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REVIEW ARTICLE

Novel challenges in spinal muscular atrophy – How to screen and whom to treat?

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Abstract

In recent years, disease-modifying and life-prolonging therapies for spinal muscular atrophy (SMA) have been developed. However, patients are currently diagnosed with significant delay and therapies are often administered in advanced stages of motor neuron degeneration, showing limited effects. Methods to identify children in presymptomatic stages are currently evaluated in newborn screening programs. Yet, not all children develop symptoms shortly after birth raising the question whom to treat and when to initiate therapy. Finally, monitoring disease progression becomes essential to individualize management. Here, we review the literature on screening approaches, strategies to predict disease severity, and biomarkers to monitor therapy.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease affecting one in 10,000 live births with a carrier frequency of 1 in 50 unaffected individuals.[1] Clinically, SMA has been divided into four subtypes based on age at onset, phenotypic severity, and the highest motor milestone achieved, which can be lost later upon disease progression[2]: Type I ("nonsitters"), type II ("sitters"), type III ("walkers"), and type IV (adult-onset). The underlying genetic causes of SMA are homozygous deletions or loss-of-function mutations in the *survival motor neuron 1 gene (SMN1)* with retained function of at least one copy of the paralogous gene *SMN2*, both located on chromosome 5q13. Due to a nucleotide substitution, the majority of *SMN2* pre-mRNA transcripts undergo alternative splicing resulting in exclusion of exon 7. The resulting truncated SMN protein is rapidly degraded and the overall lack of full-length SMN protein ultimately leads to degeneration of alpha motor neurons in the spinal cord.

In recent years, novel causal therapies for SMA have been developed. Following successful approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), a large number of SMA patients has recently been treated with antisense oligonucleotides (Nusinersen, Spinraza®). Large phase 3 trials have shown improvement in motor function and higher event-free and overall survival in infantile-onset SMA[3] as well as significant improvement in HFMSE (Expanded version of the Hammersmith Functional Motor Scale) scores in SMA patients with disease onset after 6 months of age.[4] Recently, Biogen™, the market authorization holder of Nusinersen, released interim results of a phase 2 trial evaluating the effects of Nusinersen in presymptomatic SMA patients types I-III (NURTURE, see ClinicalTrials.gov: NCT02386553), arguing that preemptive treatment led to the achievement of

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age-expected World Health Organization motor milestones, such as sitting without support in SMA type I and stable or improved motor function in SMA type II-III. Taking into account the molecular pathways affected in SMA pathology and the complex canonical and non-canonical roles that SMN protein plays in neuronal metabolism, further promising approaches including adenovirus-mediated *SMN1* gene replacement therapies, modulators of *SMN2* splicing, neuroprotective agents that modify mitochondrial pathways, compounds acting on muscles and neuromuscular junctions, and modifiers of endocytosis, actin dynamics, and ubiquitin homeostasis have been developed.[5–7] Amongst these novel approaches, gene replacement therapies hold particularly great potential to change the course of SMA and are currently investigated in advanced stages of clinical trials. Preliminary data have already been published and show very promising results.[8]

However, the advent of disease-modifying therapies raises important questions: *How do we identify affected children in the pre-symptomatic stage and how can we predict disease severity to choose the optimal therapeutic window for initiation of treatment?* Further, currently all SMA patients receive the same absolute dose of Nusinersen irrespective of age, body weight, and residual motor function, raising another crucial question: *How do we monitor patients under therapy and on what grounds can we adjust treatment doses to individual needs?*

In this review, we will discuss the literature on pre- and neonatal screening approaches for SMA, provide an overview about current strategies to predict disease severity and summarize potential candidate biomarkers to monitor therapeutic response.

Newborn Screening and Prenatal Diagnosis

Preliminary data published on the preemptive treatment of SMA patients have shown a significant increase in motor function and quality of life corroborating data from mouse models that point out that early restoration of SMN levels, preferably within the first three postnatal days, can rescue phenotypes, whereas administration of therapies beyond postnatal day 5 only showed attenuated effects and initiation of treatment after postnatal day 10 failed to improve motor function and survival.[9,10] Along these lines, different Expanded Access Programs for Nusinersen worldwide have clearly identified an early age at treatment initiation as the major determinant for therapeutic success.[11–13] However, in the vast majority of cases, SMA patients are still diagnosed with significant delay, ranging from 4 months after onset of symptoms in SMA type I to over 10 months in SMA type III.[14,15] As a result, available life-prolonging and life-saving therapies are often administered in a stage of advanced alpha motor neuron degeneration, therefore only showing limited effects.

