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Heart Transplant

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Related Policies (if applicable)
SUR703.006: Heart/Lung Transplant
SUR703.001: Organ and Tissue Transplantation (General Donor and Recipient Information)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Texas ONLY: For policies (IFM, Student, Small Group, Mid-Market, Large Group, fully-insured Municipalities/Counties/Schools, State Employee Plans, PPO, HMO, POS) delivered, issued for delivery, or renewed on or after January 1, 2024, TIC Chapter 1380 (§§ 1380.001 – 1380.003 [SB 1040 Human Organ Transplant]) prohibits coverage of a human organ transplant or post-transplant care if the transplant operation is performed in China or another country known to have participated in forced organ harvesting; or the human organ to be transplanted was procured by a sale or donation originating in China or another country known to have participated in forced organ harvesting. The commissioner of state health services may designate countries who are known to have participated in forced organ harvesting. Forced organ harvesting is defined as the removal of one or more organs from a living person by means of coercion, abduction, deception, fraud, or abuse of power or a position of vulnerability.

Coverage

Human heart transplant **may be considered medically necessary** in carefully selected individuals with irreversible, refractory, and symptomatic end-stage heart failure who meet the

United Network for Organ Sharing (UNOS) guidelines for 1-6 Status and are not currently Inactive Status (formerly known as Status 7).

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

Heart transplantation **is considered experimental, investigational and/or unproven** in all other situations.

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 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 ability to adhere to therapy.

Policy-specific potential contraindications subject to the judgment of the transplant center:

- Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance (PVR) >5 Wood units, or transpulmonary gradient (TPG) $\geq$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 medical policy SUR703.006).

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 United Network for Organ Sharing (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 (CHD), 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 individuals with refractory end-stage cardiac disease.

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 supports 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 (OPTN) and United Network for Organ Sharing (UNOS).

Heart Transplant
In 2023, 46,632 transplants were performed in the United States (U.S.) procured from 39,679 deceased donors and 6,953 living donors. (2) Heart transplants were the third most common procedure with 4,039 transplants performed from both deceased and living donors in 2023. As of June 2024, there were 3,440 patients on the waiting list for a heart transplant. (3) Rose et al. (2024) reported a 62% lower rate of heart transplants among women compared with men and a 46% lower rate in Black men compared with White men in a retrospective database review from 2010 to 2018. (4)

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 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 to the era of 2000 to 2005. (5) 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. (6) 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. (7) 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). (8) 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% versus [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). (9) A multivariate analysis identified that an estimated glomerular filtration rate (eGFR) 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). (10) 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 ratio, 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. (11)

Methods other than Vo_2max have been proposed as predictive models in adults. (12-15) 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, (17-19) but with a noted underestimation of mortality risk, particularly in blacks and device recipients. (20, 21) None of these models have been universally adopted by transplant centers.

Regulatory Status
Solid organ transplantation is a surgical procedure and, as such, is 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

This policy was originally created in 1990 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 21, 2024.

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

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. RCTs have been published on related topics (e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy) but are not germane to this medical policy.

Initial Heart Transplant

Clinical Context and Therapy Purpose

In the United States (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 policy.

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 detailed discussion of outcomes in patients with malignancy, human immunodeficiency virus (HIV), older age, pulmonary hypertension, 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.

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 versus [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 14, 2024, were 90.3% (95% CI, 89.6% to 90.9%) for men and 90.7% (95% CI, 89.6% to 91.7%) for women. (3) The 3-year survival rates were 84.7% (95% CI, 83.8% to 85.5%) for men and 84.1% (95% CI, 82.7% to 85.4%) for women, and the 5 -year survival rates were 77.8% (95% CI, 76.8% to 78.8%) and 75.9% (95% CI, 74.2% to 77.6%), respectively. There was no major difference in 1-, 3-, and 5-year survival rates between different age groups among adult recipients (See 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	406	87.4 (84.0 to 90.1)	362	83.9 (80.1 to 87.0)	317	75.0 (70.6 to 78.8)
1-5 years	345	92.4 (89.2 to 94.6)	282	85.0 (80.7 to 88.4)	257	78.1 (73.3 to 82.1)
6-10 years	223	91.9 (87.7 to 94.7)	186	87.0 (81.7 to 90.8)	166	84.1 (78.3 to 88.5)
11-17 years	507	96.6 (94.7 to 97.9)	458	91.5 (88.7 to 93.6)	356	78.4 (74.4 to 81.9)
18-34 years	840	90.9 (88.8 to 92.6)	722	82.1 (79.4 to 84.5)	597	72.3 (69.2 to 75.2)
35-49 years	1588	90.6 (89.1 to 91.8)	1399	84.8 (83.0 to 86.4)	1233	78.2 (76.1 to 80.1)
50-64 years	3896	90.4 (89.5 to 91.3)	3373	84.8 (83.7 to 85.9)	2972	78.3 (76.9 to 79.5)
65+ years	1514	88.2 (86.6 to 89.6)	1191	82.1 (80.0 to 83.9)	879	75.4 (72.9 to 77.8)

Source: Organ Procurement and Transplantation Network. (3)
CI: confidence interval; No: number; NR: not reported.
[a] One-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 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 9,404 patients who had survived 10 years after heart transplant, and 10,373 patients who had died before 10 years. Among individuals who had died, 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, 0-23.6 years). Overall

graft survival was 82% at 1 year and 68% at 5 years; the most common causes of graft loss were an 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 held 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 (see 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 ages 6-to-10 years old (n=1743), and 12.7 years for those ages 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 vs. 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, 13-18 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 the 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 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 policy.

