Genetic Testing for Statin Induced Myopathy

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Services Are Considered Not Medically Necessary
Based on review of the available data, the use of 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 to be not medically necessary.**

Background/Overview
HMG-CoA reductase inhibitors, or statin drugs, are the primary pharmacologic treatment for hypercholesterolemia worldwide. In the United States, an estimated 38 million people took statins in 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, which are the most common adverse effects of statin drugs. Myopathy is a general term for muscle toxicity. Three categories of statin-induced myopathy have been defined by a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute:

• 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; it 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 clinical trials, these have been reported in 1.5% to 3.0% of patients; in most trials, the rate of myalgias in patients on statin therapy is not increased compared with placebo treatment. In observational studies, higher rates of 10% to 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 U.S. Food and Drug Administration (FDA) adverse events reporting system has estimated a rate of 0.7 per 100,000 patient-years. A 2006 systematic review 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. FDA estimated that deaths from rhabdomyolysis occur at a rate of less than 1 death per million prescriptions.

A number of clinical factors 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 (eg, gemfibrozil, amiodarone) have been associated with higher rates of statin myopathy in clinical trials. Other factors that may be associated with myopathy include female sex and intense physical exercise.

The perceived risk of statin-induced myopathy may contribute to suboptimal statin use in patients with indications. Less than 50% of patients in the United States who would benefit from statins are currently taking them, a substantial percentage of whom do not adhere to prescribed statin regimens.

GENETIC FACTORS ASSOCIATED WITH STATIN-INDUCED MYOPATHY

A variety of genetic factors are 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, or variations in the coenzyme Q pathway.

Variations in the \textit{SLCO1B1} gene also affect statin metabolism and are among the most well studied genetic variants. These variants are 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 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 the highest 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.

Other genes have also been studied, including \textit{ABCB1}, which encodes ATP-binding cassette (ABC) transporters subfamily B member 1 (ABCB1/P-glycoprotein 1), \textit{ABCG2}, which encodes ABC transporters subfamily G member 2 (ABCG2/breast cancer resistance protein), and the coenzyme Q2 (\textit{COQ2}) homolog gene. Other studies have evaluated the association between polymorphisms in the \textit{GATM} gene, which encodes a glycine amidinotransferase that is the rate-limited enzyme in creatine biosynthesis, and statin-induced myopathy, although this association has not been consistently replicated.
Commercially Available SLCO1B Molecular Diagnostic Tests

Several commercial and academic labs offer genetic testing for statin-induced myopathy (SLCO1B1) variants. For example, Boston Heart Diagnostics™ markets a test for the (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.

Some labs offer panel tests 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, that sequences the SLCO1B1 gene.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Boston Heart Statin Induced Myopathy (SLCO1B1) Genotype test and ARUP Laboratories Statin Sensitivity SLCO1B1 are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Select published articles have reported on the analytic validity, clinical validity, and clinical utility of genetic testing for statin-induced myopathy.

ANALYTIC VALIDITY

At least 2 labs (Boston Heart Diagnostics, ARUP Laboratories) perform the statin-induced myopathy test using real-time PCR. This technique permits detection and amplification of deoxyribonucleic acid (DNA) fragments simultaneously. While an accepted method of genetic analysis with generally high accuracy, no published information was found on the accuracy of this technique for detecting genetic variants associated with statin-induced myopathy. ARUP Laboratories has reported that the test's analytic sensitivity and specificity are greater than 99% for identification of the presence of 1 or 2 copies of SLCO1B1*5.

CLINICAL VALIDITY

We found no studies that reported the sensitivity or specificity of genetic testing for statin-induced myopathy in populations with suspected statin-induced myopathy. Studies identified have reported the degree of risk for myopathy associated with the SLCO1B1 genetic variants. They include genome-wide association
studies (GWAS), case-control studies, cohort analyses, and clinical trials. Representative types of each study are discussed next.

**Randomized Controlled Trials**

GWAS have reported that \textit{SLCO1B1} variants are associated with statin-induced myopathy. The SEARCH study group published a GWAS in 2008 based on data from a randomized controlled trial (RCT) of 12,064 patients with a prior myocardial infarction (MI) assigned to simvastatin 80 mg or simvastatin 20 mg. Of the 6031 patients in the 80-mg statin group, 48 (0.8%) had elevated serum CK level more than 10 times normal, and an additional 48 (0.8%) patients had a CK level that was more than 3 times normal and more than 5 times the baseline level. These subjects were matched with 96 control subjects without CK elevation, matched for sex, age, renal function, and ancillary medication use. Adequate DNA samples were available for 85 patients with myopathy and 90 controls, and these patients formed the study group for derivation of the genome associations.

