SMA NBS Alliance

Spinal muscular atrophy: Screen at birth, save lives

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European Alliance for Newborn Screening in SMA

Foreword

NEWBORN SCREENING: "ZERO POINT" IN TIME

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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 only important for the early diagnosis of treatable RDs, but it is also important for all RD patients to ensure an accurate genetic diagnosis as early as possible. There are certainly ethical and economic aspects that are important to consider, but the future of genomic medicine is diagnosing RDs at birth.

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 and the best standards of care. 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 guilt for families resulting from a late diagnosis and full respect and compliance with data and privacy regulations. 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

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1 Executive Summary

In the UN Convention on the Rights of the Child - which was ratified by all European countries - Article 24 refers to the right to optimal health care. Newborn screening (NBS) can help identify children that are in particular need of specialised health care. To not screen children at birth however, means depriving them of the optimal care pathway they may need.

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 structured following 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 with an incidence of 1 in 6,000 to 10,000 live births
- Based on age of onset of symptoms and the maximum motor function achieved, SMA is currently classified into four main types which broadly reflect the severity of the condition
- Without treatment and depending on the severity of the condition, babies may not reach two years of age or their ability to sit, walk and breathe may be significantly impaired. SMA is therefore an important health problem.

2. **There are accepted treatment options for patients with SMA**
- Three disease-modifying treatment options for SMA have now been approved in Europe
- More treatments are under development
- There is growing evidence which indicates that earlier treatment leads to greater potential outcomes

3. **Facilities for diagnosis and treatment of SMA are available**
- There are numerous health care institutions across Europe that provide 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 symptom onset. However, even before the first symptoms, damage to the motor neurons may have already occurred
- This “window of opportunity” is often wasted due to the lack of availability of newborn screening

5. **There is a suitable newborn screening test for SMA**
- A reliable blood test is available for use in SMA newborn screening
- The test identifies a homozygous *SMN1* exon 7 deletion
- The sensitivity of this test 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 the general population

7. **The natural history of SMA, including its development from latent to diagnosed disease, is adequately understood**
- Sufficient information on the natural history of SMA is available
- Subject to its type, SMA inevitably affect children and causes a marked delay or complete halt in the development of neuromuscular 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, through the dried blood spot specimen already taken for newborn screening
- The cost of screening outweighs the cost of illness
- Detecting SMA early and treating promptly may also have a financial advantage for health care systems, in addition to improving the quality of life of treated children

10. **Case finding is a continuing process and not a "once and for all" project**
- Once a newborn screening programme for SMA has started in a country, it should be made available for all babies born in that country from that point onwards.
- 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 proposes 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 positive screening 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 is available, without need for additional blood sampling

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 optimisation through screening
- With treatment now 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

- SMA newborn screening pilot trials in Europe further support clinical trial results, showing that pre-symptomatic treatment results in age-appropriate motor development
- In Europe, there are inequities with some babies having access to newborn screening for SMA, whilst most others do not
- Some European countries such as Germany and Norway started nationwide programmes recently
- For the current status of SMA newborn screening in Europe please visit: www.sma-screening-alliance.org/map

15. Experiences from outside Europe

- The United States (US) is well ahead of Europe in implementing NBS for SMA
    a. 38/50 US states are now screening for SMA
    b. 85% 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
- In Taiwan all newborn babies are being screened for SMA

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 led by 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:

- We take into consideration the UN convention on the Rights of the Child ratified by all European Countries, mandating governments to secure optimal health care for children,
- We recognise the European Union's commitment to achieve Universal Health Coverage in its territory by 2030,
- We acknowledge 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,
- We consider 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),
- We emphasise 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,
- We strongly oppose the inequality of access to SMA newborn screening for babies born in Europe,
- We recognise that this lack of access to newborn screening for SMA contradicts the policy of the European Union to ensure appropriate health care for children as one of the most basic rights children can enjoy and
- We express 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 the EU to take action on making the aspirations of **the European Alliance for Newborn Screening in Spinal Muscular Atrophy (SMA**) a reality:

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 EU Member states in ensuring sufficient access to health care, we interpret the principle of subsidiarity regarding health care, in a way that the EU has a strong remit in fostering equal access to health care across the EU.

