CLINICAL MEDICAL POLICY	
Policy Name:	Genetic Testing for Cystic Fibrosis
Policy Number:	MP-006-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	12/01/2024; 11/01/2023; 12/01/2022; 11/19/2021; 11/23/2020; 04/20/2020; 01/20/2020; 01/15/2019; 04/15/2018; 07/01/2016
Effective Date:	01/01/2025; 12/01/2023; 01/01/2023; 12/20/2021; 12/21/2020; 05/18/2020; 01/20/2020; 01/15/2019; 04/15/2018; 07/01/2016
Next Annual Review:	10/2024
Revision Date:	11/20/2024; 10/18/2023; 10/19/2022; 10/20/2021; 10/21/2020; 03/18/2020; 10/16/2019; 10/17/2018; 12/06/2017; 08/09/2017; 03/06/2017
Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
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Policy History

Date	Activity
01/01/2025	Provider Effective date
11/20/2024	QI/UM Committee review
11/20/2024	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
12/01/2023	Provider Effective date
10/18/2023	QI/UM Committee review
10/18/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
01/01/2023	Provider Effective date
10/19/2022	QI/UM Committee review
10/19/2022	Annual Review: No changes to clinical criteria. Revised 'Procedure' section wording. Added TAG Option #1 determination information. Updated 'Summary of Literature' and 'Reference Sources' section. Corrected code description for the following CPT codes: 81221, 81222. 81223, & 81224.
12/20/2021	Provider effective date
10/20/2021	QI/UM Committee review

10/20/2021	Annual Review: No changes to clinical criteria. Minor formatting changes made to Procedures section. Updated Summary of Literature and Reference sections. Updated description for diagnosis code N46.01. Removed deleted diagnosis code N46.02, added diagnosis code N46.11.
01/15/2019	Provider Effective Date

Disclaimer

Highmark Wholecare℠ 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 Wholecare℠ may provide coverage under the laboratory benefits of the Company's Medicaid products for medically necessary genetic testing for cystic fibrosis utilizing appropriate mutation panels.

Genetic testing coverage is provided when the information is needed to adequately assess risk in the Highmark Wholecare℠ member, and the information is expected to make an impact on the member's treatment plan, or the responsible family member/legal guardian intends to use the information in making decisions about his/her care or treatment plan.

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 Commonwealth of Pennsylvania (PA) Department of Human Services (DHS) and all applicable state and federal regulations.

Definitions

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

1. Highmark Wholecare℠ considers standard genetic testing for cystic fibrosis (CF) (CPT code 81220) medically necessary for individuals in which alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or if available, will only provide an indeterminate result. Testing should only be performed **once** per lifetime.

2. Diagnostic or confirmatory genetic testing for CF in symptomatic individuals is considered medically necessary when ANY of the following conditions exist:
   A. Testing will provide confirmation of a diagnosis of CF when the diagnosis is in doubt (e.g., individuals with a negative sweat chloride test but have symptoms of CF); OR
   B. Testing will provide a diagnosis for otherwise healthy males with infertility issues due to ANY of the following conditions:
      1) congenital bilateral absence of the vas deferens (CBAVD); OR
      2) azoospermia; OR
      3) severe oligospermia (e.g., <5 million sperm/milliliter) with palpable vas deferens; OR
   C. 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
   D. Infants with elevated immunoreactive trypsinogen (IRT) value on a newborn screening; OR
   E. When testing will be performed to identify individuals who may respond to select pharmacologic treatments (e.g., Kalydeco, Orkambi, Symdeko).

   Note: 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 CF 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.

3. Carrier genetic testing for CF should only be performed in adults, and only **once** per lifetime. Carrier genetic testing for CF is considered medically necessary when ANY of the following conditions exist:
   A. Testing will be performed on a parent with a positive family history of CF (e.g., parent has a previously affected child with CF); OR

B. Testing will be performed on one or both parent(s) with a 1st degree relative identified as a CF carrier; OR
C. Testing will be performed on both prospective parents, who are both Highmark Wholecare℠ members, seeking prenatal care for an ongoing pregnancy or who are planning a pregnancy; OR
D. Testing will be performed on a reproductive partner of a person with CF; OR
E. As part of routine care in women who are pregnant or wanting to become pregnant; OR
F. When one or both parents are in a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for CF.

