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Lung and Lobar Lung Transplant

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Disclaimer

Carefully check state regulations and/or the member contract.
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Legislative Mandates

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

Coverage

Lung transplantation **may be considered medically necessary** for carefully selected individuals with end-stage pulmonary disease (ESPD), including but not limited to, one of the conditions listed below.

A lobar lung transplant from a living or deceased donor **may be considered medically necessary** for carefully selected individuals with ESPD, including but not limited to one, of the conditions listed below.

- Alpha-1 antitrypsin deficiency,
- Bilateral bronchiectasis,
- Bronchiolitis obliterans,
- Bronchopulmonary dysplasia,
- Pulmonary hypertension,
- Chronic obstructive pulmonary disease (COPD),
- Cystic fibrosis (CF) (both lungs to be transplanted),
- Eisenmenger's syndrome,
- Emphysema,
- Eosinophilic granuloma,
- Idiopathic or interstitial pulmonary fibrosis,
- Lymphangiomyomatosis,
- Post-inflammatory pulmonary fibrosis,
- Sarcoidosis,
- Scleroderma.

Lung or lobar lung transplantation, after a failed lung or lobar lung transplant, **may be considered medically necessary** in individuals who meet the criteria for lung transplantation.

Lung or lobar lung transplantation **is considered experimental, investigational and/or unproven** in all other clinical situations.

Ex-vivo lung perfusion systems (static [for use in a hospital] and/or portable), including but not limited to the following systems **are considered experimental, investigational and/or unproven:**

- XVIVO Perfusion System (XPS; XVIVO Perfusion AB, Goteborg, Sweden),
- Organ Care System (OCS) Lung (TransMedics, Andover, MA, USA),
- VivoLine LS1 (VivoLine Medical; Lund, Sweden) (acquired by XVIVO Perfusion June 2016), Lung Assist (Organ Assist; Groningen, The Netherlands).

Policy Guidelines

None.

Description

A lung transplant consists of replacing all or part of diseased lungs with healthy lung(s) or lobes. Transplantation is an option for patients with end-stage lung/pulmonary disease (ESPD).

Background

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life. (1) Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and United Network of Organ Sharing.

Lung Transplant

In 2022, 42,880 transplants were performed in the United States procured from more than 14,900 deceased donors and 6,400 living donors. (2) Lung transplants were the fourth most common procedure with 2,692 transplants performed from both deceased and living donors in 2022.

End-stage lung disease may derive from different etiologies. The most common indications for lung transplantation are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis (CF), alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension (PAH). Before consideration for transplant, patients should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung-volume reduction surgery for COPD. Lung or lobar lung transplantation is an option for patients with ESPD despite these measures.

A lung transplant refers to single-lung or double-lung replacement. In a single-lung transplant, only 1 lung from a deceased donor is provided to the recipient. In a double-lung transplant, both the recipient's lungs are removed and replaced by the donor's lungs. In a lobar transplant, a lobe of the donor's lung is excised, sized appropriately for the recipient's thoracic dimensions, and transplanted. Donors for lobar transplant have primarily been living-related donors, with 1 lobe obtained from each of 2 donors (generally friends or family members) in cases for which bilateral transplantation is required. There are also cases of cadaver lobe transplants.

Potential recipients who are 12 years of age and older are ranked according to the Lung Allocation Score (LAS). (3) A score may range between 0 and 100 and incorporates predicted survival after transplantation and predicted survival on the waiting list; the LAS takes into consideration the patient's disease and clinical parameters. The waiting list incorporates the LAS, geography, and blood type classifications. Children younger than 12 years old receive a priority for lung allocation. Under this system, children younger than 12 years old with respiratory lung failure and/or pulmonary hypertension who meet criteria are considered

"priority 1", and all other candidates in the age group are considered "priority 2". A lung review board has the authority to adjust scores on appeal for adults and children.

Potential Contraindications to Transplantation

General

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 lung disease;
- History of cancer with a moderate risk of recurrence;
- Systemic disease that could be exacerbated by immunosuppression; and
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

Additional Disease State Specific

- Coronary artery disease (CAD) not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function[a]; or
- Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria.

[a] Some patients may be candidates for combined heart and lung transplantation (see Medical Policy SUR703.006).

Individuals must meet United Network for Organ Sharing (UNOS) guidelines for a LAS greater than zero.

Lung-Specific Guidelines

Bilateral lung transplantation is typically required when chronic lung infection and disease is present (i.e., associated with CF and bronchiectasis). Some, but not all, cases of pulmonary hypertension will require bilateral lung transplantation.

Bronchiolitis obliterans is associated with chronic lung transplant rejection, and thus may be the etiology of a request for lung retransplantation.

Malignancy

Malignancies are common after lung transplantation, with 21% and 40% of patients reporting 1 or more malignancies at 5 and 10 years posttransplantation, respectively. (4) Skin cancer occurred most frequently, and lymphoproliferative disorders were the malignancies most associated with morbidity posttransplantation.

