Lung transplants

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Policy contains: Heart-lung transplant; lung transplant, pulmonary transplant.

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Coverage policy

Lung transplantation is clinically proven and, therefore, medically necessary in cases of end-stage lung disease, when all of the following general selection criteria are met:

- A > 50% risk of death due to lung disease within two years if lung transplantation is not performed.

- A > 80% likelihood of five-year post-transplant survival from a general medical perspective provided there is adequate graft function.

- No absolute contraindications (See limitations) (Leard, 2021).

Heart-lung transplantation is clinically proven and, therefore, medically necessary for members with intrinsic lung disease or severe pulmonary artery hypertension and severe structural or cardiac dysfunction unlikely to improve with normalization of pulmonary pressures (Bermudez, 2021; Leard, 2021).

Limitations

The transplanting institution may require additional general selection criteria or disease-specific criteria for medical necessity determination.

CCP.1202

Absolute contradictions to lung transplantation include (Leard, 2021):

- Lack of patient willingness or acceptance of transplant.

- Malignancy with high risk of recurrence or death related to cancer.

- Glomerular filtration rate < 40 mL/min/1.73m^2 unless being considered for multi-organ transplant.

- Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia).

- Stroke within 30 days.

- Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant.

- Acute liver failure.

- Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery.

- Septic shock.

- Active extrapulmonary or disseminated infection.

- Active tuberculosis infection.

- Human immunodeficiency virus infection with detectable viral load.

- Limited functional status (e.g., non-ambulatory) with poor potential for post-transplant rehabilitation.

- Progressive cognitive impairment.

- Repeated episodes of non-adherence without evidence of improvement (Note: This is not an absolute contraindication for pediatric members. Ongoing assessment of non-adherence should occur as they progress through different developmental stages.)

- Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or intravenous drug use.

- Other severe uncontrolled medical conditions expected to limit survival after transplant.

Relative contraindications are listed in the Appendix.

Alternative covered services

Guideline-directed maximum medical management of underlying disease.

Background

Lung transplantation or pulmonary transplantation is a surgical procedure in which a patient's diseased lung(s) are partially or totally replaced by healthy lungs from a donor. Donor lungs can be retrieved from a living donor or a deceased donor. A living donor can only donate one lung lobe. With some lung diseases, a recipient may only need to receive a single lung. With other lung diseases, such as cystic fibrosis, it is imperative that a recipient receive two lungs. While lung transplants carry certain associated risks, such as life-threatening complications and infections, especially in the first year after surgery, they can also extend life expectancy and enhance the quality of life for patients with end-stage pulmonary disease (U.S. National Heart, Lung, and Blood Institute, 2022).

The number of Americans undergoing a lung transplant was 2,562 in 2018, an increase of 31% from five years earlier (Valapour, 2020). As of August 23, 2022, 1,011 registered Americans were awaiting a lung transplant, plus an additional 31 for heart/lung transplants (U.S. Health Services Resource Administration, 2022b).

The United Network for Organ Sharing maintains a national U.S. registry for organ matching. Its purposes are to operate and monitor a system for allocation of organs donated for transplantation, maintain a waiting list of potential recipients, and match potential recipients with organ donors according to established medical criteria (U.S. Health Services Resource Administration, 2022a). Over time, the system for lung allocation has evolved to increase the availability of organs for transplant and their success through better donor matching.

The expanding waiting list for lung transplants prompted a 2005 change in the United States to assign priority to candidates based on a greater predicated survival benefit from transplantation and waitlist urgency, calculated as the Lung Allocation Score, instead of waiting time. These changes impacted patients aged 12 years and older. Subsequent changes included exceptions for younger patients and geographic distribution. On December 6, 2021, the Continuous Distribution system was approved to replace the Lung Allocation Scoring system and is anticipated to take effect early in 2023 (Benvenuto, 2021).

A deceased donor, also known as cadaveric donor, is the most common donor source used for lung transplantation. Use of a live donor as a source for lung transplantation was initiated in 1993 due to the higher demand than supply for patients waiting for lung transplantation. Deceased donor transplantation is preferred, and the proportion of transplants from live donors is falling due to the change in allocating lungs from deceased donors (Date, 2017). In 2022, there were 1,617 deceased donor lungs and no living donor lungs transplanted in U.S. recipients (U.S. Health Services Resource Administration, 2022c).

