Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/22**
(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]

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 (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

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
Stain-Induced Myopathy

Statins are associated with a known risk of muscle-related symptoms, which are the most common adverse effects of statin drugs. Myopathy is a general term for muscle toxicity. Three categories of statin-induced myopathy were defined in 2002 by a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute: [3]

- Statin-induced myalgia, defined as any muscle symptoms that occur without an elevation of serum creatinine kinase;
- Statin-induced myositis, defined as muscle symptoms with an elevation of serum creatinine kinase; and
- Statin-induced rhabdomyolysis, defined as markedly severe muscle symptoms with an elevation of creatinine kinase greater than 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.[4] Myalgias without other clinical manifestations are not associated with clinically important adverse events and resolve when the statin is discontinued.

The incidence of myalgia varies widely. In clinical trials, these have been reported in 1.5% to 3.0% of patients; in most trials, the rate of myalgias in patients on statin therapy is not increased compared with placebo treatment.[5] In observational studies, higher rates of 10% to 15% have been reported.[2]

Myositis is much less common than myalgias, with an estimated rate of 5 per 100,000 patient-years, and an estimated per-person incidence of 0.01%.[5] In virtually all cases, myositis resolves with discontinuation of the statin.

Rhabdomyolysis is the most severe clinical manifestation of statin-induced myopathy and can be life-threatening. The National Lipid Association estimated that rhabdomyolysis occurs at a rate of 1.6 per 100,000 patient-years, and the U.S. Food and Drug Administration (FDA) adverse events reporting system has estimated a rate of 0.7 per 100,000 patient-years.[5] A

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.[6] Fatalities from statin-induced rhabdomyolysis can occur, but the mortality rate is not well-defined. FDA estimated that deaths from rhabdomyolysis occur at a rate of less than 1 death per million prescriptions. [3]

A number of clinical factors are associated with an increased risk of statin myopathy. Statin dose is probably the strongest risk factor, with an estimated 6-fold increase for patients on high-dose7 (age is also a strong risk factor). 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.[8] 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.7 Other factors that may be associated with myopathy include female sex and intense physical exercise.[7] The perceived risk of statin-induced myopathy may contribute to suboptimal statin use in patients with indications. It is estimated that less than 50% of patients in the U.S. who would benefit from statins are currently taking them, a substantial percentage of whom do not adhere to prescribed statin regimens.[1]

Genetic Factors Associated with Statin-Induced Myopathy

A variety of genetic factors are associated with statin myopathy. The cytochrome p450 system in the liver is the main pathway by which statins are metabolized. Numerous genetic variants in cytochrome p450 proteins affect the pharmacokinetics of statin metabolism and serum statin levels.[2] Other genetic variants affect statin metabolism, efficacy, and susceptibility to adverse effects; these genetic variants involve variations in the apolipoproteins such as apo E, variations in the cholesterol ester transfer proteins, or variations in the coenzyme Q pathway. [1]

Variations in the *SLCO1B1* gene also affect statin metabolism and are among the most well studied genetic variants. These variants are the genetic markers for which there are commercially available tests. This gene codes for a transporter protein that is part of the solute carrier organic ion transporter system, which mediates the influx and metabolism of statins in the liver.(2) Single nucleotide variants (SNVs) in this gene are associated with variations in the risk of statin-induced myopathy. The T/T allele is the wild-type and associated with the lowest risk of myopathy. The C/C allele is associated with the highest risk of myopathy, and the T/C allele with an intermediate risk. The T allele has a prevalence of approximately 87%, and the C allele has a prevalence of approximately 13%.[4]

Other genes have also been studied, including *ABCB1*, which encodes ATP-binding cassette (ABC) transporters subfamily B member 1 (ABCB1/P-glycoprotein 1), *ABCG2*, which encodes ABC transporters subfamily G member 2 (ABCG2/breast cancer resistance protein), and the coenzyme Q2 (*COQ2*) homolog gene. Other studies have evaluated the association between variants in the *GATM* gene and statin-induced myopathy (the *GATM* gene encodes a glycine amidinotransferase that is the rate-limited enzyme in creatine biosynthesis). However, it should be noted that the association between variants has not been consistently replicated.[9]

