Protocol

Genetic Testing for Cystic Fibrosis

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 11/17
Preauthorization	No	**Review Dates**: 11/16	

Preauthorization is not required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Description

Cystic Fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis trans-membrane conductance regulator (CFTR) protein. Genetic testing is available to identify pathogenic mutations for diagnostic purposes as well as to identify unaffected individuals who are carriers and therefore risk passing this disease to their offspring.

Policy

Genetic testing to determine the carrier status for CFTR mutations may be **medically necessary** when any one of the following are met:

- A woman of reproductive age either planning a pregnancy or in the early stages of pregnancy; OR
- Reproductive partners of women who are either a carrier of or with cystic fibrosis who are either planning a pregnancy or in the early stages of pregnancy.

Genetic testing to diagnose a CFTR mutation in Cystic Fibrosis or a related disorder may be considered **medically necessary** with any one of the following (see Policy Guidelines for Testing Strategy):

- Prenatal testing for pregnancy at risk for CF; OR
- Prenatal ultrasound findings that indicate an increased risk for CF (e.g., echogenic bowel or dilated loops of bowel); OR
- Follow-up study of newborn with an elevated level of immunoreactive trypsinogen (IRT) on dry blood spot screening test; OR
- Ashkenazi Jewish Children; OR
- Inconclusive biochemical test (e.g., sweat chloride or IRT) with a physical exam when CF continues to be suspected; OR
- Male infertility due to congenital bilateral absence of the vas deferens (CBAVD).

Genetic testing for the treatment of CFTR mutation related disorders may be considered **medically necessary** in the following situations***** (see Policy Guidelines for Testing Strategy):

- Mutation testing in children with CF for treatment with Kalydeco if 2 years of age or older; OR
- Mutation testing in children for treatment of CF with Orkambi (lumacaftor 200 mg/ivacaftor 125 mg) if 12 years of age or older.

***Note:** Please refer to Drug Therapy Guidelines for guidance on appropriate use of Kalydeco or Orkambi® in the treatment of Cystic Fibrosis. This Protocol addresses testing requirements, not treatment criteria.

The following uses of genetic testing for Cystic Fibrosis would be considered **not medically necessary**:

- Routine carrier screening by complete sequencing CFTR Gene.
- Routine newborn carrier screening by complete sequencing CFTR Gene.

Expanded carrier screening panels are considered to be **not medically necessary**. (See Policy Guidelines**)

Policy Guidelines

Carrier Testing

A carrier of a genetic disorder has one abnormal allele for a disorder. When associated with an autosomal recessive disorder such as CF, carriers of the causative mutation are typically unaffected. Homozygous-affected offspring (those who inherit the mutation from both parents) manifest the disorder.

Carrier testing is performed to identify couples at risk of having offspring with a genetic disease. Carrier testing may be performed before conception or during a pregnancy and is only appropriate when the individual(s) are planning a pregnancy or are currently pregnant.

Carrier testing should be performed for diseases that have high penetrance and do not have (highly) variable expression.

Population screening should only be performed if the disease prevalence is high and disease morbidity is high.

Expanded carrier screening (ECS) panels may provide the opportunity to test carriers for a greatly expanded number of diseases for a lower cost than the conventional forms of carrier testing. However, the current limitations of these expanded panels include technical and interpretive limitations and ethical and genetic counseling challenges.

**The ACMG defines expanded panels as those that use next-generation sequencing to screen for mutations in many genes, as opposed to gene-by-gene screening (e.g., ethnic-specific screening or panethnic testing for cystic fibrosis). An ACMG position statement states that although commercial laboratories offer expanded carrier screening panels, there has been no professional guidance as to which disease genes and mutations to include.[1]

Invasive Prenatal Testing

Invasive prenatal (fetal) diagnostic testing may be used to confirm the presence of a pathogenic abnormality after it has been determined by prenatal screening that the fetus is at increased risk for one of these conditions.

Invasive prenatal testing refers to the direct testing of fetal tissue, typically by chorionic villus sampling (CVS) or amniocentesis. Invasive prenatal procedures are typically performed in pregnancies of women who have been identified as having a fetus at increased risk for a chromosomal abnormality, or if there is a family history of a single-gene disorder. Women may be identified as being at increased risk for having a fetus with an inherited genetic condition because of previously affected pregnancies, a family history in a suggestive pattern of inheritance, or being a member of a subpopulation with elevated frequencies of certain autosomal recessive conditions.

Preimplantation Genetic Testing

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure and is used to detect a specific inherited disorder to prevent the birth of affected children in couples at high risk of transmitting a disorder.

CF is one condition for which preimplantation genetic diagnosis has been frequently performed. However, CF has a variable presentation and can be treatable.

Testing Strategy

Diagnostic Testing Strategy

Testing for CFTR mutations to determine carrier status or to confirm diagnosis of CF is required only once in an individual's lifetime.

The *diagnostic* testing strategy for the applicable policy statement above (with the exception of male infertility due to congenital bilateral absence of the vas deferens) is:

- First a biochemical test (e.g., sweat chloride or IRT) with a clinical physical exam.
- If this is inconclusive and Cystic Fibrosis continues to be suspected then CFTR gene analysis for detection of common variants. (Approximately 88% identification).
- If CFTR gene analysis for detection of common variants is not conclusive and Cystic Fibrosis continues to be suspected then CFTR full sequence gene analysis. (Approximately an additional 10%).
- If CFTR full sequence gene analysis is not conclusive and Cystic Fibrosis continues to be suspected then CFTR gene analysis for detection of deletion/duplication variant. (Approximately an additional 2%).

