Name of Policy:
High Sensitivity C-Reactive Protein

Policy #: 062
Category: Laboratory

Latest Review Date: September 2008
Policy Grade: Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
C-reactive protein (CRP) is a nonspecific acute phase reactant produced by the liver as a marker to monitor inflammatory processes, such as infection and autoimmune diseases. Studies suggest the association of low-level chronic inflammation during atherogenesis, and thus measurement of C-reactive protein has been investigated in various settings of atherosclerotic cardiovascular disease. This included patients with known atherosclerotic cardiovascular disease, patients with risk factors for cardiovascular disease, and as a general risk assessment tool for cardiovascular disease. Conventional methodologies for the measurement of C-reactive protein in acute inflammatory diseases have a detection limit of 3-5 mg/L. In the setting of the low levels of chronic inflammation in otherwise healthy individuals, this level of detection is not adequate. To be used as a risk assessment tool, a greater precision of lower levels of C-reactive protein is needed such that the range of values collected in epidemiologic studies can be subdivided into quartiles and quintiles; in this way, the data from large epidemiologic studies can be applied to individual patients. It is theorized that the increased sensitivity of high-sensitivity C-reactive protein (hs-CRP) tests should be able to detect that activity as a marker for atherosclerotic cardiovascular disease.

**Policy:**

**High sensitivity C-reactive protein** (hs-CRP) **meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a marker of increased risk for cardiovascular disease when the patient has documented clinical coronary heart disease (CAD), diabetes mellitus, hyperlipidemia, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, and/or first degree family member with history of early (males before age 55 and females before age 65) cardiovascular event.

Measurement of high sensitivity C-reactive protein **does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** when performed for screening or first line testing.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
Half of all heart attacks occur among persons without overt hyperlipidemia. Ridker, et al, in the Women’s Health Study, stated that high-sensitivity C-reactive protein (hs-CRP) was the most significant predictor of the risk of cardiovascular events of 12 plasma measures evaluated in this study. In the Physicians’ Health Study, also by Ridker, et al, the observation that C-reactive protein testing combined with standard lipid screening appears to provide an improved method of detecting subclinical atherosclerosis. This marker may lead to better clinical identification of
patients who might benefit from primary prevention and for whom the cost-to-benefit ratio for long-term use of statins would be improved.

An issue with the studies is that the findings are cast in terms of relative risk only, not in terms of traditional predictive value. Ridker also states that examining both C-reactive protein levels (which cannot be predicted from cholesterol measures) and cholesterol levels provides a more accurate indication of risk than assessing cholesterol alone. In addition, Ridker found that high-C-reactive protein values signify markedly elevated risk for heart attack or stroke even in individuals with seemingly reassuring cholesterol values.

In a July 4, 2006 article published in the Annals of Internal Medicine by Cook et al, over 15,000 women were followed for an average of 10 years for the development of cardiovascular disease using global cardiovascular risk prediction models with and without hs-CRP. 390 women developed incident cardiovascular events. It was determined that a global risk prediction model that includes hs-CRP improves cardiovascular risk classification in women, particularly among those with a 10-year risk of 5% to 20%. In models that include age, blood pressure, and smoking status, hs-CRP improves prediction at least as much as do lipid measures.

A July 10, 2006 article in the Archives of Internal Medicine studied nearly 16,000 adults in a prospective study using 19 novel risk factors as predictors. Of the 19 markers studied, lipoprotein-associated phospholipase A, vitamin B, interleukin 6, and soluble thrombomodulin added the most to the prediction of coronary heart disease. The findings suggested that routine measurement of these novel markers is not warranted for risk assessment.

September 2008 Update
A literature search was performed and a large number of publications on the topic of CRP and cardiovascular disease were identified. Most evaluated the predictive ability of hs-CRP for a variety of cardiovascular and related outcomes. A smaller number of studies addressed the use of hs-CRP as a treatment target, or examined genetic polymorphisms of hs-CRP and their association with hs-CRP levels and cardiovascular risk.

Several large prospective studies were identified that added to the already substantial body of literature on hs-CRP as a predictor of cardiovascular risk. Analysis of data from the Cardiovascular Health Study, consisting of 5,020 patients without baseline cardiovascular disease followed up for 12 years, examined whether hs-CRP was an independent predictor of future cardiovascular events. An elevated hs-CRP (>3mg/l) was an independent predictor of cardiovascular death in patients with pre-existing carotid atherosclerosis (RR 1.72, 95% CI 1.46 to 2.01), but was not an independent predictor of outcomes in patients without pre-existing carotid atherosclerosis. Ridker et al published the Reynolds Risk Score, which is an empirically derived prediction model for cardiovascular outcomes based on data from 24,558 initially healthy women enrolled in the Women’s Health Study and followed up for a median of 10.2 years. A total of 35 potential predictors of cardiovascular disease were considered as potential predictors in both derivation and validation models. Hs-CRP was one of nine independent predictors of cardiovascular events that were included in the final model. Zakai et al evaluated 13 potential biomarkers for independent predictive ability compared to established risk factors, using data from 4,510 individuals followed up for nine years in the Cardiovascular Health
Study. Hs-CRP was one of seven biomarkers that had incremental predictive ability above established risk factors. The adjusted hazard ratio for each standard deviation increase in hs-CRP was 1.13 (95% CI 1.05 of 1.21). Kozan et al evaluated the ability of hs-CRP to impact classification of cardiac risk. These authors classified 1,817 hypertensive patients from the Intensive/Initial Cardiovascular Examination Regarding Blood Pressure Levels: Evaluation of Risk Groups (ICEBERG study) into risk categories according to the European Society of Hypertension/European Society of Cardiology guidelines. The addition of hs-CRP to risk prediction models significantly increased the absolute number of patients classified into “high” or “very high” risk categories by 11%–13%.

