Medical Policy

Genetic Testing for Lactase Insufficiency

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Policy Number: 565
BCBSA Reference Number: 2.04.94
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency is INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Commercial Managed Care (HMO and POS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This is not a covered service.</td>
</tr>
</tbody>
</table>


Commercial PPO and Indemnity

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

### CPT Codes

<table>
<thead>
<tr>
<th>CPT code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis) includes the following test effective 7/1/13: LCT (lactase-phlorizin hydrolase) (e.g., lactose intolerance), 13910 C&gt;T variant</td>
</tr>
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</table>

**Description**

Genetic testing of adults with suspected lactase insufficiency is proposed as an alternative to current diagnostic practices. Studies have demonstrated a tight correlation between a single nucleotide polymorphism (SNP) -13910 C>T upstream of the gene coding for the enzyme lactase and lactase insufficiency in persons of European ancestry. Currently, two indirect tests of lactose digestion, the hydrogen breath test (HBT) and lactose tolerance blood test (LTT), are the most preferred diagnostic tests for confirmation of lactase insufficiency.

**Background**

The predominant carbohydrate in milk is the disaccharide lactose consisting of the simple sugars glucose and galactose. The brush-border enzyme lactase hydrolyzes lactose into its monosaccharide components that are absorbable by the intestinal mucosa. Except for 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. (1)

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. (2) 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). (3) 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. (Table 1)

**Table 1. Prevalence of Lactase Insufficiency by Country or Ethnicity**

<table>
<thead>
<tr>
<th>Population</th>
<th>Lactase Insufficiency*%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europeans</td>
<td>2 to 15%</td>
</tr>
<tr>
<td>American Whites</td>
<td>6 to 22%</td>
</tr>
<tr>
<td>Central Europeans</td>
<td>9 to 23%</td>
</tr>
<tr>
<td>Northern Indians</td>
<td>20 to 30%</td>
</tr>
<tr>
<td>Southern Indians</td>
<td>60 to 70%</td>
</tr>
</tbody>
</table>
Hispanics 50 to 80%
Ashkenazi Jews 60 to 80%
Blacks 60 to 80%
American Indians 80 to 100%
Asians 95 to 100%
*Identified through HBT or LTT

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. (5) Lactase insufficiency is highly correlated with the C/C genotype at -13910 in the lactase promoter region. In adults with a homozygous lactase persistence genotype (T/T) lactase levels are approximately 10-times higher than for the lactase insufficient genotype (C/C) with heterozygous individuals (C/T) showing intermediate levels. (6) These heterozygous individuals may experience symptoms of lactose intolerance when ingesting quantities of lactose greater than their intermediate level of lactase can digest.

**Lactose malabsorption** – indicates that a sizable fraction 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. (5)

**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 (Table 2). Diagnosis of lactose intolerance is highly susceptible to the placebo effect and studies should appropriately conduct a blinded lactose challenge with an indistinguishable placebo. (3) A meta-analysis by Jellema and colleagues indicated that no specific patient complaint could predict lactose malabsorption with sensitivity and specificity ranging from 0-90% and 18-96% for the most common lactose intolerance symptoms. (7) Similarly, patient self-reported milk tolerance was also not found to be accurate in predicting lactose malabsorption with sensitivity and specificity ranging from 30-70% and 25-87% respectively. (7)

**Table 2. Symptoms of Lactose Intolerance** (2)

<table>
<thead>
<tr>
<th>Gut-related symptoms</th>
<th>% of total patients who experience symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>100</td>
</tr>
<tr>
<td>Gut distention</td>
<td>100</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>100</td>
</tr>
<tr>
<td>Flatulence</td>
<td>100</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
</tr>
<tr>
<td>Nausea</td>
<td>78</td>
</tr>
<tr>
<td>Vomiting</td>
<td>78</td>
</tr>
</tbody>
</table>

**Systemic symptoms**

<table>
<thead>
<tr>
<th></th>
<th>% of total patients who experience symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache and light headedness</td>
<td>86</td>
</tr>
<tr>
<td>Loss of concentration and poor short-term memory</td>
<td>82</td>
</tr>
<tr>
<td>Long-term severe tiredness</td>
<td>63</td>
</tr>
</tbody>
</table>
Lactase insufficiency is a common condition which occurs in approximately (70%) of persons after weaning. (8) An insufficiency of lactase results in the malabsorption of lactose, which may lead to symptoms of lactose intolerance such as abdominal pain, bloating, diarrhea and increased flatulence, caused by bacterial fermentation of undigested lactose in the colon. (9) However, the demonstration of lactose malabsorption does not necessarily indicate that an individual will be symptomatic. Many variables determine if a person who malabsorbs lactose develops symptoms, including: the dose of lactose ingested, residual intestinal lactase activity, ingestion of food along with lactose, the ability of the colonic flora to ferment lactose and the individual sensitivity to the products of lactose fermentation. Because of these factors, the number of persons reporting symptoms of lactose intolerance is likely only a fraction of those who are lactase insufficient. In addition, lactose malabsorption may be secondary (secondary hypolactasia) to an acquired condition such as: small bowel bacterial overgrowth, infectious enteritis, mucosal damage from celiac disease, inflammatory bowel disease, antibiotics, gastrointestinal surgery, short bowel syndrome, radiation enteritis or other conditions which may lead to reduction of lactase expression in the small intestine. (6)