2. Newborn screening pilot programmes for SMA, in a range of member states are completed / ongoing / planned, including in Belgium, Italy, Germany, Spain, France as well as the United Kingdom. We now ask that 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, are financially and organisationally supported.

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 the 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 EU level, to monitor and support all measures that help improve newborn screening for SMA.

5. We also encourage EU institutions to recommend adding SMA to a list of recommended diseases to be screened 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 competent national authorities to include SMA in the list of diseases eligible for inclusion in national and/or regional newborn screening programmes without 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 affected children. Almost five 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 for 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 support their advocacy efforts for newborn screening to include SMA.

The **European Alliance for Newborn Screening in Spinal Muscular Atrophy** demands that, national governments and authorities in Europe 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, with input from other experts and 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 European SMA patient organisations. The Whitepaper received independent scientific advice and was written and reviewed by 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. Cornelis Boersma and Dr. Maarten Postma.

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

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4 Introduction

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular condition which causes progressive muscle wasting (atrophy) and weakness, leading to loss of movement. This may affect crawling and walking ability, arm, hand, head, and neck movement, breathing and swallowing. There are different forms of SMA and a wide spectrum of how severely children and adults are affected.
The most common form is known as ´5q SMA` due to its genetic cause. 5q SMA is a severe, rare disease that has a big impact on affected individuals and their families. Yet despite being a rare disease, if left untreated, it is the leading genetic cause of death in infants (3). It is also a challenging condition for health care systems in Europe. Until 2017, when the first disease-modifying therapy (DMT) nusinersen (Spinraza®) was approved, there was no treatment.

Before the advent of Spinraza®, treatment approaches consisted of symptom management in an attempt to slow down the loss of motor-function, maintain the quality of life, prolonging life for as long as possible. Today, two additional therapies have been approved for use in SMA, meaning that now children with SMA, when diagnosed and treated early with state-of-the art disease-modifying therapies, have a completely different, improved prognosis.

Studies (see 5.2) indicate that the key is early detection and treatment as this dramatically improves the effectiveness of all currently available therapies. Newborn screening is the best way to obtain this early diagnosis and ensure every child diagnosed with SMA has the best possible chance at a healthy life.

In Europe, SMA is not widely included in the panel of conditions tested at birth and because the European Union has no direct responsibility for newborn screening, each member state must compile its own dossier to have SMA added to the panel. As national patient organisations are increasingly frustrated about this situation, SMA Europe hopes this Whitepaper will go some way to facilitate this process and at the same time, support SMA patient organisations in their advocacy initiatives.

This Whitepaper was initiated by the European Alliance for Newborn Screening in Spinal Muscular Atrophy, a multi-stakeholder initiative led by SMA Europe e.V., a European umbrella organisation of national patient and research organisations focused on spinal muscular atrophy. The aim of this paper is to inform a systematic dialogue in European health care systems, 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 public, the main criteria that will be considered are the severity of the disease, the importance of early detection that drives a therapeutic intervention with a reasonable risk/benefit profile and the precision of the screening methodology. Wilson and Jungner´s principles (4) used to determine if a disease should be included in the NBS screening panel are widely known and accepted. In the following sections, we review these 10 principles for SMA NBS.

5.1 SMA is an important health problem

SUMMARY

- 5q SMA is a rare, genetic disease with an incidence of 1 in 6,000 to 10,000 live births
- Based on age of onset of symptoms and the maximum motor function achieved, SMA is currently classified into four main types which broadly reflect the severity of the condition
- Without treatment and depending on the severity of the condition, babies may not reach two years of age or their ability to sit, walk and breathe may be significantly impaired. SMA is therefore an important health problem.