One large prospective study reported results that differed from the above studies. Olsen et al followed up 2,656 individuals from Denmark over a period of 9.4 years, and evaluated the incremental predictive ability a number of emerging risk markers including hs-CRP, N-terminal BNP, and urine albumin/creatinine ratio. When controlled for both traditional risk markers, N-terminal BNP added significant predictive information for future cardiovascular events while hs-CRP did not (HR 1.17, p=NS).

One large study examined the use of hs-CRP as a treatment target for lipid-lowering therapy. Sattar et al used data from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) to evaluate whether hs-CRP levels were associated with degree of response to statin therapy. While this analysis reported that hs-CRP levels were a predictor of adverse cardiovascular outcomes, there was no correlation between hs-CRP levels and response to statin therapy.

A number of studies addressed whether genetic polymorphisms of hs-CRP have an impact on its predictive ability. Kivimaki et al evaluated five different genetic polymorphisms of the hs-CRP gene and their relation to hs-CRP levels in 1,609 patients from the Cardiovascular Risk in Young Finns Study. These authors reported that there were significant differences in hs-CRP levels according to genetic status. However, in a multivariate model, the total amount of variation in hs-CRP explained by genetic status was relatively low ($r^2=3.3\text{-}5.0\%$). In a separate publication from the same study, Eklund et al found that there was a correlation between genetic polymorphisms and measures of carotid artery compliance, a surrogate marker for atherosclerotic disease.

The majority of the new studies identified for this update confirms or extends what is known about hs-CRP as a predictor of cardiovascular risk. This information alone is not sufficient to justify the use of hs-CRP in routine care without having adequate tools and guidelines to incorporate hs-CRP into routine clinical decision-making. Researchers have started to address these needs with studies such as Kozan et al, in which hs-CRP was used to reclassify individuals into clinically relevant risk categories, and The Reynolds Risk Score, which offers clinicians an alternative risk prediction model for cardiovascular disease in women that includes hs-CRP. Questions have been raised about the reclassification study because of lack of an additional step of evaluating the impact of the reclassification. Also, including revascularization as an end-point has been raised as an issue with the article on the Reynolds Risk Score. In addition, these potential tools for using hs-CRP measurements have not yet become widely

disseminated nor have they been incorporated into existing clinical guidelines concerning cardiac risk assessment.

**August 2010 Update**
In a recent literature search numerous studies were identified that evaluated the predictive ability of hs-CRP in different clinical situations. For example, studies reported that hs-CRP is an independent predictor of future cardiac events for patients with acute myocardial infarction, following stents with drug-eluting stents, post-CABG, and following vascular surgery. These studies extend the literature on the predictive ability of hs-CRP to different populations.

One published study evaluated CRP as a marker of treatment response to statins. MacMurray and colleagues performed a retrospective analysis of the CORONA trial, stratifying patients into high (>2.0) or low (<2.0) CRP groups. The CORONA trial randomized 4,961 patients with heart failure to rosuvastatin or placebo, and followed patients for the development of major adverse cardiovascular events. The retrospective analysis of this trial compared the degree of benefit from statin therapy in the low CRP group. For patients with high CRP, there was a significant reduction in adverse cardiovascular events for patients treated with rosuvastatin (HR [hazard ratio] 0.87; 95% CI: 0.77-0.98), while for patients with low CRP, there was no benefit reported (HR 1.09; 95% CI: 0.89-1.3). Statistical testing for interaction between CRP and treatment was marginally significant at p= 0.062. Other published studies, continued to debate the interpretation of the JUPITER trial, which has been controversial.

The existing observational evidence establishes that CRP is an independent predictor of cardiovascular disease across a wide spectrum of patient populations. The evidence also suggests that using CRP as a component of a risk assessment tool will result in a more accurate cardiac risk predictions. There is no scientific literature that directly tests the hypothesis that measurement of C-reactive protein to assess CHD risk results in improved patient outcomes.

There is some clinical trial evidence reporting that patients with high CRP levels benefit more than patients with low CRP levels. This data is derived primarily from post-hoc analysis of existing randomized, controlled trials that originally selected patients on factors other than CRP.

**Key Words:**
C-reactive protein, high-sensitivity C-reactive protein, hs-CRP, CRP, cardiovascular risk assessment

**Approved by Governing Bodies:**
The ELISA test is still primarily used as a research tool, various immunoassays have been automated and are commercially available. Several of the high-sensitivity C-reactive protein tests have received 510(k) marketing clearance from the U. S. Food and Drug Administration (FDA).
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.
FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity
Pre-certification/Pre-determination requirements: Not applicable

**Current Coding:**
CPT codes: 86141 C-reactive protein, high sensitivity

**References:**


Policy History:
Medical Policy Group, August 2002 (2)
Medical Policy Administration Committee, August 2002
Available for comment August 26-October 9, 2002
Medical Policy Group, September 2006 (1)
Medical Policy Group, September 2008 (1)
Medical Policy Group, September 2010 (1): Description updated, Key Points updated and Governing Bodies information added
Medical Policy Group, September 2012 (3): Active Policy but no longer scheduled for regular literature reviews and updates.
Medical Policy Group, October 2013 (3): Removed ICD-9 Diagnosis codes; no change to policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review)in Blue Cross and Blue Shield’s administration of plan contracts.