

Corporate Medical Policy

Genetic Testing for Cystic Fibrosis AHS – M2017

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Description of Procedure or Service

Definitions

Cystic fibrosis (CF) is an autosomal recessive genetic disease in which dysfunctional epithelial chloride channels lead to excessively thick mucus affecting multiple organ systems. Common complications include mucous plugging of the airway, lung inflammation, chronic pulmonary infections, intestinal malabsorption, pancreatic insufficiency and infertility (Pritchard, 2016).

Related Policies

Pediatric Preventive Screening AHS – G2042
Preimplantation Genetic Testing AHS – M2039

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for genetic testing for cystic fibrosis when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Cystic Fibrosis is covered

Reimbursement for testing for CFTR mutations is allowed once per lifetime.

1. Carrier screening for cystic fibrosis, using a panel containing mutations proven as causative of CF (as defined by the CFTR2 project) and including the ACMG-recommended panel of the most common mutations (see Policy Guideline #1 below), is covered in all of the following situations:
 - a. For all pregnant women OR
 - b. For all women seeking pre-conception counseling OR
 - c. For individuals who have a family history of cystic fibrosis or have a first degree relative who is a known carrier of cystic fibrosis. (Testing needs to include any known familial mutations if not already included in the panel) OR

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- d. For the male reproductive partners of women who have been identified as cystic fibrosis carriers OR
 - e. For the reproductive partners of individuals diagnosed with cystic fibrosis
2. Testing of a fetus for mutations in the CFTR gene (including all known parental mutations) is covered when:
 - a. Both biological parents are cystic fibrosis carriers
 - b. One or both biological parents are affected with cystic fibrosis
 - c. One biological parent is a cystic fibrosis carrier and the other parent is not available for testing
 - d. Echogenic bowel is detected by fetal ultrasound
 3. Testing for mutations in the CFTR gene, using a panel containing mutations proven as causative of CF (as defined by the CFTR2 project) and including the ACMG-recommended panel of the most common mutations is covered, in order to make the diagnosis or to confirm clinical diagnosis in the following situations:
 - a. In a newborn after an abnormal newborn screening result using immunoreactive trypsinogen, OR
 - b. For infants with meconium ileus, OR
 - c. For males with congenital absence of the vas deferens (CAVD), OR
 - d. For individuals with idiopathic pancreatitis
 4. Testing for mutations in the CFTR gene is covered as an adjunct to sweat testing in individuals presenting with symptoms of cystic fibrosis, as follows:
 - a. When there are known familial mutations, testing needs to include the familial mutations.
 - b. When there are no known familial mutations, or if only one familial mutation is known, testing can be done with a panel containing mutations proven as causative of CF (as defined by the CFTR2 project) as well as include the ACMG-recommended panel of the most common mutations or testing can be done for the known mutation.
 - c. Sequencing of the CFTR gene and testing for deletions and duplications in CFTR gene meets coverage criteria if no mutations or only one mutation are found using the above panel, and the clinical suspicion of cystic fibrosis remains.
 5. Testing for mutations in the CFTR gene, using a panel containing mutations proven as causative of CF (as defined by the CFTR2 project) and including the ACMG-recommended panel of the most common mutations, **along with** testing for the IVS8 5T/7T/9T variant, is covered in males with CBAVD. If mutations are not detected with the standard panel, and a diagnosis of cystic fibrosis-related CBAVD remains a consideration, sequencing of the CFTR gene meets coverage criteria.
 6. Testing for the IVS8 5T/7T/9T variant is covered for cystic fibrosis carrier screening only as a reflex test when the R117H mutation is detected on carrier screening.
 7. Reimbursement for genetic counseling is allowed for:
 - a. Individuals found to be cystic fibrosis carriers
 - b. Individuals with a diagnosis of cystic fibrosis
 - c. Individuals with a family history of cystic fibrosis
 - d. Individuals who are the reproductive partner of a cystic fibrosis carrier
 - e. Individuals who are the reproductive partner of a person diagnosed with cystic fibrosis or CBAVD.

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Policy Guideline #1: A core panel of 23 mutations are recommended by the American College of Medical Genetics (ACMG) is considered medically necessary for cystic fibrosis genetic testing. The standard mutation panel is as follows:

ΔF508	ΔI507	G542X	G551D	W1282X	N1303K
R553X	621+1G→T	R117H	1717-1G→A	A455E	R560T
R1162X	G85E	R334W	R347P	711+1G→T	1898+1G→A
2184delA	3120+1G→A	3849+10kbC→T	2789+5G→A	3659delC	

When Genetic Testing for Cystic Fibrosis is not covered

Sequencing of the *CFTR* gene is considered not medically necessary for cystic fibrosis carrier screening.

