

Spinal Muscular Atrophy Update in Best Practices

Recommendations for Diagnosis Considerations

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Abstract

Background and Objectives

Spinal muscular atrophy (SMA) is an autosomal recessive progressive neurodegenerative primary motor neuron disorder caused by biallelic variants of the survival motor neuron 1 (*SMN1*) gene. The most recent SMA best practice recommendations were published in 2018 shortly after the approval of the first SMN-enhancing treatment. The availability of disease-modifying therapies for 5q SMA and implementation of SMA newborn screening (NBS) has led to urgency to update the SMA best practice recommendations for diagnosis and to reevaluate the current classification of SMA. In addition, the availability of disease-modifying therapies has opened the door to explore improved diagnosis of adult-onset SMA.

Methods

A systematic literature review was conducted on SMA NBS. An SMA working group of American and European health care providers developed recommendations through a modified Delphi technique with serial surveys and virtual meeting feedback on SMA diagnosis to fill information gaps for topics with limited evidence. A community working group of an individual with SMA and caregivers provided insight and perspective on SMA diagnosis and support through a virtual meeting to guide recommendations.

Results

The health care provider working group achieved consensus that SMA NBS is essential to include in the updated best practice for SMA diagnosis (100%). Recommendations for the following are described: characterizing NBS-identified infants before treatment; minimum recommendations for starting or offering SMA NBS in a state or country; recommendations for activities and services to be provided by an SMA specialty care center accepting SMA NBS referrals; and recommendations for partnership with individuals with SMA and caregivers to support NBS-identified infants and their caregivers. Limited data are available to advance efficient diagnosis of adult-onset SMA.

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Coinvestigators are listed in the appendix at the end of the article.

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Discussion

Updating best practice recommendations for SMA diagnosis to include SMA NBS implementation is essential to advancing care for individuals with SMA. In addition to testing, processes for the efficient management of positive newborn screen with access to knowledgeable and skilled health care providers and access to treatment options is critical to successful early diagnosis. Additional evidence is required to improve adult-onset SMA diagnosis.

Introduction

Spinal muscular atrophy (SMA) linked to chromosome 5q (SMA) is an autosomal recessive disorder caused primarily by biallelic (homozygous) variants in the survival motor neuron 1 (*SMN1*) gene¹ affecting approximately 1 in 15,000 live births.²

SMA is characterized by dysfunction and loss of the spinal cord alpha motor neurons, causing progressive muscular weakness and atrophy.³ SMA has a wide range of clinical severity. *SMN2* gene copy number, a low-functioning *SMN1* paralog,^{1,4} correlates with disease phenotype although there are exceptions. Historically, SMA was classified into types based on the natural history of the disease. In the new therapeutic era, phenotypes are shifting. Before disease-modifying therapies, SMA types were defined by age at symptom onset and maximum motor function achieved.^{3,5} The uncommon SMA type 0 phenotype has prenatal onset associated with decreased fetal movement, significant motor weakness, respiratory distress, difficulty feeding, contractures, and cardiac defects noted at birth.⁶ The most incident phenotype, type 1 SMA, occurs in approximately 60% of infants born with SMA with weakness during the first 6 months and never achieving independent sitting.^{3,5,7,8} SMA type 2 phenotype has been defined by weakness between 6 and 18 months of life after achieving independent sitting but not walking independently. Approximately 10% of individuals born with SMA presented with SMA type 3⁸ and achieved walking independently with abnormal gait and were diagnosed after 18 months of age.^{3,5,8} An estimated <1% of individuals with SMA present during adulthood (usually fourth decade) and are classified as type 4 or adult-onset SMA and have mild motor impairment.^{3,5,9} Although symptoms are milder and progression is slower, people with adult-onset SMA often experience a long process of testing and evaluations before diagnosis.¹⁰

