7.03.07	Lung and Lobar Lung Transplant		
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Policy Statement

Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy (see Policy Guidelines).

A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease (see Policy Guidelines).

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

Lung or lobar lung transplantation is considered **investigational** in all other situations.

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

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

Policy Guidelines

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

Contraindications
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 diseases not attributed to lung disease
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

Policy specific:

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

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

Patients must meet United Network for Organ Sharing (UNOS) guidelines for a Lung Allocation Score greater than zero.

Lung-Specific Guidelines
Bilateral lung transplantation is typically required when chronic lung infection and disease is present (i.e., associated with cystic fibrosis 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.

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 disease.

Related Policies

- Heart/Lung Transplant

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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.

Rationale

Background
Solid organ transplantation offers a treatment option for patients with different types of endstage 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 2020, 39,036 transplants were performed in the United States procured from more than 12,500 deceased donors and 5,700 living donors.[2] Lung transplants were the fourth most common procedure with 2,539 transplants performed from both deceased and living donors in 20 20. End-stage lung disease may derive from different etiologies. The most common indications for lung transplantation are chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, a_1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. 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. Lung or lobar lung transplantation is an option for patients with end-stage lung disease 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.[3] A score may range between 0 and 100 and incorporates predicted survival after transplantation and predicted survival on the waiting list; the Lung Allocation Score takes into consideration the patient's disease and clinical parameters. The waiting list incorporates the Lung Allocation Score, 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

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 US Public Health Service guideline also allows for transplantations in HIV-positive recipients with proper screenings and effective regimens for HIV infections.[5]

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.[6] 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.[7] 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.[8] 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 (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 Lung Allocation Scores 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*).[9]

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.[10] 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.

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

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

Lung Transplantation for End-Stage Pulmonary Disease
Clinical Context and Therapy Purpose
The purpose of lung transplantation in patients who have end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing therapies. The question addressed in this evidence review is: Does lung transplantation improve the net health outcome in patients with end-stage pulmonary disease?

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

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 post-surgery to 30 days post-transplantation; lifelong follow-up (10 years or more given current survival data) is necessary due to 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.

Review of Evidence
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 Registry.[11] 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 in comparison to the pediatric subgroup (73%; p=.006) and adults 25 to 34 years old (75%; p<.001) and 35 to 49 years old (71%; p<.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%; p<.001) and 20- to 24-year old year patients (66%; p<.001). The registry study was biased toward the 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 International Society for Heart and Lung Transplantation registries contained data from 49,453 adult recipients who received lung transplantation (including lung retransplantation) through June 30, 2015, at 134 transplant centers.[10] 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 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%); however 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 International Society for Heart and Lung Transplantation registry contained a total of 2,229 pediatric lung transplants.[12] 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.[13] A retrospective review was conducted of 3,327 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% CI, 4.3 to 6.7 years) than the single-lung group at 3.8 years (95% CI, 3.6 to 4.1 years; p<.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 and single- versus double-lung transplant in 8778 patients (8050 had a Lung Allocation Score <75 vs. 728 had a Lung Allocation Score ≥75).[14] A significant decrease in survival was seen in single-lung transplant patients with a high Lung Allocation Score compared with double-lung transplant patients with a high Lung Allocation Score (p<.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).[15] 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 Lung Allocation Score on lung transplantation by comparing statistics for the period before and after its implementation in 2005.[16] 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 the implementation of the Lung Allocation Score system, from approximately 500 per 5,000 patients to 300 per 5,000 patients. However, it is expected that the implementation of the Lung Allocation Score affected patient characteristics of transplant applicants. One-year survival posttransplantation did not improve after implementation of the Lung Allocation Score 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 Lung Allocation Score and mortality in 537 adults wait-listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010.[17] Patients on the waitlist who had a higher Lung Allocation Score had a higher mortality rate (p<.001). In the highest quartile of Lung Allocation Score (range, 47-95), within 1 year of listing, there was a 75% mortality rate. A higher Lung Allocation Score was also associated with early posttransplant survival (p=.05) but not late posttransplant survival (p=.4). When other predictive factors of early mortality were taken into account, pretransplant Lung Allocation Score was not independently related to posttransplant mortality (p=.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 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, 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 Therapy Purpose
The purpose of lobar lung transplantation in patients who have end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does lobar lung transplantation improve the net health outcome in patients with end-stage pulmonary disease?

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

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 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.[18,] Procedures in the U.S. 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 the 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 post-surgery to 30 days post-transplantation; lifelong follow-up (10 years or more given current survival data) is necessary due to 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.

Review of Evidence

Systematic Reviews

Eberlein et al (2017) reported a systematic review of studies on lobar lung transplantation from deceased donors.[19] 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=2,777) (relative risk, 1.85; 95% CI, 1.52 to 2.25; p<.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 U.S.[20] 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 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 a retrospective study comparing 42 living-donor lobar lung transplants with 37 cadaveric lung transplants.[21] 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=.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.[22] 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 was lower in patients experiencing severe graft dysfunction (54.5%) than in the other patients (66.5%). The authors postulated that this suggested size mismatching in patients with severe graft dysfunction.

Slama et al (2014) compared 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.[23] Survival rates in the lobar lung transplant group at 1 and 5 years were 65.1% and 54.9% versus 84.8% and 65.1% in the whole-lung and downsized by wedge resection group (p<.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=.168).