The *diagnostic* testing strategy for male infertility due to congenital bilateral absence of the vas deferens (CBAVD) is CFTR gene analysis with intron 8 poly-T analysis in addition to CFTR gene analysis for detection of common variant.

Note: Conclusive indicates confirmation or exclusion of the disease.

Treatment Testing Strategy

If treatment testing guidance is required (the doctor plans to treat with a prescription of either Orkambi (ivacaftor and lumacaftor) (12 years of age or older) or Kalydeco (ivacaftor) (2 years of age or older)) the treatment testing strategy is:

- If the mutation was determined with the CFTR full sequence gene analysis then no additional testing is required (the CFTR full sequence gene analysis will determine if Kalydeco or Orkambi is appropriate).
- If the mutation was determined with CFTR gene analysis for detection of common variants then CFTR gene analysis known familial variants x 6 may be required if it is to be treated with Kalydeco (CFTR gene analysis for detection of common variants would have determined the appropriateness of Orkambi and could have determined the appropriateness of Kalydeco).
- If the clinical diagnosis was determined with a biochemical test (sweat chloride) and with a clinical physical exam, then if testing for Orkambi, CFTR gene analysis known familial variants x 1 should be performed and if it is for Kalydeco then CFTR gene analysis known familial variants x 10 should be performed.

Note: Diagnosis does not always (100%) result in treatment.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend

formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

Genetic testing for Cystic Fibrosis is unlikely to impact therapeutic decision making in the clinical management of the patient and is considered **not medically necessary**.

Background

Cystic Fibrosis

CF is a life-limiting disease inherited in an autosomal recessive fashion. Mutations in the CFTR gene disrupt the function of the chloride channels, resulting in a loss of regulation of the flow of chloride ions and water across cell membranes. There is no cure for this disease in which the cells that line the passageways of the lungs, pancreas, and other organs produce mucus that is unusually thick and sticky causing airways and various ducts to become clogged. This buildup of abnormal mucus damages many of the body's organs including the pancreas, intestine, lungs, sweat glands, and it may impact male fertility. Progressive damage to the respiratory system may cause airway obstruction with life threatening infection, bronchiectasis and end stage lung disease. Chronic digestive system problems may include malabsorption and pancreatic insufficiency resulting from obstruction, including diabetes. Respiratory and digestive signs and symptoms are among the most common although severity is varied among affected individuals. There is interest in continued research to investigate the variance in severity of this condition which may be explained by environmental factors or additional genetic mutations unrelated to CFTR.

CF affects approximately 70,000 people worldwide including 30,000 children and young adults in the United States. CF is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. Carrier rates are one in 24 in the Ashkenazi Jewish population and one in 25 in the non-Hispanic white general population.

Screening and Treatment

Each year, about 1,000 babies are born with CF, with diagnosis occurring at a mean age of three to four years, and up to 10% of affected individuals with delayed diagnosis beyond the age of 18. In the United Sates, CF is identified in 3% of infants by prenatal diagnosis and 7% by newborn screening.

Without treatment CF will result in death for 95% of affected children before age five emphasizing the importance of accurate and early diagnosis. Symptomatic treatment includes close attention to diet and nutrition, physical therapy to manage secretions in the lungs, pancreatic enzymes and medications to combat infection. Currently, with vigilant management, nearly 80% of patients with CF will live to adulthood with approximately 50% surviving past age 37.

Carrier screening for CF will neither detect every possible mutation that could be present nor can it estimate the residual risk for the patient of developing CF despite negative testing.

For couples who have one child with CF or who are known to be carriers, prenatal diagnosis of CF is available.

In 2011, ACOG issued an update on carrier screening for CF and the Committee on Genetics concluded that it is important to continue offering CF screening to women of reproductive age, and, because it is difficult to assign a single ethnicity to individuals, it is reasonable to offer CF carrier screening to all patients (ACOG No. 486, 2011).

Current guidelines, revised by the ACMG in 2004 (Watson et al, 2004) and reaffirmed in 2013, use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice. Using the 23-mutation panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.

The ACMG and the American College of Obstetricians and Gynecologists (ACOG) both recommend carrier screening for Ashkenazi Jewish individuals for (ACOG No. 442, 2009) cystic fibrosis (1/2,500-3,000; 1/29).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Two CLIA-certified laboratories, Progenity™ (Ann Arbor, Michigan; formerly aMDx Laboratory Sciences and Ascendant MDx) and Sequenom® Laboratories (San Diego, CA), offer single disease carrier testing (CFnxt and HerediT® Cystic Fibrosis Carrier Screen, respectively), and disease panels for Ashkenazi Jewish patients (AJPnxt Basic [nine diseases] or AJPnxt Expanded [19 diseases] and HerediT™ Ashkenazi Jewish Panel Carrier Screen [17 diseases], respectively). Progenity™ also offers nxtPanel for simultaneous CF, SMA, and fragile X syndrome testing.

Related Protocols

Carrier Testing for Genetic Diseases

General Approach to Genetic Testing

Invasive Prenatal (Fetal) Diagnostic Testing

Preimplantation Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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3. ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. Obstet Gynecol. Apr 2011; 117(4):1028-1031. PMID 21422883
4. Ramsey BW, Davies J, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. The New England Journal of Medicine. November 3, 2011; 365:18. 1663-1672.
5. Budey MM, Mehta AC. Cystic Fibrosis. Cleveland Clinic. August 2010. http://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/basics/definition/CON-20013731
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7. Farrell PM, Rosenstein BJ, et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report. Journal of Pediatrics. August 2008; 153(2):S4-S14
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9. Wainwright CE, Elborn JS, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220-31.
10. Richards S, Nazneen A, et al. ACMG Standards and Guidelines. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet med March 2015.