
Medical Policy



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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Statin-Induced Myopathy

Description/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 (Salt Lake City, UT). Other labs offer panel tests for drug metabolism that include the *SLCO1B1* gene; for example, ApolloGen (Irvine, CA).

Regulatory Status

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, FDA has chosen not to require any regulatory review of this test.

Medical Policy Statement

The peer reviewed medical literature has not demonstrated the clinical utility of genetic testing for the presence of variants in the *SLCO1B1* gene to identify patients at risk of statin-induced myopathy. Therefore, this service is considered **experimental/investigational**.

Inclusionary and Exclusionary Guidelines

NA

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

NA

Other codes (investigational, not medically necessary, etc.):

81328

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the 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 effects 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](#)

- Statin-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

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 ten 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, 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.^{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 100,000 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 100,000 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 100,000 patient-years.¹³ 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 1 death per million prescriptions.¹¹

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 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 four times higher than for younger patients.¹⁶ Some statins may be associated with higher risk than others, and concomitant administration of certain drugs (eg, 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.^{15,93} 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 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. 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 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.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 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 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 controls¹² 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 six 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 50% with 2 variant alleles (p=0.01 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 (JUPITER) 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 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 initiation of 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.
- 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 (ie, 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 on 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 (Table 1).²⁶ Voora et al (2017) recruited patients who had discontinued statin therapy due to suspected side effects (73% reported myalgia and 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 (Table 2). Limitations in trial design might have affected adherence to medications and self-reporting on questionnaires (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-naïve 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.

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 <i>SLCO1B1</i> variant testing	n=76 Delayed (8 mo) results of <i>SLCO1B1</i> variant testing
Vassy et al (2020) ²⁸ -PICC Study	U.S.	2015-2019	8	408 statin-naïve 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 <i>SLCO1B1</i> variant testing	n=215 Delayed (12 mo) results of <i>SLCO1B1</i> variant testing

RCT: randomized controlled study

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; RN: not reported; NS: not significant; RCT: randomized controlled trial; SF-12: 12-Item Short-Form Health Survey; DC: standard deviation.

The purpose of the limitations tables (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 medication adherence		1, 2. 8 mo might be insufficient to evaluate 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 a patients' *SLCO1B1* status.^(7,16) 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.

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.

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 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 Association

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 *SLCO1B1* genotypes and simvastatin-induced myopathy, which were updated in 2014¹⁶ 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Government Regulations

National:

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

Local:

Wisconsin Physicians Service Insurance Corporation

Local Coverage Determination (LCD): MoIDx: Pharmacogenomics Testing (L38435)

Original Effective Date 07/26/2020

Revision Effective Date 08/24/2023

Coverage Indications, Limitations, and/or Medical Necessity

This is a limited coverage policy for pharmacogenomics testing (PGx) including single gene, multi-gene panels, and combinatorial tests. These tests are generally covered (with a few exceptions) as described in further detail below to improve safety in the use of specific medications by avoiding potentially harmful medications, doses and/or adverse reactions known to occur with certain genotypes.

PGx testing is considered reasonable and necessary in limited circumstances as described below as an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to specific medications under consideration for use, or is already using a specified medication, based on other clinical considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgement, clinical science and basic science pertinent to the drug, and the patient's preferences and values.¹

PGx tests must demonstrate analytical validity, clinical validity, and clinical utility to be considered reasonable and necessary for coverage. This is demonstrated through a required technical assessment of the test. PGx Tests are considered germline tests and must adhere to other relevant germline testing policies published by this contractor.

It is understood that some panel/combinatorial tests may include content that has demonstrated clinical utility and some that has not. In such circumstances, this contractor may provide coverage for the components of tests that have demonstrated clinical utility when used in the proper clinical context described below.

Clinical Indications

PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be

considered reasonable and necessary when the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.

PGx testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Unless the record reflects that the treating clinician has already considered non-genetic factors to make a preliminary drug selection, PGx testing is not considered reasonable and necessary.

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: MoIDx: Pharmacogenomics Testing (A58395)
Original Effective Date 07/26/2020
Revision Effective Date 10/24/2024

81328 is listed in the CPT code set relevant to the policy; and also in the Group 1 Codes

CPT code 81328 is also listed in Group 1 codes in the following WPS articles:

- Local Coverage Article: MoIDx: Molecular Diagnostic Tests (MDT) (A57772)
Original Effective Date 11/01/2019
Revision Effective Date 10/01/2024
- Local Coverage Article: MoIDx: Repeat Germline Testing (A57100)
Original Effective Date 06/14/2020
Revision Effective Date 10/01/2024
- Local Coverage Article: MoIDx: Testing of Multiple Genes (A57880)
Original Effective Date 12/26/2019
Revision Effective Date 12/28/2023

