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Corporate Medical Policy

Cardiac Biomarkers for Myocardial Infarction AHS – G2150

File Name:	cardiac_biomarkers_for_myocardial_infarction
Origination:	01/2019
Last CAP Review:	04/2021
Next CAP Review:	04/2022
Last Review:	04/2021

Description of Procedure or Service

Cardiac biomarkers are the biochemical markers released in blood from the injured myocardial tissue. They become elevated in blood after a certain period and can be measured. The examples of cardiac biomarkers commonly used in clinical setting include Troponin and Creatine Kinase MB isoenzyme (CKMB) (Thygesen, Alpert, & White, 2007).

Related Policies
Cardiovascular Disease Risk Assessment AHS – G2050

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for cardiac biomarkers for myocardial infarction when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Cardiac Biomarkers For Myocardial Infaction is covered

Reimbursement is allowed for measurement of cardiac troponin (troponin T or I) for the diagnosis of myocardial infarction (MI) in all patients presenting with signs and symptoms of acute coronary syndrome* (please see Note 1)

When Cardiac Biomarkers For Myocardial Infaction is not covered

1. Reimbursement is not allowed for measurement of the following cardiac biomarkers for the diagnosis and/or prognosis of MI in patients presenting with signs and symptoms of acute coronary syndrome*:

    a) Aspartate aminotransferase (AST/SGOT)
    b) Cardiac creatine kinase isoenzyme MB (CKMB)
    c) Creatine kinase (CK)
    d) Creatine kinase Isoenzymes
    e) Lactate Dehydrogenase (LD, LDH)

f) Myoglobin

2. Reimbursement is not allowed for measurement of cardiac biomarkers in patients presenting with signs and symptoms of acute coronary syndrome* in an outpatient setting which is not capable of performing adequate clinical MI evaluation (eg. independent lab or physician's office).

3. Reimbursement is not allowed for measurement of the following cardiac biomarkers for the diagnosis and/or prognosis of MI in patients presenting with signs and symptoms of acute coronary syndrome*:
   a) Copeptin
   b) Troponin C
   c) C-reactive protein
   d) Heart-type fatty acid binding protein (H-FABP)
   e) any other cardiac biomarkers not listed above

*Note 1:
Acute Coronary Syndrome/Myocardial Infarction Common Signs and Symptoms (Reeder, 2020):

Ischemic chest pain with radiation to an upper extremity, radiation to both arms, and pain associated with diaphoresis or with nausea and vomiting.

Squeezing, tightness, pressure, constriction, crushing, strangling, burning, heartburn, fullness in the chest, band-like sensation, knot in the center of the chest, lump in throat, ache, heavy weight on chest and toothache (when there is radiation to the lower jaw).

Ischemic pain often radiates to other parts of the body including the upper abdomen (epigastrium), shoulders, arms (upper and forearm), wrist, fingers, neck and throat, lower jaw and teeth (but not upper jaw), and not infrequently to the back (specifically the interscapular region).

Shortness of breath, belching, nausea, indigestion, vomiting, diaphoresis, dizziness, lightheadedness, clamminess, and fatigue.

Atypical Signs and Symptoms (Reeder, 2020):

Dyspnea alone, weakness, nausea and/or vomiting, epigastric pain or discomfort, palpitations, syncope, or cardiac arrest.

Reimbursement Limitations:
Maximum of 4 serial troponin tests will be reimbursed (eg. Repeat troponin measurements) in the first 24-72 hours after presentation.

Policy Guidelines

Background

Acute coronary syndromes (ACS) represent continuous events starting with angina, reversible injury, progressing to unstable angina, are frequently associated with minor myocardial damage, and myocardial infarction (MI) that results in extensive tissue necrosis (Thygesen et al., 2007). Patients with ACS usually present with chest pain and associated signs and symptoms. These patients are subdivided into two major categories based on the 12-lead electrocardiogram (ECG). If an ST-segment elevation is observed on the ECG, it is indicative of acute ST-elevation myocardial infarction (STEMI) type of ACS. If the ECG shows ST-segment depression, T-wave changes, or no ECG abnormalities, it is indicative of non-ST elevation myocardial infarction (NSTEMI) and unstable angina. ACS are complex. However, the most common cause is

atherosclerotic coronary artery disease with rupture of atherosclerotic plaque (Amsterdam et al., 2014). The first documented definition of acute MI was established in 1979 by the World Health Organization (WHO). It included in the criteria for MI diagnosis the recommendation to use the rise or fall patterns of cardiac biomarkers, such as creatine kinase (CK), creatine kinase's MB isoenzyme (CK-MB), lactate dehydrogenase (LDH) or aspartate aminotransferase (AST) activities (WHO, 1979). Since then, other societies have proposed their own criteria for diagnosis. The third universal definition of MI includes typical clinical symptoms, suggestive ECG changes, or imaging evidence of new loss of viable myocardium or new regional wall abnormality with a rise and/or fall of cardiac biomarkers (Thygesen et al., 2012). Nonetheless, the universal criteria are being refined by cardiovascular societies and will likely change with scientific progress and better understanding of MI pathophysiology.

