Medical Policy
ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection

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Policy Number: 723
BCBSA Reference Number: 2.04.130
NCD/LCD: Local Coverage Determination (LCD): Non-covered Services (L33629)

Related Policies
Laboratory Tests for Heart Transplant Rejection, #530

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of the Presage ST2 Assay to evaluate the prognosis of patients diagnosed with chronic heart failure is considered INVESTIGATIONAL.

The use of the Presage ST2 Assay to guide management (pharmacological, device-based, exercise, etc.) of patients diagnosed with chronic heart failure is considered INVESTIGATIONAL.

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 INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

This is not a covered service.

Local Coverage Determination (LCD): Non-covered Services (L33629)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED if the procedure is performed inpatient.
Outpatient

- For services described in this policy, see below for situations where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>This is not a covered service.</th>
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<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare HMO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare PPO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
<td>This is not a covered service.</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tr>
<td>83006</td>
<td>Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)</td>
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Description

Heart Failure

Heart failure (HF) 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, an estimated 600,000 individuals live with chronic HF. HF 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 HF remain near 50% within 5 years of diagnosis.

HF can be caused by disorders of the pericardium, myocardium, endocardium, heart valves or great vessels, or metabolic abnormalities. Individuals with HF 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.

Initial evaluation of a patient with suspected HF is typically based on clinical history, physical examination, and chest radiograph. Because people with HF 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 identify or exclude HF 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 HF 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 HF.
Patients with HF 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 HF. They include diuretics (eg, furosemide, hydrochlorothiazide, spironolactone), angiotensin-converting enzyme inhibitors (eg, captopril, enalapril, lisinopril), angiotensin receptor blockers (eg, losartan, valsartan, candesartan), β-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 HF who have failed all other therapies and are also used as a bridge to cardiac transplantation in select patients.1

**HF Biomarkers**

Because of limitations inherent to usual assessment of suspected HF patients, a number of objective disease biomarkers have been investigated to diagnose HF and assess patient prognosis, with the additional goal of using biomarkers to guide therapy.6 They include a number of proteins, peptides, or other small molecules whose production and release into the circulation reflect the activation of remodeling and neurohormonal pathways that lead to LV impairment. Examples include B-type natriuretic peptide (BNP), its analog N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin T and I, renin, angiotensin, arginine vasopressin, C-reactive protein, and norepinephrine.1,6

BNP and NT-proBNP are considered the reference standards for biomarkers in assessing HF patients. They have had substantial impact on the standard of care for the diagnosis of HF and are included in the recommendations of all major medical societies, including the American College of Cardiology Foundation,1 European Society of Cardiology,7 and the Heart Failure Society of America.8 Although natriuretic peptide levels are not 100% specific for the clinical diagnosis of HF, 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 HF patients, with elevated blood levels portending poorer prognosis.

In addition to diagnosing and assessing prognosis of HF patients, blood levels of BNP or NT-proBNP have been proposed as an aid for managing patients diagnosed with chronic HF.1,9,10 Levels of either biomarker rise in response to myocardial damage and LV remodeling, whereas they tend to fall as drug therapy ameliorates symptoms of HF. Evidence from a large number of randomized controlled trials (RCTs) that have compared BNP- or NT-proBNP-guided therapy to clinically guided adjustment of pharmacologic treatment of patients with chronic HF has been assessed in recent systematic reviews and meta-analyses. However, these analyses have not consistently reported a benefit for BNP-guided management. The largest meta-analysis to date is a patient-level meta-analysis of 2686 patients from 12 RCTs.9 This meta-analysis showed that NT-proBNP-guided management was associated with significant reductions in all-cause mortality and HF-related hospitalization compared with clinically guided treatment.

Although BNP-guided management in this meta-analysis 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 included 11 RCTs with 2000 patients randomized to natriuretic peptide-guided pharmacologic therapy or usual care.10 The results showed that, among patients 75 years of age or younger with chronic HF, most of whom had impaired left ventricular ejection fraction (LVEF), 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 HF or cardiovascular disease.

**Suppression of Tumorigenicity-2 Protein Biomarker**

A new protein biomarker, referred to as suppression of tumorigenicity-2 (ST2), has elicited interest as a
potential aid to predict prognosis and manage therapy of chronic HF. 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 also is 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 HF. The soluble isoform of ST2 is produced by lung epithelial cells and cardiomyocytes, and is secreted into the 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 HF, 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. In 1 published study, a limit of detection of 2.0 ng/mL for sST2 was reported. In the same study, the assay had a within-run coefficient of variation (CV) of 2.5% and a total CV 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 HF, 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 HF. Although the natriuretic peptides (BNP, NT-proBNP) reflect different physiologic aspects of HF compared with sST2, they are considered the reference standard biomarkers when used with clinical findings to diagnose, prognosticate, and manage HF and as such are the comparator to sST2.

**Summary**

Evidence on the prognostic use of the Presage® ST2 Assay to predict clinical outcomes in patients diagnosed with chronic heart failure (HF) consists of studies that report a correlation between ST2 (suppression of tumorigenicity-2) levels and poor clinical outcomes. In some cases, but not all, ST2 provided incremental prognostic information above that of standard clinical exam and BNP levels. There is no evidence that ST2 provides clinically actionable information that can be used to improve outcomes. As a result, there is insufficient evidence to conclude that ST2 improves outcomes compared with standard care using either B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide measurements, and it therefore is considered investigational.

No evidence was identified on the use of the Presage® ST2 Assay to guide management of patients diagnosed with chronic HF. Therefore, the use of this assay for guiding management decisions for patients with HF is considered investigational. There is also very little evidence on the use of this test in the posttransplantation period, including its use for predicting prognosis and predicting acute cellular rejection, as a result soluble ST2 (sST2) is also considered investigational for use in the postcardiac transplantation period.

**Policy History**

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<tr>
<td>6/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2016</td>
<td>BCBSA National medical policy review.</td>
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<tr>
<td></td>
<td>Policy statement unchanged. “Heart Transplant Rejection” added to policy title.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References

7. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. Aug 2012;14(8):803-869. PMID 22828712