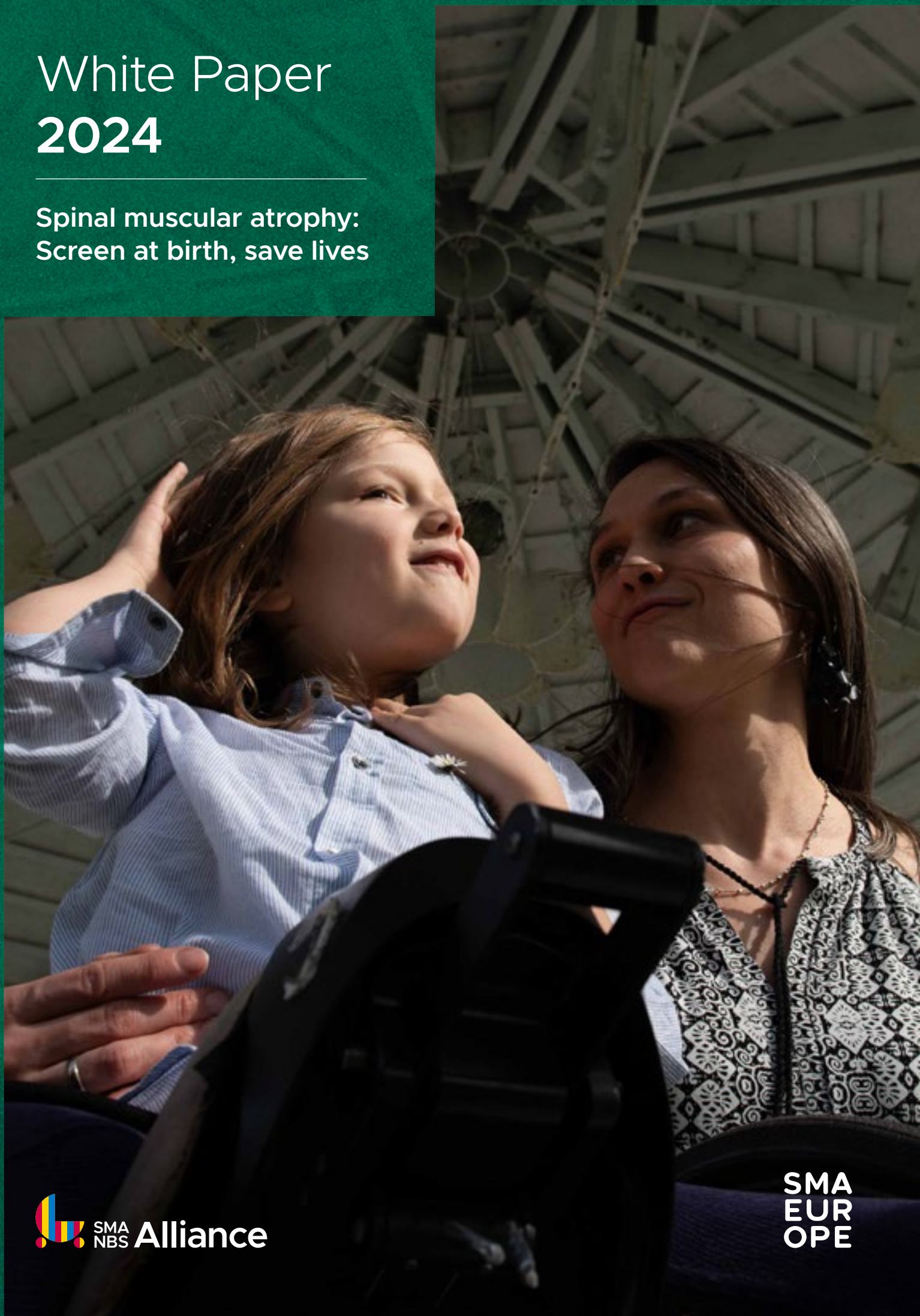
White Paper 2024

Spinal muscular atrophy: Screen at birth, save lives



SMA NBS Alliance

SMA EUROPE

Foreword

“Sometimes the questions are complicated, and the answers are simple.” Dr. Seuss

There are more than 7,000 rare diseases and new ones continue to be identified. For most people living with rare diseases, the journey to receiving a diagnosis is long and arduous with visits to many specialists and multiple mis-diagnoses along the way.

Rare diseases affect millions of people around the world, yet many people remain undiagnosed or misdiagnosed for years. Diagnosis of rare diseases is difficult and lengthy, which causes considerable challenges for patients, families, and healthcare systems.

A timely and accurate diagnosis is essential for people living with a rare disease, as it can mean access to the right treatments and support, and ultimately improve their quality of life.

The answer is simple: including SMA in screening for all newborns is an urgent priority. SMA newborn screening saves lives.

“Life can only be understood backwards; but it must be lived forwards.” Søren Kierkegaard

Spinal muscular atrophy (SMA) is a rare disease which can be diagnosed at birth, further to a simple inexpensive test added to existing nationwide programmes for newborn screening. After diagnosis, there are treatment options that can dramatically change the lives of the person living with SMA and their families, and reduce the requirements for health care and support with daily living.

Foreword

People living with SMA, diagnosed after symptoms and irreversible damage, are living every day with the effects of the devastating disease. Together with scientists and clinical experts, they are advocating for the next generation of babies that will be born with SMA. This next generation of people with SMA, not yet born, have the chance and opportunity for a different life.

“A journey of a thousand miles begins with a single step.” Lao Tzu

Today, there is inequity in Europe and indeed worldwide for newborn babies. In some regions, a baby will be screened for over 50 rare diseases. In other regions, there might be little to no screening. This inequity is intolerable.

Since our campaign began, considerable progress has been made to include SMA in nationwide newborn screening programmes in many countries. However, there are still thousands of babies born every day that do not have the opportunity to be screened.

Step-by-step, in collaboration with diverse partners, we will campaign for change. SMA newborn screening creates possibilities and opportunities for life. There is no time to waste.

Marie-Christine Ouillade
Chair of the SMA Newborn Screening Alliance

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Executive Summary

01 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 means depriving them of the optimal care pathway they may need.

For the current status of SMA newborn screening in Europe please visit: 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 in Europe of 1 in 10,000 live births.

— Historically, SMA was classified into types, based on age of symptom onset and the maximum motor function achieved, with the most common and most severe being Type I.

— Without treatment, babies with Type I SMA typically do not reach two years of age. SMA is therefore an important health problem.

— Further to the introduction of disease-modifying therapies, people with SMA are classified by functional motor capabilities, such as “non-sitters”, “sitters”, and “walkers”.

2. There are accepted treatment options for patients with SMA

— Three disease-modifying therapies for SMA are approved and available in Europe.

— Clinical studies in all three disease-modifying therapies have demonstrated that earlier treatment leads to better outcomes.

— Published real world evidence, from Germany and the U.S., reinforces the benefits of expedited diagnosis and treatment of SMA further to newborn screening.

— Taken together, the clinical trial results and the real world evidence data demonstrate that pre-symptomatic treatment results in improved functional outcomes and can result in age-appropriate motor development.

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 pre-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 wasted where newborn screening is not available.

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

— SMA care is not limited to disease-modifying therapies (SMA medicines) alone and also comprises best-supportive care including non-pharmacological treatments.

— SMA care is a shared decision-making process between the SMA experts and the child´s parents.

— The latest policy comes from the 270th ENMC International Workshop Consensus for SMN2 genetic analysis in SMA patients, which took place on 10-12 March 2023 in Hoofddorp, the Netherlands.

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 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 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, multiple analyses have shown the cost-effectiveness of newborn screening and demonstrated improved economic value for patients, payers and healthcare systems.

14. Status of newborn screening in Europe

— In Europe, inequities remain with some, but not all, babies having access to newborn screening for SMA.

— Nationwide SMA newborn screening programmes are running across much of Europe, and 72% of newborns having access to screening (as of 8 August 2024).

— 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 ahead of Europe in implementing NBS for SMA.

— 50/50 US states are now screening for SMA.

— 100% of all babies born in the USA are now screened for SMA.

— Australia has introduced NBS for SMA nationally.

— In Taiwan all newborn babies are being screened for SMA.