Myocardial infarction results in cardiac injury and extensive tissue necrosis. The cellular membranes become compromised and release structural proteins and other macromolecules into cardiac interstitial, called cardiac biomarkers. The levels of these cardiac biomarkers in blood will rise and fall with time after MI (Thygesen et al., 2007). The first cardiac biomarker, aspartate aminotransferase (AST), was used for MI diagnosis in 1954. AST is present in human tissues as two isoenzymes: cytoplasmic and mitochondrial. AST is a non-specific biomarker and its activity could also be elevated in other conditions such as hepatic congestion secondary to congestive heart failure. Since then, other cardiac biomarkers were used as an aid in diagnosis of MI, but due to their non-specificity and other reasons, many of them are no longer used in clinical practice or their use remains very limited (Danese & Montagnana, 2016). The most common cardiac biomarkers and their characteristics are well summarized in the table from Danese & Montagnana, 2016:

Table 1 Characteristics of AMI biomarkers

Biomarker	First assay development, year	Molecular weight, Da	Kinetics			Sensitivity for myocyte necrosis	Specificity for myocyte necrosis
			First detection, hours	Maximum value, hours	Return to normal values, days		
AST	1954	105,000	3–4	15–28	5	++	+
LDH	1955	140,000	5–10	60–144	12	++	+
CK total enzyme activity	1960	83,000	3–9	10–20	3	++	+
CK-MB activity	1972	83,000	3–8	10–20	3	++	++
Myoglobin	1978	17,800	1–3	4–7	1–1.5	+++	+
CK-MB mass	1985	83,000	3–12	12–18	2–3	+++	+++
cTnI	1987	23,900	3–7	10–20	10	++++	++++
cTnT	1989	37,000	3–8	15–120	14	++++	++++

AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; cTnI, cardiac troponin I; cTnT, cardiac troponin T.

Proprietary tests for various biomarkers are available in several clinical settings. Platforms including Roche's "CARDIAC Trop T Sensitive test" and Responsebio's battery of cardiac tests emphasize their speed (on the scale of minutes) and versatility (ResponseBio, 2020; Roche, 2020).

Lactate Dehydrogenase (LDH, also known as LD)

Lactate dehydrogenase is a cytoplasmic enzyme present in many different tissues, such as skeletal muscle, liver, heart, kidney, and red blood cells. Five isoenzymes have been identified by gel electrophoresis and other techniques (Marshall, Williams, & Williams, 1991). The heart isoenzymes, LD1 and LD2, have activity increases in blood five to ten hours after MI symptoms onset and remains elevated for up to ten days (Danese & Montagnana, 2016). LD has poor

specificity for cardiac tissue and is generally not recommended as a biomarker for the diagnosis of MI (Amsterdam et al., 2014; Jaffe & Morrow, 2019).

Myoglobin

Myoglobin is an oxygen-binding, cytoplasmic, heme protein. It is one of the first cardiac biomarkers measurable in the serum that appears between one and three hours after MI symptoms onset. Myoglobin is present in skeletal and cardiac muscles and is cleared by the kidneys (Vaidya, 1994). Its clinical utility is limited by its poor specificity. The main reason of using myoglobin in a clinical setting was its sensitivity for MI (Danese & Montagnana, 2016); but with appearance of sensitive troponin assays, myoglobin use offers little advantage for the diagnosis of MI (Eggers, Oldgren, Nordenskjold, & Lindahl, 2004; Kavsak et al., 2007). Currently, there are no recommendations for myoglobin to be used in the diagnosis of MI (Amsterdam et al., 2014), and its use as cardiac biomarker is discouraged (Jaffe & Morrow, 2017).

