Please Note: All treatment plans provided within this guide are for educational purposes only. Patient-specific treatment plans should be provided and reviewed by the treating practitioner.
About Cleveland HeartLab, Inc.

Cleveland HeartLab offers innovative, scientifically proven, and medically relevant biomarkers that are predictive of cardiovascular risk. We offer inflammatory and other advanced biomarker testing that practitioners from across the United States use in the management and prevention of heart disease. Our novel biomarker technologies are offered through our CAP-accredited and CLIA-certified clinical reference laboratory. We also run a research and development laboratory where next-generation cardiovascular disease biomarkers are being developed for use through our clinical laboratory.

Cleveland HeartLab is committed to Innovation:
We maintain a robust research and development program that partners with leading academic and medical institutions to bring unique biomarker technologies to market. Our first biomarker – Myeloperoxidase (MPO) – was the result of research and development at the Cleveland Clinic, and initially received 510(k) clearance from the FDA within 13 months of discovery. We have an expansive, global intellectual property portfolio that includes over 50 issued and pending patents. We consistently bring new, novel biomarkers to the market and maintain an active pipeline in development.

Cleveland HeartLab is committed to Inflammation Testing:
Cleveland HeartLab is an established, premier inflammation testing laboratory with the most experience in the field. Our scientifically-proven, peer-reviewed multimarker approach of adding inflammation-specific tests to traditional lipid testing provides additional insight into an individual’s cardiovascular risk. In addition, our approach measures risk across a spectrum, allowing for long-, mid-, and near-term assessment. This enables healthcare providers to identify ‘hidden risk’ and treat more aggressively when appropriate. Our testing is supported by over 100 peer-reviewed articles. Most recently, a seminal, peer-reviewed study published in the Journal of Medical Economics shows Cleveland HeartLab’s inflammation testing could reduce the average heart attack and stroke rate by approximately 10%. Over five years, this reduction would avert $187 million in healthcare costs for cardiovascular disease – the number one killer of men and women in the U.S.

Cleveland HeartLab is committed to Clinical Education:
We are committed to educating healthcare providers and patients on the advancements in identifying cardiovascular risk. We organize signature CME-accredited events and local Medical Forums which attract hundreds of medical professionals from across the United States. Our clinical Education Team provides access to peer-to-peer support, the latest articles on the clinical utility of inflammatory biomarkers and individual case management support. We developed and provide a CME website for healthcare professionals (chlcme.com) and a website designed for patients (knowyourrisk.com).
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Inflammation and Heart Disease

Approximately 50% of patients experiencing a heart attack or stroke have ‘normal’ cholesterol levels\(^1\).

In 1948, the Framingham Study initially established standard risk factors for heart disease, or atherosclerosis (hardening of the arteries), that include high blood pressure, age, family history, cholesterol, obesity, diabetes, an unhealthy diet and whether an individual smokes. However, evidence is continually accumulating that the Framingham risk analysis is limited and fails to accurately detect the presence of heart disease in individuals\(^2\).

The risk of developing heart disease has traditionally been assessed by measurement of LDL-C (low-density lipoprotein cholesterol; the carrier of “bad” cholesterol) and HDL-C (high-density lipoprotein cholesterol; the carrier of “good” cholesterol). Research has shown that about 50% of heart attacks and strokes occur in people with ‘normal’ cholesterol levels\(^1\). This suggests that many people at risk are presumed low-risk because they have ‘normal’ or controlled cholesterol levels. Therefore, routine cholesterol tests may fail to fully identify people at risk for heart attack and stroke.

Although it is essential to assess your cholesterol levels, adverse cardiac events (such as heart attack, stroke or death) have been associated with inflammation\(^3\), specifically vulnerable plaque related to increased white blood cell activation.
References


Inflammation Testing

Cleveland HeartLab, Inc. offers inflammatory biomarker testing to help practitioners evaluate cardiovascular risk in patients. This group of tests covers a patient's biomarker profile which may result from lifestyle concerns (F2-IsoPs, OxLDL) to the development of metabolic or cardiovascular disease (ADMA/SDMA, Microalbumin, hsCRP) and formation of vulnerable plaque and increased risk for an adverse event (MPO, Lp-PLA2 Activity).

Inflammation testing provided by Cleveland HeartLab includes the following tests:

- F2-IsoPs
- OxLDL
- ADMA
- Microalbumin
- hsCRP
- Lp-PLA2 Activity
- Myeloperoxidase
- Troponin T
- CK-MB

These tests are reviewed on the next pages, and can be ordered individually.
A Multimarker Approach Can Aid in Stratifying Cardiovascular Risk

The literature supports the concept that combining multiple markers increases our ability to risk-stratify for cardiovascular disease. We have recently published the utility of combining inflammation tests to better define a patient’s risk.

Where Inflammation Meets Lipids®

The JUPITER Trial was the first landmark trial to demonstrate increased identification and stratification of individuals at risk of adverse cardiovascular events using a multimarker approach. Prior to the results of this publication, most research focused solely on lowering LDL-C with statin therapy to reduce cardiovascular risk. The JUPITER Trial went beyond this traditional measurement to demonstrate that hsCRP, a marker of general- and cardiovascular-related inflammation within the body, can improve risk stratification of individuals who may benefit from rosuvastatin therapy. As shown in the figure here, individuals with low LDL-C, but high inflammation - measured by hsCRP - had twice the risk of a cardiovascular event compared to individuals with low LDL-C and low hsCRP. These findings highlight the importance of a multimarker strategy in assessing cardiovascular risk, and measuring inflammation levels alongside traditional measurements such as LDL-C.

Incident cardiovascular events in the JUPITER Trial following initiation of rosuvastatin therapy. This figure was adapted from [ref 5].
References

A Deeper Dive Into Inflammation

In addition to the landmark JUPITER Trial, other impactful, peer-reviewed publications exist that demonstrate the utility of a multimarker approach to individualize cardiovascular risk assessment. Multimarker approaches, when carefully designed with their physiological relevance in mind, can have additive utility of identifying the acuity of the risk.1

Systemic and Vascular Inflammation

In 2009, Heslop et al. published a study in the Journal of the American College of Cardiology which examined the clinical utility of hsCRP and MPO – two inflammatory biomarkers with different pathophysologies.2 Unlike hsCRP, free MPO within the bloodstream is a vascular-specific marker for vulnerable plaque formation. As shown in the figure here, individuals with elevated levels of both hsCRP (atheroma burden) and free MPO (active atheroma) in the bloodstream had approximately 4X increased risk of cardiovascular mortality compared to those with elevations in either hsCRP or MPO.

Cardiovascular mortality according to elevations in hsCRP and MPO. This figure was adapted from [ref 2].

*Represents hazard ratio.
References


A Multimarker Approach Can Aid in Stratifying Cardiovascular Risk

**Vascular Inflammation - Two Sides to the Story**

In 2013, Penn and Klemes published a study in *Future Cardiology* which examined the utility of a multimarker approach - when designed with the physiology of each marker in mind - to identify risk and acuity of risk¹. In particular, this study highlighted the ability of Lp-PLA₂ and free MPO in the bloodstream to identify vulnerable plaque by measuring distinct physiologies. Lp-PLA₂ examines macrophage activation underneath the collagen cap within the artery wall while free MPO examines the white blood cell response in the bloodstream due to vulnerable plaque/erosions/fissures in the artery wall. As shown in the figure here, the combined use of both Lp-PLA₂ and MPO provides additional stratification of risk for plaque rupture beyond that of using each biomarker individually¹.

Risk based on vulnerable plaque risk markers in a stable clinical population of patients. For discussion, see [ref 1].
References

F\textsubscript{2}-Isoprostanes (F\textsubscript{2}-IsoPs)

CPT Code 82542/82570
Sample Type Urine

Order Code C261
Tube Type Yellow Top

Description
F\textsubscript{2}-IsoPs are prostaglandin-like compounds formed from the free radical-mediated oxidation of arachidonic acid\textsuperscript{1}, and are the ‘gold standard’ for measuring oxidative stress in the body. F\textsubscript{2}-IsoPs also have potent biological effects associated with inflammation and therefore may mediate chronic disease initiation and progression. Additionally, F\textsubscript{2}-IsoPs may also act as potent vasoconstrictors\textsuperscript{2} via thromboxane formation in the endothelium, which can promote platelet activation resulting in thrombus formation\textsuperscript{3}.

Clinical Use
F\textsubscript{2}-IsoPs may be performed on individuals at risk of future cardiovascular disease due to lifestyle risks, or those with a family history of cardiovascular disease.

Clinical Significance
- Elevated levels of urinary F\textsubscript{2}-IsoPs are seen in conditions associated with increased risk for atherosclerosis\textsuperscript{4} and certain forms of cancer\textsuperscript{5,6}.
- F\textsubscript{2}-IsoPs are elevated in smokers\textsuperscript{7} and with increased intake of red meat\textsuperscript{8} and are decreased with exercise\textsuperscript{9}.
- Lower steady-state levels are associated with cardiovascular fitness and reduced risk.

REFERENCE RANGE
F\textsubscript{2}-Isoprostanes (ng/mg creatinine)

- \(<0.86\) Low
- \(\geq0.86\) High
**Treatment Considerations**

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess LDL-C levels.**
  - If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

- **Assess smoking habits.**
  - NOTE: Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

- **Assess lifestyle habits.**
  - Consider diet/exercise/weight reduction efforts as appropriate.
  - Consider improving cardiovascular conditioning. Individuals who are not conditioned may have increased oxidation, but this will reduce as conditioning improves.
  - Consider optimal caloric intake as individuals who exercise a lot may not be taking in enough calories for their activity level. In short, they may be at risk for increased oxidation in their bodies due to lack of nutritional balance.

---

**References**

Oxidized LDL (OxLDL)

CPT Code 83516
Sample Type Serum/EDTA Plasma

Description
OxLDL measures protein damage due to the oxidative modification of the ApoB subunit on LDL cholesterol. The oxidation of LDL cholesterol is one of the first steps in the development of atherosclerosis. Briefly, LDL-C enters the artery wall where it becomes oxidized. OxLDL is then recognized by scavenger receptors on macrophages which engulf OxLDL, resulting in foam cell formation, vascular inflammation and the initiation of atherosclerosis.

Clinical Use
The OxLDL test may be performed on individuals at risk of metabolic syndrome.

