# Prior Authorization Review Panel
## MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<th>Plan: Aetna Better Health</th>
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**Type of Submission – Check all that apply:**
- ☒ New Policy*
- □ Revised Policy
- □ Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0598 Lung Transplantation**

Policy is new to Aetna Better Health of Pennsylvania.

<table>
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<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>[Signature]</td>
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Lung Transplantation

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers lung transplantation medically necessary for any of the following qualifying conditions for members who meet the transplanting institution's selection criteria. In the absence of an institution's selection criteria, members must meet both the general selection criteria (see section on General Selection Criteria) and any applicable disease-specific selection criteria (see Disease-Specific Selection Criteria accompanying the list of Qualifying Conditions below):

Qualifying Conditions for Lung Transplantation (not an all-inclusive list):

A. Alpha1-antitrypsin deficiency: Persons who meet the emphysema/alpha1-antitrypsin deficiency disease-specific selection criteria below

B. Broncho-pulmonary dysplasia

C. Congenital heart disease (Eisenmenger's defect or complex): Persons who meet the disease-specific criteria for Eisenmenger's below

Policy History

Last Review: 03/29/2018
Effective: 03/12/2002
Next Review: 06/27/2019

Review History

Definitions

Additional Information

Clinical Policy Bulletin
Notes

D. Cystic fibrosis: Persons who meet the disease-specific selection criteria for cystic fibrosis

E. Graft-versus-host disease or failed primary lung graft

F. Lymphangioleiomyomatosis (LAM) with end-stage pulmonary disease

G. Obstructive lung disease (e.g., bronchiectasis, bronchiolitis obliterans, chronic obstructive pulmonary disease (COPD), emphysema): For persons with pulmonary fibrosis, see the disease-specific selection criteria for pulmonary fibrosis below

H. Primary pulmonary hypertension: Persons who meet the disease-specific selection criteria for primary pulmonary hypertension.

I. Restrictive lung disease (e.g., allergic alveolitis, asbestosis, collagen vascular disease, desquamative interstitial fibrosis, eosinophilic granuloma, idiopathic pulmonary fibrosis, post-chemotherapy, sarcoidosis, and systemic sclerosis [scleroderma]): For persons with sarcoidosis, see the disease-specific selection criteria below.

Disease-Specific Selection Criteria:

A. Lung transplant for cystic fibrosis (CF) is considered medically necessary for persons who meet the general selection criteria for lung transplantation and exhibit at least 2 of the following signs and symptoms of clinical deterioration:

- Cycling intravenous antibiotic therapy
- Decreasing forced expiratory volume in 1 second (FEV1)
- Development of carbon dioxide (CO2) retention (pCO2 greater than 50 mm Hg)
- FEV1 less than 30 % predicted
- Increasing frequency of hospital admission
• Increasing severe exacerbation of CF – especially an episode requiring hospital admission
• Initiation of supplemental enteral feeding by percutaneous endoscopic gastrostomy or parenteral nutrition
• Non-invasive nocturnal mechanical ventilation
• Recurrent massive hemoptysis
• Worsening arterial-alveolar (A-a) gradient requiring increasing concentrations of inspired oxygen (FiO2)
• Recurrent pneumothorax.

B. Lung transplant for emphysema (including alpha 1-antitrypsin deficiency) is considered medically necessary for persons who meet the general criteria for lung transplantation and both of the following clinical criteria:

1. Hospitalizations for exacerbation of COPD associated with hypercapnia in the preceding year. Hypercapnia is defined as pCO2 greater than or equal to 50 mm Hg with hospitalizations and/or the following associated factors:

   a. Declining body mass index
   b. Increasing oxygen requirements
   c. Reduced serum albumin
   d. Presence of cor pulmonale (defined as clinical diagnosis by a physician or any 2 of the following:

      • Enlarged pulmonary arteries on chest X-ray
      • Mean pulmonary artery pressure by right heart catheterization of greater than 25 mm Hg at rest or 30 mm Hg with exercise
      • Pedal edema or jugular venous distention
      • Right ventricular hypertrophy or right atrial enlargement on EKG
2. BODE index of 7 or above (indicating 2 years or less survival) (see appendix).

C. Lung transplant for *Eisenmenger’s complex* is considered medically necessary for persons who meet the general criteria for lung transplantation and any of the following disease-specific criteria:

- Marked deterioration in functional capacity (New York Heart Association (NYHA) Class III)
- Pulmonary hypertension with mean pulmonary artery pressure by right heart catheterization greater than 25 mm Hg at rest or 30 mm Hg with exercise
- Signs of right ventricular failure -- progressive hepatomegaly, ascites.

D. Lung transplant for *pulmonary fibrosis* is considered medically necessary for persons who meet the general criteria for lung transplantation and any of the following disease-specific criteria:

- Diffusing capacity for carbon monoxide (DLCO) less than 60 % predicted
- Presence of cor pulmonale (indicative of severe pulmonary fibrosis) or pulmonary hypertension
- Total lung capacity (TLC) less than 70 % predicted.

E. Lung transplant for *pulmonary hypertension* is considered medically necessary for persons who meet the general criteria for lung transplantation plus any of the following criteria, and valvular disease has been excluded by echocardiography:

- Persons who are NYHA III, failing conventional vasodilators (calcium channel blockers or endothelin receptor antagonists)
- Persons who are NYHA III, and have initiated or being considered for initiation of parenteral or subcutaneous vasodilator therapy
- Pulmonary hypertension with mean pulmonary artery pressure by right heart catheterization of greater than 25 mm Hg at rest or 30 mm Hg with exercise, or pulmonary artery systolic pressure of 50 mm Hg or more defined by echocardiography or pulmonary angiography.

**Note:** NYHA Class III for heart failure is defined as follows:

Persons with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity (i.e., mild exertion) causes fatigue, palpitation, dyspnea, or anginal pain.

F. Lung transplant for **sarcoidosis** is considered medically necessary for persons who meet the general criteria for lung transplantation plus any of the following disease-specific criteria:

- DLCO less than 60 % predicted
- Presence of cor pulmonale (indicative of severe pulmonary fibrosis) or pulmonary hypertension
- Total lung capacity less than 70 % predicted.

**General Selection Criteria:**

The member must meet the transplanting institution's selection criteria. In the absence of an institution's selection criteria, all of the following selection criteria must be met, and none of the contraindications listed below should be present:
A. Absence of acute or chronic active infection (pulmonary or non-pulmonary) that is not adequately treated; and

B. Adequate cardiac status (e.g., no angiographic evidence of significant coronary artery disease, ejection fraction greater than 40%, no myocardial infarction in last 6 months, negative stress test). Persons with any cardiac symptoms may require heart catheterization to rule out significant heart disease; and

C. Adequate functional status. Under established guidelines, active rehabilitation is considered important to the success of transplantation. Mechanically-ventilated or otherwise immobile persons are considered poor candidates for transplantation; however, short-term mechanical ventilation (less than 2 weeks) or bridge to transplant with ambulatory ECMO does not, in itself, rule out candidacy for lung transplantation; and

D. Adequate liver and kidney function, defined as a bilirubin of less than 2.5 mg/dL and a creatinine clearance of greater than 50 ml/min/kg; and

E. Limited life expectancy of less than 2 years; and

F. No active alcohol or chemical dependency that interferes with compliance to a strict treatment regimen. Persons with a history of drug or alcohol abuse must be abstinent for at least 3 months before being considered an eligible transplant candidate; and

G. No uncontrolled and/or untreated psychiatric disorders that interfere with compliance to a strict treatment regimen; and

H. Absence of inadequately controlled HIV/AIDS infection, defined as

   - CD4 count greater than 200 cells/mm3 for greater than 6 months; and
   - HIV-1 RNA (viral load) undetectable; and
   - No other complications from AIDS, such as opportunistic infection (e.g., aspergillus,
tuberculosis, coccidioidomycosis, resistant fungal infections) or neoplasms (e.g., Kaposi's sarcoma, non-Hodgkin's lymphoma); and

• On stable antiviral therapy greater than 3 months.