Creatine Kinase (CK) Isoenzymes and Isoform MB (CKMB)

The cytosolic enzyme creatine kinase (CK), formerly known as creatine phosphokinase (Danese & Montagnana, 2016), is present as three cytosolic isoenzymes and one mitochondrial isoenzyme. These isoenzymes are dimers of M (muscle) and B (brain) chains that exist in three combinations: MM, MB and BB (Bessman & Carpenter, 1985). The CKMM is predominant in both heart and skeletal muscle, but CKMB is more specific for the myocardium. The total CK activity could be detected in blood 3-9 hours after MI, but it reaches the maximum levels in blood in 10-20 hours and returns to normal in about 72 hours (Penttila, Penttila, & Rantanen, 2000). The measurement of total CK activity is not specific to MI because it also increases in liver, biliary tract, kidneys, and skeletal muscle disease, and its measurement is problematic in older individuals with lower muscle mass (Dillon et al., 1982; Heller, Blaustein, & Wei, 1983; Yusuf et al., 1987). CKMB mass (CKMB protein concentration measurements) was once the cardiac biomarker of the choice that replaced CK, CKMB activity, AST, and LDH (Danese & Montagnana, 2016). However, with arrival of cardiac troponin assays, the use of CKMB became less popular. Some clinicians advocate for the use of CKMB for diagnosis and prognosis of MI, but cardiac troponins have shown either equally reliable or superior results compared to CKMB; consequently, troponin is the recommended test for MI diagnosis now (Amsterdam et al., 2014; Jaffe & Morrow, 2017).

Troponins

The regulatory protein troponin in the troponin complex is composed of three isoforms. Troponin C (TnC) is responsible for calcium binding and has no role to play as a cardiac biomarker. Troponin I (TnI) and Troponin T (TnT) are responsible for inhibition of ATPase activity and tropomyosin binding, respectively (Greaser & Gergely, 1971). Contrary to all previously used cardiac biomarkers, cardiac troponins have high specificity for cardiac tissue. The cardiac troponins have a specific pattern of expression because they have different amino sequences encoded by different genes for skeletal and cardiac muscles. Cardiac TnI has an additional 31-amino acid residue compared to skeletal muscle. This protein is not expressed in normal, regenerating, or diseased skeletal muscle from human or animal origin (Bodor, Porterfield, Voss, Smith, & Apple, 1995). Cardiac TnT has an additional 11-amino acid residue, but this protein was also found in regenerating rat skeletal muscle, during human fetal development, and in diseased human skeletal muscle (Anderson, Malouf, Oakeley, Pagani, & Allen, 1991; Bodor et al., 1997; Saggin, Gorza, Ausoni, & Schiaffino, 1990). In addition, cardiac TnT was also found in skeletal muscle specimens from patients with muscular dystrophy, polymyositis, and chronic renal disease (Bodor et al., 1997; McLaurin, Apple, Voss, Herzog, & Sharkey, 1997).

Neumann et al evaluated high-sensitivity troponin (troponin I and T)'s ability to predict myocardial infarction and subsequent 30-day outcomes. The authors developed a risk assessment tool based on patients presenting to the emergency department with "symptoms suggestive of myocardial infarction". Concentrations of troponin I or T were measured at presentation and after

early or late serial sampling. Cutoffs were then determined to create cutoffs for risk assessment. Among the 22651 patients (9604 in derivation cohort, 13047 in validation cohort), the total prevalence of myocardial infarction was 15.3%. The authors found that "lower high-sensitivity troponin concentrations at presentation and smaller absolute changes during serial sampling were associated with a lower likelihood of myocardial infarction and a lower short-term risk of cardiovascular events" (Neumann et al., 2019).

Anand et al evaluated the adoption rate of the universal definition of myocardial infarction and the corresponding recommendations. 1902 medical centers over 23 countries were surveyed, and the authors obtained answers regarding the primary biomarker, diagnostic thresholds, and clinical pathways used to identify myocardial infarction. The authors found that cardiac troponin was the primary biomarker used at 96% of surveyed sites, with 41% of these sites using high-sensitivity troponins. The sites using high-sensitivity assays were also more likely to use serial sampling (91% vs 78% using "contemporary" sensitivity troponin) and the 99% percentile diagnostic threshold (74% vs 66%). Use of creatine kinase-MB (CKMB) was "very limited" outside of Latin America (Anand, Shah, Beshiri, Jaffe, & Mills, 2019).

In addition, other cardiac biomarkers, such as heart-type fatty acid binding protein (H-FABP) and copeptin, have been reported in the scientific literature. However, they are not commonly used in clinical settings (Jaffe & Morrow, 2017).