The European Alliance for Newborn Screening in Spinal Muscular Atrophy demands that by 2025, newborn screening programmes in all European countries include a test for spinal muscular atrophy for all newborn children.

02

Call to Action

Recommendations by the Alliance Steering Committee

02 Call to Action Recommendations by the Alliance Steering Committee

In 2021, a Call to Action was initiated by the European Alliance for Newborn Screening for spinal muscular atrophy, a multi-stakeholder initiative led by SMA Europe e.V. As we approach the start of 2025, the Alliance is proud of the changes in newborn screening programmes across Europe to include SMA.

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 UNICEF member states, 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 (EURORDIS, 2021) and the call-to-action of the Screen4Rare initiative (IPOPI, 2020) 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.

— 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 appropriate treatment. For the vast majority of people living with SMA, early diagnosis can prevent severe disability and 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 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.

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

Call to Action for policy makers at the EU level

1. Coordinate the exchange of knowledge and best practices on newborn screening in SMA and other eligible rare diseases, including learnings from pilots and national programmes. 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 programmes for SMA are in place and standard in a majority of EU Member States. We now ask that the European Commission financially and organisationally supports a meta-analysis of the results of the SMA NBS programmes and identification of key implementation-related learnings to support the minority of EU Member States who have yet to implement nationwide SMA NBS.

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:

— Gathering evidence and natural history data on efficacy from studies on newborn screening for sma.

— Identifying and agreeing upon criteria and mechanisms for expanding the number of diseases to be included in screening panels.

— Implementation strategies for expanding existing newborn screening programmes.

— Suitable screening procedures and processes.

— Requirements for the education and training of healthcare 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 advocate that EU institutions develop a list of recommended diseases to be screened for at birth and to support countries in the implementation of expanding newborn screening. The list of recommended diseases would include SMA.

Call to Action for policy makers at the national level, where SMA is not included in NBS

1. We urge national authorities to include SMA in the list of diseases eligible for inclusion in national and/or regional newborn screening programmes without further delay. SMA clearly meets the widely-accepted Wilson and Jungner criteria to be included in newborn screening programmes. Early, timely diagnosis and prompt treatment initiation can prevent early death in infancy and can significantly change the course of the disease. Identifying and treating SMA early provides a better outcome for affected children.

2. We call on national governments and parliaments to ensure sufficient funding for newborn screening for SMA, and fast, sustainable implementation in existing programmes.

3. We ask national authorities to draw on the experiences from the ongoing programmes in 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 the national SMA patient organisations' advocacy efforts for newborn screening to include SMA

Where SMA is not standard and in place nation-wide, 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 calls on decision-makers in European countries to implement this essential health service in all European countries without any further delay.

The SMA Europe Newborn Screening Alliance and this White Paper can inspire other countries beyond Europe and other disease areas beyond spinal muscular atrophy.

03

Authors and writing process

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This White Paper 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 White Paper summarises the major reasons for introducing SMA newborn screening.

The initial White Paper (2021) was authored by a multi-stakeholder Steering Committee, with input from other experts and with admedicum acting as the secretariat of the Alliance, under the leadership of SMA Europe e.V., the umbrella organisation of European SMA patient organisations. The White Paper **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 Tizzano. 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.

SMA Europe e.V. decided to update the White Paper to include the additional data that is now available around the benefits of early diagnosis that enables timely treatment of SMA in terms of the outcomes and longer-term prognosis of infants born with SMA. There was also the objective to share the history of the SMA Europe NBS Alliance, including its mission and objectives. The history of the SMA Europe NBS Alliance and its achievements could be relevant to inspire advocacy in other geographies and in other disease areas.

The updated White Paper (2024) was again written under the leadership of SMA Europe e.V., the umbrella organisation of European SMA patient organisations. Again, the White Paper **received independent scientific advice and was written and reviewed by a multi-professional scientific** advisory panel including Dr. Eduardo Tizzano, Dr. Liesbeth de Waele and Dr. Monika Gos.

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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— **For version 2:** 161 Consulting Ltd (Michelle Levene, London, UK).

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04

Introduction

04 Introduction

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular condition which causes progressive muscle wasting (atrophy) and progressive muscle wasting and weakening of muscles. As a result, SMA affects crawling and walking ability; arm, hand, head and neck movement; breathing and swallowing. The experience of people living with SMA is dominated by the downstream complications such as respiratory, nutritional, orthopedic and limited functional ability.

There are different forms of SMA and a wide spectrum of how severely children and adults are affected. The most common form of SMA 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. Despite being a rare disease, if left untreated, SMA is the leading genetic cause of death in infants (Farrar, 2015). It is a challenging condition for health care systems in Europe.

Before the advent of disease-modifying treatments for SMA, the clinical approach consisted of symptom management in an attempt to slow down the loss of motor-function, maintain the quality of life, and prolong life for as long as possible.

There was no treatment until as recently as 2017, when the first disease-modifying therapy (DMT) was approved. Today, there are 3 DMTs which have demonstrated that they are safe and effective for SMA and therefore approved for use.

Clinical studies and real world data indicate that early detection and treatment of SMA is key, as this dramatically improves the effectiveness of all currently available disease-modifying therapies. The magnitude of the effect is related to the timing of diagnosis and treatment. Newborn screening is the best way to obtain an early genetic and clinical diagnosis and to ensure every child with SMA has the best possible chance to tackle the disease.

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 of diseases in its NBS programme. Since the publication of our first White Paper, many European countries have taken action to assess, approve and implement SMA in their newborn screening programmes. SMA Europe believes this White Paper helped to facilitate this process and at the same time, supported SMA patient organisations in their advocacy initiatives.

Specifically, SMA Europe created the Alliance in December 2020, when there was a single pilot programme of SMA NBS that covered just two federal states of Germany, specifically Bavaria and North Rhine Westphalia. Now in November 2024, 72% of children in wider Europe are screened for SMA at birth (including the three South Caucasus countries and all of Russia and Turkey). In the EU, 64% of children are screened for SMA at birth.

As of writing in November 2024, not all children born in Europe have access to SMA newborn screening. SMA Europe and the national SMA patient organisations in those countries are increasingly frustrated about this situation.

Introducing newborn screening for SMA mandates a well thought-through process taking into perspective the medical, ethical, social, and economic context. This White Paper provides fact-based insights on these aspects to inform and support better decision-making and implementation.

Introducing newborn screening for SMA mandates a well thought-through process taking into perspective the medical, ethical, social, and economic context.

05

How and why SMA meets the criteria for newborn screening

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When a health care system evaluates whether newborn screening 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; a therapeutic intervention with a reasonable risk/benefit profile; and the precision of the screening methodology. Following a seminal paper published over 50 years ago (Wilson, 1968), Wilson and Jungner´s enduring 10 principles are the de facto starting point to assess and determine if a disease should be included in a screening panel. In the following sections, we review the 10 Wilson and Junger principles as applied to NBS for SMA.

5.1 SMA is an important health problem

SUMMARY

— 5q SMA is a rare genetic disease with an incidence in Europe of 1 in 10,000 live births.

— Historically, SMA was classified into types, based on age of symptom onset and the maximum motor function achieved, with the most common and most severe being Type I.

— Without treatment, babies with Type I SMA typically do not reach two years of age. SMA is therefore an important health problem.

— Further to the introduction of disease-modifying therapies, people with SMA are classified by functional motor capabilities, such as “non-sitters”, “sitters”, and “walkers”.

SMA is the second most common genetic disorder in the paediatric population after cystic fibrosis, with an overall incidence of 1 in 10,000 live births (Verhaart, 2017). Before the availability of disease-modifying therapies, SMA was the most common genetic cause of child mortality (Dangouloff T., 2019). In 2015, SMA was reported as the leading genetic cause of death in infants (Farrar, 2015).

The neuromuscular condition 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. SMN is a ubiquitously expressed protein, critical for snRNP (small nuclear ribonuclear protein) assembly and processing of mRNA. SMN protein is abundantly found in motor neuron axons where it fulfils other functions, including transport of mRNA (Kolb S. J., 2011) (Singh, 2017). 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 Neuron2 (SMN1 and SMN2), both located on chromosome5. 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 (Alías, 2009). 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 (Feng, 2017). It is estimated that only about 10% of the SMN protein made from SMN2 is functional (Calucho M. B., 2018) (Vitte, 2007).

