



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Lung and Lobar Lung Transplant

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for lung and lobar lung transplant when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy, including but not limited to one of the conditions listed below.

A lobar lung transplant from a living or cadaver donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease including but not limited to one of the conditions listed below.

	CODES
Alpha-1 antitrypsin deficiency	E88.01
Bilateral bronchiectasis	J47.0-J47.1; Q33.4 for congenital bronchiectasis
Bronchiolitis obliterans	J42
Bronchopulmonary dysplasia	P27.1
Chronic obstructive pulmonary disease	J44.0-J44.9
Cystic fibrosis (both lungs to be transplanted)	E84.0
Eisenmenger's syndrome	I27.83
Emphysema	J43.0-J43.9
Eosinophilic granuloma	C96.6
Idiopathic/Interstitial pulmonary fibrosis	J84.10; J84.112
Postinflammatory pulmonary fibrosis	J84.10
Lymphangiomyomatosis	J84.81
Primary pulmonary hypertension	I27.0
Pulmonary hypertension due to cardiac disease	I27.21; I27.22
Recurrent pulmonary embolism	I27.82; I26.01-I26.99
Sarcoidosis	D86.0; D86.2; D86.9
Scleroderma	M34.0-M34.9

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.

When Policy Topic is not covered

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

Considerations

Lung and lobar lung transplants should be considered for coverage under the Transplant Benefit.

General

Potential contraindications subject to the judgment of the transplant center:

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

Policy-specific

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

*Some patients may be candidates for combined heart-lung transplantation. Patients must meet UNOS guidelines for lung allocation score (LAS) greater than zero.

Lung Specific

Bilateral lung transplantation is typically required when chronic lung infection 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.

Transplant Benefit

Lung transplants should be considered for coverage under the Transplant benefit.

Items covered under the scope of the Human Organ Transplant (HOT) benefit need to be considered.

Typically, the following are covered under the HOT benefit:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis;
- hospital room, board, and general nursing in semiprivate rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ;
- diagnostic services;
- drugs that require a prescription by federal law.

Expenses incurred in the evaluation and procurement of organs and tissues are benefits when billed by the hospital. Included in these expenses may be specific charges for participation with registries for organ procurement, operating rooms, supplies, use of hospital equipment, and transportation of the tissue or organ to be evaluated.

Administration of products with a specific transplant benefit needs to be defined as to:

- when the benefit begins (at the time of admission for the transplant or once the patient is determined eligible for a transplant, which may include tests or office visits prior to transplant);
- when the benefit ends (at the time of discharge from the hospital or at the end of required followup, including the immunosuppressive drugs administered on an outpatient basis).

Coverage usually is not provided for:

- HOT services for which the cost is covered/funded by governmental, foundational, or charitable grants;
- organs sold rather than donated to the recipient;
- an artificial organ.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With end-stage pulmonary disease 	Interventions of interest are: <ul style="list-style-type: none"> • Lung transplant 	Comparators of interest are: <ul style="list-style-type: none"> • Medical management 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity

<p>Individuals:</p> <ul style="list-style-type: none"> • With end-stage pulmonary disease 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Lobar lung transplant 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical management 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity
<p>Individuals:</p> <ul style="list-style-type: none"> • With a prior lung or lobar transplant who meet criteria for a lung transplant 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Lung or lobar retransplant 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical management 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity

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.

For individuals who have end-stage pulmonary disease who receive lung transplantation, the evidence includes case series and registry studies. Relevant outcomes are overall survival, 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 patients 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 a meaningful improvement in the net health outcome.

For individuals who have end-stage pulmonary disease who receive lobar lung transplantation, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, 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 the available published studies ranging from 50% to 100%. The evidence is sufficient to determine that the technology results in a meaningful 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 overall survival, change in disease status, 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 without retransplantation of patients who have exhausted other treatments, evidence of a moderate level of posttransplant

survival is sufficient in this patient population. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Background

End-stage lung disease may be the consequence of a number of different etiologies. The most common indications for lung transplantation are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension (IPAH).

Prior to the 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 end-stage lung disease despite these measures.

A lung transplant refers to single-lung or double-lung replacement. In a single-lung transplant, only one 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 one lobe obtained from each of two donors (e.g., mother and father) in cases for which bilateral transplantation is required. There are also cases of cadaver lobe transplants. Combined lung-pancreatic islet cell transplant is being studied for patients with cystic fibrosis. (1)

Since 2005, potential recipients have been ranked according to the Lung Allocation Score (LAS). (2) Patients 12 years of age and older receive a score between 1 and 100 based on predicted survival after transplantation reduced by predicted survival on the waiting list; the LAS takes into consideration the patient's disease and clinical parameters. In 2010, a simple priority system was implemented for children under the age of 12. Under this system, children under 12 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 (LRB) has authority to adjust scores on appeal for adults and children.

