2.02.24	Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting		
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Section:	2.0 Medicine	**Page:**	Page 1 of 26

Policy Statement

In the ambulatory care and outpatient setting, cardiac hemodynamic monitoring for the management of heart failure is considered **investigational** when using **any** of the following:

I. Arterial pressure during the Valsalva maneuver
II. Implantable direct pressure monitoring of the pulmonary artery
III. Inert gas rebreathing
IV. Thoracic bioimpedance

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy refers only to the use of stand-alone cardiac output measurement devices designed for use in ambulatory care and outpatient settings. The use of cardiac hemodynamic monitors or intrathoracic fluid monitors that are integrated into other implantable cardiac devices, including implantable cardioverter defibrillators, cardiac resynchronization therapy devices, and cardiac pacing devices, is addressed in Blue Shield of California Medical Policy: Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure.

Coding

The following CPT code is specific for bioimpedance:

- **93701**: Bioimpedance-derived physiologic cardiovascular analysis

The following CPT codes are specific to the implantation of a pulmonary artery pressure sensor and monitoring:

- **33289**: Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed
- **93264**: Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional

The following category III CPT codes may be reported for pulmonary fluid monitoring:

- **0607T**: Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment
- **0608T**: Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional

Description

A variety of outpatient cardiac hemodynamic monitoring devices are intended to improve quality of life and reduce morbidity for patients with heart failure by decreasing episodes of acute decompensation. Monitors can identify physiologic changes that precede clinical symptoms and thus allow preventive intervention. These devices operate through various mechanisms, including implantable pressure sensors, thoracic bioimpedance measurement, inert gas rebreathing, and estimation of left ventricular end-diastolic pressure by arterial pressure during the Valsalva maneuver.

Related Policies

- Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Noninvasive Left Ventricular End-Diastolic Pressure Measurement Devices
In 2004, the VeriCor® (CVP Diagnostics), a noninvasive left ventricular end-diastolic pressure measurement device, was cleared for marketing by U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for the following indication:

"The VeriCor is indicated for use in estimating non-invasively, left ventricular end-diastolic pressure (LVEDP). This estimate, when used along with clinical signs and symptoms and other patient test results, including weights on a daily basis, can aid the clinician in the selection of further diagnostic tests in the process of reaching a diagnosis and formulating a therapeutic plan when abnormalities of intravascular volume are suspected. The device has been clinically validated in males only. Use of the device in females has not been investigated."

FDA product code: DXN.

Thoracic Bioimpedance Devices
Multiple thoracic impedance measurement devices that do not require invasive placement have been cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices used for peripheral blood flow monitoring. Table 1 presents an inexhaustive list of representative devices (FDA product code: DSB).

Table 1. Noninvasive Thoracic Impedance Plethysmography Devices

Device	Manufacturer	Clearance Date
BioZ® Thoracic Impedance Plethysmograph	SonoSite	2009
Zoe® Fluid Status Monitor	Noninvasive Medical Technologies	2004
Cheetah Starling SV	Cheetah Medical	2008
PhysioFlow® Signal Morphology-based Impedance Cardiography (SM-ICG™)	Vasocom, now NeuMeDx	2008
ReDSTM Wearable System	Sensible Medical Innovations	2015

Also, several manufacturers market thoracic impedance measurement devices integrated into implantable cardiac pacemakers, cardioverter defibrillator devices, and cardiac resynchronization therapy devices. Thoracic bioimpedance devices integrated into implantable cardiac devices are addressed in Blue Shield of California Medical Policy: Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure.

Inert Gas Rebreathing Devices
In 2006, the Innocor® (Innovision), an inert gas rebreathing device, was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing inert gas rebreathing devices for use in computing blood flow. FDA product code: BZG.

Implantable Pulmonary Artery Pressure Sensor Devices
In 2014, the CardioMEMS™ Champion Heart Failure Monitoring System (CardioMEMS, now Abbott) was approved for marketing by the FDA through the premarket approval process. This device consists of an implantable pulmonary artery (PA) sensor, which is implanted in the distal PA, a transvenous delivery system, and an electronic sensor that processes signals from the implantable PA sensor and transmits PA pressure measurements to a secure database.[3] The device originally underwent FDA review in 2011, at which point FDA found no reasonable assurance that the monitoring system would be effective, particularly in certain subpopulations, although the FDA agreed this monitoring system was safe for use in the indicated patient population.[4]

Several other devices that monitor cardiac output by measuring pressure changes in the PA or right ventricular outflow tract have been investigated in the research setting but have not received the FDA approval. They include the Chronicle® implantable continuous hemodynamic monitoring device (Medtronic), which includes a sensor implanted in the right ventricular outflow tract, and the ImPressure® device (Remon Medical Technologies), which includes a sensor implanted in the PA.

Note: This evidence review only addresses the use of these technologies in ambulatory care and outpatient settings.

Rationale

Background
Chronic Heart Failure
Patients with chronic heart failure are at risk of developing acute decompensated heart failure, often requiring hospital admission. Patients with a history of acute decompensation have the additional risk of future episodes of decompensation and death. Reasons for the transition from a stable, chronic state to an acute, decompensated state include disease progression, as well as acute events such as coronary ischemia and dysrhythmias. While precipitating factors are frequently not identified, the most common preventable cause is noncompliance with medication and dietary regimens.[1]

Management

Strategies for reducing decompensation, and thus the need for hospitalization, are aimed at early identification of patients at risk for imminent decompensation. Programs for early identification of heart failure are characterized by frequent contact with patients to review signs and symptoms with a health care provider, education, and medication adjustments as appropriate. These encounters may occur face-to-face in the office or at home, or via cellular or computed technology.[2,]

Precise measurement of cardiac hemodynamics is often employed in the intensive care setting to carefully manage fluid status in acutely decompensated heart failure. Transthoracic echocardiography, transesophageal echocardiography, and Doppler ultrasound are noninvasive methods for monitoring cardiac output on an intermittent basis for the more stable patient but are not addressed herein. A variety of biomarkers and radiologic techniques may be used for dyspnea when the diagnosis of acute decompensated heart failure is uncertain.

