BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Laboratory Tests for Chronic Heart Failure and Heart Transplant Rejection

Policy #: 592
Category: Laboratory

Latest Review Date: October 2020
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

For dates of service on or after March 24, 2020:

Blue Advantage will treat the use of **Presage® ST2 Assay** as a **non-covered benefit** and as **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 Advantage will treat the **measurement of volatile organic compounds** to assist in the detection of moderate grade 2R/grade 3 heart transplant rejection as a **non-covered benefit** and as **investigational.**

Effective for dates of service February 26, 2018, through March 23, 2020, refer to LCD L36954.

Effective for dates of service prior to February 26, 2018:

Blue Advantage will treat the use of the **Presage® ST2 Assay** as a **non-covered benefit** and as **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 Advantage 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 Advantage administers benefits based on the members' contract and 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.

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.

Commercially marketed laboratory testing is available to assess heart transplant rejection, including the Heartsbreath™ test which measures breath markers of oxidative stress. This test is proposed as an alternative or as an adjunct invasive endomyocardial biopsy.

Chronic Heart Failure: 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 their study. 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 diagnose 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 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.

Noninvasive Heart Transplant Rejection Testing
Heartsbreath Test
The Heartsbreath™ test, a noninvasive test that measures breath markers of oxidative stress, has been developed to assist in the detection of heart transplant rejection. In heart transplant recipients, oxidative stress appears to accompany allograft rejection, which degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes that are in turn, excreted as volatile organic compounds in breath. The Heartsbreath test analyzes the breath methylated alkane contour (BMAC), which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes and has been identified as a marker to detect Grade 3 (clinically significant) heart transplant rejection.

Presage ST2 Assay
In addition to its use as a potential aid to predict prognosis and manage therapy of heart failure, elevated serum ST2 levels have also been associated with increased risk of antibody-mediated rejection following heart transplant. For this reason, ST2 has also been proposed as a prognostic marker post heart transplantation and as a test to predict acute cellular rejection (graft-versus-host disease). The Presage ST2 Assay, described above, is a commercially available sST2 test that has been investigated as a biomarker of heart transplant rejection.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most of these have had low diagnostic accuracy in diagnosing rejection. Preliminary studies have evaluated the association between heart transplant rejection and micro-RNAs or high-sensitivity cardiac troponin in cross-sectional analyses, but the clinical use has not been evaluated.

KEY POINTS:
The most recent literature update was performed through August 25, 2020.

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 two meta-analyses. 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, and prospective and retrospective cross-sectional studies made up a large part of one meta-analysis. Studies have 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 outcomes.

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.

The evidence includes a diagnostic accuracy study for individuals who have a heart transplant who receive measurement of volatile organic compounds to assess cardiac allograft rejection. Relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The published study found that, for identifying Grade 3 (now Grade 2R) rejection, the negative predictive value of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test 78.6% was better than that for biopsy (42.4%). However, the breath test had lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing Grade 3 rejection than biopsy (specificity, 97%; positive predictive value, 45.2%). The breath test was also not evaluated for Grade 4 rejection. This single study is not sufficient to determine the clinical validity of the test measuring volatile organic compounds and no studies on clinical utility were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Positions Statements
American College of Cardiology et al
In 2017, the American College of Cardiology Foundation, American Heart Association, and Heart Failure Society published a focused update of their 2013 guideline on the management of heart failure. Part of the focus of the update was on biomarkers. The guidelines stated that soluble suppression of tumorigenicity-2 (ST2) is a biomarker for myocardial fibrosis that may predict hospitalization and death in patients with heart failure and provides additive prognostic information to natriuretic peptide levels. The guidelines were based on a class IIb recommendation (weak; benefit ≥ risk) with level B-NR evidence (moderate-quality, nonrandomized) for the use of ST2 as an option to provide additive prognostic information to established clinical evaluation and biomarkers. The guidelines did not address other uses of ST2.

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), Heartsbreath test

APPROVED BY GOVERNING BODIES:

Test	Manufacturer	FDS Clearance Type, Product Number	FDA Clearance Date	Indicated Use
Heartsbreath™	Menssana Research	Humanitarian device exemption, H030004	2004	To aid in diagnosing grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The device is intended as an adjunct to, and not as a substitute for, endomyocardial biopsy and is also limited to patients who have had endomyocardial biopsy within the previous month.
Presage® ST2 Assay kit	Critical Diagnostics	510(k), k093758	2011	For use with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)
86849	Unlisted immunology procedure

PREVIOUS CODING:
CPT Codes:

0085T	Breath test for heart transplant rejection (**Deleted 12/31/2020**)

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POLICY HISTORY:

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Available for comment March 3 through April 17, 2015
Medical Policy Group, June 2016
Medical Policy Group, June 2017
Medical Policy Group, February 2018
Medical Policy Group, October 2020: Reinstated policy effective March 24, 2020.