KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Policy # 00284
Original Effective Date: 02/16/2011
Current Effective Date: 09/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers kinesin-like protein 6 (KIF6) Genotyping for predicting cardiovascular risk and/or the effectiveness of statin therapy to be investigational.*

Background/Overview
Genetic testing to determine the KIF6 Trp719Arg variant status of patients is being evaluated as a prognostic test to predict risk of future cardiovascular events and/or as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

The KIF6 protein 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. Rather, it is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. In contrast, a study presented at the American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology 2010 Scientific Sessions reported data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is as yet no strong evidence that KIF6 protein plays a direct biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

Analysis of prospective observational studies of cardiovascular health and of the placebo arm of randomized controlled trials (RCTs) of statin intervention in at-risk populations has suggested a significant association between the Trp719Arg single nucleotide polymorphism (SNP; 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 risk, or at decreased risk, of CAD or recurrent MI, depending on the intensity of the statin therapy. These results supported the development of a KIF6 Trp719Arg genotyping test for use as a predictor of CAD risk and of the likely effectiveness of statin therapy.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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
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Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

In January 2011, Celera submitted a premarket approval application to FDA for its KIF6 Genotyping Assay performed using Abbott’s m2000™ instrument system. On April 7, FDA sent a letter to Celera indicating 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." FDA indicated that additional data on clinical utility may be required, which could include conducting a randomized controlled trial. An online search in February 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.

Centers for Medicare and Medicaid Services (CMS)
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 for all molecular diagnostic tests for Medicare. In 2015, Palmetto GBA completed a review on 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.”

Rationale/Source
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.
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**KIF6 GENOTYPING**

**Clinical Context and Test Purpose**
The purpose of testing for KIF6 gene variants in patients receiving statins therapy for 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 (eg, smoking, weight, diet, diabetes, family history of CAD). The intensity of therapies is based on a continued monitoring of response to treatment (eg, 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 undertreatment.

**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.
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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%.

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); retrospective evaluations of the placebo arms of RCTs of statin therapy (see Table 1, part 2); large meta-analysis of 19 case-control studies (see Table 1, part 3); 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, 719Arg variant carriers had larger decreases in coronary heart disease risk in association with statin treatment than noncarriers.

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. 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. 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.

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. 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.
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The conflicting results on the KIF6 variant, CHD, and treatment outcomes might have been explained in a meta-analysis by Ference et al (2011). 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.” 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>Observational Study or Placebo Arm, KIF6 Variant Carriers vs Noncarriers (95% CI)</th>
<th>Statin Arm vs Placebo Arm (unless otherwise stated) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1. KIF6 variant association with CAD outcomes in retrospective evaluations of prospective, observational studies</td>
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<tr>
<td>Morrison et al (2007)</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) NA</td>
<td></td>
</tr>
<tr>
<td>Shiffman et al (2008)</td>
<td>Adults ages ≥65 y</td>
<td>Incident MI</td>
<td>HR=1.29 (90% CI, 1.1 to 1.52) NA</td>
<td></td>
</tr>
<tr>
<td>Shiffman et al (2010)</td>
<td>Healthy white American women</td>
<td>Incident CHD event (MI, coronary revascularization, or CV-related death) or incident ischemic stroke</td>
<td>CHD HR=1.24 (1.04 to 1.46) MI HR=1.34 (1.02 to 1.75) Stroke HR=NS NA</td>
<td></td>
</tr>
<tr>
<td>Part 2. KIF6 variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy</td>
<td></td>
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</tr>
<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>HR=1.50 (1.05 to 2.15)</td>
<td>Among KIF6 variant carriers: HR=0.63 (0.46 to 0.87) Among noncarriers: HR=0.80 (0.52 to 1.24)</td>
</tr>
<tr>
<td>Shiffman et al (2010)</td>
<td>MI survivors (all)</td>
<td>Recurrent fatal or Adjusted for self-reported</td>
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</table>

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### Study | Patients Evaluated | KIF6 Association Evaluated | Results
--- | --- | --- | ---
Retrospective evaluation of CARE study 6 | ethnicities) with total cholesterol <240 mg/dL | nonfatal MI | ethnicity among:  
- KIF6 variant carriers: HR=0.63 (0.49 to 0.83)  
- Noncarriers: HR=1.01 (0.69 to 1.45)

Ikoubova et al (2008)  
Nested case-control study from WOSCOPS trial 7 | Men with hypercholesterolemia but no history of MI | Nonfatal MI, revascularization procedures, or death from CHD | OR=1.55 (1.14 to 2.09)  
- Among KIF6 variant carriers: HR=0.50 (0.38 to 0.68)  
- Among noncarriers: HR=0.91 (0.64 to 1.28)

