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Genetic Testing for Cystic Fibrosis

Policy Number: AHS – M2017	**Prior Policy Name and Number:** Not applicable
Initial Effective Date: June 01, 2023	**Current Effective Date:** January 1, 2027
Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

I. Policy Description

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.[1]

~~When pursuing genetic testing for cystic fibrosis, genetic counseling is strongly recommended.~~

For guidance on pre-implantation genetic testing, please see AHS-M2039-Pre-Implantation Genetic Testing. For guidance on prenatal screening and preconception screening for cystic fibrosis, please see AHS-M2179-Prenatal Screening (Genetic).

II. Related Policies

Policy Number	Policy Title
AHS-M2039	Pre-Implantation Genetic Testing
AHS-M2179	Prenatal Screening (Genetic)

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) Genetic counseling **IS REQUIRED** for individuals prior to and after undergoing genetic testing for cystic fibrosis.

~~1)~~2) Common variant testing (see Note 1) or comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis) **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) In a newborn after an abnormal newborn screening result using immunoreactive trypsinogen.

b) For infants with meconium ileus.

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c) For individuals with congenital absence of the vas deferens (CAVD).

d) For individuals with idiopathic pancreatitis or bronchiectasis.

~~2)~~3) As an adjunct to sweat testing in an individual presenting with symptoms of cystic fibrosis, common variant testing (see Note 1) or comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis) **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) When there are no known familial pathogenic or likely pathogenic (P/LP) variants.

b) When one or more familial P/LP variants are known; testing must include the familial P/LP variants.

4) For individuals for whom both parents are carriers of P/LP *CFTR* variants that are associated with milder/nonclassic cystic fibrosis (e.g., normal newborn screening results, normal sweat test results, normal pancreatic function), common variant or comprehensive analysis of the *CFTR* gene **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) When both familial P/LP variants are part of the ACMG variant set (see Note 1), common variant testing must be performed.

b) If one or more P/LP variant(s) is not on the common variant list (see Note 1), comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis) must be performed.

~~3)~~5) For individuals with congenital bilateral absence of the vas deferens (CBAVD), common variant testing (see Note 1) or comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis), including testing for the *CFTR* IVS8 5T/7T/9T variant, **MEETS COVERAGE CRITERIA**.

~~4)~~6) When the *CFTR* R117H variant is detected on carrier screening, reflex genetic testing for the *CFTR* IVS8 5T/7T/9T variant **MEETS COVERAGE CRITERIA**.

~~5)~~7) For individuals for whom common variant testing (see Note 1) identified no variants or only one variant, but for whom the clinical suspicion of cystic fibrosis still remains, comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis) **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) For individuals that presented with symptoms of cystic fibrosis and who received panel testing as an adjunct to sweat testing.

b) When a diagnosis of cystic fibrosis related CBAVD remains a consideration in individuals with CBAVD.

~~6)~~8) For the family members of individuals with CFTR-related metabolic disorder/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID), comprehensive analysis of the *CFTR* gene (i.e., full gene sequencing, deletion/duplication analysis) **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) For parents of the individual: When phasing of the *CFTR* variants would inform the diagnostic status of the individuals by confirming the inheritance pattern.

b) For siblings of the individual.

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~~7)~~9) For all other situations not described above, genetic testing for variants in the *CFTR* gene **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Common variant testing for *CFTR* mutations must include the American College of Medical Genetics' (ACMG) *CFTR* carrier screening variant set (n=100). Please see the "Guidelines and Recommendations" section of this policy for a table of ACMG's *CFTR* minimum variant set.