In 2007, an International Conference convened to develop the first publication on SMA standards of care.⁵ In 2018, SMA best practice recommendations were updated by convening an International Conference of SMA experts¹¹; 2 publications were produced^{12,13} and globally distributed. Subsequently, 3 SMN-enhancing treatments, nusinersen (Spinraza®, Biogen, Cambridge, MA), onasemnogene abeparvovec-xioi (Zolgensma®, Novartis Gene Therapies, Bannockburn, IL), and risdiplam (Evrysdi®, Genentech, South San Francisco, CA) have been approved by multiple regulatory bodies worldwide, and treatment approval is heterogeneous by country. The approval of nusinersen¹⁴

and successful SMA newborn screening (NBS) pilot programs^{15,16} facilitated implementation of SMA NBS resulting in dramatic change in SMA natural history. Furthermore, the historical classification of SMA by type no longer adequately characterizes outcomes for infants and children with SMA who received early disease-modifying treatment.

Historically, SMA was diagnosed through 2 pathways: (1) symptomatic presentation to primary care followed by referral for physical therapy or developmental/neurologic evaluation or waiting and observing symptom progression¹⁷ and (2) prenatal or early postnatal genetic testing associated with family history of SMA or known familial SMA carrier status.¹² Several studies report that during symptomatic presentation, significant irreversible motor neuron loss has already occurred.¹⁷⁻¹⁹ By contrast, clinical trials of presymptomatic SMA treatment have demonstrated the dramatic impact of early treatment initiation.²⁰⁻²³ Real-world evidence of NBS-identified infants confirmed impact of symptom status at treatment initiation.² Thus, early treatment provides the best outcomes for SMA,²⁴⁻²⁷ and individuals with SMA must be identified urgently and ideally before the occurrence of first symptoms. Thus, SMA NBS is paramount. However, approximately 3%–5% of infants with SMA will not be identified by current SMA NBS genetic testing based on PCR due to having a heterozygous *SMN1* deletion and a single-nucleotide variant on the other allele rather than homozygous deletion of the *SMN1* allele.

The aim of this work was to update the SMA best practice recommendations for diagnosis through systematic literature review and sequential modified Delphi surveys and discussions. Emphasis is on NBS because of the significant impact of early diagnosis and treatment on disease outcomes and on adult-onset 5q SMA because of the frequent diagnostic delay. This work is intended for health care providers, individuals with SMA, and caregivers.

Methodology

Systematic Literature Review

In November 2021, Cure SMA enlisted RTI Health Solutions to conduct a systematic literature review (SLR) to understand the diagnostic NBS and treatment landscape for SMA over the previous 10 years. The objective of the SLR was to assess the availability and efficacy of NBS and diagnostic tools for SMA. See eAppendix 1.

SMA Diagnosis Working Groups

Health care professionals with SMA expertise, individuals with SMA, and caregivers were invited to participate.

Health Care Provider Working Group

Participants included Cure SMA Care Center Network directors, SMA Clinical Trial Investigators, and Cure SMA Medical Advisory Council members. SMA Europe, a partner patient advocacy organization, identified European providers. Respondents were invited to participate in the modified Delphi process. The Health care provider working group (HCPWG), supported by the largest US SMA patient advocacy organization, Cure SMA, was invited to an introductory virtual meeting. Members were invited to complete sequential surveys and attend virtual meetings to review results. The HCPWG included 18 members plus 2 organizing and nonvoting Cure SMA staff members who moderated discussions and had no stake in the decisions. The HCPWG included 5 European physician neurologists, 12 US physician neurologists, and 1 U.S. genetic counselor. All HCPWG members participated voluntarily without compensation.

Achieving Consensus Through the Modified Delphi Technique

The HCPWG used a modified Delphi technique^{28,29} to reach consensus on recommendations. Data were collected using 3 iterative online survey rounds³⁰ (Alchemer, Louisville, CO). Sequential surveys started with broad questions during round 1 that motivated more specific questions about SMA diagnosis journey and diagnostic tools. Members answered subsequent survey questions anonymously by choosing from a selection of responses or rank-ordering responses and providing comments. Following each survey, responses were consolidated. Results with 90% or more agreement were considered highly significant. Results with 60%–89% agreement were considered significant. Results were reported back to members for further discussion through a virtual meeting. During follow-up discussion, members shared additional considerations.