Human Immunodeficiency Virus Infection

Current OPTN policy permits human immunodeficiency virus (HIV)-positive transplant candidates. The 2020 U.S. Public Health Service guideline also allows for transplantations in HIV-positive recipients with proper screenings and effective regimens for HIV infections; it

recommended that all transplant candidates receive HIV, hepatitis b virus (HBV), and hepatitis C virus (HCV) testing during hospital admission for transplant surgery. (5) In 2022, the U.S. Public Health Service published updated guidance for testing transplant candidates aged less than 12 years of age. (6) They recommended that children less than 12 years of age who have received postnatal infectious disease testing are exempt from repeat pretransplant HIV, HBV, and HCV testing during hospital admission for transplant surgery.

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease. (7) These criteria for adding a patient to the waitlist 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 Infections

Infection with *Burkholderia cenocepacia* is associated with increased mortality in some transplant centers, a factor that may be considered when evaluating the overall risk of transplant survival. (8) Two articles have evaluated the impact of infection with various species of *Burkholderia* on outcomes for lung transplantation for cystic fibrosis. In a study by Murray et al. (2008), multivariate Cox survival models were applied to 1026 lung transplant candidates and 528 transplant recipients. (9) Of the transplant recipients, 88 were infected with *Burkholderia*. Among transplant recipients infected with *B. cenocepacia,* only those infected with nonepidemic strains (n=11) had significantly greater posttransplant mortality than uninfected patients (Hazard ratio [HR], 2.52; 95% CI, 1.04 to 6.12; p=.04). Transplant recipients infected with *Burkholderia gladioli* (n=14) also had significantly greater posttransplant mortality than uninfected patients (HR, 2.23; 95% CI, 1.05 to 4.74; p=.04). When adjustments for specific species or strains were included, the LAS of *Burkholderia multivorans*-infected transplant candidates were comparable with uninfected candidate scores, and scores for patients infected with nonepidemic *B. cenocepacia* or *B. gladioli* were lower. In a smaller study of 22 patients colonized with *Burkholderia cepacia* complex who underwent lung transplantation in 2 French centers, Boussaud et al. (2008) reported that the risk of death by univariate analysis was significantly higher for the 8 patients infected with *B. cenocepacia* than for the other 14 colonized patients (11 of whom had *B. multivorans*). (10)

An analysis of international registry data by Yusen et al. (2016) found that non-cytomegalovirus (CMV) infection is a major cause of mortality within 30 days of a lung transplant in adults. (11) A total of 655 (19%) of 3424 deaths after transplants between 1990 and 2015 were due to non-CMV infection. Only 3 (0.1%) of the deaths were due to CMV infection.

<u>Ex-vivo Lung Perfusion Systems</u>

There is large discrepancy between the supply of donor lungs and the number of potential lung transplant recipients. As a result, 20% to 30% of patients on the lung transplant waiting list die each year waiting for suitable lungs. Two main factors contribute to this discrepancy: 1) an increase in lung transplant candidates while the donor rates remain unchanged; and 2) low utilization rates of donated lungs because of stringent donor-selection criteria due to limitations of the standard lung-preservation method, cold static storage (CSS). (12)

Approximately 80% of donor lungs are unsuitable for transplant in part because of CSS's limitations. Lungs sustain injuries during donor end-of-life care from aspiration, resuscitation attempts and ventilation, as well as after donor death (e.g., neurogenic edema, inflammatory responses). Transplant teams cannot reassess lungs in CSS and cannot predict how marginal-quality lungs and lungs that sustained injury will perform until after transplant. Additionally, lungs in CSS cannot recover from injuries sustained during donor end-of-life care. Therefore, lung procurement teams adopt a conservative approach for lung selection and decline marginal-quality lungs because of high complication rates for patients who receive poor-performing lungs. (13)

Ex vivo lung perfusion systems (EVLP) preserve donor lungs at a near physiologic state outside the body for several hours to allow lung transplant surgeons the opportunity to continuously assess lung function. Lung transplant teams can use EVLP systems to preserve lungs meeting transplant criteria and to evaluate and recondition lungs that initially do not meet transplant criteria but meet criteria for EVLP. During EVLP, reassessed lungs satisfying transplant criteria are selected for transplant. Using EVLP systems, surgeons may recondition lungs by removing donor immune cells and inflammatory cytokines, recruiting collapsed lung areas, and removing excess fluid from the lungs. Additionally, EVLP systems may preserve lungs initially meeting transplant criteria substantially longer than what is possible using CSS. Disadvantages associated with receiving EVLP reconditioned lungs as opposed to lungs initially deemed suitable for transplant are not known. (12)

Regulatory Status

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

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

<u>Ex-vivo Lung Perfusion Systems</u>

The FDA granted marketing approval for the XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate through a humanitarian device exemption (HDE) in 2014, followed by premarket approval (PMA) in 2019. It is indicated for flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which

time the ex-vivo function of the lungs can be reassessed for transplantation. FDA product code: PHO. (13-14)

The Organ Care System (OCS™) Lung System (TransMedics, Andover, MA, USA) received premarket approval from the FDA in March 2018 for the preservation of standard criteria donor lungs in a near physiologic, ventilated, and perfused state for double lung transplantation. FDA product code: PHO, QBA. (15)

The FDA does not have information available for the VivoLine LS1 (VivoLine Medical; Lund, Sweden) or the Lung Assist (Organ Assist; Groningen, The Netherlands).