In 2015, SMA was the leading genetic cause of death in infants (3). It is a neuromuscular condition with an incidence of 1 in 6,000 to 10,000 live births (5) (6). 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 is a ubiquitously expressed protein, 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 (7) (8). 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.

This SMN protein is encoded by two genes called *Survival Motor Neuron* 1 and *Survival Motor Neuron* 2 (*SMN1 and SMN2*), both located on chromosome 5. These genes are almost identical. 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 (9). Both *SMN1* and *SMN2* contain 8 exons and are 99% homologous in sequence. They differ only by five nucleotides and produce an almost identical protein, the SMN protein. The differences lie in exons 7 and 8, introns 6 and 7. However, only one difference between the SMN1 and SMN2 protein is functionally important: a silent transition in exon 7, on the *SMN2* gene, which disrupts an exonic splice enhancer (ESE) and creates a new exonic splice silencer (ESS). This substitution (C to T) causes exon 7 to be excluded from most of the *SMN2* transcripts, resulting in the production of a truncated SMN

protein that is unstable *in vivo* and rapidly degrades (10). It is estimated that only about 10% of the SMN protein made from *SMN2* is functional (11) (12).

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 (11). Thus, in some patients, the information of *SMN*2 copy number alone may be insufficient to correlate with the observed phenotype (13).

SMA is a single disease with a continuum of severity, which generally decreases in severity the later the first symptoms manifest themselves. For simplicity, it is generally classified into four different types depending on age of onset and motor milestone reached (6).

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 (6). Swallowing and breathing complications lead to an early death (14).

From a motor function point of view, people living with Type I SMA never sit, those living with Type II never walk, and those living with Type III walk independently but will lose this ability later in life if left untreated (Figure 1). People living with SMA Type I have a reduced median life expectancy of around one year whereas the majority of people living with Type II can live long, fulfilling lives due to improvements in care standards.
People living with Type III patients have a normal life expectancy (15).

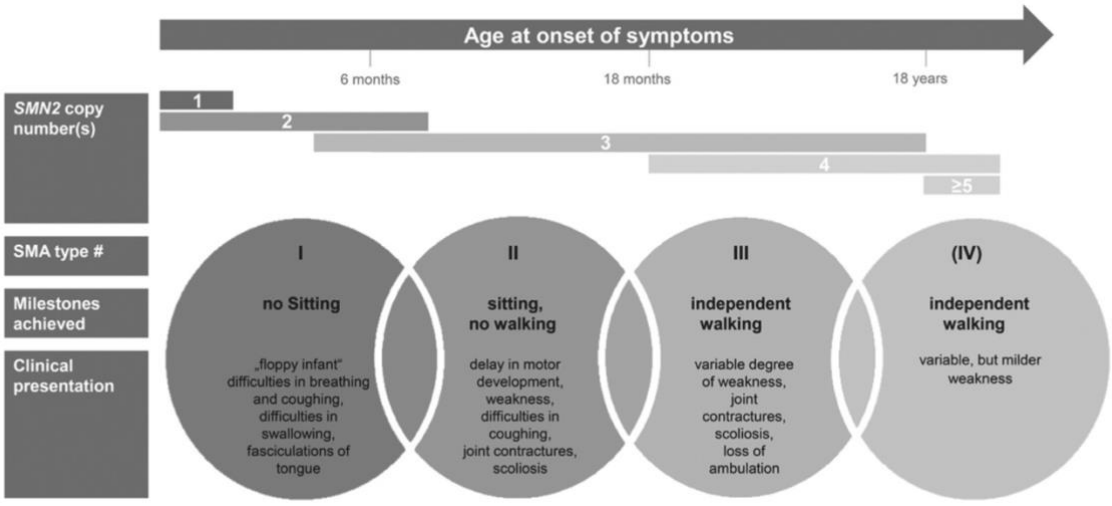

Figure 1 Clinical classification of SMA subtypes according to onset, milestones achieve, and clinical presentation. Typically associated SMN2 copy numbers are displayed. (16)