The advantages of this technique include allowing voting members to provide their opinions anonymously, without undue influence from more outspoken individuals within the group. This method allowed for easy topic identification for which the HCPWG did not initially reach consensus and could be further examined. In addition, this technique uses online tools that allow global communication among physically distant voting members. Consequently, the Delphi method has been increasingly used to reach consensus in many fields, including medicine, education, and research.³¹

Community Working Group

Individuals with SMA and caregivers were invited to participate in a workgroup virtual meeting to gain their perspective. One adult with SMA and 4 caregivers participated in 1 meeting and discussed questions as a group. Questions focused on diagnosis, resources, and information that would be helpful during diagnosis to make informed decisions. The

Community working group (CWG) was asked comparable questions as the HCPWG. Consensus was achieved through discussion across the CWG. Qualitative responses were compiled.

Standard Protocol Approvals, Registrations, and Patient Consents

Standard protocol approvals, registrations, and patient consents are not applicable for this work.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Updating SMA Diagnosis Best Practice Recommendations

The 5q SMA diagnostic process as described in previous consensus statements remains accurate for symptomatic presentation.^{5,12} The HCPWG achieved highly significant consensus that SMA NBS is essential to be included in updated best practice recommendations for SMA diagnosis (100%). Additional topics selected by more than 60% of the HCPWG included the importance of reducing time to diagnosis (94%) and better understanding of SMN2 copy number impact (75%). Another topic raised for consideration was adult-onset SMA (SMA type 4).

SMA Newborn Screening

SMA NBS is in varied stages of development as a pathway to reduce the prolonged SMA diagnostic journey throughout the world.^{16,32-35} SMA NBS is based on genetic screening for homozygous deletion of *SMN1*; the most common first-tier methodology is quantitative PCR (qPCR).³⁶ Of note, advancing SMA NBS has benefitted from implementation of Severe combined immunodeficiency (SCID) NBS, which relies on qPCR technique. SMA NBS is frequently multiplexed to SCID NBS testing.³⁶ SMA NBS has been implemented in multiple countries throughout the world.³⁷ For the most current status of SMA NBS in Europe, please see: odysma.sma-europe.eu/data-views/status-sma-newborn-screening/,³⁷ and for that in United States, please see: <https://www.curesma.org/newborn-screening-for-sma/>.

Recommendations

The processes in place to manage positive SMA NBS results affect the timeline and efficacy of treatment. The following recommendations provide insight into core considerations to implement and standardize SMA NBS management and care to achieve best outcomes (Table 1). Recommendations 1–3 were developed with the HCPWG. Recommendation 4 was developed with the CWG.

Recommendation 1

SMA infants identified by NBS and before treatment initiation should be characterized by *SMN2* copy number, current

Table 1 Recommendations Summary**Recommendation 1**

SMA infants identified by NBS and before treatment initiation should be characterized by *SMN2* copy number, current motor function, age at symptom onset, and severity of symptoms

Recommendation 2

Minimum requirements for starting or offering SMA NBS and responsible team:

	Public Health NBS Laboratories	Primary Care Provider	SMA Specialty Care Clinic Team
1. Process to notify infant's caregivers and coordinate initial visit after SMA NBS identification	X	X	X
2. Process for referring infants with SMA to appropriate specialists	X	X	X
3. Collaborative team that includes experts who evaluate motor function			X
4. Process to prevent delays starting treatment			X
5. Efficient process for determining coverage, cost, and reimbursement of treatment			X

Recommendation 3

Every SMA specialty care center accepting SMA NBS referrals should provide

1. Prompt initial evaluation and follow-up visits
2. Education and resources for caregivers
3. Confirmatory diagnostic testing and other laboratory monitoring
4. Multidisciplinary care and coordination
5. Efficient process for treatment access

