Cystic Fibrosis Genetic Testing

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Introduction

Cystic fibrosis testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CFTR targeted mutation analysis	81220
CFTR known familial mutation analysis	81221
CFTR full gene sequencing	81223
CFTR deletion/duplication analysis	81222
CFTR Poly T Tract (5T) Genotyping	81224

Criteria

Introduction

Requests for cystic fibrosis (CF) genetic testing are reviewed using the following criteria.

CFTR Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would identify the familial mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals who have a suspected diagnosis of cystic fibrosis and the familial mutations to be tested were identified in 1st degree biological relative(s), OR
- Mutation Identification to Guide Pharmacologic Therapy Selection

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  - Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR
- Carrier Screening:
  - Be of reproductive age and have potential and intention to reproduce, and
  - Familial CFTR mutation(s) in known biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Targeted Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for CFTR mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals with an intermediate range/equivocal sweat chloride test (30-59mmol/L), or
  - Individuals with a negative sweat chloride test when symptoms of CF are present, or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  - Infants with an elevated IRT value on newborn screening, or
  - Fetus with finding of echogenic bowel on ultrasound, or
  - Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD), OR
- Mutation Identification to Guide Pharmacologic Therapy Selection
  - Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR
- Carrier Screening:
  - Individuals of reproductive age and have potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Sequencing

- Genetic Counseling:

- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Diagnostic Testing for Symptomatic Individuals:
  - Previous CFTR standard panel, if performed, was non-diagnostic (fewer than 2 pathogenic mutations detected), and
  - Individuals with a negative or equivocal sweat chloride test, and unexplained chronic obstructive pulmonary disease (COPD) or bronchiectasis with unexplained chronic or recurrent sinusitis and abnormal pulmonary function tests (PFTs), or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  - Infants with an elevated immunoreactive trypsinogen (IRT) value on newborn screening and fewer than 2 pathogenic mutations identified on standard panel testing, OR

- Mutation Identification to Guide Pharmacologic Therapy Selection
  - Individuals who meet diagnostic criteria for CF and are eligible for CFTR FDA-approved genotype-based therapies, OR

- Carrier Screening:
  - General Population Screening (e.g., no family history of CF):
    - No previous CFTR testing, and
    - Be of reproductive age and have potential and intention to reproduce, OR
  - High-risk Screening (e.g., family history of CF):
    - Previous CFTR standard panel, if performed, was negative, and
    - An individual with a family history of CF with an unknown mutation(s), or
    - An individual whose reproductive partner is a known CF carrier, has a diagnosis of CF, or has a diagnosis of CFTR-related CAVD, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous CFTR deletion/duplication testing, and

  - Previous CFTR gene sequencing was non-diagnostic (fewer than 2 pathogenic mutations detected), and
  - No known familial mutation, AND
- Member meets criteria for CFTR sequencing in symptomatic or high-risk carrier individuals, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Intron 9 Poly T Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous CFTR intron 9 poly T testing, AND
- Diagnostic Testing:
  - CFTR mutation analysis performed and R117H mutation detected, or
  - Diagnosis of male infertility (congenital absence of vas deferens [CAVD], obstructive azoospermia), or
  - Diagnosis of non-classic CF, OR
- Carrier Testing:
  - CFTR mutation analysis performed and R117H mutation detected, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- For information regarding CFTR testing for individuals with pancreatitis, please refer to the guideline *Hereditary Pancreatitis Genetic Testing*, as this testing is not addressed here.
- For information regarding carrier screening for Cystic Fibrosis performed as part of a large carrier screening panel, please see the guideline *Carrier Screening Panels, Including Targeted, Pan-Ethnic, Universal, and Expanded*, as this testing is not addressed here.

What is cystic fibrosis?

Definition

Cystic fibrosis (CF) is a genetic disorder that can cause chronic lung disease, pancreatic insufficiency, and male infertility.[1,2]

Prevalence

CF affects at least 100,000 individuals worldwide.[1] While CF is most common in individuals with northern European ancestry, it can occur in any ethnic group.[2]

Symptoms

Symptoms associated with CF may include:[1]

- Frequent respiratory infections
- Bronchiectasis
- Pancreatic exocrine insufficiency
- Elevated sweat chloride levels
- Meconium ileus in newborns
- Congenital absence of the vas deferens (CAVD; can be unilateral or bilateral).

Pulmonary disease is the major cause of morbidity and mortality in individuals with CF.[1]

CFTR-Related Disorders

Several other conditions that share some clinical similarities to CF, are also caused by mutations in the CFTR gene, but do not meet the diagnostic criteria for CF. These are called "CFTR-related disorders" and include congenital bilateral absence of vas deferens (CBAVD/CAVD), acute recurrent or chronic pancreatitis, and some respiratory tract conditions such as bronchiectasis, sinusitis, and nasal polyps.[1,3]

CAVD is frequently identified after semen analysis shows absent sperm (azoospermia). CAVD is often caused by one severe CFTR mutation and one non-CF causing mutation or 2 non-CF causing mutations.[1]

CFTR-Related Metabolic Syndrome / CF Screen Positive, Inconclusive Diagnosis

CFTR-related metabolic syndrome/CF screen-positive, inconclusive diagnosis (CRMS/CF-SPID) is defined as "[a]n asymptomatic infant with a positive NBS result for CF and either a sweat chloride value <30 mmol/L and two CFTR variants at least one of which has unclear phenotypic consequences OR an intermediate sweat chloride value (30–59 mmol/L) and one or zero CF causing variants".[4] The majority of infants with CRMS/CF-SPID remain healthy. Some will convert to a CF diagnosis, and there is potential for developing a CFTR-Related Disorder (CFTR-RD) later in life.[4]

Cause

CF is caused by mutations in the CFTR gene.