Rationale

This medical policy was created in 1990 and has been updated with searches of the PubMed database. The most recent literature update was performed through December 12, 2023.

Medical policies assess clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: relevance, quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Lung Transplantation for End-Stage Pulmonary Disease

Clinical Context and Test Purpose

The purpose of lung transplantation in individuals who have end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this medical policy.

Populations
The relevant population of interest is individuals with end-stage pulmonary disease.

Before consideration for transplant, patients should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung volume reduction surgery for chronic obstructive pulmonary disease (COPD).

Interventions
The therapy being considered is a lung transplant.

Comparators
The following practice is currently being used to make decisions about reducing the risk of end-stage pulmonary disease: medical management, such as maximal medical therapy, including oxygen supplementation, or surgical options, such as lung volume reduction surgery for COPD.

Outcomes
The general outcomes of interest are overall survival (OS), change in disease status, treatment-related mortality, and treatment-related morbidity (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary to due immunosuppression drugs and risk of graft failure.

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.

Registry Studies
Paraskeva et al. (2018) analyzed survival rates of adolescent lung transplant recipients using data from the International Society for Heart and Lung Transplantation (ISHLT) Registry. (16) Patients between 10 and 24 years old represented 9% of the registry data (n=2319) and they were compared with both old and young cohorts. Overall survival in the adolescent cohort was 65% at 3 years, which was similar to that observed in adults between 50 and 65 years of age, but significantly lower than 3-year survival rate among the pediatric subgroup (73%; p=0.006) or adults 25 to 34 years old (75%; p<0.001) and 35 to 49 years old (71%; p<0.001). Within the adolescent group, patients between 15 and 19 years of age had the poorest survival rates at 3 years (59%) compared with 10- to 14-year old patients (73%) and 20- to 24-year old patients (66%,) (both p<0.001). The registry study was biased toward inclusion of North American data

and potential data entry errors or missing data. There were no data reported on the cause of mortality, differences in regimens, or rates of graft dysfunction between the groups.

One of the ISHLT registries contained data from 49,453 adult recipients who received lung transplantation (including lung retransplantation) through June 30, 2015, at 134 transplant centers. (12) A total of 55,795 lung transplants were performed, of which 53,522 (95.9%) were primary transplants and 2273 (4.1%) were retransplants. The overall median survival of patients who underwent lung transplantation was 5.8 years. Estimated unadjusted survival rates were 89% at 3 months, 80% at 1 year, 65% at 5 years, and 32% at 10 years. Patients who survived a year after primary transplantation had a median survival of 8.0 years. In the first 30 days after transplantation, the major reported causes of mortality were graft failure (24.5%) and non-cytomegalovirus (CMV) infections (19.1%) while non-CMV infections became the major cause of death for the remainder of the first year. Beyond the first year, the most commonly reported causes of mortality were obstructive bronchiolitis/bronchiolitis obliterans syndrome, graft failure, and non-CMV infections. Beyond 10 years posttransplant, the major causes of mortality were obstructive bronchiolitis/bronchiolitis obliterans syndrome (21.5%), non-CMV infection (16.5%), and nonlymphoma malignancy (13.7%).

Through 2014, another ISHLT registry contained 2229 pediatric lung transplants. (17) Most transplants (73%) were done in children between the ages of 11 and 17 years. Median survival in children who underwent lung transplantation was 5.4 years, similar to survival in adults (mean survival, 5.7 years). However, median survival in children was lower (2.2 years) than in adults (5.6 years) for single-lung transplants.

Thabut et al. (2010) reported on a comparison between patients undergoing single- and double-lung transplantation for idiopathic pulmonary fibrosis. (18) A retrospective review was conducted of 3327 patients with data in the United Network for Organ Sharing (UNOS) registry. More patients underwent single-lung transplant (64.5%) compared with double-lung transplant (35.5%). Median survival time was greater for the double-lung group at 5.2 years (95% confidence interval [CI], 4.3 to 6.7 years) than 3.8 years (95% CI, 3.6 to 4.1 years; $p<0.001$). After adjusting for baseline differences, however, survival times did not differ statistically. The authors concluded that OS did not differ between the groups: single-lung transplants offered improved short-term survival but a reduced long-term benefit, whereas double-lung transplant increased short-term harm but was associated with a long-term survival benefit. Black et al. (2014) reported on Lung Allocation Score (LAS) and single versus double-lung transplant in 8778 patients (8050 had a LAS <75 vs 728 had a LAS ≥75). (19) A significant decrease in survival was seen in single-lung transplant patients with a high LAS compared with double-lung transplant patients with a high LAS ($p<0.001$). Yu et al. (2019) compared double-lung with single-lung transplantations for outcomes of survival, pulmonary function, surgical indicators, and complications in a meta-analysis of 30 studies (n=1980 recipients of single-lung transplants and n=2112 recipients of double-lung transplants). (20) Overall survival, in-hospital mortality, and postoperative complications besides bronchiolitis obliterans syndrome were similar between the 2 groups. Recipients of double-lung transplants had lower rates of bronchiolitis obliterans syndrome, better postoperative lung function, and improved long-term survival, while

recipients of single-lung transplants spent less time in surgery, the postoperative intensive care unit, and the postoperative hospital stay.

