Patient Name: Johnny Health  
DOB: 01/01/1980  
Lab ID Number: 000000000  
Ordering Physician: Dr. KCL  
Date Sample Collected: 00/00/14  
Date Sample Received/Tested: 00/00/14  
Date Reported: 00/00/14  
Ordering Facility: Acme Center

**Genes Tested:**
- 9P21  
- Factor II Prothrombin  
- AGT  
- Factor V Leiden  
- eNOS/NOS3  
- APOE  
- MTHFR  
- SLCO1B1*5

**KEY:**  
- GREEN: NON-RISK ALLELE  
- RED: RISK ALLELE

### 9p21 Mutation

**BACKGROUND**
Coronary artery disease (CAD) risk is approximately 40-60% genetically determined.1 One of the first and most researched risk factors associated with coronary artery disease is 9p21.2 The 9p21 variant is located in a non-protein coding region near the tumor suppressor genes, cyclin-dependent kinase inhibitors 2A and 2B (CDKN2A, CDKN2B), both of which exhibit anti-proliferative activity in the vascular endothelium.3 Expression studies show the 9p21 variant to be associated with decreased expression of CDKN2a/b, which may be a source for the development of atherosclerosis.4 Presence of the 9p21 C allele is associated with CAD, atherosclerotic changes, and multi-vessel disease.2,4-7 Multiple studies have shown that the degree of CAD risk is determined by the number of risk alleles present. Heterozygous carriers have an increased CAD risk however homozygous C/C allele carriers may double their risk of CAD, atherosclerotic severity, and a greater number of vessels involved in CAD.4,7 The presence of the risk allele increases CAD risk independent of other risk factors such as cholesterol.4

### INDICATIONS

**C/C** allele carriers may have an increased coronary artery disease risk of up to 50%. G/G allele carriers do not possess the 9p21 risk alleles associated with increased risk of coronary artery disease or atherosclerosis. G/C heterozygous allele carriers may have up to a 25% increased risk of coronary artery disease, an increased risk of atherosclerosis, and increased risk in number of vessels involved in CAD. C/C allele carriers may be associated with up to a 50% increased risk of CAD, higher severity of atherosclerosis, and a two-fold higher risk of three-vessel coronary artery disease.

**References**
2. The Wellcome Trust Case Consortium, Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447(7145): 661-678.
<table>
<thead>
<tr>
<th>AGT Mutation</th>
<th>BACKGROUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: [C/C]</td>
<td>Angiotensinogen is the protein produced by the AGT gene. This is the precursor to the active peptide angiotensin II (Ang II), a hormone that causes blood pressure to increase through vasoconstriction and sodium retention.(^1) The more precursor available in the blood, the more Ang II is produced, and increased levels of the hormone are significantly correlated with blood pressure in patients with hypertension.(^2) Hundreds of epidemiological studies in various populations have focused on a few common polymorphisms in the AGT gene associated with increased AGT activity and high blood pressure. High blood pressure is known to be a risk factor for cardiovascular disease and early mortality.(^3) While evidence indicates there are many genes involved with this disease condition, there is ample evidence that this variant allele in AGT is associated with poor cardiovascular health and in particular may be a marker indicating risk for developing coronary artery disease.(^4)(^6)</td>
</tr>
<tr>
<td>C/C allele carriers do not possess the risk alleles, and may not be at increased risk for coronary artery disease.</td>
<td>C/C allele carriers do not possess the AGT risk alleles, and may not be at increased risk for coronary artery disease.</td>
</tr>
<tr>
<td>C/T allele carriers possess one risk allele and may be at increased risk of coronary artery disease.</td>
<td>C/T allele carriers possess one risk allele and may be at increased risk for coronary artery disease.</td>
</tr>
<tr>
<td>T/T allele carriers possess two copies of the risk allele and are often found to be at increased risk of coronary artery disease.</td>
<td>T/T allele carriers possess two copies of the risk allele and are often found to be at increased risk of coronary artery disease.</td>
</tr>
</tbody>
</table>

References

**eNOS/NOS3**

**Results:** G/T

**INDICATIONS**

G/T allele carriers have one risk allele and may have a reduced ability to synthesize nitric oxide.

