Policy Statement

KIF6 genotyping is considered investigational for predicting cardiovascular risk and/or the effectiveness of statin therapy.

Policy Guidelines

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Coding
There is currently no specific CPT code for KIF6 genotyping. The following CPT code would likely be used:
- **81479**: Unlisted molecular pathology procedure

Description
Genetic testing to determine kinesin-like protein 6 (KIF6) Trp719Arg variant status is being evaluated as a prognostic test to predict the risk of future cardiovascular events and as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

Related Policies
- N/A

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

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In January 2011, Celera Corp. submitted a premarket approval application to the FDA for its KIF6 Genotyping Assay performed using Abbott’s m2000™ instrument system. On April 7, the FDA informed Celera that its application was not approvable “without major amendment.” The data and publications submitted were deemed “…insufficient to demonstrate the safety and effectiveness of the device for its proposed intended use.” The FDA indicated that additional data on clinical utility might be required, which could include conducting a randomized controlled trial. An online search in 2017 found no update.

Now a wholly owned subsidiary of Quest Diagnostics, Celera holds a U.S. patent on methods of determining coronary heart disease (CHD) risk through detection of the KIF6 gene variant and reduction of such increased risk by atorvastatin and pravastatin therapy and offers the Cardio IQ™ KIF6 Genotype. San Francisco General Hospital’s Clinical Chemistry Laboratory is the only non-Celera lab licensed to develop a KIF6 LDT.

Rationale
Background
Kinesin-like protein 6 (KIF6) belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the KIF6 gene product is as yet undetermined. It has been...
reported that the gene is not expressed in the vasculature, the primary site of atherosclerosis, but is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. In contrast, a study presented at a 2010 American Heart Association scientific session reported on data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is no strong evidence that KIF6 protein plays a direct biologic role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction.

Analyses of prospective observational studies of cardiovascular health and the placebo arm of randomized controlled trials (RCTs) of statin interventions in at-risk populations have suggested a significant association between the arginine-to-tryptophan substitution at position 719 (Trp719Arg) single-nucleotide polymorphism (rs20455) in KIF6 and the development of clinical CAD. Approximately 60% of the population carries the putative KIF6 high-risk 719Arg allele. Moreover, carriers of the 719Arg allele in the treatment arms of the statin trials appeared to be at no increased or decreased risk of CAD or recurrent MI, depending on the intensity of the statin therapy. These results have supported the development of a KIF6 Trp719Arg genotyping test for use as a predictor of CAD risk and the likely effectiveness of statin therapy.

**Literature Review**

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

**KIF6 Genotyping**

**Clinical Context and Test Purpose**

The purpose of testing for kinesin-like protein 6 (KIF6) gene variants in patients receiving statins therapy for coronary artery disease (CAD) is to inform a decision whether an individual who has a variant is at a higher risk of a future cardiovascular event, and therefore statin treatment should be initiated or the existing statin dose should be increased. The questions addressed in this evidence review are: (1) Is there evidence that testing for variants in the KIF6 gene has clinical validity?; and (2) Does patient management change in a way that would improve outcomes as a result of testing?

The following PICOTS were used to select literature to inform this review.

**Patients**

The population of interest includes patients who require or are being treated with statins for primary or secondary prevention of cardiovascular disease.

**Interventions**

Genetic testing for variants in the KIF6 gene to guide initiation or intensification of statin therapy.

**Comparators**

The comparator of interest is standard clinical care without genetic testing, in which decisions about medical therapy are based on standard lipid levels and risk factors for CAD (e.g., smoking, weight, diet, diabetes, family history of CAD). The intensity of therapies is based on a continued monitoring of response to treatment (e.g., achieving target low-density lipoprotein [LDL] reduction).
Outcomes
The general outcomes of interest are overall survival, test accuracy, test validity, change in disease status, and morbid events. Specific outcomes of interest are a reduction in risks of a CAD event and its associated mortality. The potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to the initiation of unnecessary treatment and adverse effects from that treatment. False-negative test results could also lead to under treatment.

Timing
Decisions about choosing statin therapy are primarily driven by risks of CAD over a 10-year horizon. Similarly, the primary outcomes of interest for this review are CAD events and mortality over a 10-year period.

