

7.03.08	Heart/Lung Transplant		
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Policy Statement

Heart/lung transplantation may be considered **medically necessary** for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, **one** of the following diagnoses:

- I. Irreversible primary pulmonary hypertension with heart failure
- II. Nonspecific severe pulmonary fibrosis, with severe heart failure
- III. Eisenmenger complex with irreversible pulmonary hypertension and heart failure
- IV. Cystic fibrosis with severe heart failure
- V. Chronic obstructive pulmonary disease with heart failure
- VI. Emphysema with severe heart failure
- VII. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

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

Heart/lung transplantation is considered **investigational** in all other situations.

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

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

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information).

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

- 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 disease 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

Heart/Lung-Specific Criteria

When the candidate is eligible to receive a heart in accordance with United Network for Organ Sharing (UNOS) guidelines for cardiac transplantation, the lung(s) shall be allocated to the heart/lung candidate from the same donor. When the candidate is eligible to receive a lung in accordance with the UNOS Lung Allocation System, the heart shall be allocated to the heart/lung candidate from the same donor "after the heart has been offered to all heart and heart-lung potential transplant recipients in allocation classifications 1 through 4" Candidates with allocation classifications 1 through 4 fall within adult status 1 or 2 or pediatric status 1A.

Cardiac-Specific Criteria

Specific criteria for prioritizing donor thoracic organs for transplant are provided by the Organ Procurement and Transplantation Network (OPTN) and implemented through a contract with UNOS. Donor thoracic organs are prioritized by UNOS on the basis of recipient medical urgency, distance from donor hospital, and pediatric status. Patients who are most severely ill (status 1A) are given highest priority.

The following factors are considered in assessing the severity of cardiac 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). Factors considered in assessing the severity of pulmonary illness include increased pulmonary artery systolic pressure pulmonary arterial hypertension, and/or elevated pulmonary vascular resistance.

Additional criteria may be considered in pediatric patients, including 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.

In both adult and pediatric patients, isolated cardiac or pulmonary transplantations are preferred to combine heart/lung transplantation when medical or surgical management—other than organ transplantation—is available.

Full OPTN guidelines are available online (at <https://optn.transplant.hrsa.gov/governance/policies/>).

Patients who are considered temporarily unsuitable to receive a thoracic organ transplant may be assigned an inactive status.

Description

Heart/lung transplantation involves a coordinated triple operative procedure consisting of procurement of a donor heart/lung block, excision of the heart and lungs of the recipient, and implantation of the heart and lungs into the recipient. Heart/lung transplantation refers to the transplantation of one or both lungs and heart from a single cadaver donor.

Related Policies

- Heart Transplant
- Lung and Lobar Lung Transplant

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

The U.S. Food and Drug Administration 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. Heart/lung transplants are included in these regulations.

Rationale

Background

Heart/Lung Candidates Requiring Transplantation

Most heart/lung transplant recipients have Eisenmenger syndrome (37%), followed by idiopathic pulmonary artery hypertension (28%) and cystic fibrosis (14%). Eisenmenger syndrome is a form of congenital heart disease in which systemic-to-pulmonary shunting leads to pulmonary vascular resistance. It is possible that pulmonary hypertension could lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation or cyanosis.¹

Treatment

Combined heart/lung transplantation is intended to prolong survival and improve function in patients with end-stage cardiac and pulmonary diseases. Due to corrective surgical techniques and improved medical management of pulmonary hypertension, the total number of patients with Eisenmenger syndrome has seen a decline in recent years. Additionally, heart/lung transplants have not increased appreciably, but for other indications, it has become more common to transplant a single or double lung and maximize medical therapy for heart failure, rather than perform a combined transplant. For those indications, patient survival rates following heart/lung transplantations are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication. One-, 5-, and 10-year patient survival rates for heart/lung transplants performed between 1982 and 2014 were estimated at 63%, 45%, and 32%, respectively.²

In 2017, 29 individuals received heart/lung transplants in the United States. As of April 2018, 51 patients were on the waiting list for heart/lung transplants.³

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common

adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. Due to the nature of the disease condition, there are no randomized controlled trials comparing heart/lung transplant with alternatives. Systematic reviews are based on case series and registry data. The extant randomized controlled trials compare surgical technique, infection prophylaxis, and immunosuppressive therapy and are not germane to this evidence review.

