Advances in Newborn Screening and Presymptomatic Diagnosis of Spinal Muscular Atrophy

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Abstract: Spinal muscular atrophy 5q (SMA5q) is one of the most severe and common genetic diseases. In the natural course, the disease leads to premature death (in acute forms) or severe motor disability (in chronic forms). As the genetic basis of SMA is very homogeneous, the diagnostics are based entirely on simple and sensitive genetic testing. In the last few years, innovative methods of therapy have been developed based on SMN2 gene modification, such as splicing, or replacement of the damaged SMN1 gene (gene therapy). Although these approaches have shown high efficacy, results depend on the age/disease stage at which therapy is initiated. The best results have been obtained in presymptomatic patients. Indeed, introduction of therapy in the pre- or early symptomatic stage of the disease seems to be crucial for maximizing effects. Thus, all the criteria for the implementation of neonatal screening for SMA have been met, and many countries, ie, the USA, Germany, Belgium, and Australia, have started NBS national/pilot programs for SMA. The initial results of these programs indicate a high frequency of the disease, reaching 1 per 7 thousand live births in Europe, as well as early symptomatology (first weeks of life in severe cases) and a high frequency of patients with 4 SMN2 copies. Overall, the time for therapy inclusion in patients with 4 SMN2 copies remain under discussion. More precise predictors/biomarkers of the clinical course are needed. At the same time, it seems advisable to offer other solutions, such as population carrier screening. As the long-term effects of different treatments on the natural history of SMA are unknown, the natural history of the disease needs to be re-evaluated.

Keywords: spinal muscular atrophy, SMA, newborn screening, NBS, presymptomatic treatment, SMN1, SMN2

Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy is associated with mutations in the SMN1 gene (SMA5q), and it is inherited as an autosomal recessive trait. The pathomechanism of the disease involves atrophy of spinal cord motor neurons, which leads to muscle weakness and atrophy. SMA is a severe and progressive disease that in most cases results in immobility and respiratory failure.

SMA is one of the most common genetic diseases, with a morbidity comparable to phenylketonuria. The largest study on SMA epidemiology ever initiated, which was conducted in the USA on a multiethnic group of 68,478 people, showed an SMA incidence of 1:11,000 births and a carrier frequency of 1 in 54 people.1 The disease appears to be more frequent in Europe. Recently, published study results on SMA epidemiology in Europe indicate an SMA incidence of 1:8400 births (11.9/100000).2
Spinal muscular atrophy is characterized by a broad age spectrum of disease onset and course, including severity of symptoms and signs and subsequent complications. Until recently, the classification of SMA was based on age of onset and motor milestones achieved and was divided into 5 forms: 0, 1, 2, 3 and 4. However, the introduction of treatment has changed the natural history of the disease. Thus, the existing classifications are becoming less relevant. Treatment modifies the course of SMA, allowing new milestones to be achieved in some cases, which creates problems with correct assignment of individual cases to known classification groups. Should, for example, children with SMA1 achieving the ability to sit independently due to treatment be reclassified to the SMA2 group? What forms of the disease should be diagnosed among presymptomatic patients? For this reason, the functional classification, which assesses lying, sitting, and walking, is increasingly widely used. This classification has been applied in clinical practice for a long time and has determined the selection of appropriate standards of care. It is currently replacing the old classification. As the long-term effects of different treatments on the natural history of SMA are completely unknown, the natural history of the disease needs to be re-evaluated.

The genetic basis of SMA is very homogeneous. Mutations in the SMN1 gene are responsible for the disease symptoms, with 95–98% involving deletions of both gene alleles. Approximately 3–4% of patients carry point mutations, which occur in a compound heterozygous state with deletion. To date, over 100 point mutations in the SMN1 gene have been described. The most frequent mutation is T274I in exon 6, which correlates with chronic forms of SMA.

