2.04.96	Genetic Testing for Statin-Induced Myopathy		
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Section:	2.0 Medicine	**Page:**	Page 1 of 15

Policy Statement

I. Genetic testing for the presence of variants in the *SLCO1B1* gene to identify individuals at risk of statin-induced myopathy is considered investigational.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

See the Codes table for details.

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 a systematic review and 2 randomized controlled trials (RCTs). Relevant outcomes are symptoms, quality of life, morbid events, and treatment-related morbidity. 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 a specific drug) has positive outcomes in terms of lower rates of myopathy with adequate lipid control and tolerability of alternative treatments. The systematic review findings suggested that certain alleles carry less risk of statin-induced myopathy compared with others. Two RCTs were identified that evaluated adherence to medication and/or lipid control in patients whose physicians were informed of the *SLCO1B1* haplotype at the beginning or at the end of the study. No significant benefits were identified in adherence to medications or in pain related to myopathy with knowledge of the *SLCO1B1* haplotype status. There was a short-term (3-month) decrease in low-density lipoprotein (LDL) in the active treatment group in 1 trial, but knowledge of *SLCO1B1* status did not provide benefit in LDL lowering in the other trial after 12 months. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

Related Policies

- N/A

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Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that requires insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. 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, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background
Statins
HMG-CoA reductase inhibitors, or statin drugs, are the primary pharmacologic treatment for hypercholesterolemia worldwide. In the U. S., 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,] A variety of socioeconomic disparities in cardiovascular outcomes and implementation of risk-reducing measures, including use of statins and other agents for managing hypercholesterolemia, have been identified. Women with coronary artery disease are less likely to be receiving a statin than men, and those taking statins are less likely to have therapy intensified and to achieve lipid control compared to men taking statins.[3,4,5,] Black individuals at high risk of atherosclerotic cardiovascular disease are significantly less likely to be prescribed statins compared to similar White individuals, and rates of lipid control are lower among Black and non-White Hispanic individuals taking statins compared to White individuals taking statins.[6,5,] These observations are mediated in part through disparities in social determinants of health, such as income, insurance, and immigration status.[7,8,]

Commercially Available *SLCO1B* Molecular Diagnostic Tests
Several commercial and academic labs offer genetic testing for statin-induced myopathy (*SLCO1B1*) variants, including Boston Heart Diagnostics and ARUP Laboratories. Other labs offer panel tests for drug metabolism that include the *SLCO1B1* gene.

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Literature Review

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.
To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Testing for *SLCO1B1* Variants To Guide Treatment

Clinical Context and Test Purpose

Statin-Induced Myopathy

Statins are associated with a known risk of muscle-related symptoms, which are the most common adverse events of statin drugs. The terminology used to describe statin-related muscle adverse effects varies among clinical trials and consensus groups. In 2019, the American Heart Association (AHA) defined the following muscle adverse events:[9,]

- Stain-associated muscle symptoms (SAMS): muscle symptoms reported during statin therapy but not necessarily caused by the statin
- Myalgia: muscle pain and aches
- Myopathy: unexplained muscle pain or weakness accompanied by creatine kinase concentration >10 times normal
- Rhabdomyolysis: Severe form of myopathy, with creatine kinase concentration typically >40 times normal, which can cause myoglobinuria and acute renal failure

Similar terminology is used in a clinical perspective publication focused on SAMS from the National Lipid Association, with the addition of the following terms:[10,]

- Myositis: muscle inflammation by skeletal muscle biopsy and/or magnetic resonance imaging
- Myonecrosis: elevations of creatine kinase concentration

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Additionally, 3 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,[11,]

