



## Spinal Muscular Atrophy

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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 greater than 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 the 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 biallelic pathogenic variants in *SMN1* identified by molecular genetic testing. Increases in *SMN2* copy number often modify the phenotype.

### Management

*Targeted therapies:* Therapies targeted to the underlying disease mechanism include risdiplam (Evrysdi®; *SMN2*-directed RNA splicing modifier), nusinersen (Spinraza®; antisense oligonucleotide), and onasemnogene abeparvovec-xioi (Zolgensma®; gene replacement therapy) for the treatment of all types of SMA. Treatment with an SMA-specific disease-modifying treatment is most efficacious when initiated presymptomatically. The FDA has issued a black box warning about Zolgensma®, noting the possibility of serious liver injury and acute liver failure; close monitoring of liver function prior to and in the months following infusion is indicated. These

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targeted treatments may prevent the development or slow the progression of some features of SMA. New phenotypes in treated individuals are arising, and long-term effects of these treatments are unknown.

*Supportive care:* Proactive supportive treatment by a multidisciplinary team is essential to reduce symptom severity, particularly in the most severe cases of SMA and/or in untreated individuals. 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 is recommended. 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 may be indicated.

*Surveillance:* Individuals with SMA require monitoring for the development of symptoms to determine appropriate timing to initiate supportive therapies. Surveillance recommendations for potential side effects and new phenotypes associated with the targeted treatments are emerging. 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 disease-modifying treatments.

*Pregnancy management:* Women with SMA may have an increased rate of preterm birth and need for cesarean section compared to unaffected women. Women with SMA may also experience a persistent worsening of their general muscle weakness after delivery, particularly if disease-modifying therapies are discontinued due to pregnancy status. 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. There is limited to no data on the effects of disease-modifying treatments on the developing human fetus. However, based on animal models, risdiplam use should be avoided in pregnant women.

## 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* pathogenic 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. Ideally preconception (but also prenatal) carrier testing for all individuals in the general population and prenatal testing for pregnancies at increased risk are possible if the diagnosis of SMA has either been confirmed by molecular genetic testing in an affected family member and/or if both parents are found to be carriers of SMA on carrier screening testing.

## 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 spinal muscular atrophy (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). *SMN2* copy number should also be obtained on confirmatory testing.

**Scenario 2. Symptomatic individual** who has EITHER findings associated with later-onset SMA OR infantile-onset SMA that has not been treated (either because NBS was not performed or because of the presence of compound heterozygous pathogenic variants that may be missed on NBS). Clinical findings include the following:

- History of motor difficulties, especially with loss of skills
- Proximal greater than 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 biallelic pathogenic (or likely pathogenic) variants in *SMN1* identified by molecular genetic testing (see Table 1). Increases in *SMN2* copy number often modify the phenotype.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SMN1* variants of uncertain

significance (or of one known *SMN1* pathogenic variant and one *SMN1* variant of uncertain significance) does not establish or rule out the diagnosis.

## 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 in an individual suspected to have SMA, sequence analysis of *SMN1* is performed. If biallelic pathogenic variants are not identified in *SMN1*, other diagnoses should be considered (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 pathogenic 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: (1) 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.** 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 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. However, some exome platforms are unable to detect deletions or duplications involving *SMN1* and *SMN2*. (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 <sup>1</sup>	Proportion of SMA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants <sup>2</sup> Identifiable by Method	
			Sequence analysis <sup>3</sup>	Gene-targeted deletion/duplication analysis <sup>4</sup>
Diagnostic, carrier, prenatal	<i>SMN1</i>	~100%	2%-5% <sup>5</sup>	95%-98% <sup>6, 7</sup>

Table 1. continued from previous page.

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			Sequence analysis <sup>3</sup>	Gene-targeted deletion/duplication analysis <sup>4</sup>
Prognostic	<i>SMN2</i>	NA	NA	See footnote 8.

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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 a range of techniques such as 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 descent have a higher proportion of the [2+0] configuration [Verhaart et al 2017] (see Carrier Detection, **Interpretation of the results of carrier testing**).

8. 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).

