7.03.09	Heart Transplant		
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Policy Statement

I. Human heart transplantation may be considered **medically necessary** for select adults and children with end-stage heart failure when the following individual selection criteria are met.

Adult Individuals

Accepted Indications for Cardiac Transplantation (**any** of the following):

A. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items,
   1. Maximal oxygen consumption (Vo_2) less than 10 mL/kg/min with achievement of anaerobic metabolism
   2. Refractory cardiogenic shock
   3. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion

B. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty

C. Recurrent symptomatic ventricular arrhythmias refractory to all accepted therapeutic modalities

Probable Indications for Cardiac Transplantation (**any** of the following):

A. Maximal Vo_2 less than 14 mL/kg/min and major limitation of the individual's activities

B. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty

C. Instability of fluid balance/renal function not due to individual noncompliance with a regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

The following conditions are inadequate indications for cardiac transplantation unless other factors as listed above are present.

A. Ejection fraction less than 20%

B. History of functional class III or IV symptoms of heart failure

C. Previous ventricular arrhythmias

D. Maximal Vo_2 greater than 15 mL/kg/min

Pediatric Individuals

Individuals with heart failure and persistent symptoms at rest who require **one or more** of the following:

A. Continuous infusion of intravenous inotropic agents

B. Mechanical ventilatory support

C. Mechanical circulatory support

Individuals with heart disease and symptoms of heart failure who do not meet the above criteria but who have **any** of the following:

A. Severe limitation of exercise and activity (if measurable, such individuals would have a maximum Vo_2 less than 50% predicted for age and sex)

B. Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease

C. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator

D. Restrictive cardiomyopathy with reactive pulmonary hypertension

E. Reactive pulmonary hypertension and risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future
F. Anatomic and physiologic conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle
G. Anatomic and physiologic conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction

II. Heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in individuals who meet the criteria for heart transplantation.

III. Heart transplantation is considered **investigational** in all other situations.

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

Policy Guidelines

General Criteria

Potential contraindications for solid organ transplant subject to the judgment of the transplant center include the following:

- Known current malignancy, including metastatic cancer
- Recent malignancy with a high risk of recurrence
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end-stage diseases not attributed to heart or lung disease
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting the ability to adhere to therapy

Policy-specific potential contraindications include:

- Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance (PVR) greater than 5 Wood units, or transpulmonary gradient (TPG) greater than or equal to 16 mm/Hg despite treatment[a];
- Severe pulmonary disease, despite optimal medical therapy, not expected to improve with heart transplantation[a]

[a] Some individuals may be candidates for combined heart and lung transplantation (see Blue Shield of California Medical Policy: Heart/Lung Transplant).

Individuals must meet the United Network for Organ Sharing (UNOS) guidelines for status 1A, 1B, or status 2 (and not currently be status 7).

Cardiac-Specific Criteria

Specific criteria for prioritizing donor thoracic organs for transplant are provided by the Organ Procurement and Transplantation Network (OPTN) and implemented through a contract with UNOS. Donor thoracic organs are prioritized by UNOS on the basis of recipient medical urgency, distance from donor hospital, and pediatric status. Individuals who are most severely ill (status 1A) are given the highest priority. The following factors are considered in assessing the severity of illness: reliance on continuous mechanical ventilation, infusion of intravenous inotropes, and/or dependency on mechanical circulatory support (i.e., total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenator, ventricular assist device).

Additional criteria, which are considered in pediatric individuals, include diagnosis of an OPTN-approved congenital heart disease, presence of ductal dependent pulmonary or systemic circulation,

and diagnosis of hypertrophic or restrictive cardiomyopathy while less than 1-year-old. Of note, pediatric heart transplant candidates who remain on the waiting list at the time of their 18th birthday without receiving a transplant continue to qualify for medical urgency status based on the pediatric criteria.

Specific criteria for prioritizing donor thoracic organs for retransplant include severe coronary allograft vasculopathy, mild or moderate coronary allograft vasculopathy with a left ventricular ejection fraction less than 45%, coronary allograft vasculopathy with restrictive physiology, or symptomatic graft dysfunction without evidence of active rejection.

Description

A heart transplant and a retransplant consist of replacing a diseased heart with a healthy donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

Related Policies

- Heart/Lung Transplant
- Immune Cell Function Assay
- Laboratory Tests Post Transplant and for Heart Failure
- Total Artificial Hearts and Implantable Ventricular Assist Devices

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

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Rationale

Background

Solid Organ Transplantation

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[1,] Many advances have been made in the last several decades to reduce perioperative complications. Available data support improvement in long-term survival as well as improved quality

of life, particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network and United Network for Organ Sharing (UNOS).

Heart Transplant

In 2022 , 42,880 transplants were performed in the United States procured from more than 14,900 deceased donors and 6,400 living donors.[2,] Heart transplants were the third most common procedure with 4,109 transplants performed from both deceased and living donors in 2022. As of June 2023 , there were 3,355 patients on the waiting list for a heart transplant.[3,]

Most heart transplant recipients now are hospitalized as status 1 patients at the time of transplant. This shift has occurred due to the increasing demand for the scarce resource of donor organs resulting in an increased waiting time for recipients. Patients initially listed as status 2 candidates may deteriorate to a status 1 candidate before a donor organ becomes available. Alternatively, as medical and device therapy for advanced heart failure improves, some patients on the transplant list will recover enough function to be delisted. Lietz and Miller (2007) reported on survival for patients on the heart transplant waiting list, comparing the era between 1990 and 1994 with the era of 2000 to 2005.[4,] One-year survival for a UNOS status 1 candidate improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared with 81.8% in the earlier time period.

Johnson et al (2010) reported on waiting list trends in the U.S. between 1999 and 2008.[5,] The proportion of patients listed as status 1 increased, even as the waiting list and posttransplant mortality for this group have decreased. Meanwhile, status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years. Bakhtiyar et al (2020) evaluated survival among patients (N=95,323) wait-listed for heart transplantation between January 1, 1987 and December 29, 2017 using UNOS data.[6,] Results revealed 1-year survival on the wait list increased from 34.1% in 1987 to 1990 to 67.8% in 2011 to 2017 (difference in proportions, 0.34%; 95% confidence interval [CI], 0.32% to 0.36%; p<.001). One-year wait list survival also significantly increased for candidates with ventricular assist devices from 10.2% in 1996 to 2000 to 70% in 2011 to 2017 (difference in proportions, 0.60%; 95% CI, 0.58% to 0.62%; p<.001).

Alshawabkeh et al (2018) reported on the 1-year probability of the combined outcome of death or delisting due to clinical worsening for patients on the heart transplant waiting list, comparing the periods of April 1, 1986 to January 19, 1999 (early era) and January 20, 1999 to June 2, 2014 (current era).[7,] For adults without congenital heart disease (CHD), the probability of the combined outcome was lower in the current era compared with the early era, regardless of whether the patient was listed in status I (14.5% vs. 22.7%; p<.0001) or 2 (9.0% vs. 12.8%, p<.0001). When comparing the current and early eras in adults with CHD, a reduction in the probability of the combined outcome was demonstrated in those listed in status I (17.6% vs. 43.3%, respectively; p<.0001), whereas the outcome remained unchanged for those listed in status 2 (10.6% vs. 10.4%, respectively; p=.94).