- Statin-induced myalgia, defined as any muscle symptoms that occur without an elevation of serum creatine kinase;
- Statin-induced myositis, defined as muscle symptoms with an elevation of serum creatine kinase; and
- Statin-induced rhabdomyolysis, defined as markedly severe muscle symptoms with an elevation of creatine 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.[12,] 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, it has 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.[13,9,] 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 5 per 100000 patient-years, and an estimated per-person incidence of 0.01%.[13,] 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 AHA estimates that the risk of rhabdomyolysis is 0.01%.[9,] Older estimates from the National Lipid Association estimated that rhabdomyolysis occurs at a rate of 1.6 per 100000 patient-years, and the U.S. Food and Drug Administration (FDA) adverse events reporting system estimated a rate of 0.7 per 100,000 patient-years.[13,] A systematic review by Law et al (2006) combined results from 20 clinical trials and estimated the rate of rhabdomyolysis to be 1.6 cases per 100000 patient-years.[14,] Fatalities from statin-induced rhabdomyolysis can occur, but the mortality rate is not well-defined. The FDA has estimated that deaths from rhabdomyolysis occur at a rate of less than 1 death per million prescriptions.[11,]

A number of clinical factors are associated with an increased risk of statin-induced myopathy. Statin dose is probably the strongest risk factor, with an estimated 6-fold increase for patients on high-dose[15,9,] Age is also a strong risk factor, with the AHA reporting that the risk of myopathy and rhabdomyolysis doubles in individuals aged 65 years or older compared to younger individuals.[9,] Additionally, a study by Schech et al (2007) 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.[16,] Some statins may be associated with a 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.[15,9,] Other factors that may be associated with myopathy include female sex, comorbid diabetes mellitus, East Asian ancestry, and intense physical exercise.[15,9,] 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 U. S. who would benefit from statins are currently taking them, a substantial percentage of whom do not adhere to prescribed statin regimens.[1,] Additionally, an estimated 10% of patients prematurely discontinue statin therapy due to statin-related adverse events.[9,]

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 events; these

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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 in this gene are associated with variations in the risk of statin-induced myopathy. A number of variant alleles with impacts on expression and/or function of *SLCO1B1* have been identified and arranged by the Clinical Pharmacogenetics Implementation Consortium into phenotypic categories, including poor, decreased, normal, and increased transporter function phenotypes.[17,] Poor and decreased function phenotypes frequently involve the well-studied rs4149056 c.521T>C variant found in the *SLCO1B1*5* and **15* haplotypes; these variants are estimated to occur in 15% of the population and are associated with increased risk of statin-induced myopathy.[12,] The estimated prevalence of poor and decreased function phenotypes is highest in individuals of Native American (42%), North African or Middle Eastern (36%), European (31%), East Asian (22%), and Central/South Asian (13%) descent.[17,]

Other genes have 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.[18,]

Genetic Testing

The purpose of genetic testing for *SLCO1B1* variants in patients who are taking statin drugs is to inform a decision whether patients identified as at risk for statin-associated myopathy should continue taking specific statin drugs. Genome-wide association studies have found that *SLCO1B1* variants are associated with statin-induced myopathy. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) was an RCT of 12,064 patients assigned to simvastatin 20 mg or 80 mg.[19,] A genome-wide association study was conducted using data for the 1.4% of patients assigned to the 80 mg simvastatin group in SEARCH, who experienced myopathy (defined by elevations in creatine kinase levels with or without muscle symptoms) and who had adequate DNA available for genomic analysis, with matched controls.[12,] The noncoding rs4363657 *SLCO1B1* single-nucleotide variant was the sole variant that had a strong association with myopathy. Further analysis indicated the identified variant was in near-complete linkage disequilibrium with the rs4149056 c.521T>C variant. The cumulative risk of developing myopathy after 6 years of treatment with simvastatin 80 mg was 0.6% for patients with the rs4149056 T/T genotype, 3% for patients with the T/C genotype, and 18% for patients with the C/C genotype. The investigators replicated the association of the *SLCO1B1* rs4149056 c.521T>C variant with myopathy in 16,664 patients from the Heart Protection Study. In this trial, all patients were treated with simvastatin 40 mg; 0.1% were identified with creatine kinase levels greater than 10 times normal. The rs4149056 c.521T>C *SLCO1B1* variant was strongly associated with myopathy in this replication analysis.