Findings

A number of guidelines affecting lung transplants have been published. The definitive work addressing criteria on selecting lung transplant patients, and contraindications against performing surgery, was written by the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation, which published versions in 1998, 2006, and 2015 (Weill, 2015, 2018). The same group of international experts that wrote the 2006 guidelines recently developed a consensus opinion on timing of referral and listing for lung transplantation. The panel included lung allocation scores and expanded indications for and contraindications to lung transplant (Weill, 2015).

In 2021, the International Society for Heart and Lung Transplantation updated its consensus guidance on selection of lung transplant candidates (Leard, 2021). This guidance differs from prior versions by creating categories for risk factors, considering the candidate as a whole and the risk tolerance and expertise of transplant centers. They stressed optimizing all potentially modifiable risk factors prior to lung transplant to improve long-term outcomes.

Two consensus papers from the International Society for Heart and Lung Transplantation provide additional guidance on cardiothoracic transplantation in patients with connective tissue disease (Bermudez, 2021; Crespo, 2021). Patients with connective tissue disease and advanced lung disease are medically complex and often regarded as poor surgical risks, but research demonstrates comparable survival and allograft dysfunction outcomes between carefully selected patients with connective tissue disease and patients undergoing lung transplantation for other indications.

The Society defined the disease states considered connective tissue diseases and described their unique extrapulmonary manifestations that require special management before, during, and after lung or heart-lung transplantation. They recommend considering lung transplantation in patients with connective tissue disease and advanced lung disease whose clinical status has progressively declined despite maximal medical therapy.

Finally, they listed absolute and relative contraindications for several connective tissue diseases to improve risk stratification and selection of candidates for lung transplantation based on consensus, recognizing the paucity of evidence on specific predictors of prognosis after cardiothoracic transplantation in this population (Crespo, 2021).

Bilateral lung transplantation is generally preferred over single lung transplantation for its theoretical survival and functional advantages over time, but single lung transplantation can be offered in the absence of secondary pulmonary hypertension when the clinical condition requires a shorter time on the waiting list. Heart-lung transplantation is reserved for patients with intrinsic lung disease or severe pulmonary artery hypertension and severe structural or cardiac dysfunction unlikely to improve with normalization of pulmonary pressures. Patients with moderate/severe left ventricular dysfunction or profound right ventricular dilation and dysfunction on high doses of inotropic support should be considered at high risk for lung transplantation alone (Bermudez, 2021).

Lung re-transplants are now being performed in increasing numbers. The median survival rate for those with re-transplants is lower than that of transplants (2.6 years versus 5.6 years), and the five-year survival rate is lower as well, at 34.5% versus 53.3%. Lower survival was associated with single lung transplants ($P = .021$), transplantations done between 2009 and 2013 ($P = .041$), multiple retransplantations (P = .023), and recipients requiring pre-transplantation ventilator support. Careful selection of candidates for re-transplant is advised (Thomas, 2015).

A systematic review/meta-analysis of 54 studies of over 5,000 subjects determined that *B. cepacia complex* significantly increased the risk of mortality after lung transplantation. Other factors that did not affect mortality included *P. aeruginosa* colonization, forced expiratory volume in one second, pulmonary hypertension, body mass index, pancreatic insufficiency, and cystic fibrosis-related diabetes (Koutsokera, 2019).

One study of 8,778 lung transplant patients showed a significantly lower survival ($P < .001$) for single lung transplants. Nearly 92% of the patients had a lung allocation score over 75, representing patients more likely to benefit from a lung transplant (Black, 2014). A study of 580 Canadian lung transplant patients with cystic fibrosis found the five- and 10-year survival rates to be 67% and 50%, with significantly higher death rates for young and old patients, plus those with pancreatic sufficiency or *B. cepacia* infection (Stephenson, 2015).

A systematic review/meta-analysis of 30 studies (n = 4,092) concluded that bilateral (versus unilateral) lung transplants had better long-term survival, better postoperative lung function and less bronchiolitis obliterans syndrome. No differences existed for in-hospital mortality and postoperative complications (Yu, 2019).

Another systematic review of 5,601 lung transplant recipients showed a clear pattern of greater survival among double transplant patients, namely 57% versus 50% after five years, 35.3% versus 27.8% after 10 years, and 24% versus 13.9% after 15 years (Wilson-Smith, 2020).

