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White Paper on the Inclusion of Spinal Muscular Atrophy in Newborn Screening

Coalition for the Newborn Screening of Spinal Muscular Atrophy

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Executive Summary

Spinal Muscular Atrophy (SMA) is the most common genetic cause of mortality during infancy, with a death rate of one in 6,000-10,000 live births. (Markowitz, et al., 2012) In its most serious and common form – SMA Type I – the loss of motor functions accelerates during the first few months of life. Without treatment, those affected by the disease never develop head control capacity, nor the ability to sit or crawl, eventually losing the capacity to swallow or breathe unassisted. Those suffering from SMA Type I have a 90% chance of death by their second birthday. (Park, et al., 2010)

With the emergence of the new disease modifying therapies, some of which have already been approved at a Portuguese and European level, the prognosis of those with SMA has been altered. The results of clinical studies demonstrate that these new therapies are most efficient in the pre-symptomatic phase, or immediately after the manifestation of the first symptoms. (Dangouloff, et al., 2019)

This change in paradigm, verified by the emergence of the new therapies and the studies that show their efficiency when applied during the pre-symptomatic phase (like, for example, one conducted in two German states which led to a favourable conclusion regarding the Newborn Screening of SMA) have led to a movement across Europe for the Newborn Screening of SMA. In 2020, the *European Alliance for Newborn Screening in Spinal Muscular Atrophy* was founded – an alliance composed of associations that represent those suffering with SMA (at both the national and international levels, like EURORDIS and SMA Europe), academic and governmental institutions, among others – all with the objective of guaranteeing that SMA will be integrated into the Newborn Screening programmes, all across Europe, by 2025. (European Alliance for Newborn Screening in SMA, 2020; European Alliance for Newborn Screening in SMA, 2021)

This White Paper will analyse and assess the extent to which the Newborn Screening is a viable, beneficial, and efficient strategy in the management of SMA, in terms of the impacts on patients, their families, the national healthcare system, and society as a whole – according to five main axes:

1) Importance of an Early Diagnosis and Treatment for Spinal Muscular Atrophy

The Early diagnosis and subsequent early treatment of Spinal Muscular Atrophy is essential in positively altering the prognosis of the disease.

- SMA is a genetic disease in which the timing of the diagnosis and beginning of treatment is essential, especially as the “window of opportunity” in which the existing disease modifying therapies are most effective – the pre-symptomatic phase – is extremely short. (European Alliance for Newborn Screening in SMA, 2021)

- Currently, there is an average delay, from the manifestation of the first symptoms to the diagnosis, of approximately four weeks to six months for patients with SMA Type 1. For Type II patients, the average delay is of approximately 14.3 months, and approximately 43.6 months for Type III patients. (Lin, et al., 2015)
- The results from clinical trials of the approved disease modifying therapies demonstrate significant impacts in the development of SMA patients when treated in the pre-symptomatic phase, as compared to those treated after the manifestation of symptoms. (Dangouloff, et al., 2019)

2) Relevance of the Newborn Screening of Spinal Muscular Atrophy

The Newborn Screening of Spinal Muscular Atrophy is an efficient strategy in the early identification and diagnosis of the disease in patients, as well as in the increase of our understanding of the disease.

- Newborn screening programmes have the objective of identifying patients in risk and, by doing so, offering the opportunity to intervene in quicker manner, either in terms of symptom management or symptom prevention. (European Alliance for Newborn Screening in SMA, 2021)
- The universality of the newborn screening programmes, as well as their well-developed operational structure and the fact that they are generally accepted by the parents, makes them an efficient strategy for the pre-symptomatic diagnosis of SMA. (Jędrzejowska, 2020)
- The newborn screening of SMA would contribute to more accurate information regarding the incidence and prevalence rates, thus leading to better planning and an improvement in the allocation of resources for healthcare, in general, and the management of SMA. (Dangouloff, et al., 2019)
- From a pedagogical point of view, the newborn screening of SMA would contribute to the increase of the general awareness of parents, and society as a whole, to the disease. (European Alliance for Newborn Screening in SMA, 2021)
- In terms of prevention, the screening would also result in the referral of families to genetic counselling consultations, which are particularly relevant as this is a disease with a 25% risk of recurrence in future pregnancies.

3) Cost-Efficiency of the Newborn Screening

The inclusion of Spinal Muscular Atrophy on the panel of screened diseases is a viable strategy, provided that the possible impacts on the Portuguese National Newborn Screening Programme are taken into account.

- Considering the operational structure already built into the newborn screening programme, adding SMA to the list of screened diseases would, at the most, require small adaptations to the testing procedures.

- Both the additional economic cost of carrying out the test – ranging from 3€ to €5 per test performed (European Alliance for Newborn Screening in SMA, 2021) – and the cost of confirming a new positive case – an average of 1,817€ PPP (purchasing power parity) (Burgard, et al., 2012) – are known and documented.
- Taking into account the data and information from the conducted pilot studies, it is possible to identify the primary operational impacts of the inclusion of SMA on the panel of screened diseases, namely in terms of meeting the requirements regarding the informed consent and the referral of screened patients (and their families) to genetic counselling consultations, treatment centres, and possible psychological support. (Dangouloff, et al., 2019)

4) Costs and Benefits of Screening and Treating Early

The newborn screening of Spinal Muscular Atrophy, and its subsequent early treatment, presents a potentially positive cost-benefit relationship for patients, their families, the healthcare system, and society.

- The already approved disease modifying therapies carry significant costs, making it necessary to analyse the costs throughout the life of the patient, as well as of the benefits of the treatments and their early application, so that decisions can be made based on complete and reliable data. (Dangouloff, et al., 2019)
- The *cost-utility analyses* for the disease modifying therapies indicate that in the cases of rare diseases, like SMA, several other factors must be considered, such as: the lack of effective alternative treatments, the ethical and social implications of the treatment, and the fact that, despite the high cost-per-patient of the treatments, the actual budgetary impact is reduced due to the small number of affected patients.
- Considering the existing models for carrying out *cost-utility analyses* for the newborn screening for rare diseases, an analysis published based on data from the US concludes that the scenario in which the newborn screening and subsequent treatment occur is preferable to the current situation, in which patients are treated only after the manifestation of the symptoms. (Jalali, et al., 2020) Another study, conducted by the University of Groningen (currently unpublished) for the Dutch context, reaches a similar conclusion - having quantified the implicit benefits of tracking and treating SMA early (i.e., the mitigation of a decrease in the economic productivity of parents of affected children), they were able to calculate the annual amount the healthcare system would save as compared to how SMA is currently handled, without newborn screening.
- *Cost-utility analyses* for health interventions aimed at rare diseases cannot be carried out based on parameters used to assess interventions for more common diseases (such as the cost-effectiveness threshold, defined as the willingness to pay determined by each country for health interventions).

Parameters used for common diseases simply do not have the capacity to assess all relevant effects of a new health intervention, especially in terms of added value to society. (Lakdawalla, et al., 2018)

5) Importance for the Families

The newborn screening of Spinal Muscular Atrophy, and the subsequent treatment of patients in the pre-symptomatic phase of the disease, alters the perspectives of families with regards to the disease and their futures, and diminishing potential destabilizing effects within the family dynamics.

- The newborn screening of SMA will allow patients to be identified immediately after birth, preventing delays in the diagnosis, that may arise from the parents' lack of access to resources or information that would permit them to identify the need for urgent medical intervention, after the manifestation of the first symptoms. (European Alliance for Newborn Screening in SMA, 2021)
- The pedagogical component is another important element of the newborn screening of SMA, as it allows for the awareness and preparation of all involved in the process and prevents the psychological strain that is inherent to the unknown. (Dangouloff, et al., 2019)
- The early diagnosis also has significant impacts on the relationship between parents and their affected children – namely in the later manifestations of the disease, which will not be immediately targeted by the disease modifying therapies (Glascock, et al., 2018), a diagnosis provides the parents with the necessary awareness and better understanding of the limitations in their child's development, preventing situations of confusion and even guilt.
- Knowing beforehand allows the parents to organize and adjust their lives to better respond to the needs of their affected child. (European Alliance for Newborn Screening in SMA, 2021)
- A diagnosis of SMA is always a painful experience for both the patients and their respective families. As such, the best scenario is one that occurs when it is possible to avoid or at least mitigate the damage inherent to the disease – especially when compared to the current context, where the disease is treated only after the damage strikes and is irreversible. (European Alliance for Newborn Screening in SMA, 2021)
- Surveys to adults with SMA in the UK (types II, III, and IV), and to their families, show that the majority of both patients (74.4%) and families (70%) support newborn screening of SMA. (Boardman, et al., 2017; Boardman, et al., 2018)

Preface: Spinal Muscular Atrophy – from the Discovery to the Treatment

Whenever science advances, however little, an enormous step is taken for all of humanity. Whenever these advances are aimed at any one of the more than 7,000 identified rare diseases, the world nurtures renewed hope for those who suffer from them and for those who live with them.

The discovery of new scientific leads, which lead to new treatments, has as its objective the increase in life expectancy, or an improvement in the quality of life. As Spinal Muscular Atrophy (SMA), especially in its Type I form, is the leading genetic cause of infant death worldwide, it is vital we find new paths to decrease its prevalence, as well as cultivate hope and trust in the families where the disease was flagged and diagnosed.

The initial diagnosis of SMA takes on the most important role in the process. Aware of its value and having accompanied the evolution and emergence of new treatments, the *Associação Portuguesa de Neuromusculares* (*APN* – Portuguese Association of Neuromuscular Diseases), as well as the whole scientific community, want SMA patients diagnosed as early as possible. In Portugal, similar to what has been happening across Europe and indeed, the rest of the world, people linked to all areas of health and genetics research, both within the private and public sectors, are interested in the emerging importance of early diagnosis, joining the various movements, patient associations, and other coalitions, all of which aim to demonstrate the advantages of newborn screening in all its aspects.

