MEDICAL POLICY

Excellus
An independent licensee of the Blue Cross Blue Shield Association

Medical Policy Title	**Genetic Testing for Cystic Fibrosis**
Policy Number	**2.02.17**
Current Effective Date	**July 16, 2026**
Next Review Date	**July 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service**.**

(Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Genetic testing for cystic fibrosis (CF) for common variants is considered **medically appropriate** when the following criteria are met:

   A. The results will impact clinical care;

   B. When offered in a setting with adequately trained health care providers to provide appropriate pre- and post-test genetic counseling; **and**

   C. When performed by a qualified CLIA laboratory, in **ANY** of the following circumstances:

      1. Diagnostic or confirmatory testing in:

         a. individuals with symptoms of CF and a negative sweat test;

         b. infants with meconium ileus or other symptoms indicative of CF who are too young to produce adequate amounts of sweat for a sweat chloride test;

         c. males with congenital bilateral absence of vas deferens (CBAVD); or

      2. Carrier testing for:

         a. individuals with a family history of CF;

         b. individuals who have a relative who is a known carrier of a cystic fibrosis transmembrane conductance regulator (CFTR) mutation;

         c. reproductive partners of an individual with a family history or a diagnosis of CF;

         d. persons seeking preconception or prenatal care, who, after informed discussions with a practitioner that include both frequency of carrier and detection (sensitivity) rates of the test in the racial or ethnic group of the parents, make a shared decision with the practitioner to undergo testing;

         e. children already diagnosed with CF, but not genetically tested for mutations, when the parents of that child are considering another pregnancy;

         f. individuals already diagnosed with CF, but not genetically tested for mutations, when a reproductive partner is found to be a carrier of a CFTR mutation;

g. women who are pregnant or wanting to become pregnant, as part of routine care;

3. Prenatal diagnostic testing or pre-implantation testing of:

a. fetuses, when both parents have a diagnosis of CF, are a known carrier of a CFTR mutation, or have a family history of CF;

b. fetuses, when fetal echogenic bowel has been identified on ultrasound;

c. embryos, when either parent has a diagnosis of CF, is a known carrier of a CFTR mutation, or has a family history of CF.

II. Expanded CFTR testing (CPT 81223) is considered **medically appropriate** when standard variant testing is insufficient to establish diagnosis or assess reproductive risk, and when results will impact clinical or reproductive decision-making.

RELATED POLICIES

Corporate Medical Policy

2.02.25 Non-Invasive Prenatal Testing

2.02.03 Genetic Testing for Inherited Disorders

4.01.03 Prenatal Genetic Testing

4.01.05 Assisted Reproductive Technologies

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Genetic testing of an at-risk fetus may be considered in consultation with an appropriately trained (genetics) health care provider to allow for situations when the paternal family history is unknown, or the parent is unavailable but comes from a population at significantly increased carrier risk.

V. Testing for cystic fibrosis should only be performed once per lifetime.

VI. A sequential screening strategy is encouraged when screening is done during the prenatal or preconception period. Sequential screening involves testing one partner (male or female), and then the second partner is tested only if the first partner tests positive as a CF carrier or if there is a known history of CF in the family of the first partner, but the mutation is not able to be detected in that family.

DESCRIPTION

Cystic fibrosis (CF) is a multi-system genetic disease in which defective chloride transport across membranes causes dehydrated secretions. It can lead to tenacious mucous in the lungs, mucous plugs in the pancreas and high sweat chloride levels. CF has a highly variable presentation and course. Other manifestations associated with CF include chronic sinusitis, nasal polyps, liver disease, pancreatitis, and congenital absence of the vas deferens. In classic CF, patients experience chronic bacterial infections of the airway and sinuses, impairment of fat digestion due to pancreatic insufficiency, infertility in males due to azoospermia, and elevated concentrations of chloride in sweat.

Cystic fibrosis is inherited as an autosomal recessive disorder. The incidence of a positive CF carrier status varies markedly by ethnicity. CF is one of the most common genetic diseases in Caucasians, being present in one in 2500 to 3300 live births. Approximately one in every 25 people of European descent and one in every 29 people of Ashkenazi Jewish descent is a carrier of a cystic fibrosis mutation. Although CF is less common in other groups, approximately one in every 46 Hispanic Americans, one in every 65 African Americans and one in every 90 Asian-Americans carry at least one abnormal CFTR gene.

