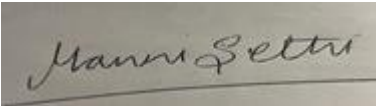


**Prior Authorization Review Panel
MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania	Submission Date: 7/1/2024
Policy Number: ccp.1207	Effective Date: 3/2016 Revision Date: June 1, 2024
Policy Name: Myocardial strain imaging	
Type of Submission – Check all that apply: New Policy <input checked="" type="checkbox"/> Revised Policy* Annual Review – No Revisions Statewide PDL	
*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below: Policy was reactivated at the request of PA Medical Directors. See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

Myocardial strain imaging

Clinical Policy ID: CCP.1207

Recent review date: 6/2024

Next review date: 10/2025

Policy contains: Chemotherapy side effects; deformation imaging; echocardiograph strain imaging; hypertrophic cardiomyopathy; myocardial strain; and speckle tracking.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania 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 Pennsylvania on a case by case basis 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 Pennsylvania 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 Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

Echocardiographic assessment of myocardial strain to measure cardiac impairment is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified for this policy.

Alternative covered services

- Cardiac magnetic resonance.
- Chest radiography.
- Computed tomography.
- Electrocardiography.
- Myocardial perfusion imaging.
- Radionuclide ventriculography.
- Stress echocardiography.
- Transthoracic or transesophageal echocardiography, including tissue Doppler imaging.

Background

Myocardial strain imaging evaluates the function of the heart muscle using cardiac ultrasound. In myocardial imaging, the terms “strain” and “strain rate” define myocardial wall deformation that occurs by the application of a force (Collier, 2017). Strain is a unitless measurement used to describe dimensional or deformational change

resulting from local shortening, thickening, and lengthening of the myocardium during the cardiac cycle. The dimensions of strain are longitudinal, radial, circumferential, and rotational (ventricular twist). Strain rate quantifies the speed of myocardial deformation.

The amount of deformation (positive or negative strain) is defined as the percent change in the length of myocardial segment from a relaxed to contractile state (Collier, 2017). Positive strain values describe thickening, and negative values describe shortening, of a given myocardial segment related to its original length. Both strain and strain rate assess systolic function (especially regional contractile function) but are not measures of contractility, because deformation is load dependent (Voigt, 2019).

Myocardial deformation data may be derived noninvasively using echocardiography or cardiac magnetic resonance (Voigt, 2019). Transthoracic echocardiography is an established modality for ventricular wall motion analysis and assessment of regional myocardial function. Through tissue Doppler imaging, calculation of myocardial strain rate deformation became possible from apical windows with left ventricular shortening and lengthening with Doppler scan lines. However, tissue Doppler imaging provides a one-dimensional view and permits limited evaluation of deformation. It is highly operator dependent, and estimation of wall motion is visual and subjective with high interobserver and intra-observer variability.

Speckle tracking echocardiography is a recent development based in two-dimensional digital gray-scale imaging on echocardiography, which is composed of several bright acoustic markers called “speckles” produced by the scatter of the ultrasound beam by the tissue (Voigt, 2019). Three-dimensional speckle tracking is now available. The motion pattern of the speckles reflects the motion pattern of myocardial tissue at the endocardial border from which strain and strain rate can be calculated. It allows the myocardium, particularly the left ventricle, to be viewed at various angles during the echocardiographic procedure and provides unique quantifiable information on regional and global myocardial function.

Speckle tracking echocardiography software is applied during post-processing to analyze regions of interest frame-by-frame, but the methods and algorithms are strongly vendor specific, leading to inter-vendor variability. The European Association of Cardiovascular Imaging and the American Society of Echocardiography initiated a consensus task force to standardize definitions and nomenclature in both atrial and ventricular strain imaging with two-dimensional speckle tracking technology (Badano, 2018; Voigt, 2015). The goal of this effort was to reduce inter-vendor differences and ambiguities in the strain algorithms.

The most studied parameter using speckle tracking data is global longitudinal strain, as it represents a shortening of the endocardial fibers that are usually the first affected in most cardiomyopathies (Voigt, 2019). Left ventricular ejection fraction is an established, but relatively late, load-dependent marker of systolic function, resulting in low sensitivity for detecting subclinical changes in ejection fraction. Myocardial strain analysis can discriminate between active and passive movement of myocardial segments and can permit separate assessment of the dimensional components of myocardial deformation that are not visually assessable on transthoracic echocardiography. As such, it has potentially wide clinical application for the diagnosis, prognosis, and provision of treatment of myocardial disease, in particular, chemotherapy-related cardiac dysfunction.

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. Treatment-related cardiac death is the most prevalent non-cancer cause of death in adult survivors of childhood cancer (Armstrong, 2015). A study of 16,456 adults with non-metastatic breast cancer identified 4.2% who had cardiotoxicity after chemotherapy (Henry, 2018). Chemotherapy drugs known to cause cardiovascular side effects in breast cancer survivors or adult survivors of childhood cancer include, but are not limited to, anthracyclines, including doxorubicin (Adriamycin) and epirubicin (Ellence), and human epidermal growth factor receptor type 2 monoclonal antibody (trastuzumab [Herceptin]).