Given our drive to be closer to the entire international community and involved in the processes that are taking place simultaneously in several countries, we have joined *SMA Europe*. In the recent months and within this entity (that aggregates the vast majority of European partners representing SMA), the *European Alliance for Newborn Screening in Spinal Muscular Atrophy* was born. Alongside them, we will monitor and share important data that will allow for a broader approach and discussion on the aspects considered most relevant for the decision-making process and their respective impact.

With the goal of introducing SMA into the National Program of Newborn Screening, we gathered all the relevant information that could add clarification to the ongoing scientific process. To debate all the related elements in an adequate way, we surrounded ourselves with a panel of experts – experienced professionals, with careers dedicated to healthcare and social causes, who did not pass on the opportunity to add their contribution to this initiative, which will serve as a complement to the proposal presented by the *Sociedade Portuguesa de Estudos de Doenças Neuromusculares* (*SPEDNM - Portuguese Society for Studies in Neuromuscular Diseases*) to the *Instituto Nacional de Saúde – Dr. Ricardo Jorge* (*INSA – National Health Institute Dr. Ricardo Jorge*).

The most sensitive topics surrounding the issue were quickly identified. Some of these concerns included the type of test to be carried out for diagnosis, the high cost of medications, informed consent, the training of professionals at various health centres, the information to be provided to parents, among others. The benefits, however, far outweigh these costs – the increases in quality of life for both patients and their families, and of the quality of service of the hospitals in which they are to be treated, are frankly immeasurable.

Aware of the difficulties in assessing and approving a process of this nature, and in the legislative authorization that is need for the introduction, in Portugal, of a pilot-project of this complexity, we are certain that a pre-symptomatic diagnosis like the one proposed, offered to the entirety of the population, is the best tool in lowering the terrible infant mortality rate already mentioned.

Prevention presents itself as a necessity.

To treat will, inevitably, be the way forward.

Finally, on behalf of all of those affected by SMA, the APN gratefully acknowledges all those involved in the debate of the different aspects surrounding this issue. A special thanks to LOYAL ADVISORY that, in a very professional and deeply committed way, produced all the summaries and structured the process, that we hope to see implemented, all to ensure the dream of a better life for all current and future patients with SMA, regardless of their type.

Joaquim Brites

President of APN – Associação Portuguesa de Neuromusculares

Spinal Muscular Atrophy – a First Person Account

Reflecting on our existence and on the nature of our circumstances can be a deep exercise in solitude.

It was on December 5th, 1982, that the eldest of the daughters, grandchildren, and nieces was born. Every heart was focused on that tiny baby that, at just nine months old, began to exhibit the symptoms of a Type II Spinal Muscular Atrophy (SMA). I cannot speak of the anguish that my parents felt at the time because, naturally, I have no memory of it. I can, however, tell you that they taught me that courage and dedication can also be genetic. They never tried to hide anything from me – for as long as I can remember, I have always known that SMA would shape my life. I adapted to the weakness of my muscles and quickly found the best that lived within me – from my independence to my resilience, and to my ceaseless curiosity. This constant adaptation is like a reminder that shows us a closed room without light.

Let us not delude ourselves into thinking that this disease does not define me – its vicissitudes have implications on my daily decisions and above all, serious implications for a life projection, in the short, medium, or long(!) term. The challenge of a SMA diagnosis begins, without a doubt, with the parents. How they react influences everything in the life of a child suffering a disease that puts them constantly between 'the sword and the wall.' It was my parents who never excluded me from any activity. By including me in the family and in all social activities, and by stressing the importance of education, they instilled in me the belief that while SMA certainly shaped our lives, it did not get to decide them for us. Living with a diagnosis of a rare disease is indeed a constant daily adaptation, but it should never mean resignation. Never. I can live with fear, with "no," and "I can't do it," and "it's impossible", but I will not live within those doubts. The disease exists within me, but the trick is to live beyond its reach, because inside me there is also joy, love, strength, and courage to see what is yet to come.

I have always been aware of my limitations. First, a different walk – slower and slower steps until I had to stop walking altogether, because of the fatigue and the effort, that were far too much to handle. I then switched to an electric wheelchair. The multidisciplinary team accompanying me had wanted me to use a manual wheelchair, but I refused; I would remain too dependent to move (though in my head, I was sure I would fly!). I refused the manual wheelchair at the age of 9, after a spinal surgery, and the next natural step was to conquer the electric wheelchair. This was my biggest achievement, but it was bittersweet as I watched my mother cry while I completed my chair-driving training with my father. I am pleased to say that since then, visits to orthopaedics offices have evolved into more positive ones.

However, I shall note here that there remains a need to improve the state's financing of such support products. It is an urgent matter that they become aware that rare diseases have

extremely specific needs. It is urgent to accept that these rare diseases exist, and it is necessary to understand that patients with such diseases should not have lives of never-ending challenges. There is nothing like the despair of waiting for a supportive product; they are what our quality of life depends on. It is on these products that our freedom rests. These products provide our dreams, our autonomy. They give our muscles relief and our families a rest, time to better spend with the people we love, the confidence to say “yes,” “it’s possible,” “of course!” Should we continue to accept that an electric wheelchair is delivered when we are no longer able to verticalize? Will we have to continue fighting for enshrined rights?

Rehabilitation therapies have always been part of my routine. I travelled more than 60 kilometres a day to do physiotherapy and hydrotherapy for years at a time. Every day after school, came rain or shine, I went, as that was the clinic best prepared to receive me. I still remember the pain I went through, the nights I slept with orthopaedic splints or braces to safeguard my spine and subsequent respiratory function. I knew that despite all of this, I still had homework to do when I got home from physiotherapy, because in that way I was no different from my peers. I am well aware of the many times my sisters were left in the care of my grandparents, because my mother could not be in all fronts. Even after when I started a higher education degree and moved to a different city, my mother came with me. My sisters? Left again to the care of others. I feel they were abandoned by my mother because of me. I still feel this guilt.

I must mention that for over three decades I have had a fantasy where I wake up one day and, for even a moment, I do not feel heaviness, fatigue, or pain. It is a fantasy of comfort. It is this fantasy that drives me, that forces me to double my efforts, because it is not just for me, but for many others. The flight I dream of is not possible without the constant support of those who have always been with me; in my case, my parents and two sisters. But this flight also brings me frustration that I attempt to camouflage, as not to increase the anxiety of those who love me. I will never know to what extent my illness affects the lives and decisions of my sisters, for example, because they will never tell me. I know they are around and there for me, but I do not know at what cost. There are things left unsaid where love is concerned. I have no idea how many times they have went out with me even though they were upset, and I do not know what will happen when my parents can no longer be my primary caregivers. Is it right to place this responsibility on my sisters’ shoulders? Is it right for their lives to always be shaped by mine?

I do not know what will happen, although I have tried to guess it several times. I know that SMA is unpredictable, but I must always be one step ahead of it. I got used to anticipating situations; it has long been part of the process. I grew up knowing that one day I would lose the capacity to walk, while on another I would not be able to lift my arms, and on yet another I might choke on a crumb and fall into distress. Perhaps it is this awareness that makes unhappiness sting less. Even so, I am certain that I will live as long as I can, aware that I face

difficulties with courage, determination, frustration and at times tears, but that I will never give up on living with joy and pursuing achievements.

Ana Isabel Gonçalves

Vice-President of APN – Associação Portuguesa de Neuromusculares

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1. Introduction

Spinal Muscular Atrophy (SMA) is the most common genetic cause of mortality during infancy, with a death rate of one in 6,000-10,000 live births. (Markowitz, et al., 2012) In its most serious and common form – SMA Type I – the loss of motor functions accelerates during the first few months of life. Without treatment, those affected by the disease never develop head control capacity, nor the ability to sit or crawl, eventually losing the capacity to swallow or breathe unassisted. Those suffering from SMA Type I have a 90% chance of death by their second birthday. (Park, et al., 2010)

With the emergence of the new disease modifying therapies, some of which have already been approved at a Portuguese and European level, the prognosis of those with SMA has been altered. The results of clinical studies demonstrate that these new therapies are most efficient in the pre-symptomatic phase, or immediately after the manifestation of the first symptoms. (Dangouloff, et al., 2019)

This change in paradigm, verified by the emergence of the new therapies and the studies that show their efficiency when applied during the pre-symptomatic phase (like, for example, one conducted in two German states which led to a favourable conclusion regarding the Newborn Screening of SMA) have led to a movement across Europe for the Newborn Screening of SMA. In 2020, the *European Alliance for Newborn Screening in Spinal Muscular Atrophy* was founded – an alliance composed of associations that represent those suffering with SMA (at both the national and international levels, like EURORDIS and SMA Europe), academic and governmental institutions, among others – all with the objective of guaranteeing that SMA will be integrated into the Newborn Screening programmes, all across Europe, by 2025. (European Alliance for Newborn Screening in SMA, 2020; European Alliance for Newborn Screening in SMA, 2021)

This White Paper will analyse and assess the extent to which the Newborn Screening is a viable, beneficial, and efficient strategy in the management of SMA, in terms of the impacts on patients, their families, the national healthcare system, and society as a whole – according to five main axes:

1) **Importance of an Early Diagnosis and Treatment of Spinal Muscular Atrophy –** *The Early diagnosis and subsequent early treatment of Spinal Muscular Atrophy is essential in positively altering the prognosis of the disease.*
2) **Relevance of the Newborn Screening of Spinal Muscular Atrophy –** *The Newborn Screening of Spinal Muscular Atrophy is an efficient strategy in the early identification and diagnosis of the disease in patients, as well as in the increase of our understanding of the disease.*
3) **Cost-Efficiency of the Newborn Screening –** *The inclusion of Spinal Muscular Atrophy on the panel of screened diseases is a viable strategy, provided that the*

possible impacts on the Portuguese National Newborn Screening Programme are considered.

