal muscular atrophy: The Wisconsin first year experience. *Neuromuscular Disorders* 2022;**32**:135–41. doi:10.1016/j.nmd.2021.07.398

9 Betts C, Dangouloff T, Montague-Johnson C, *et al.* Organisational, Ethical, and Regulatory Considerations When Setting up an NBS Program. *Journal of Neuromuscular Diseases* 2022;**9(Supplement 1)**:S73. doi:10.3233/JND-229001

10 Boemer F, Caberg JH, Beckers P, *et al.* Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. *Scientific Reports* 2021;**11**:19922. doi:10.1038/s41598-021-99496-2

11 Boemer F, Caberg JH, Dideberg V, *et al.* Newborn screening for SMA in Southern Belgium. *Neuromuscular Disorders* 2019;**29(5)**:343–9. doi:10.1016/j.nmd.2019.02.003

12 Bruno C, Aloi C, Lanza F, *et al.* Newborn Screening (NBS) program for the simultaneous early diagnosis of Spinal Muscular Atrophy (SMA) and Severe Combined immunodeficiency (SCID) in Liguria Region, Italy. *Acta Myologica* 2022;**41(3 Supplement 1)**:55–6. doi:10.36185/2532-1900-074

13 Chien YH, Chiang SC, Weng WC, *et al.* Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening. *Journal of Pediatrics* 2017;**190**:124-129.e1. doi:10.1016/j.jpeds.2017.06.042

14 Czibere L, Burggraf S, Fleige T, *et al.* High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. *European Journal of Human Genetics* 2020;**28**:23–30. doi:10.1038/s41431-019-0476-4

15 D'Silva AM, Kariyawasam DST, Best S, *et al.* Integrating newborn screening for spinal muscular atrophy into health care systems: an Australian pilot programme. *Developmental Medicine & Child Neurology* 2022;**64**:625–32. doi:10.1111/dmcn.15117

16 Elkins K, Wittenauer A, Hagar AF, *et al.* Georgia state spinal muscular atrophy newborn screening experience: Screening assay performance and early clinical outcomes. *American Journal of Medical Genetics Part C, Seminars in Medical Genetics* 2022;**190**:187–96. doi:10.1002/ajmg.c.32003

17 Gailite L, Sterna O, Konika M, *et al.* New-Born Screening for Spinal Muscular Atrophy: Results of a Latvian Pilot Study. *International Journal of Neonatal Screening* 2022;**8(1) (no pagination)**. doi:10.3390/ijns8010015

18 Hale JE, Darras BT, Swoboda KJ, *et al.* Massachusetts' Findings from Statewide Newborn Screening for Spinal Muscular Atrophy. *International Journal of Neonatal Screening* 2021;**7**:23. doi:10.3390/ijns7020026

19 Kariyawasam DST, Russell JS, Wiley V, *et al.* The implementation of newborn screening for spinal muscular atrophy: the Australian experience. *Genetics in Medicine* 2020;**22**:557–65. doi:10.1038/s41436-019-0673-0

20 Kay DM, Stevens CF, Parker A, *et al.* Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. *Genetics in Medicine* 2020;**22**:1296–302. doi:10.1038/s41436-020-0824-3

21 Kernohan KD, McMillan HJ, Yeh E, *et al.* Ontario Newborn Screening for Spinal Muscular Atrophy: The First Year. *Canadian Journal of Neurological Sciences* 2022;**49**:821–3. doi:10.1017/cjn.2021.231

22 Kimizu T, Ida S, Okamoto K, *et al.* Spinal Muscular Atrophy: Diagnosis, Incidence, and Newborn Screening in Japan. *International Journal of Neonatal Screening* 2021;**7**:20. doi:10.3390/ijns7030045

23 Kiselev A, Maretina M, Shtykalova S, *et al.* Establishment of a Pilot Newborn Screening Program for Spinal Muscular Atrophy in Saint-Petersburg. LIFE SCIENCES 2023. doi:10.20944/preprints202302.0500.v1

24 Kraszewski JN, Kay DM, Stevens CF, *et al.* Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genetics in Medicine* 2018;**20**:608–13. doi:10.1038/gim.2017.152

25 Kucera KS, Taylor JL, Robles VR, *et al.* A Voluntary Statewide Newborn Screening Pilot for Spinal Muscular Atrophy: Results from Early Check. *International Journal of Neonatal Screening* 2021;**7**:21. doi:10.3390/ijns7010020

26 Kumar B, Barton S, Kordowska J, *et al.* Novel Modification of a Confirmatory SMA Sequencing Assay that Can Be Used to Determine SMN2 Copy Number. *International Journal of Neonatal Screening* 2021;**7**:21. doi:10.3390/ijns7030047