Yusen et al. (2010) reviewed the effect of the LAS on lung transplantation by comparing statistics for the period before and after its implementation in 2005. (21) Other independent changes in clinical practice, which may affect outcomes over the same period of time, include variation in immunosuppressive regimens, an increased supply of donor lungs, changes in diagnostic mix, and increased consideration of older recipients. Deaths on the waiting list declined following implementation of the LAS system, from approximately 500 per 5000 patients to 300 per 5000 patients. However, it is expected that implementation of LAS affected patient characteristics of transplant applicants. One-year survival posttransplantation did not improve after implementation of the LAS system: patient survival data before and after were approximately 83%. Long-term survival data are not yet available. Shafii et al. (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010. (22) Patients on the wait list who had a higher LAS had a higher mortality rate ($p<0.001$). In the highest quartile of LAS (range, 47-95), within 1 year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival ($p=0.05$) but not late posttransplant survival ($p=0.4$). When other predictive factors of early mortality were taken into account, pretransplant LAS was not independently related to posttransplant mortality ($p=0.12$).

Section Summary: Lung Transplant for End-Stage Pulmonary Disease

International registry data on a large number of patients receiving lung transplantation (>50,000) found relatively high patient survival rates (89% at 3 months, 80% at 1 year, 65% at 5 years, 32% at 10 years). In patients who survived at least 1-year, median survival was 8 years. After adjusting for potential confounding factors, survival did not differ significantly after single- or double-lung transplant. A subgroup analysis of an international registry study found decreased survival for adolescent patients, especially between 15 and 19 years of age, who received lung transplantation, but the study was limited by inclusion bias and lack of data on mortality, differences in treatment regimens, and rates of graft dysfunction.

Lobar Lung Transplantation for End-Stage Pulmonary Disease

Clinical Context and Test Purpose

The purpose of lobar lung transplantation in individuals who have end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals with end-stage pulmonary disease.

Before consideration for transplant, individuals should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung volume reduction surgery for COPD.

Interventions
The therapy being considered is a lobar lung transplant.

Date (2011) published that, as of 2011, approximately 400 living-donor lobar lung transplants had been performed worldwide. (23) Procedures in the United States decreased after 2005 due to changes in the lung allocation system. Date also reported that size matching between donor and recipient is important and that, to some extent, size mismatching (oversized or undersized grafts) can be overcome by adjusting surgical technique.

Comparators
The following practice is currently being used to make decisions about end-stage pulmonary disease: medical management, such as maximal medical therapy, including oxygen supplementation, or surgical options, such as lung volume reduction surgery for COPD.

Outcomes
The general outcomes of interest are OS, change in disease status, treatment-related mortality, and treatment-related morbidity (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). Short-term follow-up ranges from immediate postsurgery to 30 days post transplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary to due immunosuppression drugs and risk of graft failure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
Eberlein et al. (2017) reported on a systematic review of studies on lobar lung transplantation from deceased donors. (24) Reviewers identified 9 studies comparing outcomes after lobar lung or lung transplant, all of which were single-center retrospective cohort studies. Seven studies were conducted in Europe, 1 in Australia and 1 in North America. One-year survival reported in individual studies ranged from 50% to 100% after lobar lung transplant and from 72% to 88% after conventional lung transplant. In a pooled analysis of data from 8 studies, lobar lung

transplant recipients (n=284) had a significantly higher risk of 1-year mortality than lung transplant recipients (n=2777) (relative risk, 1.85; 95% CI, 1.52 to 2.25; p<0.001; I^2=0%).

Retrospective Studies

Several studies have reported on lobar lung transplantation from living donors. For example, Barr et al. (2005) reported on living-donor lobar lung transplants in the United States. (25) Ninety patients were adults and 43 were children. The primary indication for transplantation (86%) was cystic fibrosis. At the time of transplantation, 67% of patients were hospitalized and 20% were ventilator dependent. Overall recipient survival rates at 1, 3, and 5 years were 70%, 54%, and 45%, respectively. There was no statistically significant difference in actuarial survival between adults and children who underwent transplantation. Moreover, survival rates were similar to the general population of lung transplant recipients. The authors also reported that rates of postoperative pulmonary function in patients surviving more than 3 months posttransplant were comparable with rates in cadaveric lung transplant recipients.

Date et al. (2015) reported on a retrospective study comparing 42 living-donor lobar lung transplants with 37 cadaveric lung transplants. (26) Survival rates at 1 and 3 years did not differ significantly between groups (89.7% and 86.1% vs 88.3% and 83.1%, respectively, p=0.55), despite living-donor lobar lung transplant patients having poorer health status preoperatively. For a program in Japan, Date et al. (2012) reported on 14 critically ill patients (10 children, 4 adults) who had undergone single living-donor lobar lung transplants. (27) Patients were followed for a mean 45 months. The 3-year survival rate was 70% and the 5-year survival was 56%. Severe graft dysfunction occurred in 4 patients. Mean forced vital capacity (FVC) was lower in patients experiencing severe graft dysfunction (54.5%) than in the other patients (66.5%). The authors postulated that this suggests size mismatching in the patients with severe graft dysfunction.

