SMA NBS Alliance

Spinal muscular atrophy: Screen at birth, save lives

Whitepaper Version 1, 26 March 2021

European Alliance for Newborn Screening in SMA

Foreword

NEWBORN SCREENING: "ZERO POINT" IN TIME

by Dr. Alessandra Ferlini, HCP representative of European Reference Networks Euro-NMD, Associate professor in medical genetics, director of the Medical Genetics Unit at the University of Ferrara (Italy)

There is full agreement that patients living with rare diseases (RDs) benefit from early diagnosis.

Receiving a precise genetic diagnosis offers RD patients the possibility of accessing all preventive and treatment measures. Diagnostic accuracy is now a reality and was not always feasible before the availability and clinical validation of the new genetic analysis approaches.

Much has been discussed about how to achieve an exhaustive diagnosis in people living with RDs. This wide brainstorming has suggested that the "zero point in time"* is at birth, where all newborns can be screened and therefore identified, allowing a genetic diagnosis. Therefore, neonatal screening is no longer considered exclusively important for early diagnosis of treatable RDs, but it is also the proper timing in which the genetic diagnosis can be assured to everyone. Certainly, there are ethical and economic aspects that are important to consider, but the future of genomic medicine looks in that direction.

Spinal muscular atrophy (SMA) is a clear and typical example of the need for genetic neonatal screening capable of identifying patients at the **"zero point" in time.*** This enables patients access to new innovative therapeutic treatments, the best standards of care, and family prevention. It gives young patients and their families the confidence that they will be taken care of, treated, and never left alone in managing their disease. Other important aspects of neonatal screening include minimising the risk of psychological harm to families and full respect and compliance with data and privacy concerns. When considering newborn screening policy decisions, the benefit to the individual SMA patients and their families from newborn screening is the primary concern we should have.

*Zero point in time: is the way we refer to the most ancient Neolithic Temple, Göbekli Tepe (Turkey) where humanity was born.

Göbekli Tepe. Photo credit: De Beytullah eles, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=90872078

TABLE OF CONTENTS

1 Executive Summary

In the UN Convention on the Rights of the Child - which has been ratified by all European countries - Article 24 refers to the right to have optimal health care. Newborn screening (NBS) can help to point to these children that are in particular need of specialised health care. Vice versa, withholding newborn screening from children, however, translates into depriving them of an optimal care pathway.
For the current status of SMA newborn screening in Europe please visit: https:/www.sma-screening-alliance.org/map.

Newborn screening for SMA should be available for all babies in Europe

This paper is organized according to the Wilson & Jungner criteria used to judge if a disease should be included in the newborn screening panel. Since SMA newborn screening meets all the established criteria, newborn screening for SMA should be made available for all babies born in Europe.
Detecting and treating 5q SMA early leads to a better clinical outcome for the babies and helps reduce the burden of care for their families.

1. **SMA is an important health problem**
- 5q SMA is a rare, genetic disease affecting approximately 1 in 6.000 - 10.000 people (most of them children)
- Based on age of onset of symptoms and the maximum motor function achieved, SMA is classified in four main types with different degrees of severity
- Without treatment and depending on the severity of the condition, life expectancy in the severe forms may not reach two years and the ability to sit, walk and breathe may be substantially impaired, therefore SMA is an important health problem

2. **There are accepted treatment options for patients with SMA**
- Two disease modifying treatment options for SMA are already approved on the European market, with a third expected to follow in early 2021
- More treatments are under development
- There is growing evidence earlier treatment leads to greater potential outcomes

3. **Facilities for diagnosis and treatment of SMA are available**
- There is a wide network of health care institutions across Europe providing state-of-the-art care to people living with SMA

4. **There is a recognisable latent or early symptomatic stage of SMA**
- There is a time window between birth and age of the first symptom onset. However, even before the first symptoms, damage to the motor neurons may occur
- This “window of opportunity” is often wasted without availability of newborn screening

5. **There is a suitable newborn screening test for SMA**

- A reliable blood test is available that can be used in SMA newborn screening
- The test identifies the presence of a homozygous *SMN1* exon 7 deletion
- Sensitivity is estimated to be 95% and specificity is nearly 100%. This means that false positives are very unlikely to occur
- It is a simple, inexpensive (approximately 3-5 Euros), automated, and high-throughput test

6. **SMA newborn screening is acceptable to the population**

- Studies demonstrate that SMA newborn screening is acceptable to both the general population and families affected by SMA and adults living with SMA

7. **The natural history of SMA, including development from latent to diagnosed disease, is adequately understood**

- Sufficient information on the natural history of SMA is available
- Subject to its type, SMA will inevitably affect children and is causing a marked delay or complete halt in the development of muscular function early in life
- Without early diagnosis and treatment, children with SMA may suffer from severe impairment, accumulation of comorbidities or early death

8. **There is an agreed policy on whom to treat**

- "Treatment" is not limited to disease modifying drugs only but includes best-supportive care including non-pharmacological treatment (e.g., specialised physiotherapy)
- Treatment is a shared decision-making process between the SMA experts and the child´s parents
- The number of *SMN2* copies (a paralogous gene to *SMN1* which can partially replace its function) on its own is not sufficient to decide on a treatment with disease-modifying drugs

9. **The cost of case finding (including diagnosis) by SMA newborn screening is economically balanced in relation to possible expenditure on health care as a whole**

- Newborn screening for SMA can be conducted without major costs from the dried blood spot specimen already collected for newborn screening
- The cost of screening outweighs the cost of illness
- Detecting SMA early and prompt treatment may also have a financial advantage to the health care system in addition to the improvement of quality of life of the treated children

10. **Case finding is a continuing process and not a "once and for all" project**

- SMA newborn screening must be available to all children consecutively born in a given country
- Introducing SMA newborn screening is a contribution toward a more inclusive health care system

After establishing that SMA NBS meets the Wilson & Jungner criteria, the paper suggests to also take into consideration the following points:

11. SMA newborn screening process proposal

- Every SMA newborn screening programme must ensure proper information for all parents. In case of a screening positive result, equity of access to care, including a clearly defined diagnosis, management and long-term follow-up of the disease shall be ensured by the standard newborn screening procedure.
- All involved health care professionals (HCPs) must have received appropriate training to fulfil their roles in the newborn screening programme
- Participation in an SMA newborn screening programme should be voluntary, parents should have the right to opt-out
- A reliable screening test with no need for additional blood sampling is available

12. SMA newborn screening is ethically required

- When discussing the advantages and potential disadvantages of early diagnosis in SMA, it becomes clear that the advantages of early screening outweigh the disadvantages
- Early diagnosis must not remain a privilege that is only accessible to a minority of well-informed and/or wealthy families. Offering SMA newborn screening in the health care system for all newborn babies is therefore ethically mandatory
- Newborn babies in Europe have the right to be diagnosed as early as possible by newborn screening for SMA in order to get optimal health care as written in the UN Convention on the Rights of the Child

13. Health economics

- Rare diseases' interventions increasingly face economic scrutiny in Health Technology Assessments
- Willingness-to-pay is on average higher for rare diseases' interventions, including treatment optimization through screening
- With treatment now being available, an analysis of cost-effectiveness of newborn screening in the US shows improved economic value for both patients and payers

14. The benefit of screening – Pilot trials in Europe

- The SMA newborn screening pilot trials in Europe further support the results from clinical trials, showing that pre-symptomatic treatment results in age-appropriate motor development
- Within Europe, there are inequities with some babies having access to newborn screening for SMA, while most European newborns are not screened for SMA
- For the current status of SMA newborn screening in Europe please visit: www.sma-screening-alliance.org/map

15. Babies in Europe are at a disadvantage to those outside Europe

- The United States is well in advance of Europe in implementing newborn screening for SMA
    - 34/50 US states are now screening for SMA
    - 69% of all babies born in the USA are now screened for SMA
- Australia has applied for SMA newborn screening and is planning to introduce it nationally after a final health ministry decision expected in 2021
- Also, in Asian countries (like Taiwan and Japan), pilot trials were conducted

2 Call to Action - Recommendations by the Alliance Steering Committee

This Call to Action is initiated by the European Alliance for Newborn Screening for Spinal Muscular Atrophy, a multi-stakeholder initiative under the leadership of SMA Europe e.V.

"There is no more time to waste for babies born with SMA - newborn screening programmes for SMA in all European countries no later than 2025"

The **European Alliance for Newborn Screening in SMA's** aspirations are aligned with the advocacy goals of other key ecosystem stakeholders in relation to newborn screening;

- Considering the UN convention on the Rights of the Child ratified by all European Countries mandating governments to secure optimal health care for children,
- Recognizing the European Union's commitment to achieve Universal Health Coverage in its territory by 2030,
- Acknowledging the initiatives for early detection of severe inherited diseases brought forward by EURORDIS- Rare Diseases Europe (1) and the call-to-action of the Screen4Rare initiative (2) and other academic and patient-led multi-stakeholder consortia,
- Considering that newborn screening programmes in Europe screen for a vastly different number of diseases depending on the country and sometimes region (ranging from 2-48 diseases),
- Emphasizing the overwhelming evidence that confirms that SMA meets the WHO criteria to be included in newborn screening programmes in order to ensure an early diagnosis and an appropriate treatment that can prevent or at least significantly delay severe impairment and/or early death in infancy,
- Strongly opposing the inequality of access of SMA newborn screening for babies born in Europe,
- Appreciating the fact that this lack of access to newborn screening for SMA contradicts the policy of the European Union to ensure appropriate health care to children as one of the most basic rights children can enjoy and
- Expressing our willingness to partner and join forces with all relevant stakeholders to secure better health care for children born with SMA in Europe now,

We hereby urge policymakers across EU to take action on realizing the aspirations of **the European Alliance for Newborn Screening in Spinal Muscular Atrophy (SMA);**

Call to Action for policy makers at the European level

1. Coordinate the exchange of knowledge and best practices on newborn screening in SMA and other eligible rare diseases, including learnings from ongoing pilots. While we appreciate the responsibility of the EU Member states in ensuring sufficient access to health care, we interpret the principle of subsidiarity with regard to health care in a way that the EU has a strong remit in fostering equal access to health care across the EU.

2. As newborn screening pilot programmes for SMA in a range of member states are finished / ongoing / planned including Belgium, Italy, Germany, Spain, France and the United Kingdom, we ask to support both financially and organisationally the meta-analysis of the results of these programmes and the identification of key learnings with regard to implementation in standard newborn screening programmes across Europe.

