Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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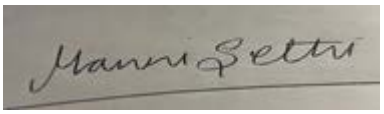
Plan: AmeriHealth Caritas Pennsylvania Community Health Choices	**Submission Date**: 4/1/2024
Policy Number: ccp.1153	**Effective Date:** 4/2015 **Revision Date:** March 1, 2024
Policy Name: Genetic testing for cystic fibrosis	
Type of Submission – Check all that apply: **New Policy** **x Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Genetic testing for cystic fibrosis

Clinical Policy ID: CCP.1153

Recent review date: 3/2024

Next review date: 7/2025

Policy contains: Cystic fibrosis transmembrane conductance regulator; genetic counseling.

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

The American College of Medical Genetics 100-variant core testing panel (herein referred to as the "core panel") for cystic fibrosis is clinically proven and, therefore, may be medically necessary, as it represents the minimum list of cystic fibrosis transmembrane conductance regulator gene variants that should be included for carrier screening (Deignan, 2023).

Cystic fibrosis transmembrane conductance regulator gene variant testing is clinically proven and, therefore, may be medically necessary, when the member displays clinical features of the disease or is at direct risk of inheriting or passing on the genetic mutation in question, for any of the following indications (American College of Obstetricians and Gynecologists, 2017; Deignan, 2020, 2023):

- Carrier screening in asymptomatic members who are considering pregnancy or are currently pregnant seeking prenatal care.
- Carrier screening of a parental Plan member of an affected child who has a positive cystic fibrosis newborn screening result.
- Diagnostic confirmation of cystic fibrosis in members (Deignan, 2020):
    - With a clinical cystic fibrosis diagnosis.
    - With meconium ileus (infants).
    - Diagnosed with isolated congenital absence of the vas deferens, idiopathic pancreatitis, or bronchiectasis.
    - With an immunoreactive trypsinogen-positive newborn screening who meet sweat chloride criteria for a cystic fibrosis diagnosis, if cystic fibrosis transmembrane conductance regulator genotyping was not available through the screening process or is incomplete.

Extended cystic fibrosis transmembrane conductance regulator gene sequencing is clinically proven and, therefore, may be medically necessary to confirm a diagnosis of cystic fibrosis for any of the following indications:

- Members with a positive newborn screen, symptoms of cystic fibrosis, or a positive family history, and sweat chloride values are in the intermediate range (30 – 59 millimoles per liter) on two separate occasions (also referred to as cystic fibrosis transmembrane conductance regulator gene-related metabolic syndrome) (Farrell, 2017).
- Initial core panel or targeted analysis is inconclusive and sweat chloride test is abnormal (at least 60 millimoles per liter), intermediate (30 – 59 millimoles per liter), inconclusive, or cannot be performed (Deignan, 2020).
- For prenatal diagnosis, when the member is a carrier of a pathogenic or likely pathogenic variant and the reproductive partner is unavailable for screening or has not been screened, and either (Deignan, 2020):
    - Screening that partner would be cost-prohibitive.
    - The results from the partner would not be available in time to allow for reproductive decision-making.
    - A diagnostic procedure (e.g., chorionic villus sampling, amniocentesis) is also being performed for other reasons (e.g., ultrasound abnormality).
- Member is diagnosed with a cystic fibrosis transmembrane conductance regulator-related disorder (e.g., isolated congenital absence of the vas deferens, idiopathic pancreatitis, or bronchiectasis) (Deignan, 2020).
- Member is diagnosed with cystic fibrosis and is under consideration for treatment with a cystic fibrosis transmembrane conductance regulator-targeted drug therapy (e.g., ivacaftor, lumacaftor, tezacaftor, or elexacaftor) (Deignan, 2020; Farrell, 2017).

Genetic counseling is clinically proven and, therefore, may be medically necessary, when provided by an obstetrician–gynecologist, pediatrician, or other health care provider with expertise in genetics, for consideration of or provided in conjunction with medically necessary genetic testing for cystic fibrosis (American College of Obstetricians and Gynecologists, 2017; Farrell, 2017).