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 SMN2 copy number and establishment of phenotype-genotype correlations (Calucho M. B., 2018). Thus, in some patients, the information of SMN2 copy number alone may be insufficient to correlate with the observed phenotype (Cuscó, 2020).

SMA is a single disease with a continuum of severity. Left untreated, the majority of children diagnosed with SMA do not survive beyond 2 years (Kolb SJ, 2015). Disease modifiying therapy treatments for SMA have caused a paradigm shift: the outlook for babies born with SMA has been transformed.

Historically, SMA was classified into four different types depending on age of onset and motor milestone reached (D'Amico, 2011), reflecting the observation in untreated patients that the disease is most severe when symptoms manifest early in life and the observation that the disease is less severe when the first symptoms manifested later in life.

The historical classification of untreated SMA is presented visually in Figure 1, and can be summarised as follows:

— SMA Type I is the most common (approx. 50 % of SMA cases) and is a severe type of SMA. Infants present with symptoms before 6 months of age, typically hypotonia and weakness, symmetrical flaccid paralysis and often no head control (D'Amico, 2011). Swallowing and breathing complications lead to an early death (Wang, 2007). From a motor function point of view, people living with Type I SMA never sit.

— Some clinical publications describe a sub-division of Type I, called SMA Type 0. SMA Type 0 is the most severe (congenital) form of SMA, where there are significant symptoms noticeable at birth.

— SMA Type II represents about 20% of cases, with typical onset of symptoms between 6-18 months. From a motor point of view, people living with Type II SMA sit independently but never stand nor walk.

— SMA Type III have symptom onset from 18 months onwards. They may walk independently but will lose this ability later in life if left untreated.

— SMA Type IV denotes a milder disease, with late symptom onset (up to 30 years of age).

Disease modifiying therapy treatments for SMA have caused a paradigm shift: the outlook for babies born with SMA has been transformed.

05. How and why SMA meets the criteria for newborn screening

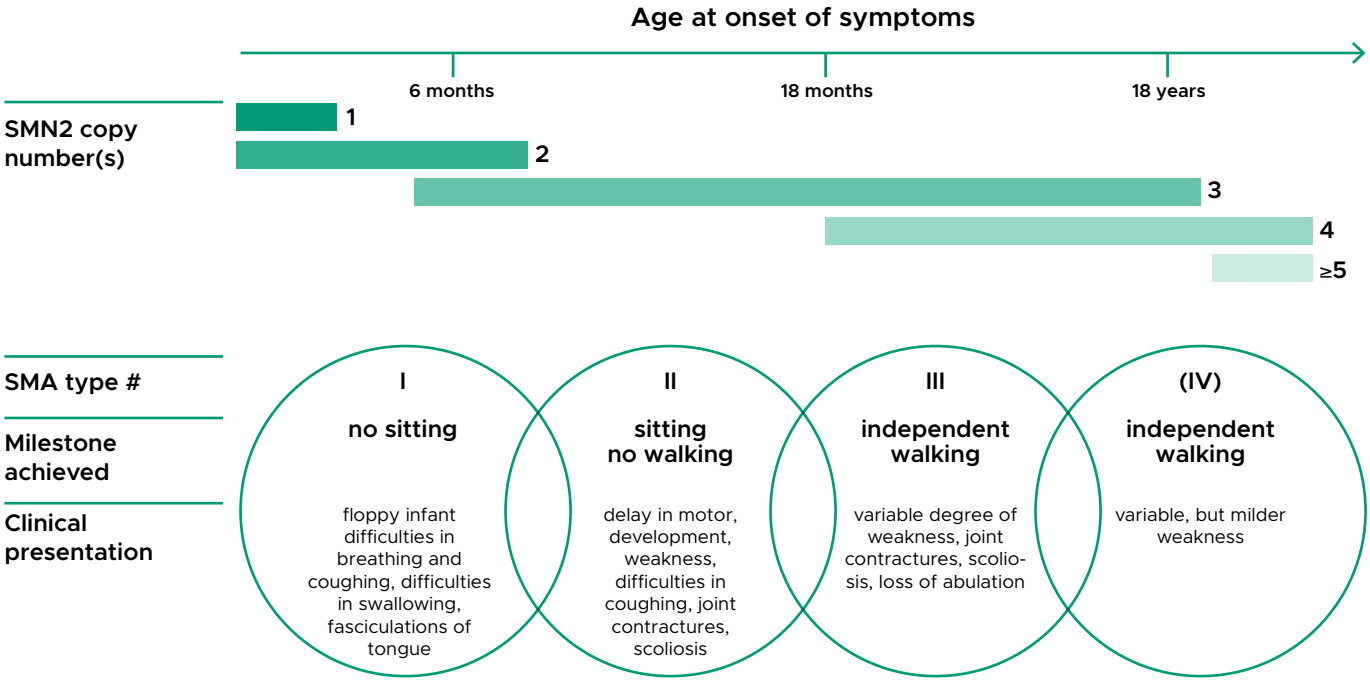


Figure 1 Clinical classification of SMA subtypes according to age at onset, milestones achieved, and clinical presentation. Typically associated SMN2 copy numbers are displayed. (Schorling D. C., 2020)

All people living with SMA have the common evolution of disease progression and thus functional decline, if the disease is not treated.

The situation above refers to SMA before disease-modifying therapies became available.

Further to the introduction of disease-modifying therapies, there has been a noticeable change in the disease. People living with SMA who are treated with disease-modifying therapies early in life have a different, milder disease. This has warranted a change in the classification of SMA. More commonly, people living with SMA are being classified according to their functional motor capability, such as “non-sitters”, “sitters”, and “walkers” (Pierzchlewicz K, 2021) which then informs recommendations for standard of care for people living with SMA (Mercuri, 2018).

All people living with SMA have the common evolution of disease progression and thus functional decline, if the disease is not treated.

5.2 There are available treatment options for patients with SMA

SUMMARY

— Three disease-modifying therapies for SMA are approved and available in Europe.

While symptomatic treatment and follow-up of SMA improved in the past (Oskoui, 2007), historically there were no disease modifying therapies available to treat the underlying cause of the disease. This changed with the European approval licensing of disease-modifying treatments for SMA between 2017 and 2021.

There are now three disease-modifying treatment options approved and available for spinal muscular atrophy patients. All three disease-modifying therapies target the underlying cause of the genetic disorder by increasing the amount of full-length SMN protein in motor neurons, therefore preventing further damage to motor neurons.

The disease-modifying therapies for SMA are the following:

— 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. The drug is administered intrathecally, with 4 loading doses (on days 0, 14, 28 and 63) followed by maintenance doses every 4 months.

— Onasemnogene abeparvovec-xioi (Zolgensma®), developed by Novartis Gene Therapies, was approved in the European Union in May 2020. It 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, one-time, intravenous (IV) infusion, Zolgensma delivers a new working copy of the SMN1 gene into a patient's cells.

— 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 is given orally and daily, allowing for treatment at home.

5.3 Earlier treatment leads to better outcomes: clinical studies

SUMMARY

— Clinical studies in all three disease-modifying therapies have demonstrated that earlier treatment leads to better outcomes.

Natural history studies indicate that without disease-modifying treatment, children with Type 1 SMA would not be able to reach such milestones, nor typically live past the age of two. All SMA clinical trials show that the earlier the treatment, the better the outcome for the patient (Dangouloff T., 2019). This is true for all three of the disease-modifying treatments for SMA.

The consensus from SMA experts at the 244th ENMC international workshop on newborn screening in SMA highlight unequivocally the need for newborn screening because the efficacy of new disease-modifying treatments in SMA is better in pre than in post-symptomatic patients (Dangouloff T, 2020).

Results from clinical trials of all three disease-modifying treatments show the significant positive impact of pre-symptomatic treatment. The relevant trials are NURTURE for Spinraza (De Vivo, 2019), SPR1NT for Zolgensma reported in 2 SMN2 copy patients (Strauss, 2022) and in 3 SMN2 copy patients (Strauss KA, 2022) and RAINBOWFISH for Evrysdi (Finkel R. F., 2023).