Contraindications: Lung transplantation is considered experimental and investigational for persons with the following contraindications to lung transplant surgery because the safety and effectiveness of lung transplantation in persons with these contraindications has not been established:

• Malignancy involving the lung (primary or metastatic). Persons with a history of non-pulmonary cancer must be in remission before being considered a lung transplant candidate. Note: Lung transplantation is considered medically necessary in persons with bronchioloalveolar carcinoma who are good surgical candidates.

• Multi-system disease. Persons with potentially multi-system diseases such as systemic sclerosis (scleroderma), other collagen vascular diseases such as systemic lupus erythematosus, or sarcoidosis must be carefully evaluated to ensure that their disease is primarily confined to the lung. Persons with diabetes must be carefully evaluated to rule out significant diabetic complications such as nephropathy, neuropathy or retinopathy.

• Other effective medical treatments or surgical options are available.

• Presence of gastrointestinal disease (e.g., bleeding peptic ulcer, chronic hepatitis, diverticulitis).

• Refractory uncontrolled hypertension.

• Single-lung transplantation is contraindicated in persons with chronic pulmonary infections (e.g., bronchiectasis, chronic bronchitis, and cystic fibrosis)
• Smoking. Persons with a history of smoking must be abstinent for 6 months before being considered eligible for lung transplantation.

II. Aetna considers lobar (from living-related donors or cadaver donors) lung transplantation medically necessary for persons with end-stage pulmonary disease when selection criteria are met (see above).

III. Aetna considers lung xenotransplantation (e.g., porcine xenografts) experimental and investigational for any pulmonary conditions because of insufficient evidence in the peer-reviewed literature.

IV. Aetna considers prophylactic anti-reflux surgery to improve lung function and survival in lung transplant recipients without gastroesophageal reflux disease as experimental and investigational because of insufficient evidence in the peer-reviewed literature.

V. Aetna considers the TransMedics Organ Care System for preservation and transport of donor lungs experimental and investigational because its effectiveness has not been established.

VI. Aetna considers ex-vivo lung perfusion for lung transplantation experimental and investigational because the effectiveness of this approach has not been established.

See also CPB 0597 - Heart-Lung Transplantation (0597.html).

Background
Lung transplantation (LTX) has become a viable treatment option for carefully selected patients with end-stage pulmonary disease (ESPD). Single, double, and lobar-lung
transplantation have all been performed successfully for a variety of diseases. Single-LTX appears to be most effective for patients with end-stage pulmonary fibrosis, while double-LTX is most effective for patients with end-stage chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) in whom cardiac function has been preserved. Lobar-LTX (from living donors or cadaver donors) is usually reserved for children or adolescents who are appropriate candidates for LTX and will not survive waiting for cadaver lungs. Indications for LTX in pediatric patients include pulmonary vascular disease, bronchiolitis obliterans, broncho-pulmonary dysplasia, graft failure due to viral pneumonitis, and CF.

Chronic obstructive pulmonary disease and alpha 1-antitrypsin deficiency, the 2 principal causes of emphysema, are responsible for approximately 60% of all single-LTX performed. Other indications for single-LTX include primary pulmonary hypertension, Eisenmenger's syndrome, as well as a variety of interstitial lung diseases (e.g., interstitial pulmonary fibrosis).

Cystic fibrosis, emphysema, and alpha 1-antitrypsin deficiency are the most common indications for double-LTX, also known as bilateral single-LTX (sequential replacement of both lungs). Comparing patients who have undergone en bloc double-LTX to patients who have undergone bilateral single-LTX, studies have shown a better outcome for those who have undergone the bilateral sequential procedure. The latter is generally considered the procedure of choice for patients with any pulmonary disorder complicated by chronic airway infection, such as bronchiectasis, CF, and chronic bronchitis. The possibility of spillover of infection from the native lung to the allograft precludes single-LTX in such patients.

Although LTX offers acceptable prospects for 5-year survival, chronic rejection and donor shortage remain to be major problems. To address the problem of donor shortage, living-donor lobar-LTX has been performed with satisfactory...
intermediate survival and functional results. In lobar-LTX, a lobe of the donor's lung is excised, sized appropriately for the recipient, and transplanted. Common indications for living-donor bilateral lobar-LTX are CF and severe primary pulmonary hypertension. Based on available scientific evidence, there is no significant difference in effectiveness between living-donor lobar-LTX and cadaver lobar-LTX.

There are currently 2 surgical therapies for the treatment of end-stage emphysema: LTX and lung volume reduction surgery (LVRS) (see CPB 0160 - Lung Volume Reduction Surgery). Ideal candidates for LVRS are those with hyper-inflation, heterogeneous distribution of disease, forced expiratory volume in 1 second (FEV1) of more than 20 %, and normal PCO2. Patients with diffuse disease, low FEV1, hypercapnia, and associated pulmonary hypertension are directed toward transplantation. Moreover, LTX provides more satisfactory results than LVRS for patients with emphysema due to alpha1-antitrypsin deficiency. Combinations of LTX and LVRS, simultaneously or sequentially, are feasible but rarely indicated.

Complications of LTX include re-implantation response and airway complications. Rejection may occur in the hyper-acute, acute, or chronic settings and requires judicious management with immunosuppression. Infection and malignancy remain potential complications of the commitment to lifelong systemic immunosuppression. Obese (greater than 20 % of ideal body weight), cachectic (less than 80 % of ideal body weight), mechanically ventilated or otherwise immobile patients are considered poor candidates for transplantation.

Advanced bronchoalveolar carcinoma (BAC) carries a poor prognosis, with median survival of approximately 1 year. More extended survivals have been reported after lung transplantation for BAC; however, fewer than 50 patients have been reported. To compare outcomes of lung transplantation for advanced BAC, Ahmad, et al. (2012) studied this
population in a compulsory, prospectively maintained database. The United Network for Organ Sharing (UNOS) database was queried for patients undergoing lung transplant from 1987 to 2010 for the diagnosis of BAC or cancer. Pathology reports of explanted specimens were reviewed. The investigators reported that 29 patients underwent lung transplantation for BAC, representing 0.13% of the 21,553 lung transplants during the study period. BAC patients had better forced expiratory volume in 1 second percent predicted (60% vs 35%, p<0.0001) and received more double-lung transplants (79% vs 54%, p=0.006). Pure BAC was present in only 52% of the explants, whereas 41% had some degree of invasive tumor, and 7% had pure adenocarcinoma. The BAC and general lung transplantation cohorts had similar 30-day mortality (10% vs 7%, p=0.44) and 5-year survival (57% vs 50%, p=0.66). The investigators concluded that survival after lung transplantation for BAC appears to be consistent with that of lung transplantation for other diagnoses and is better than that reported with chemotherapy. The investigators stated that further study is warranted to identify the subgroup of patients with lung cancer who will have a maximum survival advantage after lung transplantation.

There is a steadily increasing need for a greater supply of lung donors. Xenotransplantation offers the possibility of an unlimited supply of lungs that could be readily available when needed. However, antibody-mediated mechanisms cause the rejection of pig organs transplanted into non-human primates, and these mechanisms provide key immunological barriers that have yet to be overcome. Although porcine hearts have functioned in heterotopic sites in non-human primates for periods of several weeks, no transplanted porcine lung has functioned for even 24 hours. Currently, lung xenotransplantation is not a clinically applicable option, and is therefore considered an experimental and investigational procedure.
Amital and colleagues (2008) noted that LTX impairs surfactant activity, which may contribute to primary graft dysfunction (PGD). In an open, randomized, controlled prospective study, these researchers examined if the administration of surfactant during transplantation serves as an effective preventive measure. A total of 42 patients scheduled for single (n = 38) or double (n = 4) LTX were randomly assigned to receive, or not, intra-operative surfactant treatment. In the treated group, bovine surfactant was administered at a dose of 20 mg phospholipids/kg body weight through bronchoscope after the establishment of bronchial anastomosis. The groups were compared for oxygenation (PaO2/FiO2), chest X-ray findings, PGD grade, and outcome. Compared with the untreated group, patients who received surfactant were characterized by better post-operative oxygenation mean PaO2/FiO2 (418.8 +/- 123.8 versus 277.9 +/- 165 mm Hg, p = 0.004), better chest radiograph score, a lower PGD grade (0.66 versus 1.86, p = 0.005), fewer cases of severe PGD (1 patient versus 12, p < 0.05), earlier extubation (by 2.2 hrs; 95 % confidence interval (CI): 1.1 to 4.3 hrs, p = 0.027), shorter intensive care unit stay (by 2.3 days; 95 % CI: 1.47 to 3.74 days, p = 0.001), and better vital capacity at 1 month (61 % versus 50 %, p = 0.022). One treated and 2 untreated patients died during the first post-operative month. The authors concluded that surfactant instillation during LTX improves oxygenation, prevents PGD, shortens intubation time, and enhances early post-transplantation recovery. Moreover, they stated that further, larger studies are needed to evaluate if surfactant should be used routinely in LTX.