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations:

Molecular testing for cystic fibrosis instead of sweat testing is investigational/not clinically proven and, therefore, not medically necessary for widespread use (Farrell, 2017).

All other indications for genetic testing for cystic fibrosis are investigational/not clinically proven and, therefore, not medically necessary, including, but not limited to (American College of Obstetricians and Gynecologists, 2017; Deignan, 2020; Farrell, 2017):

- Carrier screening in individuals younger than reproductive age.
- Cystic fibrosis transmembrane conductance regulator deletion/duplication analysis.
- Complete cystic fibrosis transmembrane conductance regulator gene sequencing or 5T allele genotyping for routine carrier screening.

Direct-to-consumer genetic test kits sold directly to members (without a written order or prescription from a health care practitioner) are investigational/not clinically proven and, therefore, not medically necessary for genetic testing (American College of Obstetricians and Gynecologists, 2021).

Cell-free deoxyribonucleic acid blood testing is investigational/not clinically proven and, therefore, not medically necessary as a prenatal screening alternative for single-gene disorders, including cystic fibrosis (American College of Obstetricians and Gynecologists, 2022).

Alternative covered services:

- Clinical evaluation.
- Immunoreactive trypsinogen.
- Pilocarpine iontophoresis of sweat electrolytes (sweat test).
- Semen analysis.
- Transepithelial nasal potential difference.
- Direct intestinal current measurements from rectal suction biopsies.
- Pancreatic stimulation testing for pancreatic duct electrolyte secretion.

Background

Cystic fibrosis is an autosomal recessive genetic disorder that requires the presence of two copies of an abnormal gene — one from each parent — in order for the disease or trait to develop (Genetics Home Reference, 2021). Carriers of only one copy of the gene variant do not typically develop the disease but may pass the genetic variant to their children. Cystic fibrosis is a common genetic disease in the United States, occurring in 1 in 2,500 to 3,500 newborns primarily of Northern European descent.

Individuals with cystic fibrosis have one or more variants in the gene encoding for the cystic fibrosis transmembrane conductance regulator protein on both alleles of chromosome 7. The variants affect the transport of chloride and sodium across cell membranes, which can result in an imbalance of water absorption, causing dehydration and presence of thick and sticky mucus that can damage many body organs and shorten life expectancy. The most common phenotypic features include meconium ileus, progressive damage to the respiratory system, chronic digestive system problems associated with pancreatic insufficiency with malabsorption, salt loss syndromes, and infertility in males (Genetics Home Reference, 2021; Savant, 2023).

More than 2,000 variants within cystic fibrosis transmembrane conductance regulator gene have been identified in the Cystic Fibrosis Mutation Database, but most are classified as variants of unknown significance (Deignan, 2020). The most common variant is delta F508, which is a deletion of one amino acid at position 508 in the cystic fibrosis transmembrane conductance regulator protein.

The majority of new cases of cystic fibrosis are now detected through newborn screening required of all 50 states and the District of Columbia. Common to all protocols is measurement of immunoreactive trypsinogen in dried blood spots as the initial screening test to identify newborns at high risk of having cystic fibrosis followed by molecular testing and diagnostic sweat chloride testing for confirmation (Savant, 2023).

Carrier screening refers to genetic testing performed on an individual who does not have any overt phenotype for a genetic disorder but may have one variant allele within a gene(s) associated with a diagnosis (American College of Obstetricians and Gynecologists, 2017). Cystic fibrosis is primarily a clinical diagnosis based on clinical and laboratory criteria. Early recognition of cystic fibrosis on the basis of symptoms is desirable but difficult, as only 10% to 15% of infants with cystic fibrosis have symptoms at birth. The majority of symptoms are not specific to cystic fibrosis, and misdiagnosis and delay in treatment may occur. Variability of these features among unrelated individuals and within families further complicates diagnosis.

A sweat test is required for diagnostic confirmation. A sweat chloride level ≥ 60 millimoles per liter indicates a diagnosis of cystic fibrosis. A sweat chloride level < 30 millimoles per liter generally indicates that cystic fibrosis is unlikely, but in rare individuals with a sweat chloride < 30 millimoles per liter, cystic fibrosis may be considered

if other diagnoses are excluded and the other confirmatory tests support the diagnosis. Sweat chloride values in the intermediate range (30 – 59 millimoles per liter) may have the disease and require additional testing (Farrell, 2017).