The diagnosis of CF may be suspected because of clinical presentation or family history. Differential clinical diagnosis can be made by the results of the epithelial abnormality and is best accomplished by the sweat chloride test (greater than 60 mEq/L [milliequivalents per liter]). Newborn screening programs for CF measure immunoreactive trypsinogen in a dry blood heel-stick sample. A small number of patients with CF do not demonstrate abnormal chloride levels in the sweat test. For these individuals, diagnosis may be based on genetic testing for the presence of a mutated gene.

In 1989, the responsible gene, the CF transmembrane conductance regulator (CFTR) was mapped to chromosome 7, and the most common gene mutation, F508del, was identified. To date there are over 1,500 mutations identified in the CFTR gene, many of which are rare mutations. The standard core mutation analysis of the CFTR gene recommended by the American College of Medical Genetics (ACMG) includes 23 mutations that identify the majority of prevalent mutations. This panel can identify about 97% of mutations in Ashkenazi Jewish individuals, 90% in Caucasians, 69% in African Americans and 57% in Hispanic Americans.

In addition to diagnostic testing as noted above, experts recommend carrier testing in a subset of individuals to identify family members who do not have CF themselves but are at risk for producing affected children. Couples planning a pregnancy or those in early pregnancy may undergo testing to allow for informed decision-making regarding fetal diagnosis or reproductive choices. Prenatal genetic testing of fetuses may be indicated when there are known parental mutations or a family history of CF in both parents or when an echogenic bowel is found on fetal ultrasound. In addition,

preimplantation embryonic testing for CF may be indicated when either parent has a diagnosis of CF, is a known carrier of a CFTR mutation, or has a family history of CF.

SUPPORTIVE LITERATURE

Farrell et al (2017) noted that CF, caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis criteria. To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with CFTR mutations. An a priori threshold of greater than or equal to 80% affirmative votes was needed for acceptance of each recommendation statement. After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and a 2nd round of voting. It was recommended that diagnoses associated with CFTR mutations in all individuals, from newborn to adult, be established by evaluation of CFTR function with a sweat chloride test. The latest mutation classifications annotated in the Clinical and Functional Translation of CFTR project should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis; these terms are now merged; and equivalent, and CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis may be used. One of the recommendations was that for individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30 to 59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended CFTR gene analysis and/or CFTR functional analysis (90 % vote; 0 abstain).

Deignan et al (2023) analyzed CFTR variants across diverse populations in the U.S. and ranked them in order of decreasing frequency. They then tabulated, for each ancestral population, the minimum number of variants needed such that 95% of the total CFTR carrier frequency for the population is achieved. To derive the final set of CFTR variants, they merged the 95% variant lists from each component ancestry to achieve a nonoverlapping set of 100 variants. This approach was used to ensure that at least 95% of the total carrier frequency in each population is represented in the final variant set. Multiple factors play a role in the identification of variants associated with CF, particularly in the context of biogeographically diverse populations. For this statement, the minimum set of variants was evaluated for population frequency and coverage within six global ancestral populations using the genomeAD data set. The new CFTR variant set represents an updated minimum recommended variant set for CF carrier screening, and this new set now supersedes the previous set of 23 CFTR variants recommended by the ACMG. These revised recommendations apply only to carrier screening. They do not apply to CFTR variant testing for diagnosis or newborn screening.

PROFESSIONAL GUIDELINE(S)

In 1997, the National Institutes of Health (NIH) Consensus Development Conference recommended that genetic screening for CF mutations be offered to identify carriers among adults with a positive family history of CF, reproductive partners of individuals with CF, couples currently planning a pregnancy, and couples seeking prenatal care. The NIH advised against general population screening or routine CF genetic testing of all newborns.

In 2001, the American College of Obstetricians and Gynecologists (ACOG) issued a recommendation that CF testing information be made available to all couples, whatever their risk for carrying the CF gene, and that couples in ethnic or racial groups that are considered at higher risk for carrying the CF gene (e.g., Caucasians, particularly those of European or Ashkenazi Jewish descent), specifically be offered screening. If a patient has been screened previously, the test should not be repeated, but CF screening results should be documented. In 2011, ACOG updated its recommendations as follows:

I. For routine carrier screening, complete analysis of the CF transmembrane regulator (CFTR) gene by DNA sequencing is not appropriate.

