

# Spinal Muscular Atrophy Genetic Testing

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**Introduction**

Genetic testing for spinal muscular atrophy is addressed by this guideline.

**Procedures addressed**

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Unity SMN1/2 Analysis	0236U
SMN1 Gene Analysis; Dosage/Deletion Analysis (e.g., carrier testing), includes SMN2 Analysis, if performed	81329
SMN1 Full Gene Sequencing	81336
SMN1 Known Familial Mutation Analysis	81337
SMN2 Dosage/Deletion Analysis	81479
SMN2 Targeted Mutation Analysis (c.859G>C)	81479

**Criteria**

**Introduction**

Requests for genetic testing for spinal muscular atrophy (SMA) are reviewed using the following criteria.

**SMN1 Known Familial Mutation Analysis**

- Genetic Counseling:

Spinal Muscular Atrophy

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy) , AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known familial mutation(s) in biological relative, OR
- Carrier Screening
  - Known familial mutation(s) in biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### SMN1 Exon 7 Deletion

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the SMN1 gene, AND
- Diagnostic Testing:
  - Child with hypotonia and weakness (generally symmetrical, proximal more than distal), or
  - Young adult (through twenties) onset of weakness more severely affecting the legs than arms (may be associated with frequent falls, difficulty with stairs), and
  - No obvious signs of a different neurological disorder, OR
- Prenatal Testing:
  - Both parents are carriers of an SMA mutation (at least one of which is an exon 7 deletion mutation), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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#### Note:

Carrier Screening: SMN1 exon 7 deletion testing is not suitable for carrier screening. SMN1/SMN2 dosage analysis is the required test. Please see that section for required medical necessity criteria.

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### SMN1/SMN2 Deletion/Dosage Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of the SMN1 gene in the carrier testing setting, AND

- Diagnostic Testing:
  - Infants with an abnormal result on newborn screening and the diagnosis of SMA is still uncertain, or
  - Index of suspicion for SMA remains high based on:
    - Proximal greater than distal weakness, and
    - Normal creatine kinase (CK), OR
- Carrier Screening:
  - Be of reproductive age, and
  - Have potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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**Note:**

Prenatal Testing: SMN1/SMN2 Dosage Analysis is not suitable for preimplantation/ prenatal diagnosis. Other forms of SMA testing may be indicated based on the mutation status of parents. Please see those sections for guidance.

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**SMN1 Sequencing**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - SMN1 exon 7 deletion testing did not reveal a homozygous SMN1 deletion or SMN1/SMN2 gene dosage analysis identified a single copy of SMN1 exon 7 in the diagnostic setting, or
  - SMN1/SMN2 gene dosage analysis did not confirm carrier status of an exon 7 deletion in the carrier testing setting, AND
- Diagnostic Testing:
  - Individual is suspected to have compound heterozygous SMA based previous test results, and
  - Proximal greater than distal weakness, and
  - Normal creatine kinase (CK), OR
- Carrier Screening:
  - Have one of the following increased risk indications with a noninformative SMN1/SMN2 gene dosage analysis result:
    - Have a reproductive partner who is a carrier of SMA, or
    - Have a reproductive partner with SMA, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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**Note:**

Prenatal Testing: SMN1 full gene sequencing is not generally necessary for preimplantation/prenatal diagnosis as parental mutation status should have already been determined with SMN1 exon 7 deletion testing, SMN1 known familial variant analysis, and/or SMN1 sequencing.

### SMN2 Deletion/Dosage Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Member meets the following criteria:
  - Member has a genetically confirmed diagnosis of SMA, and
  - Member has a diagnosis of either SMA Type 1 or SMA Type 2, and
  - Member has not had previous SMN2 copy number analysis performed, and
  - Documentation is provided that SMN2 copy number is needed to obtain insurance approval for medication being considered for treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### SMN2 Targeted Mutation Analysis (c.859G>C)

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Member meets the following criteria:
  - Member has a genetically confirmed diagnosis of SMA, and
  - Member has a diagnosis of either SMA Type 1 or SMA Type 2, and
  - Member has not had previous c.859G>C analysis performed, and
  - Documentation is provided that c.859G>C analysis is needed to obtain insurance approval for medication being considered for treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

### Exclusions and Other Considerations

SMN2 gene copy analysis for the purpose of predicting SMA prognosis is not medically necessary.

