Medical Coverage Policy

Effective Date..... 9/15/2021
Next Review Date..... 9/15/2022
Coverage Policy Number 0129

Heart, Lung, and Heart-Lung Transplantation

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Overview

This Coverage Policy addresses transplantation of the thoracic organs (i.e., heart, lung), surgical procedures in which one or both of the diseased organs are replaced with the viable heart, lung(s), lung lobes, or combined heart and lung of an appropriate donor.

Coverage Policy

Heart transplantation in an adult is considered medically necessary for the treatment of ANY of the following:

- malignant ventricular arrhythmias unresponsive to medical and/or surgical therapy
- refractory angina that is not amenable or correctable by alternative medical or surgical therapies and leaves the individual in a New York Heart Association functional class III or IV
- end-stage heart failure with **EITHER** of the following:
  - disease that is not amenable or correctable by alternative medical therapies or leaves the individual in New York Heart Association functional class III or IV
  - disease that requires continuous intravenous inotropic or mechanical circulatory support

Heart transplantation in a child is considered medically necessary for the treatment of EITHER of the following:

- intractable heart failure
- congenital abnormality not amenable to surgical correction

Lung transplantation from a deceased donor is considered medically necessary when BOTH of the following criteria are met:

- end-stage disease of lung parenchyma, airway and pulmonary vasculature that is not amenable to maximum alternative medical or surgical therapies
- severe, progressive symptoms with a functional status of New York Heart Association class III or IV despite optimal medical management, resulting in an unacceptable quality of life

Heart-lung transplantation is considered medically necessary when BOTH of the following criteria are met:

- end-stage cardiopulmonary disease where the replacement of either organ alone is unlikely to improve survival or quality of life
- the individual remains at a New York Heart Association functional class III or IV despite maximal medical and surgical management

Note: Selected candidates may be eligible for multi-organ transplantation. For each organ, the candidate should meet all of the criteria for selection for the individual transplant being considered. For a heart-kidney transplant, please refer to Coverage Policy 0355 Liver and Liver-Kidney Transplantation for the kidney transplant criteria.

Lung transplantation is considered experimental, investigational or unproven for EITHER of following:

- coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function
- chest wall/spinal deformity that would pose a contraindication to transplantation

Heart, lung, or heart-lung transplantation is considered not medically necessary in an individual with ANY of the following contraindications to transplant surgery:

- malignancy that is expected to significantly limit future survival
- persistent, recurrent or unsuccessfully treated major or systemic infections
- systemic illness or comorbidities that would be expected to substantially negatively impact the successful completion and/or outcome of transplant surgery
- a pattern of demonstrated noncompliance which would place a transplanted organ at serious risk of failure
- human immunodeficiency virus (HIV) disease unless ALL of the following are noted:
    - CD4 count greater than 200 cells/mm^3
    - HIV-1 ribonucleic acid (RNA) undetectable
    - stable anti-retroviral therapy for more than three months
    - absence of serious complications associated with or secondary to HIV disease (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioidomycosis; resistant fungal infections; or Kaposi's sarcoma or other neoplasm)

An organ transport system (e.g. Paragonix SherpaPak™) for preservation and transportation of donor lung(s) and/or heart for transplantation is considered experimental, investigational or unproven.

Ex vivo organ perfusion (e.g., Organ Care System™) for lung and/or heart transplantation is considered experimental, investigational or unproven.

General Background

Heart Transplantation

Heart transplantation is the therapy of choice in adults with end-stage heart failure, refractory angina, and malignant ventricular arrhythmias, who have received maximal medical treatment, are unlikely to survive the next 6–12 months and for whom there is no other surgical option (Mancini, 2020; Canter, et al., 2007; Butler, et al., 2004). According to the Organ Procurement and Transplantation Network (OPTN) Administrative Rules and Definitions policy, each heart transplant candidate is assigned a status that reflects the candidate's medical urgency for transplant (OPTN, July 2021).

The 2021 OPTN adult heart allocation criteria for medical urgency status stated that the candidate must be at least 18 years old at the time of registration with the following requirements (OPTN/SRTR 2019 Annual Data Report, July 2021):

Adult Heart Status 1 requires that the patient has at least one of the following conditions:

- is supported by veno-arterial extracorporeal membrane oxygenation (VA ECMO)
- is supported by non-dischargeable, surgically implanted, non-endovascular biventricular support device
- is supported by mechanical circulatory support device (MCSD) with life-threatening ventricular arrhythmia

Adult Heart Status 2 requires that the patient has at least one of the following conditions:

- is supported by a non-dischargeable, surgically implanted, non-endovascular left ventricular assist device (LVAD)
- is supported by a total artificial heart (TAH), biventricular assist device (BiVAD), right ventricular assist device (RVAD), or ventricular assist device (VAD) for single ventricle patients
- is supported by a MCSD with device malfunction/mechanical failure
- is supported by a percutaneous endovascular mechanical circulatory support device
- is supported by an intra-aortic balloon pump (IABP)
- is experiencing recurrent or sustained ventricular tachycardia or ventricular fibrillation

Adult Heart Status 3 requires that the patient has at least one of the following conditions:

- is supported by a dischargeable left ventricular assist device and is exercising 30 days of discretionary time
- is supported by multiple inotropes or a single high dose inotrope and has hemodynamic monitoring
- is supported by VA ECMO after 7 days; percutaneous endovascular circulatory support device or IABP after 14 days
- is supported by non-dischargeable, surgically implanted, non-endovascular LVAD after 14 days
- is supported by an MCSD with one of the following:
    - hemolysis
    - pump thrombosis
    - device infection
    - mucosal bleeding
    - aortic insufficiency
    - right heart failure

Adult Heart Status 4 requires that the patient has at least one of the following conditions:

- is supported by dischargeable LVAD without discretionary 30 days

- is supported by inotropes without hemodynamic monitoring
- is a re-transplant
- has a diagnosis of one of the following:
    - congenital heart disease (CHD)
    - ischemic heart disease with intractable angina
    - hypertrophic cardiomyopathy
    - restrictive cardiomyopathy
    - amyloidosis

Adult Heart Status 5 is for patients who are on the waitlist for at least one other organ at the same hospital and status 6 is for all remaining active candidates.