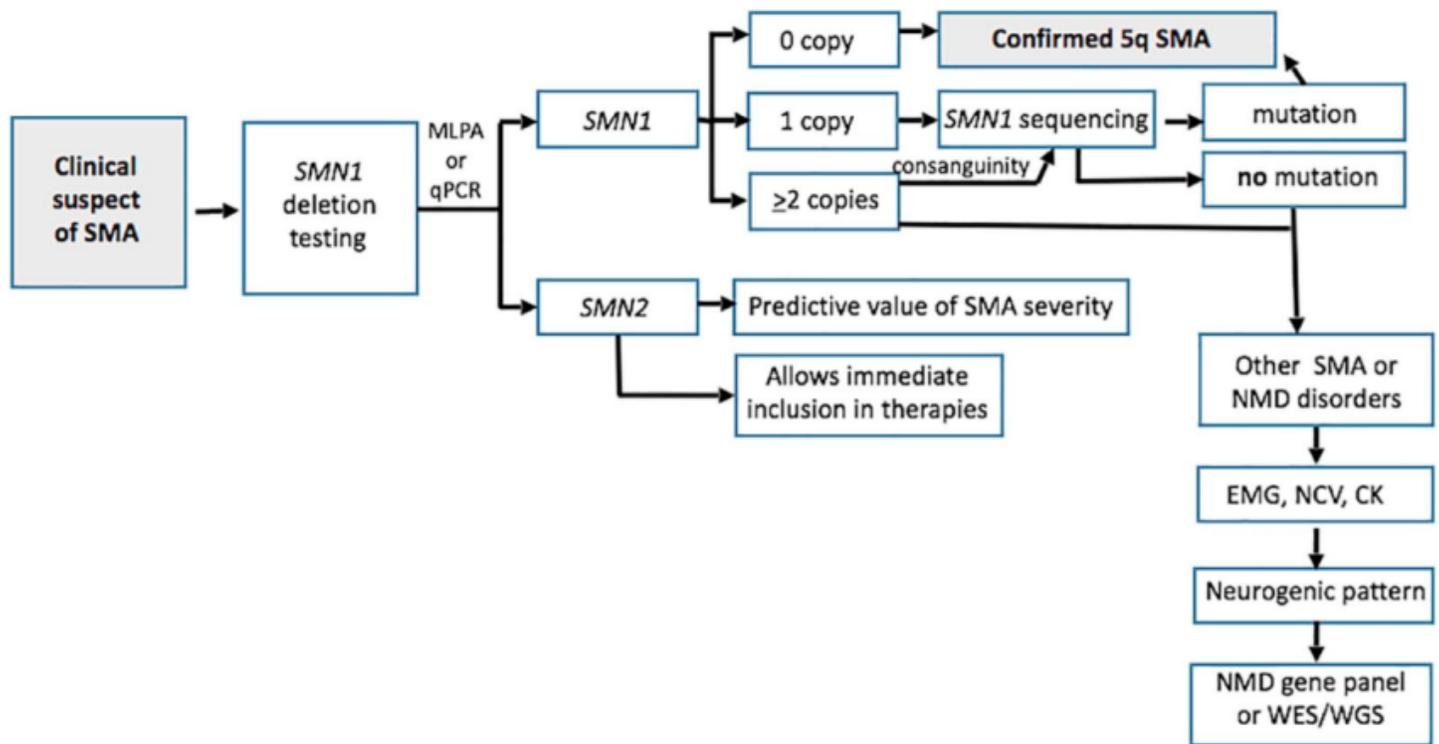
**Testing to determine carrier status** is reviewed in Genetic Counseling.

## Clinical Characteristics

### Clinical Description

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



**Figure 1.** Diagnostic algorithm for spinal muscular atrophy

CK = creatine kinase; EMG = electromyography; MLPA = multiplex ligation-dependent probe amplification; NCV = nerve conduction velocity; NMD = neuromuscular disorder; SMA = spinal muscular atrophy; qPCR = quantitative polymerase chain reaction; WES = whole-exome sequencing; WGS = whole-genome sequencing

