Spinal Muscular Atrophy Testing

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.

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What is spinal muscular atrophy

Definition

Spinal muscular atrophy (SMA) is a severe, autosomal recessive neuromuscular disease that affects 1 in 8000 to 1 in 10,000 people.\(^1\)\(^2\)

- SMA is caused by loss of lower motor neurons (anterior horn cells) in the spinal cord, resulting in progressive symmetrical muscle weakness and atrophy.\(^1\)\(^3\)
- SMA has historically been divided into three to 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:\(^1\)\(^3\)
  - Prenatal onset form ("Type 0" proposed) is characterized by polyhydramnios, decreased fetal movements, breech presentation, arthrogryposis multiplex congenita, respiratory failure at birth, and life span less than 6 months.
  - Type I (infantile or Werdnig-Hoffmann type) is the most common form (60-70\% of cases). It presents before 6 months of age with death often before age 2 due to 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 often survive early childhood. Intelligence is normal.
- Type III (juvenile, Kugelberg-Welander type) is milder. Onset ranges from infancy to youth, but affected people usually walk unassisted albeit with frequent falls or trouble with stairs. Survival is prolonged and intelligence is normal.

- Type IV (adult type) has much later onset with muscle weakness generally presenting at 20-30 years of age. People may or may not become wheelchair dependent, have normal lifespan and normal intelligence.

- 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.\(^3\)
  - The remaining 2-5% of individuals with SMA have a deletion in one SMN1 gene and a different mutation in the other.\(^3\)

- SMN2 is another gene that is almost identical to SMN1 and 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. However, SMN2 has been shown to modify the disease severity in people with SMA. More copies (usually 3 or more) of SMN2 are associated with milder disease course. Individuals may have between 0-5 copies of SMN2.\(^3\)

- SMA is inherited in an autosomal recessive manner.
  - An affected person has two SMN1 gene mutations.\(^2,3\) Most do not have a known family history of the condition.
  - People with only one mutation in the SMN1 gene are called carriers. Carriers do not show symptoms of SMA, but have a 50% chance of passing on their mutation to their children.
  - SMA is present in all ethnic groups. About 1 in 40 to 1 in 60 people are carriers.\(^2\)
  - Two carriers of SMA have a 25% chance of having a child with the disorder.
  - About 2% of SMA patients have a de novo (new) mutation in one of their two SMN1 genes. In this case, only one parent is a carrier of SMA.\(^3\)

**Test information**

- **SMN1 Deletion Analysis:** 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 both SMN1 genes do not have an exon 7 deletion, SMN1 gene sequencing can be considered.

- **SMN1 Sequencing Analysis** is typically performed in reflex, when one or no deletions are identified by deletion analysis. About 2-5% of affected individuals fall into this group. Sequencing detects the other mutation in virtually all cases.\(^2,3\)
• **Carrier testing** is usually performed by quantitative analysis that determines the dosage, or copy number, of exon 7-containing SMN1 genes.\(^3\)\(^-\)\(^5\)
  
  o Gene dosage ranges from one to three copies in most people. Asymptomatic carriers typically have one intact copy of the SMN1 gene and one SMN1 gene with the common deletion.
  
  o 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. 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 reduces the carrier risk but cannot completely rule out that a person is an SMA carrier.\(^3\)\(^-\)\(^5\)
  
  o The detection rate of carrier screening varies based on ethnicity, ranging from 71\% in African Americans to 95\% in Caucasians.\(^2\)

• **SMN2 Gene Copy Number Analysis** is performed by quantitative PCR to determine the number of copies of the SMN2 gene.
  
  o Most people have 0-3 copies of SMN2, although copy numbers as high as 5 have been reported.\(^3\)
  
  o The clinical severity of SMA can be influenced by the number of copies a person has of the SMN2 gene.\(^3\) Although a higher copy number of SMN2 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 sequence variation in SMN2 may also influence disease course regardless of copy number.\(^4\)

• **Known Familial Mutation Testing**: Once mutations have been identified in carriers or affected individuals, family members can be tested for the known familial mutation(s). Preimplantation diagnosis and prenatal testing can be considered when both parents are known SMA carriers.