The \textit{SLCO1B1} locus was the single-nucleotide polymorphism that had a strong association with myopathy, at a corrected p value of 0.001. The estimated odds ratio (OR) for myopathy in patients with a single C allele was 4.3 (95% confidence interval [CI], 2.5 to 7.2), and the estimated OR for patients homozygous for the C allele was 17.4 (95% CI, 4.8 to 62.9). Based on these data, the cumulative risk of developing myopathy after 6 years of treatment with simvastatin 80 mg was 0.6% for patients with the T/T allele, 3% for patients with the T/C allele, and 18% for patients with the C/C allele. Other clinical factors that predicted a risk of myopathy were female sex (relative risk [RR], 1.8; 95% CI, 1.1 to 2.8), age 65 and older (RR=2.2; 95% CI, 1.4 to 3.4), impaired renal function (RR=2.2; 95% CI, 1.4 to 3.4), use of amiodarone (RR=6.4; 95% CI, 3.4 to 12.1), use of calcium antagonists (RR=1.7; 95% CI, 1.2 to 2.6), and diabetes (RR=1.7; 95% CI, 1.0 to 2.9).

SEARCH investigators replicated the association of the \textit{SLCO1B1} genetic variant with myopathy in 16,664 patients from a separate RCT, the Heart Protection Study. In this study, all patients were treated with simvastatin 40 mg, and 23 (0.1%) were identified with CK levels greater than 10 times normal. \textit{SLCO1B1} variants were also strongly associated with myopathy in this replication study, with a corrected p value of 0.004. The estimated OR for the presence of 1 C allele was 2.6 (95% CI, 1.3 to 5.0).

The STRENGTH (Statin Response Examined by Genetic Haplotype Markers) study was a randomized trial that examined statin response and safety by dose of statin, statin type, and presence of genetic markers. A total of 509 patients were randomized to various doses of atorvastatin, pravastatin, or simvastatin and followed for adverse events, including myopathy. The presence of at least 1 variant on the \textit{SLCO1B1} gene was associated with an increased rate of adverse events (37% vs 25%, p=0.03). There was also evidence of a “dose-response” effect, with the risk of adverse events being 19% with no variant alleles, 27% with 1 variant allele, and 50% with 2 variant alleles (p=0.01 for trend). The association between \textit{SLCO1B1} gene status and adverse event rates did not appear to be present for patients who received pravastatin.
Case-Control and Cohort Studies

A case-control study reporting on the risk of myopathy associated with SLCO1B1 variants was reported in 2012. This study by Brunham et al identified cases with statin-induced myopathy, defined as muscle symptoms with a CK elevation at least 10 times normal, from 2 large lipid clinics in the Netherlands. Twenty-five cases of myopathy were identified from 9000 total patients, for a prevalence of 0.26%. These patients were matched for age, sex, statin type, and statin dose, with 84 patients who did not have myopathy. In the whole cohort of patients taking any statin, there was a nonsignificant trend toward an increase in myopathy for patients with a SLCO1B1 variant (OR=1.5; 95% CI, 0.58 to 3.69; p=0.21). When restricted to patients on simvastatin, the association was stronger but not statistically significant (OR=3.2; 95% CI, 0.83 to 11.96; p=0.06).

Carr et al reported results from a similar case-control study evaluating the risk of statin-induced myopathy associated with SLCO1B1 variants. The authors identified 77 statin-induced myopathy patients (serum CK >4 times the upper limit of normal) and 372 statin-tolerant controls from a U.K. large database of anonymous longitudinal medical records. In multiple logistic regression analyses to determine statin-associated myopathy risk, the presence of the C allele in the SLCO1B1 gene was significantly associated with myopathy: for all myopathy, the adjusted OR per C allele was 2.08 (95% CI, 1.3 to 3.32); for severe myopathy, the adjusted OR per C allele was 4.47 (95% CI, 1.84 to 10.84). When analysis was restricted to only those patients receiving simvastatin (n=281), there was a significant association between the SLCO1B1 gene status and myopathy (adjusted OR per C allele, 2.13; 95% CI, 1.29 to 3.54; p=0.014). In contrast, when the analysis was restricted to only those patients receiving atorvastatin (n=121), no significant association was found. Variations in the COQ2 gene were not associated with statin-induced myopathy.

Some evidence, including the Carr results, has suggested that the association between myopathy and SLCO1B1 genotype is most pronounced for simvastatin. Danik et al evaluated the role of SLCO1B1 polymorphisms as effect modifiers for clinical myalgia in the Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which randomly allocated subjects to rosuvastatin (20 mg/d) or placebo. Among the 4404 subjects allocated to rosuvastatin, there was no significant association between SLCO1B1 gene status and either muscle symptoms or a diagnosis of rhabdomyolysis, myopathy, or myositis.

In a subanalysis of a prospective population-based cohort study of chronic diseases in the elderly population, de Keyser et al evaluated whether SLCO1B1 polymorphisms modify the risk of adverse drug reactions during statin therapy among 2080 patients who received simvastatin or atorvastatin and had SLCO1B1 genotype available. The study’s primary outcome was a reduction in statin dose or a switch to another statin-lowering drug as an indicator for an adverse drug reaction. Among simvastatin users, the T>C polymorphism was significantly associated with the primary outcome. Patients with the CC genotype had a hazard ratio for dose decrease or switch of 1.74 (95% CI, 1.05 to 2.88). A similar association was not seen among atorvastatin users.

