Medical Policy

7.03.09 Heart Transplant

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Section: 11.0 Transplant

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Policy Statement

Human heart transplantation may be considered medically necessary for selected adults and children with end-stage heart failure when the following patient selection criteria are met:

Adult Patients

Accepted Indications for Transplantation (any of the following):

- Hemodynamic compromise due to heart failure demonstrated by any of the following three bulleted items:
  - Maximal oxygen consumption (Vo2) less than 10 mL/kg/min with achievement of anaerobic metabolism
  - Refractory cardiogenic shock
  - Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
- Recurrent symptomatic ventricular arrhythmias refractory to all accepted therapeutic modalities
- Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty

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

- Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction
- Maximal Vo2 less than 14 mL/kg/min and major limitation of the patient’s activities
- Recurrent unstable ischemia not amenable to bypass surgery or angioplasty

The following conditions are inadequate indications for heart transplantation unless other factors as listed above are present:

- Ejection fraction less than 20%
- History of functional class III or IV symptoms of heart failure
- Maximal Vo2 greater than 15 mL/kg/min
- Previous ventricular arrhythmias

Pediatric Patients

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

- Continuous infusion of intravenous inotropic agents
- Mechanical ventilatory support
- Mechanical circulatory support

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

- Anatomic and physiologic conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle
- Anatomic and physiologic conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction
- Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease
- Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator
- Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future
• Restrictive cardiomyopathy with reactive pulmonary hypertension
• Severe limitation of exercise and activity (if measurable, such patients would have a
  peak maximum oxygen consumption (Vo2) less than 50% predicted for age and sex)

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

Heart transplantation is considered investigational in all other situations.

### Policy Guidelines

The factors below are potential contraindications subject to the judgment of the transplant center:

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

Policy-specific potential contraindications include:

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

* Some patients may be candidates for combined heart-lung transplantation (see Blue Shield of
  California Medical Policy: Heart/Lung Transplantation).

Patients must meet the United Network for Organ Sharing (UNOS) guidelines for status 1A, 1B, or s
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 the
United Network for Organ Sharing (UNOS). Donor thoracic organs are prioritized by UNOS on
the basis of recipient medical urgency, distance from donor hospital, and pediatric status.
Patients who are most severely ill (status 1A) are given 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 (ECMO),
ventricular assist device). Additional criteria, which are considered in pediatric patients, include
diagnosis of an OPTN-approved congenital heart disease diagnosis, 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.

Full guidelines are available at https://optn.transplant.hrsa.gov/governance/policies/.

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.

Status 7 patients are considered temporarily unable to receive a thoracic organ transplant.

**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**

- Laboratory Tests for Heart Transplant Rejection
- Immune Cell Function Assay
- Heart/Lung Transplant
- 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**

Heart transplantation is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

**Rationale**

**Background**

**Heart Failure**

In the United States, approximately 6.5 million people 20 years of age and older have heart failure and 309,000 die each year from this condition.¹ The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body’s needs under minimal exertion. Heart transplantation can potentially improve both survival and quality of life in patients with end-stage heart failure.

Heart failure may be due to a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart defects. The leading indication for 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.² Ischemic cardiomyopathy was the dominant underlying primary diagnosis among the 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 the heart transplants during this time period were in adults with congenital heart disease.
Treatment
The demand for heart transplants far exceeds the availability of donor organs, and the length of
time patients are on the waiting list for transplants has increased. According to data from the
Organ Procurement and Transplantation Network, in 2016, a total of 3191 heart transplants were
performed in the United States. As of July 16, 2017, there were 3996 patients on the waiting list
for a heart transplant. In recent years, innovations in medical and device therapy for patients
with advanced heart failure has also improved the survival of patients awaiting heart
transplantation. The chronic shortage of donor hearts has led to the prioritization of patients
awaiting transplantation to ensure greater access for patients most likely to derive benefit.
Prioritization criteria are issued by the Organ Procurement and Transplantation Network and
fulfilled through a contract with the United Network for Organ Sharing.

