

**6.01.56 Myocardial Sympathetic Innervation Imaging in Patients With Heart Failure**

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**Policy Statement**

- I. Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine (MIBG) is considered **investigational** for individuals with heart failure.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

**Policy Guidelines****Coding**

The following are specific CPT category III codes for this imaging:

- **0331T**: Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment
- **0332T**: Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT

The following HCPCS code is specific for AdreView:

- **A9582**: Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 mCi

The following HCPCS code is specific for AZEDRA:

- **A9590**: Iodine I-131, iobenguane, 1 mCi

**Description**

In patients with heart failure, activation of the sympathetic nervous system is an early response to compensate for decreased myocardial function. The concentration of iodine 123 meta-iodobenzylguanidine (MIBG) over several hours after the injection of the agent is a potential marker of sympathetic neuronal activity. Iodine 123 meta-iodobenzylguanidine activity is proposed as a prognostic marker in patients with heart failure to aid in the identification of patients at risk of 1- and 2-year mortality. The marker could also be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

In 2008, AdreView® (Iobenguane I 123) Injection (GE Healthcare) was approved via the U.S. Food and Drug Administration (FDA) new drug application process (22-290) for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests.<sup>5</sup>

The FDA (2013) approved a supplemental new drug application (22-290/S-001) for AdreView and expanded the labeled indication to include scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the H/M ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and LVEF less than 35%.<sup>6</sup>

## Rationale

### Background Heart Failure

An estimated 6.2 million adults in the U.S. have heart failure. In 2018, heart failure was mentioned on 379,800 death certificates in the U.S.<sup>1</sup> According to data in the 2022 Heart and Stroke Statistics Update, 1 in 6 patients with heart failure and reduced ejection fraction developed worsening disease within 18 months of diagnosis and these individuals were more likely to be Black, >80 years of age, and have increased comorbidity burden.<sup>2</sup> Black individuals also have the highest risk of developing heart failure in the future, followed by Hispanic, White, and Chinese American individuals, reflecting disparities in the incidence of hypertension, diabetes, and socioeconomic status among these populations. Black individuals also have the highest proportion of incident heart failure not preceded by myocardial infarction (75%). Underlying causes of heart failure include coronary artery disease, hypertension, valvular disorders, and primary cardiomyopathies. These conditions reduce myocardial pump function and decrease left ventricular ejection fraction (LVEF). An early mechanism to compensate for this decreased myocardial function is activation of the sympathetic nervous system. The increased sympathetic activity initially helps compensate for heart failure by increasing heart rate and myocardial contractility to maintain blood pressure and organ perfusion. However, over time, this places additional strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease and/or myocardial damage. As the ability of the heart to compensate for reduced myocardial function diminishes, clinical symptoms of heart failure develop. Another detrimental effect of heightened sympathetic activity is an increased susceptibility to potentially fatal ventricular arrhythmias.

Overactive sympathetic innervation associated with heart failure involves increased neuronal release of norepinephrine (NE), the main neurotransmitter of the cardiac sympathetic nervous system. In response to sympathetic stimulation, vesicles containing NE are released into the neuronal synaptic cleft. The released NE binds to postsynaptic  $\beta_1$ ,  $\beta_2$ , and  $\alpha$  receptors, enhances adenylyl cyclase activity, and brings about the desired cardiac stimulatory effects. Norepinephrine is then taken back into the presynaptic space for storage or catabolic disposal, terminating the synaptic response by the uptake-1 pathway. The increased release of NE is usually accompanied by decreased NE reuptake, thereby further increasing circulating NE levels.

### Diagnostic Imaging

Guanethidine is a false neurotransmitter that is an analogue of NE; it is also taken up by the uptake-1 pathway. Iodine 123 meta-iodobenzylguanidine (<sup>123</sup>I-MIBG or MIBG) is chemically-modified guanethidine labeled with radioactive iodine. Iodine 123 meta-iodobenzylguanidine moves into the synaptic cleft and then is taken up and stored in the presynaptic nerve space in a manner similar to NE. However, unlike NE, MIBG is not catabolized and thus concentrates in myocardial sympathetic nerve endings. This concentrated MIBG can be imaged with a conventional gamma camera.<sup>3</sup> The concentration of MIBG over several hours after injection is thus a reflection of sympathetic neuronal activity, which in turn may correlate with the severity of heart failure.