Justification for pediatric heart status 1A includes patients less than 18 years old at the time of registration with at least one of the following conditions:

- requires continuous mechanical ventilation or assistance of an intra-aortic balloon pump and is admitted to the hospital that registered the patient
- has ductal dependent pulmonary or systemic circulation, with ductal patency maintained by stent or prostaglandin infusion and is admitted to the hospital that registered the patient
- has a hemodynamically significant congenital heart disease diagnosis, requires infusion of multiple intravenous inotropes or a high dose of a single intravenous inotrope and is admitted to the hospital that registered the patient
- requires assistance of a mechanical circulatory support device

Requirements for pediatric heart status 1B includes at least one of the following criteria:

- requires infusion of one or more inotropic agents but does not qualify for pediatric status 1A
- younger than one year old at the time of the candidate's initial registration and has a diagnosis of hypertrophic or restrictive cardiomyopathy

The OPTN's national data for primary heart transplantation performed between 2008-2015 states that one-, three-, and five-year patient overall survival (OS) rates for primary transplantation were 90.9%, 85.6% and 78.6% respectively (based on OPTN data as of July 23, 2021). Risk factors for mortality after transplantation include re-transplantation, inter-transplant time (i.e., time between primary and re-transplantation) of < 180 days, and the use of a total artificial heart as a bridge to transplant. Furthermore, the need for end-organ support with mechanical ventilation or dialysis, conferred the greatest risk of one-year mortality. Additional risk factors include the use of amiodarone pre-transplantation, prior coronary artery bypass grafting (CABG) before transplantation, and transplantation of a female heart into a male recipient (Pham, 2019; Mahle, 2008; Canter, et al., 2007).

Indications for Heart Transplantation: An individual with refractory angina or end-stage intractable heart failure that is not amenable or correctable by alternative medical or surgical therapies and who has a New York heart Association (NYHA) III or IV functional class may be an appropriate candidate for heart transplantation. The New York Heart Association (NYHA) Functional Classification of Patients with Heart Disease is a subjective measure of functional capacity which describes the amount of activity an individual can do before the onset of heart failure symptoms is noted. Heart transplantation may also be indicated for an individual with malignant ventricular arrhythmias which are unresponsive to medical or surgical therapies.

In an infant or child, heart transplantation is indicated for end-stage cardiomyopathy when refractory to medical therapy, as well as previously repaired or palliated congenital heart disease when the individual has developed ventricular dysfunction or other non-operable late-term complications. An infant or child with complex congenital heart disease (e.g., pulmonary atresia with intact septum and coronary arterial stenosis, some forms of hypoplastic left heart syndrome) for whom standard surgical procedures are extremely high risk may also be an appropriate candidate for heart transplantation (Bernstein, 2016).

According to UNOS (2021a), the equity in access to heart transplants correspond to five key factors:

- Donation Service Area (DSA)
    - The DSA in which a candidate is listed is the factor most associated with unintended disparities in deceased donor heart transplant access
- Blood Type
    - blood type A and AB candidates have higher rates of transplantation compared to B and O candidates
- Age:
    - older candidates have higher rates of transplantation compared to younger candidates
- Height:
    - taller individuals have greater access to deceased donor transplantation
- Weight:
    - heavier individuals have less access to deceased donor transplantation

Differences associated with other factors beyond these five are relatively small.

The OPTN/SRTR 2019 Annual Data Report (July 2021) stated that notable demographic trends in heart transplant since 2008 include stable proportions of women and men, lower proportions of whites, higher proportions of blacks, and Hispanics. In patients who underwent transplant from 2012 to 2014 recipients 65 and older had lower survival rates at one year compared with younger age groups. At two and five years, survival was highest in recipients aged 50-64 (87.6%). Recipients aged 18-35 had the lowest five year survival rate. Recipients categorized as “other” race had the best one year survival rate (93.9%), followed by Asians (92.7%). By year five, blacks fared substantially worse (75.9%), followed by whites (80.0%). Survival did not meaningfully differ by sex.

Literature Review for Heart Transplantation: Heart transplantation is considered a standard of care for selected individuals. No prospective randomized study comparing heart transplantation to optimal medical therapy has been reported; however, several retrospective reviews and database analyses have demonstrated improved long-term outcomes with heart transplantation for selected individuals (OPTN/SRTR 2019 Annual Data Report, July 2021); Deuse, et al., 2008; Tjang, et al., 2008; Weiss, et al., 2008).

Professional Societies/Organizations
American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA): The 2018 ACC/AHA guideline for the management of adults with congenital heart disease (ACHD) stated that cardiac transplantation is reasonable in adults with Fontan palliation with signs and symptoms of protein-losing enteropathy. Additionally, in patients with ACHD and Eisenmenger syndrome exhibiting deteriorating functional ability, mechanical circulatory and pulmonary support, lung transplantation with concomitant repair of anatomic cardiovascular defects, and heart–lung transplantation have been applied (Stout, et al., 2019).

The 2013 ACC/AHA guideline for the management of heart failure (Yancy, et al., 2013; focused update 2017) noted that heart transplantation is the gold standard for the treatment of refractory end-stage heart failure. Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D heart failure despite guideline-directed medical therapy, device, and surgical management.

A 2011 ACC/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy (HCM) (Gersh, 2011) noted that patients with advanced (i.e., end-stage) heart failure and nonobstructive HCM not otherwise amenable to other treatment interventions with ejection fraction (EF) ≤ 50%, or occasionally with preserved EF, should be considered for heart transplantation. Symptomatic children with HCM with restrictive physiology who are not responsive to, or appropriate candidates for, other therapeutic interventions should be considered for heart transplantation. In general, indications for heart transplantation included advanced heart disease, typically with NYHA functional class III or IV symptoms that are refractory to all other reasonable interventions. Heart transplantation should not be performed in mildly symptomatic patients of any age with HCM.

American Heart Association (AHA): The 2016 AHA scientific statement on chronic heart failure in congenital heart disease stated that transplantation is a reasonable consideration in pediatric patients with heart failure associated with systemic ventricular dysfunction with previously repaired or palliated chronic heart disease

(CHD) when it is associated with significant growth failure attributable to the heart disease and CHD with severe limitation of exercise and activity. Additional indications included: CHD with normal ventricular function if the following anatomic and physiological conditions are present and not amenable to surgical intervention (Stout, et al., 2016):

- proximal coronary arteries have severe stenosis or atresia
- atrioventricular or systemic semilunar valve(s) with moderate to severe stenosis or insufficiency
- symptomatic arterial oxygen desaturation (cyanosis)
- persistent protein-losing enteropathy despite optimal medical-surgical therapy

Lung Transplantation

Lung transplantation is the surgical replacement of the lung(s) of an individual with end-stage pulmonary disease with the partial (lobar) or whole lung or lungs of a living or deceased donor. For most recipients, lung transplantation is a palliative, rather than curative treatment, the primary goal being the projected survival benefit. It is an accepted treatment of last resort for persons with end-stage lung disease who do not respond to alternative medical or surgical treatment. Improvements in quality of life, in addition to survival, should be used to assess the effectiveness of the procedure (Orens, et al., 2006).

The type of lung transplantation procedure used (i.e., lobar, single, or double) and donor type (i.e., deceased or living) are based upon the candidate's condition and indication for transplantation, and the availability of donor organs. As donor organs are scarce relative to the number of candidates needing transplantation, conservation of acceptable donor organs is also taken into consideration.