Slama et al. (2014) reported on a comparison of outcomes in 138 cadaveric lobar lung transplants (for size discrepancies) with 778 patients who received cadaveric whole-lung transplants, 239 of whom had downsizing by wedge resection of the right middle lobe and/or the left lingula. (28) Survival rates in the lobar lung transplant group at 1 and 5 years was 65.1% and 54.9% vs 84.8% and 65.1% in the whole-lung and downsized by wedge resection group (p<0.001). The lobar lung transplantation group experienced significantly inferior early postoperative outcomes, but in patients who were successfully discharged, survival rates were similar to standard lung transplantation (p=0.168).

Section Summary: Lung Lobar Transplant for End-Stage Pulmonary Disease

There are less data on lung lobar transplants than on whole-lung transplants. The available data reported in case series have suggested reasonably similar survival outcomes, and lung lobar transplants may be the only option for patients unable to wait for a whole lung. A 2017 systematic review found 1-year survival rates ranging from 50% to 100%.

Lung or Lobar Retransplantation When Meeting Criteria for Lung Transplant

Clinical Context and Therapy Purpose

The purpose of lung retransplantation in individuals who have had a prior lung or lobar transplant and who meet criteria for a lung transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations
The relevant population of interest is individuals with a prior lung or lobar transplant who meet criteria for a lung transplant.

Interventions
The therapy being considered is lung or lobar retransplantation.

Comparators
The following practice is currently being used to make decisions about treating those whose lung or lobar transplant has failed and would still be considered as meeting eligibility criteria for an initial transplant: medical management, such as maximal medical therapy, including oxygen supplementation, or surgical options, such as lung volume reduction surgery for COPD.

Outcomes
The general outcomes of interest are OS, change in disease status, treatment-related mortality, and treatment-related morbidity (e.g., immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). Short-term follow-up ranges from immediate postsurgery to 30 days posttransplantation; lifelong follow-up.

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.

Case Series
Registry data and case series have demonstrated favorable outcomes with lung retransplantation in certain populations, such as in patients who meet criteria for initial lung transplantation. (4, 29-30)

Biswas Roy et al. (2018) published a single-center retrospective study comparing survival outcomes in 29 patients who received retransplantation for chronic lung allograft dysfunction with 390 patients receiving a primary lung transplant at the same center. (31) Patients receiving retransplantation had significantly higher use of extracorporeal membrane oxygenation

support for severe primary graft dysfunction (p=0.019) and underwent cardiopulmonary bypass and re-exploration for bleeding (p=0.019) more frequently than patients receiving primary transplantation (p=0.029). At 1-year follow-up, 89.7% of primary transplant patients were living, as were 89.2% of retransplantation patients. At 5-year follow-up, a greater percentage of the retransplantation group had survived, compared with the primary transplantation group (64.3% vs 58.2%), although the difference was not statistically significant. While high LAS and extended hospital length of stay were both identified as independent mortality risk factors, retransplantation was not (hazard ratio [HR], 1.58; 95% CI, 0.31 to 8.08; p=0.58). Study limitations included its single-center, retrospective design, the potential selection bias for younger patients, and the small size of the retransplantation group. Further, follow-up data at 3 and 5 years were incomplete for some patients and patients who were refused retransplantation were not considered in the analyses. However, for appropriately selected patients, retransplantation after chronic lung allograft dysfunction resulted in 1- and 5-year survival rates comparable to those seen after primary lung transplantation.

Registry Studies

The Organ Procurement and Transplantation Network (OPTN) reported data on lung transplants performed between 2008 and 2015. (32) Patient survival rates after repeat transplants were lower than primary transplants, but a substantial number of patients survived. For example, 1-year patient survival was 87.2% (95% CI, 86.4% to 87.9%) after a primary lung transplant and 76% (95% CI, 71.0% to 80.2%) after a repeat transplant. Five-year patient survival rates were 53.4% (95% CI, 52.2% to 54.7%) after a primary lung transplant and 32.9% (95% CI, 27.7% to 38.2%) after repeat transplant.

The ISHLT Registry contained data on 2273 retransplantation patients performed through June 2015 (4.4% of lung transplantations). (11) The major causes of death in the first 30 days after retransplantation were graft failure and non-CMV infection, followed by multiorgan failure, cardiovascular causes, and technical factors related to the transplant procedure. Beyond the first year, the most commonly reported causes of mortality were obstructive bronchiolitis/ bronchiolitis obliterans, graft failure, and non-CMV infections.

Section Summary: Lung or Lobar Retransplant When Meeting Criteria for a Lung Transplant

Data from registries and case series have found favorable outcomes with lung retransplantation in patients who meet criteria for initial lung transplantation. Given the exceedingly poor survival without retransplantation of patients who have exhausted other treatments, evidence of a moderate level of posttransplant survival is sufficient to suggest treatment efficacy in this patient population.

