MEDICAL POLICY

POLICY TITLE	KIF6 GENOTYPING FOR PREDICTING CARDIOVASCULAR RISK AND/OR EFFECTIVENESS OF STATIN THERAPY
POLICY NUMBER	MP-2.309

Original Issue Date (Created):	**4/1/2012**
Most Recent Review Date (Revised):	**6/13/2018**
Effective Date:	**8/1/2018**

I. POLICY

KIF6 Genotyping is considered **investigational** for predicting cardiovascular risk and/or the effectiveness of statin therapy. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure

Policy Guidelines

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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.

Cross-references:

MP-2.233 Genetic Testing for Cardiac Ion Channelopathies

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.67, KIF6 Genotyping for Predicting Cardiovascular Risk and/or the Effectiveness Statin Therapy. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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

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

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 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 (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.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy who receive testing for kinesin-like protein 6 (*KIF6*) Trp719Arg variant status, the evidence includes secondary analyses of randomized controlled trials (RCTs), case-control studies, and 1 quasi-experimental single-arm study. Relevant outcomes are overall survival, test accuracy and validity, change in disease status, morbid events, and medication use. Data supporting the association between *KIF6* variant status and coronary artery disease (CAD)

outcomes are contradictory. The most recent evidence from large populations with different vascular disease risk levels has not supported a significant association between CAD risk and the presence of the variant. Further, studies of the association between response to statin therapy and *KIF6* variant status are also mixed. However, a large meta-analysis has shown that carriers of the *KIF6* variant derive greater clinical benefit from low-density lipoprotein cholesterol reduction (a 13% reduction in the risk of CAD outcomes) compared with noncarriers. However, no prospective RCTs have evaluated the impact of testing for *KIF6* variants on changes in clinical management (e.g., intensifying the statin treatment in carriers, use of alternate approaches for lipid management in noncarriers) or outcomes. One nonrandomized study has suggested that subjects who received *KIF6* genotype results had greater adherence to statin therapy, but, overall, it is uncertain whether testing for *KFI6* 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.

MEDICARE NATIONAL COVERAGE

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

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, andHawaii). Palmetto GBA's decisions apply to all molecular diagnostic tests for Medicare. In 2015, Palmetto GBA completed a review of the *KIF6* genotype test and concluded: "To date, there is insufficient evidence to support the required clinical utility for the established Medicare benefit category. This was last updated September 21, 2017. Therefore, the *KIF6* genotype test is a statutorily excluded test."[26]

V. DEFINITIONS

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GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded,

and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

The following codes are investigational when used to report KIF6 genotyping for predicating cardiovascular risk and/or effectiveness of stating therapy as outlined in the policy statement:

CPT Codes®								
81479								

HCPCS Code	Description
G0452	Molecular pathology procedure; physician interpretation and report

IX. REFERENCES

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1. *Marian AJ. Surprises of the genome and "personalized" medicine. J Am Coll Cardiol. Jan 29 2008;51(4):456-458. PMID 18222356*
2. *Rosenfeld ME, Preusch M, Shiffman D, et al. KIF6, an emerging coronary heart disease risk marker expressed by macrophages in atherosclerotic lesions in humans and mice [Abstract P692]. Paper presented at: American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions; April 8-10, 2010; San Francisco, CA.*

