Overview

Useful For

Confirming a diagnosis of spinal muscular atrophy due to nucleotide variants in \textit{SMN1} gene

Second-tier carrier screening when there is a family history of spinal muscular atrophy, but an affected individual is not available for testing, or when disease-causing variants are unknown

Second-tier carrier screening for the reproductive partner of a known SMA carrier

Genetics Test Information

Testing includes full gene sequencing of the \textit{SMN1} gene.

Reflex Tests

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<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
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<tbody>
<tr>
<td>FIBR</td>
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<tr>
<td>CRYOB</td>
<td>Cryopreserve for Biochem Studies</td>
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</table>

Testing Algorithm

If a skin biopsy is received, fibroblast culture and cryopreservation for biochemical studies will be added at an additional charge.

See \textit{Inherited Motor Neuron Disease Testing Algorithm} in Special Instructions.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Inherited Motor Neuron Disease Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies
Ordering Guidance

This is not the preferred genetic test for carrier screening or diagnosis in individuals with suspicion of spinal muscular atrophy (SMA). For these situations, order SMNCS / Spinal Muscular Atrophy Carrier Screening, Deletion/Duplication Analysis, Varies or SMNDX / Spinal Muscular Atrophy Diagnostic Assay, Deletion/Duplication Analysis, Varies.

This test is appropriate for second-tier carrier screening following SMNCS / Spinal Muscular Atrophy Carrier Screening, Deletion/Duplication Analysis, Varies when:

- There is a family history of SMA, but an affected individual is not available for testing
- The disease-causing variants are unknown
- Testing the reproductive partner of a known SMA carrier

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:**

- **Preferred:** Lavender top (EDTA) or yellow top (ACD)
- **Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Specimen Type:** Cultured fibroblasts

**Container/Tube:** T-75 or T-25 flask

**Specimen Volume:** 1 Full T-75 or 2 full T-25 flasks

**Specimen Stability Information:** Ambient (preferred)/Refrigerated <24 hours

**Supplies:** Fibroblast Biopsy Transport Media (T115)
Specimen Type: Skin biopsy

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Supplies: Card - Blood Spot Collection (Filter Paper) (T493)

Specimen Type: Blood spot

Container/Tube:

Preferred: Collection card (Whatman Protein Saver 903 Paper)

Acceptable: Ahlstrom 226 filter paper, or Blood Spot Collection Card

Specimen Volume: 5 Blood spots on collection card

Collection Instructions:

1. An alternative blood collection option for a patient >1 year of age is finger stick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Additional Information:

1. For collection instructions, see Blood Spot Collection Instructions in Special Instructions.
2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777) in Special Instructions.
3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800) in Special Instructions.

Forms

1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

   - Informed Consent for Genetic Testing (T576)

   - Informed Consent for Genetic Testing-Spanish (T826)
Specimen Minimum Volume
Blood: 1 mL
Blood Spots: 3 punches 3-mm diameter

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
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Clinical and Interpretive

Clinical Information
Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics and Genomics (ACMG) recommends offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy.

The most common form of SMA is associated with the loss of survival motor neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the survival motor neuron 1 (SMN1) gene, but a small portion of SMN is also contributed by the survival motor neuron 2 (SMN2) gene. Indeed, SMN1 produces more than 90% of SMN protein, while SMN2 produces less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotides, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 are detected. In addition, individuals may also have 0 to 5 copies of SMN2.

SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a nucleotide variant in the other allele. The severity of a patient's disease course is associated with the number of copies of SMN2 that are present, and 3 or more SMN2 copies are associated with a milder SMA phenotype.

This test aims to specifically identify nucleotide variants in SMN1 by direct sequencing and to distinguish these nucleotide variants from changes within SMN2. However, SMN1 exon 1 variants are still unable to be distinguished from changes within SMN2 exon 1.

Reference Values
An interpretive report will be provided.

Interpretation
All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with
interpretive comments detailing their potential or known significance.

**Cautions**

Variants detected in *SMN1* exon 1 cannot be distinguished from variants in *SMN2* exon 1. Therefore, additional molecular analyses are required to confirm results in this region.

A small percentage of individuals who are carriers or have a diagnosis of spinal muscular atrophy may have a variant that is not identified by this method (e.g., large genomic deletions, promoter alterations). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of spinal muscular atrophy. For carrier testing, it is important to first document the presence of an *SMN1* gene variant in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare alterations exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in the interpretation of results may occur if information given is inaccurate or incomplete.

**Clinical Reference**


**Performance**

**Method Description**

Long-range-PCR of *SMN1* exons 2-8, followed by bidirectional Sanger sequence analysis for nucleotide variants in all protein-coding regions and intron/exon boundaries of *SMN1*. *SMN1* exon 1 is PCR-amplified and bidirectionally Sanger-sequenced. (Unpublished Mayo method)

**PDF Report**

No
Day(s) Performed
Varies

Report Available
14 to 20 days

Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81336
88233-Tissue culture, skin, or solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

LOINC® Information

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