Clinical Significance
- Individuals with high levels of OxLDL are 3.5X times more likely to develop metabolic syndrome in the next 5 years.\(^1\)
- Increased OxLDL levels are associated with the presence of coronary artery disease.\(^2\)\(^-\)\(^4\)
- In healthy middle-aged men, high OxLDL levels are associated with a 4X greater risk of developing coronary heart disease.\(^5\)
- Levels of OxLDL increase in a step-wise fashion as the severity of CAD increases.\(^6\)
- OxLDL levels may be elevated in patients with kidney disease and polycystic ovary syndrome. OxLDL levels should also be interpreted with caution in patients with known autoimmune disorders and those with diseases associated with oxidative stress, such as Alzheimer’s disease.

RELATIVE RISK

<table>
<thead>
<tr>
<th>OxLDL (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 Low</td>
</tr>
<tr>
<td>60-69 Moderate</td>
</tr>
<tr>
<td>≥70 High</td>
</tr>
</tbody>
</table>
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess lifestyle habits.**
  - Consider diet/exercise/weight reduction efforts if appropriate.

- **Assess LDL-C levels.**
  - If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

- **Assess insulin sensitivity.**
  - Consider an OGTT since metabolic syndrome is associated with an insulin insensitive state. This is especially prudent if other markers such as hsCRP, Lp-PLA₂ and/or MPO are elevated.

References

ADMA/SDMA

CPT Code 82542
Sample Type Serum

Description
One of the earliest manifestations of endothelial dysfunction is nitric oxide (NO) deficiency, which promotes atherosclerosis. ADMA (asymmetric dimethylarginine) and SDMA (symmetric dimethylarginine), its structural isomer, are metabolites of L-arginine, an amino acid that is catalyzed to L-citrulline and NO by nitric oxide synthase (NOS).

Both ADMA and SDMA have distinct pathophysiologies and manifestations. ADMA is a competitive inhibitor of NOS thereby reducing NO production and promoting endothelial dysfunction. SDMA also interferes with NO production, but does so indirectly by reducing the cellular availability of arginine. ADMA is primarily cleared through enzymatic degradation in the bloodstream and identifies subclinical cardiovascular disease. Conversely, SDMA is primarily excreted in the urine and identifies reduced renal function.

Clinical Use
ADMA/SDMA may be measured in individuals with multiple risk factors for the development of cardiovascular disease. Fasting is recommended, but not required.

Clinical Significance
Cardiovascular Significance:
- Elevated ADMA levels are associated with the presence of hypertension\(^1\), insulin resistance\(^1\), and hyperlipidemia\(^2\).
- Elevated ADMA levels are associated with subclinical atherosclerosis:
  - Elevated ADMA concentrations correlate with internal carotid artery bulb intimal media thickness\(^3\), a hemodynamically unstable region vulnerable to nitric oxide deficiency\(^4\) and plaque formation.
  - Elevated ADMA in young adults has been associated with increased coronary artery calcification (CAC) score\(^5\).
- Individuals with established coronary artery disease and elevated ADMA levels have more than twice the risk for adverse events (MI, stroke) than those with normal ADMA levels\(^6\).

Renal Significance:
- Elevated SDMA levels positively correlate with reduced renal function as measured by eGFR\(^7\).

Order Code C301
Tube Type Tiger Top

ADMA/SDMA

<table>
<thead>
<tr>
<th>RELATIVE RISK</th>
<th>ADMA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 Low</td>
<td></td>
</tr>
<tr>
<td>100-123 Moderate</td>
<td></td>
</tr>
<tr>
<td>&gt;123 High</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REFERENCE RANGE</th>
<th>SDMA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73-135 Low</td>
<td></td>
</tr>
<tr>
<td>&gt;135 High</td>
<td></td>
</tr>
</tbody>
</table>

CPT Code
Sample Type Serum
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess LDL-C levels.
  • If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

✓ Assess blood pressure.
  • If not at goal, consider initiating, or titrating, antihypertensive therapy.
  NOTE: An elevated blood pressure may contribute to endothelial dysfunction and the development of coronary artery disease and subsequent renal disease.
  • Consider L-Arginine or L-Citrulline supplementation to improve vasodilation and vascular tone.
  NOTE: L-Arginine and L-Citrulline enhance the production of nitric oxide which has anti-inflammatory, antithrombotic, antihypertensive, and antioxidant effects.

✓ Assess risk for pre-diabetes/diabetes.
  • If abnormal fasting glucose or oral glucose tolerance test, consider proliferator-activated receptor (PPAR) agonists, metformin or dipeptidyl peptidase-4 (DPP-IV) inhibitor if not contraindicated.

✓ Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
  • Consider aspirin therapy if not contraindicated.
  • Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke)

References

Microalbumin

CPT Code 82043/82570
Sample Type Urine

Description
Microalbumin is the quantification of small amounts of albumin, a serum protein, in urine that can be used to identify microvascular endothelial dysfunction. The presence of small amounts of albumin in the urine may suggest the presence of systemic endothelial dysfunction - an early indicator of heart disease. This test is more sensitive than a standard dipstick test routinely performed in an office setting.

Clinical Use
Microalbumin may be performed on individuals with type 1 or type 2 diabetes, hypertension, a family history of chronic kidney disease, those at intermediate (10-20%) risk for cardiovascular disease (CVD) or those with known vascular disease.

Clinical Significance
Cardiovascular Significance:
- Increases in microalbumin excretion in the ‘normal’ range (<30 mg/g) are associated with increased risk for development of cardiovascular morbidity and mortality, as well as all-cause mortality³⁸.
- In particular, it was shown that healthy individuals (defined as non-hypertensive, non-diabetic, and without prevalent CVD) with low microalbumin levels had approximately 3x greater risk for developing cardiovascular disease⁵. These levels were gender-specific and noted to be ≥3.9 mg/g for men and ≥7.5 mg/g for women.
- A direct, linear relationship exists between microalbuminuria and the risk of heart attack, stroke and death⁵.

Renal Significance:
- The American Diabetes Association has defined microalbuminuria as a microalbumin value of 30-300 mg/g creatinine¹. A persistent microalbumin of >30 mg/g indicates a loss of kidney function and is used in the diagnosis of chronic kidney disease⁷.

RELATIVE RISK¹
Microalbumin (mg/g creatinine)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.5 Low</td>
<td></td>
<td>&lt;3.9 Low</td>
</tr>
<tr>
<td>≥7.5 High</td>
<td></td>
<td>≥3.9 High</td>
</tr>
</tbody>
</table>

Order Code C919
Tube Type Yellow Top
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess blood pressure.**
  - If not at goal, consider initiating, or titrating, antihypertensive therapy.
  - NOTE: An elevated blood pressure may damage the endothelium in the kidney and contribute to disease. The presence of urinary microalbumin may suggest systemic endothelial dysfunction and the presence of CAD.
  - Retest urinary microalbumin levels in 2-3 months.

✓ **Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.**
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).

✓ **Assess risk for pre-diabetes/diabetes.**
  - If abnormal fasting glucose or oral glucose tolerance test, consider PPAR agonists, metformin or DPP-IV inhibitors if not contraindicated.

References

Description
The hsCRP test is a highly sensitive quantification of CRP, an acute-phase protein released into the blood by the liver during inflammation, which has been associated with the presence of heart disease.

Clinical Use
The hsCRP test may be performed on individuals at intermediate risk (10-year risk of 10-20%) of developing coronary heart disease (CHD) who are metabolically stable without inflammatory or infectious conditions.

Clinical Significance
- hsCRP is a well-documented clinical marker of general and cardiac-related inflammation.
- Apparently healthy individuals with elevated hsCRP values are up to 4X as likely to have coronary heart disease\(^1,2\).
- Elevated hsCRP is associated with the risk of future adverse cardiovascular events (heart attack, stroke and death) in apparently healthy individuals\(^1,3\) and in individuals with stable CAD\(^4\).
- Reductions in both hsCRP and LDL-C are associated with reduction in the rate of atherosclerosis progression\(^5\) and improved clinical outcomes\(^6\).
- Introduction of statin therapy in patients with elevated hsCRP, even with normal lipid levels, significantly reduces risks for heart attack, stroke and death\(^7\).

CPT Code 86141
Sample Type Serum/EDTA Plasma

Order Code C121
Tube Type Tiger Top or Lavender Top

High-Sensitivity C-Reactive Protein (hsCRP)

Relative Risk

<table>
<thead>
<tr>
<th>hsCRP (mg/L)</th>
<th>&lt;1.0 Low</th>
<th>1.0-3.0 Moderate</th>
<th>&gt;3.0 High</th>
</tr>
</thead>
</table>

Note: Levels >10 mg/L warrant follow-up for consideration of a non-cardiovascular-related cause\(^8\).
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess presence of acute (flu, cold, etc.) or chronic (bronchitis, chronic obstructive pulmonary disease, rheumatoid arthritis (RA)) illness.
✓ Assess LDL-C levels.
  • If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.
✓ Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
  • Consider aspirin therapy if not contraindicated.
  • Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e., TIA or stroke)
✓ Assess dental health (periodontal disease).
  • Refer to dentist to identify gum disease.
  NOTE: Poor dental health may cause significant inflammation and is associated with the presence of atherosclerosis8.
✓ Assess blood pressure.
  • If not at goal, consider initiating, or titrating, antihypertensive therapy.
  NOTE: An elevated blood pressure may contribute to endothelial dysfunction and coronary disease formation.
✓ Assess lifestyle habits.
  • Consider diet/exercise/weight reduction efforts if appropriate.

References
Lp-PLA₂ Activity

CPT Code 83698
Sample Type Serum/EDTA Plasma

Description

Lp-PLA₂, or lipoprotein-associated phospholipase-A₂, measures disease activity within the artery wall below the collagen or calcified cap due to the activation of macrophages. Lp-PLA₂ is not an acute phase reactant. When disease is active in the artery, increased levels of Lp-PLA₂ are produced by macrophages and foam cells within the intima of the artery¹. Lp-PLA₂ also interacts with oxidized LDL, which increases inflammation and enhances a proatherogenic state, as well as plaque vulnerability². Research suggests that it plays a direct role in the atherosclerotic disease process³.

Clinical Use

The Lp-PLA₂ Activity test may be performed on individuals at intermediate or high risk for developing coronary heart disease.

Clinical Significance

- Lp-PLA₂ accumulates within human atherosclerotic plaques and vulnerable lesions⁴.
- Individuals with elevated Lp-PLA₂ Activity are nearly twice as likely to develop CHD at 7 years regardless of non-HDL cholesterol levels⁵.
- Individuals with elevated Lp-PLA₂ Activity are twice as likely to experience a CHD event (MI, coronary revascularization or CHD-related death) at 5 years⁶.