In adults with CHD, factors associated with waitlist death or delisting due to clinical worsening within 1 year were also examined by Alshawabkeh et al (2016).[8,] A multivariate analysis identified that an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 (hazard ratio [HR], 1.4; 95% CI, 1.0 to 1.9; p=.043), albumin less than 3.2 g/dl (HR, 2.0; 95% CI, 1.3 to 2.9; p<.001), and hospitalization at the time of listing in the intensive care unit (HR, 2.3; 95% CI, 1.6 to 3.5; p<.001) or a non-intensive care hospital unit (HR, 1.9; 95% CI, 1.2 to 3.0; p=.006) were associated with waitlist death or delisting due to clinical worsening within 1 year.

Magnetta et al (2019) reported outcomes for children on the heart transplant waiting list, comparing the periods of December 16, 2011 to March 21, 2016 (era 1) and March 22, 2016 to June 30, 2018 (era 2).[9,] There was a significant decrease from era 1 to era 2 in the proportion of patients listed as status 1 (70% vs. 56%; p<.001), while the proportion of patients with CHD significantly increased across eras (49% to 54%; p=.018). The median time on the waitlist increased from 68 days to 78 days (p=.005). There were no significant differences across eras in the cumulative incidence of death on the waitlist among all candidates (subdistribution HR, 0.96; 95% CI, 0.80 to 1.14; p=.63) and among those listed status 1A (subdistribution HR, 1.16; 95% CI, 0.95 to 1.41; p=.14). Graft survival at 90 days was also similar across eras in the overall population and in those with CHD (p>.53 for both).

As a consequence, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (Vo_2max), which is measured during maximal exercise, is a measure suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology and American Heart Association have adopted Vo_2max as a criterion for patient selection.[10,] Studies have suggested that transplantation can be safely deferred in those patients with a Vo_2max greater than 14 mL/kg/min. The importance of Vo_2max has also been emphasized by the American Heart Association when addressing heart transplant candidacy.[11,] In past years, a left ventricular ejection fraction of less than 20% or a New York Heart Association class III or IV status might have been used to determine transplant candidacy. However, as indicated by the American College of Cardiology criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than Vo_2max have been proposed as predictive models in adults.[12,13,14,15,] The Heart Failure Survival Scale and the Seattle Heart Failure Model (SHFM) are examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information on pharmacologic and device usage is incorporated into the model, permitting some estimation on the effects of current, more aggressive heart failure treatment strategies. Levy et al (2006) introduced the model using a multivariate analysis of data from the Prospective Randomized Amlodipine Survival Evaluation-1 heart failure trial (N=1125).[16,] Applied to the data of 5 other heart failure trials, SHFM correlated well with actual survival (r=0.98). SHFM has been validated in both ambulatory and hospitalized heart failure populations,[17,18,19,] but with a noted underestimation of mortality risk, particularly in Black adults and device recipients.[20,21,] None of these models has been universally adopted by transplant centers.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 a technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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 randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Due to the nature of the population discussed herein, there are no RCTs comparing heart transplantation with alternatives, including left ventricular assist devices (LVADs). Systematic reviews are based on case series and registry data. Randomized controlled trials have been published on related topics (e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy) but are not germane to this evidence review.

Initial Heart Transplant

Clinical Context and Therapy Purpose

In the U.S., approximately 6 million people 20 years of age and older have heart failure and 1 in 8 deaths have heart failure mentioned on the death certificate.[22,] The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion.

Heart failure may be due to a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart disease (CHD). The leading indication for a heart transplant has shifted over time from ischemic to nonischemic cardiomyopathy. From 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18 to 39 years (64%) and 40 to 59 years (51%) undergoing transplant operations.[23,] Ischemic cardiomyopathy was the dominant underlying primary diagnosis among heart transplant recipients 60 to 69 years (50%) and 70 years and older (55%). Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of heart transplants during this time period were in adults with CHD.

The purpose of a heart transplant in individuals who have end-stage heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals who have end-stage heart failure.

Interventions

The therapy being considered is a heart transplant.

Comparators

The following therapies and practices are currently being used to make decisions about reducing the risk of end-stage heart failure: guideline-directed medical therapy ; surgery including coronary bypass surgery, heart valve repair or replacement, and ventricular assist devices.

Outcomes

The general outcomes of interest are overall survival (OS), symptoms, and morbid events (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for a detailed discussion of outcomes in

patients with malignancy, HIV, older age, pulmonary hypertension, and renal insufficiency, and children with intellectual disability. Follow-up of 1, 2, 5, and 10 years is of interest for heart transplant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, 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 events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Retrospective Studies

A study by Jaramillo et al (2013) examined characteristics of patients who survived more than 20 years after heart transplantation at a single-center in Spain.[24,] Thirty-nine heart transplant recipients who survived over 20 years posttransplant were compared with 98 patients who died between 1 and 20 years posttransplant. Independent factors associated with long-term survival were younger recipient age (i.e., <45 years vs. ≥45 years; odds ratio [OR], 3.9; 95% confidence interval [CI], 1.6 to 9.7) and idiopathic cardiomyopathy (i.e., vs. other etiologies; OR, 3.3; 95% CI, 1.4 to 7.8).

Registry Studies

According to the Organ Procurement and Transplantation Network (OPTN), 1-year Kaplan-Meier survival estimates for heart transplants performed between 2008 and 2015, based on available U.S. data as of June 3, 2022 , were 90.5% (95% CI, 89.9% to 91.2%) for men and 91.1% (95% CI, 90.1% to 92.1%) for women.[3,] The 3-year survival rates were 85.2% (95% CI, 84.3% to 86%) for men and 85.3% (95% CI, 83.9% to 86.5%) for women, and the 5-year survival rates were 78.4% (95% CI, 77.4% to 79.4%) and 77.7% (95% CI, 76% to 79.3%), respectively. There was no major difference in 1-, 3-, and 5-year survival rates between different age groups among adult recipients (Table 1).

Table 1. Kaplan-Meier Patient Survival Rates for Heart Transplants Performed From 2008 to 2015

Recipient Age	Years Posttransplant					
	1 Year[a]		3 Years[a]		5 Years[a]	
	No. Alive	Survival Rate (95% CI), %	No. Alive	Survival Rate (95% CI), %	No. Alive	Survival Rate (95% CI), %
<1 year	407	87.6 (84.3 to 90.3)	363	85.0 (81.3 to 88.0)	317	77.2 (72.8 to 80.9)
1-5 years	345	92.4 (89.2 to 94.6)	282	87.1 (83.0 to 90.2)	257	81.4 (76.8 to 85.2)
6-10 years	223	92.3 (88.2 to 95.0)	186	89.8 (84.9 to 93.1)	166	89.3 (84.1 to 92.9)
11-17 years	507	96.8 (94.9 to 98.0)	459	92.3 (89.6 to 94.3)	356	80.0 (76.1 to 83.4)
18-34 years	845	91.8 (89.8 to 93.4)	727	83.7 (81.1 to 85.9)	600	75.0 (71.9 to 77.8)
35-49 years	1590	90.9 (89.4 to 92.1)	1402	85.4 (83.6 to 87.0)	1243	79.1 (77.0 to 81.0)
50-64 years	3900	90.7 (89.8 to 91.6)	3382	85.3 (84.1 to 86.3)	2982	78.5 (77.2 to 79.8)
65+ years	1516	88.4 (86.7 to 89.8)	1196	82.2 (80.1 to 84.1)	NR	NR

Source: Organ Procurement and Transplantation Network.[3,]
CI: confidence interval; NR: not reported.
[a]1 year survival based on 2012-2015 transplants, 3-year survival based on 2010-2013 transplants, 5-year survival based on 2008-2011 transplants.