The criterion standard for hemodynamic monitoring is pulmonary artery catheters and central venous pressure catheters. However, they are invasive, inaccurate, and inconsistent in predicting fluid responsiveness. Several studies have demonstrated that catheters fail to improve outcomes in critically ill patients and may be associated with harm. To overcome these limitations, multiple techniques and devices have been developed that use complex imaging technology and computer algorithms to estimate fluid responsiveness, volume status, cardiac output and tissue perfusion. Many are intended for use in outpatient settings but can be used in the emergency department, intensive care unit, and operating room. Four methods are reviewed here: implantable pressure monitoring devices, thoracic bioimpedance, inert gas rebreathing, and arterial waveform during the Valsalva maneuver. Use of the last 3 is not widespread because of several limitations including use of proprietary technology making it difficult to confirm their validity and lack of large randomized controlled trials to evaluate treatment decisions guided by these hemodynamic monitors.

Literature Review

For the first indication, because there is direct evidence from a large randomized controlled trial (RCT), we focus on it and assess the evidence it provides on clinical utility. Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For indications 2, 3, and 4, we assess the evidence as a medical test. Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Implantable Pulmonary Artery Pressure Monitoring (CardioMEMS Device)

Clinical Context and Therapy Purpose

The purpose of the CardioMEMS system in patients who have heart failure is to provide remote monitoring for early symptoms of heart failure in order to modify therapy and prevent or reduce hospitalization.

The question addressed in this evidence review is: Does use of an implantable pulmonary artery sensor device (CardioMEMS) improve net health outcomes in individuals with heart failure in the outpatient setting?

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest is patients with New York Heart Association (NYHA) Class III heart failure who have had a hospitalization in the past year.

Interventions

Left ventricular end-diastolic pressure (LVEDP) can be approximated by direct pressure measurement of an implantable sensor in the pulmonary artery wall or right ventricular outflow tract. The sensor is implanted via right heart catheterization and transmits pressure readings wirelessly to external monitors. One device, the CardioMEMS Champion Heart Failure Monitoring System, has approval from the U.S. Food and Drug Administration (FDA) for the ambulatory management of heart failure patients. The CardioMEMS device is implanted using a heart catheter system fed through the femoral vein and generally requires patients to have an overnight hospital admission for observation after implantation.

Comparators

The comparator of interest is standard clinical care without testing.

Outcomes

The International Consortium for Health Outcomes Measurement has identified 3 domains of outcomes for a standard outcome set for patients with heart failure.[5]

- Survival and disease control (i.e., mortality)
- Functioning and disease control (i.e., symptom control including dyspnea, fatigue and tiredness, disturbed sleep, and peripheral edema, activities of daily living including health-related quality of life, maximum physical exertion, independence and psychosocial health including depression and anxiety, confidence and self-esteem)
- Burden of care to patient (i.e., hospital visits including admissions and appointments, treatment side effects, complications)

The Heart Failure Association of the European Society of Cardiology has published a consensus document on heart failure outcomes in clinical trials.[6] They likewise categorize important outcomes for clinical trials as mortality outcomes (all-cause and cause-specific), morbidity and clinical composites (including hospitalizations, worsening of heart failure, implantable cardioverter device shocks) and symptoms and patient-reported outcomes. The consensus document recommends that hospitalization for heart failure be defined as a hospitalization requiring at least an overnight stay caused by substantive worsening of symptoms and/or signs requiring augmentation of therapy.

Measurements of maximal oxygen consumption during exercise, the 6-minute walk test, stair climb test, Short Physical Performance Battery or hand-grip strength are functional measures. Patient-reported outcome measures include the Kansas City Cardiomyopathy Questionnaire, the NYHA Functional Classification, and the Minnesota Living with Heart Failure Questionnaire. Generally, demonstration of outcomes over a 1-year period is meaningful to assess outcomes for the intervention.

Study Selection Criteria
Methodologically credible studies were selected using the following principles.

- Comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations will be considered.
- Larger sample size studies and longer duration studies are preferred.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
Abraham et al (2011, 2016) have reported on the results of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients trial (CHAMPION), a single-blind RCT in which all enrolled patients were implanted with the CardioMEMS device.[7,8] Patients were randomized to the CardioMEMS group, in which daily uploaded pulmonary artery pressures were used to guide medical therapy, or to the control group, in which daily uploaded pressures were not made available to investigators and patients continued to receive standard of care management, which included drug adjustments in response to patients' clinical signs and symptoms. An independent clinical endpoints committee, blinded to the treatment groups, reviewed abstracted clinical data and determined if hospitalization was related to heart failure hospitalization. The randomized phase ended when the last patient enrolled completed at least 6 months of study follow-up (average, 18 months) and was followed in an open-access phase during which investigators had access to pulmonary artery pressure for all patients (former control and treatment group). The open-access phase lasted for an average of 13 months. In the randomized phase of the trial, if the investigator did not document a medication change in response to an abnormal pulmonary artery pressure elevation, a remote CardioMEMS nurse could send communications to the investigator related to clinical management. No such activity occurred in the nonrandomized phase. Trial characteristics and results are summarized in Tables 2 and 3. The trial met its primary efficacy endpoint, with a statistically significant 28% relative reduction in the rate of heart failure-related hospitalizations at 6 months. However, members of the FDA advisory committee in 2011 were unable to distinguish the effect of the device from the effect of nurse communications, and so the FDA denied approval of CardioMEMS and requested additional clarification from the manufacturer.[3] Subsequently, the FDA held a second advisory committee meeting in 2013 to review additional data (including open-access phase) and address previous concerns related to impact of nurse communication on the CHAMPION trial.[9,10]

The 2 major limitations in the early data were related to the potential impact of nurse communication and lack of treatment effect in women.

The sponsor conducted multiple analyses to address the impact of nurse intervention on heart failure-related hospitalizations. These analyses included: (1) independent auditing of all nurse communication to estimate quantitatively the number of hospitalizations that could have been influenced by nurse communication, (2) using a propensity-based score to match patients in the

CardioMEMS group who did not receive nurse communications with those in the control base, (3) comparing whether the new knowledge of pulmonary arterial pressure in the former control during the open-access phase led to reductions in heart failure-related hospitalizations, (4) comparing whether the ongoing access to pulmonary artery pressures in the treatment group during the open-access phase was accompanied by continued reduced rates of heart failure hospitalizations, and (5) comparing whether if similar access to pulmonary artery pressures in the former control group and treatment group during the open-access phase was associated with similar rates of heart failure-related hospitalizations.[9] The FDA concluded that all such analyses had methodologic limitations. Propensity matching cannot balance unmeasured characteristics and confounders, and therefore conclusions drawn from propensity analysis were not definitive.[3] While the FDA concluded that the third-party audit of nurse communication was valid, it was difficult to estimate accurately how many heart failure-related hospitalizations were avoided by the nurse communications. The FDA stated that the longitudinal analyses (see points 3 to 5 above) were the most useful regarding supporting device effectiveness. Therefore, only data from analyses 3 to 5 are summarized in Table 4 and discussed next. It is important to acknowledge that all such analyses were post hoc and were conducted with the intent to test the robustness of potentially biased RCT results; therefore, results from these analyses should be evaluated to assess consistency and not as an independent source of evidence to support efficacy. As indicated in Table 4, the longitudinal analyses of individual patient data showed that the device appears to be associated with reducing heart failure-related hospitalization rate. However, there are important trial limitations, notably, subject dropouts were not random, and patient risk profiles could have changed from the randomized phase to the open-access phase. In the open-access phase, 93 (34%) of 270 subjects in the treatment group and 110 (39%) of 280 subjects in the control group remained in the analysis.