Iodine 123 meta-iodobenzylguanidine myocardial imaging has been in use in Europe and Japan, and standardized procedures for imaging have been proposed by European organizations.<sup>4</sup> Administration of MIBG is recommended by slow (1 to 2 minute) injection. Planar images of the thorax are acquired 15 minutes (early image) and 4 hours (late image) after injection. In addition, optional single photon emission computed tomography (SPECT) can be performed following the early and late planar images. Iodine 123 meta-iodobenzylguanidine uptake is semi-quantified by determining the average count per pixel in regions of interest drawn over the heart and the upper mediastinum in the planar anterior view. There is no single universally used myocardial MIBG index. The most commonly used myocardial MIBG indices are the early heart to mediastinum (H/M) ratio, late H/M ratio, and the myocardial MIBG washout rate. The H/M ratio is calculated by taking the average count per pixel in the myocardium divided by the average count per pixel in the mediastinum. The myocardial washout rate is expressed as the rate of decrease in myocardial counts over time between early and late imaging (normalized to mediastinal activity).

Iodine 123 meta-iodobenzylguanidine activity is proposed as a prognostic marker in patients with heart failure, to be used in conjunction with established markers or prognostic models to identify heart failure patients at increased risk of short-term mortality. Iodine 123 meta-iodobenzylguanidine activity could also be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

### Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

The U.S. Food and Drug Administration (FDA) approved indication for the scintigraphic imaging agent iodine 123 meta-iodobenzylguanidine (MIBG) in heart failure patients is to measure the heart to mediastinum (H/M) ratio, which can be used to predict the risk of 1- and 2-year mortality. While the H/M ratio can be used as a dichotomous or a continuous variable, the FDA approved indication is a dichotomous variable with an H/M cutoff of 1.6. A ratio of less than 1.6 indicates higher risk, and a ratio of 1.6 or greater indicates a lower risk.<sup>7</sup> Thus, evaluation of this technology involves first searching for evidence that an H/M ratio of at least 1.6 is statistically associated with mortality in heart failure patients.

### Myocardial Sympathetic Innervation Imaging in Heart Failure

#### Clinical Context and Test Purpose

The purpose of prognostic imaging using MIBG in individuals with heart failure is to risk-stratify them to determine the appropriate next steps.

The following PICO was used to select literature to inform this review.

### ***Population***

The relevant population of interest is individuals with heart failure.

### ***Interventions***

The test being considered is imaging with MIBG for prognosis.

### ***Comparators***

The following practice is currently being used to make decisions about managing individuals with heart failure: management with standard heart failure prognostic markers.

### ***Outcomes***

The general outcomes of interest are overall survival, disease-specific survival, functional outcomes, health status measures, quality of life, hospitalizations, and medication use. Outcomes of interest for heart failure are overall survival (i.e., cardiac death), heart failure progression, and arrhythmic events. Adverse outcomes for MIBG injection are infrequent, typically a short-term spike in blood pressure and side effects of radiation.

Given 1-year mortality rates from heart failure, follow-up monitoring will be necessary for the short term for those at high risk of heart failure and over the long term for those at low risk.

### **Study Selection Criteria**

For the evaluation of the clinical validity of MIBG, studies that met the following eligibility criteria were considered:

- 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.

### **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).

### **Review of Evidence**

The first step in evaluating MIBG is assessing its prognostic accuracy, specifically, whether an H/M ratio of less than 1.6 is associated with a higher risk of heart failure mortality.

### **Systematic Reviews**

Verschure et al (2014) published the results of an individual patient data meta-analysis to assess which heart failure-related endpoint had the strongest association with MIBG results.<sup>8</sup> The meta-analysis included 636 patients with congestive heart failure from 6 studies from the U.S. and Europe. Inclusion criteria were studies reporting survival in patients with heart failure stratified by the H/M ratio, which yielded 8 studies, 6 of which were willing to share individual patient data. Over a mean follow-up of 36.9 months, 159 patients had 172 events: 83 deaths (67 of which were cardiac), 33 arrhythmic events, and 56 cardiac transplantations. In univariate analysis, the H/M ratio was significantly associated with all cardiac-related outcomes, but the lowest hazard ratios (HR) were associated with the composite endpoint of any event (HR, 0.30; 95% confidence interval [CI], 0.19 to 0.46), all-cause mortality (HR, 0.29; 95% CI, 0.16 to 0.53), and cardiac mortality (HR, 0.28; 95% CI, 0.14 to 0.55).

