Clinical Policy Title: Echocardiographic assessment of myocardial strain for cancer patients having undergone chemotherapy

Clinical Policy Number: 04.01.07

Effective Date: April 1, 2016
Initial Review Date: November 18, 2015
Most Recent Review Date: January 11, 2018
Next Review Date: January 2019

Related policies: None.

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of echocardiographic assessment of myocardial strain to measure cardiac impairment in cancer patients treated with chemotherapy to be clinically proven and, therefore, medically necessary. Left ventricular ejection fraction should be measured just before, just after, and six months after chemotherapy (Bovelli, 2010; Plana, 2014; Smiseth, 2016).

Limitations:

All other uses of echocardiographic assessment of myocardial strain may or may not be medically necessary depending on the purpose of the test.

Alternative covered services:

Various uses of echocardiography.
**Background**

Myocardial strain, also known as echocardiographic strain imaging or deformation imaging, reflects left ventricular function. Longitudinal and radial strain increases with heart rate, and decreases with age (Kuznetsova, 2008). Echocardiographic assessment of myocardial strain is a relatively new means of assessing myocardial function. This technology, introduced in the late 1990s, is one of the diagnostic methods considered potentially more advanced than conventional echocardiography, as it is able to evaluate components of cardiac function, including those functions not visually accessible. Strain and strain-rate imaging are often effective means of measuring prognosis of cardiac disease, along with effects of various therapies on the heart (Dandel, 2009). Strain is another means of describing “stretching” of the myocardial system — a lengthening, shortening, or thickening as a measure of regional left ventricular function — while strain rate is the rate of this deformity.

Strain imaging provides greater understanding of the pathophysiology of cardiac ischemia and infarction, primary diseases of the myocardium, assessment of the dys-synchrony for cardiac resynchronization therapy, effects of valve disease on myocardial function, and the mechanics of diastolic function. Most labs use echocardiographic visual assessment of wall motion for clinical use. Strain imaging has been generally used in research, but is becoming more commonly used in practice over time. One study discovered that longitudinal speckle strain had greater power to predict mortality (hazard ratio [HR] 1.45, p<0.0001) than did ejection fraction (HR 1.23, p<0.03) or wall motion score index (HR 1.28, p<0.01) (Stanton, 2009).

The original myocardial strain technique uses tissue Doppler imaging to assess longitudinal strain from Apical windows with left ventricular shortening and lengthening with Doppler scan lines. A newer technique uses “speckle tracking” a digital image that creates blocks of pixels to identify strain vectors; three-dimensional (3-D) speckle tracking strain is now available as well (Geyer, 2010; Gorscan, 2011).

The high prevalence of cancer and the growing number of chemotherapy drugs used to treat cancer patients make precise measurements of various organ functions a vital part of treatment. In particular, chemotherapy can be cardiotoxic; treatment-related cardiac death is the most prevalent noncancer cause of death in adult survivors of child cancer (Armstrong, 2015).

Patients with heart failure after chemotherapy are treated according to standard heart failure protocols. When the reduction in left ventricular ejection fraction during chemotherapy is established, it sometimes may not be in time for effective treatment. This is especially true in cases when global longitudinal strain reduction is clinically significant — greater than 15 percent. A general requirement is that patients should have left ventricular ejection fraction measured just before, just after, and six months after chemotherapy (Smiseth, 2016).

The most commonly measured cardiac functions in post-chemotherapy patients are left ventricular systolic function and left ventricular ejection fraction.
Chemotherapy-related cardiac dysfunction was originally measured by periodic surveillance of left ventricular ejection fraction through nuclear imaging, magnetic resource imaging, and other means. Echocardiography now has surpassed these modalities as the preferred method of measuring cardiac dysfunction, as it is more accurate, available, and portable, and less radioactive (Abdel-Qadir, 2015).