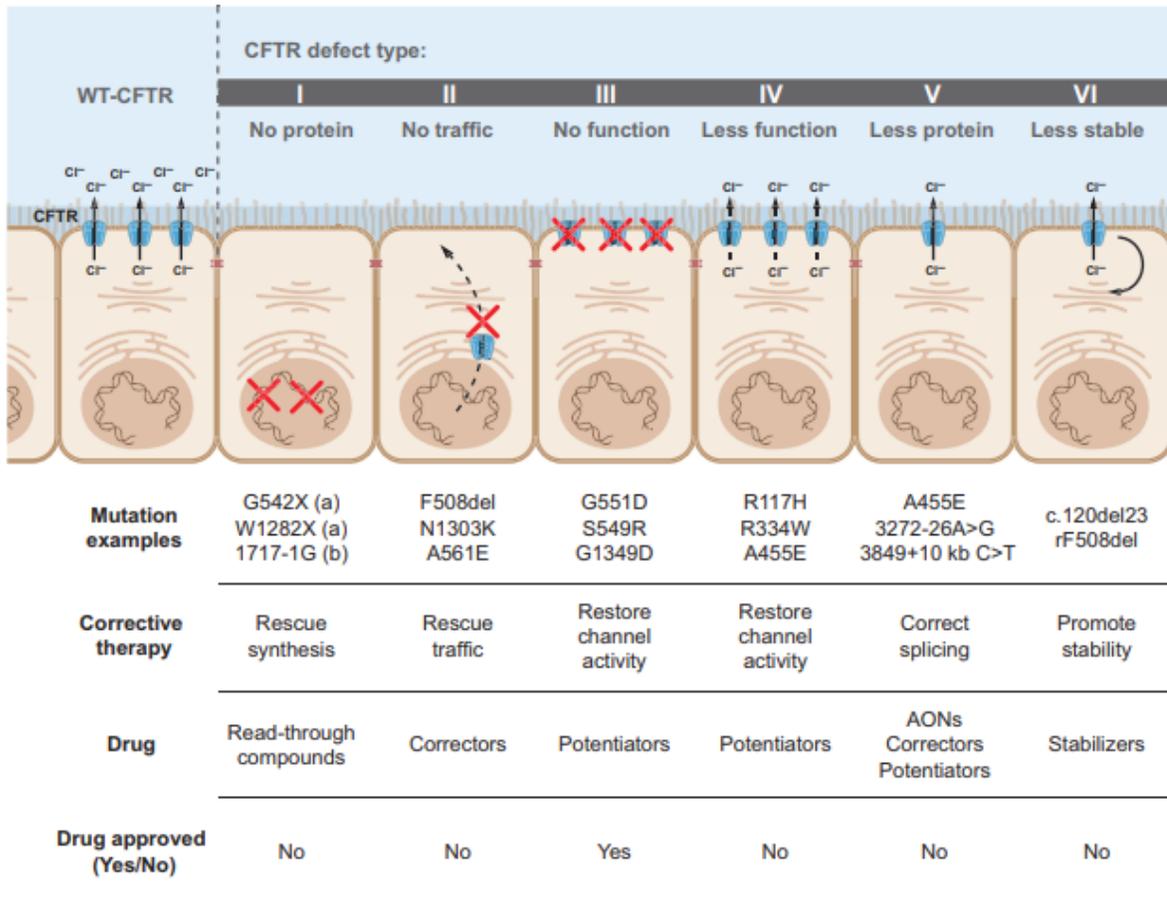
Policy Guidelines

Background

Cystic fibrosis (CF) is a common life-limiting autosomal recessive genetic disorder caused by the mutation of a gene that encodes an epithelial chloride-conducting transmembrane channel called the cystic fibrosis transmembrane conductance regulator (*CFTR*). This gene regulates anion (negatively charged ion) transport and mucociliary clearance. Mucociliary clearance is the process by which particles and gases dissolved in the mucus are moved unidirectionally from the respiratory tract. The *CFTR* protein was first identified as a chloride channel but has been shown to facilitate or regulate the transport of other ions, such as sodium, thiocyanate, bicarbonate, as well as water absorption and excretion (Clancy & Jain, 2012; Cohen-Cymerknoh, Shoseyov, & Kerem, 2011). The *CFTR* protein is present in the epithelia of various tissues, including that of the lungs, sweat glands, gastrointestinal tract, and pancreas (Barrett, Alagely, & Topol, 2012). *CFTR* dysfunction mainly affects epithelial cells; although, there is evidence of a role in immune cells.

Mutations in the *CFTR* gene which impede protein production, stability, or activity result in less available functional protein (Clancy & Jain, 2012). Functional failure of *CFTR* results in defective mucociliary clearance, chronic infection, and abnormal inflammatory response leading to progressive, irreversible lung damage (Cohen-Cymerknoh et al., 2011). Other manifestations of dysfunctional *CFTR* include pancreatic insufficiency and meconium ileus (Barrett et al., 2012). The early identification and treatment of patients by multidisciplinary teams have resulted in improvements in both quality of life and clinical outcomes in patients with cystic fibrosis, with life expectancy reaching 50 or even 60 years (Clancy & Jain, 2012).

Most mutations of the *CFTR* gene are missense alterations, but other mutations, deletions and insertions have been described (Bell, De Boeck, & Amaral, 2015). Missense mutations occur when a single nucleotide is changed, resulting in a different amino acid which may affect the overall protein functionality. To date, over 2000 mutations have been identified in the *CFTR* gene (CF Foundation, 2021). *CFTR* mutations can be divided into six classes according to their effects on protein function as depicted in the figure below (Bell et al., 2015).



Class I, II, and III mutations are associated with no residual CFTR function and patients with these mutations have a severe phenotype, whereas individuals with class IV, V, and VI mutations have some residual function of CFTR protein and have a mild lung phenotype and pancreatic sufficiency (Elborn, 2016; Wilschanski et al., 1995).