Prioritization of Candidates

Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the U.S. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from 1 based on length of time on the waiting list to a system that incorporates the severity of the patient's underlying disease, as well as the likelihood of survival.⁷ However, it has been noted that the individual systems underestimate the severity of illness in patients with both end-stage heart and lung failure, and modification of the lung allocation score can be appealed for patients with pulmonary hypertension who meet the following criteria⁸:

- Deterioration of optimal therapy, and
- Right arterial pressure greater than 15 mm Hg or
- Cardiac index less than 1.8 L/min/m².

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.¹

Yusen et al (2016) analyzed data on heart/lung transplantations performed among adults between 1982 and 2015 using the registry of the International Society for Heart and Lung Transplantation (ISHLT).⁴ Among the 3397 heart/lung transplant recipients for whom the diagnosis was reported, 35% had congenital heart disease (CHD), 27% had pulmonary arterial hypertension, and 14% had cystic fibrosis as the primary indication. There has been a shift in indications for heart/lung transplantation over time. From 2004 to 2015, CHD (35%), pulmonary arterial hypertension (27%), and cardiomyopathy (11%) were the 3 most common indications for heart/lung transplantation. Of the 883 heart/lung transplant recipients during 2004 and 2015, 36% were 18 to 34 years old, 40% were 35 to 49 years old, and 24% were 50 years or older.

Pediatric Considerations

In an analysis of data from the OPTN, Spahr and West (2014) provided indications for pediatric heart/lung transplantation.⁹ The number of pediatric heart/lung transplants has decreased in recent years (56 cases from 1993 to 1997; 32 cases from 2008 to 2013). The 3 most common indications for pediatric heart/lung transplant were primary pulmonary hypertension (n=55), CHD (n=37), and Eisenmenger syndrome (n=30). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, no transplants for this syndrome have been performed since then. Pediatric heart/lung transplants have also been performed for other indications, including alpha₁-antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

Using ISHLT Registry data, Benden et al (2012) reported on pediatric heart/lung transplant data collected through June 2011.¹⁰ Overall survival rates after heart/lung transplants are comparable in children (median half-life, 4.7 years) and adults (median half-life, 5.3 years). For pediatric heart/lung transplants performed between 1990 and 2010, the 5-year survival rate was 49%. The 2 leading causes of death in the first year after transplantation were a non-cytomegalovirus infection and graft failure. Beyond 3 years posttransplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report by Benden et al (2014) on pediatric lung and heart/lung transplant from the same registry did not include updated data on pediatric heart/lung transplants due to the small number of patients available.¹¹

Initial Combined Heart/Lung Transplant

Clinical Context and Therapy Purpose

The purpose of combined heart/lung transplant in patients who have an end-stage cardiac and pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a combined heart/lung transplant improve the net health outcome in patients who have end-stage cardiac and pulmonary disease?

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

Populations

The relevant population of interest is patients with end-stage cardiac and pulmonary disease.

Interventions

The therapy being considered is a combined heart/lung transplant.

Comparators

The following practices are currently being used to make decisions about end-stage cardiac and pulmonary disease: medical management, double-lung transplant, and single-lung transplant.

Outcomes

The general outcomes of interest are overall survival, graft failure, improved function, and adverse events (e.g., infections). Follow-up after surgery focuses on monitoring for graft failure. Long-term follow-up can continue out to 3 to 5 years and beyond.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Registry Studies and Case Series

Sertic et al (2020) compared outcomes of bilateral lung transplantation with cardiac defect repair to combined heart/lung transplantation in adult patients with Eisenmenger syndrome using the UNOS database of heart/lung transplantations performed from 1987 to 2018.¹² Among 442 patients who underwent thoracic transplantation, 316 patients underwent heart/lung transplantation and 126 patients underwent double-lung transplantation with concomitant cardiac defect repair. Overall survival was similar between patients who underwent double-lung transplantation and those who underwent heart/lung transplantation at 1 year (63.1% vs 68.0%, respectively), 5 years (38.5% vs 47.3%), and 10 years (30.2% vs 30.5%) posttransplant (p=.6). Overall survival did not differ among patients who received transplantation between 1987 to 1999 and those who received transplantation between 2000 to 2018 (p=.7).