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

There is 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 a Lung Transplant

Clinical Context and Therapy Purpose

The purpose of lung retransplantation in patients 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 question addressed in this evidence review is: Does lung or lobar retransplantation improve the net health outcome in patients with a failed prior lung or lobar transplant?

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

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 post-surgery to 30 days post-transplantation; 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.

Review of Evidence
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.[4,24,25.]

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.[26.] Patients receiving retransplantation had significantly higher use of extracorporeal membrane oxygenation support for severe primary graft dysfunction (p=.019) and underwent cardiopulmonary bypass and re-exploration for bleeding (p=.019) more frequently than patients receiving primary transplantation (p=.029). At 1-year follow-up, 89.7% of primary transplant patients were living compared with 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 Lung Allocation Score 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=.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) has reported data on lung transplants performed between 2008 and 2015.[27] 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 International Society for Heart and Lung Transplantation Registry contained data on 2273 retransplantation patients performed through June 2015 (4.4% of lung transplantations).[10] 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.

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 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 with a prior lung or lobar transplant who meet criteria for a lung transplant and 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.

Supplemental Information

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

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.[33] Key findings and recommendations are summarized in Table 6.

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

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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Society for Heart and Lung Transplantation

Initial Transplant

In 2006, the International Society for Heart and Lung Transplantation published consensus-based guidelines on the selection of lung transplant candidates.[28,] The guidelines stated that:

- "Lung transplantation is now a generally accepted therapy for the management of a wide range of severe lung disorders, with evidence supporting the quality of life and survival benefit for lung transplant recipients. However, the number of donor organs available remains far fewer than the number of patients with end-stage lung disease who might potentially benefit from the procedure. It is of primary importance, therefore, to optimize the use of this resource, such that the selection of patients who receive a transplant represents those with realistic prospects of favorable long-term outcomes..."

In 2014, these recommendations were updated for pulmonary vascular disease.[29,] The Society recommended including a transplant list for patients with New York Heart Association class III or IV disease, despite 3 months or more of combination therapy. Additional clinical indications included a cardiac index of less than 2 L/min/m^2, a mean right atrial pressure of greater than 15 mmHg, and a 6-minute walk distance of fewer than 350 meters. Also recommended for transplant listing were patients with significant hemoptysis, pericardial effusion, or signs of progressive right heart failure. Other common indications for lung transplant include interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, and chronic obstructive pulmonary disease.

Retransplant

The 2014 guideline update briefly addressed lung retransplantation, with the consensus statement noting that "criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation."[29,]

American Thoracic Society et al

Evidence-based recommendations from the American Thoracic Society and 3 international cardiac societies were published in 2011 for the diagnosis and management of patients with idiopathic fibrosis.[30] For appropriately selected patients with idiopathic pulmonary fibrosis, the international guideline panel recommended lung transplantation (strong recommendation, low-quality evidence)

In 2014, the American Thoracic Society published guidelines on the management of bronchiolitis obliterans syndrome in lung transplant recipients in conjunction with the International Society for Heart and Lung Transplantation and the European Respiratory Society.[31] 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Lung transplantation is covered under Medicare when performed in a facility approved by Medicare as meeting institutional coverage criteria.[32] The Centers for Medicare & Medicaid Services have stated that, under certain limited cases, exceptions to the facility-related criteria may be warranted if there is justification and the facility ensures safety and efficacy objectives.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00905463	Analysis of Prognosis and Patients Reported Outcomes in Lung Transplant Candidates	272	Mar 2022
NCT00177918	Prospective Evaluations of Infectious Complication in Lung Transplant Recipients	600	Dec 2025

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- Referring physician history and physical
- Pulmonary consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiological reports including:
  - Chest x-ray (CXR)
  - Chest CT
- Colonoscopy report if > 50 years of age
- Cardiology procedures and respiratory function reports:
  - EKG
  - Cardiac echocardiogram, stress test, and cardiac catheterization (if needed)
  - Pulmonary function tests (PFTs)
  - 6 minute walk study
- Laboratory reports

Coding

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

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
HCPCS	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor

Policy History

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

Effective Date	Action
06/01/1988	Policy adopted
06/01/1991	Policy Revision
05/17/2001	Policy clarification
06/01/2001	Policy Review Policy statement unchanged.
01/07/2011	Policy title change from Single and Double Lung Transplantation Policy revision with position change
03/28/2014	Policy revision with position change
04/30/2015	Policy revision without position change
04/01/2017	Policy revision without position change
10/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Literature review updated.
10/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Lung and Lobar Lung Transplant 7.03.07 **Policy Statement:** Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy (see Policy Guidelines). A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease (see Policy Guidelines). Lung or lobar lung retransplantation after a failed lung or lobar lung transplant may be considered **medically necessary** in patients who meet criteria for lung transplantation. Lung or lobar lung transplantation is considered **investigational** in all other situations. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.	**Lung and Lobar Lung Transplant 7.03.07** **Policy Statement:** Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy (see Policy Guidelines). A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease (see Policy Guidelines). Lung or lobar lung retransplantation after a failed lung or lobar lung transplant may be considered **medically necessary** in patients who meet criteria for lung transplantation. Lung or lobar lung transplantation is considered **investigational** in all other situations. The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.