Heart-type fatty acid binding protein (H-FABP)

H-FABP, a small cytoplasmic protein present in cardiomyocytes, is believed to have a function in myocardial lipid homeostasis (Glatz & van der Vusse, 1990). Because of its small size, this protein appears in the blood after MI almost as early as myoglobin, but it has better specificity than myoglobin for cardiac tissue (Van Nieuwenhoven et al., 1995). Seino et al compared the use of H-FABP with rapid troponin in 371 patients with acute chest pain (Seino et al., 2003). Their study demonstrated that H-FABP had significantly higher sensitivity (89%) than troponin T (22%) and myoglobin (38%), but it has lower specificity (52%) than troponin (94%). Other studies were performed to compare H-FABP to troponins; however, they were unable to demonstrate superior results compared to troponins. H-FABP is not encouraged for assessment of MI as troponins are generally superior (Jaffe & Morrow, 2017).

Copeptin

Copeptin is the 39 amino acid C-terminal fragment cleaved from pro-arginine vasopressin (AVP). After MI, copeptin levels increase rapidly and decline over the next two to five days (Khan et al., 2007). In the Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction (CHOPIN) 16-site study involving 1,967 patients presenting within 6 hours of pain onset, copeptin was shown to have a potential value in ruling out MI with a negative predictive value greater than 99% when combined with TnI measurements (Maisel et al., 2013). The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) multicenter study, involving 1,439 patients presenting with MI symptoms, demonstrated no benefit in using copeptin as a an early rule-out cardiac biomarker for MI (Hillinger et al., 2015). Copeptin is not encouraged for assessment of MI as troponins are generally superior (Jaffe & Morrow, 2017).

Guidelines and Recommendations

2018 ESC/ACC/AHA/WHF Fourth Universal Definition of Myocardial Infarction (Jaffe et al., 2018)

Both cTnI and cTnT are recommended for evaluation of myocardial injury, and high-sensitivity cTn assays are recommended for routine clinical use. An acute MI is designated when a rising/falling pattern is seen with cTn levels and if there is at least one measurement greater than the 99th percentile of the upper reference limit (URL) (Jaffe et al., 2018).

CKMB is considered less sensitive and specific than either troponin. However, in the absence of a cTn assay, CK-MB is considered the best alternative. A measurement of CK-MB above the 99th percentile of the URL should be "designated as the decision level for the diagnosis of MI". Sex-specific CK-MB values should be used (Jaffe et al., 2018).

In the 2019 AHA guideline discussing the "Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease [MINOCA]", the AHA notes that the diagnostic criteria of MINOCA follows the "Fourth Universal Definition of Myocardial Infarction" above, specifically the rise or fall of cardiac troponin levels with at least one value above the 99th percentile of the reference limit. The guideline considers this definition "fundamental" to identifying and defining MINOCA (Tamis-Holland Jacqueline et al., 2019).

2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes (NSTE-ACS) (Amsterdam et al., 2014)

The American College of Cardiology (ACC) and the American Heart Association (AHA) have developed clinical practice guidelines to provide recommendations applicable to patients with or at risk of developing cardiovascular disease and to provide guidance to clinicians on optimal management of patients with NSTE-ACS. In their comprehensive document, the AHA/ACC panel has provided recommendations for initial evaluation and management of patients presenting with ACS symptoms, for the early hospital care, myocardial revascularization, late hospital care, hospital discharge and posthospital discharge care, special patient groups and quality of care and outcomes for ACS. The Task Force recommended to stratify patients with suspected ACS based on the likelihood of ACS and those with high-risk features should be referred immediately to the emergency department (ED). They have provided specific recommendations for the use of cardiac biomarkers in the diagnosis and prognosis of MI. They specifically recommended using troponin (troponin I or T when contemporary assay is used) for the diagnosis of MI. According to AHA/ACC guidelines, the cardiac troponin is recommended and should be measured at presentation and 3 to 6 hours after symptom onset in all patients who present with ACS symptoms. The panelists recommended identifying rising and/or falling pattern of troponin. In addition, they recommended measuring troponin levels beyond 6 hours after symptom onset in patients with normal troponins on serial examination when ECG changes and/or clinical presentation suggests ACS. If the onset of symptoms is not clearly identified, they recommended using the time of presentation as the time of onset for measuring troponin. The AHA/ACC guideline clearly highlighted that CKMB or myoglobin should not be used for the diagnosis of ACS. All recommendations for the use of cardiac biomarkers in the diagnosis of MI were level A evidence.

