1. WHAT IS THE PULs CARDIAC TEST™?

The PULs Cardiac Test is a simple, non-invasive blood test that identifies individuals with active, yet undetected subclinical Coronary Heart Disease (the “vulnerable patients”) who are at risk of experiencing a coronary event, and in whom early intervention can help.

2. WHAT DOES THE PULs CARDIAC TEST MEASURE?

The PULs Cardiac Test measures the most clinically-significant biomarkers related to cardiac lesion formation and predicts the likelihood of rupture:

- Detects asymptomatic, subclinical disease (formation of cardiac lesions)
- Diagnoses Coronary Heart Disease stage
- Provides a score tied to likelihood of ACS (acute coronary syndrome), MI due to unstable cardiac lesion rupture, unstable angina requiring hospitalization, or sudden cardiac death within a 5 year period, considered the optimal interval for intervention and change.

3. HOW DOES THE PULs TEST COMPLEMENT AND COMPARE TO OTHER CHD BLOOD TESTING?

The PULs Cardiac Test was developed as an advanced diagnostic and predictive tool designed to compliment current tests. Using the PULs Cardiac Test in conjunction with lipid profiles provides a comprehensive approach in identifying the vulnerable patient. The PULs Cardiac Test:

- Has been independently validated in multi-ethnic populations (MESA).
- Conforms to ACC/AHA guidelines
- Has demonstrated improved clinical utility. In a large clinical trial the PULs Cardiac Test identified 61% of patients who went on to have a cardiac event, and who would have been missed by established risk factors.

4. HOW IS THE PULs CARDIAC TEST ABLE TO DIAGNOSE SUBCLINICAL CHD AND UNSTABLE CARDIAC LESIONS?

Through a 15 year research period involving collaboration with multiple university centers, all available biomarkers and clinical risk factors were evaluated statistically to determine which ones were highly indicative of subclinical coronary artery disease and unstable lesion formation and subsequent rupture.

The researchers then determined the biomarkers that provided the highest predictive value for diagnosing subclinical disease at baseline in patients who went on to experience ACS (Acute Coronary Syndrome). Validating the biomarkers in independent and prospective cohorts including the Multi-Ethnic Study of Atherosclerosis (MESA). The validation study also outperformed Framingham Risk Score.

Nine markers were chosen* to provide the highest predictive value and applied in an algorithm along with 4 clinical risk factors culminating in a single profile score that can be used to identify the “vulnerable patient,” or the individual with asymptomatic, subclinical CHD for whom early intervention can help.

*Note that commonly used markers in other panels including MPO and hsCRP were evaluated, but were not sufficiently predictive when compared to the other biomarkers.

5. WHO SHOULD ORDER THE PULs TEST?

The PULs Cardiac Test is recommended for anyone 40 years of age or older, and who has at least one AHA defined risk factor.

6. HOW DO I INTERPRET THE RESULTS OF THE PULs TEST?

The PULs Cardiac Test results provide a Heart Age and Target Heart Age based on a personalized 5-year Cardiac Profile score that will be categorized as:

- Normal (<3.5%): These patients are in the desired range. Reviewing good nutrition and exercise habits and identifying any areas of concern like heart age, rising BMI or family history will dictate if additional recommendations are encouraged.
- Borderline (3.5-7.49%): Patients in the intermediate range are generally early in disease progression. Often times, simple lifestyle modifications can bring these individuals back into the normal range.
- Elevated (>7.5%): These patients are high risk and should be treated as such using the ACC/AHA guidelines. Further evaluation is recommended to better define the clinical picture and treatment plan. If the clinical situation warrants it, and the patient is not currently under the care of a cardiologist, referral to a cardiologist might be warranted. Case studies have shown that some patients with high-risk results who have not acted on the information have experienced heart attacks within weeks or months of the test.

7. WHAT DO I DO WHEN MY PATIENT HAS NORMAL LIPID LEVELS AND A HEALTHY LIFESTYLE, BUT HAS AN ELEVATED PULs CARDIAC PROFILE SCORE?

These individuals are still at risk and, in fact, are the patients most often missed who go on to have heart attacks. They should be further evaluated to assess disease progression as outlined in question 6. Almost all individuals have some modifiable lifestyle factors that can be improved. Exercise and diet are frequent sources of opportunity to improve. As recommended in the ACC/AHA Cardiac guidelines, medication should be considered for high-risk individuals with no other evidence of disease and a lack of other lifestyle modification opportunities.

For more information, visit www.pulstest.com. | Order the PULs Cardiac Test™ by calling (866) 299-8998.
### PROTEIN BIOMARKER OVERVIEW

*9 of the most clinically-significant protein biomarkers detect unstable cardiac lesion formation, diagnose disease progression and predict the likelihood of rupture.*

<table>
<thead>
<tr>
<th>DISEASE PROCESS</th>
<th>PULs CARDIAC TEST™ BIOMARKERS</th>
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<tbody>
<tr>
<td>ENDOTHELIAL INJURY, CELL ADHESION, CHEMOTAXIS &amp; PLATELET AGGREGATION, &amp; INFLAMMATION</td>
<td>HGF</td>
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<tr>
<td>Atherosclerosis is a process of chronic endothelial injury that increases permeability of the arterial wall, allowing oxidized lipid particles to bind and aggregate on the arterial surface - contributing to the formation of lesions (atheroma). Expression of adhesion molecules and chemokines (MCP-1 and others) participate in platelet aggregation, lymphocyte, and monocyte adhesion - further activating the lesion.</td>
<td>Hepatocyte growth factor (HGF) takes part in tissue regeneration after injury. It is a potent survival and regeneration factor after severe tissue damage. It promotes cell growth and protection from apoptosis (cell death), regulates the cell migration and differentiation.</td>
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**EOTAXIN**
Eotaxin (also called CCL11 or C-C Motif Ligand 11) is a chemo-attractant for eosinophil granulocyte white blood cells that respond to inflammation by releasing reactive oxygen compounds and triggering a cascade of other chemokines and interleukins.

