DRAFT Medical Coverage Policy | ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection

EFFECTIVE DATE: 10|01|2019
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OVERVIEW

Clinical assessment and noninvasive imaging of chronic heart failure can be limited in accurately diagnosing patients with heart failure because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. For management of heart failure, clinical signs and symptoms (eg, shortness of breath) are relatively crude markers of decompensation and occur late in the course of an exacerbation. Thus, circulating biomarkers have potential benefit in heart failure diagnosis and management. A protein biomarker, soluble suppression of tumorigenicity-2 (sST2), has elicited interest as a potential aid to predict risk and manage therapy of heart failure as well as to manage in patients in the setting of heart transplant.

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Commercial Products

The use of the Presage ST2 Assay to evaluate the prognosis of patients diagnosed with chronic heart failure is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

The use of the Presage ST2 Assay to guide management (eg, pharmacologic, device-based, exercise) of patients diagnosed with chronic heart failure is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

The use of the Presage ST2 Assay in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection, is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

MEDICAL CRITERIA

Not applicable

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary benefits/coverage.

BACKGROUND

Heart Failure

Heart failure is a major cause of morbidity and mortality worldwide. The term heart failure refers to a complex clinical syndrome that impairs the heart's ability to move blood through the circulatory system. In the United States, in 2011, an estimated 600,000 individuals live with chronic heart failure. Heart failure is the leading cause of hospitalization among people older than age 65 years, with direct and indirect costs estimated at $37 billion annually in the United States. Although survival has improved with treatment advances, absolute mortality rates of heart failure remain near 50% within 5 years of diagnosis.

Physiology

Heart failure can be caused by disorders of the pericardium, myocardium, endocardium, heart valves or great vessels, or metabolic abnormalities. Individuals with heart failure may present with a wide range of left ventricular (LV) anatomy and function. Some have normal LV size and preserved ejection fraction (EF); others have severe LV dilatation and depressed EF. However, most patients present with key signs and symptoms secondary to congestion in the lungs from impaired LV myocardial function. They include dyspnea, orthopnea, and paroxysmal dyspnea. Other symptoms include weight gain due to fluid retention, fatigue, weakness, and exercise intolerance secondary to diminished cardiac output.

Diagnosis

Initial evaluation of a patient with suspected heart failure is typically based on clinical history, physical examination, and chest radiograph. Because people with heart failure may present with nonspecific signs and symptoms (eg, dyspnea), accurate diagnosis can be challenging. Therefore, noninvasive imaging (eg, echocardiography, radionuclide angiography) are used to quantify pump function of the heart, thus identifying or excluding heart failure in patients with characteristic signs and symptoms. These tests can also be used to assess prognosis by determining the severity of the underlying cardiac dysfunction. However, clinical assessment and noninvasive imaging can be limited in accurately evaluating patients with heart failure because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. Thus, invasive procedures (eg, cardiac angiography, catheterization) are used in select patients with presumed heart failure symptoms to determine the etiology (ie, ischemic vs nonischemic) and physiologic characteristics of the condition.

Treatment

Patients with heart failure may be treated using a number of interventions. Lifestyle factors such as the restriction of salt and fluid intake, monitoring for increased weight, and structured exercise programs are beneficial components of self-management. A variety of medications are available to treat heart failure. They include diuretics (eg, furosemide, hydrochlorothiazide, spironolactone), angiotensin-converting enzyme inhibitors (eg, captopril, enalapril, lisinopril), angiotensin receptor blockers (eg, losartan, valsartan, candesartan), b-blockers (eg, carvedilol, metoprolol succinate), and vasodilators (eg, hydralazine, isosorbide dinitrate). Numerous device-based therapies also are available. Implantable cardioverter defibrillators reduce mortality in patients with an increased risk of sudden cardiac death. Cardiac resynchronization therapy improves symptoms and reduces mortality for patients who have disordered LV conduction evidenced by a wide QRS complex on electrocardiogram. Ventricular assist devices are indicated for patients with end-stage heart failure who have failed all other therapies and are also used as a bridge to cardiac transplantation in select patients.