Recommendation 4

Individuals with SMA and caregivers are essential partners and must be involved at all levels throughout the diagnosis, care, and treatment decision-making process

motor function, age at symptom onset, and severity of symptoms. Highly significant consensus was achieved for Recommendation 1 (see Table 2). The classification of SMA severity based on SMA type has changed due to the effectiveness of SMN-enhancing treatments in tandem with early identification by NBS and urgent confirmatory diagnosis. Thus, the HCPWG discussed that classification of newborns by SMA type is not clinically meaningful for newly diagnosed infants with SMA and those treated early in their life with SMN-enhancing treatment(s). This initial essential characterization of the infant before treatment guides care and management discussions with parents and caregivers and guides discussion with payers regarding access to treatments. Please note that characterization of NBS-identified infants also applies to infants identified through prenatal screening.

SMN2 Copy Number

Highly significant consensus (100%) was achieved that *SMN2* copy number is very important during confirmatory diagnostic testing. *SMN2* copy number is definable and, generally, a higher *SMN2* gene copy number correlates with less severe disease, although there are exceptions.⁴ Because *SMN2* copy number is associated with disease phenotype,

progression, and outcomes, determining the number of *SMN2* copies is urgent and should be included as a component of the confirmatory diagnostic testing to include both the number of *SMN1* and *SMN2* gene copies. In addition, based on consensus recommendations by US clinicians to treat infants with 4 copies of *SMN2* urgently,³⁸ distinguishing between 4 and 5 copies of *SMN2* is necessary. Of note, an *SMN2* genetic modifier has been identified. The single base substitution in *SMN2* in exon 7, c.859G>C, results in a new exonic splicing enhancer element and increases the amount of SMN full-length transcription and may play a role in less severe disease phenotype.³⁹ Further understanding of the gene modifier mechanism is required. Testing for this specific variant is not commercially available currently.

Current Level of Motor Function

Highly significant consensus (100%) was achieved that assessing the level of function including development and motor function is an essential characteristic of an NBS-identified infant before treatment. Because motor function and weakness may vary across the musculoskeletal system of young infants with SMA, having an experienced and qualified evaluator assess function through standardized testing, e.g.,

Table 2 Diagnosis Workgroup Consensus

Delphi questions	Responses (%)	(%)
Recommendation 1	Yes	No
Do you agree that the following is an important characteristic of NBS patients (other than by types before treatment)?		
SMN2 copy number?	100	0
Current level of function?	100	0
Age at onset of symptoms?	90	10
Severity of symptoms?	90	10
During diagnosis, SMN2 copy number is very important	100	0
Recommendation 2	Yes	No
Do you agree with the following for purposes of consensus?	100	0
The following should be minimum requirements for starting NBS in your state or country:		
<ul style="list-style-type: none"> • Process to coordinate initial visit after diagnosis • Process to prevent delays starting treatment • Process for referring individuals with SMA to appropriate specialists • Collaborative team that includes someone to evaluate motor function • Efficient process for determining cover, cost, and reimbursement of treatment 		
Recommendation 3	Very important	Important
Rate level of importance for what should be provided by an SMA NBS referral center:		
• Prompt initial and follow-up visits	100	0
• Treatment options presented	100	0
• Confirmation diagnostic testing	93.3	6.7
• Education and resources for family	73.3	26.7
• Meetings for determining next steps	73.3	26.7
• Coordination with primary care provider and other specialists	60	40
• Laboratory assessments	60	33.3
How important is having a qualified evaluator assess a patient's motor function after confirmed diagnosis?	62.5	37.5

Bayley Scales of Infant Development or Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) is essential.

Age at Symptom Onset

Highly significant consensus was achieved (90%) that age at symptom onset is an important characteristic for newly diagnosed and NBS-identified infants. Having symptoms before initiation of treatment, which is consistent with

irreversible motor neuron loss,^{18,40} affects SMA disease outcomes variably. A better understanding of the correlation of symptoms, treatments, and outcomes is critical to improving care and optimal use of available treatments.

