KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Galectin-3 Blood Assay Test

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, *"*Galectin-3 Blood Assay Test*"* for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies for congestive heart failure (CHF).

The use of Galactin-3 for all other indications does not meet medical necessity because its clinical utility has not been established.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Heart failure (HF) is one of the most frequent and challenging medical disorders. It is a complex progressive disease with high morbidity and mortality. The prognosis of patients with HF is poor despite the advances made in the diagnosis, medical management, and device therapies. It is thus important to diagnose HF early and to identify the patients at higher risk of poor outcomes (Lok 2013, Browners 2014).

Accurate risk stratification of HF patients may help in the decision making for managing the disease; including individualizing the therapeutic approach and the proper use of invasive and costly therapies. However, risk prediction in acute, chronic, and new onset HF remains a challenge. Clinical parameters, such as advanced age, higher New York Heart Association (NYHA) functional class, reduced left ventricular ejection fraction (LVEF), lower body mass index, renal dysfunction, and anemia, have all been associated with poor outcomes in HF, but are not significant predictors of mortality. In recent years efforts were made to find biomarkers that might help in the risk stratification, and prognostication of acute and chronic heart failure. Brain natriuretic peptide (BNP) and its N-terminal part (NT-proBNP) have become well-established markers used in the diagnosis and management of HF patients. Both are released in response to myocyte stretch and provide useful information for HF diagnosis,

Back to Top

prognosis, and response to therapy. However, natriuretic peptides only indicate ventricular loading conditions and may not reveal other important mechanisms for HF. Other novel biomarkers from different physio pathological pathways such soluble ST2, growth differentiation factor-15, highly sensitive troponins, and Galectin-3, have recently emerged and are being evaluated for their potential use in adding value to the risk stratification of HF patients. For a biomarker to be useful to a clinician, it should be available, accurate, and reliable. It also should add incremental value to the clinical variables or other established markers, provide prognostic information, have an impact on patient management, and be responsive to interventions (Carrasco-Sanchez 2014, Coburn 2014, Filipe 2014, Gruson 2014, Pouleur 2014, Schmitter 4014, Srivatsan 2014).

Galectin-3 (Gal-3) is a member of a family of proteins comprising soluble β-galactoside-binding lectins that have regulatory roles in fibrogenesis, inflammation, tissue repair, and cell proliferation. It is mainly known for its role as a mediator of tumor growth, progression, and metastases. Gal-3 is also associated with increased age, diabetes, nephropathy, and fibrotic conditions such as liver fibrosis, renal fibrosis, idiopathic lung fibrosis, and chronic pancreatitis. Recently, it has been suggested that Gal-3 may play a role in the pathophysiology of HF through promotion of inflammation, myocardial fibrosis and myocardial remodeling, which are key processes for the development and progression of HF. It was thus suggested that an increased Gal-3 level in the circulation may reflect active and excessive myocardial fibrogenesis in patients with HF and can thus be used as a marker for poor prognosis related to excessive and potential irreversible myocardial fibrosis (Lok 2010, Gullestad 2013, Carrasco-Sanchez 2013, Suarez 2014).

GAL-3 is measured in the circulation by manual or automated assays. The enzyme linked immunosorbent assay manual assay (ELISA) is the most frequently used method in the published studies. Manual assays are, however, laborious and take considerable time for sampling, handling, incubation, and washing steps. More recently, several automated assays with faster delivery of the results, have been developed and are commercially available. A number of manual and automated assays have received FDA approval for measuring circulating Gal-3. Others are still seeking approval. The ARCHITECT Galectin-3 assay, BGM Galectin -3TM are among those approved by the FDA to be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure.

Galectin-3 testing in HF patients has not been previously reviewed by MTAC. It is being reviewed for its use as a prognostic marker in patients with heart failure based on requests from contracted providers for its coverage.

