Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Galectin-3 Testing in the Assessment and Management of Chronic Heart Failure

Description/Background

Galectin-3 is a beta-galactoside-binding protein that is associated with inflammation, fibrosis, and cardiac remodeling. Increased levels of galectin-3 have been found in individuals with acutely decompensating heart failure. There is interest in whether galectin-3 levels can be used in conjunction with clinical assessment and other diagnostic tests to identify those individuals who are at an increased risk for hospitalization and/or death. It has also been proposed that this biomarker may have a role in screening, as elevated levels of galectin-3 could indicate an increased risk of heart failure.

Regulatory Status:

The Galectin-3™ Assay (BG Medicine, Inc.) received clearance from the U.S. Food and Drug Administration in November 2010 as an aid in assessing the prognosis of patients with chronic heart failure.

Medical Policy Statement

Galectin-3 testing is considered experimental/investigational. The peer reviewed medical literature has not yet demonstrated the clinical utility of this test for the assessment and management of patients with heart failure.

Inclusionary and Exclusionary Guidelines

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.):

82777

Rationale

A study by Ghorbani et al (2018) found longitudinal changes in galectin-3 were associated with traditional cardiovascular risk factors and renal disease. Changes in galectin-3 predicted future heart failure, cardiovascular disease, and mortality. However, studies are needed to determine whether serial galectin-3 measures may be useful in disease prevention.

In a systematic review and meta-analysis, Chen et al (2016) found elevated galectin-3 levels were associated with mortality in both acute and chronic heart failure, however the sole use of galectin-3 for determining prognosis is not supported.

In a meta-analysis by Chen et al (2015), a pooled analysis (9 studies) found every 1% increase of galectin-3 level was also followed by 28% increased risk of all-cause mortality with significant heterogeneity. The studies were limited by publication bias and short follow-up periods.

Srivatsan et al (2015) conducted a systematic review to study the utility of galectin-3 as a prognostic biomarker in heart failure. Twenty-seven original articles were selected for the systematic review. Multivariate analysis showed galectin-3 to be ineffective in predicting all-cause mortality and cardiovascular mortality especially under the influence of factors such as estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NTproBNP). Galectin-3 was not found to be superior to NTproBNP, sST2, GDF-15 or C-reactive protein (CRP) as a predictor of mortality. However the combination of natriuretic peptides and galectin-3 has been observed to be superior in predicting mortality compared to either of the biomarkers alone. The role of galectin-3 in remodeling has not been conclusively proven as seen in earlier pre-clinical studies. The current weight of evidence does not suggest galectin-3 to be a predictor of mortality. However, assessment of galectin-3 in a multi-biomarker panel may have a distinct advantage in prognosticating patients with heart failure.

Ahmad et al (2014) studied whether biomarkers of myocardial stress and fibrosis (NT-proBNP, galectin-3, and ST2) improve the prediction of mode of death in those with chronic heart failure. HF-ACTION trial participants had NT-proBNP, galectin-3, and ST2 levels assessed at baseline. An independent events committee prospectively adjudicated mode of death. There were 813 participants from HF-ACTION included in this study. After a medial follow-up period of 2.5 years, there were 155 deaths (49 from pump failure, 42 from sudden cardiac death, and 64 from other causes). Elevations in all biomarkers were associated with increased risk for both pump failure and sudden cardiac death. Increased biomarkers had a stronger association with pump failure than sudden cardiac death, but this relationship weakened after adjustment for clinical risk factors. Clinical variables and NT-proBNP levels were stronger predictors of pump failure than sudden cardiac death. Galectin-3 and ST-2 provided insignificant incremental contributions. Predictability of sudden cardiac death risk was less robust and enhanced by information provided by novel biomarkers.

van der Velde et al (2013) reported on the results of a prospective study examining the association of galectin-3 levels with morbidity and mortality in patients with heart failure. The study population included a total of 1653 participants from 2 groups. The first group included 1329 individuals with chronic heart failure and New York Heart Association (NYHA) class ≥ II from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial. In this group, galectin-3 blood levels were measured at baseline and at 3 months. The second group included 324 individuals with acutely decompensated heart failure from the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) trial. In this group, galectin-3 was measured at baseline and at 6 months. An increase in galectin-3 levels was associated with hospitalization and all-cause mortality compared with stable or decreasing levels. Increases were associated with a higher risk for adverse events, even after adjusting for age, gender, diabetes, LVEF, eGFR, NTproBNP, and baseline galectin-3 level.

