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Spinal Muscular Atrophy

Thomas W Prior, PhD, FACMG,[1] Meganne E Leach, MSN, PNP,[2] and Erika Finanger, MD[2]

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Summary

Clinical characteristics

Spinal muscular atrophy (SMA) is characterized by muscle weakness and atrophy resulting from progressive degeneration and irreversible loss of the anterior horn cells in the spinal cord (i.e., lower motor neurons) and the brain stem nuclei. The onset of weakness ranges from before birth to adulthood. The weakness is symmetric, proximal > distal, and progressive. Before the genetic basis of SMA was understood, it was classified into clinical subtypes based on maximum motor function achieved; however, it is now apparent that the phenotype of *SMN1*-associated SMA spans a continuum without clear delineation of subtypes. With supportive care only, poor weight gain with growth failure, restrictive lung disease, scoliosis, and joint contractures are common complications; however, newly available targeted treatment options are changing the natural history of this disease.

Diagnosis/testing

The diagnosis of SMA is established in a proband with a history of motor difficulties or regression, proximal muscle weakness, reduced/absent deep tendon reflexes, evidence of motor unit disease, AND/OR by the identification of biallelic pathogenic variants in *SMN1* on molecular genetic testing. Increases in *SMN2* copy number often modify the phenotype.

Management

Treatment of manifestations: Therapies targeted to the underlying disease mechanism include nusinersen (Spinraza®; an antisense oligonucleotide) for the treatment of all types of SMA and onasemnogene abeparvovec-xioi (Zolgensma®; gene replacement therapy) for the treatment of type I SMA. These targeted treatments may prevent the development or slow the progression of some features of SMA; efficacy is improved when treatment is initiated before symptom onset. It is unclear what the long-term effect of these treatments will be or if new phenotypes will arise in treated individuals.

Author Affiliations: 1 Center for Human Genetics Laboratory, UH Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio; Email: thomas.prior@uhhospitals.org. 2 Division of Neurology and Pediatrics, Oregon Health and Science University, Portland, Oregon; Email: leachm@ohsu.edu; Email: finanger@ohsu.edu.

Proactive supportive treatment by a multidisciplinary team is essential to reduce symptom severity, particularly in the most severe cases of SMA. When nutrition or dysphagia is a concern, placement of a gastrostomy tube early in the course of the disease is appropriate. Standard therapy for gastroesophageal reflux disease and chronic constipation. Formal consultation and frequent follow up with a pulmonologist familiar with SMA is necessary. As respiratory function deteriorates, tracheotomy or noninvasive respiratory support may be offered. Surgical repair for scoliosis should be considered based on progression of the curvature, pulmonary function, and bone maturity. Surgical intervention for hip dislocation for those with pain.

Surveillance: Presymptomatic individuals require monitoring for the development of symptoms to determine appropriate timing to initiate targeted and/or supportive therapies. Multidisciplinary evaluation every six months or more frequently for weaker children is indicated to assess nutritional state, respiratory function, motor function, and orthopedic status, and to determine appropriate interventions.

Agents/circumstances to avoid: Prolonged fasting, particularly in the acutely ill infant with SMA.

Evaluation of relatives at risk: It is appropriate to determine the genetic status of younger, apparently asymptomatic sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of targeted treatment.

Genetic counseling

SMA is inherited in an autosomal recessive manner. Each pregnancy of a couple who have had a child with SMA has an approximately 25% chance of producing an affected child, an approximately 50% chance of producing an asymptomatic carrier, and an approximately 25% chance of producing an unaffected child who is not a carrier. These recurrence risks deviate slightly from the norm for autosomal recessive inheritance because about 2% of affected individuals have a *de novo SMN1* variant on one allele; in these instances, only one parent is a carrier of an *SMN1* variant, and thus the sibs are not at increased risk for SMA. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the diagnosis of SMA has been confirmed by molecular genetic testing in an affected family member.

GeneReview Scope

Spinal Muscular Atrophy: Included Phenotypes
• Spinal muscular atrophy 0 • Spinal muscular atrophy I • Spinal muscular atrophy II • Spinal muscular atrophy III • Spinal muscular atrophy IV

For synonyms and outdated names see Nomenclature.

Note: This review is restricted to the discussion of *SMN1*-related spinal muscular atrophy. For other genetic causes of the spinal muscular atrophy phenotype, see Differential Diagnosis.

Diagnosis

A consensus document on the diagnosis of children with SMA was initially developed by Wang et al [2007] and was updated by Mercuri et al [2018] (see Establishing the Diagnosis).

Suggestive Findings

Scenario 1. Abnormal newborn screening (NBS) result

- NBS for spinal muscular atrophy (SMA) is primarily based on real-time PCR that detects the common *SMN1* deletion and may also detect *SMN2* copy number on dried blood spots [Chien et al 2017].
- Follow-up molecular genetic testing confirmation of a positive NBS result is recommended (see Establishing the Diagnosis).

Scenario 2. Symptomatic individual who has EITHER atypical findings associated with later-onset SMA OR infantile-onset SMA that has not been treated (either because NBS was not performed or because it yielded a false negative result)

- History of motor difficulties, especially with loss of skills
- Proximal > distal muscle weakness
- Hypotonia
- Areflexia/hyporeflexia
- Tongue fasciculations
- Hand tremor
- Recurrent lower respiratory tract infections or severe bronchiolitis in the first few months of life
- Evidence of motor unit disease on electromyogram

Establishing the Diagnosis

The diagnosis of SMA **is established** in a proband with a history of motor difficulties or regression, proximal muscle weakness, reduced/absent deep tendon reflexes, and evidence of motor unit disease; AND/OR by identification of biallelic pathogenic variants in *SMN1* on molecular genetic testing (see Table 1). Increases in *SMN2* copy number often modify the phenotype.

Molecular Genetic Testing Approaches

Scenario 1. Abnormal newborn screening (NBS) result

When NBS results suggest the diagnosis of SMA, confirmatory molecular genetic testing typically includes **single-gene testing**. Gene-targeted deletion/duplication analysis to determine the dosage of *SMN1* is performed first for the *SMN1* exon 7. If one copy of *SMN1* exon 7 is present, perform sequence analysis of *SMN1*. If exon 7 is present in both copies of *SMN1*, consider other diagnoses (see Differential Diagnosis).

Because *SMN1* sequence analysis cannot determine whether a putative inactivating variant is in *SMN1* or *SMN2* (see Molecular Genetics), one of the following is required to confirm that the variant is present in *SMN1*:

- Establish that the inactivating variant has previously been reported in *SMN1*; OR
- Sequence a long-range PCR product or a subclone of *SMN1*.

Note: Gene-targeted deletion/duplication analysis to determine *SMN2* copy number can be performed to provide additional information for clinical correlation if the diagnosis of SMA is confirmed on molecular genetic testing (see Genotype-Phenotype Correlations).

See Figure 1 for a summary of the diagnostic algorithm for SMA as published by Mercuri et al [2018].

