Transcatheter Mitral Valve Repair or Replacement

Policy # 00494
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Transcatheter Aortic Valve Implantation for Aortic Stenosis is addressed separately in medical policy 00406.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider transcatheter mitral valve repair (TMVR) with a device approved by the U.S. Food and Drug Administration (FDA) for use in mitral valve repair to be **eligible for coverage****, for individuals with symptomatic, primary mitral regurgitation (MR) who are considered at prohibitive risk for open surgery (See Policy Guidelines section).

Based on review of available data, the Company may consider transcatheter mitral valve repair (TMVR) with a device approved by the U.S. FDA for individuals with heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy to be **eligible for coverage**** (See Policy Guidelines section).

Based on review of available data, the Company may consider transcatheter mitral valve-in-valve replacement (TMViVR) with a device approved by the U.S. FDA to be **eligible for coverage:****

<u>Patient Selection Criteria</u>
Coverage eligibility for transcatheter mitral valve-in-valve replacement (TMViVR) with a device approved by the U.S. FDA will be considered when all of the following conditions are present:

- Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic mitral valve; AND

- New York Heart Association heart failure class II, III, or IV symptoms; AND
- Individual is not an operable candidate for open surgery, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon); OR individual is an operable candidate but is considered at increased surgical risk for open surgery, as documented by at least 2 cardiac specialists (including a cardiac surgeon); OR individual is considered at increased surgical risk for open surgery (eg, repeat sternotomy) due to a history of congenital vascular anomalies AND/OR has a complex intrathoracic surgical history, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon) (see Policy Guidelines section).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers transcatheter mitral valve repair (TMVR) in all other situations to be **investigational.***

Policy Guidelines

"Prohibitive risk" for open surgery may be determined based on:

- Presence of a Society for Thoracic Surgeons predicted mortality risk of 12-% or greater and/or
- Presence of a logistic EuroSCORE of 20% or greater.

The FDA definition of high risk for open surgery is:

- Society of Thoracic Surgeons (STS) predicted operative risk score of 8% or higher; or
- Judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery.

Moderate to severe or severe MR may be determined by:

- Grade 3+ (moderate) or 4+ (severe) MR confirmed by echocardiography
- New York Heart Association (NYHA) functional class II, III, or IVa (ambulatory) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac

resynchronization therapy (if appropriate) administered in accordance with guidelines of professional societies.

Optimal medical therapy may be determined by guidelines from specialty societies (e.g., American Heart Association/American College of Cardiology Guideline for the Management of Individuals with Valvular Heart Disease, European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the Management of Valvular Heart Disease, American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure (refer to supplemental materials for guideline citations).

Background/Overview

Mitral Regurgitation

Epidemiology and Classification

Mitral regurgitation (MR) is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all individuals with valvular heart disease. MR with accompanying valvular incompetence leads to left ventricular (LV) volume overload with secondary ventricular remodeling, myocardial dysfunction, and left heart failure. Clinical signs and symptoms of dyspnea and orthopnea may also be present in individuals with valvular dysfunction. MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3+ to 4+ angiographic grade, respectively).

Individuals with MR generally fall into 2 categories: primary (also called degenerative) and secondary (also called functional) MR. Primary MR results from a primary structural abnormality in the valve, which causes it to leak. This leak may result from a floppy leaflet (called prolapse) or a ruptured cord that caused the leaflet to detach partially (called flail). Because the primary cause is a structural abnormality, most cases of primary MR are surgically corrected. Secondary MR results from LV dilatation due to ischemic or dilated cardiomyopathy. This causes the mitral valve (MV) leaflets not to coapt or meet in the center. Because the valves are structurally normal in secondary MR, correcting the dilated LV using medical therapy is the primary treatment strategy used in the U.S.

Standard Management

Surgical Management
In symptomatic individuals with primary MR, surgery is the main therapy. In most cases, MV repair is preferred over replacement, as long as the valve is suitable for repair and personnel with appropriate surgical expertise are available. The American College of Cardiology and the American Heart Association have issued joint guidelines on the surgical management of MV (See Supplemental Information).

