MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Genetic Testing for Cystic Fibrosis**
Policy Number	**2.02.17**
Category	**Technology Assessment**
Original Effective Date	**04/17/02**
Committee Approval Date	**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**
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Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for cystic fibrosis (CF) for common variants has been medically proven to be effective and therefore, is considered **medically appropriate** when the results will impact clinical care, when offered in a setting with adequately trained health care providers to provide appropriate pre- and post-test genetic counseling, and when performed by a qualified laboratory, in **ANY** of the following circumstances:

A. Diagnostic or confirmatory testing in:
   1. individuals with symptoms of CF and a negative sweat test;
   2. 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;
   3. males with congenital bilateral absence of vas deferens (CBAVD);

B. Carrier testing for:
   1. individuals with a family history of CF;
   2. individuals who have a relative who is a known carrier of a cystic fibrosis transmembrane conductance regulator (CFTR) mutation;
   3. reproductive partners of an individual with a family history or a diagnosis of CF;
   4. 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;
   5. children already diagnosed with CF, but not genetically tested for mutations, when the parents of that child are considering another pregnancy;

6. 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;
7. women who are pregnant or wanting to become pregnant, as part of routine care;

C. Prenatal diagnostic testing or pre-implantation testing of:
1. fetuses, when both parents have a diagnosis of CF, are a known carrier of a CFTR mutation, or have a family history of CF;
2. Fetuses, when fetal echogenic bowel has been identified on ultrasound;
3. 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. Extended panel testing (CPT: 81223): The benefit of genetic testing for CF using extended panels has not been clearly established; therefore, extended panel testing is considered **not medically necessary**.

Refer to Corporate Medical Policy #2.02.25 Non-Invasive Prenatal Testing

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing

Refer to Corporate Medical Policy #4.01.05 Assisted Reproductive Technologies - In Vitro Fertilization

POLICY GUIDELINES

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.

RATIONALE

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 recommended 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 (Deignan, et al.) where they 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.

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.

Extended CF mutation panels may have a role to play for a small subset of individuals, but definitive patient selection criteria have not been established. Evidence demonstrating the clinical utility of extended mutation panels is limited.

Information on the risks and benefits of genetic testing must be presented fully and objectively without coercion to persons contemplating genetic testing.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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 **(NMN)**	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)
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

HCPCS Codes

Code	Description
No specific code(s)	

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 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

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KEY WORDS

CF, CF transmembrane conductance regulator, CFTR, Cystic fibrosis, Newborn screening.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare members:

[https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=144&keyword=molecular+pathology&keywordType=starts&areaId=s41&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=Exact] accessed 06/24/23.

There is currently a Local Coverage Article (LCA) for Billing and Coding: Molecular Pathology Procedures (A56199). Please refer to the following LCA website for Medicare Members:

[https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=102&lcdid=35000&keyword=molecular+pathology&keywordType=starts&areaId=s41&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP&contractOption=all&sortBy=relevance&KeyWordLookUp=Doc&KeyWordSearchType=Exact&bc=AAAAAAQAIAAAAAAA&=] accessed 06/24/23.