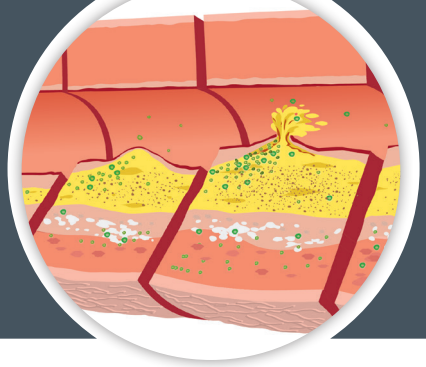
Myeloperoxidase (MPO)

CPT Code 83876
Sample Type EDTA Plasma
Order Code C133
Tube Type Lavender Top



inflammation

MPO levels are associated with an increased risk for:

- Cardiovascular disease
- Myocardial infarction

MPO levels may be measured in:

- Individuals with multiple risk factors
- Individuals at risk for pre-diabetes/diabetes
- Individuals with established cardiovascular disease

Description

MPO is a white blood cell-derived inflammatory enzyme that 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[1]. MPO mediates the vascular inflammation that propagates plaque formation[2] and activates protease cascades that are linked to plaque vulnerability[3]. 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[4,5].
- Elevated MPO levels independently predict the risk of future cardiovascular events in patients presenting with an acute coronary syndrome[6,7].
- Individuals with elevated MPO levels are more than 2x as likely to experience cardiovascular mortality[8].
- MPO enhances cardiovascular risk prediction when used independently or alongside standard biomarker testing such as hsCRP[8].
- 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.

Sample Type

The MPO test should be performed on an EDTA plasma sample.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitations. Limited information has been provided by the majority of the larger carriers (Aetna, United HealthCare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for MPO are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

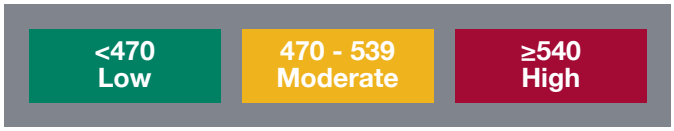
Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease	E79.0
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

RELATIVE RISK

MPO (pmol/L)



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, anti-hypertensive 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 testing (CIMT) or coronary artery calcium scoring.**
- If clinically appropriate, consider dual platelet inhibition.

✓ **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 atherosclerosis[9].

✓ **Assess HDL-C levels.**
- If not at goal, consider niacin or omega-3 fatty acids.
- Assess CoQ10 levels as recent evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels[10].

✓ **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 infarction[11].

✓ **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 runners[12] and extreme athletes and 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

1. Tavora F et al. Monocytes and neutrophils expressing myeloperoxidase occur in fibrous caps and thrombi in unstable coronary plaques. *BMC Cardiovascular Disord*. 2009; 9: 27-33.
2. Hazen SL and Heinecke JW. 3-chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima. *J Clin Invest.* 1997; 99: 2075-2081.
3. Fu X et al. Hypochlorous acid oxygenates the cysteine switch domain of pro-matrilysin (MMP-7). A mechanism for matrix metalloproteinase activation and atherosclerotic plaque rupture by myeloperoxidase. *J Biol Chem*. 2001; 276: 41279-41287.
4. Meuwese MC et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: The EPIC-Norfolk Prospective Population Study. *J Am Coll Cardiol*. 2007; 50: 159-165.
5. Karakas M et al. Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: Results from the MONICA/KORA Augsburg study. *J Intern Med*. 2012; 271: 43-50.
6. Baldus S et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation*. 2003; 108: 1440-1445.
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.
8. Heslop CL et al. Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography. *J Am Coll Cardiol*. 2010; 55: 1102-1109.
9. Buhlin K et al. Periodontitis is associated with angiographically verified coronary artery disease. *J Clin Periodontol*. 2011; 38: 1107-1014.
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.
11. Maradit-Kremers H et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A population-based cohort study. *Arthritis Rheum*. 2005; 52: 402-211.
12. Melanson SE et al. Elevation of myeloperoxidase in conjunction with cardiac-specific markers after marathon running. *Am J Clin Pathol*. 2006; 126: 888-893.

