Tătaru *et al. Rare Dis Orphan Drugs J* 2024;3:19
DOI: 10.20517/rdodj.2024.08

Rare Disease and Orphan Drugs Journal

Opinion

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Incorporating a new disease in the newborn screening programs in Europe: the spinal muscular atrophy case study

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How to cite this article: Tătaru EA, Ouillade MC, Chan CH, Pearce DA. Incorporating a new disease in the newborn screening programs in Europe: the spinal muscular atrophy case study. *Rare Dis Orphan Drugs J* 2024;3:19. https://dx.doi.org/10.20517/rdodj.2024.08

Received: 29 Feb 2024 **First Decision:** 23 Apr 2024 **Revised:** 17 May 2024 **Accepted:** 4 Jun 2024 **Published:** 2 Jul 2024

Academic Editor: Daniel Scherman **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Patient advocacy organizations have a forefront role in ensuring that patients' voices and needs are embedded as a constitutive basis in drug development, diagnosis, and policy recommendations in the healthcare ecosystem. Their sustained involvement in accelerating the policy changes for inclusion of additional diseases in the newborn screening (NBS) programs, supporting harmonization in terms of number of screened diseases across the European Union, constitutes a driving force for advancing the quality of care and the management of rare diseases by aligning NBS policies and practices internationally. In the current European landscape, NBS varies significantly across regions and countries. Patient advocacy organizations are acting to alert healthcare authorities of the existing inequity in NBS and recommending that additional diseases be added to the national NBS programs. Here, we describe the state of play for Spinal Muscular Atrophy (SMA) as a model for advancing NBS for rare diseases where a treatment regime is available. Ultimately, a broad understanding of NBS for SMA will additionally serve as a means to understand the financial impact of early therapeutic intervention for a rare disease.

Keywords: Newborn screening, rare diseases, patient advocacy organizations, spinal muscular atrophy

INTRODUCTION

Across countries, newborn screening (NBS) is implemented heterogeneously, with significant variations between high- and low-middle-income countries. A study published by Novartis and Charles River Associates (CRA) in March 2022 showed that one heel prick test can potentially diagnose up to 50 diseases, as demonstrated by Italy, which ranks as the first country in the European Union (EU) where NBS is currently implemented for 48 diseases (or more, depending on the region), while Cyprus and Romania perform NBS for only two diseases[1]. The efficiency of the diagnostic pathway remains a critical step in the management of SMA, and the inclusion of SMA in the national NBS programs, with adequate follow-up and genetic counseling, facilitates earlier treatment access and care. Across Europe, several countries have already included SMA in their national screening programs, among them Belgium, Germany, Netherlands, and Poland, while others developed pilots and provided an efficient reimbursement system for access to diagnostic resources (Austria, Czech Republic, Denmark, Finland, France, Italy, North Macedonia, Spain, Sweden, and the United Kingdom)[2,3].

Spinal Muscular Atrophy (SMA) is a genetic recessive disease caused by the mutation or absence of the Survival Motor Neuron 1 (SMN1) gene located in the q region of chromosome 5, often referred to as 5q SMA, which results in motor neuron degeneration and thus progressive muscle paralysis. In recent years, new treatments have been shown to significantly improve the motor function of symptomatic patients, but do not enable them to regain normal motor activity. In adults, they stabilize or even slightly reverse the course of the disease. Their effectiveness is largely dependent on the age of the patient and his or her ability to renew motor neurons, but above all, on the level of degeneration of the nervous system[4]. Three effective treatments have received regulatory approval from the European Medicines Agency (EMA) and at least one of them is now available for infants in some European countries[5]. Disease severity is a continuum; however, to facilitate the standard of care, the disease forms were classified by type (type 0 to 4) based on the age of disease onset[6]. The age at which a child first exhibits symptoms is a reliable predictor of the progression of the disease in terms of motor functions and associated disabilities if left untreated [Table 1].