Medical Technology Assessment Committee (MTAC)

Galectin-3 Blood Assay Test

02/09/2015: MTAC REVIEW

Evidence Conclusion: 1. Prognostic value of galectin-3 in patients with acute or chronic heart failure: The published studies on the prognostic value of Gal-3 in patients with HF are mainly secondary studies analyzing data from existing databases for RCTs examining the effect of drug therapy or other interventions on outcomes of patients with HF. In these studies, blood samples were obtained once at baseline and the plasma was stored for years at temperatures below 70o-80oC. Baseline plasma Gal-3 levels were then correlated with the incidence of CVD, HF, rehospitalization, and mortality during follow-up. The results were not validated in external cohorts and could be related to specific characteristics of the patients studied, or other unmeasured cofounders. There are several other issues with these kinds of analyses that would limit generalization of their results. Retrospective analyses may only suggest correlation and not causality; blood samples were obtained only once in the majority of studies, with no serial measurements of Gal-3 and thus cannot determine whether it varies by time and the effects of this variation if any, the plasma samples were frozen, and it is unknown if Gal-3 would degrade over the years. In addition, a number of these studies used arbitrary cutoff levels for Gal-3 to categorize patients into subgroups in order to test for interactions and associations. It was also questioned whether the detection of Gal-3 in the circulation accurately reflects activity in the tissues. The ideal study for evaluating the prognostic value of a novel biomarker would be a prospective study with long-term follow-up that examines the additive or incremental value of the new biomarker on top of existing established prognostic markers or clinical variables. The results should then be externally validated in other patient populations. In general, the analyses of the published studies suggest that the plasma concentration of Gal-3 is high in patients with HF. There is insufficient evidence however, to determine that the high plasma level of Gal-3 in these patients is an independent prognostic marker for poorer outcomes. The results of the published analyses are conflicting; some suggest that after adjusting for many clinical variables including NT-proBNP, elevated Gal-3 levels may be associated with higher rates of all-cause mortality, CV events and /or rehospitalization in patients with heart failure. Other analyses, on the other hand, show that after adjusting for similar or additional clinical variables including NT-proBNP, Gal-3 is not a significant independent prognostic marker for any of the outcomes studied (Table 3 shows the differences in the variables adjusted for). There were variations between the studies in their inclusion criteria, patient characteristics, cause,

 Back to Top

type, severity, duration, and therapies used for managing the heart failure. There were also differences in population sizes, duration of follow-up, number of covariables used in the multivariate analyses, and the cutoff for Gal-3, which was mainly arbitrarily selected. Studies that showed a significant association between Gal-3 and outcomes tended to be smaller studies that adjusted for less clinical variables in their analyses. The two largest studies HF-ACTION (Felker et al, l 2012) and CORONA (Gullestad et al, 2014) showed that Gal-3 was significantly associated with the risk of primary outcomes studies in the univariate analyses performed, but the association observed was no longer significant when series of multivariable models including NT-proBNP were performed. Chen and colleagues (2015) performed a meta-analysis of 11 studies with 8,419 participants (Evidence table 1) to assess the association between Gal-3 and adverse outcomes in HF patients. The pooled results of the analysis suggest that increased serum Gal-3 was associated with higher all-cause mortality or CV mortality after adjusting for other established factors. These results, however, have to be interpreted with caution due to several limitations. The meta-analysis pooled the results of studies including patients with acute or chronic, and with systolic or diastolic heart failure, and conducted among different patient populations. Two of the 11 studies included in the analysis were performed by the same principal authors among the same group of patients. There was significant heterogeneity between the studies as well as significant publication bias. The population sizes varied between the included studies from 240 to 1,440 patients, and the follow-up duration ranged between 1 and 8.7 years. There were also differences between the studies in the cutoff values for Gal-3 and the variables adjusted for in calculating the hazard ratios (table 3). Meijers et al's (2014) pooled analysis (Evidence table 2) of three clinical trials showed that patients with elevated Gal-3 (>17.8 ng/mL) were more likely to be re-hospitalized for HR at 30, 60, 90, and 120 days after discharge. Gal-3 was found to be an independent predictor for re-hospitalization after adjusting for age, gender, NYHA class, renal function, LVEF, and BNP. Addition of Gal-3 to the clinical risk model comprising these variables significantly improved the net risk classification of patients for postdischarge rehospitalization and fatal events at each time point. The pooled analysis had its limitations and its results should be interpreted with caution.