Some evidence has suggested that the association between myopathy and *SLCO1B1* genotype is most pronounced for simvastatin. The Statin Response Examined by Genetic Haplotype Markers study was a randomized trial that examined statin response and safety by the dose of statin, statin type, and presence of genetic markers.[20,] 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 *SLCO1B1* gene was associated with an increased rate of adverse events with the risk of adverse events being 19% with no variant alleles, 27% with 1 variant allele, and

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50% with 2 variant alleles (p=.01 for trend). The association between *SLCO1B1* gene status and adverse event rates did not appear to be present for patients who received pravastatin.

In a subanalysis of a prospective population-based cohort study of chronic diseases in the elderly population, de Keyser et al (2014) evaluated whether *SLCO1B1* variants modify the risk of adverse drug reactions during statin therapy among 2080 patients who received simvastatin or atorvastatin and had *SLCO1B1* genotype available.[21,] The study's primary outcome was a reduction in statin dose or a switch to another statin-lowering drug as an indicator of an adverse drug reaction. Among simvastatin users, the T>C variant 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% confidence interval [CI], 1.05 to 2.88). A similar association was not seen among atorvastatin users. Conversely, large retrospective studies indicate an association between the rs4149056 c.521T>C variant and likelihood of statin discontinuation or surrogate markers (such as myalgia-related diagnosis codes or new statin allergies) of statin-induced myopathy.[22,23,]

Danik et al (2013) evaluated the role of *SLCO1B1* variants as effect modifiers for clinical myalgia in the Prevention: an Intervention Trial Evaluating Rosuvastatin trial, which randomized subjects to rosuvastatin (20 mg/d) or placebo.[24,] 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.

Based on the evidence for a link between *SLCO1B1* variants and statin-associated myopathy, testing for *SLCO1B1* variants could potentially result in changes in medications that would reduce the risk of adverse drug reactions.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are on statin therapy.

Interventions
The intervention of interest is testing for *SLCO1B1* variants.

Comparators
The following practice is currently being used to manage statin therapy: standard of care treatment without *SLCO1B1* testing.

Outcomes
The general outcomes of interest are statin-associated myopathy events while on therapy and long-term cardiovascular events such as myocardial infarction and hospitalizations.

The onset of statin-associated myopathy typically occurs weeks to months after initiating statin therapy but can occur at any time.

Study Selection Criteria
Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with or without the test. Because these are intervention studies, the preferred evidence is from randomized controlled trials.

- We sought randomized controlled trials that evaluated whether the use of the *SLCO1B1* genotype to inform statin therapy (statin dose or choice of a specific drug) has positive outcomes in terms of lower rates of myopathy with adequate lipid control and tolerability of alternative treatments.

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- As the main purpose of genetic testing for statin-induced myopathy is to optimize treatment to improve quality of life and minimize risk of long-term cardiovascular events compared with standard of care, we preferred evidence on health outcomes.
- We also included studies that reported only on short-term adverse events and efficacy outcomes, such as lipid control and treatment adherence, etc.

Review of Evidence

Systematic Review

In their meta-analysis, Xiang et al (2018) assessed the association between *SLCO1B1* T521C and 521T alleles and the risk of statin-induced myopathy.[25,] Fourteen cohort and case-control studies were included, with a total of 3265 myopathy patients and 7743 controls. Findings of several studies suggested that 521TT carries a statistically significant lower risk of statin-induced myopathy compared to the other genotypes studied (i.e., 521CC, 521TC, 521CC + TC). In addition, 521C was also associated with a greater risk of statin-induced myopathy than 521T. These studies all had significant heterogeneity. The authors also evaluated the association of *SLCO1B1* T521C and the risk of myopathy when taking different types of statins. They found a statistically significant risk for 521CC + TC individuals on simvastatin (odds ratio [OR], 2.35; 95% CI, 1.08 to 5.12; p=.032) or rosuvastatin (OR, 1.69; 95% CI, 1.07 to 2.67; p=.024) compared with 521TT. The 521C allele was also associated with a greater risk of myopathy from taking cerivastatin (OR, 1.95; 95% CI, 1.47 to 2.57; p<.001). The heterogeneity among studies of statin types for *SLCO1B1* T521C and myopathy risk was not statistically significant. Publication bias could not be ruled out in several comparisons.