Due to the relatively high frequency in the U.S. population and studies demonstrating that early detection and care can improve outcomes, CF testing is included as part of the newborn screen in all states (Grosse et al., 2004). Newborn screening (NBS) for CF can include testing for immunoreactive trypsinogen (IRT), which is a pancreatic enzyme found at elevated levels in the blood of some individuals with CF, genetic testing for common CF mutations, or a combination of IRT and genetic testing. Positive newborn screens are typically followed by genetic testing (if not already done), and a sweat test, which measures the chloride concentration in sweat. The sweat test historically has been considered the “gold standard” for CF diagnosis. The presence of two disease-causing mutations also may be considered diagnostic of the disease, even in the absence of classic symptoms or in the case of a negative or inconclusive sweat test (Farrell et al., 2008).

In addition to NBS, CF carrier screening (PCS) has become commonplace in the U.S., particularly among pregnant women and couples planning a pregnancy. PCS has been found to markedly reduce CF birth rates with a shift towards milder mutations, but was often avoided for cultural reasons necessitating the use of complementary PCS and NBS (Stafler et al., 2016).

A subset of 23 mutations account for the majority of cystic fibrosis cases in the U.S. and were accepted by most guidelines as the primary genes to be screened for diagnosis of CF and carrier status. The most common CF-causing mutation is F508del, which is present in over 70% of known CF cases. The Clinical and Functional Translation of CFTR (CFTR2) project continually evaluates genotype and phenotype correlations and has confirmed many additional mutations as being causative of CF (CF Foundation, 2021). Information from over 88,000 patients with specific cystic fibrosis variants from the United

States, Canada, and Europe was collected by the CFTR2 team from national CF Patient Registries and placed in the CFTR2 database and then compiled into the CFTR2 website that contains information about the 322 most common CFTR variants (CF Foundation, 2021).

Analysis of data from the CF Foundation Patient Registry found that patients of Hispanic, black, or Asian ancestry were less likely to have two identified *CFTR* variants and more likely to carry no mutations on the commonly used 23 mutation carrier screening panel (Schrijver et al., 2016). Analysis of the Exome Aggregation Consortium dataset also found that 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 (Lim et al., 2016). This research indicates the possible need for adjustment of this panel to facilitate equity in mutation detection between white and nonwhite or mixed-ethnicity CF patients, enabling an earlier diagnosis improving their quality of life.

There are several cystic fibrosis genotyping assays approved by the FDA. eSensor Cystic Fibrosis Carrier Detection System detects 24 *CFTR* mutations (Clinical_Micro_Sensors, 2006), Tag-It™ Cystic Fibrosis Kit detects 39 mutations (Tm_Bioscience_Corporation, 2006), Cystic Fibrosis Genotyping Assay detects 30 mutations (Celera, 2007), InPlex™ CF Molecular Test detects 32 mutations (Hologic, 2008), Verigene®*CFTR* and Verigene®*CFTR* PolyT Nucleic Acid Tests detect 26 mutations (Nanosphere, 2009), xTAG® Cystic Fibrosis 71 v2 Kit detects 71 mutations (Luminex, 2016), and Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay (Illumina, 2013).

Next generation sequencing (NGS) is also being integrated into CF diagnostic protocols. A diagnostic protocol in which a quick and relatively low-cost polymerase chain reaction (PCR)-based screening for the most common CF mutation, F508del, followed by full-gene next generation sequencing of *CFTR* was shown to improve genetic diagnosis and “holds promise to be a straightforward, convenient and rapid diagnostic protocol for CF patients” (Straniero et al., 2016). A study using NGS for NBS found that 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 (Baker et al., 2016). Further, whole genome sequencing of the *CFTR* gene is also growing in popularity. This type of sequencing has revealed a high prevalence of the intronic variant c.3874-4522A>G in those affected by CF (Morris-Rosendahl et al., 2020).

CFTR modulators are a new class of medications targeting the underlying defect in CF by improving production, intracellular processing, and/or function of the defective *CFTR* protein. Ivacaftor (IVA), which improves chloride channel function, IVA combined with lumacaftor (LUM), which partially corrects the *CFTR* misfolding, and IVA combined with tezacaftor, which improves the intracellular processing and trafficking of *CFTR*, have been approved by the U.S. Food and Drug Administration for use in patients with CF. The indications and efficacy of these drugs depend upon the *CFTR* mutation in the individual patient. For example, ivacaftor has been FDA-approved and Clinical Pharmacogenetics Implementation Consortium (CPIC)-recommended only for CF patients with the *G551D* mutation. It is not recommended for any other CF mutation (Clancy et al., 2014).

Clinical Validity and Utility

Lyon et al. (2014) assessed clinical laboratories’ proficiency at evaluating genetic alterations for CF. A total of 357 labs participated, performing approximately 120,000 tests monthly. Analytical sensitivity and specificity were 98.8% and 99.6%, respectively. Clinical interpretation matched intended response for zero, one, and two mutations. The authors concluded that laboratory testing for CF in the United States is of high quality (Lyon et al., 2014).

Sosnay et al. (2013) performed a comprehensive analysis of CF genotypes and phenotypes. The authors collected genotype and phenotype data from 39696 CF patients and found 159 variants with over 0.01% allele frequency, 127 of which met both the clinical and functional criteria for CF. The phenotypic criterion used to define the pathogenic threshold was sweat chloride conductance of 10%. These 127 pathogenic genetic variants were estimated to represent 95.4% of CF alleles, leaving only 0.21% of CF

patients without an identified pathological CFTR variant. The phenotypes of these variants vary (Sosnay et al., 2013).