Motiwala et al (2013) examined the benefit of serial measurements of galectin-3 in determining prognosis and response to therapy in chronic heart failure. The study followed 151 individuals with left ventricular systolic dysfunction through 908 visits over 10 + 3 months. The study found serial galectin-3 measurements added incremental prognostic information and predicted left ventricular remodeling. The authors reported that in addition to baseline values, measurement at 6 months provided significantly greater prognostic information than baseline values alone. Galectin-3 concentrations were found to be independent predictors of cardiovascular events even after adjustment for clinically relevant variables. An increase in galectin-3 was associated with increased risk, whereas a decrease in the level of galectin-3 was associated with fewer events. However, heart failure therapies had no clear effect on galectin-3 levels.

Anand et al (2013) reported on a prospective study examining the roles of baseline and serial measurements of galectin-3 and prognosis of heart failure in 1650 patients participating in the Val-HeFT (Valsartan Heart Failure Trial). Higher levels of galectin-3 were associated with symptoms of more severe heart failure. Adjusted baseline galectin-3 levels were not associated with all-cause mortality or hospitalization for heart failure. However, increases in galectin-3 over time were independently associated with worse outcomes even after adjusting for all baseline variables. The authors noted that galectin-3 may identify late disease processes that are no longer responding to medical therapy. This study is limited by the population being comprised of a subset of patients enrolled in the Val-HeFT population,

unmeasured confounders, arbitrary galectin-3 cutoff value, and potential bias due to deaths occurring before the 4 and 12 month time points.

Felker et al (2012) reported on a study evaluating the association between galectin-3 and long-term clinical outcomes in ambulatory heart failure patients who were enrolled in the HF-ACTION study. Galectin-3 was assessed at baseline from stored plasma samples in a cohort of 895 HF-ACTION participants. Higher galectin-3 levels were associated with other measures of heart failure severity, including higher NYHA class, lower systolic blood pressure, higher creatinine, higher NTproBNP, and lower maximal oxygen consumption. Unadjusted analysis showed a significant association between elevated galectin-3 levels and hospitalization-free survival. However, multivariate modeling showed the prognostic impact of galectin-3 was significantly attenuated by the inclusion of other known predictors and galectin-3 was no longer a significant predictor when NT-proBNP was included.

Lopez-Andrès et al (2012) prospectively studied the relationship between galectin-3, fibrosis markers and long-term cardiovascular outcomes in patients with heart failure and other cardiac conditions. The study was conducted with a subset of the population from the Cardiac Resynchronization in Heart Failure trial (CARE-HF). Galectin-3 and 4 other biomarkers were measured at baseline, 3 months, and 18 months. There were no significant differences in the mean values of galectin-3 over time. Adjusting for age and gender, baseline galectin-3 was associated with death or hospitalization for heart failure. In a multivariate model, galectin-3 was associated with death or hospitalization for heart failure. However, this association did not remain significant when eGFR was included in the models. Cardiac resynchronization therapy (CRT) was not found to be associated with changes in galectin-3 levels.

A prospective study by de Boer et al (2011) examined the prognostic value of baseline galectin-3 levels in individuals with preserved and reduced LVEF and compared the findings with other biomarkers. This was a substudy of the COACH trial and included 592 patients (out of a total of 1023 participants) Galectin-3 levels were measured at discharge (from a hospital admission for heart failure) and again at 6 months. The primary outcome was a composite of all-cause mortality and hospitalization for heart failure. The study found galectin-3 levels had independent prognostic value even after adjusting for known risk factors associated with poor outcomes in heart failure patients, however this finding appears to be stronger in those with preserved LVEF. Serial sampling in this study did not increase the prognostic yield.

Lok et al (2013) reported on a prospective study assessing the association of galectin-3 with ventricular remodeling and long-term outcomes in individuals with severe chronic heart failure. The study population included 240 individuals from the Deventer-Alkmaar Heart Failure (DEAL-HF) study. Serial echocardiography was performed by blinded investigators at baseline and again at 3 months. Individuals who had decreased left ventricular end diastolic volume (LVEDV) over time had significantly lower levels of baseline galectin-3 compared to those with stable or increased LVEDV. Among these groups, there were no significant differences in levels of NTproBNP. Galectin-3 predicted cardiac remodeling as measured by regression of LVEDV and it remained a significant predictor of remodeling even after baseline LVEDV, gender, etiology of heart failure, NYHA class, and duration of heart failure were adjusted for. Baseline galectin-3 measurements at baseline were found to be as useful as serial measurements. In multivariate linear regression analyses, galectin-3 was positively associated

with change in LVEDV. Galectin-3 was also a significant predictor of long term mortality even after adjusting for age, gender, NTproBNP, and renal function.

Lok et al (2010) assessed the utility of baseline levels of galectin-3 as a biomarker in individuals with stable, advanced heart failure. The study population included 232 of the 240 patients from the DEAL-HF study who had baseline plasma sample volumes sufficient to measure galectin-3. Increasing quartiles of galectin-3 was associated with older age, lower eGFR, higher NTproBNP, and lower body mass index. There was a gradual increase in all-cause mortality across increasing quartiles of galectin-3 levels. Galectin-3 was also significantly associated with mortality after adjusting for age, gender, pro-BNP, and eGFR.