In LTX recipients, gastro-esophageal reflux disease (GERD) is associated with increased incidence of acute rejection, earlier onset of chronic rejection, and higher mortality. Surgical treatment of GERD in LTX recipients seems to prevent early allograft dysfunction and improve overall survival. A total (360 degrees) fundoplication is shown to be a safe and effective method for treating GERD in LTX recipients for this high-risk patient population. The principal goal should be to minimize
reflux of enteric contents that may lead to micro- or macro-
aspiration events in this complicated group of patients. Peri-
operative care should involve a multi-disciplinary approach,
including physicians and other health care providers familiar
with the complexities of LTX recipients (Hartwig et al, 2005).

Molina et al (2009) identified outcomes in LTX recipients with
clinical evidence of GERD. Retrospective review of 162 LTX
recipients at the authors’ institution between January 1994 and
June 2006 was performed. Gastro-esophageal reflux disease
was confirmed in symptomatic patients by esophago-gastro-
duodenoscopy (EGD) and/or esophagography. Occurrence of
biopsy-proven obliterative bronchiolitis (OB) and bronchiolitis
obliterans syndrome (BOS) were analyzed. Kaplan-Meier
analysis of survival and Cox proportional hazard analysis of
risk factors were performed. Gastro-esophageal reflux
disease was diagnosed in 21 (13 %) of patients, usually
following LTX (71 %). There was no difference in mean
survival (1,603 +/- 300 versus 1,422 +/- 131 days; log rank p >
0.05), or development of OB (5 % versus 6 %, respectively; p
> 0.05) in patients with GERD compared with patients without
GERD. However, there was correlation between GERD and
BOS (p = 0.01). The authors concluded that symptomatic
GERD is increased following LTX. Patients with symptomatic
GERD demonstrated an increased incidence of BOS, but
survival was not affected in this study. They stated that more
sensitive and specific diagnostic tools should be implemented
in all LTX recipients to investigate the impact of symptomatic
and silent GERD and thus improve outcomes after LTX.

Burton et al (2009) stated that GERD in LTX recipients has
gained increasing attention as a factor in allograft failure.
There are few data on the impact of fundoplication on survival
or lung function, and less on its effect on symptoms or quality
of life. Patients undergoing fundoplication following LTX from
1999 to 2005 were included in the study. Patient satisfaction,
changes in GERD symptoms, and the presence of known side
effects were assessed. The effect on lung function, body
mass index, and rate of progression to the BOS were recorded. A total of 21 patients (13 males), in whom reflux was confirmed on objective criteria, were included, with a mean age of 43 years (range of 20 to 68). Time between transplantation and fundoplication was 768 days (range of 145 to 1,524). The indication for fundoplication was suspected micro-aspiration in 13 and symptoms of GERD in 8. There was 1 peri-operative death, at day 17. There were 3 other late deaths. Fundoplication did not appear to affect progression to BOS stage 1, although it may have slowed progression to stage 2 and 3. Forced expiratory volume-1 % predicted was 72.9 (20.9), 6 months prior to fundoplication and 70.4 (26.8), 6 months post-fundoplication, p = 0.33. Body mass index decreased significantly in the 6 months following fundoplication (23 kg/m(2) versus 21 kg/m(2), p = 0.05). Patients were satisfied with the outcome of the fundoplication (mean satisfaction score 8.8 out of 10). Prevalence of GERD symptoms decreased significantly following surgery (11 of 14 versus 4 of 17, p = 0.002). Fundoplication does not reverse any decline in lung function when performed at a late stage post-LTX in patients with objectively confirmed GERD. It may, however, slow progression to the more advanced stages of BOS. Reflux symptoms were well-controlled and patients were highly satisfied. The authors stated that whether performing fundoplication early post-LTX in selected patients can prevent BOS and improve long-term outcomes requires formal evaluation.

King et al (2009) examined the relationship between BOS and GERD measured by esophageal impedance. After the initiation of routine screening for GERD, 59 LTX recipients underwent ambulatory esophageal impedance monitoring. Exposure to acid reflux and non-acid liquid reflux was recorded. Clinical outcomes were reviewed to analyze any effect of reflux on the time to development of BOS. A total of 37 patients (65 %) had abnormal acid reflux and 16 (27 %) had abnormal non-acid reflux. There was no relationship between acid reflux and BOS. The hazard ratio (HR) for
development of BOS in the presence of abnormal non-acid reflux was 2.8 (p = 0.043). The HR for development of BOS increased to 3.6 (p = 0.022) when the number of acute rejection episodes was also taken into account. The authors concluded that GERD is prevalent in LTX recipients and may represent a modifiable risk factor for BOS. This study found non-acid reflux, measured by esophageal impedance to be associated with the development of BOS. They stated that prospective studies are now needed to investigate a causal association between GERD and the development of BOS and to establish the role of surgery for GERD in preventing progression to BOS.

Robertson et al (2010) noted that LTX is an accepted treatment strategy for end-stage lung disease; however, BOS is a major cause of morbidity and mortality. These investigators reviewed the role of GERD in BOS and the evidence suggesting the benefits of anti-reflux surgery in improving lung function and survival. There is a high prevalence of gastro-esophageal reflux in patients post-LTX. This may be due to a high pre-operative incidence, vagal damage and immunosuppression. Reflux in these patients is associated with a worse outcome, which may be due to micro-aspiration. Anti-reflux surgery is safe in selected LTX recipients; however there has been 1 report of a post-operative mortality. Evidence is conflicting but may suggest a benefit for patients undergoing anti-reflux surgery in terms of lung function and survival; there are no controlled studies. The precise indications, timing, and choice of fundoplication are yet to be defined, and further studies are required.

Zheng et al (2011) examined the safety and possible benefits of laparoscopic anti-reflux surgery in pediatric patients following LTX and heart-lung transplantation. An Institutional Review Board-approved retrospective chart review was performed to evaluate the outcomes and complications of laparoscopic anti-reflux surgery in pediatric LTX and heart-lung transplant patients. Spirometry data were collected for
BOS staging using BOS criteria for children. A total of 25 LTX and heart-lung transplants were performed between January 2003 and July 2009. Eleven transplant recipients, including 6 double-lung and 5 heart-lung, with a median age of 11.7 years (range of 5.1 to 18.4 years), underwent a total of 12 laparoscopic Nissen fundoplications at a median of 427 days after transplant (range of 51 to 2310 days). The diagnosis of GERD was made based upon clinical impression, pH probe study, gastric emptying study, and/or esophagram in all patients. Three patients already had a gastrostomy tube in place and 2 had one placed at the time of fundoplication.