Patients with heart failure after chemotherapy are treated according to standard heart failure protocols. The most commonly measured cardiac functions in post-chemotherapy patients are left ventricular systolic function and left ventricular ejection fraction (Smiseth, 2016). A general requirement is that patients should have left ventricular ejection fraction measured just before, just after, and six months after chemotherapy. 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, 2016).

Findings

Some professional societies have produced guidelines on types of echocardiography, including assessment of myocardial strain for chemotherapy drugs with Type 1 or 2 cardiotoxicity.

According to the American Society of Echocardiography, global longitudinal strain using speckle-tracking echocardiography may be added to tissue Doppler imaging to monitor myocardial function in pediatric patients undergoing cancer treatment, although the Society acknowledges a lack of evidence supporting the prognostic significance of early changes in left ventricular function determined by global longitudinal strain. The Society recommends more data before incorporating strain measurement routinely in therapeutic decisions to monitor cardiotoxicity in cancer treatment (Mertens, 2023).

In 2019, the American College of Cardiology, leading a group of ten professional medical organizations, issued appropriate use criteria for multimodality imaging in the assessment of cardiac structure and function in nonvalvular heart disease, including indications for strain and strain rate imaging (Doherty, 2019). Their consensus panel rated numerous indications as “appropriate,” “may be appropriate,” or “rarely appropriate” based on an assessment of benefits and risks and judgment that the procedure is generally acceptable and reasonable for the indication.

For strain or strain rate imaging, only four indications were rated as “appropriate” and represent clinical scenarios where the expected incremental information from speckle or tissue Doppler, combined with clinical judgment, may exceed the expected negative consequences. All other 77 indications were rated as “may be appropriate” (n = 14) or “rarely appropriate” (n = 63), reflecting the uncertainty in the clinical value of myocardial strain data using two-dimensional speckle tracking for these scenarios. The four indications rated as “appropriate” are (Doherty, 2019):

- Initial evaluation prior to exposure to medications/radiation that could result in cardiotoxicity/heart failure.
- Re-evaluation (one year) in a patient previously or currently undergoing therapy with potentially cardiotoxic agents.
- Periodic re-evaluation in a patient undergoing therapy with cardiotoxic agents with worsening symptoms.
- Evaluation of suspected hypertrophic cardiomyopathy to clarify initial diagnostic testing (commonly when transthoracic echocardiography is nondiagnostic).

The American Society for Clinical Oncology guideline for prevention and monitoring of cardiac dysfunction of adult cancers endorsed routine echocardiography in metastatic breast cancer. It also recommended echocardiography in post-chemotherapy patients with signs and symptoms of cardiac disease, 6-12 months after chemotherapy in high-risk patients. If echocardiography is unavailable or not technically feasible, cardiac magnetic resonance imaging or multi-gated acquisition scans can be used. Reports in the professional medical literature address these indications for myocardial strain imaging. However, none address whether the procedure affects eventual patient outcomes (Amerinian, 2017).

Several recent systematic reviews and meta-analyses that compared efficacy (in terms of myocardial strain) of different types of echocardiography updated earlier findings:

A systematic review found that for 1,504 chemotherapy patients, tissue Doppler strain imaging most consistently detected early myocardial changes during treatment, 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, reviewed patients with normal left ventricular ejection fractions after three-dimensional echocardiography; 28.0% had evidence of cardiac dysfunction when global longitudinal strain was used, compared to just 8.7% when American Society of Echocardiography-graded diastolic assessment was used (Armstrong, 2015).

A systematic review and meta-analysis of 14 studies of children, adolescents, and young adults addressed changes in myocardial dysfunction after anthracycline therapy for childhood cancer. Global longitudinal strain abnormalities are common during and just after chemotherapy, but changes in global circumferential strain/global radial strain occur after long-term follow-up. Authors conclude myocardial strain by echocardiography is useful for evaluating subclinical myocardial injury (Tuzovic, 2018).

A systematic review of six studies (n = 2,545) of subjects with cancer documented that, after a multi-gated acquisition scan or echocardiograph before treatment, 2.5% had abnormal left ventricular ejection fraction, and 1.6% had a change in chemotherapy decision. Authors recommend efforts to better identify low-risk patients that do not need left ventricular assessment at baseline, preventing delay in chemotherapy administration (O'Brien, 2019).

A systematic review and meta-analysis of 16 studies of breast cancer patients given anthracyclines or trastuzumab showed significant reductions in two-dimensional left ventricular ejection fraction and speckle tracking echocardiography parameters early in chemotherapy. Peak systolic global longitudinal strain was the most consistently detected early myocardial change, upholding the role of monitoring and starting cardioprotective treatment (Bergamini, 2019).

