Genetic Testing for Statin-induced Myopathy

Statin drugs are widely used and 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 SLCO1B1 gene. Commercially available tests for the presence of SLCO1B1 variants are currently marketed for use in predicting the risk of myopathy for patients taking statins.

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 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 defined 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 than 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 estimated that rhabdomyolysis occurs at a rate of 1.6 per 100,000 patient-years, and the FDA adverse events reporting system has estimated a rate of 0.7 per 100,000 patient-years. A systematic review
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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 six-fold increase for patients on high dose statins. Age is also a strong risk factor. One study reported that patients over 65 years of age required hospitalization for statin-induced myositis at a rate that was four 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.

The perceived risk of statin-induced myopathy may contribute to suboptimal statin use in patients with indications. Less than 50% of patients in the US 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 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.

While SLCO1B1 variants have been the most studied in statin metabolism, other genes have also been studied, including ABCB1, which encodes ATP-binding cassette (ABC) transporters subfamily B member 1 (ABCB1/P-glycoprotein 1), ABCG2, which encodes ABC transporters subfamily G member 2 (ABCG2/breast cancer resistance protein), and the coenzyme Q2 (COQ2) homolog gene. Other studies have evaluated the association between polymorphisms in the GATM gene, which encodes a glycine amidinotransferase that is the rate-limited enzyme in creatine biosynthesis, and statin-induced myopathy, although this association was not been consistently replicated.

Commercially Available SLCO1B Molecular Diagnostic Tests

Several commercial and academic labs 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.

Arup Laboratories markets a test for SLCO1B1 genetic variants that uses real-time PCR with high resolution melting analysis to identify the rs4149056C variant in the SLCO1B1 gene.
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Some labs offer panels test for drug metabolism, which may use Sanger sequencing or next-generation sequencing that include the SLCO1B1 gene. For example, ApolloGen (Irvine, CA) markets a pharmacogenomics panel, the iGene Pharmacogenomics Panel, which includes sequencing of the SLCO1B1 gene.

***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 statin-induced myopathy is considered not medically necessary. BCBSNC does not provide coverage for not medically necessary 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 Statin-induced Myopathy is covered

Not Applicable

When Genetic Testing for Statin-induced Myopathy is not covered

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. BCBSNC does not provide coverage for not medically necessary services or procedures.

Policy Guidelines

The evidence for genetic testing for SLCO1B1 variants for individuals taking statin drugs, includes secondary analyses of randomized controlled trials (RCTs) and prospective observational studies. Relevant outcomes are test accuracy and validity, morbid events, and hospitalizations. No published information was found on the analytic validity of the marketed tests for detecting genetic variants associated with statin-induced myopathy. The available evidence from genome-wide association studies has suggested that SLCO1B1 polymorphisms are associated with risk of statin-induced myopathy. Observational studies and RCTs have been mixed in demonstrating an association between SLCO1B1 polymorphisms and statin-associated myopathy. No studies identified reported direct evidence on the clinical utility of genetic testing for statin myopathy.

Statins are associated with a definite decreased risk of cardiovascular events such as 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. The evidence in 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 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.
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*Applicable service codes: 81328, 81400, 81479.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support 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 8/2014

Specialty Matched Consultant Advisory Panel review 8/2014


Specialty Matched Consultant Advisory Panel review 8/2015

Medical Director review 8/2015


Medical Director review 7/2016
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Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017


Policy Implementation/Update Information

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<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>8/13/13</td>
<td>New policy developed. 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. Medical Director review 7/2013. (mco)</td>
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<tr>
<td>12/30/16</td>
<td>Minor revisions to description section. No change to policy statement/intent. (jd)</td>
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<tr>
<td>12/29/17</td>
<td>Code update; adding 81328 effective 1/1/18. (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.