Myeloperoxidase (MPO)

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.

<table>
<thead>
<tr>
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<tbody>
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<td>Mixed Hyperlipidemia</td>
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<tr>
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<td>Essential (primary) Hypertension</td>
<td>I10</td>
</tr>
<tr>
<td>Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris</td>
<td>I25.10</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 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.

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.
**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$^2$.
- 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.

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<tr>
<td>Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris</td>
<td>I25.10</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 omega-3 fatty acid levels.**
  - Omega-3 fatty acid supplementation, along with statin therapy, may reduce Lp-PLA₂ levels³.

- **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 levels¹¹.

- **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-PLA₂ levels⁵.

- **Assess smoking habits.**
  - If not at goal, consider initiating, or titrating, anti-hypertensive therapy.
  - **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**

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.
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

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\(^1\)\(^2\) and in individuals with stable coronary artery disease\(^3\).
- Reductions in both hsCRP and LDL cholesterol are associated with a reduction in the rate of atherosclerosis progression\(^4\) and improved clinical outcomes\(^5\).
- Introduction of statin therapy in patients with elevated hsCRP, even with normal lipid levels, significantly reduces risk for heart attack, stroke and death\(^6\).

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.

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

- **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**

Urinary Microalbumin

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

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

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
**RELATIVE RISK**
Urinary Microalbumin/Creatinine (mg/g)

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

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.

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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
## 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

**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.

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</table>

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**F$_2$-Isoprostanes levels are increased with:**

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

---

**CPT Code**

82542/82570

**Order Code**

C261

**Sample Type**

Urine

**Tube Type**

Yellow Top
References


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.

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 pathophysiology 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.

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

CPT Code 82542
Sample Type Serum
Tube Type Tiger Top

Order Code C301

N=O

N=O

ClevelandHeartLab®
Know your risk.
References


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).

**RELATIVE RISK**

<table>
<thead>
<tr>
<th>ADMA</th>
<th>SDMA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Normal endothelial function</td>
</tr>
<tr>
<td>Med</td>
<td>High</td>
<td>Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Reduced renal function</td>
</tr>
<tr>
<td>Med</td>
<td>High</td>
<td>Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Possible renal failure</td>
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</tbody>
</table>

**REFERENCE RANGE**

<table>
<thead>
<tr>
<th>SDMA (ng/mL)</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
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</tr>
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<td>High</td>
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