Ex-vivo Lung Perfusion (EVLP) Systems

Van Raemdonck et al. (2010) noted that the critical organ shortage has forced lung transplant teams to extend their donor criteria, thereby compromising a good early outcome in the recipient. (33) Better preservation solutions for longer storage are welcomed to further reduce incidence of primary graft dysfunction. New ex-vivo techniques to assess and to condition lungs prior to transplantation are hoped to increase the number of available pulmonary grafts.

Although no prospective clinical trial has been carried out so far, clinical and experimental evidence suggest that an extracellular solution is currently the preservation fluid of choice for lung transplantation. The combination of an antegrade and retrograde pulmonary flush and technique to control reperfusion and ventilation are becoming common practice, although the evidence to support this method is low. Ex-vivo lung perfusion to assess and to re-condition lungs has been demonstrated to be well-tolerated and effective in small clinical series. The author concluded that new extracellular preservation solutions have contributed in decreasing the incidence of primary graft dysfunction over the last decade leaving more room to extend the donor criteria and ischemic time. Ex-vivo lung perfusion is now on the horizon as a potential method to prolong the preservation time and to resuscitate lungs of inferior quality.

Warnecke et al. (2012) stated that cold flush and static cold storage is the standard preservation technique for donor lungs before transplantations. (34) Several research groups have assessed normothermic perfusion of donor lungs, but all devices investigated were non-portable. In a pilot study, these investigators reported first-in-man experience of the portable Organ Care System (OCS) Lung device for concomitant preservation, assessment, and transport of donor lungs. Between February 18 and July 1, 2011, 12 patients were transplanted at 2 academic lung transplantation centers in Hanover, Germany and Madrid, Spain. Lungs were perfused with low potassium dextran solution, explanted, immediately connected to the OCS Lung, perfused with Steen's solution supplemented with 2 red-cell concentrates. These researchers assessed donor and recipient characteristics and monitored extended criteria donor lung scores; primary graft dysfunction scores at 0, 24, 48, and 72 hours; time on mechanical ventilation after surgery; length of stays in hospital and the intensive-care unit after surgery; blood gases; and survival of grafts and patients. Eight donors were female and 4 were male (mean age of 44.5 years, range of 14 to 72). Seven recipients were female and 5 were male (mean age of 50.0 years, range of 31 to 59). The pre-harvest donor ratio of partial pressure of oxygen (PaO_2) to fractional concentration of oxygen in inspired air (FiO_2) was 463.9 (SD 91.4). The final ratio of PaO_2 to FiO_2 measured with the OCS Lung was 471.58 (127.9). The difference between these ratios was not significant ($p = 0.72$). All grafts and patients survived to 30 days; all recipients recovered and were discharged from hospital. The authors concluded that lungs can be safely preserved with the OCS Lung, resulting in complete organ use and successful transplantation in this series of high-risk recipients.

In November 2011, Warnecke et al. (2018) began recruitment for a prospective, randomized, multi-center trial (INSPIRE) to compare preservation with OCS Lung with standard cold storage. (35) Eligible donors were ages 18 years or older and younger than 65 registered as standard criteria primary double lung transplant candidates. In this non-inferiority, phase 3 trial 370 patients were randomly assigned and 320 underwent transplantation with a follow-up completed November 2016. The authors reported that the trial met its primary effectiveness and safety endpoints. Although no short-term survival benefit was reported, further research is needed to see whether the reduced incidence of pulmonary graft dysfunction of grade 3 within 72 hours of a transplant might translate into earlier recovery and improved long-term outcomes after lung transplantation.

Warnecke et al. (2018) assess physiological donor lung preservation using the OCS Lung device compared with cold static storage in a non-inferiority, randomized, controlled, open-label, phase 3 trial (INSPIRE). Participants were aged 18 years or older and were registered as standard criteria primary double lung transplant candidates. (36) Transplant recipients were randomly assigned (1:1) with permuted blocks, stratified by center, to receive standard criteria donor lungs preserved in the OCS Lung device (OCS arm) or cold storage at 4°C (control arm). The composite primary effectiveness endpoint was absence of primary graft dysfunction of grade 3 (PGD3) within the first 72 hours after transplant and 30-day survival in the per-protocol population, with a stringent 4% non-inferiority margin. Superiority was tested upon meeting non-inferiority. The primary safety endpoint was the mean number of lung graft-related serious adverse events within 30 days of transplant. Researchers randomly assigned 370 patients, and 320 (86%) underwent transplantation (n=151 OCS and n=169 control); follow-up was completed in November 2016. The primary endpoint was met in 112 (79·4%) of 141 patients (95% CI 71·8 to 85·8) in the OCS group compared with 116 (70·3%) of 165 patients (62·7 to 77·2) in the control group (non-inferiority point estimate -9·1%; 95% CI -∞ to -1·0; p=0·0038; and superiority test p=0·068). Patient survival at day 30 post-transplant was 135 (95·7%) of 141 patients (95% CI 91·0-98·4) in the OCS group and 165 patients (100%; 97·8-100·0) in the control group (p=0·0090) and at 12 months was 126 (89·4%) of 141 patients (83·1-93·9) for the OCS group compared with 146 (88·1%) of 165 patients (81·8-92·8) for the control group. Incidence of PGD3 within 72 h was reported in 25 (17·7%) of 141 patients in the OCS group (95% CI 11·8 to 25·1) and 49 (29·7%) of 165 patients in the control group (22·8 to 37·3; superiority test p=0·015). 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 [point estimate -0·045%; 95% CI -∞ to 0·047; non-inferiority test p=0·020]). In the intention-to-treat population, causes of death at 30 days and in hospital were lung graft failure or lung infection (n=2 for OCS vs n=7 for control), cardiac causes (n=4 vs n=1), vascular or stroke (n=3 vs n=0), metabolic coma (n=0 vs n=2), and generalized sepsis (n=0 vs n=1). Researchers concluded that the INSPIRE trial met its primary effectiveness and safety endpoints. Although no short-term survival benefit was reported, further research is needed to see whether the reduced incidence of PGD3 within 72 hours of a transplant might translate into earlier recovery and improved long-term outcomes after lung transplantation.