5.2 There are accepted treatment options for patients with SMA

SUMMARY

- Three disease-modifying treatment options for SMA have now been approved in Europe
- More treatments are under development
- There is growing evidence which indicates that earlier treatment leads to greater potential outcomes

While symptomatic treatment and follow-up of SMA has improved over the past two decades (17), no disease modifying therapies were available. However, over the course of the past four years, three therapeutic options involving the SMN genes were approved. These target the underlying cause 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 which targets exon 7 of the *SMN2* gene, leading to an increased production of functional, full-length SMN protein. This drug is administered 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 in the European Union in March 2021. This drug increases and sustains the production of fully functional SMN protein throughout the central nervous system and peripheral tissues via the *SMN2* gene. Risdiplam can be given orally, allowing for a treatment at home.

Additional potentially disease modifying products are under development.

Results from clinical trials of both Spinraza® (NURTURE) and Zolgensma® (SPR1NT) show the significant positive impact of pre-symptomatic treatment (18), (Novartis Gene Therapies data on file) and a trial of Evrysdi® in pre-symptomatic babies has been initiated.

The NURTURE trial by Biogen on pre-symptomatic infants with two or three *SMN2* copies showed a clear benefit of treatment with nusinersen, when compared to the ENDEAR trial, which looked at the effects of nusinersen on early symptomatic infants, analysis limited to infants with 2 *SMN2* copies (19). The NURTURE interim analysis carried out in March 2019 on data obtained from 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 (February 2020), children treated pre-symptomatically maintained and made progressive gains in motor function compared to the natural history of the disease (Biogen, data on file).

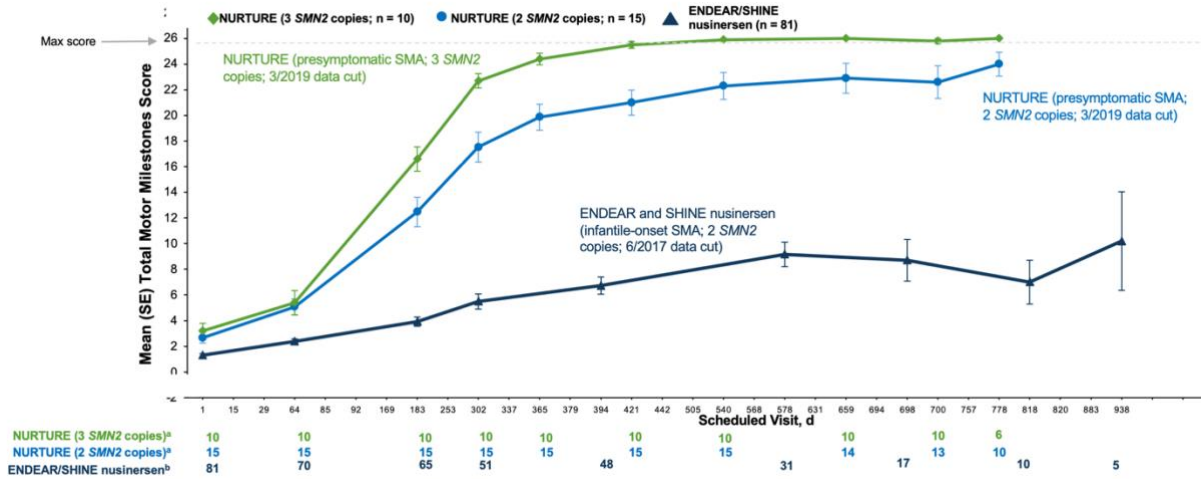

Figure 2 HINE Motor Milestone Scores Over Time Across Studies (Source: Swoboda, et al. Cure SMA Annual Conference 2020, adapted)

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).

In addition, infants treated pre-symptomatically with Zolgensma® achieved early, age-appropriate motor milestones, did not require ventilatory support nor enteral feeding (SPR1NT study, Novartis Gene Therapies, data on file).

