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**
  - Individuals: Who are asymptomatic with risk of cardiovascular disease and undergoing treatment with statin therapy

- **Interventions**
  - Interventions of interest are: Testing for KIF6 Trp719Arg variant status

- **Comparators**
  - Comparators of interest are: Standard clinical management without genetic testing

- **Outcomes**
  - 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 the risk of future cardiovascular events and as a pharmacogenetic 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 kinesin-like protein 6 (KIF6) Trp719Arg variant status, the evidence includes secondary analyses of randomized controlled trials (RCTs), case-control studies, and one 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 \textit{KIF6} variants will alter the clinical management decisions. The clinical utility of \textit{KIF6} testing has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

\textbf{Policy}

\textit{KIF6} genotyping is considered investigational for predicting cardiovascular risk and/or the effectiveness of statin therapy.

\textbf{Policy Guidelines}

\textit{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 protocol updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

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.

\textbf{Table PG1. Nomenclature to Report on Variants in DNA}

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

\textbf{Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification}

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

\textit{Genetic Counseling}

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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. 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 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. An online search in 2017 found no update.

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. San Francisco General Hospital’s Clinical Chemistry Laboratory is the only non-Celera lab licensed to develop a KIF6 LDT.

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.

15. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. Jul 7 2007; 447(7145):661-678. PMID 17554300