IV. Table of Terminology

Term	Definition
ACMG	American College of Medical Genetics
ACOG	American College of Obstetrics and Gynecology
CAVD	Congenital absence of the vas deferens
CBAVD	Congenital bilateral absence of the vas deferens
CF	Cystic fibrosis
CFCD	Cystic fibrosis carrier detection
CFF	Cystic Fibrosis Foundation
CFSPID	Cystic fibrosis screen positive, inconclusive diagnosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR2	Clinical and functional translation of CFTR
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers For Medicare and Medicaid
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRMS	CFTR-related metabolic disorder
CVS	Chorionic villus sampling
DNA	Deoxyribonucleic acid
ECFS	European Cystic Fibrosis Society
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
ICM	Intestinal current measurement
IRT	Immunoreactive trypsinogen
IVA	Ivacaftor
LDT	Laboratory-developed test
LUM	Lumacaftor
MMWR	Morbidity And Mortality Weekly Report
MVCC	Mutation of varying clinical consequence
NBS	Newborn screening
NGS	Next generation sequencing
NICE	National Institute for Health and Care Excellence
NPD	Nasal potential difference
NSGC	National Society of Genetic Counselors
P/LP	Pathogenic/likely pathogenic

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PCR	Polymerase chain reaction
PCRM	Physicians Committee for Responsible Medicine
PCS	Cystic fibrosis carrier screening
QALY	Quality adjusted life year
RT-PCR	Reverse transcription polymerase chain reaction
TDAS	XTAG Data Analysis Software
TDN	Therapeutics Development Network
TOP	Termination of pregnancy
UNK	Uncharacterized mutation
VUS	Variant of uncertain significance

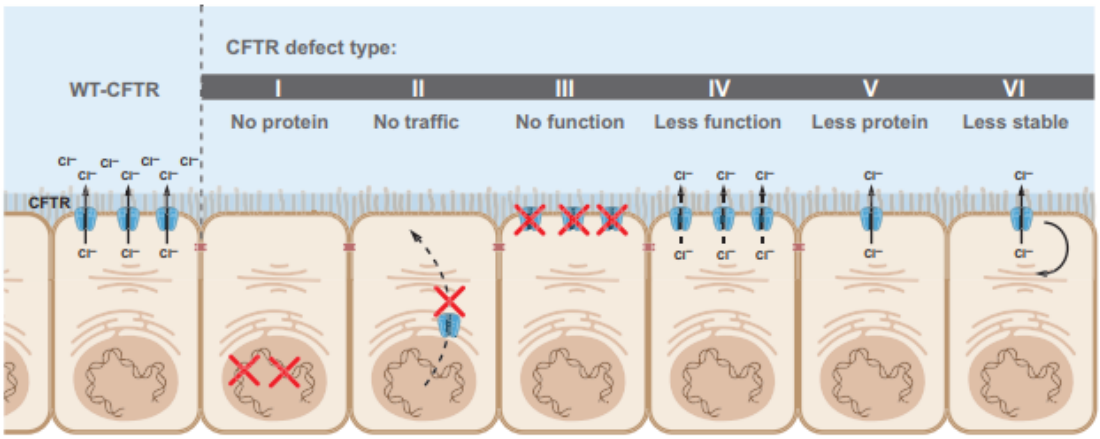
V. Scientific Background

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.[2,3] The CFTR protein is present in the epithelia of various tissues, including that of the lungs, sweat glands, gastrointestinal tract, and pancreas.[4] 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.[3] Functional failure of CFTR results in defective mucociliary clearance, chronic infection, and abnormal inflammatory response leading to progressive, irreversible lung damage.[2] Other manifestations of dysfunctional CFTR include pancreatic insufficiency and meconium ileus.[4] 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.[3]

Most mutations of the *CFTR* gene are missense alterations, but other mutations, deletions and insertions have been described.[5] 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.[6] *CFTR* mutations can be divided into six classes according to their effects on protein function as depicted in the figure below.[5]

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	I	II	III	IV	V	VI
Mutation examples	G542X (a) W1282X (a) 1717-1G (b)	F508del N1303K A561E	G551D S549R G1349D	R117H R334W A455E	A455E 3272-26A>G 3849+10 kb C>T	c.120del23 rF508del
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability
Drug	Read-through compounds	Correctors	Potentiators	Potentiators	AONs Correctors Potentiators	Stabilizers
Drug approved (Yes/No)	No	No	Yes	No	No	No