The twin-similar SMN2 gene acts as the main phenotype modifier. The SMN2 gene encodes an identical protein to the SMN1 gene. However, due to the mononucleotide difference in exon 7 (c.840C>T), the SMN2 gene undergoes alternative splicing, and a mostly defective product is produced, which undergoes rapid degradation. Only 10% of the SMN2 gene product is a full-length SMN protein. In patients with spinal muscular atrophy, the SMN protein is expressed only from the preserved SMN2 gene. Therefore, increasing the number of copies of the SMN2 gene as a result of duplication or conversion alleviates the clinical course of SMA: the more copies of the gene are present, the milder is the course of the disease. In patients with the acute form of SMA, 1–2 SMN2 copies are usually observed, whereas 2–3 copies are observed in patients with the intermediate form; in patients with the mild form, 3–4 copies are observed, but even 5–6 copies may be present. Thus, the number of SMN2 copies does not fully explain phenotype variability in SMA; however, it is still a good and the most sensitive phenotype modifier. Others, such as the substitution c.859G>C in exon 7 of the SMN2 gene and over- or underexpression of PLS and NCALD, are rare, or their influence on the SMA phenotype is not fully understood.

Currently, the diagnostics of SMA are based entirely on genetic testing. The most commonly used test is the MLPA technique (MRC-Holland, the test is CE-IVD certified), which shows the number of SMN1 and SMN2 copies. Loss of both SMN1 alleles confirms the clinical diagnosis of the disease; the presence of one copy requires further research, aiming to identify a potential point mutation. The number of SMN2 copies is routinely assessed as the main phenotype modifier.

**SMA Therapy**

In the last few years, innovative methods of SMA treatment have been developed. They are based on the change in SMN2 gene splicing or on delivering a correct copy of the SMN1 gene to cells (gene therapy). Nusinersen (Spinraza), the first drug approved to treat SMA, is a synthetic oligonucleotide (ASO) that binds to intron 7 of the SMN2 pre-mRNA. This intron includes the transcriptional silencer (ISS), to which transcription-inhibiting factors (hnRNPs) bind under natural conditions. Blocking this site by ASO allows the binding of transcription factors (U1 snRNPs) and, as a consequence, increased incorporation of exon 7 into the transcript. This, in turn, results in a higher amount of full-length protein. The effectiveness of this therapeutic approach was confirmed in an animal model and later developed by the Biogen company and introduced into therapy. Nusinersen has been registered for the treatment of all forms of SMA, regardless of the patient’s age, in the USA (December 2016), in the European Union (June 2017) and in Japan (September 2017). The effectiveness of treatment observed in randomized drug trials is confirmed by the results of open clinical trials and real-world data. In drug trials, 323 patients with various forms of SMA (SMA1, 2, 3 and presymptomatic) were treated with nusinersen. Currently, over 11,000 patients worldwide receive the drug (October 2020).

A different therapeutic approach is gene therapy, ie, introducing the correct sequence of the SMN1 gene into
the cell. Medical products for gene therapy of SMA were developed by Avexis under the name onasemnogene abeparvovec (Zolgensma, AVXS-101). The therapy consists of a single intravenous administration of the cDNA sequence of the SMN1 gene, inserted into a carrier that is the capsid of AAV9 devoid of the original viral genome. The transgene embedded in the vector is under control of the cytomegalovirus enhancer/chicken beta-actin gene promoter. The vector delivers genetic material to the nuclei of cells (including motor neurons), which allows production of the SMN protein. DNA does not integrate into the genetic material of the host but is deposited in the form of an episome. As administration of a drug carried by a virus stimulates the development of permanent immunity to that type of virus, onasemnogene abeparvovec can be administered only once. Some people have antibodies against AAV9 viruses; approximately 50% of the adult population is resistant to scAAV9. The prevalence of resistance to AVXS-101 in children in clinical trials range from 5% in the US to 15% in Europe. Onasemnogene abeparvovec was registered in the USA, Japan and the Middle East in May 2019 for children with SMA under 2 years of age, including those who are presymptomatic. In May 2020, the drug was conditionally approved in the European Union for the treatment of patients with no more than 3 copies of SMN2 and a body weight of less than 21 kg. Information on treatment outcomes is very promising but limited. In total, 120 patients were included in clinical trials, and the drug was commercially administered to an additional 600 patients.