According to the FDA documents, the apparent lack of reduction in heart failure-related hospitalization in women resulted from a greater number of deaths among women in the control group early in the trial, and this early mortality resulted in a competing risk for future heart failure hospitalizations. While both the FDA and sponsor conducted multiple analyses to understand device effectiveness in women, the FDA statisticians concluded that such analyses did clearly delineate the limited treatment effect in women.[9] The decrease in heart-failure related hospitalizations observed in the CardioMEMS post-approval study (see Tables 7 and 8) was also observed in the subgroup analysis of women, which comprised 37.7% of the study population.

Other subgroup analyses of the CHAMPION trial in patients with reduced ejection fraction,[11] preserved ejection fraction,[12] Medicare-eligible patients,[13] and chronic obstructive pulmonary disease[14] are out of scope and not discussed in this evidence review.

Table 2. Summary of Key RCT Characteristics

Author; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Abraham et al (2011, 2016)[7,8]; CHAMPION	U.S.	64	2007-2009	• At least 1 previous HFH in the past 12 mo and NYHA class III HF for at least 3 mo • 40% patients from academic setting and 60% from community setting	Disease management by daily measurement of pulmonary artery pressures (via CardioMEMS) plus standard of care (n=270)	Disease management by standard of care alone (n=280)

CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients trial; HF: heart failure; HFH: heart failure hospitalization; NYHA: New York Heart Association; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

Trial	HFH, n (events per patient)		Device- or System-Related Complications, n (%)		Pressure-Sensor Failures at 6 or 12 Months
	At 6 Months	*At 12 Months*	*At 6 Months*	*At 12 Months*	

Trial	HFH, n (events per patient)		Device- or System-Related Complications, n (%)		Pressure-Sensor Failures at 6 or 12 Months
Abraham et al (2011, 2016)[7,8]; CHAMPION	550	550	550	550	550
CardioMEMS	84 (0.32)	182 (0.46)	3 (1)	0	0
Control	120 (0.44)	279 (0.68)	3 (1)	0	0
HR (95% CI)	0.72 (0.60 to 0.85)	0.67 (0.55 to 0.80)	NA	NA	NA
NNT	8	4	NA	NA	NA

CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients trial; CI: confidence interval; HFH: heart failure hospitalization; HR: hazard ratio; NA: not applicable; NNT: number needed to treat; RCT: randomized controlled trial.

Table 4. Summary of Additional Analyses of the CHAMPION RCT

Trial Period	Randomized Group	CardioMEMS Data Available	Nurse Communications	Comparison	HR for HFH (95% CI)
Randomized access	Treatment	Yes	Yes	Former control to control	0.52 (0.40 to 0.69)
	Control	No	No	Former treatment to treatment	0.93 (0.70 to 1.22)
Open access	Former control	Yes	No	Former control to former treatment	0.80 (0.56 to 1.14)
	Former treatment	Yes	No	NR	NR

Adapted from Abraham et al (2016) and FDA (2013).[10,9]
CI: confidence interval; HFH: heart failure hospitalization; HR: hazard ratio; NR: not reported.
Tables 5 and 6 display notable limitations identified in each study.

Table 5. Study Relevance Limitations

Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Abraham et al(2011, 2016)[7,8]; CHAMPION		1. Delivery not similar intensity as comparator. Treatment group received additional nurse communication for enhanced protocol compliance. Trial intention was to assess physician's ability to use PA pressure information and not capabilities of sponsor's nursing staff to monitor and correct physician-directed therapy.			

CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients trial; PA: pulmonary artery.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Abraham (2011,		1. Physicians not blinded to treatment assignment but outcome assessment				

Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
2016)[7,8]; CHAMPION		was independent and blinded				

CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Studies

As previously described in the selection criteria, studies will be included here to assess long-term outcomes and adverse effects if they capture longer periods of follow-up and/or larger populations than the RCTs.

Shavelle et al (2020) reported 1 year outcomes from the open-label, observational, single-arm, post-approval study of CardioMEMS in 1200 patients (37.7% female) across 104 centers in the U.S. with NYHA Class III heart failure and a heart failure-related hospitalization in the prior year.[15] Study characteristics and results are summarized in Tables 7 and 8. Study visits were planned at 1, 6, 12, 18, and 24 months. The primary efficacy outcome was the difference between rates of adjudicated heart failure-related hospitalization 1 year after compared to 1 year prior to device implantation. The 12-month visit was completed in 875 patients (72.9%). Prior to 1 year, 76 patients (6.3%) withdrew from the study and 186 patients (15.5%) died. The heart failure-related hospitalization rate was significantly lower at 1 year post-implantation (0.54 versus 1.25 events/patient-year; hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.39 to 0.47; $P<0.0001$). The rate decreases remained significant regardless of the number of pre-enrollment heart failure-related hospitalizations, with a trend towards a more significant benefit in a small subgroup of patients (n=21) with ≥ 5 pre-enrollment heart failure-related hospitalizations. The rate of all-cause hospitalization (ACH) was also significantly lower (1.67 versus 2.28 events/patient-year; HR, 0.73; 95% CI, 0.68 to 0.78; $P<0.0001$). These results were consistent across subgroups defined by ejection fraction, sex, race, cardiomyopathy cause, and presence or absence of implantable cardiac defibrillator or cardiac resynchronization therapy. The mean rate of daily pressure transmission was 76 ± 24%. Pressure changes differed according to baseline mean pulmonary artery pressure, with the largest decreases observed in patients with baseline pulmonary artery pressure ≥ 35 mmHg (n=550). Pulmonary artery pressure also decreased in the subgroup of patients that died in the year postimplantation. During the study, 94.1% of patients had a medication change, with an average of 1.6 medication changes per month. Medication changes related to an increase or decrease in pulmonary artery pressure were implemented in 81.8% and 55.8% of patients, respectively. The primary safety outcome was defined as freedom from device- or system-related complications and pressure sensor failure at 2 years. Two year safety follow-up has not yet been concluded. At 1 year, freedom from device- or system-related complications was 99.6% (5 events) and freedom from pressure sensor failure was 99.9% (1 event). The nature of these events and the frequency of procedure-related adverse events was not reported. Study interpretation is limited by the lack of a randomized control group and the potential influence of both information and survivor bias. Assessing heart failure-related hospitalizations as a study entry requirement and an endpoint may also reflect a bias of prior hospitalization in favor of any intervention. Notably, 82.8% of patients had a medication change that was unrelated to changes in pulmonary artery pressure (e.g., uptitration of neurohormonal modulation in stable patients). Therefore, it is unclear to what degree heart failure-related hospitalization reduction can be explained by a more intensive follow-up and drug uptitration plan in the year following implantation. Details regarding the frequency of nursing and/or provider communications were not reported.