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.[5,7]

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.[8] 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.[9]

In addition to NBS, CF carrier screening (PCS) has become commonplace in the U.S., particularly among pregnant individuals and couples planning a pregnancy. PCS has been found to markedly reduce CF birth rates with a shift towards milder mutations, but it was often avoided for cultural reasons necessitating the use of complementary PCS and NBS.[10]

A subset of 23 mutations accounts for most 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

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correlations and has confirmed many additional mutations as being causative of CF.[6] Information from over 88,000 ~~patients~~individuals 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.[6]

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.[11] Analysis of the Exome Aggregation Consortium dataset also found that none of the current genetic screening panels or existing *CFTR* mutation databases covered most 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.[12] 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.

Proprietary Testing

There are several traditional cystic fibrosis genotyping assays approved by the FDA. eSensor Cystic Fibrosis Carrier Detection System detects 24 CFTR variants,[13] Tag-It™ Cystic Fibrosis Kit detects 39 variants,[14] Cystic Fibrosis Genotyping Assay detects 30 variants,[15] InPlex™ CF Molecular Test detects 32 variants,[16] Verigene®CFTR and Verigene®CFTR PolyT Nucleic Acid Tests detect 26 variants,[17] Diasorin xTAG® Cystic Fibrosis (CFTR) 39 kit v2 detects 39 variants and the Diasorin xTAG® Cystic Fibrosis (CFTR) 60 kit v2 detects an additional 21 variants,[18] and Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay detects 139 variants.[19] These panels target common mutations prevalent in certain populations, providing rapid and cost-effective results. However, they may miss rare or novel mutations not included in the panel, potentially leading to incomplete genetic assessments.

Next generation sequencing (NGS) offers a comprehensive analysis by sequencing the entire *CFTR* gene enabling the detection of both common and rare mutations, including novel variants that traditional panels might overlook. FDA-approved platforms, such as the Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay, facilitate the detection of both common and rare *CFTR* mutations.[20] 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.[21] Further studies have shown that implementing NGS has improved diagnostic accuracy and increased the positive predictive value in newborn screening.[22] Additionally, 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.[23]

Cystic fibrosis transmembrane conductance regulator (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. Additional approval of Trikafta, a combination therapy of elexacaftor, tezacaftor, and ivacaftor, has expanded treatment options by demonstrating efficacy in patients with a broader spectrum of CFTR mutations.[24] The indications and efficacy of these

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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.[25]

Analytical Validity

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.[26]

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%."[27] Overall, the presence and/or absence of *CFTR* variants was strongly related to a CF diagnosis.

Hendrix, et al. (2020) assessed the performance of dried blood spot DNA extraction methods in NGS for cystic fibrosis. A total of 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."[28]

Sicko, et al. (2021) validated the use of a custom NGS assay, Archer CF assay, for CF newborn screening. According to the New York State, CF NBS had high false positive rates. However, after the implementation of this three-tier IRT-DNA-SEQ approach using commercially available tests, the positive predictive value of CF NBS improved from 3.7% to 25.2%. The Archer CF assay involves full gene sequencing, analyzing a specific panel of 338 clinically relevant CFTR variants (second tier), followed by unblinding of all sequence variants and bioinformatic assessment of deletions/duplications (third tier). A total of 227 infant samples were taken, and 190 of 227 carries one or more of the 338 panel variants. The second-tier panel variants were all called correctly, detecting 44 different variants with a 100% sensitivity and 100% specificity. All 227 samples also underwent third tier analysis which detected 62 additional unique SNV/indel variants.[22]