A systematic review by Verberne et al (2008) selected studies that reported survival in patients with heart failure stratified by MIBG myocardial parameters (early H/M, late H/M, and/or myocardial

washout).<sup>9</sup> Eighteen studies met the eligibility criteria. Thirteen studies were prospective, and all but 1 had at least 3 months of follow-up. Sample sizes ranged from 37 to 205 patients; 5 studies included more than 100 patients. Patient populations varied across studies. Some studies included the whole heart failure spectrum (i.e., New York Heart Association [NYHA] functional status class I through IV) and others focused on a narrower range of functional status. Fourteen studies included patients with depressed left ventricular ejection fraction (LVEF; <40%). Acquisition of early H/M ratio was performed at 15 to 20 minutes in 9 studies and ranged from 30 to 60 minutes in the other 6 studies. Seventeen studies acquired late H/M ratio at 240 minutes after injection. Reviewers evaluated methodologic quality using a tool they developed to rate each study; the scoring range was 0 to 9. The median quality score of the included studies was 6; 2 studies scored 9.

In reviewers' initial calculations, the pooled HR for death and late H/M ratio and for a cardiac event and late H/M ratio showed significant heterogeneity among studies and therefore pooled results were not presented for the entire body of studies. Reviewers eliminated statistical heterogeneity by selecting the highest quality studies (i.e., top fifth in terms of quality score, n=3 studies). When findings from these 3 highest quality studies were pooled, there was a statistically significant effect of MIBG on cardiac events (HR, 1.98; 95% CI, 1.57 to 2.50). However, when findings from the 2 highest-quality studies reporting the outcome of cardiac death were pooled, there was no statistically significant effect of MIBG on this outcome (HR, 1.82; 95% CI, 0.80 to 4.12). Reviewers did not pool findings on the prognostic value of early H/M or myocardial washout due to failure to identify a subset of studies without heterogeneity.

## Prospective Studies

### ADMIRE-HF Study

Jacobson et al (2010) published data from 2 prospective, multicenter, industry-sponsored studies, together known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study.<sup>10</sup> This study was the primary evidence used by the FDA to grant approval for AdreView. The analysis presented the combined primary efficacy results of the 2 studies. The study included patients with NYHA functional class II or III heart failure and LVEF of 35% or lower, which are the clinical parameters specified by the FDA documents as the appropriate criteria for use of AdreView in heart failure patients. In addition, patients had to be treated with optimum pharmacotherapy. Major exclusion criteria were serum creatinine above 3.0 mg/dL, functioning ventricular pacemaker and cardiac revascularization, myocardial infarction, or implantable cardioverter-defibrillator implantation within the past 30 days.

Patients received an injection of MIBG and then underwent planar and single photon emission computed tomography (SPECT) imaging of the thorax at 15 minutes after injection (early) and at 3 hours and 50 minutes after injection (late). The H/M ratio, on a scale from 0 to 4, was determined from both the early and late images. Patients then received standard clinical care and were followed for 2 years. The primary analysis evaluated the association between time to first cardiac event occurrence and the late H/M ratio categorized as under 1.6 or 1.6 and higher. The authors also evaluated the association between time to first cardiac event occurrence and late H/M ratio as a continuous variable. The composite outcome of cardiac events was defined as the occurrence of either (1) heart failure progression (i.e., increase of  $\geq 1$  NYHA functional class); (2) potentially life-threatening arrhythmic event (i.e., spontaneous ventricular tachyarrhythmia for >30 seconds, resuscitated cardiac arrest, or appropriate discharge of implantable cardiac defibrillator); or (3) cardiac death.

A total of 985 patients underwent MIBG imaging (435 in the first study, 532 in the second study) and 961 (98%) patients were available for analysis. There were 760 (79%) patients with an H/M ratio less than 1.6 and 201 (21%) patients with an H/M ratio of at least 1.6. Patients were followed for a median of 17 months (range, 2 days to 30 months). Cardiac events occurred in 237 (25%) of 961 patients. The mean late H/M ratio (standard deviation [SD]) was 1.39 (0.18) in the group of patients with events and 1.46 (0.21) in the group of patients without events. The risk of cardiac events was significantly lower for

patients who had an H/M at least 1.6 compared with those who had an H/M ratio less than 1.6 (HR, 0.40; 97.5% CI, 0.25 to 0.64;  $p < .001$ ). In addition, there was a statistically significant association between the cardiac event rate and H/M ratio as a continuous variable, with lower event rates in patients with higher H/M ratios (HR, 0.22; 95% CI, 0.10 to 0.47;  $p < .001$ ). The estimate of 2-year all-cause mortality was 16.1% for patients with an H/M less than 1.6 and 3.0% for patients with an H/M ratio at least 1.6 ( $p < .001$ ). The authors also compared H/M ratios with other prognostic markers. In a multivariate model including the H/M ratio, b-type natriuretic peptide, LVEF, and NYHA functional class, all 4 markers were independently associated with time to cardiac events.