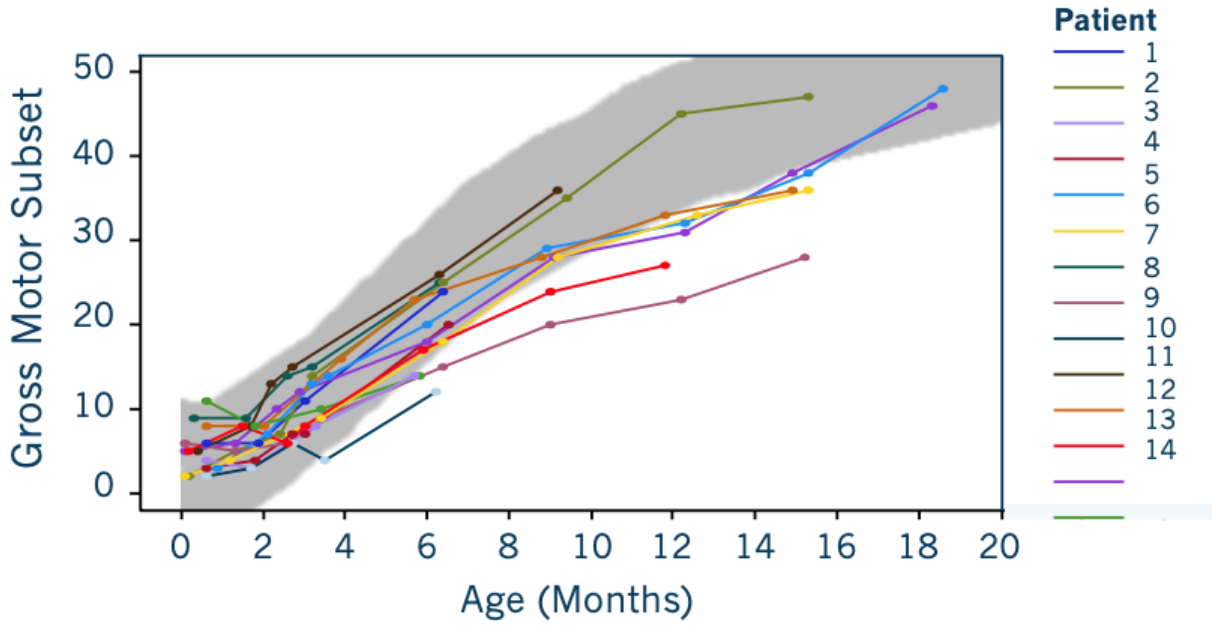

*Figure 3 Infants with 2 SMN2 copies: **7 of 14 (50%)** have **gross motor performance** similar to normal development; **14 of 14 (100%)** have **fine motor performance** similar to normal development (SPR1NT study update 31 Dec 2019, Novartis Gene Therapies, data on file). The gray shaded area denotes 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 are numerous health care institutions across Europe that provide state-of-the-art care to people living with SMA

Critical for SMA care, specialised teams of health care providers diagnose and initiate both symptomatic and disease-modifying therapies and ensure a proper follow-up of the patient.
Moreover, to ensure a holistic treatment approach, psychological and psychosocial counselling, as well as physiotherapy services should be made available. Depending on the local health care system, a close cooperation with primary care physicians (general/family practitioners and/or paediatricians) should be ensured.
A variety of SMA centres of expertise exists across Europe: 29 countries have specialised centres that treat young children living with SMA, including with disease-modifying therapies; 14 countries are home of 61 European Reference Network for neuromuscular diseases (ERN-EURO-NMD) centres (www.ern-euro-nmd.eu). However, for some countries, access to disease-modifying therapies 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 symptom onset. However, even before the first symptoms, damage to the motor neurons may have already occurred
- This "window of opportunity" is often wasted due to the lack of availability of newborn screening

The majority of 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 $\pm$ 0.6 months for the most common SMA Type, Type I and 8.3 $\pm$ 1.6 months for SMA Type II (22). Knowing that the damage to the motor neurons may occur before the onset of symptoms, there is an urgent need to use this "window of opportunity" to diagnose SMA as early as possible, through NBS.
Even though most babies born with SMA are asymptomatic at birth, there are exceptions, as seen in the German NBS pilot trial (23). From the 165,525 children screened within 13 months, 22 SMA cases were identified, 4 of which were already symptomatic on first examination. Because of this quick diagnosis, immediate treatment following the NBS result could be administered, giving these babies a much improved prognosis.
Unfortunately, this "window of opportunity" is often wasted without the availability of NBS.