Pedersen, et al. (2024) evaluated the 11-year performance of the cystic fibrosis newborn bloodspot screening (CF-NBS) and found strong sensitivity (96%) but moderate positive predictive value (PPV) (25%). The program uses an immunoreactive trypsinogen (IRT)-DNA algorithm with a second IRT (IRT-2) as a safety net. Optimal cut-offs for IRT-1 and IRT-2 were identified at 2.7 and 5.9 z-scores, respectively. Simulated algorithm modifications suggested that removing the safety net could increase PPV to 30%,

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reduce unnecessary second heel-prick tests, and maintain sensitivity at 95%. The findings highlight the potential for optimizing CF-NBS algorithms to improve PPV and reduce follow-up testing while maintaining high diagnostic sensitivity.[29]

Clinical Utility and Validity

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.[30]

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.[31]

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 one 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.[32]

Kessels, et al. (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%)."[33] The authors conclude by stating that genetic testing for CF had good diagnostic performance and lead to fewer births affected by CF.

Avram, et al. (2021) studied the cost-effectiveness of genotyping versus sequencing for prenatal CF carrier screening using three strategies: genotyping ("genotyping included the standard 23-variant panel recommended by ACMG/ACOG") both partners, genotyping one partner then sequencing the second, and sequencing both partners. The authors used a decision-analytic model to generate a theoretical cohort of four million pregnant people and their partners. Sequencing both partners identified 1,099 carrier couples that would have been missed by genotyping of both partners, resulting in 273 fewer missed prenatal diagnoses, 152 more terminations, 152 fewer affected newborns, and screening with genotyping followed by sequencing identified 477 more carrier couples as compared to genotyping both partners, resulting in 119 fewer missed prenatal diagnoses, 66 more terminations, and 66 fewer affected newborns. The incremental cost-effectiveness ratio of genotyping followed by sequencing compared to

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genotyping both partners was $180,004/ quality-adjusted life year (QALY) and the incremental cost-effectiveness ratio of sequencing both partners compared to genotyping followed by sequencing was $17.6 million/QALY. “Compared to genotyping both partners, the cost per CF case averted for genotyping/sequencing was $1.2 million and sequencing both partners was $49.4 million. . . Sequencing both partners was cost-effective when the cost of sequencing fell below $339 per test. Genotyping/sequencing was cost-effective when the cost of sequencing was between $340 and 1837 per test. Lastly, genotyping both partners was cost-effective when sequencing cost above $1838 per test". The authors concluded that “before being routinely recommended, sequencing for CF carrier screening requires greater examination at a population-based level.[34]

VI. Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG)

The ACMG recommends offering CF carrier screening to all individuals capable of becoming pregnant who are of reproductive age, regardless of ethnic background. Ideally, the testing would occur prior to pregnancy, but if the individual is pregnant, then they should be tested as early as possible during the pregnancy. ACMG also indicates that if the individual is found to be a CF carrier, then their reproductive partner should also be tested.[35] If the individual presents for testing late in the pregnancy, simultaneous testing of both reproductive partners of the fetus should be considered. When there is a paternal family history of CF, carrier testing of the father is warranted.

In 2020, the ACMG introduced technical guidelines for CFTR variant testing, particularly emphasizing considerations during pregnancy. These guidelines suggest that simultaneous testing might be necessary based on various factors like gestational age, family history, ethnicity, or patient preferences. Carrier testing is recommended for individuals with a family history of CF, partners of those with such history, partners of males with CAVD, reproductive age women, and gamete donors. Additionally, CFTR variant testing can be conducted for prenatal diagnosis using cells obtained through procedures like amniocentesis or chorionic villus sampling (CVS). To ensure inclusivity, “the ACMG recommends either a classification-based reporting approach or a classification-based (targeted) testing approach (which has historically been used for CFTR carrier screening). For those laboratories who wish to continue using a targeted testing approach, the ACMG-23 variant panel remains as the minimum list of CFTR variants that should be included. Laboratories may want to consider adding additional variants to their panel depending on the ethnic composition of their expected test population. However, the minimum list of CFTR variants recommended for pan-ethnic carrier screening has not been increased at this time.”[36]