Studies measuring cardiac dysfunction have typically focused on breast cancer survivors or adult survivors of childhood cancer. Various chemotherapy drugs known to cause cardiovascular side effects have been studied, including but not limited to:

- Anthracyclines, including doxorubicin (Adriamycin) and epirubicin (Ellence).
- Human epidermal growth factor receptor type 2 monoclonal antibody.
- Trastuzumab (Herceptin).

Many reports are not controlled trials assessing which type of echocardiography best detects cardiovascular problems, but merely address the efficacy of a particular form of echocardiography.

Some professional societies have produced guidelines on the topic. One is from the European Society for Medical Oncology (Bovelli, 2010). A more recent version is from the American Society of Echocardiography and European Association of Cardiovascular Imaging (Plana, 2014). Both extol the benefits of echocardiography due to its ability to assess more than ventricular function in a relatively low-cost, noninvasive, and radiation-free manner.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on November 22, 2017. Search terms were: “myocardial strain,” “chemotherapy” “echocardiography,” “tissue doppler,” “echocardiograph strain imaging,” “deformation imaging,” and “speckle tracking.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
• **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

As echocardiography technology evolved and newer models were used, several experts raised the question of whether more specialized echocardiographs could be more sensitive to any reductions in cardiac functions after chemotherapy than conventional testing. As early as 2008, experts recommended that Doppler-based myocardial deformation imaging should monitor cardiac function during chemotherapy, instead of conventional echocardiography (Jurcut, 2008). One relatively early study used two-dimensional (2-D) echocardiography to document lower global myocardial strain, strain rates, and time to peak systolic strain in long-term child cancer survivors versus healthy controls, and speculated that 2-D echocardiography might provide superior results to conventional echocardiography (Mavinkurve-Groothuis, 2010).

Another early study stated that myocardial strain imaging had the potential to detect changes in cardiac function from chemotherapy earlier than conventional echocardiography (Stoodley, 2011a). The same research team documented that 2-D myocardial strain imaging detected changes in left ventricular systolic function immediately after chemotherapy in 52 women with breast cancer (Stoodley, 2011b).

Several more recent systematic reviews and meta-analyses that compared efficacy of different types of echocardiography updated earlier findings:

• A meta-analysis of 10 studies (n=458) found that in five studies, compared with healthy controls, patients with arrhythmogenic right ventricular cardiomyopathy, which can lead to sudden death, had a significantly lower myocardial strain (17 versus 30 percent (p<0.001) (Qasem, 2016).

• A systematic review of seven studies (n=3,138) used speckle tracking echocardiography for myocardial strain to assess effectiveness for prognostication. In five studies, global longitudinal strain predicted the development of adverse left ventricular (p values varied from <0.05 to <0.001), and in four studies, it also predicted the development of major adverse cardiac events (p<0.006 to p<0.05); authors concluded it is a predictor of poor prognosis (Sheyte, 2015).

• A meta-analysis of 10 studies (n=486) with normal echocardiograms and with no cardiopulmonary disease or risk factors showed the weighted estimate of right ventricular free wall strain using tissue Doppler and with speckle tracking including were equal at -27, estimating a right ventricular strain range in subjects without cardiopulmonary disease (Fine, 2015).

• A systematic review found that for 1,504 chemotherapy patients, tissue Doppler strain imaging most consistently detected early myocardial changes during therapy, while speckle tracking echocardiography most consistently detected peak systolic global longitudinal strain (Thavendiranathan, 2014).
A study of 1,820 adult survivors of pediatric cancer, most of whom were treated with anthracycline chemotherapy, found 32.1 percent with normal left ventricular ejection fractions after 3-D echocardiography had evidence of cardiac dysfunction when global longitudinal strain was used (Armstrong, 2015).

A study of 75 patients with non-Hodgkin’s lymphoma were followed after chemotherapy, measuring changes in global longitudinal, circumferential, and radial strain using speckle tracking. Based on those who developed cardiotoxicity after treatment, global radial strain was the only significant predictor of cardiotoxicity (Kang, 2014).