Wainwright et al. (2015) evaluated the combination of IVA and LUM in CF patients homozygous for the *F508D* mutation (labeled Phe508del). A total of 1108 patients were examined. The mean baseline forced expiratory volume in one second “FEV1” was 61% of the predicted value. The absolute mean improvement in FEV1% was found to be 2.6-4%, which corresponded to a 4.3-6.7% relative treatment difference. The rate of pulmonary exacerbations was found to be 30-39% less in the treatment group compared to the placebo group. However, the rate of discontinuation due to an adverse event was 4.2% in the treatment group compared to the placebo group (Wainwright et al., 2015).

Sharma et al. (2018) performed a cost-effectiveness analysis of the FDA-approved IVA-LUM combination for the *F508D* mutation. The authors built a Markov-state model to assess the IVA-LUM for 12-year-old CF patients over several periods of time. “Markov states included mild CF (percentage of predicted forced expiratory volume in 1 second or FEV1 > 70%), moderate (FEV1 40–70%), severe (FEV1 < 40%) disease, post-transplant, and death. Pulmonary exacerbation and lung transplant were included as transition states.” The IVA-LUM combination resulted in higher quality adjusted life years (QALY, 7.29 vs 6.84 for usual care) but at a cost of \$1,778,920.88 per QALY compared to \$116,155.76 for usual care. Both monetary amounts were over a 10-year period. The IVA-LUM combination was cost-effective at a threshold of \$150,000 / QALY, which was estimated to occur at an annual drug cost of \$4153 (Sharma et al., 2018).

Sugunaraj et al. (2019) completed a cross-sectional study which included the analysis of *CFTR* variants in 50,778 exomes. Only 24 patients were identified to contain bi-allelic pathogenic *CFTR* variants; the authors identified 21 of these cases as true-positives and three as potential false positives. Therefore, “genomic screening exhibited a positive predictive value of 87.5%, negative predictive value of 99.9%, sensitivity of 95.5%, and a specificity of 99.9% (Sugunaraj et al., 2019).” Overall, the presence and/or absence of *CFTR* variants was strongly related to a CF diagnosis.

Kessels, Carter, Ellery, Newton, and Merlin (2020) completed a systematic review of prenatal genetic testing for CF. Eight different databases were researched for this review. The authors found that after genetic testing “A change in clinical management was observed: termination of pregnancy (TOP) occurred in most cases where two pathogenic variants were identified in a fetus of carrier parents (158/167; 94.6%) (Kessels et al., 2020).” The authors conclude by stating that genetic testing for CF had good diagnostic performance and lead to fewer births affected by CF.

Hendrix, Cuthbert, and Cordovado (2020) assessed the performance of dried blood spot DNA extraction methods in NGS for cystic fibrosis. 20 DNA samples were used in this study and sequenced using Illumina's MiSeqDx™ Cystic Fibrosis 139-Variant Assay and Swift Biosciences' Accel-Amplicon™ *CFTR* panel. The MiSeqDx *CFTR* Clinical Sequencing Assay identified 37 CF-causing variants in the 20 samples tested, for a total of 141 benign variants which were all confirmed with Sanger sequencing. The Swift Biosciences' Accel-Amplicon™ *CFTR* panel identified 39 CF-causing variants for a total of 123 benign variants which were all confirmed with Sanger sequencing. Illumina's MiSeqDx performed well with a very high average coverage per method (>3000×) despite most DNA extraction methods being low-concentration and relatively crude. Because of the higher input of samples on a single flow cell, the average coverage per target was lower in the Accel-Amplicon™ *CFTR* panel in comparison to the clinical sequencing assay, but still often had >1000× coverage. The authors conclude that “both these tests are appropriate DNA extraction methods that can be used with dried blood spots that will result in consistent, high-quality sequencing results (Hendrix et al., 2020).”

Guidelines and Recommendations

Cystic Fibrosis Foundation (Farrell et al., 2017)

The Cystic Fibrosis Foundation (Farrell et al., 2017) convened a group to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with *CFTR* mutations. The experts determined 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 (<http://www.cftr2.org/index.php>) should be used to aid in diagnosis. ”

The committee approved 27 consensus statements (Farrell et al., 2017):

- 1 Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the CLSI 2009 Guidelines.
- 2 Newborns with a positive CF newborn screen, to increase the likelihood of collecting an adequate sweat specimen, should have the test performed bilaterally and when the infant weighs >2 kg, and is at least 36 wk of corrected gestational age.
- 3 Newborns greater than 36 wk gestation and >2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 d of age, ideally by the end of the neonatal period (4 wk of age).
- 4 In infants with presumptive CF identified through NBS, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.
- 5 Sweat chloride analysis should be performed within a few hours of sweat collection and the results and interpretations should be reported to clinicians and parents or patients, as soon as possible and certainly on the same day.
- 6 In individuals presenting with a positive newborn screen, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made if the sweat chloride value is ≥ 60 mmol/L.
- 7 Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo *CFTR* genetic testing if the *CFTR* genotype was not available through the screening process or is incomplete.
- 8 In individuals with a positive newborn screen, a sweat chloride <30 mmol/L indicates that CF is unlikely.
- 9 Individuals with clinical features that may be consistent with CF who have a sweat chloride <30 mmol/L indicates that CF is less likely. It may, however, be considered if evolving clinical criteria and/or *CFTR* genotyping support CF and not an alternative diagnosis.
- 10 Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on two separate occasions may have CF. They should be considered for extended *CFTR* gene analysis and/or *CFTR* functional analysis.
- 11 The latest classifications identified in the CFTR2 project (<http://www.cftr2.org/index.php>) should be used to aid with CF diagnosis:
 - CF-causing mutation: individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed)
 - Mutation of varying clinical consequence (MVCC): a mutation that in combination with a CF-causing mutation or another MVCC mutation may result in CF
 - Uncharacterized mutation/mutation of UNK: mutation that has not been evaluated by CFTR2 and may be disease causing or of variable clinical consequence or benign
 - Non-CF-causing mutation: individuals with 1 or more are unlikely to have CF (as a result of that allele)

