Extracorporeal Photopheresis

Policy # 00099
Original Effective Date: 06/05/2002
Current Effective Date: 03/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider extracorporeal photopheresis (ECP) to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment to be **eligible for coverage.**

Based on review of available data, the Company may consider ECP as a technique to treat acute graft-versus-host disease (GVHD) that is refractory to medical therapy to be **eligible for coverage.**

Based on review of available data, the Company may consider ECP as a technique to treat chronic GVHD that is refractory to medical therapy to be **eligible for coverage.**

Based on review of available data, the Company may consider ECP as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma (CTCL) to be **eligible for coverage.**

Based on review of available data, the Company may consider ECP as a technique to treat early stage (I/II) CTCL that is progressive and refractory to established nonsystemic therapies to be **eligible for coverage.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers ECP in all other situations related to treatment or prevention of rejection in solid-organ transplantation to be **investigational.***

Based on review of available data, the Company considers ECP as a technique to treat acute GVHD or chronic GVHD that is either previously untreated or is responding to established therapies to be **investigational.***

Based on review of available data, the Company considers ECP as a technique to treat either the cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, multiple sclerosis, diabetes, autoimmune bullous disorders, severe atopic dermatitis, or Crohn disease to be **investigational. ***

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Based on review of available data, the Company considers ECP as a technique to treat early stage (I/II) CTCL that is either previously untreated or is responding to established nonsystemic therapies to be **investigational.***

Based on review of available data, the Company considers ECP for all other indications to be **investigational.***

Policy Guidelines

ORGAN REJECTION AFTER SOLID ORGAN TRANSPLANT

A regimen of immunosuppressive therapy is standard of care for the treatment of solid organ rejection. Therefore, refractory rejection is defined as rejection that fails to respond adequately to a standard regimen of immunosuppressive therapy.

Recurrent allograft rejection is defined as having at least 2 rejection episodes that recurred after standard immunosuppressive therapy.

There is no standard schedule for ECP, and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with 2 consecutive days of ECP in month 1, followed by biweekly therapy on 2 consecutive days in months 2 and 3, then monthly on 2 consecutive days in months 4 through 6.

GRAFT-VERSUS-HOST DISEASE

Methylprednisolone is considered first-line treatment of acute GVHD. For chronic GVHD, an alternating regimen of cyclosporine and prednisone is commonly used; other therapies include antithymocyte globulin, corticosteroid monotherapy, and cytotoxic immunosuppressive drugs such as procarbazine, cyclophosphamide, or azathioprine. Therefore, refractory disease is defined as GVHD that fails to respond adequately to a trial of any of these therapies.

Treatment schedule and duration of ECP for GVHD have not been optimally defined. Guidelines and consensus statements have generally recommended 1 cycle (i.e., ECP on 2 consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response; discontinuation is generally recommended for no or minimal response.

CUTANEOUS T-CELL LYMPHOMA STAGING

CTCL staging is based on the tumor, node, metastases (TNM) classification system (see Table PG1).

Table PG1. Cutaneous T-cell Lymphoma Staging

Stage	Tumor T, N, and M Categories
IA	T1N0M0
IB	T2N0M0
IIA	T1-2N1M1
IIB	T3N0-1M0

III	T4N0-1M0
IVA	T1-4N2-3M0
IVB	T1-4N0-3M1

Sézary Syndrome
According to the World Health Organization–European Organization for Research and Treatment of Cancer, Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. The International Society of Cutaneous Lymphomas recommends an absolute Sézary cell count of at least 1000 cells per cubic millimeter, in the presence of immunophenotypical abnormalities (CD4/CD8 ratio >10; loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5; or both), or the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.

Background/Overview

ORGAN REJECTION TREATMENT AFTER SOLID ORGAN TRANSPLANT
The standard of care for treatment of organ transplant rejection is immunosuppression, with the particular regimen dictated by the organ being transplanted. As organ transplantation success rates have improved, more patients are facing the morbidity and mortality associated with immunosuppressive therapies developed to prevent rejection of the transplanted organ. Immunosuppressive therapies are used to lower the responsiveness of the recipient's immune system, decreasing the chance of rejection. Unfortunately, portions of the immune system responsible for the prevention of viral, fungal, and bacterial infection also are affected. This can, in turn, lead to serious infections, including opportunistic infections.