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 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.

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 retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range, 5%-38%). Some factors associated with poorer outcome 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 retransplantation was 4.6 years vs. 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 patents 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 (see 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; No: number.

[a] One-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=0.88). In subgroup analysis, the retransplant group (n=65) had longer survival than the medically managed group at 1 year after development of coronary allograft vasculopathy (n=124; p=0.02).

In an analysis of the OPTN data from 1995 to 2012, Belli et al. (2014) reported that 987 (3.5%) retransplants 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 [RR], 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=0.73). (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 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<0.01).

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, 0-14 years) and 14 years (range, 1-26 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 retransplantation). 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 the 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 both 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 and 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 or other 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, 7-1117 patients; mean age range, 6-52 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 increased risk of overall posttransplant malignancy (subhazard ratio [SHR], 1.51; $p<0.01$), skin malignancies (SHR=1.55, $p<0.01$), and solid organ malignancies (SHR=1.54, $p<0.01$) on multivariate analysis.

One large series by Oliveira et al. (2012) reported similar short- and long-term posttransplant 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 lower 5-year survival (<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, 1-5 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 work-up. The guidelines also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

Human Immunodeficiency Virus (HIV) Infection

Solid organ transplant for patients who are HIV-positive has historically been controversial. The availability of highly active antiretroviral therapy (HAART) has changed the natural history of the disease. Aguero et al. (2016) reported on a review on heart transplants among HIV-infected patients. (46) In this review, since 2001, 12 heart transplantations in HIV-infected patients have been 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 vs. 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%) of recipients were 65 years and older and 185 were younger; there were no significant differences in posttransplant morbidity (all p>0.12) or at 1-year survival between groups (p=0.88). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; p=0.037). 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 old, 26.8% (n=13,527) were 60 to 69 years old, and 1.4% (n=715) were 70 years old of age or older. The 5-year mortality rate was 26.9% for recipients 18 to 59 years old, 29.3% for recipients 60 to 69 years old, 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=0.48).

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 (n=659). (53) The older and younger groups had similar 1-year (93.0 vs. 92.1; p=0.79), 5-year (84.2 vs. 73.4; p=0.18), and 10-year (51.2 vs. 50.2; p=0.43) survival rates, respectively.

Kilic et al. (2012) analyzed UNOS data on 5,330 patients age 60 and older (mean age, 63.7 years) who underwent heart transplantation between 1995 and 2004. (54) A total of 3,492 (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 heart transplant. (55-58) 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<0.001) to a level similar that in the low PVR group (2.70 Wood units, p=0.91) and remained low after heart transplantation. The mean follow-up period 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<0.05). 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=0.45).

De Santo et 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 heart transplant. Oral sildenafil treatment resumed following 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, 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 vs. 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 postheart transplantation and measured glomerular filtration rate (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 posttransplantation year (HR=1.62; 95% Cl, 1.04 to 2.53; p=0.03). Preoperative measured GFR was not predictive of mortality or end-stage renal disease, but older patients (HR=1.03; 95% Cl, 1.02 to 1.04; p<0.001) or patients with a ventricular assisted device (HR=2.23; 95% Cl, 1.43 to 3.46; p<0.001) 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 has the poorest prognosis. Study limitations included selection bias of patients, the retrospective study design, the exclusion of the sickest patients eligible undergoing postheart transplantation, changes in ventricular assisted 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 35 to 49 mL/min/1.73 m^2 or an eGFR greater than 49 mL/min/1.73 m^2 ($p<0.001$). 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 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 eGFR 35 to 49 mL/min/1.73 m^2 were significant risk factors for death at 1 year ($p<0.001$). 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 prolonged waitlist time ($p<0.001$). 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 probable intellectual disability group, and 91.8% and 86.2% for no intellectual disability group. Patient survival did not differ between groups at any time posttransplant ($p=0.578$). 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 1,204 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 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=0.07), however, they did suggest poorer patient survival among the intellectual disability group during the first 4 years following transplantation (p=0.05). In unadjusted Cox regression, intellectual disability was associated with poorer graft (HR=1.66; 95% CI, to 1.01 to 2.72; p=0.05) and patient survival (HR=1.71; 95% CI, 0.99 to 2.94; p=0.05). 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=0.89) or patient survival (HR=0.80; 95% CI, 0.36 to 1.75; p=0.58). 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 3,722 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 (2004-2014) with data reporting academic progress in the OPTN database (n=2,245). (66) Of the patients with complete academic progress data, 1,707 (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 posttransplant survival than patients within 1 grade level of peers and those who required special education ($p<0.001$). Delayed grade level remained as an independent predictor of posttransplant graft loss (adjusted HR=1.4; 95% CI, 1.02 to 1.79; p=0.03) 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=0.57). Cognitive delay remained a statistically nonsignificant predictor in multivariate analysis (adjusted HR=1.01; 95% CI, 0.83 to 1.22; p=0.953).