II. Maternal carrier screening is not replaced by newborn screening panels that include CF screening.

III. If a woman with CF wishes to become pregnant, a multidisciplinary team may assist in management of issues regarding pulmonary function, weight gain, infections, and higher risks for diabetes and preterm delivery.

IV. When both parents are CF carriers, they should undergo genetic counseling to review prenatal testing and reproductive options.

V. When neither parent is affected by CF, but one or both has a family history of CF, CFTR mutation analysis in the affected family member may be identified from medical record review, and the couple should undergo genetic counseling.

VI. If a woman's reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens, mutation analysis and consultation by a geneticist is recommended.

In 2002, the American College of Medical Genetics (ACMG) published the following recommended indications for CF genetic testing (revised 2004):

I. Diagnostic testing for possible diagnosis of CF, definite diagnosis of CF, infants with meconium ileus, or males with congenital bilateral absence of the vasa deferens (CBAVD);

II. Carrier testing for reproductive partners of individuals with positive family history of CF, reproductive partners of males with congenital bilateral absence of the vasa deferens (CBAVD), the general population of reproductive couples, persons with a positive family history of CF, or gamete donors;

III. Preimplantation testing;

IV. Prenatal diagnostic testing for individuals with positive family history of CF, couples having a CF mutation in both partners, or fetuses with echogenic bowel during second trimester; and

V. Newborn screening.

ACOG and ACMG introduced guidelines for prenatal and preconception carrier screening for CF and recommended screening for CF to be performed as part of routine obstetric practice for all patients (2001). Given that CF screening has been a routine part of reproductive care for women since 2001, it is prudent to determine if the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated.

In an effort to standardize the laboratory approach to screening, the Subcommittee on Cystic Fibrosis Screening, the Accreditation of Genetic Services Committee, ACMG, and ACOG have recommended the use of a pan-ethnic screening panel that includes all mutations with an allele frequency of at least 0.1% in the general U.S. population. The initial ACMG 25-mutation panel has been considered the standard-of-care for population-based carrier testing. This panel can identify about 97% of mutations in Ashkenazi Jewish individuals, 90% in Caucasians, 69% in African Americans and 57% in Hispanic Americans. In 2004, two of these mutations were dropped, leaving the current recommendation at 23 mutations.

In 2020, the ACMG published an updated set of technical standards for CFTR variant testing, which recommended that laboratories could now use either targeted or comprehensive (i.e., next-generation sequencing [NGS]) methods for testing and reaffirmed the original set of 23 variants as the minimum set for CF carrier screening; an overlapping workgroup subsequently convened to evaluate whether an update to the minimum CFTR variant set was necessary. In addition, in 2021, the ACMG published a new carrier screening clinical practice resource, which continued to recommend offering testing of CFTR (now along with many additional genes) to all pregnant patients, as well as those planning a pregnancy.

The original ACMG-23 CF variant set was derived primarily from databases comprising individuals with well characterized CF who were Non-Hispanic White or Ashkenazi Jewish, thereby allowing individuals from those ancestries to be more easily identified during carrier screening. However, given that CF has been reported across all races, ethnicities, and ancestries, improved equity in variant detection was both necessary and desirable.

The ACMG released new CFTR variant set recommendations in 2023. The new CFTR variant set represents an updated minimum recommended variant set for CF carrier screening, and this new set now supersedes the previous set of 23 CFTR variants recommended by the ACMG. These revised recommendations apply only to carrier screening. Benefit from the use of mutation testing panels that extend beyond the ACMG-recommended mutations has not been clearly established. These larger panels range in scope from testing for over 80 mutations to full-length CFTR gene sequencing. Extended panels are proposed for use in:

I. Patients with a family history of CF, when the standard mutation panel results are negative;

II. Reproductive couples who test positive/negative with the standard mutation panel;

III. Parents of an affected CF child to identify a rare familial mutation, when the standard mutation panel test results are negative; and