Order Code C570
Tube Type Tiger Top or Lavender Top

RELATIVE RISK

Lp-PLA₂ Activity (nmol/min/mL)

<75 Low
≥75 High
Assess LDL-C levels.
- If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

Assess omega-3 fatty acid levels.
- Omega-3 fatty acid supplementation, along with statin therapy, may reduce Lp-PLA2 levels.

Assess HDL-C levels.
- If low, assess CoQ10 levels as evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels.

Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).

Assess dental health (periodontal disease).
- Refer to dentist to identify gum disease.

Assess blood pressure.
- If not at goal, consider initiating, or titrating, antihypertensive therapy.
  NOTE: An elevated blood pressure may contribute to endothelial damage and coronary disease formation.

Assess lifestyle habits.
- Consider diet/exercise/weight reduction efforts if appropriate.
- Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

References
7. Schaefer EJ. Effects of atorvastatin versus other statins on fasting and postprandial C-reactive protein and lipoprotein-associated phospholipase A2 in patients with coronary heart disease versus control subjects. Am J Cardiol. 2005; 95(9):1025-1032.
10. Toyama K et al. Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease. Atherosclerosis. 2011; 217: 158-164.
Myeloperoxidase (MPO)

CPT Code 83876
Sample Type EDTA Plasma

Description
MPO is a white blood cell-derived inflammatory enzyme and measures disease activity from the luminal aspect of the arterial wall.

Briefly, when the artery wall is damaged, or inflamed, MPO is released by invading white blood cells where it accumulates. MPO mediates the vascular inflammation that propagates plaque formation and activates protease cascades that are linked to plaque vulnerability. White blood cell activation in the bloodstream, in response to luminal injury of the artery wall including fissures, erosions or a degrading collagen cap, leads to MPO release in the bloodstream. This combination of detrimental effects demonstrates that MPO is actively involved in the progression of atherosclerosis. The Cleveland HeartLab MPO test measures free MPO in the bloodstream.

Clinical Use
The MPO test may be performed on individuals with multiple risk factors for cardiovascular disease, or those with established disease.

Clinical Significance
- Elevated MPO levels predict the risk of heart disease in subgroups otherwise associated with low risk.
- Elevated MPO levels independently predict the risk of future cardiovascular events in patients presenting with an acute coronary syndrome.
- Individuals with elevated MPO levels are more than 2x as likely to experience cardiovascular mortality.
- MPO enhances cardiovascular risk prediction when used independently or alongside standard biomarker testing such as hsCRP.
- MPO levels are not likely to be elevated due to chronic infections or rheumatologic disorders due to the fact that free MPO in the blood is a specific marker of vascular inflammation and vulnerable plaque/erosions/fissures.
- The p-ANCA test (anti-MPO antibody test) is not the same as the MPO test performed by Cleveland HeartLab. The p-ANCA test primarily measures the amount of antibodies directed against the MPO protein.

RELATIVE RISK
MPO (pmol/L)

Note: Numerous studies have documented that increasing MPO levels predict increasing risk for adverse events in various cohorts of individuals. Please visit www.clevelandheartlab.com for literature supporting the clinical utility of MPO testing.

<470 Low
470-539 Moderate
≥540 High

Note: CPT codes are for informational purposes only and do not constitute medical advice.
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess LDL-C levels.
  • If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.
✓ Assess lifestyle habits.
  • Consider diet/exercise/weight reduction efforts if appropriate.
✓ Assess blood pressure.
  • If not at goal, consider initiating, or titrating, antihypertensive therapy.
  NOTE: An elevated blood pressure may contribute to endothelial dysfunction and coronary disease formation.
✓ Assess smoking habits.
  NOTE: Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.
✓ Assess risk for pre-diabetes/diabetes.
  • If abnormal oral glucose tolerance test or insulin levels, consider insulin sensitizing therapy.
✓ Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
  • Consider aspirin therapy if not contraindicated.
  • Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e., TIA or stroke).
✓ Assess dental health (periodontal disease).
  NOTE: Poor dental health may cause significant inflammation and is associated with the presence of atherosclerosis9.
✓ Assess HDL-C levels.
  • If low, assess CoQ10 levels as evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels10.
✓ Assess, if known to be present, the treatment of inflammatory conditions such as Crohn's disease, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). 
  NOTE: Chronic inflammatory diseases may exhibit elevated MPO values due to increased vascular disease associated with these conditions. For example, RA is associated with a 5X increased risk for myocardial infarction11.
✓ Assess the presence of vasculitis.
  NOTE: MPO values may be elevated in individuals with vasculitis as it is characterized by increased vascular inflammation.
✓ Assess the presence of bone marrow dyscrasias.
  NOTE: MPO values may be elevated in individuals with chronic lymphocytic leukemia or other leukemias that cause increased white blood cell destruction.
✓ Assess level of exercise.
  NOTE: MPO values may be elevated in marathon runners12 and extreme athletes may identify those with increased oxidative stress and basal levels of inflammation

If asymptomatic, with all of the above factors ruled out, an elevated MPO value may in fact be the patient’s baseline. MPO levels should be monitored every 3-6 months.

References
7. Cavusoglu E et al. Usefulness of baseline plasma myeloperoxidase levels as an independent predictor of myocardial infarction at two years in patients presenting with acute coronary syndrome. Am J Cardiol. 2007; 99: 1364-1368.
10. Toyama K et al. Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease. Atherosclerosis. 2011; 217: 158-164.
Abnormal cholesterol levels are a well-known risk factor for CVD and are a part of routine clinical testing. Current recommendations focus on LDL-C as a target of therapy for CVD risk reduction. The LDL-C result is typically calculated from a fasting specimen according to the Friedewald formula, which indirectly determines the amount of LDL-C based on the measurement of other lipoproteins (total cholesterol (TC), HDL-C, and very low-density lipoprotein cholesterol (VLDL-C) based on triglyceride (TG) results). These tests themselves are subject to measurement uncertainty. Therefore, calculated LDL-C results can vary as much as 15% in some patients.

Knowing your patient’s lipid levels is a useful clinical and diagnostic tool, even with the aforementioned limitations. However, advanced lipid testing is currently available to provide a more powerful insight into your patient’s true lipid risk.
References


Cleveland HeartLab offers advanced lipid testing to aid in determining cardiovascular risk in patients, alongside a Standard Lipid Panel which is commonly performed at least once a year in most medical practices. While a Standard Lipid Panel provides cholesterol and triglyceride measurements, other measurements readily available can address additional risk factors for disease including the number of atherogenic particles, the size of these particles and the inherent risk of developing CVD.

Advanced lipid testing provided by Cleveland HeartLab includes the following tests:
- Standard Lipid Panel (includes non-HDL cholesterol and automatic reflex to direct LDL when TGs >400 mg/dL)
- ApoB
- ApoA1
- ApoB/ApoA1 Ratio
- sdLDL
- Lp(a)
- HDL2b

These tests are reviewed on the next pages, and can be ordered individually.
Standard Lipid Panel

CPT Code 80061  
Sample Type Serum  
Order Code C909  
Tube Type Tiger Top

Description
The lipid panel is a well-established group of tests that provide general information used to identify patients at risk for CVD. The standard lipid panel includes: total cholesterol, LDL-C, HDL-C, triglycerides, and non-HDL cholesterol.

Clinical Use
The lipid panel may be used to identify individuals at risk of, or with, CVD or dyslipidemia. It also may be used to monitor an individual's progress on anti-lipid therapy.

Clinical Significance
- Numerous laboratory and clinical studies have demonstrated that lipid abnormalities are associated with cardiovascular disease risk1.
- National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII) guidelines recommend a complete lipid profile as the preferred initial test for determination of CVD risk1.
- NCEP/ATPIII guidelines state that LDL-C is the primary target for cholesterol treatment1 and therefore should be monitored routinely.
- Lipid panels are an easy way to monitor therapeutic response to various drugs including statins, niacin, and fibrates2.

RELATIVE RISK

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 Low</td>
<td>&lt;100 Low</td>
<td>≥50 Low</td>
</tr>
<tr>
<td>200-239 Moderate</td>
<td>100-129 Moderate</td>
<td>≥40 Low</td>
</tr>
<tr>
<td>≥240 High</td>
<td>≥130 High</td>
<td>&lt;50 High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triglycerides (mg/dL)</th>
<th>Non-HDL Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 Low</td>
<td>&lt;130 Low</td>
</tr>
<tr>
<td>150-199 Moderate</td>
<td>130-159 Moderate</td>
</tr>
<tr>
<td>≥200 High</td>
<td>≥160 High</td>
</tr>
</tbody>
</table>
**Treatment Considerations**

*These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.*

- **Assess LDL-C levels.**
  - If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.

- **Assess HDL-C levels.**
  - If low, assess CoQ10 levels as recent evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels.

- **Assess risk for pre-diabetes/diabetes.**

- **Assess smoking habits.**
  - **NOTE:** Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

- **Assess triglyceride levels.**
  - If not at goal, first consider fasting status at time of blood draw, risk of pre-diabetes/diabetes, alcohol intake, thyroid status, renal function, smoking status or pregnancy.
  - Once the aforementioned have been addressed, consider statins, niacin, fenofibrate, omega-3 fatty acid supplementation, PPAR agonist or combination therapy if not contraindicated.

- **Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.**
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).

- **Assess lifestyle habits.**
  - Consider diet/exercise/weight reduction efforts if appropriate.

---

**References**


3. Toyama K et al. Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease. *Atherosclerosis*. 2011; 217: 158-164.
Apolipoprotein B (ApoB) and A1 (ApoA1)

CPT Code 82172 (same for both biomarkers)
Sample Type Serum

Description
ApoB is the primary apolipoprotein found on the surface of all atherogenic lipoproteins: LDL, IDL, VLDL, and Lp(a). ApoB acts as a... ... ApoA1 is the major lipoprotein of HDL and promotes cholesterol efflux from the artery wall to the liver for excretion.

Clinical Use
The ApoB test may be performed on individuals undergoing management for lipoprotein abnormalities, individuals with established coronary heart disease or diabetes, or individuals with two or more major risk factors for coronary heart disease. The ApoA1 test may be performed on individuals with hyperlipidemia, those with decreased levels of HDL-C, those at risk of cardiovascular disease or those with a family history of cardiovascular disease. Both may be used to monitor the efficacy of lifestyle and therapeutic interventions in individuals with established cardiovascular disease.