Although first approved for the treatment of CTCL, ECP has more recently been used as a supplement to conventional therapies in the area of solid organ transplantation. Reports of the successful use of ECP in human cardiac transplant recipients were published in 1992 and use in other transplant patients followed. Although the specific mechanism of action of ECP is unknown, the reinfusion of treated leukocytes seems to specifically suppress the patient's immune response to the donor organ, although maintaining the body's ability to respond to other antigens. The specificity of ECP to target the immune response to the transplanted organ allows ECP to decrease organ rejection without an increased risk of infection, common with immunosuppressive drugs.

GRAFT-VERSUS-HOST DISEASE
Given that GVHD is an immune mediated disease, ECP can be used to treat GVHD after a prior allogeneic cell transplant. In fact, GVHD can be categorized in 2 ways: (1) as an acute disease, occurring within the first 100 days after the infusion of allogeneic cells; or (2), as a chronic disease, which develops sometime after 100 days. Acute GVHD is commonly graded from I to IV, ranging from mild disease, which is characterized by a skin rash without involvement of the liver or gut, to grades III and IV, which are characterized by generalized erythroderma, elevated bilirubin levels, or diarrhea. Grade III acute GVHD is considered severe, and grade IV is considered life-threatening. Chronic GVHD typically presents with more diverse symptomatology resembling autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, or rheumatoid arthritis. Chronic GVHD may affect the mouth, eyes,

respiratory tract, musculoskeletal system, and peripheral nerves, as well as the skin, liver, or gut—the usual sites of acute GVHD.

AUTOIMMUNE DISEASE

The use of ECP as a treatment of autoimmune disease is based on the premise that pathogenic lymphocytes form an expanded clone of cells, which are damaged when exposed to ultraviolet light in the presence of agent 8-methoxypsoralen (8-MOP). It is hypothesized that the resulting damage induces a population of circulating suppressor T cells targeted against the light-damaged cells. It is further hypothesized that these suppressor T cells are targeted at a component of the cell that is common to the entire clone of abnormal cells (i.e., not just the light-sensitized cells), thus inducing a systemic effect. However, although scleroderma and other autoimmune diseases are associated with the presence of circulating autoantibodies, it is unknown how these antibodies are related to the pathogenesis of the disease. As discussed in this evidence review, photopheresis is not associated with consistent changes in autoantibody levels.

T-CELL LYMPHOMA

Cutaneous T-Cell Lymphoma

According to the National Cancer Institute, CTCL is a neoplasia of malignant T lymphocytes that initially presents as skin involvement. CTCL is extremely rare, with an estimated incidence of approximately 0.4 per 100,000 annually, but because most are low-grade malignancies with long survival, overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sézary syndrome, account for approximately 60% and 5% of new cases of CTCL, respectively.

CTCL is included in the Revised European-American Lymphoma classification as a group of low-grade T-cell lymphomas, which should be distinguished from other T-cell lymphomas that involve the skin, such as anaplastic large cell lymphoma, peripheral T-cell lymphoma (PTCL), adult T-cell leukemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitis T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis.

Mycosis fungoides typically progresses from an eczematous patch/plaque stage, covering less than 10% of the body surface (T1), to a plaque stage, covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sézary syndrome is an advanced form of mycosis fungoides with generalized erythroderma (T4) and peripheral blood involvement (B1) at presentation. Cytologic transformation from a low-grade lymphoma to a high-grade lymphoma sometimes occurs during the course of these diseases and is associated with poor prognosis. A common cause of death during the tumor phase is sepsis from *Pseudomonas aeruginosa* or *Staphylococcus aureus* caused by chronic skin infection with staphylococcus species and subsequent systemic infections.

