

(20496)

<b>Medical Benefit</b>		<b>Effective Date:</b> 01/01/14	<b>Next Review Date:</b> 09/17
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***This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.***

*The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

### Description

Statin drugs, which are widely used, can cause muscle-related adverse 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.

### Summary of Evidence

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 is not consistently demonstrated across studies. Evidence from studies that evaluate whether a clinical strategy guided by testing for *SLCO1B1* or other genes involved in statin metabolism leads to improved patient outcomes does not exist.

Statins are associated with a definite decreased risk of cardiovascular events such as myocardial infarction, 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

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**.

### Background

Statin drugs are the primary pharmacologic treatment for hypercholesterolemia throughout the world. In the

United States, there are an estimated 38 million people taking statins as of 2008.<sup>1</sup> Use of statins is associated with an approximately 30% reduction in cardiovascular events across a wide variety of populations.<sup>2</sup>

### *Statin-Induced Myopathy*

Statins are associated with a known risk of muscle-related symptoms, and these are the most common adverse 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 American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute advisory committee<sup>3</sup>:

- 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.<sup>4</sup> 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% to 3.0% of patients, and in most trials, the rate of myalgias in patients on statin therapy is not increased compared with placebo treatment.<sup>5</sup> In observational studies, higher rates of 10% to 15% have been reported.<sup>2</sup>

Myositis is much less common than myalgias, with an estimated rate of five per 100,000 patient-years and an estimated per-person incidence of 0.01%.<sup>5</sup> 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.<sup>5</sup> 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.<sup>6</sup> Fatalities from statin-induced rhabdomyolysis can occur, but the mortality rate is not well-defined. FDA estimated that deaths for rhabdomyolysis occur at a rate of less than one death per million prescriptions.<sup>3</sup>

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.<sup>7</sup> 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 four times higher than for younger patients.<sup>8</sup> 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.<sup>7</sup> Other factors that may be associated with myopathy include female sex and intense physical exercise.<sup>7</sup>

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, and a substantial part of this is the result of nonadherence to prescribed statins.<sup>1</sup>

### *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.<sup>2</sup> 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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>4</sup>

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 which is the rate-limited enzyme in creatine biosynthesis, and statin-induced myopathy, although this association has not been consistently replicated.<sup>9</sup>

#### Commercially Available *SLCO1B1* Molecular Diagnostic Tests

Several commercial and academic labs offer genetic testing for *SLCO1B1* variants. For example, 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. (Available at: [http://www.bostonheartdiagnostics.com/science\\_portfolio\\_statin.php](http://www.bostonheartdiagnostics.com/science_portfolio_statin.php)).

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. (Available at: <http://ltd.aruplab.com/tests/pub/2008426>).

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, which includes sequencing of the *SLCO1B1* gene.<sup>10</sup>

#### **Regulatory Status**

There are no currently available genetic tests for statin-induced myopathy that are cleared for marketing by the FDA.

The commercially available tests for *SLCO1B1* are laboratory-developed tests and not subject to approval by FDA. 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 Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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