Setting
Patients being treated with statins for primary prophylaxis of CAD are typically treated by primary care providers; those requiring statin therapy for secondary prevention may be treated by specialists or primary care providers. Consultations generally occur in outpatient care.

Analytic Validity
Measures of analytic validity include sensitivity (detection rate), specificity (1 – false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

The KIF6 Trp719Arg single-nucleotide variant (SNV) testing is conducted using real-time polymerase chain reaction (PCR), with PCR amplification of target sequences from genomic DNA, followed by allele-specific oligonucleotide ligation. No studies were identified that specifically addressed the analytic validity of commercially available assays for the KIF6 Trp719Arg SNV. One study (2008) reported that the proportion of samples with successful genotype determination was 97.9%.3

Section Summary: Analytic Validity
No studies were identified that specifically addressed the analytic validity of available assays for the KIF6 Trp719Arg SNV.

Clinical Validity
Multiple studies have reported on the association between the KIF6 Trp719Arg SNV and the risks of CAD and response to statin therapy, with varying results about the strength and direction of the association. These studies include early retrospective evaluations of prospective, observational studies (see Table 1, part 1)3,5; retrospective evaluations of the placebo arms of randomized controlled trials (RCTs) of statin therapy (see Table 1, part 2)6,7; large meta-analysis of 19 case-control studies (see Table 1, part 3)8 and finally retrospective evaluation of more recently conducted RCTs (see Table 1, part 4).

Patient populations in these studies include relatively unselected prevention cohorts and those with a higher risk of a CAD event. In prospective, observational studies and the placebo arms of RCTs, the Trp719Arg variant was positively associated with some CAD-related outcomes. In some RCTs,6,7,9,10 719Arg variant carriers had larger decreases in coronary heart disease risk in association with statin treatment than noncarriers.10

However, a large meta-analysis of 19 case-control studies (see Table 1, part 3) found no association between the Trp719Arg SNV and nonfatal CAD.8 A major limitation of this trial was the exclusion of fatal coronary disease events and inability to examine whether the effect on risk was modified by statin therapy. In addition to the findings of the meta-analysis, none of several, large genome-wide association studies for CAD or myocardial infarction reported any SNVs at the KIF6 locus as significant.11-15 Retrospective analyses of data from major RCTs published from
2011 to 2012 was consistent with the meta-analytic results and statins were equally effective at reducing cardiovascular event rates among carriers and noncarriers of the KIF6 variant.\textsuperscript{16-18}

In a retrospective analysis of 2 prospective trials, Arsenault et al (2012) investigated whether KIF6 variant carriers obtain more benefit from high-dose statin therapy.\textsuperscript{19} The benefit was similar across all groups, except for those with homozygous variants, in whom there was a statistically significant benefit with a higher statin dose. However, the genotype by treatment interaction was not significant.

The conflicting results on the KIF6 variant, CHD, and treatment outcomes might have been explained in a meta-analysis by Ference et al (2011).\textsuperscript{20} Reviewers selected 37 case-control studies, prospective cohort studies, or randomized trial treatment allocation arms (each considered as a separate cohort), which together enrolled 144,931 participants and reported 27,465 CHD events. The KIF6 genotype, particularly the Trp719Arg SNV carrier status, was not associated with increased risk of CHD event. However, for each millimole per liter increase in low-density lipoprotein cholesterol (LDL-C), KIF6 variant carriers experienced a 15% greater increase in the relative risk of CHD compared with noncarriers (ratio of relative risk, 1.15; 95% confidence interval [CI], 1.06 to 1.25, \( p = 0.001 \)). Similarly, the decrease in risk for each mmol/L decrease in LDL was 13% higher for variant carriers. Also included in the meta-analysis were 8 randomized trials of statin therapy involving 50,060 participants and 7307 CHD events. KIF6 variant carriers derived a greater clinical benefit for each millimole per liter reduction in LDL-C during treatment with a statin than did noncarriers (ratio of relative risk, 0.87; 95% CI, 0.77 to 0.99; \( p = 0.038 \)). Thus, the results suggest that the KIF6 Trp719Arg variant increases vulnerability to LDL-C. This result may explain why KIF6 variant carriers appear to derive greater clinical benefit from a statin even though the variant itself does not appear to affect the ability of the statin to lower LDL-C, nor does it appear to be independently associated with the risk of CHD on average. However, “the association between the KIF6 variant and the risk of CHD will vary according to the average LDL cholesterol level of the population(s) under study.”\textsuperscript{20} This association may explain some of the conflicting reports of KIF6 genotype association with CHD.

