BlueCross BlueShield of Alabama

Name of Policy:

ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection

Policy #: 592
Category: Laboratory

Latest Review Date: May 2018
Policy Grade: B

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:

Clinical assessment and noninvasive imaging of chronic heart failure (CHF) can be limited in accurately diagnosing patients with heart failure (HF) because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. For management of HF, clinical signs and symptoms (e.g., 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 HF diagnosis and management. A new protein biomarker, referred to as soluble suppression of tumorigenicity-2 (sST2), has elicited interest as a potential aid to predict risk and manage therapy of CHF. Soluble ST2 is also proposed for use in patients after heart transplant.

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, in 2011, approximately 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, the absolute mortality rates of HF remain at about 50% within 5 years of diagnosis.

Physiology

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 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 that are secondary to congestion in the lungs from impaired LV myocardial function. These 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 HF may present with signs and symptoms that are relatively nonspecific, for example dyspnea, an accurate diagnosis can be a challenge. Therefore, noninvasive imaging such as echocardiography and radionuclide angiography, are used to quantify to pump function of the heart, thus identifying or excluding 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 methods can be limited in accurately evaluating patients with HF because symptoms and signs can be poorly correlated with objective methods of assessing cardiac dysfunction. Thus, invasive procedures such as cardiac angiography or catheterization are used in selected patients with presumed HF symptoms to determine the etiology (i.e., ischemic vs non-ischemic) and physiologic characteristics of the condition.

Treatment

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 as components of self-management. A variety of medications are available to treat HF. These include diuretics (e.g., furosemide, hydrochlorothiazide, spironolactone), angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, lisinopril), angiotensin receptor blockers (e.g., losartan, valsartan, candesartan), β- blockers (e.g., carvedilol, metoprolol succinate), and vasodilators (e.g., 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.

HF Biomarkers

Because of limitations inherent to standard clinical assessment of 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. 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.

BNP and NT-proBNP are considered the reference standard 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 societies including the American College of Cardiology Foundation, European Society of Cardiology, and the Heart Failure Society of America. 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 identifies 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. 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 clinical trials (RCTs) that 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 (MA). However, these analyses have not consistently reported a benefit for BNP-guided management. The largest meta-analysis to date was a patient-level MA that included 2686 patients from 12 RCTs. This MA 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 MA was not associated with significant reductions in these parameters, differences in patient numbers and characteristics may explain the discrepancy. A second patient-level MA included 11 RCTs and 2000 patients' randomized to natriuretic peptide-guided pharmacologic therapy or usual care. These results show 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 protein biomarker, referred to as suppression of tumorigenicity-2(ST2), has elicited interest as a potential aid to predict prognosis and manage therapy of 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 II 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 anti-remodeling 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, systolic and diastolic function.

An enzyme-linked immunosorbent (ELISA) –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 one 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 and 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.

Policy:

The use of the **Presage® ST2 Assay does not meet** Blue Cross and Blue Shield of Alabama's medical criteria and is considered **investigational** for all indications, including but not limited to the following:

- to evaluate the prognosis of patients diagnosed with chronic heart failure;
- to guide management (pharmacological, device-based, exercise, etc.) of patients diagnosed with chronic heart failure
- in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection

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 member's 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:

The most recent literature review was performed through March 6, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Use of Soluble Suppression of Tumorigenicity-2-Levels in Chronic Heart Failure Patients

Clinical Context and Test Purpose

The purpose of biomarker testing in patients who have chronic heart failure is to inform decisions about treatment goals and choice of treatment, and to provide patients and their families with realistic expectations about prognosis. This review evaluates whether the biomarker soluble suppression of tumorigenicity-2 (sST2) assay provides improved prognostic information compared with standardly used biomarkers.

The question addressed in this evidence review is: In individuals with chronic heart failure, does testing for sST2 levels change patient management decisions, especially choice of treatment, improve quality of life, and/or lead to improvements in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with chronic heart failure.

Interventions
The intervention of interest is an sST2 assay cleared by the Food and Drug Administration (FDA).

Comparators
The comparators of interest are standard prognostic markers such as B-type natriuretic peptide levels.

