I. POLICY

Myocardial sympathetic innervation imaging with $^{123}$Iodine meta-iodobenzylguanidine (MIBG) 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.

**Cross-reference:**
- MP-2.204 Lab Tests for Cardiac Risk Management
- MP-2.309 KIF6 Genotyping for Predicting Cardiovascular Risk and or Effectiveness of Statin Therapy
- MP-2.313 Gene Expression Testing to Predict Coronary Artery Disease

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

*The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

III. DESCRIPTION/BACKGROUND
In patients with heart failure, activation of the sympathetic nervous system is an early mechanism to compensate for decreased myocardial function. The concentration of 123Iodine meta-iodobenzylguanidine (known as MIBG) over several hours after injection of the agent is a potential marker of sympathetic neuronal activity and may correlate with the severity of heart failure. 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 potentially be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

An estimated 5.7 million adults in the United States have heart failure, and heart failure is the main cause of death for approximately 55,000 Americans each year. (1) Underlying causes of heart failure include coronary artery disease (CAD), 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 in order 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), which is 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 post-synaptic beta-1, beta-2 and alpha receptors, enhances adenyl cyclase activity and brings about the desired cardiac stimulatory effects. NE is then taken back into the presynaptic space for storage or catabolic disposal that terminates the synaptic response by the uptake-1 pathway. The increased release of NE is usually accompanied by decreased NE reuptake, thereby further increase circulating NE levels.

Guanethidine is a false neurotransmitter that is an analogue of NE; it is also taken up by the uptake-1 pathway. 123Iodine meta-iodobenzylguanidine (known as 123I-MIBG or MIBG) is guanethidine that is chemically modified and labeled with radioactive iodine. MIBG moves into the synaptic cleft and then is taken up and stored in the presynaptic nerve space in a manner that is 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. (2) The concentration of MIBG over several hours after injection of the agent is thus a reflection of sympathetic neuronal activity, which in turn may correlate with the severity of heart failure.
MIBG myocardial imaging has been in use in Europe and Japan and standardized procedures for imaging have been proposed by European organizations. (3) Administration of MIBG is recommended by slow (1 to 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) imaging can be performed following the early and late planar images. MIBG uptake is semi-quantified by determining the average count per pixel in regions of interest (ROI) 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).

MIBG 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. MIBG activity could also potentially be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

**Regulatory Status**

In March 2013, the U.S. Food and Drug Administration (FDA) approved AdreView™ (lobenguane I 123 injection, GE Healthcare) for “scintigraphic measurement of sympathetic innervations of the myocardium by measurement of the heart to mediastinum (H/M) ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and left ventricular ejection fraction (LVEF) <35%” (4) The product label states that AdreView can be used for identifying patients with lower 1- and 2-year mortality risk; this lower risk is indicated by an H/M ratio of at least 1.6.

**IV. RATIONALE**

The most recently literature update is through May 12, 2015. Following is a summary of the key literature published to date.

The U.S. Food and Drug Administration (FDA)–approved indication for the scintigraphic imaging agent meta-iodobenzylguanidine (MIBG) in heart failure patients is to measure the heart to mediastinum (H/M) ratio, which can be used to predict risk of 1- and 2-year mortality. While the H/M ratio can be used as either a dichotomous or continuous variable, the FDA-approved indication is a dichotomous variable with a cutoff in H/M of 1.6. A ratio less than 1.6 indicates higher risk, and a ratio of 1.6 or greater indicates lower risk. 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. Then, to demonstrate that this technology improves health outcomes, direct or indirect evidence is needed that managing patients with MIBG imaging significantly impacts treatment decisions in a way that will lead to improved outcomes, compared with managing patients without MIBG imaging.

**Do MIBG Imaging Findings Predict Health Outcomes in Patients With Heart Failure?**

**Systematic Review**

A systematic review was published in 2008 by Verberne et al. Studies were eligible for inclusion in the review if they reported survival in patients with heart failure stratified by MIBG myocardial parameters (early H/M, late H/M, and/or myocardial washout). 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 of the studies included more than 100 patients. Patient populations varied among studies. Some studies included the whole heart failure spectrum (ie, New York Heart Association [NYHA] functional status class 1 to IV) and others focused on a smaller range of functional status. Fourteen of the studies included patients with depressed left ventricular ejection fraction (LVEF), ie, less than 40%. Acquisition of early H/M was performed at 15 to 20 minutes in 9 studies and ranged from 30 to 60 minutes in the other 6 studies. Seventeen of the studies acquired late H/M at 240 minutes after injection. The investigators evaluated methodologic quality using a tool they developed to rate each study; the possible range of the score was 0 to 9. The median quality score of the included studies was 6; 2 studies received a score of 9.