Yusen et al (2016) reported on the survival of adult heart/lung transplant recipients using the ISHLT database.⁴ Among the 3775 primary heart/lung transplants performed during 1982 and 2014, the 3-month, 1-year, 3-year, 5-year, and 10-year survival rates were 71%, 63%, 52%, 45%, and 32%, respectively. The overall median survival during this period (1982 to 2014) was 3.4 years. Those who survived to 1 year had a conditional median survival of 10.3 years. Survival improved

over time, with a median survival of 2.1 years for patients (n=1596) who received the transplant between 1982 and 1993, 3.9 years for patients (n=1392) between 1994 and 2003, and 5.8 years for patients between 2004 and 2014 (n=843) ($p < .05$ for all pairwise comparisons). Heart/lung transplant recipients in the 2004 to 2014 group had a median conditional survival beyond 10 years. Compared with lung-only transplantation (median conditional survival, 8.0 years), heart/lung transplant recipients had a better long-term survival (median conditional survival, 10.3 years).

Hill et al (2015) compared survival following heart/lung transplantation with double-lung transplantation for idiopathic pulmonary arterial hypertension among adult transplant recipients in the Scientific Registry of Transplant Recipients database during 1987 and 2012.¹³ Among the 928 idiopathic pulmonary arterial hypertension patients, 667 underwent double-lung transplantation, and 261 underwent heart/lung transplantation. Overall, the adjusted survival was similar between double-lung transplantation and heart/lung transplant recipients. However, for recipients hospitalized in the intensive care unit, double-lung transplantation was associated with worse outcomes than heart/lung transplantation recipients (hazard ratio [HR], 1.83; 95% confidence interval [CI], 1.02 to 3.28).

Jayarajan et al (2014) compared the mortality rates (at 1 month and 5 years posttransplant) of heart/lung transplant recipients who required pretransplant ventilation (n=22) or extracorporeal membrane oxygenation (ECMO; n=15) with controls.¹⁴ Median survival times were 10 days, 181 days, and 1547 days among patients with pretransplant ECMO, patients with a mechanical ventilator, and the control group, respectively. Patients with pretransplant ECMO had poorer survival than the control group at 30 days (20.0% vs 83.5%) and 5 years (20.0% vs 47.4%; $p < .001$). Similarly, patients requiring ventilation prior to transplantation had worse survival at 1 month (77.3% vs 83.5%) and 5 years (26.5% vs 47.4%; $p < .001$) compared with the control group. The use of ECMO (HR, 3.82; 95% CI, 1.60 to 9.12; $p = .003$) or mechanical ventilation (HR, 2.01; 95% CI, 1.07 to 3.78; $p = .030$) as a bridge to transplantation was independently associated with mortality on multivariate analysis. The findings of the study raise concern whether combined heart/lung transplant should be carried out in patients requiring ECMO; further, the findings suggest a need for additional research to improve survival in this high-risk group of patients.