According to UNOS (2021a), the equity in access to lung transplants correspond to four key factors:

- Donation service area (DSA):
    - the DSA in which a candidate is listed is the factor most associated with unintended disparities in deceased donor lung transplant access
- Height:
    - taller individuals have greater access to size-compatible lung donors
- Gender:
    - higher transplant rates are observed for males
- Blood type:
    - blood type A and AB candidates have higher rates of transplantation compared to B and O candidates

Differences associated with other factors are relatively small.

The OPTN/SRTR 2019 Annual Data Report (July 2021) stated that most lung transplant candidates were white (73.1%), with increasing proportions of Black (11.5%), Hispanic (11.5%), and Asian (3.2%). Across all recipients, 1-year survival was 88.8%; 3 year, 74.4%; 5 year, 59.2%, and 10 year, 33.1%. Five-year survival differed by age, and was lowest for recipients aged 65 years or older, followed by those aged 18-34, 50-64, and 35-49 years. Survival also differed by race, and was lowest for Black recipients after the first year compared with other racial groups Survival did not meaningfully differ by sex

Deceased Donor Lung Transplantation: A deceased donor, also known as cadaveric donor, is the most common donor source used for lung transplantation. Deceased donors are categorized into either donation after brainstem death (DBD) or donation after circulatory death (DCD). The management of the donation after brain death (DBD) donor includes optimizing cardiac filling pressures, maintaining adequate arterial pressure for donor organ perfusion, ensuring a patent airway and maintaining protective ventilation strategies, and maintaining metabolic homeostasis. DCD donor lungs are proposed to increase lung transplant activity, decreasing duration on the waiting list and waitlist mortality. The standard criterion for determination of circulatory death is the permanent absence of respiration and circulation. Because circulatory death occurs in differing circumstances, the severity of the ischemic injury to the donor lungs may vary. DCD grafts sustain a greater degree of ischemic insult prior to harvesting, when they are subsequently cooled and perfused. This is because, during DBD, organs

undergo cold perfusion prior to organ harvesting, whilst in DBD grafts there is a definitive period between cardiac arrest and organ retrieval. This period is known as the “warm ischemic time” and has been shown to affect organ quality. When lungs are transported, the lungs are flushed and then preserved in a cold storage device for transport to their destination hospital. The lungs are cooled to prevent damage ex vivo before being gradually warmed for placement into the recipient. Cold storage is based around the concept that it slows metabolism, reduces oxygen consumption and substrate requirements thus preventing end organ deterioration. In 2018, there were 2426 DBD donations and 121 DCD donations in transplant candidates age 12 years or older (Copeland, et al., 2020; Jin, et al., 2020; OPTN/SRTR 2019 Annual Data Report, July 2021).

The 2021 OPTN policy on the allocation of lungs stated that lung candidates < 12 years old are assigned a priority for lung allocation that is based on medical urgency and patients at least 12 years old use a Lung Allocation Score (LAS), geography and blood type to determine lung allocation.

According to the Organ Procurement and Transplantation Network (OPTN) national data for deceased donor primary lung transplantation performed between 2008 and 2015, graft survival rates were 86.7%, 67.8% and 52.5%, respectively, at one-, three-, and five years (based on OPTN data as of July 23, 2021).

Living Donor Lung Transplantation (LDLT): Use of a live donor as a source for lung transplantation was initiated in 1993 due to the higher demand than supply for patients waiting for lung transplantation. Although LDLT may be appropriate for a highly selected individual who likely would not survive waiting times for a deceased donor, it is now rarely performed. According to the 2019 OPTN/SRTR annual report, only one living donor lung transplant (LDLT) was performed in 2013. In 2019 there were not any living donor lung transplants performed (OPTN/SRTR 2019 Annual Data Report). This procedure requires the donation of one lung lobe from each of two living donors. Major complications have included pleural effusion, bronchial stump fistula, bi-lobectomy, hemorrhage phrenic nerve injury, pulmonary artery thrombosis, and bronchial stricture. Minor complications include persistent air leak, arrhythmia, and pneumonia. Deceased donor transplantation is preferred to avoid the risk to two healthy donors (Solomon, et al., 2010).

Indications for Lung Transplantation: Lung transplantation should be considered for adults with chronic, end-stage lung disease, progressive symptoms, a New York Heart Association (NYHA) functional class III or IV that has not responded to medical or surgical therapies. There are four primary diagnostic groupings of lung disease for which transplantation may be indicated. Along with examples of each category, these include (Yusen, et al., 2016):

- chronic obstructive lung disease (COPD) (e.g., alpha-1 antitrypsin deficiency, non alpha-1 antitrypsin deficiency)
- interstitial lung disease (ILD) (e.g., idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonia [IIP])
- cystic fibrosis (e.g., bronchiectasis)
- pulmonary vascular disease (e.g., primary/idiopathic pulmonary hypertension, Eisenmenger syndrome)

Disease-specific parameters used to determine appropriateness for lung transplantation have been suggested by the International Society for Heart and Lung Transplantation (ISHLT) (Yusen, et al., 2016; Weill, et al., 2015; Orens, et al., 2006), the American Society of Transplantation (Faro, et al., 2007; Steinman, et al., 2001) and other published scientific literature (Kotloff, 2010; Lynch, et al., 2006) and include the following (Weill, et al., 2015):

Chronic Obstructive Airway Disease:

- BODE index (i.e., body mass index [B], degree of obstruction [O], dyspnea [D], exercise capacity [E]), score of ≥ 7
- FEV1 (i.e., forced expiratory volume in the first second) < 15% to 20% predicted
- three or more severe exacerbations during the preceding year with one severe exacerbation with acute hypercapnic respiratory failure
- moderate to severe pulmonary hypertension

Interstitial Lung Disease (ILD):

- a 10% or greater decrease in FVC (i.e., forced vital capacity) during six months of follow-up
- a decline in diffusion capacity (corrected for alveolar volume) ≥15% during 6 months of follow-up
- decrease in pulse oximetry <88% during a six-minute walk test
- confirmed pulmonary hypertension
- hospitalization for decline in respiratory status, pneumothorax or acute exacerbation

Cystic Fibrosis:
- chronic respiratory failure with hypoxia
- hypercapnia
- long-term non-invasive ventilation
- pulmonary hypertension
- frequent hospitalization
- rapid decline in lung function
- World Health Organization Functional Class IV

Pulmonary Vascular Disease:
- persistent NYHA functional class III or IV
- cardiac index of less than two liters per minute per square meter
- right atrial pressure of more than 15 mmHg
- low, or declining six-minute walk test (less than 350 meters)
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure

Literature Review for Lung Transplantation: Lung transplantation recipients represent a heterogeneous population, with different diagnostic groups having different survival rates; however, in a cohort study of 1997 patients, 1143 of whom received lung transplantation, improved survival was noted for all diagnosis groups (Titman, et al., 2009). Although there are no randomized controlled clinical trials demonstrating the safety and effectiveness of lung transplantation, several registry analyses and retrospective cohort studies note improved overall survival with transplantation compared with other medical and surgical therapies (OPTN/SRTR 2019 Annual Data Report, July 2021; Chambers, et al., 2017; Christie, et al., 2010).

