Test Definition: CFSMN

Cystic Fibrosis and Spinal Muscular Atrophy Carrier Screen Panel, Varies

Overview

Useful For

Reproductive risk refinement via carrier screening for individuals in the general population for cystic fibrosis (CF) and spinal muscular atrophy (SMA).

Reproductive risk refinement via carrier screening for individuals with a family history of CF and/or SMA when familial variants are not available

This test is **not useful for** clinical diagnosis of an affected individual.

Genetics Test Information

This test includes targeted testing to evaluate over 500 genetic variants including the 23 cystic fibrosis transmembrane conductance regulator (*CFTR*) variants recommended by the American College of Medical Genetics and Genomics as well as targeted testing of survival motor neuron 1 (*SMN1*) and *SMN2*.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Variants Detected by Focused Carrier Screening Tests

Highlights

A targeted genotyping array is utilized to detect over 500 genetic targets associated with cystic fibrosis or cystic fibrosis-related disorder for the purpose of carrier screening.

Method Name

Targeted Genotyping Array

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is specifically for carrier screening purposes and is not intended for diagnostic purposes. For diagnostic testing, order CFMP / Cystic Fibrosis, *CFTR* Gene, Variant Panel, Varies.

If the reproductive partner is also having this test performed, call the lab for a revised risk assessment.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel under FMTT / Familial Variant, Targeted Testing, Varies. Call 800-533-1710 to obtain more information about this testing option.

Necessary Information

If there is a family history of cystic fibrosis or spinal muscular atrophy, the known genetic variant in the family should be supplied for best interpretation of results.

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**.
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 are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base
Acceptable: Matrix tube, 1 mL
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.

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)

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

An individual may be a carrier of an autosomal recessive condition without exhibiting signs or symptoms, which is often reflected in the absence of a relevant family history. As such, a couple without a known family history may be unaware of their potential risk of having a child with a genetic condition. Carrier screening, either prior to or during pregnancy, can help couples assess their risk of having a child affected by a genetic disorder.

Carrier screening for genetic variants associated with cystic fibrosis (CF) and spinal muscular atrophy (SMA) are considered standard of care by American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) for all couples regardless of ancestry.(1,2)

Cystic Fibrosis:
Cystic fibrosis, in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. Since the incidence of CF varies among different populations, the genetic variant detection rates for variant screening tests also vary between different ethnic and racial groups. To date, over 1500 variants have been described within the gene that causes CF, named cystic fibrosis transmembrane conductance regulator (*CFTR*). The most common variant, deltaF508, accounts for approximately 67% of the variants worldwide and approximately 70% to 75% in the North American population of Northern European descent. Most of the remaining variants are rare, although some show a relatively higher prevalence in certain ethnic groups or in certain atypical presentations of CF such as congenital bilateral absence of the vas deferens (CBAVD). Genetic variants detected by this assay include the 100 variants recommended by the ACMG as well as over 350 other variants.

Of note, *CFTR* potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at

least one copy of a select subset of variants.

Detection rates for several ethnic and racial groups are listed in the table below. Note that interpretation of test results and risk calculations are also dependent on clinical information and family history.

Racial or ethnic group	Carrier frequency	Variant detection rate*
European American	1/25	94%
Ashkenazi Jewish	1/25	95%
African American	1/65	87%
Hispanic American	1/46	87%
Asian American**	1/90	65%
General US population	1/35	86%

*Rates are for classic CF. Rates are lower for atypical forms of CF and for CBAVD.
**Does not apply to individuals of Japanese ancestry.

Spinal Muscular Atrophy:
Spinal muscular atrophy 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 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, 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 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 one 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 *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 one copy of *SMN1* on each chromosome. However, following a study performed by Luo et al,(3) 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. See the table below for details.