- 12 In individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, the identification of 2 CF-causing mutations (defined by CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to confirm the diagnosis.
- 13 The absence of detection of 2 CF-causing *CFTR* mutations does not exclude a diagnosis of CF.
- 14 If further CF functional testing is needed (NPD and ICM), it should be performed in a validated reference center with trained staff certified by the CF Foundation TDN or ECFS Clinical Trial Network.
- 15 In individuals with a positive newborn screen but variable or uncharacterized *CFTR* mutations (<2 CF-causing mutations), the diagnosis of CF can be made by demonstrating CFTR dysfunction (a sweat chloride \geq 60 mmol/L or CF-typical NPD or ICM).
- 16 The term CRMS is used in the US for healthcare delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS.
- 17 The term CRMS/CFSPID is reserved for individuals who screen positive without clinical features consistent with a diagnosis of CF.
- 18 The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either:

A sweat chloride value <30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences

OR

An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations
- 19 Children designated as CRMS/CFSPID should undergo at least one repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center.
- 20 Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms.
- 21 Children designated as CRMS/CFSPID can be considered for extended *CFTR* gene analysis (sequencing and or deletion duplication testing), as well as CFTR functional analysis (NPD/ICM) testing to further define their likelihood of developing CF.
- 22 The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of CFTR (sweat chloride, and possibly NPD/ICM), *CFTR* genetic analysis, and clinical assessment by the CF clinicians caring for the patient.
- 23 Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies.
- 24 Research Recommendation: Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow-up.
- 25 For individuals presenting with CF symptoms, the same diagnostic criteria recommended for the screened population for sweat chloride testing, *CFTR* genetic analysis, and CFTR functional testing should be used to confirm a CF diagnosis.

- 26 The diagnosis of CFTR-related disorder has been defined as a monosymptomatic clinical entity (CBAVD/pancreatitis/bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF.
- 27 Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF, because these terms have no harmonized definition and could be confusing for families or caregivers.

The Cystic Fibrosis Foundation (Ren et al., 2018) also convened a multidisciplinary committee of CF caregivers to develop evidence-based guidelines for CFTR modulator therapy. The committee defined patients with CF as individuals who met the above CFF criteria for diagnosis of CF, combined with evidence of abnormal CFTR function, as demonstrated by elevated sweat chloride, detection of two CF-causing CFTR mutations, or abnormal nasal potential differences.

For adults and children aged 6 years and older with CF due to gating mutations other than G551D or R117H, the guideline panel made a conditional recommendation for treatment with IVA. For those with the R117H mutation, the guideline panel made a conditional recommendation for treatment with IVA for 1) adults aged 18 years or older, and 2) children aged 6–17 years with a forced expiratory volume in 1 second (FEV₁) less than 90% predicted. For those with the R117H mutation, the guideline panel made a conditional recommendation against treatment with IVA for 1) children aged 12–17 years with an FEV₁ greater than 90% predicted, and 2) children less than 6 years of age. Among those with two copies of F508del, the guideline panel made a strong recommendation for treatment with IVA/LUM for adults and children aged 12 years and older with an FEV₁ less than 90% predicted; and made a conditional recommendation for treatment with IVA/LUM for 1) adults and children aged 12 years or older with an FEV₁ greater than 90% predicted, and 2) children aged 6–11 years.

American College of Obstetrics and Gynecology (ACOG) (ACOG, 2017) (reaffirmed 2020)

The ACOG recommends offering CF carrier screening to all women who are considering pregnancy or are currently pregnant. Expanded mutation panels which enhance the sensitivity for carrier screening can be considered for carrier detection, especially in non-Caucasian ethnic groups, but testing should not be repeated if performed previously (e.g. during previous pregnancy). If the patient is found to be a carrier, then her partner should be tested. They also indicate that newborn screening is not a replacement for carrier screening in a population.

Prenatal diagnosis is indicated after genetic counseling if both parents are carriers, or if the mother is a carrier and the father is unknown or unavailable for testing.

ACOG recommends that complete gene sequencing of the CFTR gene is not appropriate for use in carrier screening, rather reserved for patients with cystic fibrosis, patients with negative carrier screening but a family history of cystic fibrosis, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening after the standard 23 gene screen has a negative result.

They also recommend referral to genetic counseling for couples in which both partners are CF carriers, prenatal diagnosis and advanced reproductive technologies to decrease the risk of affected offspring should be discussed (ACOG, 2017).

American College of Medical Genetics and Genomics (ACMG) (ACMG, 2011; Pletcher & Bocian, 2006; Watson et al., 2004)

The ACMG also recommends offering CF carrier screening to all women of reproductive age, regardless of ethnic background. Ideally, the testing would occur prior to pregnancy, but if the woman is pregnant, then she should be tested as early as possible during the pregnancy. ACMG also indicates that if the woman is found to be a CF carrier, then her reproductive partner should also be tested (Pletcher & Bocian, 2006). If the woman presents for testing late in the pregnancy, simultaneous testing of both the woman and the biologic father of the fetus should be considered. When there is a paternal family history of CF, carrier testing of the father is warranted.