Randomized Controlled Trials

Vassy et al (2018) conducted a systematic review of *SLCO1B1* testing of patient and clinical outcomes.[26,] They identified 5 pilot studies and an RCT by Voora et al (2017) that studied how *SLCO1B1* test results influence patient outcomes (see Table 1).[27,] Voora et al (2017) recruited patients who had discontinued statin therapy due to suspected side effects (73% reported myalgia, 25% of patients were *SLCO1B1*5* carriers). Patients were randomized to immediate or delayed results of *SLCO1B1* testing, stratified based on *SLCO1B1*5* genotype (carriers vs noncarriers) and clinic site. The primary outcome was adherence as assessed by the Morisky Medication Adherence Scale. Secondary outcomes included low-density lipoprotein cholesterol (LDL-C), Brief Pain Inventory, and 12-Item Short-Form Health Survey. Voora et al (2017) reported a significant difference between groups in LDL-C at 3 months, but not in other outcome measures (see Table 2). Limitations in trial design might have affected adherence to medications and self-reporting on questionnaires (see Tables 3 and 4).

The Integrating Pharmacogenetics in Clinical Care (I-PICC) Study, conducted by Vassy et al (2020), assessed the effect of *SLCO1B1* testing in statin-naive patients eligible for statin therapy due to cardiovascular disease risk factors (Table 1).[28,] The study was conducted at 8 Veterans Affairs primary care facilities. Similar to the Voora et al RCT, participants were randomized to either immediate *SLCO1B1* testing or delayed testing after 12 months. In the immediate testing group, *SLCO1B1* test results were delivered to treating physicians via the patient's electronic health record, but it was left to the discretion of the physician regarding when (or if) test results were communicated to the patient. Ultimately, only 15.5% of physicians documented communicating *SLCO1B1* test results to patients. The primary outcome of the study was change from baseline in LDL-C after 12 months follow-up (Table 2). Physician assessed statin-associated muscle symptoms were a secondary outcome. After 12 months, there was less LDL lowering in the immediate group than the delayed group (between-group difference -1.1 mg/dL, 90% CI -4.1 to 1.8). This mean difference between groups was within the prespecified noninferiority margin of 10 mg/dL, indicating that *SLCO1B1* testing did not cause harm to patients in this study, nor did it provide benefit. There was no difference between groups in physician-reported statin-associated muscle symptoms (1% vs. 1.4%; p>.99). This study was limited by the low uptake of statin prescriptions in statin-eligible patients in both the immediate and delayed groups (40% and 34.8%, respectively). Other limitations appear in Tables 3 and 4.

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Table 1. Summary of Key RCT Characteristics

Study	Countries	Dates	Sites	Participants	Interventions	
					Active	Comparator
Voora et al (2017)[27],	U.S.	2013-2016	3	159 nonusers of statin therapy due to suspected side effects; approximately 57% female, 20% non-White (16% Black, less than 5% other race)	n=83 Immediate results of *SLCO1B1* variant testing	n=76 Delayed (8 mo) results of *SLCO1B1* variant testing
Vassy et al (2020)[28], I-PICC Study	U.S.	2015-2019	8	408 statin-naive patients with elevated risk of cardiovascular events being managed by a primary care physician; approximately 6% female, 14% non-White	n=193 Immediate results of *SLCO1B1* variant testing	n=215 Delayed (12 mo) results of *SLCO1B1* variant testing

RCT: randomized controlled trial.