Outcomes
The primary outcome of interest is overall survival. Other relevant outcomes are cardiovascular mortality, quality of life, and hospitalizations.

Time
The timing of survival outcomes are short-term (in hospital and 30-day mortality) and longer term (e.g., 1- and 5-year) mortality. The timing for other outcomes are also short-term (30-days) and longer term.

Setting
The assay could be used in either the inpatient or outpatient setting.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A number of clinical studies in which soluble ST2 (sST2) blood levels were determined using the Presage® ST2 Assay have reported that there is an association between ST2 levels and adverse outcomes in patients diagnosed with chronic HF. A substantial body of biomarker evidence has been reported retrospectively from subsets of patients who were enrolled in RCTs of HF interventions. These RCTs include Val-HeFT (Valsartan Heart Failure Trial); HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training); CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure); and, PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure study). Although the patients in these RCTs were well-characterized and generally well-matched between study arms, the trials were neither intended nor designed to specifically evaluate biomarkers as risk predictors. At present, no prospectively gathered evidence is available from an RCT in which sST2 levels were compared with levels of a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro B-type natriuretic peptide [NT-proBNP]) to predict risk for adverse outcomes among well-defined cohorts of patients with diagnosed chronic HF. Key results of larger individual studies are summarized in Table 1.

Findings of studies on the prognostic value of soluble ST2 for chronic heart failure were pooled in a 2016 meta-analysis by Aimo et al. The meta-analysis included seven studies, including post hoc analyses of RCTs, and calculated the association between the Presage ST2 assay and health outcomes. A pooled analysis of seven studies found that soluble ST2 was a statistically significant predictor of overall mortality (hazard ratio [HR], 1.75; 95% confidence interval [CI], 1.37 to 2.22). Moreover, a pooled analysis of five studies found that sST2 was a significant predictor of cardiovascular mortality (HR=1.79; 95% CI, 1.22 to 2.63).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No evidence is available from randomized or nonrandomized controlled studies in which outcomes from groups of well-matched patients who were managed using serial changes in sST2 blood levels were compared to reference standard BNP or NT-proBNP levels.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

No inferences can be drawn about the clinical utility of sST2 levels for chronic heart failure.

Section Summary: Use of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure Patients
Several analyses, mainly retrospective, have evaluated whether sST2 levels are associated with disease prognosis, especially mortality outcomes. Studies mainly found that elevated sST2 levels were statistically associated with elevated risk of mortality. A pooled analysis of study results found that sST2 levels significantly predicted overall mortality and cardiovascular mortality. Several studies, however, found that sST2 test results did not provide additional prognostic information compared with or NT-proBNP levels. In general, it appears that elevated sST2 levels predict higher risk of poor outcomes than lower levels. The available evidence is limited by interstudy inconsistency and differences in patient characteristics, particularly the severity of HF, its etiology, duration, and treatment. Furthermore, most of the evidence was obtained from retrospective analyses of sST2 levels in subsets of larger patient cohorts within RCTs, potentially biasing the findings. The evidence primarily shows associations between elevated sST2 levels and poor outcomes, but does not go beyond that in demonstrating a clinical connection between biomarker status, treatment received, and clinical outcomes.

Use of SST2 in Post Heart Transplantation Patients
Clinical Context and Test Purpose
The purpose of biomarker testing in patients who underwent heart transplantation is to predict acute cellular rejection and/or provide information on prognosis to inform patient management decisions.

The question addressed in this evidence review is: In individuals who underwent heart transplantation, does testing for sST2 levels reduce the need for endomyocardial biopsy, contribute to patient management decisions such as dosing of anti-rejection medications, and/or lead to improvements in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients who have had heart transplantation.

Interventions
The intervention of interest is an FDA-cleared sST2 assay.

Comparators
The comparator of interest for predicting acute cellular rejection is endomyocardial biopsy.

Outcomes
The primary outcomes of interest are overall survival and morbid events (i.e., acute cellular rejection). Another outcome of interest is hospitalizations.