In 2023, the ACMG issued updated recommendations for CFTR carrier screening, introducing a new minimum CFTR variant set (Table 1) that replaces the previous set of 23 variants. These revised recommendations specifically apply to carrier screening and do not affect CFTR variant testing for diagnosis or newborn screening. However, all other aspects of the 2020 ACMG CFTR technical standards remain unchanged.[37]

Table 1 (adapted from Deignan, et al. (2023)) : *CFTR* Carrier Screening Variant Set (n=100)

DNA Variant	Protein Variant	Legacy Name
c.4C>T	p.Gln2Ter	Q2X

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DNA Variant	Protein Variant	Legacy Name
c.178G>T	p.Glu60Ter	E60X
c.200C>T	p.Pro67Leu	P67L
c.223C>T	p.Arg75Ter	R75X
c.254G>A	p.Gly85Glu	G85E[a]
c.262_263del	p.Leu88IlefsTer22	394delTT
c.271G>A	p.Gly91Arg	G91R
c.274-1G>A	p.?	406-1G->A
c.292C>T	p.Gln98Ter	Q98X
c.293A>G	p.Gln98Arg	Q98R
c.313del	p.Ile105SerfsTer2	444delA
c.328G>C	p.Asp110His	D110H
c.349C>T	p.Arg117Cys	R117C
c.350G>A	p.Arg117His	R117H[a]
c.489+1G>T	p.?	621+1G->T[a]
c.571T>G	p.Phe191Val	F191V
c.579+1G>T	p.?	711+1G->T[a]
c.579+3A>G	p.?	711+3A->G
c.617T>G	p.Leu206Trp	L206W
c.653T>A	p.Leu218Ter	L218X
c.695T>A	p.Val232Asp	V232D
c.803del	p.Asn268IlefsTer17	935delA
c.868C>T	p.Gln290Ter	Q290X
c.988G>T	p.Gly330Ter	G330X
c.1000C>T	p.Arg334Trp	R334W[a]
c.1013C>T	p.Thr338Ile	T338I
c.1021_1022dup	p.Phe342HisfsTer28	1154insTC
c.1029del	p.Cys343Ter	1161delC
c.1040G>A	p.Arg347His	R347H
c.1040G>C	p.Arg347Pro	R347P[a]
c.1055G>A	p.Arg352Gln	R352Q
c.1155_1156dup	p.Asn386IlefsTer3	1288insTA
c.1327_1330dup	p.Ile444ArgfsTer3	1461ins4
c.1364C>A	p.Ala455Glu	A455E[a]
c.1367T>C	p.Val456Ala	V456A
c.1373del	p.Gly458AspfsTer11	1504delG
c.1393-1G>A	p.?	1525-1G->A
c.1397C>G	p.Ser466Ter	S466X
c.1400T>C	p.Leu467Pro	L467P
c.1519_1521del	p.Ile507del	I507del[a]
c.1521_1523del	p.Phe508del	F508del[a]
c.1572C>A	p.Cys524Ter	C524X