ClevelandHeartLab®

Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

Lp-PLA$_2$

CPT Code 83698
Sample Type EDTA Plasma or Serum

Order Code C167
Tube Type Lavender Top or Tiger Top

inflammation

Increased levels of Lp-PLA$_2$ may lead to increased risk of:

- Coronary heart disease
- Stroke
- Myocardial infarction

Lp-PLA$_2$ levels can be reduced by:

- Treatment with statins
- Supplementation with niacin
- Lifestyle modifications

Description

Lp-PLA$_2$, or lipoprotein-associated phospholipase-A$_2$, measures disease activity within the artery wall below the collagen or calcified cap due to the activation of macrophages. Lp-PLA$_2$ is not an acute phase reactant. When disease is active in the artery, increased levels of Lp-PLA$_2$ are produced by macrophages and foam cells within the intima of the artery[1]. Lp-PLA$_2$ also interacts with oxidized LDL, which increases inflammation and enhances a proatherogenic state, as well as plaque vulnerability[2]. Research suggests that it plays a direct role in the atherosclerotic disease process[3].

Clinical Use

The Lp-PLA$_2$ test may be performed on individuals at intermediate or high risk for developing coronary heart disease who are any age with at least two major risk factors, those ≥65 years of age with one major risk factor, smokers, those with a fasting blood glucose of ≥100 mg/dL, or those who have metabolic syndrome.

Clinical Significance

- Lp-PLA$_2$ accumulates within human atherosclerotic plaques and vulnerable lesions[4].
- Elevated Lp-PLA$_2$ levels can predict the development of coronary artery disease in apparently healthy individuals[5,6] and the risk of future adverse cardiac and cerebrovascular events[7].
- Individuals with normal systolic blood pressure, but high Lp-PLA$_2$ levels, are 2x as likely to have a stroke[7], while those with elevated systolic blood pressure and Lp-PLA$_2$ levels are 7x more likely to experience a stroke[8].
- Post-menopausal women not using hormone therapy who have an elevated Lp-PLA$_2$ have a 64% increased risk of ischemic stroke[9].

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be performed alongside a standard lipid panel in patients at moderate to high risk for CHD or ischemic stroke. These patients may have two or more risk factors such as a family history of CVD or hypertension.

Sample Type

The Lp-PLA$_2$ test should be performed on a serum or EDTA plasma sample.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitations. Limited information has been provided by the majority of the larger carriers (Aetna, United HealthCare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for Lp-PLA$_2$ are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease	E79.0
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

REFERENCE RANGE

Lp-PLA$_2$ (ng/mL)

≤200 Low	>200 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 omega-3 fatty acid levels.**

- Omega-3 fatty acid supplementation, along with statin therapy, may reduce Lp-PLA$_2$ levels[10].

✓ **Assess HDL-C levels.**

- If not at goal, consider niacin or fenofibrate therapy.
- Assess CoQ10 levels as recent evidence suggests that low ApoA1 and/or HDL-C levels are associated with low CoQ10 levels[11].

✓ **Assess the presence of CAD with imaging techniques such as CIMT or coronary artery calcium scoring.**

- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e., myocardial infarction 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: Periodontal therapy may reduce Lp-PLA$_2$ levels[12].

✓ **Assess smoking habits.**

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

✓ **Assess blood pressure.**

- If not at goal, consider initiating, or titrating, anti-hypertensive 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.

