Protocol

Genetic Testing for Statin-Induced Myopathy

(20496)

Medical Benefit		**Effective Date**: 01/01/14	**Next Review Date**: 09/19
Preauthorization	No	**Review Dates**: 09/13, 09/14, 09/15, 09/16, 09/17, 09/18	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are taking statin drugs	Interventions of interest are: • Genetic testing for SLCO1B1 variants	Comparators of interest are: • Standard care without genetic testing for SLCO1B1 variants	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Hospitalizations

DESCRIPTION

HMG-CoA reductase inhibitors, or statins, which are widely used to treat hypercholesterolemia, can cause muscle-related adverse events. Serious myopathy (i.e., myositis, rhabdomyolysis) can also occur and may be associated with variants in the SLCO1B1 gene. Commercially available tests for the presence of SLCO1B1 variants are marketed for use in predicting the risk of myopathy for patients taking statins.

SUMMARY OF EVIDENCE

For individuals who are taking statin drugs who receive genetic testing for SLCO1B1 variants, the evidence 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 variants are associated with risk of statin-associated myopathy. Observational studies and RCTs have been mixed in demonstrating an association between SLCO1B1 variants 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 myocardial infarction, and this benefit of reduced cardiovascular events is likely to far outweigh the risk of myopathy—even in individuals with the highest risk of myopathy (i.e., those with two 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.

POLICY

Genetic testing for the presence of variants in the SLCO1B1 gene to identify patients at risk of statin-induced myopathy is considered **not medically necessary**.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

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.[1] The use of statins is associated with an approximately 30% reduction in cardiovascular events across a wide variety of populations.[2]

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 were defined in 2002 by a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute[3]:

- Statin-induced myalgia, defined as any muscle symptoms that occur without an elevation of serum creatinine kinase;
- Statin-induced myositis, defined as muscle symptoms with an elevation of serum creatinine kinase; and
- Statin-induced rhabdomyolysis, defined as markedly severe muscle symptoms with an elevation of creatinine kinase 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.[4] 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.[5] In observational studies, higher rates of 10% to 15% have been reported.[2]

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%.[5] 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.[5] 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.[6] 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 one death per million prescriptions.[3]

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 six-fold increase for patients on high-dose statins[7] (age is also a strong risk factor). One 2007 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.[8] Some statins may be associated with higher risk than others, and concomitant administration of certain drugs (e.g., gemfibrozil, amiodarone) has been associated with higher rates of statin myopathy in clinical trials.[7] Other factors that may be associated with myopathy include female sex and intense physical exercise.[7] The perceived risk of statin-induced myopathy may contribute to suboptimal statin use in patients with indications. It is estimated that 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.[1]

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.[2] Other genetic variants affect statin metabolism, efficacy, and susceptibility to adverse effects; these genetic variants involve variations in the apolipoproteins such as apo E, variations in the cholesterol ester transfer proteins, or variations in the coenzyme Q pathway.[1]

Variations in the 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.[2] Single nucleotide variants (SNVs) 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.[4]

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 variants in the GATM gene and statin-induced myopathy (the GATM gene encodes a glycine amidinotransferase that is the rate-limited enzyme in creatine biosynthesis). However, it should be noted that the association between variants has not been consistently replicated.[9]

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 to identify patients with the T/T, T/C, or C/C genotype.[10]

ARUP Laboratories (Salt Lake City, UT) markets a test for SLCO1B1 variants that uses real-time polymerase chain reaction with high-resolution melting analysis to identify the rs4149056C variant in the SLCO1B1 gene.[11]

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.[12]

REGULATORY STATUS

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 the CLIA. Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

RELATED PROTOCOLS

Cochlear Implant

Preimplantation Genetic Testing

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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