Newborn screening programs for SMA hold tremendous potential for identifying affected children at an asymptomatic stage, allowing presymptomatic initiation of therapy before irreversible motor neuron damage occurs. Nationwide, genetic newborn screening programs for SMA have been widely discussed in the context of the novel life-prolonging therapies. A recent study convincingly demonstrated that homozygous *SMN1* mutations can be detected with high accuracy in dried blood spots, proving a feasible and practical genetic newborn screening method for SMA.[16] In the U.S., SMA newborn screening is already implemented in screening programs in a number of states and further clinical trials are currently evaluating the applicability and economic challenges implicated in a nationwide genetic newborn screening for SMA in Taiwan and Belgium (ClinicalTrials.gov: NCT03217578 and NCT03554343). Limitations to these methods include the fact that point mutations in the *SMN1* gene, accounting for approximately 5% of patients, cannot be detected. Furthermore, SMN has been shown to play a role in neuronal differentiation and formation of the neuromuscular junction in murine cell models, highlighting the demand of SMN during neurodevelopment and synaptogenesis[17] and raising the question whether treatment in neonatal SMA (sometimes referred to as SMA type 0) should already be initiated in the prenatal period.[18] These considerations gain particular importance in the context of promising results in the field of gene replacement therapies that can theoretically be administered in utero. Prenatal screening methods offer the chance to identify affected children during early pregnancy, allowing prenatal therapeutic intervention. Prenatal testing is possible and widely available. Chorionic villus sampling or amniocentesis can be performed at 10–14 or 15–20 weeks of gestation respectively and can determine a child's risk for SMA with high accuracy. However, these techniques are invasive and carry significant risks for the mother and the unborn child and are therefore only carried out in high-risk pregnancies with proven carrier status of the parents. Interestingly, noninvasive prenatal diagnosis techniques have been reported in the literature. By isolating circulating fetal trophoblastic cells[19] or cell-free fetal DNA from maternal blood,[20] it is possible to detect SMA in unborn children with 100% diagnostic sensitivity and specificity, thus holding great potential to further change the field of SMA. However, besides technical limitations, such as isolation of fetal cells and cell-free fetal DNA from maternal blood, these techniques are costly and require laboratories

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with special expertise and are thus not likely to be implemented on a nationwide scale. Finally, significant ethical concerns are implicated with genetic screening methods that have to be discussed in detail by the community before making these tests available.[21]

Approaches to Predict Disease Severity

Screening methods for SMA are important tools to detect affected children at an early stage. However, not all patients will develop clinical signs shortly after birth, and many SMA patients show a very mild disease course with late onset of symptoms and only minimal muscle weakness. In regard of the costly and invasive therapies, the question arises how we can reliably predict disease severity and derive clinical decisions from these predictions.

Recently, the *SMA NBS Multidisciplinary Working Group* released a treatment algorithm for SMA children identified through newborn screening based on *SMN1* deletion analysis in dried blood spots.[15] Recommendations for treatment decisions were based on the correlation of *SMN2* copy numbers and clinical phenotype. The group argues that all children with 2–3 copies should receive immediate treatment, patients with one copy should be treated if asymptomatic at birth and therapy should be delayed in patients with four or more copies due to a usually milder disease course. However, how closely are *SMN2* copy numbers correlated with SMA phenotype and is this quantification enough to decide whether a child should receive therapy?

A number of groups investigated the correlation of *SMN2* copy number and disease severity (Table 1). The majority of studies conclude that a correlation exists, but is not absolute, since there is significant overlap between different SMA types. The most compelling evidence comes from Calucho et al. who attempted to correlate *SMN2* copy number with clinical data in a cohort of almost 3500 SMA patients. The study concluded that while one and four copies were associated with a severe and mild phenotype respectively, there was significant overlap between patients with two and three copies, showing any possible phenotype.[22] Unfortunately, around 80% of individuals in the cohort carried 2–3 *SMN2* copies, reflecting the common problem in clinical practice, where in most cases, 2–3 *SMN2* copies are detected rendering predictions about disease severity extremely difficult. The situation becomes even more complicated considering that, in SMA families, siblings with identical *SMN2* copy numbers can have different phenotypes[23,24] and even five *SMN2* copies in the context of homozygous *SMN1* mutations were found in both SMA type I patients and asymptomatic individuals.[22,25,26]