Scenario 2. A symptomatic individual with findings associated with later-onset SMA or untreated infantile-onset SMA (resulting from NBS not performed or false negative NBS result)

Molecular genetic testing approaches can include **single-gene testing** (see above) or use of a **multigene panel** that includes *SMN1*, *SMN2*, and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic

cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Spinal Muscular Atrophy

Type of Testing	Gene [1]	Proportion of SMA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
Diagnostic, carrier, prenatal	*SMN1*	~100%	2%-5% [5]	95%-98% [6, 7]
Prognostic	*SMN2*	NA	NA	See footnote 8.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR and multiplex ligation-dependent probe amplification (MLPA) to detect single-exon deletions or duplications. Note that *SMN1* and *SMN2* are nearly identical; therefore, gene-targeted microarray cannot be used to determine *SMN1* and *SMN2* copy number.
5. Detects the 2%-5% of individuals who are compound heterozygous for an intragenic pathogenic variant and an *SMN1* deletion of at least exon 7 [Parsons et al 1998, Wirth 2000]
6. Bussaglia et al [1995], Lefebvre et al [1995], Parsons et al [1996], Hahnen et al [1997], McAndrew et al [1997], Talbot et al [1997], Ogino & Wilson [2002]
7. False negatives may occur because about 5%-8% of the population have two copies of *SMN1* on a single chromosome and a deletion on the other chromosome, known as a [2+0] configuration. Individuals of sub-Saharan African heritage have a higher proportion of the [2+0] configuration [Verhaart et al 2017] (see Carrier Detection, **Interpretation of the results of carrier testing**).
8. Note: Gene-targeted deletion/duplication analysis of *SMN2* can be performed to provide additional phenotype information if the diagnosis of SMA is confirmed on molecular genetic testing. The number of copies of *SMN2* may range from zero to five. Quantitative PCR and MLPA methods are often designed to detect both *SMN1* and *SMN2* copy number [Anhuf et al 2003, Arkblad et al 2006, Scarciolla et al 2006] (see Genotype-Phenotype Correlations).

Testing to determine carrier status is reviewed in Genetic Counseling.

Clinical Characteristics

Clinical Description

SMA is characterized by muscle weakness and atrophy resulting from progressive degeneration and irreversible loss of the anterior horn cells in the spinal cord (i.e., lower motor neurons) and the brain stem nuclei. The onset of weakness ranges from before birth to adulthood. The weakness is symmetric, proximal greater than distal, and progressive.

Before the advent of molecular diagnosis, attempts were made to classify SMA into discrete subtypes; however, it is now apparent that the phenotype of SMA associated with *SMN1* pathogenic variants spans a broad continuum without clear delineation of subtypes. Newly approved treatment options (see **Management**, **Treatment of**

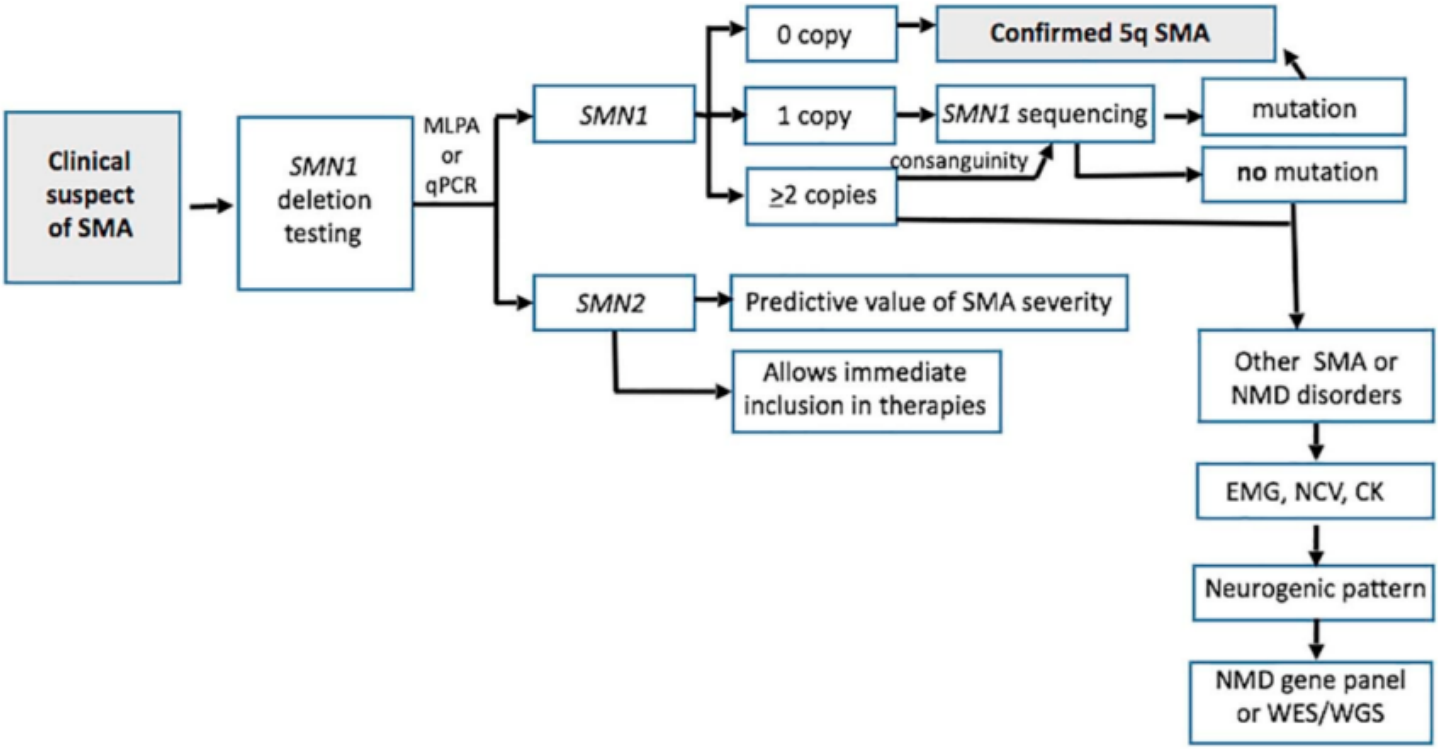

Figure 1. Diagnostic algorithm for SMA

Manifestations, Table 7) are changing the natural history of SMA phenotypes and blurring the boundaries even further [Tizzano & Finkel 2017]. Nonetheless, the existing classification system (Table 2) based on age of onset and maximum function attained with supportive care only is useful for prognosis and management.

Table 2. Spectrum of SMA Phenotypes at Presentation

Phenotype	Age of Onset	Life Span [1]	Motor Milestones [1]	Other Findings [1]
SMA 0	Prenatal	A few weeks, <6 mos	None achieved	• Severe neonatal hypotonia • Severe weakness • Areflexia • Respiratory failure at birth • Facial diplegia • ↓ fetal movements • Atrial septal defects • Arthrogryposis
SMA I	<6 mos	Median survival 8-10 mos	Some head control, sit w/support only	• Loss of head control • Mild joint contractures • Normal or minimal facial weakness • Variable suck & swallow difficulties
SMA II	6-18 mos	70% alive at age 25 yrs	Independent sitting when placed	• Developmental delay w/loss of motor skills • ↓ or absent deep tendon reflexes • Proximal muscle weakness • Postural tremor of fingers

Table 2. continued from previous page.

Phenotype	Age of Onset	Life Span [1]	Motor Milestones [1]	Other Findings [1]
SMA III	>18 mos	Normal	Independent ambulation	• Proximal muscle weakness (i.e., difficulty w/stairs, running) • Loss of motor skills • Fatigue • Postural tremor of fingers • Loss of patellar reflexes
SMA IV	Adulthood	Normal	Normal	• Fatigue • Proximal muscle weakness

1. With supportive care only

SMA 0 presents with severe weakness, hypotonia, and respiratory distress at birth. There may be a history of decreased in utero movements, joint contractures, and atrial septal defects. Infants with SMA type 0 have severe respiratory compromise/failure and, with supportive care only, rarely survive past age six months [Dubowitz 1999, MacLeod et al 1999]. There have not been any published reports of infants with SMA 0 who have been treated with nusinersen or gene therapy (see Table 7).