The first oral drug approved in August 2020 in the US for the treatment of adult patients and children over 2 months of age is risdiplam (RG7916) (Evrysdi). Risdiplam is a small molecule splicing modifier that changes assembly of the SMN2 gene. The proposed mechanism of action of this group of substances (so-called SMN-C type compounds) is their binding to two sites at exon 7 of the SMN2 gene (ESE2-exonic splicing enhancer 2 and 5'ss-5'splicing site) when U1 snRNA is bound. Interaction with the 5'ss promotes exon 7 inclusion in the splicing process, whereas binding to ESE2 results in hnRNP G dislocation and allows the U1 snRNP complex to bind to ESE2. The effectiveness of risdiplam was studied in a group of 337 patients with various types of SMA (FIREFISH [NCT02913482], SUNFISH [NCT02908685], JEWELFISH [NCT03032172], RAINBOWFISH [NCT03779334] studies). The registration procedure in Europe is currently underway.

A second mRNA folding micromolecule, branaplam (LM1070) [NCT02268552], is also the subject of advanced clinical trials.

A number of other substances with various mechanisms of action (change of SMN2 splicing, gene therapy, effects on muscles) have been analyzed as potential drugs for SMA, both in clinical and preclinical studies.

The different structure of clinical trials (as for study groups, methods, endpoints) but also different stages of research advancement do not allow us to potentially indicate the best and most effective drug. In all these studies, it was pointed out that the effectiveness of treatment depends on the severity of the disease at treatment initiation.

**Earlier – Better and Presymptomatic Treatment**

Recent advances in SMA treatment have dramatically altered SMA prognosis. However, success of treatment correlates strongly with the age of the patient at the initiation of treatment. The shorter the disease duration is, the better the prognosis for the patient is.

The treatment should be introduced when motor neurons are still viable and when upregulation of the SMN protein, whether caused by an alteration of SMN2 splicing or the introduction of a transgene, will recreate the physiological SMN-mediated processes. This idea is perfectly summed up by the term “time is motoneuron”, used by Govani et al. Of course, depending on the baseline SMN protein deficiency, the timing of treatment varies greatly. In severe and extremely severe forms, the SMN deficit is significant prenatally, and it is not possible to fully restore physiological processes after birth. On the other hand, the therapeutic window for the mild and very mild forms has not yet been defined. Nevertheless, the great majority of patients will undoubtedly benefit from early diagnosis and treatment.

The currently available data on therapeutic results in the context of the time of treatment initiation for individual approved therapies are discussed below.

**Nusinersen (Spinraza)**

The most spectacular results were obtained in patients treated presymptomatically. In the NURTURE trial (NCT02386553), 25 patients with 2 or 3 copies of SMN2 received nusinersen in the presymptomatic period. After a median of 2.9 years of follow-up, all children were alive, 0% were on permanent ventilation, 100% achieved the ability to sit independently,
and as much as 88% achieved independent walking. Such tremendous effects were especially seen in patients with 3 copies, whose psychomotor development did not differ from that of healthy peers.20

In comparison, in the ENDEAR study (NCT02193074), which involved 122 infants with SMA 1 and 2 copies of SMN2 (81 nusinersen vs 41 placebo), patients who were given the therapy earlier (disease duration less than 13.1 weeks) obtained better results with regard to motor function (93% vs 45% increase in HINE-2 score) and respiratory function (77% vs 46% for those with no permanent ventilation).21 WHO motor milestones were not assessed in ENDEAR, though the study summary showed that 8% of nusinersen-treated children (cut off day 394) had achieved the ability to sit independently.12 Children in the ENDEAR study who survived (65 from the nusinersen group and 24 from the sham control group) were further treated with nusinersen and followed in the SHINE study (NCT02594124).

The longest time of individual follow-up was 7.63 y.22 At the end of the study, these patients were scored for both CHOP-INTEND and WHO milestone scores. Among the children treated with nusinersen (both in ENDEAR and SHINE) from the beginning, the mean improvement in the CHOP INTEND scale was 16.8 points, as compared to 8.2 points for the children treated only in SHINE (sham control in ENDEAR).23 The results show a significant difference between the group that received treatment before 5.42 months (improvement by an average of 19.4 points) and the group treated between 5.42 and 7.96 months (13.8 CHOP INTEND points). Large differences depending on the age of therapy onset were also observed according to the WHO milestones scale. Sixty percent of children treated before 5.42 months vs 38% of children treated between 5.42 and 7.96 months were able to sit independently. However, none of the children treated only in the SHINE arm (the first dose 10.39–22.99 months) were able to sit up on their own. In the group treated at the earliest age (<5.42 months), 10% started walking with help.

