Medical Policy

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

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy	Interventions of interest are: • Testing for *KIF6* Trp719Arg variant status	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Overall survival • Test accuracy • Test validity • Change in disease status • Morbid events • Medication use

DESCRIPTION

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

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Objective

The objective of this evidence review is to determine whether genetic testing for kinesin-like protein 6 (KIF6) Trp719Arg variant status predicts the response to statin therapy for patients at risk for cardiovascular disease and improves the net health outcome.

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.[1] In contrast, a study presented at the 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.[2] 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 (MI).

Analysis of prospective observational studies of cardiovascular health and of 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 variant (rs20455) in *KIF6* and the development of clinical CAD. Approximately 60% of the population carries the putative *KIF6* high-risk 719Arg allele.[3] 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 of the likely effectiveness of statin therapy.

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 FDA for its *KIF6* Genotyping Assay performed using Abbott's m2000™ instrument system. On April 7, 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." FDA indicated that additional data on clinical utility may be required, which could include conducting a randomized controlled trial.

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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."

POLICY

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

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.

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). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

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.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through March 6, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.
The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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?

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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
The test being considered is genetic testing for variants in the *KIF6* gene to guide initiation or intensification of statin therapy.

Comparators
The following practice is currently being used: 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 primary outcomes of interest for this review are CAD events and mortality over a 10-year period. 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 events 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.

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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Multiple studies have reported on the association between the *KIF6* Trp719Arg single nucleotide variant-(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 randomized controlled trials (RCTs) of statin therapy (see Table 1, part 2); large meta-

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analysis of 19 case-control studies (see Table 1, part 3); and a retrospective evaluation of more recently conducted RCTs (see Table 1, part 4).

Patient populations in these studies included relatively unselected prevention cohorts and those with a higher risk of a CAD event. In prospective, observational studies and the placebo arms of RCTs, theTrp719Arg variant was positively associated with some CAD-related outcomes. In some RCTs, 719Arg variant carriers had larger decreases in coronary heart disease (CHD) risk in association with statin treatment than noncarriers.[3-6]

However, a large meta-analysis of 19 case-control studies found no association between the Trp719Arg SNV and nonfatal CAD.[7] A major limitation of this meta-analysis 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 evaluating CAD or myocardial infarction reported any SNVs at the *KIF6* locus as significant.[8-12] Retrospective analyses of data from major RCTs published from 2011 to 2012 were consistent with the meta-analytic results, and statins were equally effective at reducing cardiovascular event rates among carriers and noncarriers of the *KIF6* variant.[13-15]

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.[16] 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 the meta-analysis by Ference et al (2011).[17] 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 cholesteroal (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 millimole per liter decrease in LDL was 13% higher for variant carriers. Also included in the meta-analysis were 8 randomized trials assessing statin therapy in 50,060 participants with 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 suggested that the *KIF6* Trp719Arg variant increases vulnerability to LDL-C. This result might 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."[17] This association might also explain some of the conflicting reports of *KIF6* genotype association with CHD.

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

Study; Trial	Patients Evaluated	*KIF6* Association Evaluated	Results	
			Observational Study or Placebo Arm, *KIF6* Variant Carriers vs Noncarriers (95% CI)	Statin Arm vs Placebo Arm (unless otherwise stated) (95% CI)
Part 1. *KIF6* variant association with CAD outcomes in retrospective evaluations of prospective, observational studies				
Morrison et al (2007)[18] Retrospective evaluation of ARIC study cohort	U.S. individuals ages 45-64 y	MI, CHD death, or coronary revascularization	HR=1.09 (1.00 to 1.19)	NA
Shiffman et al (2008)[19] Retrospective evaluation of CHS	Adults ages ≥65 y	Incident MI	HR=1.29 (90% CI, 1.1 to 1.52)[a] (95% CI, 1.06 to 1.6)[b]	NA
Shiffman et al (2008)[20] Retrospective evaluation of WHS	Healthy white American women	Incident CHD event (MI, coronary revascularization, or CV-related death) or incident ischemic stroke	• CHD HR=1.24 (1.04 to 1.46) • MI HR=1.34 (1.02 to 1.75) • Stroke HR=*NS*	NA
Part 2. *KIF6* variant association with CAD outcomes in retrospective evaluations of RCTs of statin therapy				
Iakoubova et al (2008)[3] Retrospective evaluation of CARE study	White MI survivors with total cholesterol <240 mg/dL	Recurrent fatal or nonfatal MI	HR=1.50 (1.05 to 2.15)	• *KIF6* variant carriers: HR=0.63 (0.46 to 0.87) • Noncarriers: HR=0.80 (0.52 to 1.24)
Shiffman et al (2010)[5] Retrospective evaluation of CARE study	MI survivors with total cholesterol <240 mg/dL	Recurrent fatal or nonfatal MI		Adjusted for self-reported ethnicity among: • *KIF6* variant carriers: HR=0.63 (0.49 to 0.83) • Noncarriers: HR=1.01 (0.69 to 1.45)
Iakoubova et al (2008)[3] Nested case-control study from WOSCOPS trial	Men with hyper-cholesterolemia but no history of MI	Nonfatal MI, revascularization procedures, or death from CHD	OR=1.55 (1.14 to 2.09)	• *KIF6* variant carriers: HR=0.50 (0.38 to 0.68) • Noncarriers: HR=0.91 (0.64 to 1.28)
Iakoubova et al (2008)[6] Retrospective evaluation of PROVE IT-TIMI 22	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)