Professional Societies/Organizations
American Society of Transplantation (AST) and the American Society of Transplant Surgeons (ASTS): On behalf of the AST and ASTS, Faro et al. (2007) noted that, in general, lung transplantation should be considered in selected children with end-stage or progressive lung disease or life-threatening pulmonary vascular disease for which there is no other medical therapy.

Heart-Lung Transplantation

Heart-lung transplantation is the surgical replacement of the heart and lung(s) of an individual who has end-stage cardiopulmonary disease with the healthy heart and lungs of a donor. It is an accepted therapy for an individual whose disease is refractory to standard optimal medical or surgical treatment when no contraindications are present. Combined heart-lung transplantation is reserved for a candidate in whom either heart transplantation or lung transplantation alone will not improve the recipient's condition.

Indications for Heart-Lung Transplantation: Indications for heart-lung transplants have changed over time. During the time period January 2004 through June 2015 the most frequent indications for heart-lung transplant were congenital heart disease, pulmonary arterial hypertension, and cardiomyopathy (Yusen, et al., 2016). Heart-lung transplantation is usually reserved for patients with uncorrectable or previously repaired or palliated congenital heart disease associated with significant pulmonary vascular obstructive disease. Such disease includes a single-ventricle physiology with pulmonary vascular disease or left ventricular (LV) dysfunction with associated pulmonary vascular disease. In the presence of more complex intracardiac abnormalities, combined heart-lung transplantation is usually most appropriate. Indications include, but are not limited to complex congenital disease with pulmonary hypoplasia, Eisenmenger syndrome, primary pulmonary hypertension, congenital lung abnormalities, alpha-antitrypsin deficiency, and end-stage parenchymal lung disease (Weill, et al., 2016; Bernstein, 2016; Warnes, et al., 2008).

Literature Review for Heart-Lung Transplantation: There are no randomized clinical trials comparing heart-lung transplantation to optimal medical treatment. Graft survival for primary heart-lung transplant recipients at one-, three- and five-years were 80.9%, 58.3% and 49.2%, respectively, based on Organ Procurement and Transplantation Network (OPTN) data for primary heart-lung transplants performed 2008-2015 (based on OPTN data as of July 23, 2021)

Re-transplantation
Re-transplantation remains a controversial procedure, in part due to ethical concerns over the limited supply of organs. The recipient of the re-transplantation procedure often suffers from the systemic sequelae of short-or long-term immunosuppression, infection, and technical issues attributable to the initial transplantation surgery (Goldraich, et al., 2016; Kawut, et al., 2008).

Re-transplantation has remained constant at 2%–4% of adult heart transplants since 1982. Cardiac allograft vasculopathy (CAV) and myopathy are the most common reasons for re-transplantation (Lund, et al., 2014). Heart re-transplantation is indicated for those patients who develop CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Mehra, et al., 2016). Graft survival outcomes for repeat heart transplantation are 86.7%, 75.5% and 67.8% for one-, three-, and five-years, respectively, based on Organ Procurement and Transplantation network (OPTN) data as of July 23, 2021. Although outcomes are decreased for both children and adults compared to results for primary transplantation, re-transplantation may be an appropriate intervention for eligible children and adults.

Outcomes after repeat lung transplantation are generally poorer than those seen with the primary transplantation procedure. Survival rates for repeat lung transplantation performed between 2008 and 2015 were 76%, 49% and 33.8%, respectively, at one-, three-, and five-years (based on OPTN data as of July 23, 2021). Although data are limited, lung re-transplantation may be an appropriate therapeutic option for highly selected individuals for complications of transplantation that are refractory to other medical or surgical therapies. Survival rates were not available for repeat heart-lung transplants at one, three and five years due to the low number of transplants performed.

Contraindications to Heart, Lung, and Heart-Lung Transplantation

Many factors affect the outcome of solid organ transplantation; appropriate selection is the first step in attaining the best result for each recipient. Transplantation of the heart, lung(s) or heart and lungs remains a complex therapy; it is important; therefore, to consider the sum of all contraindications and comorbidities.

Heart Transplantation Contraindications: In the 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update, the following contraindications are noted (Mehra, et al., 2016):

- diabetes with end-organ damage
- irreversible renal dysfunction (eGFR < 30 ml/min/1.73 m2)
- symptomatic cerebrovascular disease
- elevated pulmonary vascular resistance
- severe extracardiac amyloid organ dysfunction
- chronic HCV or HBV infection, clinical, radiologic or biochemical signs of cirrhosis, portal hypertension or hepatocellular carcinoma

Lung and Heart-Lung Transplantation Contraindications: In the consensus document for the selection of lung transplant candidates: 2014 -an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation (Weill, et al., 2015) the following absolute contraindications are noted:

- a recent history of malignancy, (recommend a two year disease-free interval combined with a low predicted risk of recurrence after lung transplantation)
- untreatable advanced dysfunction of another major organ system (e.g., heart, liver, kidney or brain)
- uncorrected atherosclerotic disease with possible end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularization
- acute medical instability

- uncorrectable bleeding disorder
- chronic infection with highly virulent and/or resistant microbes
- active Mycobacteriumtuberculosis infection
- chest wall or spinal deformity expected to cause severe restriction after transplantation
- class II or III obesity
- current non-adherence to medical therapy or a history of non-adherence
- psychiatric or psychologic conditions associated with the inability to cooperate with care
- absence of a consistent and reliable social support system
- severely limited functional status with poor rehabilitation potential
- substance abuse or dependence

In addition to absolute contraindications, there are relative contraindications as well which include (list is not all inclusive):

- age
- obesity
- malnutrition
- severe osteoporosis
- extensive prior chest surgery with lung resection
- active infections
- other medical conditions should be treated before transplantation (diabetes, hypertension)

Organ transport systems

Sherpapak: The SherpaPak™ system (Paragonix Technologies) was developed to reduce the risk of primary graft failure by optimizing temperature during transport which can allow for longer ischemic times. It is proposed that with longer ischemic times, the heart can travel for longer time periods and therefore can expand the donor pool. The SherpaPak preserves the heart in a single-use sterile disposable box, with controlled temperature ranging between 4 to 8 ℃. Procurement with the SherpaPak involves filling the organ canister with cold preservation solution. The donor heart is perfused with standard solution followed by procurement. The procured heart is then anchored in the organ canister and the organ canister is placed within the outer canister, which is surrounded by ice packs. The current standard for donor heart transportation is cold storage. This method utilizes a three bag technique with the heart transported in a cooler filled with slush ice. Monitoring is not performed routinely and information on exact temperature of the donor heart is missing. Possible limitations of cold storage is the possibility of uneven cooling and freeze injury to the donor heart (Naito, et al., 2020; Radakovic, et al., 2020).