Severity of Symptoms

Highly significant consensus was achieved (90%) that severity of symptoms is an important characteristic and when

present before treatment provides prognostic guidance. Some infants identified by NBS are symptomatic at birth or may become symptomatic within a very short time following birth. Characterization by symptom severity informs the conversation with patients and caregivers regarding expectations and interventions and is clinically meaningful during conversations with agencies that approve treatment access. Age at symptom onset, current level of function, and severity of symptoms are linked yet distinctly different dimensions of characterizing NBS or prenatally identified infants.

Recommendation 1

Additional Considerations

Symptomatic vs presymptomatic was selected by 75% of the HCPWG to characterize NBS-identified infants. However, the delineation between presymptomatic and symptomatic for NBS-identified infants was not resolved by the HCPWG. The discussion focused on defining the clinical presentation continuum between presymptomatic and symptomatic in which the suspicious signs and symptoms of SMA begin to appear but are not confidently attributed to SMA. This in-between state is often described as vague symptoms suggestive of SMA. Suggested labels included paucisymptomatic and prodromal.⁴¹ The terminology of clinically silent, prodromal, and clinically manifest has been proposed,⁴¹ although further validation is needed.⁴²

Thus, clinical examination, though essential, may be limited and unable to distinguish between the presymptomatic and symptomatic states in some situations. Clarity of this continuum may be important as a surrogate marker for clinically meaningful progression or change of clinical disease status. In addition, several NBS pilots have reported symptom incidence of 40% in individuals with 2 copies at treatment initiation,⁴³ highlighting that progression to symptomatic state may occur rapidly. The HCPWG made the point that when an objective biomarker is identified that monitors and measures the effect of the disease on motor neuron loss and responsiveness to treatment, and is widely available for clinical application, this biomarker can be added to clinical examination, evaluation, electrophysiology, and motor function measure assessments.

Age at treatment initiation was proposed as an important characteristic; however, this characteristic may have greater prognostic impact post initial NBS-identified window and is outside the scope of this work.

Recommendation 2

Minimum requirements for starting or offering SMA NBS:

1. Process to notify infant's caregivers and coordinate initial visit after SMA NBS identification
2. Process to prevent delays starting treatment
3. Process for referring infants with SMA to appropriate specialists

4. Collaborative team that includes experts who evaluate motor function
5. Efficient process for determining coverage, cost, and reimbursement of treatment

The HCPWG achieved significant consensus (75% or more) that the abovementioned processes should be minimum requirements when initiating SMA NBS in a state or country, as listed in rank order per the second Delphi survey. These items reached highly significant consensus (100% of respondents) in the third Delphi survey (see Table 2). Depending on the location, the responsibilities for each step may vary across the testing laboratory, the primary care provider, and the neuromuscular specialty care provider.

Public Health NBS Laboratories conducting SMA NBS are responsible for the following processes:

1. Urgently (same day) notify the child's primary health care provider about positive SMA newborn screen through phone, pager, or fax. Notifying the SMA specialty care center (SCC) physician the same day may result in more efficient time to treatment.
2. Identify and ensure access to SMA SCC equipped to urgently care, counsel, and provide access to all approved treatments for individuals with SMA in their region.
3. Follow-up with the referral SMA SCC to ensure that the initial visit occurred, confirmatory testing was obtained and resulted, follow-up visits are scheduled, and whether treatment was provided.

The primary care provider notified by the public health laboratory is responsible for urgently (same day) communicating with the infants' caregivers about the results, making the urgent referral to an SMA SCC, and facilitating scheduling the infant for an initial SMA SCC evaluation appointment ideally within 2 days of notification (3 days if weekend).

The SMA SCC physician and team have the responsibility to ensure patient access to and prevent delays for the initial evaluation and treatment and referring patients to additional specialists as described further.