SMA I manifests as marked weakness and developmental motor regression before age six months. The mean age of symptom onset is 2.5 months [Lin et al 2015]. Infants may acquire head control and ability to roll, but quickly lose these abilities. With supportive care only, affected children do not achieve the ability to sit independently. Proximal, symmetric muscle weakness, lack of motor development with regression of motor function, reduced or absent deep tendon reflexes, and poor muscle tone are the major clinical manifestations. Mild contractures are often noted at the knees and, rarely, at the elbows.

With supportive care only, fasciculation of the tongue is seen in most but not all infants. While the muscles of the face are relatively spared at initial presentation, bulbar weakness is present in the neonatal period or during the first few months, and infants frequently have problems sucking or swallowing, leading to growth failure and recurrent aspiration. Weakness of the intercostal respiratory muscles with relative preservation of diaphragm musculature leads to characteristic "bell-shaped" chest and paradoxic respiration (abdominal breathing). The diaphragm is not involved until late in the course of disease. Cognitive function is normal. Severe symptomatic bradycardia has been noted in a study of the long-term survival of ventilator-dependent individuals with SMA I [Bach 2007].

With supportive care only, prospective studies of children with SMA I have shown median survival of 24 months [Oskoui et al 2007]; however, more recent studies have shown a median time to either death or >16 hours/day of ventilation of 8-13.5 months [Finkel et al 2014, Kolb et al 2017]. With proactive respiratory and nutritional supportive care, survival is improving [Grychtol et al 2018]. Promising new treatments are changing the natural history of SMA I, particularly when treatment is initiated before onset of symptoms (see Table 7).

SMA II usually manifests between ages six and 12 months; the mean age of symptom onset is 8.3 months [Lin et al 2015]. Although poor muscle tone may be evident at birth or within the first few months of life, individuals with SMA II may gain motor milestones slowly until about age five years. With supportive care only, the maximum motor milestone attained is the ability to sit independently when placed. Affected individuals then have a slow decline in motor function and on average lose the ability to sit independently by the mid-teens [Mercuri et al 2016]. Hand tremor is common. Deep tendon reflexes are decreased to absent. Scoliosis is common with progression of disease. Cognition is normal. Cardiac abnormalities are unlikely to develop [Finkel et al 2018]. Progressive respiratory muscle weakness leads to restrictive lung disease that is associated with morbidity and mortality in these individuals.

With supportive care only, the life expectancy of persons with SMA II is not known with certainty. A review of life expectancy of 240 individuals with SMA II from Germany and Poland found that 68% of individuals with SMA II were alive at age 25 years [Zerres et al 1997]. The ability to stand is directly correlated with better pulmonary function and long-term survival. This natural history, however, will likely be improved by newer treatments (see Table 7).

SMA III typically manifests after age 18 months with a mean age of onset of 39 months ± 32.6 months [Lin et al 2015]. The legs are more severely affected than the arms. With supportive care only, individuals walk independently but proximal muscle weakness may lead to more frequent falls or trouble walking up and down stairs. Fatigue can adversely affect quality of life and function significantly.

Most children with SMA III treated only with supportive care make gains in their motor function until about age six years and then experience a slow decline in function until about puberty. Puberty (until age ~20) may be associated with a more rapid decline in function for adolescents with SMA III.

With supportive care only, adulthood is then associated with another, much slower decline in function [Montes et al 2018]. Although individuals with SMA III develop the ability to walk, the vast majority will lose that ability with time. If symptom onset is before age three years, loss of ambulation typically occurs in the second decade. However, if symptom onset is between ages three and 12 years, loss of ambulation may occur in the fourth decade [Wadman et al 2017]. Individuals with SMA III have little to no respiratory muscle weakness. Cardiac and cognitive functions are normal. In a retrospective study of individuals with SMA, the life expectancy of 329 individuals with SMA III from Germany and Poland treated only with supportive care was not different from that of the general population [Zerres et al 1997]. This natural history, however, will likely be improved by newer treatments (see Table 7).

SMA IV typically presents with muscle weakness in the second or third decade of life. There is a specific pattern of muscle involvement, with weakness disproportionately affecting the deltoids, triceps, and quadriceps. There may be a loss of patellar reflexes, with sparing of the deep tendon reflexes in the upper extremities and Achilles. Individuals may have a hand tremor. Cardiac and cognitive functioning is normal. With supportive care only, findings are similar to but less severe than those described for SMA III, and if loss of ambulation occurs, it may be after the fifth decade [Brahe et al 1995, Clermont et al 1995, Zerres et al 1997, Wadman et al 2017]. Life expectancy is normal. SMA IV is the least common form of SMA and affects fewer than 5% of individuals with SMA [Kolb et al 2017].

Potential Complications of SMA

Poor weight gain with growth failure, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties are common complications of SMA in those who receive supportive care only. At this time, it is unknown what long-term complications may arise in individuals who receive early and/or presymptomatic targeted treatment.

Nutrition/gastrointestinal

- Bulbar dysfunction is universal in individuals with SMA I; the bulbar dysfunction eventually becomes a serious problem for persons with SMA II and only very late in the course of disease for those with SMA III.
- Gastrointestinal issues may include constipation, delayed gastric emptying, and potentially life-threatening gastroesophageal reflux with aspiration.
- Growth failure can be addressed with gastrostomy tube placement as needed (see Management).
- Nonambulatory individuals with SMA II and III are at risk of developing obesity [Mercuri et al 2018].

Respiratory. Children with SMA I and II (and more rarely, type III) who are treated with supportive care only have progressive decline in pulmonary function due to a combination of weak respiratory muscles, reduced chest wall and lung compliance, and a reduction in alveolar multiplication [Chng et al 2003].

- Respiratory failure is the most common cause of death in SMA I and II.
- Decreased respiratory function leads to impaired cough with inadequate clearance of lower airway secretions, hypoventilation during sleep, and recurrent pneumonia.
- Noninvasive ventilation, such as BiPAP, and airway clearance techniques are commonly used to improve respiratory insufficiency in those with SMA (see Management).

Orthopedic. Scoliosis, hip dislocation, and joint contractures are common complications in individuals with SMA. Scoliosis is a major problem in most persons with SMA II and in half of those with SMA III. With supportive care only:

- Approximately 50% of affected children (especially those who are nonambulatory) develop spinal curvatures of more than 50 degrees (which require surgery) before age ten years;
- Later in the disease course, nonambulatory individuals can develop thoracic kyphosis [Mercuri et al 2018];
- Progressive scoliosis impairs lung function and if severe can cause decreased cardiac output [Chng et al 2003].

Use of the vertical expandable prosthetic titanium rib is a possible treatment for severe scoliosis (see Management).

Metabolic. An unexplained potential complication of SMA is severe metabolic acidosis with dicarboxylic aciduria and low serum carnitine concentrations during periods of intercurrent illness or prolonged fasting [Kelley & Sladky 1986].

- Whether these metabolic abnormalities are primary or secondary to the underlying defect in SMA is unknown.
- Although the etiology of these metabolic derangements remains unknown, one report suggests that aberrant glucose metabolism may play a role [Bowerman et al 2012].
- Prolonged fasting should be avoided (see Agents/Circumstances to Avoid).