Heart Failure Biomarkers

Because of limitations inherent in standard clinical assessments of patients with heart failure, a number of objective disease biomarkers have been investigated to diagnose and assess heart failure patient prognosis, with the additional goal of using biomarkers to guide therapy. They include a number of proteins, peptides, or other small molecules whose production and release into circulation reflect the activation of remodeling and neurohormonal pathways that lead to LV impairment. Examples include B-type natriuretic peptide (BNP), its analogue N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin T and I, renin, angiotensin, arginine vasopressin, C-reactive protein, and norepinephrine.

BNP and NT-proBNP are considered the reference standards for biomarkers in assessing heart failure patients. They have had substantial impact on the standard of care for diagnosis of heart failure and are included in the recommendations of all major medical societies, including the American College of Cardiology Foundation and American Heart Association, European Society of Cardiology and the Heart Failure Society of America. Although natriuretic peptide levels are not 100% specific for the clinical diagnosis of heart failure, elevated BNP or NT-proBNP levels in the presence of clinical signs and symptoms reliably identify the presence of structural heart disease due to remodeling and heightened risk for adverse events.

Natriuretic peptides also can help in determining prognosis of heart failure patients, with elevated blood levels portending poorer prognosis.

In addition to diagnosing and assessing prognosis of heart failure patients, blood levels of BNP or NT-proBNP have been proposed as an aid for managing patients diagnosed with chronic heart failure. Levels of either biomarker rise in response to myocardial damage and LV remodeling, whereas they tend to fall as drug therapy ameliorates symptoms of heart failure. Evidence from a large number of randomized controlled trials that have compared BNP- or NT-proBNP-guided therapy with clinically guided adjustment of pharmacologic treatment of patients who had chronic heart failure has been assessed in recent systematic reviews and meta-analyses. However, these analyses have not consistently reported a benefit for BNPguided management. The largest meta-analysis to date is a patient-level meta-analysis by Savarese et al (2013) that evaluated 2686 patients from 12 randomized controlled trials. This meta-analysis showed that NT-proBNP-guided management was associated with significant reductions in allcause mortality and heart failure-related hospitalization compared with clinically guided treatment. Although BNP-guided management in this metaanalysis was not associated with significant reductions in these parameters, differences in patient numbers and characteristics may explain the discrepancy. A second patient-level meta-analysis, conducted by Troughton et al (2014), included 11 randomized controlled trials with 2000 patients randomized to natriuretic peptide-guided pharmacologic therapy or usual care. The results showed that, among patients 75 years of age or younger with chronic heart failure, most of whom had impaired left ventricular EF, natriuretic peptide-guided therapy was associated with significant reductions in all-cause mortality compared with clinically guided therapy. Natriuretic-guided therapy also was associated with significant reductions in hospitalization due to heart failure or cardiovascular disease.

Suppression of Tumorigenicity-2 Protein Biomarker
A protein biomarker, suppression of tumorigenicity-2 (ST2), has elicited interest as a potential aid to predict prognosis and manage therapy of heart failure. This protein is a member of the interleukin-1 (IL-1) receptor family. It is found as a transmembrane isoform (ST2L) and a soluble isoform (sST2), both of which have circulating IL-33 as their primary ligand. ST2 is a unique biomarker that has pluripotent effects in vivo. Thus, binding between IL-33 and ST2L is believed to have an immunomodulatory function via T-helper type 2 lymphocytes and was initially described in the context of cell proliferation, inflammatory states, and autoimmune diseases. However, the IL-33/ST2L signaling cascade is also strongly induced through mechanical strain of cardiac fibroblasts or cardiomyocytes. The net result is mitigation of adverse cardiac remodeling and myocardial fibrosis, which are key processes in the development of heart failure. The soluble isoform of ST2 is produced by lung epithelial cells and cardiomyocytes, and is secreted into circulation in response to exogenous stimuli, mechanical stress, and cellular stretch. This form of ST2 binds to circulating IL-33, acting as a "decoy," thus inhibiting the IL-33-associated antiremodeling effects of the IL-33/ST2L signaling pathway. Thus, on a biologic level, IL-33/ST2L signaling plays a role in modulating the balance of inflammation and neurohormonal activation, and is viewed as pivotal for protection from myocardial remodeling, whereas sST2 is viewed as attenuating this protection. In the clinic, blood concentrations of sST2 appear to correlate closely with adverse cardiac structure and functional changes consistent with remodeling in patients with heart failure, including abnormalities in filling pressures, chamber size, and systolic and diastolic function.