Recommendation 3

Every SMA SCC accepting SMA NBS referrals should provide the following (in rank order): prompt initial and follow-up visits; treatment options presented; confirmatory diagnostic testing; education and resources for caregivers; meetings for determining next steps; coordination with primary care provider and other specialists; and obtain necessary laboratory studies.

The HCPWG achieved highly significant consensus on the abovementioned services to be provided by the SMA NBS referral SMA SCC, ranking each either very important or important (see Table 2). Following notification of positive

SMA NBS results, the SMA SCC should begin the list of urgent activities mentioned earlier.

Prompt Initial Evaluation and Follow-Up

Every SMA SCC that accepts SMA NBS referrals should have the capacity to meet and evaluate the SMA NBS-identified infant within 2 days (3 days if weekend) after receiving notice and/or referral of positive SMA NBS. Expectations for follow-up clinic visits should be stated during the initial clinic visit including purpose, e.g., follow-up examination and assessment of motor function and development, reviewing test results, monitoring symptoms and outcomes, monitoring for treatment side effects, and discussion of next steps. Follow-up visits should be scheduled before leaving the initial visit and after each clinic visit.

Education and Resources for Caregivers

SMA SCC health care providers must have the knowledge, experience, and ability to provide unbiased education and resources and compassionate care to individuals with SMA and their caregivers to guide their decision-making. During the initial evaluation, education about predicted SMA natural history should be provided by an experienced neuromuscular physician and clinical team members both verbally and in writing. Information should be adapted and individualized to the child's condition, as assessed by the physical examination, current level of function, symptoms present and severity, and *SMN2* copy number and adapted to assist the caregiver with understanding. *SMN2* copy number may not be available at first evaluation; thus, education and counseling may be limited to a high-level overview of SMA and available treatments. Key takeaway messages include understanding that SMA is a severe disease, treatment options are available, and treatment is not a cure. Consider that the internet has vast amounts of information of varying quality and reliability. Proactively directing patients and caregivers to reliable web-based data sources is tremendously helpful, e.g., curesma.org/ and sma-europe.eu/ or respective national or local reliable websites. In addition, providing supportive resources as soon as possible including social worker, genetic counselor, care coordinator, or case manager and access to a patient advocacy organization will assist caregivers with counseling, understanding, and managing expectations and scheduling follow-up. During follow-up visits/meetings with the newly diagnosed child and caregivers, providing information and support is equally important and should include repeating educational information with treatment options and assessing caregiver understanding by asking questions.

In addition, SMA SCC teams should have the experience and resources to provide counseling about and access within their center to the SMA treatment options approved in their respective country and the follow-up care and monitoring required. Caregivers should receive information about all

available treatment options, known benefits and risks, anticipated possible and probable side effects, and required monitoring post treatment both verbally and written. Reasonable expectations and limitations about treatment should be discussed and reinforced that no current treatment cures SMA. The SMA SCC should provide the patient and caregiver with a care plan that includes clear goals, time lines, and expectations.

Confirmatory Diagnostic Testing

Whole blood for SMA diagnosis confirmation should be obtained at the first visit or before the visit along with other screening laboratory studies as feasible and in consideration of treatment options. Studies include *SMN1* and *SMN2* copy number (distinguishing between 4 and 5 copies) for SMA diagnosis confirmation and may include other screening studies, e.g., AAV9 antibody titer, liver function tests, platelet count, troponin-I level, coagulation testing, and urine protein spot testing depending on treatment considerations.

Multidisciplinary Care and Care Coordination

Care coordination for the child is essential throughout the process of diagnosis, treatment, and follow-up care. The primary care provider as a valued source of information and support for caregivers should receive communication about all clinic visits, findings, and conversations. Clinic documentation should be shared with the child's caregivers.