Targeted analysis of c.859G>C, c.835-44A>G, or any other modifier variants for the purpose of predicting SMA prognosis is not medically necessary.

For information regarding carrier screening for SMA performed as part of a large carrier screening panel, please see the guideline *Carrier Screening Panels, Including Targeted, Pan-Ethnic, Universal, and Expanded*, as this testing is not addressed here.

## What is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a severe, inherited neuromuscular disease.<sup>1-5</sup> SMA is caused by loss of lower motor neurons (anterior horn cells) in the spinal cord, resulting in progressive symmetrical muscle weakness and atrophy.<sup>1-5</sup>

### Incidence

The incidence and carrier frequencies are dependent on ethnicity. SMA affects 1/7,829 to 1/18,808 people.<sup>5</sup> The carrier frequency ranges from 1/45 to 1/100.<sup>5</sup> SMA is present in all ethnic groups.<sup>1-5</sup>

### Symptoms

SMA is commonly divided into five clinical subtypes based on age of onset and clinical course. While genetic testing has shown these clinical subtypes are not completely distinct, they are still widely used, and include:<sup>1-5</sup>

- Prenatal onset form ("Type 0" proposed): characterized by polyhydramnios, decreased fetal movements, breech presentation, arthrogryposis multiplex congenita, and respiratory failure at birth.
- Type I (infantile or Werdnig-Hoffmann type): most common form (60-70% of cases). It presents before 6 months of age and the cause of death is often respiratory failure. Affected children have severe, generalized weakness and do not ever sit without support.
- Type II (intermediate type): causes muscle weakness with onset after 6 months, although children often are able to sit alone and can survive through childhood. Intelligence is normal.
- Type III (juvenile, Kugelberg-Welander type): milder. Onset ranges from infancy to youth, but affected people usually walk unassisted albeit with frequent falls or trouble with stairs. Intelligence is normal.
- Type IV (adult type): much later onset with muscle weakness generally presenting at 20-30 years of age. People may or may not become wheelchair dependent and have normal intelligence.

### Cause

SMA is caused by mutations in the SMN1 gene.

- Large gene deletions (exon 7 +/- exon 8) cause SMA in the vast majority (95-98%) of affected individuals.<sup>5</sup>
- The remaining 2-5% of individuals with SMA have a deletion in one copy of the SMN1 gene and a different mutation in the other.<sup>5</sup>

The clinical severity of SMA can be influenced by the number of copies a person has of the SMN2 gene.<sup>5</sup> The SMN2 gene is almost identical to SMN1 and is located on the same chromosome. SMN2 gene mutations do not cause SMA. In fact, about 15% of unaffected people have no copies of the SMN2 gene. Individuals may have between 0-5 copies of SMN2 and SMN2 has been shown to modify the disease severity in people with SMA.

Although a higher copy number of SMN2 (usually 3 or more) is generally associated with a milder phenotype, SMA is still a highly variable disease. It is difficult to use SMN2 copy number to reliably predict the clinical manifestations of SMA in an affected person because other modifying factors not yet fully delineated are likely contributing to the variability in clinical presentation.<sup>5</sup> Identifying SMN2 copy number greater than 3 is technically challenging, sometimes inaccurate, and may require repeat testing for confirmation.<sup>6,7</sup>

Other potential genetic modifiers have been identified; however, the significance of these potential modifiers is yet to be determined.<sup>8</sup>

## Inheritance

SMA is an autosomal recessive disorder.

### Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

About 2% of individuals with SMA have a de novo (new) mutation in one of their two SMN1 genes. In this case, only one parent is a carrier of SMA.<sup>5</sup>

About 4% of carriers have two copies of SMN1 on a single chromosome. These 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).<sup>5</sup>

## Diagnosis

The diagnosis of SMA is established in a proband with a history of motor difficulties, evidence of motor unit disease on physical examination, and identification of biallelic pathogenic variants in SMN1 on molecular genetic testing.<sup>5</sup> Most states include SMA

testing with newborn screening, which enables earlier diagnosis and treatment for affected individuals.<sup>9</sup>