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

Literature Review
Assessment of efficacy for therapeutic intervention involves a determination of whether an
intervention improves health outcomes. The optimal study design for this purpose is a
randomized controlled trial that includes clinically relevant measures of health outcomes.
Intermediate outcome measures, also known as surrogate outcome measures, may also be
adequate if there is an established link between the intermediate outcome and true health
outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes
provide useful information on health outcomes but are prone to biases such as
noncomparability of treatment groups, placebo effect, and variable natural history of the
condition.

Due to the nature of the population discussed herein, there are no randomized controlled trials
comparing heart transplantation with alternatives, including ventricular assist devices.
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. The following is a summary of evidence based on registry and case series data.

Prioritization of Candidates
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 on 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 has
improved, some patients on the transplant list will recover enough function to become delisted.
In 2007, Lietz and Miller reported on patient survival on the heart transplant waiting list,
comparing the era between 1990 and 1994 with the era of 2000 to 2005. One-year survival for
United Network for Organ Sharing (UNOS) status 1 candidates 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.

In 2010, Johnson et al reported on waiting list trends in the United States between 1999 and
2008. The proportion of patients listed as status 1 has continued to increase, even as waiting list
and posttransplant mortality for this group has 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.
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\textsubscript{2}max), which is measured during maximal exercise, is a measure that has been 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\textsubscript{2}max as a criterion for patient selection. Studies have suggested that transplantation can be safely deferred in those patients with a VO\textsubscript{2}max of greater than 14 mL/kg/min. The importance of the VO\textsubscript{2}max has also been emphasized by the American Heart Association when addressing heart transplant candidacy. 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\textsubscript{2}max have been proposed as predictive models in adults. 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 of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy et al introduced the model using a multivariate analysis of data from the PRAISE1 heart failure trial (N=1125). 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, but with a noted underestimation of mortality risk, particularly in blacks and device recipients. None of these models has been universally adopted by transplant centers.

Initial Heart Transplant Survival

According to the Organ Procurement and Transplantation Network (OPTN), 1-year Kaplan-Meier survival rates for heart transplants performed between 2008 and 2015, based on available U.S. data as of July 10, 2017, were 90.5% (95% confidence interval [CI], 89.9% to 91.2%) for men and 91.1% (95% CI, 90.1% to 92.1%) for women. The 3-year survival rates were 85.1% (95% CI, 84.3% to 86.0%) for men and 85.2% (95% CI, 83.8% to 86.4%) for women, and the 5-year survival rates were 78.4% (95% CI, 77.3% to 79.3%) and 77.7% (95% CI, 76.0% to 79.2%), respectively. There was no major difference in 1-, 3-, and 5-year survival rates between different age groups among adult recipients (see Table 1).

Nguyen et al (2017) investigated the benefit of heart transplantation compared with 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. 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 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. Transplant recipients were compared with patients listed for transplant but who did not receive one; transplant 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, a 2012 study by Kilic et al analyzed prospectively collected data from the UNOS registry. The analysis included 9404 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 (odds ratio [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 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).

A 2013 study examined characteristics of patients who survived more than 20 years after heart transplantation at a single center in Spain. 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; OR=3.9; 95% CI, 1.6 to 9.7) and idiopathic cardiomyopathy (i.e., vs other etiologies; OR=3.3; 95% CI, 1.4 to 7.8).

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. 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.