An enzyme-linked immunosorbent-based assay is commercially available for determining sST2 blood levels (Presage ST2 Assay). The manufacturer claims a limit of detection of 1.8 ng/mL for sST2, and a limit of quantification of 2.4 ng/mL, as determined according to Clinical and Laboratory Standards Institute guideline EP-17-A. A study by Mueller and Dieplinger (2013) reported a limit of detection of 2.0 ng/mL for sST2. In the same study, the assay had a within-run coefficient of variation of 2.5% and a total coefficient of variation less than 4.0%; demonstrated linearity within the dynamic range of the assay calibration curve; and exhibited no relevant interference or cross-reactivity.

The ST2 biomarker is not intended to diagnosis heart failure, because it is a relatively nonspecific marker that is increased in many other disparate conditions that may be associated with acute or chronic manifestations of heart failure. Although the natriuretic peptides (BNP, NT-proBNP) reflect different physiologic aspects of heart failure compared with sST2, they are considered the reference standard biomarkers when used with clinical findings to diagnose, prognosticate, and manage heart failure and as such are the comparator to sST2.

Regulatory Status
In 2011, the Presage® ST2 Assay kit (Critical Diagnostics) was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for use with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure. The assay had already received Conformite Europeenne Mark in January 2011. The Presage® ST2 Assay kit is provided in a microplate configuration. The kit contains a ready-to-use 96-well microtiter plate coated with mouse monoclonal antihuman sST2 antibodies; a recombinant human sST2 standard calibrator (lyophilized); a standard diluent; an anti-ST2 biotinylated antibody reagent (mouse monoclonal antihuman sST2 antibodies) in phosphate-buffered saline; a sample diluent; a tracer concentrate and tracer diluent; a wash concentrate; a tetramethylbenzidine reagent; a stop solution; and 2 levels of controls provided in a sealed, lyophilized format (high and low control).

For individuals who have chronic heart failure who receive the sST2 assay to determine prognosis and/or to guide management, the evidence includes correlational studies and a meta-analysis. Relevant outcomes are overall survival, quality of life, and hospitalization. Most of the evidence is from reanalysis of existing randomized controlled trials and not from studies specifically designed to evaluate the predictive accuracy of sST2. Studies have mainly found that elevated sST2 levels are statistically associated with elevated risk of mortality. A pooled analysis of study results found that sST2 significantly predicted overall mortality and cardiovascular mortality. Several studies, however, found that sST2 test results did not provide additional prognostic information compared with N-terminal pro B-type natriuretic peptide levels. Moreover, no comparative studies were identified on the use of the sST2 assay to guide management of patients diagnosed with chronic heart failure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart transplantation who receive sST2 assay to determine prognosis and/or to predict acute cellular rejection, the evidence includes a small number of retrospective observational studies on the Presage ST2 Assay. Relevant outcomes are overall survival, morbid events, and hospitalization. No prospective studies were identified that provide high-quality evidence on the ability of sST2 to predict transplant outcomes. One retrospective study (N=241) found that sST2 levels were associated with acute cellular rejection and mortality; another study (N=26) found that sST2 levels were higher during an acute rejection episode than before rejection. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING
The following code is not medically necessary for Commercial Products.
83006 Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)

RELATED POLICIES
BlueCHiP for Medicare National and Local Coverage Determinations

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