For patients diagnosed through a genetic test of 5q13 SMA, a double deletion of the SMN1 gene will indicate a positive result. SMN1 and SMN2 have identical sequences except for a single nucleotide change in exon 7 of SMN2 which alters splicing. SMN2 usually produces a small amount of functional protein and the copy number of SMN2 typically influences the severity of SMA disease[4].

• 1 copy of SMN2: the child will develop a severe form of type 1 and will probably show clinical signs from birth;

• 2 copies of SMN2: the child will present the first symptoms at a very young age and will probably have SMA type 1 or 2;

• 3 copies of SMN2: first symptoms develop in childhood, and the patient will probably have SMA type 2 or 3;

• 4 copies of SMN2: the first symptoms will appear in adolescence or adulthood, and the patient will probably develop a type 3 or 4 SMA;

• Beyond 5 copies is quite rare, the patient can develop SMA type 4, and many adults diagnosed in this way are usually asymptomatic[5].

Table 1. Characteristics of 5q SMA types

	Type 1	Type 2	Type 3	Type 4
Age of onset of first symptom	Before 6 months	Between 6-18 months	After 18 months	Adult age (> 18 years)
Mobility status without treatment	Non-Sitter	Sitter	Walker	Walker
% of Incidence	50%*	25%	22%	3%

*Incidence of type 1 is quite high, but because of the short life expectancy (less than 2 years, median life expectancy 12 months) of this population, prevalence of type 1 remains quite low.

The published clinical studies results have shown that the effectiveness of all approved treatments is significantly higher when the child is treated before the onset of the first clinical sign[5-7]. Three treatments are approved in Europe, targeting the survival motor neuron gene (SMN1 and SMN2) production:

(1) Spinraza™ (nusinersen), an antisense oligonucleotide (ASO) targeting the SMN2 gene, administered via intrathecal injection every 4 months[8];

(2) Evrysdi™ (risdiplam), SMN2 splicing modifier overexpressing SMN production, medicine administered per os (PO), once per day[9];

(3) Zolgensma™ (onasemnogene abeparvovec), gene therapy, adding the SMN1 sequence, single-dose intravenous infusion[10].

Why include SMA in NBS programs?

During the clinical studies preceding the marketing submission or authorization of new treatments, in addition to symptomatic patients, pharmaceutical companies conducted a series of trials on patients diagnosed with SMA at birth via genetic screening. Most investigations were focused on patients treated presymptomatically who had two or three copies of SMN2 and who were predisposed to developing an early form of the disease. In the NURTURE study, a clinical trial conducted by Biogen, the newborns were administered intrathecal nusinersen (Spinraza™) during neonatal development, with long-term follow-up to evaluate the benefits on survival, respiratory interventions, and motor outcomes and if the treatment guaranteed a favorable safety profile. Interim results from the NURTURE study concluded that, after a follow-up of 2 years and 9 months, there were clear clinical benefits for the infants with two or three copies of the SMN2 gene who received treatment, providing an opportunity for early intervention and improvement of symptoms experienced. The ENDEAR study evaluated the motor-milestone responses and the event-free survival in infants with SMA treated with nusinersen compared with a control group. An interim analysis showed a better motor-milestone response in the group treated with nusinersen, which led to the early termination of the trial. The final analysis showed a significant improvement in motor response and survival in the arm treated with nusinersen compared with the control group[5,8].

A comparable level of efficacy has been demonstrated by Zolgensma (onasemnogene abeparvovec), the gene therapy medication developed by Novartis Gene Therapies, that was administered in a single-arm SMA patients trial who had two or three copies of SMN2. The results highlighted that 7 out of 14 (50%) infants with two SMN2 copies had gross motor performance similar to normal development, while all 14 (100%) infants had fine motor performance similar to normal development[10]. Moreover, all patients with three copies of SMN2 treated presymptomatically achieved the primary endpoint, demonstrating the ability to stand without support during the 2-year follow-up visit. More recently, Evrysdi (Roche) also showed a comparable level of efficacy based on the results presented in their publication of the RAINBOWFISH trial

result, showcasing that 80% of the infants involved in the trial were able to sit without support for at least 5 s after one year of treatment[11-13].