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DNA Variant	Protein Variant	Legacy Name
c.1584+1G>A	p.?	1716+1G->A
c.1585-1G>A	p.?	1717-1G->A[a]
c.1624G>T	p.Gly542Ter	G542X[a]
c.1646G>A	p.Ser549Asn	S549N
c.1647T>G	p.Ser549Arg	S549R
c.1651G>A	p.Gly551Ser	G551S
c.1652G>A	p.Gly551Asp	G551D[a]
c.1657C>T	p.Arg553Ter	R553X[a]
c.1673T>C	p.Leu558Ser	L558S
c.1675G>A	p.Ala559Thr	A559T
c.1679G>C	p.Arg560Thr	R560T[a]
c.1679+1G>A	p.?	1811+1G->A
c.1680-886A>G	p.?	1811+1634A->G
c.1680A>C	p.Arg560Ser	R560S
c.1682C>A	p.Ala561Glu	A561E
c.1692del	p.Asp565MetfsTer7	1824delA
c.1705T>G	p.Tyr569Asp	Y569D
c.1753G>T	p.Glu585Ter	E585X
c.1766+1G>A	p.?	1898+1G->A[a]
c.1766+5G>T	p.?	1898+5G->T
c.1837G>A	p.Ala613Thr	A613T
c.1882G>A	p.Gly628Arg	G628R
c.2052dup	p.Gln685ThrfsTer4	2184insA
c.2052del	p.Lys684AsnfsTer38	2184delA[a]
c.2125C>T	p.Arg709Ter	R709X
c.2175dup	p.Glu726ArgfsTer4	2307insA
c.2290C>T	p.Arg764Ter	R764X
c.2353C>T	p.Arg785Ter	R785X
c.2374C>T	p.Arg792Ter	R792X
c.2490+1G>A	p.?	2622+1G->A
c.2657+5G>A	p.?	2789+5G->A[a]
c.2668C>T	p.Gln890Ter	Q890X
c.2739T>A	p.Tyr913Ter	Y913X
c.2834C>T	p.Ser945Leu	S945L
c.2909G>A	p.Gly970Asp	G970D
c.2988G>A	p.Gln996=	3120G->A
c.2988+1G>A	p.?	3120+1G->A[a]
c.3067_3072del	p.Ile1023_Val1024del	3199del6
c.3107C>A	p.Thr1036Asn	T1036N
c.3140-26A>G	p.?	3272-26A->G
c.3196C>T	p.Arg1066Cys	R1066C

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DNA Variant	Protein Variant	Legacy Name
c.3197G>A	p.Arg1066His	R1066H
c.3266G>A	p.Trp1089Ter	W1089X
c.3294G>C	p.Trp1098Cys	W1098C
c.3353C>T	p.Ser1118Phe	S1118F
c.3472C>T	p.Arg1158Ter	R1158X
c.3484C>T	p.Arg1162Ter	R1162X[a]
c.3528del	p.Lys1177SerfsTer15	3659delC[a]
c.3612G>A	p.Trp1204Ter	W1204X
c.3659del	p.Thr1220LysfsTer8	3791delC
c.3717+5G>A	p.?	3849+5G->A
c.3718-2477C>T	p.?	3849+10kbC->T[a]
c.3744del	p.Lys1250ArgfsTer9	3876delA
c.3764C>A	p.Ser1255Ter	S1255X
c.3808del	p.Asp1270MetfsTer8	3940delG
c.3846G>A	p.Trp1282Ter	W1282X[a]
c.3889dup	p.Ser1297PhefsTer5	4016insT
c.3909C>G	p.Asn1303Lys	N1303K[a]

[a]Variants that were part of the previously recommended minimum 23-variant set.

The 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.[38]

The 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 individuals 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, to partners of individuals with a positive family history, to partners of individuals with CAVD, to reproductive age individuals capable of becoming pregnant, and to gamete donors.[36]

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."[36]

Comprehensive CFTR sequencing may be considered when:

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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).