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Study; Trial	Patients Evaluated	*KIF6* Association Evaluated	Results	
				• Noncarriers: HR=0.94 (0.70 to 1.27)
Iakoubova et al (2010)[4] Retrospective evaluation of PROSPER study	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)	• *KIF6* variant carriers: HR=0.66 (0.52 to 0.86) • 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)[7] Meta-analysis of 19 case-control studies	17,000 cases, 39,369 controls	CAD cases with and without 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)[13] Retrospective evaluation of prospective JUPITER study (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=0.91 (0.66 to 1.26)	• *KIF6* variant carriers: HR=0.61 (0.43 to 0.87) • Noncarriers: HR=0.59 (0.39 to 0.88) • p=0.90 (interaction)
Hopewell et al (2011)[14] Retrospective evaluation of prospective HPS (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)	• *KIF6* variant carriers: 23% (16% to 29%) • Noncarriers: 24% (17% to 31%) • p range, 0.4-0.7 (interaction)
Hoffmann et al (2011)[15] Retrospective evaluation of 4D prospective study (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)	• Statin-treated, *KIF6* variant carriers vs noncarriers: • HR=0.96 (0.76 to 1.23)
Arsenault et al (2012)[16] Retrospective evaluation of prospective TNT: atorvastatin 80- vs 10-mg/d; IDEAL: atorvastatin 80 mg/d vs simvastatin 20-40 mg/d)	• 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	• TNT *KIF6* variant carriers: 0.85 (0.66 to 1.11) • TNT homozygote carriers: 0.44 (0.23 to 0.84) • TNT noncarriers: 0.81 (0.59 to 1.11) • p=0.81 (interaction) • IDEAL *KIF6* variant carriers: 0.91 (0.58 to 1.43) • IDEAL homozygote carriers: 0.88 (0.62 to 1.07) • IDEAL noncarriers: 0.85 (0.67 to 1.10), • p=0.91 (interaction)

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Study; Trial	Patients Evaluated	*KIF6* Association Evaluated	Results	
Akao et al (2012)[21] Retrospective study of participants in PROSPER trial, randomized to pravastatin 40 mg/d or placebo	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	NA

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: Clinically Valid
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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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 is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Charland et al (2014) reported on 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.[22] 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

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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 trial and made aware that their statin adherence might be routinely monitored but who declined study participation with *KIF6* testing. The primary 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 restrict the conclusions that can be drawn about the effect of *KIF6* genotyping on adherence.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
The conflicting evidence on clinical validity does not permit conclusions on clinical utility.

Section Summary: Clinically Useful

The clinical utility of genetic testing for the *KIF6* variant has not been established. It is unclear whether genetic testing for the *KFI6* variant alters the clinical management decisions. One nonrandomized trial suggested that subjects who received *KIF6* genotype results exhibited 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 trial participation restrict 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 reduce 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 a 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 coronary artery disease outcomes are contradictory. The most recent evidence from large populations with different vascular disease risk levels has not supported a significant association between coronary artery disease risk and the presence of the variant. Further, studies of the association between response to statin therapy and *KIF6* variant status are 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 coronary artery disease outcomes) compared with noncarriers. Currently, no prospective RCTs have evaluated the impact of testing for *KIF6* variants on changes in clinical management (eg,

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intensifying the statin treatment in carriers, use of alternative approaches for lipid management in noncarriers) or outcomes. One nonrandomized study has suggested that subjects with *KIF6* genotype results showed greater adherence to statin therapy, but, overall, it is uncertain whether testing for *KFI6* variants will alter the clinical management decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

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

In 2013, the American College of Cardiology and the American Heart Association issued joint guidelines on the assessment of cardiovascular risk that did 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 use of *KIF6* genotyping to guide the selection or use of statin therapy have been identified.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2018 did not identify any ongoing or unpublished trials that would likely influence this review

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

81479 Unlisted molecular pathology procedure

- There is currently no specific CPT code for this testing. The unlisted molecular pathology code (81479) would be reported.

DIAGNOSIS

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

03-10-2011	Policy added to the bcbsks.com web site.
06-05-2012	Description section updated
	Rationale section updated
	References updated
01-15-2013	In Coding section: ▪ Added CPT code: 81479 (effective 01-01-2013)

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	▪ Updated coding instructions to remove reference to 83890-83912 which are no longer effective as of 12-31-2012.
05-10-2013	Description section updated
	Rationale section updated
	In Coding section: ▪ Updated coding instructions
	References updated
09-16-2015	Description section updated
	Rationale section updated
	References updated
04-25-2016	Description section updated
	Rationale section updated
	In Policy section: ▪ Added Policy Guidelines to include a paragraph on Genetic Counseling.
	In Coding section: ▪ Coding notations updated
	References updated
	Added Appendix Table 1. Categories of Genetic Testing addressed in Policy
08-15-2017	Description section updated
	In Policy section: ▪ Policy Guidelines updated to provide general information about the Human Genome Variation Society and the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants
	Rationale section updated
	References updated
08-01-2018	Description section updated
	In Policy section: ▪ Policy Guidelines updated.
	Rationale section updated
	References updated

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