An exception to the pattern of lower mortality for double lung transplants was found in a recent systematic review/meta-analysis of 16 studies (n = 17,872) that addressed outcomes of lung transplant patients with idiopathic pulmonary fibrosis. Those with single transplants had a lower post-treatment Forced Exhaled Volume 1% than those with double transplants ($P < .001$). Survival outcomes were not significantly different at $P < .39$, but after single transplants, significantly fewer deaths were due to primary graft dysfunction and more due to malignancy, both $P < .001$ (Li, 2020).

A systematic review of six studies (n = 1,305) showed enhancement in quality of life for lung transplant candidates in five of the studies, using the SF-36 questionnaire and the six-minute walk test (Hoffman, 2017). A large systematic review of 73 studies showed that quality of life after lung transplants is enhanced, especially during the first year after the procedure in physical health and functioning domains, and may improve more after bilateral transplants and heart and liver transplants than after single lung transplants (Singer, 2013).

Some studies have identified factors that increase the risk of mortality in lung transplant patients. A review of 13 cohort studies (n = 40,742) reviewed weight at surgery and found significantly elevated relative risks compared to normal weight for underweight (1.36), obese (1.90), and overweight plus underweight (1.36) (Upala, 2016). Clinical risk factors were identified in 13 studies (n = 10,042) of primary graft dysfunction; the main causes of elevated morbidity and mortality include female gender, African American race, idiopathic pulmonary fibrosis, sarcoidosis, primary pulmonary hypertension, elevated body mass index, and use of cardiopulmonary bypass (Liu, 2014).

Non-adherence to medical regimens after transplants was the focus of a systematic review. While non-adherence rates varied across risk factors, they were not a significant factor in mortality (Hu, 2017).

While lung transplantations from deceased donors remain a small minority of all such procedures, one meta-analysis of nine studies (n = 301) compared the mortality of patients who received a graft from deceased and live (conventional) donors. One year survival ranged from 50% to 100% among transplants from deceased donors, compared to 72% to 88% from live donors. One of the studies included nearly half of the transplants (138 of 301); one-year survival was significantly lower among deceased donor transplants (65.1% versus 84.1% for live transplants, $P < .001$) (Eberlein, 2017).

A comparison of lungs transplanted after > 12 hours ex-vivo preservation by splitting one cold ischemic time into two shorter ones (n = 97, average 875.7 minutes) with lungs transplanted with single waits < 12 hours (n = 809, average 400.8 minutes) was made. Median length of stay for both hospital and intensive-care unit lengths of stay did not differ significantly between groups (23.0 days versus 25.5 days, $P = .60$, and 4.0 days versus 4.0 days, $P = .53$). Primary graft dysfunction grade was not significantly different between the groups 72 hours after transplantation ($P = .85$), and there was no significant difference in survival ($P = .61$) (Yeung, 2017).

A systematic review of 13 studies found the ability of cardiopulmonary exercise testing to assist in making decisions in optimal timing for lung transplantation was limited due to problems of retrospective studies, patient selection, insufficient adjustment for confounders, and inadequate statistical analyses (Barratt, 2020).

An analysis of 65,265 lung transplant patients (median age 50.3 years) followed an average of 5.2 years found 17.3% died of cancer after surgery, a rate 4.28-fold higher than the general population. The most common types of malignancies causing death were lymphatic/hematological, integumentary, respiratory, digestive, and reproductive/urinary. Use of immunosuppressive therapy contributed in part to high rates. Authors state findings can improve individualized guidance for transplant patients (Ge, 2020).

In 2022, we added three updated consensus statements (Bermudez, 2021; Crespo, 2021; Leard, 2021), described earlier, and three new systematic reviews and meta-analyses. A meta-analysis of 72 eligible studies found no donor variables and only post-transplantation need for extra-corporeal membrane oxygenation that predicted one-year mortality with high certainty (hazard ratio 1.91, 95% confidence interval 1.79 to 2.04) in adult recipients. The authors stated lack of prognostic significance for some widely accepted factors (e.g., donor smoking, age) may relate to limits in the range of these variables found in selected donors and recipients (Foroutan, 2022).