Table. SMA carrier residual risk estimates.(3)

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
European descent	1/35	95%	1/632	N/A	1/769	1/28
Ashkenazi Jewish	1/41	90%	1/345	94%	1/580	2+0 Carrier
Asian	1/53	92%	1/628	93%	1/701	2+0 Carrier
African American	1/66	71%	1/121	N/A	1/395	1/33
Latinx	1/117	90%	1/1061	N/A	1/1762	1/139
General population	1/54	90%	1/536	N/A	N/A	N/A

For details regarding the specific variants identified by this test see Targeted Variants Detected by Focused Carrier Screening Tests.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A negative result does not eliminate the risk of carrier status for any of the included conditions, due to the possibility that the patient carries a variant that is not interrogated with this assay or the rare chance of a false-negative result for a tested variant. For tested variants, the negative predictive value of this screen is greater than 98%. The patient's residual risk to be a carrier after a negative screen is dependent on ethnic background and family history.

A positive control was not available for all variants targeted on this panel. For more information regarding availability of a positive control for each variant see Targeted Variants Detected by Focused Carrier Screening Tests. The negative predictive value of these targets is unknown.

Rare variants (ie, polymorphisms) 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.

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) This assay was designed to specifically target known pathogenic or likely pathogenic variants. In rare cases, DNA variants of undetermined significance may be identified. The laboratory encourages health care professionals to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Multiple in-silico evaluation tools may have been used to assist in the interpretation of these results. Of note, the sensitivity and specificity of these tools for the determination of pathogenicity is currently unvalidated.

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

Hematopoietic stem cell transplants from allogenic donors will interfere with testing. Call Mayo Clinic Laboratories for instructions for testing patients who have received a hematopoietic stem cell transplant.

An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects deidentified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

Clinical Reference

1. Langfelder-Schwind E, Karczeski B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014;23(1):5-15. doi:10.1007/s10897-013-9636-9
2. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32. doi:10.1038/ejhg.2011.134
3. 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
4. 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;17(5):405-424. doi:10.1038/gim.2015.30
5. Carrier Testing for Cystic Fibrosis. Cystic Fibrosis Foundation; Accessed April 9, 2025. Available at www.cff.org/What-is-CF/Testing/Carrier-Testing-for-Cystic-Fibrosis/
6. Deignan JL, Gregg AR, Grody WW, et al. Updated recommendations for CFTR carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(8):100867. doi:10.1016/j.gim.2023.100867.
7. Prior TW. Professional Practice and Guidelines Committee: Carrier screening for spinal muscular atrophy. Genet Med. 2008;10:840-842. doi:10.1097/GIM.0b013e318188d069
9: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55. doi:10.1097/AOG.0000000000001952
10: Gregg AR, Aarabi M, Klugman S, et al. ACMG Professional Practice and Guidelines Committee: Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-1806. doi:10.1038/s41436-021-01203-z

Performance

Method Description

The targeted genotyping array utilizing the ThermoFisher GeneTitan platform is used to detect select genetic variants in the following genes associated with heritable conditions: cystic fibrosis transmembrane conductance regulator (*CFTR*) and survival motor neuron 1 (*SMN1*). *SMN2* may be reported in conjunction with relevant genotype findings.

For details regarding the targeted mutations identified by this test see Targeted Variants Detected by Focused Carrier Screening Tests.

Multiplex ligation-dependent probe amplification, polymerase chain reaction (PCR), relative quantitative PCR, droplet digital PCR, and Sanger sequencing are used to confirm alterations detected by microarray when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Varies

Report Available

7 to 21 days

Specimen Retention Time

Whole blood: 28 days (if available); Extracted DNA: 3 months

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

81220
81329
81222
81479 (if appropriate for government payers)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CFSMN	CF and SMA Carrier Screen Panel	98039-1

Result ID	Test Result Name	Result LOINC® Value
608350	Result Summary	50397-9
608351	Result	82939-0
608352	Interpretation	69047-9
608353	Additional Information	48767-8
608354	Method	85069-3
608355	Specimen	31208-2
608356	Source	31208-2
608357	Released By	18771-6