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

<table>
<thead>
<tr>
<th>Recipient Age</th>
<th>No. Alive</th>
<th>1 Year Survival Rate (95% CI), %</th>
<th>No. Alive</th>
<th>3 Years Survival Rate (95% CI), %</th>
<th>No. Alive</th>
<th>5 Years Survival Rate (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>378</td>
<td>87.6 (84.2 to 90.3)</td>
<td>327</td>
<td>85 (81.3 to 88.0)</td>
<td>277</td>
<td>77.1 (72.8 to 80.8)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>313</td>
<td>92.3 (89.1 to 94.6)</td>
<td>253</td>
<td>87 (82.9 to 90.2)</td>
<td>232</td>
<td>81.4 (76.8 to 85.2)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>198</td>
<td>92.2 (88.1 to 95.0)</td>
<td>168</td>
<td>89.7 (84.8 to 93.1)</td>
<td>154</td>
<td>89.3 (84.1 to 92.9)</td>
</tr>
<tr>
<td>11-17 years</td>
<td>478</td>
<td>96.8 (94.9 to 98.0)</td>
<td>417</td>
<td>92.3 (89.5 to 94.3)</td>
<td>318</td>
<td>80 (76.0 to 83.4)</td>
</tr>
<tr>
<td>18-34 years</td>
<td>791</td>
<td>91.8 (89.8 to 93.4)</td>
<td>659</td>
<td>83.6 (81.0 to 85.9)</td>
<td>550</td>
<td>74.8 (71.7 to 77.7)</td>
</tr>
<tr>
<td>35-49 years</td>
<td>1478</td>
<td>90.9 (89.4 to 92.1)</td>
<td>1286</td>
<td>85.4 (83.6 to 87.0)</td>
<td>1148</td>
<td>79 (76.9 to 80.9)</td>
</tr>
<tr>
<td>50-64 years</td>
<td>3647</td>
<td>90.7 (89.8 to 91.6)</td>
<td>3103</td>
<td>85.2 (84.1 to 86.3)</td>
<td>2723</td>
<td>78.5 (77.1 to 79.7)</td>
</tr>
<tr>
<td>65+ years</td>
<td>1414</td>
<td>88.3 (86.7 to 89.8)</td>
<td>1088</td>
<td>82.1 (80.0 to 84.0)</td>
<td>808</td>
<td>75.2 (72.6 to 77.5)</td>
</tr>
</tbody>
</table>


CI: confidence interval.

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.

### Pediatric Considerations

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. 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. 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.

Authors conducted a multivariable analysis of pediatric patients undergoing heart transplant between 2003 and 2013 to identify the factors associated with 1-year mortality. 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=626), donor cause of death (cerebrovascular accident vs head trauma; HR=1.59; 95% CI, 1.20 to 2.09; n=396), diagnosis (congenital heart disease [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<0.001), donor weight (p<0.001), estimated glomerular filtration rate (eGFR; p=0.002), and pediatric center volume (p<0.001) were risk factors for 1-year mortality. Earlier era (1999-2000 vs 2007-2009), 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.

Data from the Pediatric Heart Transplant Study (2013), which includes data on all pediatric transplants at 35 participating institutions, suggest 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).

A retrospective analysis of the OPTN data focusing on the adolescent population was published by Savla et al (2014). From 1987 to 2011, heart transplants were performed in 99 adolescents (age, 13-18 years) with myocarditis and 456 adolescents with CHD. Among adolescent 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. Of 3098 children (<18 years of age) listed between 1999 and 2006, a total of 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 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 nonwhite 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.

A retrospective review of pediatric cardiac transplantation patients was published by Auerbach et al in 2012. A total of 191 patients who underwent primary heart transplantation at a single center in the United States 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 acute rejection and graft vasculopathy. Overall patient 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 requiring 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. Limitations of the study included its retrospective design and single center sample.

Section Summary: Initial Heart Transplant
The evidence supports a net benefit for heart transplantation compared with waitlist for status 1A and 1B candidates. Data from national and international registries have also found high patient survival rates after initial heart transplant among adult and pediatric patients (e.g., a 5-year survival rate, 78%).

Heart Retransplantation Survival
An analysis of the OPTN data from 2008 to 2015 reported that 724 (3.9%) retransplants (of 18,676 heart transplants) were performed. Kaplan-Meier patient survival rates at 1, 3, and 5 years were lower among the retransplant recipients than among primary transplant recipients (see Table 2). A 2014 analysis of the OPTN data from 1995 to 2012 reported that 987 (3.5%) retransplants were performed from a sample of 28,464 heart transplants. 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).

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

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Primary Transplant</th>
<th>Repeat Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Alive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Survival Rate, %</td>
</tr>
<tr>
<td>1 year</td>
<td>8396</td>
<td>90.9</td>
</tr>
<tr>
<td>3 years</td>
<td>7038</td>
<td>85.5</td>
</tr>
<tr>
<td>5 years</td>
<td>5991</td>
<td>78.5</td>
</tr>
</tbody>
</table>

CI: confidence interval.
<sup>a</sup> 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.

A number of studies have reviewed the clinical experience with heart retransplantation in adults. In 2008, Tjiang et al published a systematic review of the literature on clinical experience with adult heart retransplantation; reviewers identified 22 studies. 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.