Clinical Significance
- Because the amount of LDL cholesterol per LDL particle varies within and between individuals, ApoB measurements provide a true indication of the number of atherogenic particles.
- ApoB and ApoA1 are measured directly, unlike LDL-C which is calculated from measurements of total cholesterol, TG, and HDL-C using the Friedewald formula (this is only accurate if TG values are ≤400 mg/dL).
- Elevated levels of ApoB may signify increased risk of fatal MI even when LDL levels are within normal range.
- Low levels of ApoA1 are associated with low levels of HDL-C and reduced cholesterol clearance.
- The ApoB/ApoA1 ratio indicates ‘cholesterol balance’ and provides a strong, direct relationship for the risk of virtually all ischemic events.
- The ApoB/ApoA1 ratio was more strongly related to risk of MI than either smoking or diabetes, and individuals with a high ApoB/ApoA1 ratio have more than a 3X greater risk of having an MI.

RELATIVE RISK
ApoB/ApoA1 Ratio

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.70 Low</td>
<td>&lt;0.75 Low</td>
</tr>
<tr>
<td>0.70-0.80 Moderate</td>
<td>0.75-0.90 Moderate</td>
</tr>
<tr>
<td>&gt;0.80 High</td>
<td>&gt;0.90 High</td>
</tr>
</tbody>
</table>

ApoB (mg/dL)

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 Low</td>
<td>&lt;100 Low</td>
</tr>
<tr>
<td>100-120 Moderate</td>
<td>100-120 Moderate</td>
</tr>
<tr>
<td>&gt;120 High</td>
<td>&gt;120 High</td>
</tr>
</tbody>
</table>

ApoA1 (mg/dL)

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;130 Low</td>
<td>&gt;120 Low</td>
</tr>
<tr>
<td>≤130 High</td>
<td>≤120 High</td>
</tr>
</tbody>
</table>
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess LDL-C levels.
  • If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.
  • Consider diet/exercise/weight reduction efforts if appropriate.
✓ Assess HDL-C levels.
  • Assess CoQ10 levels as recent evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels.
✓ Assess risk for pre-diabetes/diabetes.
✓ Assess smoking habits.
  NOTE: Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

References
Small-Dense LDL (sdLDL)

Description
LDL exists either as large, more buoyant particles or as smaller, more dense particles (sdLDL). sdLDL is more easily oxidized, has a higher affinity for vessel walls, and remains in the circulation longer because it is less likely to be cleared by the liver, making it more atherogenic than larger LDL particles.

Clinical Use
The sdLDL test may be performed on individuals at risk of metabolic syndrome, those with established/progressing coronary artery disease, those with triglyceride levels between 70 and 140 mg/dL, as well as those with a diet high in trans-fat or carbohydrates.

Clinical Significance
- Increased levels of sdLDL are found in patients with metabolic syndrome and are part of the “atherogenic lipoprotein profile”, which includes increased levels of TG and reduced levels of HDL-C.
- An increased level of sdLDL is a strong predictive factor for CVD independent of total LDL levels.
- Increased sdLDL levels at baseline are associated with increased rates of CVD progression.
- The amount of cholesterol in sdLDL is associated with risk of ischemic heart disease, and is independent of lipid and non-lipid risk factors, as well as ApoB.

REFERENCE RANGE
Small-Dense LDL (mg/dL)

≤40.0 Low

>40.0 High
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess LDL-C levels.**
  - If not at goal, consider lipid-lowering therapy, ideally with a statin-based regimen if not contraindicated.
  - Consider diet/exercise/weight reduction efforts if appropriate.

- **Assess risk for pre-diabetes/diabetes.**
  - If abnormal fasting glucose or oral glucose tolerance test, consider PPAR agonists, metformin or DPP-IV inhibitors if not contraindicated.

- **Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.**
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).

- **Assess smoking habits.**
  - NOTE: Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

- **Consider statin, niacin, omega-3 fatty acid supplementation, or combination therapy if not contraindicated.**

---

References

5. Rosensen RS et al. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol. 2002; 90: 89-94.
Lipoprotein (a) (Lp(a))

Description
Lp(a) is a plasma lipoprotein consisting of a cholesterol-rich LDL particle attached to an additional apolipoprotein called apo(a). Lp(a) levels are genetically determined and not affected by changes in lifestyle.

Clinical Use
The Lp(a) test may be performed on individuals with a family history of premature coronary heart disease, a genetic predisposition for hypercholesterolemia, established atherosclerosis but with a normal routine lipid profile, hyperlipidemia refractory to treatment, or a history of recurrent arterial stenosis.

Clinical Significance
- Lp(a) possesses potent atherogenic and thrombogenic properties.
- Elevated Lp(a) levels signify increased risk for coronary heart disease and are associated with increased risk for myocardial infarction.
- Lp(a) levels are elevated in ischemic stroke patients and correlate well with carotid artery atherosclerosis.

Relative Risk

<table>
<thead>
<tr>
<th>Lp(a) (mg/dL)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess family history of heart disease.
✓ Assess Lp-PLA2 and MPO levels.
   - If abnormal, treat individual biomarkers and retest in 3-6 months.
   NOTE: Lp-PLA2 and MPO may help to identify the presence of vulnerable plaque and increased risk of thrombosis in patients with early onset heart disease.
✓ Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
   - Consider aspirin therapy if not contraindicated.
   - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).
✓ If abnormal, consider niacin therapy.

References

7. Kamstrup PR et al. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009; 301: 2331-2339.
**HDL2b**

CPT Code 83701  
Sample Type Serum

### Description

HDL cholesterol, like LDL cholesterol, can be divided into several subfractions, based on density, size and protein composition. The HDL2 subfraction (HDL2a, HDL2b) consists of larger, more buoyant particles while particles in the HDL3 subfraction (HDL3a, HDL3b, HDL3c) are smaller and denser. The largest and most buoyant HDL particle is HDL2b.

One primary function of HDL particles is to promote reverse cholesterol transport, or the movement of cholesterol from the tissues to the liver for excretion. HDL is first formed in the liver as the smaller HDL3 particles. Once released, HDL3 particles travel in the blood, where they receive cholesterol by various enzymatic events, eventually resulting in the formation of HDL2b particles. Assessment of HDL2b particles may provide a more powerful measure of cardiovascular risk than other HDL2 or HDL3 subfractions, individually or combined.

### Clinical Use

The HDL2b test may be used for individuals at risk of diabetes or cardiovascular disease, those with cardiovascular disease or those with low total HDL levels or high triglyceride levels.

### Clinical Significance

- Elevated total cholesterol and low HDL cholesterol levels, as well as high triglyceride levels, are associated with low HDL2b levels\(^1\). \(^4\).
- Reduced HDL2b levels have been associated with insulin resistance\(^6\).
- Women tend to have higher levels of HDL2b than men, and HDL2b levels tend to decrease as a person's BMI increases\(^6\).
- HDL2b levels may be significantly increased by a combination of caloric restriction and high-intensity exercise\(^7\).

### RELATIVE RISK

<table>
<thead>
<tr>
<th>HDL2b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;28 Low</td>
</tr>
<tr>
<td>18-28 Moderate</td>
</tr>
<tr>
<td>&lt;18 High</td>
</tr>
</tbody>
</table>

**WOMEN**

- >28 Low
- 18-28 Moderate
- <18 High

**MEN**

- >26 Low
- 18-26 Moderate
- <18 High

---

\(^1\) --- \(^7\) Refer to sources for detailed information.
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess HDL-C levels.
  - Assess CoQ10 levels as recent evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels.
✓ Assess risk for pre-diabetes/diabetes.
✓ Assess smoking habits.
  NOTE: Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.
✓ Assess triglyceride levels.
  - If triglyceride levels are not at goal, first consider fasting status at time of blood draw, risk of pre-diabetes/diabetes, alcohol intake, thyroid status, renal function, smoking status or pregnancy.
  - If the aforementioned have been addressed and triglycerides remain high, consider fenofibrate, prescription omega-3 fatty acids, niacin, statins, or combination therapy if not contraindicated.
✓ Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).
✓ Assess lifestyle habits.
  - Consider diet/exercise/weight reduction efforts if appropriate.

References
8. Toyama K et al. Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease. Atherosclerosis. 2001; 217: 158-164.
Metabolic Testing

Cleveland HeartLab also offers metabolic tests that are additive and complementary to our inflammatory and advanced lipid testing.

Some of these tests are reviewed on the following pages.

Metabolic tests include:
- TMAO
- Adiponectin

For a complete listing, see the test menu on our website.
Trimethylamine N-oxide (TMAO)

CPT Code 82542
Sample Type Serum

Order Code C524
Tube Type Tiger Top

Description
Gut microbes live symbiotically within the human digestive tract and play important roles in host defense, immunity, and nutrient processing and absorption. This diverse community is unique to each person and influenced by both acute and chronic dietary exposures to various food sources.

Nutrients such as phosphatidylcholine (also known as lecithin), choline, and L-carnitine are abundant in animal-derived products such as red meat, egg yolk and dairy products. When consumed, these nutrients are processed by gut bacteria resulting in the release of various metabolites including TMA (trimethylamine) into the blood. TMA is then transported to the liver where it is converted into TMAO (trimethylamine N-oxide). TMAO has been shown to regulate various physiological processes which are involved in the development of atherosclerosis1,2 as well as reverse cholesterol synthesis3 and platelet function4.

Clinical Use
TMAO may be measured in individuals with one or more risk factors for the development of cardiovascular disease and/or individuals whom may benefit from intensive dietary intervention.

Clinical Significance
- There is a dose-response relationship between TMAO and atherosclerotic burden1 and major adverse cardiovascular events incidence (MACE: MI, stroke or death)5,6.
- In stable individuals undergoing elective cardiac evaluation, elevated TMAO levels are associated with increased risk of cardiovascular disease1 and MACE5.
- Increased plasma L-Carnitine (a dietary precursor to TMAO) is associated with cardiovascular risk only when TMAO is simultaneously elevated via the metabolism by specific gut microbes2.
- In subsets of this population considered ‘low risk’ (<65 years old, <100mg/dL LDL-C, normal blood pressure, non-smokers, low levels of MPO), elevated TMAO remained a significant predictor of MACE risk2.
- Elevated TMAO increases 7-year mortality risk in patients admitted to the ER who presented with acute coronary syndrome5 as well as 5-year mortality risk in patients with CAD receiving optimal therapy7 and PAD patients8.