Rationale

Literature Review

This evidence review was created in July 1996 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 21, 2018.

Evidence reviews assess the 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: the relevance and the 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 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 Test 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 PICOTS were used to select literature to inform this review.

Patients

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

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.

Outcomes

The general outcomes of interest are overall survival and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for detailed discussion.

Timing

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.

Setting

Lung retransplantation is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

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.² 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 year 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 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.³ 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 (non-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 International Society for Heart and Lung Transplantation registry contained a total of 2229 pediatric lung transplants.⁴ 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.⁵ A retrospective review was conducted of 3327 patients with data in the United Network for Organ Sharing 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 the single-lung group at 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 overall survival 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- vs double-lung transplant in 8778 patients (8050 had a LAS < 75 vs 728 had a LAS ≥ 75).⁶ 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, even though operative morbidity was higher ($p < 0.001$).

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 2005.⁷ 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 wait-listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010.⁸ 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 a 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 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 PICOTS were used to select literature to inform this review.

Patients

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

Date (2011) stated that, as of 2011, approximately 400 living-donor lobar lung transplants had been performed worldwide.⁹ Procedures in the United States decreased after 2005 due to changes in the lung allocation system. Date (2011) 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.

Interventions

The therapy being considered is a lobar lung transplant.

Comparators

The following practice is currently being used to make decisions about end-stage pulmonary disease: medical management.

Outcomes

The general outcomes of interest are overall survival and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for detailed discussion.

Timing

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.

Setting

Lung retransplantation is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

Systematic Reviews

Eberlein et al (2017) reported on a systematic review of studies on lobar lung transplantation from deceased donors.¹⁰ 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 and one in Australia and one 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; $p < 0.001$; $I^2 = 0\%$).

Case Series

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.¹¹ 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 actuarial 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.¹² 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.¹³ 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 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.¹⁴ Survival rates in the lobar lung transplant group at 1 and 5 years were 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 a lung transplant

Clinical Context and Test 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 PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals receiving a lung retransplant after failing a prior lung or lobar transplant and who would be eligible 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.

Outcomes

The general outcomes of interest are overall survival and treatment-related adverse events (eg, immunosuppression, graft failure, surgical complications, infections, cardiovascular complications, malignancies). See the Potential Contraindications section for detailed discussion.

Timing

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.

Setting

Lung retransplantation is provided in a hospital setting with specialized staff and equipped to perform the surgical procedure and postsurgical intensive care.

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.¹⁵⁻¹⁷

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.¹⁸ 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, 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 has reported data on lung transplants performed between 2008 and 2015.¹⁹ 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 87.9% (95% CI, 87.2% to 88.7%) after a primary lung transplant and 76% (95% CI, 70.9% to 80.2%) after a repeat transplant. Five-year patient survival rates were 55.9% (54.7% to 57.2%) after a primary lung transplant and 33.8% (28.5 to 39.1%) 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).³ 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.

Potential Contraindications (Applies to all Indications above)

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.¹⁵ Skin cancer occurred most frequently, and lymphoproliferative disorders were the malignancies most associated with morbidity posttransplantation.

HIV Infection

Current Organ Procurement and Transplantation Network policy permits HIV-positive transplant candidates.²⁰

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.²¹ These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- Cluster of Differentiation 4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

Other Infections

Infection with *Burkholderia cenocepacia* is associated with increased mortality in some transplant centers. A factor that may be considered when evaluating overall risk for transplant survival.²² 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 assessing hazard ratios were applied to 1026 lung transplant candidates and 528

transplant recipients.²³ 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, 2.52; 95% CI, 1.04 to 6.12; p=0.04). Transplant recipients infected with *Burkholderia gladioli* (n=14) also had significantly greater posttransplant mortality than uninfected patients (hazard ratio, 2.23; 95% CI, 1.05 to 4.74; p=0.04). 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*).²⁴

An analysis of international registry data by Yusen et al (2016) found that non-CMV infection is a major cause of mortality within 30 days of a lung transplant in adults.³ 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.