2. Incremental value of galectin-3: The most commonly used way to evaluate the ability of a prognostic HF biomarker in predicting an event is to assess the area under the Receiver Operator Curve (AUC) which is a balance of sensitivity and specificity of the test or tool, and to compare it with a gold standard (C-statistics). However, a small but statically significant difference between the AUC for the gold standard and biomarker studied, may be clinically irrelevant, and there is no generally agreed upon clinically improvement in the C-statistics (Januzzi 2014). Area under Receiver Operator Curve (AUC) for Gal-3, NT-proBNP, and combinations

Author/ Study	N of patients	Outcome	AUC						
			Clinical model	Ref. † model	Gal-3	NT-proBNP Or BNP	Clinical or Reference model +Gal-3	Clinical model +BNP	Gal-3 +BNP
Zhang et al, 2015	1,440	All-cause death		0.82	0.71	0.79	0.83		0.81
		CV death		0.83			0.83		
Ahmad et al 2014/ HF-ACTION	813	Pump failure	0.82		0.76	0.83	0.83	0.87	
		SCD	0.68		0.66	0.67	0.71	0.73	
De Boer et al, 2010/COACH	592	Death or HF hospitalization			0.67	0.65 (BNP)			0.69
Lok, et al, 2010/ DEAL-HF* 2013	232	All-cause mortality			0.612	0.611			
	209				0.68	0.63			0.69
Van Kimmenade 2006**	599	Mortality			0.74	0.67			

†Reference model included sex, age, DM, ischemic HD, SBP, NYHA functional class, LVEF, ARB/ACE I, B-blocker, hemoglobin, sodium, and NT-proBNP.

*Patients with high baseline levels of both markers were observed to have approximately 1.5-2-fold higher mortality rate compared to those in other categories.

** The combination of an elevated galectin-3 with NT-proBNP was a better predictor of mortality than either of the 2 markers alone.

Back to Top

oCutoff values for Gal-3 were: 22.4 for in-hospital death in Zhang et al's study (sensitivity =0.69 and specificity =0.62), 13.9 ng/mL in HF-ACTION, and 18.05 ng/mL in DEAL-HF
oCutoff values for NT-proBNP were: 2,472 pg/mL in Zhang et al's study, and 852 pg/mL in HF-ACTION.
Accuracy of Gal-3 in the diagnosis of HF was studied in a small study with N= 35 patients with HF and 43 controls (Sheng et al, 2014) showing the following results:

	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %	AUC
Gal-3	94.3	65.1	78.2	68.8	93.3	0.891
NT-proBNP	77.1	90.7	84.6	87.1	83.0	0.896

At a cutoff of 17.8 ng/mL for Gal-3 and 100 pg/mL for NT-proBNP

90.7 84.6 87.1
83.0 0.896

3. Clinical utility of Galectin-3: The literature search did not identify any randomized controlled trial that examined the use of Gal-3 as a target in HF therapy, or that evaluated its impact on selecting a management strategy for patients with HF. Published studies on the disruption of galectin-3 gene to block myofibroblast activation are experimental, with the hypothesis that direct inhibition of Gal-3 may be possible by N-acetyle-seryl-aspartyl-lysyl-proline (Ac-SDKP), a naturally occurring tetrapeptide that prevents and reverses inflammation and collagen deposition in heart after hypertension or myocardial infarction (Hrynchyshyn 2013). Studies on anti-galectin-3 therapy for heart failure are ongoing. The effect of measuring the concentration of circulating Gal-3 on patient management was indirectly examined in post hoc analyses of data obtained from RCTs evaluating different therapies for HF; rosuvastatin in the CORONA study and valsartan in the Val-HeFT.
The CORONA study (Kjekshus et al, 2007) aimed at examining the beneficial effects of rosuvastatin among patients with chronic, symptomatic, systolic, ischemic heart failure. The trial randomized 5,011 patients over the age of 60 years, with chronic ischemic heart failure to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. After a median follow-up of 32.8 months the results of the trial showed that rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in these older patients with systolic heart failure but reduced the number of cardiovascular hospitalizations. In a post hoc analysis of CORONA study, Gullestad and colleagues (2012) investigated whether plasma Gal-3 can identify patients with chronic HF for whom statins are effective. Of the 5,011 patients enrolled in the CORONA study, 1,462 (29%) patients had baseline plasma specimens available for measuring Gal-3. These were obtained from nonfasting blood samples obtained at baseline and stored at -80oC. There were significant baseline differences between this subset of patients and the entire CORONA participants. For this secondary analysis, the investigators categorized patients into two groups based on the median Gal-3 baseline level (19.0 ng/mL) and found that after a median follow-up of 32.8 months, patients with Gal-3 below the median level who were assigned to rosuvastatin had significantly lower primary event rate, lower total mortality, and lower rates for the composite outcome of all-cause mortality and HF hospitalization, compared to placebo. No benefits were observed for patients with Gal-3 above the median level. The authors noted that the combination of Gal-3 and NT-proBNP (at cutoff of 102.7 pmol/L) identified patients with a large benefit from rosuvastatin treatment. Val-HeFT trial (Cohn et al, 2001) was a randomized placebo-controlled trial that enrolled 5,010 patients >18 years of age with symptomatic HF to evaluate the efficacy of valsartan. Blood was sampled, and the separated plasma was stored at -70oC. The primary outcomes of Val-HeFT were all-cause mortality and the first morbid event (defined as death, sudden death with resuscitation, hospitalization for HF, or the administration of intravenous inotropic drug or vasodilator for four or more hours without hospitalization). The results of the trial showed that after a median follow-up duration of 23 months, valsartan had no effect on mortality, but reduced the first morbid event by13% and hospitalization for HF by 28%. These 3 endpoints were analyzed in the Galectin-3 substudy by Anand and colleagues (2013). This post hoc analysis of Val-HeFT trial examined whether circulating Gal-3 levels can predict the response to valsartan. Baseline samples for measuring Gal-3 were available for 1,650 patients (~30% of the participants). The overall results of this secondary analysis indicate that the use of valsartan was not associated with a beneficial effect on any outcome in this subgroup of patients with available baseline Gal-3 measurements. The authors then arbitrarily categorized patients into two groups based on the median level of Gal-3 (16.2 ng/mL) and found that valsartan treatment was associated with a significant decrease in hospitalization only among patients with Gal-3 below the median level and not for those with levels above the median. This is a posthoc analysis with several limitations and does not directly examine the impact of measuring Gal-3 levels on patient management, and/or treatment outcomes. The results of these post hoc analyses should be interpreted with caution due to several limitations. The studies did not directly examine the impact of