RELATIVE RISK
TMAO (µM)

- <6.2 Low
- 6.2-9.9 Moderate
- ≥10.0 High
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess dietary habits**
  - Consider implementing a Mediterranean or plant-based diet.
  - A more diverse diet rich in vegetables can improve the health of the gut microbiota.
  - Consider limiting the intake of foods rich in TMA precursors such as red meat, eggs, and/or dairy products.

  NOTE: Certain types of seafood contain high levels of TMAO particularly saltwater fish, sharks, rays, mollusks, and crustaceans. Arctic deep sea fishes are known to be rich in TMAO while surface fishes (trout) contain much less TMAO. These food sources may falsely elevate TMAO levels.

✓ **Assess supplementation**
  - Consider probiotic/prebiotic supplementation to promote gut bacterial biodiversity.
  - Consider discontinuing the use of lecithin or L-carnitine containing supplements in individuals with elevated TMAO levels.

Implement global risk reduction strategies

✓ **Assess LDL-C levels.**
  - If elevated, consider LDL-lowering therapies.

✓ **Assess BMI.**
  - If overweight/obese, consider weight management strategies.

References

Adiponectin

CPT Code 83516
Sample Type Serum

Order Code C314
Tube Type Tiger Top

Description
Adiponectin is an abundant hormone released by adipocytes (or fat cells), commonly referred to as an adipokine. Adiponectin plays a large metabolic role in the body, participating in the regulation of glucose levels, insulin sensitivity and lipid catabolism. Adiponectin also helps support proper endothelial functioning and has multiple anti-inflammatory properties, including inhibiting the transformation of macrophages to foam cells, one of the first steps of atherosclerosis.

Unlike other adipokines, adiponectin levels are lower in obese individuals. As adipocytes become larger with weight gain, they release less adiponectin. Among healthy individuals, women typically have higher adiponectin levels than men, and adiponectin levels tend to decrease as a person ages.

Clinical Use
The adiponectin test may be used to assess future risk of metabolic syndrome or diabetes in individuals who make poor lifestyle choices.

Clinical Significance
- Individuals with low adiponectin levels have a 3X greater risk of developing metabolic syndrome¹.
- Men with two or more risk factors for metabolic syndrome and high adiponectin levels are half as likely to develop metabolic syndrome as men with low adiponectin levels².
- Individuals with the lowest levels of adiponectin are up to 9X as likely to develop type 2 diabetes³.
- Individuals with low adiponectin levels have a 2X increase in the prevalence of CAD⁴.

REFERENCE RANGE
Adiponectin (μg/mL)

<table>
<thead>
<tr>
<th></th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td>5-37</td>
<td>4-26</td>
</tr>
<tr>
<td>BMI 25-30 kg/m²</td>
<td>5-28</td>
<td>4-20</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>4-22</td>
<td>2-20</td>
</tr>
</tbody>
</table>
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess lifestyle habits.
  • Consider diet/exercise/weight reduction efforts if appropriate.
Note: The Look AHEAD Study demonstrated that intensive lifestyle interventions (resulting in moderate weight loss in obese diabetic individuals) resulted in higher HDL-C levels which were significantly associated with and possibly mediated by adiponectin levels.

References


Vitamin & Supplement Testing

Cleveland HeartLab also offers vitamin and supplement testing that are additive and complementary to our inflammatory and advanced lipid testing.

Some of these tests are reviewed on the following pages.

Vitamin & Supplement tests include:

- OmegaCheck™
- Coenzyme Q10
- Vitamin D, 25 OH
- AspirinWorks®

For a complete listing, see the test menu on our website.
Description

Omega-3 and omega-6 fatty acids (FA) are polyunsaturated long chain FA required by the body for proper functioning, normal growth and the formation of neural synapses and cellular membranes. Omega-3 and -6 FA are considered “essential” and obtained primarily from dietary sources.

Three of the most important omega-3 FA are eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). Omega-3 FA are primarily obtained from oily fish. They have antioxidant\(^1\), anti-inflammatory\(^2\) and antithrombotic\(^3\) effects, and can help to reduce triglyceride levels\(^4-6\). Two of the most abundant omega-6 FA are arachidonic acid (AA) and linoleic acid (LA). Omega-6 FA are obtained from animal sources and plant oils, and have pro-inflammatory\(^2,7\) and pro-thrombotic\(^7\) properties at high levels.

Clinical Use

OmegaCheck™ may be performed on individuals with hypercholesterolemia, hypertriglyceridemia, hypertension, and/or those at high metabolic or cardiovascular risk.

Clinical Significance

- Consumption of omega-3 FA reduces the occurrence of major acute cardiac events in healthy individuals or patients with cardiovascular risk factors or who have cardiovascular disease\(^5-14\).
- Consumption of omega-3 FA leads to a reduction in triglyceride\(^4-6\), non-HDL\(^5\) and Lp-PLA\(_2\) levels\(^6\).
- A high intake of omega-6 FA precursors can interfere with the absorption of omega-3 FA\(^12\).
- The mean omega-6:omega-3 ratio of the standard American diet is approximately 10:1\(^12\), while a diet with a ratio of 4:1 or less may reduce total mortality up to 70% over 2 years\(^11\).

RELATIVE RISK

OmegaCheck™ (% by weight)

- ≥5.5 Low
- 3.8-5.4 Moderate
- ≤3.7 High

The OmegaCheck™ was developed and validated at Cleveland HeartLab with the support of Nutrasource Diagnostics, Inc.
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess dietary intake of omega-3 and omega-6 fatty acids.**
  • Dietary sources of omega-3 fatty acids include fatty fishes, such as salmon or sardines, nuts, and plant oils. Foods high in omega-6 fatty acids include poultry and eggs, plant oils, and nuts.

✓ **Consider omega-3 fatty acid supplementation.**
  • If currently taking, consider adjusting dosage and retest in 1-2 months.

✓ **Assess lifestyle habits.**
  • Consider diet/exercise/weight reduction efforts if appropriate.

References

Coenzyme Q10 (CoQ10)

CPT Code 82542
Sample Type Serum/EDTA Plasma

Order Code C295
Tube Type Tiger Top or Lavender Top

Description
Coenzyme Q10 (CoQ10) is a fat-soluble, vitamin-like substance present in most cells, primarily in mitochondria. CoQ10 has two major roles within the human body: it participates in aerobic cellular respiration generating energy (i.e., ATP) and is a powerful antioxidant. CoQ10 exists in two forms in the body: ubiquinone and ubiquinol (the active form of CoQ10, which is made from ubiquinone).

Endogenous synthesis of CoQ10 is a very complex process requiring an adequate supply of numerous precursors and cofactors, and deficiencies in one or more of these components can adversely affect the production of adequate amounts of CoQ10. CoQ10 deficiency may also be caused by one or more of the following: insufficient dietary intake, impairment of CoQ10 biosynthesis, poor gastrointestinal absorption, and/or excessive utilization of CoQ10 by the body.

Exogenous sources of CoQ10 include animal products such as beef, pork and chicken. Plant products such as broccoli, spinach, soybean oil and palm oil are also good sources of CoQ10. Supplements are also widely available over-the-counter, either as ubiquinol or ubiquinone. As a person ages, their body makes less ubiquinone, and the body’s ability to convert ubiquinone to ubiquinol is reduced. Therefore, the choice of CoQ10 supplement may depend in part on the person’s age.

Clinical Use
The CoQ10 test may be performed on individuals on statin therapy who may or may not be experiencing myalgia symptoms, hypercholesterolemic individuals, and asymptomatic individuals at risk for vascular disease who may have low ApoA1 and/or HDL levels.

Clinical Significance
- CoQ10 deficiency contributes to mitochondrial dysfunction and muscle dysfunction without myonecrosis.
- Statin use may inhibit the production of CoQ10 in a dose-dependent fashion by as much as 40% in hypercholesterolemic individuals.
- Exercise, in combination with statin therapy, can improve HDL levels and preserve CoQ10 levels.
- Low CoQ10 levels may be associated with low ApoA1 and/or HDL levels and poor outcomes, and may increase infarct size if/when an individual has an acute myocardial infarction or stroke.

REFERENCE RANGE
CoQ10
(µg/mL)

0.36-1.59
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess dietary intake of CoQ10.
  - Dietary sources of CoQ10 include animal products such as beef, pork or chicken, and vegetables such as spinach, cauliflower and broccoli.
✓ Consider CoQ10 supplementation.
  - If currently taking, consider adjusting dosage and retest in 1-2 months.
✓ Assess ApoA1 and/or HDL levels.
  - If low, consider treatment with niacin or fenofibrate therapy.

References
3. Toyama K et al. Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease. Atherosclerosis. 2011; 217: 158-164.
Vitamin D, 25 OH

CPT Code 82306
Sample Type Serum/EDTA Plasma

Order Code C339
Tube Type Tiger Top or Lavender Top

Description
Vitamin D is a fat-soluble vitamin naturally present in some foods, but the main source is synthesis within the body after exposure to sunlight. Vitamin D has various roles within the body, but primarily regulates the absorption of calcium in the gut, maintaining adequate serum calcium and phosphate concentrations that contribute to mineralization of bone.

Vitamin D is available in two forms. Vitamin D3 (cholecalciferol) is mainly made in the skin upon exposure to UV light, and is also found in fish. The main source of Vitamin D2 (ergocalciferol) is fortified foods and supplements. Although commonly considered bioequivalent, Vitamin D2 may not be as bioavailable to the body as Vitamin D3. Vitamin D is metabolized in the liver to the prohormone Vitamin D, 25 OH which is the primary circulating form of Vitamin D.

Clinical Use
The Vitamin D, 25-OH test is used to determine the levels of Vitamin D in blood, particularly in individuals with bone weakness or malformation, or those with impaired calcium metabolism. The test may also be used to monitor Vitamin D levels in individuals with conditions that impair fat absorption.

Clinical Significance
- Vitamin D deficiency is implicated in increased risk for CVD.
- Vitamin D deficiency is associated with an increased risk for hypertension, common cancers, autoimmune diseases and infectious diseases.
- Vitamin D is critical for the maintenance of healthy bones, and deficiency can cause osteoporosis, muscle weakness and muscle wasting.