Ketchum et al (2012) published an analysis incorporating MIBG imaging findings into the Seattle Heart Failure Model (SHFM) using survival data from the 961 patients included in the primary efficacy analysis of the ADMIRE-HF study.<sup>11</sup> The late H/M ratio from MIBG imaging was divided into 5 categories: less than 1.2, 1.2 to 1.39, 1.40 to 1.59, 1.6 to 1.79, and at least 1.8. (Note that this differs from the dichotomous late H/M variable used in the main ADMIRE-HF analysis.) In a Cox proportional hazards model, SHFM and H/M were both independent predictors of overall survival. There was an 82.1% increase in risk for each 1 SD change in the SHFM ( $p < .001$ ) and a 60.3% increase in risk for each 1 SD change in the late H/M ratio ( $p < .001$ ). For the outcome of cardiac mortality, each SD increase in SHFM was associated with an 86.1% increase in risk ( $p < .001$ ), and each SD increase in the late H/M ratio was associated with a 57.9% increase in risk ( $p = .002$ ). In an area under the curve analysis, the addition of H/M to the SHFM significantly improved the prediction of all-cause mortality compared with the SHFM alone. When H/M was added to the SHFM, the area under the curve increased by 0.039 ( $p = .026$ ) for 1-year mortality, and the area under the curve increased by 0.028 ( $p < .05$ ) for 2-year mortality.

Sood et al (2013) published a subgroup analysis of the ADMIRE-HF study to evaluate whether resting perfusion defects on myocardial perfusion imaging with SPECT, representing scarring or fibrosis, improved risk stratification beyond the H/M ratio in the prediction of ventricular arrhythmias in ischemic and nonischemic cardiomyopathy patients.<sup>12</sup> In 317 nonischemic cardiomyopathy patients, myocardial perfusion imaging with SPECT score (summed rest score,  $>8$ ) had an incremental predictive value for ventricular arrhythmias for those with a low H/M ratio. Among the 612 patients with ischemic cardiomyopathy, myocardial perfusion imaging with SPECT results did not have an incremental predictive value.

Al Badarin et al (2014) conducted another subgroup analysis of the ADMIRE-HF study to evaluate whether the addition of MIBG scintigraphy to conventional markers of arrhythmic risk had an incremental predictive value for arrhythmic events in patients with heart failure.<sup>13</sup> This analysis included 778 patients from ADMIRE-HF with an LVEF less than 35% and NYHA class II or III heart failure symptoms who did not have an implantable cardioverter-defibrillator at the time of enrollment. Of these, 6.9% experienced the primary endpoint of an arrhythmic event, which was a composite of sudden cardiac death, appropriate implantable cardioverter-defibrillator therapy, resuscitated cardiac arrest, or sustained ventricular tachycardia. An H/M ratio of less than 1.6 was significantly associated with risk of arrhythmic events (HR, 3.48; 95% CI, 1.52 to 8;  $p = .02$ ). Other predictors of arrhythmic events were LVEF less than 25% and systolic blood pressure less than 120 mm Hg. The authors derived a risk score, incorporating the H/M ratio, systolic blood pressure, and LVEF. Risk scores ranged from -3 to 20, with higher scores associated with an increased risk of arrhythmic events. Stratified by tertiles, patients with low ( $<4$ ), intermediate (4 to 15), and high ( $>15$ ) risk scores had significantly different arrhythmic event rates (2%, 10%, 16%, respectively;  $p < .001$ ). The integrated discrimination improvement by adding MIBG imaging, systolic blood pressure, and LVEF results to the risk model was 0.45 (absolute integrated discrimination improvement, 0.01; 95% CI, 0.001 to 0.014), which demonstrated a 45% improvement in discriminatory ability with the addition of MIBG results.

Jain et al (2014) evaluated the incremental predictive value of adding MIBG imaging to 4 published heart failure risk models using data from ADMIRE-HF.<sup>14</sup> The 4 risk models varied by predictor

variables and the patient populations from which the models were derived. In the ADMIRE-HF population, the 4 models had modest discrimination for identifying patients at risk of experiencing the composite primary endpoint of heart failure progression necessitating hospital admission, life-threatening arrhythmia, or cardiac death (C statistic range, 0.611 to 0.652). When the H/M ratio was added to the risk prediction models, the integrated discrimination improvement had an absolute improvement of 2.1% to 3.0% in each model, representing a relative improvement in predictive utility ranging from 33% to 59%.