3. *Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. J Am Coll Cardiol. Jan 29 2008;51(4):435-443. PMID 18222353*
4. *Iakoubova OA, Robertson M, Tong CH, et al. KIF6 Trp719Arg polymorphism and the effect of statin therapy in elderly patients: results from the PROSPER study. Eur J Cardiovasc Prev Rehabil. Aug 2010;17(4):455-461. PMID 20215968*
5. *Shiffman D, Sabatine MS, Louie JZ, et al. Effect of pravastatin therapy on coronary events in carriers of the KIF6 719Arg allele from the cholesterol and recurrent events trial. Am J Cardiol. May 1 2010;105(9):1300-1305. PMID 20403483*
6. *Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. J Am Coll Cardiol. Jan 29 2008;51(4):449-455. PMID 18222355*
7. *Assimes TL, Holm H, Kathiresan S, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies. J Am Coll Cardiol. Nov 2 2010;56(19):1552-1563. PMID 20933357*
8. *Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. N Engl J Med. Aug 2 2007;357(5):443-453. PMID 17634449*
9. *Myocardial Infarction Genetics Consortium, Kathiresan S, Voight BF, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. Mar 2009;41(3):334-341. PMID 19198609*
10. *McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science. Jun 8 2007;316(5830):1488-1491. PMID 17478681*
11. *Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. Jun 8 2007;316(5830):1491-1493. PMID 17478679*
12. *Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. Jun 7 2007;447(7145):661-678. PMID 17554300*
13. *Ridker PM, MacFadyen JG, Glynn RJ, et al. Kinesin-like protein 6 (KIF6) polymorphism and the efficacy of rosuvastatin in primary prevention. Circ Cardiovasc Genet. Jun 2011;4(3):312-317. PMID 21493817*
14. *Hopewell JC, Parish S, Clarke R, et al. No impact of KIF6 genotype on vascular risk and statin response among 18,348 randomized patients in the Heart Protection Study. J Am Coll Cardiol. May 17 2011;57(20):2000-2007. PMID 21458191*
15. *Hoffmann MM, Marz W, Genser B, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: The 4D study. Atherosclerosis. Dec 2011;219(2):659-662. PMID 21871624*
16. *Arsenault BJ, Boekholdt SM, Hovingh GK, et al. The 719Arg variant of KIF6 and cardiovascular outcomes in statin-treated, stable coronary patients of the treating to new*

targets and incremental decrease in end points through aggressive lipid-lowering prospective studies. Circ Cardiovasc Genet. Feb 1 2012;5(1):51-57. PMID 22135385

17. *Ference BA, Yoo W, Flack JM, et al. A common KIF6 polymorphism increases vulnerability to low-density lipoprotein cholesterol: two meta-analyses and a meta-regression analysis. PLoS One. Jan 2011;6(12):e28834. PMID 22216121*
18. *Morrison AC, Bare LA, Chambless LE, et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. Jul 1 2007;166(1):28-35. PMID 17443022*
19. *Shiffman D, O'Meara ES, Bare LA, et al. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. Jan 2008;28(1):173-179. PMID 17975119*
20. *Shiffman D, Chasman DI, Zee RY, et al. A kinesin family member 6 variant is associated with coronary heart disease in the Women's Health Study. J Am Coll Cardiol. Jan 29 2008;51(4):444-448. PMID 18222354*
21. *Akao H, Polisecki E, Kajinami K, et al. 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*
22. *Charland SL, Agatep BC, Herrera V, et al. Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. Pharmacogenomics J. Jun 2014;14(3):272-280. PMID 23979174*
23. *Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. Dec 21 2010;122(25):e584-636. PMID 21098428*
24. *Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Dec 14 2010;56(25):e50-103. PMID 21144964*
25. *Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jul 1 2014;63(25 Pt B):2935-2959. PMID 24239921*
26. *Palmetto GBA. KIF6 Genotype Coding and Billing Guidelines (M00017, V6). 2017; https://palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Excluded%20Tests~8W4T2H6800?open&navmenu=%7C%7C. Accessed June 13, 2018.*
27. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.67 KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy. May 2018*

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X. POLICY HISTORY

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MP-2.309	**CAC 11/22/11** New policy. Adopt BCBSA. CBC was silent related to coverage for this testing. Considered investigational.
	04/08/13 Admin Code review.
	7/18/13 Admin code review complete.
	CAC 9/24/13 Consensus review. References updated. No changes to the policy statements. Rationale added.
	CAC 7/22/14 Consensus review. No changes to the policy statements. References and rationale updated.
	CAC 7/21/15 Consensus review. No change to policy statements. Rationale and references updated. Codes reviewed.
	CAC 7/26/16 Consensus review. No change to the policy statement. Policy Guidelines and Appendix added. Cross-References, Description/Background and Rationale sections updated. Coding reviewed/updated.
	Admin Update 11/9/16 Variation section reformatted.
	CAC 9/26/17 Consensus. No change to policy statements. References and rationale updated. Coding Reviewed.
	6/13/18 Consensus. No change to policy statements. References updated. Rationale condensed.

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