Prognosis

The availability of new targeted treatment options (see Table 7) will likely change the natural history of this condition. Furthermore, diagnosis prior to symptom onset through newborn screening programs, coupled with targeted therapies, will likely decrease the morbidity and mortality regardless of treatment strategy.

Genotype-Phenotype Correlations

***SMN1*.** No correlation exists between the type of *SMN1* pathogenic variants and the severity of disease: the homozygous exon 7 deletion is observed with approximately the same frequency in all phenotypes.

***SMN2*.** Small amounts (up to a quarter) of full-length transcripts generated by *SMN2* produce functional protein and result in the milder SMA II or SMA III phenotype. The number of copies (dosage) of *SMN2* (arranged in tandem in *cis* configuration on each chromosome) ranges from zero to five (see Molecular Genetics). The presence of two copies of *SMN2* is approximately 80% predictive of the SMA I phenotype, whereas the presence of four or more copies of *SMN2* is approximately 88% predictive of achieving the ability to ambulate with supportive care only (SMA III/IV) [Calucho et al 2018]. Modifying factors that are not fully understood are likely to contribute to the variability in clinical severity, as can be easily demonstrated with individuals who have three copies of *SMN2*. Data from Calucho et al [2018] are summarized in Table 3.

Table 3. *SMN2* Copy Number and SMA Clinical Phenotype

SMN2 Copy Number	SMA Clinical Phenotype [1]		
	SMA I	SMA II [2]	SMA III/IV [3]
1	96%	4%	0%
2	79%	16%	5%
3	15%	54%	31%
>=4 [4]	1%	11%	88%

Adapted from Calucho et al [2018]
1. Clinical phenotype with supportive care only
2. With supportive care only, the maximum motor function achieved is sitting.
3. With supportive care only, ambulation is achieved but may not be maintained.
4. Prior et al [2004] reported three asymptomatic, unrelated individuals homozygous for an *SMN1* deletion who had five copies of *SMN2*, demonstrating that expression levels consistent with five copies of *SMN2* may compensate for the lack of *SMN1* expression.

Other putative modifiers of SMA phenotype

- A single-base substitution – c.859G>C (p.Gly287Arg) – in exon 7 of *SMN2* has been identified as a disease modifier resulting in a milder disease [Prior et al 2009]. This substitution creates a new exon splicing enhancer (ESE) element. The new ESE increased the amount of exon 7 inclusion and number of full-length transcripts generated from *SMN2*.
- In some rare families with unaffected females who have biallelic *SMN1* deletions, the expression of plastin 3 (encoded by *PLS3* at chromosome locus Xq23) was higher than in their SMA-affected counterparts. *PLS3* was shown to be important for axonogenesis and therefore may act as a protective modifier [Oprea et al 2008].

Nomenclature

SMA I was previously known as Werdnig-Hoffmann disease or acute SMA [Hoffmann 1892, Werdnig 1971].

SMA II was called chronic SMA or Dubowitz disease prior to the current classification.

SMA III has had the eponym "Kugelberg-Welander disease" and has also been referred to as juvenile SMA [Kugelberg & Welander 1956].

SMA IV may also be referred to as adolescent- or adult-onset SMA.

Prevalence

The exact prevalence of SMA is unknown. Historical studies evaluating the prevalence of SMA were limited by lack of genetic confirmation and may underestimate the prevalence of more severe phenotypes due to the shortened life span. It has been suggested that the overall prevalence of SMA is between one and two per 100,000 people [Verhaart et al 2017]. In regions or groups with high consanguinity rates, the incidence of SMA can be higher.

Table 4. Carrier Frequency and Incidence of SMA

Population	Carrier Frequency	Estimated Incidence
Arab	1:59	Not reported
Asian	1:48	1:8009
Asian Indian	1:71	1:9655

Table 4. continued from previous page.

Population	Carrier Frequency	Estimated Incidence
Black (sub-Saharan African heritage)	1:100	1:18,808
White	1:45	1:7829
Hispanic	1:77	1:20,134
Jewish	1:56	1:10,000

Adapted from Verhaart et al [2017]

Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* are known to be associated with pathogenic variants in *SMN1*.

Differential Diagnosis

Table 5. Disorders to Consider in the Differential Diagnosis of Spinal Muscular Atrophy (SMA)

Age of Onset	Disorder	Gene(s) or Region	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/SMA	Distinguishing from SMA
Congenital to <6 mos	X-linked infantile SMA	*UBA1*	XL	Hypotonia, weakness, areflexia	Multiple congenital contractures, intrauterine fractures
	SMARD1 [1] (OMIM 604320)	*IGHMBP2*	AR	Weakness, respiratory failure, hypo- or areflexia	Distal predominant weakness, diaphragmatic paralysis
	GARS1-related infantile-onset SMA [2] (OMIM 619042)	*GARS1*	AD	Hypotonia, weakness, areflexia	Diaphragmatic paralysis, sensory involvement
	Prader-Willi syndrome	15q11.2-q13 [3]	See footnote 3.	Hypotonia, feeding difficulties	Poor respiratory effort is rare.
	Myotonic dystrophy type 1	*DMPK*	AD	Hypotonia, muscle weakness	Marked facial weakness
	Congenital muscular dystrophy	Many genes	AR AD	Hypotonia, muscle weakness	CNS, eye involvement, possible increased tone
	Zellweger spectrum disorder	PEX family of genes	AR	Hypotonia	Hepatosplenomegaly, CNS
	Congenital myasthenic syndromes	*CHAT* *CHRNE* *COLQ* *DOK7* *GFPT1* *RAPSN* [4]	AR AD	Hypotonia	Ophthalmoplegia, ptosis, episodic respiratory failure
	Pompe disease	*GAA*	AR	Hypotonia	Cardiomegaly
	Other: congenital myopathies, [5] metabolic/mitochondrial myopathies, [6] peripheral neuropathies [7]				
>6 mos	Botulism	NA	NA	Proximal muscle weakness, decreased reflexes	Prominent cranial nerve palsies, acute onset

Table 5. continued from previous page.

Age of Onset	Disorder	Gene(s) or Region	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/SMA	Distinguishing from SMA
Later childhood	Guillain-Barré syndrome	NA		Muscle weakness	Subacute onset, sensory involvement
	Duchenne muscular dystrophy	*DMD*	XL	Muscle weakness, motor regression	Serum creatine kinase concentration 10-20x > normal
	Hexosaminidase A deficiency (juvenile, chronic, & adult-onset variants)	*HEXA*	AR	Lower motor neuron disease	Slow progression, progressive dystonia, spinocerebellar degeneration, cognitive/ psychiatric involvement
	Fazio-Londe syndrome (See Riboflavin Transporter Deficiency Neuronopathy.)	*SLC52A2* *SLC52A3*	AR	Progressive bulbar palsy	Limited to lower cranial nerves; progresses to death in 1-5 yrs
	Monomelic amyotrophy (Hirayama disease) (OMIM 602440)	Unknown		Muscle weakness	Predominantly cervical; tongue may be affected (rare); other cranial nerves spared
	Other: peripheral neuropathies, [7] muscular dystrophies [8]				
Adulthood	Spinal and bulbar muscular atrophy (Kennedy disease)	*AR*	XL	Proximal muscle weakness, muscle atrophy, fasciculations	Gradually progressive; gynecomastia, testicular atrophy, ↓ fertility
	Amyotrophic lateral sclerosis	Many genes [9]	AD AR XL	May begin w/pure lower motor neuron signs	Progressive neurodegeneration; involves both upper & lower motor neurons

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; SMARD = spinal muscular atrophy with respiratory distress; XL = X-linked

1. SMARD spans a phenotypic spectrum [Guenther et al 2007].

2. Pathogenic variants in *GARS1* are also associated with Charcot-Marie-Tooth neuropathy type 2D (CMT2D) and distal spinal muscular atrophy V (dSMA-V) (see *GARS1*-Associated Axonal Neuropathy). CMT2D and dSMA-V are characterized by adolescent or early-adult onset of unique patterns of motor and sensory manifestations with age of onset ranging from eight to 36 years.