According to Lin et al., there is a delay in diagnosis of 3.6 months for SMA Type I, 14.3 months for Type II and 43.6 months for Type III (22). According to patient organisations, the delay in

diagnosis for Type I SMA ranges from 4 weeks to 6 months, depending on the health care system. This odyssey is very stressful for parents of a child with SMA and precious time is wasted, 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 HCPs, the “wait and see” approach to rule out other disease possibilities 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 for use in SMA newborn screening
- The test identifies a homozygous *SMN1* exon 7 deletion
- The sensitivity of this test 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). In most studies, the specificity of these assays was nearly 100% 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 ranging from 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 the general population

SMA newborn screening is performed on the same DBS specimen usually collected between 24h and 72h after birth from the newborn's heel and placed on a specimen collection device. As this procedure is 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 public, parents, and adults with SMA? Boardman et al. (33) administered an online survey to families affected by SMA and the

UK public. Eighty-four percent of the public were in favour of introducing SMA NBS, mainly due to 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) as were a mixed population of families and adults (70%), despite preferring 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 treatment unavailability), the situation may now be different, as discussed elsewhere (36).

5.7 The natural history of SMA, including its 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 inevitably affect children and causes a marked delay or complete halt in the development of neuromuscular function early in life
- Without early diagnosis and treatment, children with SMA may suffer from severe impairment, accumulation of comorbidities or early death

The trajectories of SMA have changed over the years. A more proactive management of the condition (including the introduction of non-invasive ventilation and tube feeding) has 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 has 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 on 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. Natural history data can therefore 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 (TREAT-NMD, data on file). Therefore, the application of disease-modifying drugs might also be favourable 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
≥ 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 (13).
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.

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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, through the dried blood spot specimen already taken for newborn screening
- The cost of screening outweighs the cost of illness
- Detecting SMA early and treating promptly may also have a financial advantage for health care systems, in addition to improving the quality of life of treated children

NBS aims to detect SMA through genetic analysis of a DBS specimen. 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 compared to the cost of illness. There are cost estimations available from a German study group which calculated 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 for 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 to be 33,723 Euro. Another study which investigated the cost of illness in the UK, France and Germany, estimated the 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 do not 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

- Once a newborn screening programme for SMA has started in a country, it should be made available for all babies born in that country from that point onwards.
- 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 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 newborn screening for SMA. Hence, introduction of SMA NBS in the national screening policy is an important aspect to creating 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 positive screening 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 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 is available, without need for additional blood sampling

Although NBS programmes have historically focused on screening, truly effective NBS programmes provide an infrastructure for universal access, education, and rapid follow-up of 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 meaning each makes its own decisions regarding NBS. Depending on the country, NBS may be governed by national or regional 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, equal access to and availability of appropriate resources for the diagnosis and treatment of newborns detected must be ensured. The NBS programme should include the assessment of resources available for disease diagnosis, treatment, and follow-up in the geographic location where it is conducted. An SMA diagnosis will need to be confirmed using molecular studies. The use of potentially complex therapies, in terms of accessibility, cost, and the urgency in initiating them, will be recommended 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. For example, this was a crucial aspect when NBS for cystic fibrosis (CF) was introduced in a couple of European countries in recent years. Like SMA, CF is considered a rare disease that requires special care structures including specialised health care providers. As these are available – as 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 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 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 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) (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. It should be made clear to parents that participation is in their child's best interest. This, along with general education on the programme and its benefits, should be offered before or at the time the DBS specimen is collected.