Additionally, ACMG defines a panel of 23 mutations that includes the most common mutations found in a pan-ethnic population in the U.S. for use in routine CF carrier screening (ACMG, 2011; Watson et al., 2004). This 23-mutation panel incorporates all CF-causing mutations with a frequency of greater than or equal to 0.1% in the general U.S. population. ACOG also endorses the ACMG panel, and both organizations recommend against use of expanded mutation panels for routine CF carrier screening.

ACMG also recommends that testing for the IVS8 polyT variant be performed only when carrier screening reveals a R117H mutation, as the polyT variant influences the clinical severity of the mutation but does not cause CF by itself (ACMG, 2011).

ACMG provides guidance on indications for CFTR variant testing. Diagnostic testing can be used for the molecular confirmation of a clinical CF diagnosis, for infants with meconium ileus, for males with CAVD, individuals with idiopathic pancreatitis or bronchiectasis, and as a follow-up to newborn screening. Regarding carrier testing, ACMG recommends that carrier testing be offered to “individuals with a positive family history of CF, in partners of individuals with a positive family history, in partners of CAVD males, to reproductive age women, and to gamete donors (Deignan et al., 2020).”

Prenatal testing can be performed using cells obtained for diagnostic cytogenetic testing (i.e., amniocentesis or chorionic villus sampling [CVS]). Testing can take place on cultured or uncultured amniocytes or villous trophoblasts. According to the guidelines, targeted sequencing for specific CFTR variants may be considered when:

- a. “A pathogenic or likely pathogenic variant is confirmed in both partners.
- b. A pathogenic or likely pathogenic variant is confirmed in one partner and a VUS or variant associated with variable expressivity is confirmed in the other partner
- c. As part of preimplantation genetic testing when both biological parents are confirmed carriers of a pathogenic or likely pathogenic variant (Deignan et al., 2020).”

Comprehensive CFTR sequencing may be considered when:

- a. “One member of a couple is known to be a carrier of a pathogenic or likely pathogenic variant and any of the following is also true:
 - The partner is unavailable for screening
 - The partner has not been screened and any of the following is also true:
 - 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., CVS, amniocentesis) is also being performed for other reasons (e.g., ultrasound abnormality).
- b. An ultrasound finding (i.e., fetal echogenic bowel) suggests an affected fetus and CFTR variant information is not available from either biological parent (Deignan et al., 2020).”

ACMG recommends the following regarding testing of intronic variants, deletions/duplications, reporting VUS and variable expressivity, and reporting of intron 9 polyT and TG regions:

- “ACMG recommends the reporting of the c.2657+5G>A and c.3718–2477C>T intronic variants. If these variants are not detectable with the laboratory’s methodology (e.g., exome sequencing), then a separate assay should be performed to test for these variants.
- For all prenatal, postnatal, and adult diagnostic testing and carrier screening indications for CFTR testing, the ACMG does not recommend the testing of any specific exon-level or gene-level deletion or duplication variants.
- For all prenatal, postnatal, and adult diagnostic testing indications for CFTR where comprehensive methods are used, the ACMG recommends the reporting of VUS. For all adult carrier screening indications for CFTR where comprehensive methods are used, VUS should generally not be reported. However, laboratories may want to consider reporting

VUS in the partner of an individual who had a pathogenic or likely pathogenic variant detected during screening.

- For all prenatal, postnatal, and adult diagnostic testing indications for CFTR where comprehensive methods are used, the ACMG recommends the reporting of any variants associated with variable expressivity.
- For all prenatal, postnatal, and adult diagnostic testing indications for CFTR, the ACMG recommends the reporting of R117H status as well as the results from at least the associated polyT tract. For all adult carrier screening indications for CFTR, polyT status should be reported when the R117H variant is detected; laboratories may also want to consider reporting the results from the associated polyT tract in the partner of an individual who had a pathogenic or likely pathogenic variant detected during screening (Deignan et al., 2020)."

National Society of Genetic Counselors (NSGC) (Langfelder-Schwind et al., 2014)

The National Society of Genetic Counselors (NSGC) recommends that "Carrier testing for CF should be offered to all women of reproductive age, regardless of ancestry; preferably pre-conceptionally. CF carrier testing should also be offered to any individual with a family history of CF and to partners of mutation carriers and people with CF (Langfelder-Schwind et al., 2014)."

Regarding what mutations should be included in the carrier screening test, the NSGC states, "Carrier testing panels should include the mutations recommended by ACOG and ACMG. For individuals of non-Northern European descent, pan-ethnic panels that include additional mutations more commonly identified in minority populations are appropriate to consider. Focus general population CF screening practices on identifying carriers of established disease-causing CFTR mutations (Langfelder-Schwind et al., 2014)."

The NSGC agrees with the ACMG regarding testing for IVS 8 5T/7T/9T as a reflex when mutation R117H is found in the CF carrier screen. They also assert that "in the absence of an R117H mutation, assessment of the intron 8 polyT or TG tracts is not recommended for routine CF carrier testing (Langfelder-Schwind et al., 2014)."

European Cystic Fibrosis Society (ECFS) (Castellani et al., 2018; Smyth et al., 2014)

The European Cystic Fibrosis Society mentioned CFTR modulators in their standards of care guideline. They recommended that "in patients with the G551D mutation ivacaftor should be part of standard of care". At the time of writing, only one CFTR modulator had been shown to "demonstrate clinical efficacy" (Smyth et al., 2014).