3. As best practice sharing can help member states to implement newborn screening for SMA by learning both from other Member States and non-EU countries, we ask the European Commission to gather key learnings including but not limited to
    a. gathering evidence and natural history data on efficacy from pilot studies on newborn screening for SMA
    b. identifying and agreeing upon criteria and mechanisms for expanding the number of diseases to be included in screening panels
    c. implementation strategies for expanding existing newborn screening programmes
    d. suitable screening procedures
    e. requirements for education and training of professionals and communication with families and citizens.

4. Newborn screening in rare diseases, including but not limited to SMA, is a key instrument to ensure equal access to diagnosis and subsequent appropriate therapy for children with rare diseases in Europe. We therefore ask the European Commission and other stakeholders at the EU level to monitor and support all measures helping to improve newborn screening for SMA.

5. We also encourage EU institutions to recommend adding SMA to a list of recommended diseases to screen for at birth and support countries in the implementation of expanding newborn screening.

Call to Action for policy makers at the national level

1. We urge national competent authorities to include SMA in the list of diseases eligible to be included in national and/or regional newborn screening programmes without any further delay.
   Based on growing evidence, SMA clearly meets the WHO criteria to be included in the newborn screening programmes. Early diagnosis and treatment initiation can prevent early death in infancy and significantly delay severe impairment in later stages. Identifying and treating SMA early on provides a better outcome for children affected by SMA. Almost four years after the first new generation treatment for SMA became available, patients in the vast majority of European countries still lack access to timely diagnosis through newborn screening.

2. We further call on national governments and parliaments to ensure sufficient funding of newborn screening for SMA including an appropriate, fast and sustainable implementation.

3. We ask national competent authorities to draw on the experiences from the ongoing pilot programmes in other European countries and to make use of the support provided by the European Union in reducing access barriers to newborn screening for SMA.

4. National SMA patient organisations play a crucial role in providing patient insights, family support and public guidance during the implementation of newborn screening in SMA. We strongly suggest national parliaments to support their advocacy efforts for newborn screening to include SMA.

The **European Alliance for Newborn Screening in Spinal Muscular Atrophy** demands to national governments and authorities in Europe to immediately include a test for spinal muscular atrophy for all newborn children in national newborn screening programmes. There is no more time to waste for babies born with SMA to start adequate treatment.

The Alliance therefore calls on all decision-makers in Europe to implement this essential health service in all European countries without any further delay.

3 Authors and writing process

This Whitepaper summarises the major reasoning for introducing SMA newborn screening. It is authored by a multi-stakeholder Steering Committee, and with input from other experts with admedicum acting as the secretariat of the Alliance.

This Whitepaper was written under the leadership of SMA Europe e.V., the umbrella organisation of the European SMA patient organisations. The Whitepaper is informed, written, and reviewed including independent scientific advice from a multi-professional scientific advisory panel including Dr. Raquel Yahyaoui, Dr. Nathalie Goemans, and Dr. Eduardo Tizanno. The chapter on SMA NBS process proposal was written by Dr. Raquel Yahyaoui. The chapter on health economics was written by Dr. Cornelius Boersma and Dr. Maarten Postma.

The writing and dissemination process is financially supported by a multi-stakeholder funding circle in full compliance with the principles of independence and transparency.

Steering committee members:

- Chair: Marie-Christine Ouillade, SMA Europe e.V.
- Kacper Rucinski, SMA Europe e.V.
- Dr. Nathalie Goemans, Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven, Belgium
- Jana Popova, European Alliance of Neuromuscular Disorders Associations (EAMDA)
- Gulcin Gumus, PhD., EURORDIS
- Dr. Eduardo Tizzano, Pediatrician and Director Department of Clinical and Molecular Genetics, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Additional experts:

- Dr. Raquel Yahyaoui, Clinical Biochemistry Specialist. Newborn Screening Center of Eastern Andalusia. Málaga Regional University Hospital. Málaga, Spain
- Dr. Cornelis Boersma, Founder & CEO of Health-Ecore BV, Netherlands
- Dr. Maarten Postma, Professor Global Health Economics, University of Groningen, Netherlands

Secretariat:

- admedicum Business for Patients (Dr. Andreas Reimann, Robert Pleticha, Dr. Meike Neukirchen), Cologne, Germany and Barcelona, Spain

This Whitepaper was sponsored by unrestricted educational grants from Biogen, Novartis Gene Therapies, Roche, PerkinElmer and LaCAR MDX Technologies.

4 Introduction

Spinal muscular atrophy (SMA) is a severe rare disease that has a big impact on affected children and their families. At the same time, it is a challenging disease for health care systems in Europe. There was no treatment until the approval of the first disease-modifying therapy (DMT) nusinersen (Spinraza®) in 2017.

Treatment approaches until then involved symptom management to slow down the loss of motor-function and maintain the quality of life as much as possible, while delaying death for as long as possible. The landscape has now changed. For the first time, children with SMA, when diagnosed early and treated as soon as possible with state-of-the art disease-modifying therapies, now have a completely different and improved prognosis.

As the European Union has no direct responsibility in newborn screening (NBS), patient organizations and their members are growing increasingly frustrated at the national bureaucracy of the newborn screening committees which require that similar dossiers are completed to approve SMA newborn screening in each of the member states. This Whitepaper is meant to facilitate this process and support national SMA patient organisations in their advocacy efforts.

This Whitepaper was initiated by the European Alliance for Newborn Screening in Spinal Muscular Atrophy, a multi-stakeholder initiative under the leadership of SMA Europe e.V., a European umbrella organisation of national patient and research organisations focused on spinal muscular atrophy. It is intended to inform a systematic dialogue in the health care systems in Europe to help foster the introduction of SMA newborn screening for all children in Europe.

The authors are aware, however, that introducing newborn screening for SMA mandates a well thought-through process taking medical, ethical, social and economic context into perspective. This Whitepaper aims to provide fact-based insights on these aspects.

5 How and why SMA meets the criteria for newborn screening

When a health care system evaluates whether newborn screening (NBS) for a given disease should be made available to the general public, the main dimensions that will be taken into account are the severity of the disease, the importance of an early detection that drives a therapeutic intervention with a reasonable risk/benefit profile and the precision of the screening methodology. The principles by Wilson and Jungner (3) used to judge if a disease should be included in the NBS screening panel are widely known and accepted. In the following, we review these 10 principles for the case of SMA NBS.

5.1 SMA is an important health problem

SUMMARY

- 5q SMA is a rare, genetic disease affecting approximately 1 in 6.000 - 10.000 people (most of them children)
- Based on age of onset of symptoms and the maximum motor function achieved, SMA is classified in four main types with different degrees of severity
- Without treatment and depending on the severity of the condition, life expectancy in the severe forms may not reach two years and the ability to sit, walk and breathe may be substantially impaired, therefore SMA is an important health problem

In 2015, SMA was the leading genetic cause of death in infants (4). It is a neuromuscular condition with an incidence of 1 in 6.000 to 10.000 live births (5). It is an autosomal recessive disorder caused by pathogenic variants in the *survival motor neuron 1 gene* (*SMN1)*, mapped to chromosome 5q13, resulting in very low levels of survival motor neuron (SMN) protein. This protein is critical for snRNP (small nuclear ribonuclear protein) assembly and processing of mRNA. It is abundantly found in motor neuron axons where it fulfils other functions, including transport of mRNA (6) (7). Lack of SMN protein will result in motor neuron loss, inducing a progressive muscle weakness and atrophy, affecting bulbar, skeletal and respiratory muscles. Clinical symptoms span a wide range of severity, but common aspects are loss of strength, difficulty breathing, general mobility issues and problems in swallowing.

In the general population the SMN protein, encoded by the wild-type *SMN1* gene, is normally biosynthesized and functional. Homozygous absence of exon 7 of *SMN1* is the cause of the disease in most (95%) SMA patients, whereas a heterozygous mutation on one allele and other deleterious variants on the other is the cause in the remaining cases (8). A paralogous gene, *SMN2,* differs by only a few nucleotides from *SMN1*, including a C → T transition in exon 7, which affects the splicing of the gene, resulting in the exclusion of exon 7 from ~90% of the protein produced. The resulting protein, missing exon 7, is unstable and rapidly degraded (9). Thus, only approx. 10% of the produced protein by each *SMN*2 copy is functional (10) (11). A greater number of *SMN2* copies has been associated with a milder disease course in SMA patients, however, the correlation is not absolute, and discordances are observed. Several technical pitfalls and biological inter-individual variations account for reported discrepancies in the estimation of *SMN*2 copy number and establishment of phenotype-genotype

correlations (10). Thus, in some patients, the information of *SMN*2 copy number alone may be insufficient to correlate with the observed phenotype (12).
SMA is a single disease with a continuum of severity more or less decreasing with the age of onset of first symptoms. For simplicity, it is generally classified into four different types depending on age of onset and motor milestone reached (13).
SMA Type I is the most common (approx. 50 % of SMA cases) and most severe type of SMA. Infants present with severe hypotonia and weakness, symmetrical flaccid paralysis and often no head control (13). Swallowing and breathing complications will lead to an early death (14). From a motor function point of view, type I patients never sit, type II never walk, and type III walk independently but will lose the ability to walk later in life without treatment (Figure 1). SMA Type 1 patients have a reduced median life expectancy of around one year whereas Type II patients survive more than 20 years and Type III patients have a normal life expectancy (15).