RELATIVE RISK
Status of Vitamin D Sufficiency
Vitamin D, 25 OH (ng/mL)

<table>
<thead>
<tr>
<th>Status</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.0-80.0</td>
<td>Sufficient</td>
</tr>
<tr>
<td>10.0-29.9</td>
<td>Insufficient</td>
</tr>
<tr>
<td>80.1-100.0</td>
<td>Excess</td>
</tr>
<tr>
<td>&lt;10.0</td>
<td>Deficient</td>
</tr>
<tr>
<td>&gt;100.0</td>
<td>Potential Toxicity</td>
</tr>
</tbody>
</table>
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess dietary intake of vitamin D.
  ▪ If not at goal, consider vitamin D-rich foods such as cheese, vitamin D-fortified milk, shiitake and button mushrooms (dried by sunlight), or supplementation with vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol).

✓ Consider an increase in direct sun exposure to 10-15 minutes a day.

References

Description
AspirinWorks® is an enzyme-linked immunoassay (ELISA) for the quantitative measurement of 11-dehydrothromboxane B₂ (11-dhTXB₂) levels in urine which aids in the qualitative detection of aspirin effect in apparently healthy individuals post-ingestion.

Clinical Use
The AspirinWorks® test may be used to assess clotting risk in individuals on aspirin therapy.

Clinical Significance
- The effectiveness of aspirin therapy varies from individual to individual. Aspirin-insensitive individuals are twice as likely to have a cardiovascular event¹.
- High levels of 11-dhTXB₂ are associated with increased risk of heart attack and cardiac death in aspirin-treated patients¹.
- Hyperlipidemia and diabetes are associated with a diminished response to aspirin²-⁴.
- 11-dhTXB₂ levels demonstrate a dose-related effect of aspirin treatment and have been shown to correlate with a Framingham Risk Score⁵,⁶.

REFERENCE RANGE
Status of Aspirin Effect
11-dhTXB₂ (pg/mg creatinine)

≤1500 ASA Effect
>1500 Lack of ASA Effect
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ If not at goal, confirm that aspirin was ingested and/or patient compliance.
✓ Assess concomitant ibuprofen or NSAID use, LDL-C levels, and risk for pre-diabetes/diabetes.
  • These can reduce the effectiveness of aspirin therapy.
✓ If not at goal, and all of the aforementioned have been addressed, consider adjusting aspirin dosage and retest in 2-3 weeks.
  • If not at goal following retest, consider clopidogrel therapy as the patient may be non-responsive to aspirin therapy.

References

Other Advanced Cardiovascular Tests

Cleveland HeartLab also offers other advanced cardiovascular testing that are additive and complementary to our inflammatory and advanced lipid testing.

Some of these tests are reviewed on the following pages.

Other advanced cardiovascular tests include:
- Galectin-3
- NT-proBNP
- PULS Cardiac Test™

For a complete listing, see the test menu on our website.
Galectin-3 (Gal-3)

CPT Code 82777
Sample Type Serum/EDTA Plasma

Order Code C315
Tube Type Tiger Top or Lavender Top

Description
Galectin-3 is one of the most widely studied galectins, a family of soluble B-galactoside-binding lectins that play a regulatory role in inflammation\(^1\). Galectin-3 affects the synthesis of matrix compounds, such as type I collagen\(^2\). When cardiac tissue is injured, macrophages infiltrate the tissue and secrete galectin-3, which promotes collagen synthesis and ultimately leads to cardiac fibrosis and adverse cardiac remodeling\(^3\).

Clinical Use
The galectin-3 test may be used to identify individuals at risk of future chronic heart failure due to hypertension.

Clinical Significance
- Elevated levels of galectin-3 in hypertensive individuals may suggest increased inflammation, collagen deposition and fibrosis that can lead to adverse cardiac remodeling\(^4\).
- Galectin-3 levels may be used to guide the selection of medications in hypertensive individuals, as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to more effectively reduce left ventricular mass\(^5\).

RELATIVE RISK
Galectin-3 (ng/mL)

- <17.9 Low
- 17.9-25.9 Moderate
- ≥26.0 High
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess blood pressure.**
  - If abnormal, consider switching current hypertensive medication to an ACE inhibitor or ARB to prevent/reduce adverse cardiac remodeling or titrate dose if currently taking either drug.

- **Assess the presence of conditions associated with organ fibrosis, cancer, human anti-mouse antibodies or rheumatoid factor, or high levels of gamma globulins (>2.5 g/dL) as these may contribute to abnormal galectin-3 results.**

References

**N-Terminal proBNP (NT-proBNP)**

**CPT Code** 83880  
**Sample Type** Serum  
**Order Code** C125  
**Tube Type** Tiger Top

**Description**  
During periods of increased volume or pressure overload, cardiomyocytes synthesize proBNP, a prohormone, which is cleaved to release B-type natriuretic peptide (BNP, an active hormone) and NT-proBNP (an inactive fragment) into the bloodstream.

**Clinical Use**  
A NT-proBNP test may be used to assess myocardial stretch and support risk stratification of individuals with stable CAD or acute heart failure (HF).

**Clinical Significance**  
- NT-proBNP is co-secreted in quantities directly proportional to BNP, but has a much longer half-life\(^1,2\).
- NT-proBNP levels positively correlate with New York Heart Association (NYHA) function class of dyspnea and echocardiographic findings\(^3\).
- NT-proBNP levels fall in tandem with treatment of decompensated HF\(^4,5\).
- In hospitalized patients with decompensated HF, changes in NT-proBNP levels were the strongest independent predictor of death or hospital readmission in the ensuing 6 months\(^5,6\).

**RELATIVE RISK**  
NT-proBNP (pg/mL)  

<table>
<thead>
<tr>
<th>NT-proBNP (pg/mL)</th>
<th>&lt;75 yrs. old</th>
<th>≥75 yrs. old</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤125 Low</td>
<td>≤125 Low</td>
<td>≤125 Low</td>
</tr>
<tr>
<td>&gt;125 High</td>
<td>126–450 Moderate</td>
<td>&gt;450 High</td>
</tr>
</tbody>
</table>
Treatment Considerations
These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ Assess exercise regimen.
   NOTE: Younger individuals may have slightly elevated levels due to increased load on the heart with chronic exercise.

✓ Assess cardiac function.
   • If abnormal, consider diuretics or nitrates to reduce preload, or ACE inhibitor or ARB therapy to improve cardiac function.

References
Sample Type
Serum and EDTA Whole Blood

Tube Type
Tiger Top and Lavender Top

Description
Atherosclerotic disease progression is characterized by chronic endothelial damage and an accumulation of fatty plaque within the arterial wall. Unstable plaque can rupture and lead to arterial blockage causing a heart attack. The first steps in prevention are the identification of individuals at near-term risk of a heart attack, and allowing for more aggressive therapy to potentially avoid a future event.

The PULS (Protein Unstable Lesion Signature) Cardiac Test measures key clinical risk factors including age, sex, diabetic status, family history of heart attack, and distinct protein biomarkers. These markers are associated with the biological pathways underlying cardiac lesion formation, progression and rupture. This refined methodology of cardiac risk assessment provides an improved calculation of a patient’s near-term (5 year) risk for a heart attack.

Clinical Significance
- Cardiovascular risk prediction models such as the Framingham Risk Score calculate risk of a cardiovascular event within the next 10 years. When used, these calculations rely heavily on established clinical risk factors which may not fully estimate the prevalence of cardiovascular disease in the general population.
- The PULS Cardiac Test measures clinically significant proteins in the blood associated with active unstable lesion formation and when combined with established clinical risk factors, predicts whether a cardiac lesion could rupture within a 5 year period.
- In the Multi-Ethnic Study of Atherosclerosis (MESA), the PULS Cardiac Test outperformed a common risk calculator, yielding a net reclassification index of 42.7% in individuals defined as intermediate risk by the Framingham Risk Score. Reclassification of those initially defined as intermediate risk to high risk may result in more appropriate therapeutic intervention.
- In a large clinical trial, the PULS Cardiac Test identified 61% of patients who went on to have a cardiac event who otherwise would have been missed using established risk factors alone.

Clinical Use
The PULS Cardiac Test may be performed on individuals at intermediate risk with one or more risk factors for coronary heart disease.

RELATIVE RISK
PULS CARDIAC TEST™ (%)
- <3.50 Normal
- 3.5-7.49 Borderline
- ≥7.50 Elevated

LIPID PATHWAY
HDL (mg/dl)
- ≥50 Normal
- <50 Elevated

WOMEN
- ≥40 Normal
- <40 Elevated

MEN

INSULIN/GLUCOSE PATHWAY
HbA1c (%)
- 4.0-5.6 Normal
- 5.7-6.4 Borderline
- >6.4 Elevated
Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

- **Assess LDL-C Levels**
  - If elevated, consider LDL-lowering therapies.

- **Assess lifestyle habits**
  - Consider diet/exercise/weight reduction efforts if appropriate.

- **Assess blood pressure**
  - If not at goal, consider initiating, or titrating, antihypertensive therapy.

- **Assess smoking habits**
  - Smoking cessation is essential as individuals who smoke are at increased risk of heart disease and blood clots.

- **Assess risk for pre-diabetes/diabetes**
  - If abnormal oral glucose tolerance test or insulin levels, consider insulin sensitizing therapy.

- **Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.**
  - Consider aspirin therapy if not contraindicated.
  - Consider clopidogrel if history of CAD (i.e., MI or revascularization) and/or a history of cerebrovascular disease (i.e. TIA or stroke).

References


Genetic Testing

Cleveland HeartLab also offers genetic tests which are reviewed on the following pages.

Genetic tests include:
- CYP2C19
- Apolipoprotein E
- MTHFR

For a complete listing, see the test menu on our website.
CYP2C19

CPT Code 81225  Order Code C603
Sample Type EDTA Whole Blood  Tube Type Lavender Top

Description
CYP2C19 is a member of the cytochrome P450 family of enzymes involved in the metabolism and bioactivation of drugs. In particular, CYP2C19 is integral for the generation of the active form of clopidogrel (Plavix®), which is prescribed in a prodrug form. This prodrug is converted by CYP2C19 to the active form in the liver. Several variants of CYP2C19 have been identified which have an impact on its ability to metabolize drugs. The main CYP2C19 alleles include the non-functional alleles *2 and *3, as well as the hyperactive *17 allele.

Clinical Use
CYP2C19 testing may be performed on individuals who are candidates for or are currently taking clopidogrel (Plavix®), or those who have a family history of clopidogrel (Plavix®) inefficacy. Coverage is limited to once in a lifetime.