The natural history of mycosis fungoides is typically indolent. Symptoms may present for long periods of time (mean, 2-10 years) as waxing and waning cutaneous eruptions. The prognosis of patients with mycosis fungoides or Sézary syndrome is based on the extent of disease at presentation and its stage.

Lymphadenopathy and involvement of peripheral blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. Median survival after diagnosis varies by stage. Median survival in patients with stage IA disease exceeds 20 years, with most deaths in this group typically unrelated to mycosis fungoides. In contrast, median survival in patients with stage III or IV disease is less than 5 years; more than 50% of these patients die of their disease.

Appropriate therapy of CTCL depends on a variety of factors, including stage, the patient's overall health, and the presence of symptoms. In general, therapies can be categorized into topical and systemic treatments that include ECP. In contrast to more conventional lymphomas, CTCL is usually not curable (unless caught in its earliest stages). Thus, systemic cytotoxic chemotherapy is avoided except for advanced stage cases. Partial or complete remission is achievable, although most patients require lifelong treatment and monitoring.

Peripheral T-Cell Lymphoma
PTCL, is a group of rare and usually aggressive non-Hodgkin lymphomas that develop from mature T cells. This disease comprises approximately 10% to 15% of all cases of non-Hodgkin lymphoma in the United States and generally occurs in adults 60 years of age or older. Standards of care are evolving, including the use of hematopoietic cell transplantation.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Two photopheresis systems (Therakos, West Chester, PA) were approved by the U.S. FDA through the premarket approval process. Both systems are approved for use in ultraviolet-A (UVA) irradiation treatment, in the presence of the photoactive drug 8-MOP, of extracorporeally circulating leukocyte-enriched blood, in the palliative treatment of skin manifestations of CTCL, in persons who have not been responsive to other forms of treatment. The 2 systems are:

- UVAR®‡ XTS Photopheresis System (FDA approved in 1987).
- CELLEX®‡ (FDA approved in 2009).

8-MOP (UVADEX®)‡ is FDA approved for extracorporeal administration with the UVAR XTS or CELLEX Photopheresis System in the palliative treatment of the skin manifestations of CTCL unresponsive to other forms of treatment.

The use of either Therakos Photopheresis System or UVADEX for other conditions is off-label. FDA product code: LNR.

Centers for Medicare and Medicaid Services (CMS)
Solid Organ Transplants
Based on a 2006 evidence review, the CMS concluded that ECP is reasonable and necessary for persons with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment.

Effective 2012, Medicare also provided coverage for ECP for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation only when ECP is provided under a clinical research study that meets certain conditions.

Graft-Versus-Host Disease
Effective 2006, Medicare provided coverage of ECP for patients with chronic GVHD whose disease is refractory to standard immunosuppressive drug treatment.

Autoimmune Disorders
There are no national coverage decisions on the use of ECP for the treatment of autoimmune disease.

T-Cell Lymphoma
Based on a 1988 evidence review, the CMS concluded that ECP is reasonable and necessary for palliative treatment of skin manifestations of CTCL that has not responded to other therapy.

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition. The following is a summary of the key literature to date.

ORGAN REJECTION AFTER SOLID ORGAN TRANSPLANT

Heart Transplant

Acute Rejection
A 1992 RCT compared the efficacy of ECP with corticosteroids for the treatment of heart transplant rejection. Costanzo-Nordin et al enrolled 16 heart transplant patients and randomized to ECP (n=9) or corticosteroids (n=7). Recipients of orthotopic transplanted hearts were eligible if endomyocardial biopsy (EMB) showed moderate rejection (grades 2, 3A, 3B). Participants were excluded for leukopenia; hemodynamic compromise (HC rejection), manifested clinically or by a minimum 25% decrease in cardiac output and a minimum 25% increase in mean pulmonary artery wedge pressure; and/or allergy or intolerance to psoralen. Corticosteroids were dosed at oral prednisone 100 mg/d for 3 days or intravenous methylprednisolone 1 g/d for 3 days at the discretion of the managing physician. If on the seventh day EMB had not demonstrated improvement in rejection grade, treatment was repeated. If rejection grade persisted after retreatment, patients were given oral methotrexate 10-mg at weekly intervals for 8 weeks. Participants were followed for a mean of 6.2 months, and all participants completed the study. Those who participated in ECP treatment generally only received the treatment once. The only reason for multiple treatment was if an