Pediatric Considerations

Riggs et al (2020) assessed outcomes for pediatric heart/lung transplantation among children with congenital heart disease (CHD) with Eisenmenger syndrome, CHD without Eisenmenger syndrome, primary pulmonary hypertension, and "other" categories using the UNOS database of heart/lung transplantations performed from 1987 to 2018.¹⁵ Among 209 heart/lung transplantations performed during the specified time frame, 37 (17.7%) had CHD with Eisenmenger syndrome, 40 (19.1%) had CHD without Eisenmenger syndrome, 70 (33.5%) had primary pulmonary hypertension, 6 (2.9%) were retransplants, and 56 (26.8%) had another diagnosis. One-year, 5-year, and 10-year survival rates post-transplant, respectively, were 75%, 44%, and 32% for pediatric patients with CHD with Eisenmenger syndrome, 56%, 21%, and 16% for patients with CHD without Eisenmenger syndrome, 77%, 41%, and 33% for patients with primary pulmonary hypertension, 40%, 0%, and 0% for retransplanted patients, and 70%, 44%, and 20% for patients with other diagnoses. Compared to the reference group of pediatric patients with primary pulmonary hypertension, patients with CHD without Eisenmenger syndrome ($p = .03$) and patients who were retransplanted ($p = .008$) had significantly lower survival rates. Other survival comparisons were not significant. Survival rates were not different when comparing patients who received transplants between 1987 to 1999 and 2000 to 2018. Infants (HR, 2.2; 95% CI, 1.04 to 4.55; $p = .04$), 1 to 11 year old patients (HR, 1.78; 95% CI, 1.12 to 2.8; $p = .015$), and patients on ECMO (HR, 4.1; 95% CI, 1.3 to 12.8; $p = .016$) had the highest risk of mortality post-transplant.

Goldfarb et al (2016) reported on the survival of pediatric lung and heart/lung transplant recipients using the ISHLT database.¹⁶ Among the 698 pediatric heart/lung transplant recipients, median survival was 3.0 years, and conditional median survival was 7.8 years. There was no

statistically significant difference in survival by indication, recipient age group, or time period of transplant for pediatric heart/lung transplant recipients.

Section Summary: Initial Heart/Lung Transplant

Data from transplantation registries have found longer patient survival rates after initial heart/lung transplant among adult and pediatric patients over time. The net benefit of heart transplantation compared with lung-only transplantation is also evident, especially among patients with idiopathic pulmonary arterial hypertension.

Heart/Lung Retransplantation

Clinical Context and Therapy Purpose

The purpose of combined heart/lung retransplants in patients who have had a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung is to provide a treatment option that is an alternative to or an improvement on existing therapies. The question addressed in this evidence review is: Does a combined heart/lung retransplant improve the net health outcome in patients whose combined heart/lung transplant has been complicated by graft failure or severe dysfunction of the heart/lung? The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung.

Interventions

The therapy being considered is a combined heart/lung retransplant.

Comparators

The following practices are currently being used to make decisions about a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung: medical management, double-lung transplant, and single-lung transplant.

Outcomes

The general outcomes of interest are overall survival, graft failure, improved function, and adverse events (e.g., infections). Follow-up after surgery focuses on monitoring for graft failure. Long-term follow-up can continue out to 3 to 5 years and beyond.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Registry Studies

While uncommon, repeat heart/lung transplant procedures have been performed. Yusen et al (2014) reported on outcomes for adult heart/lung transplants, with a focus on retransplantation, using data from the ISHLT Registry.¹⁷ From 1982 to 2012, 90 adults had a first heart/lung retransplant after a previous heart/lung transplant. These 90 patients had a median survival of 0.3 years, with unadjusted survival rates of 52%, 43%, 36%, and 27% at 3 months, 1 year, 3 years, and 5 years, respectively. Those who survived to 1 year had a conditional median survival of 7.9 years.

A study by Shuhaiber et al (2008) reviewed data from the UNOS registry.¹⁸ They identified 799 primary heart/lung transplants and 19 repeat heart/lung transplants. Using Kaplan-Meier survival analysis, the observed median survival times were 2.08 years after primary transplant and 0.34 years after repeat transplants. In addition, reviewers analyzed survival data in matched pairs of primary and repeat transplant patients who were matched on a number of potentially confounding demographic and clinical characteristics. Matches were not available for 4 repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly between groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis was the low number of repeat transplant procedures performed.

Section Summary: Heart/Lung Retransplantation

Analysis has suggested that patients undergoing heart/lung retransplantation have a lower median survival compared with patients undergoing primary heart/lung transplantation. However, after controlling confounding variables, survival times did not differ significantly between groups. Also, the conditional mean survival of 7.9 years among those who survived to 1 year posttransplant would suggest a survival benefit of heart/lung retransplant.