Nguyen et al (2017) investigated the benefit of heart transplantation compared with surveillance while on a waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in OPTN between 2006 and 2015.[25,] The net benefit from heart transplantation was evident across all estimates of donor-recipient status 1A candidates (lowest risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR, 0.52; 95% CI,

0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR, 0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR, 0.66; 95% CI, 0.58 to 0.74). Status 2 candidates also showed a benefit from heart transplantation; however, the survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Rana et al (2015) retrospectively analyzed solid organ transplant recipients registered in the United Network for Organ Sharing (UNOS) database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.[26,] Transplant recipients were compared with patients listed for transplant but who did not receive one; heart recipients were awarded the transplant based on propensity score matching, which served to measure a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

Several studies have analyzed factors associated with survival in heart transplant patients. For example, Lund et al (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation between 2000 and 2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.[23,] Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR, 1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR, 1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR, 1.16; 95% CI: 1.10 to 1.23; n=7822), congenital (HR, 1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR, 1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs. nonischemic cardiomyopathy), and retransplant (HR, 1.18; 95% CI, 1.02 to 1.35; n=489) were associated with posttransplant mortality risk at 10 years.

A study by Kilic et al (2012) analyzed prospectively collected data from the UNOS registry.[27,] The analysis included 9404 patients who had survived 10 years after a heart transplant and 10,373 patients who had died before 10 years. Among individuals who had died, the mean survival was 3.7 years posttransplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included age younger than 55 years (OR, 1.24; 95% CI, 1.10 to 1.38), younger donor age (OR, 1.01; 95% CI, 1.01 to 1.02), shorter ischemic time (OR, 1.11; 95% CI, 1.05 to 1.18), White race (OR, 1.35; 95% CI, 1.17 to 1.56), and annual center volume of 9 or more heart transplants (OR, 1.31; 95% CI, 1.17 to 1.47). Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included the use of mechanical ventilation (OR, 0.53; 95% CI, 0.36 to 0.78) and diabetes (OR, 0.67; 95% CI, 0.57 to 0.78).

Pediatric Considerations

Retrospective Studies

An analysis of data from the Pediatric Heart Transplant Study (2013), which includes data on all pediatric transplants at 35 participating institutions, suggests that 5-year survival for pediatric heart transplants has improved over time (76% for patients transplanted from 2000 to 2004 vs. 83% for patients transplanted from 2005 to 2009).[28,]

Auerbach et al (2012) published a retrospective review of pediatric cardiac transplantation patients.[29,] A total of 191 patients who underwent primary heart transplantation at a single-center in the U.S. were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at 1 year and 68% at 5 years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall survival was 82% at 1 year and 72% at 5 years. In multivariate analysis, the authors found that CHD (HR, 1.6; 95% CI, 1.02 to 2.64) and mechanical ventilation at the time of transplantation (HR, 1.6; 95% CI, 1.13 to 3.10) were both significantly and independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small size of the study group. Study limitations included the retrospective design and single-center sample.

Registry Studies

According to OPTN, patients between the ages of 11 and 17 years old had the highest 1- and 3-year survival rates among pediatric patients who underwent a heart transplant in the U.S. between 2008 and 2015.[3,] Patients younger than 1 year of age had the lowest 1-, 3-, and 5-year survival rates among pediatric patients (Table 1).

Rossano et al (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry.[30,] Among 12,091 pediatric patients undergoing heart transplantation between 1982 and 2014, the overall median survival was 20.7 years for infants (n=2994), 18.2 years for children between the ages of 1 to 5 years old (n=2720), 14.0 years for those 6 to 10 years old (n=1743), and 12.7 years for those 11 to 17 years old (n=4684). Because the first year posttransplant represents the greatest risk for mortality, survival conditional on survival to 1 year was longer.

Rossano et al conducted a multivariable analysis of pediatric patients undergoing a heart transplant between 2003 and 2013 to identify the factors associated with 1-year mortality.[30,] Infection requiring intravenous drug therapy within 2 weeks of transplant (HR, 1.36; 95% CI, 1.10 to 1.68; n=681), ventilator use (HR, 1.41; 95% CI, 1.13 to 1.76; n=826), donor cause of death (cerebrovascular accident vs. head trauma; HR, 1.59; 95% CI, 1.20 to 2.09; n=396), diagnosis (CHD vs. cardiomyopathy; HR, 1.91; 95% CI, 1.46 to 2.52; n=1979; retransplant vs. cardiomyopathy; HR, 2.23; 95% CI, 1.53 to 3.25; n=304), recipient dialysis (HR, 2.36; 95% CI, 1.57 to 3.57; n=146), extracorporeal membrane oxygenation (ECMO) with a diagnosis of CHD versus no ECMO (HR, 2.42; 95% CI, 1.74 to 3.35; n=145), ischemic time (p<.001), donor weight (p<.001), estimated glomerular filtration rate (eGFR; p=.002), and pediatric center volume (p<.001) were risk factors for 1-year mortality. Earlier era (1999 to 2000 vs. 2007 to 2009), CHD (vs. dilated cardiomyopathy), use of ECMO (vs. no device), and pediatric center volume were risk factors for 5-, 10-, and 15-year mortality. A panel-reactive antibody greater than 10% was associated with worse 5- and 10-year survival and eGFR was associated with 5- and 10-year mortality.

A retrospective analysis of the OPTN data focusing on the adolescent population was reported by Savla et al (2014).[31,] From 1987 to 2011, heart transplants were performed in 99 adolescents (age, 13 to 18 years) with myocarditis and 456 adolescents with CHD. Among transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly lower than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond et al (2009) analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine whether the pediatric heart allocation system, as revised in 1999, was prioritizing patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.[32,] Of 3098 children (<18 years of age) listed between 1999 and 2006, 1874 (60%) were listed as status 1A. Of these 1874, 30% were placed on ventilation, and 18% were receiving ECMO. Overall, 533 (17%) died, 1943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that status 1A patients were a heterogeneous population with a large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included ECMO support (HR, 3.1), ventilator support (HR, 1.9), listing status 1A (HR, 2.2), CHD (HR, 2.2), dialysis support (HR, 1.9), and non-White race/ethnicity (HR, 1.7). The authors concluded that the pediatric heart allocation system was capturing medical urgency poorly, specific high-risk subgroups could be identified, and further research would be needed to better define the optimal organ allocation system for pediatric heart transplantation.