Ferrari et al conducted a case-control study among patients treated with atorvastatin, rosuvastatin, or simvastatin to assess the contribution of polymorphisms in the SLCO1B1, ABCB1, and ABCG2 genes to
Genetic Testing for Statin Induced Myopathy

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the risk of statin-induced myopathy. Cases (n=33) included patients with statin-induced elevations in serum CK levels of greater than 3 times the upper limit of normal; they were compared with 33 matched controls. Patients with increased CK levels had significantly increased odds for the SLCO1B1 C allele (OR, 8.86; p<0.01) or the ABCB1 T allele (OR=4.67; p<0.05). Patients with increased CK levels did not have a significantly increased odds of having the ABCG2 genotype.

Canestero et al conducted a systematic review of studies evaluating the association between a number of genetic variants, including SLCO1B1, and statin serum concentrations and subsequent myopathy. Thirteen studies were identified, which evaluated 7 genes in classes: 3 cytochrome p450 enzymes (CYP2D6, CYP3A4, CYP3A5), the mitochondrial enzyme glycine amidinotransferase (GATM), SLCO1B1, and the cell efflux transporters genes (ABCB1, ABCG2). The STRENGTH and SEARCH studies, along with the Brunham study, were included in the systematic review. Reviewers concluded that the evidence for an association between the *5 allele of the SLCO1B1 gene and statin-related myopathy was strong and replicated in multiple studies, particularly for simvastatin. A meta-analysis of case-control studies supported these findings; the variant C allele, in particular, increased the risk of severe myopathy. The increased risk was observed for simvastatin but not atorvastatin.

Section Summary: Clinical Validity
The available evidence from GWASs has suggested that SLCO1B1 polymorphisms are associated with risk of statin-associated myopathy. Prospective case-control studies and RCTs have been mixed in demonstrating an association between SLCO1B1 polymorphisms and statin-associated myopathy.

CLINICAL UTILITY
No studies identified reported direct evidence on the clinical utility of genetic testing for statin myopathy. Direct evidence for clinical utility in this setting would come from studies demonstrating that using the SLCO1B1 genotype to inform statin therapy (statin dose or choice of specific drug) has positive outcomes in terms of lower rates of myopathy with adequate lipid control and tolerability of alternative treatments. Indirect evidence includes the predicted number of patients who avoid statin myopathy as a result of genetic testing. This number is uncertain because there are a number of actions that can be taken as a result of genetic testing. Statins can be stopped or not started, a lower dose can be used, and other risk factors can be avoided, such as use of amiodarone. Despite the uncertainty in the precise number of events avoided, the number will necessarily be low because of the low underlying rate of serious events.

Several institutions have implemented electronic medical record–based clinical decision support systems to guide statin dosing and follow-up for patients started on a statin based on patients’ SLCO1B1 status, including Vanderbilt University Medical Center and St. Jude Children’s Research Hospital. However, studies that demonstrate that such systems are associated with improved clinical outcomes are lacking.

When statin use is reduced or eliminated, the reduction in statin myopathy needs to be weighed against the increased cardiovascular events that may occur as a result of this change. In patients with a moderate-to-high risk of cardiovascular events, the probability of MI over a 10-year period may be in the range of 10% to 20%. This event rate is substantially higher than the probability of serious myositis and rhabdomyolysis.
Genetic Testing for Statin Induced Myopathy

Policy # 00377
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a result, if statin drugs are avoided because of genetic testing, the number of MIs that will result may exceed the number of myopathy episodes avoided, and net harm may result. Because there are no alternative agents that can reduce the rate of cardiovascular events to the extent as do statins, it may not be possible to ameliorate this net harm by a change to an alternative lipid-lowering strategy.

Section Summary: Clinical Utility
The available evidence is insufficient to demonstrate that the clinical use of SLCO1B1 genotyping is associated with subsequent changes in patient management and/or improved outcomes, or with increased adherence to statin therapy.

SUMMARY OF EVIDENCE
For individuals who are taking statin drugs who receive genetic testing for SLCO1B1 variants, the evidence includes secondary analyses of RCTs and prospective observational studies. Relevant outcomes are test accuracy and validity, morbidity 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 GWAS has suggested that SLCO1B1 polymorphisms are associated with risk of statin-associated 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 definitive 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 those at the highest risk of myopathy (ie, 2 abnormal SLCO1B1 alleles). Therefore, there is a possibility of harm if the results of a positive test for statin-induced myopathy are used as part of the decision-making process for prescribing statins. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
Genetic Testing for Statin Induced Myopathy

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08/19/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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Coding
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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