### Table 1. Results of Individual Studies Investigating the Differential Effects of KIF6 Genotype on CV Outcomes and a Meta-Analysis of the Association Between KIF6 Genotype and CAD Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observational Study or Placebo Arm, KIF6V Carriers vs Noncarriers (95% CI)</td>
<td>Statin Arm vs Placebo Arm (unless otherwise stated) (95% CI)</td>
</tr>
<tr>
<td><strong>Part 1. KIF6 variant association with CAD outcomes in retrospective evaluations of prospective, observational studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrison et al (2007) Retrospective evaluation of ARIC study cohort\textsuperscript{4}</td>
<td>U.S. individuals ages 45-64 y</td>
<td>MI, CHD death, or coronary revascularization</td>
<td>HR=1.09 (1.00 to 1.19)</td>
</tr>
<tr>
<td>Shiffman et al (2008) Retrospective evaluation of CHS\textsuperscript{5}</td>
<td>Adults ages ( \geq 65 ) y</td>
<td>Incident MI</td>
<td>HR=1.29 (90% CI, 1.1 to 1.52)\textsuperscript{a} (95% CI, 1.06 to 1.6)\textsuperscript{b}</td>
</tr>
<tr>
<td>Shiffman et al (2008) Retrospective evaluation of WHS\textsuperscript{6}</td>
<td>Healthy white American women</td>
<td>Incident CHD event (MI, coronary revascularization, or CV-related death) or • CHD HR=1.24 (1.04 to 1.46) • MI HR=1.34 (1.02 to 1.75) • Stroke HR=NS</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Part 2. KIF6 variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iakoubova et al (2008)</td>
<td>White MI survivors with total cholesterol &lt;240 mg/dL</td>
<td>Recurrent fatal or nonfatal MI</td>
<td>• Among KIF6V carriers: HR=0.63 (0.46 to 0.87)&lt;br&gt;• Among noncarriers: HR=0.80 (0.52 to 1.24)</td>
</tr>
<tr>
<td>Shiffman et al (2010)</td>
<td>MI survivors (all ethnicities) with total cholesterol &lt;240 mg/dL</td>
<td>Recurrent fatal or nonfatal MI</td>
<td>• Adjusted for self-reported ethnicity:&lt;br&gt;• Among KIF6V carriers: HR=0.63 (0.49 to 0.83)&lt;br&gt;• Among noncarriers: HR=1.01 (0.69 to 1.45)</td>
</tr>
<tr>
<td>Iakoubova et al (2008)</td>
<td>Men with hypercholesterolemia but no history of MI</td>
<td>Nonfatal MI, revascularization procedures, or death from CHD</td>
<td>• Among KIF6V carriers: HR=0.50 (0.38 to 0.68)&lt;br&gt;• Among noncarriers: HR=0.91 (0.64 to 1.28)</td>
</tr>
<tr>
<td>Iakoubova et al (2008)</td>
<td>Patients hospitalized for MI or high-risk unstable angina</td>
<td>Composite: all-cause mortality, MI, unstable angina, or stroke</td>
<td>No placebo arm&lt;br&gt;Intensive vs moderate statin therapy arms among:&lt;br&gt;• KIF6V carriers: HR=0.59 (0.45 to 0.77)&lt;br&gt;• Non-KIF6V carriers: HR=0.94 (0.70 to 1.27)</td>
</tr>
<tr>
<td>Iakoubova et al (2010)</td>
<td>Older patients with: preexisting vascular disease, increased risk for vascular disease</td>
<td>Composite: death from CHD, nonfatal MI, or fatal/nonfatal stroke</td>
<td>• Among KIF6V carriers: HR=0.66 (0.52 to 0.86)&lt;br&gt;• Among noncarriers: HR=0.94 (0.69 to 1.28)&lt;br&gt;No benefit</td>
</tr>
</tbody>
</table>

### Part 3. Meta-analysis of KIF6 variant association with CAD outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assimes et al (2010)</td>
<td>(Various) 17,000 cases, 39,369 controls</td>
<td>OR=0.98 (0.95 to 1.02)&lt;br&gt;NA&lt;br&gt;&lt;br&gt;NA</td>
</tr>
</tbody>
</table>