Angermann et al (2020) published results from the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF).[16.] This was an industry-sponsored, prospective, observational, non-randomized study designed to assess the safety and feasibility of the CardioMEMS HF system over 12-month follow up in 31 centers across Germany, the Netherlands, and Ireland. A total of 239 patients (22% female) with NYHA class III heart failure and ≥ 1 heart failure-related hospitalization in the prior year were enrolled for remote pulmonary artery pressure-guided heart failure management. Patients were also contacted by nursing staff on a weekly basis during the first month, and biweekly or monthly based on current NYHA class. NYHA class improved in 83 patients (35.5%) and worsened in 4 patients (1.7%) at 12 months. Mean daily adherence to pulmonary artery pressure transmission was 78.1 ± 23.5% (median, 87.6% [interquartile range, 69.4% to 94.9%]). Co-primary outcome measures, 1-year rates of freedom from device- or system-related complications and sensor failure, were 98.3% (95% CI, 95.8 to 100.0) and 99.6% (95% CI, 97.6 to 100), respectively. Twenty-one serious adverse events (8.9%) were reported during 236 implant attempts, of which 4 were categorized as device- or system-related and 21 as procedure-related. Three procedure-related cardiac deaths were reported. The overall 12-month mortality rate was 13.8%, with no device- or system-related deaths. The secondary outcome measures included heart failure-related hospitalization rate at 12 months compared to the prior year before implantation and health-related quality of life. Heart failure-related hospitalizations decreased 62% (0.60 versus 1.55 events/patient year; HR, 0.38; 95% CI, 0.31 to 0.48; P<0.0001). These reductions were consistent across subgroups defined by sex, age, heart failure etiology, device use, ejection fraction, baseline pulmonary artery pressure, and various comorbidities. Patient-reported health-related quality of life outcomes were assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ), 9-Item Patient Health Questionnaire (PHQ-9), and the EQ-5D-5L. All measures significantly improved at 6 months and were sustained through 12 months. Cumulative medication changes and the average rate of monthly per-patient medication changes were highest in months 0 to 3 postimplant, with diuretics adjusted most often. While the observed heart failure-related hospitalization rate reduction in MEMS-HF is consistent with U.S. experience with the CardioMEMS device, the authors note that study results may have been impacted by information bias, regression to the mean, asymmetrical data handling, and confounding or selection of patients thought to be adherent to remote patient management requirements. Although helpful for evaluating safety and feasibility, prospective registries using historical events for within-patient comparisons cannot provide definitive effectiveness data. The Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF) randomized controlled trial of the CardioMEMS device is currently ongoing in the U.S., with a planned enrollment of 3600 patients across 139 centers.

Abraham et al (2019) published a retrospective matched cohort study of Medicare beneficiaries who received the CardioMEMS device between 2014 and 2016.[17.] Patients were matched to 1087 controls by demographics, history and timing of heart failure-related hospitalizations, and number of ACH. Propensity scoring based on arrhythmia, hypertension, diabetes, pulmonary disease, and renal disease was used for additional matching. Follow-up was censored at death, ventricular assist device implant, or heart transplant. At 12 months postimplantation, 616 and 784 heart failure-related hospitalizations occurred in the treatment and control cohorts, respectively. Study characteristics and results are summarized in Tables 7 and 8. The rate of heart failure-related hospitalizations was lower in the treatment cohort at 12 months (HR, 0.76; 95% CI, 0.65 to 0.89; *P*<0.001). Percentage of days lost to heart failure-related hospitalizations (HR, 0.73; 95% CI, 0.64 to 0.84; *P*<0.001) and ACH or death (HR, 0.77; 95% CI, 0.68 to 0.88; *P*<0.001) were both significantly lower in the treatment group. The treatment cohort had 241 deaths and 20 ventricular assist device implants or heart transplants; over the same period, the control cohort had 325 deaths and 13 ventricular assist device implants or heart transplants. Mean (standard deviation [SD]) length of hospital stay was 6.6 (6.5) and 6.5 (5.8) days in the control and treatment cohorts, respectively (*P* =0.70). Mean (SD) total days spent in hospital for heart failure was 3.7 (9.5) and 4.4 (10.3), respectively. The percentage of days lost owing to heart failure-related hospitalization or death was reduced in the treatment cohort (relative risk [RR], 0.73; 95% CI, 0.63 to 0.83). Limitations of this study include lack of medical history data, including ejection fraction, natriuretic peptide levels, renal function, and medication use. Residual confounding by unmeasured covariates remains possible, including the role of heightened health care team involvement in implanted patients.

Desai et al (2017) published a retrospective cohort study of Medicare administrative claims data for individuals who received the CardioMEMS device following the FDA approval.[18.] Of 1935 Medicare enrollees who underwent implantation of the device, 1114 were continuously enrolled and had evaluable data for at least 6 months before, and following, implantation. A subset of 480 enrollees had complete data for 12 months before and after implantation. Study characteristics and results are summarized in Tables 7 and 8. The cumulative incidence of heart failure-related hospitalizations were significantly lower in the postimplantation period than in the preimplantation period at both 6- and 12-month follow-ups. Limitations of this pre-post retrospective study include lack of data on medical history, ejection fraction, indication for implantation and possible confounding due to amplified touchpoints with the health care system necessitated by the device's implantation.