Gullestad et al (2012) prospectively studied the prognostic value of galectin-3 in individuals with chronic systolic HF who were participants in the CORONA study. The CORONA study population included individuals over 60 years of age with chronic heart failure of ischemic cause, NYHA classes II to IV, LVEF ≤ 40% (≤ 35% if NYHA class II), and did not require treatment with a cholesterol-lowering drug. The primary composite endpoint was cardiovascular death, nonfatal myocardial infarction (MI) or stroke. This study found baseline galectin-3 levels were significantly associated with older age, lower eGFR, higher NTproBNP, female gender, higher CRP, and use of aldosterone antagonists. In multivariable analyses, galectin-3 was significantly associated with the primary composite and all-cause, cardiovascular mortality, sudden death, and coronary events, but not with death due to worsening of heart failure or hospitalization. Adding NTproBNP to the models, galectin-3 was no longer found to be a significant predictor of any endpoint, suggesting that galectin-3 may have limited use in the determining the prognosis of elderly patients with systolic HF.

Summary
While studies suggest that there is an association between increased levels of galectin-3 and poor outcomes in individuals with heart failure, additional studies are needed to clearly define this association and determine the role of this biomarker in the clinical assessment and management of patients.

Supplemental Information

Practice Guidelines and Position Statements

The American Heart Association/American College of Cardiology (AHA/ACC) published guidelines in 2013 stating that emerging biomarkers of myocardial fibrosis, soluble ST2 and galectin-3 are predictive of hospitalization and death in patients with heart failure. These biomarkers are also additive to natriuretic peptide levels in their prognostic value. A Class IIb Evidence Level B rating was given, indicating that while the benefits of testing are equal to or greater than the risk, that efficacy and usefulness are uncertain, and studies on this technology may have conflicting results.

In 2017 the ACA/AHA Task Force on Clinical Practice Guidelines published an update: ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

"In addition to natriuretic peptides and troponins multiple other biomarkers, including those of inflammation, oxidative stress, vascular dysfunction, and myocardial and matrix remodeling, have been implicated in HF. Biomarkers of myocardial fibrosis, soluble ST2 receptor, and galectin-3 are predictive of hospitalization and death and may provide incremental prognostic value over natriuretic peptide levels in patients with HF. Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future, but multicenter studies with larger derivation and validation cohorts are needed. Several emerging biomarkers await validation with well-defined outcome measures and prognostic accuracy before they can reach the clinical arena."

Clinical Trials
A review of the clinicaltrials.gov site 2/9/21 did not identify any ongoing clinical trials that may influence this review.

Government Regulations
National/Local:

There is no national or local coverage determination on this topic.

The CMS 2023 Clinical Laboratory Fee Schedule does not list a fee for CPT code 82777. A fee is not a guarantee of coverage.

(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

- Lipoprotein-associated Phospholipase A2 (Lp-PLA2) and Secretory Type II Phospholipase A2 (sPLA2-IIA) in the Assessment of Cardiovascular Risk, Measurement of
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease
- Skin Advanced Glycation End Products (AGE) Measurement By Multi-Wavelength Fluorescent Spectroscopy
- Skin Cholesterol Testing (ie PREVU) (Retired)
- ST2 Assay for Chronic Heart Failure
- Troponin and Creatinine Kinase Isoforms (Retired)

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3. Chen YS, Gi WT, Liao TY, et al. Using the galectin-3 test to predict mortality in heart failure : a systematic review and meta-analysis. Biomark Med, 2016, Vol 10, Issue 3, pp. 329-42.
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17. Van der Velde AR et al. Prognostic value of changes in galectin-3 levels over time in patients with heart failure: Data from CORONA and COACH. Circ Heart Fail, 2013, Volume 6, pp. 219-226.
18. Yancy CW et al. Writing Committee Members. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013, Volume 128, Issue 16, pp. e240-e319.
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Heart Failure Society of America. Circulation. Aug 2017. Vol 136, Issue 6. https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000509 Accessed 1/30/23.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/30/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/13	2/19/13	3/4/13	Joint policy established
9/1/14	6/20/14	6/23/14	Routine review; rationale and references updated; added "assessment" to policy title.
7/1/16	4/19/16	4/19/16	Routine review; rationale and references updated
7/1/17	4/18/17	4/18/17	Routine review; rationale and references updated
7/1/18	4/17/18	4/17/18	Routine maintenance
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance Ref 19 added
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Vendor Managed: NA

Next Review Date: 2nd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GALECTIN-3 TESTING IN THE ASSESSMENT AND MANAGEMENT OF CHRONIC HEART FAILURE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section.
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.