MAYO CLINIC LABORATORIES

Test Definition: SMNDX

Spinal Muscular Atrophy Diagnostic Assay, Deletion/Duplication Analysis, Varies

Overview

Useful For

First-tier newborn screening for spinal muscular atrophy (SMA)

Prenatal testing for SMA

Diagnostic testing to confirm a suspected diagnosis of SMA

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No

Genetics Test Information

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

Testing Algorithm

For prenatal specimens only: If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture/genetic test will be added at an additional charge.

If chorionic villus specimen (nonconfluent cultured cells) is received, fibroblast culture for genetic test will be added per laboratory protocol at an additional charge.

For any prenatal specimen that is received, maternal cell contamination testing will be added per laboratory protocol at an additional charge.

For more information see Newborn Screening Act Sheet Spinal Muscular Atrophy: Zero Functioning Copies of *SMN1*.

The following algorithms are available:
-Inherited Motor Neuron Disease and Dementia Testing Algorithm
-Spinal Muscular Atrophy Testing Algorithm

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 and Dementia Algorithm
- Newborn Screening Act Sheet Spinal Muscular Atrophy: Zero Functioning Copies of SMN1
- Informed Consent for Genetic Testing (Spanish)
- Spinal Muscular Atrophy Testing Algorithm
- Blood Spot Collection Instructions

Method Name

Dosage Analysis by Digital Droplet Polymerase Chain Reaction (ddPCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

Additional Testing Requirements

All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

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. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.

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.
Additional Information: To ensure a minimum DNA amount and concentration, the preferred blood volume must be submitted. Testing may be canceled if the specimen supplied is inadequate.
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days

Prenatal Specimens
Due to its complexity, consultation with the laboratory is required for all prenatal testing; call 800-533-1710 to speak to a genetic counselor.

Submit only 1 of the following specimens:

Specimen Type: Amniotic fluid
Container/Tube:
Preferred: Screw-capped, sterile centrifuge tubes
Acceptable: T-25 flasks of confluent cultured cells
Specimen Volume: 20 mL
Specimen Stability Information: Refrigerated (preferred)/Ambient

Specimen Type: Chorionic villi
Container/Tube:
Preferred: 15-mL tube containing 15 mL of transport media
Acceptable: T-25 flasks of confluent cultured cells
Specimen Volume: 20 mg
Specimen Stability Information: Refrigerated

Specimen Type: Blood spot
Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: Perkin Elmer 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 >1 year of age is a finger stick.
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. 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.
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

Blood: 1 mL
Amniotic Fluid: 10 mL
Chorionic villi: 5 mg

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 & 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) and The American Congress 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 less than 10% of residual SMN protein. This occurs because *SMN2* differs from *SMN1* by 5 nucleotide changes, one 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 alteration 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 or more *SMN1* copies may, in fact, have 2 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 one copy of *SMN1* on each chromosome. However, following a study performed by Luo et al,(1) 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* alteration g.27134T>G. The presence of this alteration 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. See the table below for details.

SMA carrier residual risk estimates.(1)

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* g.27134T>G	Residual risk of being a 2+0 carrier after presence of *SMN1* 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. 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. doi: 10.1038/gim.2013.84
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. doi: 10.1136/jmg.2009.066969
3. Carre A, Empey C: Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. J Genet Couns. 2016;25:32-43. doi: 10.1007/s10897-015-9859-z
4. Committee on Genetics: Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. 2017;129:e35-e40. doi: 10.1097/AOG.0000000000001951
5. Committee on Genetics: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. March 2017;129;e41-e55. doi: 10.1097/AOG.0000000000001952
6. D'Amico A, Mercuri E, Tiziano FD, Bertini E: Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71. doi: 10.1186/1750-1172-6-71
7. Prior TW, Nagan N: Spinal muscular atrophy: overview of molecular diagnostic approaches. Curr Protoc Hum Genet. 2016;1:88 unit 9.27. doi: 10.1002/0471142905.hg0927s88
8. Prior TW, Nagan N, Sugarman EA, Batish SD, Braastad C: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med, 2011;13:686-694. doi: 10.1097/GIM.0b013e318220d523

Performance

Method Description

Droplet digital polymerase chain reaction 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). Variant 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
88235 (if appropriate)
88240 (if appropriate)
88233 (if appropriate)
88240 (if appropriate)
81265 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SMNDX	SMA Diagnostic by Del/Dup	49857-6

Result ID	Test Result Name	Result LOINC® Value
113452	Result Summary	50397-9
113453	Result	49857-6
113454	Interpretation	69047-9
113455	Additional Information	48767-8
113456	Specimen	31208-2
113457	Source	31208-2
113458	Released By	18771-6