
Medical Policy



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***Current Policy Effective Date: 3/1/21**
(See policy history boxes for previous effective dates)

Title: Molecular Testing for Chronic Heart Failure and Heart Transplant

Description/Background

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.

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.(1) The prevalence of heart failure in the U.S. between 2013 and 2016 was an estimated 6.2 million for Americans ≥ 20 years old, up from 5.7 million from between 2009 and 2012.(2,3) Heart failure is the leading cause of hospitalization among people older than age 65 years, with direct and indirect costs estimated at about \$37 billion annually in the United States.(3) Although survival has improved with treatment advances, the absolute mortality rates of heart failure remain at about 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 exhibit a wide range of LV anatomy and function. Some have normal LV size and preserved ejection fraction; others have severe LV dilatation and depressed ejection fraction. However, most patients present with key signs and symptoms that are secondary to congestion in the lungs

from impaired LV myocardial function.(1) They include dyspnea, orthopnea, and paroxysmal dyspnea. Other symptoms include weight gain due to fluid retention, fatigue, weakness and exercise intolerance that also are 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 procedures, (eg, echocardiography, radionuclide angiography) are used to quantify the 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.(1) However, clinical assessment and noninvasive imaging methods can be limited in accurately evaluating patients with heart failure because symptoms and signs can be poorly correlated with objective methods of assessing cardiac dysfunction.(4-6) Thus, invasive procedures (eg, cardiac angiography, catheterization) are used in select patients with presumed HF symptoms to determine the etiology (ie, ischemic vs non-ischemic) 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 as components of self-management. A variety of medications are available to treat heart failure. These include diuretics (eg, furosemide, hydrochlorothiazide, spironolactone, etc.), angiotensin converting enzyme inhibitors (eg, captopril, enalapril, lisinopril, etc.), angiotensin receptor blockers (eg, losartan, valsartan, candesartan), beta blockers (eg, carvedilol, metoprolol succinate, etc.), 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 left ventricle conduction evidenced by a wide QRS complex on EKG. 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 selected patients.(1)

Heart Failure Biomarkers

Because of limitations inherent in standard clinical assessment of patients with heart failure, a number of objective disease biomarkers have been investigated to diagnose heart failure and patient prognosis, with the additional goal of using biomarkers to guide therapy.(7) 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 left ventricular 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.(1,7)

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,(1)

European Society of Cardiology,(8) and the Heart Failure Society of America.(9) 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.(1,10,11) Levels of either biomarker rise in response to myocardial damage and left ventricular remodeling, whereas they tend to fall as drug therapy ameliorates symptoms of heart failure. Evidence from a large number of randomized controlled trials (RCTs) 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 BNP-guided management. Savarese et al (2013) published the largest meta-analysis to date, a patient-level meta-analysis that evaluated 2686 patients from 12 randomized controlled trials.(10) This meta-analysis showed that NT-proBNP-guided management was associated with significant reductions in all-cause mortality and heart failure-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. Troughton et al (2014) conducted a second patient-level meta-analysis that included 11 randomized controlled trials with 2000 patients randomized to natriuretic peptide-guided pharmacologic therapy or usual care.(11) The results showed that, among patients 75 years of age or younger with chronic heart failure, most of whom had impaired left ventricular ejection fraction, 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.(12-18) 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.(19) 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.(20) 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.(7,14,16)

An enzyme-linked immunosorbent–based assay is commercially available for determining sST2 blood levels (Presage ST2 Assay).(17) 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. Mueller and Dieplinger (2013) reported a limit of detection of 2.0 ng/mL for sST2 in their study.(17) 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.(16,17) 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.

myTAI_{HEART} Biomarker

myTAI HEART is a laboratory developed test which examines the cell-free DNA in patients' blood sample as a marker for transplanted organ injury in heart transplant recipients. Using proprietary myTAI_{HEART} software, the myTAI_{HEART} test uses multiplexed, high-fidelity amplification followed by allele-specific qPCR of a panel of 94 highly informative bi-allelic single nucleotide polymorphisms (SNPs) and two controls to quantitatively genotype cell free DNA in the patient's plasma after cardiac transplant, and accurately distinguish "donor specific" cell free DNA originating from the engrafted heart from "self-specific" cell free DNA originating from the recipient's native cells.(21) The ratio of donor specific cell free DNA to total cell free DNA is reported as the donor fraction(%) and categorizes the patient as at low or increased risk of moderate (grade 2R) to severe (grade 3R) acute cellular rejection: low donor fractions indicate less damage to the transplanted heart and a lower risk for rejection, while increased donor fractions indicate more damage to the transplanted heart and an increased risk for rejection. Testing with myTAI_{HEART} does not require a donor specimen. The test is indicated for use in heart transplant recipients who are two months of age or older and ≥ 8 days post-transplant, restricted to use in single organ post-heart transplant patients, and is contraindicated in patients who:

