BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Genetic Testing for Statin-Induced Myopathy AHS – M2089

File Name:	genetic_testing_for_statin_induced_myopathy
Origination:	01/01/2019
Last CAP Review:	N/A
Next CAP Review:	01/01/2020
Last Review:	01/01/2019

Description of Procedure or Service

Statins are a class of medicines used to lower serum cholesterol. Statins work by reducing the inhibiting the conversion of HMG-CoA to mevalonic acid, which is a key step in cholesterol synthesis (Rosenson, 2016).

Statin-Induced myopathy is a common side effect, affecting up to 29% of patients taking the medication (Mayo Clinic, 2017) reporting muscle pain. It is also a common reason for patients to discontinue use of statins. Less often, severe myopathy, including rhabdomyolysis, may develop from statin use.

******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, specifically for the presence of variants in the SLCO1B1 gene is considered not medically necessary.

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

N/A

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.

Policy Guidelines

Literature Review

The mechanism for statin-induced myopathy is not well understood, and the incidence varies by the statin prescribed and dosage. Rosenson (2016) states, “Individual statins may have distinct effects on the synthesis of coenzyme Q10 (CoQ10, ubiquinone), which plays an important role in muscle cell energy production. It has been speculated that a reduction in ubiquinone in skeletal

muscle may contribute to statin-induced muscle injury. Some studies have found that statins decrease skeletal muscle and plasma concentrations of ubiquinone; however, other studies have not, and studies have come to different conclusions about whether statin treatment decreases levels of ubiquinone in skeletal muscle."

Clinical Validity ad Utility

Rosensen and Baker (2016) stated that genetic factors might increase the risk of statin myopathy. However, they concluded that "it seems unlikely that such a test would be clinically useful or worth the expense in most situations."

Talameh and Kitzmiller (2014) reviewed pharmacokinetic genetic variants and their association with statin-induced myopathy clinical outcomes. Eighteen studies of SIM clinical outcome and pharmacokinetic genetic variants were identified. The authors stated that for simvastatin, it seems unlikely that pharmacokinetic genes other than *SLCO1B1* will be clinically important for predicting risk of simvastatin-induced myopathy. *SLCO1B1* may also have potential to be clinically important in pravastatin and pitavastatin-induced myopathy, however further studies of *SLCO1B1* and pravastatin and pitavastatin statin-induced myopathy clinical outcomes are needed. The authors further stated that current available data does not support *SLCO1B1* genotyping for predicting atorvastatin-, rosuvastatin- or lovastatin-induced myopathy as the clinical utility is unknown. The currently available literature does not support genes other than *SLCO1B1* and SIM clinical outcome, except for possibly *CYP2D6* and atorvastatin-induced myopathy. *CYP2D6*4* may be clinically relevant for atorvastatin-induced myopathy, but mechanistic studies are needed.

The SEARCH Collaborative Group (2008) carried out a genomewide association study using approximately 300,000 markers in 85 subjects with definite or incipient myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. The genomewide scan yielded a single strong association of myopathy with the rs4363657 single-nucleotide polymorphism located within SLCO1B1 on chromosome 12. The association of rs4149056 with myopathy was replicated in the trial of 40 mg of simvastatin daily, which also showed an association between rs4149056 and the cholesterol-lowering effects of simvastatin. No SNPs in any other region were clearly associated with myopathy. The investigators concluded that they had identified common variants in SLCO1B1 that are strongly associated with an increased risk of statin-induced myopathy. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively.

The STRENGTH (Statin Response Examined by Genetic Haplotype Markers) study was a randomized trial that examined statin efficacy and safety by dose of statin, type of statin and by presence of genetic markers (Voora et al, 2009). Composite adverse events were observed in 99 subjects (54 discontinuations, 49 myalgias, and nine CK elevations). The investigators concluded that SLCO1B1*5 genotype and female sex were associated with mild statin-induced side effects. These findings expand the results of a recent genome wide association study of statin myopathy with CK > 3 times normal to milder, statin-induced, muscle side effects.

Brunham et al (2012) conducted a case-control study to evaluate the association of the rs4149056 variant in SLCO1B1 with severe statin-associated myopathy. 25 cases of severe statin-associated myopathy and 84 controls matched for age, gender, statin type and dose were identified. The results confirmed that the SLCO1B1 rs4149056 genotype was significantly associated with myopathy in patients who received simvastatin, but not in patients who received atorvastatin. The investigators concluded that the results provide further support for the important role of SLCO1B1 in influencing simvastatin-related myopathy.