27 Lakhotia A, Toupin D, Thamann A, *et al.* Demographic and Clinical Profiles of Neonates Diagnosed with Spinal Muscular Atrophy (SMA) via the Kentucky Newborn Screening (NBS) Program: A Two-Year Experience. *Neurology Conference: 74th Annual Meeting of the American Academy of Neurology, AAN* 2022;**98**.https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=638416987

28 Lee BH, Deng S, Chiriboga CA, *et al.* Newborn Screening for Spinal Muscular Atrophy in New York State: Clinical Outcomes From the First 3 Years. *Neurology* 2022;**14**:14. doi:10.1212/WNL.0000000000200986

29 Lin Y, Lin CH, Yin X, *et al.* Newborn Screening for Spinal Muscular Atrophy in China Using DNA Mass Spectrometry. *Frontiers in Genetics* 2019;**10**:1255. doi:10.3389/fgene.2019.01255

30 Liu Z, Zhang P, He X, *et al.* New multiplex real-time PCR approach to detect gene mutations for spinal muscular atrophy. *BMC Neurology* 2016;**16**:141. doi:10.1186/s12883-016-0651-y

31 Matteson J, Wu CH, Mathur D, *et al.* California's experience with SMA newborn screening: A successful path to early intervention. *Journal of neuromuscular diseases* 2022;**9**:777–85. doi:10.3233/JND-221561

32 McMillan HJ, Kernohan KD, Yeh E, *et al.* Newborn Screening for Spinal Muscular Atrophy: Ontario Testing and Follow-up Recommendations. *Canadian Journal of Neurological Sciences* 2021;**48**:504–11. doi:10.1017/cjn.2020.229

33 Muller-Felber W, Vill K, Schwartz O, *et al.* Infants Diagnosed with Spinal Muscular Atrophy and 4 SMN2 Copies through Newborn Screening - Opportunity or Burden? *Journal of neuromuscular diseases* 2020;**7**:109–17. doi:10.3233/JND-200475

34 Müller-Felber W, Blaschek A, Schwartz O, *et al.* Newbornscreening SMA - From Pilot Project to Nationwide Screening in Germany. *J Neuromuscul Dis* 2023;**10**:55–65. doi:10.3233/JND-221577

35 Pan J, Zhang C, Teng Y, *et al.* Detection of Spinal Muscular Atrophy Using a Duplexed Real-Time PCR Approach With Locked Nucleic Acid-Modified Primers. *Annals of Laboratory Medicine* 2021;**41**:101–7. doi:10.3343/alm.2021.41.1.101

36 Prior TW, Snyder PJ, Rink BD, *et al.* Newborn and carrier screening for spinal muscular atrophy. *American Journal of Medical Genetics Part A* 2010;**152A**:1608–16. doi:10.1002/ajmg.a.33474

37 Sawada T, Kido J, Sugawara K, *et al.* Newborn screening for spinal muscular atrophy in Japan: One year of experience. *Molecular Genetics and Metabolism Reports* 2022;**32**:100908. doi:10.1016/j.ymgmr.2022.100908

38 Shinohara M, Niba ETE, Wijaya YOS, *et al.* A Novel System for Spinal Muscular Atrophy Screening in Newborns: Japanese Pilot Study. *International Journal of Neonatal Screening* 2019;**5**:41. doi:10.3390/ijns5040041

39 Vill K, Kolbel H, Schwartz O, *et al.* One Year of Newborn Screening for SMA - Results of a German Pilot Project. *Journal of neuromuscular diseases* 2019;**6**:503–15. doi:10.3233/JND-190428

40 Vill K, Schwartz O, Blaschek A, *et al.* Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. *Orphanet Journal Of Rare Diseases* 2021;**16**:153. doi:10.1186/s13023-021-01783-8

41 Weng WC, Hsu YK, Chang FM, *et al.* CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening. *Genetics in Medicine* 2021;**23**:415–20. doi:10.1038/s41436-020-00987-w

42 Adams SP, Gravett E, Kent N, *et al.* Screening of Neonatal UK Dried Blood Spots Using a Duplex SMN1 Screening Assay. *International Journal of Neonatal Screening* 2021;**7**:26. doi:10.3390/ijns7040069

43 Ar Rochmah M, Harahap NIF, Niba ETE, *et al.* Genetic screening of spinal muscular atrophy using a real-time modified COP-PCR technique with dried blood-spot DNA. *Brain & Development* 2017;**39**:774–82. doi:10.1016/j.braindev.2017.04.015

44 Cavdarli B, Ozturk FN, Guntekin Ergun S, *et al.* Intelligent Ratio: A New Method for Carrier and Newborn Screening in Spinal Muscular Atrophy. *Genetic Testing & Molecular Biomarkers* 2020;**24**:569–77. doi:10.1089/gtmb.2020.0085