NURTURE

Long-term follow up of nusinersen initiated in 25 infants in the presymptomatic stage of SMA[a]

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 (IQWIG, 2020). 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 (De Vivo, 2019).

After ~5 years, all children achieved previously unattainable motor milestones, many within normal developmental timeframes, emphasizing the value of early diagnosis and early initiation of nusinersen (Crawford, 2023).

Results in the ongoing NURTURE study demonstrate continued benefit and a favorable safety profile over ~5 years after early initiation of nusinersen treatment in children with 2 or 3 SMN2 copies in the presymptomatic stage of SMA.[b]

Children achieved previously unattainable motor milestones, many within normal developmental timeframes.[1]

Subgroup analyses suggest inclusion/exclusion criteria and baseline characteristics should be considered when interpreting presymptomatic SMA trial data.

[a] Data cut: 15 February 2021. *Median (range) follow-up of 4.9 (3.9–5.7) years.

[1] World Health Organization Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006;450:86-95.

* Nusinersen was well tolerated; its favorable safety profile remains unchanged over ~5 years.[b]

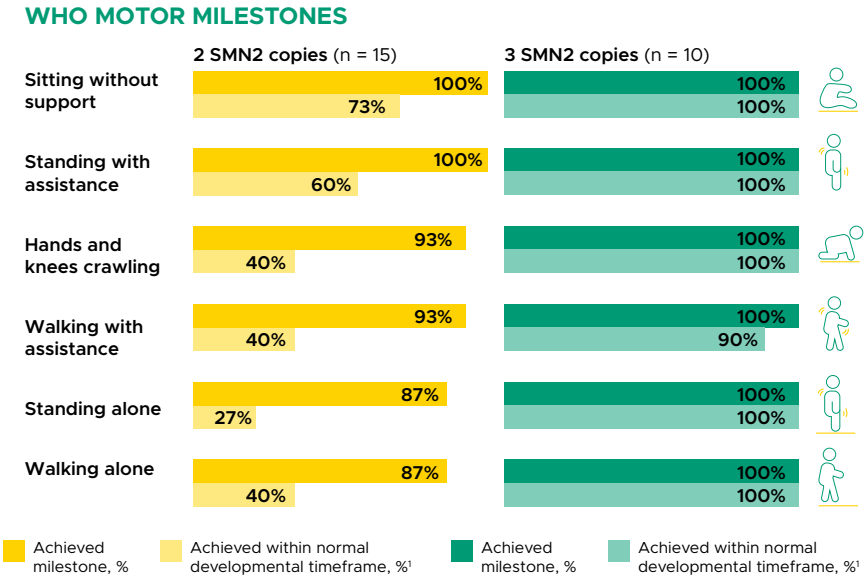


Figure 2 Graphic from 5 year readout of NURTURE trial of nusinersen in presymptomatic SMA (Crawford, 2023)

SPR1NT

In the SPR1NT study, infants treated pre-symptomatically with Zolgensma achieved early, age-appropriate motor milestones, and did not require ventilatory support nor enteral feeding (Strauss, 2022).

Patients from the SPR1NT study had the option to enrol in LT-002, a 15-year, ongoing, open-label follow-up study. 25 patients from the SPR1NT trial enrolled in LT-001. As of May 2022, all patients from the SPR1NT study were alive and none required permanent ventilation. The mean time since treatment was 3.5 (range 2.9-4.1) years and 3.2 (range 2.8-3.7) years for patients with 2 and 3 copies of SMN2, respectively (Data on file. Novartis Gene Therapies, Inc. 2023).

Patients achieved and maintained all motor milestones assessed in the presymptomatic SPR1NT study[9]

All four patients who did not achieve walking alone in the SPR1NT study achieved this milestone during LT-002 (as of May 2022)[9]

2 of these 4 patients had received other add-on therapy during LT-002 (1 of these 2 patients achieved walking alone before receiving add-on therapy)[9,a,b]

a Add-on was defined by treatment with any other disease modifying therapy.[9]

b In long-term follow-up some milestone achievements occurred after add-on therapy. Crawls (2/4); Pulls to stand (2/3); Walks with assistance (1/2), Stands alone (1/3), Walks alone (1/4).[9]

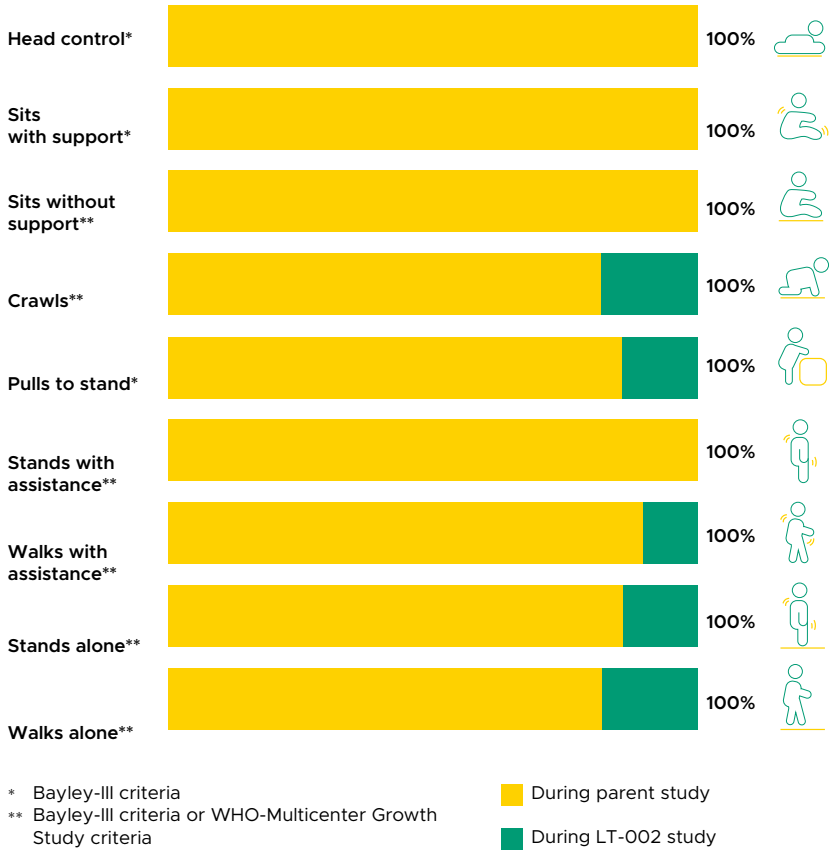


Figure 3 Infants treated pre-symptomatically in the SPR1NT parent study were invited to enrol in LT-002. The 25 patients in LT-002 achieved the nine motor milestones assessed, either during the parent study or during the LT-002 study (Data on file. Novartis Gene Therapies, Inc. 2023).

RAINBOWFISH

RAINBOWFISH (NCT03779334) is an open-label, single-arm, multicenter study assessing the efficacy, safety and pharmacokinetics/pharmacodynamics (PK/PD) of risdiplam in infants with genetically diagnosed and presymptomatic spinal muscular atrophy (SMA) from birth–6 weeks of age (at first dose), regardless of SMN2 copy number. A preliminary analysis was published in 2023 (Finkel R. F., 2023) and further publications of the study can be expected.

5.4 Earlier treatment leads to better outcomes: real world evidence

SUMMARY

— Published real world evidence, from Germany and the U.S., reinforces the benefits of expedited diagnosis and treatment of SMA further to newborn screening.

Published real world evidence supports the benefits of early diagnosis of SMA via newborn screening.

Germany

Babies born in 2 federal states in Germany underwent screening in a newborn screening pilot project for SMA. Babies from the 'exposure to SMA NBS' cohort were diagnosed with SMA early as the newborn screening for SMA pilot project expedited their diagnosis.

The 'exposure to SMA NBS' cohort were then compared to other SMA patients that were diagnosed after clinical symptom onset, with a focus on clinically relevant outcomes.

The clinically relevant outcome data was taken from the SMARTCARE registry. The SMARTCARE registry includes data from 70 participating centres in Germany, Austria, and Switzerland. Data analysis was performed for patients with a minimal follow-up of 18 months. All patients received standard care within the same health care system.