**REFERENCES**


**Folate (Vitamin B9)**

**MTHFR Mutations**

**MTHFR-1: C677T**

<table>
<thead>
<tr>
<th>Results: C/T</th>
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</thead>
</table>

**MTHFR-2: A1298C**

<table>
<thead>
<tr>
<th>Results: A/C</th>
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</table>

**INDICATIONS**

**MTHFR-1: C677T**

<table>
<thead>
<tr>
<th>C/T allele carriers have one risk allele but are not at risk for elevated levels of homocysteine.</th>
</tr>
</thead>
</table>

**MTHFR-2: A1298C**

<table>
<thead>
<tr>
<th>A/C allele carriers may have reduced levels of enzyme activity, but typically do not have increased homocysteine levels.</th>
</tr>
</thead>
</table>

**REFERENCES**

1. Impaired folate metabolism due to MTHFR enzyme inactivity, or a low folate level, results in elevated plasma homocysteine. Homocysteine is an amino acid synthesized by the body through demethylation of methionine. In the presence of adequate B-vitamins, homocysteine is either irreversibly degraded to cysteine or it is re-methylated back to methionine, an essential amino acid. An elevated homocysteine level has been identified as an independent risk factor for ischemic stroke, thrombotic and cardiovascular diseases. However, it is important to remember that this is a multifactorial condition, involving a combination of genetic, physiologic, and environmental factors, and clinical relevance of MTHFR testing should be interpreted in light of clinical information. Two single nucleotide variants known to affect MTHFR function are C677T (a change from cytosine to thymine at position 677 within the gene) and the A1298C mutation (a change from adenine to cytosine at position 1298 within the gene). It is not uncommon for some individuals to have both MTHFR variants. Clinical relevance for hyperhomocysteinemia is associated with homozgyosity for the C677T variant allele. In general, these genotypes produce an MTHFR enzyme with reduced function and activity.

**MTHFR-1: C677T**

<table>
<thead>
<tr>
<th>C/C allele carriers do not carry the risk allele and are not at risk for elevated levels of homocysteine. C/T allele carriers have one risk allele but are not at risk for elevated levels of homocysteine. T/T allele carriers of two risk alleles are associated with increased homocysteine levels.</th>
</tr>
</thead>
</table>
### MTHFR-2: A1298C

<table>
<thead>
<tr>
<th>Allele Carriers</th>
<th>Enzymatic Activity and Homocysteine Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/A</td>
<td>Full enzymatic activity and most often do not exhibit high levels of homocysteine.</td>
</tr>
<tr>
<td>A/C</td>
<td>May have reduced levels of enzyme activity, but typically do not have increased homocysteine levels.</td>
</tr>
<tr>
<td>C/C</td>
<td>Have two risk alleles and are often found to have decreased enzyme activity but not elevated homocysteine levels.</td>
</tr>
</tbody>
</table>

### References


### Factor II Prothrombin

#### Background

Coronary heart disease and stroke remain the leading causes of death and disability for individuals of most ethnicities within the United States. The prothrombin gene, also known as coagulation Factor II (F2) has been considered as a candidate gene for venous thrombosis and stroke. Prothrombin is the precursor protein of thrombin, a component of the coagulation cascade. Thrombin is the key enzyme involved in the processes of hemostasis and thrombosis that exhibits procoagulant, anticoagulant, and antifibrinolytic activities. Individuals with this particular mutation in F2 have a 2-3-fold increased risk for developing thrombosis and venous thromboembolism (VTE). Additionally, for individuals carrying both the F2 and the Factor V Leiden mutations, the risk of VTE is even further increased. This mutation is also associated with significantly increased stroke risk in adults ≤55 years.

### Results: G/G

<table>
<thead>
<tr>
<th>Allele Carriers</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>Do not possess the risk alleles and are typically not at increased risk for thrombosis.</td>
</tr>
</tbody>
</table>

### Indications

- **G/G** allele carriers do not possess the risk alleles and are typically not at increased risk for thrombosis.
- **G/A** heterozygotes may be associated with increased risk for thrombosis and embolism.
- **A/A** allele carriers possess two copies of risk alleles and are often associated with increased risk of thrombosis, embolism, and stroke.

### References

<table>
<thead>
<tr>
<th>Factor V Leiden</th>
<th>BACKGROUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: A/A</td>
<td>Factor V Leiden thrombophilia is an inherited blood clotting disorder. Factor V Leiden is a rare variant of the human factor V protein that causes an increase in blood clotting (hypercoagulability). The mutation prevents efficient inactivation of factor V; prolonged activation of factor V allows for the overproduction of thrombin. Thrombin catalyzes the formation of fibrin, a key protein involved in clot formation. In people with the factor V mutation, excess fibrin is formed causing excess clotting. In a comprehensive meta-analysis it was determined that individuals that are heterozygous for the factor V mutation have a fivefold increased relative risk for idiopathic venous thromboembolism (VTE), while those who are homozygous for the mutation have a nine to tenfold increase in risk. Additionally, there have been statistically significant associations with deep vein thrombosis, ischemic stroke, as well as pre-eclampsia also identified for factor V Leiden. G/G allele carriers do not possess the risk alleles. G/A heterozygous allele carriers possess one risk allele and may be at increased risk for thrombophilia and VTE. A/A individuals carry two copies of risk alleles and are at increased risk for thrombophilia, VTE and stroke.</td>
</tr>
</tbody>
</table>