- are pregnant
 - currently have or in the past have had another transplanted organ (solid organ or allogeneic bone marrow)
 - have post-transplant lymphoproliferative disease
 - have cancer or have had cancer within the previous 2 years
 - are on mechanical circulatory support
 - are closely related to the transplant donor
-

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 Conformité Européenne 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). FDA product code: OYG.

myTAI_{HEART} is a laboratory developed test (LDT) developed for clinical diagnostic performance exclusively in the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) accredited TAI Diagnostics Clinical Reference Laboratory.(21) This test was developed and its performance characteristics determined by TAI Diagnostics, and has not been cleared or approved by the U.S. Food and Drug Administration.

Medical Policy Statement

The use of the Presage ST2 Assay to (1) evaluate the prognosis of patients diagnosed with chronic heart failure, (2) guide management (eg, pharmacological, device-based, exercise) of patients diagnosed with chronic heart failure **OR** (3) in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection is considered experimental/investigational.

The use of myTAI_{HEART} assay in the post cardiac transplantation period to predict (1) prognosis **OR** (2) acute cellular rejection is considered experimental/investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

83006

0055U

Rationale

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 the ST2 assay is to determine prognosis and/or to guide management in patients with chronic heart failure as an alternative to or an improvement on existing tests and clinical assessment.

The question addressed in this evidence review is: Do ST2 assays determine prognosis and/or guide treatment in patients with chronic heart failure and improve net health outcomes?

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

Patients

The relevant population of interest are individuals with chronic heart failure.

Interventions

The test being considered is soluble suppression of tumorigenicity-2 assay determine prognosis and/or to guide management. Elevated sST2 levels are purported to predict higher risk of poor outcomes.

Patients with chronic heart failure are actively managed by cardiologists.

Comparators

Comparators of interest include standard prognostic markers, including B-type natriuretic peptide levels and clinical assessment.

Patients with chronic heart failure are actively managed by cardiologists.

Outcomes

The general outcomes of interest are overall survival (OS), quality of life, and hospitalizations. Follow-up of 6 -12 months would be appropriate to assess quality of life outcomes.

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).

Study Selection Criteria

For the evaluation of clinical validity of sST2 testing, methodologically credible studies were selected using the following principles:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort.

A number of clinical studies in which 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 heart failure. A substantial body of biomarker evidence has been reported retrospectively from subsets of patients who were enrolled in RCTs of heart failure interventions. These RCTs include the Valsartan Heart Failure Trial (Val-HeFT);(22) Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION);(23) Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA);(24) and, ProBNP Outpatient Tailored Chronic Heart Failure study (PROTECT).(25) 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 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 4.

Aimo et al (2017) pooled findings of studies on the prognostic value of soluble sST2 for chronic heart failure were pooled in a meta-analysis.(26) The meta-analysis selected 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).

Huang et al (2020) conducted a meta-analysis examining the diagnostic values of several novel biomarkers for heart failure, including ST2.(27) Of the 45 studies included, 13 were on ST2 (all were prospective or retrospective cross-sectional studies; N = 3362 patients). No significant publication bias was found for the ST2 studies, but they had high heterogeneity. The pooled sensitivity for the ST2 biomarker was 0.81 (95% CI, 0.79-0.82); specificity was 0.76

(95% CI, 0.74-0.78); positive likelihood ratio was 2.82 (95% CI, 2.17-3.65); negative likelihood ratio was 0.30 (95% CI, 0.22-0.40); positive predictive value was 0.76 (95% CI, 0.74-0.77); negative predictive value 0.81 (0.79-0.73); and area under the curve was 0.83 (indicating a “good” diagnostic tool). The pooled diagnostic odds ratio for ST2 was 11.91 (95% CI, 7.53-18.83). Overall, ST2 was shown to have value for diagnosing heart failure.

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 managed using serial changes in sST2 blood levels were compared with those managed using the reference standard of 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 sST2 in Chronic Heart Failure Patients

Several analyses, mostly 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 BNP or NT-proBNP levels. In general, it appears that elevated sST2 levels predict higher risk of poor outcomes better than lower levels. The available evidence is limited by interstudy inconsistency and differences in patient characteristics, particularly the severity of heart failure, 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 among biomarker status, treatment received, and clinical outcomes.