Genetic testing facilitates carrier screening and early diagnosis by providing molecular confirmation of the presence of associated cystic fibrosis gene variants. Genetic counseling and comprehensive educational programs are available for the public and health professionals to help providers and families navigate the diagnostic process and understand the risks and benefits associated with genetic testing (Savant, 2023).

Findings

Cystic fibrosis transmembrane conductance regulator gene variant testing is used postnatally for diagnosis and in adults for diagnosis and carrier screening of asymptomatic individuals.

According to the American College of Obstetricians and Gynecologists (2017), all women currently pregnant or considering pregnancy should be offered carrier screening, genetic counseling, and medical record review to determine if mutation analysis is available, and counseling if a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens.

The Cystic Fibrosis Diagnosis Consensus Conference Committee conducted a survey of 32 experts, who agreed on 27 consensus recommendations on cystic fibrosis transmembrane conductance regulator testing or diagnostic criteria for newborns to adults (Farrell, 2017). The recommendations relating to genetic analysis are as follows:

- In individuals who fall into the intermediate sweat chloride level (30 – 59 millimoles per liter), genetic analysis is required.
- Individuals who are screen-positive and meet sweat chloride criteria for a cystic fibrosis diagnosis should undergo cystic fibrosis transmembrane conductance regulator genetic testing if genotyping was not available through the screening process or is incomplete.
- Individuals with clinical features that may be consistent with cystic fibrosis who have a sweat chloride < 30 millimoles per liter indicates that cystic fibrosis is less likely. It may, however, be considered if evolving clinical criteria and/or cystic fibrosis transmembrane conductance regulator genotyping support cystic fibrosis and not an alternative diagnosis.
- Individuals presenting with a positive newborn screen, symptoms of cystic fibrosis, or a positive family history, and sweat chloride values in the intermediate range (30 – 59 millimoles per liter) on two separate occasions may have cystic fibrosis and should be considered for extended cystic fibrosis transmembrane conductance regulator gene analysis and/or cystic fibrosis transmembrane conductance regulator functional analysis.
- The latest classifications identified in the Clinical and Functional Translation of CFTR (CFTR2) project should be used to aid with diagnosis.

Carrier testing for the cystic fibrosis transmembrane conductance regulator variant is highly accurate. This is based on a study of 357 labs (322 of which were in the United States) between 2003 and 2013, which performed nearly 120,000 tests monthly. Sensitivity and specificity of U.S. lab testing were 98.8% and 99.6%, respectively. Sensitivity improved from 97.9% to 99.3% from 2003 to 2008 and remained steady thereafter (Lyon, 2015).

A review of three million screening tests for 23 mutations for cystic fibrosis in fetuses and newborns found that 1 in 37.6 were carriers of the disease, or a detection rate of 77% (the estimated U.S. frequency was 1 in 29). The ratios for whites and Ashkenazi Jews, who are known to have the highest carrier rates, were 1 in 29 and 1 in 27, respectively, with a detection rate of 90% (Strom, 2011).

A review of eight databases determined a high level of accuracy of genetic tests in prenatal testing for cystic fibrosis. In cases where two pathogenic variants were identified in a fetus of carrier parents, 94.6% (158/167) elected to terminate the pregnancy (Kessels, 2020).

A systematic review of 85 studies covering 23 years of population-based carrier screening for cystic fibrosis documented a strong association with relatively high uptake, positive attitudes, correct recall and understanding of carrier status, and no long-term psychological harm of screening. Information on how to offer screening, factors influencing decision-making, and follow-up after screening are also included in the study (Ioannou, 2014).

As a result of widespread newborn screening, the majority of new diagnoses of cystic fibrosis in the United States now occur in asymptomatic or minimally symptomatic infants following a positive immunoreactive trypsinogen screening result. While most can be diagnosed with a confirmatory test showing high sweat chloride concentration, sweat and initial molecular test results may be inconclusive. In these cases, follow-up at three, six, and 12 months after birth and thereafter should be performed (Sermet-Gaudelus, 2017). These “screen-positive, inconclusive diagnosis” newborns are the subject of management recommendations (Munck, 2015).