Vaduganathan (2017) analyzed mandatory and voluntary reports of device-related malfunctions reported to the FDA to identify CardioMEMS HF System-related adverse events within the first 3 years of the FDA approval.[19.] From among the more than 5500 CardioMEMS implants in the first 3 years, there were 155 adverse event reports covering 177 distinct adverse events for a rate of 2.8%. There were 28 reports of pulmonary artery injury/hemoptysis (0.5%) that included 14 intensive care unit stays, 7 intubations, and 6 deaths. Sensor failure, malfunction, or migration occurred in 46 cases, of which 35 required recalibrations. Compared with a reported 2.8% event rate, the serious adverse event rate in CHAMPION trial was 2.6% with 575 implant attempts, including 1 case of pulmonary artery injury and 2 deaths. Limitation of the current analysis primarily included lack of adjudication and limited clinical data.

Table 7. Summary of Key Nonrandomized Study Characteristics

Author	Study Type	Country/Institution	Dates	Participants	Treatment	Follow-Up
Shavelle et al (2020)[15.]	Post-approval multicenter study	U.S./Abbott	2014-2017	Individuals with a diagnosis of NYHA class III heart failure and at least 1 HFH within the previous 12 months.	CardioMEMS implant	12 mo
Angermann et al (2020)[16.]	Prospective multicenter study	Germany, the Netherlands, Ireland/Abbott	2016-2018	Individuals with a diagnosis of NYHA class III heart failure and at least 1 HFH within the previous 12 months	CardioMEMS implant; communications with trained non-physician staff	12 mo
Abraham et al (2019)[17.]	Retrospective matched cohort	U.S./Medicare/Abbott	2014-2016	Individuals with CPT codes consistent	CardioMEMS implant	12 mo

Author	Study Type	Country/Institution	Dates	Participants	Treatment	Follow-Up
				with use of procedure and at least 1 HFH within the previous 12 months		
Desai et al (2017)[18]	Retrospective cohort	U.S./Medicare	2014-2015	Individuals with inpatient CPT codes consistent with use of procedure	CardioMEMS implant	2 cohorts: • 6-mo preimplant and postimplant data (n=1114) • 12-mo preimplant and postimplant data (n=480)
Vaduganathan et al (2017)[19]	Postmarketing surveillance study	U.S./FDA and Abbott	2014-2017	Individuals reporting Cardio-MEMS-related adverse event	CardioMEMS implant	Not applicable

FDA: U.S. Food and Drug Administration; HFH: heart failure-related hospitalization; NYHA: New York Heart Association,

Table 8. Summary of Key Nonrandomized Study Results

Study	HFH at 6 Months	HFH at 12 Months	Safety
Shavelle et al (2020)[15]	1013	875	NR
HR (95% CI); *P*	NR	0.43 (0.39 to 0.47); <0.0001	Freedom from DSRC: 99.6% Freedom from pressure sensor failure: 99.9%
Angermann et al (2020)[16]	198	234[a];180[b]	236
HR (95% CI); *P*	NR	0.38 (0.31 to 0.48); <0.0001[a] 0.34 (0.26 to 0.44); <0.0001[b]	Freedom from DSRC: 1.7% Freedom from pressure sensor failure: 0.4% SAE: 21/236 (8.9%) Delivery system-related events: 4 Implant procedure-related events: 21 Pulmonary artery perforation: 1 (0.4%) Procedure-related cardiac deaths: 3 (1.3%)
Abraham et al (2019)[17]	NR	1087	NR
HR (95% CI); *P*	NR	0.76 (0.65 to 0.89); <0.001	NR
Desai et al (2017)[18]	1114	480	NR
Preimplant, n	1020	696	NR
Postimplant, n	381	300	NR
HR (95% CI); *P*	0.55 (0.49 to 0.61); <0.001	0.66 (0.57 to 0.76); <0.001	NR
Vaduganathan et al (2017)[19]			Estimated 5500 received CardioMEMS

Study	HFH at 6 Months	HFH at 12 Months	Safety
AE cohort identified from MAUDE database	NR	NR	155 (2.8%) AEs; 28 pulmonary artery injury or hemoptysis (0.5%), and 2 (0.4%) deaths

AE: adverse event; CI: confidence interval; DSRC: device- or system-related complications, HFH: heart failure hospitalization; HR: hazard ratio; NR: not reported; SAE: serious adverse event.
[a] The primary efficacy analysis consisted of all 234 patients implanted with the CardioMEMS device.
[b] Results at 12-month follow-up as completed by 180 patients.

Case Series

Heywood et al (2017) reported pulmonary artery pressure data for the first 2000 consecutive patients with at least 6 months of follow-up who were implanted with CardioMEMS. No clinical data were reported except for pulmonary artery measurement.[20] Study characteristics and results are summarized in Tables 9 and 10. The mean age of the cohort enrolled was 70 years and the mean follow-up period was 333 days. There was a median of 1.2 days between remote pressure transmissions and greater than 98% weekly use of the system, demonstrating a high level of adherence.

Table 9. Summary of Key Case Series Characteristics

Author	Country/Institution	Participants	Treatment Delivery	Follow-Up (SD)
Heywood et al (2017)[20]	U.S./Abbott	First 2000 individuals who received CardioMEMS with follow-up data for a minimum of 6 mo	CardioMEMS	333 (125) d

SD: standard deviation.

Table 10. Summary of Key Case Series Results

Author	Treatment	AUC (mm Hg day)	Adherence
Heywood et al (2017)[20]	CardioMEMS device	• -32.8 mm Hg/d (1 mo) • -156.2 mm Hg/d (3 mo) • -434.0 mm Hg/d (6 mo)	• Median days between transmissions: 1.07 d (first 30 d) and 1.27 days (after 6 mo) • Use of the system: 98.6% (IQR, 82.9%-100.0%)

AUC: area under the curve; IQR: interquartile range.

