Medical Policy
Genetic Testing for Lactase Insufficiency

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Policy Number: 565
BCBSA Reference Number: 2.04.94

Related Policies
- None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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

Prior Authorization Information
Commercial Members: Managed Care (HMO and POS)
This is NOT a covered service.

Commercial Members: PPO, and Indemnity
This is NOT a covered service.

Medicare Members: HMO Blue℠
This is NOT a covered service.

Medicare Members: PPO Blue℠
This is NOT a covered service.
CPT Codes / HCPCS Codes / ICD-9 Codes

The following codes are included below for informational purposes. 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 codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, 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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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 (4)

<table>
<thead>
<tr>
<th>Population</th>
<th>Lactase Insufficiency*%</th>
</tr>
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<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>
<tr>
<td>Hispanics</td>
<td>50 to 80%</td>
</tr>
</tbody>
</table>
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>
<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>
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<table>
<thead>
<tr>
<th>Systemic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache and light headedness</td>
</tr>
<tr>
<td>Loss of concentration and poor short-term memory</td>
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</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 \textit{MCM6} gene that is upstream of the lactase gene (\textit{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 \textit{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

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<th>Date</th>
<th>Action</th>
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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