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, 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 a meaningful 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 overall survival, 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 a meaningful 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 overall survival, change in disease status, 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 a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

International Society for Heart and Lung Transplantation

Initial Transplant

The International Society for Heart and Lung Transplantation (2006) published consensus-based guidelines on selection of lung transplant candidates.²⁵ 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 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.²⁶ 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/m², a mean right atrial pressure of greater than 15 mm Hg, and a 6-minute walk distance of fewer than 350 meters. Also, recommended for transplant listing were 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

Lung retransplantation was addressed briefly, with the consensus statement noting that “criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation.”

American Thoracic Society et al

Evidence-based recommendations from the American Thoracic Society and 3 international cardiac societies were published in 2011.²⁷ For appropriately selected patients with idiopathic pulmonary fibrosis, the group et al recommended lung transplantation (strong recommendation, low-quality evidence)

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.²⁸ 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 unpublished trials that might influence this review are listed in Table 1.

Table 1. 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.

References

1. Organ Procurement and Transplantation Network (OPTN). Policy 10: Allocation of Lungs. 2018; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed July 20, 2018.
2. Paraskeva MA, Edwards LB, Levvey B, et al. Outcomes of adolescent recipients after lung transplantation: An analysis of the International Society for Heart and Lung Transplantation Registry. *J Heart Lung Transplant*. Feb 17 2018;37(3):323-331. PMID 28320631
3. Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. Oct 2016;35(10):1170-1184. PMID 27772669
4. Goldfarb SB, Levvey BJ, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Lung and Heart-Lung Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. Oct 2016;35(10):1196-1205. PMID 27772671
5. Thabut G, Christie JD, Kremers WK, et al. Survival differences following lung transplantation among US transplant centers. *JAMA*. Jul 07 2010;304(1):53-60. PMID 20606149
6. Black MC, Trivedi J, Schumer EM, et al. Double lung transplants have significantly improved survival compared with single lung transplants in high lung allocation score patients. *Ann Thorac Surg*. Nov 2014;98(5):1737-1741. PMID 25110334
7. Yusen RD, Shearon TH, Qian Y, et al. Lung transplantation in the United States, 1999-2008. *Am J Transplant*. Apr 2010;10(4 Pt 2):1047-1068. PMID 20420652
8. Shafii AE, Mason DP, Brown CR, et al. Too high for transplantation? Single-center analysis of the lung allocation score. *Ann Thorac Surg*. Nov 2014;98(5):1730-1736. PMID 25218678

9. Date H. Update on living-donor lobar lung transplantation. *Curr Opin Organ Transplant*. Oct 2011;16(5):453-457. PMID 21836512
10. Eberlein M, Reed RM, Chahla M, et al. Lobar lung transplantation from deceased donors: A systematic review. *World J Transplant*. Feb 24 2017;7(1):70-80. PMID 28280698
11. Barr ML, Schenkel FA, Bowdish ME, et al. Living donor lobar lung transplantation: current status and future directions. *Transplant Proc*. Nov 2005;37(9):3983-3986. PMID 16386604
12. Date H, Sato M, Aoyama A, et al. Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients. *Eur J Cardiothorac Surg*. Jun 2015;47(6):967-972; discussion 972-963. PMID 25228745
13. Date H, Shiraishi T, Sugimoto S, et al. Outcome of living-donor lobar lung transplantation using a single donor. *J Thorac Cardiovasc Surg*. Sep 2012;144(3):710-715. PMID 22717276
14. Slama A, Ghanim B, Klikovits T, et al. Lobar lung transplantation--is it comparable with standard lung transplantation? *Transpl Int*. Sep 2014;27(9):909-916. PMID 24810771
15. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report--2013; focus theme: age. *J Heart Lung Transplant*. Oct 2013;32(10):965-978. PMID 24054805
16. Kilic A, Beaty CA, Merlo CA, et al. Functional status is highly predictive of outcomes after redo lung transplantation: an analysis of 390 cases in the modern era. *Ann Thorac Surg*. Nov 2013;96(5):1804-1811. PMID 23968759
17. Kawut SM. Lung retransplantation. *Clin Chest Med*. Jun 2011;32(2):367-377. PMID 21511096
18. Biswas Roy S, Panchanathan R, Walia R, et al. Lung retransplantation for chronic rejection: a single-center experience. *Ann Thorac Surg*. Nov 1 2018;105(1):221-227. PMID 29100649
19. Organ Procurement and Transplantation Network (OPTN). National Data. n.d.; <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>. Accessed July 20, 2018.
20. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2018; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed July 20, 2018.
21. Working Party of the British Transplantation Society. Kidney and Pancreas Transplantation in Patients with HIV. Second Edition (Revised). British Transplantation Society Guidelines. Macclesfield, UK: British Transplantation Society; 2017.
22. Alexander BD, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex. *Am J Transplant*. May 2008;8(5):1025-1030. PMID 18318775
23. Murray S, Charbeneau J, Marshall BC, et al. Impact of burkholderia infection on lung transplantation in cystic fibrosis. *Am J Respir Crit Care Med*. Aug 15 2008;178(4):363-371. PMID 18535253
24. Boussaud V, Guillemain R, Grenet D, et al. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with *Burkholderia cepacia* complex: results from two French centres. *Thorax*. Aug 2008;63(8):732-737. PMID 18408050
25. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. Jul 2006;25(7):745-755. PMID 16818116
26. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* Jun 26 2015 34(1):1-15. PMID 25085497
27. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. Mar 15 2011;183(6):788-824. PMID 21471066
28. Centers for Medicare & Medicaid. Medicare-approved transplant programs: Lung-only. 2018; <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandComplianc/downloads/ApprovedTransplantPrograms.pdf>. Accessed July 20, 2018.