The use of standard open MV repair is limited by the requirement for thoracotomy and cardiopulmonary bypass, which may not be tolerated by elderly or debilitated individuals due to their underlying cardiac disease or other conditions. In a single-center evaluation of 5737 individuals with severe MR in the U.S., Goel et al (2014) found that 53% of individuals did not have MV surgery performed, suggesting an unmet need for such individuals.

Isolated MV surgery (repair or replacement) for severe chronic secondary MR is not generally recommended because there is no proven mortality reduction and an uncertain durable effect on symptoms. Recommendations from major societies regarding MV surgery in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement are weak because the current evidence is inconsistent on whether MV surgery produces a clinical benefit.

Transcatheter Mitral Valve Repair
Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among inoperable individuals who face prohibitively high surgical risks due to age or comorbidities. MV repair devices under development address various components of the MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass. Approaches to MV repair include direct leaflet repair, repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

Direct Leaflet Approximation
Devices currently approved by the FDA for transcatheter mitral valve repair (TMVR) undergo direct mitral leaflet repair (also referred to as transcatheter edge-to-edge repair). Of the TMVR devices

under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008. The MitraClip system is deployed percutaneously and approximates the open Alfieri edge-to-edge repair approach to treating MR. The delivery system consists of a catheter, a steerable sleeve, and the MitraClip device, which is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene fabric. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.

The PASCAL (PAddles Spacer Clasps ALfieri) Mitral Repair System (Edwards Lifesciences) is also a direct coaptation device and works in a similar manner to the MitraClip system. PASCAL has been in clinical use since 2016 and was approved for use in Europe in 2019. The delivery system consists of a 10-mm central spacer that attaches to the MV leaflets by 2 paddles and clasps.

Other Mitral Valve Repair Devices
Devices for TMVR that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc device (Edwards Lifesciences). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by a manual pull back on the catheter. The Carillon system was evaluated in the Carillon Mitral Annuloplasty Device European Union Study and the follow-up Tighten the Annulus Now study, with further studies planned. The Monarc system also involves 2 self-expanding stents connected by a nitinol bridge, with one end implanted in the coronary sinus via the internal jugular vein and the other in the great cardiac vein. Several weeks after implantation, the biologically degradable coating over the nitinol bridge degrades, allowing the bridge to shrink and the system to shorten. It has been evaluated in the Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation trial.

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty System (Mitralign) and the AccuCinch®‡ System (Guided Delivery Systems), both of which involve transcatheter placement of anchors in the MV; they are cinched or connected to narrow the mitral annulus. Other transcutaneous direct annuloplasty devices under investigation include the enCorTC™‡ device

(MiCardia), which involves a percutaneously insertable annuloplasty ring that is adjustable using radiofrequency energy, a variation on its CE-marked enCor$_{SQ}$ Mitral Valve Repair System, and the Cardioband Annuloplasty System (Valtech Cardio), an implantable annuloplasty band with a transfemoral venous delivery system.

Transcatheter Mitral Valve-in-Valve Replacement
Mitral valve-in-valve replacement is a minimally invasive procedure designed to treat patients with failing surgical bioprosthetic mitral valves who are at high risk for complications with repeat open-heart surgery. The Edwards SAPIEN 3 Transcatheter Heart Valve received FDA approval in June 2017 (PMA #P140031) for patients with a failing surgical bioprosthetic mitral valve who are at high or prohibitive risk for repeat surgery. The procedure involves deploying the replacement valve within the failing bioprosthetic valve using a catheter-based transapical or transseptal approach. Once in position, the replacement valve is expanded, pushing the leaflets of the failing bioprosthetic valve aside and taking over the valve function.

Medical Management
The standard treatment for individuals with chronic secondary MR is medical management. Individuals with chronic secondary MR should receive standard therapy for heart failure with reduced ejection fraction; standard management includes angiotensin-converting enzyme inhibitor (or angiotensin II receptor blocker or angiotensin receptor-neprilysin inhibitor), beta-blocker and mineralocorticoid receptor antagonist, and diuretic therapy as needed to treat volume overload. Resynchronization therapy may provide symptomatic relief, improve LV function, and in some individuals, lessen the severity of MR.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In October 2013, the MitraClip Clip Delivery System (Abbott Vascular) was approved by the FDA through the premarket approval process for treatment of "significant symptomatic mitral regurgitation (MR ≥3+) due to primary abnormality of the mitral apparatus (degenerative MR) in individuals who have been determined to be at a prohibitive risk for mitral valve surgery by a heart team."

