

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

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

Policy Guidelines

Genetics Nomenclature Update

The 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 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

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.

Coding

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

- **81479:** Unlisted molecular pathology procedure

Description

Genetic testing to determine kinesin-like protein 6 (*KIF6*) Trp719Arg variant status is being evaluated as a test to predict the risk of future cardiovascular events and as a 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 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the 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. In April, 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.

Now a wholly owned subsidiary of Quest Diagnostics, Celera holds a U.S. patent on methods of determining coronary heart disease 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.

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.¹ 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.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.

Analyses of prospective observational studies of cardiovascular health and the placebo arm of randomized controlled trials 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 myocardial infarction, 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

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?

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 (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 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.

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-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, the Trp719Arg 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.^{13,14,15}

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 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 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.

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	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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 hypercholesterolemia	Nonfatal MI, revascularization	OR=1.55 (1.14 to 2.09)	<ul style="list-style-type: none">• KIF6 variant carriers: HR=0.50 (0.38 to 0.68)• Noncarriers:

Study; Trial	Patients Evaluated	KIF6 Association Evaluated	Results
	but no history of MI	procedures, or death from CHD	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) • 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) • 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)
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 • 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)
Akao et al (2012) ²¹ Retrospective study of participants in PROSPER	Individuals with history of, or risk	MI or stroke	• Homozygote HR=0.47 (p=0.03) NA

Study; Trial	Patients Evaluated	KIF6 Association Evaluated	Results
trial, randomized to pravastatin 40 mg/d or placebo	factors for, vascular disease		<ul style="list-style-type: none"> 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: Clinically Valid

There is 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 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 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 *KIF6* 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 (e.g., 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 *KIF6* variants will alter the clinical management decisions. 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 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.

Medicare National Coverage

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

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA's decisions apply to all molecular diagnostic tests for Medicare.

In 2017, 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 March 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

Type	Code	Description
CPT®	81479	Unlisted molecular pathology procedure
HCPCS	None	
ICD-10 Procedure	None	

Policy History

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

Effective Date	Action	Reason
05/29/2015	BCBSA Medical Policy adoption	Medical Policy Committee
06/01/2016	Policy revision without position change	Medical Policy Committee
07/01/2017	Policy revision without position change	Medical Policy Committee
07/01/2018	Policy revision without position change	Medical Policy Committee
07/01/2019	Policy revision without position change	Medical Policy Committee

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 governmental 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.