In 2022, we added a guideline from the American College of Medical Genetics and Genomics (Deignan, 2020) that updated the technical standards for cystic fibrosis transmembrane conductance regulator gene variant testing. We modified the coverage criteria to align with these recommendations.

Genetic testing techniques typically involve methods that target the detection of known variants and more comprehensive methods (e.g., sequencing and deletion and duplication testing) that attempt to detect all variants without a need for any prior knowledge regarding the identity or precise location of any particular variant. Laboratories often use one or a combination of methods. Specific genetic testing recommendations are as follows (Deignan, 2020):

- Targeted and comprehensive testing approaches are both acceptable for genetic testing of individuals regardless of race, ethnicity, or test indication.
- The American College of Medical Genetics and Genomics 23-variant core panel remains as the minimum list of cystic fibrosis transmembrane conductance regulator variants that should be included in pan-ethnic carrier screening. Laboratories may include additional variants to their panel depending on the ethnic composition of their expected test population.
- For all prenatal, postnatal, and adult diagnostic testing and carrier screening indications for cystic fibrosis transmembrane conductance regulator variant testing, testing of any specific exon-level or gene-level deletion or duplication variants is not recommended.
- For prenatal diagnosis, targeted sequencing for specific cystic fibrosis transmembrane conductance regulator variants may be considered when a pathogenic or likely pathogenic variant is confirmed in both partners or when a pathogenic or likely pathogenic variant is confirmed in one partner and a variant of unknown significance or variant associated with variable expressivity is confirmed in the other partner.
- For prenatal diagnosis, comprehensive cystic fibrosis transmembrane conductance regulator sequencing may be considered when one member of a couple is known to be a carrier of a pathogenic or likely pathogenic variant and the partner is either unavailable for screening or has not been screened, and either:
    - Screening would be cost-prohibitive.
    - The results from the partner would not be available in time to allow for reproductive decision-making.
    - The diagnostic procedure (e.g., chorionic villus sampling, amniocentesis) is also being performed for other reasons (e.g., ultrasound abnormality).

- Carrier testing is recommended for individuals with a positive family history of cystic fibrosis, for partners of individuals with a positive family history, for partners of individuals with isolated congenital absence of the vas deferens, and for women of reproductive age.
- If pathogenic or likely pathogenic core panel variants have been confirmed in both biological parents or in an affected full sibling, only targeted methods should be used.
- A genetic diagnosis is recommended in individuals with a clinical cystic fibrosis diagnosis, for infants with meconium ileus, for males with isolated congenital absence of the vas deferens, for individuals with idiopathic pancreatitis or bronchiectasis, and as a follow-up to newborn screening.

In 2023, we updated the references and added a practice advisory that did not recommend cell-free deoxyribonucleic acid as a noninvasive prenatal screening alternative for single-gene disorders, including cystic fibrosis (American College of Obstetricians and Gynecologists, 2022). No other policy changes are warranted.

In 2024, we updated the references and a guideline from the American College of Medical Genetics and Genomics that expands the minimum recommended variant set for cystic fibrosis carrier screening from 23 variants to 100 variants (Deignan, 2023). We added two systematic reviews of carrier screening for cystic fibrosis:

- While carrier screening uptake among different populations and testing methods varied across studies, pre-conception or prenatal carrier screening is likely effective for identifying at-risk couples and informing reproductive decision-making (Ontario Health, 2023; 107 studies).
- There was insufficient evidence supporting the effectiveness of population-based cystic fibrosis carrier screening in adults of reproductive age with no *a priori* increased risk of having an affected pregnancy (Banzi, 2023; 71 studies).

References

On November 27, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “Cystic Fibrosis Transmembrane Conductance Regulator “(MeSH), “genetic testing” (MeSH), “cystic fibrosis,” and “genetic testing.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

1/2015: initial review date and clinical policy effective date: 4/2015

2/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated. Coverage modified.

2/2023: Policy references updated.

3/2024: Policy reference updated. Coverage modified.