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Medical Benefit		Effective Date: 01/01/12	Next Review Date: 07/19
Preauthorization	No	Review Dates: 09/11, 09/12, 09/13, 07/14, 07/15, 07/16, 07/17, 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy 	Interventions of interest are: <ul style="list-style-type: none"> Testing for KIF6 Trp719Arg variant status 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> 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 test to predict the risk of future cardiovascular events and as a test to predict response to statin therapy, particularly in high-risk patients.

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 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.

POLICY

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 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 protocol 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 and the Association for Molecular Pathology 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.

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 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 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by the 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. 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 an RCT.

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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