Goldraich et al (2016) examined the survival in adult heart recipients with cardiac allograft vasculopathy who were retransplanted (n=65) or managed medically (n=4530). During a median follow-up of 4 years, there were 24 deaths 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, overall the retransplant group (n=65) had longer survival than medically managed group with systolic graft dysfunction at 1 year after development of coronary allograft vasculopathy (n=124; p=0.02).
A representative study was published in 2013 by Saito et al.\textsuperscript{31} This retrospective review of data evaluated 593 heart transplant patients performed at their institution, 22 (4\%) of whom required retransplants. The mean interval between initial and repeat transplant 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 transplant 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.

A 2014 study using UNOS data 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).\textsuperscript{32} However, conclusions from this study’s results may be 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 2015 study by Bock et al 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.\textsuperscript{33} 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 mortality 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 transplantation among pediatric (<18 years of age) heart transplant recipients from 1998 to 2010.\textsuperscript{34} 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 when 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. Perhaps in doing so, retransplantation could be limited to highly selected patients with cardiac allograft vasculopathy.

Potential Contraindications to Heart Transplant (Applies to all Indications)
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, 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 over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population, Mistiaen et al (2015) conducted a systematic review to study posttransplant outcomes of patients with pretransplant malignancy. 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. One large series (2012) reported similar short- and long-term posttransplant survival rates for patients who received chemotherapy-related (n=232) and for those with other nonischemic-related cardiomyopathy (n=8890). The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients, respectively. Similar findings were observed for 1-year survival 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 smaller 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).

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 posttransplant malignancy. 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.

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 was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART) has markedly changed the natural history of the disease. Aguero et al (2016) reported of a review on heart transplants among HIV-infected patients. 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/mm³, 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. There are few data directly comparing outcomes for patients with and without HIV.

As of February 2013, the OPTN policy 4 on HIV-positive transplant candidates stated: “A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy.”

In 2017, the British HIV Association and the British Transplantation Society updated their guidelines on kidney transplantation in patients with HIV disease. 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 an issue for debate. While the maximum recipient age for heart transplantation was set at 55 years during the early years of heart transplantation, with increasing evidence of comparable survival rates among older population following heart transplantation, transplant centers have been accepting older recipients. However, the upper age limit for heart transplant candidates is still controversial and is generally defined by the transplant centers.

Cooper et al (2016) analyzed UNOS data to assess the long-term outcomes of older recipients of orthotopic heart transplantation (OHT) in the United States between 1987 and 2014. 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 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). 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.

In 2012, Kilic et al analyzed UNOS data on 5330 patients age 60 and older (mean age, 63.7 years) who underwent heart transplantation between 1995 and 2004. 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 (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 of them.

**Section Summary: Age**

There is consistent evidence that there is no significant difference in posttransplant survival rates between heart transplant recipients greater than 70 years and those who are younger.

**Pulmonary Hypertension**

Findings from several studies published in 2012 and 2013 have suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant. For example, Tsukashita et al (2015) retrospectively investigated the effect of continuous-flow left ventricular assist device support on pulmonary hypertension and compared posttransplantation outcomes among 227 potential OHT candidates with preexisting pulmonary hypertension. 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 left ventricular assist device 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. 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 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 heart transplant due to severe pulmonary hypertension were treated with bosentan. 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 in the study 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**

The 2016 ISHLT criteria for heart transplantation recommended irreversible renal dysfunction (eGFR <30 mL/min/1.73 m²) as a relative contraindication for heart transplantation alone. The cutoff for eGFR in the previous recommendation was 35 mL/min/1.73 m². Hong et al (2016) conducted a study among 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. Posttransplant graft survival in the group with an eGFR less than 34 mL/min/1.73 m² was...
significantly worse than in the groups with an eGFR 35 to 49 mL/min/1.73 m² or an eGFR greater than 49 mL/min/1.73 m² (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 m², an eGFR 35 to 49 mL/min/1.73 m², and an eGFR greater than 49 mL/min/1.73 m², respectively. In multivariable logistic regression analysis, eGFR less than 34 mL/min/1.73 m² and eGFR 35 to 49 mL/min/1.73 m² were significant risk factors for death at 1 year (p<0.001). Rosano 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 under pediatric considerations for survival after heart transplant).

