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):	**5/12/2021**
Effective Date:	**9/1/2021**

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

Cross-references:

MP-2.233 Genetic Testing for Cardiac Ion Channelopathies

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Benefit Brochure for information on KIF6 Genotyping
https://www.fepblue.org/benefit-plans/benefit-plans-brochures-and-forms
Note* - The Federal Employee Program (FEP) Service Benefit Plan does not have a medical policy related to these services. “

III. DESCRIPTION/BACKGROUND

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Kinesin-like protein 6 (*KIF6*) belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the *KIF6* gene product is as yet undetermined. It has been reported that the gene is not expressed in the vasculature, the primary site of atherosclerosis, but is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. In contrast, a study presented at a 2010 American Heart Association scientific session reported on data derived from tissue immunohistochemistry, locating KIF6 protein in

macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is no strong evidence that KIF6 protein plays a direct biologic role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction.

Analyses of prospective observational studies of cardiovascular health and the placebo arm of randomized controlled trials (RCTs) of statin interventions in at-risk populations have suggested a significant association between the arginine-to-tryptophan substitution at position 719 (Trp719Arg) single-nucleotide variant (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 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.

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 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 FDA for its *KIF6* Genotyping Assay performed using Abbott's m2000™ instrument system. In April, 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 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 *KIF6* Trp719Arg variant status, the evidence includes secondary analyses of randomized controlled trials (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 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 evidence is insufficient to determine the effects of the technology on health outcomes.

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 health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's 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. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or

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Member Services. 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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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.

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	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.
	11/9/16 Administrative update. Variation section reformatted.
	CAC 9/26/17 Consensus review. No change to policy statements. References and rationale updated. Coding Reviewed.
	6/13/18 Consensus review. No change to policy statements. References updated. Rationale condensed.
	4/12/2019 Consensus review. Policy statement unchanged. References updated.
	7/1/2020 Consensus Review. Background, Rationale and FEP coverage updated. References reviewed. Product and Benefit Variation as well as Disclaimer updated. No change in policy statement.
	5/12/2021 Consensus Review. Reference updated. Coding reviewed. Policy guidelines removed.

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