**Table 2.** Spinal Muscular Atrophy: Spectrum of Phenotypes at Presentation

Phenotype	Age of Onset	Life Span <sup>1</sup>	Motor Milestones <sup>1</sup>	Other Findings <sup>1</sup>
<b>SMA 0</b>	Prenatal	A few weeks, <6 mos	None achieved	<ul style="list-style-type: none"> <li>• Severe neonatal hypotonia</li> <li>• Severe weakness</li> <li>• Areflexia</li> <li>• Respiratory failure at birth</li> <li>• Facial diplegia</li> <li>• ↓ fetal movements</li> <li>• Atrial septal defects</li> <li>• Arthrogyrosis</li> </ul>
<b>SMA I</b>	<6 mos	Median survival 8-10 mos	Some head control, sit w/support only	<ul style="list-style-type: none"> <li>• Loss of head control</li> <li>• Mild joint contractures</li> <li>• Normal or minimal facial weakness</li> <li>• Variable suck &amp; swallow difficulties</li> </ul>
<b>SMA II</b>	6-18 mos	70% alive at age 25 yrs	Independent sitting when placed	<ul style="list-style-type: none"> <li>• Developmental delay w/loss of motor skills</li> <li>• ↓ or absent deep tendon reflexes</li> <li>• Proximal muscle weakness</li> <li>• Postural tremor of fingers</li> </ul>
<b>SMA III</b>	>18 mos	Normal	Independent ambulation	<ul style="list-style-type: none"> <li>• Proximal muscle weakness (i.e., difficulty w/stairs, running)</li> <li>• Loss of motor skills</li> <li>• Fatigue</li> <li>• Postural tremor of fingers</li> <li>• Loss of patellar reflexes</li> </ul>

Table 2. continued from previous page.

Phenotype	Age of Onset	Life Span <sup>1</sup>	Motor Milestones <sup>1</sup>	Other Findings <sup>1</sup>
<b>SMA IV</b>	Adulthood	Normal	Normal	<ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Proximal muscle weakness</li> </ul>

1. With supportive care only

## SMA Subtypes

**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, Tiberi et al 2020, Erbas & Gusset 2021].

**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. At the time of diagnosis, 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 develop 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 paradoxical respiration (abdominal breathing). The diaphragm is not involved until late in the course of disease. In the past, cognitive function was thought to be normal, but with newer disease-modifying therapies, this premise does not always seem to be true and is being actively investigated. 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]. Disease-modifying 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 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]. A history of having the ability to stand is directly correlated with better pulmonary function and long-term survival. This natural history, however, is changing with newer treatments (see Table 7).

**SMA III** typically manifests after age 18 months with a mean age of onset of 39 months  $\pm$  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 significantly adversely affect quality of life and function.

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 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, is changing with 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 manifestations may arise in individuals who receive early and/or presymptomatic targeted treatment (see Table 7).

### 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, SMA III) who are treated with supportive care only have progressive decline in pulmonary function due to a combination of weak respiratory muscles and reduced chest wall and lung compliance [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 bilevel positive airway pressure 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].

**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 disease-modifying treatment options (see Table 7) will likely change the natural history of this condition. 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 one quarter) of full-length transcripts generated by *SMN2* produce functional protein and result in the milder SMA phenotypes. 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 demonstrated with individuals who have three copies of *SMN2*. Data from Calucho et al [2018] are summarized in Table 3.

**Table 3.** Spinal Muscular Atrophy: *SMN2* Copy Number and Clinical Phenotype

<i>SMN2</i> Copy Number	SMA Clinical Phenotype <sup>1</sup>		
	SMA I	SMA II <sup>2</sup>	SMA III/IV <sup>3</sup>
1	96%	4%	0%
2	79%	16%	5%
3	15%	54%	31%

Table 3. continued from previous page.

SMN2 Copy Number	SMA Clinical Phenotype <sup>1</sup>		
	SMA I	SMA II <sup>2</sup>	SMA III/IV <sup>3</sup>
≥4 <sup>4</sup>	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 in 100,000 people [Verhaart et al 2017]. In regions or groups with high consanguinity rates, the incidence of SMA can be higher.

**Table 4.** Spinal Muscular Atrophy: Carrier Frequency and Incidence

Population	Carrier Frequency	Estimated Incidence
Arab	1:59	Not reported
Asian	1:48	1:8,009
Asian Indian	1:71	1:9,655
Black (sub-Saharan African descent)	1:100	1:18,808
White	1:45	1:7,829
Hispanic	1:77	1:20,134

Table 4. continued from previous page.