This nonrandomized study in Germany was able to compare real world data from two cohorts: (1) from people living with SMA diagnosed early, further to newborn screening of SMA in a pilot project, and (2) from people living with SMA diagnosed further to clinical symptom onset before newborn screening of SMA was implemented in Germany.

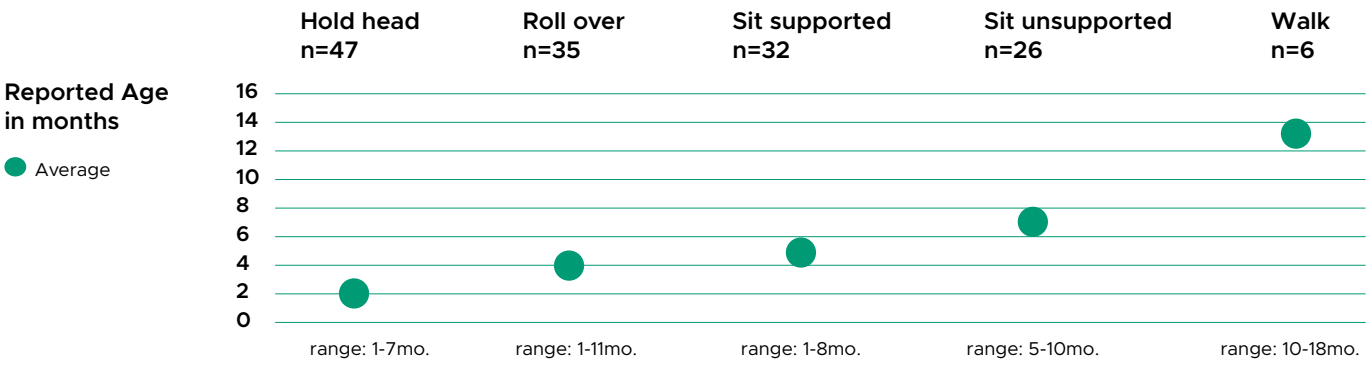
A total of 234 children were included in the analysis: 44 (18.8%) in the newborn screening cohort and 190 children (81.2%) in the clinical symptom onset cohort. The mean (SD) age at start of treatment with 1 of the approved disease-modifying drugs was 1.3 (2.2) months in the newborn screening cohort and 10.7 (9.1) months in the clinical symptom onset cohort. In the newborn screening cohort, 40 of 44 children (90.9%) gained the ability to sit independently vs 141 of 190 (74.2%) in the clinical symptom onset cohort. For independent ambulation, the ratio was 28 of 40 (63.6%) vs 28 of 190 (14.7%).

This nonrandomized trial demonstrated effectiveness of newborn screening for infants with SMA in the real-world setting. Functional outcomes and thus the response to treatment were significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group. The authors conclude that functional outcomes and the response to treatment are significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group (Schwartz, 2024).

United States of America

In the US, cross-sectional analysis was undertaken using data taken from four Cure SMA databases. In the NBS Registry, a parent/caregiver-reported database collected through an online survey with over 65 individuals identified by NBS, median reported ages at milestone achievements were within published normal ranges for development.

Parent/Caregiver reported

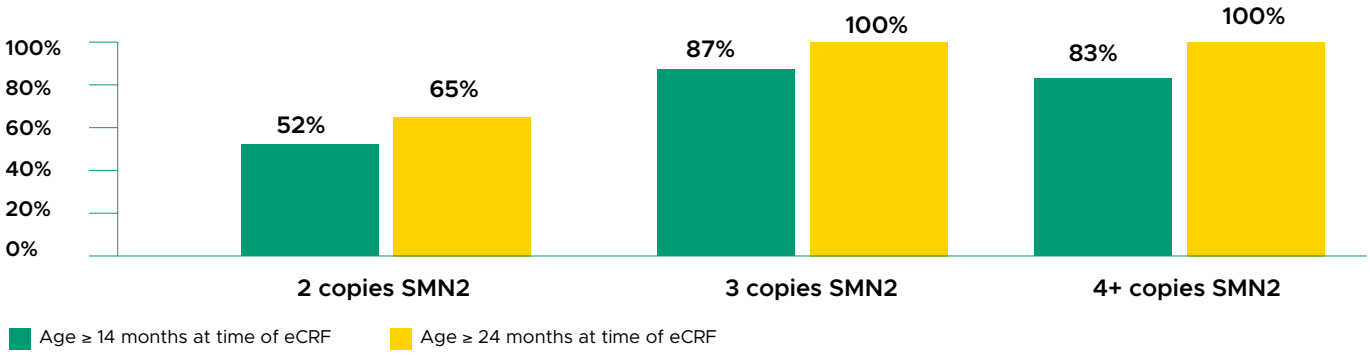


Distribution of *SMN2* Copy Number

Note: n=35 who reported the age at which the individual achieved either "rolling from back to stomach" or "rolling from stomach to back". The minimum of both reported ages was used

Figure 4 Reported median age at milestone achievement, in months, of Infants diagnosed with SMA further to NBS in the US. Source: NBS Registry (NBSR): a parent/caregiver-reported database compiled and maintained by Cure SMA (Whitmire S., 2023, June 28-30)

Clinician reported



Note: eCRF completion is based on information in the medical chart at time of submission and may be outdated. Most recent functional status had a "SELECT ONE" response. Two individuals with "stand independently" as the current functional status were not included in this analysis due to uncertainty of whether they were also able to walk assisted.

Figure 5 Achievement of assisted or unassisted walking in infants diagnosed with SMA further to NBS in the US. Source: Clinical Data Registry (CDR): an IRB-governed database comprised of EMR-sourced data linked to clinician entered electronic CRFs, N=87 (Whitmire S., 2023, June 28-30)

In the Clinical Data Registry, an IRB-governed database comprised of electronic medical record-sourced data from the Cure SMA Care Center Network (CCN) which is linked to clinician-entered electronic case report forms, there are details of over 800 SMA affected individuals of which 87 were identified by NBS and eligible for inclusion. Clinicians reported that 65% of individuals with 2 copies of SMN2 and 100% of individuals with 3+ copies of SMN2 over 24 months old could walk assisted or unassisted (Whitmire S., 2023, June 28-30).

5.5 Earlier treatment leads to better outcomes: summary

SUMMARY

— Taken together, the clinical trial results and the real-world evidence data demonstrate that pre-symptomatic treatment results in improved functional outcomes and can result in age-appropriate motor development.

As Oskoui, Dangouloff and Servais wrote: "There is no doubt that initiating disease-modifying therapy (DMT) earlier in newborns who will otherwise develop symptoms of SMA in infancy or childhood results in improved outcomes. The magnitude of this benefit is dependent on SMN2 copy number, clinical condition at treatment onset, and time to treatment initiation. In this context, improving the processes to remove barriers for rapid diagnosis confirmation and treatment onset is key" (Oskoui M, 2024).

In summary, both clinical trial data and real-world evidence demonstrate that early treatment facilitates and may be necessary to maximise the potential benefits for people affected by SMA.

5.6 Facilities for diagnosis and treatment of SMA are available

SUMMARY

— There are many health care institutions across Europe that provide good care to people living with SMA.

Critical for SMA care, specialised teams of health care providers diagnose and initiate the international recognised basic standard of care and disease-modifying therapies. Then the specialised teams ensure proper follow-up of the patient.

The 2018 SMA Standards of Care recommendations were published in Neuromuscular Disorders as Part 1 in February 2018 (Mercuri, 2018) and Part 2 in March 2018 (Finkel R. S., 2018). These documents are updates of the Standard of Care document issued in 2007. The 2018 recommendations emphasise that "a multidisciplinary approach is the key element in the management of SMA patients."

For the best outcomes in SMA patients, healthcare providers representing a variety of specialties should work together across specialties and with families. The multidisciplinary care team may include specialists in neuromuscular conditions, palliative care, respiratory medicine, physiotherapy, occupational therapy, speech and language therapy, dietetics, psychologists, pain specialists and a hospital or community consultant paediatrician. Where available, a key worker should assist in the co-ordination of services for the family. Depending on the local health care system, close cooperation with primary care physicians (general/family practitioners and/or paediatricians) should be ensured.