Loor et al. (2019) evaluated the efficacy of normothermic portable OCS Lung perfusion and ventilation on donor lung use from extended-criteria donors and donors after circulatory death. (37) In this single-arm, pivotal trial done in eight institutions across the USA, Germany, and Belgium, lungs from extended-criteria donors were included if fulfilling one or more of the following criteria: a ratio of partial pressure of arterial oxygen (PaO_2) to fractional concentration of oxygen inspired air (FiO_2) in the donor lung of 300 mm Hg or less; expected ischemic time longer than 6 hours; donor age 55 years or older; or lungs from donors after circulatory death that were recruited and assessed using OCS Lung. Lungs were transplanted if they showed stability of OCS Lung variables, PaO_2:FiO_2 was more than 300 mm Hg, and they were accepted by the transplanting surgeon. Patients were adult bilateral lung transplant recipients. The primary efficacy endpoint was a composite of patient survival at day 30 post-transplant and absence of ISHLT PGD3 within 72 hours post-transplantation, with a prespecified objective

performance goal of 65%. The primary analysis population was all transplanted recipients. The primary endpoint was achieved in 43 (54%) of 79 patients and did not meet the objective performance goal. 35 (44%) of 79 patients had PGD3 within the initial 72 h. 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 (SD 0·5). Despite missing the objective primary endpoint, the portable OCS Lung resulted in 87% donor lung use for transplantation with excellent clinical outcomes. Many lungs declined by other transplant centres were successfully transplanted using this new technology, which implies its use has the potential to increase the number of lung transplants performed worldwide. Whether similar outcomes could be obtained if these lungs were preserved on ice is unknown and remains an area for future research.

An UpToDate review on "Lung transplantation: Donor lung procurement and preservation" (Hartwig et al., 2023) states that the cold static preservation system "was developed in an era with younger organ donors and good-quality organs. (38) However, the need to use acceptable, but less than ideal donor lungs to expand donor lung availability and difficulties assessing lung function in donation after cardiac death have made it necessary to explore alternative preservation techniques, such as EVLP, also known as ex vivo reconditioning. Normothermic EVLP is being increasingly investigated and applied clinically. EVLP is an important assessment and treatment platform to manage donor lungs and is generally used with a period of protective cold static preservation before and after normothermic EVLP." Although there is mounting evidence that normothermic ex vivo perfusion and ventilation of lungs is an effective method in assessing organs outside of the context of a multiorgan donor, this method of organ preservation and assessment has not been shown to be safer or superior to cold static preservation.

Summary of Evidence

For individuals who have end-stage pulmonary disease who receive a lung transplant, the evidence includes case series and registry studies. Relevant outcomes are overall survival (OS), change in disease status, and treatment-related mortality and morbidity. International registry data on a large number of patients receiving lung transplantation (>50,000), found relatively high patient survival rates, especially among those who survived the first year posttransplant. After adjusting for potential confounding factors, survival did not differ significantly after single- or double-lung transplant. Lung transplantation may be the only option for some patients with end-stage lung disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have end-stage pulmonary disease who receive a lobar lung transplant, the evidence includes case series and systematic reviews. Relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. There are less data on lung lobar transplants than on whole-lung transplants, but several case series have reported reasonably similar survival outcomes between the procedures, and lung lobar transplants may be the only option for patients unable to wait for a whole-lung transplant. A 2017 systematic review found 1-year survival rates in available published studies ranging from 50% to 100%. The evidence is

sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a prior lung or lobar transplant who meet criteria for a lung transplant who receive a lung or lobar lung retransplant, the evidence includes case series and registry studies. Relevant outcomes are OS, change in disease status, and treatment-related mortality and morbidity. Data from registries and case series have found favorable outcomes with lung retransplantation in patients who meet criteria for initial lung transplantation. Given the exceedingly poor survival prognosis without retransplantation of patients who have exhausted other treatments, the evidence of a moderate level of posttransplant survival may be considered sufficient in this patient population. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have end-stage pulmonary disease who receive a lung transplant, lobar lung transplant, and/or lung or lobar lung retransplant, to date, there is insufficient evidence to permit scientific conclusions regarding the use of ex vivo lung perfusion systems. Well-conducted long term randomized controlled trials (RCTs) with sufficiently large sample sizes are needed to draw conclusions on the impact to health outcomes.