Per previous SMA best practice recommendations, multidisciplinary care is core to achieve optimal outcomes for SMA and includes referrals, evaluations, and follow-up visits with multiple specialists.⁸ Care coordination is often led by the SMA SCC physician and may be delegated to designated staff. The HCPWG recommends that staff responsibilities be clear and contact information is provided to patients and caregivers. Individuals with SMA and caregivers should receive assistance to schedule appointments and coordinate care across the SMA SCC multidisciplinary team. In addition to the SMA specialty physician, genetic counselor, care coordinator, or case manager listed earlier, the team should include experienced SMA health care providers in Physical Medicine and Rehabilitation, (e.g., physical therapist, occupational therapist, speech and feeding therapy, physician), Nutrition, Pulmonology/Respirology, Orthopedic Surgery, and Mental and Emotional Health support, e.g., social work and/or counselor. Multidisciplinary and interdisciplinary care assisted by care coordination to navigate care is essential to optimize level of function and manage symptoms.⁸

Motor function and developmental milestones are the primary outcome measures used to monitor SMA disease and treatment outcomes in early childhood. HCPWG achieved significant consensus that the SMA SCC team should include a qualified evaluator to complete formal assessments of

motor function and development to establish the infant's baseline during confirmed diagnosis and before treatment initiation. Longitudinal assessments of motor function and development are necessary during watchful waiting to support continued access to treatment as applicable and to contribute to knowledge about SMA treatments and related outcomes. Greater understanding of the variables contributing to treatment outcomes will contribute to best use of treatments. The longitudinal motor function evaluator is often a physical therapist or occupational therapist.

Efficient Process for Treatment Access

Within a state or country, the process to secure approval or authorization for SMA treatment must be well established by the SMA SCC to efficiently initiate treatment. Globally, the process requires that patient information be submitted for review. In countries with a national health care system, the process requires a request for access to a treatment through a national health governing agency; in countries with government-funded and/or employment-based insurance, access to the nationally approved treatments requires a prior authorization for each patient specific to insurer. This process often requires close follow-up by the prescribing provider to ensure that documentation has been received and is being processed. When a denial determination is received, the next step is urgent submission of an appeal. To minimize delay, an established process within each SMA SCC is required and must include the allocation of dedicated staff time. The most successful programs have dedicated staff who complete the submission documentation and coordinate the communication process for approval. Authorization request submission should occur within 24 hours of having all required information.

Recommendation 4

Individuals with SMA and caregivers are essential partners and must be involved at all levels throughout the diagnosis, care, and treatment decision-making process. The CWG shared insights and recommended the following to support NBS-identified and newly diagnosed individuals with SMA and their caregivers.

Information About SMA

Patient/parent/caregiver should be provided with nonbiased education about SMA diagnosis, current functional status of patient, and information about supportive care. Information should be presented at the patient/parent/caregivers' level of understanding and culturally aligned. The HCPWG and CWG agreed that education, information, and access to resources including patient advocacy organization materials are necessary to guide shared decision-making. In addition, CWG recommended that these conversations be with health care professionals who will guide them through the process and collaborate with them on decision-making. After all information has been provided to individuals with SMA and

caregivers, time to ask questions and consider the options should be provided. Decisions about care are between individuals with SMA/caregivers and their health care providers.⁴⁴

SMA Care in Addition to Approved SMA Treatments

CWG achieved consensus that individuals with SMA and caregivers benefit from access to multidisciplinary specialists who will provide additional education and information about the multiorgan system impact and risks of SMA including actively monitoring and managing symptoms. These multidisciplinary specialists, specific to their expertise, should monitor nutrition, motor function and development, orthopedic concerns, respiratory status, and illness management and provide a care plan. Essential information includes the importance of addressing and providing care for active symptoms without delay. CWG identified that overreliance on treatments without integration of supportive care results in increased risk of morbidity and mortality, and CWG recommended setting expectations that ongoing SMA care is essential and concurrent with SMA treatments.

CWG recommended access to SMA SCC staff who assist with care coordination and case management to facilitate patient and caregiver navigation through the health care system including scheduling follow-up appointments with SMA SCC multidisciplinary care team members and navigating treatment access.