There are accessible centres with SMA expertise across Europe.

5.7 There is a recognisable latent or pre-symptomatic stage of SMA

SUMMARY

— There is a time window between birth and age of symptom onset. However, even before the first clinical symptoms, damage to the motor neurons may have already occurred.

— This "window of opportunity" is wasted where newborn screening is not available.

The majority of babies born with SMA are clinically asymptomatic at birth, in that we do not see the symptoms of the condition. In the literature and without newborn screening, the age of symptom onset is reported to be 2.5 + 0.6 months for the most common SMA types and 8.3 + 1.6 months for later-onset SMA types (Lin C. W., 2015). Knowing that the damage to the motor neurons occurs before the onset of symptoms, there is an urgent need to use the "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 (Vill, 2019). From the 165,525 children screened within 13 months, 22 SMA cases were identified and 4 babies were already symptomatic on first examination. Some babies may be presymptomatic at the time of NBS, and then become symptomatic after a few weeks. Further to a quick diagnosis following the NBS result, immediate treatment can be administered, giving these babies a much improved prognosis.

Unfortunately, this "window of opportunity" is wasted without the availability of NBS.

According to a meta-analysis by 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 (Lin C. W., 2015). This has been confirmed in later publications from individual countries in Ireland (Michael Carter, 2023) and France (HAS-sante-fr, 2024). According to patient organisations, the delay in diagnosis for Type I SMA ranges from 4 weeks to 9 months, depending on the health care system.

This odyssey between onset of symptoms and finally reaching a diagnosis 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 (Lawton, 2015).

In contrast, screening close to birth is best in order to provide a sufficient time window to identify the disease, communicate with the family and, eventually, treat the disease successfully. In most European countries, the heelprick bloodspot sample is taken for screening soon after birth for all babies nationwide (e.g. 72 hours after birth in France and Germany). Every day matters.

5.8 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 (Dangouloff T. B., 2021) as no specific biochemical marker has been validated for the disease. A homozygous SMN1 exon deletion has been found in most patients with SMA and is thus used as a reliable and sensitive SMA NBS test in dried blood spot (DBS) specimens (Prior, 2010).

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 (Kraszewski, 2018), (Chien, 2017), (Kariyawasam, 2020) (Kay, 2020) (Weng, 2020) (Boemer, 2019) (Vill, 2019). In most studies, the specificity of these assays was nearly 100% and the cost of conducting the test is approximately €3 - €5 per sample (Heijnen, 2020).

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% (IQWIG, 2020).

The cost of conducting the test is approximately €3 - €5 per sample (Heijnen, 2020).

5.9 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 a blood-spot specimen from a heelprick, which is a skin puncture on the heel to a depth of 2 mm or less. The heelprick is undertaken by a trained healthcare professional who collects the bloodspots from the newborn's heel onto a Guthrie paper, which is a specimen collection device designed for this purpose. A heelprick blood procedure is routine in all newborn screening programmes, so adding SMA to the existing newborn screening panel is not creating a new procedure nor exposing the newborn to an additional intervention.

In Europe, countries inform parents differently about their NBS programme, potentially including different knowledge aspects in their information. Parents and healthcare professionals often view NBS as a routine procedure. Informed participation is of great importance and strived for with informed consent procedures in place in around half of European countries. Both opt-in and opt-out systems are used for consent (Ijzebrink, 2021).

Performance of NBS programmes is reportedly high. In an analysis performed by the International Society of Neonatal Screening (ISNS) across 51 countries in Europe including EU, EFTA members, potential candidate EU members and Europe-other including Russia and former Soviet countries, ISNS found that in the majority of the countries, the coverage, defined as the percentage of newborns included in neonatal screening, is higher than 90%. In many countries, coverage is even higher than 99% despite the fact that NBS is not mandated in most countries (Loeber JG, 2021).

However, how is SMA newborn screening perceived by the public, parents, and adults with SMA? Boardman et al. (Boardman F. K., 2018) 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%) (Boardman, 2018) as were a mixed population of families and adults (70%), despite preferring pre-conception and / or prenatal screening (Boardman, 2017).

In May 2024, Eurordis conducted a Rare Barometer survey with the Screen4Care project (Eurordis, 2024) The study gathered the views of more than 6,179 people living with a rare disease and family members worldwide, 5,569 of whom were living in Europe with more than 1,300 distinct rare diseases, hence representing the diversity of the rare disease community.

"Respondents' answers confirm the strong support for newborn screening from the rare disease community. They also show that people living with a rare disease and their family members mostly see newborn screening as a way to alleviate the burden of the diagnosis odyssey and to enable parents to make informed choices for their child living with severe and early onset conditions, regardless of their access to a treatment or intervention." (Eurordis, 2024)

5.10 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.
— SMA inevitably affects 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.

There are natural history studies and observational trials published on SMA infants (Kolb S. J., 2017) (Finkel R. S., 2014) and young children living with SMA (Annoussamy M, 2021). These natural history studies have described the rapid loss of motor function, lack of weight gain and early death in young children with SMA. The effects of untreated SMA are devastating, causing a marked delay or complete halt in the development of neuromuscular function early in life.

Before the availability of disease-modifying therapies, the trajectory for people living with SMA was already changing. A 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 (Oskoui, 2007).

In 2007, Wang et al. published a first "Standard of Care" document for SMA, emphasizing that the disease has a large clinical spectrum and requires multidisciplinary care (Wang, 2007). This consensus was updated in two parts in 2018 (Mercuri, 2018) (Finkel R. S., 2018).

Now that three different disease-modifying treatments for SMA are available, it is important to have these natural history data on hand, so we can remember what severe SMA looks like when left untreated.

5.11 There is an agreed policy on whom to treat

SUMMARY

— SMA care is not limited to disease-modifying therapies (SMA medicines) alone and also comprises best-supportive care including non-pharmacological treatments.

— SMA care is a shared decision-making process between the SMA experts and the child´s parents.

— The latest policy comes from the 270th ENMC International Workshop Consensus for SMN2 genetic analysis in SMA patients, which took place on 10-12 March 2023 in Hoofddorp, the Netherlands.

The focus of all treatment decisions needs to be on the patient, the family, and the multi-disciplinary management of the disease. Treatment 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. Treatment can range from best supportive care to treatments to alleviate symptoms to disease-modifying therapies (SMA treatments). 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.

To correctly diagnose these children, specialised personnel are needed, also allowing for a second or third opinion. SMN2 copy number is a good predictor of disease. However, multiple publications have reported that there are patients who perform better or worse than the expected phenotype based on SMN2 copies (Calucho M. B., 2018), (Schorling D. C., 2019), (Costa-Roger, 2021), (Abiusi, 2024), (Schwartz, 2024), (Groulx-Boivin, 2024). This could be due to technical reasons, with discordance between laboratories about the number of SMN2 copies. It could also be due to biological reasons with differences in the quality of SMN2 genes in producing functional SMN protein (Schorling D. B., 2019).

To make treatment decisions for a newborn baby living with SMA, a physician's recommendation to the parents is guided by the presence or absence of early symptoms and the number of SMN2 copies. There is consensus that the reported number of SMN2 copies alone is not a sufficient base for a treatment decision for each individual child.

The latest discussion and consensus came from 270th ENMC International Workshop: Consensus for SMN2 genetic analysis in SMA patients which took place on 10-12 March, 2023 in Hoofddorp, the Netherlands. At the end of the workshop, the attendees defined a set of recommendations divided into four topics: SMA molecular prognosis assessment, newborn screening for SMA, SMN2 copies and treatments, and modifiers and biomarkers (Abiusi, 2024).

Clinical recommendations could be discussed and updated in the future. Costa-Roget et al. argue that the SMN2 gene warrants a deeper study beyond the determination of the number of SMN2 gene copies. In the future, routine analysis after a positive newborn screening result could be adapted to detect SMN2 variants that may impact disease severity (Costa-Roger, 2021).

At the time of writing, the implications of SMN2 modifier variants and hybrid genes are not fully understood. In the future, the availability of better biomarkers together with a better understanding of SMN2 modifier variants and hybrid genes, might provide additional support for decision making.

Given the principle of autonomy, after joint consultation with supporting health care professionals, the family has the responsibility for the final decision regarding initiation of treatment.