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 this Alliance is to accelerate the inclusion of SMA in the NBS program in Europe. It emphasizes that delays in adding SMA to the screening programs could result in children not being identified early enough, thus missing out on available life-saving treatments.

The Alliance has developed tools to assist clinicians and national patient organizations in advocating for the implementation of NBS screening in their countries, such as flyers or posters to support the advocacy actions, and developed a white paper that addresses most of the questions related to access to diagnosis, treatments, and care, and that, at the same time, may encourage the introduction of SMA screening in the national programs in Europe.

How does SMA address the Wilson & Jungner criteria and why should it be included in all NBS programs

The Wilson and Jungner criteria were first published in 1968, and it comprises 10 principles of population screening with the scope of guiding the screening decisions[14-16]. The principles are explained below in Table 2, together with arguments to screen for SMA at birth based on each criterion.

In reality, the inclusion of SMA screening in NBS programs in Europe has been moderately successful so far. In 2020, less than 25% of the babies born in the EU were screened, and this rate drops to 15% in continental Europe[22]. In comparison, three years after SMA was added to the federal recommended list of diseases for screening at birth, 98% of the newborns in the United States of America are now screened for SMA at birth[23].

Main obstacles encountered - cumbersome, redundant and complicated administrative procedures

The implementation of NBS in the EU member states is disparate, and sometimes, as it happens in Spain or Italy, it is a decision at the regional level. This multiplies the number of dossiers to be submitted, sometimes with contradictory analyses from one country to another. In order to facilitate the constitution of the different dossiers, the Alliance has produced a white paper answering the main questions asked by the national or regional agencies with the associated scientific references[22].

The national procedures for implementing screening might sometimes be unclear, not fully transparent and therefore difficult to understand for many stakeholders including patient associations. The Alliance, with the support of the CRA, has carried out a mapping of the different procedures by country and identified points of contact, as well as a series of good practices or success stories based on the feedback received. This study shows that in some countries, there is no formal procedure and usually, in a vast majority of them, a patient association is not authorized to initiate a request for NBS for a disease. The patient advocacy associations are sometimes consulted during the development of a new series of procedures, but in most cases, their input remains minimal, and it is not captured either through formal or informal meetings[22].

Data privacy concerns

Genetic data are considered sensitive data according to the EU General Data Protection Regulation (GDPR). Furthermore, many countries, including France, have a very strict legislation regarding the protection of genetic data of their citizens. Consequently, the implementation of genetic screening requires a specific national legislative change.

Table 2. Why SMA should be screened at birth based on Wilson & Jungner criteria

Wilson & Jungner criteria	Argument for SMA
1. The condition sought should be an important health problem	Half of the children affected by the disease die before the age of 2 years old
2. There should be an accepted treatment	Three treatments are showing efficiency And all trials have demonstrated improved efficacy if administered presymptomatically
3. Facilities for diagnosis and treatment should be available	Monogenic diseases due to double deletion of the SMN 1 gene
4. There should be a recognized latent or early symptomatic stage	Floppy Infant Syndrome
5. There should be a suitable test or examination	Genetic Polymerase Chain Reaction (PCR) test is available[17]
6. The test should be acceptable to the population	Early treatment prevents the death of babies or permanent disabilities
7. The natural history of the condition should be adequately understood	The natural history of the disease is published and well documented[18,19]
8. There should be an agreed policy on whom to treat as patients	Scientific publications recommend whom to treat[9,20]
9. The cost of case-finding should be economically balanced	Cost-effectiveness studies show efficiency in all countries where they were performed[21]
10. Case-finding should be a continuing process	SMA is a recessive disease, and NBS should be applied permanently to identify new cases