There were no conversions to open surgery, 30-day re-admissions, or 30-day mortalities. Complications included 1 exploratory laparoscopy for free air 6 days after laparoscopic Nissen fundoplication for a gastric perforation that had spontaneously sealed. Another patient required a revision laparoscopic Nissen 822 days following the initial fundoplication for a para-esophageal hernia and recurrent GERD. The average length of hospital stay was 4.4 +/- 1.7 days. Nine of the 12 fundoplications were performed in patients with baseline spirometry values prior to fundoplication and who could also complete spirometry reliably. One of these 9 operations was associated with improvement in BOS stage 6 months after fundoplication; 7 were associated with no change in BOS stage; and 1 was associated with a decline in BOS stage. The authors concluded that it is feasible to perform laparoscopic Nissen fundoplication in pediatric LTX and heart-lung transplant recipients without mortality or significant morbidity for the treatment of GERD. The real effect on pulmonary function can not be assessed due to the small sample size and lack of reproducible spirometry in the younger patients. The authors stated that additional studies are needed to elucidate the relationship between anti-reflux surgery and the potential for improving pulmonary allograft function and survival in children that has been previously observed in adult patients.
Robertson et al (2012) evaluated the safety of fundoplication in LTX recipients and its effects on quality of life. Between June 1, 2008 and December 31, 2010, a prospective study of LTX recipients undergoing fundoplication was undertaken. Quality of life was assessed before and after surgery. Body mass index (BMI) and pulmonary function were followed-up. A total of 16 patients, mean +/- SD age of 38 +/-11.9 yrs, underwent laparoscopic Nissen fundoplication. There was no peri-operative mortality or major complications. Mean +/- SD hospital stay was 2.6 +/- 0.9 days; 15 out of 16 patients were satisfied with the results of surgery post-fundoplication. There was a significant improvement in reflux symptom index and DeMeester questionnaires and gastro-intestinal quality of life index scores at 6 months. Mean BMI decreased significantly after fundoplication (p = 0.01). Patients operated on for deteriorating lung function had a statistically significant decrease in the rate of lung function decline after fundoplication (p = 0.008). The authors concluded that laparoscopic fundoplication is safe in selected LTX recipients. Patient benefit is suggested by improved symptoms and satisfaction. Thye stated that this procedure is acceptable, improves quality of life and may reduce deterioration of lung function. These preliminary findings need to be validated by well-designed studies.

Fisichella and colleagues (2012) hypothesized that laparoscopic anti-reflux surgery (LARS) alters the pulmonary immune profile in LTX patients with GERD. In 8 LTX patients with GERD, these researchers quantified and compared the pulmonary leukocyte differential and the concentration of inflammatory mediators in the broncho-alveolar lavage fluid (BALF) 4 weeks before LARS, 4 weeks after LARS, and 12 months after LTX. Freedom from BOS (graded 1 to 3 according to the International Society of Heart and Lung Transplantation guidelines), FEV1 trends, and survival were also examined. At 4 weeks after LARS, the percentages of neutrophils and lymphocytes in the BALF were reduced (from 6.6 % to 2.8 %, p = 0.049, and from 10.4 % to 2.4 %, p =
0.163, respectively). The percentage of macrophages increased (from 74.8% to 94.6%, \( p = 0.077 \)). Finally, the BALF concentration of myeloperoxide and interleukin-1-beta tended to decrease (from 2,109 to 1,033 U/mg, \( p = 0.063 \), and from 4.1 to 0 pg/mg protein, \( p = 0.031 \), respectively), and the concentrations of interleukin-13 and interferon-gamma tended to increase (from 7.6 to 30.4 pg/mg protein, \( p = 0.078 \) and from 0 to 159.5 pg/mg protein, \( p = 0.031 \), respectively). These trends were typically similar at 12 months after transplantation. At a mean follow-up of 19.7 months, the survival rate was 75% and the freedom from BOS was 75%. Overall, the FEV1 remained stable during the first year after transplantation. The authors concluded that these preliminary findings indicated that LARS can restore the physiological balance of pulmonary leukocyte populations and that the BALF concentration of pro-inflammatory mediators is altered early after LARS. These results suggested that LARS could modulate the pulmonary inflammatory milieu in LTX patients with GERD.

There is great disparity between the supply of donor lungs and the number of potential lung transplant recipients. The shortage of donor lungs for transplantation demands optimal utilization of the donor organ. For many years hypothermic preservation has been the universal standard for organ preservation. Although limited in terms of the duration of preservation, hypothermic preservation has had the major advantages of simplicity, portability and affordability. Recently, organ preservation and transportation by normothermic perfusion has been reported to be superior over static cold storage in experimental settings; however, all devices examined were non-portable. The Organ Care System (TransMedics, Inc., Andover, MA) is a portable device for preservation and transport of donor lungs. However, its role in lung transplantation has not yet been established.
Van Raemdonck et al (2010) noted that the critical organ shortage has forced lung transplant teams to extend their donor criteria, thereby compromising a good early outcome in the recipient. Better preservation solutions for longer storage are welcomed to further reduce incidence of primary graft dysfunction. New ex-vivo techniques to assess and to condition lungs prior to transplantation are hoped to increase the number of available pulmonary grafts. Although no prospective clinical trial has been carried out so far, clinical and experimental evidence suggest that an extracellular solution is currently the preservation fluid of choice for lung transplantation. The combination of an antegrade and retrograde pulmonary flush and technique to control reperfusion and ventilation are becoming common practice, although the evidence to support this method is low. Ex-vivo lung perfusion to assess and to re-condition lungs has been demonstrated to be well-tolerated and effective in small clinical series. The author concluded that new extracellular preservation solutions have contributed in decreasing the incidence of primary graft dysfunction over the last decade leaving more room to extend the donor criteria and ischemic time. Ex-vivo lung perfusion is now on the horizon as a potential method to prolong the preservation time and to resuscitate lungs of inferior quality.

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

Also, an UpToDate review on “Lung transplantation: Donor lung preservation” (Cypel et al, 2012) states that “The cold static preservation system described above was developed in an era with younger organ donors and good-quality organs. However, in order to increase the availability of donor organs, older and sometimes injured donor organs are being used. The use of suboptimal donor lungs and difficulties assessing lung function in donation after cardiac death have made it necessary to explore alternative preservation techniques. Hypothermic preservation inhibits cellular metabolism and eliminates the possibility of substantial reparative processes occurring after donor organ injury. For this reason, normothermic (37° C) or near-normothermic (25 to 34° C) ex vivo perfusion is becoming popular as a preservation
alternative in kidney and liver transplantation. Attempts at using a ventilating and perfusing machine for lung preservation have failed in the past, largely due to the development of lung edema and increases in pulmonary vascular resistance. However, investigators have used an animal model to develop a perfusion system that allows evaluation of lung function ex vivo. A key part of ex vivo perfusion is the identification of a specific solution (Steen® solution) that allows for ex vivo perfusion of lungs without development of pulmonary edema. In an animal model and a single human case, after a short period (60 to 90 minutes) of ex vivo evaluation, lungs were successfully transplanted. An acellular, ex vivo lung perfusion (EVLP) technique that can maintain donor lungs for at least 12 hours at body temperature without inducing injury has been tested in porcine and human lungs. After prolonged EVLP, lung function after transplantation was excellent. Using this acellular perfusion technique also allowed evaluation of lung function ex vivo. However, another animal model of EVLP was less successful; six hours of EVLP resulted in impaired lung function, manifest by increased pulmonary vascular resistance (PVR) and increased airway pressures towards the end of the procedure. A clinical trial is underway using normothermic ex vivo lung perfusion as a method to reassess and optimize donor lungs that are initially unsuitable for transplantation.”

TramsMedics is currently conducting a clinical trial “International Randomized Study of the TransMedics Organ Care System (OCS Lung) for Lung Preservation and Transplantation (INSPIRE)”, which compares preservation of donor lungs using OCS-Lung perfusion device to cold flush and storage (last verified December 2012).

Uhlving and co-workers (2012) stated that BO following allogeneic hematopoietic SCT (HSCT) is a serious complication affecting 1.7 to 26 % of the patients, with a reported mortality rate of 21 to 100 %. It is considered a manifestation of chronic graft-versus-host disease (cGVHD), but its etiology and pathogenesis is still unclear. Diagnostic
criteria are being developed, and will allow more uniform and comparable research activities between centers. At present, no randomized controlled trials have been completed that could demonstrate an effective treatment. Steroids in combination with other immunosuppressive drugs still constitute the mainstay of the treatment strategy, and results from the authors and other centers suggested that monthly infusions of high-dose pulse intravenous methylprednisolone might stabilize the disease and hinder progression.