Carrier screening for SMA is recommended preconceptionally or prenatally.<sup>10</sup> Asymptomatic carriers typically have one intact copy of the SMN1 gene and one SMN1 gene with the common deletion. However, some unaffected carriers have two intact copies of the SMN1 gene. These may be on the same chromosome with no intact SMN1 gene on the other chromosome. Carriers of rare mutations and those carrying two SMN1 genes on the same chromosome will not be detected by gene dosage analysis. Therefore, a negative gene dosage analysis result reduces the carrier risk but cannot completely rule out that a person is an SMA carrier.<sup>5,11</sup> The detection rate of carrier screening varies based on ethnicity, ranging from 71% in African Americans to 95% in Caucasians.<sup>2-4</sup>

## Management

Since 2016, three medications for SMA have met FDA Approval. Spinraza/nusinersen, Zolgensma/onasemnogene abeparvovec-xioi, and Evrysdi/risdiplam are used to treat disease manifestations for specific types of SMA. These treatments have the best efficacy when treatment is started before symptoms appear. Onset of symptoms may be prevented or delayed; however, long-term effects of these treatments are unknown.<sup>5</sup> For symptomatic individuals, treatment and care are best coordinated through a multidisciplinary team. Care may include support for feeding, neuromuscular, pulmonary, gastrointestinal, and skeletal symptoms.<sup>5</sup>

## Survival

Treatment with Spinraza/nusinersen, Zolgensma/onasemnogene abeparvovec-xioi, and/or Evrysdi/risdiplam impacts the natural history of SMA with longer survival. Historically, the survival of individuals with SMA with supportive care only has correlated with the subtype:<sup>5</sup>

- Prenatal onset form: survival less than 6 months
- Type I: median survival 8-10 months
- Type II: approximately 70% of affected individuals are alive at 25 years
- Types III and IV: normal life span

## Test information

### Introduction

Testing for SMA may include known familial mutation analysis, deletion analysis, gene dosage analysis, sequencing, or targeted mutation analysis.



## Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

## SMN1 Exon 7 Deletion

Diagnostic testing in an affected individual begins with deletion or copy number analysis, which will identify a deletion of exon 7 in the SMN1 gene. For most affected individuals, both SMN1 genes will be missing exon 7. If one or both SMN1 genes do not have an exon 7 deletion, SMN1 gene sequencing can be considered.

## SMN1/SMN2 Deletion/Dosage Analysis

SMN1/SMN2 deletion/dosage analysis is performed by multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) to determine the number of full copies of the SMN1/SMN2 genes. Dosage analysis is commonly performed in the diagnostic testing of affected individuals and in carrier testing.<sup>5,11</sup>

## SMN1 Sequencing

SMN1 sequencing is typically performed in reflex, when one or no deletions are identified by deletion/dosage analysis in a symptomatic individual. About 2-5% of affected individuals fall into this group. Sequencing detects the other mutation in virtually all cases.<sup>2-5</sup>

## SMN2 Deletion/Dosage Analysis

SMN2 deletion/dosage analysis is performed in individuals following SMN1 genetic testing that established a diagnosis of SMA. SMN2 genetic testing serves to provide a better understanding of the expected severity and to determine eligibility for certain treatments.<sup>5</sup>

## SMN2 Targeted Mutation Analysis

The c.859G>C mutation in SMN2 is a positive modifier variant.<sup>5,8</sup> This testing may be indicated when treatment is being considered. Other positive modifier variants have been identified in SMN2, including the c.835-44A>G mutation.<sup>8</sup>



## Guidelines and evidence

### Diagnostic Testing

The following organizations have published guidelines regarding diagnostic testing for SMA.

#### European Neuromuscular Centre

The 218th European Neuromuscular Centre (ENMC, 2017) workshop revisited the consensus statement that was published in 2007 from the International Standard of Care Committee for Spinal Muscular Atrophy.<sup>11</sup> They stated the following regarding testing for SMA:<sup>12</sup>

- "There was consensus that genetic testing is the first line investigation when this condition is suspected in a typical case and that muscle biopsy or electromyography should not be performed in a typical presentation."
- "There was also consensus that, at variance with previous recommendations, the current gold standard is SMN1 deletion/mutation and SMN copy number testing, with a minimal standard of SMN1 deletion testing. Other areas concerning the value of SMN2 copy number were more controversial and a further Delphi round was planned to complete the task."

