CARRIER TESTING FOR GENETIC DISEASES

Policy Number: LABORATORY 021.2 T2

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INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

<table>
<thead>
<tr>
<th>Applicable Lines of Business/Products</th>
<th>This policy applies to Oxford Commercial plan membership.</th>
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<tbody>
<tr>
<td>Benefit Type</td>
<td>General Benefits Package</td>
</tr>
<tr>
<td>Referral Required</td>
<td>No</td>
</tr>
<tr>
<td>(Does not apply to non-gatekeeper products)</td>
<td></td>
</tr>
<tr>
<td>Authorization Required</td>
<td>Yes¹</td>
</tr>
<tr>
<td>(Precertification always required for inpatient admission)</td>
<td></td>
</tr>
<tr>
<td>Precertification with Medical Director Review Required</td>
<td>Yes¹</td>
</tr>
<tr>
<td>Applicable Site(s) of Service</td>
<td>Laboratory</td>
</tr>
<tr>
<td>(If site of service is not listed, Medical Director review is required)</td>
<td></td>
</tr>
<tr>
<td>Special Considerations</td>
<td>¹Precertification with review by a Medical Director or their designee is required.</td>
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</table>

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Related Policies

- Chemosensitivity and Chemoresistance Assays in Cancer
- Fetal Aneuploidy Testing Using Cell-Free Fetal Nucleic Acids in Maternal Blood
Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person. For information regarding noninvasive prenatal screening (NIPT) for fetal aneuploidy, refer to the medical policy titled Fetal Aneuploidy Testing Using Cell-Free Fetal Nucleic Acids in Maternal Blood.

Ashkenazi Jewish Carrier Screening

Ashkenazi Jewish carrier screening is proven and medically necessary for evaluating the following:

- Individuals who are seeking prenatal care or planning a pregnancy who have had not previously had informative Ashkenazi Jewish carrier screening; and
- At least one of the following additional criteria is met:
  - At least one reproductive partner is Ashkenazi Jewish (this individual has at least one Ashkenazi Jewish grandparent); or
  - The reproductive partners have a previously affected child with one of the genetic diseases included in the Ashkenazi Jewish carrier screening test and the results of this test will inform a current or future pregnancy; or
  - One or both individuals have a first- or second-degree relative who is affected and the results of this test will inform a current or future pregnancy; or
  - One or both individuals have a first-degree relative with an affected offspring and the results of this test will inform a current or future pregnancy; or
  - One of the reproductive partners is already known to be a carrier for one of the genetic disease included in the Ashkenazi Jewish carrier screening test and the results of this test will inform a current or future pregnancy.

Carrier testing for any additional genetic diseases as part of Ashkenazi Jewish carrier screening is considered unproven and not medically necessary.

Ashkenazi Jewish carrier screening is considered unproven and not medically necessary for all other indications.

Expanded Carrier Screening Panel Testing

Expanded Carrier Screening Panel Testing is considered unproven and not medically necessary for all indications.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

<table>
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<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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Carrier screening is performed to detect genetic mutations that may increase the risk of a genetic disorder. This testing may impact the reproductive decision-making for parents or prospective parents.

Carrier screening may be available for autosomal recessive conditions, autosomal dominant less penetrant conditions, X-linked conditions, and certain chromosome abnormalities. In general, carrier screening may be performed for conditions that are found in the general population (pan-ethnic), for diseases that are more common in a particular population, or based on family history. For individuals of Ashkenazi Jewish descent (Gross et al., 2008), certain autosomal recessive conditions are more prevalent and many of these disorders are lethal in childhood or associated with significant morbidity.

Diagnostic genetic testing of a heritable disease may also be performed using similar methods as carrier screening. It may be medically necessary to use genetic testing to establish a molecular diagnosis when an individual has clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic) and the result of the test will directly impact the treatment being delivered.