Vogl and associates (2013) noted that BO is a detrimental late pulmonary complication after allogeneic HSCT associated with cGVHD. When systemic immunosuppressive treatment fails to improve, severe BO patients should be considered for LTX. These researchers presented 7 patients undergoing LTX for severe refractory BO after HSCT. Evaluation for LTX was initiated after failure of a median of 4 immunosuppressive regimens. Between 1996 and 2012, a total of 7 patients with severe refractory BO were evaluated for LTX. The median time from HSCT to diagnosis of chronic lung GVHD was 8.2 months (range of 3.7 to 16.6). At a median time of 18.1 months (range of 6 to 120) after diagnosis of BO, 6 patients received a bilateral sequential LTX, and 1 patient received a single LTX. Six post-operative courses were uneventful; the patient with single LTX died from septic multi-organ failure. Three LTX recipients had a mild acute rejection after 1 to 3 months after LTX, and 1 patient experienced fatal chronic rejection and hemolytic uremic syndrome; 3 (43 %) LTX recipients remained alive at a median observation time of 26 months (range of 1 month to 16 years) after LTX. The median overall survival from LTX was 24 months (95 % CI: 0.5 to 78); the median overall survival time after allogeneic HCT was 98 months (95 % CI: 46 to 198). The authors concluded that the findings of this case series illustrated that LTX is a possible therapeutic option for selected patients with severe treatment-refractory BO.
Soubani and colleagues (2014) stated that non-infectious pulmonary complications following HSCT are major cause of morbidity and mortality with limited treatment options. Lung transplantation has been rarely reported as a treatment option for selected HSCT recipients with these problems. These researchers described the outcome of HSCT recipients who underwent LTX. A total of 2 cases of LTX following HSCT from the authors’ institution were presented. Cases reported in literature were identified using English language PubMed/Medline with keywords hematopoietic stem cell transplantation, bone marrow transplantation or bronchiolitis obliterans cross-referenced with lung transplantation. These investigators extracted data on baseline characteristics and survival data following LTX. A total of 84 patients were analyzed. Median age at time of LTX was 22 years (range of 1 to 66); 79 patients were recipients of allogeneic HSCT. The indications for LTX were BOS (n = 63), pulmonary fibrosis (n = 13), BOS/pulmonary fibrosis (n = 5), and GVHD of lung (n = 3). The median time between HSCT and LTX was 52.3 months (range of 6 to 240). The median follow-up after LTX was 36 months (range of 0 to 168). During this time, BOS was documented in 25 patients. Relapse of hematological malignancy was reported in 2 patients and new malignancy developed in 4 patients. At the end of follow-up, 60 patients were alive and 24 patients died. The probability of survival following LTX at 24 and 36 months was 0.88 (95% CI: 0.78 to 0.93) and 0.79 (95% CI: 0.67 to 0.87), respectively. The authors concluded that LTX is a potential therapeutic option in selected patients with severe chronic pulmonary disease following HSCT. Moreover, they stated that further studies are needed to determine the appropriate timing and the outcome of this approach.

In an exploratory analysis, Schaffer et al (2015) compared outcomes in single- and double-LTX recipients since the Lung Allocation Score was implemented. Adults with idiopathic pulmonary fibrosis (IPF) or COPD who underwent LTX in the United States between May 4, 2005, and December 31, 2012,
were identified in the UNOS thoracic registry, with follow-up to December 31, 2012. Post-transplantation graft survival was assessed with Kaplan-Meier analysis. Propensity scores were used to control for treatment selection bias. A multi-variable flexible parametric prognostic model was used to characterize the time-varying hazard associated with single- versus double-LTX. Main outcome measures were composite of post-transplant death and graft failure (re-transplantation). Patients with IPF (n = 4,134, of whom 2,010 underwent single-lung and 2,124 underwent double-LTX) or COPD (n = 3,174, of whom 1,299 underwent single-LTX and 1,875 underwent double-LTX) were identified as having undergone LTX since May 2005. Median follow-up was 23.5 months. Of the patients with IPF, 1,380 (33.4 %) died and 115 (2.8 %) underwent re-transplantation; of the patients with COPD, 1,138 (34.0 %) died and 59 (1.9 %) underwent re-transplantation. After confounders were controlled for with propensity score analysis, double-LTX were associated with better graft survival in patients with IPF (adjusted median survival, 65.2 months [interquartile range {IQR}, 21.4 to 91.3 months] versus 50.4 months [IQR, 17.0 to 87.5 months]; p < 0.001) but not in patients with COPD (adjusted median survival, 67.7 months [IQR, 25.2 to 89.6 months] versus 64.0 months [IQR, 25.2 to 88.7 months]; p = 0.23). The interaction between diagnosis type (COPD or IPF) and graft failure was significant (p = 0.049). Double-LTX had a time-varying association with graft survival; a decreased instantaneous late hazard for death or graft failure among patients with IPF was noted at 1 year and persisted at 5 years post-operatively (instantaneous hazard at 5 years, HR, 0.67 [95 % CI: 0.52 to 0.84] in patients with IPF and 0.89 [95 % CI: 0.71 to 1.13] in patients with COPD). The authors concluded that in an exploratory analysis of registry data since implementation of a medical need-based lung allocation system, double-LTX was associated with better graft survival than single-LTX in patients with IPF. In patients with COPD, there was no survival difference between single- and double-LTX recipients at 5 years.
Anti-Fungal Prophylaxis:

Pilarczyk and colleagues (2016) stated that LTX recipients are at high risk of invasive Aspergillus infections (IAI). However, no randomized-controlled trials (RCT) or international guidelines on anti-fungal prophylaxis (AFP) in the LTX population exist. These investigators performed a meta-analysis to determine whether AFP reduces the rate of IAI after LTX. A total of 6 eligible observational studies (5 with no prophylaxis, 1 with targeted prophylaxis, 3 studies including heart/lung transplantation) with a total of 748 patients were included. The pooled odds ratio (OR) for IAI (62 IFI in the intervention arm, and 82 in the control group) was 0.234 (95% CI: 0.097 to 0.564, p = 0.001, z = -3.237). Pooled studies were characterized by substantial heterogeneity (I² = 66.64 %); number needed to treat was 6.8. A subgroup analyses with exclusion of heart transplant recipients also showed a statistically significant reduction in IAI with AFP (OR 0.183, 95% CI: 0.0449 to 0.744, p = 0.018). The authors concluded that the findings of this study suggested that universal anti-fungal prophylaxes reduced incidence of IAI after LTX. However, included studies were limited by small sample size, single-center structure without randomization, mixed population (including heart/heart-lung transplant), and heterogeneity due to variations in immunosuppression, type, and duration of AFP. Thus, there is a clear need for an adequately powered RCT.

Intraoperative Extracorporeal Membrane Oxygenation (ECMO):

Ius and associates (2012) stated that patients requiring extracorporeal cardio-respiratory support during lung transplantation can be treated with conventional cardiopulmonary bypass (CPB) or veno-arterial extracorporeal membrane oxygenation (ECMO). In a retrospective analysis, these investigators compared the post-operative course and outcomes of patients treated using these approaches.
Between August 2008 and September 2011, a total of 92 consecutive patients underwent lung transplantation with extracorporeal support (CPB group, n = 46; and, since February 2010, ECMO group, n = 46) at the authors’ institution. They evaluated survival, secondary organ failure, bleeding complications, and the need for blood and platelet transfusions in these 2 patient populations. Intra-operatively, the CPB group required more packed red blood cell (RBC) transfusions (12 ± 11 versus 7 ± 9 U; p = 0.01) and platelet concentrates (2.5 ± 1.6 versus 1.5 ± 1 U; p < 0.01) than the ECMO group. In-hospital mortality (39 % versus 13 %; p = 0.004), the need for hemodialysis (48 % versus 13 %; p < 0.01), and new post-operative ECMO support (26 % versus 4 %; p < 0.01) were greater in the CPB group than in the ECMO group, respectively. After propensity score analysis, multivariate analysis identified re-transplantation (OR, 7; 95 % CI: 1 to 43; p = 0.034) and transplantation with CPB support (OR, 4.9; 95 % CI: 1.2 to 20; p = 0.026) as independent risk factors for in-hospital mortality. The survival rate at 3, 9, and 12 months was 70 %, 59 %, and 56 % in the CPB group, and 87 %, 81 %, and 81 % in the ECMO group (p = 0.004). The authors concluded that intra-operative ECMO allowed for better peri-procedural management and reduced post-operative complications and conferred a survival benefit compared with CPB, mainly because of lower in-hospital mortality. They stated that it is now the standard of care in their lung transplantation program.