3. Prader-Willi syndrome (PWS) is caused by an absence of expression of imprinted genes in the paternally derived PWS / Angelman syndrome region (15q11.2-q13) of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy 15, and rarely an imprinting defect). The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

4. Pathogenic variants in one of multiple genes encoding proteins expressed at the neuromuscular junction are currently known to be associated with subtypes of CMS. The most commonly associated genes include those listed in the table (see Congenital Myasthenic Syndromes).

5. Congenital myopathies: see X-Linked Centronuclear Myopathy

6. Metabolic/mitochondrial myopathies: see Glycogen Storage Diseases (GSD I, GSD II, GSD III, GSD IV, GSD V, GSD VI) and Mitochondrial Disorders Overview

7. Peripheral neuropathies: see Charcot-Marie-Tooth Hereditary Neuropathy Overview

8. Muscular dystrophies: see Dystrophinopathies

9. See Amyotrophic Lateral Sclerosis: Phenotypic Series to view genes associated with this phenotype in OMIM.

Trauma of the cervical spinal cord can be considered as well, especially with breech delivery.

Management

Detailed recommendations on management of care in individuals with SMA have been published; see Finkel et al [2018] (full text) and Mercuri et al [2018] (full text). Furthermore, treatment algorithms for infants diagnosed through newborn screen have been published [Glascock et al 2018] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with SMA, the affected individual should be referred to a multidisciplinary clinic.

Regardless of SMA subtype, clinical care should be based on an individual's current functional status. Issues to consider are listed in Table 6.

Table 6. Evaluations to Consider Following Initial Diagnosis in Individuals with Spinal Muscular Atrophy

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth parameters	Plotted on a standard growth chart
Gastrointestinal/ Feeding	Assessment for feeding dysfunction & gastroesophageal reflux disease	• Incl evaluation of aspiration risk, [1] nutritional status, & time required to complete a feed • Consider evaluation for gastric tube placement in those w/ dysphagia &/or aspiration risk.
	Assessment for constipation	
Respiratory	Assessment of pulse oximetry & capnography	Consider referral to pulmonologist familiar w/SMA. [2]
	Consider forced vital capacity (FVC), as appropriate to age.	• In children age >4-6 yrs, a handheld spirometer is accurate. • When FVC is >40%, decompensation during respiratory infection is less likely than when FVC is ˂40%.
	Assessment of airway clearance function by pediatric pulmonologist	
	Consider sleep study (polysomnogram)	In all individuals w/type I SMA, in those w/type II who are weak, & if clinical evidence of or concern for nocturnal hypoventilation
Musculoskeletal	Orthopedic, physical medicine & rehabilitation, PT, & OT evaluation	Incl assessment of: • Gross motor & fine motor skills • Contractures, hip dislocation, & scoliosis • Mobility, activities of daily living, & need for adaptive devices [3] • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family support/resources	Assess: • Use of community or online resources such as Parent to Parent • Need for social work involvement for parental support • Need for home nursing referral

OT = occupational therapy; PT = physical therapy
1. Including consideration of a formal videofluoroscopic swallowing study
2. Wang et al [2007]
3. Assess equipment needed for safety (car seat / car bed) and independence, such as power chair and other equipment in the home to improve the quality of life for the affected individual and the caregiver.

Treatment of Manifestations

Currently, there is no cure for SMA. Two treatment options that are targeted to the underlying mechanism that leads to SMA have become available and have been shown to have a positive effect on disease progression (see Table 7). These treatments are likely to also have a positive impact on the natural history of SMA [Finkel et al 2017, Mendell et al 2017, Finkel et al 2018, Mercuri et al 2018], particularly if treatment is initiated prior to symptom onset.

The decision of when to initiate targeted therapy after detection of an affected individual via newborn screening relies on genotype and presence of symptoms [Glascock et al 2018]. After confirmatory *SMN1* genetic testing:

- Targeted treatment is recommended for all individuals who have two or three copies of *SMN2*, regardless of whether symptoms are present;
- For individuals who have one copy of *SMN2*, targeted treatment is left to the discretion of the treating physician, taking into account the severity of symptoms, which may have been present prenatally or at birth;
- For individuals with four or more copies of *SMN2*, targeted treatment can be deferred until symptom onset, although careful monitoring for the development of symptoms by a neuromuscular expert is recommended.

Table 7. Targeted Treatment of Spinal Muscular Atrophy

SMA Subtype	Treatment	Dosage	Mechanism
All subtypes of SMA	Nusinersen (Spinraza®) [1-4]	Treatment regimen: [5] 1. Intrathecal loading dose of 12 mg (equivalent dose; 4-5 mL depending on age) every 14 days for a total of 3 loading doses 2. 4th loading dose 30 days after 3rd dose 3. Then, maintenance doses every 4 mos	Antisense oligonucleotide [6]

Table 7. continued from previous page.

SMA Subtype	Treatment	Dosage	Mechanism
SMA type I	Onasemnogene abeparvovec-xioi (Zolgensma®; formerly AVXS-101) [7, 8]	One-time intravenous injection	Gene replacement therapy w/ viral delivery of *SMN1*

Treatments discussed in this table are targeted to address the underlying mechanism of disease causation and not specifically the signs and symptoms experienced by an affected individual (see Table 8).
1. In the double-blind, sham-controlled Phase III clinical trial of nusinersen in 121 infants with SMA type I, 51% of treated infants showed acquisition of a new motor milestone as assessed by the Hammersmith Infant Neurological Examination (HINE) compared with 0% of controls [Finkel et al 2017].
2. Further, event-free survival ("event" defined as death or requirement for permanent assisted ventilation) was higher in the nusinersen group than in the control group (hazard ratio 0.53; P=0.005) as was the likelihood of overall survival (hazard ratio 0.37; P=0.004) [Finkel et al 2017].
3. In the parallel double-blind, sham-controlled, Phase III trial including 126 children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group [Mercuri et al 2018].
4. The efficacy of treatment with nusinersen in those who already have symptoms is not completely understood [Shorrock et al 2018, Gidaro & Servais 2019].
5. Shorrock et al [2018]
6. The antisense oligonucleotide is a single-stranded RNA molecule that is specifically designed to bind to the ISS-N1 regulatory motif in the intron downstream of exon 7 in the *SMN2* pre-mMRA [Rigo et al 2014]. Binding at this site promotes inclusion of exon 7, leading to increased full-length *SMN* mRNA and thus full-length SMN protein.
7. A Phase I trial in 15 individuals with SMA type I showed event-free survival ("event" = death or need for permanent ventilator assistance) at age 20 months in all 15 compared with only 8% of historical controls [Mendell et al 2017].
8. Treated individuals showed an improvement in motor milestones and an increase from baseline in objective motor function scales.

Supportive treatment of children with SMA is guided by the underlying subtype but should be individualized to the affected individual and his/her current functional status (nonsitter, sitter, or walker) [Finkel et al 2018]. The proportion of affected individuals who develop a given complication and the severity of the complication depends on which subtype of SMA is involved and whether targeted treatment is initiated before or after symptom onset [Shorrock et al 2018] (see Table 8).