The AHA/ACC guideline considered all recommendations in the use of cardiac biomarkers for ACS prognosis as level of evidence B. They considered the presence and magnitude of troponin elevations useful for short and long-term prognosis. The re-measurement of troponin once on day 3 or day 4 in patients with MI was considered reasonable to estimate the infarct size and dynamics of necrosis. Finally, they considered the use of B-type natriuretic peptide to be reasonable for additional prognostic information.

The recommendations for the use of cardiac biomarkers in the diagnosis and prognosis of MI was well summarized in Table from 2014 AHA/ACC guidelines p.2655 (Amsterdam et al, 2014):

TABLE 5 Summary of Recommendations for Cardiac Biomarkers and the Universal Definition of MI

Recommendations	COR	LOE
Diagnosis		
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values	I	A
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A
Prognosis		
Troponin elevations are useful for short- and long-term prognosis	I	B
Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis	IIb	B
BNP may be reasonable for additional prognostic information	IIb	B

ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; CK-MB, creatine kinase myocardial isoenzyme; COR, Class of Recommendation; LOE, Level of Evidence; and MI, myocardial infarction.

2013 (published 2014) Society for Cardiovascular Angiography and Interventions (SCAI) (Moussa et al., 2013)

In their expert consensus document titled Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization, the SCAI expert panel introduced a new definition of clinically relevant MI after coronary revascularization percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). In their definition of clinically relevant MI after both PCI and CABG procedures, authors gave recommendations according to 3 different types of clinical presentation. In the first case, when patient has a normal CKMB baseline: "The peak CK-MB measured within 48 hours of the procedure rises to >10x the local laboratory ULN, or to >5x ULN with new pathologic Q-waves in >2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to >70x the local laboratory ULN, or >35x ULN with new pathologic Q-waves in >2 contiguous leads or new persistent LBBB". In case when patients have elevated baseline CKMB (or cTn) with stable of falling biomarkers levels, they issued the following recommendation: "The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level". And, in patients with elevated CKMB (or cTn), but without stable or falling biomarkers level, the recommendation was: "The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension". The authors have expressed preference to use CKMB instead of cTn, but they have included cTn in their definition if CKMB was not available.

2015 AHA Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (O'Connor et al, 2015)

In their review of previously issued guidelines, the expert panel introduced new recommendations for diagnostic interventions in ACS regarding cardiac biomarkers. They still recommended to use Troponin in following situations: "We recommend against using hs-cTnT and cTnI alone measured at 0 and 2 hours (without performing clinical risk stratification) to identify patients at low risk for ACS (Class III: Harm, LOE B-NR). We recommend that hs-cTnI measurements that are less than the 99th percentile, measured at 0 and 2 hours, may be used together with low-risk stratification (TIMI score of 0 or 1 or low risk per Vancouver rule) to predict a less than 1% chance of 30-day MACE (Class IIa, LOE B-NR). We recommend that negative cTnI or cTnT measurements at 0 and between 3 and 6 hours may be used together with very low-risk stratification (TIMI score of 0, low-risk score per Vancouver rule, North American Chest Pain score of 0 and age less than 50 years, or low-risk HEART score) to predict a less than 1% chance of 30-day MACE (Class IIa, LOE B-NR)". They did not express a preference in cardiac biomarkers to use, nor did they gave any recommendations regarding CKMB (O'Connor Robert et al., 2015).

European Society of Cardiology (ESC)

The ESC notes measurement of cardiac troponins as "mandatory" in all patients with suspected non-ST-elevation acute coronary syndromes. The guidelines assert that cardiac troponins are more sensitive and specific biomarkers of cardiomyocyte injury than CK, CKMB, and myoglobin. However, if troponin measurement is not possible, measurement of copeptin is recommended.

The ESC also acknowledges the natriuretic peptides (B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide and midregional pro-A-type natriuretic peptide) as providing useful prognostic information along with the troponins. The ESC mentions other biomarkers such as midregional pro-adrenomedullin, growth differentiation factor 15 and copeptin, but they cannot recommend them at this time as their added value in risk assessment seems "marginal" (Gencer et al., 2016).

The 2019 ESC guidelines focusing on chronic coronary syndromes states that for "clinical suspicion of coronary artery disease instability…management should follow the Guidelines for ACS without persistent ST-segment elevation", which is discussed above (Knuuti et al., 2019).

ACC/AATS/AHA/ASE/ASNC/SCAI/ SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes Guidelines (Patel et al., 2016)

In 2016 The American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Thoracic Surgeons (STS), and American Association for Thoracic Surgery (AATS), along with key specialty and subspecialty societies created an Appropriate Use Task Force with the mission to revise the appropriate use criteria (AUC) for coronary revascularization. They have used clinical scenarios to mimic patient presentations seen in everyday clinical practice and included information on symptom status, presence of clinical instability or ongoing ischemic symptoms and other characteristics. They follow 2014 AHA/ACC recommendations for the use of cardiac biomarkers (Amsterdam et al., 2014).