In a retrospective, single-center study, Hoechter and co-workers (2015) analyzed transfusion requirements, coagulation parameters, and outcome parameters in patients undergoing lung transplantation (LuTx) with intra-operative extracorporeal circulatory support, comparing CPB and ECMO. Over a 3-year period, 49 of a total of 188 LuTx recipients were identified being set intra-operatively on either conventional CPB (n = 22) or ECMO (n = 27). Intra- and post-operative transfusion and coagulation factor requirements as well as early outcome parameters were analyzed. LuTx
patients on CPB had significantly higher intra-operative transfusion requirements when compared with ECMO patients, that is, packed RBCs (9 units [5 to 18] versus 6 units [4 to 8], p = 0.011), platelets (3.5 units [2 to 4] versus 2 units [0 to 3], p = 0.034), fibrinogen (5 g [4 to 6] versus 0 g [0 to 4], p = 0.013), prothrombin complex concentrate (3 iU [2 to 5] versus 0 iU [0 to 2], p = 0.001), and tranexamic acid (2.5 mg [2 to 5] versus 2.0 mg [1 to 3], p = 0.002). Also, ventilator support requirements (21 days [7 to 31] versus 5 days [3 to 21], p = 0.013) and lengths of ICU stays (36 days [14 to 62] versus 15 days [6 to 44], p = 0.030) were markedly longer in CPB patients. There were no differences in 30-day and 1-year mortality rates. The authors concluded that these findings indicated a peri-operative advantage of ECMO usage with low-dose heparinization over conventional CPB for extracorporeal circulatory support during LuTx; however, long-term outcome is not affected.

In a meta-analysis, Hoechter and colleagues (2017) stated that extracorporeal circulation is an invaluable tool in lung transplantation. Over the past years, an increasing number of centers changed their standard for intra-operative extracorporeal circulation from CPB to ECMO with differing results. These investigators reviewed the existing evidence. An online literature research on Medline, Embase, and PubMed has been performed; 2 persons independently judged the papers using the ACROBAT-NRSI tool of the Cochrane collaboration. Meta-analyses and meta-regressions were used to determine whether veno-arterial ECMO resulted in better outcomes compared to CPB. A total of 6 papers -- all observational studies without randomization -- were included into the analysis. All were considered to have serious bias due to heparinization as co-intervention. Forest plots showed a beneficial trend of ECMO regarding blood transfusions (packed red blood cells with an average mean difference of -0.46 units [95 % CI: -3.72 to 2.80], fresh-frozen plasma with an average mean difference of -0.65 units [95 % CI: -1.56 to 0.25], platelets with an average mean difference of -1.72 units
Duration of ventilator support with an average mean difference of -2.86 days [95 % CI: -11.43 to 5.71] and intensive care unit (ICU) length of stay with an average mean difference of -4.79 days [95 % CI: -8.17 to 1.41] were shorter in ECMO patients; ECMO treatment tended to be superior regarding 3-month mortality (odds ratio [OR] = 0.46, 95 % CI: 0.21 to 1.02) and 1-year mortality (OR = 0.65, 95 % CI: 0.37 to 1.13). However, only the ICU length of stay reached statistical significance. Meta-regression analyses showed that heterogeneity across studies (sex, year of ECMO implementation and underlying disease) influenced differences. The authors concluded that these data indicated a benefit of the intra-operative use of ECMO as compared to CPB during lung transplant procedures regarding short-term outcome (ICU stay). However, there was no statistical significant effect regarding blood transfusion needs or long term outcome. They stated that the superiority of ECMO in lung transplantation patients remains to be determined in larger multi-center randomized trials.

Ex-Vivo Lung Perfusion:

Popov and colleagues (2016) stated that LTX remains the gold standard for patients with ESPD. However, the number of suitable donor lungs for the increasing number of patients on the waiting list necessitates alternative tools to expand the lung donor pool. Modern preservation and lung assessment techniques could contribute to improved function in previously rejected lungs. Ex-vivo lung perfusion (EVLP) already demonstrated its value in identification of transplantable grafts from the higher risk donor pool. Moreover, lungs from EVLP did not show significantly different post-operative results compared to standard criteria lungs. This could be explained by the reduction of the ischemia-reperfusion injury through EVLP application. The authors concluded that the usage of EVLP resulted in raising the amount of lung transplants by determining grafts from the suboptimal donor pool whose performance is considered equal to those regarded standard.
Since EVLP is being utilized more extensively and new ways of therapy are being adapted for the clinical environment, its application promises a new era in LTX. They stated that advancing the development of this technique might result in extending the safe ex-vivo perfusion time and treatment of different pathologies besides pulmonary edema.

In a multi-center, un-blinded, non-randomized, non-inferiority, observational study, Fisher and associates (2016) compared transplant outcomes between EVLP-assessed and standard donor lungs. Participants included patients aged greater than or equal to 18 years with advanced lung disease who were accepted onto the lung transplant waiting list. The study intervention was EVLP assessment of donor lungs before determining suitability for LTX. The primary outcome measure was survival during the first 12 months following LTX; secondary outcome measures were patient-centered outcomes that were influenced by the effectiveness of LTX and that contribute to the health-care costs. Lungs from 53 donors unsuitable for standard transplant were assessed with EVLP, of which 18 (34 %) were subsequently transplanted. A total of 184 participants received standard donor lungs. Owing to the early closure of the study, a non-inferiority analysis was not conducted. The Kaplan-Meier estimate of survival at 12 months was 0.67 [95 % CI: 0.40 to 0.83] for the EVLP arm and 0.80 (95 % CI: 0.74 to 0.85) for the standard arm. The HR for overall 12-month survival in the EVLP arm relative to the standard arm was 1.96 (95 % CI: 0.83 to 4.67). Patients in the EVLP arm required ventilation for a longer period and stayed longer in an intensive therapy unit (ITU) than patients in the standard arm, but duration of overall hospital stay was similar in both groups. There was a higher rate of very early grade-3 PGD in the EVLP arm, but rates of PGD did not differ between groups after 72 hours. The requirement for ECMO support was higher in the EVLP arm (7/18, 38.8 %) than in the standard arm (6/184, 3.2 %). There were no major differences in rates of chest radiograph abnormalities, infection, lung function or rejection by 12 months. The cost of EVLP
transplants was approximately £35,000 higher than the cost of standard transplants, as a result of the cost of the EVLP procedure, and the increased ECMO use and ITU stay. Predictors of cost were quality of life (QOL) on joining the waiting list, type of transplant and number of lungs transplanted. An exploratory model comparing a NHS lung transplant service that included EVLP and standard lung transplants with one including only standard lung transplants resulted in an incremental cost-effectiveness ratio of £73,000. Interviews showed that patients had a good understanding of the need for, and the processes of, EVLP. If EVLP could increase the number of usable donor lungs and reduce waiting, it is likely to be acceptable to those waiting for LTX.

Study limitations included small numbers in the EVLP arm, limiting analysis to descriptive statistics and the EVLP protocol change during the study. The authors concluded that 1/3 of donor lungs subjected to EVLP were deemed suitable for transplant. Estimated survival over 12 months was lower than in the standard group, but the data were also consistent with no difference in survival between groups. Patients receiving these additional transplants experienced a higher rate of early graft injury and need for unplanned ECMO support, at increased cost. The small number of participants in the EVLP arm because of early study termination limited the robustness of these conclusions. The reason for the increased PGD rates, high ECMO requirement and possible differences in lung injury between EVLP protocols needs evaluation. They noted that EVLP using a Lund protocol has the potential to offer an increased chance of achieving effective LTX in patients at high risk of death on the waiting list. Moreover, they stated that although the overall findings of the DEVELOP-UK study were not what was hoped for, and did not allow the original research question to be definitively answered, there are still a significant number of factors to consider that will help to direct further research in the area of EVLP.

