MEDICAL POLICY

POLICY TITLE	MYOCARDIAL SYMPATHETIC INNERVATION IMAGING IN PATIENTS WITH HEART FAILURE
POLICY NUMBER	MP-5.054

Effective Date:	2/1/2023

I. POLICY

Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine is considered **investigational** for patients with heart failure. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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 injection of the agent is a potential marker of sympathetic neuronal activity. MIBG 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.

Heart Failure

An estimated 6.2 million adults in the United States have heart failure, which is the main cause of death for approximately 58,300 Americans each year. In 2018, heart failure was mentioned on 379,800 death certificates in the U.S. 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. 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 β_1, β_2, and α receptors, enhances adenyl 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 (^{123}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. 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. Administration of MIBG is recommended by slow (1-2 minutes) 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.

Regulatory Status

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

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%.

IV. RATIONALE TOP

Summary of Evidence

For individuals with heart failure who receive imaging with MIBG for prognosis, the evidence includes numerous studies that MIBG cardiac imaging findings predict outcomes in patients with heart failure. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, health status measures, quality of life, hospitalizations, and medication use. While the available studies vary in their patient inclusion criteria and methods for analyzing MIBG parameters, the highest quality studies have demonstrated a significant association between MIBG imaging results and adverse cardiac events, including cardiac death. Moreover, MIGB findings have been shown to improve the ability of the Seattle Heart Failure Model and other risk models to predict mortality. However, there is no direct published evidence on the clinical utility of MIBG (ie, whether findings of the test would lead to patient management changes that improve health outcomes) and no chain of evidence can be constructed to support clinical utility. Management changes made as a result of MIBG imaging are uncertain, and it is not possible to determine whether management changes based on MIBG results lead to improved health outcomes compared with management without MIBG imaging. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. Coding Information

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational, therefore not covered:

Procedure Codes								
0331T	0332T	A9582						

IX. References

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X. POLICY HISTORY

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MP-5.054	**CAC 7/30/13 New policy** adopting BCBSA. Previously silent now investigational. Policy coded
	CAC 5/20/14 Consensus review. References updated. No changes to the policy statements. Codes reviewed.
	CAC 6/2/15. Consensus review. No change to policy statements. Referrences and rationale updated. Added reference to LCD L31686 Services that are not Reasonable and Necessary. Coding reviewed.
	11/2/15 Administrative change. LCD number changed from L31686 to L35094 due to Novitas update to ICD-10.
	CAC 5/31/16 Consensus review. No change to the policy statement. References and rationale updated. Coding reviewed.
	11/22/16 Administrative Update. Variation reformatting
	CAC 7/25/17 Consensus review. No change to the policy statement. References and rationale updated**.**
	2/28/18 Admin coding review. No changes.
	5/09/18 Consensus review. Policy statement unchanged. Description/Background, Rationale and Reference sections updated.
	4/15/19 Consensus review. No change to the policy statement.
	6/2/20 Consensus review. No change to policy statement or references.
	4/30/2021 Consensus review. No changes to policy statement. Updated background and references. Added code A9582.
	10/28/2022 Consensus Review. No change to policy statement. FEP language updated. Background, Rationale and References revised.

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