5.12 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 dried bloodspot specimen that is already taken on a routine basis in the newborn screening programmes that exist across Europe. SMA can easily be added to the existing European NBS programmes. SMA screening can be done cost effectively for approximately 3-5 Euros per child (Heijnen, 2020).

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 (Klug, 2016). 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. (López-Bastida, 2017) 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 (Peña-Longobardo, 2020).

These figures do not 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.

5.13 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 in selected regions or provinces of a country may help to establish test routines and the appropriate processes, it is unfair if regional pilot studies are 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 creating an inclusive health care system.

06

SMA newborn screening process proposal

06 How and why SMA meets the criteria for newborn screening

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-positivwe result. A complete NBS programme comprises six main components (Therrell BL, 2001):

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, nor the European Union (Loeber J. G., 2018). Although the European Commission has published recommendations for European policymakers (Burgard, 2011) (Cornel, 2011), health care falls under the competency of the individual member states of the European Union meaning each member state 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 (Loeber J. G., 2021). 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 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. In some countries, an official nationwide national newborn screening programme has not yet been established (Loeber J. G., 2021).

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.

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 NBS programmes have been set up, funded, and managed (Loeber J. G., 2018). Typically, NBS programmes in Europe are funded comprehensively, from the pre-analytical 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 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 (Ijzebrink, 2021). In a few countries, the procedure for providing information to parents is still unregulated. 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 not participate.

Depending on local regulations, SMA could be added to an NBS programme utilising the same consent practices that are in place for the existing programme. Alternatively, specific consent may be required, which is the case in countries where genetic information is treated differently from 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 dried blood spot specimen for SMA NBS can be easily added to standard NBS programmes. Capillary blood is collected through a heel prick. The blood spots are applied onto the filter paper section of the specimen collection device. In limited situations, other sources of blood may be used for SMA NBS (CLSI, 2013). For most NBS programmes, dried blood spot 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 (Taylor, 2015), 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.

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 (Pyatt, 2007), (Dobrowolski, 2012) (Lin Y. L., 2019) (Kato, 2015) (Vandermeulen, 2020). 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 (Vandermeulen, 2020).

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) (Gutierrez-Mateo, 2019). 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 (Vidal-Folch, 2018) (Chien, 2017). The use of second-tier testing has proven that a false positive rate of 0.0% can be reached (Kay, 2020) (Chien, 2017).

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 is required to a neuropaediatrician at an SMA/neuromuscular specialty centre for diagnostic confirmation and subsequent information on treatment options. 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 (Cuscó, 2020).

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 (Alías, 2009) (Dangouloff T, 2020). Thus, the introduction of SMA NBS does not diminish the importance of a differential diagnosis for SMA when compatible symptoms are present even in countries where SMA is included in the national NBS programme.

6.6 Management

Recently, consensus statements on treatment of SMA with disease-modifying therapies have clearly stressed that the time between diagnosis and initiation of treatment should not exceed two weeks (Kirschner, 2020).

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 (Kariyawasam, 2020) (Vill, 2019). The therapeutic effects of a disease-modifying therapy may be less when treating a symptomatic patient. This should be considered when discussing treatment plans with the child´s parents (Jędrzejowska, 2020).

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 (Vill, 2019) (Kariyawasam, 2020).

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 (ACMG, 2006).

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.

07

SMA newborn screening is ethically required

07 SMA newborn screening is ethically required

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 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 (Loeber J. G., 2018). In this vein, withholding NBS from children, translates to depriving them of an optimal pathway towards care.

The complex ethical and legal landscape surrounding consent in the context of incorporating genomic sequencing into existing newborn bloodspot screening programmes was explored by a consortium from Canada, Australia and the UK (Knoppers, 2024). The authors introduced the 'right of the asymptomatic at-risk child to be found' as a useful concept to draw on when considering consent to newborn screening.

In the future, with the possibility of genomic studies and whole genome sequencing of newborns, the right of the asymptomatic at-risk child to be found could become increasingly relevant to healthcare systems and societies.

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 (Boardman, Newborn screening for spinal muscular atrophy: The views of affected families and adults., 2017).

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 (Botkin, 2016). 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

The risk of a false positive result is very low if a confirmative test is done in an additional laboratory (Prior TW, Updated 2024 Sep 19).

The risk of a false negative result is more challenging due to laboratory errors or subtle pathogenic variant not identifiable by the NBS method. 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 (Dangouloff T, 2020).

The situation for children who are false-negative, will probably be slightly different after the introduction of nationwide NBS for SMA. The responsible physician may be less likely to check for SMA as the physician assumes that the child has already been screened in NBS. Therefore, the delay to diagnose SMA from the onset of symptoms could become longer.

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 the possibility and to the symptoms of SMA.

As 95% of all children with SMA will benefit from NBS, denying those children and their families 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. These are caused by alterations in other genes and do not have specific treatments (Peeters, 2014).

08

Health economics

08 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, multiple analyses have shown the cost-effectiveness of newborn screening and demonstrated improved economic value for patients, payers and healthcare systems

Health economics is a field in Health Technology Assessment (HTA) that has become and still continues to be increasingly important, including in the field of population-based screening for rare diseases. For decades, interventions in rare diseases were relatively exempt from health economic analysis. For example, new drugs would come on the market and were reimbursed relatively straightforwardly. Recently, however, we have seen HTA jurisdictions also make rare disease interventions the target of economic scrutiny, in particular, cost-effectiveness/cost-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 status quo without newborn screening for SMA. This analysis 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/cost-effectiveness analysis is the cost-effectiveness (CE) ratio, reflecting the difference in costs divided by the difference in health benefits. Health benefits can be 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 (Rawlins, 2010); as well as generally higher WTPs being used in the context of rare diseases (Schlander, 2016).

It is often argued that for rare diseases, cost-effectiveness analysis fails to grasp all the relevant prevailing societal values that apply to rare diseases and corresponding interventions, including gene-therapies and screening (Schlander, 2016). If severity justifies an increased WTP (as applied by several HTA bodies), other aspects of creating value through treating rare diseases may warrant further WTP increases.

Firstly, rarity per se may reflect a societal value in itself (Medic, 2017). 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 been identified by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) as an additional value for new drugs, potentially warranting higher WTPs (Neumann, 2022). 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. Conforming to standard health-economics methodologies, the 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 (Jalali, 2020). It was concluded from this study that NBS for SMA provides improved economic value for payers and patients when nusinersen is available.

In England, an analysis was undertaken to evaluate the cost-effectiveness of newborn screening (NBS) versus no NBS for 5q spinal muscular atrophy (SMA). The analysis demonstrated that NBS improves health outcomes for patients with SMA and is less costly compared with no screening. Therefore, NBS for 5q SMA is a cost-effective use of resources from the perspective of the NHS in England. (Weidlich D, 2023)

In Italy, an evaluation of the cost effectiveness of universal NBS for SMA yielded the results that universal NBS followed by presymptomatic treatment resulted in 318 life years gained, 386 quality-adjusted life years gained, and incremental costs of –€143,167 over a lifetime time horizon. Thus, NBS was less costly and more effective than a scenario without NBS. The NBS strategy has a 100% probability of being cost-effective assuming a willingness-to-pay of >€40,000. The publication concluded that "our analysis demonstrated that NBS followed by presymptomatic SMA treatment is good value for money and cost-effective from the Italian National Health Service perspective". (Ghetti, 2022)

Additional studies have produced similar findings in lower population countries including the Netherlands which identified a lifetime savings of EURO 12 million for patients identified and treated through NBS compared with patients identified through non-NBS treatment pathways (Velikanova, 2022), Belgium based on real world data (Dangouloff T. T., 2024) and Portugal (Fonseca, et al., 2024).

"Our analysis demonstrated that NBS followed by presymptomatic SMA treatment is good value for money and cost-effective from the Italian National Health Service perspective".

09

Status of SMA newborn screening in Europe

09 Status of SMA newborn screening in Europe

SUMMARY

— In Europe, inequities remain with some, but not all, babies having access to newborn screening for SMA.

— Nationwide SMA newborn screening programmes are running across much of Europe, and 72% of newborns having access to screening (as of 8 August 2024).

