MAYO CLINIC LABORATORIES

Test Definition: SMNCS

Spinal Muscular Atrophy Carrier Screening, Deletion/Duplication Analysis, Varies

Overview

Useful For

General population carrier screening for spinal muscular atrophy (SMA)

Carrier screening for reproductive partners of known SMA carriers

Carrier screening for parents of a child with a known deletion of the survival motor neuron 1 gene (*SMN1*) or other family history of SMA

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

SMN1 exon 7 copy number and SMN2 exon 7 copy number are determined. Also ascertains whether the g.27134T>G polymorphism is present or absent in patients found to have 2 copies of SMN1.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Muscle Biopsy Specimen Preparation Instructions
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Dosage Analysis by Digital Droplet Polymerase Chain Reaction (ddPCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

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 Mayo Clinic Laboratories 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 whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Blood spot
Supplies: Card-Blood Spot Collection (Filter paper) T493

Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: PerkinElmer 226 (formerly Ahlstrom 226) filter paper or blood spot collection card
Specimen Volume: 5 Blood spots
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see How to Collect Dried Blood Spot Samples.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 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. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.
2. For collection instructions, see Blood Spot Collection Instructions
3. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)

4. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

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
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
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. Tubes can be supplied upon request (Eagle's minimum essential medium with 1% penicillin and streptomycin [T115]).
Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Tissue biopsy
Supplies: Muscle Biopsy Kit (T541)
Collection Instructions: Prepare and transport specimen per instructions in Muscle Biopsy Specimen Preparation Instructions.
Additional Information: Muscle Biopsy Shipping Kits (T541) are available.
Specimen Volume: 10-80 mg
Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

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
Tissue Biopsy: 200 mg

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & 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 (ACMG) and The American College of Obstetricians and Gynecologists (ACOG) currently recommend 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 *SMN1* gene but a small portion of SMN is also contributed by the *SMN2* gene. In fact, *SMN1* produces more than 90% of SMN protein, while *SMN2* produces about less than 10% of residual SMN protein. This occurs because *SMN2* differs from *SMN1* by 5 nucleotide changes, 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* have been observed. 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 point mutation in the other allele. The severity of a patient's disease 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.

As the SMA test is a quantitative assay for the number of *SMN1* exon 7 deletions, any result showing 2 *SMN1* copies may in fact have 2 normal copies of *SMN1* in cis (on the same chromosome) and a copy of *SMN1* with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry. Previously, it was not possible to distinguish a "2+0" carrier from an individual with 1 copy of *SMN1* on each chromosome. However, following a study performed by Luo et al,(6) it is now possible to provide an adjusted genetic residual carrier risk specific to one’s ancestry, based on the presence or absence of the *SMN1* polymorphism g.27134T>G. The presence of this polymorphism is linked to being a "2+0" carrier in the Ashkenazi Jewish and Asian populations and it increases the chances that one is a "2+0" carrier in other populations. Please see the table below for details.

SMA carrier residual risk estimates.(6)

Ancestry	Carrier frequency	Detection rate based on copy number alone	Residual risk after detection of 2 copies of *SMN1*	Detection rate with addition of *SMN1* g.27134T>G	Residual risk of being a 2+0 carrier after absence of *SMN1*	Residual risk of being a 2+0 carrier after presence of *SMN1*

					g.27134T>G	g.27134T>G
Ashkenazi Jewish	1 in 41.1	90%	1 in 345	94%	1 in 580	2+0 Carrier
Asian	1 in 53	92.6%	1 in 628	93.3%	1 in 701.8	2+0 Carrier
African American	1 in 66	71.1%	1 in 121	N/A	1 in 395.7	1 in 33.5
Hispanic	1 in 117	90.6%	1 in 1,061	N/A	1 in 1,762	1 in 139.6
European	1 in 35	94.9%	1 in 632	N/A	1 in 769.3	1 in 28.6

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

Cautions

Point mutations are undetectable by this assay. Nor can this assay definitively discriminate between 2 copies of survival motor neuron 1 (*SMN1*) on the same chromosome versus 2 copies on separate chromosomes for patients of most ancestries.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match 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 our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. D'Amico A, Mercuri E, Tiziano FD, Bertini E: Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71
2. Hendrickson BC, Donohoe C, Akmaev VR, et al: Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet 2009;46:641-644
3. Carre A, Empey C: Review of Spinal Muscular Atrophy (SMA) for Prenatal and Pediatric Genetic Counselors. 2016;25:32-43
4. Committee on Genetics: Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol 2017;129:e35-e40
5. Committee on Genetics: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol March 2017;129;e41-e55
6. Luo M, Liu L, Peter I, et al: An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med 2014;16:149-156
7. Prior TW, Nagan N: Spinal muscular atrophy: overview of molecular diagnostic approaches. Curr Protoc Hum Genet 2016;1:88 unit 9.27
8. Prior TW, Nagan N, Sugarman EA, et al: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2011;13:686-694

Performance

Method Description
Droplet digital PCR method for detection and quantification of survival motor neuron 1 (*SMN1*) exon 7, *SMN2* exon 7, and *SMN1* rs143838139 (g.27134T>G) associated with spinal muscular atrophy (SMA). Mutation nomenclature is based on the following GenBank Accession numbers (build GRCh37 [hg19]): NM_022874.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Varies

Report Available
5 to 10 days

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

Performing Laboratory Location
Rochester

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81329
88233 (if appropriate)
88240 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SMNCS	SMA Carrier by Del/Dup	49857-6

Result ID	Test Result Name	Result LOINC® Value
113445	Result Summary	50397-9
113446	Result	49857-6
113447	Interpretation	69047-9
113448	Additional Information	48767-8
113449	Specimen	31208-2
113450	Source	31208-2
113451	Released By	18771-6