Section Summary: Initial Heart Transplant

The evidence supports a net benefit for heart transplantation compared with a waitlist for status 1A and 1B candidates. Status 2 candidates also show a benefit from heart transplantation; however, the survival benefit is delayed. Data from national and international registries have found high patient

survival rates after initial heart transplant among adult and pediatric patients (e.g., a 5-year survival rate, 78%).

Heart Retransplantation

Clinical Context and Therapy Purpose

From 2008 to 2015, approximately 4% of heart transplants were repeated transplantations.[3,] Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The UNOS does not have separate organ allocation criteria for repeat heart transplant recipients.

The purpose of heart retransplants in individuals who have had a prior heart transplant complicated by graft failure or severe heart dysfunction is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals who have had a prior heart transplant complicated by graft failure or severe heart dysfunction.

Interventions

The therapy being considered is a heart retransplant.

Comparators

The following therapies and practices are currently being used to make decisions about reducing the risk of end-stage heart failure: guideline-directed medical therapy ; surgery including coronary bypass surgery, heart valve repair or replacement, and ventricular assist devices.

Outcomes

The general outcomes of interest are OS, symptoms, and morbid events (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for a detailed discussion of outcomes in patients with malignancy, HIV, older age, pulmonary hypertension, and renal insufficiency, and children with intellectual disability. Follow-up of 1, 2, 5, and 10 years is of interest for heart transplant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, 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 events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A number of studies have reviewed the clinical experience with heart retransplantation in adults. Tjang et al (2008) published a systematic review of the literature on the clinical experience with adult heart retransplantation; reviewers identified 22 studies.[33,] The most common indications for re-transplantation were cardiac allograft vasculopathy (55%), acute rejection (19%), and primary graft failure (17%). The early mortality rate in individual studies was 16% (range, 5% to 38%). Some factors associated with poorer outcomes after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure, and an initial diagnosis of ischemic cardiomyopathy.

Retrospective Reviews

Zhu et al (2022) evaluated outcomes after heart retransplantation for 123 patients (112 adult and 11 pediatric patients) as compared to those who received a primary heart transplant at a single-center over a 50-year period (January 6, 1968 to June 2019).[34] The indications for retransplantation included cardiac allograft vasculopathy (80%), primary graft dysfunction (15%), and refractory acute rejection (5%). The mean time interval between the primary and re-transplant was 6.4 years. Patients who underwent a retransplantation were significantly more likely to have hypertension (73.3% vs. 53.3%; p=.0022), hyperlipidemia (66.7% vs. 30.7%; p<.0001), and require dialysis (11.7% vs. 2.9%; p=.0025) as compared to those undergoing a primary heart transplant. After matching, postoperative outcomes and complications including hospital stay (mean 22.9 vs. 25.8 days; p=.49), intensive care unit stay (mean 12.2 vs. 9.9 days; p=.48), respiratory failure (41.7% vs. 20.6%; p=.083), dialysis (21.2% vs. 24.2%; p=.82), pneumonia (12.9% vs. 9.6%; p=.48), septicemia (1.6% vs. 9.4%; p=.10), and rejection within the first year after transplantation requiring hospitalization (21.5% vs. 26.2%; p=.82) were similar between the retransplant and primary transplant groups, respectively. Matched median survival after re-transplantation was 4.6 years versus 6.5 years after primary heart transplantation (p=.36).

In a retrospective review, Saito et al (2013) evaluated 593 patients with heart transplants performed at their institution, 22 (4%) of whom required retransplants.[35] The mean interval between initial and repeat transplants was 5.1 years. The indications for a repeat transplant were acute rejection in 7 (32%) patients, graft vascular disease in 10 (45%) patients, and primary graft failure in 5 (23%) patients. The 30-day mortality rate after cardiac retransplantation was 32% (7/22 patients). Among patients who survived the first 30 days (n=15), 1-, 5-, and 10-year survival rates were 93.3%, 79%, and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82%, and 63%, respectively. An interval of 1 year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of 9 (33.3%) patients with less than 1 year between the primary and retransplantation survived to 30 days; by comparison, 12 (92%) of 13 patients with at least 1 year between primary and retransplantation were alive at 30 days after surgery.

Registry Studies

An analysis of OPTN data from 2008 to 2015 found that 724 (3.9%) retransplants (of 18,676 heart transplants) were performed. Kaplan-Meier patient survival estimates at 1, 3, and 5 years were lower among the retransplant recipients than among primary transplant recipients (Table 2).

Table 2. Kaplan-Meier Patient Survival Estimates for Primary and Repeat Heart Transplants Performed Between 2008 and 2015

Years Posttransplant	Transplant Type					
	Primary Transplant			Repeat Transplant		
	No. Alive	Survival Rate, %[a]	95% CI, %	No. Alive	Survival Rate, %[a]	95% CI, %
1 year	9013	90.9	90.3 to 91.4	320	87.0	83.1 to 90.0
3 years	7711	85.6	84.8 to 86.3	286	76.5	71.8 to 80.4
5 years	6572	78.6	77.7 to 79.4	237	69.7	64.6 to 74.2

Source: Organ Procurement and Transplantation Network.[3]
CI: confidence interval.
[a] 1 year survival rates based on 2012-2015 transplants, 3-year survival rates based on 2010-2013 transplants, 5-year survival rates based on 2008-2011 transplants.

In a study analyzing UNOS data from January 1996 and November 2017, Miller et al (2019) reported that 349 (0.6%) early/acute retransplants (occurring ≤1 year after the previous transplant) and 2202 (3.5%) late retransplants (occurring >1 year after the previous transplant) were performed from a sample of 62,112 heart transplants.[36] Compared with a matched group of patients undergoing initial transplantation, patients undergoing late retransplantation were not at an increased risk of death (HR, 1.08; p=.084) or the combined outcome of death or retransplantation (HR, 1.07; p=.114). Additionally, patients undergoing late retransplant had comparable rates of 1-year all-cause

mortality when compared to patients undergoing initial transplant (13.8% vs. 14.5%, respectively; p=.517). Conversely, patients undergoing early/acute transplant had higher rates of 1-year all-cause mortality when compared to patients undergoing initial transplant (35% vs. 21.6%; p<.001). Furthermore, early/acute retransplantation was associated with an increased risk of all-cause mortality (HR, 1.79; p<.001) and the combined outcome of death or retransplantation (HR, 1.72; p<.001).

Goldraich et al (2016) examined the survival data for adult heart recipients with cardiac allograft vasculopathy who were retransplanted (n=65) or managed medically (n=4530).[37,] During a median follow-up of 4 years, 24 deaths occurred among those who underwent retransplantation and 1466 deaths among those medically managed. There was no significant difference in survival rates at 9 years (55% in retransplant recipients vs. 51% in medically managed patients, p=.88). In a subgroup analysis, the retransplant group (n=65) had longer survival than the medically managed group at 1 year after the development of coronary allograft vasculopathy (n=124; p=.02).

In an analysis of the OPTN data from 1995 to 2012, Belli et al (2014) reported that 987 (3.5%) re-transplants were performed from a sample of 28,464 heart transplants.[38,] Median survival among retransplant recipients was 8 years. The estimated survival rates at 1, 5, 10, and 15 years following retransplant were 80%, 64%, 47%, and 30%, respectively. Compared with primary transplant recipients, retransplant patients had a somewhat higher risk of death (relative risk, 1.27, 95% CI, 1.13 to 1.42).