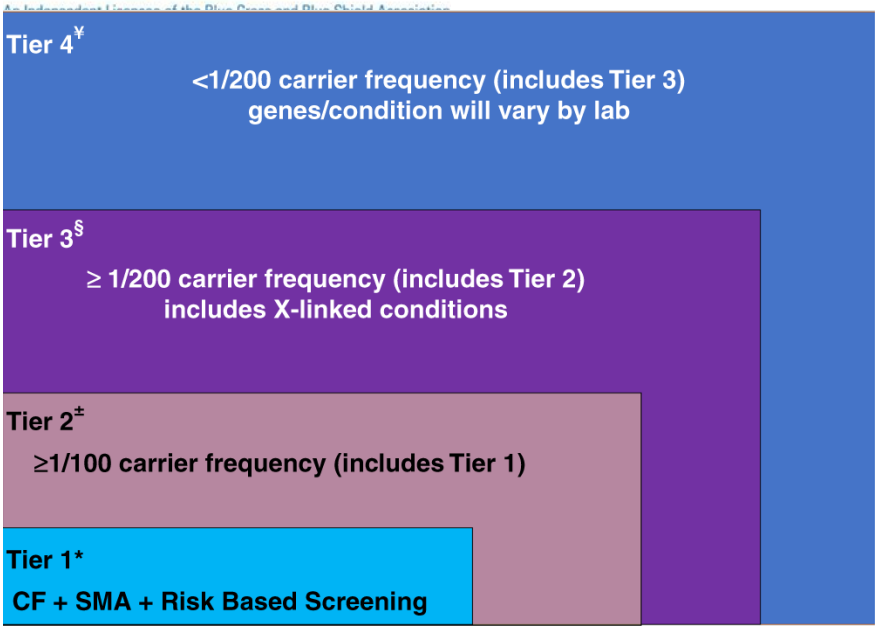
b. An ultrasound finding (i.e., fetal echogenic bowel) suggests an affected fetus and CFTR variant information is not available from either biological parent."[36]

The 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."[36]

The ACMG released recommendations for preconception and prenatal carrier screening. The following tier-based approach to carrier screening was produced and recommendations were made:[39]

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CF: cystic fibrosis, SMA: spinal muscular atrophy.

- Preconception screening is recommended over prenatal screening.
- Concurrent partner testing should be offered if testing done during pregnancy.
- Tier 3 screening is recommended which includes 97 autosomal recessive genes and 16 X-linked genes, including DMD and Fragile X.
- The second biological parent may be offered Tier 3 carrier screening (for autosomal recessive conditions) when carrier screening is being performed at the same time in their reproductive partner who is capable of becoming pregnant.
- All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.
- Tier 4 screening should be considered when a pregnancy arises from a known or possible consanguineous relationship (second cousins or closer) or when a family or personal medical history warrants further risk assessment.
- ACMG does not recommend offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups and routine offering of Tier 4 panels.[39]

Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation convened a group ~~of~~ 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."[40]

The committee approved 27 consensus statements:[40]

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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:

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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 ≥ 60 mmol/L or CF-typical NPD or ICM).

16 The term CRMS [CFTR-related metabolic disorder] is used in the US for healthcare delivery purposes and CFSPID [cystic fibrosis screen positive, inconclusive diagnosis] 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.

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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 also convened a multidisciplinary committee of CF caregivers to develop evidence-based guidelines for CFTR modulator therapy. The committee approves and prescribes CFTR modulators based on specific mutations (as seen below), therefore testing to identify the exact CFTR genotype is recommended. 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.[41]

For adults and children aged six 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

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one second (FEV_1) 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 FEV_1 greater than 90% predicted, and *2*) children less than six 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 FEV_1 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 FEV_1 greater than 90% predicted, and *2*) children aged 6–11 years.[41]

In an updated 2024 report, a multidisciplinary committee with the Cystic Fibrosis Foundation released additional recommendations as described below:

Genetic Testing:

- "The CFF recommends that people with CRMS/CFSPID who have <2 disease-causing variants identified by NBS should undergo sequencing of the coding and flanking regions and deletion/duplication (del/dup) analysis of the coding and exon flanking regions of CFTR (Grade B).
- The CFF recommends, for people with CRMS/CFSPID, selectively offering full gene CFTR sequencing including intronic regions when the CFTR genotype remains incomplete after coding and flanking region sequencing and del/dup (Grade C)
- The CFF recommends CFTR genetic evaluation for parents of people with CRMS/CFSPID when phasing the CFTR variants (ie, in cis or trans) would inform the diagnostic status of the individual by confirming the inheritance pattern (Grade A).
- The CFF recommends offering CFTR genetic evaluation for siblings of people with CRMS/CFSPID (Grade B).
- The CFF recommends, for families of people with CRMS/CFSPID, that health care professionals (HCPs) providing genetic counseling should have training or clinical expertise in CF and genetics. A licensed or certified genetic counselor (GC) should be accessible to families of people with CRMS/CFSPID for further support, including discussions regarding future reproductive decision-making (Grade B)."[42]

