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 18, 2017
Next Review Date: January 2018

Related policies:

None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s 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 Keystone First 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. Keystone First’s 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. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First 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.

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
Echocardiographic assessment of myocardial strain, also known as echocardiographic strain imaging or deformation imaging, is a relatively new means of assessing myocardial function. This technology 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. Strain is another means of describing “stretching” of the myocardial system, while strain rate is the rate of this deformity.

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).

Historical studies of early changes in myocardial function have used conventional echocardiography to assess biological impact, but in recent years other technologies have offered the potential to improve this diagnostic function. Among these new methods are two-dimensional (2-D) and three-dimensional (3-D) echocardiography, tissue Doppler-derived strain imaging, and speckle tracking echocardiography (STE).

The most commonly-measured cardiac functions in postchemotherapy patients are left ventricular systolic (LVS) function and left ventricular ejection fraction (LVEF).

**Searches**

Keystone First 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 4, 2016. Search terms were: “myocardial strain,” “chemotherapy” AND “echocardiography,” OR “Tissue Doppler.”

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**

Chemotherapy-related cardiac dysfunction was originally measured by periodic surveillance of LVEF 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.

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. One relatively early study used 2-D echocardiography to document lower global myocardial strain, strain rates, and time to peak systolic strain in long-term child cancer survivors vs. healthy controls, and speculated that 2-D echocardiography might provide superior results to conventional echocardiography (Mavinkurve-Groothuis, 2010). Another stated that myocardial strain imaging had the potential to detect changes in cardiac function from chemotherapy earlier than conventional echocardiography (Stoodley, 2011a).

Several more recent controlled trials that compared efficacy of different types of echocardiography updated earlier findings:
• One systematic review found that for 1,504 chemotherapy patients, tissue Doppler strain imaging most consistently detected early myocardial changes during therapy, while STE most consistently detected peak systolic global longitudinal strain (GLS) (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 LVEFs after 3-D echocardiography had evidence of cardiac dysfunction when GLS was used (Armstrong, 2015).

• A study of 57 pediatric cancer survivors treated with chemotherapy found that the most sensitive parameters identifying subjects with subclinical myocardial dysfunction were 1) 3-D echocardiographic ejection fraction, 2) end-systolic volume index, 3) 3-D STE peak GLS magnitude, and 4) a decrease in early atrial myocardial velocity at the interventricular septum by Doppler tissue imaging (Toro-Salazar, 2016).

• STE was found to identify significantly more subjects with abnormal peak systolic strain and peak circumferential strain in pediatric cancer patients vs. controls (Pignatelli, 2015).

• 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 LVEF and LV volume (Thavendiranathan, 2013).

Echocardiography of myocardial strain might also be helpful in predicting adverse cardiac events prior to chemotherapy. A report on patients with hematologic cancer who were given echocardiography prior to chemotherapy found pretreatment LVEF was lower in patients with subsequent events, compared to those with no events (Ali, 2016).

More comparisons of types of echocardiographic assessment of cardiac damage after chemotherapy are warranted to better understand relative efficacy of each method on various populations.

Policy updates:

Six new peer-reviewed references were added to this policy in November 2016.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali (2016)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Comparison of several diagnostic tests in patients with hematologic cancer</td>
<td>• Patients with hematologic cancer, treated with anthracyclines, who also underwent prechemotherapy echocardiography 2006–2011, mean follow-up over four years.</td>
</tr>
<tr>
<td></td>
<td>• 450 patients (6%) experienced cardiac events.</td>
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<tr>
<td></td>
<td>• Prechemotherapy LVEF and GLS were lower in patients with cardiac events.</td>
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<tr>
<td></td>
<td>• Diabetes, hypertension, LVEF, and GLS were linked with cardiac events.</td>
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</tbody>
</table>
**Citation** | **Content, Methods, Recommendations**
--- | ---
Armstrong (2015) | **Prechemotherapy GLS can stratify patients at high risk for cardiac events after anthracycline chemotherapy.**
| **Key points:**
| • 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 LVEF, 32.1% were found to have cardiac dysfunction by GLS (28%), American Society of Echocardiography (ASE)-graded diastolic assessment (8.7%), or both.
| • GLS 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**
| **Key points:**
| • Systematic review, 35 articles, n=1504 (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 GLS most consistently detected early myocardial changes during therapy when STE was used.
| • Echocardiographic myocardial deformation parameters for early detection of myocardial changes and prediction of cardiotoxicity for chemotherapy patients are effective.

Thavendiranathan (2013) | **Reproducibility of methods to assess LVEF using echocardiography for chemotherapy patients**
| **Key points:**
| • 56 female breast cancer chemotherapy patients, stable for GLS up to 12 months posttreatment.
| • Each given echocardiogram at 3, 6, 9, and 12 months after treatment, including 2-D and 3-D procedures with and without contrast administration.
| • Noncontrast 3-D echocardiography was the most reproducible technique for LVEF and LV volume measurements.

**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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<thead>
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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
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<td>0399T</td>
<td>Myocardial strain imaging (quantitative assessment of myocardial mechanics using image-based analysis of local myocardial dynamics) (List separately in addition to code for primary procedure)</td>
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<tr>
<td>93306</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, with spectral Doppler echocardiography, and with color flow Doppler echocardiography</td>
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<tr>
<td>93307</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography</td>
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<td>I51.89</td>
<td>Chemotherapy-related cardiac dysfunction (CTRCD)</td>
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<td>T45.1X5</td>
<td>Adverse effect of Doxorubicin, Mitoxantrone, 5-FU</td>
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<tr>
<td>Z08</td>
<td>Encounter for follow-up examination after completed treatment for malignant neoplasm</td>
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<th>HCPCS Code</th>
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