Test Definition: SMN1Z

SMN1 Full Gene Analysis

Overview

Useful For

Confirming a diagnosis of spinal muscular atrophy due to nucleotide variants in *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 *SMN1* gene.

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
FIBR	Fibroblast Culture	Yes	No
CRYOB	Cryopreserve for Biochem Studies	No	No

Testing Algorithm

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

See 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)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions.

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

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

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 (eg, 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

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

2. Wirth B: An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mutat. 2000;15:228-237

3. Clermont O, Burlet P, Benit P, et al: Molecular analysis of SMA patients without homozygous SMN1 deletions using a new strategy for identification of SMN1 subtle mutations. Hum Mutat. 2004;24:417-427

4. Kubo Y, Nishio H, Saito K: A new method for SMN1 and hybrid SMN gene analysis in spinal muscular atrophy using long-range PCR followed by sequencing. J Hum Genet. 2015;60: 233-239

5. Prior T, Leach ME, Finanger E: Spinal muscular atrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. Gene Reviews [Internet]. University of Washington, Seattle; 2000. Updated November 14, 2019. Accessed September 28, 2020. Available at www.ncbi.nlm.nih.gov/sites/books/NBK1352/

6. The Human Gene Mutation Database (HGMD), Professional version 2017.2 from BIOBASE. A database of germline mutations in genes associated with human inherited disease. Accessed Sep 12, 2017. Available at https://portal.biobase-international.com/hgmd/pro/start.php

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 U.S. Food and Drug Administration.

CPT Code Information

81336

88233-Tissue culture, skin, or solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
SMN1Z	SMN1 Full Gene Analysis	94221-9

Result ID	Test Result Name	Result LOINC Value
602754	Result Summary	50397-9
602755	Result	82939-0
602756	Interpretation	69047-9
602757	Additional Information	48767-8
602758	Specimen	31208-2
602759	Source	31208-2
602760	Released By	18771-6