inadequate number of cells had been treated; in those cases, an additional treatment was given 48 hours later. Eight of 9 rejection episodes treated with ECP improved; all 7 rejection episodes treated with corticosteroid ds resolved. Improvement was seen a mean of 7 days (range, 5-20 days) after ECP and 8 days (range, 6-67 days) after corticosteroid treatment. Seven infections occurred during follow-up, five in the corticosteroid group, and two in the ECP group. No other adverse events were observed with ECP. The authors noted that major limitations of the trial included small sample size and a wide range in time from transplant to study entry. They concluded that ECP and corticosteroid in this small group with short-term follow-up appeared to have similar efficacies for the treatment of moderate heart transplant rejection. They also noted the reduced number of infections and no other observed harms associated with ECP.

Recurrent and/or Refractory Rejection

In 2006, Kirklin et al published a comparative study of 343 heart transplant recipients. Thirty-six patients were treated with ECP for rejection and formed the treatment group. Patients were 18 years of age or older, treated from 1990-1993, and followed to May 2004. Indications for ECP were episodes of rejection with HC rejection (n=12); recurrent (n=9), or persistent (n=11) rejection; or prophylaxis in the presence of antidonor antibodies (n=4). ECP consisted of psoralen in a 2-day treatment protocol every 3 to 6 weeks for 18 months; maintenance immunosuppression used cyclosporine- or tacrolimus-based therapy with prednisone for the first 4 to 6 months and azathioprine, which was replaced by mycophenolate mofetil during the later years of the study. The primary outcome was incidence of HC rejection or death from rejection (rejection death). Hazard functions were used for analysis. Patients with at least 3 months of ECP were considered to have effective photopheresis treatment; patients who received less than 3 months of treatment were considered untreated but were analyzed as part of the photopheresis group. The period after 3 months of ECP was associated with a reduction in risk of HC rejection or rejection death (risk reduction, 0.29). A sustained decrease in the risk of HC rejection or HC death was observed for the photopheresis group through 2 years of follow-up. This study was not randomized; risk factor analysis showed that the ECP group had higher baseline risk of HC rejection or rejection death. Changes in maintenance immunotherapy over time may confound the results, as patients in the comparison group did not receive a consistent regimen. However, improvements in maintenance immunotherapy would tend to obscure any treatment effect of ECP compared with evolving immunotherapy regimens. This bias, therefore, strengthens the authors' conclusion that ECP reduces the risk of subsequent HC rejection and/or death from rejection in patients at high risk of rejection.

In 2000, Dall'Amico et al reported on a case series of 11 heart transplant recipients with recurrent rejection. Participants were eligible if they had acute rejection and at least 2 rejection episodes after standard immunosuppressive therapies in the 3 months before ECP. ECP was administered with ultraviolet-A radiation (UVAR) photopheresis instruments in 2 consecutive treatments at weekly intervals for 1 month, at 2-week intervals for 2 months, and then monthly for 3 months. One patient with grade 3B rejection received an intravenous pulse of corticosteroids during the first ECP cycle. Patients were followed for 60 months. During follow-up, 1 patient died from hepatitis C virus and another dropped out due to rejection unresponsive to ECP and high-dose corticosteroids; all others completed the study. All acute rejection episodes were successfully reversed after a mean of 14.2 days (range, 7-32 days). In terms of rejection relapse, the fraction of EMBs with grade 0/1A rejection increased during ECP from 46% to 72%, and those

showing 3A/3B rejection decreased from 42% to 18%. One of 78 EMBs during ECP showed 3B rejection compared with 13 of 110 during the pre-ECP period. Six rejection relapses were observed during follow-up, two of which occurred during the tapering of oral corticosteroids. Four were reversed by ECP, one by intravenous corticosteroids, and one by methotrexate after the failure of both ECP and intravenous corticosteroids. The mean dose of immunosuppressive drugs (corticosteroids, cyclosporine, azathioprine) was reduced after 6 months of ECP therapy. One patient with anemia and low body weight experienced symptomatic hypotension during treatment, and another had interstitial pneumonia. The authors concluded that ECP was a well-tolerated treatment, which permitted better recurrent rejection control and reductions in immunosuppressive therapy. Follow-up time and patient population are adequate; the study was limited by its small size and lack of comparison group.

