BSC2.04	Genetic Testing for Cystic Fibrosis		
Original Policy Date:	October 11, 2000	**Effective Date:**	June 1, 2019
Section:	2.0 Medicine	**Page:**	Page 1 of 6

Policy Statement

Genetic testing for cystic fibrosis (CF) utilizing the American College of Medical Genetics (ACMG) mutation core panel may be considered **medically necessary** when **any** of the following criteria are met:

- Testing of either or both partners for carrier status before conception or early in pregnancy (prior to 20 weeks gestation)
- Testing of neonates with clinical features consistent with CF

Genetic counseling services for CF may be considered **medically necessary** in conjunction with the above criteria.

Genetic testing for CF is considered **investigational** in the following situations:

- Screening for CF carrier status in whole populations
- Screening of asymptomatic neonates without a family history of CF

Policy Guidelines

Note: In accordance with recommendations set forth by American College of Obstetrics and Gynecology (ACOG), complete analysis of the cystic fibrosis transmembrane conductance regulator (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 generally 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 a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.[1]

Coding

The following CPT codes may be used for genetic testing for CF:

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

There is a genetic testing code modifier:

- 8A CFTR (cystic fibrosis)

Description

Cystic fibrosis is an inherited disease involving a genetic mutation that affects the respiratory, gastrointestinal, and reproductive systems. Cystic fibrosis is one of the most common autosomal

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recessive diseases in the North American Caucasian population with an incidence of one in 2500 to 3300 live births.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Literature Review
Cystic fibrosis is an autosomal recessive disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for a protein that functions as a chloride channel and is regulated by cyclic adenosine monophosphate (cAMP). These mutations result in abnormalities of cAMP-regulated chloride transport across epithelial cells on the mucosal surfaces. Over 1,400 CFTR mutations have been identified.

In 1997, the National Institute of Health issued the following statement:

> Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing. The panel does not recommend offering CF genetic testing to the general population or newborn infants.[2]

The American College of Obstetrics and Gynecology advised preconception carrier screening for CF allows carrier couples to consider all reproductive options.[3] The decision to have CF carrier screening should be with the patient's informed consent. The following are recommended for CF screening:

- Information about CF screening should be accessible to all couples
- Cystic fibrosis carrier screening should be offered before conception or early in pregnancy when both partners are Caucasian, European, or of Ashkenazi Jewish ethnicity
- In individuals with a family history of CF, medical records of the affected family members should be obtained
- Reproductive partners with CF or congenital bilateral absence of vas deferens may benefit from an expanded panel of mutations, or a complete analysis of the CFTR gene by sequencing
- When both partners are CF carriers, genetic counseling is recommended to review reproductive options
- Cystic fibrosis carrier screening may identify individuals with two CF mutations who have not been previously diagnosed with CF

According to the American College of Medical Genetics (ACMG), a panel of 23 mutations accounts for 94.04% of detectable mutations.[4] This panel includes all mutations with an allele

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frequency greater than or equal to 0.1% of the general United States (US) population. The ACMG mutation panel is considered the standard of care for population-based carrier testing and is performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The test does not require US Food and Drug Administration (FDA) approval. An example of this kit is the eSensor platform (Osmotech Molecular Diagnostics, Pasadena, CA).[4]

A randomized control study (RCT) completed by Loukas et al, advised that a 23-mutation panel for CFTR carrier screening is recommended to women of reproductive age by the American College of Obstetricians and Gynecologists. In this study the optimized efficiency regarding the carrier rate of Next-Generation sequencing (NGS) technology is compared to the one of limited mutation detection panels. A total of 824 consequent cases were subjected to the commercial Cystic Fibrosis Genotyping Assay. Some 188 negative samples randomly selected from the initial group of probands were further subjected to an extended mutation panel characterized by 92% detection rate, as well as to massive parallel sequencing. Twenty-two probands subjected to the commercial assay proved to carry one mutation included in the ACOG panel (carrier rate 0.0267). The latter panels revealed the presence of mutations not included in the ACOG panel in four probands, resulting to an increase of carrier rate of 0.0106 in the case of in-house panel and an increase of rate of 0.0213 if NGS was used. The above data seem to support the implementation of NGS in the routine CFTR carrier screening.[6]