In 2018, the ECFS published a revised version of their best practice guidelines. The ECFS has published the following requirement to when providing a CF diagnosis:

- "To be able to perform genetic testing for the most appropriate panel of *CFTR* mutations for the local population. Access to extended exon DNA analysis should be available when required (Castellani et al., 2018)."

The ECFS also states that genetic counseling should be offered when reporting a CF diagnosis to a patient.

National Institute for Health and Care Excellence (NICE) (NICE, 2017)

In 2017, the NICE published guidelines on the diagnosis and management of CF. NICE includes the following recommendations on CF diagnoses:

- "Be aware that cystic fibrosis can be diagnosed based on:
 - positive test results in people with no symptoms, for example infant screening (blood spot immunoreactive trypsin test) followed by sweat and gene tests for confirmation or
 - clinical manifestations, supported by sweat or gene test results for confirmation or

- clinical manifestations alone, in the rare case of people with symptoms who have normal sweat or gene test results.
- Assess for cystic fibrosis and, when clinically appropriate, perform a sweat test (for children and young people) or a cystic fibrosis gene test (for adults) in people with any of the following:
 - family history
 - congenital intestinal atresia
 - meconium ileus
 - symptoms and signs that suggest distal intestinal obstruction syndrome
 - faltering growth (in infants and young children)
 - undernutrition
 - recurrent and chronic pulmonary disease, such as:
 - recurrent lower respiratory tract infections
 - clinical or radiological evidence of lung disease (in particular bronchiectasis)
 - persistent chest X-ray changes
 - chronic wet or productive cough
 - chronic sinus disease
 - obstructive azoospermia (in young people and adults)
 - acute or chronic pancreatitis
 - malabsorption
 - rectal prolapse (in children)
 - pseudo-Bartter syndrome.
- Refer people with suspected cystic fibrosis to a specialist cystic fibrosis center if:
 - they have a positive or equivocal sweat test result
 - their assessment suggests they have cystic fibrosis, but their test results are normal
 - gene testing reveals 1 or more cystic fibrosis mutations (NICE, 2017)."

Royal College of Paediatrics and Child Health (RCPCH) (RCPCH, 2014)

The RCPCH has published guidelines on the performance of the sweat test for the investigation of CF. These guidelines state that for patients less than six months of age and a sweat chloride level less than 30 mmol/L, "Cystic fibrosis is unlikely but requires genetic and clinical correlation"; also, for those older than six months and a sweat chloride level less than 40 mmol/L, "Cystic fibrosis is unlikely but requires genetic and clinical correlation (RCPCH, 2014)." Finally, the RCPCH notes that "The presence of two mutations of the *CFTR* gene known to cause CF may provide confirmatory evidence but the demonstration of mutations is not necessary to make a diagnosis of CF. The genetic diagnosis of CF by the demonstration of two *CFTR* mutations (known to be associated with clinical disease) does not require confirmation by a sweat test, however the UK Newborn Screening Program does currently require a sweat test after a positive newborn screening test, even in the presence of two *CFTR* mutations (RCPCH, 2014)."

Physicians Committee For Responsible Medicine (PCRM) (PCRM, 2021)

PCRM has published guidelines on diagnosis of cystic fibrosis. Below are the recommended guidelines:

1. A sweat chloride test can be performed as early as 48 hours after birth, which is the mainstay of laboratory confirmation.
2. Newborn Screening is mandatory in all 50 states.
A patient with symptoms may require a sweat chloride test or genetic testing. "Patients who exhibit signs and symptoms but do not have a positive sweat test should have a genetic test. Prenatal testing and newborn screening may be used. Early detection renders a better clinical course."

Applicable Federal Regulations

A search for “cystic fibrosis” on the FDA website on May 10, 2021, yielded 12 results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

On March 28, 2006 the FDA (2006a) approved eSensor Cystic Fibrosis Carrier Detection System as a device for the detection of carrier status for cystic fibrosis for all adult couples contemplating pregnancy, regardless of ethnicity. It is a qualitative genotyping assay that simultaneously detects mutations currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG). The eSensor® CFCD System is not indicated for prenatal screening or to establish a diagnosis for cystic fibrosis.

On June 7, 2006 the FDA (2006b) approved Tag-It™ Cystic Fibrosis Kit as a device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in human blood specimens. The panel includes mutations and variants currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG), plus some of the world’s most common and North American-prevalent mutations. The Tag-It™ Cystic Fibrosis Kit is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and 2 in confirmatory diagnostic testing in newborns and children.

On September 9, 2007 the FDA (2007) approved Cystic Fibrosis Genotyping Assay as a qualitative in vitro diagnostic device used to genotype a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic deoxyribonucleic acid (DNA) isolated from human whole blood specimens. The panel includes mutations and variants recommended by the American College of Medical Genetics (ACMG, 2004) and the American College of Obstetricians and Gynecologists (ACOG, 2005) plus additional multiethnic mutations. The Cystic Fibrosis Genotyping Assay provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening and in confirmatory diagnostic testing of newborns and children. This test is not indicated for use in fetal diagnostic or pre-implantation testing. This test is also not indicated for stand-alone diagnostic purposes.

On March 13, 2008 the FDA (2008) approved InPlex™ CF Molecular Test as an in vitro diagnostic device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA samples isolated from human peripheral whole blood specimens. The panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG). The InPlex™ CF Molecular Test is a qualitative genotyping test that provides information intended to be used for cystic fibrosis carrier screening as recommended by ACMG and the 2005 American College of Obstetricians and Gynecologists (ACOG) for adults of reproductive age, as an aid in newborn screening for cystic fibrosis, and in confirmatory diagnostic testing for cystic fibrosis in newborns and children. The test is not indicated for use in fetal diagnostic or pre-implantation testing. This test is also not indicated for stand-alone diagnostic purposes and results should be used in conjunction with other available laboratory and clinical information.