In June 2017, the Edwards SAPIEN 3 Transcatheter Heart Valve received FDA approval through the premarket approval process for the treatment of patients with a "failing surgical bioprosthetic mitral valve who have been determined to be at high or greater risk for open-heart surgery by a heart team."

In March 2019, the FDA approved a new indication for MitraClip, for "treatment of individuals with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe mitral regurgitation because of diminished left heart function (commonly known as secondary or functional mitral regurgitation) despite being treated with optimal medical therapy. Optimal medical therapy includes combinations of different heart failure medications along with, in certain individuals, cardiac resynchronization therapy and implantation of cardioverter defibrillators."

In September 2022, the FDA approved the PASCAL Precision Transcatheter Valve Repair System through the premarket approval process for treatment of "significant, symptomatic mitral regurgitation (MR ≥3+) due to primary abnormality of the mitral apparatus (degenerative MR) in individuals who have been determined to be at prohibitive risk for mitral valve surgery by a heart team."

FDA product code for MitraClip and PASCAL: NKM.

FDA product code for Edwards SAPIEN 3: NPV

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Transcatheter mitral valve repair (TMVR) is an alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from a primary structural abnormality of the mitral valve (MV) complex or a secondary dilatation of an anatomically normal MV due to a dilated left ventricle caused by ischemic or dilated cardiomyopathy. Surgical therapy

may be underutilized, particularly in individuals with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for MV repair.

Two devices, MitraClip™‡ and PASCAL™‡, have approval from the U.S. Food and Drug Administration for the treatment of severe symptomatic MR due to a primary abnormality of the MV (primary MR) in patients considered at prohibitive risk for surgery. MitraClip is also approved for patients with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy. The Edwards SAPIEN 3 transcatheter heart valve has been approved by the U.S. Food and Drug Administration for transcatheter mitral valve-in-valve replacement (TMViVR) in patients with a failing surgical bioprosthetic mitral valve who are at high or greater risk for repeat surgery.

Summary of Evidence
For individuals who have symptomatic primary mitral regurgitation (MR) and are at prohibitive risk for open surgery who receive transcatheter mitral valve repair (TMVR) using MitraClip or PASCAL, the evidence includes a noninferiority randomized controlled trial (RCT) and single-arm prospective cohort with historical cohort and registry studies. Relevant outcomes are overall survival (OS), morbid events, functional outcomes, and treatment-related morbidity. The primary evidence includes the pivotal EVEREST II HRR and EVEREST II REALISM studies, the Transcatheter Valve Therapy Registry study, and the CLASP IID/IIF study. Studies evaluating MitraClip have demonstrated that MitraClip implantation is feasible with a procedural success rate greater than 90%, 30-day mortality ranging from 2.3% to 6.4% (less than predicted Society of Thoracic Surgeons [STS] mortality risk score for MR repair or replacement; range, 9.5% to 13.2%), post implantation MR severity grade of 2+ or less in 82% to 93% of individuals, and a clinically meaningful gain in quality of life (5- to 6-point gains in ySF-36 scores). At 1 year, freedom from death and MR more than 2+ was achieved in 61% of individuals but the 1-year mortality or heart failure (HF) hospitalization rates remain considerably high (38%). Conclusions related to the treatment effect on mortality based on historical controls cannot be made because the control groups did not provide unbiased or precise estimates of the natural history of individuals eligible to receive MitraClip. Given that primary MR is a mechanical problem and there is no effective medical therapy, an RCT comparing TMVR with medical management is not feasible or ethical. The post marketing data from the U.S. is supportive that MitraClip surgery is being performed with short-term effectiveness and safety in a select patient population. The CLASP IID/IIF randomized cohort demonstrated that PASCAL is noninferior to MitraClip in safety and effectiveness for individuals with primary MR at