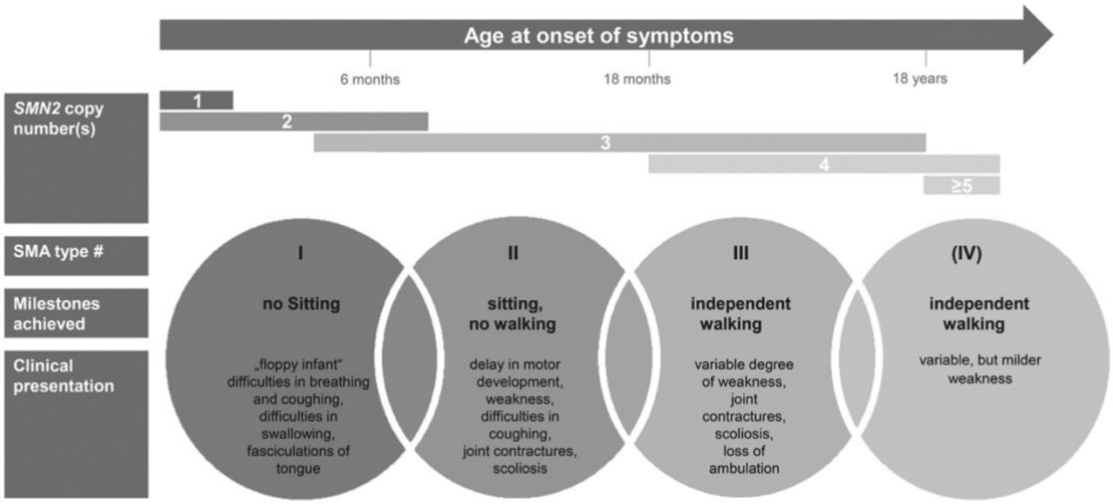


Figure 1 Clinical classification of SMA subtypes according to onset, milestones achieve, and clinical presentation. Typically associated SMN2 copy numbers are displayed. (16)

5.2 There are accepted treatment options for patients with SMA

SUMMARY

- Two disease modifying treatment options for SMA are already available on the European market, with a third to follow early 2021
- More treatments are under development
- There is growing evidence earlier treatment leads to greater potential outcomes

While symptomatic treatment and follow-up of SMA has improved over the last two decades (17), no disease modifying therapies were available. However, three therapeutic options involving the SMN genes were approved during the last years (three in the US and two in Europe, the third underway) that target the underlying mechanism of the disease:

- Nusinersen (Spinraza®), developed by Biogen, was the first drug for spinal muscular atrophy approved in the European Union (May 2017). It is an antisense oligonucleotide, targeting exon 7 of the *SMN2* gene, which is able to enhance the production of functional, full-length SMN protein by the *SMN*2 gene. It has to be given

intrathecally with loading doses on Days 0, 14, 28 and 63 and sustained doses quarterly.

- Onasemnogene abeparvovec-xioi (Zolgensma®), developed by Novartis Gene Therapies, is a one-time gene therapy designed to address the genetic root cause of the disease by replacing the function of the missing or nonworking *SMN1* gene. Administered during a single, intravenous (IV) infusion, Zolgensma delivers a new working copy of the *SMN1* gene into a patient's cells, halting disease progression. It was approved in the European Union in May 2020.
- Risdiplam, (Evrysdi®) developed by Roche in collaboration with the SMA Foundation and PTC Therapeutics, was approved by the FDA in August 2020. This drug also increases the production of complete SMN protein via the *SMN2* gene. Risdiplam can be given orally, allowing for a treatment at home. Approval in the European Union is expected soon, as the Committee for Medicinal Products for Human Use granted a positive opinion in February 2021.

Additional potentially disease modifying pharmacotherapeutic approaches are underway.

There are already results from clinical trials for both Spinraza® and Zolgensma® available showing the significant positive impact of pre-symptomatic treatment (18), (Novartis Gene Therapies data on file). In the case of Evrysdi® a trial in pre-symptomatic babies is still enrolling.

The NURTURE trial by Biogen including pre-symptomatic infants with two or three *SMN2* copies showed a clear benefit of treatment with nusinersen in comparison to the ENDEAR trial that included early symptomatic infants, analysis limited to infants with 2 *SMN2* copies (19). The NURTURE interim analysis in March 2019 with 25 children revealed that all children were alive, had passed the age of expected SMA Type I and II symptom onset and did not require permanent ventilation (18). After an additional year of follow-up (Feb 2020) children in whom treatment was initiated in the pre-symptomatic stage of SMA made progress in motor function which is unusual for the natural history of the disease (Biogen, data on file).

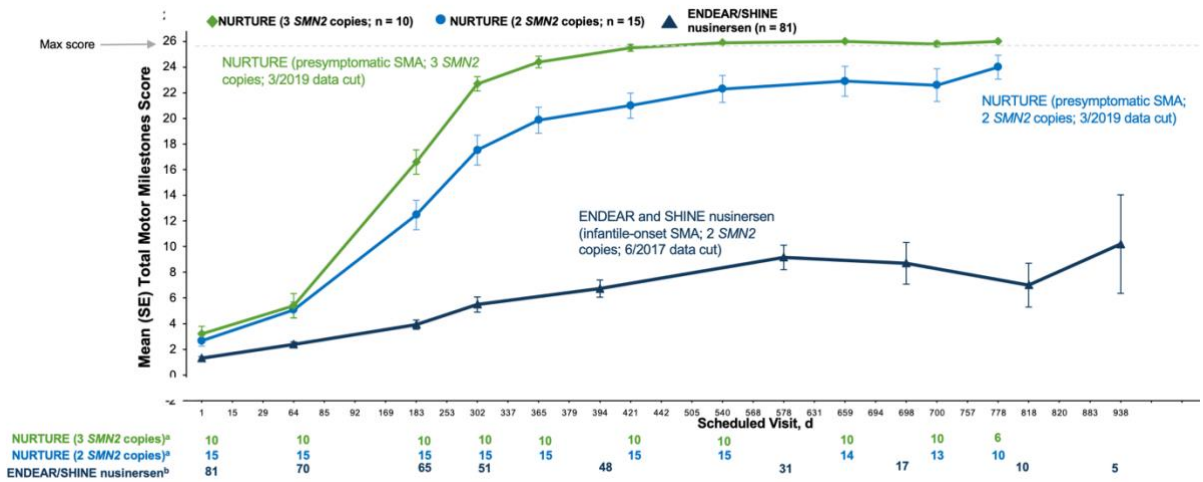
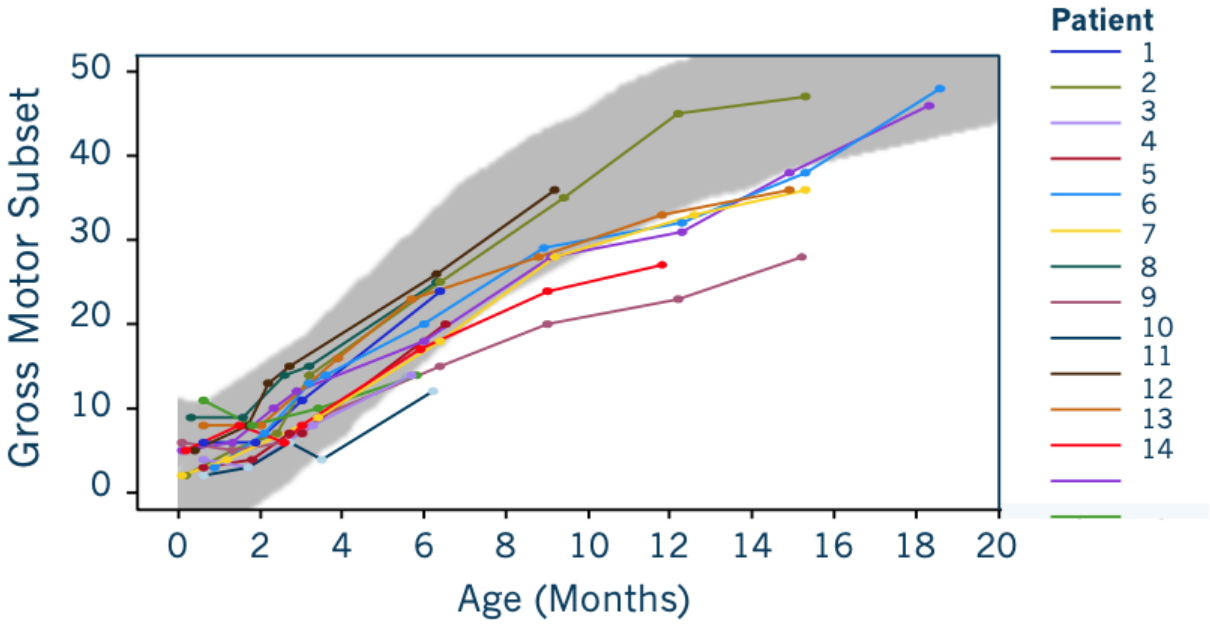


Figure 2 HINE Motor Milestone Scores Over Time Across Studies (Source: Swoboda, et al. Cure SMA Annual Conference 2020, adapted)

NURTURE study interim analysis data cutoff date: 29 March 2019; ENDEAR/SHINE integrated analysis data cutoff date: 30 June 2017. [a]HINE Section 2 was assessed in NURTURE participants up until the Day 778 study visit. [b]ENDEAR participants with 2 SMN2 copies in the intention-to-treat population. ENDEAR data were windowed into intervals based on time from baseline. Data are reported from the first interim data

cut of SHINE. For each study, n ≥ 5 are plotted. Data presented are from the individual studies and are not head-to-head comparisons (Biogen data on file).

Also, for the infants treated pre-symptomatically with Zolgensma® achievement of early, age-appropriate motor milestones was seen, and no ventilatory support or tube feeding was



needed (SPR1NT study, Novartis Gene Therapies, data on file

*Figure 3 Infants with 2 SMN2 copies: **7 of 14 (50%)** have **gross motor performance** similar to normal development; **14 of 14 (100%)** have **fine motor performance** similar to normal development (SPR1NT study update 31 Dec 2019, Novartis Gene Therapies, data on file). The gray shaded area denotes the normal range of raw Bayley-III Gross Motor scores (mean ± 2SD).*

All SMA trials showed that the earlier the treatment, the better the outcome for the patient (20).

In particular, these findings on pre-symptomatic treatment highlight the need for newborn screening (21).
In general, both clinical trial and real-world evidence suggests that early treatment may be necessary to maximise the potential benefits.

5.3 Facilities for diagnosis and treatment of SMA are available

SUMMARY

- There is a wide network of health care institutions across Europe providing state-of-the-art care to SMA patients

Critical for SMA care are specialized teams of health care providers establishing the diagnosis, initiating both symptomatic and disease-modifying therapy and ensuring a proper follow-up of the patient. Moreover, to ensure a holistic treatment approach, psychological and psychosocial counselling as well as physiotherapy services should also be available. Depending on the local health care system, a close cooperation with primary care physicians

(general/family practitioners and/or paediatricians) should be achieved. Across Europe, a variety of SMA centres of expertise are available. In 29 European countries there are specialized centres to treat young children living with SMA, including disease-modifying therapy. The European Reference Network for neuromuscular diseases (ERN-EURO-NMD) is present in 14 countries with 61 centres (www.ern-euro-nmd.eu). In some countries, access to disease-modifying therapy may require cross-border care.