NBS programmes differ considerably in terms of approaches used to obtain parental consent, 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.

Depending on local regulations, SMA could be added to an NBS programme using the same consent practices used for the programme. Alternatively, specific consent may be required, as is the case in some countries where legislation on genetic information is treated differently from that of other sensitive health information. 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

Newborn DBS specimen for SMA NBS can be easily added to standard NBS programmes without additional specimen collection. Capillary blood collected through 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 used 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.
There are no validated biochemical markers of SMA. However, several approaches based on molecular testing to detect homozygous *SMN1* exon 7 deletion have been developed. Some have been designed so that SMA can be detected from the same DBS punch used to screen newborns for severe combined immunodeficiency (SCID) screening (52), an advantage when it comes to adding SMA to programmes that already screen for SCID. Assays for SMA NBS are specifically tailored to NBS laboratories so just modest adaptations and personnel training would be required to perform these genetic analyses. More advanced molecular technology and other analytical innovations together with therapeutic advances 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 these, the technique most used in SMA NBS pilot

studies and programmes in the US, has been qPCR. However, 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 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 recommended. An 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 NBS programme protocols, SMA screen-positive results should be reported immediately. NBS programmes need to arrange, or help coordinate, follow-up diagnostic testing so 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 needed. 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 (13).

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 (9) (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 suitable information to parents 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. Having an appropriate understanding of the disease, prognostic factors, and therapeutic options, will allow parents to participate in decision-making freely and actively.

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 caregivers.

6.8 Newborn screening programme evaluation and quality assurance

Quality indicators for SMA NBS programmes must be established before implementation and continuously evaluated, 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 ideally be analysed.

All these quality indicators must be periodically reviewed 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

Article 24 of the UN Convention on the Rights of the Child - ratified by all European Countries - refers 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). In this vein, withholding children NBS, translates to depriving them from an optimal pathway towards care.

7.2 Newborn screening applies to babies 2-3 days after birth

Newborn screening is for babies only and should therefore not be confused with pre-conception or prenatal screening. The intention is to detect affected infants rather than carriers or foetuses / unborn children. This is important to understand as these approaches are still subject to controversial debates reflecting religious, political and historical experiences, and traditions in various 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, thereby sparing families from difficulties associated with a late diagnosis, such as economic and psychological burden.

7.3 Newborn screening in SMA is a way ensuring 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 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 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

All families have the "right to know at the right time". Knowing that there is a reason for their child´s slow development prevents parents´ potential attempts to "push" the child into activities she or he cannot perform because of the disease. It also helps parents to better understand the limited span of control they have over their child´s development, thus preventing excessive parental guilt. The diagnosis of SMA is a painful experience for the affected families. However, a survey of families and people living 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 parents have a "right not to know" about the diagnosis.

It is mainly the threat of an over medicalised childhood leading to excessive treatment and a disturbed parent/child relationship that may come up as arguments against NBS for 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 the family some time in apparent "peace", it will inevitably lead to a waste of precious time to take urgent action to treat and halt irreversible damage to the motor neurons when these can still be preserved, or their deterioration slowed down significantly. So, not to know about 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 diagnosed with SMA, would an early diagnosis be considered unethical. However, in this case, one may challenge the parental right to deny appropriate treatment, as it conflicts with the Right of the Child for optimal health care.

7.6 Newborn screening allows informed decisions

Informed parents can make informed decisions. They could, for example, decide to move closer to hospitals or places which offer better medical care and educational opportunities as well as allow planning for more children (62). Members of the wider family, as potential carriers, might also take this possible risk into consideration for family planning reasons.

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 for detecting the deletion of *SMN1* on the long arm of chromosome 5 (5q-SMA) due to *SMN1* point mutations (21). The situation for children who are false-negative, 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 the first contact with the family, and responsible physicians to alert them to this possibility and to 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 optimisation through screening
- With treatment now available, an analysis of cost-effectiveness of newborn screening 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 continues to be 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 on the market and were reimbursed relatively straightforwardly. Recently, however, we have seen how HTA-jurisdictions have also made rare disease interventions the target of economic scrutiny, in particular, cost-effectiveness/utility analysis.