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Vladutiu GD. Genetic predisposition to statin myopathy. *Curr Opin Rheumatol*. Nov 2008;20(6):648-655. PMID 18946323
2. Maggo SD, Kennedy MA, Clark DW. Clinical implications of pharmacogenetic variation on the effects of statins. *Drug Saf*. Jan 1 2011;34(1):1-19. PMID 21142270
3. Arnold SV, Spertus JA, Tang F, et al. Statin use in outpatients with obstructive coronary artery disease. *Circulation*. Nov 29 2011; 124(22): 2405-10. PMID 22064595
4. Virani SS, Woodard LD, Chitwood SS, et al. Frequency and correlates of treatment intensification for elevated cholesterol levels in patients with cardiovascular disease. *Am Heart J*. Oct 2011; 162(4): 725-732.e1. PMID 21982666
5. Aggarwal R, Bhatt DL, Rodriguez F, et al. Trends in Lipid Concentrations and Lipid Control Among US Adults, 2007-2018. *JAMA*. Aug 23 2022; 328(8): 737-745. PMID 35997731
6. Dorsch MP, Lester CA, Ding Y, et al. Effects of Race on Statin Prescribing for Primary Prevention With High Atherosclerotic Cardiovascular Disease Risk in a Large Healthcare System. *J Am Heart Assoc*. Nov 19 2019; 8(22): e014709. PMID 31707943
7. Guadamuz JS, Durazo-Arvizu RA, Daviglius ML, et al. Immigration Status and Disparities in the Treatment of Cardiovascular Disease Risk Factors in the Hispanic Community Health Study/Study of Latinos (Visit 2, 2014-2017). *Am J Public Health*. Sep 2020; 110(9): 1397-1404. PMID 32673107
8. He J, Zhu Z, Bundy JD, et al. Trends in Cardiovascular Risk Factors in US Adults by Race and Ethnicity and Socioeconomic Status, 1999-2018. *JAMA*. Oct 05 2021; 326(13): 1286-1298. PMID 34609450
9. Newman CB, Preiss D, Tobert JA, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*. Feb 2019; 39(2): e38-e81. PMID 30580575
10. Warden BA, Guyton JR, Kovacs AC, et al. Assessment and management of statin-associated muscle symptoms (SAMS): A clinical perspective from the National Lipid Association. *J Clin Lipidol*. 2023; 17(1): 19-39. PMID 36115813
11. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *Circulation*. Aug 20 2002;106(8):1024-1028. PMID 12186811
12. Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *N Engl J Med*. Aug 21 2008;359(8):789-799. PMID 18650507
13. McKenney JM, Davidson MH, Jacobson TA, et al. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. Apr 17 2006;97(8A):89C-94C. PMID 16581336
14. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol*. Apr 17 2006;97(8A):52C-60C. PMID 16581329
15. Wilke RA, Ramsey LB, Johnson SG, et al. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther*. Jul 2012;92(1):112-117. PMID 22617227
16. Schech S, Graham D, Staffa J, et al. Risk factors for statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Saf*. Mar 2007;16(3):352-358. PMID 16892458

17. Luzum JA, Kitzmiller JP, Isackson PJ, et al. GATM polymorphism associated with the risk for statin-induced myopathy does not replicate in case-control analysis of 715 dyslipidemic individuals. *Cell Metab.* Apr 7 2015;21(4):622-627. PMID 25863251
18. Boston Heart Diagnostics Corp. The science behind the Boston Heart Statin Induced Myopathy (SLCO1B1) Genotype test 2016;
<https://bostonheartdiagnostics.com/test/boston-heart-statin-induced-myopathy-slco1b1-genotype-test/> Accessed 11/25/24.
19. de Keyser CE, Peters BJ, Becker ML, et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. *Pharmacogenet Genomics.* Jan 2014;24(1):43-51. PMID 24263182
20. Danik JS, Chasman DI, MacFadyen JG, et al. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. *Am Heart J.* Jun 2013;165(6):1008-1014. PMID 23708174
21. Xiang Q, Chen SQ, Ma LY et al. Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. *Pharmacogenomics J.*, 2018 Sep 27;18(6). PMID 30250148.
22. Vassy JL, Chun S, Advani S, et al. Impact of SLCO1B1 Pharmacogenetic Testing on Patient and Healthcare Outcomes: A Systematic Review. *Clin Pharmacol Ther.* Aug 23 2018. PMID 30137643
23. Voora D. Genetically Guided Statin Therapy (Report no. AFRL-SA-WP-TR-2017-0005). Wright-Patterson Air Force Base, OH: USAF School of Aerospace Medicine; 2017.
24. Vassy JL, Gaziano JM, Green RC, et al. Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol: A Randomized Clinical Trial. *JAMA Netw Open.* Dec 01 2020; 3(12): e2027092. PMID 33270123
25. Hoffman JM, Haidar CE, Wilkinson MR, et al. PG4KDS: A model for the clinical implementation of pre-emptive pharmacogenetics. *Am J Med Genet C Semin Med Genet.* Mar 2014;166(1):45-55. PMID 24619595
26. Ramsey LB, Johnson SG, Caudle KE, et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther.* Oct 2014;96(4):423-428. PMID 24918167
27. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD) MoIDX: Pharmacogenomics Testing (L38435). Revision effective date: 10/01/2023
28. Wisconsin Physicians Service Insurance Corporation. Billing and Coding: MoIDX: Repeat Germline Testing (A57100) Revision effective date: 10/01/2023
29. Wisconsin Physicians Service Insurance Corporation. Billing and coding: MoIDX: Molecular Diagnostic Tests (MDT) A57772. Revision effective date: 10/01/2023
30. Wisconsin Physicians Service Insurance Corporation. Billing and Coding: MoIDX: Testing of Multiple Genes. A57880 Revision effective date: 02/24/2022

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/25/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/18	2/20/18	2/20/18	Joint policy established
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance References 10 and 13 added
5/1/21	2/16/21		Routine maintenance
5/1/22	2/15/22		Routine maintenance Ref 16 added
5/1/23	2/21/23		Routine maintenance (jf) Vendor Managed: NA
5/1/24	2/20/24		Routine maintenance (jf) Vendor Managed: NA
5/1/25	2/18/25		Routine maintenance (jf) Vendor Managed: NA Ref Added: 9,10

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR STATIN-INDUCED MYOPATHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.