Carr et al. (2013) reported results from a similar case-control study evaluating the risk of statin-induced myopathy associated with *SLCO1B1* variants. Seventy-seven statin-induced myopathy patients and 372 statin-tolerant controls were identified. 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. In patients receiving simvastatin (n = 281), statistically significant associations between c.521T>C (rs4149056) and risk of both myopathy (P = 0.014) and severe myopathy (P = 0.0004) were observed. The authors concluded that in terms of the clinical utility of the genetic association between the *SLCO1B1* polymorphism and statin-induced myopathy, there is now convincing evidence for simvastatin, but not for other statins, for which more studies are needed.

Canestaro et al (2014) conducted a systematic review to identify relevant research evaluating the significance of genetic variants predictive of altered statin concentrations and subsequent statin-related myopathy. 13 studies were identified that associated genetic variants with some form of the clinical outcome of muscle toxicity and weakness. Seven genes (*CYP2D6, CYP3A4, CYP3A5, GATM, SLCO1B1, ABCB1,* and *ABCG2*) and all statins were included in this review. The authors concluded that the evidence for an association between the *5 allele of *SLCO1B1* and statin-related myopathy is strong and convincing, especially for simvastatin, for which this relationship appears to be strongest. The authors further state that although the evidence for this association is clear and consistent, it is still unclear whether the use of prospective genotyping and subsequent statin personalization will be cost effective.

Ferrari et al. (2014) conducted a case-control study in which patients treated with atorvastatin, rosuvastatin or simvastatin were genotyped for polymorphisms in the SLCO1B1, *ABCB1 and ABCG2* genes. Patients carrying SLCO1B1 T521C or ABCB1 C1236T single nucleotide polymorphisms (SNPs) had an odds ratio (OR) for statin-induced elevated serum CK levels of 8.86 ($p<0.01$) and 4.67 ($p<0.05$), respectively, while patients carrying the SLCO1B1 A388G SNP had an OR of 0.24 ($p<0.05$). The investigators concluded that genotyping of the SLCO1B1, ABCB1 and ABCG2 genes should be considered to improve statin safety while concomitantly reducing the burden of blood tests for CK measurements.

Applicable Federal Regulations
This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

In 2012, the Clinical Pharmacogenomics Implementation Consortium (CPIC) issued guidelines for *SLCO1B* and simvastatin-induced myopathy, which were updated in 2014 (Wilke et al, 2012; Ramsey et al, 2014). CPIC stated that "a single coding single-nucleotide polymorphism, rs4149056T>C, in *SLCO1B1* increases systemic exposure to simvastatin and the risk of muscle toxicity." According to CPIC, "a potential benefit of preemptive *SLCO1B1* testing is a significant reduction in the incidence of simvastatin-induced myopathies and rhabdomyolysis, by identifying those at significant risk and recommending a lower simvastatin dose or an alternative statin as appropriate. In addition, genotyping may promote statin adherence and lower low-density lipoprotein cholesterol levels." CPIC concluded that "for simvastatin, the evidence linking myopathy to rs4149056 in *SLCO1B1* is of high quality, and this association has been reproduced in randomized trials and clinical practice–based cohorts. Conversely, the association of rs4149056 with myopathy has been less compelling for other statins." CPIC recommended that at lower simvastatin doses (e.g., 40 mg daily), this information should be used to warn providers about modest increases in myopathy risk for subjects with a C allele at rs4149056.

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.

Applicable service codes: 81328, 81479

Code Number	PA Required	PA Not Required	Not Covered
81328	X		
81479	X		

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

Brunham, L.R., Lansberg, P.J., Zhang, L. et al (2012). Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J., 12*(3):233-237.

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Voora, D., Shah, S. H., Spasojevic, I., Ali, S., Reed, C. R., Salisbury, B. A., & Ginsburg, G. S. (2009). The *SLCO1B1**5 Genetic Variant is Associated with Statin-Induced Side Effects. *Journal of the American College of Cardiology*, *54*(17), 1609–1616. http://doi.org/10.1016/j.jacc.2009.04.053

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Policy Implementation/Update Information

1/1/2019	BCBSNC will not provide coverage for genetic testing for the presence of variants in the SLCO1B1 gene because it is considered not medically necessary. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)