The above developments could impact the assessment of screening for SMA. In particular, proof of cost-effectiveness is required for SMA screening, as well as the cost-effectiveness of giving treatment to babies found to be positive, when compared to the natural course of the symptomatic condition treated or untreated. 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®, Evrysdi® 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, the WHO states that the Gross Domestic Product (GDP) per capita sets 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 by 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 tend to involve innovative scientific technologies, such as gene therapies, potentially allowing scientific spill-overs to other disease areas, within or outside the rare diseases field, 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 identification (screening) stimulates continued investment in the development of orphan drugs, satisfying an important societal need.

Health economic evaluation of NBS for SMA needs to be conducted against the current practice of diagnosis 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 that of other children of the same age.

Cost-effectiveness models for newborn screening for rare and genetic diseases exist but are rare. Previously, cost-effectiveness results were 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 in the long run. In 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 be similar 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

- SMA newborn screening pilot trials in Europe further support clinical trial results, showing that pre-symptomatic treatment results in age-appropriate motor development
- In Europe, there are inequities with some babies having access to newborn screening for SMA, whilst most others do not
- Some European countries such as Germany and Norway started nationwide programmes recently
- For the current status of SMA newborn screening in Europe please visit: www.sma-screening-alliance.org/map

Norway began nationwide screening for SMA on 1 September 2021, becoming one of the first European countries to test all newborns.
Currently, there are some NBS ongoing pilot trials in Europe (Italy and Spain with France and the United Kingdom following soon).
In Belgium, a 3-year pilot trial started in 2018 and was completed (31). SMA NBS has now become permanent policy for the Belgian regions of Wallonia and Brussels.
In Germany, the pilot trial started in 2018. Data can be found here (72) (23) (21). In December 2020, the federal joint committee in Germany agreed to implement screening for SMA into the national NBS panel (73). Due to technical prerequisites the actual screening is expected to start in October 2021.
The pilot trial in Italy started in September 2019. The Spanish pilot trial will start in 2021 in Valencia and is expected to include Andalucía later this year. Also, in Russia a pilot trial started in 2019 in 3 clinics in Moscow. Further pilot trials are planned for France and the United Kingdom. Dangouloff et al. present a comprehensive overview on worldwide SMA NBS programmes (74).

In addition to Germany and Norway, SMA is approved as part of the national newborn screening programme and awaiting implementation in the Netherlands (75), and Slovenia (status Sept 2021). SMA newborn screening in Poland was approved in March 2021 and is now undergoing staggered implementation, province by province, starting in April 2021. The last province is planned to enter the programme in November 2022. The implementation is currently ahead of schedule and as of now, it covers 12 out of 16 provinces which account for approx. 70% of live births in Poland. (status Nov. 2021).
For the regularly updated 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 ahead of Europe in implementing NBS for SMA
  - 38/50 US states are now screening for SMA
  - 85% 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
- In Taiwan all newborn babies are being screened for SMA

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 respective, state-specific screening panels. As of September 2021, 38 out of 50 States are screening for SMA, resulting in a screening rate of 85% 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 in.

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 recognised the importance of this pilot and has continued to provide funding for testing now that the pilot has ended. An application was made to the national newborn screening committee to add SMA to the national NBS programme after birth (smaaustralia.org.au). This addition is expected to happen in 2021.

In Canada screening for SMA is added to the NBS screening panel in Ontario and in other provinces of the country respective projects are planned (https://muscle.ca/services-support/newborn-screening).

Pilot trials have also been conducted in Asian countries (e.g. like Taiwan and Japan) (27) (76). In Taiwan all newborn babies born in the whole country are being screened for SMA (74).

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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
ESE	Exonic splice enhancer
ESS	Exonic splice silencer
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

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14 Declaration on conflicts of interest

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