Monitoring CFTR diagnosis:

- "The CFF recommends, for people with CRMS/CFSPID, at least annual follow-up by a CF clinician and nurse, with an initial assessment to include a social worker, a mental health coordinator (MHC), and/or a genetic counseling provider. Continued follow-up by a social worker, MHC, and/or genetic counselor should be part of the care of CRMS/CFSPID, depending on the needs of that individual and family (Grade B)
- The CFF recommends for people with CRMS/CFSPID to repeat SCT at 6 months of life and annually, at least until age 8 years (Grade B)."[42]

American College of Obstetrics and Gynecology (ACOG)

The ACOG recommends offering CF carrier screening to all individuals who are considering becoming pregnant or who 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

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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.

The ACOG recommends that complete gene sequencing of the CTFR 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, individuals 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.[43]

These statements were reaffirmed in ~~2023~~2025.

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors (NSGC) recommends that for all individuals capable of becoming pregnant and who are of reproductive age, carrier screening for CG should be offered "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."[44]

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."[44]

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."[44]

European Cystic Fibrosis Society (ECFS)

The ECFS mentioned CFTR modulators in their standards of care ~~guideline~~guidelines. Recommendations state 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."[45]

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."[46]

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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)

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."[47]

These statements were reviewed and reasserted in 2024.

Physicians Committee for Responsible Medicine (PCRM)

The PSRM 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.

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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. While not widely available, nasal potential difference measurements can confirm the diagnosis if sweat testing and genetic testing results are inconclusive."[48]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

On March 28, 2006, the FDA 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.[49]

On June 7, 2006, the FDA 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 two in confirmatory diagnostic testing in newborns and children.[14]

On September 9, 2007, the FDA 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.[15]

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On March 13, 2008, the FDA 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.[50]

On July 6, 2009, the FDA 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.[51]

On July 24, 2009, the FDA 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.[17]

On December 11, 2009, the FDA approved 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.[52] On December 15, 2016, a modification to this test was approved for new software thresholds for 2183/2184 variants.[53]

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On November 19, 2013, the FDA 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.[54]

On November 19, 2013, the FDA also approved Illumina MiSeqDxTM 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 nonclassic 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.[20]

On December 15, 2016, the FDA approved the XTAG Cystic Fibrosis 39 Kit V2 by Luminex Molecular Diagnostics, Inc. This test can identify the 23 CFTR mutations related to cystic fibrosis and could aid in carrier screening, newborn screening, and diagnostic testing.[~~55~~53]

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination

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as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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)
81479	Unlisted molecular pathology procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Evidence-based Scientific References

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XI. Revision History

Revision Date	Summary of Changes
06/03/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Addition of new CC1 requiring genetic counseling: "1) Genetic counseling IS REQUIRED for individuals prior to and after undergoing genetic testing for cystic fibrosis." New CC4: "4) For individuals for whom both parents are carriers of P/LP CFTR variants that are associated with milder/nonclassic cystic fibrosis (e.g., normal newborn screening results, normal sweat test results, normal pancreatic function), common variant or comprehensive analysis of the CFTR gene MEETS COVERAGE CRITERIA in any of the following situations: a) When both familial P/LP variants are part of the ACMG variant set (see Note 1), common variant testing must be performed. b) If one or more P/LP variant(s) is not on the common variant list (see Note 1), comprehensive analysis of the CFTR gene (i.e., full gene sequencing, deletion/duplication analysis) must be performed."

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