Taking into account that some lack of correlation between *SMN2* copy number and phenotype may lie in the accuracy of *SMN2* copy number quantitation, which becomes technically demanding with more than three copies, one might argue that the discordance between *SMN2* copy number and phenotype could also lie in the fact that *SMN2* is not equally transcribed among different individuals. Indeed, many studies have shown that *SMN2* transcripts do not correlate with *SMN2* copy number.[27–30] *SMN2* full-length (*SMN2*-fl) mRNA and *SMN2* mRNA lacking exon 7 (*SMN2Δ7*) as downstream readouts of *SMN2* copy number have been studied in SMA patients. Interestingly, some studies identified a correlation between SMN expression and SMA phenotype.[26,31,32] Tiziano et al., for instance, report that SMA type III patients have significantly higher *SMN2*-fl transcript levels than SMA type II patients and unraveled a correlation between motor function scores and *SMN2*-fl transcripts levels in the SMA type II population.[31] Similarly, SMA type III patients with higher transcript levels were associated with more advanced age at disease onset, and a dosage of *SMN2*-fl levels $\geq$58 mol/ng predicted a threefold lower risk of disease onset below the age of 3 years, thus discriminating between SMA IIIA and IIIB. Along these lines, Tiziano et al. report that in ambulant SMA type III patients, *SMN2*-fl mRNA levels correlated with motor performance, thus predicting disease severity.[28] Further evidence comes from families with several SMA children. In siblings with discordant phenotypes, the more severely affected sibling showed significantly lower *SMN2*-fl mRNA levels, while in phenotypically similar siblings, both showed similar *SMN2*-fl transcripts.[31] By contrast, Sumner et al. found relatively normal *SMN2*-fl mRNA in SMA type II and III patients compared to healthy children[33] and Vezain et al. state that in SMA patients with three *SMN2* copies and different phenotypes, *SMN2*-fl and *SMN2Δ7* mRNA levels did not differ.[32] Thus, conclusions about the use of *SMN2* transcripts in predicting disease severity cannot be made with certainty based on the current literature. Nevertheless, despite discordant results, *SMN2* transcript measurements might be helpful in predicting SMA disease severity and should not be completely left out of considerations when it comes to therapeutic decisions. Interestingly, no robust correlations between *SMN2* copy number and SMN protein levels could be established. However, SMN expression seems to be tissue dependent, since unlike in peripheral blood, quantification of SMN levels in fibroblasts did correlate with *SMN2* copy number arguing that blood might not be the adequate biomaterial to monitor SMA.[30]

Moreover, the significant overlaps between *SMN2* copy numbers and phenotype, as well as the lacking correlation between *SMN2* copy numbers and *SMN2* transcript levels

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Table 1. Correlation of *SMN2* copy number and disease severity.

# SMA patients	SMA types	Correlation of SMN2 copy number and disease severity	Reference
Strong correlation			
142	I/III	Good correlation	Mailman et al.[61]
50	I/II/III	Good correlation	Kesari et al.[62]
87	II	Good correlation to HFMS in SMA type II	Tiziano et al.[63]
143	I/II/III	1–2 *SMN2* copies predict early disease onset and poor survival	Taylor et al.[64]
26	I	Correlation with risk of death or permanent invasive ventilatory support	Kolb et al.[47]
3	asymptomatic	Five *SMN2* copies are protective in case of homozygous *SMN1* deletion	Prior et al.[25]
Modest correlation			
115	III/IV	Strong correlation of 1–2 copies with severe phenotype and four or more copies with mild phenotype, strong overlap in cases of three copies	Wirth et al.[65]
NA	I/II/III	Modifying role in MUNE and CMAP and overall functional status	Swoboda et al.[50]
36	I/II/III	Modest correlation	Czech et al.[29]
42	I/II/III	Correlation exists, but better predictor when combined with *NAIP* mutation analysis	Watihayati et al.[66]
375	I/II/III	Correlation exists, but great overlap between groups	Feldkotter et al.[67]
27	I/II/III	Correlation exists, but great overlap between groups	Harada et al.[68]
51	I/II/III	Correlation exists, but great overlap between groups	Tiziano et al.[31]
144	I/II/III	Correlation exists, but great overlap between groups	Medrano et al.[69]
3459	I/II/III/IV	Correlation exists, but great overlap between groups, especially in cases of 2–3 copies	Calucho et al.[22]
45	I/II/III	Correlation exists, but siblings with different phenotypes show identical *SMN2* copy numbers	Cusco et al.[23]
Poor correlation			
48	I/II/III	No correlation	Vezain et al.[32]
45	III	No correlation	Tiziano et al.[28]
61	II/III	Four *SMN2* copies in a family member with SMA type III and unaffected sibling and five *SMN2* copies in unaffected family member	Zheleznyakova et al.[24]
108	I/II/III	SMA type I patients with four or five copies exist	Crawford et al.[26]