Practice Guidelines and Position Statements

International Society for Heart and Lung Transplantation (ISHLT)

Initial Transplant

In 2021, the ISHLT published consensus-based guidelines on selection of lung transplant candidates. (39) The guidelines state that:

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

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

The guideline also notes risk factors to be considered in the evaluation of transplant candidates, along with pediatric and disease-specific considerations. ISHLT does not have a guideline addressing EVLP.

Retransplant

The 2021 guideline update briefly addressed lung retransplantation, with the consensus statement noting that "The outcomes after re-transplants are inferior compared to first lung transplants, particularly if the re- transplant is done within the first year after the original transplant or for patients with restrictive allograft syndrome (RAS) [...] In the pre-transplant evaluation of such patients, particular emphasis should be focused on understanding the possible reasons for the graft failure, such as alloimmunization, poor adherence, gastroesophageal reflux, or repeated infections". (39)

American Thoracic Society (ATS) et al.

Evidence-based recommendations from the ATS and 3 international cardiac societies were published in 2011 for the diagnosis and management of patients with idiopathic fibrosis. (40) For appropriately selected patients with idiopathic pulmonary fibrosis, the international guideline panel recommended lung transplantation (strong recommendation, low-quality evidence). An update to this document was published in 2015 in which the committee did not make a recommendation regarding single versus bilateral lung transplantation in patients with idiopathic fibrosis. (41) The committee stated that "it is unclear whether single or bilateral lung transplantation is preferential for long-term outcomes".

In 2022, the American Thoracic Society along with the 3 other international cardiac societies published updated guidance on diagnosis and management of idiopathic pulmonary fibrosis and progressive pulmonary fibrosis. (42) In terms of treatment considerations, the committee stated that "patients at increased risk of mortality should be referred for lung transplantation at diagnosis".

In 2014, the ATS published guidelines on the management of bronchiolitis obliterans syndrome in lung transplant recipients in conjunction with the ISHLT and the European Respiratory Society. (43) The guideline recommends referral to a transplant surgeon to be evaluated for retransplantation for end-stage bronchial obliterans syndrome that is refractory to other therapies.

The ATS does not have a guideline addressing EVLP.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Lung Transplant: Unpublished			
NCT00905463	Analysis of Prognosis and Patients Reported Outcomes in Lung Transplant Candidates	272	Mar 2022 (No results posted)
Lung Transplant: Ongoing			
NCT00177918	Prospective Evaluations of Infectious Complication in Lung Transplant Recipients	600	Dec 2025
EVLP: Ongoing:			
NCT0510146	An all comers registry for normothermic Ex Vivo Lung Perfusion as assessment of donor lungs for transplant	315	Apr 2029

NCT03641677	Increasing lung transplant availability using normothermic EVLP at a dedicated EVLP facility	186	Mar 2024

EVLP: Ex vivo lung perfusion systems; NCT: national clinical trial.

Coding

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

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

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

CPT Codes	32850, 32851, 32852, 32853, 32854, 32855, 32856, 0494T, 0495T, 0496T
HCPCS Codes	S2060, S2061, S2152

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

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Centers for Medicare and Medicaid Services (CMS)

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

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

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

Policy History/Revision

Date	Description of Change
10/15/2024	Reviewed. No changes.
02/01/2024	Document updated with literature review. Coverage unchanged. Added references: 6, 39, 41, 42; others updated and some removed.
10/15/2022	Reviewed. No changes.
12/01/2021	Document updated with literature review. The following change was made to Coverage: Modified end-stage pulmonary disease example list. Added/updated the following references: 1-3, 5, 13, 19, 35-37, and 41.
12/15/2020	Reviewed. No changes.
04/01/2019	Document updated with literature review. Coverage unchanged. References 5-7, 13, 21-24, 30, 33-34 were added and some references removed.
01/01/2018	Document updated with literature review. The following change was made to Coverage: Experimental, investigational and/or unproven coverage statement added for Ex vivo lung perfusion systems.

12/01/2017	Reviewed. No changes.
09/01/2016	Document updated with literature review. Coverage unchanged.
01/15/2015	Document updated with literature review. The following changes were made to coverage: 1) A lobar lung transplant may be considered medically necessary for carefully selected patients with end-stage pulmonary disease; 2) Postinflammatory and interstitial pulmonary fibrosis was added to list of example conditions; 3) Lung or lobar lung transplantation, after a failed lung or lobar lung transplant, may be considered medically necessary in patients who meet the criteria for lung transplantation; and 4) Lung or lobar lung transplantation is considered experimental, investigational and/or unproven in all other clinical situations. The Rationale and References were substantially revised and reorganized. CPT/HCPCS codes updated.
10/01/2012	CPT/HCPCS code(s) updated
05/15/2003	Revised document
08/01/1999	Revised document
09/01/1998	Revised document
05/01/1996	Revised document
04/01/1996	Revised document
10/01/1994	Revised document
07/01/1993	Revised document
04/01/1992	Revised document
01/01/1992	Revised document
05/01/1990	New medical document