4) **Costs and Benefits of Screening and Treating Early –** *The Newborn Screening of Spinal Muscular Atrophy, and its subsequent early treatment, presents a potentially positive cost-benefit relationship for patients, their families, the healthcare system, and society.*
5) **Importance for the Families –** *The Newborn Screening of Spinal Muscular Atrophy, and the subsequent treatment of patients in the pre-symptomatic phase of the disease, alters the perspectives of families with regards to the disease and their futures, and diminishing potential destabilizing effects within the family dynamics.*

2. Methodology

The present document is based on the contributions of experts from different fields of knowledge – from Paediatrics, Neurology, Neuropediatric, Neonatology, Human Genetics, namely Medical Genetics and Laboratorial Genetics, Bioethics, Child Welfare – as well as a long process of research and compilation of information from scientific publications. The process was structured in three phases, between the months of December 2020 and May 2021, namely:

1) Individual meetings with specialists from the aforementioned fields, which served to gather their takes on the topic.
2) A literature review process, which allowed us to collect information that would provide answers to the identified issues and challenges.
3) Working group meetings (four, between January and May of 2021), where the five main axes were discussed.

3. Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA) is responsible for the highest mortality during infancy, in terms of genetic diseases, and is characterized clinically by the progressive loss of spinal cord motor neurons, resulting in severe hypotonia, progressive skeletal muscular atrophy, and the increase of generalized muscle weakness that, in its most severe form, leads to death before the child reaches its second birthday. It is an autosomal recessive disease caused by the homozygous deletion or mutation of the *SMN1* gene (*Survival Neuron Motor* 1). Its phenotype is modified by other genes, being the *SMN2* the most important, whose copy number is the biggest determinant, or modifier, of the severity of the disease. (Lunn, et al., 2008) The calculated incidence is one patient in every live 6,000 to 10,000 live births, with an

estimated rate of one to two healthy carriers for every 100 individuals. (Markowitz, et al., 2012)

3.1. Clinical Onsets

SMA's most common forms are divided, in the literature, into four clinical types, based on the patient's age at the time of the onset of symptoms, and on the motor functions affected: a) Type I – the most severe and precocious manifestation of the disease; b) Type II – the intermediate onset; c) Type III – less severe and later onset; and d) Type IV – manifesting itself during adulthood. (Russman, 2007) Most specialists tend to define the type of clinical manifestation according to the level of function that the patient achieves – for example, sitting or walking. (**See Table 1**)

Table 1 – Clinical classification of Spinal Muscular Atrophy

Types of SMA	OMIM No.	Age of Onset	Maximum motor function achieved	Average death age
I	253300	< 6 months	Do not achieve sitting capacity	< 2 years
II	253550	6–18 months	Sitting independently	> 2 years
III	253400	>18 months	Stand up and walk	Adulthood
IV	271150	Adulthood (2nd or 3rd decade)	Walk during adulthood	Adulthood

Source: *OMIM Online Mendelian Inheritance in Man* (OMIM®)

Type I SMA (also known as Werdnig-Hoffman disease) is the most common and serious manifestation of the disease, accounting for approximately 60% of all positively diagnosed patients. (Verhaart, et al., 2017) It manifests before the child's six months of age and, in 90% of the cases, results in death before their second birthday. It affects the development of the motor functions of the patients, with those afflicted losing control over head support and movement, never achieving the capacity to sit up unsupported, and suffering diminishing capacity of sucking, swallowing, and airways protection, increasing the risk of aspiration pneumonia and inevitably leading to respiratory failure – a common cause of morbidity and mortality in patients with Type I SMA. (Lunn, et al., 2008)

Type II SMA is the intermediate form of the disease, in terms of the severity of the symptoms, which manifest between seven and 18 months of age. The patients have the capacity to sit without support, with a few able to stand up with help from splints supporting the legs, but none walk independently, and develop a severe and progressive scoliosis. Poor swallowing and low muscle mass tend to prevent patients from gaining weight. Breathing difficulties may arise, with respiratory failure being the leading cause of death in patients with Type II, usually during adolescence. (Lunn, et al., 2008)

Patients with Type III SMA (also known as Kugelberg-Welander) typically achieve all major motor function milestones, such as walking independently. Some eventually lose the capacity

to walk independently and require the assistance of a wheelchair during childhood, while others maintain the ability and develop productive lives, with only minor manifestations of muscle weakness. (Lunn, et al., 2008)

Finally, patients with Type IV SMA typically see their symptoms manifest between the second and third decade of their lives, with a milder onset in terms of motor impairment, without any respiratory or nutritional problems, allowing patients to continue walking through adulthood. (Lunn, et al., 2008)

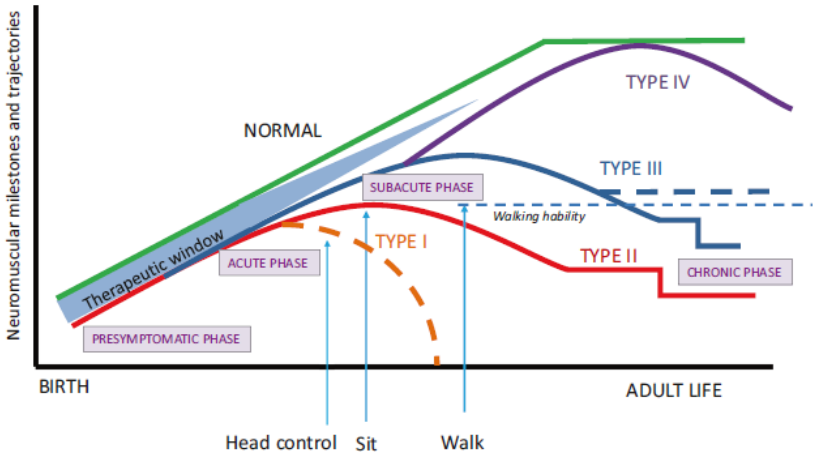
The prognosis of survival in each of the four types described above is ultimately dependent on the involvement of the respiratory muscles, and not just on the degree of weakness of the skeletal muscles, although they often occur simultaneously. The careful clinical evaluation of each case is critical, in order to assess the severity, potential prognosis (both in vital and functional terms), and appropriate interdisciplinary management of each individual case.

3.2. Patient Treatment and Follow-Up

The treatment and clinical follow-up of patients with SMA has advanced significantly over the last two decades. This is mainly due to the improvement of proactive standard-of-care measures, that aim to minimize the delay from prognosis to early intervention and to optimize the quality of life and independent functionality, and to the development of innovative pharmacological disease modifying therapies. (Serra-Juhe, et al., 2019; Mercuri, et al., 2018)

Standard-of-care and support measures include, above all, physical therapy, respiratory aid, and nutritional support. However, these measures do not modify the natural progression of the disease. As a result, without treatment, Type I patients see their motor functions deteriorate, and become increasingly dependent on ventilators until the end of their lives. In less severe manifestations of the disease, patients reach stability in their motor trajectories, only later observing the decline in their functions (as can be seen in **Figure 1**).

Figure 1 – Motor Trajectories, from birth, in all types of SMA. The orange dashed line represents the stage at which patients require respiratory intervention. The thick blue dashed line represents Type III cases that maintain walking ability.



Source: *Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review* (Verhaart, et al., 2017)

The disease's prognosis, and the patients' own perspectives, change with the emergence of the innovative disease modifying therapies aimed at the treatment of SMA – with results showing that, through the prevention of the loss of motor neurons, they successfully alter the natural evolution of the disease, drastically reducing the mortality rate and resulting in a significant increase in the quality of life of the patients. (Dangouloff, et al., 2019)

There are three disease modifying therapies available to patients with SMA, with the *oligonucleotide antisense nusinersen* approved and reimbursed in Portugal (Infarmed; Administração Central do Sistema de Saúde, 2019), and both the gene replacement therapy *omnasemnogene abeparvovec* and *risdiplam* already approved by the European Medicines Agency (European Medicines Agency, 2020; European Medicines Agency, 2021). Encouraging results from phases II and III of the clinical trials point to the possibility of more therapeutic options becoming available in the near future. (Messina, et al., 2020)

The concept of SMA as an untreatable disease evolved fundamentally with the emergence of these therapies, and with the results of the patients treated. However, these therapies also carry significant costs, raising the question of the approach and timing of administration that will yield the best possible results for treated patients – as SMA is a neurodegenerative disease that leads to the death of motor neurons, it is essential that treatments start as early as possible, preventing any irreversible damage to the motor neurons and, consequently, the manifestation of any symptoms. For this to happen, patients must be identified, diagnosed and treated early.

The availability of these therapies, and the need to begin the treatment before the loss of motor neurons (especially in Type I patients, in which 90% of motor neurons die before the patient is six months old), has led several countries to begin studying the feasibility of carrying out the newborn screening for SMA.