Population	Carrier Frequency	Estimated Incidence
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

Age of Onset	Disorder	Gene(s) or Region	MOI	Clinical Features of Disorder	
				Overlapping w/SMA	Distinguishing from SMA
Congenital to <6 mos	X-linked infantile SMA	<i>UBA1</i>	XL	Hypotonia, weakness, areflexia	Multiple congenital contractures, intrauterine fractures
	SMARD1 <sup>1</sup> (OMIM 604320)	<i>IGHMBP2</i>	AR	Weakness, respiratory failure, hypo- or areflexia	Distal predominant weakness, diaphragmatic paralysis
	GARS1-related infantile-onset SMA <sup>2</sup> (OMIM 619042)	<i>GARS1</i>	AD	Hypotonia, weakness, areflexia	Diaphragmatic paralysis, sensory involvement
	Prader-Willi syndrome	15q11.2-q13 <sup>3</sup>	See footnote 3.	Hypotonia, feeding difficulties	Poor respiratory effort is rare.
	Myotonic dystrophy type 1	<i>DMPK</i>	AD	Hypotonia, muscle weakness	Marked facial weakness
	Congenital muscular dystrophy	Many genes	AR AD	Hypotonia, muscle weakness	CNS, eye involvement, possible ↑ tone
	Zellweger spectrum disorder	PEX family of genes	AR	Hypotonia	Hepatosplenomegaly, CNS
	Congenital myasthenic syndromes	<i>CHAT</i> <i>CHRNE</i> <i>COLQ</i> <i>DOK7</i> <i>GFPT1</i> <i>RAPSN</i> <sup>4</sup>	AR AD	Hypotonia	Ophthalmoplegia, ptosis, episodic respiratory failure
	Pompe disease	<i>GAA</i>	AR	Hypotonia	Cardiomegaly
	Other: congenital myopathies, <sup>5</sup> metabolic/mitochondrial myopathies, <sup>6</sup> peripheral neuropathies <sup>7</sup>				
>6 mos	Botulism	NA		Proximal muscle weakness, ↓ reflexes	Prominent cranial nerve palsies, acute onset
Later childhood	Guillain-Barré syndrome	NA		Muscle weakness	Subacute onset, sensory involvement
	Duchenne muscular dystrophy	<i>DMD</i>	XL	Muscle weakness, motor regression	Serum creatine kinase concentration 10-20x > normal

Table 5. continued from previous page.

Age of Onset	Disorder	Gene(s) or Region	MOI	Clinical Features of Disorder	
				Overlapping w/SMA	Distinguishing from SMA
	<a href="#">Hexosaminidase A deficiency</a> (juvenile, chronic, & adult-onset variants)	<i>HEXA</i>	AR	Lower motor neuron disease	Slow progression, progressive dystonia, spinocerebellar degeneration, cognitive/psychiatric involvement
	Fazio-Londe syndrome (See <a href="#">Riboflavin Transporter Deficiency Neuronopathy</a> .)	<i>SLC52A2</i> <i>SLC52A3</i>	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, <sup>7</sup> muscular dystrophies <sup>8</sup>				
Adulthood	<a href="#">Spinal &amp; bulbar muscular atrophy</a> (Kennedy disease)	<i>AR</i>	XL	Proximal muscle weakness, muscle atrophy, fasciculations	Gradually progressive; gynecomastia, testicular atrophy, ↓ fertility
	<a href="#">Amyotrophic lateral sclerosis</a>	Many genes <sup>9</sup>	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; CNS = central nervous system; 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 [Phenotypic Series: Amyotrophic Lateral Sclerosis](#) 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 spinal muscular atrophy (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 [Glascocock et al 2018] ([full text](#)).

