Genetic Testing for Lactase Insufficiency

Description of Procedure or Service

Genetic testing of adults with suspected lactase insufficiency is proposed as an alternative to current diagnostic practices, which include hydrogen breath test (HBT), lactose tolerance blood test (LTT), and intestinal biopsy.

The predominant carbohydrate in milk is the disaccharide lactose, consisting of simple sugars, glucose and galactose. The brush-border enzyme, lactase (also called lactase-phlorizin hydrolase), hydrolyzes lactose into its monosaccharide components that are absorbable by the intestinal mucosa. Except in rare instances of congenital hypolactasia, most infants are able to produce lactase with enzyme levels highest at birth. Sometime after weaning in the majority of children, there is a decrease in lactase production through a multifactorial process that is regulated at the gene transcription level.

The decrease in lactase level varies significantly by ethnic group both in terms of the lowest level of lactase and time from weaning necessary to reach the nadir of lactase activity. By 2 to 12 years of age, two groups emerge: a group with insufficient levels of lactase activity (primary hypolactasia or lactase non-persistence) and a group that retains the infant level of lactase activity through adulthood (lactase-persistence). The ethnic groups with the highest rates of lactase insufficiency are Asian, Native American and Blacks with the lowest rates in people of northern European origin.

Problems with the absorption of lactose can be described in several terms:

- Lactase insufficiency (lactase non-persistence or primary hypolactasia) – indicates that lactase activity is a fraction of the original infantile level. Direct measurement of lactase activity is tested biochemically through duodenal biopsy.
- Lactose malabsorption – indicates that a large portion of lactose is not able to be absorbed in the small bowel and is delivered to the colon. Malabsorption is tested by HBT or LTT.
- Lactose intolerance – indicates that lactose malabsorption causes gastrointestinal symptoms. There is no genetic test for lactose intolerance and demonstration of lactose intolerance requires patients to self-report symptoms after lactose ingestion.

In 2002, Enattah and colleagues identified the first DNA variant to control transcription of lactase. This variant, MCM6-13910 C>T, is located in a non-coding region of the MCM6 gene which is upstream of the lactase gene (LCT). The less common T allele has been associated with lactase persistence and has demonstrated an autosomal dominant pattern of inheritance. This variant is thought to be related to the domestication of animals during the last 10,000-12,000 years, and persons with the C/C genotype have been shown to be strongly associated with lactase insufficiency phenotype in Caucasians. Other variants have been identified in the same MCM6 regulatory region which are associated with other ethnic groups (such as Africans and Arabs), but...
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prevalence of these vary geographically and to date, no commercially available testing kits have incorporated these variants.

Prometheus’s LactoTYPE® is a commercially available polymerase chain reaction-based test that assesses the most common lactase nonpersistence variant, MCM6-13910 C>T, in patients with suspected lactose intolerance. Fulgent Clinical Diagnostics Lab also offers MCM6 sequencing and deletion/duplication analysis using next-generation sequencing. Demonstration of the C/C genotype can be used as indirect evidence of lactase insufficiency and lactose malabsorption.

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

Policy
Genetic testing for lactase insufficiency is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

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

When Genetic Testing for Lactase Insufficiency is covered
Not Applicable

When Genetic Testing for Lactase Insufficiency is not covered
The use of targeted MCM6-13910 C>T variant analysis (genetic testing) for the prediction of lactase insufficiency is considered investigational.

Policy Guidelines
For individual with suspected lactase insufficiency who receive targeted testing for the MCM6-13910C>T variant, the evidence includes genotype-phenotype studies and meta-analysis. Relevant outcomes are symptoms, morbid events, functional outcomes, health status measures and quality of life. Studies have demonstrated a high correlation between the -13910C>T single-nucleotide variant upstream of the gene encoding the enzyme lactase, and lactase insufficiency in persons of European ancestry. Studies in white populations have reported a high degree of agreement for the diagnosis of lactase insufficiency between genotyping and both hydrogen breath test and lactose tolerance blood test. However, there is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms. Therefore, an empirical diagnosis of lactose intolerance in the absence of confirmation by HBT, LTT, or genotyping, followed by treatment with dietary restriction of lactose, is suitable. Currently the evidence does not support conclusion that assessment of the genetic etiology of lactose intolerance would affect patient management or improve clinical outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

*Applicable service codes: 81400*

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

**Scientific Background and Reference Sources**


Medical Director review 1/2014


Specialty Matched Consultant Advisory Panel review 8/2014

Medical Director review 8/2014


Specialty Matched Consultant Advisory Panel review 8/2015

Medical Director review 8/2015


Medical Director review 7/2016

Specialty Matched Consultant Advisory Panel review 7/2017

Medical Director review 7/2017


Medical Director review 9/2017


Medical Director review 5/2018

Specialty Matched Consultant Advisory Panel review 7/2018

Medical Director review 7/2018
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Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
<th>Review Details</th>
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<tbody>
<tr>
<td>1/28/14</td>
<td>New policy developed. The use of targeted mutation analysis (genetic testing) of -13910 C&gt;T for the prediction of lactase insufficiency is considered investigational. Medical Director review 1/2014. (mco)</td>
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<tr>
<td>7/29/14</td>
<td>Description section updated. References updated. No changes to Policy Statements. (mco)</td>
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<tr>
<td>5/26/15</td>
<td>References updated. Policy Statement remains unchanged. (td)</td>
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<tr>
<td>10/1/15</td>
<td>Specialty Matched Consultant Advisory Panel review 8/26/2015. Medical Director review</td>
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<tr>
<td>8/2015</td>
<td>References updated. Policy intent remains unchanged. (td)</td>
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<tr>
<td>10/13/17</td>
<td>Minor revision to Description section and extensive update to Policy Guidelines. Genetic nomenclature updated throughout policy; no change to policy intent. References updated. Medical Director review. (jd)</td>
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<td>6/8/18</td>
<td>Minor revision to “When Not Covered” section; added the following terminology “MCM6” with no change to policy intent. Policy guidelines and references updated. Medical Director review. (jd)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.