5.4 There is a recognisable latent or early symptomatic stage of SMA

SUMMARY

- There is a time window between birth and age of the first symptom onset. However, even before the first symptoms damage to the motor neurons may occur
- This "window of opportunity" is often wasted without availability of newborn screening

The majority of the babies born with SMA are asymptomatic at birth. This is also seen in the pilot trials conducted so far. In the literature the age of symptom onset is reported to be 2.5 ± 0.6 months for the most common SMA Type I and 8.3 ± 1.6 months for SMA Type II (22). Knowing that the damage to the motor neurons may occur before the first symptoms occur, there is an urgent need to use this "window of opportunity" to identify SMA as early as possible by NBS.
Even though in most cases the babies born with SMA are asymptomatic a birth, there are exceptions as seen in the German pilot trial (23). From the 165.525 children screened within 13 months, 22 SMA cases were identified from which 4 were already symptomatic at the first examination. But also, these symptomatic babies take advantage of the quick diagnosis and immediate treatment following the NBS result.
Unfortunately, this "window of opportunity" is often wasted without availability of NBS.

According to Lin et al., the delay in diagnosis is 3.6 months for SMA Type I, 14.3 months for Type II and 43.6 months for Type III (22). According to patient organizations, the delay in diagnosis for Type 1 SMA is ranging from 4 weeks to 6 months, depending on the respective health care system. This odyssey is very stressful for parents of a child with SMA and wastes precious time during which there is progressive and irreversible damage to motor neurons. With earlier, pre-symptomatic diagnosis, the urgent need to treat can be met and motor neurons can be protected. The delay in diagnosis is often the result of visits to different health care professionals, the "wait and see" approach, to rule out other possibilities of diseases before a genetic test is done (24). In contrast, sampling for NBS, for example in Germany 72 hours after birth at the latest, gives a sufficient time window to identify the disease, communicate to the family and eventually, treat it successfully. Every day matters.

5.5 There is a suitable newborn screening test for SMA

Summary

- A reliable blood test is available that can be used in SMA newborn screening
- The test identifies the presence of a homozygous *SMN1* exon 7 deletion
- Sensitivity is estimated to be 95% and specificity is nearly 100%. This means that false positives are very unlikely to occur
- It is a simple, inexpensive (approximately 3-5 Euros), automated, and high-throughput test

Early detection of SMA during the neonatal period can only be accomplished through molecular diagnostics, as no specific biochemical marker has been validated for the disease. However, a homozygous *SMN1* exon deletion has been found in most patients with SMA and is being used as a reliable and sensitive SMA NBS test in dried blood spot (DBS) specimens (25).

The clinical sensitivity of SMA NBS assays is predicted to be approximately 95%, given that they would not identify affected individuals who are compound heterozygotes with one deleted *SMN1* allele and a second allele with a point mutation. At present, results from several pilot studies on SMA NBS have demonstrated the feasibility of DNA-based SMA NBS (26), (27), (28) (29) (30) (31) (23). The specificity of these assays was nearly 100% in most studies and the cost of conducting the test is approximately €3 - €5 per sample.

A growing number of NBS programmes include SMA testing, so there is a greater demand for reliable SMA screening methods that are cost-efficient; have a high throughput; and are easy to perform, automate, and interpret (32). Significant advances in the development and improvement of these assays are expected in the coming years.

A systematic review by the German Institute for Quality and Efficiency in Health Care (IQWIG) based on the German pilot project and three other studies in Australia, the United States and Taiwan, reported a positive predictive value of the screening between 90% (one study) and 100% (three studies) with a specificity of 100% (19).

5.6 SMA newborn screening is acceptable to the population

Summary

- Studies demonstrate that SMA newborn screening is acceptable to both the general population and families affected by SMA and adults living with SMA

SMA newborn screening is performed from the same DBS specimen that is usually collected between 24h and 72h after birth from the newborn's heel and placed on a specimen collection device. As this procedure is part of the routine in all countries with newborn screening programmes, the newborn will not be exposed to any additional intervention. However, how is SMA newborn screening perceived by the general public, parents and adults with SMA? Boardman et al. (33) administered an online survey to families affected by SMA as well as to the general public in the UK. The general public voted 84% in favour to introduce

SMA NBS. Major reasons were the belief that this would result in better health care and life expectancy for the affected infants. The majority of SMA adults were also in favour of newborn screening (74%) (34). A mixed population of families and adults were also in favour of newborn screening (70%), even though they preferred pre-conception and / or prenatal screening (35). Since the survey was done before a treatment for SMA was available (one key reason not to support NBS is the fact that no treatment is available), the scene may have changed here as discussed elsewhere (36).

5.7 The natural history of SMA, including development from latent to diagnosed disease, is adequately understood

Summary

- Sufficient information on the natural history of SMA is available
- Subject to its type, SMA will inevitably affect children and is causing a marked delay or complete halt in the development of muscular function early in life
- Without early diagnosis and treatment, children with SMA may suffer from severe impairment, accumulation of comorbidities or early death

The natural history of SMA has changed over the years. The turn to more proactive management of the condition (including the introduction of non-invasive ventilation and tube feeding) had an impact on the survival of affected children (17). In 2007, Wang et al. published a first "Standard of Care" document for SMA. The disease manifests with a large clinical spectrum and requires multidisciplinary care (14). This consensus was updated in two parts in 2018 (37) (38).

There are natural history and observational trials published for SMA infants (39) (40). These demonstrate the rapid loss of motor function, lack of weight gain and early death. Now that disease-modifying treatments are available, it is important to have this natural history data on hand. The inclusion of a placebo arm into a clinical trial is from an ethical standpoint no longer possible therefore the natural history data can support the design of upcoming clinical trials.

5.8 There is an agreed policy on whom to treat

Summary

- "Treatment" is not limited to disease modifying drugs only but is comprising best-supportive care including non-pharmacological treatment (e.g., specialised physiotherapy)
- Treatment is a shared decision-making process between the SMA experts and the child´s parents
- The number of *SMN2* copies (a paralogous gene to *SMN1* which can partially replace its function) on its own is not sufficient to decide on a treatment with disease-modifying drugs

The term "treatment" per se is not limited to disease modifying drugs only. In the focus of all decisions needs to be the patient, the family and the multi-disciplinary management of the disease. Treatment therefore means the best possible medical care according to the judgement of SMA experts and agreed in a shared decision-making process with the child's parents. It can reach from best supportive care over symptomatic treatment up to disease-modifying drug therapy. Applying this definition, no baby diagnosed with SMA should be left without any treatment. However, the type of treatment applied should be chosen based on a holistic assessment of the clinical situation of the child and the context of the family.

There is clear consensus, that the sheer number of *SMN2* copies is not a sufficient base to decide on a drug treatment. Instead, the presence or absence of (early) symptoms in combination with the number of *SMN2* copies should guide the physician's recommendation to the parents. To correctly diagnose these children specialized personnel is needed, also allowing for a second or third opinion.

In general, there is agreement to treat babies with two and three *SMN2* copies, as underpinned by a roundtable with European SMA specialists*, and patient representatives**, except in case of very severe and early symptoms, where palliative care should be discussed. This is also in line with the treatment algorithms published and adapted by Glascock et al. in 2020 in the US (41). With regards to babies with 4 *SMN2* copies, there are data available suggesting that the onset of symptoms may be earlier than expected (TreatNMD, data on file). Therefore, the application of disease-modifying drugs might also be favorable here (also in line with (41)). The guiding principle for patients with four or more *SMN2* copies should be an individual decision of both SMA specialist and caregivers based on the medical assessment, the severity of symptoms and the family context.

Taking this conceptional framework into account, the following table might be the basis for this individual treatment decision (Table 1).

No. of *SMN2* copies	**No symptoms**	**Mild symptoms**	**Severe symptoms**
1	DMT	BSC+DMT	BSC only
2	DMT	BSC+DMT	BSC only
3	DMT	BSC+DMT	BSC and revisit genetic findings
$\geq$ 4	DMT (define monitoring and potential start of DMT)	BSC+DMT	BSC and revisit genetic findings (check for modifiers)

Table 1 decision-making grid for the consideration by the medical team and the parents. Symptoms refer to the presentation at time of diagnosis as a neonate.

DMT: disease-modifying therapy, BSC: best supportive care including symptomatic treatment.

Cuscó et al. also present factors to consider when treating neonates with SMA presenting with or without symptoms and 4 *SMN2* copies (12).

In the future, the availability of better biomarkers might support decision making also in those cases where today disease-modifying-drug therapy is only considered an option.

*Dr. Nathalie Goemans, Dr. Wolfgang Müller-Felber, Dr. Laurent Servais, Dr. Eduardo Tizzano, Dr. Danilo Francesco Tiziano

** Olga Germanenko, Marie-Christine Ouillade

5.9 The cost of case finding (including diagnosis) by SMA NBS is economically balanced in relation to possible expenditure on health care as a whole

SUMMARY

- Newborn screening for SMA can be conducted without major costs from the dried blood spot specimen already collected for newborn screening
- The cost of screening outweighs the cost of illness
- Detecting SMA early and prompt treatment may also have a financial advantage to the health care system, in addition to the improvement of quality of life of the treated children

NBS is aiming to detect SMA via a DBS specimen genetic analysis. This can easily be added to the existing European NBS programmes. SMA screening can be done cost effectively for approximately 3-5 Euros per child.

These costs are economically balanced when comparing them to the cost of illness. There are cost estimations available from a German study group calculating the cost of illness for SMA patients in Germany (42). The costs correlate clearly with the severity of the illness. They found mean total costs of 107.807 Euro/year for SMA Type I patients, 90.267 Euro/year in SMA Type II patients and 52.440 Euro/year for SMA Type III patients (in 2013). For the Spanish health care system, López-Bastida et al. (43) estimate the average annual cost of healthcare for SMA 33.723 Euro. Another study investigating cost of illness in the UK, France and Germany, estimates annual average cost associated with SMA to be as high as 54.295 Euro in the UK, 32.042 Euro in France and 51.983 Euro in Germany, respectively (44).

These figures cannot yet include the economic benefit of treating SMA as soon as possible after identifying children by NBS. Modifying the disease severity may have an economic benefit. For further discussions on health economics, please see chapter 8.

5.10 Case finding is a continuing process and not a “once and for all” project

SUMMARY

- SMA newborn screening must be available to all children consecutively born in a given country
- Introducing SMA newborn screening is a contribution toward a more inclusive health care system

NBS for SMA must include all newborns rather than a selected – often privileged – cohort. While pilot testing may help to establish test routines and the appropriate processes, they are unfair if continued endlessly. Every child born in Europe must have equal opportunities to access newborn screening for SMA. Hence, introduction of SMA NBS in the national screening policy is an important aspect to create an inclusive health care system.

