C-REACTIVE PROTEIN, HIGH SENSITIVITY

Policy Number: CMP - 024
Effective Date: January 21, 2017

INSTRUCTIONS FOR USE
This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BACKGROUND
C-reactive protein (CRP) is an immunomodulatory protein produced by the liver. Acute inflammation mediates the IL-6-dependent transcription of CRP, an acute phase reactant. The protein is immediately released after synthesis, is not stored in the body, and has a half-life of about 19 hours. It is normally present in trace amounts in healthy individuals but increases quickly and significantly in response to infection and inflammation. Early clinical use of the protein centered on the measurement of standard CRP in patients with autoimmune disease and infections. More recently, interest in the biomarker has stemmed from the use of high-sensitivity C-reactive protein (hs-CRP) in predicting coronary heart disease (CHD) in asymptomatic patients.

Heart disease is the leading cause of death in the United States. More than 1 in 3 adults are affected by cardiovascular disease. It has been estimated that heart disease and stroke cost more than $500 billion in
health care dollars in 2010.\textsuperscript{1} Traditional CHD risk factors include advanced age, genetics (familial hypercholesterolemia), lifestyle factors (inactivity, smoking), and diagnosis of diabetes mellitus, hypertension, and hyperlipidemia. One half of deaths attributed to CHD occur without warning from symptoms or clinical diagnoses, and these deaths can occur in individuals with normal or even below-average cholesterol levels.\textsuperscript{2, 3} In the late 1980s, at the same time that drugs known as statins were introduced to decrease the risk of CHD in patients with hyperlipidemia, researchers were striving to identify novel risk factors for CHD.

Because of the role of inflammation in the pathogenesis of CHD, interest grew in exploring CRP and the risk of a CHD event in apparently healthy individuals. Due to the need to measure low concentrations of CRP, newer assays were developed. Subsequently, high-sensitivity C-reactive protein assays came to market in the late 1990s to offer the type of performance characteristics necessary for atherosclerotic risk prediction.\textsuperscript{4} The current risk stratification categories of low, intermediate and high risk were approved at the 1996 American College of Cardiology Bethesda Conference, but the model is not evidence-based.\textsuperscript{5} According to this stratification scheme, lifestyle changes are recommended for low-risk patients, and pharmaceutical intervention is recommended for high-risk patients. Individuals at intermediate risk may benefit from further testing to establish the best route to risk reduction.

A multicenter, prospective trial, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), was sponsored by AstraZeneca, the manufacturer of prescription rosvastatin, to determine if the use of the drug could decrease the rate of coronary events in apparently healthy individuals with increased hs-CRP levels.\textsuperscript{5} This study, with strict enrollment criteria, enrolled men who were over the age of 50 and women over the age of 60 without CHD or hyperlipidemia. Additionally, the study participants could not have inflammatory conditions or a diagnosis of diabetes mellitus. There could be no current or previous use of lipid-lowering drugs, immunosuppressant drugs or hormone therapy. In total, 17,802 asymptomatic persons were enrolled. Subjects were randomized to receive either rosvastatin (20 mg daily) or placebo. The median hs-CRP level in the treatment and placebo group was 4.2 and 4.3 mg/L, respectively. Primary end point events were defined as a first coronary event and included unstable angina, myocardial infarction, stroke, revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or death from cardiovascular causes. Events were recorded, and although the study duration was initially intended to be 5 years, the randomized controlled trial was terminated due to early determination of therapeutic benefit. Rosuvastatin decreased the incidence of major cardiovascular events in men and women.

JUPITER analysis is complex and questions remain about the use of hs-CRP in CHD risk assessment. Reviewers have questioned if hs-CRP reduction mediated the decreased number of coronary events observed with statin use.\textsuperscript{6} Other studies have shown that statins decrease risk of CHD over a full spectrum of LDL concentrations. Analysts of the study have suggested that a trial that looks at benefit of statin use over a wide range of CRP concentrations would be valuable.\textsuperscript{2} The authors of the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines on assessment of cardiovascular risk in asymptomatic adults point out that JUPITER was not a study of the clinical utility of hs-CRP.\textsuperscript{3} Further, these authors and others recommend further studies to determine its cost-effectiveness.\textsuperscript{3, 7}

The ACCF/AHA guidelines on assessment of cardiovascular risk in asymptomatic adults cite the JUPITER trial. The guideline writing committee advises hs-CRP can be useful in the selection of patients for statin therapy in these populations\textsuperscript{3}:
• In men age 50 and over and women age 60 and over with LDL cholesterol <130 mg/dL, not on lipid-lowering therapy, hormone therapy or immunosuppressant therapy, without CHD, diabetes, chronic kidney disease, severe inflammatory conditions or contraindications to statins. This recommendation is Level B, Class IIa, indicating there is some conflicting evidence from a single randomized trial or nonrandomized studies.

• In asymptomatic, intermediate-risk men less than age 50 and women less than age 60. This recommendation is Level B, Class IIb, indicating usefulness is less well established due to greater conflicting evidence from a single randomized trial or nonrandomized studies.

These guidelines do not recommend the measurement of CRP for cardiovascular risk assessment in asymptomatic, high-risk adults or in low-risk men (<50 years of age) and women (≤60 years of age). Despite these guidelines, the use of hs-CRP in the prediction of CHD remains controversial, and the USPTF has stated there is insufficient evidence that hs-CRP would significantly reclassify individuals in the intermediate CHD risk category.8 Regardless of the controversy, in early 2010, the FDA approved rosuvastatin for the prevention of CHD in men over 50 years and women over 60 years with an elevated hs-CRP and at least one traditional risk factor.9

### POLICY

For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

*Table 1. HCPCS Codes (Alphanumeric, CPT® AMA)*

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>86141</td>
<td>C-Reactive Protein, High Sensitivity</td>
</tr>
</tbody>
</table>

*ICD-10 Diagnosis Codes (Proven)*

CMP-024 CRP ICD10 v1.0
REFERENCES


POLICY HISTORY/REVISION HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ ICD10 PDF files.</td>
</tr>
</tbody>
</table>