CMAP, compound muscle action potential; HFMS, Hammersmith Functional Motor Scale; MUNE, motor unit number estimation; NAIP, neuronal apoptosis inhibitory protein; SMA, spinal muscular atrophy; SMN, survival motor neuron.

highlight the importance of genetic and environmental modifiers. To date, a number of modifiers attenuating or exacerbating SMA phenotype have been reported.[34] Amongst genetic modifiers, a rare polymorphism in *SMN2* (c.859G>C, p.Gly287Arg), acting as an exonic splicing enhancer element and increasing the amount of *SMN2*-fl transcripts has been identified as disease attenuating variant.[25,35,36] Similarly, an A-44G transition in *SMN2* intron 6 has recently been reported, a variant that results in enhanced exon 7 inclusion and a milder phenotype.[37] Along these lines, upregulation of plastin 3 and neuritin 1 as well as reduction of neurocalcin delta have been reported as protective genetic modifiers.[38–40] Concerning epigenetic modifiers, Hauke et al. report that hypermethylation of *SMN2* results in gene silencing and consequently in disease aggravation.[41] These findings were confirmed by Cao et al. who found 13 differentially methylated units in *SMN2*, eight of which were associated with disease severity, thereby showing higher methylation levels in SMA type I compared to SMA type III.[42] In line with these findings, Zheleznyakova et al. carried out genome-wide methylation analysis of SMA patients of all types uncovering several differentially methylated gene loci involved in actin cytoskeleton dynamics, neuronal metabolism, transcriptional regulation, and cell death.[43]

Thus, the exact pathophysiological mechanisms in SMA, especially those determining disease severities, are currently not well understood and the contribution of a number of genetic and epigenetic disease modifiers has been shown in the literature, raising the question whether therapeutic decisions solely based on *SMN2* copy number will suffice in clinical practice.

Candidate Biomarkers for Therapeutic Monitoring

Currently, all SMA patients receive an absolute dose of 12 mg Nusinersen, which is administered via intrathecal administration in 4-month intervals following a loading phase of five intrathecal injections within the first 180 days of treatment. These recommendations are based on phase 1 trials and pharmacological studies that pointed out a half-life of Nusinersen in the cerebrospinal fluid (CSF) of around 163 days and further showed that

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no correlations between age, body weight, and CSF concentration of Nusinersen exist.[44,45] However, while Luu et al. argue that age-based dosing produced more comparable median exposures of Nusinersen in the CSF, no dose-limiting toxicity was reported, leading to consensus of using fixed-dosing schemes across all age groups. Following these results, Finkel et al. carried out a phase 2 dose-escalation study demonstrating that an absolute dose of 12 mg of Nusinersen was superior to 6 mg.[46] Outcome measures included achievement of motor milestones, motor function tests, dependence on permanent ventilation, electrophysiological measurements, and overall survival. However, so far only 20 patients were studied and all patients were under 1 year of age and below 10 kg body weight. Ultimately, the question arises if these pharmacologic investigations and the small cohorts studied in phase 2 clinical trials can accurately reflect clinical practice. Considering the broad variability of SMA patients concerning age at disease onset, body weight, and residual motor function, a uniform dose and equal dosing intervals across all patients seem highly inaccurate. But how can we monitor therapies and on what grounds can we base decisions for adjusting therapeutic doses and dosing intervals to optimize therapeutic success? In order to answer these questions, reliable biomarkers dynamically reflecting disease progression under pharmacotherapy are needed. Candidate biomarkers for SMA have therefore been extensively studied in the past.

Recently, the NeuroNEXT study evaluated different instrumental and molecular biomarkers.[47] Amongst others, compound muscle action potential (CMAP) responses and SMN protein blood levels have been identified as possible biomarkers to monitor therapies.