Table 2. Summary of Key RCT Results

Study	Adherence	LDL-C (mg/dL), interim	LDL-C (mg/dL), final	Brief Pain Inventory Score	SF-12 Score
Voora et al (2017)[27],	Morisky Medication Adherence Scale (SD)	3 months (SD)	8 months (SD)		
N	119	148	119	119	119
Immediate	6.8 (1.7)	132 (42)	129 (38)	NR	NR
Delayed	7.1 (1.3)	144 (43)	141 (44)	NR	NR
p	.75	.04	.07	NS	NS
Vassy et al (2020)[28],	Proportion adherent among those prescribed a statin		12 months (SE); mean change from baseline (SE)		
N	40	408	408	408	408
Immediate	45% (9/20)	NR	105.1 (2.3); -1.1 (1.2)	NR	NR
Delayed	45% (9/20)	NR	106.7 (1.9); -2.2 (1.3)	NR	NR
p	1.00	NR	<.001	NR	NR

LDL-C: low-density lipoprotein cholesterol; NR: not reported; NS: not significant; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-12: 12-Item Short-Form Health Survey.

The purpose of the limitations tables (see Tables 3 and 4) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. The study limitations stated in these tables are specific to the current review and do not reflect a comprehensive gaps' assessment.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Voora (2017)[27],			2. Participation in the study might have increased		1, 2. 8 mo might be insufficient to evaluate

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
			medication adherence		medication adherence
Vassy et al (2020)[28],	4. Women represented 6% of the study population				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Voora (2017)[27],		1, 2. Patients were not blinded, which might have affected adherence and questionnaire responses				
Vassy et al (2020)[28],	3. Randomization method, including allocation, not described	1, 2, 3. Neither treating physicians nor patients were blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

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 using patients' *SLCO1B1* status.[15,29,30,31] It should be noted that all studies seeking to demonstrate that such support systems are associated with improved clinical outcomes have been found to be lacking.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

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guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Assocaition

In 2019, the American Heart Association (AHA) published a scientific statement focused on statin safety and associated adverse events.[9] Regarding genetic testing for SLCO1B1 variants, the AHA noted that: *"..polymorphisms in the SLCO1B1 gene account for a small proportion of cases of statin-induced myopathy."* No specific recommendations for or against testing were provided.

Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium

In 2012, the Clinical Pharmacogenetics and Pharmacogenomics Implementation Consortium issued guidelines for *SLCO1B* genotypes and simvastatin-induced myopathy, which were updated in 2014 and again in 2022.[17] The 2022 guideline update reorganized genotype-phenotype categories and expanded upon recommendations for statin selection and dosing recommendations according to phenotype, statin intensity according to 2018 American College of Cardiology/American Heart Association guidelines, and strength of supportive data.

National Lipid Association

In 2023, the National Lipid Association (NLA) published a clinical perspective focused on the assessment and management of statin-associated muscle symptoms (SAMS).[10] Regarding genetic testing for SLCO1B1 variants, the NLA noted: *"The SLCO1B1 rs4149056 variant...has the most evidence supporting its association with the SAMS phenotype, but it has not been routinely measured in clinical care."* Furthermore, the publication notes that: *"Genetic testing has not become the standard of care because some patients with pharmacologic SAMS may have no identifiable causative variants, while others with known causative variants never develop SAMS."*

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2024 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (e.g., adverse drug reaction), gene analysis, common variant(s) (e.g., *5)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2017	BCBSA Medical Policy adoption
01/01/2018	Policy revision without position change Coding Update
01/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
11/01/2025	Policy reactivated. Previously archived from 09/01/2020 to 10/31/2025.

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Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) 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 the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into

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consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Statin-Induced Myopathy 2.04.96** **Policy Statement:** I. Genetic testing for the presence of variants in the *SLCO1B1* gene to identify individuals at risk of statin-induced myopathy is considered investigational.

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