prohibitive surgical risk, and the single-arm registry cohort demonstrated that PASCAL is safe and effective in individuals with complex mitral valve (MV) anatomy precluding the use of MitraClip. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have HF and symptomatic secondary mitral regurgitation (SMR) despite the use of maximally tolerated guideline-directed medical therapy who receive TMVR using MitraClip, the evidence includes a systematic review, 2 RCTs, and multiple observational studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The trials had discrepant results potentially related to differences in primary outcomes. The larger trial, with individuals selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip up to 5 years compared to medical therapy alone, including benefits in overall survival and hospitalization for heart failure. Improvements in MR severity, quality of life measures, and functional capacity persisted to 36 months in individuals who received TMVR. The systematic review confirmed the benefit of MitraClip found in the larger RCT, but had important methodological limitations. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic primary or secondary MR and are surgical candidates who receive TMVR using MitraClip, the evidence includes a systematic review, 1 RCT, and a retrospective comparative observational study in individuals aged ≥75 years. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The RCT found that MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and was associated with fewer adverse events at 1 year. Long-term follow-up from the RCT showed that significantly more MitraClip individuals required surgery for MV dysfunction than conventional surgery individuals. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. The observational study in individuals aged ≥75 years found that although MitraClip was associated with improved 1-year survival and a lower rate of all acute complications compared with surgical repair, it had lower 5-year survival and greater MR recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic primary or secondary MR who receive TMVR using devices other than MitraClip or PASCAL, the evidence includes a randomized study, nonrandomized prospective studies, and noncomparative feasibility studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The randomized, sham-controlled trial for the indirect annuloplasty device Carillon offers promising safety data; however, further studies are needed to determine efficacy and long-term outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have valve dysfunction and mitral stenosis or regurgitation after prior bioprosthetic mitral valve replacement, who are at a high or prohibitive risk for redo surgical mitral valve replacement (rSMVR), and who receive a transcatheter mitral valve-in-valve replacement (TMViVR) using an FDA-approved device, the evidence includes 2 meta-analyses, 8 comparative retrospective cohort studies, and 9 observational studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The meta-analyses had mixed early-term findings, with one observing a benefit for in-hospital mortality favoring TMViVR over rSMVR, but at 30 days, 1-year, and 2-year follow-up, no difference between groups in OS was observed in either review. Both analyses found that complications of stroke, renal dysfunction, vascular complications, pacemaker implantation, and bleeding were more common in the rSMVR group. The comparative studies generally found that mortality was equivalent or favored TMViVR through 1-year follow-up; however, several studies that reported longer-term outcomes observed that the trend in mortality was reversed with numerically higher rates in the TMViVR group. TMViVR was associated with a shorter hospital or ICU stay than rSMVR. Several adverse events (acute kidney injury, cardiac arrest, cardiogenic shock, major bleeding, pacemaker implantation, pneumonia, sepsis, stroke, and vascular complications) were more commonly reported in the rSMVR group compared to TMViVR. These results were supported by observational data, which provided data on mortality, functional outcomes, and complications through up to 7 years post-implantation. The evidence base is limited primarily by the lack of experimental studies, but assigning patients who are at high or prohibitive risk for open surgery to rSMVR is ethically prohibitive so retrospective comparisons will likely continue to represent the best available evidence for this intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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 and American Heart Association
In 2020, the American College of Cardiology and American Heart Association presented updated expert consensus on the management of mitral regurgitation (MR). The recommendations are as follows: "At present, transcatheter mitral repair using an edge-to-edge clip device can be considered for the treatment of individuals with primary MR and severe symptoms who are felt to be poor surgical candidates. Surgical or transcatheter treatment for secondary MR is undertaken only after appropriate medical and device therapies have been instituted and optimized, as judged by the multidisciplinary team with input from a cardiologist with experience managing heart failure and MR."