Note: Genetic testing or expanded screening panels for CFTR mutations to determine the *carrier status* of an individual may be considered medically necessary on a case-by-case basis 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.

4. Prenatal genetic testing for CF is considered medically necessary when ANY of the following conditions exist:
   A. Both parents are CF carriers; OR
   B. One parent is a CF carrier and the other parent has CF; OR
   C. One parent is a CF carrier or has CF and genetic testing on the other parent is unavailable/unknown; OR
   D. The fetus presents with fetal echogenic bowel during the second trimester ultrasound.

5. Highmark Wholecare recognizes the following American College of Obstetricians and Gynecologists (ACOG) recommendations on carrier screening for CF:
   - CF 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 CF, 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 CF 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.

6. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform patient being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has previously evaluated the patient, and intends to see the patient after genetic testing has been performed:
   - 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 of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

7. When genetic testing for CF is considered not medically necessary
   Genetic carrier and diagnostic testing for CF is considered not medically necessary any indication other than those listed above. Any other indication requests will require case-by-case review by a Medical Director. All of the following are considered not medically necessary:
   - Carrier panels for more than one condition, unless all components of the panel have been determined to be medically necessary based on criteria listed above.
   - Direct-to-consumer genetic self-testing home kits due to potential risks, including but not limited to inappropriate testing, misinterpretation of testing results, testing that is not clinically valid, and lack of follow-up care.
   - General newborn screenings

8. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

9. Place of Service
   The proper place of service for genetic testing for CF is outpatient.

10. Related Policy
    - MP-010-MD-PA Testing for Genetic Disease

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 CMS 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 rather there is procedural compliance.

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

As of August 2020, the TAG workgroup assigned cystic fibrosis testing an Option # 1, specifically for CPT codes 81221, 81222, & 81223.

Summary of Literature

Cystic fibrosis (CF) is a progressive, genetic disease that affects the lungs, pancreas, and other organs. Approximately 40,000 children and adults are living with CF in the United States. CF effects people of every racial and ethnic group (CFF, 2022).

In people with CF, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene cause CFTR protein to become dysfunctional. When the protein is not operating correctly, it is unable to help move chloride, which is a component of salt, to the cell surface. Without chloride to attract water to the cell surface, the mucus in multiple organs becomes thick and sticky (CFF, 2022).

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 CF 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 (LeGrys et al, 2007).

CFTR 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.

In 1989, the CFTR gene 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 (ACMG, 2001).

It is 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 (Farrell, 2017).

The ACMG published the following recommended indications for performing 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 donors
3. Preimplantation testing
4. Prenatal diagnostic testing – positive family history, couples having a CF mutation in both partners, or fetus with echogenic bowel during second trimester
5. Newborn screening

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),
- 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 ACMG has updated recommendations in which the recommended variant set for CF carrier screening supersedes the previous group of 23 CFTR variants. The revised recommendations apply to carrier screening and do not apply to CFTR variant testing for diagnosis or newborn screening. The updated minimum variant set for CF carrier screening is based on evidence that the variant has been established as CF-causing and is present in the Genome Aggregation Database (gnomAD) (Deignan, et al., 2023).

The following are various carrier screening scenarios with associated management recommendations:

- A woman is a carrier of a cystic fibrosis mutation and her partner is unavailable for testing or paternity is unknown. Genetic counseling to review the risk of having an affected child and prenatal testing options and limitations is recommended.
- Prenatal diagnosis is being performed for other indications and cystic fibrosis carrier status is unknown. Cystic fibrosis screening can be performed concurrently on the patient and partner.

Chorionic villi or amniocytes may be maintained in culture by the diagnostic laboratory until cystic fibrosis screening results are available for the patient or couple. If both partners are carriers, diagnostic testing for cystic fibrosis can be performed on the chorionic villi or amniocytes.

- Both partners are cystic fibrosis carriers. Genetic counseling is recommended to review prenatal testing and reproductive options. Prenatal diagnosis should be offered for the couple's specific, known mutations.
- 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. Carrier screening should be offered for both partners, with attention to ensure that the familial mutation is included in the assessment.
- 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.
- An individual has two cystic fibrosis mutations but has not previously received a diagnosis of cystic fibrosis. The individual usually has a mild form of the disease and should be referred to a specialist for further evaluation. Genetic counseling is recommended (ACOG, 2020).