6 SMA newborn screening process proposal

Summary

- Every SMA newborn screening programme must ensure proper information for all parents. In case of a screening positive result, equity of access to care, including a clearly defined diagnosis, management and long-term follow-up of the disease shall be ensured by the standard newborn screening procedure
- All involved health care professionals must have received appropriate training to fulfil their roles in the newborn screening programme
- Participation in an SMA newborn screening programme should be voluntary, parents should have the right to opt-out
- A reliable screening test with no need for additional blood sampling is available

Although NBS programmes have historically focused on screening testing, truly effective NBS programmes provide an infrastructure for universal access, education, and rapid follow-up for newborns with a screen-positive result. A complete NBS programme comprises six main components (45):

-Education
-Screening
-Diagnosis
-Management
-Follow-up
-Evaluation

Currently, there are no policy recommendations or universal standards or guidelines for the implementation of NBS programmes in Europe, not even within the European Union (46). Although the European Commission has published recommendations for European policymakers (47) (48), health care falls under the competency of the individual member states of the European Union and thus each makes its own decisions on NBS. Depending on the country, NBS may be governed by national or local laws, policies, regulations, or rules that affect NBS programmes (49). Furthermore, in some countries, health care policymaking is decentralised to regions or provinces that operate with a greater or lesser degree of autonomy, which adds an additional layer of complexity.

There is now some kind of institutionalised newborn screening in nearly all European countries, but there are significant variations among them. NBS programmes in several countries are poorly developed and, in some countries, an official NBS programme has not yet been established (49).

When an NBS programme is implemented, it must ensure equal access to and coverage of appropriate resources for the diagnosis and treatment of newborns detected. The NBS programme should assess the resources for disease diagnosis, treatment, and follow-up that are available in the geographic location where it is conducted. Molecular studies will be needed to definitively diagnose SMA. The use of potentially complex therapies in terms of accessibility, cost, and urgency for initiating them will be indicated for babies identified as

having SMA. A lack of resources may limit the value of the screening and indeed SMA NBS may not be advisable if sufficient resources for care are not available. By way of example, this was a crucial aspect when NBS on cystic fibrosis (CF) was introduced in a couple of European countries in the most recent years. Like SMA, CF is considered a rare disease that requires special care structures including specialized health care providers. As these are available – as it is the case for SMA – CF NBS could therefore be introduced after the need for it was established.

6.1 Access, equity and funding

NBS in European countries is heterogeneous and there is no consensus on which diseases the programmes should screen for. Although the value of NBS has been widely recognised, its introduction depends on the health care structure, available funds, local politics, and input from professional groups and the general public. This has led to quite varying approaches in the way these programmes have been set up, funded, and managed (46). Typically, NBS programmes in Europe are funded comprehensively, from the preanalytical through the diagnostic and management/follow-up phases. If it is financed with public funds, NBS offered by health services usually has an underlying legal basis that supports it or is an implicit public health measure.

In order to provide equal access, SMA NBS should be offered to all newborns in Europe. Its provision should be governed by the appropriate legal provisions and must ensure compliance with the same quality requirements found in other types of health legislation (such as patient rights, personal data protection, biobanks, research approval by ethics committees, genetic testing, and genetic counselling). Each national health service should cover the costs associated with these programmes.

For ongoing pilot trials and the status of the implementation of SMA NBS in Europe, please see chapter 9.

6.2 Awareness, education and training

An integral component of NBS is ensuring awareness, education, and training for all relevant stakeholders. These stakeholders include prenatal, primary care, and specialty care providers; hospital personnel; families; NBS programme personnel; policymakers; and advocates. Awareness and education will enable informed participation in SMA NBS and will improve parents' experience, especially for those whose children are screen-positive.

Most European countries provide information on NBS to parents in the form of online information, brochures, or other educational materials. These materials address the purpose of NBS and the importance of participation in the programme. Many of them also provide a list of diseases that are screened for, information about the possibility of false positive and false negative findings, and the medical implications of screening (50) (also see chapter 7.7). In a few countries, the procedure for providing information to parents is still unregulated and significant variations exist; establishing regulations in this regard is a goal that should be

worked towards. When preparing to add SMA to an NBS programme, it is necessary to create or update educational materials as well as offer specific training to all relevant stakeholders.

6.3 Consent practices

Participation in an SMA NBS programme should be voluntary. The fact that participation in an SMA NBS programme is in their child's best interest should be made clear to parents. This information, along with education, should be offered to them before or at the time the DBS specimen is collected.

NBS programmes differ considerably in terms of approaches to parental consent for NBS, regardless of the nature of the test (biochemical or genetic). Written consent is required in only a few countries. Some NBS programmes allow parents to refuse to participate in NBS testing but may require them to actively opt out in order to do so. In a few European countries, NBS is mandatory (Poland, Hungary, Croatia, and the Czech Republic) (49).

Depending on local regulations, the addition of SMA to an NBS programme could be implemented using the same consent practices used for the programme or may require a specific consent, as in some countries, legislation on genetic information is treated differently from that on other sensitive health information. The consent protocols for SMA NBS should be defined at the jurisdictional level following consultation with the appropriate stakeholders. Specific consent should be obtained for activities that are not strictly for the benefit of the newborn, such as reporting incidental findings, the storage of DBS specimens, and the use of residual DBS specimens for research purposes.

6.4 Screening

The newborn DBS specimen collection for SMA NBS can be easily added to standard NBS programmes without additional specimen collection. Capillary blood collected by a heel prick with direct application on the filter paper section of the specimen collection device is the preferred method for NBS. In limited situations, other sources of blood may be valid for SMA NBS (51). For most NBS programmes, DBS specimen collection occurs between 24 and 72 hours after birth. The demographic data and other information requested on the specimen collection device must be accurately completed either manually or electronically.

No biochemical markers of SMA have been validated. However, several approaches based on molecular testing to detect homozygous *SMN1* exon 7 deletion have been developed. Some of these assays have been designed for multiplexing SMA and severe combined immunodeficiency (SCID) screening (52), which is an advantage when it comes to adding SMA to programmes that already screen for severe combined immunodeficiency (SCID). Assays for SMA NBS are specifically tailored for NBS laboratories and would only require modest laboratory adaptations and personnel training in order to perform these genetic analyses. More advanced molecular technology and other analytical innovations will inexorably lead to even more disorders being included in NBS programmes.

Many methods have been evaluated for SMA NBS testing with DBS specimens. They include liquid microbead suspension arrays, high-resolution DNA melting analysis (HRMA), quantitative real-time polymerase chain reaction (qPCR), competitive oligonucleotide priming PCR (COP-PCR), loop-mediated isothermal amplification (LAMP) technology, and DNA mass spectrometry (53), (54) (32) (55) (56). Of them, the technique most used in SMA NBS pilot studies and programmes in the United States of America has been qPCR. LAMP technology has the advantage of not requiring DNA extraction, which simplifies the sample analysis process (56).

For an SMA screening method to be suitable for NBS programmes, it must be cost-efficient, capable of high-throughput, and easy to implement in NBS laboratories. In addition to multiplexing with SCID, SMA can also be combined with screening for X-linked agammaglobulinemia (XLA) (57). Quality assurance measures must be established to ensure assay performance and the use of DBS reference materials, such as those provided by the US Centers for Disease Control and Prevention (CDC), is recommendable. A SMA proficiency testing programme is currently being piloted within the CDC's Newborn Screening Quality Assurance Programme (NSQAP).

Droplet digital PCR (ddPCR) has been used as a second-tier test for excluding false positives and measuring *SMN2* copy number (58) (27). The use of second-tier testing has proven that a false positive rate of 0.0% can be reached (29) (27).

6.5 Diagnosis confirmation

According to the NBS programme protocols, SMA screen-positive results should be reported immediately. NBS programmes need to arrange or help coordinate follow-up diagnostic testing so the newborns can receive a prompt diagnosis. For newborns with a screen-positive result for SMA, a rapid referral to a neuropaediatrician at an SMA/neuromuscular specialty centre for diagnostic confirmation and subsequent information on treatment options is necessary. It is essential to perform a proper neurological and clinical examination and take a family medical history.

All possible SMA cases identified through SMA NBS must be confirmed with a reliable diagnostic test in another blood specimen as soon as possible. The multiplex ligation-dependent probe amplification (MLPA) technique is most frequently used for diagnostic confirmation. Diagnostic confirmation should include genetic testing for *SMN1* exon deletions and *SMN2* copy number as a predictive marker (12).

It should be noted that approximately 5% of patients with SMA will present a subtle *SMN1* variant and will not be detected by current screening methods (8) (21). Thus, the introduction of SMA NBS does not diminish the importance of a differential diagnosis for SMA when compatible symptoms are present.

6.6 Management

Recently, consensus statements on gene therapy have clearly stressed that the time between diagnosis and initiation of treatment should not exceed two weeks (59).

It should be noted that for some babies / infants with very severe forms of SMA, detection of the disease through NBS does not allow for pre-symptomatic treatment (28) (23). The therapeutic effects are less when treating a symptomatic patient. This should be considered when discussing treatment plans with the child´s parents (60).

In pilot studies, attention was drawn to a very narrow therapeutic window for patients with acute SMA. Therefore, the time periods between obtaining the initial screening results, confirmatory testing results, and the initiation of therapy should be as short as possible (23) (28).

The aim of treatment will always be to improve the child's survival and quality of motor function, achieving developmental milestones that were not seen in the natural history of the disease without treatment and ensuring a higher quality of life for the patient and the family.

6.7 Follow-up

Follow-up, which determines whether NBS programmes have achieved and continue to meet their primary aims of preventing or minimising morbidity and mortality, is vital to evaluating the benefits of NBS to an individual throughout his or her lifetime as well as to the family and society (61).

Communication of a screen-positive result and confirmed diagnosis should include the provision of information to parents that is suitable, and which serves to ease their anxiety. At present, the availability of digital or printed materials on the meaning and the consequences of a positive result of an SMA NBS can help parents understand and cope with the diagnosis of this disease. If they have an appropriate understanding of the disease, prognostic factors, and therapeutic options, they will be able to freely and actively participate in decision-making.

Multidisciplinary care is essential in this phase. This includes follow-up with a genetic counsellor in the form of a consultation which would ideally take place shortly after diagnosis as well as psychological support for the family.

Greater parent and patient empowerment may improve the management of care and families' quality of life. Patients' and parents' organisations may play a role in assuring optimal quality of care for SMA patients and in providing respite initiatives for family caregivers.