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in 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.** Spinal Muscular Atrophy: Evaluations to Consider Following Initial Diagnosis

System/Concern	Evaluation	Comment
<b>Constitutional</b>	Assessment of growth parameters	Plotted on standard growth chart
<b>Gastrointestinal/ Feeding</b>	Assessment for feeding dysfunction & GERD	<ul style="list-style-type: none"> <li>Incl evaluation of aspiration risk, <sup>1</sup> nutritional status, &amp; time required to complete a feed</li> <li>Consider eval for gastrostomy tube placement in those w/ dysphagia &amp;/or aspiration risk.</li> </ul>
	Assessment for constipation	
	Assessment of liver function	Prior to consideration of onasemnogene abeparvovec-xioi (Zolgensma <sup>®</sup> ; gene replacement therapy) (See Table 7.)
<b>Respiratory</b>	Assessment of pulse oximetry & capnography	Consider referral to pulmonologist familiar w/SMA. <sup>2</sup>
	Consider FVC, as appropriate to age.	<ul style="list-style-type: none"> <li>In children age &gt;4-6 yrs, a handheld spirometer is accurate.</li> <li>Greater reduction in FVC is assoc w/↑ risk of decompensation during respiratory infection.</li> </ul>
	Assessment of airway clearance function by pediatric pulmonologist	
	Consider sleep study (polysomnogram).	In all persons w/SMA I, in those w/SMA II who are weak, & if clinical evidence of or concern for nocturnal hypoventilation
<b>Musculoskeletal</b>	Orthopedic / physical medicine & rehab / PT & OT eval	Incl assessment of: <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills</li> <li>Contractures, hip dislocation, &amp; scoliosis</li> <li>Mobility, ADL, &amp; need for adaptive devices <sup>3</sup></li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> </ul>
<b>Hematologic</b>	Assessment for thrombocytopenia & coagulation abnormalities	Prior to administration of nusinersen (Spinraza <sup>®</sup> ; antisense oligonucleotide) & onasemnogene abeparvovec (Zolgensma <sup>®</sup> ) (See Table 7.)
<b>Miscellaneous/ Other</b>	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family support & resources	Assessment of family & social structure to determine need for: <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a></li> <li>Social work involvement for parental support</li> <li>Home nursing referral</li> </ul>

ADL = activities of daily living; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy; SMA = spinal muscular atrophy

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.

### Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED*

Three treatment options that are targeted to the underlying mechanism that leads to SMA are available and have a positive effect on disease progression (see Table 7). These treatments 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, three, or four copies of *SMN2*, regardless of whether symptoms are present [Glascock et al 2020];
- For individuals who have one copy of *SMN2*, targeted treatment is left to the discretion of the treating provider, taking into account the severity of symptoms, which may have been present prenatally or at birth;
- For individuals with five copies of *SMN2*, targeted treatment may be deferred until symptom onset, although careful monitoring for the development of symptoms by a neuromuscular expert is recommended.

**Table 7.** Spinal Muscular Atrophy: Targeted Treatment <sup>1, 2</sup>

Mechanism	Treatment	Dosage	Considerations
Small molecule; <i>SMN2</i> -directed RNA splicing modifier	Risdiplam (Evrysdi®) <sup>3</sup>	<p>Oral 1x/day dosing depending on age &amp; body weight:</p> <ul style="list-style-type: none"> <li>• Age &lt;2 mos: 0.15 mg/kg</li> <li>• Age 2 mos to &lt;2 yrs: 0.2 mg/kg</li> <li>• Age ≥2 yrs w/weight &lt;20 kg: 0.25 mg/kg</li> <li>• Age ≥2 yrs w/weight &gt;20 kg: 5 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Evrysdi® must be refrigerated once reconstituted.</li> <li>• In animal studies, use during pregnancy resulted in teratogenic effects, incl fetal demise &amp; reproductive impairment in offspring.</li> </ul>
Antisense oligonucleotide <sup>4</sup> ; <i>SMN2</i> -directed RNA splicing modifier	Nusinersen (Spinraza®) <sup>5, 6, 7</sup>	<p>Treatment regimen: <sup>8</sup></p> <ul style="list-style-type: none"> <li>• 12 mg per dose</li> <li>• Intrathecal loading doses every 14 days for total of 3 loading doses</li> <li>• 4th loading dose 30 days after 3rd dose</li> <li>• Then, maintenance doses every 4 mos</li> </ul>	<ul style="list-style-type: none"> <li>• Side effects are primarily related to mode of delivery (lumbar puncture).</li> <li>• Monitor for thrombocytopenia/coagulation abnormalities &amp; renal toxicity.</li> </ul>

Table 7. continued from previous page.