IV. Patients affected with CF, to identify rare mutations when the standard mutation panel test results are negative.

The 2025 United States Cystic Fibrosis Foundation published a consensus guideline that supports the use of expanded CFTR testing as a secondary approach when initial variant panel testing is insufficient to detect relevant mutations or clarify risk. Expanded testing, including sequencing, may be used to improve detection and better characterize genetic findings, particularly when results are needed to support a diagnosis or inform reproductive risk. The guidelines emphasize that expanded CFTR testing should be used selectively based on clinical need, and the results must be interpreted in the context of follow-up diagnostic evaluation, as genetic testing alone does not establish a diagnosis of cystic fibrosis.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: Clinical Laboratory Improvement Amendments (CLIA) | FDA [accessed 2026 Jun 22]

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (ego, male infertility)

Code	Description
81401	Molecular Pathology Procedure Level 2
81402	Molecular Pathology Procedure Level 3
81403	Molecular Pathology Procedure Level 4
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7
81407	Molecular Pathology Procedure Level 8
81408	Molecular Pathology Procedure Level 9

Copyright © 2026 American Medical Association, Chicago, IL

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
E84.0-E84.9	Cystic fibrosis (code range)
Z14.1	Cystic fibrosis carrier
Z31.430-Z31.438	Encounter for genetic testing of female for procreative management (code range)
Z31.440-Z31.448	Encounter for genetic testing of male for procreative management (code range)
Z31.5	Encounter for procreative genetic counseling
Z33.1	Pregnant state, incidental
Z34.00-Z34.93	Encounter for supervision of normal pregnancy (code range)
Z36	Encounter for antenatal screening of mother

REFERENCES

American College of Obstetrics and Gynecologists, American College of Medical Genetics. Preconception and prenatal carrier screening for cystic fibrosis: clinical and laboratory guidelines. Obstet Gynecol. 2001;98:907-918.

American College of Obstetrics and Gynecologists. ACOG Committee Opinion. Number 325, December 2005. Update on carrier screening for cystic fibrosis. Obstet Gynecol. 2005 Dec;106(6):1465-8.

American College of Obstetrics and Gynecologists. ACOG Committee Opinion. Number 442, Oct 2009. Update on preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. Obstet Gynecol. 2009 Oct;114(4):950-53.

American College of Obstetrics and Gynecologists. ACOG Committee Opinion. Number 691. March 2017. Update on carrier screening for cystic fibrosis. Obstet Gynecol. 2017 Mar;129:41-51.

American College of Medical Genetics. Standards and Guidelines for CFTR Mutation Testing, ACMG Statement. Genet Med. 2002 Sep/Oct;4(5):379–90.

Deignan JL, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 May;22(8):1288–1295.

Deignan J, et al. Updated recommendations for CFTR carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Jun:100867. Epub ahead of print.

Farrell P, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb:181S:S4-S15.

McGarry ME, et al. Cystic fibrosis newborn screening: A systematic review-driven consensus guideline from the United States Cystic Fibrosis Foundation. Int J Neonatal Screen. 2025 Apr 2;11(2):24.

Ong T, et al. [Internet] Cystic fibrosis and congenital absence of the vas deferens. Posted 2001 Mar 26, Last revision: Mar 9, 2023. [accessed 2026 Jun 22] Available from: https://www.ncbi.nlm.nih.gov/books/NBK1250/

SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

LCD - Molecular Pathology Procedures (L35000) [accessed 2026 Jun 22]

Article - Billing and Coding: Molecular Pathology Procedures (A56199) [accessed 2026 Jun 22]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.

- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
04/17/02, 02/20/03, 01/15/04, 12/16/04, 12/15/05, 10/19/06, 08/16/07, 07/17/08, 07/16/09, 07/15/10, 07/21/11, 07/19/12, 07/18/13, 07/17/14, 07/16/15, 07/21/16, 07/20/17, 07/19/18, 07/18/19, 07/16/20, 07/15/21, 07/21/22, 07/20/23, 07/18/24, 07/17/25, 07/16/26	
Date	**Summary of Changes**
07/16/26	• Annual review. Expanded CTFR testing stance updated to medically necessary when specific criteria are met.
07/17/25	• Annual review; policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
04/17/02	• Original effective date