 Back to Top

measuring Gal-3 levels on patient management, and/or treatment outcomes. They were secondary analyses that included less than one third of the population in each of the two trials, there were some significant baseline differences between the patients with Gal-3 measurements and the entire participants in each of the studies, Gal-3 was measured from specimens obtained at baseline and stored for years, and the results of the trials did not show any significant effect of either drug used (rosuvastatin or valsartan) on the primary outcomes studied. *Conclusions:* There is insufficient evidence from longitudinal studies with long-term follow-up and serial measurements of Gal-3 to determine that elevated circulating Gal-3 levels are independent prognostic markers for poor outcomes in patients with HF. There is insufficient evidence to determine that Gal-3 adds clinically significant incremental value to established markers and clinical variables. There is insufficient evidence to determine that circulating Gal-3 has an impact on management decisions made for patients with HF.
Articles: The literature search revealed over 200 articles on Galectin-3 and heart failure. The great majority were unrelated to the current review. There were several published studies on the prognostic value of Gal-3 in patients with heart failure. These were mainly secondary analyses of data or subsets of data collected for patients enrolled in large cohort studies or randomized controlled trials that investigated different other therapies or interventions. The search also identified a pooled analysis of the results of 3 trials (Meijers 2014), and a more recent meta-analysis (Chen et al, 2015) that pooled the results of 11 studies. The literature search did not identify any RCT that directly studied the impact of using the plasma levels Gal-3 on the management of patients with HF. The two meta-analyses were selected for critical appraisal (Evidence tables 1 & 2). The characteristics of the studies included in the larger meta-analysis as well as selected studies published in the last 5 years and not included in the meta-analyses were reviewed and summarized in Evidence Table 3. Chen A, Hou W, Zhang Y et al. Prognostic value of serum galectin-3 in patients with heart failure: a meta-analysis. Int J Cardiol 2015; 182:168-170. See Evidence Table 1. Meijers WC, Januzzi JL, de Filippi C, et al. Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: a pooled analysis of 3 clinical trials. Am Heart J. 2014 Jun;167(6):853-60.e4.See Evidence Table 2.

The use of Galectin-3 Blood Assay Test does not meet the Kaiser Permanente *Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
82777	Galectin-3

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
03/03/2015	03/03/2015[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC]	08/04/2015

[MPC] Medical Policy Committee

Revision History	Description
08/04/2015	Addendum: Insufficient Evidence for all other indications Addendum: Congestive Heart Failure (CHF) as an indication

Back to Top