Genetic testing for the presence of variants in the *SLCO1B1* gene to identify patients at risk of statin-induced myopathy is considered **not medically necessary**.

**POLICY GUIDELINES**

**GENETICS NOMENCLATURE UPDATE**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
</table>
### GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### CODING

See the Codes table for details.

### BENEFIT APPLICATION

**BLUECARD/NATIONAL ACCOUNT ISSUES**

Some Plans may have contract or benefit exclusions for genetic testing.

### BACKGROUND

**STATINS**

HMG-CoA reductase inhibitors, or statin drugs, are the primary pharmacologic treatment for hypercholesterolemia worldwide. In the United States, an estimated 38 million people took statins in 2008. The use of statins is associated with an approximately 30% reduction in cardiovascular events across a wide variety of populations.

**Statin-Induced Myopathy**

Statin-induced myopathy is the most common manifestation of myopathy; it is characterized by muscle pain, cramps, fatigue, and/or weakness. 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. In observational studies, higher rates of 10% to 15% have been reported.

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%. 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 adverse events reporting system has estimated a rate of 0.7 per 100,000 patient-years. 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. Fatalities from statin-induced rhabdomyolysis can occur, but the mortality rate is not well-defined. The Food and Drug Administration has estimated that deaths from rhabdomyolysis occur at a rate of less than 1 death per million prescriptions.

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 statins (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 4 times higher than for younger patients. Some statins may be associated with a 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. Other factors that may be associated with myopathy include female sex and intense physical exercise. 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 United States who would benefit from statins are currently taking them, a substantial percentage of whom do not adhere to prescribed statin regimens.

**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. Other genetic variants affect statin metabolism, efficacy, and susceptibility to adverse events; 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.

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. Single nucleotide variants 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%.

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...
MP 2.04.96
Genetic Testing for Statin-Induced Myopathy

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.\(^9\)

**Commerci**ally 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; for example, ApolloGen.

**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, the Food and Drug Administration has chosen not to require any regulatory review of this test.

**RATIONALE**

This evidence review was created in June 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through September 4, 2018.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in 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 a 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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
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) Collaboration Group (2008) published a genome-wide association study based on data from an RCT of 12,064 patients assigned to simvastatin 20 mg or 80 mg. 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 6 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 SEARCH 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 ten 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 (STRENGTH) study was a randomized trial that examined statin response and safety by dose of statin, statin type, and presence of genetic markers. 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. The study’s primary outcome was a reduction in statin dose or a switch to another statin-lowering drug as an indicator for 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, 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. 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?

Original Policy Date: June 2013
The following PICOTS were used to select literature to inform this review.

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

**Interventions**
The intervention of interest is testing for \textit{SLCO1B1} variants.

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

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

**Setting**
Asymptomatic patients are typically placed on statin therapy by primary care physicians. Symptomatic patients are referred to cardiologists.

**Randomized Controlled Trials**
Vassy et al (2018) conducted a systematic review of \textit{SLCO1B1} testing of patient and clinical outcomes. They identified 5 pilot studies and an RCT by Voora (2017) that studied how \textit{SLCO1B1} test results influence patient outcomes (see Table 1). Voora recruited patients who had discontinued statin therapy due to suspected side effects (73\% reported myalgia, 25\% of patients were \textit{SLCO1B1}*5 carriers). Patients were randomized to immediate or delayed results of \textit{SLCO1B1} testing, stratified based on \textit{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, Brief Pain Inventory, and 12-Item Short-Form Health Survey. Voora reported a significant difference between groups in low-density lipoprotein cholesterol 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).

### Table 1. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Dates</th>
<th>Sites</th>
<th>Participants</th>
<th>Interventions</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voora (2017)</td>
<td>U.S.</td>
<td>2013-2016</td>
<td>3</td>
<td>159 nonusers of statin therapy due to suspected side effects</td>
<td>Immediate results of \textit{SLCO1B1} variant testing</td>
<td>Delayed (8 mo) results of \textit{SLCO1B1} variant testing</td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial.

### Table 2. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Morisky Medication</th>
<th>LDL-C (mg/dL) at 3 Months (SD)</th>
<th>LDL-C (mg/dL) at 8 Months</th>
<th>Brief Pain Inventory</th>
<th>SF-12 Score</th>
</tr>
</thead>
</table>

**Original Policy Date:** June 2013
Table 3. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population a</th>
<th>Intervention b</th>
<th>Comparator c</th>
<th>Outcomes d</th>
<th>Follow-Up e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voora (2017) 14</td>
<td>1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.</td>
<td>2. Participation in the study might have increased medication adherence</td>
<td>1. No 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.</td>
<td>1, 2. 8 mo might be insufficient to evaluate medication adherence</td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps 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 Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation a</th>
<th>Blinding b</th>
<th>Selective Reporting d</th>
<th>Data Completeness e</th>
<th>Power d</th>
<th>Statistical f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voora (2017) 14</td>
<td>1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.</td>
<td>1. Patients were not blinded, which might have affected adherence and questionnaire responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.  


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).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

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. 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 randomized controlled trial. 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 specific drug) has positive outcomes in terms of lower rates of myopathy with adequate lipid control and tolerability of alternative treatments. One randomized controlled trial was identified that evaluated adherence to medication and 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 with knowledge of the SLCO1B1 haplotype status. There was a decrease in low-density lipoprotein cholesterol at 3 months but not at 8 months in the active intervention group. Interpretation of this trial is limited due to the lack of blinding of participants and short-term outcomes, which might have affected adherence to medications and patient responses on questionnaires. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 5.
Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Comple tion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT0287193</td>
<td>Clinical Safety and Efficacy of Pharmacogenetics in Veteran Care</td>
<td>408</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81328</td>
<td>SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg. *5)</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>G71.14</td>
<td>Drug induced myotonia</td>
</tr>
<tr>
<td></td>
<td>T46.6X5S</td>
<td>Adverse effect of antihyperlipidemic and antiarteriosclerotic drugs, sequela</td>
</tr>
</tbody>
</table>

**ICD-10-PCS**

Not applicable. There are no ICD procedure codes for laboratory tests.

**Type of Service** Laboratory

**Place of Service** Outpatient

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>05/22/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 1, 2014; references 9 and 12-16 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>05/21/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 17, 2015; references 9-10, 18, and 20 added. Policy statement unchanged.</td>
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<td>12/23/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 3, 2016; references 11-12 and 21 added. Policy statement unchanged.</td>
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<tr>
<td>11/30/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through September 11, 2017; references 10-13 and 15 updated. Policy statement unchanged.</td>
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<tr>
<td>11/15/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 11/15/2018. Policy updated with literature review through September 4, 2018; references 13-14 added. Policy statement unchanged.</td>
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