References

1. Ferguson JF et al. Translational studies of lipoprotein-associated phospholipase A(2) in inflammation and atherosclerosis. *J Am Coll Cardio*. 2012; 59: 764-772.
2. Gonçalves I et al. Evidence supporting a key role of Lp-PLA$_2$-generated lysophosphatidylcholine in human atherosclerotic plaque inflammation. *Arterioscler Thromb Vasc Biol*. 2012; 32: 1505-1512.
3. Serruys PW et al. (2008). Effects of the direct lipoprotein-associated phospholipase A$_2$ inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation*. 2008; 118: 1172-1182.
4. Kolodgie FD et al. Lipoprotein-associated phospholipase A$_2$ protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2006; 26: 2523-2529.
5. Ballantyne CM et al. Lipoprotein-associated phospholipase A$_2$, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2004; 109: 837-842.
6. Daniels LB et al. Lipoprotein-associated phospholipase A$_2$ is an independent predictor of incident coronary heart disease in an apparently healthy older population: The Rancho Bernardo Study. *J Am Coll Cardiol*. 2008; 51: 913-919.
7. Ballantyne CM et al. Lipoprotein-associated phospholipase A$_2$, high sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med*. 2005; 165: 2479-2484.
8. Gorelick PB. Lipoprotein-associated phospholipase A$_2$ and risk of stroke. *Am J Cardiol*. 2008; 101 (suppl): 34F-40F.
9. Wassertheil-Smoller S et al. Lipoprotein-associated phospholipase A$_2$, hormone use, and the risk of ischemic stroke in postmenopausal women. *Hypertension*. 2008; 51: 1115-1122.
10. Davidson MH et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: An 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2007; 39: 1354-1367.
11. 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.
12. Zhou SY et al. Lipoprotein-associated phospholipase A2 and serum lipid levels in subjects with chronic periodontitis and hyperlipidemia. *Chin J Dent Res.* 2012; 15: 25-29.

ClevelandHeartLab®

Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

High Sensitivity C-Reactive Protein (hsCRP)

CPT Code 86141
Sample Type EDTA Plasma or Serum

Order Code C121
Tube Type Lavender Top or Tiger Top

inflammation

Moderate hsCRP levels (1-10 mg/L) are associated with:

- Cardiovascular disease
- Periodontal disease

High hsCRP levels (>10 mg/L) are associated with:

- Acute illness (cold, flu or infection)
- Chronic illness (bronchitis or COPD)
- Autoimmune disorders (RA or SLE)

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 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 coronary artery disease[4].
- Reductions in both hsCRP and LDL cholesterol are associated with a 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 risk for heart attack, stroke and death[7].

Testing Frequency

The frequency of testing is determined by an individual's medical history, but an elevated hsCRP level should be confirmed with an additional measurement at least one month later. For levels >10 mg/L, the test should be repeated in 2-3 weeks as levels above 10 mg/L can reflect acute infection.

Sample Type

The hsCRP test should be performed on a serum or EDTA plasma sample.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitations. Limited information has been provided by the majority of the larger carriers (Aetna, United HealthCare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for hsCRP are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Pure Hypercholesterolemia	E78.0
Pure Hyperglyceridemia	E78.1
Mixed Hyperlipidemia	E78.2
Hyperchylomicronemia	E78.3
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10
Imparied Fasting Glucose	R73.01
Encounter for Screening for Cardiovascular Disorders	Z13.6
Long Term (current) Use of Hormonal Contraceptives	Z79.3
Family History of Ischemic Heart Disease and Other Diseases of the Circulatory System	Z82.49

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

RELATIVE RISK
hsCRP (mg/L)

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, 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 CAD with imaging techniques such as CIMT or coronary artery calcium scoring.**

- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e., myocardial infarction or revascularization) and/or a history of cerebrovascular disease (i.e., TIA or stroke).
- If the presence of vascular disease is confirmed by imaging studies, consider statin-based lipid-lowering therapy unless contraindicated.

✓ **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 atherosclerosis[8].

✓ **Assess blood pressure.**

- If not at goal, consider initiating, or titrating, anti-hypertensive 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

1. Ridker PM et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997; 336: 973-979.
2. Ridker PM et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002; 347: 1557-1565.
3. Rost NS et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: The Framingham study. *Stroke*. 2001; 32: 2575-2579.
4. Ndrepepa G et al. N-terminal probrain natriuretic peptide and C-reactive protein in stable coronary heart disease. *Am J Med*. 2006; 119: 355.e1-355.e8.
5. Nissen SE et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005; 352: 29-38.
6. Ridker PM et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005; 352: 20-28.
7. Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359: 2195-2207.
8. Buhlin K et al. Periodontitis is associated with angiographically verified coronary artery disease. *J Clin Periodontol*. 2011; 38: 1007-1014.