6.8 Newborn screening programme evaluation and quality assurance

SMA NBS programmes must establish quality indicators before their implementation begins and must continuously evaluate them in order to identify best practices. Some indicators should be related to the analytical performance of the NBS methodology (sensitivity,

specificity, positive predictive value, negative predictive value, false positive and false negative rates). Other commonly evaluated parameters are related to the programmes' response times (days of life of the newborn when reporting the NBS/diagnosis results as well as when therapy is initiated). Finally, other objectives concerning infants' health outcomes throughout long-term follow-up should be ideally analysed.

All these quality indicators must be periodically reviewed so as to identify weaknesses in the NBS programme that can be corrected with improvement plans or actions. In order to achieve best practices, it can be helpful to follow the recommendations of groups of experts or international quality standards, if available, or failing that, the programme can be compared to other NBS programmes' performance indicators and outcomes.

7 Ethical considerations

Summary

- When discussing the advantages and potential disadvantages of early diagnosis in SMA, it becomes clear that the advantages of early screening outweigh the disadvantages
- Early diagnosis must not remain a privilege that is only accessible to a minority of well-informed and/or wealthy families. Offering SMA newborn screening in the health care system for all newborn babies is therefore ethically mandatory
- Newborn babies in Europe have the right to be diagnosed as early as possible by newborn screening for SMA in order to get optimal health care as written in the UN Convention on the Rights of the Child

7.1 The Rights of the Child

In the UN Convention on the Rights of the Child - which were ratified by all European Countries - Article 24 is referring to the right to have optimal health care. NBS can help to point to these children that are in special need of elevated health care (46). Vice versa, withholding children NBS, however, translates into depriving them from an optimal pathway towards care.

7.2 Newborn screening addresses babies 2-3 days after birth

Newborn screening includes only babies and should therefore not be confused with pre-conception or prenatal screening. The intention is to detect affected infants rather than carriers or a foetus / unborn child. This is important to understand as these approaches are still subject to controversial debates reflecting religious, political and historical experiences and traditions in the varying societies. Hence, when making decisions for the public health care system, it should be made clear that the introduction of NBS for SMA is by no means pre-empting any of the aforementioned approaches. Early testing reduces the long and stressful pathway to diagnosis, thus an early diagnosis would spare the family from difficulties associated with a late diagnosis, such as economic and psychological burden.

7.3 Newborn screening in SMA is a means to ensure equality of access to appropriate health care

The most striking ethical argument for NBS in SMA is an early diagnosis ideally before symptoms occur allowing initiation of an appropriate treatment. This way, the onset of symptoms affecting the patient's quality of life can be significantly delayed or even prevented and his/her life-expectancy can be improved.

NBS for SMA available to the general population also supports the equity of access to both diagnosis and therapy across the population as opposed to a policy that would leave the choice of NBS to parents that are well-informed and financially prepared to seek out and to

pay for NBS for their newborn. NBS is therefore a means to improve equity and inclusivity in the health care system and in society.
To ensure true equality of access, NBS in SMA must be free of charge for parents.

7.4 Newborn screening can prevent parental guilt

There is also the aspect of the "right to know at the right time" for all families. Knowing that the child is developing slowly for a reason prevents potential parental attempts to "push" the child to activities she or he cannot perform due to the disease. It also helps parents to better understand the limited span of control they have over the development of their child, thus preventing excessive parental self-guilt. The diagnosis of SMA is a painful experience for the affected families. A survey in SMA families and patients with SMA showed that the majority did not agree that the identification of SMA at birth would interfere with the early bonding process (35).

7.5 There is no "right not to know"

From an ethical point, one may argue that the parents have a "right not to know" about the diagnosis.

It is mainly the threat of an overmedicalized childhood leading to excessive treatment and a disturbed parent/child relationship that may come up as points against NBS in SMA. It has also been discussed that identifying SMA before symptoms emerge will prevent families and children enjoying life while they are symptom free. However, while not knowing about the child's disease may give some time to the family – in apparent "peace", it will inevitably lead to a waste of precious time needed to take urgent action to treat and halt irreversible damage when motor neurons can still be preserved, or the deterioration can at least be slowed down significantly. So, not to know the disease, is not an acceptable ethical option if parents would choose therapy if they knew. Only in those few cases where parents would choose not to seek appropriate treatment for their child that has been diagnosed with SMA, an early diagnosis could be considered unethical. However, in this case one may challenge the parental right to deny appropriate treatment that is in conflict with the Right of the Child for optimal health care.

7.6 Newborn screening allows informed decisions

Informed parents can make informed decisions and could for example, decide to move closer to hospitals or places with better medical care and educational opportunities. They can also decide on further reproduction plans (62). The wider family as potential carriers might also take this possible risk into consideration for family planning.

7.7 The risk of false positive or false negative results do not outweigh the benefit of newborn screening in SMA

While the risk of a false positive result is low if a confirmative test is done in an additional laboratory, the risk of a false negative result is more challenging (laboratory errors, subtle pathogenic variant not identifiable by the NBS method, etc.). Approximately 5% of SMA patients will not be identified by available screening methods detecting the deletion of *SMN1* on the long arm of chromosome 5 (5q-SMA) due to *SMN1* point mutations (21). The situation for false negative tested children will probably be slightly different after a general NBS in SMA has been introduced, because the responsible physician is unlikely to check for SMA as the child has already been tested in NBS and the time for diagnosis could even be longer than before. Hence, to minimize this risk, the introduction of NBS in SMA must be accompanied by appropriate countermeasures such as medical education of health care professionals who have first contact with the family and responsible physicians to alert them to this possibility and the symptoms of SMA. However, 95% of all children with SMA will benefit from NBS, so denying them access to an early diagnosis and earlier treatment cannot be considered an ethically appropriate option. Furthermore, it is opportune to comment here that there are other SMA types, (non-5q-SMA) that are much less frequent than 5q-SMA, caused by alterations in other genes and without specific treatment (63).

8 Health economics

Summary

- Rare diseases' interventions increasingly face economic scrutiny in Health Technology Assessments
- Willingness-to-pay is on average higher for rare diseases' interventions, including treatment optimization through screening
- With treatment now being available, an analysis of cost-effectiveness of NBS in the US shows improved economic value for both patients and payers

Health economics is a field in Health Technology Assessment (HTA) that has become and still becomes increasingly important, generally, but also in the field of population-based screening for rare diseases. For decades, interventions in rare diseases have been relatively exempt from economic analysis, for example, new drugs would come to the market and were reimbursed relatively straightforward. Recently, however, we have seen how HTA-jurisdictions also have made rare disease interventions the target of economic scrutiny, in particular, cost-effectiveness/utility analysis.

The above developments could impact on the assessment of screening for SMA. In particular, cost-effectiveness is required for screening for SMA, as well as the cost-effectiveness of giving treatment asymptomatically to those found to be positive, compared to the natural course of SMA patients. This involves evaluation of the cost-effectiveness of NBS with the inclusion of different treatment scenarios, notably the recent disease-modifying therapies such as Spinraza® and Zolgensma®.
The core concept in cost-utility/effectiveness is the cost-effectiveness (CE) ratio, reflecting the difference in costs divided by the difference in health benefits, expressed in quality-adjusted life years (QALYs). Willingness-to-Pay (WTP) thresholds have been developed for health care interventions (e.g., medicines, vaccination programmes) with broad-scale use. Typically, WHO propagates that the Gross Domestic Product (GDP) per capita is leading to set the WTP. If the CE-ratio is below 1 GDP/capita the label is "very cost-effective", if between 1- and 2-times GDP/capita "cost-effective", if between 2- and 3-times GDP/capita "potentially cost-effective" and if above 3 times GDP/capita "not cost-effective". Targeted therapies/immune therapies as well as rare diseases' treatments have changed the landscape of WTP-thresholds in introducing differentiated thresholds for various countries. Notably, the more serious the index disease, the higher the WTP, as illustrated with NICE's end-of-life criteria (64); as well as generally higher WTPs being used in the context of rare diseases (65).

It is often argued that for rare diseases, cost-effectiveness fails to grasp all the relevant prevailing societal values that apply to this class of diseases and corresponding interventions, including gene-therapies and screening (65). If severity justifies an increased WTP (as applied by several HTA bodies), other aspects of value may warrant further increases.

Firstly, rarity per se may reflect a societal value in itself (66). Secondly, whereas cost-effectiveness HTA methodology was developed for drugs with large-scale use and corresponding high budget impact, due to low patient numbers, rare diseases' interventions, including gene therapies and corresponding identification of eligible patients (screening), may

have relatively modest budget impact. Modest or low budget impact reflects an important value for society, allowing affordability of health care systems. Thirdly, drugs for rare diseases – more than on average – apply innovative scientific technologies potentially allowing scientific spill-overs to other disease areas within or outside the rare diseases field such as gene therapies, warranting stimulation of its development and use (screening). Scientific spill-overs have recently been identified by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR, flower paper) as an additional value for new drugs, potentially warranting higher WTPs. Finally, there is societal value in developing drugs for rare diseases, reflecting a field with difficult return-on-investment potentials. Relatively higher pricing as well as patient finding (screening) stimulates continued investment in development of orphan drugs, satisfying an important societal need.

Health economic evaluation of NBS for SMA needs to be conducted versus the current practice of diagnoses and treatment of symptomatic SMA patients. NBS will allow for early pre-symptomatic diagnosis and treatment of SMA patients. This in combination with the most optimal treatment option has enormous potential to improve a patient's prognosis to live a life comparable to other children of the same age.

Cost-effectiveness models for newborn screening for rare and genetic diseases are existing but rare. Previously, cost-effectiveness results have been published for severe combined immunodeficiency, cystic fibrosis and biotinidase deficiency diseases (67) (68) (69) (70). Conforming to standard health-economics methodologies, these analyses generally use a decision-tree model to compare the impact of screening in combination with a so-called Markov-model for the differences in costs and effects on the long run. For the United States a cost-effectiveness analysis was conducted for NBS for SMA with subsequent nusinersen treatment (71). It was concluded from this study that NBS for SMA provides improved economic value for payers and patients when nusinersen is available. It is likely, this conclusion would not be very different for gene therapy. A core economic model will need to provide health care decision-makers with relevant cost-effectiveness results to inform country-specific implementation of NBS for SMA. Notably, such core models are in development. Such a model needs to be adapted based on country-specific parameter input and in line with the guidelines for health-economic studies that apply (e.g., discounting, time-horizon, health care or societal perspective). Cost-effectiveness results will depend on these country-specific input values, the clinical treatment guidelines, whether there is an existing NBS programme and if SMA treatment is available for patients.