**Guidelines and evidence**

**Diagnostic Testing**

• The International Standard of Care Committee for Spinal Muscular Atrophy issued a consensus statement in 2007 that stated the following:\(^5\)
  
  o “The first diagnostic test for a patient suspected to have spinal muscular atrophy should be the SMN gene deletion test.” \(^5\)
  
  o “The current literature suggests SMN2 copy numbers correlate with spinal muscular atrophy clinical phenotypes. However, although a higher copy number of SMN2 is correlated with milder phenotype, phenotypes can vary substantially
given SMN2 copy number. Therefore, predicting clinical phenotype using SMN2 copy number can be risky and is not currently recommended."

- The European Federation of Neurological Societies (EFNS, 2011) published guidelines on the molecular diagnosis of various neuromuscular disorders. Regarding SMA testing they state:
  - “Screening for SMN1 deletions is indicated in SMA I-III to confirm the diagnosis and provide genetic counseling (Level B).”
  - “In adult-onset SMA, genetic testing for SBMA should be considered in males with bulbar manifestations, gynecomastia and X-linked inheritance (Level B).”
  - “As nearly all of these studies have a retrospective design and look for a specific mutation in a previously ascertained and clinically diagnosed cohort of patients, the highest achievable recommendation level will be B.”

### Carrier Testing

- The American College of Obstetricians and Gynecologists (ACOG, 2017) stated the following in regards to carrier testing for SMA in an updated Committee Opinion:
  - “Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.”

- The American College of Medical Genetics (ACMG, 2008; reaffirmed 2013) state the following regarding carrier testing for SMA:
  - “Because SMA is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. Ideally, the testing should be offered before conception or early in pregnancy. The primary goal is to allow carriers to make informed reproductive choices.”

- In 2011 the Association of Molecular Pathology issued their statement on SMA carrier screening stating that it is “a technology on the threshold of feasibility.” They outlined 6 concerns, 2 of which related to population carrier frequencies, another regarding the need for pilot programs, need for genotype/phenotype research, and another about technical issues with SMN1/SMN2 as outlined above.

### Spinraza

- In 2016, the FDA approved the use of Spinraza in individuals with SMA. While the FDA label does not require SMN2 copy number analysis, the study of 121 patients on which FDA approval was based used the following inclusion criteria:
  - 5q SMN1 homozygous gene deletion or mutation or compound heterozygous mutation
  - 2 copies of the SMN2 gene (98% of enrolled patients had 2 copies of SMN2)
Criteria

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 for Symptomatic Individuals:
  - 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 different neurological disorder, OR
- Carrier Screening:
  - SMN1 exon 7 deletion testing is not suitable for carrier screening. SMN1/SMN2 dosage analysis is necessary, 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.

SMN1/SMN2 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 for Symptomatic Individuals:
Index of suspicion for SMA remains high based on:

- Proximal greater than distal weakness, and
- Normal creatine kinase (CK), and
- Neurogenic EMG, OR

• Carrier Screening:
  - Have a family history of a close relative (first-, second-, or third-degree) with SMA or SMA-like disease, or
  - Have a reproductive partner who is a carrier of SMA, or
  - Have a reproductive partner with SMA, OR

• 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. See those sections for guidance, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMN1 Known Familial Mutation Analysis

• 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 for known SMN1 family mutation(s), AND

• Diagnostic Testing for Symptomatic Individuals:
  - Known family SMN1 point mutation(s) in biological relative, OR

• Carrier Screening
  - Known family SMN1 point mutation(s) in biological relative, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

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 for Symptomatic Individuals:
  - Individual suspected to have compound heterozygous SMA based previous test results and:
    - Proximal greater than distal weakness, and
    - Normal creatine kinase (CK), and
    - Neurogenic EMG, OR

• Carrier Screening:
  - Have one of the following increased risk indication with a non-informative SMN1/SMN2 gene dosage analysis result:
    ▪ Have a reproductive partner who is a carrier of SMA, or
    ▪ Have a reproductive partner with SMA, OR

• 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

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMN2 Gene Copy 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
  - Treatment with Spinraza is being considered, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.
Exclusions

Genetic testing is not approved for SMN2 gene copy analysis for the purposes of predicting SMA prognosis because it is currently considered experimental, investigational or is unproven.

References