In the European context, newborn screening for SMA has already been approved and is awaiting implementation in the Netherlands, Germany, Norway, Serbia, Poland, and Slovenia, with pilot studies being carried out in Italy, Germany, Spain, and Belgium. Pilot studies in the UK and France are expected to start soon. (SMA Newborn Screening Alliance, 2021)

Also in the European context, the *European Alliance for Newborn Screening in Spinal Muscular Atrophy* was founded – a coalition made up of associations that represent patients (either at a national level – such as *APN* – or at an international level – such as *EURORDIS* and *SMA Europe*), scientific societies, academic institutions, government institutions, non-profits, as well as the pharmaceutical and technological innovation in healthcare industries – all with the objective of, through the cooperation with government entities of the various European countries, ensuring that all SMA patients are diagnosed and treated in a timely manner through newborn screening of SMA. (European Alliance for Newborn Screening in SMA, 2020; European Alliance for Newborn Screening in SMA, 2021)

4. Newborn Screening

Newborn Screening programs are (non-mandatory) preventative healthcare programs that promote the screening of newborns for rare treatable conditions, that threaten the life or long-term health of a newborn. The objective of these programs is to identify the patients at risk as soon as possible, before the symptoms appear, confirm the diagnosis, and proceed with early clinical intervention (in the pre-symptomatic phase), in order to prevent the onset of these pathologies, ensuring the well-being of the newborn and promoting a life with better quality.

4.1. Procedure

The procedure (risk-free) is performed between the first 24 hours and seven days of life of a newborn. The methodology consists of a prick on the heel of the newborn, in order to collect a sample, consisting of a few drops of blood, onto an absorbent card – known as the Guthrie card. The sample is then analysed in a laboratory to assess the possibility of the newborn suffering from one of the conditions tracked. A second blood sample may be needed later for confirmation purposes and the reason for this is explained to the parents.

4.2. Criteria for Screening

A pathology may be screened at birth as long as it meets the ten requirements established by Wilson and Junger (Wilson, et al., 1968; Andermann, et al., 2008):

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

4.3. Portuguese Context

Created in 1979, the *Programa Nacional de Rastreio Neonatal* (*PNRN – National Newborn Screening Program*), known in Portuguese as the “*teste do pezinho*” (*little foot test*), has as its primary objective the newborn screening of rare treatable diseases, to prevent their evolution through the pre-symptomatic diagnosis and early implementation of the appropriate treatments.

The *PNRN* is a multidisciplinary program and has as a common objective the well-being of the newborn, controlling the pathology detected in the pre-symptomatic phase, and uniting in harmony the maternity hospitals, primary healthcare centres, treatment centres, and the screening laboratory. The program aims, through the early screening, to enable screened patients to receive proper monitoring and treatment, thus being able to integrate into society with a type of life similar to their peers.

Congenital hypothyroidism, cystic fibrosis, and 24 other hereditary and metabolic diseases (see **Table 2**) are systematically screened, with an average age of treatment initiation of 10 days. Since the beginning of the program, more than 3,890,677 newborns have been screened and 2,217 patients have been diagnosed, with an overall incidence rate of 1 per 1,123 for the 26 pathologies screened. The national coverage rate is close to 100%, constituting an excellent indicator of the population’s acceptance of this national public health program. (Vilarinho, et al., 2020)

Table 2 – Panel of screened diseases within the *PNRN*.

I. Congenital Hypothyroidism		
II. Cystic Fibrosis		
III. Hereditary Metabolic Diseases	Amino Acid Disorders	Phenylketonuria / Hyperphenylalaninemia
		Type I Tyrosinemia
		Types II/III Tyrosinemia
		Maple Syrup Urine Disease (MSUD)
		Classical Homocystinuria
		Hypermethioninemia (DEF. MATI/III)
	Urea Cycle Disorder	Type I Citrullinemia
		Argininosuccinic Aciduria
		Hyperargininemia
	Organic Acidurias (Organic Acid Disorders, OADs)	Propionic Acidemia (PA)
		Methylmalonic Acidemia (Methylmalonyl-Coenzyme A mutase deficiency)
		Isovaleric acidaemia (IVA)
		3-Hydroxy-3-Methylglutaric Aciduria (HMG)
		Type I Glutaric Aciduria (GA1)
		3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC Deficiency)
		Malonyl-CoA Decarboxylase Deficiency
	Mitochondrial Fatty Acid Oxidation Disorders	Short Chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency (SCHAD)
		Medium-Chain acyl-CoA Dehydrogenase (MCAD) Deficiency
		Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency
		Very long-chain acyl-CoA Dehydrogenase Deficiency (VLCADD)
		Carnitine Palmitoyltransferase I (CPT I) Deficiency
		Carnitine Palmitoyltransferase II (CPT II) Deficiency
		Multiple Acyl-CoA Dehydrogenase Deficiency (MADD / Glutaric Aciduria Type II)
		Carnitine Uptake Defect (CUD)

Source: *Relatório 2019 - Programa Nacional de Rastreio Neonatal* (Vilarinho, et al., 2020)

4.4. European and Global Context

The number of screened diseases in the newborn screening program of each country varies taking into account different factors, from the financing model of the healthcare system, autonomy in the definition of regional/state public policies (for example, in the United States, each state has autonomy over its newborn screening program), among others.

In the European context, 39 pathologies are screened, with Italy being the country that screens the most pathologies –a total of 35 diseases (4 of them in the scope of ongoing pilot studies) – and Kyrgyzstan and Moldova in last place in this regard, with each country screening for one disease only. (Loeber, et al., 2021) (see **Table 3**)

Table 3 – Number of screened diseases per country (Europe). P = Diseases screened in the scope of ongoing pilot studies.

Country	Number of Screened Diseases
Italy[1]	35 = 31 + 4P
Spain[1]	33 = 7 + 26P
Poland[1]	29 = 27 + 2P
Ukraine[1]	28 = 4 + 24P
Iceland[1]	28 = 27 + 1P
Hungary[1]	27 = 26 + 1P
Slovakia[1]	27 = 25 + 2P
Austria[1], Portugal[2]	26
Macedonia[1]	26 = 25 + 1P
Sweden[1]	25
Norway[1]	23
Finland[1]	22 = 21 + 1P
Netherlands[1]	22 = 20 + 2P
Uzbekistan[1]	21 = 2 + 19P
Denmark[1], Israel[1], Slovenia[1]	20 = 19 + 1P
Belgium[1]	20 = 17 + 3P
Estonia[1]	19
Germany[1]	19 = 17 + 2P
Czech Republic[1]	18
Switzerland[1]	10
United Kingdom[1]	9
Croatia[1], Ireland[1]	8
France[1], Latvia[1], Russia[1], Turkmenistan[1]	6
Azerbaijan[1], Luxembourg[1], Turkey[1]	5
Greece[1], Lithuania[1], Romania[1]	4
Bulgaria[1], Georgia[1], Malta[1], Serbia[1]	3
Kazakhstan[1]	3 = 2 + 1P
Armenia[1], Belarus[1], Bosnia and Herzegovina[1], Cyprus[1], Montenegro[1]	2
Kyrgyzstan[1], Moldova[1]	1
Albania[1], Kosovo[1], Tajikistan[1]	No Available Data

Sources: [1]*Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010* (Loeber, et al., 2021); [2] *Relatório 2019 - Programa Nacional de Rastreio Neonatal* (Vilarinho, et al., 2020)

5. Proposition – The 5 Axes of Analysis

The present document assesses to what extent the proposition below is verified and of an accurate nature:

"The inclusion of Spinal Muscular Atrophy in the Portuguese National Newborn Screening Program disease panel represents an added-value for the patients, their respective families, the healthcare system and Society."

The aforementioned proposition focuses on the inclusion of SMA in the panel of screened diseases of the Portuguese newborn screening program and is grounded by the following five axes of analysis:

1) **Importance of an Early Diagnosis and Treatment of Spinal Muscular Atrophy.**
2) **Relevance of the Newborn Screening of Spinal Muscular Atrophy.**
3) **Cost-Efficiency of the Newborn Screening.**
4) **Costs and Benefits of Screening and Treating Early.**
5) **Importance for the Families.**

5.1. Importance of an Early Diagnosis and Treatment of Spinal Muscular Atrophy

"The Early diagnosis and subsequent early treatment of Spinal Muscular Atrophy is essential in positively altering the prognosis of the disease."

In the field of rare diseases, the early diagnosis allows the patients to plan and to access preventive and symptom management measures, as well as treatments (when available). In the cases of the diseases for which there are still no treatments, the argument that early diagnosis allows for better preparation of patients for when the disease arrives, as well as better medical monitoring, has gained strength in recent years, due to advances in the scientific knowledge and evolution of the standards-of-care. However, this argument also raises important ethical and economic aspects that should be considered, such as the psychological burden on patients and their families. (European Alliance for Newborn Screening in SMA, 2021)

Therapeutic advances in the field of SMA demonstrate that it is a rare disease in which the moment of diagnosis is essential. Early diagnosis allows for the detection of the disease at a time when the patient's development is not yet compromised, resulting in access to treatment in the pre-symptomatic phase of the disease, or right after the onset of the first symptoms – a phase in which the available treatments present greater effectiveness.

