MAYO CLINIC LABORATORIES

Test Definition: CFTRN

Cystic Fibrosis Transmembrane Conductance Regulator, CFTR, Full Gene Analysis, Varies

Overview

Useful For

Follow-up testing to identify variants in individuals with a clinical diagnosis of cystic fibrosis (CF)

Identifying genetic variants in individuals with atypical presentations of CF (eg, congenital bilateral absence of the vas deferens or pancreatitis)

Identifying genetic variants in individuals where detection rates by targeted variant analysis are low or unknown for their ancestral background

Identifying patients who may respond to cystic fibrosis transmembrane conductance regulator (*CFTR*) potentiator therapy

Reflex Tests

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

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *CFTR* gene associated with cystic fibrosis (CF).

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for CF.

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 at an additional charge.

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

charge.

Skin biopsy or cultured fibroblast specimens:
If a skin biopsy is received, 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
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is not the preferred test for cystic fibrous carrier screening. See CFMP / Cystic Fibrosis, *CFTR* Gene, Variant Panel, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for variants identified in the CFTR gene. See FMTT / Familial Mutation, Targeted Testing, Varies. To obtain more information about testing option, call 800-533-1710.

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. **This must be a different order number than the prenatal specimen**.

For cord blood specimens: Maternal cell contamination (MCC) studies are available. **Order MATCC on both the cord blood and maternal specimens under separate order numbers**. Cord blood testing will proceed without MCC studies, but results may be compromised if MCC is present.

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 whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated

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.
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: Cultured fibroblasts
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory.
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.

Due to the complexity of prenatal testing, consultation with the laboratory is required for all prenatal testing. Prenatal specimens can be sent Monday through Thursday and must be received by 5 p.m. Central time on Friday in order to be processed appropriately.

Specimen Type: Amniotic fluid
Container/Tube: Amniotic fluid container
Specimen Volume: 20 mL
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional information:
1. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2

to 3 weeks is required to culture amniotic fluid before genetic testing can occur.
2. 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: Refrigerated
Additional Information:
1. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 2 to 3 weeks is required to culture chorionic villi before genetic testing can occur.
2. 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 cells
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured cells from another laboratory.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information: **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)

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
Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varying degree of chronic obstructive lung disease and pancreatic enzyme insufficiency.(1) Clinical diagnosis is generally made based on these features, combined with a positive sweat chloride test or positive nasal potential difference.(1) CF can also have

an atypical presentation (*CFTR*-related disorder [CFRD] or *CFTR*-related metabolic syndrome [CRMS]) and may manifest solely as congenital absence of the vas deferens or chronic idiopathic pancreatitis.(2) Several states have implemented newborn screening for CF, which identifies potentially affected individuals by measuring immunoreactive trypsinogen in a dried blood specimen collected on filter paper.(3)

To date, over 2000 variants have been described within the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that can cause CF.(3) The most common variant, deltaF508, accounts for approximately 67% of the variants worldwide and approximately 70% to 75% in the North American White population.(4) Most of the remaining variants are rare, although some show a relatively higher prevalence in certain ancestries or in some atypical presentations of CF, such as CFRD or CRMS.

If a clinical diagnosis of CF has been made or is suspected, full gene analysis of the *CFTR* gene may be utilized instead to genetically confirm the diagnosis. Full gene and deletion/duplication analysis of the *CFTR* gene can identify over 98% of the sequence variants in the coding region and splice junctions.

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.(3)

Reference Values

An interpretive report will be provided

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
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.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukoreduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(5) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These

findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Ong T, Marshall SG, Karczeski BA, et al: Cystic fibrosis and congenital absence of the vas deferens. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated November 10, 2022. Accessed January 20, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1250/
2. Bombieri C, Claustres M, De Boeck K, et al: Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros. 2011 Jun;10 Suppl 2:S86-102
3. Link SL, Nayak RP: Review of rapid advances in cystic fibrosis. Mo Med. 2020 Nov-Dec;117(6):548-554
4. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM: Cystic fibrosis: a worldwide analysis of CFTR murations--correlation with incidence data and application to screening. Hum Mutat. 2002 Jun;19(6):575-606
5. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: 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

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the *CFTR* gene, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the *CFTR* gene.

There may be regions of *CFTR* that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.

Gene symbol	Reference transcript	Additional evaluations	Technical limitations
CFTR	NM_000492.4	Poly T tract TG repeat region for 5T alleles only deletion/duplication analysis c.870-1113_870-1110del c.1393-18G>A	Copy number variation analysis in exon 13 is not performed

		c.1585-9T>A c.1585-8G>A c.1585-9412A>G c.1680-886A>G c.1680-883A>G c.1680-877G>T c.2909-15T>G c.2989-313A>T c.3140-26A>G c.3140-16T>A c.3469-1304C>G c.3717+40A>G c.3718-2477C>T c.3874-4522A>G	

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy, cord blood, amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month

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. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81223

88233- Tissue culture, skin, solid tissue biopsy (if appropriate)
88240- Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CFTRN	CFTR Gene, Full Gene Analysis	90256-9

Result ID	Test Result Name	Result LOINC® Value
619775	Test Description	62364-5
619776	Specimen	31208-2
619777	Source	31208-2
619778	Result Summary	50397-9
619779	Result	82939-0
619780	Interpretation	69047-9
619781	Additional Results	In Process
619782	Resources	99622-3
619783	Additional Information	48767-8
619784	Method	85069-3
619785	Genes Analyzed	82939-0
619786	Disclaimer	62364-5
619787	Released By	18771-6