In the investigators’ initial calculations, the pooled hazard ratio (HR) for death and late H/M and for a cardiac event and late H/M showed significant heterogeneity among studies, and therefore pooled results were not presented for the entire body of studies. The investigators were able to eliminate statistical heterogeneity by selecting the highest quality studies (ie, top 5th 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% confidence interval [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 not a statistically significant effect of MIBG on this outcome (HR=1.82; 95% CI, 0.80 to 4.12). The authors 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.

**AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) Study**

In 2010, Jacobson et al published data from 2 prospective, multicenter industry-sponsored studies, together known as ADMIRE-HF. This study was the primary evidence used by 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 FDA documents as the appropriate criteria for use of AdreView in heart failure patients. In addition, patients needed to be treated with optimum pharmacotherapy. Major exclusion criteria were serum creatinine above
**MEDICAL POLICY**

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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 (AdreView; GE Healthcare) and then underwent planar and single photon emission computer 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 (ie, increase of 1 or more NYHA functional class); (2) potentially life-threatening arrhythmic event (ie, spontaneous ventricular tachyarrhythmia for more than 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 patients (98%) were available for analysis. There were 760 (79%) patients with H/M less than 1.60 and 201 patients (21%) with H/M at least 1.60. Patients were followed for a median of 17 months (range, 2 days-30 months). Cardiac events occurred in 237 of 961 (25%) patients. The mean late H/M ratio (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 with H/M at least 1.6 compared with those with H/M less than 1.6 (HR=0.40; 97.5% CI, 0.25 to 0.64; p<0.001). 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 on patients with higher H/M ratios (HR=0.22; 95% CI, 0.10 to 0.47; p<0.001). The estimate of 2-year all-cause mortality was 16.1% for patients with H/M less than 1.60 and 3.0% for patients with H/M at least 1.60 (p<0.001). The authors also compared H/M 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.

In 2012, Ketchum et al 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.

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, <1.60 and at least 1.60, 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 1 SD change in the SHFM (p<0.001) and a 60.3% increase in risk for 1 SD change in the late H/M ratio (p<0.001). For the outcome cardiac mortality, each SD increase in SHFM was associated with an 86.1% increase in risk (p<0.001), and each SD increase in the late H/M ratio was associated with a 57.9% increase in risk (p=0.002). In an area under the curve (AUC) 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 AUC increased by...
0.039 (p=0.026) for 1-year mortality and the AUC increased by 0.028 (p<0.05) for 2-year mortality.

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

In 2014, Al Badarin et al published another subanalysis of the ADMIRE-HF study to evaluate whether the addition of MIBG scintigraphy to conventional markers of arrhythmic risk had incremental predictive value for arrhythmic events in patients with heart failure. This analysis included 778 patients from ADMIRE-HF with LVEF less than 35% and NYHA class II or III heart failure symptoms who did not have an implantable cardioverter defibrillator (ICD) at the time of enrollment. Of these, 6.9% experienced the primary end point of an arrhythmic event, which was a composite of sudden cardiac death, appropriate ICD therapy, resuscitated cardiac arrest, or sustained ventricular tachycardia. An H/M less than 1.6 ratio was significantly associated with risk of arrhythmic events (HR=3.48; 95% CI, 1.52 to 8; p=0.02). Other predictors of arrhythmic events were LVEF less than 25% and systolic blood pressure (SBP) less than 120. The authors derived a risk score, which included H/M ratio, SBP, and LVEF, with values ranging from -3 to 20 with higher scores associated with increased risk of arrhythmic events. Based on tertile of the risk score, patients with low scores (<4), intermediate (4-15), and high (>15) scores had significantly different arrhythmic events rates for (2%, 10%, 16%, respectively; p<0.001). The integrated discrimination improvement (IDI) for the addition of MIBG imaging results to a risk model which included SBP and LVEF was 0.45 (absolute IDI=0.01; 95% CI, 0.0007 to 0.014; demonstrating a 45% improvement in discriminatory ability with the addition of MIBG results).

Also in 2014, Jain et al evaluated the incremental predictive value of MIBG imaging in addition to 4 published heart failure risk models using data from ADMIRE-HF. The 4 risk models varied in the patient populations from which they were derived and in their predictor variables. In the ADMIRE-HF population, the 4 models had modest discrimination for identifying patients at risk of experiencing the composite primary endpoint, heart failure progression necessitating hospital admission, life-threatening arrhythmia, or cardiac death (C statistic range, 0.611-0.652). When the H/F ratio was added to the risk prediction models, the IDI 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%.