In a study of 78 breast cancer patients studied over 12 months, myocardial strain imaging was found to be more sensitive than left ventricular ejection fraction in early detection and intermediate-term monitoring of left ventricular systolic function after chemotherapy (Stoodley, 2013). Global longitudinal strain was found to be an effective predictor of patients at high risk for cardiac events. In a study of 450 patients, 28 of whom experienced cardiac events after chemotherapy, a low global longitudinal strain before treatment was found in 23 percent of patients, a six-fold increase, significant at p<0.0001 (Ali, 2016).

A comparison of 2-D and 3-D echocardiograms, with and without contrast, in 56 female breast cancer patients undergoing chemotherapy found that noncontrast 3-D tests best reproduced left ventricular ejection fraction and left ventricular volume (Thavendiranathan, 2013). A study of 89 patients compared 2-D and 3-D left and right ventricular global longitudinal strain to baseline, after chemotherapy; both had the same reductions in global longitudinal and circumferential strain, with 3-D having a higher sensitivity (Song, 2017). Compared with controls in a study of 91 patients, 3-D speckle tracking echocardiography resulted in significantly lower left ventricular global 3-D strain, torsion, and global performance index, with higher systolic dys-synchrony (Yu, 2013).

Policy updates:

A total of one guideline/other and eight peer-reviewed references were added, and 16 peer-reviewed references were removed from this policy in November 2017.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Qasem (2016)</td>
<td>Key points:</td>
</tr>
</tbody>
</table>
| Myocardial strain as a predictor of sudden death | - Meta-analysis of 10 studies (n=458), comparing patients with arrhythmogenic right ventricular cardiomyopathy to healthy controls.  
- Patients with cardiomyopathy, which can lead to sudden death, had a significantly lower myocardial strain (17 versus 30 percent (p<0.001). |
| Sheyte (2015)  | Key points:                       |
Speckle tracking echocardiography for myocardial strain as a predictor of adverse events

- Systematic review of seven studies (n=3,138) using speckle tracking echocardiography for myocardial strain to assess ability to predict prognosis.
- In five studies, global longitudinal strain predicted the development of adverse left ventricular (p <0.05 to <0.001).
- In four studies, global longitudinal strain predicted the development of major adverse cardiac events (p<0.006 to p<0.05).
- Authors concluded global longitudinal strain is an effective predictor of poor prognosis.

Fine (2015)

Tissue doppler vs. speckle tracking to estimate right ventricular strain range

- Meta-analysis of 10 studies (n=486) with normal echocardiograms and with no cardiopulmonary disease or risk factors.
- Weighted estimate of right ventricular free wall strain were measured using tissue Doppler and speckle tracking.
- Each method estimated a right ventricular strain range at -27.

Armstrong (2015)

Detecting treatment-related cardiac dysfunction in adult survivors of child cancer

- 1,820 adult survivors of pediatric cancer, St. Jude Children’s Research Hospital.
- All exposed to anthracycline (1,050), chest-directed radiotherapy (306), or both (464).
- Of survivors with normal 3-D left ventricular ejection fraction, 32.1% were found to have cardiac dysfunction by global longitudinal strain (28%), American Society of Echocardiography (ASE)-graded diastolic assessment (8.7%), or both.
- Global longitudinal strain and ASE-graded diastolic assessment can identify survivors who may benefit from early medical intervention.

Thavendiranathan (2014)

Review of various means of detecting cardiac dysfunction in chemotherapy patients

- Systematic review, 35 articles, n=1,504 (all with cancer and chemotherapy).
- Peak systolic longitudinal strain rate most consistently detected early myocardial changes during therapy, when tissue Doppler-based strain imaging was used.
- Peak systolic global longitudinal strain most consistently detected early myocardial changes during therapy when speckle tracking echocardiography was used.
- Echocardiographic myocardial deformation parameters for early detection of myocardial changes and prediction of cardiotoxicity for chemotherapy patients are effective.

References

Professional society guidelines/other:


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the services and items subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Z08</td>
<td>Encounter for follow-up examination after completed treatment for malignant neoplasm</td>
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