Electrophysiological measurements have been previously proposed as possible biomarkers for SMA. These measurements include CMAP, motor unit number estimation (MUNE) responses, and electrical impedance myography (EIM). Different studies have shown that both proximal and distal muscles can be used as sites for electrophysiological measurements in SMA patients.[48,49] Importantly, Swoboda et al. point out that electrophysiological measurements hold prognostic value for an individual SMA patient's expectations toward clinical improvement and response to therapy.[50] Indeed, Arnold et al. showed that electrophysiological measurements dynamically change in mice under antisense oligonucleotide therapy providing a potential tool for future treatment stratification.[51] Similarly, SMN protein levels in peripheral blood have been investigated in the past. Measurements of SMN levels in SMA patients have produced stable readouts over the first 2 years of life with little intraindividual variability and have thus been proposed as potential biomarker to monitor disease progression.[27,33,47] Recently, Otsuki et al. published a reliable flow cytometry-based approach to quantify SMN protein levels in peripheral blood. Besides reliably differentiating between SMA subjects and healthy controls, SMN quantification could be correlated to some extent to clinical phenotypes and motor scores, therefore providing a promising candidate biomarker.[52] Meanwhile, approaches for the establishment of radiological biomarkers that are already utilized in neuromuscular disorders such as Duchenne muscular dystrophy, the limb-girdle muscular dystrophies, and others are scarce in SMA and only few studies investigated the correlation between motor function tests and radiologic markers.[53,54] Further studies evaluating the dynamic changes of electrophysiological measurements, SMN protein levels, or even high-resolution magnetic resonance imaging signals in response to pharmacotherapy are needed to confirm the use of these biomarkers to monitor SMA therapies.

Along these lines, the current lack of reliable biomarkers for SMA has fostered the search for novel candidate substrates. Promising methods to detect novel biomarkers are unbiased "omics" approaches. By using proteomics technologies, Matsaers et al. identified Calreticulin and GRP75/Mortalin, proteins associated with neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease, as potential biomarkers for SMA in muscle samples of SMA patients.[55] The "Biomarkers for SMA" (BforSMA) project used a combined proteomics, metabolomics, and transcriptomics approach and detected 97 plasma proteins, 59 plasma metabolites, and 44 urine metabolites correlating with motor function tests.[56] Kobayashi et al. analyzed plasma samples from the BforSMA study in detail and found 12 candidate SMA biomarkers significantly associated with motor function and further analytes associated with nonmotor SMA outcome measures, which were included into a commercial plasma protein panel.[57] Several analytes deriving from the findings of Kobayashi et al. were subsequently investigated in the *SMNΔ7* mouse model before and under treatment with antisense oligonucleotides (ASO). Osteopontin, dipeptidyl-dipeptidase 4 (DPPIV), tetranectin, fetuin A and vitronectin were identified to significantly correlate with motor function and some of these candidate biomarkers normalized in ASO-treated mice. However, the group concludes that these candidate biomarkers are not disease-specific and the observed results most likely show compensatory changes rather than being directly attributable to SMA pathology.[58] Currently, the "NatHis-SMA study" is evaluating the value of a number of biomarkers for predicting SMA disease severity and progression and to determine their use as outcome measures for further therapeutic trials (ClinicalTrials.gov: NCT02391831). Recently published baseline results demonstrate that muscle strength and

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motor function tests, measurements of upper limb function, respiratory function tests, as well as electrophysiological and radiographic studies were able to differentiate among nonsitter and sitter SMA type II, nonambulant SMA type III and ambulant patients. Longitudinal evaluation during the 2-year observation period will unravel if these candidate biomarkers will be able to dynamically reflect disease progression determining their value as therapeutic outcome measures.[54]

Thus, the search for biomarkers for SMA has identified a number of candidates. However, none of the designated substrates has yet proven to dynamically reflect SMA disease progression. Further studies are needed to evaluate the clinical benefits of current potential candidates as well as to isolate novel disease-specific biomarkers in order to allow accurate monitoring and recommendations for individual adjustments of therapy.

Conclusion

SMA is a devastating neuromuscular disease associated with high morbidity and mortality. In light of novel therapies profoundly changing disease course and prolonging survival, reliable biomarkers and screening methods for early diagnosis and therapeutic monitoring are needed more than ever. Here, we provide a critical review about current pre- and neonatal screening approaches, strategies to predict disease severity, and potential biomarkers for therapeutic monitoring.