A systematic review of 27 low-quality studies found 95% early survival rates in recipients with end-stage lung disease from COVID-19 infection. The data suggest bilateral lung transplantation is an effective option with reasonable short-term outcomes for these patients (Hawkins, 2021).

A systematic review of 51 prospective studies examined primary or secondary patient-important outcomes. The outcomes considered were mortality, pain, physical function, pulmonary, gastrointestinal, neuropsychological, cardiac, sleep or sexual symptoms, and quality of life. Mortality was the most frequently reported patient-important outcome (29.4% of studies), and quality of life was studied in 12%. The authors concluded outcomes other than mortality were insufficiently considered in lung transplantation studies.

We updated the references and modified the coverage based on new guidance and added an appendix of risk factor considerations from an updated consensus statement by the International Society for Heart and Lung Transplantation (Leard, 2021).

References

On August 29, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "lung transplantation (MeSH)," "heart lung transplantation (MeSH)," "lung transplantation," and "pulmonary arterial hypertension." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

10/2015: initial review date and clinical policy effective date: 1/2016

10/2016: Policy references updated.

10/2017: Policy references updated.

10/2018: Policy references updated.

10/2019: Policy references updated. Policy ID changed to CCP.1202.

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Appendix

Table 1. International Society for Heart and Lung Transplantation factors associated with high or substantially increased risk.

Members with these conditions may be considered in centers with expertise specific to the condition. There may be insufficient data supporting transplantation in members with these risk factors, or currently available data suggest substantially increased risk, and further research is needed to better inform future recommendations. Presence of more than one of these risk factors may be multiplicative in terms of increasing risk of adverse outcomes. Modifiable conditions should be optimized when possible.

1. Age > 70 years.
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant.
3. Reduced left ventricular ejection fraction < 40%.
4. Significant cerebrovascular disease.
5. Severe esophageal dysmotility.
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction.

7. Body mass index > 35 kg/m^2.

8. Body mass index < 16 kg/m^2.

9. Limited functional status with potential for post-transplant rehabilitation.

10. Psychiatric, psychological, or cognitive conditions with potential to interfere with medical adherence without sufficient support systems.

11. Unreliable support system or caregiving plan.

12. Lack of understanding of disease and / or transplant despite teaching.

13. *Mycobacterium abscessus* infection.

14. *Lomentospora prolificans* infection.

15. *Burkholderia cenocepacia or gladioli* infection.

16. Hepatitis B or C infection with detectable viral load and liver fibrosis.

17. Chest wall or spinal deformity expected to cause restriction after transplant.

18. Extracorporeal life support.

19. Retransplant < one year following initial lung transplant.

20. Retransplant for restrictive chronic lung allograft dysfunction.

21. Retransplant for antibody mediated rejection as etiology for chronic lung allograft dysfunction.

Source: Leard (2021).

Table 2. Additional International Society for Heart and Lung Transplantation risk factors.

These risk factors have unfavorable implications for short- or long-term outcomes after lung transplantation. While members with these risk factors may be acceptable for lung transplantation programs to consider, multiple risk factors together may increase risk for adverse lung transplant outcomes.

1. Age 65-70 years.

2. Glomerular filtration rate 40-60 mL/min/1.73m^2.

3. Mild to moderate coronary artery disease.

4. Severe coronary artery disease that can be revascularized via percutaneous coronary intervention prior to transplant.

5. Member with prior coronary artery bypass grafting.

6. Reduced left ventricular ejection fraction 40-50%.

7. Peripheral vascular disease.

8. Connective tissue diseases (scleroderma, lupus, inflammatory myopathies).

9. Severe gastroesophageal reflux disease.

10. Esophageal dysmotility.

11. Thrombocytopenia, leukopenia, or anemia with high likelihood of persistence after transplant.

12. Osteoporosis.

13. Body mass index 30-34.9 kg/m^2.

14. Body mass index 16-17 kg/m^2.

15. Frailty.

16. Hypoalbuminemia.

17. Poorly controlled diabetes.

18. Edible marijuana use.

19. *Scedosporium apiospermum* infection.

20. Human immunodeficiency virus infection with undetectable viral load.

21. Previous thoracic surgery.

22. Prior pleurodesis.

23. Mechanical ventilation.

24. Retransplant > one year for obstructive chronic lung allograft dysfunction.

Source: Leard (2021).