In many European countries, dried blood samples are stored after the NBS test is performed for research purposes. However, the parents or caregivers need to express their consent (opt-in or opt-out) for the sample to be stored or destroyed, de-identified, used for further scientific purposes, or shared through different research platforms. Secondary use of data would be possible in collaboration with the European biobank infrastructures which can oversee the legal requirements and privacy protection regulations and compliance with GDPR and national legislation. Moreover, as data sharing and re-use may provoke certain concerns related to breach of privacy and stigmatization, it is essential to name the safeguards that are in place pre- and post-procedures. An alignment in executing the NBS programs across Europe would be possible if it is offered as a service respecting the legal provisions and funded publicly, following a specific consent related not only to the immediate benefit for the infant, but also to the research results and possible applications, such as in the identification of novel biomarkers for SMA. Specifically, analyzing the link to disease progression or predicting individual responses to therapy would enable further clarifications on the disease pathogenesis and therapeutic response.

Country-specific pilot initiatives for including a new disease in the national NBS programs

Recently, many countries have expressed their wish to develop a pilot program, often targeting a subset group of their population, as a prerequisite to the national implementation of including a new disease within their NBS program. This practice is certainly useful for the countries introducing a new disease into their screening panel, but for SMA, the pilots conducted in Germany[24] or Belgium[25], as documented in scientific publications, have displayed the inequalities between the citizens of these countries. In Belgium, for example, the Wallonia region implemented screening very quickly at the beginning of 2020, whereas the Flemish part initiated it in 2022. The existence of a country-specific coalition, along with the sustained exchange of knowledge, perspectives, procedures, and strategies, is essential to diminish the possible variations encountered per region of the same country.

Implementation of genetic NBS

In several countries, SMA screening is the first to be carried out through genetic analysis[6,26], and it has raised numerous questions from the local health authorities on both technical approaches and ethical issues.

Patient organizations consulted the learnings and facts presented by the International Society for Neonatal Screening (ISNS), and in 2020, a low level of interest was noted for screening via biological analyses. Consequently, the Alliance has tried to address this issue by organizing an online webinar to get technical answers from the genetic testing manufacturers and, at the same time, to clarify the effectiveness and the risks of false negatives and false positives, and to remove any ambiguity about the eugenic nature of this type of testing[27].

Screening findings

NBS is a fundamental public health service that identifies a potential risk for developing a rare or very rare disease. Within the framework of SMA, as each country produces or tries to produce its own genetic analyses, it becomes almost impossible to have a harmonized analysis across European countries. The number of cases remains insufficient to support a comparative analysis, as the studies developed in different countries often have conflicting results and are based on scattered data. The Rare Barometer developed by EURORDIS-Rare Diseases Europe, under the collaborative Innovative Medicines Initiative (IMI 2 JU) Screen4Care, is an open survey available in 23 languages, which can be accessed by anyone in the world suffering from a rare disease, carriers, or family members of patients. This survey systematically collects the patients' opinions on transversal topics, aiming to translate them into key facts and figures that can be shared with a wider public, including policy and decision makers, thereby ensuring direct patient involvement in exemplifying the topics that matter most to them[28].

The Rare 2030 Survey, initiated by EURORDIS-Rare Diseases Europe to explore the future of rare disease policy and conducted through the Rare Barometer program, received 3,998 responses from all over the world, and highlighted the growing interest among patient organizations to be directly involved in the research process. The report underlines that only 18% of the responders (representing patients living with a rare disease) had been previously involved in the development of treatments and therapies, and one of the reasons causing this is the lack of public/private funding for small populations. Two hundred fifty-two patient representatives expressed their willingness to contribute directly throughout the research process, including helping researchers recruit participants for the clinical trials, reviewing research proposals to ensure an alignment with patients' needs, actively participating as partners or co-investigators, contributing to raising funds, and actively disseminating information about the project research and its results, all of which would bring clear benefits including for SMA patients and their families. Being actively involved in the research process as an equal partner or co-investigator would ensure better dissemination of the available resources, knowledge sharing, and cross-border alignment in multidisciplinary care for SMA patients[29].