In a study analyzing UNOS data, Friedland-Little et al (2014) reported no survival differences between third and second transplants (76% for third transplant vs. 80% for second transplant at 1 year; 62% for third transplant vs. 58% for second transplant at 5 years; 53% for third transplant vs. 34% for second transplant at 10 years, p=.73).[39,] However, study conclusions might have been limited because of the small number (n=25) of third heart transplants.

Pediatric Considerations

As with initial heart transplants, children awaiting heart retransplantation have high waitlist mortality. A study by Bock et al (2015) evaluated data on 632 pediatric patients who were listed for a heart retransplant for at least 1 year (median, 7.3 years) after the primary transplant.[40,] Patients' median age was 4 years at the time of the primary transplant and 14 years when relisted. Median waiting time was 75.3 days, and the mortality rate was 25.2% (159/632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<.01).

Conway et al (2014) analyzed the ISHLT Registry to compare the outcomes after retransplantation with primary heart transplantation among pediatric (<18 years of age) transplant recipients from 1998 to 2010.[41,] Of the 9882 heart transplant recipients with available clinical outcomes data, 9248 (93.6%) were primary transplants, 602 (6.1%) were retransplants (second graft), and 32 (0.3%) were third or fourth grafts. The median ages at primary transplant and retransplant were 7 years (range, 0 to 14 years) and 14 years (range, 1 to 26 years), respectively. The mean intertransplant interval was 6.8 years after primary transplant. The most common indications for retransplantation were coronary allograft vasculopathy (n=352 [59%]), nonspecific graft failure (n=52 [9%]), and acute rejection (n=49 [8%]). Retransplantation was associated with similar early survival but decreased long-term survival compared with initial transplantation. After primary transplantation, the survival rate was 84% at 1 year, 72% at 5 years, 60% at 10 years, and 42% at 20 years, compared with 81% at 1 year, 63% at 5 years, 46% at 10 years, and 26% at 20 years after retransplantation, respectively. The median survival rate was longer in primary transplant recipients, reaching 15 years (vs. 8.7 years after re-transplantation). The most common causes of death after retransplantation were cardiovascular other than vasculopathy (28%), graft failure (10%), infection (9%), noncardiac organ failure (9%), coronary allograft vasculopathy (4%), and acute rejection (3%),

Section Summary: Heart Retransplantation

In both adult and pediatric studies, poorer survival after retransplantation compared with initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events. Data from national and international registries have found high patient survival rates after heart retransplant among adult and pediatric patients (e.g., a 5-year survival rate, 69%). Cardiac allograft vasculopathy is the most common indication for heart retransplantation among adult and pediatric patients. Considering the scarcity of heart donors and the few treatment options for cardiac allograft vasculopathy, additional studies must be done to further examine the survival benefit of cardiac retransplantation over medical management among patients with cardiac allograft vasculopathy.

Potential Contraindications to Heart Transplant/Retransplantation

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes (e.g., morbidity, mortality) are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer, another disease). Moreover, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Pretransplant malignancy is considered a relative contraindication for heart transplantation because malignancy has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population, Mistiaen (2015) conducted a systematic review to study posttransplant outcomes of patients with pretransplant malignancy.[42,] Most selected studies were small case series (median sample size, 17 patients; range, 7 to 1117 patients; mean age range, 6 to 52 years). Hematologic malignancy and breast cancer were the most common types of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy were the most common reasons for transplantation in 4 case series, chemotherapy-related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality rates varied between 0% and 33%, with small sample size potentially explaining the observed variation.

Yoosabai et al (2015) retrospectively reviewed data on 23,171 heart transplant recipients in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of post-transplant malignancy.[43,] Posttransplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with an increased risk of overall post-transplant malignancy (subhazard ratio, 1.51; p<.01), skin malignancies (subhazard ratio, 1.55, p<.01), and solid organ malignancies (subhazard ratio, 1.54, p<.01) on multivariate analysis.

One large series by Oliveira et al (2012) reported similar short- and long-term post-transplant survival rates for patients who received chemotherapy-related (n=232) and for those with another nonischemic-related cardiomyopathy (n=8890).[44,] The 1-, 3-, and 5-year survival rates were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients, respectively. Similar 1-year survival findings were observed in smaller series. Two-, 5-, and 10-year survival rates among patients with pretransplant malignancy were also comparable with other transplant patients. In addition to the non-malignancy-related factors such as cardiac, pulmonary, and renal dysfunction, 2 malignancy-related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with a lower 5-year survival rate (<60%) than with a longer interval (>75%). Patients with prior hematologic malignancies had increased posttransplant mortality rates in 3 small series. Recurrence of

malignancy was more frequent among patients with a shorter disease-free interval (63%, 26%, and 6% among patients with <1 year, 1 to 5 years, and >5 years of disease-free interval, respectively).[45,]

The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients for whom cancer is thought to be cured should not be excluded from consideration for transplant. ISHLT guidelines have recommended stratifying each patient with pretransplant malignancy as to his or her risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup. The guidelines also recommend that the specific amount of time to wait for transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

Human Immunodeficiency Virus Infection

Solid-organ transplant for patients who are HIV-positive has historically been controversial. The availability of highly active antiretroviral therapy has changed the natural history of the disease. Aguero et al (2016) reported on a review of heart transplants among HIV-infected patients.[46,] In this review, since 2001, 12 heart transplantations in HIV-infected patients were reported and 3 patients acquired HIV after heart transplantation. Fourteen (93%) of these 15 patients were younger than 50 years of age, with cluster of differentiation 4 (CD4) counts greater than 200 cells/mm^3, and all recipients were taking antiretroviral therapy. Thirteen were alive with normal graft function at the end of follow-up. One patient had suboptimal adherence to antiretroviral therapy and died of multiorgan failure. The cause of death in the other patient was not reported.[47,]

There are few data directly comparing outcomes for patients with and without HIV. In 2021, Doberne et al compared survival outcomes of cardiac transplantation in HIV-positive recipients with HIV-negative recipients.[48,] Utilizing UNOS data on first-time heart transplant recipients and their donors between January 2005 and June 2019, a total of 75 HIV-positive transplant recipients and 29,848 HIV-negative recipients were included in an analysis. Results revealed no difference in 30-day, 1-year, and 5-year survival of HIV-positive versus HIV-negative heart transplant recipients. However, HIV-positive recipients had significantly longer median lengths of hospital stays (18 vs. 15 days; p=.006), rate of acute rejection during initial hospitalization (38.7% vs. 17.7%; p<.001), and rate of anti-rejection treatment administration (26.7% vs. 10.4%; p<.001).

Current OPTN policy permits HIV-positive transplant candidates.[49,]

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.[50,] These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- CD4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

Age

The maximum acceptable age for heart transplantation is uncertain. While the maximum recipient age for heart transplantation had been set at 55 years, with more evidence of comparable survival rates among the older population following heart transplantation, transplant centers are accepting older recipients. Currently, the upper age limit for heart transplant candidates is generally defined by transplant centers.