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. 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 1204 children receiving a first isolated heart transplant for whom cognitive and educational data were available in the UNOS dataset between 2008 and 2013. 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, 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).

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=2245). Of the patients with complete academic progress data, 1707 (76%) were within 1 grade level of peers (WGL), 269 (12%) had delayed grade level, and 269 (12%) required special education. There was no significant difference in posttransplant survival between patients WGL and those who required special education. However, patients with delayed grade level demonstrated worse posttransplant survival than patients WGL 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. Authors conducted a secondary analysis substituting cognitive delay for academic
progress; patients were divided into 2 groups based on whether any concerns for 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 all these studies assessed the patients who received transplants and did not evaluate children who were refused listing by a transplant center or never referred to 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 case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. Despite improvements in the prognosis for many patients with advanced heart disease, 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 in patients for whom the procedure is expected to be futile due to comorbid disease or in whom posttransplantation care is expected to worsen comorbid conditions significantly. The evidence is sufficient to determine that the technology results in a meaningful 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 case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. 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 who have exhausted other medical or surgical remedies, yet are still with severe symptoms. 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 in a meaningful improvement in the net health outcome.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American College of Cardiology Foundation and American Heart Association**

Guidelines from the American College of Cardiology Foundation and American Heart Association on management of heart failure, updated in 2013, recommended evaluation for cardiac transplantation for patients with stage D heart failure despite guideline-directed medical therapy, device, and surgical management.\(^{55}\)

**International Society for Heart and Lung Transplantation**

In a 2004 statement, the International Society for Heart and Lung Transplantation (ISHLT) recommended that children with the following conditions be evaluated for heart transplantation (see Table 3).\(^{56}\)
Table 3. Recommendations for Pediatric Heart Transplant

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
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<tbody>
<tr>
<td>Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death.</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>C</td>
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</tbody>
</table>

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, ISHLT published a 10-year update to its listing criteria for heart transplantation. The guidelines recommended updates or changes to the 2006 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 is not recommended in children.
- Carefully selected patients >70 years of age may be considered for cardiac transplantation.
- Pre-existing neoplasm, BMI ≥35 kg/m², 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 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.

The 2010 guidelines from ISHLT include the following recommendations on cardiac retransplantation:

- “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
The American Heart Association indicated in 2007 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:

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E₁ 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 guidelines state 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/m² 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/m² or the transpulmonary gradient to <15 mm Hg.”

**European Society of Cardiology**

The 2016 European Society of Cardiology guidelines on the diagnosis and treatment of acute and chronic heart failure recommended considering heart transplantation for patients with end-stage heart failure with severe symptoms, poor prognosis, and no alternative treatment options. Active infection, severe peripheral arterial or cerebrovascular ischemia, pharmacologically irreversible pulmonary hypertension, cancer, renal insufficiency, systemic disease with multiorgan involvement, pretransplant body mass index greater than 35 kg/m², current alcohol or drug abuse, and insufficient social support to achieve compliant care in outpatient setting were considered relative contraindications for heart transplantation.

**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. 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 July 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**


60. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. Jul 14 2016;37(27):2129-2200. PMID 27206819


### Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- Referring physician 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 physicians (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. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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### Type | Code | Description
--- | --- | ---
CPT<sup>®</sup> | 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

### ICD-10 Procedure
02YA0Z0 | Transplantation of Heart, Allogeneic, Open Approach

### ICD-10 Diagnosis
All Diagnoses

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

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<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>05/16/1984</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/12/1994</td>
<td>Policy revision adopted</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/17/2001</td>
<td>Policy clarification</td>
<td>Transplant team review</td>
</tr>
<tr>
<td>07/02/2007</td>
<td>Policy updated. Adopted from BCBSA MPP. Benefit guidelines from BSC COE program</td>
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<td>02/20/2008</td>
<td>Formatting correction</td>
<td>Administrative Review</td>
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<td>01/07/2011</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
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<td>04/09/2014</td>
<td>Administrative Update</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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

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

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

Questions regarding the applicability of this policy should also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal at www.blueshieldca.com/provider.

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