Mechanism	Treatment	Dosage	Considerations
Gene replacement therapy w/viral delivery of <i>SMN1</i>	Onasemnogene abeparvovec-xioi (Zolgensma®; formerly AVXS-101) <sup>9</sup>	One-time intravenous injection <sup>9</sup> w/weight-based dosing of 1.1 x 10 <sup>14</sup> vector genomes (vg) per kg of body weight	<p>The FDA has issued a black box warning for Zolgensma®, noting the potential for serious liver injury &amp; acute liver failure (refer to prescribing information).</p> <ul style="list-style-type: none"> <li>• Assessment of liver function prior to infusion is recommended.</li> <li>• Care should be taken in providing this therapy to persons w/pre-existing liver impairment.</li> </ul> <p>Other risks incl thrombotic microangiopathy &amp; ↑ troponin I.</p>

1. This is also referred to as disease-modifying therapy (DMT).

2. 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).

3. Darras et al [2021], Mercuri et al [2022], Sitas et al [2024]

4. 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-mRNA [Rigo et al 2014]. Binding at this site promotes inclusion of exon 7, leading to increased full-length *SMN* mRNA and thus full-length survival motor neuron (SMN) protein.

5. In a double-blind, sham-controlled Phase III clinical trial of nusinersen in 121 infants with SMA 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. Further, event-free survival ("event" = death or need for permanent ventilator assistance) 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].

6. In a 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].

7. The efficacy of treatment with nusinersen in those who already have symptoms is not completely understood [Shorrock et al 2018, Gidaro & Servais 2019].

8. Shorrock et al [2018]

9. A Phase I trial in 15 individuals with SMA I showed event-free survival ("event" = death or need for permanent ventilator assistance) at age 20 months in all 15 individuals, compared with only 8% of historical controls. Treated individuals showed an improvement in motor milestones and an increase from baseline in objective motor function scales [Mendell et al 2017].

## Supportive Care

Supportive treatment of children with SMA is guided by the underlying subtype but should be individualized to the affected person and their 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.** Spinal Muscular Atrophy: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
<b>Bulbar dysfunction leading to poor weight gain</b>	Placement of gastrostomy tube & nutritional supplementation	<ul style="list-style-type: none"> <li>• Most untreated persons w/SMA I have a gastrostomy tube by age 12 mos. <sup>1</sup></li> <li>• Low threshold for clinical feeding eval &amp;/or radiographic swallowing study if clinical signs or symptoms of dysphagia &amp;/or bulbar dysfunction</li> </ul>
<b>Obesity</b>	Regular nutritional evals	
<b>Gastroesophageal reflux disease</b>	Standard treatment	
<b>Bowel dysfunction</b>	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	For constipation
<b>Respiratory insufficiency/failure options</b> <sup>2, 3, 4</sup>	Palliative care &/or no respiratory support	May be option depending on family preference
	Airway clearance techniques & secretion mgmt <sup>5</sup>	<ul style="list-style-type: none"> <li>• Incl mechanical in-exsufflator in conjunction w/suctioning &amp; chest physiotherapy, particularly during acute illness</li> <li>• Suctioning of secretions, careful use of medications</li> <li>• Use of mechanical in-exsufflation in treatment of children w/neuromuscular diseases (incl those w/SMA) appears to ↓ pulmonary complications.</li> </ul>
	Noninvasive ventilation <sup>5</sup> such as BiPAP	<ul style="list-style-type: none"> <li>• For hypoventilation as demonstrated by hypercarbia or on sleep study <sup>6</sup></li> <li>• Has been shown to improve sleep breathing parameters in those w/SMA I &amp; II <sup>7</sup></li> <li>• BiPAP may improve chest wall &amp; lung development, which may ↓ lung infections &amp; pulmonary comorbidity.</li> </ul>
	Tracheotomy w/permanent mechanical ventilation	Ethical questions re use of invasive ventilation in severely affected infants must be addressed. <sup>8</sup>
<b>Progressive scoliosis</b>	Standard surgical intervention per orthopedist	<ul style="list-style-type: none"> <li>• Use of spinal orthosis for curvatures &gt;20 degrees prior to surgical intervention is common. <sup>9</sup></li> <li>• Important consideration in spinal surgery: leave a window for possibility of intrathecal administration of future treatments. <sup>10</sup></li> </ul>
	Consider vertical expandable prosthetic titanium rib. <sup>11</sup>	For severe scoliosis
	Consider magnetically controlled growing rods.	<ul style="list-style-type: none"> <li>• For gradual outpatient distractions controlled by an external remote device <sup>12</sup></li> <li>• May ↓ need for repeated surgery <sup>13</sup></li> </ul>
<b>Hip dislocation</b>	Consider surgery for those who have pain.	No surgery for those who are asymptomatic <sup>14</sup>
<b>Metabolic acidosis during intercurrent illness</b>	Supportive care w/early IV fluids & glucose	Avoid prolonged periods of fasting.