Jamil et al (2017) conducted a retrospective study of age as it relates to primary graft dysfunction after heart transplantation.[51,] Of the 255 heart transplants studied, 70 (27%) recipients were 65 years and older and 185 were younger; there were no significant differences in posttransplant morbidity (all p>.12) or 1-year survival between groups (p=.88). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; p=.037). Study limitations included the single-center design, lack of data on long-term survival, and the potential for selection bias in retrospective studies.

Cooper et al (2016) analyzed UNOS data to assess the long-term outcomes of older recipients of orthotopic heart transplantation (OHT) in the U.S. between 1987 and 2014.[52,] During this period, 50,432 patients underwent OHT; 71.8% (n=36,190) were 18 to 59 years of age, 26.8% (n=13,527) were 60 to 69 years of age , and 1.4% (n=715) were 70 years of age or older. The 5-year mortality rate was 26.9% for recipients 18 to 59 years, 29.3% for recipients 60 to 69 years, and 30.8% for recipients 70 years of age and older. Survival between the oldest group and the 60 to 69-year-old group did not differ significantly (p=.48).

Awad et al (2016) reported on a single-center retrospective review of 704 adults who underwent heart transplantation from 1988 to 2012 to investigate the mortality and morbidity rates of heart transplantations among recipients 70 years of age and older (n=45) compared with recipients younger than 70 years of age (n=659).[53,] The older and younger groups had similar 1-year (93.0% vs. 92.1%; p=.79), 5-year (84.2% vs. 73.4%; p=.18), and 10-year (51.2% vs. 50.2%; p=.43) survival rates, respectively.

Kilic et al (2012) analyzed UNOS data for 5,330 patients age 60 and older (mean age, 63.7 years) who underwent heart transplantation between 1995 and 2004.[54,] A total of 3492 (65.5%) patients survived to 5 years. In multivariate analysis, statistically significant predictors of 5-year survival included younger age (OR, 0.97; 95% CI, 0.95 to 1.00), younger donor age (OR, 0.99; 95% CI, 0.99 to 1.00), White race (OR, 1.23; 95% CI, 1.02 to 1.49), shorter ischemic time (OR. 0.93; 95% CI, 0.87 to 0.99), and lower serum creatinine level (OR, 0.92; 95% CI, 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly decreased the odds of surviving to 5 years. Patients with 2 or more of these factors had a 12% lower rate of 5-year survival than those with none.

Pulmonary Hypertension

Findings from several studies have suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after a heart transplant.[55,56,57,58,] For example, Tsukashita et al (2015) retrospectively compared the effect of continuous-flow LVAD support on pulmonary hypertension with posttransplantation outcomes among 227 potential OHT candidates with preexisting pulmonary hypertension.[59,] Patients were divided into 2 groups based on preimplantation pulmonary vascular resistance (PVR): low (<5 Wood units) (n=182) and high (≥5 Wood units) (n=45). After LVAD implantation, PVR in the high PVR group decreased significantly (7.13 Wood units to 2.82 Wood units, p<.001) to a level similar to that seen in the low PVR group (2.70 Wood units, p=.91) and remained low after heart transplantation. The mean follow-up after OHT was 3.5 years (range, 1 month to 9.3 years). The in-hospital mortality rate after OHT was significantly higher in the high PVR group (20.7%) than in the low PVR group (5.8%; p<.05). The survival rates at 3 years post-OHT were 85.0% for the low PVR group and 79.0% for the high PVR group (p=.45).

De Santoet al (2012) reported on 31 consecutive patients diagnosed with unresponsive pulmonary hypertension at baseline after right heart catheterization.[55,] After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing patients to be listed for a heart transplant. Oral sildenafil treatment resumed following the transplant. One patient died in the hospital. A right heart catheterization at 3 months posttransplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at 1 year in the 29 surviving patients. Similarly, in a study by Perez-Villa et al (2013), 22

patients considered high-risk for a heart transplant due to severe pulmonary hypertension were treated with bosentan.[56,] After 4 months of treatment, the mean PVR decreased from 5.6 to 3.4 Wood units. In a similar group of 9 patients who refused participation and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation, and the 1-year survival rate was 93%.

Renal Insufficiency

A retrospective report by Arshad et al (2019) compared renal outcomes and survival in patients who received an LVAD (n=45) or heart transplant (n=58).[60,] The eGFR was similar between LVAD and transplant groups on day 30 after the procedure (75.1 mL/min/1.73 m^2 and 65.8 mL/min/1.73 m^2, respectively; p=.057), and significantly higher with LVAD versus transplant at 6 months (68.3 mL/min/1.73 m^2 and 59.4 mL/min/1.73 m^2; p=.046) and 1 year (68.3 mL/min/1.73 m^2 and 56.8 mL/min/1.73 m^2; p=.15). Survival rates were similar between LVAD and transplant groups at 1 year (84.4% and 81.0%, respectively; p=.540) and 2 years (78.3% and 78.8%, respectively; p=.687) after the procedure.

Another retrospective report by Kolsrud et al (2018) investigated the association between post-heart transplantation and measured GFR as a risk factor for death and/or end-stage renal disease.[61,] During the first year after heart transplant, 416 adults showed a 12% mean drop in measured GFR compared with preoperative values and long-term survival was significantly worse in patients who experienced a 25% or greater decrease in measured GFR during the first post-transplantation year (HR, 1.62; 95% CI, 1.04 to 2.53; p=.03). Preoperative measured GFR was not predictive of mortality or end-stage renal disease, but older patients (HR, 1.03; 95% CI, 1.02 to 1.04; p<.001) or patients with a ventricular assist device (HR, 2.23; 95% CI, 1.43 to 3.46; p<.001) were predictors of death. The authors concluded that pretransplantation measured GFR was not predictive of mortality or end-stage renal disease after heart transplantation, but in this select patient population, a simultaneous or late-stage concomitant kidney transplant was necessary. Patients who experienced a 25% or greater measured GFR decrease had the poorest prognosis. Study limitations included selection bias of patients, the retrospective study design, the exclusion of the sickest patients eligible undergoing post-heart transplantation, changes in ventricular assist device and concomitant kidney transplant methods over time, and the small sample size studied.

The 2016 ISHLT criteria for heart transplantation recommended irreversible renal dysfunction (eGFR <30 mL/min/1.73 m^2) as a relative contraindication for heart transplantation alone. The cutoff for eGFR in the previous recommendation was 35 mL/min/1.73 m^2. Hong et al (2016) assessed 17,459 adult OHT recipients with results between 2001 and 2009 in the UNOS database to determine whether survival after OHT was associated with pretransplant eGFR and to define ranges of pretransplant eGFR associated with differences in posttransplant survival.[62,] Posttransplant graft survival in the group with an eGFR less than 34 mL/min/1.73 m^2 was significantly worse than in the groups with an eGFR of 35 to 49 mL/min/1.73 m^2 or an eGFR greater than 49 mL/min/1.73 m^2 (p<.001). Median survival in the 3 groups was 8.2 years, 10.0 years, and 10.3 years, respectively. At 3 months, graft survival rates were 82.1%, 90.7%, and 94.0% in the groups with an eGFR less than 34 mL/min/1.73 m^2, an eGFR of 35 to 49 mL/min/1.73 m^2, and an eGFR greater than 49 mL/min/1.73 m^2, respectively. In multivariable logistic regression analysis, an eGFR less than 34 mL/min/1.73 m^2 and an eGFR of 35 to 49 mL/min/1.73 m^2 were significant risk factors for death at 1 year (p<.001). Rossano et al (2016) also reported eGFR to be an independent risk factor for 1-, 5-, and 10-year posttransplant mortality among pediatric transplant recipients (described in the Pediatric Considerations section for survival after heart transplant).[30,]

Children With Intellectual Disability

Considering the shortage of available donor organs, heart transplantation in children with intellectual disability has been debated. In 2016, ISHLT removed explicit mention of "mental retardation" as a relative contraindication to heart transplantation from its official guidelines. Multiple studies in recent years have examined whether intellectual disability in children is associated

with significantly lower survival following heart transplantation compared with children without intellectual disability.