Time
The timing of survival outcomes are short-term (in hospital and 30-day mortality) and longer term (e.g., 1- and 5-year) mortality. The timing of acute cellular rejection is primarily within the first year after transplantation.

Setting
The assay could be used in either the inpatient or outpatient setting.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Serum ST2 levels have been proposed as a prognostic marker post-cardiac transplantation and as a test to predict acute cellular rejection (graft-versus-host disease). There is very little evidence available for these indications. Januzzi et al 2013 performed a retrospective study in which sST2 levels were measured in 241 patients post heart transplant. Over a follow-up out to seven years, sST2 levels were predictive of total mortality (hazard ratio, 2.01; 95% confidence interval, 1.15 to 3.51; p=0.01). sST2 levels were also associated with risk of acute cellular rejection, with a significant difference between the top and bottom quartiles of sST2 levels in the risk of rejection (p=0.003).

In a study by Pascual-Figal et al (2011), 26 patients were identified who were post-cardiac transplantation and had an acute rejection episode. Levels of sST2 were measured during the acute rejection episode and compared with levels that were measured when acute rejection was not present. Levels of sST2 were higher during the acute rejection episode compared to the non-rejection period (130 ng/mL vs 50 ng/mL, p=0.002). Elevated sST2 levels greater than 68 ng/mL had a positive predictive value of 53% and a negative predictive value of 83% for the presence of acute cellular rejection. The addition of sST2 levels to serum BNP resulted in incremental improvement in identifying rejection episodes.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified using sST2 levels that directed patient management in heart transplantation patients and which assessed patient outcomes.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. No inferences can be drawn about the clinical utility of sST2 levels for patients with heart transplantation.

Section Summary: Use of sST2 in Post Heart Transplantation Patients
Few studies are available, and the literature consists of observational and retrospective studies. 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.

Table 1: Summary of Selected Clinical Studies of sST2 to Predict Outcomes in Chronic Heart Failure Patients

Author (year)	Population (N)	Mean Age (years)	Study Description and Biomarkers	Primary Endpoints (mean follow-up duration)	Synopsis of Findings
Ky et al (2011)	Chronic ambulatory HF (N=1141, 75% of Penn HF Study population)	56	Retrospective analysis of sST2 and NT-proBNP levels and their incremental usefulness over clinical Seattle Heart Failure Model (SHFM)	Mortality or cardiac transplant (2.8 years)	Elevated sST2 levels were associated with increased risk. (adjusted p= 0.002). sST2 in combination with NT-proBNP levels showed moderate improvement over SHFM in predicting outcomes. (p=0.017).
Bayes-Genis et al (2012)	Ambulatory decompensated HF (N=891)	70	Retrospective analysis of sST2 and proBNP levels from a consecutive series of patients	Mortality (2.8 years)	Elevated sST2 and NT-proBNP levels provided independent and additive prognostic information for elevated risk of mortality. (p<0.001).

Broch et al (2012)	Chronic ischemic HF (N=1149, 30% of CORONA population)	72	Retrospective analysis of sST2 NT-proBNP, and C-reactive protein levels in patient samples from CORONA RCT	Cardiovascular mortality, nonfatal myocardial infarction or stroke (2.6 years)	Elevated sST2 levels were independently associated with increased risk for mortality, hospitalization due to HF, or any cardiovascular hospitalization ($p<0.001$). sST2 did not provide additive prognostic information compared to NT-proBNP.
Felker et al (2013)	Ambulatory HF (N=910, 39% of HF-ACTION population)	59	Retrospective analysis of sST2 and NT-proBNP levels in patients samples from HF-ACTION RCT	Mortality, hospitalization, functional capacity (2.5 years)	Elevated sST2 levels were independently associated with increased risk for mortality, hospitalization due to HF, or any cardiovascular hospitalization ($p<0.000$). sST2 and NT-proBNP provided independent prognostic information. sST2 did not provide additive prognostic information compared to NT-proBNP.
Gaggin et al (2013)	Chronic recently decompensated HF (N=151, 100% of PROTECT population)	63	Retrospective analysis of sST2 and NT-proBNP levels in patient samples from PROTECT RCT	Composite outcome comprising worsening HF, hospitalization for HF, clinically significant cardiovascular events (0.8 years)	Elevated sST2 levels were associated with increased risk for adverse cardiovascular outcome ($p<0.001$). sST2 and NT-proBNP did not provide independent prognostic information.
Anand et al (2014)	Chronic HF (N= 1,650, 33% of Val-HeFT population)	63	Retrospective analysis of sST2, NT-proBNP and other biomarker levels in patient samples from Val-HeFT RCT	All-cause mortality and a composite outcome that included mortality, sudden cardiac death with resuscitation,	Elevated sST2 levels were independently associated with increased risk of poor outcomes ($p<0.000$). Baseline sST2 levels did not provide substantial prognostic