**INDICATIONS**

<table>
<thead>
<tr>
<th>A/A allele carriers possess two copies of risk alleles and are at increased risk for thrombophilia, VTE and stroke.</th>
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**References:**

<table>
<thead>
<tr>
<th>APOE</th>
<th>BACKGROUND</th>
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<tbody>
<tr>
<td>APOE-1</td>
<td>Apolipoprotein E (APOE) is a serum glycoprotein synthesized by most tissues in the body. It accumulates on the surface of very low density lipoprotein (VLDL) particles and chylomicrons as they travel through the bloodstream and helps to direct the metabolism of cholesterol and triglycerides. ApoE genetic polymorphisms are thought to contribute up to 10% of the variation in cholesterol levels, and 20–40% of variability in triglyceride levels seen in the general population. The three variants of apoE are commonly reported as a phenotype that represents the isoform present on each chromosome, such as E3/E3 or E2/E3. This is determined by cysteine and arginine amino acid substitutions at two residues in the protein. Depending on the amino acid present at these locations, the apoE protein changes conformation, which in the case of ApoE2, affects its ability to interact with the LDL receptor. ApoE2/E2 is also associated with type III hyperlipidemia (HLP III) (dysbetalipoproteinemia), however most individuals with this condition will present as normolipidemic and it may be decades before deleterious cardiovascular changes due to secondary factors, become evident. Ultimately out of all the phenotypes, ApoE4/E4 carriers are associated with the highest risk of heart disease.</td>
</tr>
<tr>
<td>APOE-2</td>
<td></td>
</tr>
<tr>
<td>Results: [C/C]</td>
<td></td>
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<tr>
<td>Genotype: [E3/E4]</td>
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</table>

INDICATIONS

APOE-1/APOE-2 allelic variants are associated with cardiovascular health.

| APOE-1: C/T; APOE-2: C/C =E3/E4 allele carriers are at increased risk for heart disease and may have higher triglycerides, and LDL cholesterol, with lower HDL levels. |

References

**SLCO1B1*5**

<table>
<thead>
<tr>
<th>Results: [C/C]</th>
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<tr>
<td></td>
<td>The SLCO1B1 gene encodes the organic anion transporting polypeptide B1 (OATPB1). This protein mediates the liver’s uptake of many compounds, including the class of medications called statins. Variants in this gene affect the function of the transport protein, causing changes in the amount of statin medication that can be taken up into the liver. Presence of the variant allele markedly reduces the uptake of certain statins which in turn reduces the efficacy of the statin medication and allows statin accumulation in the bloodstream. Due to the adverse effects of statin-induced myopathies and myalgias being dose-dependent, it may be advisable to avoid high dose statin therapy in these variant allele carriers.</td>
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**INDICATIONS**

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<tr>
<td><strong>C/C – poor metabolizer</strong></td>
<td>These patients have a significantly decreased ability to metabolize statins. They are less responsive to statin therapy and achieve less LDL-c lowering from the statin that they receive. High dose statin therapy may not be advisable.</td>
</tr>
<tr>
<td><strong>T/T – normal metabolizer</strong></td>
<td>These patients are able to metabolize statins appropriately. Standard doses are recommended for LDL-C reduction and CVD risk reduction.</td>
</tr>
<tr>
<td><strong>T/C – intermediate metabolizer</strong></td>
<td>These patients have a decreased ability to metabolize statins. They are less responsive to statin therapy and achieve less LDL-c lowering from the statin that they receive. Consider routine creatine kinase (CK) monitoring.</td>
</tr>
<tr>
<td><strong>C/C – poor metabolizer</strong></td>
<td>These patients have a significantly decreased ability to metabolize statins. They are less responsive to statin therapy and achieve less LDL-c lowering from the statin that they receive. Consider routine creatine kinase (CK) monitoring. High dose statin therapy may not be advisable.</td>
</tr>
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</table>

**References:**


*Additional information will be supplied to your provider to help inform treatment options.*

This test was developed and its performance characteristics determined by Kashi Clinical Laboratories. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

**Reported and Reviewed By:**

Zahra Mehdizadeh Kashi, Ph.D., HCLD  
CEO and Laboratory Director