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

Urinary Microalbumin

CPT Code 82043/82570
Sample Type Urine

Order Code C919
Tube Type Yellow Top

inflammation

Increased levels of urinary microalbumin may identify:

- Metabolic syndrome/diabetes
- Kidney disease
- Cardiovascular disease

Urinary microalbumin levels can be reduced by:

- Lowering blood pressure
- Lowering blood sugar levels

Description

Urinary 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

The urinary microalbumin/creatinine ratio 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 CVD or those with known vascular disease.

Clinical Significance

- **Renal Significance:** The American Diabetes Association has defined microalbuminuria as a urinary albumin/creatinine ratio of 30-300 mg/g[1]. A persistent Microalbumin/Creatinine ratio >30 mg/g indicates a loss of kidney function and is used in the diagnosis of chronic kidney disease[2].
- **Cardiovascular Significance:** Increases in urinary albumin 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 mortality[3-8].
- In particular, it was shown that healthy individuals (defined as non-hypertensive, non-diabetic, and without prevalent CVD) with low urinary microalbumin/creatinine ratios had approximately 3x greater risk for developing cardiovascular disease[3]. 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 urinary microalbumin level and the risk of heart attack, stroke and death[5].

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be monitored more frequently in diabetic or hypertensive individuals.

Sample Type

The urinary microalbumin test should be performed on a urine sample.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitations. Limited information has been provided by the majority of the larger carriers (Aetna, United HealthCare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for urinary microalbumin are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease	E79.0
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

RELATIVE RISK

Urinary Microalbumin/Creatinine (mg/g)

	Women	Men
Low	<7.5	<3.9
High	≥7.5	≥3.9

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, anti-hypertensive 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 CAD with imaging techniques such as CIMT or coronary artery calcium scoring.**

- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e., myocardial infarction or revascularization) and/or 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

1. American Diabetes Association: Clinical recommendations 2001: Diabetic nephropathy. *Diabetes Care*. 2001; 24: S69 –S72.
2. Fox CH et al. Importance of urine albumin–creatinine ratio in the diagnosis and prognosis of chronic kidney disease. *OA Nephrol*. 2013; 3: 21.
3. Arnlöv J et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation*. 2005; 112: 969-975.
4. Lambers Heerspink HJ et al. Update on microalbuminuria as a biomarker in renal and cardiovascular disease. *Curr Opin Nephrol Hypertens*. 2006; 15: 631-636.
5. Gerstein HC et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001; 286: 421-426.
6. Hillege HL et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002; 106: 1777-1782.
7. Klausen K et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation*. 2004; 110: 32-35.
8. Kistorp C et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005; 293: 1609-1616.

ClevelandHeartLab®

Know your risk.

6701 Carnegie Ave. I Suite 500 I Cleveland, OH 44103 I p 866.358.9828 I f 866.869.0148 I clevelandheartlab.com I knowyourrisk.com I chlcme.com

Oxidized LDL (OxLDL)

CPT Code 83516
Sample Type EDTA Plasma or Serum

Order Code C335
Tube Type Lavender Top or Tiger Top

inflammation

Increased OxLDL levels signify increased risk for:

- Metabolic syndrome
- Cardiovascular disease
- Acute myocardial infarction

OxLDL levels may be decreased by:

- Maintaining a healthy weight/diet
- Exercising more
- Cholesterol-lowering medications

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 the 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 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.

Testing Frequency

The OxLDL test can be ordered in conjunction with standard/advanced lipid testing and/or inflammation testing.

Sample Type

The OxLDL test should be performed on a serum or EDTA plasma sample.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have not been established or posted by CMS (Medicare and Medicaid). We have reviewed the larger carriers (Aetna, United Healthcare, Cigna, Blues) and information has not been posted or is limited.