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 Homcysteine (Collaboration Group 2008) published a genome-wide association study based on data from an RCT of 12,064 patients assigned to simvastin 20 mg or 80 mg.[4] Of the patients in the 80-mg statin group, 0.8% had elevated serum creatinine kinase levels more than 10 times normal, and an additional 0.8% had creatinine kinase levels that were more than 3 times normal. The *SLCO1B1* locus was the single-nucleotide variant that had a strong association with myopathy. The cumulative risk of developing myopathy after six years of treatment with simvastatin 80 mg was 0.6% for patients with the T/T allele, 3% for patients with the T/C allele, and 18% for patients with the C/C allele.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine investigators replicated the association of the *SLCO1B1* genetic 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 creatinine kinase levels greater than 10 times normal. *SLCO1B1* variants were strongly associated with myopathy in this replication study.

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.10 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.[11] 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.

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.[12] 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 simvastatin-associated myopathy, testing for *SLCO1B1* variants could potentially result in changes in medications that would reduce the risk of adverse drug reactions.

The question addressed in this evidence review is: Does testing for *SLCO1B1* variants improve the net health outcome in patients treated with statins?

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. Asymptomatic patients are typically placed onstatin therapy by primary care physicians. Symptomatic patients are referred to cardiologists.

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.[13] 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 less significant risk of statin-induced myopathy compared to the other alleles 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, 2.35; 95% CI, 1.08 to 5.12; p = .032) or rosuvastatin (odds ratio, 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 (odds ratio, 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 studies.

Randomized Controlled Trials

Vassy et al (2018) conducted a systematic review of *SLCO1B1* testing on patient and clinical outcomes.[14] They identified 5 pilot studies and an RCT by Voora et al (2017) that studied how *SLCO1B1* test results influence patient outcomes (Table 1).[15] 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-naive patients eligible for statin therapy due to cardiovascular disease risk factors (Table 1).[16] 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)[15]	U.S.	2013-2016	3	159 nonusers of statin therapy due to suspected side effects	n=83 Immediate results of *SLCO1B1* variant testing	n=76 Delayed (8 mo) results of *SLCO1B1* variant testing
Vassy et al (2020)[16] 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	n=193 Immediate results of SLCO1B1 variant testing	n=215 Delayed (12 mo) results of SLCO1B1 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)[15]	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)[16]	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)[15]			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)16	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)[15]		1, 2. Patients were not blinded, which might have affected adherence and questionnaire responses				
Vassy et al (2020)[16]	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 two randomized controlled trials. 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 one 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.

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.[18] These guidelines on patient management for various *SLCO1B* genotypes recommended prescribing a lower dose or considering an alternative statin and considering routine creatinine kinase surveillance in patients with *SLCO1B* genotypes consistent with intermediate or low statin metabolism.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov did not identify any ongoing or unpublised 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): MolDx: Pharmacogenomics Testing (L38435)
Original Effective Date 07/26/2020
Revision Effective Date 08/06/2020

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: MolDx: Pharmacogenomics Testing (A58395)
Original Effective Date 07/26/2020
Revision Effective Date 08/23/2021

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: MolDx: Molecular Diagnostic Tests (MDT) (A57772)
  Original Effective Date 11/01/2019
  Revision Effective Date 01/01/2022
- Local Coverage Article: MolDx: Repeat Germline Testing (A57100)
  Original Effective Date 06/14/2020
  Revision Effective Date 01/01/2022
- Local Coverage Article: MolDx: Testing of Multiple Genes (A57880)
  Original Effective Date 12/26/2019
  Revision Effective Date 01/01/2022

(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

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13. 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.

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/3/22, 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

Next Review Date: 1st Qtr, 2023

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.