U.S. Food and Drug Administration (FDA): According to the FDA, the SherpaPak Cardiac Transport System (Paragonix Technologies) received 510(k) approval on October 9, 2018. The SherpaPak is indicated for static hypothermic preservation of hearts during transportation and eventual transplantation into a recipient using cold storage solutions indicated for use with the heart. The FDA stated that “the intended organ storage time for the SherpaPak Cardiac Transport System is up to four hours. Donor hearts exceeding clinically accepted static hypothermic preservation times should be evaluated by the transplant surgeon to determine transplantability in accordance with accepted clinical guidelines and in the best medical interest of the intended recipient” (FDA, 2018).

Literature Review: The evidence in the peer-reviewed scientific literature consists mainly of case reports and retrospective studies and is insufficient to support that using the SherpaPak Cardiac Transport System results in improved clinical outcomes when compared to the standard of care (cold storage). Radakovic et al. (2020) conducted a retrospective, case control study that compared standard cold storage to the SherpaPak to evaluate the donor heart temperature during transportation, donor heart function and systemic infection rate among recipients after transplantation. There were seven heart procurements using the SherpaPak™ device and 14 using cold storage. All organs were procured from brain dead donors and stored either in the disposable SherpaPak™ system or with a standard technique consisting of three plastic bags and a cooler. There were five men and two women with an average age of 50.3±13.2 years. The matched comparison group consisted of 11

men and three women (p =0.717) with a mean age of 56.6±8.2 years (p=0.359). Recipient and donor age, gender, BMI, diagnosis leading to heart transplantation, use of any mechanical circulatory support, urgency status, reperfusion organ time and pulmonary vascular resistance were similar between groups. Cold ischemic time was significantly longer in the SherpaPak™ group when compared to the cold storage group (p=0.027). The SherpaPak kept the organ temperature at 5.1±0.8 ℃, with an average outside temperature of 21.4±3.6 ℃. Over the first hours there was not a significant difference in hemodynamic parameters, CK-MB levels or vasoactive-inotropic score. At the 30 day post-transplant follow-up, there was slightly better right heart function in the SherpaPak group (p=0.020) and no significant difference in positive blood cultures (p=0.255; 0/SherpaPak & 4/cold storage). After one year, there was not a significant difference in survival, five patients in the Sherpapak survived compared to 11 in the cold storage (p=0.717). The limitations according to the authors included the single-center retrospective study design and small patient population. That authors concluded that the SherpaPak cold storage might be a good alternative for donor heart transport at relatively low cost with continuous monitoring of adequate hypothermic state of the donor organ. Further studies are needed regarding extension of ischemic time and thereby improving donor organ availability using the SherpaPak. No health disparities were identified by the investigators.

Ex vivo organ perfusion

Ex vivo lung perfusion (EVLP): Lung transplantation is a life-saving procedure for patients with end-stage lung disease. In 2018, 3134 transplant candidates age 12 years or older were added to the lung transplant waiting list and 2562 transplants were performed. The demand for lung for transplant continues be greater than the donations. A total of 8.7% of candidates 12 years of age or older died within three years of being waitlisted for transplant. Risk of waitlist mortality plays an important role in organ allocation in the US, where lungs are allocated to candidates 12 years or older based on the lung allocation score (LAS), age, geography, ABO compatibility, and, if necessary, waiting time. Candidates younger than 12 years access transplant through an illness-based priority status, age, geography, blood type (ABO) compatibility, and waiting time. A strategy to address the shortage of donor lungs been to use lungs retrieved from DCD or to use marginal lungs (OPTN/SRTR 2018 Annual Data Report: Lung (D'Cunha and Rojas, 2018; Valapour, et al., 2018). Ex vivo lung perfusion (EVLP) is a proposed technology to assess and prepare lungs that are considered marginal for transplantation. However there are is a lack of randomized controlled trials evaluating EVLP on marginal lungs. The rationale for normothermic ex-vivo preservation as an alternative to the standard of care (cold ischemic storage) is that keeping donor lungs in a near physiologic state allows pulmonary cells and tissues to remain metabolically active and viable for additional hours between the time of cardiac death and functional evaluation by a transplant team (Hayes, 2018). EVLP is proposed to provide a window of time to evaluate and recondition lungs of inferior quality outside the donor body before transplantation. During EVLP evaluation, the lungs remain viable, as it is done at body temperature (37℃), making the lungs metabolically active and viable for hours (Makdisi, et al., 2017). Examples of lung EVLP systems are the Organ Care System™ (OCS™) Lung System, XVIVO XPS, XVIVO LS and XVIVO Disposable Lung Set

U.S. Food and Drug Administration (FDA): According to the FDA, the Organ Care System (OCS™) Lung System (TransMedics, Inc., Andover, MA) received premarket approval (PMA) on March 22, 2018. Per the FDA the TransMedics® OCS Lung System "is a portable organ perfusion, ventilation, and monitoring medical device indicated for the preservation of standard criteria donor lungs in a near physiologic, ventilated, and perfused state for double lung transplantation". According to the FDA approval letter, two post-approval studies (PAS) are required. The first is a continuation of the INSPIRE study to evaluate the long term outcomes of the INSPIRE trial patients. The second is a prospective, single-arm, multi-center, observational study designed to evaluate the short- and long-term safety and effectiveness of the OCS Lung System. The primary endpoint is patient and graft survival at 12 months. The co-secondary endpoints are total ischemic time and incidence of PGD3 within 72 hours. This study is under ClinicalTrials.gov Identifier: NCT03639025.

In a PMA supplement approved on May 31, 2019 (P160013/S002), the FDA expanded the indications for the Organ Care System (OCS™) Lung System preservation to include the preservation of donor lung pairs initially deemed unacceptable for procurement and transplantation based on limitations of cold static preservation. FDA approval was based on review of data from the EXPAND study (Loor, et al., 2019). According to the FDA approval letter, two post-approval studies (PAS) are required. The first PAS consists of continued follow-up of patients who participated in EXPAND study (Loor, et al., 2019). The EXPAND II study is designed to report the five years post transplantation outcomes on the patients that completed the EXPAND study. The primary

effectiveness endpoint is bronchiolitis obliterans syndrome (BOS) free survival through five years after transplantation. The study can be found at ClinicalTrials.gov Identifier: NCT03343535.