Ikoubova et al (2008)  
Retrospective evaluation of PROVE IT-TIMI 22 10 | Patients hospitalized for MI or high-risk unstable angina | Composite: all-cause mortality, MI, unstable angina, or stroke | No placebo arm  
- Intensive vs moderate statin therapy arms among:  
  - KIF6 variant carriers: HR=0.59 (0.45 to 0.77)  
  - Noncarriers: HR=0.94 (0.70 to 1.27)  
- No benefit

Ikoubova et al (2010)  
Retrospective evaluation of PROSPER study 6 | Older patients with:  
- preexisting vascular disease  
- increased risk for vascular disease | Composite: death from CHD, nonfatal MI, or fatal/nonfatal stroke | HR=1.28 (0.98 to 1.69)  
- Among KIF6 variant carriers: HR=0.66 (0.52 to 0.86)  
- Among noncarriers: HR=0.94 (0.69 to 1.28)  
- No benefit

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

Assimes et al (2010)  
Meta-analysis of 19 case-control studies 4 | (Various) 17,000 cases, 39,369 controls | CAD cases with and without a diagnosis of nonfatal MI | OR=0.98 (0.95 to 1.02)  
**NA**

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

Ridker et al (2011)  
Retrospective evaluation of prospective JUPITER study 15  
(rosuvastatin vs placebo) | Men and women free of diabetes or prior CVD | Composite: CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or arterial revascularization | HR=0.61 (0.66 to 1.26)  
- Among KIF6 variant carriers: HR=0.61 (0.43 to 0.87)  
- Among noncarriers: HR=0.59 (0.39 to 0.88)  
P interact, 0.90

Hopewell et al (2011)  
Retrospective evaluation of prospective HPS 17  
(simvastatin vs placebo) | Individuals at high risk for or previous diagnosis of CVD | Composite: CHD death, nonfatal MI, strokes, coronary or noncoronary revascularizations | No significant effect on risk of major CV events, regardless of modeling approach (p range, 0.54–0.76)  
- Among KIF6 variant carriers: 23% (16% to 29%)  
- Among noncarriers: 24% (17% to 31%)  
P interact, 0.4-0.7

Hoffmann et al (2011)  
Retrospective evaluation of 4D prospective study 18  
(atorvastatin vs placebo) | Patients with T2D and <2 y prior hemodialysis treatment | Composite: death from cardiac causes, MI, or stroke | HR=0.83 (0.66 to 1.05)  
- Among statin-treated, KIF6 variant carriers vs noncarriers:  
  - HR=0.96 (0.76 to 1.23)

Arsenault et al (2012)  
Retrospective evaluation of prospective TNT 80- vs 10- 
mg/d atorvastatin) and IDEAL (80 mg/d atorvastatin vs 20-40 mg/d simvastatin) studies 19 | 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 | **NA**  
- Among KIF6 variant carriers: 0.85 (0.66 to 1.11)  
- Among homozgyote carriers: 0.44 (0.23 to 0.84)  
- Among noncarriers: 0.81 (0.59 to 1.11)  
P interact, 0.81

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>KIF6 Association Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akao et al (2012) Retrospective study of participants in PROSPECT trial,(^2) randomized to pravastatin 40 mg/d or placebo</td>
<td>Individuals with history of, or risk factors for, vascular disease</td>
<td>MI or stroke</td>
<td>• Homozygote HR=0.47 (p=0.03) (^b) • For women on pravastatin only; not significant after correction for multiple comparisons</td>
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<td></td>
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<td>NA</td>
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</tbody>
</table>

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; PROSPECT: 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 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.

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 group differences limit the validity of the results. The potential for selection bias of healthier patients who volunteered 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 KIF6 Trp719Arg variant status, the evidence includes secondary analyses of RCTs, case-control studies, and 1 quasi-experimental single-arm study. Relevant outcomes are overall survival, test accuracy and validity, change in disease status, morbid events, and medication use. Data supporting the association between KIF6 variant status and 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 (eg, 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.

References
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22. KIF6, LPA, TAS2R50, and VAMP8 genetic variation, low density lipoprotein cholesterol lowering response to pravastatin, and heart disease risk reduction in the elderly. Atherosclerosis. Feb 2012;220(2):456-462. PMID 22192511


Policy History

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<td>Medical Policy Implementation Committee approval. New policy.</td>
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<td>01/01/2017</td>
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<tr>
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</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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