Potential Contraindications to Heart/Lung 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, or another disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise (e.g., 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 given that 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 et al (2015) conducted a systematic review to study the posttransplant outcomes for pretransplant malignancy patients. Most selected studies were small case series (median sample size, 17 patients; range, 7 to 1117 patients; mean age, 6 to 52 years).¹⁹ 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 ranged between 0% and 33%, with small sample sizes potentially explaining the observed variation. A large series by Oliveira et al (2012) reported similar short- and long-term posttransplant survival rates for chemotherapy-related (n=232) and other nonischemic cardiomyopathy (n=8890) patients.²⁰ 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. Further, 2-, 5-, and 10-year survival rates among pretransplant malignancy patients were found to be 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. A 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 in 3 small series. For example, as reported by Sigurdardottir et al (2012), recurrence of malignancy was

more frequent among patients with a shorter disease-free interval: 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.²¹

Yoosabai et al (2015) conducted a retrospective review of 23,171 heart transplant recipients in the OPTN/UNOS database to identify whether pretransplant malignancy increased the risk of posttransplant malignancy.²² 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, 1.51; $p < .01$), skin malignancies (subhazard ratio, 1.55; $p < .01$), and solid organ malignancies (subhazard ratio, 1.54; $p < .01$) on multivariate analysis.

Recurrence Risk

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 in whom cancer is thought to be cured should not be excluded from consideration for transplant. The ISHLT guidelines have recommended stratifying each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup. The guidelines also recommended that the specific amount of time to wait for transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

Human Immunodeficiency Virus Infection

Koval et al (2019) conducted a retrospective study to assess outcomes among 29 HIV-infected patients who underwent thoracic transplant at 14 sites in the U.S. and Europe.²³ Of the 29 patients, 21 received heart transplants, 7 received lung transplants, and 1 received heart/lung transplant. At the time of transplantation, 2 patients had detectable HIV RNA levels and the remainder were undetectable. All patients were on a 3-drug antiretroviral regimen at the time of transplantation. One year survival did not differ for patients with HIV who received heart (90%) and lung (86%) transplants compared to control patients without HIV ($p = .947$ and $p = .949$, respectively) from the ISHLT database. Three and 5-year survival rates among patients with HIV were 73% and 64%, respectively for heart transplants, and 80% and 75%, respectively for lung transplants. Acute cellular rejection occurred in 14 (67%) heart transplant patients and 2 lung transplant patients. Infections were reported in 8 (39%) heart transplant patients and 7 (86%) lung transplant patients. Six patients (5 heart transplant and 1 lung transplant) developed malignancy; none were AIDS-defining malignancies. Suppression of HIV RNA continued for at least 1 year for all patients. One patient who had a detectable viral load at the time of (heart) transplant died after 3 years from AIDS-related complications and graft failure. However, this was due to lack of adherence and lack of appropriate follow-up. The second patient with a detectable viral load at the time of transplant lived for 10 years post-transplant. There are few data directly comparing outcomes for patients with and without HIV or for combined heart/lung transplants.

Current OPTN policy permits HIV-positive transplant candidates.¹

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.²⁴ These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- Cluster of differentiation 4 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.

Other Potential Contraindications

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart/lung transplantation. For example, cystic fibrosis accounts for most pediatric candidates for heart/lung transplantation, and infection with *Burkholderia* species is associated with higher mortality in these patients.