Also in 2020, the American College of Cardiology and American Heart Association released updated guidelines on the management of valvular heart disease. The guidelines state that TMVR is of benefit to individuals with severely symptomatic primary MR who are at high or prohibitive risk for surgery, and to a subset of individuals with secondary MR who remain severely symptomatic despite guideline-directed management and therapy for heart failure. Individuals who have prosthetic valve stenosis are recommended to be offered revision surgery, but for severely symptomatic patients who are at high risk for surgery, a transcatheter aortic valve-in-valve procedure may be reasonable (B level of evidence, moderate class of recommendation); no recommendation is given regarding mitral

valve-in-valve procedures. Relevant recommendations on interventions for primary and secondary MR, and prosthetic valve stenosis are shown in Table 1.

Table 1. Recommendations on Interventions for Primary and Secondary Mitral Regurgitation

Recommendation	COR	LOE
Primary MR		
In symptomatic patients with severe primary MR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function	1 (Strong)	B-NR[1]
In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF ≤60%, LVESD ≥40 mm) (Stage C2), mitral valve surgery is recommended	1 (Strong)	B-NR[1]
In patients with severe primary MR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is a degenerative disease, if a successful and durable repair is possible	1 (Strong)	B-NR[1]
In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF ≥60% and LVESD ≥40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1% when it can be performed at a Primary or Comprehensive Valve Center	2a (Moderate)	B-NR[1]
In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD <40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on ≥3 serial imaging studies, mitral valve surgery may be considered irrespective of the probability of a successful and durable repair	2b (Weak)	C-LD[2]
In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, TEER is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year	2a (Moderate)	B-NR[1]

In symptomatic patients with severe primary MR attributable to rheumatic valve disease, mitral valve repair may be considered at a Comprehensive Valve Center by an experienced team when surgical treatment is indicated, if a durable and successful repair is likely	2b (Weak)	B-NR[1]
In patients with severe primary MR where leaflet pathology is limited to less than one half the posterior leaflet, mitral valve replacement should not be performed unless mitral valve repair has been attempted at a Primary or Comprehensive Valve Center and was unsuccessful	3:Harm (Strong)	B-NR[1]
Secondary MR		
In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg	2a (Moderate)	B-R[3]
In patients with severe secondary MR (Stages C and D), mitral valve surgery is reasonable when CABG is undertaken for the treatment of myocardial ischemia	2a (Moderate)	B-NR[1]
In patients with chronic severe secondary MR from atrial annular dilation with preserved LV systolic function (LVEF ≥50%) who have severe persistent symptoms (NYHA class III or IV) despite therapy for HF and therapy for associated AF or other comorbidities (Stage D), mitral valve surgery may be considered	2b (Weak)	B-NR[1]
In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent severe symptoms (NYHA class III or IV) while on optimal GDMT for HF (Stage D), mitral valve surgery may be considered	2b (Weak)	B-NR[1]
In patients with CAD and chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) (Stage D) who are undergoing mitral valve surgery because of severe symptoms (NYHA class III or IV) that	2b (Weak)	B-R[3]

persist despite GDMT for HF, chordal-sparing mitral valve replacement may be reasonable to choose over downsized annuloplasty repair		
Intervention for Prosthetic Valve Stenosis		
In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless the surgical risk is high or prohibitive	1 (Strong)	B-NR1
For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a comprehensive valve center	2a (Moderate)	B-NR1
For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable	2a (Moderate)	B-NR1

Source: Adapted from Otto et al (2020)
[1]Moderate, nonrandomized; [2]Limited data; [3]Moderate, randomized.
AF: atrial fibrillation; CABG: coronary artery bypass graft; CAD: coronary artery disease; COR: class of recommendation; EF: ejection fraction; GDMT: guideline-directed medical therapy; HF: heart failure; LOE: level of evidence; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameters; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; TEE: transesophageal echocardiogram; TEER: transcatheter edge-to-edge repair, ViV: valve-in-valve; VKA, vitamin K antagonist.

American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

The American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2014) issued a position statement on transcatheter therapies for MR. This statement outlined critical components for successful transcatheter MR therapies and recommended ongoing research and inclusion of all individuals treated with transcatheter MR therapies in a disease registry.