Table 8. Supportive Treatment of Manifestations in Individuals with Spinal Muscular Atrophy

Manifestation/ Concern	Treatment	Considerations/Other
Bulbar dysfunction leading to poor weight gain	Placement of gastrostomy tube & nutritional supplementation	• Most individuals w/SMA I have a gastrostomy tube by age 12 mos. [1] • Low threshold for clinical feeding evaluation &/or radiographic swallowing study if clinical signs or symptoms of dysphagia &/or bulbar dysfunction
Obesity	Regular nutritional evaluations	For nonambulatory individuals w/SMA II & III
Gastroesophageal reflux disease	Standard treatment	
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	For constipation
Respiratory insufficiency/ failure options [3, 4]	Palliative care &/or no respiratory support	May be an option depending on family preference [2]

Table 8. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	Airway clearance techniques & secretion management [5]	• Incl mechanical in-exsufflator in conjunction w/suctioning & chest physiotherapy, particularly during acute illness • Use of mechanical in-exsufflation in treatment of children w/neuromuscular diseases (incl those w/SMA) appears to reduce pulmonary complications.
	Noninvasive ventilation, [5] such as BiPAP	• For hypoventilation as demonstrated by ↓ oxygen saturation by pulse oximetry or by obstructive sleep apnea [6] • Has been shown to improve sleep breathing parameters in those w/SMA I & II [7] • BiPAP may improve chest wall & lung development, which may reduce lung infections & pulmonary comorbidity.
	Tracheotomy w/permanent mechanical ventilation	Ethical questions re use of invasive ventilation in severely affected infants must be addressed. [8]
Progressive scoliosis	Standard surgical intervention per orthopedist	• Use of spinal orthosis for curvatures >20° prior to surgical intervention is common. [9] • Important consideration in spinal surgery: leave a window for possibility of intrathecal administration of future treatments. [10]
	Consider vertical expandable prosthetic titanium rib (VEPTR). [11]	For severe scoliosis
	Consider magnetically controlled growing rods (MGR).	• For gradual outpatient distractions controlled by an external remote device [12] • May ↓ need for repeated surgery [13]
Hip dislocation	Consider surgery for those who have pain.	No surgery for those who are asymptomatic [14]
Metabolic acidosis during intercurrent illness	Supportive care w/early intravenous fluids & glucose	

Table 8. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/ Community	Ensure appropriate social work involvement to connect families w/ local resources, respite, & support.	Ongoing assessment of need for palliative care involvement &/or home nursing
	Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

1. In those who receive supportive care only [Finkel et al 2014]
2. See Table 7 for targeted treatment options that may improve lung function in affected individuals.
3. Options should be discussed with parents / care providers before respiratory failure occurs.
4. The type of respiratory support is dependent on the individual's respiratory status, quality-of-life goals, and access to equipment.
5. Noninvasive pulmonary intervention should be incorporated into the management of all types of SMA.
6. Chatwin et al [2003], Miske et al [2004]
7. Petrone et al [2007]
8. Finkel et al [2018], Grychtol et al [2018]
9. There is insufficient evidence that spinal orthotics alter scoliosis in SMA.
10. Mercuri et al [2018]
11. Chandran and colleagues [2011] described the use of VEPTR in 11 children with SMA types I and II who were followed for an average of 43 months after the initial surgery. The average age at time of surgery was six years. No surgical complications were identified. Medical complications were seen in two affected individuals: postoperative pneumonia and anemia.
12. A small case series of individuals with neuromuscular disorders (2 of whom had SMA) evaluated MGR and pulmonary function. Affected individuals showed an improvement in forced vital capacity and FEV1 (forced expired volume in 1 second) postoperatively with spinal deformity correction, with very few complications [Yoon et al 2014].
13. Finkel et al [2018]
14. Sporer & Smith [2003]

Prevention of Primary Manifestations

See Table 7.

Surveillance

Presymptomatic individuals should be monitored for the development of symptoms to determine appropriate timing to initiate targeted and/or supportive therapies. A treatment algorithm for the evaluation of presymptomatic infants has been published [Glascock et al 2018].

Individuals with SMA are evaluated at least every six months; weaker children are evaluated more frequently.

Multidisciplinary surveillance at each visit includes assessments of nutritional state, respiratory function, and orthopedic status (spine, hips, and joint range of motion).

Agents/Circumstances to Avoid

Prolonged fasting should be avoided, particularly in the acutely ill infant with SMA [Mercuri et al 2018].

Evaluation of Relatives at Risk

It is appropriate to determine the genetic status of younger, apparently asymptomatic sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of targeted treatment and preventive measures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

There have been two published studies surveying the pregnancy experience of women with SMA [Awater et al 2012, Elsheikh et al 2017] as well as an international workshop on pregnancy in neuromuscular disorders [Norwood & Rudnik-Schöneborn 2012]. From the collective experience, it appears that women with SMA may have an increased rate of preterm birth (27%) and need for cesarean section (41%) [Awater et al 2012, Elsheikh et al 2017] compared to unaffected women. While local anesthesia is preferred to general anesthesia in women with SMA, an epidural can be difficult in people with severe scoliosis or spinal fusions [Awater et al 2012, Finkel et al 2018]. Women with SMA may also experience a persistent worsening of their general muscle weakness after delivery (32%) [Awater et al 2012, Elsheikh et al 2017]. Severe respiratory distress with maternal hypercapnia and hypoxemia was attributed to one stillbirth at 26 weeks' gestation [Awater et al 2012]. Due to the risk of respiratory failure, it is recommended that women with neuromuscular disorders, including those with SMA, obtain baseline pulmonary function prior to becoming pregnant, with frequent monitoring during pregnancy [Norwood & Rudnik-Schöneborn 2012].

No human pregnancies have been reported to have occurred during/after treatment with nusinersen. It is also unknown if nusinersen is excreted through human breast milk. Animal models do not show an increased risk for adverse fetal outcome with nusinersen exposure, or risk for future male or female infertility. However, as the risk to a developing human fetus has not been determined, it has been recommended that women discontinue treatment with nusinersen prior to conception.

There have not been any reported cases of pregnant women with SMA treated with gene therapy.

Therapies Under Investigation

A number of different therapeutic approaches are in development, including further studies on the approved therapeutics discussed above. Newer approaches (including some directed at increasing full-length SMN protein from *SMN2*, use of gene therapy to restore *SMN1*, and SMN-independent approaches) are being actively investigated; see Shorrock et al [2018].

***SMN2*-targeted therapeutic approaches.** Therapeutic approaches in this category aim to alter *SMN2* splicing to increase the proportion of transcripts containing exon 7 and thus increase full-length SMN protein. Antisense oligonucleotides are single-stranded RNA molecules specifically designed to target complementary sequences in the SMN2 transcript leading to inclusion of exon 7. Nusinersen also works through this mechanism. At least two additional *SNM2* splicing modifiers are currently in clinical trials in SMA, including Novartis Pharmaceuticals LMI070 (NCT02268552) and Roche RG7916 (NCT02633709). Both of these agents are delivered orally. Results of these trials are not yet available.

SMN-independent approaches. Molecules directed at increasing muscle strength in individuals with SMA are also under investigation. CK-107 is a tropinin complex activator proposed to cause increased muscle force output [Andrews et al 2018]. This molecule is being studied in a Phase II trial (NCT02644668) in individuals with SMA II-IV. The trial has recently completed enrollment; results are not yet available.