Strategies for disease prevention, detection, and treatment represent one of the priorities of the International Consortium on Newborn Sequencing (ICoNS), a global alliance network founded in 2022 by leaders from eight sequencing projects (BabySeq, Genomics England, GUARDIAN Study, BeginNGS, Early Check, Screen4Care, ScreenPlus, and BabyBeyond) that tries through its annual conferences to represent the vision of various international stakeholders on the implementation of NBS as a public health measure[30]. The Alliance brought to attention that a robust application of the NBS programs can be achieved only through a common understanding and coordination among the parties involved. This can be sustained through the development of an effective infrastructure adapted to the population's necessities and harmonized with the industry precompetitive challenges. An ICoNS working group has been tasked with creating a functional mechanism for ensuring documentation consistency, alignment of terminology and metrics, with the final objective of consolidating data results and facilitating the data sharing in the consortium[30,31].

Cost-effectiveness analysis

Because of the high cost of treatment of Evrysdi™, Spinraza™, or Zolgensma™, the issue of the cost of genetic screening and the additional cost of treatment is often not prioritized by the health authorities[4,32]. Several studies analyzed the cost-effectiveness of implementing NBS, based on different case studies. In a study carried out in England, the introduction of SMA screening identified approximately 56 infants suffering from SMA yearly, accounting for 96% of cases, reporting savings of £62,191,531 and quality-adjusted life years of 529, compared with a scenario where NBS would not have been implemented[33]. In the Netherlands, another study highlighted the cost-utility model that estimates the lifetime health impacts and costs for identifying SMA, compared with a pathway without NBS, concluding that in the cohort studied (17 patients), the number of quality-adjusted life-years was approximately 320 years, while the total healthcare cost decreased by €12,014,949[34]. In Belgium, the lifetime cost-effectiveness showed a minimal increased economic cost for healthcare services (€ 6,858,061 *vs.* € 6,738,120), but more quality-adjusted life years, compared with a scenario of "no screening" (40.95 *vs.* 20.34), concluding that screening of SMA, accompanied by early-stage treatment, is more cost-effective and it represents a comprehensive choice from a societal perspective[35].

Newborns with fewer than four SMN2 copies typically receive partial reimbursement for treatment costs from national authorities. In contrast, babies identified with double deletions of SMN1 and 4 or more copies of SMN2, who also face a heightened risk of developing a late-onset form of SMA, have difficulties in obtaining treatment coverage.

Is the solution developed by SMA Europe by creating the alliance to support national organizations reproducible for other rare diseases?

With the development and approval of new therapeutic agents for an increasing number of rare diseases, it is increasingly important to add new diseases to national NBS programs. A number of therapies now exist for Duchenne Muscular Dystrophy (DMD) including gene therapy (Elevidys™), antisense drugs (Ataluren™, Eteplirsen™, Viltolarsen™, Casimersen™), glucocorticoids (Deflazacort™, Vamorolone™), and Histone deacetylase inhibitors (Givinostat™). While the typical age of onset is around 4 years of age, many patients may benefit from early screening to ensure that therapies can be administered to reduce muscle loss[36]. Other examples where early intervention would benefit patients are those with inherited retinal diseases such as Leber congenital amaurosis or retinitis pigmentosa for which Luxturna™ (Voretigene neparvovec) has been approved, but only in patients with enough functioning cells in the retina[37].

The work conducted by the Alliance has demonstrated that an alliance is necessary to accelerate the implementation of NBS for SMA and could be replicated for other diseases, which might contribute to accelerating the expansion of NBS programs in Europe.