Goel et al (2017) conducted a retrospective cohort study using UNOS data from 2008 to 2015 to evaluate the prevalence and outcomes of heart transplantation in this population.[63,] Intellectual disability was assessed by using the cognitive development, academic progress, and academic level (5-point Likert scale scores for each of those) reported by transplant centers to UNOS. There were 565 pediatric (<19 years) patients with definite (n=131) or probable (n=434) intellectual disability who received their first heart transplant, accounting for 22.4% of all first pediatric heart transplants (n=2524). Intellectual disability was associated with a prolonged waitlist time (p<.001). Patient survival rates at 1 and 3 years, respectively, were 88.9% and 86.0% for the definite intellectual disability group, 91.6% and 82.4% for the probable intellectual disability group, and 91.8% and 86.2% for the no intellectual disability group. Patient survival did not differ between groups at any time posttransplant (p=.578). Intellectual disability status at listing was not associated with graft mortality hazards in univariate and multivariate analyses.

Wightman et al (2017) performed a retrospective cohort analysis of 1204 children receiving a first isolated heart transplant for whom cognitive and educational data were available in the UNOS dataset between 2008 and 2013.[64,] Children were categorized as "definitely cognitive delay/ impairment" by their transplant center using the Likert scales for cognitive development. All other recipients were classified as "no intellectual disability." Kaplan-Meier curves and log-rank tests did not suggest a significant difference in graft survival during the first 4 years after transplantation (p=.07), however, they did suggest poorer patient survival among the intellectual disability group during the first 4 years following transplantation (p=.05). In an unadjusted Cox regression, intellectual disability was associated with poorer graft (HR, 1.66; 95% CI, 1.01 to 2.72; p=.05) and patient survival (HR, 1.71; 95% CI, 0.99 to 2.94; p=.05). However, after adjusting for covariates, there was no association between intellectual disability and graft survival (HR, 0.95; 95% CI, 0.49 to 1.88; p=.89) or patient survival (HR, 0.80; 95% CI, 0.36 to 1.75; p=.58). Wightman et al (2021) also investigated the prevalence and long-term outcomes of initial kidney, liver, and heart transplants from 2008 to 2017 using UNOS data in children with an intellectual disability.[65,] During this study period, children with definite intellectual disability accounted for 324 (9%) of 3722 initial heart transplant recipients. In these patients, intellectual disability was not significantly associated with patient or graft survival.

Prendergast et al (2017) assessed the impact of cognitive delay on pediatric heart transplantation outcomes using academic progress as a surrogate for cognitive performance among pediatric heart transplant recipients (2004 to 2014) with data reporting academic progress in the OPTN database (n=2245).[66,] Of the patients with complete academic progress data, 1707 (76%) were within 1 grade level of peers, 269 (12%) had delayed grade level, and 269 (12%) required special education. There was no significant difference in posttransplant survival between patients within 1 grade level of peers and those who required special education. However, patients with delayed grade level demonstrated worse post-transplant survival than patients within 1 grade level of peers and those who required special education (p<.001). Delayed grade level remained as an independent predictor of post-transplant graft loss (adjusted HR, 1.4; 95% CI, 1.02 to 1.79; p=.03) in multivariate analysis. The authors conducted a secondary analysis substituting cognitive delay for academic progress; patients were divided into 2 groups based on whether any concerns for a cognitive delay (questionable, probable, or definite) were ever reported at the time of heart transplantation or during follow-up (1176 with cognitive delay, 1783 with no documented cognitive delay). There was no significant difference in posttransplant graft survival based on the presence of cognitive delay (p=.57). Cognitive delay remained a statistically nonsignificant predictor in multivariate analysis (adjusted HR, 1.01; 95% CI, 0.83 to 1.22; p=.953).

Because these studies assessed patients who received transplants and did not evaluate children who were refused listing by a transplant center or never referred to a transplant center, the prevalence of intellectual disability among potential candidates of heart transplantation might have been

underestimated. With low-risk intellectual disability patients receiving heart transplant and individuals with intellectual disability and other high-risk conditions being excluded, results might also have a positive selection bias.

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 Foundation et al

Heart failure guidelines from the American College of Cardiology Foundation, the American Heart Association, and the Heart Failure Society of America were updated in 2022.[67,]

Recommendations for cardiac transplantation by the joint committee were as follows:

- "For selected patients with advanced HF [heart failure] despite GDMT [guideline-directed medical therapy], cardiac transplantation is indicated to improve survival and QOL [quality of life] (class of recommendation, 1; level of evidence, C-LD)
- In patients with stage D (advanced) HF despite GDMT, cardiac transplantation provides intermediate economic value (value statement: intermediate value)"

International Society for Heart and Lung Transplantation

In 2004, the International Society for Heart and Lung Transplantation (ISHLT) recommended that children with the following conditions be evaluated for heart transplantation (Table 3).[68,]

Table 3. Recommendations for Pediatric Heart Transplant

Recommendation	LOE
Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death	B
Advanced systemic right ventricular failure (Heart Failure Stage C described as patients with underlying structural or functional heart disease and past or current symptoms of heart failure) that is refractory to medical therapy	C

LOE B is based on a single randomized trial or multiple nonrandomized trials; LOE C is based primarily on expert consensus opinion.
LOE: level of evidence.

In 2016, the ISHLT published a 10-year update to its listing criteria for heart transplantation.[69,] The guidelines recommended the following updates or changes to the prior guideline:

- Recommended use of heart failure prognosis scores (e.g., Seattle Heart Failure Model, Heart Failure Survival Score) along with a cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients.
- Periodic right heart catheterization for routine surveillance was not recommended in children.
- Carefully selected patients >70 years of age may be considered for cardiac transplantation.
- Pre-existing neoplasm, body mass index of ≥35 kg/m^2, diabetes with "end-organ damage (other than non-proliferative retinopathy) or poor glycemic control … despite optimal effort," irreversible renal dysfunction, clinically severe symptomatic cerebrovascular disease, peripheral vascular disease, and frailty are considered relative contraindications to heart transplantation.

- Considering active smoking during the previous 6 months as a risk factor for poor outcomes after transplantation, active tobacco smoking is considered a relative contraindication for heart transplantation. Similarly, patients who remain active substance abusers (including alcohol) are not recommended to receive heart transplantation.