In most cases, the newborns detected are still in the asymptomatic stage of the disease – an observation supported by the recent pilot studies of the newborn screening of SMA. In Type I SMA, the symptoms appear on average at 2.5 months of age, with diagnosis occurring on average at 6.3 months of age – an average delay in diagnosis of between four weeks and six months. In the case of Type II SMA, the average delay is 14.3 months, and in the case of Type III SMA, the average delay is 43.6 months. (Lin, et al., 2015)

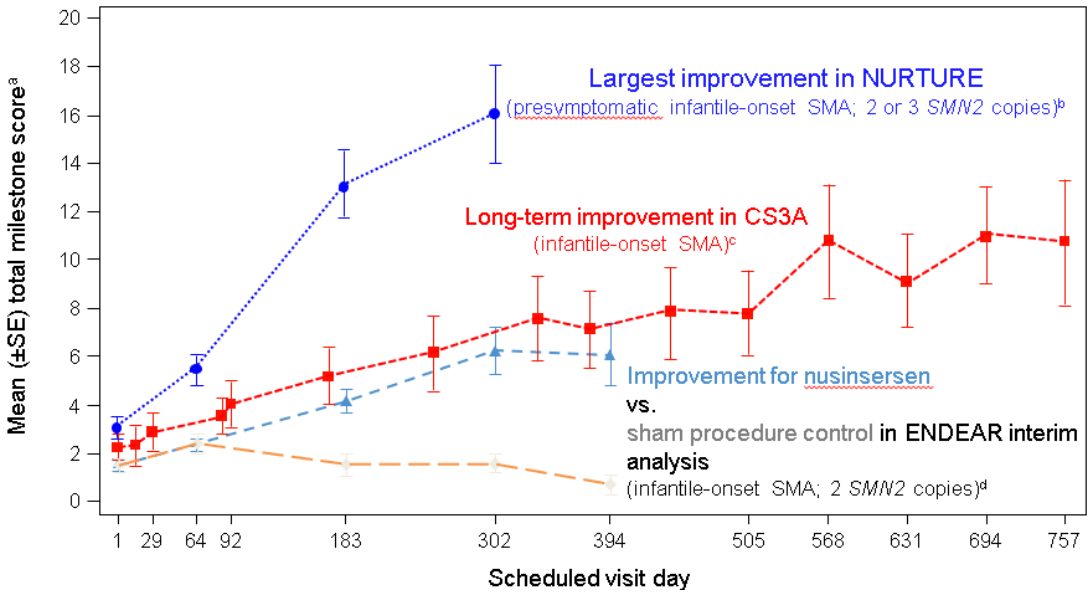
Since it has been proven that damage to motor neurons occurs before the onset of the first symptoms, starting even in the gestation period in some cases, the “window of opportunity” to detect and treat the disease before the onset is quite short. Of the 22 newborns diagnosed early in the pilot study carried out in the German states of Bavaria and North Rhine-Westphalia, there were four cases in which symptoms manifested before the treatment was able to be initiated – treatment, for these cases, started between the 17th and 39th day of life. This demonstrates just how short the “window of opportunity” actually is. (Vill, et al., 2019)

Both in the case of treating with the *oligonucleotide antisense nusinersen*, as in the case of the gene replacement therapy with *onasemnogene abeparvovec*, the results of the clinical trials demonstrate significant impacts of pre-symptomatic treatment, when compared to symptomatic treatment. (Dangouloff, et al., 2019) In the case of *risdiplam*, a clinical trial with patients treated pre-symptomatically is currently underway.

The *NURTURE* clinical trial of the *oligonucleotide antisense nusinersen*, which included patients treated in the pre-symptomatic stage with two or three copies of *SMN2*, demonstrates the benefits of pre-symptomatic treatment when compared to the “*CS3A*” and *ENDEAR “CS3B”* trials, which included patients with two copies of *SMN2*, and were initiated after the onset of the first symptoms (see **Figure 2**). (De Vivo, et al., 2019) Although a direct comparison cannot be drawn between different studies due to the heterogeneity of the disease, in global terms, the clinical results of patients treated in the pre-symptomatic phase are substantially better than the results of patients treated after the onset of the symptomology.

From the interim analysis of the *NURTURE* trials (in March 2019), we are able to observe that the 25 treated patients exceeded the age of predicted onset of symptoms achieving motor functions that are not expected when dealing with Type I and Type II SMA patients and were free from permanent assisted ventilation. In a subsequent analysis (February 2020) all patients treated in the symptomatic phase had progressed in the development of motor stages, with a significant alteration to the natural course of the disease’s natural course, as it was known to date. (European Alliance for Newborn Screening in SMA, 2021)

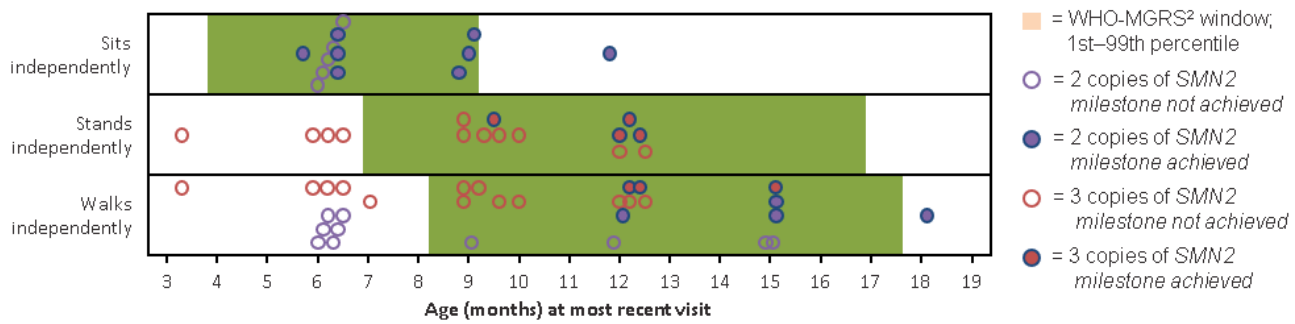
Figure 2 – Level of motor function milestones developed over time, according to the *“CS3A”* (which began in 2013, here shown as the red line), *ENDEAR “CS3B*” (which began in 2014, light blue line = treated patients, orange line = control group), and *NURTURE* (which began in 2015, shown as the dark blue line) trials.



Sources: *A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA)* (ClinicalTrials.gov, 2021)*; A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR)* (ClinicalTrials.gov, 2021)*; A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (NURTURE)* (ClinicalTrials.gov, 2019)

The clinical trial *SPR1NT*, of the pre-symptomatic treatment through the gene replacement therapy *onasemnogene abeparvovec*, was carried out with 30 patients with two or three copies of *SMN2*, demonstrates that the treated patients reached motor function states at the expected ages, not requiring any assistance with breathing or feeding. (Strauss, et al., 2020) Through **Figure 3** we may observe the development of the patients, at the date of the last consultation.

Figure 3 – Milestones reached by patients who participated in the *SPR1NT* study, at the date of the last consultation. In green we observe the periods (months of life) where each milestone is expected to occur. In blue, the patients with two copies of *SMN2* who had not yet reached the expected milestone (empty circles) and those who had already reached them (full circles). In pink, we observe the same situation for patients with three copies of *SMN2*.



Source: *Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients with Multiple Copies of SMN2 (SPR1NT)* (ClinicalTrials.gov, 2021)

Regardless of the treatment, the results of the clinical trials of both therapies, as well as the results of the experience of countries in which patients were already diagnosed and treated

in the pre-symptomatic phase, demonstrate that the earlier the disease is diagnosed and treated, the greater the efficacy of the applied treatments. (Messina, et al., 2020)

5.2. Relevance of the Newborn Screening of Spinal Muscular Atrophy

"The Newborn Screening of Spinal Muscular Atrophy is an efficient strategy in the early identification and diagnosis of the disease in patients, as well as in the increase of our understanding of the disease."

The results of the clinical trials and pilot studies that have already been carried out demonstrate that the treatments approved and available are more effective the earlier they are applied. (Dangouloff, et al., 2019) Taking this aspect into account, as well as the fact that newborn screening aims for the early identification of patients at risk, paving the way for a more rapid intervention, both in terms of symptom management and prevention, the discussion on the inclusion of SMA in newborn screening becomes not only relevant but imperative, as a strategy to provide a better quality of life to patients. (European Alliance for Newborn Screening in SMA, 2021)

Given the universality of the newborn screening programs, the fact that they have a well-developed operational structure (especially at the European level), and the general acceptance of screening programs by parents, the inclusion of SMA is the best option for early diagnosis of the disease. (Jędrzejowska, 2020) The inclusion of SMA will also contribute to increasing the parents' general knowledge on the disease – even if the parents decide not to authorize the screening for SMA, they will be better prepared to identify possible signs of the disease and seek help in a timely manner, thus mitigating the delays in referral and diagnosis currently observed. (European Alliance for Newborn Screening in SMA, 2021)

Until the emergence of the disease modifying therapies for SMA, newborn screening for SMA was not a possibility, as not all of the Wilson and Junger criteria were verified (Wilson, et al., 1968; Andermann, et al., 2008) – universally accepted as determinants for the inclusion of a disease in a newborn screening program – namely, the criterion that specifies the need for the existence of an effective treatment for the disease to be identified, the criterion that establishes that the costs of discovering new cases must be economically weighed in regarding the possible expenses with medical care, and the criterion that advocates for an agreement on whom to treat as a patient.

With the emergence and approval of the disease modifying therapies, whose costs are known, as they are already supported by the healthcare system, the context alters substantially, not only the compliance with Wilson and Junger's criteria being verified (Serra-Juhe, et al., 2019; Glascock, et al., 2018; European Alliance for Newborn Screening in SMA, 2021), but also the *Key Principles for Newborn Screening*, as established by EURORDIS for

the newborn screening of a rare disease. (EURORDIS - European Organisation for Rare Diseases, 2021; European Alliance for Newborn Screening in SMA, 2021)

In the European context, newborn screening for SMA is approved and awaiting implementation in six countries, with pilot studies taking place in five others, and with pilot studies being planned to start in three more, all in 2021. (SMA Newborn Screening Alliance, 2021)

Table 4 – Systematized analysis of the main data collected through the SMA newborn screening pilot studies, taking place in Germany (federal states Bavaria and North Rhineland-Westphalia), Belgium (regions of Wallonia and Brussels), and Italy (regions of Lazio and Tuscany).