Table 8. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Family/ Community</b>	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.	

BiPAP = bilevel positive airway pressure; IV = intravenous; SMA = spinal muscular atrophy

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/caregivers 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 et al [2011] described the use of vertical expandable prosthetic titanium rib in 11 children with SMA 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 magnetically controlled growing rods and pulmonary function. Affected individuals showed an improvement in forced vital capacity and 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]

## Surveillance

Where available, targeted therapy should be initiated as soon as possible for eligible individuals. A treatment algorithm for the evaluation of presymptomatic infants has been published [Glascock et al 2018].

Presymptomatic individuals with five copies of *SMN2* should be carefully monitored for the development of symptoms to determine appropriate timing to initiate targeted and/or supportive therapies.

For those who are receiving a targeted therapy, review of prescribing information and the package insert is suggested, as recommendations for ongoing surveillance are changing rapidly for each targeted therapy. Both potential side effects and new phenotypes associated with targeted treatments continue to emerge.

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, motor function, and orthopedic status (spine, hips, and joint range of motion) to help determine appropriate interventions.

## 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 several published studies surveying the pregnancy experience of women with SMA [Awater et al 2012, Elsheikh et al 2017, Bencivenga et al 2023] as well as an international workshop on pregnancy in neuromuscular disorders [Norwood & Rudnik-Schöneborn 2012]. From this collective experience, it appears that women with SMA may have an increased rate of preterm birth (27%) and need for cesarean section (41%-100%) [Awater et al 2012, Elsheikh et al 2017, Bencivenga et al 2023] compared to unaffected women. While local anesthesia is preferred to general anesthesia in women with SMA, an epidural can be difficult to perform 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], particularly if disease-modifying therapies are discontinued due to pregnancy status. 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].

There are no adequate data on the developmental risk associated with the use of nusinersen in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested. There has been one reported case of a pregnancy that occurred during treatment with nusinersen [Schön et al 2023]. Treatment with nusinersen was stopped at 12 weeks' gestation after the bigeminal dichorionic pregnancy was discovered. It is unknown if nusinersen is excreted through human breast milk.

No human pregnancies have been reported to have occurred during/after treatment with risdiplam. Teratogenic effects have been seen in studies of pregnant animals, including fetal demise, malformations, and reproductive impairments in the surviving offspring. Based on the results from animal studies, risdiplam use should be avoided in pregnant women. It is unknown if risdiplam is excreted in human breast milk, but it is excreted in the milk of lactating animals.

There have not been any reported cases of pregnant women with SMA treated with onasemnogene abeparvovec-xioi. No animal studies have been performed evaluating the reproductive risks or possible fetal toxicity of use of onasemnogene abeparvovec-xioi in pregnancy.

## Therapies Under Investigation

A number of different therapeutic approaches are in development, including further studies on the approved therapeutics discussed above. See the [SMA Drug Pipeline](#) maintained by [Cure SMA](#) for a list of therapies in preclinical and clinical development phases.

**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 survival motor neuron (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 and risdiplam work through this mechanism.

**SMN-independent approaches.** Molecules directed at increasing muscle strength in individuals with SMA are also under investigation.