The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) issued guidelines on the management of valvular heart disease in 2022. A new position on the management of prosthetic valve dysfunction was issued, stating, "Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical intervention." This recommendation was given a class IIb recommendation, indicating that there is conflicting evidence about the usefulness or efficacy of this treatment, with the opinion being supported by less well-established evidence.

National Institute for Health and Care Excellence

The NICE guideline on heart valve disease management (2021) makes the following recommendations related to TMVR:

- "1.5.10 - Consider transcatheter edge-to-edge repair, if suitable, for adults with severe primary mitral regurgitation and symptoms, if surgery is unsuitable.
- 1.5.14 - Consider transcatheter mitral edge-to-edge repair for adults with heart failure and severe secondary mitral regurgitation, if surgery is unsuitable and they remain symptomatic on medical management."

Another NICE guideline was issued in 2021 on the use of transapical transcathter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis:

- "1.1 - Evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis is adequate and shows some serious but well-recognised complications. Evidence on its efficacy is limited in quality. So, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

- "1.4 - Patient selection should be done by a multidisciplinary team which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging, and where appropriate, a cardiac anaesthetist and a specialist in medicine for older people. The multidisciplinary team should determine the risk level for each patient and the device most suitable for them."

- "1.6 - The procedure is technically challenging and should only be done in specialised centres, and only by clinical teams with special training and experience in complex endovascular cardiac interventions, including regular experience in transcatheter valve implantation procedures. Centres doing these procedures should have cardiac surgical support for emergency treatment of complications and subsequent patient care."

- "1.7 - NICE encourages further research into transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. Studies should include details on patient selection, type and size of valve used, functional outcomes (New York Heart Association functional class, mitral valve regurgitation), quality of life, patient-reported outcome measures, survival and complications. Studies should report long-term follow up of clinical outcomes and valve durability. NICE may update this guidance on publication of further evidence."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services issued a national coverage decision for the use of TMVR in 2015, which was updated in 2021.

The Centers for Medicare & Medicaid Services determined that it would cover TMVR under Coverage with Evidence Development for the treatment of symptomatic moderate-to-severe or severe functional (secondary) MR or significant symptomatic degenerative (primary) MR when all of the following conditions are met:

"1. The procedure is furnished with a [TMVR] system that has received FDA [Food and Drug Administration] premarket approval (PMDA).

2. The patient (preoperatively and postoperatively) is under the care of a heart team...

3. Each patient's suitability for surgical mitral valve repair, [TMVR], or palliative therapy must be evaluated, documented...

4. An interventional cardiologist or cardiac surgeon from the heart team must perform the mitral valve [TMVR]...

5. Mitral valve [TMVR] must be furnished in a hospital with appropriate infrastructure and experience...

6. The heart team and hospital are participating in a prospective, national, audited registry...

7. The registry shall collect all data necessary and have a written executable analysis plan..."

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02444338	A Randomized Study of The MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF)	650	June 2024
NCT04009434	Treatment of Concomitant Mitral Regurgitation by Mitral Valve Clipping in Patients With Successful Transcatheter Aortic Valve Implantation	1162	Aug 2023
NCT01626079[a]	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial) and COAPT CAS (COAPT)	614 in COAPT and 162 in COAPT CAS	July 2024 (5-year follow-up per protocol)[b]
NCT04198870[a]	Percutaneous MitraClip Device or Surgical Mitral Valve Repair in Patients With Primary Mitral	500	Feb 2032