9 The benefits of screening – Pilot trials and status of SMA newborn screening implementation in Europe

Summary

- The SMA newborn screening pilot trials in Europe further support the results from clinical trials, showing that pre-symptomatic treatment results in age-appropriate motor development
- Within Europe, there are inequities with some babies having access to newborn screening for SMA, while most European newborns are not screened for SMA
- For the current status of SMA NBS in Europe please visit: www.sma-screening-alliance.org/map

Currently, there are some NBS ongoing pilot trials in Europe (Germany, Italy and Spain following soon).
In Belgium, a 3-year pilot trial started in 2018 and was completed (31). The vast majority of the parents gave consent when offered SMA NBS. SMA NBS has now become permanent policy for the Belgian regions of Wallonia and Brussels.
In Germany, the pilot trial started in 2018. After more than one year, 178.000 children were screened with 25 cases of SMA identified. The incidence found is in line with known incidences, meaning that NBS does not detect SMA cases that would not be found in normal clinical practice (23). In all children with pre-symptomatic treatment, the HINE and CHOP-Intend scores show near normal development (21). In December 2020, the federal joint committee in Germany agreed to implement screening for SMA into the national NBS panel (72). Due to technical prerequisites the actual screening is expected to start mid 2021.
The pilot trial in Italy started in September 2019. Until October 2020 over 45.000 newborns were screened and 11 positive cases have been reported so far. The Spanish pilot trial will start in 2021 in Valencia and is expected to include Andalucía later this year.
As of February 2021, further pilot trials are planned for France and the United Kingdom.

	Germany	Italy	Belgium
Starting date	15 Jan 2018	05 Sept 2019	5 Mar 2018
Expected births / year (pilot duration)	150.000 / year (3 years)	55.000 / year (2 years)	60.000 / year (3 years)
Number of patients screened so far	178.000	45.112	42.000
Number of positive cases	25	11	6
Date of last update	Mar 2019	07 Oct 2020	Mar 2019

Table 2 SMA screening pilots ongoing in Europe, adapted from (21) The numbers for the Italian pilot trial were kindly updated and provided by Dr. Danilo Francesco Tiziano.

In addition to Germany, SMA is approved as part of the national newborn screening programme and awaiting implementation: the Netherlands (73), Norway, Serbia, Poland and Slovenia (status Feb 2021).
For the current status of SMA NBS in Europe please visit: www.sma-screening-alliance.org/map.

10 Experiences from outside Europe

Summary

- The United States (US) is well in advance of Europe in implementing NBS for SMA
  - 34/50 US states are now screening for SMA
  - 69% of all babies born in the USA are now screened for SMA
- Australia has applied for SMA newborn screening and is planning to introduce it nationally after a final health ministry decision expected in 2021
- Also, in Asian countries (like Taiwan and Japan), pilot trials were conducted

In the US, SMA was added to the "recommended uniform screening panel" (RUSP) in 2018. Individual states are now aiming to implement this in their State-specific screening panels. As of March 2021, 34 out of 50 States are screening for SMA, resulting in a screening rate of 69% babies born in the US (https://www.curesma.org/newborn-screening-for-sma). This State-by-State process does not treat all US babies equally, because it strongly depends in which state the infant is born.

A pilot programme in two Australian States, New South Wales (NSW) and Australian Capital Territory was performed from August 2018 to July 2020. The NSW health department has recognized the importance of this pilot and have continued to provide funding for testing now that the pilot has ended. An application was made to the national newborn screening committee in order to add SMA to the national NBS programme after birth (smaaustralia.org.au). This addition is expected to happen in 2021.

Also, in Asian countries (like Taiwan and Japan), pilot trials were conducted (27) (74).

11 References

1. *https://download2.eurordis.org/documents/pdf/eurordis_nbs_position_paper.pdf.* **EURORDIS.** 2021.
2. *https://ipopi.org/wp-content/uploads/2020/06/Call-to-Action-NBS-Screen-4-Rare.pdf.* **IPOPI.** 2020.
3. *Principles and Practice of screening for disease.* **Wilson&Jungner.** 1968, Public Health Papers 34.
4. *The Genetics of Spinal Muscular Atrophy: Progress and Challenges.* **Farrar, M. A., & Kiernan, M. C.** 2015, The journal of the American Society for Experimental NeuroTherapeutics, 12(2), pp. 290–302.
5. *Incidence, prevalence, and gene frequency studies of chronic childhood spinal muscular atrophy.* **Pearn J.** 1978, J Med Genet. Dec;15(6):, pp. 409-413.
6. *Spinal muscular atrophy: a timely review.* **Kolb, S. J., & Kissel, J. T.** 2011, Arch Neurol. Aug;68(8):, pp. 979-984.
7. *Diverse role of survival motor neuron protein.* **Singh, R. N., Howell, M. D., Ottesen, E. W., et al.** 2017, Biochim Biophys Acta Gene Regul Mech. Mar; 1860(3), pp. 299-315.
8. *Mutation update of spinal muscular atrophy in Spain: molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene.* **Alías, L., Bernal, S., Fuentes-Prior, et al.** 2009, Hum Genet., pp. 29-39.
9. *The next generation of population-based spinal muscular atrophy carrier screening: comprehensive pan-ethnic SMN1 copy-number and sequence variant analysis by massively parallel sequencing.* **Feng, Y., Ge, X., Meng, L., et al.** 2017, Genet. Med Aug;19(8), pp. 936-944.
10. *Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases.* **Calucho, M., Bernal, S., Alías, L., et al.** 2018, Neuromuscular Disorders Mar; 28 (3), pp. 208–215.
11. *Refined characterization of the expression and stability of the SMN gene products.* **Vitte, J., Fassier, C., Tiziano, F. D., et al.** 2007, Am J Pathol. Oct;171(4), pp. 1269-1280.
12. *Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy.* **Cuscó, I., Bernal, S., Blasco-Pérez, L., et al.** 2020, Neurol Genet. 18;6(6).
13. *Spinal muscular atrophy.* **D'Amico, A., Mercuri, E., Tiziano, F. D., et al.** 2011, Orphanet Journal of Rare Diseases Nov 2; 6:71.
14. *Consensus statement for standard of care in spinal muscular atrophy.* **Wang, C. H., Finkel, R. S., Bertini, E. S., et al.** 2007, J Child Neurol Aug; 22(8), pp. 1027-1049.
15. *Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review.* **Verhaart, I., Robertson, A., Wilson, I. J., et al.** 2017, Orphanet Journal of Rare Diseases Jul 4;12 (1).
16. *Advances in Treatment of Spinal Muscular Atrophy – New Phenotypes, New Challenges, New Implications for Care.* **Schorling, D. C., Pechmann, A., & Kirschner, J.** 2020, Journal of Neuromuscular Diseases 7 (1), pp. 1-13.
17. *The changing natural history of spinal muscular atrophy type 1.* **Oskoui, M., Levy, G., Garland, C. J., et al.** 2007, Neurology 13;69(20), pp. 1931-1936.

18. *Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study.* **De Vivo, D. C., Bertini, E., Swoboda, K. J., et al.** 2019, Neuromuscular Disorders Nov; 29 (11), pp. 842–856.
19. **IQWIG.** *Neugeborenenscreening auf 5q-assoziierte spinale Muskelatrophie Bericht Nr.891.* Köln 2020 : s.n.
20. *Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives.* **Dangouloff, T., Servais, L.** 2019, Ther Clin Risk Manag. Oct 2;15:, pp. 1153-1161.
21. *244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands.* **Dangouloff, T., Burghes, A., Tizzano, E. F., et al.** 2020, Neuromuscular Disorders Jan; 30 (1), pp. 93-103.
22. *Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review.* **Lin, C. W., Kalb, S. J., & Yeh, W. S.** 2015, Pediatric Neurology Oct; 53 (4), pp. 293-300.
23. *One Year of Newborn Screening for SMA – Results of a German Pilot Project.* **Vill, K., Kölbel, H., Schwartz, O., et al.** 2019, Journal of Neuromuscular Diseases ;6 (4), pp. 503–515.
24. *A mixed methods exploration of families' experiences of the diagnosis of childhood spinal muscular atrophy.* **Lawton, S., Hickerton, C., Archibald, A. D., et al.** 2015, European Journal of Human Genetics May; 23 (5), pp. 575–580.
25. *Newborn and carrier screening for spinal muscular atrophy.* **Prior, T. W., Snyder, P. J., Rink, B. D., et al.** 2010, Am J Med Genet A. Jul;152A(7), pp. 1608-1616.
26. *Pilot study of population-based newborn screening for spinal muscular atrophy in New York state.* **Kraszewski, J. N., Kay, D. M., Stevens, C. F., et al.** 2018, Genet Med. Jun;20(6), pp. 608-613.
27. *Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening.* **Chien, Y. H., Chiang, S. C., Weng, W. C., et al.** 2017, J Pediatr. Nov;190:, pp. 124-129.
28. *The implementation of newborn screening for spinal muscular atrophy: the Australian experience.* **Kariyawasam, D., Russell, J. S., Wiley, V., et al.** 2020, Genet Med.Mar;22(3), pp. 557-565.
29. *Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy.* **Kay, D. M., Stevens, C. F., Parker, A., et al.** 2020, Genet Med. Aug;22(8):, pp. 1296-1302.
30. *CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening.* **Weng, W. C., Hsu, Y. K., Chang, F. M., et al.** 2020, Genet Med. Oct 9.
31. *Newborn screening for SMA in Southern Belgium.* **Boemer, F., Caberg, J. H., Dideberg, V., et al.** 2019, Neuromuscular Disorders May; 29 (5), pp. 343–349.
32. *Newborn Screening for Spinal Muscular Atrophy in China Using DNA Mass Spectrometry.* **Lin, Y., Lin, C. H., Yin, X., et al.** 2019, Front Genet. Dec 17;10:1255.
33. *Newborn genetic screening for spinal muscular atrophy in the UK: The views of the general population.* **Boardman F. K., Sadler C, Young PJ.** 2018, Molecular Genetics & Genomic Medicine Jan; 6 (1), pp. 99–108.
34. *Impairment Experiences, Identity and Attitudes Towards Genetic Screening: the Views of People with Spinal Muscular Atrophy.* **Boardman, F. K., Young, P. J., & Griffiths, F. E.** 2018, J Genet Counsel Feb; 27 (1), pp. 69–84.