On July 6, 2009 the FDA (FDA, 2009a) approved eSensor® CF Genotyping Test as an in vitro diagnostic device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA samples isolated from human peripheral whole blood specimens. The panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG). The eSensor® CF Genotyping Test is a qualitative genotyping test that provides information intended to be used for cystic fibrosis carrier screening as recommended by ACMG and the 2005 American College of Obstetricians and Gynecologists (ACOG) for adults of reproductive age, as an aid in newborn screening for cystic fibrosis, and in confirmatory diagnostic testing for cystic fibrosis in newborns and children. The test is not indicated for use in fetal diagnostic or pre-implantation testing. This test is also not indicated for stand-alone diagnostic purposes and results should be used in conjunction with other available laboratory and clinical information.

On July 24, 2009 the FDA (FDA, 2009b) approved Verigene®CFTR and Verigene®CFTR PolyT Nucleic Acid Tests as qualitative in vitro diagnostic devices used to genotype a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens. The panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG) and the 2005 American College of Obstetricians and Gynecologists (ACOG). The Verigene®CFTR Nucleic Acid Test provides information intended to be used for carrier testing in adults of reproductive age and in confirmatory diagnostic testing of newborns and children. These tests are not indicated for use in fetal diagnostic or pre-implantation testing and not indicated for stand-alone diagnostic purposes and the results should be used in conjunction with other available laboratory and clinical information.

On December 11, 2009 the FDA (FDA, 2009c) approved e xTAG® Cystic Fibrosis 60 Kit v2 as a device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in human blood specimens. The panel includes mutations and variants currently recommended by the American College of Medical Genetics and American College of Obstetricians and Gynecologists (ACMG/ACOG), plus some of the world's most common and North American prevalent mutations. The xTAG® Cystic Fibrosis 60 Kit v2 is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children. The kit is not indicated for use in fetal diagnostic or pre-implantation testing. This kit is also not indicated for stand-alone diagnostic purposes. On December 15, 2016 a modification to this test was approved for new software thresholds for 2183/2184 variants.

On November 19, 2013 the FDA (2013b) approved Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay is a qualitative in vitro diagnostic system used to simultaneously detect 139 clinically relevant cystic fibrosis disease-causing mutations and variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens. The variants include those recommended in 2004 by the American College of Medical Genetics (ACMG) and in 2011 by the American College of Obstetricians and Gynecologists (ACOG). The test is intended for carrier screening in adults of reproductive age, in confirmatory diagnostic testing of newborns and children, and as an initial test to aid in the diagnosis of individuals with suspected cystic fibrosis. The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information. This test is not indicated for use for newborn screening, fetal diagnostic testing, preimplantation testing, or for stand-alone diagnostic purposes.

On November 19, 2013 the FDA (2013a) also approved Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing Assay as a targeted sequencing in vitro diagnostic system that re-sequences the protein coding regions and intron/exon boundaries of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens collected in K2EDTA. The test detects single nucleotide variants, and small InDels within the region sequenced, and additionally reports on two deep intronic mutations and two large deletions. The test is intended to be used on the Illumina MiSeqDx Instrument. The test is intended to be used as an aid in the diagnosis of individuals with suspected cystic fibrosis (CF). The test is most appropriate when the patient has an atypical or non-classic presentation of CF or when other mutation panels have failed to identify both causative mutations. The results of the test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available information including clinical symptoms, other diagnostic tests, and family history. This test is not indicated for use for stand-alone diagnostic purposes, fetal diagnostic testing, for pre-implantation testing, carrier screening, newborn screening, or population screening.

On December 15, 2016 the FDA approved the XTAG Cystic Fibrosis 39 Kit V2 (FDA, 2016a) by Luminex Molecular Diagnostics, Inc. This test is able to identify the 23 CFTR mutations related to cystic fibrosis and could aid in carrier screening, newborn screening and diagnostic testing.

On December 15, 2016 the FDA also approved the XTAG Cystic Fibrosis 60 Kit V2, XTAG Data Analysis Software (TDAS) CFTR by Luminex Molecular Diagnostics, Inc (FDA, 2016b). This software works with the XTAG Cystic Fibrosis 39 Kit V2 to interpret samples and identify mutant and/or wild type alleles for each variation.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81220, 81221, 81222, 81223, 81224, 81479, 96040, S0265

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Policy Implementation/Update Information

- 1/1/2019 New policy developed. BCBSNC will provide coverage for genetic testing for cystic fibrosis when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
- 8/13/19 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)
- 8/27/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Added “Related Policies” section, minor revisions to policy guidelines and coding table removed from the Billing/Coding section of the policy. References updated. No change to policy intent. Medical Director reviewed 8/2019. (jd)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Related policies added. Policy guidelines and references updated. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)
- 7/1/21 Off-cycle review by Avalon 1st Quarter 2021 CAB. CPT codes 81220 and 81221 added to Billing/Coding section for PPA effective date of 7/1/21. Medical Director review. (jd)
- 8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB review. Background, policy guidelines, and references updated. Reworded item 3, under the When Covered section for clarity, adding items b-d, and removed item d, under #4 pertaining to cascade testing, combining it within item c. Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.