Billing Coding/Physician Documentation Information

- 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
- S2060** Lobar lung transplantation
- S2061** Donor lobectomy (lung) for transplantation, living donor

ICD-10 Codes

- A15.0** Tuberculosis of lung (includes tuberculous fibrosis of lung)
- C96.6** Unifocal Langerhans-cell histiocytosis (includes eosinophilic granuloma of lung)
- D48.1** Neoplasm of uncertain behavior of connective and other soft tissue (includes lymphangiomyomatosis)
- D86.0;** Sarcoidosis of lung and sarcoidosis of lung with sarcoidosis of lymph
D86.2 nodes, respectively
- E84.0-** Cystic fibrosis code range
E84.9
- E88.01** Alpha-1-antitrypsin deficiency
- I26.01-** Pulmonary embolism, acute code range
I26.99
- I27.0** Primary pulmonary hypertension
- I27.2** Other secondary pulmonary hypertension (includes pulmonary hypertension due to cardiac disease)
- I27.82** Chronic pulmonary embolism
- I27.89** Other specified pulmonary heart diseases (includes Eisenmenger's syndrome)
- J42** Unspecified chronic bronchitis (includes bronchiolitis obliterans)
- J43.0-** Emphysema code range
J43.9
- J44.9** Chronic obstructive pulmonary disease, unspecified
- J47.0-** Bronchiectasis, acute codes
J47.1
- J60-** Lung diseases due to external agents code range (includes
J70.9 pneumoconiosis and pulmonary fibrosis due to fumes and vapors)

- J84.1** Other interstitial pulmonary diseases with fibrosis
- M34.0-** Systemic sclerosis [scleroderma] (especially M34.81 – Systemic
- M34.9** sclerosis with lung involvement)
- P27.0-** Chronic respiratory disease originating in the perinatal period (includes
- P27.9** bronchopulmonary dysplasia)
- Q33.0-** Congenital malformations of lung code range (includes congenital
- Q33.9** bronchiectasis)

Additional Policy Key Words

N/A

Policy Implementation/Update Information

- 11/1/01 New policy. Added to the Surgery / Transplant sections.
- 11/1/02 No policy statement changes.
- 11/1/03 Policy statement revised to remove pulmonary fibrosis as a covered indications. New codes added.
- 11/1/04 No policy statement changes.
- 11/1/05 No policy statement changes.
- 4/1/06 Added general criteria to the considerations section.
- 11/1/06 No policy statement changes.
- 11/1/07 No policy statement changes.
- 11/1/08 No policy statement changes.
- 11/1/09 No policy statement changes.
- 11/1/10 No policy statement changes.
- 11/1/11 Policy statement and Considerations reorganized by moving detail from Considerations to policy statements.
- 11/1/12 Absolute contraindications moved to Policy Guidelines and combined with relative complications; wording consistent with other transplant policies.
- 11/1/13 In lobar lung statement, "children and adolescents" replaced with "carefully selected patients" and coding correction: lymphangiomyomatosis corrected to 516.4
- 11/1/14 Policy statement added indicating lung or lobar lung retransplantation may be medically necessary. Policy statement added that lung or lobar lung transplantation is considered investigational in all other situations (previously considered not medically necessary)
- 11/1/15 No policy statement changes.
- 11/1/16 No policy statement changes.
- 11/1/17 ICD-10 codes for covered indications added to policy statement.
- 11/1/18 No policy statement changes.

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