Understanding Medical Necessity

The following ICD-10 codes for OxLDL are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

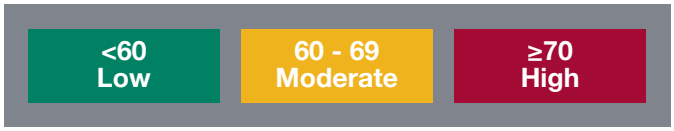
Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease	E79.0
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

RELATIVE RISK

OxLDL (U/L)



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-PLA_2 and/or MPO are elevated.

References

1. Holvoet P et al. Association between circulating oxidized low-density lipoprotein and incidence of the metabolic syndrome. *JAMA*. 2008; 299: 2287-2293.
2. Holvoet P et al. Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2001; 21: 844-848.
3. Nishi K et al. Oxidized LDL in carotid plaques and plasma associates with plaque instability. *Ateriosclr Thromb Vasc Biol*. 2002; 22: 1649-1654.
4. Tsimikas S et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005; 353: 46-57.
5. Meisinger C et al. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. *Circulation*. 2005; 112: 651-657.
6. Ehara S et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. *Circulation*. 2001; 103: 1955-1960.

ClevelandHeartLab®

Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

F_2-Isoprostanes (F_2-IsoPs)

CPT Code 82542/82570
Sample Type Urine

Order Code C261
Tube Type Yellow Top

inflammation

F_2-IsoPs levels are increased with:

- Cigarette smoking
- Poor diet (including high red meat intake)
- Sedentary lifestyle

Description

F_2-IsoPs, prostaglandin-like compounds formed from the free radical-mediated oxidation of arachidonic acid[1], are the 'gold standard' for measuring oxidative stress in the body. F_2-IsoPs also have potent biological effects associated with inflammation and therefore may mediate chronic disease initiation and progression. Additionally, F_2-IsoPs may also act as potent vasoconstrictors[2] via thromboxane formation in the endothelium, and promote platelet activation resulting in thrombus formation[3].

Clinical Use

The F_2-IsoPs test 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_2-IsoPs are seen in conditions associated with increased risk for atherosclerosis[4] and certain forms of cancer[5,6].
- F_2-IsoPs are elevated in smokers[7] and with increased intake of red meat[8] and are decreased with exercise[9].
- Lower steady state levels are associated with cardiovascular fitness and reduced risk.

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be performed yearly alongside a standard lipid panel in asymptomatic individuals with lifestyle risk factors.

Sample Type

The F_2-IsoPs test should be performed on a urine sample collected in a yellow top tube (without preservative).

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitations. Limited information has been provided by the majority of the larger carriers (Aetna, United HealthCare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for F_2-Isoprostanes are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease	E79.0
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

REFERENCE RANGE

F_2-IsoPs (ng/mg)

<0.86 Low	≥0.86 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 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

1. Morrow JD et al. A series of prostaglandin F_2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci USA*. 1990; 87: 9383-9387.
2. Morrow JD et al. The F_2-isoprostane, 8-epi-prostaglandin F_2alpha, a potent agonist of the vascular thromboxane/endoperoxide receptor, is a platelet thromboxane/endoperoxide receptor antagonist. *Prostaglandins*. 1992; 44: 155-163.
3. Minuz P et al. The F_2-isoprostane 8-epiprostaglandin F_2alpha increases platelet adhesion and reduces the antiadhesive and antiaggregatory effects of NO. *Arterioscler Thromb Vasc Biol*. 1998; 18: 1248-1256.
4. Schwedhelm E et al. Urinary 8-iso-prostaglandin F_2alpha as a risk marker in patients with coronary heart disease: A matched case-control study. *Circulation*. 2004; 109: 843-848.
5. Rossner P Jr et al. Relationship between urinary 15-F_2t-isoprostane and 8-oxodeoxyguanosine levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2006; 15: 639-644.
6. Epplein M et al. Association of plasma micronutrient levels and urinary isoprostane with risk of lung cancer: The multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev*. 2009; 18: 1962-1970.
7. Morrow JD et al. Increase in circulating products of lipid peroxidation (F_2-Isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med*. 1995; 332: 1198-1203.
8. Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68: 562-564.
9. Shi M et al. Effects of anaerobic exercise and aerobic exercise on biomarkers of oxidative stress. *Environ Health Prev Med*. 2007; 12: 202-208.