The 270<sup>th</sup> European Neuromuscular Center (ENMC, 2024) international workshop developed a consensus statement regarding SMN2 genetic analysis that included the following recommendations:<sup>13</sup>

- "It has been verified that errors in SMN2 quantification are too frequent, particularly in less-experienced laboratories. Certification and quality controls of the labs are, therefore, strongly recommended"
- "SMN2 modifier variants (c.859G>C and c.835-44A>G) should be routinely tested and reported (also in NBS [newborn screening]). Sanger sequencing is recommended for the analysis of these variants"
- "In symptomatic patients, access to therapy should be independent of SMN2 copies. Given the principle of autonomy, treatment initiation is the final decision and responsibility of the family"
- "The implications of SMN2 modifier variants and hybrid genes for treatment are not currently known and, therefore there is no indication that the therapeutic approach should be altered. Collaborative studies are recommended to obtain longitudinal data in carriers of these variants"

#### International Conference on the Standard of Care for Spinal Muscular Atrophy

An international consensus statement (2018) provided recommendations regarding the diagnosis and management of SMA and stated:<sup>14</sup>

- Clinical suspicion for SMA is often based on hypotonia with progressive symmetric proximal weakness affecting legs more than arms and sparing of facial muscles along with normal creatinine kinase (CK) levels. Electromyography is typically not needed in individuals with SMA type 1 and 2, nor is muscle biopsy.
- Genetic testing is considered a first line investigation when SMA is suspected. Multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) that allow for quantitative analysis of SMN1 and SMN2 is recommended. SMN2 copy number inversely correlates with disease severity and may be required for inclusion in therapy.
- If neither full SMN1 copy is present, a diagnosis of SMA may be made. If the phenotype is suggestive of SMA, but one or both full copies of the SMN1 gene are present, SMN1 gene sequencing is recommended. If SMN1 genetic testing is unable to make a diagnosis, "other motor neuron diseases should be considered."

### **U.S. Secretary of Health and Human Services (HHS)**

The U.S. Secretary of HHS released a national guideline (HHS, 2023) that made recommendations related to which disorders should be included in the state universal newborn screening programs, which includes screening for SMA.<sup>15</sup> The recommended follow-up for an abnormal newborn screening result is SMN1 and SMN2 gene dosage testing.<sup>16</sup>

### **Carrier Testing**

The following organizations have published guidelines regarding carrier testing for SMA.

#### **American College of Medical Genetics and Genomics**

The American College of Medical Genetics (ACMG, 2021) released an educational practice resource on carrier screening. This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic.<sup>17</sup> To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of  $>1/200$  was suggested, including SMA.

#### **American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (ACOG, 2017; Reaffirmed 2023) stated the following in regard to carrier testing for SMA in an updated Committee Opinion:<sup>10</sup>

- "Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant."

## Treatments

The FDA has approved use of Spinraza (nusinersen), Zolgensma (onasemnogene abeparvovec-xioi), and Evrysdi (risdiplam) in individuals with SMA.

### Spinraza (nusinersen)

Spinraza (nusinersen) is FDA approved for use in individuals with SMA. While the FDA label does not require SMN2 copy number analysis, the study of 121 affected individuals on which FDA approval was based used the following inclusion criteria:<sup>18</sup>

- 5q SMN1 homozygous gene deletion or mutation or compound heterozygous mutation
- 2 copies of the SMN2 gene (98% of enrolled individuals had 2 copies of SMN2)
- Onset of SMA symptoms at or before 6 months of age
- No hypoxemia at baseline screening at age 7 months or younger

### Zolgensma (onasemnogene abeparvovec-xioi)

Zolgensma (onasemnogene abeparvovec-xioi) is FDA approved for use in individuals with SMA who are full-term to 2 years old. While the FDA label does not require SMN2 copy number analysis, the study of the 21 affected individuals on which FDA approval was based used the following inclusion criteria:<sup>19</sup>

- Confirmed bi-allelic SMN1 gene deletions
- 2 copies of the SMN2 gene
- Onset of SMA symptoms before 6 months of age
- Absence of the c.859G>C positive modifier variant in exon 7 of the SMN2 gene

### Evrysdi (risdiplam)

Evrysdi/risdiplam is FDA approved for use in individuals with SMA at any age.

- Clinical studies included infantile onset SMA and later onset SMA. The overall findings of these studies support the effectiveness of Evrysdi in SMA patients of any age and appear to support the early initiation of treatment with Evrysdi.<sup>20</sup>
- Infantile onset SMA study enrolled patients with genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies.
- Later onset SMA study enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. The median age of patients at the start of treatment was 9.0 years (range 2 to 25), and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range 1 to 275).

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#### Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for spinal muscular atrophy testing will ensure

that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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