Clinical Significance
- In 2010, the FDA announced a boxed warning for clopidogrel (Plavix®) to alert patients and physicians to the drug’s inefficacy in individuals who cannot metabolize the drug to its active form. 
- Poor metabolizers (loss of CYP2C19 activity) have 2X the risk of having a subsequent adverse cardiac event while receiving treatment with clopidogrel after a myocardial infarction.
- Ultra-rapid metabolizers (increased CYP2C19 activity) have a reduced risk of major adverse cardiac events while being treated with clopidogrel, but are at an increased risk of bleeding.
### Treatment Considerations

*These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.*

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Interpretation</th>
<th>Treatment Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer</td>
<td>Two non-functional alleles (*2/*2 or *2/*3 or *3/*3)</td>
<td>Poor metabolizers do not effectively convert the drug to its active metabolite and exhibit poor anti-platelet responsiveness.</td>
<td>Consider a higher dosage of clopidogrel (Plavix®) or an alternative therapy.</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>One WT and one non-functional allele or one non-functional and one hyperactive allele (WT/*2, WT/*3, *2/*17)</td>
<td>Intermediate metabolizers convert the drug to an active metabolite at a slower rate than a normal metabolizer and exhibit decreased responsiveness to the drug.</td>
<td></td>
</tr>
<tr>
<td>Normal (Extensive) Metabolizer</td>
<td>No mutations (WT/WT)</td>
<td>Normal metabolizers effectively convert the drug to an active metabolite.</td>
<td>Consider a standard dosage of clopidogrel (Plavix®).</td>
</tr>
<tr>
<td>Ultra-Rapid Metabolizer</td>
<td>One WT and one hyperactive allele or 2 hyperactive alleles (WT/*17 or *17/*17)</td>
<td>Ultra-rapid metabolizers convert a higher percentage of the drug to an active metabolite, and have a greater therapeutic response to the drug compared to normal metabolizers. Ultra-rapid metabolizers may produce an adequate platelet response even when lower than normal doses of the drug are used, and are at increased risk of bleeding.</td>
<td>Consider a standard or reduced dosage of clopidogrel (Plavix®) and monitoring the patient for potential bleeding.</td>
</tr>
<tr>
<td>Unknown</td>
<td>One non-functional allele and one hyperactive allele (*3/*17)</td>
<td>The metabolizer status is unknown for individuals with this genotype.</td>
<td>Consider an alternative therapy.</td>
</tr>
</tbody>
</table>

The Cleveland Heartlab assay identifies the non-functional alleles *2 and *3, and the ultra-rapid allele *17 of the CYP2C19 gene. The presence of less common alleles cannot be ruled out by this test.

### References

Apolipoprotein E

CPT Code 81401
Sample Type EDTA Whole Blood
Order Code C604
Tube Type Lavender Top

Description
ApoE is an apolipoprotein found in blood that, in association with lipids, forms lipoproteins including very low-density lipoproteins (VLDL). ApoE plays multiple roles in the regulation of lipid and lipoprotein levels in the blood1. ApoE serves as a ligand for members of the low-density lipoprotein (LDL) receptor family, and is involved in the removal of lipoproteins from the circulation for excretion in the liver. ApoE is also involved in the formation of chylomicrons and VLDL, and affects the activity of other proteins and enzymes that are involved in lipid metabolism, such as hepatic lipase and lipoprotein lipase2.

Polymorphisms in the ApoE gene result in three separate alleles encoding three distinct protein isoforms: e2, e3, and e4. There are 6 possible genotypes: e2/e2, e2/e3, e2/e4, e3/e3, e4/e3, and e4/e4. The allelic frequencies differ between ethnic groups, but in general the e3/e3 genotype is the most common, while e2/e4 is the least common1.

Clinical Significance
An individual’s ApoE genotype may affect their lipid levels. The e2/e2 genotype is associated with increased triglycerides and reduced total cholesterol, while the e4/e3 and e4/e4 genotypes are associated with increased total cholesterol, triglycerides and LDL cholesterol3.

ApoE genotypes have varying impact on risk of cardiovascular disease. Carriers of an e4 allele are at 42% higher risk for CHD4.

The ApoE genotype can affect an individual’s response to lifestyle modifications. In those with the e2/e2 or e2/e3 genotype, extremely low fat diets can increase small dense LDL levels, and therefore these individuals should have moderate fat restriction5. Individuals with the e4/e3 or e4/e4 genotype, on the other hand, respond well to very low fat dietary restrictions6.

Responsiveness to treatment with statins is also affected by the ApoE genotype. Individuals with the e2/e2 or e2/e3 genotype respond well to statins7, while statins are less effective in individuals with the e4/e3 or e4/e4 genotype8.

Clinical Use
ApoE testing may be performed on individuals with premature coronary heart disease (CHD) or individuals who have high total cholesterol and triglyceride levels, but are unresponsive to treatment with medication and lifestyle changes. Coverage is limited to once in a lifetime.
## Treatment Considerations

*These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Population Frequency</th>
<th>Interpretation†</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>*e2/e2</td>
<td>1%</td>
<td>Approximately 5% of the people with the ApoE *e2/e2 genotype develop type III hyperlipoproteinemia, which is a rare inherited disorder characterized by increased cholesterol and triglyceride levels, the presence of beta-VLDL, xanthomas, and premature vascular disease.</td>
<td>• Statin therapy7 (▼LDL-C) • Moderate alcohol intake (▼LDL-C ▲HDL-C) • Moderate (35%) fat diet if elevated triglycerides5</td>
</tr>
<tr>
<td>*e2/e3</td>
<td>10%</td>
<td>This genotype is associated with lower LDL-C levels and lower risk of coronary heart disease compared to those with the *e3/e3 genotype.</td>
<td>• Normal dietary modifications</td>
</tr>
<tr>
<td>*e2/e4</td>
<td>2%</td>
<td>This genotype is associated with normal lipid metabolism and low cardiovascular disease risk. However, there is some association of this genotype with type III hyperlipoproteinemia.</td>
<td>• Statin therapy8 (Limited ▼LDL-C) • Low alcohol intake • Very low fat diet (20%) if elevated LDL-C6 (▼LDL-C ▼Triglycerides ▼sdLDL)</td>
</tr>
<tr>
<td>*e3/e3</td>
<td>62%</td>
<td>This genotype is associated with normal lipid metabolism and low cardiovascular disease risk.</td>
<td>•</td>
</tr>
<tr>
<td>*e4/e3</td>
<td>20%</td>
<td>These genotypes are associated with a predisposition to elevated total cholesterol levels and slightly elevated LDL-C levels compared to those with the *e3/e3 genotype.</td>
<td>•</td>
</tr>
<tr>
<td>*e4/e4</td>
<td>5%</td>
<td>Additionally, these genotypes are associated with an increased risk of metabolic syndrome and atherosclerosis along with a slightly higher risk of CHD when consuming a diet high in saturated fat.</td>
<td>•</td>
</tr>
</tbody>
</table>

† Relative risk and interpretations reported for each genotype are associated with cardiovascular risk only. The interpretations should not be used to determine the relative risk of other diseases.

### References

MTHFR
CPT Code 81291
Sample Type EDTA Whole Blood
Order Code C605
Tube Type Lavender Top

Description
MTHFR (5,10-methylenetetrahydrofolate reductase) is an enzyme involved in the metabolism of folate. MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the major circulating form of folate. In turn, 5-methyltetrahydrofolate is involved in the conversion of homocysteine to methionine. MTHFR has an important role in maintaining folate and methionine levels, as well as helping to keep circulating homocysteine levels low. MTHFR is also involved in the methylation pathway, which has multiple, wide-ranging roles in the body, including regulation of gene expression and enzymatic activities.

Multiple mutations have been identified within the MTHFR gene. One of the most common and best characterized mutations is the substitution of a T for a C at position 677. There are three possible MTHFR genotypes at this position: the wild type CC, CT or TT. The frequency of the 3 alleles differs between various populations, and the 677TT genotype is more common among Caucasians and Hispanics in the United States than African Americans. However, roughly 10% of the US population has the MTHFR 677TT genotype.

Other mutations are also found in the MTHFR gene. Another common mutation is at position 1298, where there is the substitution of a C for an A. There are three possible genotypes at this position: the wild type AA, AC, or CC. Approximately 30% of the population has at least one C allele at position 1298. Only one mutation in MTHFR, the C677T mutation, is associated with elevated levels of homocysteine.

Clinical Use
MTHFR testing may be performed on individuals with elevated homocysteine levels, those with a personal or family history of premature cardiovascular disease, and those who have family members with a known MTHFR mutation. Coverage is limited to once in a lifetime.

Clinical Significance
- Individuals with the 677CC genotype have:
  - Normal MTHFR enzyme activity
  - Normal levels of folate
  - Normal levels of homocysteine
  - Normal global DNA methylation levels

- Individuals with the 677CT genotype have:
  - Reduced MTHFR enzyme activity (~71% of normal)
  - Normal levels of folate
  - Normal levels of homocysteine
  - Normal global DNA methylation levels

- Individuals with the 677TT genotype have:
  - Greatly reduced MTHFR enzyme activity (~34% of normal)
  - Significantly lower levels of folate, regardless of folate intake
  - Significantly higher levels of homocysteine at low circulating folate levels
  - Significantly reduced global DNA methylation levels at low circulating folate levels
### Treatment Considerations

*These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.*

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Interpretation</th>
<th>Interpretation/Treatment Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>677CC 1298AA</td>
<td>MTHFR enzyme activity is normal</td>
<td></td>
</tr>
</tbody>
</table>
Associated with normal homocysteine levels and a normal risk for coronary artery disease or venous thrombosis. Treat other risk factors as appropriate. |
| 677CC 1298AC | MTHFR enzyme activity is slightly decreased |  
| 677CC 1298CC | MTHFR enzyme activity is decreased |  
| 677CT 1298AA | MTHFR enzyme activity is slightly decreased |  
| 677CT 1298AC | MTHFR enzyme activity is slightly decreased |  
| 677CT 1298CC | MTHFR enzyme activity is considerably decreased |  
| 677TT 1298AA | MTHFR enzyme activity is greatly decreased |  
| 677TT 1298AC | MTHFR enzyme activity is greatly decreased |  
| 677TT 1298CC | MTHFR enzyme activity is greatly decreased |  

### References

Understanding Medical Necessity

The provided ICD-10 codes are listed as a convenience for the ordering physician.