Summary of Evidence

For individuals who have end-stage cardiac and pulmonary disease who receive combined heart/lung transplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. The available literature reports on outcomes after heart/lung transplantation. Given the exceedingly poor expected survival rates without transplantation, this evidence is sufficient to demonstrate that heart/lung transplantation provides a survival benefit in appropriately selected patients. A transplant may be the only option for some patients with end-stage cardiopulmonary disease. Heart/lung transplant is contraindicated for patients in whom the procedure is expected to be futile due to comorbid disease or for whom post-transplantation care 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 a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung and who receive a combined heart/lung retransplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. A very limited amount of data has suggested that, after controlling for confounding variables, survival rates after primary and repeat heart/lung transplants are similar. Findings are inconclusive due to the small number of cases of repeat heart/lung transplants reported in the published literature. Repeat heart/lung transplantation is, however, likely to improve outcomes in patients with a prior failed transplant who meet the clinical criteria for heart/lung transplantation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.¹⁹ Key findings and recommendations are summarized in Table 1.

Table 1. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

Content Area	Key Point
1 Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2 Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3 Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period
4 OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5 Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

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

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Society for Heart and Lung Transplantation

In 2014, the International Society for Heart and Lung Transplantation updated its consensus-based guidelines on the selection of lung transplant recipients.²⁵ These guidelines made the following statements about lung transplantation:

"Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

- High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed
- High (>80%) likelihood of surviving at least 90 days after lung transplantation
- High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."

For combined heart/lung transplant, the guidelines have stated that patients with irreversible myocardial dysfunction or irreparable congenital defects in conjunction with intrinsic lung disease or severe pulmonary arterial hypertension are appropriate candidates for heart/lung transplantation. The guidelines also mentioned that isolated bilateral lung transplantation is associated with comparable or better outcomes in most patients with pulmonary hypertension associated with right ventricular failure.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Heart/lung transplantation is covered under Medicare when performed in a facility approved by Medicare as meeting institutional coverage criteria.²⁶ The Centers for Medicare & Medicaid Services has stated that, under certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures safety and efficacy objectives.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

References

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Cardiology and pulmonary 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
- Radiology reports including:
 - Chest X-ray
 - Chest CT scan
- Colonoscopy report if > 50 years of age
- Cardiology procedures and pulmonary function reports:
 - Electrocardiogram (EKG)
 - Cardiac echocardiogram
 - Cardiac stress test
 - Cardiac catheterization
 - Pulmonary function tests (PFTs)
 - 6-minute walk study
- Laboratory reports

Coding

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

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may

include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	33930	Donor cardiectomy-pneumonectomy (including cold preservation)
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
HCPCS	None	

Policy History

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

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
06/28/2013	Policy revision with position change
03/28/2014	Title change from Heart-Lung Transplant with position change
04/09/2014	Administrative Update
07/31/2015	Coding update
03/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
11/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
10/01/2020	Annual review. Policy guidelines and literature updated
10/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Heart/Lung Transplant 7.03.08</p> <p>Policy Statement: Heart/lung transplantation may be considered medically necessary for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:</p> <ul style="list-style-type: none"> I. Irreversible primary pulmonary hypertension with heart failure II. Nonspecific severe pulmonary fibrosis, with severe heart failure III. Eisenmenger complex with irreversible pulmonary hypertension and heart failure IV. Cystic fibrosis with severe heart failure V. Chronic obstructive pulmonary disease with heart failure VI. Emphysema with severe heart failure VII. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure <p>Heart/lung retransplantation after a failed primary heart/lung transplant may be considered medically necessary in patients who meet criteria for heart/lung transplantation.</p> <p>Heart/lung transplantation is considered investigational in all other situations.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>	<p>Heart/Lung Transplant 7.03.08</p> <p>Policy Statement: Heart/lung transplantation may be considered medically necessary for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:</p> <ul style="list-style-type: none"> I. Irreversible primary pulmonary hypertension with heart failure II. Nonspecific severe pulmonary fibrosis, with severe heart failure III. Eisenmenger complex with irreversible pulmonary hypertension and heart failure IV. Cystic fibrosis with severe heart failure V. Chronic obstructive pulmonary disease with heart failure VI. Emphysema with severe heart failure VII. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure <p>Heart/lung retransplantation after a failed primary heart/lung transplant may be considered medically necessary in patients who meet criteria for heart/lung transplantation.</p> <p>Heart/lung transplantation is considered investigational in all other situations.</p> <p>The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered investigational.</p>