45 Er T-K, Kan T-M, Su Y-F, *et al.* High-resolution melting (HRM) analysis as a feasible method for detecting spinal muscular atrophy via dried blood spots. *Clinica Chimica Acta* 2012;**413**:1781–5. doi:10.1016/j.cca.2012.06.033

46 Guo F, Ou Y, Mathur A, *et al.* Reducing the time to diagnosis for spinal muscular atrophy. *Molecular Genetics and Metabolism* 2021;**132(Supplement 1)**:S279. doi:10.1016/S1096-7192%2821%2900513-8

47 Gutierrez-Mateo C, Timonen A, Vaahtera K, *et al.* Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA. *International Journal of Neonatal Screening* 2019;**5**:39. doi:10.3390/ijns5040039

48 Pyatt RE, Mihal DC, Prior TW. Assessment of liquid microbead arrays for the screening of newborns for spinal muscular atrophy. *Clinical Chemistry* 2007;**53**:1879–85.

49 Pyatt RE, Prior TW. A feasibility study for the newborn screening of spinal muscular atrophy. *Genetics in Medicine* 2006;**8**:428–37.

50 Romanelli Tavares VL, Monfardini F, Lourenco NCV, *et al.* Newborn Screening for 5q Spinal Muscular Atrophy: Comparisons between Real-Time PCR Methodologies and Cost

Estimations for Future Implementation Programs. *International Journal of Neonatal Screening* 2021;**7**:11. doi:10.3390/ijns7030053

51 Strunk A, Abbes A, Stuitje AR, *et al.* Validation of a Fast, Robust, Inexpensive, Two-Tiered Neonatal Screening Test algorithm on Dried Blood Spots for Spinal Muscular Atrophy. *International Journal of Neonatal Screening* 2019;**5**:21. doi:10.3390/ijns5020021

52 Taylor JL, Lee FK, Yazdanpanah GK, *et al.* Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. *Clinical Chemistry* 2015;**61**:412–9. doi:10.1373/clinchem.2014.231019

53 Vidal-Folch N, Gavrilov D, Raymond K, *et al.* Multiplex Droplet Digital PCR Method Applicable to Newborn Screening, Carrier Status, and Assessment of Spinal Muscular Atrophy. *Clinical Chemistry* 2018;**64**:1753–61. doi:10.1373/clinchem.2018.293712

54 Wang KC, Fang CY, Chang CC, *et al.* A rapid molecular diagnostic method for spinal muscular atrophy. *Journal of Neurogenetics* 2021;**35**:29–32. doi:10.1080/01677063.2020.1853721

55 Wijaya YOS, Nishio H, Niba ETE, *et al.* Detection of Spinal Muscular Atrophy Patients Using Dried Saliva Spots. *Genes* 2021;**12**:14. doi:10.3390/genes12101621

56 Wijaya YOS, Nishio H, Niba ETE, *et al.* Dried Blood Spot Screening System for Spinal Muscular Atrophy with Allele-Specific Polymerase Chain Reaction and Melting Peak Analysis. *Genetic Testing & Molecular Biomarkers* 2021;**25**:293–301. doi:10.1089/gtmb.2020.0312

57 Biogen. Anhang zur Stellungnahme: Vergleich präsymptomatischer vs. symptomatischer Therapiebeginn [from review by IQWiG 2020). 2019.

58 Blaschek A, Kolbel H, Schwartz O, *et al.* Newborn Screening for SMA - Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies? *Journal of neuromuscular diseases* 2022;**9**:597–605. doi:10.3233/JND-221510

59 Chiang J, Sunkonkit K, Alzaid M, *et al.* Sleep Disordered Breathing in Infants with a Positive Newborn Screen for Spinal Muscular Atrophy: A Case Series. *American Journal of Respiratory and Critical Care Medicine Conference: International Conferenceof the American Thoracic Society, ATS* 2022;**205**. doi:10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A4409

60 Dangouloff T, Hiligsmann M, Deconinck N, *et al.* Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening. *Developmental Medicine & Child Neurology* 2022;**08**:08. doi:10.1111/dmcn.15286

61 De Vivo DC, Bertini E, Swoboda KJ, *et al.* Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscular Disorders* 2019;**29**:842–56. doi:10.1016/j.nmd.2019.09.007

62 D'Silva AM, Holland S, Kariyawasam D, *et al.* Onasemnogene abeparvovec in spinal muscular atrophy: an Australian experience of safety and efficacy. *Annals of Clinical & Translational Neurology* 2022;**9**:339–50. doi:10.1002/acn3.51519