The second PAS "OCS Lung PAS: Donor Lungs Initially Deemed Unacceptable (DLIDU)" is a prospective, single-arm, multi-center, observational study designed to evaluate the short and long-term safety and effectiveness of the OCS Lung System for donor lungs initially deemed unacceptable for procurement and transplantation based on limitations of cold static storage. Data will be collected through the Organ Care System (OCS™) Lung Thoracic Organ Perfusion (TOP) Registry for Donor under ClinicalTrials.gov Identifier: NCT03639025. After enrollment, the Primary Analysis Population (PAP) will be comprised of the first 266 patients who meet the recipient eligibility criteria and are transplanted with donor lungs from a donor who meets the donor eligibility criteria. The full PAS cohort will consist of the PAP and all other enrolled patients who are transplanted with OCS-preserved donor lungs initially deemed unacceptable but do not meet the PAP criteria. Study enrollment will end when all 266 patients who meet the PAP criteria have been enrolled. Patients will be transplanted at 30 U.S. sites and followed for five years post-transplantation. The primary endpoint is patient and graft survival at 12 months post double-lung transplantation. The secondary endpoints are incidence of PGD3 at 72 hours post transplantation, donor lung utilization rate, and incidence of PGD3 within the initial 72 hours post-transplantation (FDA, 2019).

The XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate (XVIVO Perfusion Inc., Englewood, CO) received premarket approval (PMA) on April 26, 2019. Per the FDA the XPS™ with STEEN Solution™ Perfusate is intended to be used on donor lungs prior to transplantation in patients with end-stage lung disease. The FDA states that "the XPS™ System warms the donor lungs to near normal body temperature and continuously flushes the lung tissue with the STEEN Solution™, which preserves the lungs and removes waste products." The system is used only for previously unaccepted donor lungs that will be transplanted into a patient with end-stage lung disease (FDA, 2019).

FDA approval was based on review of data from the NOVEL study, including its NOVEL Extension portion. According to the FDA approval letter, two post-approval studies (PAS) are required. The first PAS consists of continued follow-up of patients who participated in the NOVEL and NOVEL Extension studies. The NOVEL/NOVEL Extension Continuation Long-Term Post Approval Study of NOVEL and NOVEL Extension study primary effectiveness outcome is Bronchiolitis Obliterans Syndrome (BOS) free survival through five years after transplantation. By the one year interim report, follow-up data needs to be provided on at least 90% of study subjects. The final report to FDA is when all patients reach the five year follow-up, and need to have the five year follow-up data for at least 90% of patients. The second PAS study is a prospective, single arm, multi-center study of all patients using the XPS™ System with STEEN Solution. The primary endpoint of The Long-Term Evaluation PAS of the XPS™ System with STEEN Solution™ Perfusate study is a composite of 12-month survival and incidence of Primary Graft Dysfunction (PGD) Grade 3 at 72 hours post-transplantation, and these data will be compared to data from the United Network Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR) registry. The study will also assess, the incidence of BOS at 1–5 years post-transplantation, Quality of Life at 1–5 years post-transplantation, and patient survival at 1–5 years post-transplantation (FDA, 2019).

Literature Review: Evidence evaluating EVLP is primarily in the form of retrospective reviews and prospective case series, observational studies, review articles, and few randomized controlled trials (Buchko, et al., 2020; Chakos, et al., 2020; Cypel, et al., 2019; Hsin, et al., 2018; Makdisi, et al., 2017; Fisher, et al., 2016; Zeriouh, et al., 2016; Popov, et al., 2015).

Loor et al. (2019) conducted a single arm, pivotal trial that evaluated the efficacy of normothermic portable Organ Care System (OCS) Lung perfusion and ventilation on donor lung use from extended-criteria donors and donors after circulatory death (EXPAND). Patients (n=79) were included in the study if they were age ≥ 18 years and undergoing a bilateral lung transplantation. The study used donor lungs (n=93) if they had one or more of the following extended criteria: a ratio of partial pressure of arterial oxygen (PaO2) to fractional concentration of oxygen (FiO2) of 300 mm Hg or less; expected total ischemic time of less than six hours; donation after circulatory death (DCD); and donor older than 55 years. The primary outcome was a composite of patient survival at day 30 post-transplant and absence primary graft dysfunction grade 3 (PGD3) within 72 h after transplantation. The secondary outcomes included the incidence of PGD3 72 h after transplantation, and PGD 2 or 3 at the same time point. The primary safety outcome was the mean number of lung-graft-related serious

adverse events within 30 days post-transplant. Patient follow-up occurred at six and 12 months after transplantation. Lungs were transplanted if they showed stability of OCS Lung variables, PaO2:FiO2 was more than 300 mm Hg, and they were accepted by the transplanting surgeon. The primary outcome was achieved in 43 (54%) of 79 patients and did not meet the objective performance goal. Thirty-five (44%) of 79 patients had PGD3 within the initial 72 hours and 78 (99%) of 79 patients had survived at 30 days post-transplant. The mean number of lung graft-related serious adverse events (respiratory failure and major pulmonary-related infection) was 0.3 events per patient, which was comparable to previous studies. Author noted limitations included single-arm study design and the contraindication to use lungs with an open air leak and severe lung contusions in the OCS. Whether similar outcomes could be obtained if these lungs were preserved on ice is unknown and remains an area for future research. The secondary study outcome described bronchiolitis obliterans syndrome rather than chronic lung allograft dysfunction. Thus, FEV1 values were reviewed for presence or absence of bronchiolitis obliterans syndrome and didn't differentiate between restrictive allograft syndrome, bronchiolitis obliterans syndrome, or chronic lung allograft dysfunction. The authors concluded that the portable OCS Lung resulted in 87% donor lung use for transplantation with excellent clinical outcomes. This resulted in lungs that were declined by other transplant centers were successfully transplanted. Longer follow-up of EXPAND trial patients is underway to assess the long term survival and prevalence of bronchiolitis obliterans syndrome.