USE OF SOLUBLE ST2 IN POST HEART TRANSPLANTATION PATIENTS

Clinical Context and Test Purpose

The purpose of sST2 assay to determine prognosis and/or to predict acute cellular rejection in patients with heart transplantation an alternative to or an improvement on existing tests.

The question addressed in this evidence review is: Does the use of the sST2 assay determine prognosis and/or predict acute cellular rejection in patients undergoing heart transplantation and improve net health outcomes?

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

Patients

The relevant population of interest are individuals with heart transplantation.

Interventions

The test being considered is sST2 assay to determine prognosis and/or to predict acute cellular rejection.

Comparators

Comparators of interest include endomyocardial biopsy for predicting acute cellular rejection.

Patients undergoing heart transplant are actively managed by cardiologists and transplant specialists.

Outcomes

The general outcomes of interest are overall survival, quality of life, and hospitalizations.

Table 1. Significant Outcomes for Post-heart Transplantation Patients

Outcomes	Details	Timing
Morbid events	Short-term and long-term events, such as acute cellular rejection, myocardial infarction, and stroke	30 days: 60 months, 1-5 years
Hospitalizations	Inpatient hospital admissions	30 days, 6 months, 1-5 years

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).

Study Selection Criteria

For the evaluation of clinical validity of sST2 testing, methodologically credible studies were selected using the following principles:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

Review of Evidence

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) retrospectively assessed sST2 levels in 241 patients post-heart transplant.(28) Over a follow-up out to seven years, sST2 levels were predictive of total mortality (HR = 2.01; 95% CI 1.15-3.51; p = 0.01). Soluble ST2 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).

Pascual-Figal et al (2011),identified 26 patients with post-cardiac transplantation and an acute rejection episode.(29) Soluble ST2 levels were measured during the acute rejection episode and compared to levels that were measured when acute rejection was not present. Soluble ST2 levels were higher during the acute rejection episode(130 ng/mL) than during the non-rejection period (50ng/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.

Table 2. Summary of Key Nonrandomized Clinical Validity Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-up
Januzzi (2013) ²⁸	Retrospective	US	NR	Post cardiac transplantation	sST2 levels assessment (n=241)	Median 7.1 years
Pascual-Figal (2011) ²⁹	Retrospective	Spain	2002-2007	Post cardiac transplantation with acute rejection	sST2 levels assessment (n=26)	Median 3 months

NR: not reported, sST2: soluble suppression of tumorigenicity-2

Table 3. Summary of Key Nonrandomized Clinical Validity Study Results

Study	Total Mortality	ST2 Levels	Positive Predictive Value	Negative Predictive Value
Januzzi (2013)²⁸			NR	NR
HR (95% CI)	2.02 (1.16-3.52)	≥ 30 ng/mL at 7 year follow-up	NA	NA
p-value	0.01	NR	NA	NA
Pascual-Figal (2011)²⁹			53%	83
Rejection Episode	NR	130 ng/mL (IQR 60 to 238 ng/mL)	NA	NA
Nonrejection Period	NR	50 ng/mL (IQR 28 to 80 ng/mL)	NA	NA
p-value	NR	0.002	NA	NA

HR: hazard ratio; NA: not applicable; NR: not reported; IQR: interquartile range

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.

Table 4. Summary of Selected Clinical Studies of sST2 to Predict Outcomes in Chronic Heart Failure Patients

Study	Population	Mean Age, y	Study Description and Biomarkers	Primary Endpoints	Mean FU	Synopsis of Findings
Ky et al (2011) ³⁰	Ambulatory CHF (N = 1141, 75% of Penn HF Study population)	56	Retrospective analysis of sST2 and NT-proBNP levels and their incremental usefulness over clinical SHFM	Mortality or cardiac transplant	2.8 y	- Elevated sST2 levels associated with increased risk (adjusted $P=.002$) - sST2 in plus NT-proBNP levels showed moderate improvement over SHFM in predicting outcomes ($P=.017$)
Bayes-Genis et al (2012) ³¹	Ambulatory decompensated HF (N = 891)	70	Retrospective analysis of sST2 and NT-proBNP levels from consecutive series	Mortality	2.8 y	Elevated sST2 and NT-proBNP levels provided independent and additive prognostic information for elevated risk of mortality ($P<.001$)
Broch et al (2012) ³²	Ischemic CHF (N = 1149, 30% of CORONA RCT)	72	Retrospective analysis of sST2, NT-proBNP, and CRP levels	CV mortality, nonfatal myocardial infarction or stroke	2.6 y	- Elevated sST2 levels independently associated with increased risk for mortality, hospitalization due to HF, or any CV hospitalization ($P<.001$) - sST2 did not provide additive prognostic information vs. NT-proBNP
Felker et al (2013) ³³	Ambulatory HF (N = 910, 39% of HF-ACTION RCT)	59	Retrospective analysis of sST2 and NT-proBNP levels	Mortality, hospitalization, functional capacity	2.5 y	- Elevated sST2 levels independently associated with increased risk for mortality, hospitalization due to HF, or any CV hospitalization ($P<.000$) - sST2 and NT-proBNP provided independent