63 Finkel RS, Day JW, De Vivo DC, *et al.* RESTORE: A Prospective Multinational Registry of Patients with Genetically Confirmed Spinal Muscular Atrophy - Rationale and Study Design. *Journal of neuromuscular diseases* 2020;**7**:145–52. doi:10.3233/JND-190451

64 Finkel RS, Mercuri E, Darras BT, *et al.* Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 2017;**377**:1723–32. doi:10.1056/NEJMoa1702752

65 Kariyawasam DS, D'Silva AM, Sampaio H, *et al.* Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. *The Lancet Child & Adolescent Health* 2023;**7**:159–70. doi:10.1016/S2352-4642(22)00342-X

66 Kirschner J, Crawford T, Ryan M, *et al.* Impact of Nusinersen on Caregiver Experience and HRQoL in Presymptomatic SMA: NURTURE Study Results. *Journal of Neuromuscular Diseases* 2022;**9(Supplement 1)**:S113–4. doi:10.3233/JND-229001

67 Ngawa M, Farra FD, Marinescu A, *et al.* SMA CLINICAL DATA: EP.248 Longitudinal developmental profile of newborns and toddlers treated for spinal muscular atrophy. *Neuromuscular Disorders* 2021;**31(Supplement 1)**:S124–5. doi:10.1016/j.nmd.2021.07.273

68 Sansone V, Swoboda K, De Vivo D, *et al.* Preserved swallowing function in infants who initiated nusinersen treatment with presymptomatic SMA: Nurture study results. *Journal of Neuromuscular Diseases* 2021;**8(SUPPL 1)**:S130. doi:10.3233/JND-219006

69 Schwartz O, Kolbel H, Blaschek A, *et al.* Spinal Muscular Atrophy - Is Newborn Screening Too Late for Children with Two SMN2 Copies? *Journal of neuromuscular diseases* 2022;**9**:389–96. doi:10.3233/JND-220789

70 Servais L, De Vivo DC, Kirschner J, *et al.* The RESTORE Registry: Comparative outcomes in patients with spinal muscular atrophy (SMA) in the United States identified by newborn screening (NBS) or clinical diagnosis. *Developmental Medicine and Child Neurology* 2022;**64(SUPPL 1)**:68. doi:10.1111/dmcn.15123

71 Servais L, De Vivo D, Kirschner J, *et al.* Newborn Screening (NBS) for Spinal Muscular Atrophy (SMA) in the United States (US): Early Findings from the RESTORE Registry. *Annals of Neurology* 2021;**90(SUPPL 26)**:S152–3. doi:10.1002/ana.26177

72 Servais L, Farrar M, Vlodavets D, *et al.* RAINBOWFISH: Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Presymptomatic Spinal Muscular Atrophy. *Journal of Neuromuscular Diseases* 2022;**9(Supplement 1)**:S114–5. doi:10.3233/JND-229001

73 Stettner GM, Hasselmann O, Tscherter A, *et al.* Treatment of spinal muscular atrophy with Onasemnogene Abeparvovec in Switzerland: a prospective observational case series study. *BMC Neurol* 2023;**23**:88. doi:10.1186/s12883-023-03133-6

74 Strauss KA, Farrar MA, Muntoni F, *et al.* Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nature Medicine* 2022;**28**:1390–7. doi:10.1038/s41591-022-01867-3

75 Strauss KA, Farrar MA, Muntoni F, *et al.* Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nature Medicine* 2022;**28**:1381–9. doi:10.1038/s41591-022-01866-4

76 Waldrop MA, Karingada C, Storey MA, *et al.* Gene Therapy for Spinal Muscular Atrophy: Safety and Early Outcomes. *Pediatrics* 2020;**146**:09. doi:10.1542/peds.2020-0729

77 Albrechtsen SS, Born AP, Boesen MS. Nusinersen treatment of spinal muscular atrophy - a systematic review. *Danish Medical Journal* 2020;**67**:07.

78 Chiriboga CA. Pharmacotherapy for Spinal Muscular Atrophy in Babies and Children: A Review of Approved and Experimental Therapies. *Paediatric Drugs* 2022;**24**:585–602. doi:10.1007/s40272-022-00529-8

79 Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives. *Therapeutics and Clinical Risk Management* 2019;**15**:1153–61. doi:10.2147/TCRM.S172291

80 Markati T, Fisher G, Ramdas S, *et al.* Risdiplam: an investigational survival motor neuron 2 (SMN2) splicing modifier for spinal muscular atrophy (SMA). *Expert Opinion on Investigational Drugs* 2022;**31**:451–61. doi:10.1080/13543784.2022.2056836

81 Yang M, Awano H, Tanaka S, *et al.* Systematic Literature Review of Clinical and Economic Evidence for Spinal Muscular Atrophy. *Advances in Therapy* 2022;**39**:1915–58. doi:10.1007/s12325-022-02089-2