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.

Summary of Evidence
For individuals who have end-stage heart failure who receive a heart transplant, the evidence includes retrospective studies and registry data. Relevant outcomes are overall survival (OS), symptoms, and morbid events. Heart transplant remains a viable treatment for those with severe heart dysfunction despite appropriate medical management with medication, surgery, or medical devices. Given the exceedingly poor survival rates without transplantation for these patients, evidence of posttransplant survival is sufficient to demonstrate that heart transplantation provides a survival benefit. Heart transplantation is contraindicated for patients for whom the procedure is expected to be futile due to comorbid disease or for whom the procedure is expected to worsen comorbid conditions significantly. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have had a prior heart transplant complicated by graft failure or severe dysfunction of the heart who receive a heart retransplant, the evidence includes systematic reviews, retrospective studies, and registry data. Relevant outcomes are OS, symptoms, and morbid events. Despite improvements in the prognosis for many patients with graft failure, cardiac allograft vasculopathy, and severe dysfunction of the transplanted heart, heart retransplant remains a viable treatment for those whose severe symptoms persist despite treatment with other medical or surgical remedies. Given the exceedingly poor survival rates without retransplantation for patients who have exhausted other treatments, evidence of posttransplant survival is sufficient to demonstrate that heart retransplantation provides a survival benefit in appropriately selected patients. The evidence is sufficient to determine that the technology results an improvement in the net health outcome.

Practice Guidelines and Position Statements
American College of Cardiology Foundation (ACCF), American Heart Association (AHA) and Heart Failure Society of America
Heart failure guidelines from the ACCF, AHA, and the Heart Failure Society of America were updated in 2022. (11)

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)."

American Heart Association (AHA)
In 2007, the AHA 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: (67)
- 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."

International Society for Heart and Lung Transplantation (ISHLT)

In 2004, the 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 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 guidelines cite the published consensus by Johnson et al. (2007) on indications for retransplantation. (6) 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 six 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 guidelines 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 the 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."

Medicare National Coverage

Cardiac transplantation is covered under Medicare when performed in a facility approved by Medicare. (71) 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 from June 2024 did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	33940, 33944, 33945
HCPCS Codes	S2152

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/15/2024	Document updated with literature review. Coverage unchanged. Added reference 4; others updated and some removed.
02/01/2024	Document updated with literature review. Coverage unchanged. Added references 34, 67; others updated.
12/01/2022	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. The following references were added/updated: 1, 2, 3, 6-9, 22, 24, 35, 47, 48, 59, 64 and 72.

01/15/2021	Reviewed. No changes.
06/01/2020	Document updated with literature review. The follow change was made to the Coverage section: The medically necessary statement was changed from including 1A, 1B, or 2 Status to now including the United Network for Organ Sharing (UNOS) guidelines for 1-6 Status. References 42, 51 and 56 were added and some references removed.
11/15/2018	Reviewed. No changes.
12/15/2017	Document updated with literature review. The following change was made to Coverage: Updated terminology from “Status 7” to “Inactive Status”.
03/01/2016	Reviewed. No changes.
06/01/2015	Document updated with literature review. Coverage unchanged.
12/01/2014	Document updated with literature review. The following statements were added to coverage: 1) Heart retransplantation after a failed primary heart transplant may be considered medically necessary in patients who meet criteria for heart transplantation. 2) Heart transplantation is considered experimental, investigational and/or unproven in all other situations.
11/01/2013	Document updated with literature review. Coverage changed to: Human heart transplant may be considered medically necessary in carefully selected patients with irreversible, refractory, and symptomatic end-stage heart failure who meet the United Network for Organ Sharing (UNOS) guidelines for 1A, 1B, or 2 Status and are not currently Status 7. CPT/HCPCS code(s) updated.
04/15/2009	Editorial revision to clarify end-stage cardiomyopathy coverage criteria; references revised
06/01/2008	Revised/updated entire document; this policy is no longer scheduled for routine literature and update
02/01/2005	Revised/updated entire document
09/01/1998	Revised/updated entire document
05/01/1996	Medical policy number changed
04/01/1996	Revised/updated entire document
01/01/1992	Revised/updated entire document
05/01/1990	New medical document