Real-world data indicate that up to 30% of symptomatically treated SMA1 patients (15/47 in the group treated for 14 msc, aged 2.5–102.8 msc and 2/61 and 3/16 treated for 6 msc) achieved sitting ability.15,16,24

Thus, the ability to achieve independent sitting in children with SMA1 treated symptomatically with nusinersen might be estimated at 30–50%, depending on the age of treatment initiation. This efficacy of symptomatic treatment is incomparably lower than the results of symptomatic treatment.

The importance of age and disease stage is also evident in the treatment outcomes of patients with chronic forms of SMA.

The CHERISH study (NCT 02292537) included 126 patients with SMA2, aged 2–12 years.25 One hundred patients (66 treated vs 34 placebo) completed the 15-month follow-up period. In the group younger than 6 years of age, 64% (38/59) showed an improvement of >3 HFMSE points compared with 14% (1/7) in the group older than 6 years of age. Patients in this trial were followed up in the open arm of the study. In the analysis conducted 690 days after the start of treatment, the greatest improvement by as much as 8.6 points on the HFMSE scale was shown by children younger than 3.69 years (n = 39). In slightly older children, aged 3.69–4.92, an improvement of 3.0 points on the HFMSE scale was observed (n = 35). In patients older than 4.92 years (n = 6), the results were worsened by approximately 2 points on the HFMSE scale.

Onasemnogen Abeparvovec (Zolgensma)

In an open-label study of children with SMA1 and 2 copies of SMN2, after a long, over two-year follow-up of 12 children, eleven were able to sit independently, four to stand, and two to walk.26 In the same group, a correlation of motor achievements with treatment age and baseline functional status was observed.27 Patients treated before the age of 3 months achieved the ability to sit independently earlier than did patients treated after 3 months. The initial functional state was also important. Patients with high functional status who received treatment before the age of 3 months (early dosing/high motor = 3 patients; mean age of sitting 9.4 months) achieved the ability to sit most quickly. Despite a lower baseline motor score, the early dosing/low motor group achieved sitting unassisted earlier than did the late dosing group (mean age: 17.0 vs 22.0 months). This indicates the role of patient age/disease duration in establishing prognosis; nevertheless, the baseline functional status is also important.

Open-label studies for patients with SMA1 and SMA2 and presymptomatic patients (studies STRIVE [NCT03306277], SPR1NT [NCT03505099] and STRONG [NCT03381729]) are still ongoing. Final data are not yet available.

Sparse real-world data on the effectiveness of Zolgensma depending on the age of treatment initiation are available. Based on recently published outcomes for patients aged 1–23 months with 2–4 copies of SMN2, 89%
(n = 17) experienced improvement of motor function, and 11% (n = 2) experienced stabilization.²⁸

In the summary of the US arm of the STR1VE study for infants with SMA1 (treated at the age of 0.5–5.9 months), 90.9% (20/22) survived up to 18 months of age, and 59% (13/22) achieved independent sitting.²⁹ In the European arm of this study, 33 infants treated at the age of 1.8–6.0 months had a shorter follow-up (6.9–18.9 months).³⁰ Of this group, 18.8% (6/32) started to sit independently, and one child started to walk.

The SPR1NT study evaluated children with 2 and 3 copies of SMN2 treated presymptomatically.³¹ Thirty children were qualified (14 of 2 and 16 with 3 copies of SMN2), and the study is ongoing. In the summary from December 2019, among patients with 2 copies, 8 were able to sit and 4 to walk (observation period from 6 to 18 msc); in the group with 3 copies, 4 were able to stand and 3 to walk (observation period 3.3–15 msc). Taking into account the relatively short follow-up time, the results are promising and indicate a much higher effectiveness of presymptomatic in comparison to symptomatic treatment.