						prognostic information • sST2 did not provide additive prognostic information vs. NT-proBNP
Gaggin et al (2013) ³⁴	Recently decompensated CHF (n=151, 100% of PROTECT RCT)	63	Retrospective analysis of sST2 and NT-proBNP levels	Composite outcome (worsening HF, hospitalization for HF, clinically significant CV events)	0.8 y	• Elevated sST2 levels associated with increased risk for adverse CV outcome ($P<.001$) • sST2 and NT-proBNP did not provide independent prognostic information
Anand et al (2014) ³⁵	CHF (n=1650, 33% of Val-HeFT RCT)	63	Retrospective analysis of sST2, NT-proBNP, and other biomarker levels	All-cause mortality and composite outcome (mortality, SCD with resuscitation, hospitalization for HF, or administration of IV inotropic or vasodilator drug for ³⁴ h without hospitalization)		• Elevated sST2 levels independently associated with increased risk of poor outcomes ($P<.001$) • Baseline sST2 levels did not provide substantial prognostic information when added to a clinical model that included NT-proBNP levels
Zhang et al (2015) ³⁶	De novo HF or decompensated CHF (N = 1161)	58	Prospective analysis of sST2 in hospitalized sample at 1 center in China	All-cause mortality	1 y	• Elevated sST2 levels independently associated with increased risk of all-cause mortality ($P<.001$) after adjustment for clinical risk factors and NT-proBNP levels
Dupuy et al (2016) ³⁷	HF for ≥ 6 mo (N = 178)	75	Prospective analysis of sST2, NT-proBNP, and other biomarker levels in sample from 1 center in France	All-cause mortality and CV mortality	42 mo ^a	• Elevated sST2 levels independently associated with increased risk for all-cause mortality and CV mortality ($P<.001$) • 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; FU: follow-up; 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.
 a Median.

Section Summary: Use of Soluble Suppression of Tumorigenicity-2 in Post Heart Transplantation Patients

Few studies are available and they are observational and retrospective. No prospective studies were identified that provide high-quality evidence on the ability of sST2 levels 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.

Use of myTAI_{HEART} in Post Heart Transplantation Patients

Clinical Context and Test Purpose

The purpose of myTAI_{HEART} is to determine prognosis and/or to predict acute cellular rejection in patients with heart transplantation as an alternative to or an improvement on existing tests.

The question addressed in this evidence review is: Does the use of the myTAI_{HEART} assay determine prognosis and/or predict acute cellular rejection in patients undergoing heart transplantation and improve net health outcomes?

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

Patients

The relevant population of interest is individuals with heart transplantation.

Patients undergoing heart transplant are actively managed by cardiologists and transplant specialists.

Interventions

The test being considered is myTAI_{HEART} assay to determine prognosis and/or to predict acute cellular rejection.

Comparators

Comparators of interest include endomyocardial biopsy for predicting acute cellular rejection.

Patients undergoing heart transplant are actively managed by cardiologists and transplant specialists.

Outcomes

The general outcomes of interest are overall survival, quality of life, and hospitalizations.

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).

Study Selection Criteria

For the evaluation of clinical validity of myTAI_{HEART} testing, methodologically credible studies were selected using the following principles:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort

Review of Evidence

Serum donor fraction (%), defined as the ratio of donor specific cell free DNA to total cell free DNA, has been proposed as a test to predict acute cellular rejection. In study funded by TAI Diagnostics, Inc., North et al (2020) performed a blinded clinical validation study on 158 matched pairs of endomyocardial biopsy-plasma samples collected from 76 volunteer adult and pediatric heart transplant recipients (ages 2 months or older, and 8 days more post-transplant) between June of 2010 and Aug 2016 from two Milwaukee transplant centers.(21) Based on acute cellular rejection grade as defined by the 2004 International Society for Heart and Lung Transplantation (ISHLT) classification, Receiver Operating Characteristic (ROC) analysis was performed to evaluate diagnostic accuracy across all possible cutoffs. To maximize diagnostic accuracy, Youden's Index was used to select the optimal cutoff, found to correspond to a donor fraction value of 0.32%. Using this cutoff, clinical performance characteristics of the assay included a negative predictive value (NPV) of 100.00% for grade 2R or higher acute cellular rejection, with 100.00% sensitivity and 75.48% specificity; Area under the Curve (AUC) for this analysis was 0.842, indicative of robust ability of the donor fraction assay to rule out 2R or greater acute cellular rejection for donor fraction values less than 0.32%. There was no statistically significant correlation of donor fraction with age. Donor fraction elevation can also be caused by other forms of injury to the donor heart such as acute cellular rejection 1R, acute antibody-mediated rejection (AMR), and presence of coronary artery vasculopathy (CAV), thereby requiring correlation of myTAI_{HEART} results with other clinical indicators.