Narula et al (2015) reported on the ADMIRE-HF extension study (ADMIRE-HFX), which extended the follow-up to a median of 24 months and focused specifically on the predictive value of MIBG imaging for mortality prediction.<sup>15</sup> The primary endpoint for this extension study was all-cause mortality, which was analyzed using 2 coprimary analysis methods, proportional hazards and logistic regression. In both the multivariate Cox proportional hazards analysis and the multivariate logistic regression analysis with receiver operating characteristic curve comparisons, the H/M ratio was a significant additional predictor for all-cause mortality (HR, 0.08;  $p < .001$ ; odds ratio, 0.07; 95% CI, 0.20 to 0.238, respectively).

Agostini et al (2021) continued to evaluate the value of MIBG imaging for predicting mortality, cardiac death, and arrhythmic events in the ADMIRE-HF study at a median follow-up of 62.7 months.<sup>16</sup> Results revealed that all-cause mortality (38.4% vs. 20.9%) and cardiac mortality (16.8% vs. 4.5%) were significantly increased for those patients with a H/M ratio  $< 1.6$  versus those with a ratio  $\geq 1.6$  ( $p < .05$  for both comparisons). Patients with preserved sympathetic innervation of the myocardium (H/M  $\geq 1.6$ ) also had a significantly lower risk of 5-year mortality (17.1% vs. 34.3%;  $p < .0001$ ), 5-year cardiac mortality (4.6% vs. 15.8%;  $p < .0001$ ), and sudden cardiac death or potentially life-threatening arrhythmias (10.9% vs. 21.1%;  $p = .0002$ ). A trend toward a higher mortality for subjects with H/M  $< 1.6$  was seen reaching significance for patients with a LVEF of 25 to  $\leq 35\%$  only.

### Other Prospective Studies

For patients with heart failure without reduced LVEF (i.e., LVEF of at least 50%), several prospective studies have found that MIBG is an independent predictor of cardiac outcomes.<sup>17,18,19,20,21</sup> For example, Nakata et al (2013) published the results of a pooled patient-level analysis of 6 prospective heart failure studies from Japan in which cardiac MIBG imaging was used.<sup>22</sup> The 6 studies initially included 1360 patients, but 38 patients were excluded (32 due to loss to follow-up, 6 due to follow-up  $< 1$  year) for the present analysis. The H/M ratio and the washout rate of MIBG activity were the primary cardiac sympathetic innervation markers. In a multivariate Cox proportional hazards model, the late H/M ratio was significantly associated with the primary outcome of all-cause mortality ( $p < .001$ ). The addition of the H/M ratio to a model of cardiac risk based on clinical information led to a net reclassification improvement of 0.175 ( $p < .001$ ).

A prospective single-center study by Doi et al (2012) evaluated the prognostic value of MIBG activity assessment in 178 heart failure patients without reduced LVEF.<sup>18</sup> Eligibility for the trial included symptomatic heart failure and LVEF more than 50%. Mean LVEF in the sample was 64.5%. Cardiac planar and tomographic MIBG images were obtained 15 to 30 minutes (early) and 4 hours (late) after the agent was injected. Iodine 123 meta-iodobenzylguanidine activity was quantified as the H/M ratio by an experienced technician blinded to clinical data. Patients were followed for a mean of 80 months (minimum, 3 months). The primary endpoints were cardiac events consisting of death, sudden cardiac death, pump failure, or rehospitalization due to the progression of heart failure. During follow-up, cardiac events were documented in 34 (19%) of 178 patients. Events included 7 deaths due to pump failure, 2 sudden deaths, and 25 readmissions due to heart failure progression. There were significantly lower early and late MIBG levels in patients who experienced cardiac events compared with those without events. This study evaluated MIBG activity as a continuous variable; it did not use a cutoff (e.g., an H/M ratio of at least 1.6), as was used to indicate decreased risk in the ADMIRE-HF study.<sup>10</sup> The mean early H/M ratio level was 1.86 in the group with cardiac events and 2.00 in the group without cardiac events. The mean late H/M ratio was 1.64 in the group with, and

1.89 in the group without, cardiac events. In a multivariate analysis, use of diuretics, late atrial diameter, and late H/M ratio were all independent predictors of cardiac events.