Screening methods are currently being evaluated in clinical trials and offer tremendous opportunities for early diagnosis. However, technical and ethical issues are yet to be discussed. Predictions of disease severity remain a challenging topic. Taking into account the discordance between phenotype and *SMN2* copy numbers, as well as the many exceptions ranging from asymptomatic to severely-affected patients with high copy numbers and mildly-affected individuals with low copy numbers in combination with the many genetic and epigenetic modifiers contributing to disease severity, the decision upon initiation of costly and invasive SMA therapies based solely on *SMN2* copy numbers appears highly unsatisfactory. In addition, *SMN2* copy number, to date, holds no prognostic value concerning response to therapy as recently published interim results of the NURTURE trial demonstrate for presymptomatic SMA individuals corroborating the previously shown data for symptomatic patients.[11,12,59] In the absence of reliable predictive biomarkers, assessment of SMN protein levels and genetic and epigenetic modifiers, providing at least some information about disease severity, should in our opinion be considered in cases with more than three *SMN2* copies before denying affected children potentially life-saving therapies. Further, the question arises how to monitor untreated individuals to catch the optimal time point for treatment initiation. The *SMA NBS Multidisciplinary Working Group* suggests regular clinical follow-up visits for individuals with four and more *SMN2* copies with age-dependent assessment of EMG, CMAP, myometry, physical exam, and motor function tests such as the HFMSE and the 6-Minute Walk Test (6MWT).[15] Indeed, recently Montes et al. demonstrated high sensitivity of the 6MWT in predicting phenotypic severity in ambulant SMA patients, reliably capturing small prognostic changes.[60] Similarly, sensitive changes in quantitative MRI of the thighs have been reported as powerful monitoring tool.[53] Additional studies are needed to optimize medical care and develop more sensitive tests for untreated individuals with SMA to avoid missing the critical window of opportunity for treatment initiation with potentially devastating consequences for the affected individuals.

Finally, therapeutic monitoring is essential to adjust treatment and optimize outcome. Electrophysiological studies and measurements of SMN protein levels provide possibilities for therapeutic monitoring. Further studies need to evaluate the benefits of these biomarkers. Due to the discordant findings regarding the value of currently available biomarkers, the search for novel candidates is more pressing than ever. This point becomes even more important in light of ongoing and upcoming clinical trials to evaluate novel therapeutics such as the orally administered small molecules risdiplam (FIREFISH, RAINBOWFISH) and branaplam, intravenous and intrathecal adenovirus-mediated *SMN1* gene replacement therapies (SPRINT, STRIVE-EU, REACH), and others. Monitoring and clinically comparing patient cohorts treated with these novel therapies will become particularly challenging since subtle subclinical changes have to be detected to evaluate the benefits of the specific therapeutics and different routes of administration, adjust therapeutic management in case of disease progression and define cutoffs for considering add-on and combination therapies to maximize clinical outcomes. Promising approaches to identify novel biomarkers could come from "omics" studies, providing a useful untargeted tool to screen for candidate biomarkers. However, results are often difficult to interpret. To date, disease-specific biomarkers could not be identified.

In conclusion, the exciting field of SMA is currently being transformed due to novel disease-modifying therapies. Novel screening methods, strategies to predict disease severity and candidate biomarkers allowing therapeutic monitoring are being identified and developed, however, as yet all of these techniques show limitations, and none of them accurately reflects the complexity of SMA pathology. Further research is needed to identify more accurate

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methods for diagnosis, disease prediction, and therapeutic monitoring in SMA and to establish individualized dosing recommendations. This will be the next major step in the transition of a recently untreatable rare neuromuscular disease to precision medicine and satisfactory long-term therapy and outcome.

Author Contributions

All the authors designed the manuscript. A.S. and A.Z. wrote the initial draft. All the authors read, amended, and approved the final manuscript.

Conflicts of Interest

A.S. reports grants from Biogen which manufactures and develops therapies for spinal muscular atrophy. S.K. has nothing to report. G.F.H. has nothing to report. M.W. reports financial support for conference attendance from Biogen which manufactures and develops therapies for spinal muscular atrophy, and from Pfizer. A.Z. reports grants from Biogen and Avexis which manufacture and develop therapies for spinal muscular atrophy.

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