**Risdiplam (Evrysdi)**

The Firefish Part 2 study investigated the effectiveness of risdiplam in children with SMA1 aged 1–7 months and 2 copies of the SMN2 gene. Ninety-three percent (38/41) of the children survived, and 29% (12/41) achieved the ability to sit independently.³² Long-term observation of patients from the Firefish Part 1 study revealed that 59% (10/17) achieved the ability to sit unaided after 24 months of treatment.³³ These studies did not analyze the effectiveness of treatment in the context of the patient’s age. However, such an initial analysis was performed in the Sunfish Part 2 study, which included a much more diverse group of SMA2 and SMA3 patients aged 2–25 years. After 12 months of treatment, patients aged 2–5 years showed an improvement of 5.34 points on the MFM32 and 4.34 points on the RULM, as compared to +0.82 and +1.55 in the group of patients aged 6–11, respectively, and –0.05 and –0.56 in the group of patients aged 12–17 years.³⁴ Unfortunately, we do not have data from the Rainbowfish trial (study enrollment is still ongoing) to analyze the effectiveness of presymptomatic treatment.

Clinical evidence supporting the early treatment of patients with SMA was clearly presented recently by Dangouloff et al.²¹

**Newborn Screening for SMA**

Newborn screening (NBS) seems to be the best solution to guarantee early diagnosis of SMA. Neonatal screening tests are mass screening tests covering all newborns, enabling the detection of diseases that, if untreated, lead to serious developmental disorders and even death. The criteria for including the disease in neonatal screening were developed by Wilson and Junger in 1968.³⁵ The basic criteria for introducing screening tests are economic, taking into account the incidence of disease in the population and the availability of treatment and care. Currently, with the development of medicine and diagnostic techniques, this approach is being revised. The economic factor is important but no longer the main criterion for introducing newborn screening tests.

SMA meets all screening criteria according to Wilson and Junger. An important element of these criteria, apart from the severity and frequency of the disease and the effectiveness of early therapy, is the availability of a sensitive and relatively inexpensive diagnostic test. The situation of SMA is rare in clinical genetics, whereby the genetic basis of the disease is extremely homogeneous. In approximately 95–98% of SMA patients, the disease is caused by bilateral loss of the SMN1 gene. This has enabled the development of very sensitive (95–98%), specific (100%) and relatively inexpensive (up to a few Euro/sample) genetic tests for SMA, which can be used on a mass scale and implemented for screening.³⁶⁻³⁸ These tests are performed on DNA isolated from a dry blood drop, with the real-time PCR technique most often being employed. In some centers, screening for SMA is combined with testing for SCID.³⁹ The result of the screening test requires confirmation and evaluation of the SMN2 gene copy number. The MLPA technique is most frequently used for verification/diagnostic tests. However, it is worth mentioning that 2–4% of SMA patients whose symptoms are related to point mutations will not be diagnosed with this type of test. Thus, the introduction of NBS does not negate the importance of differential diagnosis for SMA in the case of floppy infant or limb-girdle syndrome.