### **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, more effective therapy, or avoid unnecessary therapy or 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.

As noted, numerous prospective studies have indicated that MIBG imaging is associated as a prognostic marker with heart failure mortality. No studies were identified that evaluated the impact of cardiac sympathetic innervation assessed by MIBG on treatment decisions for heart failure or that evaluated whether managing heart failure patients with this test (vs. managing patients without the test) leads to patient management decisions that improve health 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.

A systematic review by Treglia et al (2013) included 33 studies, primarily performed in Europe and Japan, that compared MIBG imaging results in patients with heart failure before and after receiving medication treatment.<sup>23</sup> Reviewers provided brief descriptions of the findings of individual studies; they did not pool study results. Studies addressed different classes of medications (e.g.,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers) and different MIBG parameters used. Reviewers did not report the number of studies with statistically significant findings but described a number of studies that found significant associations between medication treatment and changes in 1 or more MIBG parameters. They also described some studies that found significant associations between changes in 1 or more MIBG parameters and cardiac outcomes in patients receiving medication treatment. However, none of the studies used MIBG imaging results to guide medication treatment choices or compared management strategies that did and did not include MIBG imaging.

Management changes that might be made as a result of MIBG myocardial imaging are uncertain. It is possible that medication therapy could be intensified based on MIBG scanning that indicated a poor prognosis. However, the evidence is lacking that such a management change would result in improved outcomes. It is also possible that medications that block sympathetic overactivity (e.g.,  $\beta$ -blockers or angiotensin-converting enzyme inhibitors) could be adjusted to achieve an optimal H/M ratio. It is also not known whether such medication adjustments made as a result of MIBG imaging would lead to improvements in health outcomes.

Klein et al (2015) reported on the results of a pilot study that used MIBG imaging to map substrates for ventricular tachycardia ablation<sup>24</sup>, but the use of MIBG imaging for this purpose is still in preliminary investigations.

### **Section Summary: Myocardial Sympathetic Innervation Imaging in Heart Failure**

The available evidence has demonstrated that MIBG imaging is a predictor of future cardiac events and mortality in patients with heart failure. Numerous prospective studies have evaluated this question and a systematic review that pooled the highest quality studies estimated that cardiac events were approximately 2 times more frequent for patients with a lower MIBG ratio than for those with a higher ratio. The primary study on which the FDA approval was based reported that a low



MIBG ratio was associated with a substantially higher mortality rate at 2 years. Data from this same study reported that the addition of the MIBG score to a known prognostic index (the SHFM) resulted in improved predictive accuracy. The evidence does not support a finding that MIBG imaging can be used to direct management in patients with heart failure. Numerous studies have correlated medication changes with changes in MIBG imaging. However, these studies do not provide evidence on the type of management changes that might follow from MIBG imaging. Further studies are needed to determine the impact of MIBG imaging on health outcomes.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (2011) published a report on the translation of cardiovascular molecular imaging.<sup>25</sup> In regard to heart imaging with meta-iodobenzylguanidine (MIBG), the report cited the ADMIRE-HF trial,<sup>10</sup> and stated that additional clinical trials would be needed to determine the efficacy of heart failure management strategies using MIBG compared with usual care without MIBG imaging.

### American Heart Association et al

The American Heart Association, American College of Cardiology, and Heart Failure Society of America published joint guidelines on the management of heart failure in 2022.<sup>26</sup> These guidelines did not address the use of MIBG imaging in heart failure management.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2023 did not identify any studies that might influence this review.

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### Documentation for Clinical Review

- No records required

### Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment;
	0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT
HCPCS	A9582	Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 mCi
	A9590	Iodine I-131, iobenguane, 1 mCi

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2016	BCBSA Medical Policy adoption
11/01/2016	Policy revision without position change
11/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
12/16/2019	Policy revision without position change
03/01/2020	Coding update
11/01/2020	Annual review. No change to policy statement. Literature review updated.
11/01/2021	Annual review. No change to policy statement. Literature review updated.
11/01/2022	Annual review. Policy statement and literature review updated.
11/01/2023	Annual review. No change to policy statement. Policy guidelines and literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Myocardial Sympathetic Innervation Imaging in Patients With Heart Failure 6.01.56</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine (MIBG) is considered <b>investigational</b> for patients with heart failure.</li> </ul>	<p><b>Myocardial Sympathetic Innervation Imaging in Patients With Heart Failure 6.01.56</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine (MIBG) is considered <b>investigational</b> for individuals with heart failure.</li> </ul>