BlueCross BlueShield Federal Employee Program.

FEP 2.04.96 Genetic Testing for Statin-Induced Myopathy

Effective Date: April 15, 2018 **Related Policies:** None

Genetic Testing for Statin-Induced Myopathy

Description

HMG-CoA reductase inhibitors, or statins, which are widely used to treat hypercholesterolemia, can cause muscle-related adverse events. Serious myopathy (ie, 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.

FDA 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). Exome or genome sequencing tests as a clinical service 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. Food and Drug Administration has chosen not to require any regulatory review of this test.

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] The Boston Heart Statin Induced Myopathy (SLCO1B1) Genotype test and ARUP Laboratories Statin Sensitivity SLCO1B1 are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

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]

POLICY STATEMENT

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**.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

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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 evidence 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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

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 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 randomized controlled trials 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 (ie, those with 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

In 2012, the Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium issued guidelines for *SLCO1B* genotypes and simvastatin-induced myopathy, which were updated in 2014.[26] These guidelines on patient management for various *SLCO1B* genotypes recommended prescribing a lower dose or considering an alternative statin and considering routine creatinine kinase surveillance in patients with *SLCO1B* genotypes consistent with intermediate or low statin metabolism.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY

Date	Action	Description
March 2018	New 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

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