	Belgium	**Germany**	**Italy**
Beginning of the Pilot Study	05-Mar-2018	15-Jan-2018	05-Sep-2019
Predicted Births / Year (Duration of the Pilot)	60.000 / year (3 years)	150.000 / year (3 years)	55.000 / year (2 years)
Number of Patients at the Date of the Final Update	42.000	178.000	45.112
Number of Positive Cases (Incidence)	6 (1 in 7.000)	25 (1 in 7.120)	11 (1 in 4.101)
Date of the Last Update	Mar-2019	Mar-2019	Oct-2020

Source: *Spinal muscular atrophy: Screen at birth, save lives* (European Alliance for Newborn Screening in SMA, 2021)

As can be observed in **Table 4**, the SMA newborn screening allows access to more accurate information regarding the incidence rates, allowing for the ability to demonstrate whether the actual incidence of the disease in each country is in line with the estimated incidence rate in the literature, thus leading to better planning and allocation of resources to management of SMA. The early identification will allow for the referral of patients to treatment centres but will also allow the referral of families to genetic counselling consultations – allowing for cascade screenings that will lead to the identification of possible carriers of the pathogenic mutation. In the context of SMA, genetic counselling consultations gain particular relevance due to it being a disease with a 25% risk of reoccurrence in future pregnancies.

5.3. Cost-Efficiency of the Newborn Screening

"The inclusion of Spinal Muscular Atrophy on the panel of screened diseases is a viable strategy, provided that the possible impacts on the Portuguese National Newborn Screening Programme are considered."

As mentioned in the second axis, the option of an early screening for SMA through the inclusion in the national screening program benefits from the existence of an operational structure already in place, which, at the most, will be adapted to the needs of testing for the new pathology to be included. For this reason, when analysing the cost-effectiveness of the SMA newborn screening, one should look at the additional economic cost of carrying out the test – which ranges from 3€ and 5€ per test performed (European Alliance for Newborn Screening in SMA, 2021) – as well as to the impacts that carrying out the test will have on the operational structure of the screening program. To the costs of carrying out the test, one must add the costs inherent to the discovery of new positive cases – all costs related to the process of confirming a positive result, from healthcare costs to additional testing procedures. As part of an analysis of European newborn screening programs, it was estimated that the confirmation of a positive result implies an average cost of €1,817 PPP (adjusted for purchasing power parity). (Burgard, et al., 2012)

Table 5 – Data regarding the operationalization of the SMA newborn screening pilot studies in Germany, Belgium, and Italy.

	Belgium	**Germany**	**Italy**
Type of Consent	No consent (as for other NBS), informed consent for confirming	Information of the parents, additional Informed consent	Consent (information during pregnancy, flyer, social media camping, consent signature)
Type of Test	Real time PCR + MLPA for positive cases	Real-time PCR	Real-time PCR (dedicated DBS)
Test Site Network	1 Central Lab	Central for Bavaria	1 Central Lab
Testing Costs per Newborn	2,5€ / sample + Tech	N/A	2,35€ - 3,35€

Source: *244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12* (Dangouloff, et al., 2019)

As shown in **Table 5**, despite the possibility of small variations in the overall testing approach, the test performed is genetic, which raises the need for "informed consent." This is an issue whose approach varies from country to country – in the Belgian case, the local Ethics Commission considered that the introduction of informed consent would create a situation of unnecessary additional anxiety for the parents, as the other diseases did not imply the need for consent, and therefore it was decided to introduce consent only for the confirmation of

positive cases. (Boemer, et al., 2019) Both in the German and Italian cases, this situation does not apply, with the informed consent being signed during the newborn screening.

In the Portuguese context, Law. n.º 12/2005 determines that the performance of diagnostic genetic or pharmacogenetic tests must be preceded by a signed informed consent. (Assembleia da República, 2005) Accordingly, Decree n.º 131/2014 establishes the principles by which the carrying out of genetic tests should be governed, reinforcing the need for an informed consent to carry out genetic tests and to maintain genetic information in databases, as well as the need to provide all relevant information about the genetic test (including its purpose, the risks and consequences of processing the genetic information, and the right to revoke consent). (Assembleia da República, 2014)

In this sense, newborn screening for SMA should, considering current legislation, be preceded by an informed consent from the parents. In order for this requirement not to become a deterrent for parents, it is necessary to develop a pedagogical effort on the training of the healthcare professionals who will accompany parents throughout the pregnancy, and who will inform them about the *PNRN* and the pathologies tracked within the test, as well as the health professionals who will present the issue to the parents when the test is performed – the message should be conveyed in a calm, clear, and understandable way. There should be a pedagogical effort with parents, so that they understand the meaning of a positive result, the consequences of it, and the characteristics of the test to be performed (including the possibility of false positives/negatives) and the existence and availability of effective treatments.

In the case of SMA, the risk of false positives is reduced because of the confirmation test. However, approximately 5% of patients with SMA will not be identified using the available methods, due to *SMN1* point mutations. Once again, the training of healthcare professionals will be essential for them to be aware of possible manifestations of symptoms in these "false negatives," and for parents to be alerted to the disease and its characteristics, thus being able to identify any abnormal occurrence. (European Alliance for Newborn Screening in SMA, 2021)

Finally, for the identified positive cases, coordination between the diagnostics laboratory, the genetics centre, and the treatment centre is essential, so that there are no delays between the detection of a positive case and the referral of patients for treatment, and parents for genetic counselling – not losing the advantage gained from the early diagnosis. (Dangouloff, et al., 2019) This fluidity of processes is paramount both in cases where treatment will begin immediately (patients with two or three copies of *SMN2*) and in cases of patients whose treatment will only begin when symptoms appear (patients with four copies of *SMN2*), but which must be monitored regularly by specialists. (Glascock, et al., 2018) (European Alliance for Newborn Screening in SMA, 2021)

5.4. Costs and Benefits of Screening and Treating Early

"The Newborn Screening of Spinal Muscular Atrophy, and its subsequent early treatment, presents a potentially positive cost-benefit relationship for patients, their families, the healthcare system, and society."

The emergence, and subsequent approval, of the disease modifying therapies for SMA, as well as the published results of the application of those therapies, means that the prognosis of the disease has changed substantially, with the natural course of the disease being mitigated, and in some cases even stagnated. These therapies have dramatically decreased the mortality rate and increased the average life expectancy of patients by preventing neuronal death, resulting in a significant increase in the quality of life of patients. (Messina, et al., 2020) Additionally, the results also demonstrate that the effectiveness of these therapies is greater when patients are treated in the pre-symptomatic phase of the disease, reinforcing the need to screen patients at an earlier stage, through newborn screening. (Dangouloff, et al., 2019)

However, any of the already approved disease modifying therapies also include significant costs, which raises the need to analyse the costs of the disease throughout life, from diagnosis to the monitoring and treatment, as well as the benefits of treatments and their early applications, so that the managers of the healthcare system, namely the *Serviço Nacional de Saúde* (*SNS - National Health Service*), in the Portuguese context, can make informed decisions regarding the allocation of health resources. (Dangouloff, et al., 2019)

Economic analyses, carried out within the scope of *health economics*, aim to quantify all the costs and benefits inherent to a given medical intervention, to be able to compare them with existing alternative interventions, and thus be able to conclude on the *cost-effectiveness* of each one, determining the intervention with the best results. The most common type of analyses in health economics are the *cost-utility analyses*, where the results are calculated based on *Quality-Adjusted Life Years* (QALYs) – which correspond to the number of healthy life years, thus allowing for the capture of the effects of the health intervention, both in mortality and morbidity. These results are typically expressed as an *Incremental Cost-Effectiveness Ratio* (ICER) – defined based on the differences in costs and outcomes of interventions under analysis – and resulting in the incremental cost per *QALY* gained. Once the ICER is calculated, the resulting ratio is compared with the *Cost-Effectiveness Threshold* – defined by the health authorities of each country for health interventions, taking into account specific economic factors, such as GDP and the typology of the health system. (Drummond, et al., 2015)

Table 6 – Data regarding the annual costs related to the management of SMA through standard-of-care (estimated with 2014 data, before the approval of modifying therapies) in Germany, Spain, France, and the United Kingdom.

	France[2]	Germany[2]	Spain[1]	United Kingdom[2]
Direct Healthcare Costs	**4.672**	**7.313**	**10.882**	**11.081**
• Drugs	14	35	83	560
• Medical Tests	384	158	603	874
• Medical Visits	1.870	1.954	7.732	4.569
• Hospitalizations	1.229	3.170	1.297	2.219
• General Practice and Emergency	144	617	244	842
• Medical Material	990	1.379	920	1.958
• Healthcare Transport	41	0	3	58
Direct Non-Healthcare Costs	**27.370**	**44.670**	**22.839**	**43.214**
• Social Services	1.029	4.380	746	2.187
• Main Informal Carer	17.468	27.436	11.508	27.012
• Other Informal Carers	8.151	12.490	9.619	13.516
• Other Non-Healthcare Family Costs	722	364	966	501
Total Annual Costs	**32.042**	**51.983**	**33.721**	**54.295**

Sources: [1]*Socia/economic costs and health-related quality of life in patients with spinal muscular atrophy in Spain* (López-Bastida, et al., 2017) e [2]*The Economic Impact and Health-Related Quality of Life of Spinal Muscular Atrophy. An Analysis across Europe* (Peña-Longobardo, et al., 2020)

As shown in **Table 6**, the total annual costs of managing SMA through the standard-of-care were estimated considering 2014 data from the French, German, Spanish and British health systems. (López-Bastida, et al., 2017; Peña-Longobardo, et al., 2020) The values described do not include the costs of the disease modifying therapies (the decision regarding the therapy is up to the specialists who follow the patient and the specificities of each case), and it is estimated that these values decrease when patients undergo treatment with the aforementioned therapies (especially when treated in the pre-symptomatic phase). This decrease is due to the reduction in need for healthcare services – such as hospitalizations, assisted ventilation and hospital equipment, among others – and, above all, due to the reduction in auxiliary services and care, that represent 66% (Spain) to 86% (Germany) of the total annual cost – such as informal caregivers, speech therapy, among many other services. (Dangouloff, et al., 2019) Through these values, it is possible to estimate the total cost of a patient with SMA, based on the average life expectancy of each clinical type, and then to carry out more detailed comparative analyses between different health interventions – the update of these values is advisable.