The World Health Organization guideline on the "Standards for improving the quality of care for small and sick newborns in health facilities" acknowledges that "every child has the inherent right to life" (Art. 6) and mentions that the goal is to "strive to ensure that no child is deprived of his or her right of access to such health care services" and they should pursue full implementation of this right to diminish infant and child mortality and to develop a preventive healthcare system (Art. 24)[38,39]. The guidance highlights the need to respect, protect, and fulfill the newborns' rights without any discrimination. However, despite sustained international efforts to align different roles and responsibilities and to ensure a transparent and robust model, the processing of requests at local per country or per region levels remains constrained by different factors (absence of registries, qualified personnel, availability and complexity of diagnostic services, healthcare expenditure, lack of clear procedures, *etc.*).

Is it possible to have a European strategic recommendation for inclusion?

In the USA, the Advisory Committee on Heritable Disorders in Newborns and Children recommended a Uniform Screening Panel to ensure the adequacy and uniformity of the evaluation programs, meant to overcome various barriers and establish a national framework for scientific evaluation of conditions, standardization of cases and reporting, better oversight of implementation procedures, data collection, surveillance and re-use, as well as addressing the financial needs to deliver the relevant services to a wider population[40]. In Europe, patient advocacy organizations, with technical and scientific support from the EMA, could propose recommendations for the inclusion of a new pathology in the panel of EU states, but in this case, each state should define clear rules for meeting certain criteria to achieve the expected outcomes.

When faced with a lack of procedure, those wishing to propose the inclusion of a new condition are often confronted with a missing action plan in terms of: who are the stakeholders that can initiate an application? what scientific data and evidence should be provided to endorse it? what is the validation process for inclusion of a new disease in the national panel? and what is the usual timeframe for handling such requests?

An international alignment at the European level for SMA could improve equitable access in the provision of NBS and ensure that newborns receive a qualitative screening for multiple diseases regardless of their nationality, race, or socioeconomic background. Creating an ecosystem that gathers all experiences reported, initiatives, and diagnostic approaches would move forward in the alignment of NBS screening programs, and would diminish the current discrepancies and limitations that exist between countries. However, taking into account the complexity of implementation in real-world settings, with the development of accessible pathways, changes related to ethical and informed consent, data and scientific sharing, including linkage of registries, the process of introducing new conditions in the national screening panels remains difficult at this stage.

Is it necessary to have an innovative interconnected database?

To have more reliable statistical analysis, it will be necessary to gather all results with a pathophysiological description in a single database. The European Reference Networks (ERNs) could play an important role in centralizing the data at the European level. An identical analysis at the level of the other continents would be desirable. Ideally, the interconnection of these data could advance the understanding of the disease and serve as a basis for economic benefit-risk analyses.

CONCLUSION

There are still many areas for improvement to speed up and facilitate the procedures for including a new condition in NBS programs in the European member states. A stronger commitment from countries and healthcare organizations is essential for addressing the bottlenecks experienced by patients and their caregivers. The EU can set the example by endorsing genetic screening as a fair procedure in terms of human rights, and can take part in deciding if the screening techniques can be approved for more than one disease, while EMA can play a role by providing treatment recommendations that have been proved to be successful in the past and showed efficacy when administered presymptomatically. The engagement of different stakeholders, especially the direct involvement of patients and patient advocacy organizations across all NBS-related activities, remains a critical point in public health discussions, not limited just to ethical or societal concerns, but also in connection with the advancement and harmonization of equitable access to screening techniques and treatment options. Learnings from SMA therapy development and the introduction of NBS in SMA in a consistent and European-wide manner can serve as a model for additional rare diseases in the future.

DECLARATIONS

Authors' contributions

Manuscript concept: Ouillade MC, Tătaru EA
Contributed to the first and subsequent drafts: Tătaru EA, Ouillade MC
Contributed to multiple critical revisions: Tătaru EA, Chan CH, Pearce DA

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Pearce DA is an Editorial Board member of *Rare Disease and Orphan Drugs Journal*, while the other authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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