— For the current status of SMA newborn screening in Europe please visit: www.sma-screening-alliance.org/map

In Europe, as of August 2024, nationwide newborn screening programmes are operating in Austria, Belgium, Croatia, Denmark, Estonia, Germany, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Russia, Serbia, Slovakia, Slovenia, Sweden, Switzerland, Turkey and the Ukraine.

SMA newborn screening is approved in some provinces in France (Nouvelle Aquitaine, Bordeaux, and Grand Est, Strasbourg), Italy (in most of the 20 regions and 33% of births) and Spain (pilot studies ongoing in Madrid and Comunidad Valenciana; Newborn Screening Programme includes SMA in Galicia, the Balearic Islands and Canary Islands).

SMA was approved as part of the national newborn screening programme and is awaiting implementation in Ireland.

A pilot of SMA newborn screening is underway in the Thames Valley region (Oxford) in England. There are active pilots underway in the Czech Republic, Hungary, Macedonia, Romania,

As of August 2024, 72% of children are screened for SMA at birth in wider Europe (including the three South Caucasas countries as well as all of Russia and Turkey). In geographical Europe, 66% of children are screened for SMA at birth. In the EU, 64% of children are screened for SMA at birth.

For the regularly updated status of SMA NBS in Europe please visit:
www.sma-screening-alliance.org/map

10

Experiences from outside Europe

10 Experiences from outside Europe

SUMMARY

— The United States (US) is ahead of Europe in implementing NBS for SMA
– 50/50 US states are now screening for SMA
– 100% of all babies born in the USA are now screened for SMA

— Australia has introduced NBS for SMA nationally.
— In Taiwan all newborn babies are being screened for SMA.

In the **US**, in July 2018, the federal government added spinal muscular atrophy (SMA) to the Recommended Uniform Screening Panel (RUSP)—the list of suggested conditions that states should screen for within their statewide universal newborn screening programs. As of August 2024, advocates have successfully encouraged the adoption of newborn SMA screening in all 50 states, plus Washington, D.C. Within 6 years of SMA being added to the federally recommended list of diseases to screen for at birth, Cure SMA and its advocates have ensured that 100% of babies born in the U.S. are now screened for SMA at birth
www.curesma.org/newborn-screening-for-sma

In **Australia**, 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 has taken place
www.health.gov.au/our-work/newborn-blood-spot-screening/what-is-screened

In **Canada**, screening for SMA was first added to the NBS screening panel in Ontario
https://muscle.ca/services-support/newborn-screening/

A cross-sectional survey published in April 2024 reports that NBS for SMA is performed in five provinces f(Alberta, British Columbia, Manitoba, Ontario and Saskatchewan, as well as in Nunavut and the Northwest Territories), with 72% of Canadian newborns screened for SMA at birth (Groulx-Boivin, 2024).

Multiple pilot trials have been conducted in **China** (Chien, 2017) (Shinohara, 2019) (Lin Y. L., 2019). In **Taiwan**, following a pilot project in 2014-2016, all newborn babies born in the country are being screened for SMA (Dangouloff T. V., 2021).

For **Japan**, following pilots (Shinohara, 2019), SMA newborn screening programmes have been started in various parts of the country, including Hyogo, Osaka, Chiba, Kumamoto, Ehime, Miyagi, Nagano, and Gifu. However, in 2023 it was reported that only about 20% of newborns in Japan are screened for SMA at birth (Tomokazu, 2023). In April 2023, Tokyo Health Service Association introduced a “expanded newborn screening programme” which includes SMA as an optional screening test for babies born in the Tokyo Metropolitan Area
www.yobouigaku-tokyo.or.jp/baby/optional/en

For **Mexico** and **Latin America**, IRDiRC reviews the progress made in implementing and expanding newborn screening programmes and reported that despite significant advancements over the past 50 years, many children in the region still do not fully benefit from this vital public health strategy
www.oaepublish.com/articles/rdodj.2024.02

11

The story of the SMA newborn screening alliance

11 The story of the SMA newborn screening alliance

In February 2020, at the SMA Europe Scientific Congress (Évry, France), SMA patient organizations and leading clinicians in the field expressed their concern about an important loss of opportunity for early intervention for infants not screened at birth. Subsequently, they created the European Alliance for SMA NBS. The goal of the Alliance was to accelerate the inclusion of SMA in the NBS programme in Europe, because delays in adding SMA to the screening programmes result in children not being identified early enough, thus missing out on available life-saving treatments.

The Alliance was ground-breaking because of the breadth of the multi-stakeholder initiative.

SMA Europe brought together a wide audience, with other patient organisations like EURORDIS or EAMDA (European Alliance for neuromuscular association), but also medical and scientific networks like EURO NMD (European reference network for neuromuscular diseases) and TREAT-NMD, academic research and university institutions like Groningen University and Health-Ecore from the Netherlands and IBIMA Institute in Malaga Spain.

Initially, the partners in the Alliance included the three pharma companies that have an approved treatment for SMA (Biogen, Roche, and Novartis Gene Therapies) and testing kit manufacturers, PerkinElmer (now Revvity). In 2021 and 2022, additional companies joined the Alliance including Scholar Rock, LaCAR MDX Technologies (ZenTech), ImmunoIVD and Asuragen (a Biotechne brand). admedicum provided secretariat support for the Alliance for 2020-2022. Subsequently, SMA Europe took over the secretariat function.

The Alliance developed, produced and disseminated multiple tools to support national patient organisations in advocating for the implementation of NBS screening in their countries. The tools included policy flyers, conference posters and presentations, videos, media and social media materials. The Alliance also developed a toolkit which is intended to assist national patient organisations in identifying and preparing for potential challenges

The status map can be found here:

www.sma-screening-alliance.org/map

The toolkit and other resources can be found here:

www.sma-screening-alliance.org/resources

they may face, in their countries, when advocating for high quality and equitable screening and including suggestions on how patient advocacy groups can better engage in the processes to support good decision making. This toolkit may be applicable to other countries globally and to other diseases beyond SMA.

The Alliance also hosted webinars for member organisations to educate the different stakeholders about NBS for SMA. In addition, the Alliance has provided support for individual countries in collaboration with local SMA patient organisations and policy work at country level and at the EU level in Brussels.

All the up-to-date information, the toolkit and other resources are collated and made accessible on the Alliance's website, where there is also an updated map tracking the progress towards SMA NBS throughout all of Europe.

In 2021, the Alliance published a White Paper that summarised the current understanding and scientific consensus on neonatal screening for spinal muscular atrophy and made a case for a wider introduction of this diagnostic method population-wide. The White Paper addressed key topics and questions to encourage the introduction of SMA screening in the national programmes in Europe, and was a "go to" collection of scientific and technical evidence that is requested by national screening committees. Further to requests from national SMA patient organisations, the White Paper was translated into Spanish, Portuguese, Romanian and Chinese.

In 2022, the Alliance won the EURORDIS 2022 Black Pearl Award in the category: "EURORDIS Company Award for Patient Engagement" in recognition for its work to promote the early implementation of newborn screening for spinal muscular atrophy throughout Europe.

The work to add a new disease into the national panel in any European country is huge and time consuming. It is necessary to go country-by-country, sometimes region-by-region in some states, with the same data and similar arguments. As an urgency for another rare disease, the work of the Alliance can be replicated. However, the Alliance advocates at EU level to have European recommendations for all NBS panels, to avoid such a heavy burden for each individual rare disease community. After a EU recommendation in favour of adding a new rare disease to NBS, each EU Member State can decide to implement the recommendation or not. Yet the scientific rationale will be challenged, assessed and validated only once, more or less as EMA undertakes evaluation of applications for marketing authorisation of drugs.

The work conducted by the Alliance has demonstrated that an alliance is able to accelerate the implementation of newborn screening for spinal muscular atrophy. The Alliance's work could be replicated in other geographies and in other rare diseases, which might contribute to accelerating the expansion of newborn screening programmes in Europe and globally.

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13 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

EAMDA
European Alliance for Neuromuscular Disease Association

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

IRDiRC
International Rare Diseases Research Consortium

IQWIG
Institute for Quality and Efficiency in Health Care (Germany)

ISNS
International Society for Neontal Screening

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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