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. This test 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, an amniotic fluid culture will be added at an additional charge. If a chorionic villus specimen (nonconfluent cultured cells) is received, a fibroblast culture will be added at an additional charge.

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

If the patient has abnormal newborn screening result for spinal muscular atrophy, immediate action should be taken. Refer to the appropriate American College of Medical Genetics and Genomics Newborn Screening ACT Sheet.(1)

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
- Hereditary Peripheral Neuropathy Diagnostic Algorithm
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Inherited Motor Neuron Disease Testing and Dementia Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Spinal Muscular Atrophy Testing Algorithm
- Blood Spot Collection Instructions

Method Name

Droplet Digital Polymerase Chain Reaction (ddPCR)

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

Patient Preparation: A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA) or yellow top (ACD)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure

test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

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 filter paper or blood spot collection card
Specimen Volume: 2 to 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 a Dried Blood Spot Sample.
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. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.
2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.
3. For collection instructions, see Blood Spot Collection Instructions
4. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
5. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2mL with skirted conical base
Acceptable: Matrix tube, 1mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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.

Specimen Type: Amniotic fluid
Container/Tube: Amniotic fluid container
Specimen Volume: 20 mL
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information: Direct testing of an uncultured specimen may be attempted for this test. Contact the laboratory at 800-533-1710 if direct testing is desired.
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2 to 3 weeks are required to culture amniotic fluid before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Confluent cultured amniocytes
Container/Tube: T-25 flask
Specimen Volume: 2 Full flasks
Collection Instructions: Submit confluent cultured amniocytes from another laboratory
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Chorionic villi
Container/Tube: 15-mL tube containing 15 mL of transport media
Specimen Volume: 20 mg
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information: Specimen will only be tested after culture.
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Cultured chorionic villi
Container/Tube: T-25 flasks
Specimen Volume: 2 full flasks
Collection Instructions: Submit confluent cultured cells from another laboratory

Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Congenital Inherited Diseases Patient Information(T521)
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

See Specimen Required

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*.

Spinal muscular atrophy is most frequently 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 this 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 in trans (on the other chromosome). 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,(2) 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.

Table. SMA carrier residual risk estimates(2)

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

The interpretive report includes an overview of the findings as well as the associated clinical significance.

Cautions

Point alterations are undetectable by this assay. This assay also cannot 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 alterations (previously 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 the interpretation of results may occur if the information given is inaccurate or incomplete.

Clinical Reference

1. Newborn Screening ACT Sheet [Exon 7 Deletion (Pathogenic Variant) in Survival Motor Neuron Gene (SMN1)] Spinal Muscular Atrophy (SMA). American College of Medical Genetics and Genomics; 2020. Accessed May 19, 2025. Available at www.acmg.net/PDFLibrary/SMA-ACT-Sheet.pdf
2. 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(2):149-156. doi:10.1038/gim.2013.84
3. Hendrickson BC, Donohoe C, Akmaev VR, et al. Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet. 2009;46(9):641-644. doi:10.1136/jmg.2009.066969
4. Carre A, Empey C. Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. J Genet Couns. 2016;25(1):32-43. doi:10.1007/s10897-015-9859-z
5. Committee on Genetics: Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. 2017;129(3):e35-e40. doi:10.1097/AOG.0000000000001951
6. Committee on Genetics: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. March 2017;12(3):e41-e55. doi:10.1097/AOG.0000000000001952
7. 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
8. 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
9. 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: 28 days (if available); Extracted DNA: 3 months, Blood spots: 1 year (if available)

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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