Genetic Testing for Cystic Fibrosis

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Page Number(s):	1 of 9

Disclaimer

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under medical surgical benefits of the Company's Medicaid products for medically necessary genetic testing for cystic fibrosis.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Highmark Health Options (HHO) – Managed care organization serving vulnerable populations that have complex needs and qualify for Medicaid. Highmark Health Options members include individuals and families with low income, expecting mothers, children, and people with disabilities. Members pay nothing to very little for their health coverage. Highmark Health Options currently services Delaware Medicaid: Delaware Healthy Children Program (DHCP) and Diamond State Health Plan Plus members.

Carrier – An individual that 'carries' a genetic change that can cause a disease. Carriers typically show no signs of the disorder; however, they can pass on the genetic variation to their children, who may develop the disorder or become carriers themselves.

Diagnostic Testing – When genetic testing is performed to identify a genetic condition or disease-causing signs or symptoms currently or will cause signs and symptoms in the future.

Newborn Screening – Testing performed on infants one to two days after birth to determine if the infant has a certain disease known to cause issues with health and development.

Prenatal Screening – Testing performed during pregnancy to help identify fetuses that may have a certain disease.

Cystic Fibrosis (CF) – An autosomal recessive inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) – A gene located on chromosome 7 that is mutated in cystic fibrosis.

Family – For the purposes of this policy, a family is defined as:

- First degree relatives are the parents, brothers, sisters, or children of an individual
- Second degree relatives are the people with whom one quarter of an individual's genes is shared (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling)
- Third degree relatives are the people with whom one eighth of an individual's genes is shared (i.e., cousin, great-grandparent, great-aunt, or great-uncle)

PROCEDURES

A prior authorization is required.

Highmark Health Options considers standard genetic testing for cystic fibrosis (CF) (81220) medically necessary for members in which alternative biochemical or other clinical tests to definitively diagnose carrier status are not available or if available provided an indeterminate result. The following criteria must be met:

- Diagnostic or Confirmatory Testing for Symptomatic individuals:
  - Testing should only be performed one per lifetime; AND
  - Confirmation of a diagnosis of cystic fibrosis when the diagnosis is in doubt (e.g., individuals with a negative sweat chloride test) but have symptoms of cystic fibrosis, OR
  - Diagnosis for otherwise healthy males with infertility issues due to congenital bilateral absence of the vas deferens (CBAVD); OR
  - Analysis of DNA for mutations is not a primary screening method for any of the disorders for which newborn screening is performed. The diagnosis of cystic fibrosis is generally confirmed by means of sweat chloride testing and does not require documentation of genetic mutation. In cases of clinically suspected CF, in which sweat chloride values are normal or non-diagnostic, documentation of CFTR mutation may be needed to confirm a diagnosis; OR
  - 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, OR
  - Infants with an elevated IRT value on newborn screening.

- Carrier Testing:
  - Carrier testing should only be performed in adults and only once per lifetime; AND
  - Parent with a positive family history of cystic fibrosis (e.g., member has a previously affected child with CF); OR
  - One or both parents with a 1st degree relative identified as a cystic fibrosis carrier, OR
  - Both prospective parents, who are Highmark Health Options members, seeking prenatal care for ongoing pregnancy or who are planning a pregnancy, OR
  - Reproductive partners, who are Highmark Health Options members, of persons with cystic fibrosis; OR
  - As part of routine care in women who are pregnant or wanting to become pregnant, OR
  - One or both parents are in a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for CF

Genetic testing or expanded screening panels for CFTR mutations to determine the carrier status of an individual may be considered medically necessary if medical necessity has been confirmed by appropriately trained health care providers in genetics when the paternal family history is unknown, or the parent is unavailable but comes from a population at significantly increased carrier risk.

- Prenatal Testing:
  - Both parents are carriers, OR
  - One parent is a carrier, and the other parent has CF: OR
  - One parent is a carrier or has CF and genetic testing on the other parent is unavailable/unknown; OR
  - The fetus presents with fetal echogenic bowel per ultrasound during second trimester.

In accordance with the 2011 ACOG update on carrier screening for CF, Highmark Health Options recognizes the following recommendations:

- When a member has been screened previously, the CF screening results should be documented, but the test should not be repeated; AND
- Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.
- Prenatal Diagnostic Testing
- Fetuses when both parents have any combination of either a diagnosis of CF, are a known carrier of a CFTR mutation, or have family history of CF, OR
- Prenatal diagnosis where ultrasound demonstrates fetal meconium ileus, echogenic bowel, or obstructed bowel

Diagnostic Testing Strategy:

- A biochemical test (e.g., sweat chloride) is performed with a clinical exam. If the test is inconclusive and cystic fibrosis remains, there are other considerations mentioned below.
- A CFTR gene analysis for the detection of common variants should be performed (Section 2 & 5). If the testing is inconclusive and cystic fibrosis remains, there are other considerations mentioned below.
- A full sequence analysis should be performed (Section 3). If this test is inconclusive, there is a final consideration mentioned below.
- A CFTR gene analysis for detection/duplication variant (Section 4)

Highmark Health Options considers CFTR Known Familial Mutation Analysis (81221) medically necessary for members who meet the following criteria:

- Genetic Counseling: Pre and post-test genetic counseling by an appropriate provider; AND
- Previous Testing:
  - No previous genetic testing for known CFTR family mutation(s); OR
  - Previous CFTR panel testing was not inclusive of known family mutation; AND C. Carrier Screening: Family CFTR mutation(s) in known biologic relative; OR D. Prenatal Testing: Either biological parent is known carrier of a CFTR mutation.