Warnecke et al. (2018) published the results of a prospective, randomized, controlled, open-label, phase 3 trial (INSPIRE) which assessed physiological donor lung preservation using the Organ Care System (OCS) Lung device compared with cold static storage. The included patients were over 18 years old and were registered as standard criteria primary double lung transplant candidates. The eligible donors were younger than age 65, had a ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen of more than 300 mmHg, no active primary pulmonary disease, and were suitable for preservation with OCS or the current cold storage standard of care. The transplant recipients were randomly assigned to receive standard criteria donor lungs preserved in the OCS Lung device (n=141) or cold storage at 4°C (n=165). The primary outcome was absence of primary graft dysfunction grade three (PGD3) within the first 72 hours after transplant and survival at day 30. The primary safety outcome was the mean number of lung graft-related serious adverse events per patient within 30 days of transplant. PGD3 was assessed at post-surgical intensive care unit admission (0 hours) and at 24, 48, and 72 hours. Long-term follow-up was measured at months six, 12, and 24. The INSPIRE study was designed to show non-inferiority of the OCS treatment to the control treatment with a 4% non-inferiority margin (OCS treatment had to perform at least five percentage points higher than the control treatment.) The primary outcome (absence of primary graft dysfunction grade three (PGD3) within the first 72 hours after transplant and survival at day 30) was met in 112/141 (79.4%) OCS patients compared to 116/165 (70.3%) control group patients (p=0.0038). The difference satisfied the predefined 4% non-inferiority test, but not a subsequent test for superiority (p=0.068). The incidence of PGD3 within 72 hours, included 25/141 (17.7%) OCS patients and 49/165 (29.7%) control group patients indicating a clinically significant lower rate of PGD3 (p=0.015) in the OCS group. Patient survival at day 30 post-transplant was 135/141 (95.7%) OCS patients and 165 (100%) control group patients, indicating a clinically significant lower rate of survival at 30 days post-transplant (p=0.009) in the OCS group. Patient survival at 12 months was 126/141 (89.4%) OCS patients compared with 146/165 (88.1%) control group patients. The primary safety endpoint was met (0.23 lung graft-related serious adverse events in the OCS group compared with 0.28 events in the control group) (non-inferiority test p=0·020). Author noted limitations of the study included: its unblinded nature; randomization occurred before final acceptance of the donor lung for transplantation; and an interruption in supply of the OCS Lung Solution, which led to greater use of the commercially available LPD solution than was originally anticipated. Additional randomized controlled trials with larger patient populations and long-term follow-up are needed to support the outcomes of this study.

Slama et al. (2017) reported their results of a prospective randomized clinical trial which compared patients who underwent transplant with ex vivo (EVLP) evaluated donor lungs (n=39) using a perfusion system with STEEN solution with an equivalent patient population without previous EVLP (n=41). In the EVLP group, two sets of lungs (n=2) ultimately did not qualify for transplant and were rejected for lung transplant owing to technical reasons. There were 76 transplants performed within this trial (EVLP, n=35; control, n=41). Donor lungs were considered standard and eligible for inclusion when they met all of the criteria. The criteria were donation after brain death, arterial oxygen partial pressure of inspired oxygen ratio (PaO_2/FiO_2 ratio) on100% O_2 > 300 mmHg, donor age > 18 years, clear chest x-ray, no major purulent secretions found during bronchoscopy, no major mechanical lung trauma, no gross gastric aspiration, no evidence of significant infection, no evidence for human immunodeficiency virus, hepatitis virus, hepatitis C virus, or any other relevant viral disease and no history or

evidence of malignant disease. All recipients on the waiting list were considered except for patients presenting with no consent, pediatric recipient < 18 years old, diagnosis of primary pulmonary arterial hypertension, patient ventilated or on mechanical support before transplant, previous transplant of any solid organ and the need for combined heart-lung transplant, lobar lung transplant or single-lung transplant. The primary study end-points were the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2 ratio) (FiO_2=1.0) and primary graft dysfunction (PGD) > 1 at 24 hours after lung transplant. The secondary end-points were PaO_2/FiO_2 ratio and PGD scores measured at 12, 48 and 72 hours post-transplant, duration of intubation, length of ICU stay and hospitalization time. The median PaO_2/FiO_2 at 24 hours after transplant between the two groups was not statistically significant (p=0.63) and the difference between the two groups at all other time points did not reach statistical significance. Incidence of primary graft dysfunction > 1 was lower in the EVLP group at all times points compared with the control group and the need for post-operative prolonged extracorporeal membrane oxygenation was lower in the EVLP group, however the differences did not meet statistical significance (p=0.10, p=0.44, respectively). Short-term clinical outcomes did not differ between recipients in the two groups. The author noted limitation of the study was the small patient population. The authors concluded that in a clinical setting EVLP applied in donor lungs that meet the standard acceptance criteria was at least equivalent to standard lung procurement. However, statistical significance for superiority of EVLP was not achieved in this study. The authors suggested that the focus of future studies should focus on prolonged perfusion and protocol modifications. Additional studies are needed to support the safety and effectiveness of EVLP.

Hayes (2018) published a Prognosis Overview report on the Organ Care System (OCS) Lung (TransMedics) for ex vivo lung perfusion system for the preservation of donor lungs. Hayes concluded that there is insufficient published evidence to assess the risks and benefits of the OCS Lung System over standard cold storage techniques for preservation of donor lungs. According to Hayes, there is no published evidence to date demonstrating that the OCS Lung improves post-transplant clinical morbidity or mortality outcomes compared with standard cold storage.

Ex vivo Heart perfusion: Currently there is an organ donor shortage that limits the number of heart transplants that can be performed and this shortage impacts pretransplant waitlist mortality. The Registry of the International Society for Heart and Lung Transplantation reported 5149 heart transplants performed worldwide from July 1, 2016, to June 30, 2017 (Khush, et al., 2018). In the United States, it is mandatory to report transplants to the United Network for Organ Sharing (UNOS). According to United Network for Organ Sharing (UNOS, 2021b), heart transplants performed increased to 3658 in 2020 from 3552 in 2019. A portable heart perfusion system has been proposed to increase donor supply. Ex vivo heart perfusion (EVHP) is an emerging technique for the procurement of heart allografts. This technique provides mechanically supported warm circulation to an explanted donor heart and before transplantation. EVHP can be sustained for several hours which can facilitate extended travel time, enable administration of pharmacological agents to optimize cardiac recovery and function and allow assessment of allograft function before implantation (Beuth, et al., 2019)

An examples of the ex vivo heart perfusion systems is the Organ Care System™ (OCS™) Heart System.

U.S. Food and Drug Administration (FDA): The OCS heart system has not received FDA approval.

Literature Review: Evidence evaluating ex vivo heart perfusion is primarily in the form of retrospective reviews and prospective case series, observational studies, review articles, and a randomized controlled trial (Beuth, et al., 2019; Chan, et al., 2017; Ardehali, et al., 2015)

Ardehali et al. 2015 conducted a prospective, open-label, multicenter, non-inferiority randomized controlled trial at ten heart-transplant centers in the USA and Europe. The study assessed the clinical outcomes of the ex-vivo perfusion system (organ care system [OCS]) compared to standard cold storage of human donor hearts for transplantation (PROCEED II). The recipient of the heart transplantation was included if the following criteria were met: registered male or female primary heart transplant candidate, ≥ 18 years old, signed consent document and authorization to use and disclose protected health information. The donor hearts met the following criteria: age < 60 years, mean systolic blood pressure > 60 mmHg at the time of final heart assessment and satisfactory echocardiography assessment. Patients (n=130) were randomized (1:1) to receive donor hearts preserved with either the OCS (n=67) or standard cold storage (n=63). The primary outcome measured the 30 day patient and graft survival with the originally transplanted heart and no mechanical circulatory assist device,