**Clinical Diagnosis of Lactase Insufficiency**

Mucosal biopsy of the duodenum followed by biochemical lactase assay to directly measure lactase activity is the reference standard for diagnosis of lactase insufficiency. This approach may also exclude other causes of secondary lactose malabsorption through endoscopy. However, this approach is limited in utility due to the invasiveness of the procedure and the patchy expression of lactase in the duodenum.

Two common alternatives to this direct method of measuring lactase level are the hydrogen breath test (HBT) and lactose tolerance blood test (LTT) which measure lactose malabsorption. Because lactose malabsorption is nearly always attributable to lactase insufficiency, this can typically be imputed from measurements of lactose malabsorption. (3)

The HBT measures the amount of hydrogen exhaled by gas chromatography for up to 3 hours after ingesting 25-50 g of lactose. Persons undergoing HBT are required to fast overnight and refrain from activities that may elevate breath hydrogen during testing. A rise in breath hydrogen of 0.31–2.5 mL/min is indicative of bacterial fermentation from the malabsorbed lactose. A negative HBT can exclude lactose malabsorption as the cause of symptoms, and a positive result indicates that the symptoms may be attributable to ingestion of lactose. (3) The following factors are associated with a rise in breath hydrogen and may cause false-positive results if present at time of testing:

- Diabetes
- Small bowel disease (e.g., celiac, giardiasis)
- Bacterial overgrowth
- Altered colon pH
- Antibiotic usage
- Probiotic usage
- Smoking
- Exercise
- Aspirin usage
- Colonic bacterial adaptation
The LTT measures blood glucose increase over time with blood drawn at 15, 30, 60, and 90 minutes after ingesting a 25-50 g dose of lactose. A glucose increase of less than 20 mg/dL above an 8-hour fasting level indicates an abnormal test. The following factors are associated with a rise in blood sugar when undergoing a lactose tolerance test and may cause false-positive results:

- Diabetes
- Small-bowel disease (e.g., celiac, giardiasis)
- Thyroid disorders
- Motility disorders (stomach, small bowel)
- Bacterial overgrowth

Molecular Diagnosis of Lactase Insufficiency
Enattah and colleagues identified the first DNA variant to control transcription of lactase in 2002. (10) This polymorphism, -13910 C>T, is located in a noncoding region of the MCM6 gene that 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 polymorphism 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 polymorphisms have been identified in the same MCM6 regulatory region which are associated with additional ethnic groups (such as Africans and Arabs), but these have not been as commonly observed and to date no commercially available testing kits have incorporated these polymorphisms. (6)

Prometheus's LactoType® is a commercially available PCR-based test that assesses the most common lactase non-persistence variant, -13910 C>T, in patients with suspected lactose intolerance. Demonstration of the C/C genotype can be used as indirect evidence of lactase insufficiency and lactose malabsorption.

Treatment of Lactase Insufficiency
The goal of treatment should be to ensure adequate nutrients important for skeletal health. (1) Dietary adjustment to restrict the consumption of foods containing lactose is the principal form of therapy for patients with lactase insufficiency. However, even lactose maldigesters can usually tolerate small amounts of lactose (12 g/day) with no or minimal symptoms. Lactase enzyme preparations are available for symptom relief but may not be effective in all patients.

Summary
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. Studies have demonstrated a tight correlation between a single nucleotide polymorphism (SNP) -13910 C>T upstream of the gene coding for the enzyme lactase and lactase insufficiency in persons of European ancestry, and studies in Caucasian populations report a high degree of agreement for the diagnosis of lactase insufficiency between genotyping and both the HBT and LTT.

Genetic testing has the potential advantage of sparing patients the discomfort of fasting and experiencing symptoms of lactose intolerance during the administration of HBT or LTT. Genotyping may also have additional utility in the diagnosis of secondary hypolactasia.

However, because there is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms alone, an empiric diagnosis of lactose intolerance in the absence of confirmation with HBT, LTT or genotyping followed by treatment with dietary restriction of lactose is suitable. There is currently insufficient evidence that the assessment of the genetic etiology of lactose intolerance would affect patient management or improve clinical outcomes, and therefore the use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency is considered investigational.
Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
</tr>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References

37. Enko D, Rezanka E, Stolba R, Halwachs-Baumann G. Lactose malabsorption testing in daily clinical practice: a critical retrospective analysis and comparison of the hydrogen/methane breath test and