### Part 4. Recent publications: KIF6 variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ridker et al (2011)</td>
<td>Men and women free of diabetes or prior CVD</td>
<td>HR=0.91 (0.66 to 1.26)&lt;br&gt;• Among KIF6V carriers: HR=0.61 (0.43 to 0.87)&lt;br&gt;• Among noncarriers: HR=0.59 (0.39 to 0.88)&lt;br&gt;P interact, 0.90</td>
</tr>
<tr>
<td>Study</td>
<td>Patients Evaluated</td>
<td>KIF6 Association Evaluated</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hopewell et al (2011)</td>
<td>Individuals at high risk for or previous diagnosis of CVD</td>
<td>Composite: CHD death, nonfatal MI, strokes, coronary or noncoronary revascularization(s)</td>
</tr>
</tbody>
</table>
| Hoffmann et al (2011)                     | Patients with T2D and <2 y prior hemodialysis treatment                              | Composite: death from cardiac causes, MI, or stroke                                         | • Among KIF6V carriers: 23% (16% to 29%)  
• Among noncarriers: 24% (17% to 31%)  
P interact, 0.4-0.7                                                                                                                                   |
| Arsenault et al (2012)                    | TNT: patients with stable CHD and LDL-C levels <130 mg/dL  
IDEAL: patients with a history of MI | Composite: coronary death, nonfatal MI, resuscitation after cardiac arrest and fatal or nonfatal stroke | HR=0.83  
(0.66 to 1.05)  
NA  
• Among statin-treated, KIF6V carriers vs noncarriers:  
• HR=0.96 (0.76 to 1.23)  
• Among KIF6V carriers: 0.85 (0.66 to 1.11)  
• Among homozygote carriers: 0.44 (0.23 to 0.84)  
• Among noncarriers: 0.81 (0.59 to 1.11)  
P interact, 0.81  
• Among KIF6V carriers: 0.91 (0.58 to 1.43)  
• Among homozygote carriers: 0.88 (0.62 to 1.07)  
• Among noncarriers: 0.85 (0.67 to 1.10), P interact, 0.91                                                                                   |
| Akao et al (2012)                         | Individuals with history of, or risk factors for, vascular disease                 | MI or stroke                                                                               | • Homozygote HR=0.47  
p=0.03  
• For women on pravastatin only; not significant after correction for multiple comparisons                                                                                                         |

ARIC: Atherosclerosis Risk in Communities; CAD: coronary artery disease; CARE: Cholesterol and Recurrent Events trial; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; HPS: Heart Protection Study; HR: hazard ratio; IDEAL: Incremental Decrease in End Points Through Aggressive Lipid-Lowering; JUPITER: Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NA: not applicable; OR: odds ratio; PROSPER: PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy; Thrombolysis in Myocardial Infarction 22 trial; RCT: randomized controlled trial; TNT: treating to new targets; T2D: type 2 diabetes; WHS: Women’s Health Study; WOSCOPS: West of Scotland Coronary Prevention Study.

a Published.
b Calculated from published data.

Section Summary: Clinical Validity
There uncertainty about the clinical validity of genetic testing for KIF6 Trp719Arg SNV due to conflicting results on the association between KIF6 variant carrier status and the risks of CAD and
to conflicting results of the association between KIF6 variant carrier status and response to statin therapy.

**Clinical Utility**
The potential clinical utility of genetic testing for KIF6 includes confirming a diagnosis and evaluating whether there is a modifiable treatment option that would lower the risk of CAD for that individual.

**Direct Evidence**
Direct evidence of clinical utility would be provided by studies comparing health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs.