Ordering practitioners should report the diagnosis code that best describes the reason for performing the test.
## Diagnosis of Inflammation: Understanding Medical Necessity

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Code</th>
<th>F₂-IsoPs</th>
<th>OxLDL</th>
<th>ADMA/SDMA</th>
<th>Microalbumin</th>
<th>hsCRP</th>
<th>MPO</th>
<th>Lp-PLA₂ Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes Mellitus with Hyperglycemia</td>
<td>E11.65</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus without Complications</td>
<td>E11.9</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Other Specified Diabetes Mellitus without Complications</td>
<td>E13.9</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Pure Hypercholesterolemia, unspecified</td>
<td>E78.00</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>E78.01</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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</tr>
<tr>
<td>Pure Hyperglyceridemia</td>
<td>E78.1</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Mixed Hyperlipidemia</td>
<td>E78.2</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hyperchylomicronemia</td>
<td>E78.3</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Other Hyperlipidemia</td>
<td>E78.4</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hyperlipidemia, Unspecified</td>
<td>E78.5</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease</td>
<td>E79.0</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Code</td>
<td>F$_2$-IsoPs</td>
<td>OxLDL</td>
<td>ADMA/SDMA</td>
<td>Microalbumin</td>
<td>hsCRP</td>
<td>MPO</td>
<td>Lp-PLA$_2$ Activity</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
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# Lipids: Understanding Medical Necessity

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# Metabolic: Understanding Medical Necessity

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## Vitamins & Supplements: Understanding Medical Necessity

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Other Cardiovascular Testing: Understanding Medical Necessity

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<td>Code</td>
<td>Galectin-3</td>
<td>NT-proBNP</td>
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<td>Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease</td>
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## Genetics: Understanding Medical Necessity

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<th>Apo-E</th>
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<td>Mixed Hyperlipidemia</td>
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<td>ST Elevation (STEMI) Myocardial Infarction Involving Other Sites</td>
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<td>Acute Coronary Thrombosis Non Resulting in Myocardial Infarction</td>
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<td>Impaired Fasting Glucose</td>
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## Quick Reference: Test Menu

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<th>Order Code</th>
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<th>Sample Type</th>
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<td>Serum</td>
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<td>C301</td>
<td>ADMA/SDMA</td>
<td>82542</td>
<td>Serum</td>
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<td>C122</td>
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<td>ApoB</td>
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<td>ApoE Genotype†‡</td>
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<tr>
<td>C922</td>
<td>AspirinWorks®</td>
<td>84431/82570</td>
<td>Urine Whole Blood</td>
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<td>C295</td>
<td>Coenzyme Q10**</td>
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<td>Serum or EDTA Plasma</td>
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<td>Urine</td>
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<td>hsCRP</td>
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<td>Microalbumin/Creatinine</td>
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<td>Urine</td>
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<td>PULS Cardiac Test™</td>
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<td>sdLDL</td>
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<td>C906</td>
<td>Standard Lipid Panel (includes non-HDL cholesterol)</td>
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<td>C524</td>
<td>TMAO</td>
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<td>C339</td>
<td>Vitamin D, 25 OH</td>
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<td>Serum or EDTA Plasma</td>
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</tbody>
</table>

*Sample must be shipped the same day collected. **Sample must be protected from light. †A single separate tube is required. ‡Requires an ABN for Medicare patients.
Quick Reference: Sample Rejection and Shipping

Sample Rejection Policy (Samples will be rejected for any of the following reasons):

- Samples were shipped on Saturday.
- Friday blood draws arrived on Monday.
- Sample types were incorrect or samples were received in damaged condition (i.e. tube open or cracked, sample not at correct temperature).
- Sample tube is not properly labeled with full name and date of birth.
- Transport tube not properly labeled with sample type.
- Requisition form is not completely filled out. First and last name, date of birth and gender are required.
- Physician signature is missing.

Office Packing

Samples should be stored at 2–8°C immediately after they are collected and processed.

1) Place cold or frozen sample(s) in the biohazard bags.
2) Place completed requisition (and insurance information if applicable) for each sample in the pouch of the biohazard bag.
3) Place biohazard bag (with sample(s) and requisition form) in the Styrofoam box.
4) Place a frozen ice pack on top of the samples in the Styrofoam box.
5) Place Styrofoam box into a Laboratory Shipping Pak.

FEDEX Pick-Up

<table>
<thead>
<tr>
<th>FedEx</th>
<th>(800) 463-3339, 0, 0</th>
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<tbody>
<tr>
<td>Phone</td>
<td></td>
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<tr>
<td>Number</td>
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<tr>
<td>Request</td>
<td>“I would like to schedule a FedEx Express Billable Stamp pick-up and I do not have the account number.”</td>
</tr>
<tr>
<td>Instructions</td>
<td></td>
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</tbody>
</table>

Have your shipping label available when calling for a pick-up.

Ship for next day delivery (with provided label) to: Cleveland HeartLab, Inc. 6701 Carnegie Ave, Suite 500, Cleveland, OH 44103, Phone: 866-358-9828. Samples can be shipped Monday through Friday.
Serum
(Tiger Top)

Sample Handling
1. Draw.
2. Gently invert 5x (DO NOT SHAKE!).
3. Let blood clot for 30 min. at room temperature.
4. Centrifuge at 1300 rcf for 10 min.
5. Store and transport refrigerated.

Note:
A minimum of 0.5 mL of serum is required per test or panel.

EDTA Plasma (Lavender Top, 6mL and Transport Tube)

Sample Handling
1. Draw.
2. Gently invert 8-10x (DO NOT SHAKE!).
3. Centrifuge immediately at 1300 rcf for 10 min.
4. Pre-squeeze transfer pipet bulb and draw off approximately 2/3 of the upper plasma layer. Aliquot plasma into labeled transport tube and cap tightly. Discard original tube. Label the transport tube as EDTA Plasma and ship to Cleveland HeartLab.
5. Store and transport refrigerated.

Note:
A minimum of 0.5 mL of plasma is required per test.

EDTA Whole Blood (Lavender Top, 4mL)

Sample Handling
1. Draw.
2. Gently invert 8-10x (DO NOT SHAKE!).
3. Do not centrifuge
4. Store and transport refrigerated.

Note:
A single separate tube is required for genetic tests. A minimum of 1.0 mL of whole blood is required per genetic test.
Urine Specimen Tube (Yellow Top)

Sample Handling
1. Collect random urine into the vacutainer cup system.
2. Transfer urine sample into the yellow top tube using the vacutainer system.
3. Store and transport refrigerated. Please discard the vacutainer cup system and do not ship the cup.

Note:
A minimum of 1.0 mL of urine is required per test.

Urine Specimen Tube (Cherry Red/Yellow Top)

Sample Handling
1. Collect random urine into the vacutainer cup system.
2. Transfer urine sample into the cherry/yellow top tube using the vacutainer system.
3. Gently invert 8-10x (DO NOT SHAKE!).
4. Store and transport same day refrigerated. Please discard the vacutainer cup system and do not ship the cup.

Note:
A minimum of 3.0 mL of urine is required per test.
Glossary

AA - Arachidonic Acid
ACE Inhibitor - Angiotensin-Converting Enzyme Inhibitor
ADMA - Asymmetric Dimethylarginine
ApoA - Apolipoprotein A
ApoB - Apolipoprotein B
ApoE - Apolipoprotein E
ARB - Angiotensin II Receptor Blockers
ATP - Adenosine Triphosphate
BMI - Body Mass Index
BNP - B-type Natriuretic Peptide
CAC - Coronary Artery Calcification score
CAD - Coronary Artery Disease
CAP - College of American Pathologists
CHD - Coronary Heart Disease
CIMT - Carotid Intima-Media Thickness test
CLIA - Clinical Laboratory Improvement Amendments
CoQ10 - Coenzyme Q10
CME - Continuing Medical Education
CVD - Cardiovascular Disease
DHA - Docosahexaenoic Acid
DPA - Docosapentaenoic Acid
DPP-IV Inhibitor - Dipetidyl Peptidase-4 Inhibitor
EDTA - Ethylenediaminetetraacetic Acid
eGFR - Estimated Glomerular Filtration Rate
EPA - Eicosapentaenoic Acid
ER - Emergency Room
F2-IsoPs - F2-Isoprostanes
FA - Fatty Acids
FDA - Food & Drug Administration
HDL-C - High-Density Lipoprotein Cholesterol
HF - Heart Failure
hsCRP - High Sensitivity C-Reactive Protein
IDL - Intermediate-Density Lipoprotein
LA - Linoleic Acid
LDL-C - Low-Density Lipoprotein Cholesterol
Lp(a) - Lipoprotein (a)
Lp-PLA2 - Lipoprotein-associated Phospholipase-A 2
MACE - Major Adverse Cardiovascular Events
MESA - Multi-Ethnic Study of Atherosclerosis
MI - Myocardial Infarction
MPO - Myeloperoxidase
MTHFR - 5,10-Methylene tetrahydrofolate Reductase
NCEDP/ATPIII - National Cholesterol Education Program/Adult Treatment Panel III
NO - Nitric Oxide
NOS - Nitric Oxide Synthase
NSAID - Non-Steroidal Anti-Inflammatory
NT-proBNP - N-Terminal-pro B-type Natriuretic Peptide
NYHA - New York Heart Association
OGTT - Oral Glucose Tolerance Test
OxLDL - Oxidized Low-Density Lipoprotein
PAD - Peripheral Artery Disease
p-ANCA - Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
PPAR Agonist - Proliferator-Activated Receptor Agonist
PULS - Protein Unstable Lesion Signature
RA - Rheumatoid Arthritis
sdLDL - Small Dense Low-Density Lipoprotein
SDMA - Symmetric Dimethylarginine
SLE - Systemic Lupus Erythematosus
STEMI - ST Elevation Myocardial Infarction
TIA - Transient Ischemic Attack
TMA - Trimethylamine
TMAO - Trimethylamine N-Oxide
Cleveland HeartLab, Inc.
6701 Carnegie Avenue, Suite 500
Cleveland, Ohio 44103

If you have general questions, please contact **Customer Support:**

- PHONE  866.358.9828, option 1
- FAX     866.869.0148
- EMAIL   chlcustomerservice@clevelandheartlab.com

If you have general billing questions, please contact **Billing:**

- PHONE  866.358.9828, option 2
- EMAIL   chlbilling@clevelandheartlab.com

If you have quality-related questions, please contact **Inquiries:**

- EMAIL   chlinquiries@clevelandheartlab.com

If you have general clinical/testing questions, please contact **Consulting:**

- EMAIL   consult@clevelandheartlab.com