A myostatin inhibitor SRK-015 has recently initiated enrollment in a Phase II trial (NCT03921528) in those with SMA II or III [Long et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Spinal muscular atrophy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Approximately 98% of parents of an affected child are heterozygotes (i.e., carriers of one *SMN1* pathogenic variant).
- About 2% of parents are not carriers of an *SMN1* pathogenic variant, as their affected child has a *de novo* pathogenic variant [Wirth et al 1997]. The majority of *de novo* pathogenic variants are paternal in origin [Wirth et al 1997].
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has an approximately 25% chance of being affected, an approximately 50% chance of being an asymptomatic carrier, and an approximately 25% chance of being unaffected and not a carrier.

  Note: Recurrence risk in sibs is the same (i.e., ~25%) if one parent of the proband has a [2+0] *SMN1* genotype (see Carrier Detection) and the other parent has an *SMN1* exon 7 deletion [1+0] or *SMN1* intragenic variant.

- Recurrence risk in sibs of a proband with one pathogenic variant known to have been inherited from a carrier parent and one apparently *de novo* pathogenic variant (i.e., one of the parents does not have an identifiable *SMN1* pathogenic variant) is presumed to be low. However, due to the possibility that the parent in whom an *SMN1* pathogenic variant was not identified has germline mosaicism for an *SMN1* variant, these sibs should still be considered at risk for SMA [Campbell et al 1998].

Offspring of a proband

- The offspring of an individual with SMA are obligate heterozygotes for an *SMN1* pathogenic variant.
- The unrelated reproductive partner of an individual with SMA should be offered carrier testing. If the partner shows at least two *SMN1* copies, the partner has a one-in-670 probability of being a carrier (taking into consideration the 2% frequency of two *SMN1* copies on the same chromosome and the small risk of an intragenic *SMN1* pathogenic variant). Thus, the risk to such a couple of having an affected child is one in 1,340.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SMN1* pathogenic variant.

Carrier Detection

Molecular genetic testing to determine carrier status is recommended for:

- Parents of more than one child with molecularly confirmed SMA;
- Parents of a child with molecularly confirmed SMA who represents a simplex case (i.e., a single occurrence in a family);
- Parents of a child with suspected but not molecularly confirmed SMA;
- Persons not known to have a family history of SMA (see Population Screening) who are reproductive partners of known carriers.

Note: Preconception carrier screening for SMA in individuals with and without a family history of SMA has been recommended by the ACMG and ACOG (see Population Screening).

Interpretation of the results of carrier testing. Approximately 6% of parents of a child with SMA resulting from a homozygous *SMN1* deletion have normal results of *SMN1* dosage testing for the following two reasons:

- About 4% of carriers have two copies of *SMN1* on a single chromosome [McAndrew et al 1997]. These carrier individuals with two copies of *SMN1* on one chromosome (a [2+0] genotype) are misdiagnosed as non-carriers by the *SMN1* dosage test (i.e., a false negative test result). A specific haplotype block is associated with a [2+0] genotype in the Ashkenazi Jewish population [Luo et al 2014] and in black individuals of sub-Saharan African heritage [Verhaart et al 2017].
- *De novo* deletion of exon 7 of one *SMN1* allele occurs in 2% of individuals with SMA; thus, only one parent is a carrier.
- In the United States pan ethnic population, the calculated a priori carrier frequency is 1/54 with a detection rate of 91.2%. Therefore, an individual from this pan ethnic population with normal *SMN1* dosage testing would have a ~1/500 residual risk of being a carrier [Sugarman et al 2012].

Determining Carrier Status

In parents of a child with molecularly confirmed SMA. If the child is confirmed to have exon 7 deleted from both copies of *SMN1*, first perform *SMN1* dosage analysis on both parents:

- If exon 7 is found to be deleted from one copy of *SMN1* in both parents, carrier status is confirmed in the parents.
- If exon 7 is found to be deleted from one copy of *SMN1* in only one parent, the following are possible explanations:
  - The parent in whom the exon 7 *SMN1* deletion was not identified may have one chromosome 5 with two copies of *SMN1* and one chromosome 5 with no copies of *SMN1* (i.e., a [2+0] *SMN1* genotype).
  - Note: (1) Testing additional family members of the parent with the [2+0] *SMN1* genotype may be informative: usually one of his/her parents has a deletion (1/0 *SMN1* genotype) and the other parent has three or more *SMN1* copies (2/1 *SMN1* genotype). (2) If the parent of a child with SMA who has one chromosome 5 with two copies of *SMN1* and one chromosome 5 with no copies of *SMN1* (i.e., a [2+0] *SMN1* genotype) has children with a known carrier, the children are at 25% risk of having SMA as the result of inheriting the chromosome 5 with no copies of *SMN1* from this parent and the chromosome 5 with the *SMN1* exon 7 deletion or *SMN1* intragenic pathogenic variant from the carrier parent.
  - The child may have a *de novo* deletion of exon 7 (if the child represents a simplex case [i.e., a single occurrence in a family]).
  - Non-paternity

If the child is confirmed to have exon 7 deleted from one copy of *SMN1* and an intragenic pathogenic variant in the other copy of *SMN1*, first perform *SMN1* dosage analysis on both parents:

- Typically, one parent is found to have the *SMN1* deletion.

- Molecular genetic testing for the intragenic *SMN1* pathogenic variant identified in the child should be performed on the parent in whom the exon 7 deletion was not detected.
- If the intragenic *SMN1* pathogenic variant is identified in the parent, carrier status is confirmed in that parent.
- If the intragenic *SMN1* pathogenic variant identified in the child is not identified in the parent, possible explanations include:
  - A *de novo* intragenic *SMN1* pathogenic variant in the child (if the child represents a simplex case [i.e., a single occurrence in a family]);
  - Germline mosaicism for the intragenic *SMN1* pathogenic variant in the parent;
  - Non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption.

In parents of a deceased child with suspected but not molecularly confirmed SMA. As a first step, attempt to test any available tissue samples, such as muscle biopsies (even if imbedded in paraffin) and blood spots from newborn screening, as these samples can **often** provide enough DNA for molecular genetic testing.

If DNA is not available, perform *SMN1* dosage analysis on both parents:

- If exon 7 is found to be deleted from one copy of *SMN1* in both parents, carrier status is confirmed in the parents.
- If exon 7 is found to be deleted from one copy of *SMN1* in only one parent, sequence analysis of *SMN1* should be considered in the parent in whom the deletion was not detected.
- If exon 7 is not found to be deleted from one copy of *SMN1* in either parent, alternate diagnoses should be considered.

Population Screening

Preconception carrier screening for SMA in individuals not known to have a family history of SMA has been recommended by the ACMG and ACOG. Carrier screening for persons not known to have a family history of SMA requires *SMN1* dosage analysis. If such an individual is found to have at least two *SMN1* copies, the probability of being a carrier is approximately 1/670 (taking into consideration the 2% frequency of two *SMN1* copies on the same chromosome and the small risk of being a carrier for an intragenic *SMN1* pathogenic variant).