				hospitalization for HF, or administration of an intravenous inotropic or vasodilator drug for 4 hours or more without hospitalization	information when added to a clinical model that included NT-proBNP levels.
Zhang et al (2015)	De novo HF or decompensated CHF (N=1161)	58	Prospective analysis of sST2 in hospitalized patients at a single center in China	All-cause mortality (1 year)	Elevated sST2 levels independently associated with increased risk of all-cause mortality ($p<0.001$) after adjustment for clinical risk factors and NT-proBNP levels.
Dupuy et al (2016)	HF for at least 6 mo (n=178)	75	Prospective analysis of sST2, NT-proBNP, and other biomarker levels in patient samples from a single center in France	All-cause mortality and CV mortality Median 42 mo	Elevated sST2 levels independently associated with increased risk for all-cause mortality and CV mortality ($p<0.001$) In multivariate analysis, sST2 and CRP significantly associated with all-cause mortality and CV mortality

CHF: chronic heart failure; CRP: C-reactive protein; CV: cardiovascular; HF: heart failure; IV: intravenous; NT-proBNP: N-terminal pro B-type natriuretic peptide; RCT: randomized controlled trial; SCD: sudden cardiac death; SHFM: Seattle Heart Failure Model; sST2: soluble suppression of tumorigenicity-2; y=years; mo=months.

Summary of Evidence

For individuals who have chronic heart failure (CHF) who receive soluble suppression of tumorigenicity-2 (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 mainly found that elevated sST2 levels were 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 or 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 HF. The evidence is insufficient to determine the effects of the technology on health outcome.

For individuals who have heart transplantation who receive sST2 assay to determine prognosis and 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 outcome.

Practice Guidelines and Position Statements
In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) published joint evidence-based guidelines based on a systematic review of the literature on the management of HF. In the review, ACC/AHA stated that sST2 is a biomarker for myocardial fibrosis that predicts hospitalization and death in patients with HF and provides additive prognostic information to natriuretic peptide levels. In the ambulatory HF setting, ACC/AHA applies a class IIb recommendation and assigns a level B of evidence for the use of sST2 as an option to provide additive prognostic information to established clinical evaluation and biomarkers. The guidelines are silent on other uses of sST2.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Heart Failure, Heart transplant, HF, Presage® ST2 Assay, ST2 (suppression of tumorigenicity), soluble suppression of tumorigenicity-2 (sST2)

Approved by Governing Bodies:
In 2011, the Presage® ST2 Assay kit (Critical Diagnostics, San Diego, CA) was cleared for marketing by the FDA through the 510(k) process for use in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic HF. The assay had previously received Conformite Europeenne (CE) 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 two levels of controls provided in a sealed, lyophilized format (high and low control).

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: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)

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Policy History:

Medical Policy Panel, January 2015
Medical Policy Group, March 2015 (**3**): Adopting as new medical policy
Medical Policy Administration Committee, March 2015
Available for comment March 3 through April 17, 2015
Medical Policy Group, June 2016 (**3**): Updates to Title, Description, Key Points, Key Words & References; clarified policy statement to be able to add to list of investigational indications – no change in policy intents – remains investigational
Medical Policy Panel, May 2017
Medical Policy Group, May 2017 **(3):** 2017 Updates to Description, Key Points, & References. No change in policy statement.
Medical Policy Panel, May 2018
Medical Policy Group, May 2018 **(4)**: Updates to Description and Key Points. No change to Policy statement.