Section Summary: Implantable Pulmonary Artery Pressure Monitoring (CardioMEMS Device)

The pivotal CHAMPION RCT reported a statistically significant decrease in heart failure-related hospitalizations in patients implanted with CardioMEMS device compared with usual care. However, trial results were potentially biased in favor of the treatment group due to use of additional nurse communication to enhance protocol compliance with the device. The trial intended to assess the physician's ability to use pulmonary artery pressure information and not the capabilities of the sponsor's nursing staff to monitor and correct physician-directed therapy. The manufacturer conducted multiple analyses to address the potential bias from the nurse interventions. These analyses were reviewed favorably by the FDA. While these analyses demonstrated the consistency of benefit from the CardioMEMS device, all such analyses have methodologic limitations. With greater adoption of this technology, it is likely to be used by a broader group of clinicians with variable training in the actual procedure and used in patients at a higher risk compared with those in the CHAMPION trial. Early safety data have been suggestive of a higher rate of procedural complications, particularly related to pulmonary artery injury. While the U.S. CardioMEMS post-approval study and European MEMS-HF study reported a significant decrease in heart-failure related hospitalizations with few device- or system-related complications at 1 year, the impact of nursing interventions remains unclear. Complete 2-year safety outcomes from the CardioMEMS post-approval study are pending, and the serious adverse event rate in the MEMS-HF trial was 8.9%. Given that the intervention is invasive and intended to be used for a highly prevalent condition, in the light of limited safety data, lack of demonstrable mortality benefit, and pending questions related to its benefit for reduction in hospitalization, the net benefit remains uncertain. Concerns may be clarified by the ongoing GUIDE-HF RCT that proposes to enroll 3600 patients.

Noninvasive Thoracic Bioimpedance/Impedance Cardiography

Clinical Context and Test Purpose

The purpose of thoracic bioimpedance in patients who have heart failure in an outpatient setting is (1) to guide volume management, (2) to identify physiologic changes that precede clinical symptoms and thus allow preventive interventions, and (3) to prevent hospitalizations.

The question addressed in this evidence review is: Does the use of thoracic bioimpedance/ impedance cardiography improve net health outcomes in individuals with heart failure in the outpatient setting?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with chronic heart failure who are at risk of developing acute decompensated heart failure (ADHF).

Interventions

The test being considered is thoracic bioimpedance.

Bioimpedance is defined as the electrical resistance of current flow through tissue. For example, when small electrical signals are transmitted through the thorax, the current travels along the blood-filled aorta, which is the most conductive area. Changes in bioimpedance, measured during each beat of the heart, are inversely related to pulsatile changes in volume and velocity of blood in the aorta. Cardiac output is the product of stroke volume by heart rate and, thus, can be calculated from bioimpedance. Cardiac output is generally reduced in patients with systolic heart failure. Acute decompensation is characterized by worsening of cardiac output from the patient's baseline status. The technique is alternatively known as impedance cardiography.

Comparators

The comparator of interest is standard clinical care without testing. Decisions on guiding volume management are being made based on signs and symptoms.

Outcomes

The general outcomes of interest are the prevention of decompensation episodes, reductions in hospitalization and mortality, and improvements in quality of life.

Generally, demonstration of outcomes over a 1-year period is meaningful for interventions.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several studies were excluded from the evaluation of the clinical validity of the thoracic bioimpedance testing because they did not include information needed to assess clinical validity.[21,22,23,]

Packer et al (2006) reported on use of impedance cardiography measured by BioZ impedance cardiography monitor to predict decompensation in patients with chronic heart failure.[24,] In this study, 212 stable patients with heart failure and a recent episode of decompensation underwent serial evaluation and blinded impedance cardiography testing every 2 weeks for 26 weeks and were followed for the occurrence of death or worsening heart failure requiring hospitalization or emergent care. Results are summarized in Table 11. A composite score of 3 impedance cardiography parameters was a predictor of an event during the next 14 days (p<0.001).

Table 11. Clinical Validity of 3-Level Risk Score for BioZ Impedance Cardiography Monitor

Author	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity:Mean Probability of Outcome (95% CI), %		
					Low Risk	*Medium Risk*	*High Risk*
Packer et al (2006)[24.]	212	212	None	59 patients had 104 episodes of decompensated HF including 16 deaths, 78 hospitalizations, 10 ED visits	1.0 (0.5 to 1.9)	3.5 (2.4 to 4.8)	8.4 (5.8 to 11.6)

CI: confidence interval; ED: emergency department; HF: heart failure.

Section Summary: Clinically Valid

The clinical validity of using thoracic bioimpedance for patients with chronic heart failure who are at risk of developing ADHF has not been established. Association studies are insufficient evidence to determine whether thoracic bioimpedance can improve outcomes in patients with chronic heart failure who are at risk of developing ADHF. There are no studies reporting the clinical validity regarding sensitivity, specificity, or predictive value.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Amir et al (2017) reported on results of a prospective study in which 59 patients recently hospitalized for heart failure were selected for ReDS-guided treatment for 90 days.[25.] The number of heart failure hospitalizations during 90-day ReDS-guided therapy were compared with hospitalizations in the preceding 90 days before enrollment and the 90 days following discontinuation of ReDS monitoring. During treatment, patients were equipped with the ReDS wearable vest, which was worn once a day at home to measure lung fluid content. Study characteristics and results are summarized in Tables 12 and 13. The rate of heart failure hospitalizations was lower during the ReDS-guided follow-up compared with pre and posttreatment periods. Interpretation of results is uncertain due to the lack of concurrent control and randomization, short-term follow-up, large CIs, and lack of clarity about lost-to-follow-up during the post-ReDS period. An RCT comparing ReDS monitoring with standard of care (SMILE; NCT02448342) was initiated but terminated before its completion.

Table 12. Summary of Key Nonrandomized Study Characteristics

Author	Study Type	Country	Dates	Participants	Treatment	Mean FU (SD), d
Amir et al (2017)[25.]	Pre-post prospective cohort	Israel	2012-2015	Patients ≥18 y with stage C heart failure, regardless of LVEF (n=59)	ReDS Wearable System	83.0 (25.4)

FU: follow-up; LVEF: left ventricular ejection fraction; SD: standard deviation.

Table 13. Summary of Key Nonrandomized Study Results

Study	Heart Failure-Related Hospitalizations (events/patient/3 mo)	Deaths
Amir et al (2017)[25.]	50	50
Pre-90-day period (control)	0.04	0

Study	Heart Failure-Related Hospitalizations (events/patient/3 mo)	Deaths
90-day treatment period	0.30	2
Post-90-day period (control)	0.19	2
Hazard ratio (95% confidence interval); p	• 0.07 (0.01 to 0.54); 0.01[a] • 0.11 (0.014 to 0.88); 0.037[b]	

[a] Treatment versus pretreatment period;
[b] Treatment versus posttreatment period.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Because the clinical validity of using thoracic bioimpedance has not been proved, a chain of evidence to support its clinical utility cannot be constructed.