2017 International Liaison Committee on Resuscitation (ILCOR) Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations Summary (Olasveengen et al., 2017).

No recommendations were given regarding the use of cardiac markers.

American Society for Clinical Pathology (ASCP, 2015)

The ASCP recommends against testing CK-MB or myoglobin to diagnose an acute myocardial infarction. Instead, they recommend testing either troponin I or T. They also assert that both troponins are specific to cardiac injury and that there is much support for relying solely on troponin (ASCP, 2015).

National Institute for Health and Care Excellence (NICE, 2016)

NICE recommends diagnosis of MI using the "detection of rise and/or fall of cardiac biomarkers values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

- symptoms of ischaemia
- new or presumed new significant ST-segment-T wave (ST-T) chanages or new left bundle branch block (LBBB)
- development of pathological Q waves in the ECG
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- identification of an intracoronary thrombus by angiography (NICE, 2016)"

Applicable Federal Regulations

There is a multitude of FDA-approved cardiac biomarkers tests for Troponin and CKMB currently available in high and moderate complexity formats. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 82550, 82552, 82553, 82554, 82725, 83615, 83625, 83874, 84450, 84484, 84512, 84588, 86140, 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Specialty Matched Consultant Advisory Panel review 4/2020

Medical Director review 4/2020

Amsterdam, E. A., Wenger, N. K., Brindis, R. G., Casey, D. E., Ganiats, T. G., Holmes, D. R., . . . Zieman, S. J. (2014). 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 130*(25), e344-e426. doi:10.1161/cir.0000000000000134

Anand, A., Shah, A. S. V., Beshiri, A., Jaffe, A. S., & Mills, N. L. (2019). Global Adoption of High-Sensitivity Cardiac Troponins and the Universal Definition of Myocardial Infarction. *Clin Chem, 65*(3), 484-489. doi:10.1373/clinchem.2018.298059

Anderson, P. A., Malouf, N. N., Oakeley, A. E., Pagani, E. D., & Allen, P. D. (1991). Troponin T isoform expression in humans. A comparison among normal and failing adult heart, fetal heart, and adult and fetal skeletal muscle. *Circ Res, 69*(5), 1226-1233.

ASCP. (2015). Retrieved from https://www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-myoglobin-to-diagnose-acute-myocardial-infarction/

Bessman, S. P., & Carpenter, C. L. (1985). The creatine-creatine phosphate energy shuttle. *Annu Rev Biochem, 54*, 831-862. doi:10.1146/annurev.bi.54.070185.004151

Bodor, G. S., Porterfield, D., Voss, E. M., Smith, S., & Apple, F. S. (1995). Cardiac troponin-I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. *Clin Chem, 41*(12 Pt 1), 1710-1715.

Bodor, G. S., Survant, L., Voss, E. M., Smith, S., Porterfield, D., & Apple, F. S. (1997). Cardiac troponin T composition in normal and regenerating human skeletal muscle. *Clin Chem, 43*(3), 476-484.

Danese, E., & Montagnana, M. (2016). An historical approach to the diagnostic biomarkers of acute coronary syndrome. *Ann Transl Med, 4*(10), 194. doi:10.21037/atm.2016.05.19

Dillon, M. C., Calbreath, D. F., Dixon, A. M., Rivin, B. E., Roark, S. F., Ideker, R. E., & Wagner, G. S. (1982). Diagnostic problem in acute myocardial infarction: CK-MB in the absence of abnormally elevated total creatine kinase levels. *Arch Intern Med, 142*(1), 33-38.

Eggers, K. M., Oldgren, J., Nordenskjold, A., & Lindahl, B. (2004). Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J, 148*(4), 574-581. doi:10.1016/j.ahj.2004.04.030

Gencer, B., Brotons, C., Mueller, C., Mukherjee, D., Chew, D. P., Andreotti, F., . . . Group, E. S. C. S. D. (2016). 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal, 37*(3), 267-315. doi:10.1093/eurheartj/ehv320

Glatz, J. F., & van der Vusse, G. J. (1990). Cellular fatty acid-binding proteins: current concepts and future directions. *Mol Cell Biochem, 98*(1-2), 237-251.