The emergence of real prospects for the treatment of SMA a few years ago started discussions on the implementation of neonatal screening for SMA. One of the firsts pilot studies were in Taiwan (in the period 11.2014–09.2016).⁴⁰ In a group of 120,267 newborns who were examined there, seven cases of SMA were identified. Another study was conducted in three hospitals
in New York between 01.2016 and 01.2017, and it allowed the identification of SMA in 1 of 3,826 newborns tested.\textsuperscript{41} Currently, the US is the first country to gradually implement the NBS toward SMA for the entire population.\textsuperscript{37} The first countries in Europe that introduced a pilot screening for SMA were Belgium and Germany. In the former, a pilot study under the (S)un (M)ay (A)rise on SMA project covered the Liege region and later was extended to southern Belgium in the period 03.2018–06.2019.\textsuperscript{42} This study identified SMA in 5 of 35,000 newborns, indicating a higher than previously assumed incidence of SMA in Europe. This was confirmed in German studies conducted in Bavaria and North Westphalia from January 2019 to February 2019. Homozygous deletion of SMA was identified in 22 of 165,525 newborns examined, indicating a frequency of SMA of 1:7524.\textsuperscript{43} In the identified group of patients, as many as 36% (8/22) of the children carried 4 copies of SMN2. Two and 3 copies were identified in 45% (10/22) and 18% (4/22) of newborns, respectively. Preliminary results were confirmed in the update from January 2020, and the estimated population incidence of SMA was corrected to 1:7,350 births (38/278,970 newborns), and 4 copies of SMN2 were identified in as many as 40% of newborns with molecularly confirmed SMA.\textsuperscript{44} On the other hand, the Australian pilot study reported only patients with 2 and 3 copies.\textsuperscript{45} This was to avoid possible psychological harm by providing an early diagnosis with no immediate option for therapeutic intervention due to the reimbursement of nusinersen in Australia only for patients younger than 18 years and with disease onset <3 years. SMA was diagnosed in 9/103,903 newborns (frequency of potential SMA1 and SMA2 1:11545). In 6 and 3 children, two and three copies of the SMN2 gene were identified, respectively.

The current situation of neonatal screening for SMA is very promising. Pilot studies are underway in some countries, while in others, decisions or negotiations have already been made to add SMA to national screening programs. High hopes are attached to the initiative of the European Alliance for Newborn Screening in Spinal Muscular Atrophy. On August 31, 2020, nineteen national SMA patient organizations, which are part of SMA Europe, EURORDIS – European Organization for Rare Diseases, European Alliance of Neuromuscular Diseases (EAMDA), TREAT-NMD and AveXis, Biogen and Roche, formed a European alliance for neonatal screening for spinal atrophy.\textsuperscript{46} The goal of the Alliance is to introduce population screening tests for newborns for SMA in all European countries by 2025. Members of the Alliance will create the White Paper on Newborn Screening for SMA, which will gather scientific evidence to support the need to include SMA in national neonatal screening programs. In addition, Allies will organize activities in their countries to urge health authorities to evaluate the inclusion of SMA in the neonatal screening panel.

**Patients Diagnosed in NBS – Too Late or Too Early for Treatment?**

In the previously cited German and Australian pilot studies, attention was drawn to a very narrow therapeutic window for patients with acute SMA.\textsuperscript{43–45} Four of the nine children identified in the Australian study had symptoms of the disease between 16 and 33 days of life. In one child, the full symptoms of SMA were present on day 16. The initial screening result was obtained, on average, at 8 days of life (5–18), and the diagnostic result was obtained at 18.5 days of life (13–24). Treatment was initiated on average at 26.5 days of life (16–37). In the 10 German patients with 2 and 3 copies of SMN2, three were symptomatic (CMAP ulnar <1 mV and/or CHOP Intend <30 points) at the time of therapy introduction (15–29 days of age). The above observations allow two conclusions to be drawn. At all costs, the time between the final result of the screening test and the onset of the therapy should be shortened. Recently, published consensus on gene therapy have clearly stressed that the time between diagnosis and treatment initiation should not exceed 2 weeks.\textsuperscript{47} On the other hand, it should be realized that for some patients with very severe forms, detection of the disease in NBS does not allow for presymptomatic treatment. Thus, therapeutic effects are likely to be limited. This should be considered when discussing therapeutic plans with the child’s parents.

Among patients identified in NBS are newborns with 4 copies of the SMN2 gene. German studies indicate that this number may reach 40%.\textsuperscript{44} Four copies of the SMN2 gene most often correlate with the mild form of the disease and the onset of symptoms at the age of several years. The presence of 4 copies, unfortunately, does not exclude the acute (rarely) or intermediate form.\textsuperscript{4,9} Regardless, there are reports of completely asymptomatic patients with 4 copies of SMN2.\textsuperscript{48} The question therefore arises when to start therapy in these patients. The recommendations of the American NBS Multidisciplinary Working Group published in 2018 suggest follow-up for this group every
3–6 months before 2 years of age and then every 6–12
months, taking into account clinical and electrophysiolo-
gical tests, functional scales and myometry adjusted to the
patient’s age. In the case of alteration of any of the above
parameters, they recommend immediate treatment. A
revision of the above recommendations from 2020 sug-
gests that therapy should be started immediately after
diagnosis.