Loor and associates (2017) reported the ability to extend lung preservation up to 24 hours (24H) by using autologous whole
donor blood circulating within an EVLP system. This approach facilitated donor lung re-conditioning in a model of extended normo-thermic EVLP. These researchers analyzed comparative responses to cellular and acellular perfusates to identify these benefits. A total of 12 pairs of swine lungs were retrieved after cardiac arrest and studied for 24H on the Organ Care System (OCS) Lung EVLP platform; 3 groups (n = 4 each) were differentiated by perfusate: (i) isolated red blood cells (RBCs) (current clinical standard for OCS); (ii) whole blood (WB); and (iii) acellular buffered dextran-albumin solution (analogous to STEEN solution). Only the RBC and WB groups met clinical standards for transplantation at 8 hours; primary analysis at 24H focused on perfusion with WB versus RBC. The WB perfusate was superior (versus RBC) for maintaining stability of all monitored parameters, including the following mean 24H measures: pulmonary artery pressure (6.8 versus 9.0 mm Hg), reservoir volume replacement (85 versus 1607 ml), and PaO2:FIO2 ratio (541 versus 223). Acellular perfusion was limited to 6 hours on the OCS system due to prohibitively high vascular resistance, edema, and worsening compliance. The authors concluded that the use of an autologous whole donor blood perfusate allowed 24 hours of preservation without functional deterioration and was superior to both RBC, and buffered dextran-albumin solution for extended lung preservation in a swine model using OCS Lung. They stated that this finding represented a potentially significant advance in donor lung preservation and re-conditioning.

In a pilot study, Luc and co-workers (2017) reported their initial experience with the use of portable EVLP with the OCS Lung device for evaluation of donation after circulatory death (DCD) lungs. These researchers performed a retrospective review of the DCD LTX experience at a single-center through the use of a prospective database. From 2011 to 2015, a total of 208 LTX were performed at the University of Alberta, of which 11 were DCD LTX with 7 (64 %) that underwent portable EVLP.
DCD lungs preserved with portable EVLP had a significantly shorter cold ischemic time (161 ± 44 versus 234 ± 60 mins, p = 0.045), lower grade of PGD at 72 hours after LTX (0.4 ± 0.5 versus 2.1 ± 0.7, p = 0.003), similar mechanical ventilation time (55 ± 44 versus 103 ± 97 hrs, p = 0.281), and hospital length of stay (29 ± 11 versus 33 ± 10 days, p = 0.610). All patients were alive at 1-year follow-up after LTX with improved functional outcomes and acceptable QOL compared with before LTX, although there were no inter-group differences. The authors concluded that in their pilot cohort, portable EVLP was a feasible modality to increase confidence in the use of DCD lungs with validated objective evidence of lung function during EVLP that translates to acceptable clinical outcomes and QOL after LTX. They stated that further studies are needed to validate these initial findings in a larger cohort.

D'Cunha and Rojas (2017) noted that EVLP has emerged as a new technology with the potential of re-conditioning human donor lungs previously unsuitable for transplantation. Since the first successful transplant of a lung treated using EVLP in the year 2000, multiple clinical trials had demonstrated, in several transplant centers around the world, the feasibility and the potential of EVLP to increase the total number of lungs available for transplant.

Sales and co-workers (2017) stated that despite the increment in LTX rates, in 2016 the overall mortality while on waiting list in Italy reached 10 %, whereas only 39 % of the wait-list patients were successfully transplanted. A number of approaches, including protective ventilatory strategy, accurate management of fluid balance, administration of a hormonal resuscitation therapy have been reported to improve lung donor performance before organ retrieval. These approaches, in conjunction with the use of EVLP technique contributed to expand the lung donor pool, without affecting the harvest of other organs and the outcomes of lung recipients. But the efficacy of issues related to the EVLP technique, such as the optimal ventilation strategy, the ischemia-reperfusion induced...
lung injury management, the prophylaxis of germs transmission from donor to recipient and the application of targeted pharmacologic therapies to treat specific donor lung injuries are still to be explored.

Himmat and associates (2017) stated that normo-thermic EVLP is an evolving technology to evaluate function of donor lungs to determine suitability for transplantation. These researchers hypothesized that hypoxic pulmonary vasoconstriction (HPV) during EVLP will provide a more sensitive parameter of lung function to determine donor lung quality for LTX. A total of 8 porcine lungs were procured, and subsequently underwent EVLP with autologous blood and STEEN solution for 10 hours. Standard physiologic parameters including dynamic compliance, peak airway pressure, and pulmonary vascular resistance (PVR) remained stable ($p = 0.055$), mean oxygenation ($PO_2 /FiO_2$) was 400 ± 18 mm Hg on average throughout perfusion. Response to hypoxia resulted in a robust increase in PVR ($\Delta PVR$) up to 4 hours of perfusion, however the HPV response then blunted beyond 6 hours ($p < 0.01$). The decrease in HPV response inversely correlated to cytokine concentrations of interleukin-6 and tumor necrosis factor-α ($p < 0.01$). The authors concluded that despite acceptable lung oxygenation and standard physiologic parameters during 10 hours of EVLP, there was a subclinical deterioration of lung function. They stated that HPV challenges can be performed during EVLP as a simple and more sensitive index of PVR.

Hsin and colleagues (2018) identified potential biomarkers during EVLP using metabolomics approach. EVLP perfusate taken at 1- and 4 hr-perfusion were collected from 50 clinical EVLP cases, and submitted to untargeted metabolic profiling with mass spectrometry. The findings were correlated with early LTX outcomes. Following EVLP, 7 cases were declined for LTX. In the remaining transplanted cases, 9 cases developed PGD 3. For the metabolic profile at EVLP-1hr, a logistic regression model based on palmitoyl-sphingomyelin,
5-aminovalerate, and decanoylcarnitine yielded a receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.987 in differentiating PGD 3 from non-PGD 3 outcomes. For the metabolic profile at EVLP-4hr, a logistic regression model based on N2-methylguanosine, 5-aminovalerate, oleamide, and decanoylcarnitine yielded a ROC curve with AUC 0.985 in differentiating PGD 3 from non-PGD 3 outcomes. The authors concluded that metabolomics of EVLP perfusate revealed a small panel of metabolites highly correlated with early LTX outcomes, and may be potential biomarkers that can improve selection of marginal lungs on EVLP. Moreover, they stated that further validation studies are needed to confirm these findings.

Appendix

The BODE Index (Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise) is a multidimensional capacity index for COPD. The index uses the four factors for predicting the risk of death from the disease: FEV1, body mass index, dyspnea score and 6 minute walk test.

Table: The BODE Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE Index</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>FEV1 (% predicted)</td>
<td>≥65</td>
</tr>
<tr>
<td>6-Minute Walk Test (meters)</td>
<td>≥350</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale</td>
<td>0-1</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>&gt;21</td>
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</tbody>
</table>
An online tool for calculating the BODE Index is available at the following website:

[BODE Index for COPD Survival Prediction](http://reference.medscape.com/calculator/bode-index-copd)