As with all carrier screening, it is generally more cost effective and practical to perform initial carrier screening only for the patient. CF carrier screening should be offered to all women who are considering pregnancy or are currently pregnant. If the patient is a cystic fibrosis carrier, then her partner should be tested. During pregnancy, concurrent screening of the patient and her partner is suggested if there are time constraints for decisions regarding prenatal diagnostic evaluation. Given that cystic fibrosis 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 repeat cystic fibrosis screening. If a patient has been screened previously, cystic fibrosis screening results should be documented, but the test should not be repeated. Although some mutation panels have been expanded over the past decade, the incremental yield of the addition of those mutations is small for most patients. Before repeat testing, the clinical scenario should be discussed with an obstetrician–gynecologist or other health care provider with expertise in genetics (ACOG, 2020).

Consensus guidelines from the Cystic Fibrosis Foundation note that although newborn screening is now widely implemented, the diagnosis of CF is not always clear. A sweat test is required for confirmation of CF; a sweat chloride level ≥60 mmol/L indicates a diagnosis of CF and a sweat chloride level <30 mmol/L indicates that CF is unlikely. In individuals who fall into the intermediate sweat chloride level, 30-59 mmol/L, genetic analysis is required. Further testing for CFTR function such as NPD and ICM may also be indicated but should be performed in a specialized center approved for such studies. Some infants with a positive newborn screening and sweat chloride levels from 30 to 59 mmol/L or even ≤29 mmol/L and inconclusive genetic testing may be designated as CRMS/CFSPID. Further research is needed to determine their prognosis, best practice, and frequency of follow-up (Farrell, 2017).

An in-depth look into CFTR sequence variants in nonwhite US patients is an important step toward future studies that correlate CFTR sequence changes (and combinations thereof) observed in nonwhite individuals with clinical severity of symptoms. Knowledge of sequence variants in each population and improved genotype-phenotype correlations can affect results reporting, counseling, prognosis predictions, and therapeutic decisions. This information can be used to optimize newborn screening programs in the United States based on the ethnic composition of state populations, resulting in earlier diagnosis and intervention, timely clinical treatment, and enhanced prognosis. For both screening and

diagnostic testing it could propel equity in mutation detection for white and nonwhite CF patients (Schrijver, 2016).

A study reviewed the risks of cystic fibrosis-related conditions in nearly 100,000 cystic fibrosis carriers. Their results suggest that CF carriers are at increased risk for most conditions associated with CF. Given that there are more than 10 million CF carriers in the US, the disease burden attributable to the CF carrier state is likely substantial. We believe that identifying CF carriers may aid the prevention, diagnosis, and treatment of several common and uncommon disorders. The widespread availability of CF genotyping made this discovery possible, and with increased genetic screening, it may be possible to apply a similar approach to people who are carriers of other recessive genetic diseases (Miller, 2020).

This genetic carrier screening program for CF, Fragile X syndrome, and spinal muscular atrophy has proven to be successful in identifying individuals and couples at increased risk of having a child affected by one of these conditions. Offering screening through a coordinated clinical and laboratory service ensures patients are supported to make informed reproductive choices. This program has demonstrated that despite individual recessive conditions being relatively rare, when tested collectively, the combined chance of an affected child with one of the conditions is comparable to that of Down syndrome (Archibald, 2020).

Coding Requirements

Covered Procedure Codes

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

Noncovered Procedure Code

Requests for this procedure code is to be reviewed on a case-by-case basis by a Medical Director.

CPT Code	Description
CFTR Intron 8 Poly T Analysis	
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; intron 8 pol-T analysis (e.g. male infertility)

Diagnosis Codes

ICD-10 Code	Description
E84.0	Cystic fibrosis with pulmonary manifestations
E84.11	Meconium ileus in cystic fibrosis
E84.19	Cystic fibrosis with other intestinal manifestations

E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified
N46.01	Organic azoospermia
N46.11	Organic oligospermia
Q55.3	Atresia of vas deferens
Z14.1	Cystic fibrosis carrier
Z31.430	Encounter for genetic testing of female for genetic disease carrier status for procreative management
Z31.440	Encounter for genetic testing of male for genetic disease carrier status for procreative management
Z33.1	Pregnant state, incidental
Z84.81	Family history of carrier of genetic disease

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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