Section Summary: Clinical Utility

The clinical utility of using thoracic bioimpedance for patients with chronic heart failure who are at risk of developing ADHF has not been established. One prospective longitudinal study reported that ReDS-guided management reduced heart failure readmissions in ADHF patients recently discharged from the hospital. However, interpretation of results is uncertain due to the lack of concurrent controls and randomization, short-term follow-up, large CIs, and lack of clarity about lost-to-follow-up during the post-ReDS monitoring period. An RCT comparing ReDS monitoring with standard of care was initiated but terminated before its completion.

Inert Gas Rebreathing

Clinical Context and Test Purpose

The purpose of inert gas breathing in patients who have heart failure in an outpatient setting is (1) to guide volume management, (2) to identify physiologic changes that precede clinical symptoms and thus allow preventive interventions, and (3) to prevent hospitalizations.

The question addressed in this evidence review is: Does the use of inert gas breathing improve net health outcomes in individuals with heart failure in the outpatient setting?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with chronic heart failure who are at risk of developing ADHF.

Interventions

The test being considered is inert gas breathing.

Inert gas rebreathing is based on the observation that the absorption and disappearance of a blood-soluble gas are proportional to cardiac blood flow. The patient is asked to breathe and rebreathe from a bag filled with oxygen mixed with a fixed proportion of 2 inert gases, typically nitrous oxide and sulfur hexafluoride. The nitrous oxide is soluble in blood and is therefore absorbed during the blood's passage through the lungs at a rate proportional to the blood flow. The sulfur hexafluoride is insoluble in blood and therefore stays in the gas phase and is used to determine the lung volume from which the soluble gas is removed. These gases and carbon dioxide are measured continuously and simultaneously at the mouthpiece.

This noninvasive procedure is administered by a cardiologist in an outpatient clinical setting.

Comparators

The comparator of interest is standard clinical care without testing. Decisions on guiding volume management are being made based on signs and symptoms.

Patients with heart failure are managed by cardiologists in an outpatient clinical setting.

Outcomes
The general outcomes of interest are the prevention of decompensation episodes, reduction in hospitalization and mortality, and improvement in quality of life.

Trials of using inert gas rebreathing for this population were not found. Generally, demonstration of outcomes over a 1-year period is meaningful for interventions.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No studies on the clinical validity were identified that would establish how the use of inert gas rebreathing measurements helps detect the likelihood of decompensation.

Section Summary: Clinically Valid
The clinical validity of using inert gas breathing for patients with chronic heart failure who are at risk of developing ADHF has not been established.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies were identified that determined how the use of inert gas rebreathing measurements is associated with changes in patient management or evaluated the effects of this technology on patient outcomes.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Because the clinical validity of using inert gas breathing has not been proved, a chain of evidence to support clinical utility cannot be constructed.

Section Summary: Clinically Valid
No studies of clinical utility were identified that determined how the use of inert gas breathing measurements in managing heart failure affects patient outcomes. It is unclear how such devices will improve patient outcomes.

Noninvasive Left Ventricular End-Diastolic Pressure Estimation
Clinical Context and Test Purpose
The purpose of LVEDP estimation in patients who have heart failure in an outpatient setting is (1) to guide volume management, (2) to identify physiologic changes that precede clinical symptoms and thus allow preventive interventions, and (3) to prevent hospitalizations.

The question addressed in this evidence review is: Does the use of noninvasive LVEDP estimation improve health outcomes in individuals with heart failure in the outpatient setting?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with chronic heart failure who are at risk of developing ADHF.

Interventions
The test being considered is noninvasive LVEDP estimation.

LVEDP is elevated with acute decompensated heart failure. While direct catheter measurement of LVEDP is possible for patients undergoing cardiac catheterization for diagnostic or therapeutic reasons, its invasive nature precludes outpatient use. Noninvasive measurements of LVEDP have been developed based on the observation that arterial pressure during the strain phase of the Valsalva maneuver may directly reflect the LVEDP. Arterial pressure responses during repeated Valsalva maneuvers can be recorded and analyzed to produce values that correlate to the LVEDP.

This noninvasive procedure is administered by a cardiologist in an outpatient clinical setting.

Comparators
The comparator of interest is standard clinical care without testing. Decisions guiding volume management are being made based on signs and symptoms.

Patients with heart failure are managed by cardiologists in an outpatient clinical setting.

Outcomes
The general outcomes of interest are the prevention of decompensation episodes, reduction in hospitalization and mortality, and improvement in quality of life.

Trials of using noninvasive LVEDP estimation for this population were not found. Generally, demonstration of outcomes over a 1-year period is meaningful for interventions.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Silber et al (2012) reported on finger photoplethysmography during the Valsalva maneuver performed in 33 patients before cardiac catheterization.[26] LVEDP was measured via a catheter placed in the left ventricle and used as the reference standard. For identifying LVEDP greater than 15 mm Hg, finger photoplethysmography during the Valsalva maneuver was 85% sensitive (95% CI, 54% to 97%) and 80% specific (95% CI, 56% to 93%).

Section Summary: Clinically Valid
Only 1 study was identified assessing the use of LVEDP monitoring in this patient population; it reported an 85% sensitivity and an 80% specificity to detect LVEDP greater than 15 mm Hg.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies were identified that determined how the use of noninvasive LVEDP estimation is associated with changes in patient management or evaluated the effects on patient outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of using noninvasive LVEDP estimation has only been demonstrated in a small, single study, a chain of evidence to support clinical utility cannot be constructed.

Section Summary: Clinically Useful

No studies of clinical utility were identified that assessed how the use of noninvasive LVEDP estimation in managing heart failure affects patient outcomes. A chain of evidence on the clinical utility of noninvasive LVEDP estimation cannot be constructed because it is unclear how these devices will improve patient outcomes.