Inheritance

CF is an autosomal recessive condition.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis of CF can be made based on clinical symptoms and evidence of CFTR dysfunction, which may include elevated sweat chloride or nasal potential difference, or the identification of 2 CFTR mutations.[1] In newborns, the diagnosis is made based on elevated trypsinogen on newborn screening and the presence of 2 CFTR mutations.[1]

Most signs of CF cannot be identified on prenatal ultrasound examination. However, pregnancies in which fetal echogenic bowel is identified on ultrasound are at an increased risk to be affected with CF.[1]

Prenatal diagnosis for CF can be performed on a sample from chorionic villus sampling (CVS) or amniocentesis:[1]

- If both parents are known carriers, a mutation panel that includes both parental mutations is typically the test of choice.
- If only one parent is a carrier, or if testing is indicated because of echogenic bowel, testing with a large mutation panel or sequencing and deletion/duplication analysis offers greater sensitivity.

Newborn screening (NBS) programs include screening for CF, though the screening protocol may vary by state.[5]

The American College of Medical Genetics has defined a panel of 23 common, pan-ethnic mutations that occur at a frequency of at least 0.1% in patients with cystic fibrosis.[6,7] While this panel was created for carrier screening purposes, the CF diagnostic guidelines also endorse its use in that setting for most patients.[2] In 2023, the ACMG-recommended mutation list was updated to 100 variants.[8] Laboratories performing mutation panel testing routinely include all of these mutations. Many laboratories expand their panels with more mutations intended to increase the detection rate, particularly in non-Caucasian populations. Expanded mutation panels

generally test for 70 or more CFTR mutations. The detection rates of targeted mutation panels vary by laboratory and depend on the mutations included and the patient's ethnicity.[1]

CFTR-sequencing detects more than 97% of mutations.[1] The frequency of deletions and duplications is estimated to be less than 5% of all detected CFTR variants, but this may be an underestimate.[7]

Management

Management of CF addresses respiratory and digestive issues through inhaled medications and replacement of pancreatic enzymes.

There are several FDA-approved mutation-specific therapies.[9]

Survival

CF Foundation Patient registry data from 2022 indicate that the median predicted survival for people with CF is about 56 years.[10]

Test information

Introduction

Testing for cystic fibrosis tests may include known familial mutation analysis, targeted mutation analysis, NGS sequencing, deletion/duplication analysis, and intron 9 poly-T and TG analysis (previously called intron 8 or IVS8 poly-T analysis).

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene

sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Intron 9 poly-T and TG analysis

Intron 9 (formerly intron 8 or IVS 8) poly-T analysis identifies the number of thymidine bases in intron 9 of the CFTR gene. The three common variants are 5T, 7T, and 9T, with 7T and 9T being considered normal variants.[1]

“The 5T allele by itself is associated with variable penetrance for CF and CAVD based on the status of an adjacent poly TG tract, which usually contains 11, 12, or 13 repeats (c.1210–34TG[11], c.1210–34TG[12], c.1210–34TG [13]). When paired with a known CF-causing variant, 5T and 11TG variants in cis rarely confer an increased risk for CAVD in males while 5T in cis with 12TG or 13TG confers risk for CAVD and rarely for nonclassic CF. Given the commonness of the 5T allele (one in ten individuals carry a 5T variant), interpretation of its disease liability should ideally be performed in the context of the number of associated TG repeats.” [7]

Guidelines and evidence

The American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) technical standard for CFTR variant testing stated:[7]

- “As a way to ensure that CFTR variant testing for carrier screening and diagnostic testing purposes remains comprehensive, pan-ethnic, and up-to-date, the ACMG recommends either a classification-based reporting approach or a classification-based (targeted) testing approach (which has historically been used for CFTR carrier screening.”
- “For those laboratories who wish to continue using a targeted testing approach, the ACMG-23 variant panel remains as the minimum list of CFTR variants that should be included. Laboratories may want to consider adding additional variants to their panel depending on the ethnic composition of their expected test population.

However, the minimum list of CFTR variants recommended for pan-ethnic carrier screening has not been increased at this time."