Charland et al (2014) reported the results of a prospective, nonrandomized, open-label, single-center trial designed to compare statin adherence at 6 months in those who learned about their KIF6 carrier status with those who did not. Patients older than 18 years of age who were new to statin therapy (with no pharmacy electronic claims for statins in prior 6 months before the index date) were enrolled, and KIF6 genotyping was performed. KIF6 carrier status results were mailed to all individuals, including information on the association between KIF6 carriers and higher coronary heart disease risk reduction with statins. Patients not contacted for study participation were matched 1:1 with the final KIF6-tested group based on age, sex, index statin prescription fill channel (mail or retail pharmacy), and a number of unique chronic medications within 180 days of the statin index date to serve as controls. A secondary control cohort was created from patients who were contacted about the study and made aware that their statin adherence might be routinely monitored but who declined study participation with KIF6 testing. The primary study outcomes were statin prescription adherence and persistence, assessed using prescription claims records. Adherence was calculated as the proportion of days covered; subjects were adherent if they had 80% or more of the days covered. The proportion of patients categorized as adherent to statin therapy was 18.4% higher for the KIF6-tested group (63.4% 95% CI, 59.6% to 67.1%) than for the matched controls (45.0% 95% CI, 41.1% to 48.8% p<0.001) and 12.7% higher than for the secondary control group (50.7% 95% CI, 47.7% to 52.6% p<0.001). While this trial reported an association between receipt of KIF6-genotype testing results and higher statin adherence, the nonrandomized trial design and the baseline group differences limit the validity of the results. The potential for bias in the self-selection of healthier patients for KIF6 genotyping and the inability to isolate the incremental effects of receiving the KIF6 genotype results over other aspects of study participation limit the conclusions that can be drawn about the effect of KIF6 genotyping on adherence.

**Chain of Evidence**
Genetic testing could have utility if diagnosis led to management changes that improved outcomes.

**Section Summary: Clinical Utility**
The clinical utility of genetic testing for the KIF6 variant has not been established. It is unclear whether genetic testing for the KIF6 variant alters the clinical management decisions. One nonrandomized study suggested that subjects who received KIF6 genotype results had greater adherence to statin therapy, but the nonrandomized trial design and the baseline differences between groups limit the validity of the results. The potential for bias in the self-selection of healthier patients for KIF6 genotyping and the inability to isolate the incremental effects of receiving the KIF6 genotype results over other aspects of study participation limit the conclusions that can be drawn about the effect of KIF6 genotyping on adherence. More importantly, no study has demonstrated whether KIF6 testing leads to changes in clinical management that leads to a reduction in the risk of CAD.

**Summary of Evidence**
For individuals who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy who receive testing for kinesin-like protein 6 (KIF6) Trp719Arg variant
status, the evidence includes secondary analyses of randomized controlled trials (RCTs), case-control studies, and 1 quasi-experimental single-arm study. Relevant outcomes are overall survival, test accuracy and validity, change in disease status, morbidity events, and medication use. Data supporting the association between KIF6 variant status and coronary artery disease (CAD) outcomes are contradictory. The most recent evidence from large populations with different vascular disease risk levels has not supported a significant association between CAD risk and the presence of the variant. Further, studies of the association between response to statin therapy and KIF6 variant status are also mixed. However, a large meta-analysis has shown that carriers of the KIF6 variant derive greater clinical benefit from low-density lipoprotein cholesterol reduction (a 13% reduction in the risk of CAD outcomes) compared with noncarriers. However, no prospective RCTs have evaluated the impact of testing for KIF6 variants on changes in clinical management (e.g., intensifying the statin treatment in carriers, use of alternate approaches for lipid management in noncarriers) or outcomes. One nonrandomized study has suggested that subjects who received KIF6 genotype results had greater adherence to statin therapy, but, overall, it is uncertain whether testing for KIF6 variants will alter the clinical management decisions. The clinical utility of KIF6 testing has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

No reference to KIF6 genotyping was found in the 2010 joint American College of Cardiology Foundation and American Heart Association practice guidelines on the assessment of cardiovascular risk in asymptomatic adults.23,24

In 2013, ACC and AHA issued joint guidelines on the assessment of cardiovascular risk that does not address KIF6 genotyping.25

**U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations for KIF6 genotyping in coronary heart disease risk or the selection or use of statin therapy have been identified.

**Medicare National Coverage**

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

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA’s decisions apply to all molecular diagnostic tests for Medicare. In 2015, Palmetto GBA completed a review of the KIF6 genotype test and concluded: “To date, there is insufficient evidence to support the required clinical utility for the established Medicare benefit category. Therefore, the KIF6 genotype test is a statutorily excluded test.”26

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in April 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

### Appendix

#### Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.67

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td>X</td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
</tbody>
</table>
2.04.67  KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy
Page 10 of 13

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

References

15. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. Jun 7 2007;447(7145):661-678. PMID 17554300

**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

**Policy History**

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/29/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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