Reldesemtiv is a tropinin complex activator proposed to cause increased muscle force output [Andrews et al 2018]. This molecule was studied in a Phase II trial ([NCT02644668](#)) in individuals with SMA II-IV. Results from the study have not been published.

At least three myostatin inhibitor agents are currently in clinical trials for use in SMA. Results have not been published, but long-term extension studies are under way.

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 gonadal 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 (carriers) for an *SMN1* pathogenic variant.
- The 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 1/670 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 1/1,340.

**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 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 descent [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 the grandparents has a deletion ([1+0] *SMN1* genotype) and the other grandparent 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 identified in the child is identified in the parent in whom the exon 7 deletion was not detected, carrier status is confirmed in that parent.
- If the intragenic *SMN1* pathogenic variant identified in the child is not identified in the parent in whom the exon 7 deletion was not detected, 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]);
  - Gonadal 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 multiple national physician organizations. 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] *SMN1* genotype); 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] *SMN1* genotype. Black individuals of sub-Saharan African descent have a higher proportion of the [2+0] genotype and have a lower detection rate (70%) than other populations [Verhaart et al 2017]. Individuals with a [2+0] *SMN1* genotype 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.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## 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 and preimplantation genetic testing for SMA are possible [Moutou et al 2003, Malcov et al 2004]. 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**  
**Phone:** 800-886-1762  
**Email:** [info@curesma.org](mailto:info@curesma.org)  
[curesma.org](http://curesma.org)
- **Gwendolyn Strong Foundation**  
**Phone:** 805-203-0334  
**Email:** [info@nevergiveup.org](mailto:info@nevergiveup.org)

[nevergiveup.org](http://nevergiveup.org)

- **Muscular Dystrophy Association (MDA) - USA**  
**Phone:** 833-275-6321  
**Email:** [ResourceCenter@mdausa.org](mailto:ResourceCenter@mdausa.org)  
[mda.org](http://mda.org)
- **National Organization for Rare Disorders (NORD)**  
[Spinal Muscular Atrophy](#)
- **MedlinePlus**  
[Spinal Muscular Atrophy](#)
- **Newborn Screening in Your State**  
 Health Resources & Services Administration  
[newbornscreening.hrsa.gov/your-state](http://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
<i>SMN1</i>	5q13.2	Survival motor neuron protein	<a href="#">alsod/SMN1 genetic mutations</a> <a href="#">SMN1 homepage - Leiden Muscular Dystrophy pages</a>	<a href="#">SMN1</a>	<a href="#">SMN1</a>
<i>SMN2</i>	5q13.2	Survival motor neuron protein	<a href="#">alsod/SMN2 genetic mutations</a> <a href="#">SMN2 database</a>	<a href="#">SMN2</a>	<a href="#">SMN2</a>

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 (SMN) protein necessary for lower motor neuron function [Lefebvre et al 1995]. *SMN2* predominantly produces a SMN protein that is lacking in exon 7, a less stable protein.

SMN protein 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 small nuclear ribonuclear protein (snRNP) biogenesis and function [Fischer et al 1997, Liu et al 1997, Pellizzoni et al 1998]. Small nuclear RNPs and possibly other splicing components require regeneration from inactivated to activated functional forms. SMN protein is required for reassembly and regeneration of these splicing components [Pellizzoni et al 1998]. SMN protein 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.

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 protein modulates apoptosis by blocking the activation of several caspases and other key regulators of cell survival [Anderton et al 2013]. SMN protein regulates translation by associating with polysomes, resulting in repression of translation [Sanchez et al 2013].

Spinal muscular atrophy (SMA) may be the result of a genetic defect in the biogenesis and trafficking of the spliceosomal snRNP complexes. Mutated SMN protein, such as that found in individuals with SMA, lacks the splicing-regeneration activity of wild type SMN protein. Reduced SMN protein 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].

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 SMA II or III phenotype.

**Mechanism of disease causation.** Loss of function. 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).

***SMN1*- and *SMN2*-specific laboratory technical considerations.** 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, survival motor neuron

protein, which is required for efficient assembly of snRNP complexes. The high degree of homology may make detection of *SMN1* sequence variants more difficult to detect by whole-exome sequencing.

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

## Chapter Notes

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