- "Targeted and comprehensive approaches are both acceptable for the testing of individuals regardless of race, ethnicity, or test indication."
- "The ACMG recommends that laboratories performing initial CFTR variant testing on an individual can use either targeted or comprehensive methods to evaluate the gene…If pathogenic or likely pathogenic CFTR variants have been confirmed in both biological parents, or an affected full sibling, only targeted methods should be used."
- "For all prenatal, postnatal, and adult diagnostic testing indications for CFTR, the ACMG recommends the reporting of R117H status as well as the results from at least the associated polyT tract. For all adult carrier screening indications for CFTR, polyT status should be reported when the R117H variant is detected; laboratories may also want to consider reporting the results from the associated polyT tract in the partner of an individual who had a pathogenic or likely pathogenic variant detected during screening."

ACMG (2023) issued a position statement updating the minimum set of CFTR variants to be included for CF carrier screening that stated:[8]

- "The new set of 100 variants represents an updated minimum CFTR carrier screening variant set, but it does not represent a limit on the total number of variants that a laboratory can choose to assess, and it is likely that laboratories may already have many (but likely not all) of these variants included as a part of their tests."
- "The workgroup is also aware that there are not likely any existing targeted CF tests available that contain all of the newly recommended variants. However, some laboratories may have previously chosen to offer CF carrier screening using either Sanger or NGS of CFTR, and these methods should encompass all of the genomic regions containing the recommended variants."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2017; Reaffirmed 2023) issued a committee opinion on carrier screening for genetic conditions that stated:[11]

- "Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant."
- "Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening."
- "For couples in which both partners are unaffected but one or both has a family history of cystic fibrosis, genetic counseling and medical record review should be performed to determine if CFTR mutation analysis in the affected family member is available."

- "If a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens, the couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation."
- "If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed."
- "Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations."

American Urological Association in partnership with the American Society for Reproductive Medicine

The American Urological Association in partnership with the American Society for Reproductive Medicine (2020) published guidelines on the diagnosis and treatment of infertility in males that stated:[12]

- "Clinicians should recommend Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation carrier testing (including assessment of the 5T allele) in men with vasal agenesis or idiopathic obstructive azoospermia. (Expert Opinion)"
- "For men who harbor a CFTR mutation, genetic evaluation of the female partner should be recommended. (Expert Opinion)"
- "Specifically, studies suggest that mutations in the CFTR gene are present in up to 80% of men with congenital bilateral absence of the vas deferens (CBAVD), 20% of men with CUAVD and 21% of men with idiopathic epididymal obstruction."
- "As the goal of genetic testing is to help identify the etiology as well as provide counseling on potential offspring transmission, expanded carrier screening or gene sequencing should be considered. In addition to classic mutations, the 5-thymidine (5T) variant of the polythymidine tract in the splice site of intron 8 (which regulates exon 9 splicing efficiency) is also commonly found in men with obstructive azoospermia due to CFTR abnormalities."

Cystic Fibrosis Foundation

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017) outline the ways in which a CF diagnosis can be established (see below). Characteristic features of CF include chronic sinopulmonary disease (such as persistent infection with characteristic CF pathogens, chronic productive cough, bronchiectasis, airway obstruction, nasal polyps, and digital clubbing), gastrointestinal/nutritional abnormalities (including meconium ileus, pancreatic insufficiency, chronic pancreatitis, liver disease,

and failure to thrive), salt loss syndromes, and obstructive azoospermia in males (due to CAVD).[2]

When at least one characteristic feature is present, a diagnosis of CF can be established by:

- Two abnormal sweat chloride values; or
- Identification of two CF-causing CFTR gene mutations; or
- Characteristic transepithelial nasal potential difference (NPD)

In the absence of symptoms, a CF diagnosis can be established in:

- A newborn with two CF-causing CFTR gene mutations identified via newborn screening

"Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo CFTR genetic testing if the CFTR genotype was not available through the screening process or is incomplete." "Even in the presence of a positive sweat test, the identification of 2 CF-causing mutations should be confirmed in a clinical genetics laboratory capable of performing in-depth genetic analysis when required to further define CF risk (eg, the length of polyT tracts with the c.350G>A [legacy:R117H] CFTR mutation). Confirmation of genetic testing results with an FDA-approved companion diagnostic test also has additional value in therapy selection and access."[2]

These guidelines further state that, “Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30- 59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended CFTR gene analysis and/ or CFTR functional analysis."[2]

A CFF evidence-based guideline (2024) on management of CRMS/CFSPID stated:[13]

- "The CFF recommends that people with CRMS/CFSPID who have <2 disease-causing variants identified by NBS, should undergo sequencing of the coding and flanking regions and del/dup analysis of the coding and exon flanking regions of CFTR." Grade B; Certainty: Moderate
- "The CFF recommends CFTR genetic evaluation for parents of people with CRMS/CFSPID when phasing of the CFTR variants (ie, in cis or trans) would inform the diagnostic status of the individual by confirming the inheritance pattern." Grade A; Certainty: High

Society for Maternal-Fetal Medicine

The Society for Maternal Fetal Medicine (SMFM, 2021) statement on the evaluation of soft ultrasound markers such as fetal echogenic bowel identified during ultrasound stated:[14]

- "...for fetuses with isolated echogenic bowel, we recommend an evaluation for cystic fibrosis and fetal cytomegalovirus infection and a third-trimester ultrasound examination for reassessment and evaluation of growth (GRADE 1C)".

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for cystic fibrosis testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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