	Regurgitation Who Are Candidates for Surgery (REPAIR MR)		
NCT05090540	Transcatheter Edge to Edge Mitral Valve Repair Versus Standard Surgical Mitral Valve Operation for Secondary Mitral Regurgitation	600	Dec 2023
NCT05051033	Percutaneous or Surgical Repair In Mitral Prolapse And Regurgitation for ≥65 Year-Olds (PRIMARY)	450	Jan 2032
NCT05021614[a]	Evaluation of the Efficacy and Safety of the Transcatheter Mitral Valve Repair System in Patients With Moderate and Above Degenerative Mitral Regurgitation at High Surgical Risk	150	Sep 2027
NCT04734756[a]	A Prospective, Multicenter, Objective Performance Criteria Study to Evaluate the Safety and Effectiveness of Dragonfly Transcatheter Mitral Valve Repair System for the Treatment of Degenerative Mitral Regurgitation (DMR) Subjects	120	May 2027
NCT04733404[a]	A Prospective, Multicenter, Objective Performance Criteria Study to Evaluate the Safety and Effectiveness of Dragonfly Transcatheter Mitral Valve Repair System for the Treatment of Functional Mitral Regurgitation (FMR) Subjects	120	Sep 2027
NCT04430075[a]	Transcatheter Repair of Mitral Regurgitation With Edwards PASCAL Transcatheter Valve Repair System: A European Prospective, Multicenter Post Market Clinical Follow-Up (PMFC)	500	June 2028
NCT03706833[a]	Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial (CLASP IID/IIF): A Prospective, Multicenter, Randomized, Controlled Pivotal Trial to Evaluate the Safety and Effectiveness of Transcatheter Mitral Valve Repair	1275	Jan 2028

	With the Edwards PASCAL Transcatheter Valve Repair System Compared to Abbott MitraClip in Patients With Mitral Regurgitation		
NCT05332782	Outcomes of Patients Treated with Mitral Transcatheter Edge-to-edge Repair for Primary Mitral Regurgitation Registry (PRIME-MR)	2000	Jan 2026
NCT05496998[a]	Transcatheter Mitral Valve Replacement With the Medtronic Intrepid™ ‡ TMVR Transfemoral System in Patients With Severe Symptomatic Mitral Regurgitation - APOLLO-EU Trial	360	Nov 2026
NCT05417945[a]	A Prospective, Multicenter Study to Evaluate the JensClip Transcatheter Valve Repair System	124	Dec 2024
NCT05455489	GISE Registry of Transcatheter Treatment of Mitral Valve Regurgitation With the MitraClip G4	264	Aug 2029
NCT03271762	Multicentre and Randomized Study of MITRACLIP®‡ Transcatheter Mitral Valve Repair in Patients With Severe Primary Mitral Regurgitation Eligible for High-risk Surgery	330	May 2027
NCT04402931	Randomized Trial of Transcatheter Valve-in-Valve Intervention vs Redo Surgery for the Treatment of Structural Mitral Bioprosthetic Dysfunction	150	Dec 2031
NCT03193801	PARTNER 3 Trial - SAPIEN 3 Transcatheter Heart Valve Implantation in Patients With a Failing Mitral Bioprosthetic Valve	53	Aug 2031

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.
[b]Primary results have been published, long-term follow-up ongoing

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Policy History

Original Effective Date: 02/17/2016
Current Effective Date: 09/01/2024
02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. New Policy

01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Degenerative mitral regurgitation was replaced with primary mitral regurgitation and functional mitral regurgitation was replaced with secondary mitral regurgitation including the policy statement to be in consistent with language used in the guidelines.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added "Based on review of available data, the Company may consider transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration for patients with heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy to be eligible for coverage**" Added Policy Guidelines section.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. No change to coverage.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. Policy updated with literature review through March 6, 2024; title changed to 'Transcatheter Mitral Valve Repair or Replacement'; new indication for transseptal valve-in-valve replacement; references added. Policy statement added:

Transcatheter mitral valve-in-valve replacement (TMViVR) with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve (valve-in-valve) is considered medically necessary for individuals when all of the following conditions are present:

- Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic mitral valve; AND
- New York Heart Association heart failure class II, III, or IV symptoms; AND
- Individual is not an operable candidate for open surgery, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon); OR individual is an operable candidate but is considered at increased surgical risk for open surgery, as documented by at least 2 cardiac specialists (including a cardiac surgeon); OR individual is considered at increased surgical risk for open surgery (eg, repeat sternotomy) due to a history of congenital vascular anomalies AND/OR has a complex intrathoracic surgical history, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon). Title changed from "Transcatheter Mitral Valve Repair" to "Transcatheter Mitral Valve Repair or Replacement."

Next Scheduled Review Date: 08/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0345T, 0544T, 33418, 33419 Add codes effective 09/01/2024: 0483T, 0484T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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 eligibility for coverage.