ClevelandHeartLab®

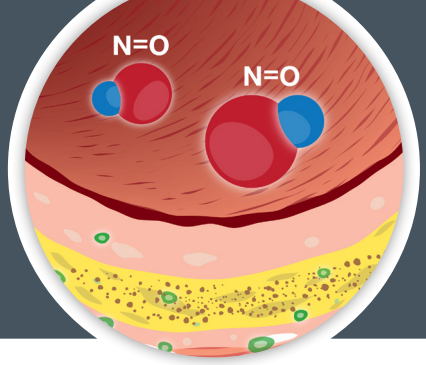
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

ADMA/SDMA

CPT Code 82542
Sample Type Serum

Order Code C301
Tube Type Tiger Top



endothelial dysfunction

Elevated ADMA levels may identify:

- Endothelial dysfunction
- Pre-diabetes/diabetes
- Subclinical cardiovascular disease

Elevated SDMA levels may identify:

- Reduced renal function and progressive kidney failure

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.

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 CT coronary artery calcification[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].

Sample Type

The ADMA/SDMA test should be performed on a serum sample, and fasting is recommended, but not required.

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be monitored in individuals with hyperlipidemia, hypertension, pre-diabetes/diabetes, or those who are at moderate to high risk for developing cardiovascular disease.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitation. Limited information has been provided by the majority of the larger carriers (Aetna, United Healthcare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for ADMA/SDMA are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia	E78.0
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Metabolic Syndrome	E88.81
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10
Atherosclerotic Heart Disease of Native Coronary Artery with Unstable Angina Pectoris	I25.110
Impaired Fasting Glucose	R73.01
Impaired Glucose Tolerance Test (oral)	R73.02
Abnormal Finding of Blood Chemistry, Unspecified	R79.9

ClevelandHeartLab®
Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com

RELATIVE RISK
ADMA (ng/mL)

<100 Low	100 - 123 Moderate	>123 High

REFERENCE RANGE
SDMA (ng/mL)

73 - 135 Low	>135 High

TEST ADMA	TEST SDMA	Interpretation
Low	Low	• Normal endothelial function
Med / High	Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low	High	• Reduced renal function
Med / High	High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Possible renal failure

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 supplementation to improve vasodilation and vascular tone.

  Note: *L-Arginine enhances the production of nitric oxide which has anti-inflammatory, anti-thrombotic, anti-hypertensive, and anti-oxidant effects.*

✓ **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 CAD with imaging techniques such as CIMT or coronary artery calcium scoring.**
- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e. myocardial infarction or revascularization) and/or cerebrovascular disease (i.e. TIA or stroke).

References

1. Stühlinger MC et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA*. 2002; 287: 1420-1426.
2. Böger RH et al. Asymmetric dimethylarginine (ADMA): A novel risk factor for endothelial dysfunction its role in hypercholesterolemia. *Circulation*. 1998; 98: 1842-1847.
3. Maas R et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke*. 2009; 40: 2715-2719.
4. Malek AM et al. Hemodynamic shear stress and its role in atherosclerosis. *JAMA*. 1999; 282: 2035-2042.
5. Iribarren C et al. Asymmetric dimethyl-arginine and coronary artery calcification in young adults entering middle age: the CARDIA Study. *Eur J Cardiovasc Prev Rehabil*. 2007; 14: 222-229.
6. Schnabel R et al. Asymmetric dimethylarginine and the risk of cardiovascular events and death in patients with coronary artery disease: Results from the AtheroGene study. *Circ Res*. 2005; 97: e53-e59.
7. Kielstein JT et al. Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol*. 2002; 13: 170-176.

ClevelandHeartLab®

Know your risk.

6701 Carnegie Ave. | Suite 500 | Cleveland, OH 44103 | p 866.358.9828 | f 866.869.0148 | clevelandheartlab.com | knowyourrisk.com | chlcme.com