Highmark Health Options considers CFTR Sequencing (81223) medically necessary for members who meet the following criteria:

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider; AND

- Previous Genetic Testing:
  - Previous CFTR Standard Panel was negative (no mutation found) or only one mutation was found; AND
  - Individuals with a negative or equivocal sweat chloride test; AND
    - Unexplained COPD or bronchiectasis with unexplained chronic or recurrent sinusitis and abnormal pulmonary function tests (PFTs); OR
    - Idiopathic chronic (acute recurrent) pancreatitis is 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 and a negative 23 mutation panel; OR
- Carrier Screening:
  - An individual with a family history of CF with an unknown mutation; OR
  - An individual whose reproductive partner is a known CF carrier, has a diagnosis of CF, or has a diagnosis of CAVD.

Highmark Health Options considers CFTR Deletion/Duplication Analysis (81222) medically necessary for members who meet the following criteria:

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider; AND
- Previous Genetic Testing:
  - Previous CFTR Standard Panel was negative (no mutation found) or only one mutation was found; AND
  - No previous CFTR deletion/duplication testing; AND
  - No known familial mutation.

Highmark Health Options considers CFTR Intron 8 Poly T Analysis (81224) medically necessary for members who meet the following criteria:

- Genetic Counseling: Pre and post-test genetic counseling by an appropriate provider; AND
- Previous Genetic Testing: No previous CFTR intron 8 poly T testing; AND
- Diagnostic testing: Diagnosis of non-classic CF; AND
- Carrier testing: CFTR mutation analysis performed and R117H mutation detected.

Genetic Counseling:

Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary to inform people being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board-Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board-Certified Clinical Geneticist
- A physician with experience in genetic medicine and genetic testing methods

When genetic testing for cystic fibrosis is not covered:

- Highmark Health Options considers genetic carrier and diagnostic testing for cystic fibrosis medically necessary for the indications listed above. Any other condition will require case-by case review.
- Carrier panels for more than one condition are not covered unless all components of the panel have been determined to be medically necessary based on criteria above.

Post-payment Audit Statement

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

Place of Service: Outpatient

CODING REQUIREMENTS

CPT code	Description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMOG/ACPG guidelines).

Covered Diagnosis Codes

E84.0	E84.11	E84.19	E84.8	E84.9
Q55.3	Z13.71	Z14.1	Z31.430	Z31.440
Z31.5	Z33.1	Z34.00	Z34.01	Z34.02
Z34.03	Z34.80	Z34.81	Z34.82	Z34.83
Z34.90	Z34.91	Z34.92	Z34.93	Z36.0
Z84.81				

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF THE LITERATURE

Cystic fibrosis is a rare genetic disease, found in about 30,000 people in the United Sates and 70,000 worldwide. The disease is an example of a recessive disease, meaning that a person must have a mutation in both copies of the cystic fibrosis gene to have cystic fibrosis. If a person only has one copy of the CF gene and the other copy are normal, the person does not have CF but is considered a CF carrier. About 10 million people in the Unites States are CF carriers.

There are more than 1,900 mutations in the CF gene. Many of the mutations are common while others are rare and found in a relatively few persons. The disease occurs mostly in whites whose ancestors came from northern Europe, although it affects all races and ethnic groups. Accordingly, it is less common in African Americans, Native Americans, and Asian Americans. Approximately 2,500 babies are born with CF each year in the United States. Also, about 1 in every 20 Americans is an unaffected carrier of an abnormal "CF gene."

The most common test for CF is called the sweat test, which is the gold standard for accurately diagnosing (LeGrys et al, 2007). The sweat test measures the amount of sodium chloride in the sweat. In

this test, an area of the skin (usually the forearm) is made to sweat by using a chemical called pilocarpine and applying a mild electric current. To collect the sweat, the area is covered with a gauze pad or filter paper and wrapped in plastic. After 30 to 40 minutes, the plastic is removed, and the sweat collected in the pad or paper is analyzed. Higher than normal amounts of sodium and chloride suggest that the person has cystic fibrosis. The sweat test may not work well in newborns because they do not produce enough sweat. In that case, another type of test, such as the immune-reactive trypsinogen test (IRT), may be used. In the IRT test, blood drawn 2 to 3 days after birth is analyzed for a specific protein called trypsinogen. Positive IRT tests must be confirmed by second tier tests, such as sweat tests and CFTR genetic mutation tests. Also, a small percentage of people with CF have normal sweat chloride levels. They can only be diagnosed by chemical tests for the presence of the mutated gene. Some of the other tests that can assist in the diagnosis of CF are chest X- rays, lung function tests, and sputum (phlegm) cultures. Stool examinations can help identify the digestive abnormalities that are typical of CF.