A systematic review/meta-analysis of 21 studies (n = 1,782) of cancer therapy-related cardiac dysfunction diagnosed by echocardiographic left ventricular global longitudinal strain included patients with breast cancer, hematologic malignancies, or sarcomas treated with anthracyclines with or without trastuzumab. The rate of positive tests ranged from 9.3% to 43.8% after a mean follow-up of 4.2 to 23.0 months. Worse global longitudinal strain was associated with a higher risk of cardiac dysfunction. Authors characterized the results as “good prognostic performance” of strain for cardiac dysfunction (Oikonomou, 2019).

In 2021, we updated the references and added several systematic reviews published since Doherty (2019). Significant limitations in the literature prevented meaningful evaluation of clinical efficacy through meta-analysis in most instances. The main limitations are the inclusion of only retrospective or prospective cohort studies and the large degree of heterogeneity among studies, particularly the variation in strain values among methods, modalities, and software versions that prevented determination of a clearly defined threshold value for left ventricular global longitudinal strain that would trigger clinical action and any subsequent impact on clinical care. The diagnostic and prognostic roles for myocardial strain imaging of the atria or right ventricle, or in pediatric populations, have not been established.

The following indications are unrelated to provision of cardiotoxic agents, primarily for early detection and outcome prediction, the results of which would not alter American College of Cardiology findings:

- To evaluate hypertrophic cardiomyopathy. Two systematic reviews (Dorobantu, 2021, 14 studies, n = 809 total patients; Tower-Rader, 2019, 14 studies, n = 3,154 total patients) confirm an association between abnormal left ventricular global longitudinal strain and adverse composite cardiac outcomes and ventricular arrhythmias, and the ability of left ventricular global longitudinal strain data derived from

speckle tracking echocardiography to detect left ventricular dysfunction, especially in the setting of a normal left ventricular ejection fraction. Another American College of Cardiology guideline (Ommen, 2020) stated that while changes in left ventricular systolic strain and diastolic function can precede definitive hypertrophy on echocardiography, the clinical significance of subclinical structural and functional abnormalities, such as myocardial strain, is unclear and treatment decisions are usually not based on these findings alone.

- After repair of Tetralogy of Fallot using speckle tracking echocardiography, tissue Doppler imaging, or cardiac magnetic resonance feature tracking (Cheung, 2019, 10 studies).
- To predict response to catheter ablation (Bajraktari, 2020, 13 studies, n = 1,179 total patients; Nielsen, 2020, 12 studies, n = 1,025 total patients).
- To predict response to cardiac resynchronization therapy using ventricular strain (Bazoukis, 2022; n = 12 studies with 1,004 total patients).
- For early detection of subclinical ventricular dysfunction associated with:
 - Systemic lupus erythematosus (Di Minno, 2020, nine studies).
 - Sickle cell disease (Whipple, 2021, 17 studies, n = 887 total patients of all genotypes).
 - Hypertensive pregnancy disorders (Moors, 2020, 16 studies, n = 870 index cases and 693 normotensive controls).
 - Acute cellular rejection in heart transplant recipients (Elkaryoni, 2020, 10 studies, n = 511 total patients; Zhu, 2020, seven studies).
- For prognosis using ventricular longitudinal strain:
 - In patients with coronavirus disease 2019 (Wibowo, 2021, seven studies, n = 612 total patients).
 - In patients with sepsis (Vallabhajosyula, 2019, five studies, n = 561 patients).
 - In patients with subclinical primary mitral regurgitation, to guide timing of mitral valve surgery (Modaragamage Dona, 2021, 12 studies).
 - In fetuses during gestation (van Oostrum, 2020a, 23 studies; van Oostrum, 2020b, four studies).

In 2022, we added a systematic review/meta-analysis of 42 studies (n = 5,403) of children with cancer undergoing chemotherapy. While myocardial strain imaging by speckle-tracking echocardiography documents early evidence of myocardial injury, additional evidence on risk parameters is needed to support its adoption for clinical use, and more data are required for the better understating of myocardial deformation parameters in risk stratification (Li, 2022). We also added a systematic review of eight studies (n = 979) that showed left ventricular global longitudinal strain was significantly lower in all hypertensive groups compared with controls without hypertension (Tadic, 2021).

In 2024, we added a systematic review/meta-analysis that included three studies (n = 1,332). Myocardial strain by strain-encoded magnetic resonance imaging accurately predicted all-cause mortality and other endpoints ($P < .001$). However, subjects had heart failure or coronary artery disease, with no mention of prior cancer or chemotherapy (Korosoglou, 2024). The policy was reactivated, updated, and changed from medically necessary to investigational, based on guideline recommendations (Mertens, 2023) stating a lack of evidence that myocardial strain imaging affects outcomes.

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On February 28, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “echocardiographic strain imaging,” “deformation imaging,” “myocardial strain,” and “speckle tracking.” We included the best available evidence

according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

11/2015: initial review date and clinical policy effective date: 3/2016

11/2016: Policy references updated.

11/2017: Policy references updated.

11/2018: Policy references updated. Policy ID changed to CCP.1207.

1/2020: Policy references updated.

8/2021: Policy references updated. Coverage limitation clarified.

8/2022: Policy references updated.

4/2024: Policy re-activated and updated. Coverage modified from medically necessary to investigational.