**Ashkenazi Jewish Carrier Screening**

Carrier screening for individuals of Ashkenazi Jewish descent is focused on identifying reproductive partners who are at risk to have a child with a disorder that has a higher prevalence in this population. For individuals of Ashkenazi Jewish descent, certain autosomal recessive conditions are more prevalent and many of these disorders are lethal in childhood or associated with significant morbidity. The disorders generally screened in this population are Tay-Sachs, Canavan, Cystic fibrosis, Familial Dysautonomia, Fanconi Anemia, Niemann-Pick type A, Bloom syndrome, Mucolipidosis IV, and Gaucher disease. Since carrier screening includes only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a carrier. If an individual has no mutations detected on a carrier screening test, the individual still has some remaining risk of being a carrier. (Gross et al., 2008; ACMG, 2017; ACOG, 2017)

Ashkenazi Jewish carrier screening should include testing for the genetic diseases recommended by American College of Obstetricians and Gynecologists (ACOG) and/or the American College of Medical Genetics (ACMG):

- Tay Sachs disease
- Canavan disease
- Cystic fibrosis
- Familial dysautonomia
- Bloom syndrome
- Fanconi anemia
- Niemann-Pick disease
- Gaucher disease
- Mucolipidosis IV

**Expanded Carrier Screening Panels**

For carrier screening, new technologies, such as next generation sequencing technology or chromosomal microarray, have created the ability to screen for genetic mutations using genetic panels instead of single genes. These expanded genetic panels are able to analyze many genes simultaneously; however, there is a lack of evidence to establish the clinical utility of gene test panels that include genes that are not associated with a specific inherited disorder. Furthermore, there is a lack of standardization in the genetic panel composition, thus panels for the similar conditions, may evaluate different set of genes. Currently, there are no existing professional guidelines to support the ordering and evaluation of carrier screening by expanded panels. (Grody et al., 2013)

Additionally, for every disorder, the gene/mutation/mutation frequency should be known in the population being tested so that negative test results can be translated into an expected residual risk of the disorder (Grody et al., 2013). Unfortunately, many laboratories are unable to calculate the residual risk as they lack the knowledge of the carrier frequency within the testing population and the proportion of disease-causing mutations on the assay platform.
CLINICAL EVIDENCE

Ashkenazi Jewish Carrier Screening
The American College of Medical Genetics and Genomics (ACMG) 2017, and the American College of Obstetricians and Gynecologists (ACOG) 2017, both recommend carrier screening for Ashkenazi Jewish individuals for:
- Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30), and
- Canavan disease (1/6,400; 1/40), and
- Cystic fibrosis (1/2,500-3,000; 1/29) and
- Familial Dysautonomia (1/3,600; 1/32).

In addition, the ACMG recommends that the following also be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy:
- Fanconi Anemia (group C) (1/32,000; 1/89), and
- Niemann-Pick (type A) (1/32,000; 1/90), and
- Bloom syndrome (1/40,000; 1/100), and
- Mucolipidosis IV (1/62,500; 1/127), and
- Gaucher disease (1/900; 1/15).

If only 1 member of the couple is Jewish, ideally, that individual should be tested first. One Jewish grandparent is sufficient to offer testing. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be tested for variants associated with that particular disorder. (ACMG 2017)

Expanded Carrier Screening
An ACMG position statement states that although some commercial laboratories offer expanded carrier screening panels, there is little consensus on which disease genes and mutations to include in these panels. (Grody et al., 2013; Edwards et al., 2015) Panels for that include multiple carrier screening tests may be useful if they include the diseases that are present with increased frequency in a specific population (i.e., Ashkenazi Jewish Carrier Screening), but do not have clinical utility when they include a larger number of genetic diseases for which the individual does not have an increased risk of being a carrier.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm.

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2017T0586A]


**POLICY HISTORY/REVISION INFORMATION**

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<tr>
<th>Date</th>
<th>Action/Description</th>
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<tr>
<td>05/01/2018</td>
<td>• Updated list of applicable CPT codes; removed 81161</td>
</tr>
<tr>
<td></td>
<td>• Archived previous policy version LABORATORY 021.1 T2</td>
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