**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CPT codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td>32850</td>
<td>Donor pneumonectomy(s) (including cold preservation), from cadaver donor</td>
</tr>
<tr>
<td>32851</td>
<td>Lung transplant, single; without cardiopulmonary bypass</td>
</tr>
<tr>
<td>32852</td>
<td>with cardiopulmonary bypass</td>
</tr>
<tr>
<td>32853</td>
<td>Lung transplant, double (bilateral sequential or en bloc); without cardiopulmonary bypass</td>
</tr>
<tr>
<td>32854</td>
<td>with cardiopulmonary bypass</td>
</tr>
<tr>
<td>34714</td>
<td>Open femoral artery exposure with creation of conduit for delivery of endovascular prosthesis or for establishment of cardiopulmonary bypass, by groin incision, unilateral (List separately in addition to code for primary procedure)</td>
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<td></td>
<td><strong>CPT codes not covered for indications listed in the CPB:</strong></td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>43257</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease</td>
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<td>43280</td>
<td>Laparoscopy, surgical; esophagogastric fundoplasting (e.g., Nissen, Toupet procedures) [not covered if patient is asymptomatic]</td>
</tr>
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<td>43281</td>
<td>Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplastic, when performed; without implantation of mesh [not covered if patient is asymptomatic]</td>
</tr>
<tr>
<td>43282</td>
<td>Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplastic, when performed; with implantation of mesh [not covered if patient is asymptomatic]</td>
</tr>
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<td>43325</td>
<td>Esophagogastric fundoplasty with fundic patch (Thal-Nissen procedure) [not covered if patient is asymptomatic]</td>
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<tr>
<td>43327</td>
<td>Esophagogastric fundoplasty partial or complete; laparotomy [not covered if patient is asymptomatic]</td>
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<tr>
<td>43328</td>
<td>Esophagogastric fundoplasty partial or complete; thoracotomy [not covered if patient is asymptomatic]</td>
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<td>43332</td>
<td>Repair paraesophageal hiatal hernia, via laparotomy except neonatal; without implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>43333</td>
<td>Repair paraesophageal hiatal hernia, via laparotomy except neonatal; with implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
</tr>
<tr>
<td>43334</td>
<td>Repair paraesophageal hiatal hernia, via thoracotomy, except neonatal; without implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
</tr>
<tr>
<td>43335</td>
<td>Repair paraesophageal hiatal hernia, via thoracotomy, except neonatal; with implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
</tr>
<tr>
<td>43336</td>
<td>Repair paraesophageal hiatal hernia, via thoracoabdominal incision, except neonatal; without implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
</tr>
<tr>
<td>43337</td>
<td>Repair paraesophageal hiatal hernia, via thoracoabdominal incision, except neonatal; with implantation of mesh or other prosthesis [not covered if patient is asymptomatic]</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C34.00</td>
<td>Malignant neoplasm of bronchus and lung [good surgical candidates]</td>
</tr>
<tr>
<td>C34.92</td>
<td></td>
</tr>
<tr>
<td>C96.6</td>
<td>Unifocal Langerhans-cell histiocytosis [eosinophilic granuloma]</td>
</tr>
<tr>
<td>D86.0</td>
<td>Sarcoidosis of lung [must be carefully evaluated to ensure diseases is primarily confined to lung]</td>
</tr>
<tr>
<td>D89.810</td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td>D89.813</td>
<td></td>
</tr>
<tr>
<td>E84.0</td>
<td>Cystic fibrosis [contraindicated for single-lung transplant]</td>
</tr>
<tr>
<td>E84.9</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>E88.01</td>
<td>Alpha-1-antitrypsin deficiency</td>
</tr>
<tr>
<td>I27.0</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>I27.83</td>
<td>Eisenmenger's syndrome</td>
</tr>
<tr>
<td>J41.8</td>
<td>Mixed simple and mucopurulent chronic bronchitis [contraindicated for single-lung]</td>
</tr>
<tr>
<td>J42</td>
<td>Unspecified chronic bronchitis [bronchiolitis obliterans]</td>
</tr>
<tr>
<td>J43.0</td>
<td>Emphysema</td>
</tr>
<tr>
<td>J43.9</td>
<td></td>
</tr>
<tr>
<td>J44.0</td>
<td>Chronic obstructive pulmonary disease [contraindicated for single-lung]</td>
</tr>
<tr>
<td>J44.9</td>
<td></td>
</tr>
<tr>
<td>J47.0</td>
<td>Bronchiectasis [contraindicated for single-lung]</td>
</tr>
<tr>
<td>J47.9</td>
<td></td>
</tr>
<tr>
<td>J61</td>
<td>Pneumoconiosis due to asbestos and other mineral fibers</td>
</tr>
<tr>
<td>J67.4</td>
<td>Allergic alveolitis (extrinsic)</td>
</tr>
<tr>
<td>J67.9</td>
<td></td>
</tr>
<tr>
<td>J84.10</td>
<td>Pulmonary fibrosis, unspecified</td>
</tr>
<tr>
<td>J84.111</td>
<td>Idiopathic interstitial pneumonia</td>
</tr>
<tr>
<td>J84.117</td>
<td></td>
</tr>
<tr>
<td>J84.81</td>
<td>Lymphangioleiomyomatosis [with end-stage pulmonary disease]</td>
</tr>
<tr>
<td>J84.89</td>
<td>Other specified interstitial pulmonary diseases</td>
</tr>
<tr>
<td>J99</td>
<td>Respiratory disorders in diseases classified elsewhere</td>
</tr>
<tr>
<td>M31.0</td>
<td>Hypersensitivity angitis [must be carefully evaluated to ensure diseases is primarily confined to lung]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>M34.81</td>
<td>Systemic sclerosis with lung involvement [must be carefully evaluated to ensure diseases is primarily confined to lung]</td>
</tr>
<tr>
<td>P27.0 - P27.9</td>
<td>Chronic respiratory disease arising in the perinatal period [bronchopulmonary dysplasia]</td>
</tr>
<tr>
<td>Q33.0</td>
<td>Congenital cystic lung</td>
</tr>
<tr>
<td>Q33.3</td>
<td>Agenesis of lung</td>
</tr>
<tr>
<td>Q33.4</td>
<td>Congenital bronchiectasis</td>
</tr>
<tr>
<td>Q33.6</td>
<td>Congenital hypoplasia and dysplasia of lung</td>
</tr>
<tr>
<td>T86.810 - T86.819</td>
<td>Complications of lung transplant</td>
</tr>
</tbody>
</table>

ICD-10 codes contraindicated for this CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A00.0 - B99.9</td>
<td>Infectious and parasitic diseases [acute or chronic active infection not adequately treated including HIV/AIDS and complications such as aspergillus, tuberculosis, coccidoidomycosis, or fungal]</td>
</tr>
<tr>
<td>C34.00 - C34.92</td>
<td>Malignant neoplasm of bronchus and lung</td>
</tr>
<tr>
<td>C46.0 - C46.9</td>
<td>Kaposi's sarcoma [complication from AIDS]</td>
</tr>
<tr>
<td>C82.00 - C85.99</td>
<td>Non-Hodgkin's lymphoma [complication from AIDS]</td>
</tr>
<tr>
<td>D02.0</td>
<td>Carcinoma in situ of larynx</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>E10.21 - E10.29</td>
<td>Diabetes mellitus with renal complications</td>
</tr>
<tr>
<td>E11.21 - E11.29</td>
<td></td>
</tr>
<tr>
<td>E13.21 - E13.29</td>
<td></td>
</tr>
<tr>
<td>E10.311 - E10.39</td>
<td>Diabetes mellitus with ophthalmic complications</td>
</tr>
<tr>
<td>E11.311 - E11.39</td>
<td></td>
</tr>
<tr>
<td>E13.311 - E13.39</td>
<td></td>
</tr>
<tr>
<td>E10.40 - E10.49</td>
<td>Diabetes mellitus with neurologic complications</td>
</tr>
<tr>
<td>E10.610</td>
<td></td>
</tr>
<tr>
<td>E11.40 - E11.49</td>
<td></td>
</tr>
<tr>
<td>E11.610</td>
<td></td>
</tr>
<tr>
<td>E13.40 - E13.49</td>
<td></td>
</tr>
<tr>
<td>E13.610</td>
<td></td>
</tr>
<tr>
<td>F01.50 - F99</td>
<td>Mental and behavioral disorders [uncontrolled and/or untreated that interfere with compliance including alcohol, chemical, or tobacco dependency]</td>
</tr>
<tr>
<td>I10 - I16.2</td>
<td>Hypertensive disease [refractory uncontrolled]</td>
</tr>
<tr>
<td>I21.01 - I22.9</td>
<td>ST elevation (STEMI) and non-ST (NSTEMI) myocardial infarction [in last 6 months]</td>
</tr>
<tr>
<td>I25.1 - I25.9</td>
<td>Atherosclerotic heart disease of native coronary artery [significant]</td>
</tr>
<tr>
<td>K25.0 - K25.9</td>
<td>Gastic ulcer</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


17. Cohen RG, Barr ML, Schenkel FA, et al. Living-related donor lobectomy for bilateral lobar transplantation in


64. D'Cunha HC, Rojas M. Ex vivo lung perfusion: Past, present, and future. ASAIO J. 2017 Aug 29 [Epub ahead of print]


increased inflammation during extended normothermic ex vivo lung perfusion. Artif Organs. 2017 Dec 20 [Epub ahead of print].

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0598 Lung Transplantation

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania  new 11/01/2018