In the USA, registration of gene therapy for children up
to 2 years of age, regardless of the number of SMN2
copies, enables the use of this therapy in presymptomatic
children with 4 copies. European registration is more
restrictive and limits administration only to patients with
2 and 3 copies of SMN2. Thus, presymptomatic newborns
with 4 copies can currently only be treated with nusinersen.
Considering the route of administration, the long-term
treatment of asymptomatic children with nusinersen raises
some doubts. On the other hand, German experience
shows that it is difficult to carry out the recommended
follow-up without starting treatment. As many as three
of the patients they supervised were lost to medical fol-
low-up (two because of socioeconomic reasons and one to
avoid the psychological stress associated with the appoint-
ments). High hopes are associated with the possibility of
oral treatment with risdiplam.

Population SMA Carrier Screening
Reproductive carrier screening involves testing of indi-
duals or couples assessing their risk of having a child
affected with autosomal or X-linked recessive diseases.
Reproductive carrier screening started in the 1970s for
Tay-Sachs disease and hemoglobinopathies. Israel,
where the national population program of carrier screening
has been run since the 1980s, has the most extensive
experience in this field. Since 2013, it includes all known
severe diseases with frequencies above 1 in 15,000 live
births or/and carrier frequencies above 1:60. Carrier
testing is voluntary, free of charge and population specific
(according to disease frequency in the different popula-
tions/communities in Israel). Additionally, in some coun-
tries (including Australia, USA, Cyprus, Italy, UK, Saudi
Arabia), preconceptual carrier testing is carried out, free of
charge, depending on ancestry or consanguinity. Commer-
cial tests are also broadly available. Such studies are
becoming increasingly widespread, and their scope
with the development of NGS technology has become
available for hundreds of diseases at relatively low costs.

The aim of reproductive carrier screening is to inform
people about their risk of having affected children and to
allow for informed decisions on reproductive options
(changing the marriage/reproductive plans, prenatal diag-
nosis or preimplantation genetic diagnosis). Reproductive
carrier screening is also considered and discussed in the
context of spinal muscular atrophy. It appears to be a good
solution, enabling an informed decision for couples with
a high risk of having a child affected with SMA. As
treatment develops, pregnancy maintenance and adminis-
tration of the therapy in the first days of life, even before
the NBS result is obtained, have become the real manage-
ment option. In severe forms, each day is important for
prognosis. In the future, prenatal disease treatment will
likely be possible.

Regardless of the positive results that reproductive
carrier screening for SMA may bring, at present, newborn
screening seems to be the most effective option in the
population context. On the one hand, the sensitivity of
SMA carrier tests is limited. Due to the complexity of
the genetic basis of the disease (the presence of the
SMN1 2–0 allele in the population), it is estimated only
at approximately 96%. Thus, a person with 2 copies of
SMN1 gene still have a risk to be an SMA carrier. On the
other hand, it is difficult to imagine obligatory carrier
testing at present, taking into account the worldview issues
and cultural diversity of societies.

Final Remarks
Early treatment of SMA seems to be crucial for maximizing
therapeutic effects. Up to 30–60% (depending on the age of
treatment initiation and the patient’s baseline functional
status) of children with SMA1, treated after the onset of
disease symptoms, achieve the ability to sit independently.
Individual patients acquire the ability to walk with help.
However, the chance of acquiring new milestones is lower
in the case of chronic forms. Nonetheless, presymptomatic
treatment results in (based on previous experience) fully
normal motor development in most patients. Therefore,
every effort should be made to diagnose spinal muscular
atrophy in the presymptomatic period. At present, the best
solution is to screen all newborns for SMA. Given the
homogeneity of the genetic background of the disease and
well-developed screening programs in most countries, the
introduction of universal testing of newborns for SMA does
not appear difficult. The European Alliance for Newborn
Screening in Spinal Muscular Atrophy can also help. In the
future, it is worth considering conducting population
studies of SMA carrier status while taking into account the cultural, philosophical and genetic differences of various social groups and populations.

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