Other Prospective Studies
For patients with heart failure who do not have reduced LVEF (ie, LVEF of at least 50%), several prospective studies have found MIBG to be an independent predictor of cardiac outcomes. For example, a 2012 prospective single-center study by Doi et al evaluated the
prognostic value of MIBG activity assessment in 178 heart failure patients without reduced LVEF. 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. MIBG 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 end points 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 of 178 patients (19%). Events included 7 deaths due to pump failure, 2 sudden deaths, and 25 readmissions due to heart failure progression. There was a 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; they did not use a cutoff, eg, an H/M ratio of at least 1.60, which was used to indicate decreased risk in the ADMIRE-HF study. The mean (SD) early H/M ratio level was 1.86 (0.38) in the group with cardiac events and 2.00 (0.31) in the group without cardiac events. The mean (SD) late H/M ratio was 1.64 (0.35) in the group with cardiac events and 1.89 (0.33) 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.

In 2013, Nakata et al published results of a pooled patient-level analysis of 6 prospective heart failure studies from Japan in which cardiac MIBG imaging was used. The 6 studies initially included 1360 patients, but 32 patients were excluded due to loss to follow-up, and 6 were excluded due to follow-up less than a 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<0.001). The addition of H/M ratio to a model of cardiac risk based on clinical information lead to a net reclassification improvement of 0.175 (p<0.001).

In 2014, Verschure et al published results of an individual patient meta-analysis to assess which heart failure-related end point had the strongest associated with MIBG results. The study included 636 patients with congestive heart failure from 6 studies from the United States and Europe. Inclusion criteria were studies reporting survival in patients with heart failure stratified by 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, H/M ratio was significantly associated with all cardiac-related outcomes, but the lowest HRs were associated with the composite end point of any event (HR=0.30; 95% 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).
Section Summary
The available evidence demonstrates that MIBG imaging is a predictor of future cardiac events and mortality in patients with heart failure. Numerous prospective studies have been completed on this question, and a systematic review that pooled the highest quality studies estimated that cardiac events were approximately 2 times as frequent for patients with a lower MIBG ratio compared with those with a higher ratio. The primary study on which 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 addition of the MIBG score to a known prognostic index, the SHFM, resulted in improved predictive accuracy.

Do MIBG Imaging Findings Lead to Patient Management Changes That Improve Health Outcomes?
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 (compared with managing patients without the test) leads to patient management decisions that improve health outcomes.

A systematic review by Treglia et al 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. The authors provided brief descriptions of the findings of individual studies; they did not pool study results. Studies addressed different classes of medications (eg, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers) and varied in the MIBG parameters that were used. The authors did not report the number of studies that had statistically significant findings, but they 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 as a result of MIBG scanning that indicates poor prognosis. However, evidence is lacking that such a management change would result in improved outcomes. It is also possible that medications that block sympathetic overactivity, such as β-blockers or ACE 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 lead to improvements in health outcomes.

Klein et al reported results of a pilot study which used MIBG imaging to map substrates for ventricular tachycardia ablation, but use of MIBG imaging for this purpose is still in preliminary investigations.
Section Summary
The evidence is not sufficient to determine whether 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 be made following MIBG imaging. Further studies are needed to determine the impact of MIBG imaging on health outcomes. The preferred study design to evaluate clinical utility is a randomized controlled trial comparing health outcomes in a group of heart failure patients managed with MIBG activity assessment and a group of patients managed without MIBG activity assessment. Well-controlled prospective studies that examine clinicians’ treatment decisions based on MIBG findings compared with treatment decisions made without MIBG findings may also inform the question whether MIBG imaging can improve outcomes in patients with heart failure.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in May 2015 did not identify any ongoing or unpublished trials that would likely influence this policy.

Summary of Evidence
There is evidence from numerous studies that findings on cardiac imaging with 123Iodine meta-iodobenzylguanidine (MIBG) predict outcomes in patients with heart failure. While the available studies vary in their patient inclusion criteria and methods for analyzing MIBG parameters, the highest quality studies demonstrate a significant association of MIBG results with adverse cardiac events, including cardiac death. Moreover, MIBG findings have been shown to improve the ability of the Seattle Heart Failure Model and other risk prediction models to predict mortality. 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. There is no clear chain of indirect evidence of 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 superior outcomes compared with management without MIBG imaging. As a result, the available evidence is insufficient to determine that the use of MIBG myocardial imaging improves the net health outcome for patients with heart failure.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
National Heart, Lung, and Blood Institute
In 2011, a working group of the National Heart, Lung, and Blood Institute published a report on translation of cardiovascular molecular imaging. In regard to imaging the heart with MIBG, the report cited the ADMIRE-HF trial (discussed earlier), and stated that additional clinical trials are needed to determine the efficacy of heart failure management strategies with MIBG compared with usual care without MIBG imaging.
American College of Cardiology Foundation and the American Heart Association
In 2013, the American College of Cardiology Foundation and the American Heart Association published updated guidelines on the management of heart failure. These guidelines include recommendations about the use of noninvasive cardiac imaging in the management of heart failure, but do 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 (NCD).

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’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. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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:

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<th>CPT Codes®</th>
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<th>0332T</th>
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IX. REFERENCES


Other Sources:
Medical Policy

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<tr>
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X. Policy History

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