According to a RCT completed by Baker et al, many regions have implemented newborn screening (NBS) for cystic fibrosis (CF) using a limited panel of cystic fibrosis transmembrane regulator (CFTR) mutations after immunoreactive trypsinogen (IRT) analysis. The authors tried to determine the feasibility of further improving the screening using next-generation sequencing (NGS) technology. A NGS assay was used to detect 162 CFTR mutations/variants characterized by the CFTR2 project. 67 dried blood spots (DBSs) were used, containing 48 distinct CFTR mutations to validate the assay. NGS assay was retrospectively performed on 165 CF screen-positive samples with one CFTR mutation. The NGS assay was successfully performed using DNA isolated from DBSs, and it correctly detected all CFTR mutations in the validation. Among 165 screen positive infants with one CFTR mutation, no additional disease-causing mutation was identified in 151 samples consistent with normal sweat tests. Five infants had a CF-causing mutation that was not included in this panel, and nine with two CF-causing mutations were identified. The NGS assay was 100% concordant with traditional methods. Retrospective analysis results indicate an IRT/NGS screening algorithm would enable high sensitivity, better specificity and positive predictive value (PPV). This study lays the foundation for prospective studies and for introducing NGS in NBS laboratories. [7]

Cystic fibrosis transmembrane regulator (CFTR) allele and genotype frequencies were obtained from a non-patient cohort with more than 60,000 unrelated personal genomes collected by the Exome Aggregation Consortium in a RCT by Lim et al. Likely disease-contributing mutations were identified with the use of public database annotations and computational tools. The authors identified 131 previously described and likely pathogenic variants and another 210 untested variants with a high probability of causing protein damage. None of the current genetic screening panels or existing CFTR mutation databases covered a majority of deleterious variants in any geographical population outside of Europe. Both clinical annotation and mutation coverage by commercially available targeted screening panels for CF are strongly biased toward detection of reproductive risk in persons of European descent. South and East Asian populations are severely underrepresented, in part because of a definition of disease that preferences the phenotype associated with European-typical CFTR alleles.[8]

Extended mutation panels, which would test for the standard 23 mutations plus additional mutations, have been proposed by some, however the ACMG, the ACOG, and the Cystic Fibrosis Foundation recommend against this testing.[3,4,8] Extended mutation panels are approved by the FDA as 510(k) Class II devices. Examples include Tag-It™ Cystic Fibrosis Kit (Tm Bioscience Corporation, Toronto, Ontario), CF v3 OLA ASR (Abbott Laboratories and Celera Diagnostics, Abbott Park, IL), and InPlex CFTR ASR (Third Wave Technology Inc., Madison, WI).[5]

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References

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2. National Institute of Health Consensus Development Program. Genetic Testing for Cystic Fibrosis. 1997 Apr 14-16. Retrieved on May 15, 2019 from http://consensus.nih.gov/1997/1997GeneticTestCysticFibrosis106html.htm.
3. American College of Obstetrics and Gynecology (ACOG). ACOG Committee on Genetics. Number 324, December 2005. Update on carrier screening for cystic fibrosis. Obstet Gynecol. 2005 Dec; 106(6):1465-8.
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5. United States Food and Drug Administration. Medical Devices. Tag-It™ Cystic Fibrosis Kit - K043011. Retrieved on May 15, 2019 from https://www.accessdata.fda.gov/cdrh_docs/reviews/k043011.pdf.
6. Loukas YL, Thodi G, Molou E, et al. Clinical diagnostic Next-Generation sequencing: The case of CFTR carrier screening. Scand J Clin Lab Invest. 2015 Sep;75(5):374-81. doi: 10.3109/00365513.2015.1031689. Epub 2015 Apr 15.
7. Baker MW, Atkins AE, Cordovado SK, et al. Improving newborn screening for cystic fibrosis using next-generation sequencing technology: a technical feasibility study. Genet Med. 2015 Feb 12. doi: 10.1038/gim.2014.209. [Epub ahead of print]
8. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr.2008 Aug; 153(2):S4-S14.
9. Grody WW, Cutting GR, Klinger KW, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Genet Med. 2001 Mar-Apr; 3(2):149-54.
10. Sharma GD. eMedicine. Cystic Fibrosis. Retrieved May 15, 2019 from http://emedicine.medscape.com/article/1001602-overview.

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history of cystic fibrosis (CF) including:
    - Family relationship (if applicable)
    - Genetic mutation analysis results in that relative (if applicable)
- Lab results documenting both partners carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

Post Service

- Results/reports of tests performed

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Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	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
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	81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/11/2000	Policy adoption	Medical Policy Committee
03/13/2002	Policy clarification	Administrative Review
08/01/2002	Policy clarification	Administrative
01/07/2011	Policy revision with position change	Medical Policy Committee
03/13/2012	Coding update	Administrative Review
06/13/2012	Coding update	Administrative Review
06/28/2013	Policy clarification	Administrative Review
06/30/2015	Coding update	Administrative Review
04/01/2016	Policy revision without position change	Medical Policy committee
05/01/2017	Policy revision without position change	Medical Policy committee
06/01/2018	Policy revision without position change	Medical Policy committee
06/01/2019	Policy revision without position change	Medical Policy committee

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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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