with a 10% non-inferiority margin. The secondary outcomes measured cardiac graft-related serious adverse events, acute rejection determined by biopsy during the 30 day follow up and the ICU length of stay. At 30 days, the patient and graft survival rates were not significant in the intention to treat group, with 94% (n=63) in the OCS group and 97% (n=61) in the standard cold storage group (p=0.45). Cardiac-related serious adverse events were reported in eight (13%) patients in the OCS group and nine (14%) patients in the standard cold storage group. The severe rejection and stay in the intensive-care unit also did not differ significantly between the groups. The results were similar in the as-treated and per-protocol study populations. Five donor hearts selected for four patients were deemed unacceptable for transplantation while on the Organ Care System and were discarded. The OCS indicated rising total perfusate lactate concentrations, which indicated persistent myocardial ischemia despite optimization of myocardial perfusion. Author noted limitations included: the protocols for myocardial protection before and after the Organ Care System were not standardized among all participating centers and may have affected clinical outcomes in the Organ Care System group. Additionally, the discarding of Organ Care System donor hearts before transplantation was not anticipated. Another limitation of the study was that the population studied only included heart-transplant centers in the USA and Europe and the results may not be applicable to other races or ethnic groups. The authors concluded that the clinical outcomes of donor hearts adequately preserved with the Organ Care System platform are non-inferior to the outcomes of those preserved with standard cold storage. Further studies are needed to assess the metabolic assessment capability of the Organ Care System. No health disparities were identified by the investigators.

There is insufficient evidence to support that using the OCS ex vivo perfusion improves clinical outcomes when compared to static cold storage.

Use Outside of the US:
Canadian Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care update on cardiac transplantation indicated that cardiac transplantation should be considered for eligible patients with advanced heart failure (HF) who are ≤ 70 years of age and for carefully selected patients with advanced HF > 70 years of age. Additionally, it is recommended to perform an assessment of frailty using the Fried Frailty Phenotype score, Deficit Index, or Edmonton Frailty Scale. Frailty in patients with advanced HF is associated with increased morbidity and mortality. The position statement indicated that the contraindications to heart transplant included: repeated medical nonadherence, active alcohol or drug abuse, active smoking, and mental health and social conditions that are likely to affect compliance. Furthermore, significant pulmonary hypertension (PH), defined as pulmonary vascular resistance > 3 Wood Units, transpulmonary gradient > 15 mm Hg and/or pulmonary artery systolic pressure > 50 mm Hg, is a contraindication for heart transplant because of greater risk of post transplantation right ventricular failure and early mortality (Chih, et al., 2020).

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) issued a position statement on advanced heart failure (Crespo-Leiro, et al., 2018) which indicated that heart transplantation remains the treatment of choice for patients with advanced or end-stage heart failure without contraindications. Data from the latest International Society for Heart and Lung Transplantation (ISHLT) Registry showed one-year survival of around 90% and median survival of 12.2 years. Transplantation not only improves survival but also functional status and quality of life (Lund, et al., 2014). Contraindications included active infection, severe peripheral arterial/cerebrovascular disease, pharmacologic irreversible pulmonary hypertension, cancer, irreversible renal dysfunction, systemic disease with multi-organ involvement, other serious co-morbidity with poor prognosis, pre-transplant BMI > 35 kg/m^2, current alcohol or drug abuse and any patient for whom social supports are deemed insufficient.

Following a systematic review of the literature that included two studies (one comparative cohort study and one report of three cases) that, the Ontario Health Technology Advisory Committee (2020) reported that based on very low quality of evidence the outcomes for patients who received hearts donated after cardiocirculatory death using a portable normothermic cardiac perfusion system appear to be similar to those for people who received hearts donated after brain death. The committee stated that the occurrence of rejection and graft failure did not significantly differ between the groups (GRADE: Very Low). Additionally, cardiac function in the early post-operative period was better in DCD hearts than NDD hearts (GRADE: Very Low). There were no differences in outcomes between DCD procurement techniques. The investigators noted that they did not detect potential

health inequities related to the effectiveness of a portable normothermic cardiac perfusion systems in DCD during the literature search.

In May 2021, NICE issued an Interventional Procedure Guidance on ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant. The guidance stated that current evidence on the efficacy and safety of ex-situ machine perfusion for extracorporeal preservation of lungs for transplant is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. The committee review of the published literature was comprised of the evidence from seven sources and included three meta-analyses, three retrospective cohort studies and one prospective case series.

In February 2016, NICE issued an Interventional Procedure Guidance on normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death. The guidance stated that current evidence on the efficacy of normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death shows that the procedure extends preservation times compared to cold storage. The evidence on safety is adequate in the short term to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit. The committee recommended further research and the outcomes should include primary graft function, long term graft function and complications related to the device.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Heart Transplants (260.9)	5/1/2008

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	**Description**
32850	Donor pneumonectomy(s) (including cold preservation), from cadaver donor
32851	Lung transplant, single; without cardiopulmonary bypass
32852	Lung transplant, single; with cardiopulmonary bypass
32853	Lung transplant, double (bilateral sequential or en bloc); without cardiopulmonary bypass
32854	Lung transplant, double (bilateral sequential or en bloc); with cardiopulmonary bypass
32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; unilateral
32856	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; bilateral
33929	Removal of a total replacement heart system (artificial heart) for heart transplantation (List separately in addition to code for primary procedure)
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

CPT®* Codes	Description
33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
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 Codes	Description
S2060	Lobar lung transplantation
S2061	Donor lobectomy (lung) for transplantation, living donor
S2152	Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition

Considered Experimental, Investigational or Unproven when used to report organ transport systems for preservation and transportation of donor lung(s) and/or heart for transplantation:

HCPCS Codes	Description
E1399	Durable medical equipment, miscellaneous

Considered Experimental, Investigational or Unproven when used to report Ex-vivo perfusion (e.g., Organ Care System™) for lung and/or heart transplantation:

CPT®* Codes	Description
0494T	Surgical preparation and cannulation of marginal (extended) cadaver donor lung(s) to ex vivo organ perfusion system, including decannulation, separation from the perfusion system, and cold preservation of the allograft prior to implantation, when performed
0495T	Initiation and monitoring marginal (extended) cadaver donor lung(s) organ perfusion system by physician or qualified health care professional, including physiological and laboratory assessment (eg, pulmonary artery flow, pulmonary artery pressure, left atrial pressure, pulmonary vascular resistance, mean/peak and plateau airway pressure, dynamic compliance and perfusate gas analysis), including bronchoscopy and X ray when performed; first two hours in sterile field
0496T	Initiation and monitoring marginal (extended) cadaver donor lung(s) organ perfusion system by physician or qualified health care professional, including physiological and laboratory assessment (eg, pulmonary artery flow, pulmonary artery pressure, left atrial pressure, pulmonary vascular resistance, mean/peak and plateau airway pressure, dynamic compliance and perfusate gas analysis), including bronchoscopy and X ray when performed; each additional hour (List separately in addition to code for primary procedure)

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