In the case of SMA, there are currently very few published *cost-utility analyses*, although some reports have already been published that address the *cost-effectiveness* of the treatments for the purposes of their approval, particularly in Scotland (of the *oligonucleotide antisense nusinersen*) (Scottish Medicines Consortium, 2018), the United States (of the *oligonucleotide antisense nusinersen* and *onasemnogene abeparvovec*) (ICER - Institute for Clinical and Economic Review, 2019), the United Kingdom (of the *oligonucleotide antisense nusinersen* and *onasemnogene abeparvovec*) (National Institute for Health and Care Excellence, 2019; National Institute for Health and Care Excellence, 2021) and Sweden (of the *oligonucleotide antisense nusinersen*) (Tandvårds-och Läkemedelsförmånsverkets, 2017; Zuluaga-Sanchez, et al., 2019). These reports show high ICER values, suggesting that

the disease modifying therapies for SMA are not *cost-effective*, given the *cost-effectiveness threshold* defined by their respective countries. However, they conclude favourably as to their approval and financing, considering that in the case of rare diseases, and SMA especially, factors such as the lack of effective alternatives, the impact of treatments in ethical and social terms, and the budgetary impact – despite the high cost per patient, the budgetary impact is considered low because of the small number of patients affected – must be considered.

With the increase in the number of patients treated during the pre-symptomatic stage due to the implementation of newborn screening or pilot projects for the same purpose (such as those in Belgium, Germany, and Italy), more data will be available to carry out assessments of socioeconomic impacts, through the preparation of *cost-utility analyses* done while tracking and treating SMA in the pre-symptomatic phase, and comparing this with the current practice – in which patients are only treated after the manifestation of symptoms. This type of information will be essential for decision-makers and managers in the healthcare field, in both the planning and allocation of available resources. (European Alliance for Newborn Screening in SMA, 2021)

Currently, there are already models for carrying out *cost-utility analyses* for the newborn screening of rare diseases, although there are few in number. (van der Ploeg, et al., 2015; Bessey, et al., 2019; van der Ploeg, et al., 2019)

For the context of the United States, a *cost-utility analysis* for the newborn screening of SMA and subsequent treatment (with the *oligonucleotide antisense nusinersen*) was published in 2020. The analysis shows that the ICER of the *"don't screen– treat"* scenario – as is the case for Portugal, where treatment is approved and reimbursed, but where newborns are not screened for SMA at birth– is $522,118 per QALY when compared to the *"don't screen–don't treat"* scenario (standard-of-care). The *"screen–treat"* scenario resulted in an ICER of $330,558 per QALY, when compared to the same standard-of-care scenario. The analysis thus concludes that the scenario in which newborn screening and subsequent early treatment is performed is preferable to the scenario in which patients are treated without newborn screening, after the onset of symptoms (see **Table 7**). (Jalali, et al., 2020) A similar conclusion is anticipated for the treatment with *onasemnogene abeparvovec*. (Dangouloff, et al., 2021)

Table 7 – Conclusions of the *cost-utility analysis* (ICER) of newborn screening for SMA accompanied by pre-symptomatic treatment with *oligonucleotide antisense nusinersen.*

	Don't Screen – Don't Treat
Don't Screen – Treat	$522.118 per QALY
Screen – Treat	$330.558 per QALY

Source: *Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy* (Jalali, et al., 2020)

It is important to note that the results of this type of analysis will always be sensitive to country-specific factors (such as the health system model or the existing newborn screening

program), especially between the United States and European countries, such as Portugal. It is, therefore, imperative to carry out similar studies for other countries, namely at the European and Portuguese levels.

Following this need, a *cost-utility analysis* performed by the University Medical Center of Groningen (Netherlands) has been completed, and is pending publishing, taking into account the Dutch context. This analysis considered the costs associated with the newborn screening of SMA and with the discovery of new cases (cost of confirmation, follow-up, genetic counselling, treatment, among others), and all the benefits resulting from the application of treatment in the pre-symptomatic phase – which include not only the mitigation of healthcare costs inherent to the late treatment (after the onset of symptoms) but also the mitigation of losses to society, such as the loss of productivity resulting from the need for parents to be absent from their jobs to be able to accompany the treatment of their child. All these factors are quantified throughout the analysis, resulting in the conclusion that newborn screening for SMA, and subsequent treatment (through either *oligonucleotide antisense nusinersen* or the gene replacement therapy *onasemnogene abeparvovec*) is preferable when compared to the current scenario – treatment after the manifestation of symptoms.

Another relevant factor that should be considered is the fact that, in the context of rare diseases, the existing *cost-utility analysis* model is not able to assess all the relevant effects of a new health intervention, especially in terms of added value to society. (Lakdawalla, et al., 2018) In addition to the possibility of mitigating the effects of a serious illness like SMA, there are other factors that justify a higher willingness to pay that should be taken into account when performing future analyses.

Firstly, the *cost-utility analysis* models and the values defined as the *cost-effectiveness threshold* were developed and designed for large-scale diseases – with a high incidence rate – and consequently, their high budgetary impact due to the incidence rate. Therefore, by not quantifying all the socioeconomic benefits, *cost-utility analyses* of health interventions for rare diseases may overestimate the budgetary impact of the interventions being studied. (Schlander, et al., 2016)

Secondly, interventions aimed at rare diseases imply, in most cases, an important effort in technological innovation (i.e., gene therapies), which will potentially impact areas related to combating other diseases (both rare and common). The effects of this effort in technological innovation will spill over into these areas, stimulating the development of other health interventions – as stated by the International Society of Pharmacoeconomics and Outcomes Research. (Lakdawalla, et al., 2018)

Thirdly, the higher prices for interventions for rare diseases are often due to the high investment in the research that is devoted to that area – an area with a difficult return-on-investment (resulting in the designation of orphan drugs for interventions developed in this

area) – and which results in the satisfaction of an important need for society – combating diseases that would otherwise lead to a low quality of life or even a low average life expectancy of those affected. For this reason, meeting this need also implies added value for society as a whole. (Dangouloff, et al., 2021; European Alliance for Newborn Screening in SMA, 2021)

Last but not least, the rarity of a disease entails socioeconomic value, and the willingness to pay verified in European countries is inversely correlated with the incidence of a certain disease. This was the conclusion of a study that, based on the costs of orphan drugs approved by the European Medicines Agency and the incidence of each disease, analysed the correlation between the rarity of the disease and the willingness to pay in seven European countries – Germany, Spain, France, Italy, Norway, the United Kingdom, and Sweden. The study concluded that the willingness to pay for a certain medication increased, the lower the incidence of the disease. (Medic, et al., 2017)

5.5. Importance for the Families

"The Newborn Screening of Spinal Muscular Atrophy, and the subsequent treatment of patients in the pre-symptomatic phase of the disease, alters the perspectives of families with regards to the disease and their futures, and diminishing potential destabilizing effects within the family dynamics."

Article 24.º of the United Nations Convention on the Rights of the Child, ratified by all European countries, guarantees to all children the right to enjoy the best possible state of health and access to medical services, primary healthcare and prevention measures, public health education, and the reduction of child mortality, ensuring that no child is deprived of the right to health services. (UNICEF, 1989) The fundamental right to the best available healthcare is also enshrined in the Hospitalized Children's Charter, drawn up by various European associations for the defence of the rights of the child and recognized by the European Parliament. (Instituto de Apoio à Criança, 1988)

Taking into account the severity of SMA, its incidence and manifestation in paediatric age, and the fact that current data points to greater effectiveness of the disease modifying therapies when applied during the pre-symptomatic phase, newborn screening is the adequate response in ensuring an effective fight against the disease, as it is performed within the first few days of life, and in the prevention of infant mortality, which in Type I SMA usually occurs within the first two years of life. (Dangouloff, et al., 2019)

European newborn screening programs are usually managed and funded by the public health authorities of each country, although there are exceptions, being heterogeneous in terms of the diseases screened, comprehensively designed from the pre-analytical stage through

diagnosis and communication of the final result, and ending in the referral and follow-up by specialists' phase. (Loeber, et al., 2021) In regards to the Portuguese National Health Service, the referral to genetic counselling consultations, as well as the follow-up by specialists and psychosocial support are defined by the Portuguese legislation as rights available to any citizen, both before and after a genetic test.