In study funded by a grant from the National Institutes of Health and TAI Diagnostics, Inc., Richmond et al (2019) assessed 174 post-cardiac transplant patients from seven centers (ages 2.4 months-73.4 years) days with myTAI_{HEART} testing (before transplant; 1, 4, and 7 days following transplant; and at discharge from transplant hospitalization) using blinded analysis of biopsy-paired samples.(38) All the patients were followed for at least one year. Donor fraction, defined as the ratio of cell free DNA specific to the transplanted organ to the total amount of cell free DNA present in a blood sample was higher in acute cellular rejection 1R/2R (n = 15) than acute cellular rejection 0R (healthy) (n = 42) (P = 0.02); an optimal donor fraction threshold (0.3%) was determined by the use of Receiver Operating Characteristic (ROC) analysis, revealing an AUC of 0.814 with a sensitivity of 0.65, specificity of 0.93, and an NPV of 81.8% for the absence of any allograft rejection.

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 RCTs.

No studies were identified using myTAI_{HEART} 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 myTAI_{HEART} levels for patients with heart transplantation.

Section Summary: Use of myTAI_{HEART} in Post-Heart Transplantation Patients

Few studies are available, and they are observational and of small sample size. No high-quality evidence was found supporting the ability of myTAI_{HEART} levels to predict transplant outcomes. A clinical validation study (n=76) reports donor fraction cutoff value of 0.32% cutoff provides a negative predictive value (NPV) of 100.00% for grade 2R or higher acute cellular rejection, with 100.00% sensitivity and 75.48% specificity; an additional prospective study (N = 174) found that myTAI_{HEART} levels were associated with acute cellular rejection with an optimal donor fraction threshold of 0.3% to rule out the presence of either acute cellular rejection or antibody-mediated rejection.

Summary of Evidence

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 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 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.

For individuals who have heart transplantation who receive myTAI_{HEART} assay to determine acute cellular rejection, the evidence includes observational studies. A validation study using 158 matched endomyocardial biopsy-plasma pairs from 76 pediatric and adult heart transplant recipients (ages 2 months or older, and 8 days more post-transplant) found a donor-specific fraction cutoff (0.32%) that produced a 100% negative predictive value for Grade 2 or higher acute cellular rejection. A prospective observational blinded study (n=174; pediatric=101, adult=73) using biopsy-paired samples found that myTAI_{HEART} level was associated with acute cellular and antibody-mediated rejection in both adult and pediatric heart transplant populations, and that an optimal donor fraction threshold (0.3%) ruled out the presence of either acute cellular rejection or antibody-mediated rejection. Both studies received industry funding. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

In 2017, the American College of Cardiology, American Heart Association and Heart Failure Society published a focused update of their 2013 guideline on the management of heart failure.(39,1) 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 or myTAI_{HEART}.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable

Government Regulations

There is no national or local coverage determination for ST2 assays.

The Medicare Clinical Diagnostic Laboratory Fee Schedule lists a fee for 83006.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Galectin-3 Testing in the Assessment and Management of Chronic Heart Failure
 - Laboratory Tests for Heart and Kidney Transplant Rejection
 - Measurement of Lipoprotein-associated Phospholipase A2 (Lp-PLA2) and Secretory Type II Phospholipase A2 (sPLA-IIA) in the Assessment of Cardiovascular Risk
 - Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease
 - Skin Advanced Glycation End Products (AGE) Measurement By Multi-Wavelength Fluorescent Spectroscopy
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through October 6, 2020, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/15	4/21/15	5/8/15	Joint policy established
7/15/16	4/19/16	4/19/16	Routine approval
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		- myTAI HEART (0055U) added (EI) - Title changed from: ST2 Assay for Chronic Heart Failure

Next Review Date: 4th Qtr, 2021

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MOLECULAR TESTING FOR CHRONIC HEART FAILURE AND HEART TRANSPLANT

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*