**MCP-3**
MCP-3 is Monocyte-Specific Chemokine 3, also known as CCL-7. It regulates macrophage function and acts as a chemo-attractant for monocytes to inflamed or infected tissues.

**CTACK**
CTACK is Cutaneous T-cell-Attracting Chemokine (also called CCL27 which refers to C-C Motif Ligand 27) that is primarily released by epithelial cells as part of the chemo-attraction of white blood cells and their activation-dependent adhesion at sites of inflammation.

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<tr>
<th>ANGIOGENESIS, CELL PROLIFERATION &amp; VASCULAR REMODELING</th>
<th>IL-16</th>
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<td>The presence of such compounds stimulates the vessel cells to produce molecules and recruit leukocytes (monocytes, granulocytes, and T-cells) to the arterial walls, and stimulates the proliferation of smooth muscle cells. The recruited leukocytes are transformed into lipid-laden foam cells and are responsible for the growth of the lesion. Growth factors then are released and stimulate the generation of new capillaries through the process of angiogenesis, providing the growing lesion with an adequate blood supply.</td>
<td>IL-16 is Interleukin 16, a cytokine protein that attracts and activates monocytes, T-cells, and eosinophils in response to inflammation and immunoreactions. IL-16 is released by lymphocytes and epithelial cells, such as those that line the wall of blood vessels.</td>
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<th>APOPTOSIS</th>
<th>FAS LIGAND</th>
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<td>A physical change in the smooth muscle cells, and the process of cell turnover (apoptosis) produces excessive amounts of collagen, elastin and proteoglycans. This transforms the endothelial injury into a lesion comprised of a thin fibrous cap and lipid core (plaque) that is unstable and prone to rupture.</td>
<td>Fas Ligand is also called tumor necrosis factor ligand superfamily member 6 (TNFSF6) and is part of the cell death (apoptosis) pathways that clear the body of immune cells activated by inflammation and infection by binding to the Fas protein. Apoptosis is a key component of vulnerable plaque progression and rupture.</td>
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</table>

**sFAS**
{sFas} is the secreted form of tumor necrosis factor receptor superfamily member 6 (TNFRSF6). Fas binds to Fas Ligand triggering cell death (apoptosis) pathways that clear the body of immune cells activated by inflammation and infection. Apoptosis is a key component of vulnerable plaque progression and rupture.

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<tr>
<th>LIPID PATHWAY</th>
<th>HDL</th>
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<td>HDL have relevant role regarding vascular protection. Macrophages in the vessel wall take up (oxidized) LDL, turn into foam cells, and add to a pro-inflammatory environment that promotes atherosclerotic lesion formation and ultimately lesion instability. HDL has been shown to inhibit the expression of endothelial adhesion molecules and to inhibit LDL-induced monocyte transmigration.</td>
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<th>INSULIN/GLUCOSE PATHWAY</th>
<th>HBA1C</th>
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<td>Increasing levels of HbA1c in asymptomatic individuals are associated with the presence of coronary atherosclerosis, but more specifically with the presence and burden of mixed coronary lesion. Elements of lesion instability have been associated with mixed coronary plaque/lesion.</td>
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UNDERSTANDING RESULTS

PULs Protein Biomarker & Clinical Risk Factor Measurements
Protein biomarkers combined with clinical risk factors calculates the Cardiac Profile score. Read measurements from right to left to understand what is contributing the most to the Cardiac Profile score for your patient.

PULs Cardiac Profile Score & Disease Stage
This section shows Cardiac Profile Score that categorizes disease stage as Normal, Borderline, or Elevated disease stage. Physicians can use this categorization to treat according to clinical guidelines. See below for recommendations for each disease stage.

Heart Age
The PULs Cardiac Score determines the patient "Heart Age".

Normal (<3.50%)
These patients are in the desired range. Reviewing good nutrition and exercise habits and identifying any areas of concern like heart age, rising BMI or family history will dictate if additional recommendations are encouraged.

Borderline (3.5-7.49%)
Patients in the Borderline range are generally early in disease progression. Often times, simple lifestyle modifications can bring these individuals back into the normal range.

Elevated (>7.50%)
These patients are high risk and should be treated as such using the ACC/AHA guidelines. A low threshold for additional testing should be applied to these patients including stress test, CAC, and CCTA to better define the clinical picture and treatment plan. If the clinical situation warrants it, and the patient is not currently under the care of a cardiologist, referral to a cardiologist might be warranted. Case studies have shown that some patients with high-risk results who have not acted on the information have experienced heart attacks within weeks or months of the test.

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