Medical Policy

Genetic Testing for Statin-Induced Myopathy

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Policy Number: 575
BCBSA Reference Number: 2.04.96
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy

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

Genetic testing for the presence of variants in the SLCO1B1 gene for the purpose of identifying patients at risk of statin-induced myopathy is considered NOT MEDICALLY NECESSARY.

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>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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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>
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<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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)</td>
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Description
Statin drugs, which are widely used, can cause muscle-related side effects. Serious myopathy, i.e., myositis or rhabdomyolysis, can also occur and may be associated with genetic factors such as variants in the SLC01B1 gene. Commercially available tests for the presence of SLC01B1 variants are currently marketed for use in predicting the risk of myopathy for patients taking statins.

Background
Statin drugs are the primary pharmacologic treatment for hypercholesterolemia throughout the world. In the United States, there are an estimated 38 million individuals taking statins as of 2008. Use of statins is associated with an approximately 30% reduction in cardiovascular events across a wide variety of populations.

Statin-induced myopathy
Statins are associated with a known risk of muscle-related symptoms, and these are the most common side-effects of statin drugs. Myopathy is a general term for muscle toxicity. The following three categories of statin-induced myopathy have been recommended by an ACC/AHA/NHLBI advisory committee:

- Statin-induced myalgia, defined as any muscle symptoms that occur without an elevation of serum creatinine kinase (CK);
- Statin-induced myositis, defined as muscle symptoms with an elevation of serum CK; and
- Statin-induced rhabdomyolysis, defined as markedly severe muscle symptoms with an elevation of CK greater than 10 times normal with an elevation in serum creatinine.

Statin-induced myalgia is the most common manifestation of myopathy and is characterized by muscle pain, cramps, fatigue, and/or weakness. Myalgias without other clinical manifestations are not associated with clinically important adverse events and resolve when the statin is discontinued.

The incidence of myalgia varies widely in the published literature. In clinical trials, these symptoms have been reported in 1.5-3.0% of patients, and in most trials, the rate of myalgias in patients on statin therapy is not increased compared to placebo treatment. In observational studies, higher rates of 10-15% have been reported.

Myositis is much less common that myalgias, with an estimated rate of 5 per 100,000 patient-years, and an estimated per-person incidence of 0.01%. In virtually all cases, myositis resolves with discontinuation of the statin. Rhabdomyolysis is the most severe clinical manifestation of statin-induced myopathy and can be life-threatening. The National Lipid Association Statin Safety Assessment Task Force estimated that rhabdomyolysis occurs at a rate of 1.6 per 100,000 patient years, and the U.S. Food and Drug Administration (FDA) adverse events reporting system has estimated a rate of 0.7 per 100,000 patient-
years. As a systematic review published in 2006 combined results from 20 clinical trials, and estimated the rate of rhabdomyolysis to be 1.6 cases per 100,000 patient-years. Fatalities from statin-induced rhabdomyolysis can occur, but the mortality rate is not well-defined. The FDA estimated that deaths for rhabdomyolysis occur at a rate of less than 1 death per million prescriptions.

There are a number of clinical factors that are associated with an increased risk of statin myopathy. Statin dose is probably the strongest risk factor, with an estimated 6-fold increase for patients on high-dose statins. Age is also a strong risk factor. One study reported that patients older than 65 years of age required hospitalization for statin-induced myositis at a rate that was 4 times higher than for younger patients. Some statins may be associated with higher risk than others, and concomitant administration of certain drugs such as gemfibrozil and amiodarone is associated with higher rates of statin myopathy in clinical trials. Other factors that may be associated with myopathy include female gender and intense physical exercise.

The perceived risk of statin-induced myopathy may be a contributing reason for suboptimal statin use in patients with indications. Less than 50% of patients in the U.S. who would benefit from statins are currently taking them, and a substantial part of this is the result of non-adherence to prescribed statins.

Genetic factors associated with statin-induced myopathy
There are a variety of genetic factors associated with statin myopathy. The cytochrome p450 system in the liver is the main pathway by which statins are metabolized. Numerous genetic variants in cytochrome p450 proteins affect the pharmacokinetics of statin metabolism and serum statin levels. Other genetic variants that affect statin metabolism, efficacy, and susceptibility to adverse effects involve variations in the apolipoproteins such as apo E, variations in the cholesterol ester transfer proteins (CETP), or variations in the coenzyme Q pathway.

Variations in the SLCO1B1 gene also affect statin metabolism and are among the most well-studied genetic variants. These are also the genetic markers for which there are commercially available tests. This gene codes for a transporter protein that is part of the solute carrier organic ion transporter (SLCO) system, which mediates the influx and metabolism of statins in the liver. Single nucleotide polymorphisms (SNPs) in this gene are associated with variations in the risk of statin-induced myopathy. The T/T allele is the wild-type and associated with the lowest risk of myopathy. The C/C allele is associated with a higher risk of myopathy, and the T/C allele with an intermediate risk. The T allele has a prevalence of approximately 0.87, and the C allele has a prevalence of approximately 0.13.

There are at least two commercial labs that offer genetic testing for SLCO1B1 variants. Boston Heart Diagnostics™ markets a test for the statin-induced myopathy (SLCO1B1) genotype. This test uses real-time polymerase chain reaction (PCR) to identify patients with the T/T, T/C, or C/C genotype.

Berkeley Heart Lab™ offers a similar genetic test for SLCO1B1 variants. Details of how this test is performed are not provided on the company website.

Available online at: http://www.bhlinc.com/clinicians/test-descriptions/SLCO1B1-Genotype-Test

Summary
Statin muscle symptoms are the most common side effect of statins, and serious myopathy or rhabdomyolysis occurs in a very small number of patients treated with statins. An association between genetic variants of the SLCO1B1 gene and statin myopathy has been reported. This association has been found in genome-wide association studies that indicate a several-fold risk of statin myopathy associated with genetic variants. Evidence from case-control studies and clinical trials also show a possible association, but the quantity of evidence is small and the association has not been demonstrated to be strong. Statins are associated with a definite decreased risk of cardiovascular events such as myocardial infarction (MI), and this benefit of reduced cardiovascular events is likely to far outweigh the risk of myopathy, even in patients with the highest risk of myopathy, i.e., two abnormal SLCO1B1 alleles.
Therefore, there is a possibility of harm if the results of genetic testing for statin-induced myopathy are used as part of the decision-making process for prescribing statins. As a result, genetic testing for statin-induced myopathy is considered not medically necessary.

**Policy History**

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<td>12/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2015</td>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</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**