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.

The normal gene product of cystic fibrosis is a transmembrane conductance regulator (CFTR) that allows the normal passage of chloride, along with sodium to make a salt, into and out of certain cells, including those that line the lungs and pancreas. Mutations in the normal gene protein can affect the CFTR protein quantitatively, qualitatively, or both.

As a result, these cells produce thick, sticky mucus and other secretions. The mucus clogs the lungs, causing breathing problems. Affected individuals also have frequent lung infections, which eventually damage the lungs and contribute to early death. The thickened digestive fluids made by the pancreas are prevented from reaching the small intestine, where they are needed to digest food.

The American College of Obstetricians and Gynecologists (2001) has issued similar recommendations on genetic carrier testing for CF. The recommendations include:

1. For routine carrier screening, complete analysis of the CF transmembrane regulator (CFTR) gene by DNA sequencing is not appropriate.
2. Maternal carrier screening is not replaced by newborn screening panels that include CF screening.
3. 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.
4. When both parents are CF carriers, they should undergo genetic counseling to review prenatal testing and reproductive options.
5. 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.
6. 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.

ACOG also recommends that screening should be made available to couples in other racial and ethnic groups. To date, over 900 mutations in the CF gene have been identified. As it is impractical to test for every known mutation, the ACMG Accreditation of Genetic Services Committee has compiled a standard screening panel of 25 CF mutations, which represents the standard panel that ACMG recommends for screening in the U.S. population (Grody, et al, 2001). This 25-mutation panel incorporates all CF-causing

mutations with an allele frequency of greater than or equal to 11% in the general U.S. population, including mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans. This standard panel of mutations is intended to provide the greatest pan- ethnic detectability that can practically be performed.

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

1. Diagnostic testing – Possible diagnosis of CF, definite diagnosis of CF, infants with meconium ileus, or males with congenital bilateral absence of the vasa deferentia (CBAVD)
2. Carrier testing – Partners of individuals with positive family history of CF, partners of males with congenital bilateral absence of the vasa deferentia (CBAVD), general population of reproductive couples, persons with a positive family history of CF, or gamete donor
3. Preimplantation testing
4. Prenatal diagnostic testing – Positive family history, couples having a CF mutation in both partners, and fetus with echogenic bowel during second trimester
5. Newborn screening

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. Carrier rates are 1 in 24 in the Ashkenazi Jewish population and 1 in 25 in the non-Hispanic white general population. In 2011, ACOG issued an update on carrier screening for CF and the Committee on Genetics concluded that it is important that CF screening continues to be offered to women of reproductive age, and that because it is difficult to assign a single ethnicity to individuals, it is reasonable to offer CF carrier screening to all patients.

Current guidelines, revised by the ACMG in 2004 and reaffirmed in 2013, use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice. Using the 23-mutation panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population. The ACMG and the American College of Obstetricians and Gynecologists (ACOG) both recommend carrier screening for Ashkenazi Jewish individuals for:

- Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30), and
- Canavan disease (1/6,400; 1/40), and
- Cystic Fibrosis (1/2,500-3,000; 1/29) and
- Familial Dysautonomia (1/3,600; 1/32)

In addition, the ACMG recommends that the following also be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy:

- Fanconi anemia (group C) (1/32,000; 1/89), and
- Niemann-Pick (type A) (1/32,000; 1/90), and
- Bloom syndrome (1/40,000; 1/100), mucolipidosis IV (1/62,500; 1/127), and
- Gaucher disease (1/900; 1/15).

The ACOG's update on carrier screening for CF (2011) provided the following recommendations. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated. Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.

ACOG published an update on carrier screening for CF (2014). They have determined that screening is most efficacious in non-Hispanic white and Ashkenazi Jewish populations. Because testing is offered for only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a CF carrier and having an affected offspring. In addition, complete analysis of the CFTR

gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret.

This type of testing is reserved for patients with CF, patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.

GOVERNING BODIES APPROVAL

Genetic tests are laboratory developed tests that do not require premarket approval by the FDA. These types of tests are regulated by the Centers for Medicare & Medicaid Services as part of the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The regulations of the CLIA Amendments do not include validation of specific tests but there is procedural compliance.

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POLICY UPDATE HISTORY

11/24/2021	Approved in medical policy committee
11/30/2022	Annual review; approved in medical policy committee
12/2022	Approved in QI/UM