Summary of Evidence

For individuals who have heart failure in outpatient settings who receive hemodynamic monitoring with an implantable pulmonary artery pressure sensor device, the evidence includes RCTs. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. One implantable pressure monitor, the CardioMEMS device, has U.S. FDA approval. The pivotal CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA III Heart Failure Patients RCT reported a statistically significant decrease in heart failure-related hospitalizations in patients implanted with CardioMEMS device compared with usual care. However, trial results were potentially biased in favor of the treatment group due to use of additional nurse communication to enhance protocol compliance with the device. The manufacturer conducted multiple analyses to address potential bias from the nurse interventions. Results were reviewed favorably by the FDA. While these analyses demonstrated the consistency of benefit from the CardioMEMS device, all such analyses have methodologic limitations. Early safety data have been suggestive of a higher rate of procedural complications, particularly related to pulmonary artery injury. While the U.S. CardioMEMS post-approval study and CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF) study reported a significant decrease in heart-failure related hospitalizations with few device- or system-related complications at 1 year, the impact of nursing interventions remains unclear. Complete 2-year safety outcomes from the CardioMEMS post-approval study are pending, and the serious adverse event rate in the MEMS-HF trial was 8.9%. Given that the intervention is invasive and intended to be used for a highly prevalent condition, in the light of limited safety data, lack of demonstrable mortality benefit, and pending questions related to its benefit in reducing hospitalizations, the net benefit remains uncertain. Concerns may be clarified by the ongoing GUIDE-HF RCT that proposes to enroll 3600 patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart failure in outpatient settings who receive hemodynamic monitoring by thoracic bioimpedance, the evidence includes uncontrolled prospective studies and case series. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. There is a lack of RCT evidence evaluating whether the use of these technologies improves health outcomes over standard active management of heart failure patients. The case series have reported physiologic measurement-related outcomes and/or associations between monitoring information and heart failure exacerbations, but do not provide definitive evidence on device efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart failure in outpatient settings who receive hemodynamic monitoring with inert gas rebreathing, no studies have been identified on clinical validity or clinical utility. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart failure in outpatient settings who receive hemodynamic monitoring of arterial pressure during the Valsalva maneuver, a single study was identified. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. The study assessed the use of LVEDP monitoring and reported an 85% sensitivity and an 80% specificity to detect LVEDP greater than 15 mm Hg. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology et al

In 2017, the American College of Cardiology, the American Heart Association, and the Heart Failure Society of America issued joint guidelines on the management of heart failure that offered no recommendations for the use of ambulatory monitoring devices.[27]

National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence (NICE) updated their guidelines on chronic heart failure management and did not include outpatient hemodynamic monitoring as a recommendation. [28]

In 2013, the Institute issued guidance on the insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure.[29] The recommendations concluded that "Current evidence on the safety and efficacy of the insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure is limited in both quality and quantity."

Heart Failure Society of America

In 2018, the Heart Failure Society of America Scientific Statements Committee (2018) published a white paper consensus statement on remote monitoring of patients with heart failure.[30]
The committee concluded that: "Based on available evidence, routine use of external RPM devices is not recommended. Implanted devices that monitor pulmonary arterial pressure and/or other parameters may be beneficial in selected patients or when used in structured programs, but the value of these devices in routine care requires further study."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

In 2014, the Centers for Medicare & Medicaid Services updated its 2006 decision memorandum on thoracic electrical bioimpedance.[31] Medicare's national coverage determination found thoracic bioimpedance to be reasonable and necessary for the following indications:

- Differentiation of cardiogenic from pulmonary causes of acute dyspnea;
- Optimization of atrioventricular interval for patients with atrioventricular sequential cardiac pacemakers;

- Monitoring of continuous inotropic therapy for patients with terminal heart failure;
- Evaluation for rejection in patients with a heart transplant as a predetermined alternative to myocardial biopsy; and
- Optimization of fluid management in patients with congestive heart failure.

While Medicare permits coverage of thoracic bioimpedance in these conditions, it has acknowledged that there is a "...general absence of studies evaluating the impact of using thoracic bioimpedance for managing patients with cardiac disease...." Medicare does not cover the use of thoracic bioimpedance in the management of hypertension due to inadequate evidence.

Medicare has also specified that thoracic bioimpedance is not covered for "the management of all forms of hypertension (with the exception of drug-resistant hypertension...)."
Further, Medicare specified that:

> "[Contractors] have discretion to determine whether the use of TEB [thoracic bioimpedance] for the management of drug-resistant hypertension is reasonable and necessary. Drug resistant hypertension is defined as failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic."

There is no Medicare national coverage determination on implantable direct pressure monitoring, inert gas rebreathing, and arterial pressure with Valsalva.

Effective April 7, 2016, Novitas Solutions issued a noncoverage local coverage determination (ID L36419) for outpatient wireless pulmonary artery pressure monitoring for heart failure (CardioMEMS). As of July 1, 2020, this local coverage determination has been retired.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04223271[a]	Heart Failure Event Advance Detection Trial (HEADstart)	165	Apr 2021 (recruiting)
NCT03476590	A New Model of Medical Care With Use of Modern Methods of Non-invasive Clinical Assessment and Telemedicine in Patients With Heart Failure (AMULET)	605	Jun 2021 (ongoing)
NCT02954341[a]	CardioMEMS HF System OUS Post Market Study	800	Dec 2023 (recruiting)
NCT03387813[a]	Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF)	3600	Feb 2024 (recruiting)
NCT04398654	Pulmonary Artery Sensor System Pressure Monitoring to Improve Heart Failure (HF) Outcomes	554	May 2024 (recruiting)
NCT04441203	Patient SELF-management With HemodynamIc Monitoring: Virtual Heart Failure Clinic and Outcomes (SELFIe-HF)	150	Jun 2024 (not yet recruiting)
NCT03020043	CardioMEMS Registry of the Frankfurt Heart Failure Center	500	Dec 2025 (recruiting)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0607T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment
	0608T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional
	33289	Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed
	93264	Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional
	93701	Bioimpedance-derived physiologic cardiovascular analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/16/2008	New Medical Policy Adoption
10/07/2011	Policy title change from Thoracic Bioimpedance (TEB) & Inert Gas Rebreathing in the Outpatient Setting with adoption of BCBSA policy

Effective Date	Action
08/29/2014	Policy title change from Cardiac Hemodynamic Monitoring in the Outpatient Setting Policy title change without position change
01/01/2015	Coding update
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
02/01/2019	Coding update
07/01/2019	Policy revision without position change
07/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2020	Coding update
07/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting 2.02.24 **Policy Statement:** In the ambulatory care and outpatient setting, cardiac hemodynamic monitoring for the management of heart failure is considered **investigational** when using **any** of the following: • Arterial pressure during the Valsalva maneuver • Implantable direct pressure monitoring of the pulmonary artery • Inert gas rebreathing • Thoracic bioimpedance	**Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting 2.02.24** **Policy Statement:** In the ambulatory care and outpatient setting, cardiac hemodynamic monitoring for the management of heart failure is considered **investigational** when using **any** of the following: I. Arterial pressure during the Valsalva maneuver II. Implantable direct pressure monitoring of the pulmonary artery III. Inert gas rebreathing IV. Thoracic bioimpedance