Note: In the general population most people have one copy of *SMN1* on each chromosome ([1+1] configuration); however, about 5%-8% of the population have two copies of *SMN1* on a single chromosome and a deletion on the other chromosome, known as a [2+0] configuration. Black individuals of sub-Saharan African heritage have a higher proportion of the [2+0] configuration and have a lower detection rate (70%) than other populations [Verhaart et al 2017]. Individuals with a [2+0] *SMN1* configuration will have a false negative carrier screening result with the most common forms of carrier testing.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancy. Once the *SMN1* pathogenic variants in both parents are known or linkage has been established in the family, prenatal testing and preimplantation genetic testing for SMA [Moutou et al 2003, Malcov et al 2004] are possible. Although it would be predicted that a fetus with the same genotype (i.e., molecular genetic test result) as a previously affected sib would have similar clinical findings, there can be intrafamilial variability in phenotypic presentation. An *SMN2* copy number determination on the prenatal specimen may help to better predict the phenotype of the affected child.

Note: Interpretation of test results and prediction of clinical findings in an affected child may be difficult and should be done in the context of formal genetic counseling.

Low-risk pregnancy. For the fetus with reduced fetal movement at no known increased risk for SMA, SMA needs to be considered, as do the disorders discussed in the Differential Diagnosis [MacLeod et al 1999].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Cure SMA**
  925 Busse Road
  Elk Grove Village IL 60007
  Phone: 800-886-1762 (toll-free)
  Email: familysupport@curesma.org
  www.curesma.org
- **Medical Home Portal**
  Spinal Muscular Atrophy
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **National Organization for Rare Disorders (NORD)**
  55 Kenosia Avenue
  PO Box 1968
  Danbury CT 06813-1968
  Phone: 800-999-6673 (toll-free); 203-744-0100; 203-797-9590 (TDD)
  Fax: 203-798-2291
  Email: RN@rarediseases.org; genetic_counselor@rarediseases.org; orphan@rarediseases.org
  Spinal Muscular Atrophy

- **NCBI Genes and Disease**
  Spinal muscular atrophy
- **The Gwendolyn Strong Foundation**
  27 West Anapamu Street
  Suite 177
  Santa Barbara CA 93101
  www.thegsf.org
- **Claire Altman Heine Foundation, Inc.**
  A foundation whose focus is support and funding of population-based SMA carrier screening, and increasing awareness of SMA in both the public and medical communities
  1112 Montana Avenue
  #372
  Santa Monica CA 90403
  Phone: 310-260-3262
  Fax: 310-393-7154
  Email: deb@preventsma.org
  www.clairealtmanheinefoundation.org
- **Medline Plus**
  Spinal Muscular Atrophy
- **National Library of Medicine Genetics Home Reference**
  Spinal muscular atrophy
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Spinal Muscular Atrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMN1	5q13.2	Survival motor neuron protein	alsod/SMN1 genetic mutations SMN1 homepage - Leiden Muscular Dystrophy pages	SMN1	SMN1
SMN2	5q13.2	Survival motor neuron protein	alsod/SMN2 genetic mutations SMN2 database	SMN2	SMN2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Spinal Muscular Atrophy (View All in OMIM)

253300	SPINAL MUSCULAR ATROPHY, TYPE I; SMA1
253400	SPINAL MUSCULAR ATROPHY, TYPE III; SMA3
253550	SPINAL MUSCULAR ATROPHY, TYPE II; SMA2
271150	SPINAL MUSCULAR ATROPHY, TYPE IV; SMA4
600354	SURVIVAL OF MOTOR NEURON 1; SMN1
601627	SURVIVAL OF MOTOR NEURON 2; SMN2
602595	GEM NUCLEAR ORGANELLE-ASSOCIATED PROTEIN 2; GEMIN2
603519	SURVIVAL MOTOR NEURON DOMAIN-CONTAINING PROTEIN 1; SMNDC1

Molecular Pathogenesis

SMN1 produces a full-length survival motor neuron protein necessary for lower motor neuron function [Lefebvre et al 1995]. *SMN2* predominantly produces a survival motor neuron protein that is lacking in exon 7, a less stable protein. SMA is caused by loss of *SMN1* because *SMN2* cannot fully compensate for loss of *SMN1*-produced protein. However, when the *SMN2* (dosage) copy number is increased, the small amount of full-length transcript generated by *SMN2* is often able to produce a milder type II or type III phenotype.

SMN1 and *SMN2*

Gene structure. The SMN region on chromosome 5q12.2-q13.3 is unusually complex, with repetitive sequences, pseudogenes, retrotransposable elements, deletions, and inverted duplications [Biros & Forrest 1999]. Unaffected individuals have two genes encoding SMN protein that are arranged in tandem on each chromosome: *SMN1* (telomeric copy, NM_000344.3) and *SMN2* (centromeric copy, NM_017411.3).

- Other terms that have been used to identify *SMN1*: telSMN, SMNt (t for telomeric), SMNT
- Other terms that have been used to identify *SMN2*: cenSMN, SMNc (c for centromeric), BCD541, SMNC

SMN1 and *SMN2* each comprise nine exons and differ only in eight nucleotides (5 intronic; 3 exonic, 1 each located within exons 6, 7, and 8) [Biros & Forrest 1999]. *SMN1* and *SMN2* share more than 99% nucleotide identity, and both are capable of encoding a 294-amino acid RNA-binding protein, SMN, which is required for efficient assembly of snRNP complexes.

For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Loss of *SMN1* causes SMA. Individuals with SMA are either homozygous for a deletion of at least exon 7 of *SMN1* or are compound heterozygous for such a deletion along with an intragenic *SMN1* inactivating pathogenic variant. Exon 7 of *SMN1* is undetectable in more than 95% of individuals with SMA irrespective of the clinical subtype of SMA, either as a result of homozygous deletions or gene conversion of *SMN1* sequence into *SMN2* sequences (possible because of their high nucleotide identity).

Table 9. *SMN2* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.859G>C	p.Gly287Arg	NM_017411.3 NP_059107.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. SMN is localized to novel nuclear structures called "gems"; gems appear similar to (and possibly interact with) coiled bodies, which are thought to play a role in the processing and metabolism of small nuclear RNAs [Liu & Dreyfuss 1996]. Evidence supports a role for SMN protein in snRNP (small nuclear ribonuclear protein) biogenesis and function [Fischer et al 1997, Liu et al 1997, Pellizzoni et al 1998]. SnRNPs and possibly other splicing components require regeneration from inactivated to activated functional forms. SMN is required for reassembly and regeneration of these splicing components [Pellizzoni et al 1998]. SMN accomplishes this in a modular way, bringing together several RNA-binding proteins with several RNAs, facilitating the assembly of specific proteins on the target RNAs.

The SMN protein has also been reported to influence other cellular activities such as apoptosis and translational regulation [Strasswimmer et al 1999, Lefebvre et al 2002, Vyas et al 2002]. SMN modulates apoptosis by blocking the activation of several caspases and other key regulators of cell survival [Anderton et al 2013]. SMN regulates translation by associating with polysomes, resulting in repression of translation [Sanchez et al 2013].

Abnormal gene product. SMA may be the result of a genetic defect in the biogenesis and trafficking of the spliceosomal snRNP complexes. Mutated SMN, such as that found in individuals with SMA, lacks the splicing-regeneration activity of wild type SMN. Reduced SMN lowers the capacity of cells to assemble the snRNPs, which leads to altered levels of spliceosomal components and defects in splicing, and impaired capacity to produce specific mRNAs and their encoded proteins that are necessary for cellular growth and function. It remains unclear how a defect of splicing results in a motor neuron-specific disorder [Workman et al 2012].

Chapter Notes

Author History

Erika Finanger, MD (2016-present)
Meganne E Leach, MSN, PNP (2019-present)
Thomas W Prior, PhD, FACMG (2000-present)
Barry S Russman, MD; Oregon Health and Science University (2000-2016)

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