Greaser, M. L., & Gergely, J. (1971). Reconstitution of troponin activity from three protein components. *J Biol Chem, 246*(13), 4226-4233.

Heller, G. V., Blaustein, A. S., & Wei, J. Y. (1983). Implications of increased myocardial isoenzyme level in the presence of normal serum creatine kinase activity. *Am J Cardiol, 51*(1), 24-27.

Hillinger, P., Twerenbold, R., Jaeger, C., Wildi, K., Reichlin, T., Gimenez, M. R., . . . Mueller, C. (2015). Optimizing Early Rule-Out Strategies for Acute Myocardial Infarction: Utility of 1-Hour Copeptin. *Clin Chem, 61*(12), 1466-1474. doi:10.1373/clinchem.2015.242743

Jaffe, A. S., Chaitman, B. R., Morrow, D. A., Bax, J. J., White, H. D., Alpert, J. S., . . . Group, E. S. C. S. D. (2018). Fourth universal definition of myocardial infarction (2018). *Eur Heart J, 40*(3), 237-269. doi:10.1093/eurheartj/ehy462

Jaffe, A. S., & Morrow, D. A. (2017, 07/03/2017). Biomarkers of cardiac injury other than troponin. *UpToDate*. Retrieved from https://www.uptodate.com/contents/biomarkers-of-cardiac-injury-other-than-troponin

Jaffe, A. S., & Morrow, D. A. (2019, 3/21/2019). Biomarkers of cardiac injury other than troponin. *UpToDate*. Retrieved from https://www.uptodate.com/contents/biomarkers-of-cardiac-injury-other-than-troponin

Kavsak, P. A., MacRae, A. R., Newman, A. M., Lustig, V., Palomaki, G. E., Ko, D. T., . . . Jaffe, A. S. (2007). Effects of contemporary troponin assay sensitivity on the utility of the early markers myoglobin and CKMB isoforms in evaluating patients with possible acute myocardial infarction. *Clin Chim Acta, 380*(1-2), 213-216. doi:10.1016/j.cca.2007.01.001

Khan, S. Q., Dhillon, O. S., O'Brien, R. J., Struck, J., Quinn, P. A., Morgenthaler, N. G., . . . Ng, L. L. (2007). C-Terminal Provasopressin (Copeptin) as a Novel and Prognostic Marker in Acute Myocardial Infarction. *Leicester Acute Myocardial Infarction Peptide (LAMP) Study, 115*(16), 2103-2110. doi:10.1161/circulationaha.106.685503

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., . . . Group, E. S. C. S. D. (2019). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal, 41*(3), 407-477. doi:10.1093/eurheartj/ehz425

Maisel, A., Mueller, C., Neath, S.-X., Christenson, R. H., Morgenthaler, N. G., McCord, J., . . . Peacock, W. F. (2013). Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction: Primary Results of the CHOPIN Trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction). *Journal of the American College of Cardiology, 62*(2), 150-160. doi:https://doi.org/10.1016/j.jacc.2013.04.011

Marshall, T., Williams, J., & Williams, K. M. (1991). Electrophoresis of serum isoenzymes and proteins following acute myocardial infarction. *J Chromatogr, 569*(1-2), 323-345.

McLaurin, M. D., Apple, F. S., Voss, E. M., Herzog, C. A., & Sharkey, S. W. (1997). Cardiac troponin I, cardiac troponin T, and creatine kinase MB in dialysis patients without ischemic heart disease: evidence of cardiac troponin T expression in skeletal muscle. *Clin Chem, 43*(6 Pt 1), 976-982.

Moussa, I. D., Klein, L. W., Shah, B., Mehran, R., Mack, M. J., Brilakis, E. S., . . . Stone, G. W. (2013). Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular

Angiography and Interventions (SCAI). *J Am Coll Cardiol, 62*(17), 1563-1570. doi:10.1016/j.jacc.2013.08.720
Neumann, J. T., Twerenbold, R., Ojeda, F., Sorensen, N. A., Chapman, A. R., Shah, A. S. V., . . . Blankenberg, S. (2019). Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. *N Engl J Med, 380*(26), 2529-2540. doi:10.1056/NEJMoa1803377
NICE. (2016). Chest pain of recent onset: assessment and diagnosis. Retrieved from https://www.nice.org.uk/guidance/cg95/chapter/Recommendations
O'Connor Robert, E., Al Ali Abdulaziz, S., Brady William, J., Ghaemmaghami Chris, A., Menon, V., Welsford, M., & Shuster, M. (2015). Part 9: Acute Coronary Syndromes. *Circulation, 132*(18_suppl_2), S483-S500. doi:10.1161/CIR.0000000000000263
Olasveengen, T. M., de Caen, A. R., Mancini, M. E., Maconochie, I. K., Aickin, R., Atkins, D. L., . . . Nolan, J. P. (2017). 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary. *Circulation, 136*(23), e424-e440. doi:10.1161/cir.0000000000000541
Patel, M. R., Calhoon, J. H., Dehmer, G. J., Grantham, J. A., Maddox, T. M., Maron, D. J., & Smith, P. K. (2016). ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes. *A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons*. doi:10.1016/j.jacc.2016.10.034
Penttila, I., Penttila, K., & Rantanen, T. (2000). Laboratory diagnosis of patients with acute chest pain. *Clin Chem Lab Med, 38*(3), 187-197. doi:10.1515/cclm.2000.027
Reeder, G., S., Awtry, E., Mahler, S., A. (2020). Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department. Retrieved from http://www.uptodate.com UpToDate Inc http://www.uptodate.com
ResponseBio. (2020). POINT OF CARE CARDIAC. Retrieved from https://responsebio.com/acute-care-diagnostics/cardiovascular/
Roche. (2020). Roche CARDIAC Trop T Sensitive test (visual). Retrieved from https://diagnostics.roche.com/global/en/products/params/roche-cardiac-trop-t-sensitive-test-visual.html
Saggin, L., Gorza, L., Ausoni, S., & Schiaffino, S. (1990). Cardiac troponin T in developing, regenerating and denervated rat skeletal muscle. *Development, 110*(2), 547-554.
Seino, Y., Ogata, K., Takano, T., Ishii, J., Hishida, H., Morita, H., . . . Kitaura, Y. (2003). Use of a whole blood rapid panel test for heart-type fatty acid-binding protein in patients with acute chest pain: comparison with rapid troponin T and myoglobin tests. *Am J Med, 115*(3), 185-190.
Tamis-Holland Jacqueline, E., Jneid, H., Reynolds Harmony, R., Agewall, S., Brilakis Emmanouil, S., Brown Todd, M., . . . null, n. (2019). Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation, 139*(18), e891-e908. doi:10.1161/CIR.0000000000000670
Thygesen, K., Alpert, J. S., Jaffe, A. S., Simoons, M. L., Chaitman, B. R., & White, H. D. (2012). Third Universal Definition of Myocardial Infarction. *Circulation, 126*(16), 2020-2035. doi:10.1161/CIR.0b013e31826e1058
Thygesen, K., Alpert, J. S., & White, H. D. (2007). Universal Definition of Myocardial Infarction. *Circulation, 116*(22), 2634-2653. doi:10.1161/circulationaha.107.187397
Van Nieuwenhoven, F. A., Kleine, A. H., Wodzig, W. H., Hermens, W. T., Kragten, H. A., Maessen, J. G., . . . Glatz, J. F. (1995). Discrimination between myocardial and skeletal muscle injury by assessment of the plasma ratio of myoglobin over fatty acid-binding protein. *Circulation, 92*(10), 2848-2854.
WHO. (1979). Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Retrieved from https://www.ahajournals.org/doi/pdf/10.1161/01.CIR.59.3.607

Yusuf, S., Collins, R., Lin, L., Sterry, H., Pearson, M., & Sleight, P. (1987). Significance of elevated MB isoenzyme with normal creatine kinase in acute myocardial infarction. *Am J Cardiol, 59*(4), 245-250.

Specialty Matched Consultant Advisory Panel review 4/2021

Medical Director review 4/2021

Policy Implementation/Update Information

1/1/2019	New policy developed. BCBSNC will provide coverage for cardiac biomarkers for myocardial infarction when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
10/01/19	Policy Statement revised to read: BCBSNC will provide coverage for cardiac biomarkers for myocardial infarction when it is determined the medical criteria or reimbursement guidelines noted below are met. Wording revised in the Not Covered section. "Not Medically Necessary" and "investigational" changed to read "Reimbursement is not allowed…" Deleted coding grid. Notification given 10/1/2019 for policy effective date 12/2/2019. (an)
4/28/20	Specialty Matched Consultant Advisory Panel review 4/2020. Medical Director review 4/2020. (jd)
7/28/20	Reviewed by Avalon 2nd Quarter 2020 Quarter CAB. Related policies section added. Policy guidelines and references updated. Medical Director review 7/2020. (jd)
5/4/21	Specialty Matched Consultant Advisory Panel review 4/2021. Medical Director review 4/2021. (jd)