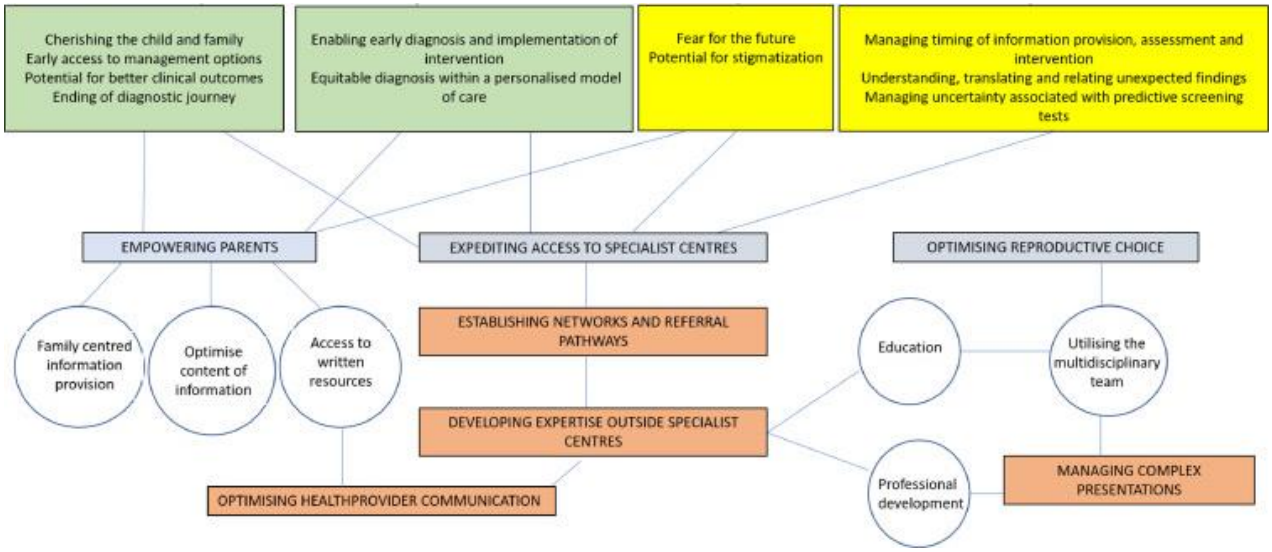
Given the nature of newborns screening programs, they represent an adequate solution to ensure equity among all – allowing all children to be screened at birth, newborn screening programs avoid possible delays in diagnosis, which may stem from the lesser ability of the parents to seek healthcare support in a timely manner, or poor access to the information they would require to identify the need for healthcare support, when the symptoms first appear. (European Alliance for Newborn Screening in SMA, 2021)

The pedagogical component is another of the advantages of newborn screening programs, as they allow for the awareness and preparation of everyone involved in the process for each of the diseases screened, from healthcare professionals to families, through hospital staff and legislators, and society as a whole. This awareness leads to better preparation by the parents at the moment of deciding whether or not to participate in the program (which should always be voluntary) (Instituto de Apoio à Criança, 1988), as well as the better preparation for parents to react to a positive diagnosis.

Following the pilot study for newborn screening of SMA in Australia, a survey was carried out among the healthcare professionals involved and the parents of patients identified through screening, which aimed to assess the perception of these two groups with regards to newborn screening. (Kariyawasam, et al., 2021) Through the questionnaire, it was possible to identify the successes and benefits of the program, the challenges and disadvantages, the recommendations from both groups for the future of the program, and the effects of these recommendations. The main success perceived by the families is the easing of the odyssey that is the process leading to a diagnosis, that due to the delays leads to the weariness of parents and healthcare professionals who participate in the process – delays which are harmful to the disease management process. This is linked directly to the success identified by healthcare professionals, who highlighted the possibility of starting the planning and management of a health intervention in a timely manner, obtaining the best results possible. The main challenge identified was communicating a positive diagnosis to the parents. As mentioned above, the way the diagnosis is communicated influences the parents' reaction to the news and the way they process it, especially at the psychological level. Through the responses collected, the relationship between each of these factors was identified, resulting in the schematic illustrated in **Figure 4**.

Figure 4 – Map of interactions between recommendations and perceptions of parents of diagnosed patients and healthcare professionals involved in SMA newborn screening in Australia. In green – newborn screening benefits and successes (left – identified by parents,

right – identified by healthcare professionals); in yellow – disadvantages and challenges of the newborn screening program (left – parents, right – healthcare professionals); in blue – parents' recommendations; in orange – healthcare professionals' recommendations; in circles, the potential outcomes of recommendations by parents and healthcare professionals.



Source: *"We needed this": perspectives of parents and healthcare professionals involved in a pilot newborn screening program for spinal muscular atrophy* (Kariyawasam, et al., 2021)

In most European countries, parents begin to be informed about the existence of newborn screening, its importance and benefits, the diseases being screened for, and the types of procedures involved in screening, during the pregnancy follow-up. This information is usually conveyed through brochures, online, and other educational contents. (IJzebrink, et al., 2021) When including SMA on the panel of screened diseases, it is important that this content is updated to contain all relevant information in order to properly inform parents and train healthcare professionals involved in the monitoring of the pregnancy, through to the screening and ending with the monitoring of patients and their families. (Instituto de Apoio à Criança, 2021)

The correct and assertive communication of a positive diagnosis, followed by multidisciplinary monitoring, is essential for parents to be able to understand the information and feel better supported during the decision-making period, reducing the anxiety and psychological disorder inherent to receiving the results. (Kariyawasam, et al., 2021) A correct understanding of what the disease entails, its prognosis, and therapeutic options allows parents to participate in the management of the disease actively and consciously, but also the management of their expectations regarding the effects and limitations of treatments. The right attitude toward the disease is essential for parents, as it will inevitably be projected onto their children, who will have to live with the disease for the rest of their lives.

As mentioned throughout this document, the main argument for screening patients in the newborn period is the fact that treatment can be started during the pre-symptomatic stage, where the available therapies are most effective. However, early diagnosis also has

significant impacts on the relationship between parent and child – namely in the cases of later manifestations of symptoms that will not be immediately targeted by the disease modifying treatments (Glascock, et al., 2018), early screening allows parents to better understand the limitations in their child's development, thus preventing the guilt they may feel (for example, in situations where parents pressure their children to join certain activities, without knowing that the disease may hinder them). Knowing in advance also allows parents to organize and adjust their lives, so that they can respond in the best way to their new reality (such as moving to locations closer to treatment centres or designating who will monitor and accompany their child). (European Alliance for Newborn Screening in SMA, 2021)

The diagnosis of SMA is always a painful experience for patients and their respective families. However, the ideal scenario for receiving it will be one that occurs when it is still possible to avoid or mitigate the damage of the disease – especially when compared to a scenario where the fight against the disease only starts after the first and irreversible damages occur. (European Alliance for Newborn Screening in SMA, 2021)

Two studies, based on surveys answered by adult patients with SMA (Types II, III, and IV) and relatives of those patients in the United Kingdom, show that the majority of patients (85%), as well as the majority of families (also 85%), do not believe that the diagnosis at birth interferes with the process of developing affective bonds between parents and children. Both studies also demonstrate that the majority of patients (74.4%), as well as the majority of parents (70%), support newborn screening for SMA. (Boardman, et al., 2017; Boardman, et al., 2018) This view also corresponds to that of members of the general population in the United Kingdom who, in a similar survey, responded favourably (84%) to the implementation of newborns screening for SMA. (Boardman, et al., 2018)

Finally, it should be noted that the burden of diagnosis, especially in cases of later onset of the disease and which will possibly not be immediately treated (patients with 4 or more copies of *SMN2* – Type IV and some cases of Type III) (Glascock, et al., 2018; European Alliance for Newborn Screening in SMA, 2021), also falls on the patients themselves, who live with the stigma and emotional effects of the disease. Once again, a multidisciplinary follow-up (not only in terms of disease management, but also at the psychological level) will be essential in the patient's development. The survey of adult patients with SMA in the United Kingdom showed that 74% believed that newborn screening would save patients from difficulties associated with discovering the disease later, at a stage when the patient would already have defined and robust life plans that would not account for the limitations of the disease, resulting in severe psychological consequences. Of the 74% that responded favourably, 36% had Type III and 28% had Type IV. (Boardman, et al., 2018)

6. Conclusion

Given its characteristics and primary objective (screening of rare diseases, in order to avoid the evolution of the pathology, through pre-symptomatic diagnosis and early implementation of adequate therapy), the information from clinical trials of the disease modifying therapies already approved and pilot studies already completed, and the existing knowledge about SMA, the PNRN presents itself as a viable and effective solution for the diagnosis and initiation of SMA treatment in the pre-symptomatic phase, taking advantage of the “window of opportunity” in which the currently approved disease modifying therapies are most effective.

Throughout this document, the various dimensions of SMA and newborn screening have been addressed, having been listed the costs and benefits of including SMA in the PNRN, as well as the challenges it faces, based on the existing literature to date, the testimonies of those who accompany and/or live with the disease, and the experience of countries where the same solution is being put to the test.

Despite the costs inherent to the inclusion of SMA in the panel of screened diseases in the PNRN, and the other challenges that this inclusion may entail, this analysis indicates that the benefits achieved may represent an added value, both in terms of quality of life for patients and their families, but also in terms of added value for society as a whole.

Taking all that has been mentioned into consideration, the present document concludes that a pilot study of the newborn screening of SMA is warranted in Portugal, within the PNRN, similar to those ongoing or that have undergone in other European countries, to better allow for the assessment of the real costs and benefits, as well as for the fine tuning of the conditions in which testing is to occur, all the while taking advantage of the “window of opportunity” for the pre-symptomatic treatment of patients.

7. Technical Sheet

White Paper on the Inclusion of Spinal Muscular Atrophy in Newborn Screening

Associação Portuguesa de Neuromusculares > Coalition for the Newborn Screening of Spinal Muscular Atrophy.

Executive Development: Loyal Advisory

Scientific Discussion and Review:

Carmen Carvalho, Neonatologist

Joana Ribeiro, Neurologist

José Pedro Vieira, Neuropaediatrician

Mónica Vasconcelos, Neuropaediatrician

Teresa Moreno, Neuropaediatrician

Heloísa Santos, Medical Geneticist / Paediatrician

João Lavinha, Human Genetics Researcher

Melanie Tavares, Psychologist

Signatories:

International Partners: *SMA Europe > European Alliance for Newborn Screening in Spinal Muscular Atrophy*.

With the Support of: *Biogen Portugal*, *Novartis Gene Therapies*; *Roche Portugal*

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