Access to Community Resources

Because SMA is a rare disorder, CWG recommends referral and access to multiple community-based resources including:

1. Peer support through the SMA community of people with SMA and caregivers and access to community resources to facilitate ongoing learning surrounding the diagnosis and treatment options. This may occur in the form of support groups online or in person.
2. Patient advocacy organizations are often the most reliable source of complete and current information about SMA and support. Referral to patient advocacy organizations should occur shortly after diagnosis.
3. Caregiver psychological support to manage the impact of the SMA diagnosis on expectations and personal mental health.
4. Programs for early developmental monitoring, e.g., Birth-to-3 Program (United States) or Child Health Center assessments (Europe) can be reassuring and facilitate identification of therapy needs.

Adult-Onset 5q SMA Diagnosis

Adult-onset 5q SMA represents a small proportion of all who are diagnosed with 5q SMA. Individuals with adult-onset

SMA typically present with proximal muscle weakness over the age of 18 years. Some fit the characteristics and natural history of SMA type 3b individuals with SMA, while others (usually starting symptoms at age older than 30 years) seem to have a less progressive disease and are classified as type 4 SMA.^{45,46} Ambulation is maintained. EMG is consistent with a neurogenic etiology, and compound muscle action potential (CMAP) amplitude correlates with clinical severity.^{10,47} Typically, 4–6 copies of *SMN2* are present,⁴⁸ and the c.859G>C variant in exon 7 of the *SMN2* gene is more frequent than in infantile-onset SMA.¹⁰ Moreover, compound heterozygous for exon 7 deletion and an intragenic variant in *SMN1* gene are frequently found.¹⁰

The HCPWG prioritized the following as typical presenting symptoms for adult-onset SMA with 81% or more consensus (highly significant): proximal weakness, frequent falls, cramps-fasciculation syndrome or minipolymyoclonus, mild proximal lower limb weakness with selective quadricep weakness, and reduced sports performance or endurance combined with increased CK, also known as paucisymptomatic hyperCKemia. The signs and symptoms of adult-onset SMA are not specific or unique and are often confused with myopathic disorders. A patient presenting with the above-mentioned findings and EMG with neurogenic findings suggests consideration of adult-onset SMA and SMA genetic testing should be completed. Creatinine kinase may be variably elevated. Elevated CK is not specific to adult-onset SMA and does not exclude the diagnosis of SMA.¹⁰ Further studies assessing the natural history of adult-onset SMA are needed.

Discussion

SMA NBS is the first step to optimizing outcomes for SMA. The SMA community has a low tolerance for delays to evaluate infants and offer treatment after identification by SMA NBS. The working groups agreed that additional work includes defining which signs and symptoms to monitor and how to define SMA stages (presymptomatic, prodromal/paucisymptomatic, and symptomatic) in a clinically meaningful and easily understandable way. Deeper understanding of SMA pathophysiology (especially those factors that modify prognosis), the natural history, and disease-defining biomarkers are needed. Understanding of adult-onset SMA natural history will facilitate efficient diagnosis and may be best accomplished by combining real-world datasets.

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TAKE-HOME POINTS

- Efficient and early diagnosis and treatment of 5q spinal muscular atrophy (SMA) is essential for best disease outcomes.
- SMA infants identified by newborn screening and before treatment initiation should be characterized by *SMN2* copy number, current motor function, age at symptom onset, and severity of symptoms.
- Processes to manage newborn screening-identified infants with SMA must be in place and require communication, collaboration, and coordination across the public health newborn screening laboratory, the primary care provider and the SMA specialty care center team.
- Every SMA specialty care center accepting SMA newborn screening referrals should provide prompt initial (within 2 days) and follow-up visits, access to treatment options, confirmatory diagnostic testing, education and resources for caregivers, and coordination with primary care provider and other specialists.
- Individuals with SMA and caregivers are essential partners and must be involved throughout the diagnosis, care, and treatment decision-making process.

Disclosure

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Appendix 1 (continued)

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Appendix 1 (continued)

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Appendix 2 (continued)

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