In 2016, this same ISHLT guideline update states the following regarding retransplantation indications:

> "Retransplantation is indicated for those patients who develop significant CAV [(cardiac allograft vasculopathy)] with refractory cardiac allograph dysfunction, without evidence of ongoing acute rejection (Class IIa, Level of Evidence: C)."

The guideline cites the published consensus by Johnson et al (2007) on indications for retransplantation.[5,] It states that based on available data, appropriate indications for retransplantation include "the development of chronic severe CAV with symptoms of ischemia or heart failure, CAV without symptoms but with moderate to severe LV [(left ventricle)] dysfunction, or symptomatic graft dysfunction without evidence of active rejection." Retransplantation within the first 6 months after previous transplantation, especially with immunologic complications as a primary cause, was considered high-risk.

As a note on heart transplantation in children, the 2016 guideline update states, "although nearly half of all HTs [(heart transplants)] in children are done for CHD [(congenital heart disease)],... it should be noted that general considerations vary for more traditional indications, such as idiopathic dilated cardiomyopathy, for transplantation in the pediatric population....Thus, as these guidelines are translated to the younger patient, such prudence will need to be exercised."

In 2010, the guidelines from ISHLT on the care of heart transplant recipients include the following recommendations on cardiac retransplantation[70,]:

- "Retransplantation is indicated in children with at least moderate systolic heart allograft dysfunction and/or severe diastolic dysfunction and at least moderate CAV (*cardiac allograft vasculopathy*)."
- "It is reasonable to consider listing for retransplantation those adult HT [heart transplant] recipients who develop severe CAV not amenable to medical or surgical therapy and symptoms of heart failure or ischemia."
- "It is reasonable to consider listing for retransplantation those HT recipients with heart allograft dysfunction and symptomatic heart failure occurring in the absence of acute rejection."
- "It is reasonable to consider retransplantation in children with normal heart allograft function and severe CAV."

American Heart Association

In 2007, the American Heart Association indicated that, based on level B (nonrandomized studies) or level C (consensus opinion of experts) evidence, heart transplantation is indicated for pediatric patients as therapy for the following indications:[71,]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E_1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previous repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death

and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension;

The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, "in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m^2 and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m^2 or the transpulmonary gradient to <15 mm Hg."

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

Medicare National Coverage
Cardiac transplantation is covered under Medicare when performed in a facility approved by Medicare.[72,] The Centers for Medicare & Medicaid Services has stated that, under certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures safety and efficacy objectives.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in June 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring provider history and physical
- Cardiology consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring providers (when applicable)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Chest x-ray (CXR) and other radiology reports (when applicable)
- Colonoscopy report if > 50 years of age
- Cardiology procedures and respiratory function reports:
  - EKG
  - Cardiac echocardiogram
  - Cardiac stress test
  - Cardiac catheterization

- Pulmonary Function Tests (PFTs)
- Laboratory reports

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®	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of cadaver donor heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
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
05/16/1984	BCBSA Medical Policy adoption
10/12/1994	Policy revision adopted
05/17/2001	Policy clarification
07/02/2007	Policy updated. Adopted from BCBSA MPP. Benefit guidelines from BSC COE program
02/20/2008	Formatting correction
01/07/2011	Policy revision with position change
03/14/2014	Policy revision with position change
04/09/2014	Administrative Update
07/31/2015	Coding update
03/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
11/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Literature review updated.
10/01/2021	Annual review. No change to policy statement. Policy guidelines and literature review updated.
10/01/2022	Annual review. Policy statement, guidelines and literature review updated.
10/01/2023	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 and Feedback (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.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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**
Heart Transplant 7.03.09 **Policy Statement:** I. Human heart transplantation may be considered **medically necessary** for select adults and children with end-stage heart failure when the following individual selection criteria are met. **Adult Individuals** Accepted Indications for Cardiac Transplantation (**any** of the following): A. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items, 1. Maximal oxygen consumption (Vo_2) less than 10 mL/kg/min with achievement of anaerobic metabolism 2. Refractory cardiogenic shock 3. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion B. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty C. Recurrent symptomatic ventricular arrhythmias refractory to all accepted therapeutic modalities Probable Indications for Cardiac Transplantation (**any** of the following): A. Maximal Vo_2 less than 14 mL/kg/min and major limitation of the individual's activities B. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty C. Instability of fluid balance/renal function not due to individual noncompliance with a regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction The following conditions are inadequate indications for cardiac transplantation unless other factors as listed above are present.	**Heart Transplant 7.03.09** **Policy Statement:** I. Human heart transplantation may be considered **medically necessary** for select adults and children with end-stage heart failure when the following individual selection criteria are met. **Adult Individuals** Accepted Indications for Cardiac Transplantation (**any** of the following): A. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items, 1. Maximal oxygen consumption (Vo_2) less than 10 mL/kg/min with achievement of anaerobic metabolism 2. Refractory cardiogenic shock 3. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion B. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty C. Recurrent symptomatic ventricular arrhythmias refractory to all accepted therapeutic modalities Probable Indications for Cardiac Transplantation (**any** of the following): A. Maximal Vo_2 less than 14 mL/kg/min and major limitation of the individual's activities B. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty C. Instability of fluid balance/renal function not due to individual noncompliance with a regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction The following conditions are inadequate indications for cardiac transplantation unless other factors as listed above are present.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
A. Ejection fraction less than 20% B. History of functional class III or IV symptoms of heart failure C. Previous ventricular arrhythmias D. Maximal Vo_2 greater than 15 mL/kg/min **Pediatric Individuals** Individuals with heart failure and persistent symptoms at rest who require **one or more** of the following: A. Continuous infusion of intravenous inotropic agents B. Mechanical ventilatory support C. Mechanical circulatory support Individuals with heart disease and symptoms of heart failure who do not meet the above criteria but who have **any** of the following: A. Severe limitation of exercise and activity (if measurable, such individuals would have a maximum Vo_2 less than 50% predicted for age and sex) B. Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease C. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator D. Restrictive cardiomyopathy with reactive pulmonary hypertension E. Reactive pulmonary hypertension and risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future F. Anatomic and physiologic conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle G. Anatomic and physiologic conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction	A. Ejection fraction less than 20% B. History of functional class III or IV symptoms of heart failure C. Previous ventricular arrhythmias D. Maximal Vo_2 greater than 15 mL/kg/min **Pediatric Individuals** Individuals with heart failure and persistent symptoms at rest who require **one or more** of the following: A. Continuous infusion of intravenous inotropic agents B. Mechanical ventilatory support C. Mechanical circulatory support Individuals with heart disease and symptoms of heart failure who do not meet the above criteria but who have **any** of the following: A. Severe limitation of exercise and activity (if measurable, such individuals would have a maximum Vo_2 less than 50% predicted for age and sex) B. Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease C. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator D. Restrictive cardiomyopathy with reactive pulmonary hypertension E. Reactive pulmonary hypertension and risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future F. Anatomic and physiologic conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle G. Anatomic and physiologic conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
II. Heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in individuals who meet the criteria for heart transplantation.	II. Heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in individuals who meet the criteria for heart transplantation.
III. Heart transplantation is considered **investigational** in all other situations.	III. Heart transplantation is considered **investigational** in all other situations.