35. *Newborn screening for spinal muscular atrophy: The views of affected families and adults.* **Boardman, F. K., Young, P. J., & Griffiths, F. E.** 2017, Am J Med Genet A. Jun;173(6):, pp. 1546-1561.
36. *Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors.* **Serra-Juhe, C., & Tizzano, E. F.** 2019, Eur J Hum Genet. Dec;27(12), pp. 1774-1782.
37. *Request Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care.* **Mercuri, E., Finkel, R. S., Muntoni, F., et al.** 2018, Neuromuscular Disorders Feb; 28 (2), pp. 103-115.
38. *Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics.* **Finkel, R. S., Mercuri, E., Meyer, O. H., et al.** 2018, Neuromuscul Disord. Mar;28 (3), pp. 197-207.
39. *Natural history of infantile-onset spinal muscular atrophy.* **Kolb, S. J., Coffey, C. S., Yankey, J. W., et al.** 2017, Ann Neurol Dec; 82(6), pp. 883-891.
40. *Observational study of spinal muscular atrophy type I and implications for clinical trials.* **Finkel, R. S., McDermott, M. P., Kaufmann, P.,et al.** 2014, Neurology. Aug 26;83(9), pp. 810-817.
41. *Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2.* **Glascock, J., Sampson, J., Connolly, A.M., et al.** 2020, J Neuromuscul Dis.; 7(2):97-100.
42. *Disease burden of spinal muscular atrophy in Germany.* **Klug, C., Schreiber-Katz, O., Thiele, S., et al.** 2016, Orphanet Journal of Rare Diseases May 4; 11 (1):58.
43. *Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain.* **López-Bastida, J., Peña-Longobardo, L. M., Aranda-Reneo, I., et al.** 2017, Orphanet journal of rare diseases, 12(1), 141.
44. *The Economic Impact and Health-Related Quality of Life of Spinal Muscular Atrophy. An Analysis across Europe.* **Peña-Longobardo, L. M., Aranda-Reneo, I., Oliva-Moreno, J., et al.** 2020, International journal of environmental research and public health, 17(16), 5640.
45. *U.S. newborn screening policy dilemmas for the twenty-first century.* **Therrell BL.** 2001, Mol Genet Metab. Sep-Oct;74(1-2):, pp. 64-74.
46. *European Union Should Actively Stimulate and Harmonise Neonatal Screening Initiatives.* **Loeber, J. G.** 2018, International Journal of Neonatal Screening Nov 14; 4 (4).
47. *Short executive summary of the report on the practices of newborn screening for rare disorders in member states of the European Union, candidate and potential candidate, and EFTA countries.* **Burgard, P., Cornel, M.C., Di Filippo, et al.** 2011, http://www.isns-neoscreening.org/wp-content/uploads/2016/06/Summary20111018.pdf.
48. *Newborn screening in Europe; expert opinion document.* **Cornel, M.C., Rigter, T., Weinreich, S.S., et al.** 2011, https://www.isns-neoscreening.org/wp-content/uploads/2018/11/Expert-opinion-document-on-NBS-FINAL.pdf.
49. *Neonatal screening in Europe revisited; an ISNS-perspective on the current state and developments since 2010.* **Loeber, J. G., Platis, D., Zetterström, R. H., et al.** 2021, Int J Neonatal Screen. 7(1), 15.
50. *Informing parents about newborn screening: a European comparison study.* **Ijzebrink, A., van Dijk, T., Franková, V., et al.** 2021, Int J Neonatal Screen.(in press).
51. *Blood collection on filter paper for newborn screening programs; approved standard-sixth edition.* **CLSI.** 2013, CLSI document NBS01-A6. Clinical and Laboratory Standards Institute.

52. *Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency.* **Taylor, J. L., Lee, F. K., Yazdanpanah, G. K.,et al.** 2015, Clin Chem.; 61(2), pp. 412-419.
53. *Assessment of liquid microbead arrays for the screening of newborns for spinal muscular atrophy.* **Pyatt, R. E., Mihal, D. C., & Prior, T. W.** 2007, Clin Chem. Nov;53(11), pp. 1879-85.
54. *Newborn screening for spinal muscular atrophy by calibrated short-amplicon melt profiling.* **Dobrowolski, S. F., Pham, H. T., Downes, F. P., et al.** 2012, Clin Chem. Jun; 58(6):, pp. 1033-1039.
55. *SMA screening system using dried blood spots on filter paper: application of COP-PCR to the SMN1 deletion test.* **Kato, N., Sa'Adah, N., Ar Rochmah, M., et al.** 2015, Kobe J Med Sci. Jan 19;60(4):, pp. E78-85.
56. *An innovative SMA screening method directly from dried blood spots.* **Vandermeulen, C., Giltay, A., Detemmerman, L.** 2020, 6. Int J Neonatal Screen https://www.mdpi.com/2409-515X/6/1/12/htm.
57. *Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA.* **Gutierrez-Mateo, C., Timonen, A., Vaahtera, K., et al.** 2019, Int J Neonatal Screen. Nov 2;5(4):, p. 39.
58. *Multiplex Droplet Digital PCR Method Applicable to Newborn Screening, Carrier Status, and Assessment of Spinal Muscular Atrophy.* **Vidal-Folch, N., Gavrilov, D., Raymond, K., et al.** 2018, Clin Chem. Dec;64(12), pp. 1753-1761.
59. *European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy.* **Kirschner, J., Butoianu, N., Goemans, N., et al.** 2020, Eur J Paediatr Neurol. Sep;28:., pp. 38-43.
60. *Advances in Newborn Screening and Presymptomatic Diagnosis of Spinal Muscular Atrophy.* **Jędrzejowska, M.** 2020, Degener Neurol Neuromuscul Dis. Dec 15;10:, pp. 39-47.
61. *American College of Medical Genetics' Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system.* **ACMG.** 2006, Genet Med.;8 (suppl 1):1S-252S.
62. *Whole genome sequencing and newborn screening.* **Botkin, J. R., & Rothwell, E.** 2016, Curr Genet Med Rep. Mar 1; 4 (1), pp. 1-6.
63. *Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies.* **Peeters, K., Chamova, T., & Jordanova, A.** 2014, Brain Nov; 137 (Pt11), pp. 2879-96.
64. *Pharmacoeconomics: NICE's approach to decision-making.* **Rawlins, M., Barnett, D., & Stevens, A.** 2010, Br J Clin Pharmacol. Sep; 70(3):, pp. 346–349.
65. *Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement.* **Schlander, M., Garattini, S., Kolominsky-Rabas, P., et al.** 2016, J Mark Access Health Policy.
66. *Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe.* **Medic, G., Korchagina, D., Young, K. E., et al.** 2017, J Mark Access Health Policy Apr 10;5(1).
67. *A cost-effectiveness analysis of newborn screening for severe combined immunodeficiency in the UK.* **Bessey, A., Chilcott, J., Leaviss, J., et al.** 2019, Internat. Journal Neonatal Screen. Aug 30; 5 (3).
68. *Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data.* **van der Ploeg, C. P., van den Akker-van Marle, M. E., Vernooij-van Langen, A. M., et al.** 2015, J Cyst Fibros Mar; 14 (2), pp. 194-202.

69. *Cost-effectiveness of newborn screening for severe combined immunodeficiency.* **van der Ploeg, C. P., Blom, M., Bredius, R.G.M., et al.** 2019, Eur J Pediatr May; 178 (5), pp. 721-729.
70. *Cost-Effectiveness Analysis of a National Newborn Screening Program for Biotinidase Deficiency.* **Vallejo-Torres, L., Castilla, I., Couce, M. L., et al.** 2015, Pediatrics Aug; 136 (2), pp. 424-432.
71. *Cost-effectiveness of nusinersen and universal newborns screening for spinal muscular atrophy.* **Jalali, A., Rothwell, E., Botkin, J. R., et al.** 2020, J Pediatr Dec; 227, pp. 274-280.
72. *https://www.g-ba.de/presse/pressemitteilungen-meldungen/919/.* **GBA.** 2020.
73. *https://www.healthcouncil.nl/documents/advisory-reports/2019/07/23/neonatal-screening-for-spinal-muscular-atrophy.* **NL, Health Council.** 2019.
74. *A Novel System for Spinal Muscular Atrophy Screening in Newborns: Japanese Pilot Study.* **Shinohara, M., Niba, E., Wijaya, Y., et al.** 2019, Int J Neonatal Screen. Nov 12;5(4):41.

12 Glossary of abbreviations

BSC	best supportive care
CDC	Centers for Disease Control and Prevention
CE	Cost-effectiveness
CF	cystic fibrosis
CHOP-INTEND:	Children´s Hospital of Philadelphia Infant Test of Neuromuscular Disorders score
COP-PCR	Competitive oligonucleotide priming polymerase chain reaction
DBS	Dried blood spot
ddPCR	Droplet digital polymerase chain reaction
DMT	Disease-modifying therapy
GDP	Gross domestic product
HCPs	Health care professionals
HINE	Hammersmith Infant Neurological Examination
HRMA	High-resolution DNA melting analysis
HTA	Health technology assessment
IQWIG	Institute for Quality and Efficiency in Health Care (Germany)
LAMP	Loop-mediated isothermal amplification
MLPA	Multiplex ligation-dependent probe amplification
mRNA	messenger ribonucleic acid
NBS	Newborn screening
NSQAP	Newborn Screening Quality Assurance Programme
PCR	Polymerase chain reaction
QALYs	Quality-adjusted life years
qPCR	Quantitative real-time polymerase chain reaction
SCID	Severe combined immunodeficiency
SMA	Spinal muscular atrophy
SMN	Survival of motor neuron
snRNP	Small nuclear ribonuclear protein
WTP	Willingness-to-Pay
XLA	X-linked agammaglobulinemia

13 Acknowledgements

In-kind contributions were given by volunteers from SMA Europe e.V. (Marie-Christine Ouillade, Kacper Rucinski, and Vanessa Christie-Brown), TREAT-NMD, EURORDIS, and admedicum Business for Patients. Liz Ryburn from SMA UK kindly reviewed the Whitepaper.

Additional expert input was generously given by Dr. Raquel Yahyaoui, Dr. Cornelis Boersma, and Dr. Maarten Postma.

Thank you to Dr. Nathalie Goemans, Dr. Wolfgang Müller-Felber, Dr. Laurent Servais, Dr. Eduardo Tizzano, Dr. Danilo Francesco Tiziano, Olga Germanenko, and Marie-Christine Ouillade for taking part in the roundtable that resulted in the text that is contained in Chapter 5.8 There is an agreed upon policy on whom to treat.

This Whitepaper was made possible by funding from the companies as mentioned in chapter three.

A special thanks and immense gratitude go to the members of the Steering Committee who met regularly on a volunteer basis and ensured the success of the Whitepaper.

14 Declaration on conflicts of interest

Declarations on conflicts of interest were collected by all authors and are available on file.