In 2001, Maccherini et al presented a case series of 12 patients treated with ECP for recurrent rejection. Inclusion criteria were recurrent rejection (n=5), recurrent infections associated with acute rejection (n=2), and a grade 3A acute rejection 2 years after transplantation (n=5). Mean post-ECP follow-up was 23.3 months. ECP was performed as 2 treatments weekly for 1 month, once weekly for 2 months, and then once monthly for 2 months. The total number of rejection episodes decreased from a mean of 3 per patient pre-ECP to 0.4 per patient post-ECP. All patients reduced immunosuppressive therapy. There were no adverse events or infections reported during follow-up. The authors concluded that ECP was safe and effective for heart transplant patients with recurrent rejection and reduced both rejection episodes and immunosuppressive therapy.

Lehrer et al (2000) presented similar results in 4 patients treated with ECP for severe refractory (grade 3A-4) cardiac allograft rejection. All 4 patients experienced reversal of their rejection. Three patients improved following 2 consecutive days of treatment, and the fourth responded after three 2-day treatments. Two patients subsequently died of acute rejection at 9 weeks and 10 weeks, respectively, after completing ECP. The other two showed no signs of rejection, one at 6 years and the other at 4 months after completion of ECP. The results of this small case series are consistent with the results of the previous two slightly larger studies.

Carlo et al (2014) reported their experience with ECP in 20 pediatric heart transplant recipients between 1990 and 2012 at a U.S. university. Patients who had transplants at a median age of 12.7 years (range, 0.3-18.5) and received their first ECP treatment at a median age of 15.3 years (range, 7.3-31 years). Indications for ECP included rejection with HC, rejection without HC, and prophylaxis. One- and 3-year survival rates after ECP were 84% and 53%, respectively. Survival outcomes were worse in noncompliant than compliant patients.

Prevention of Rejection

A 1998 RCT by Barr et al investigated ECP for the prevention of rejection after cardiac transplant. Sixty consecutive adult cardiac transplant recipients at 12 clinical sites (9 in U.S., 3 in Europe) were randomized to both immunosuppressive therapy plus ECP (n=33) or immunosuppressive therapy alone (n=27). Standard immunosuppressive therapy consisted of cyclosporine, azathioprine, and prednisone. Entry criteria were adequate peripheral venous access and residence less than 2 hours away from the transplant

center. ECP treatment was delivered on days 1, 2, 5, 6, 10, 11, 17, 18, 27, and 28 in month 1; then for 2 consecutive days every 2 weeks in months 2 and 3; and then for 2 consecutive days every 4 weeks in months 4 to 6 for a total of 24 ECP procedures per patient. The primary end point was the number and frequency of histologic acute rejection episodes. Pathologists were blinded to treatment assignment. Follow-up for the primary end point was 6 months; an additional 6 months of follow-up was completed to assess safety and survival.

After 6 months of follow-up, the mean number of acute rejection episodes per patient was statistically greater in the standard therapy group (1.4) than in the ECP group (0.9). In the standard therapy group, 5 patients had no rejection episodes, nine had one, nine had two, and four had three or more. In the ECP group, 13 had none, 14 had one, 3 had two, and 3 had three or more. These differences were statistically significant. There were no differences in 6- or 12-month survival rates, number of infections, or time to first rejection between groups. During a subsequent 6 months of follow-up, there was no difference between groups in the number of acute rejection episodes; however, because of time management issues, institutions reverted to nonstandardized protocols during this interval. The authors concluded that ECP plus standard immunosuppressive therapy significantly reduced the risk of cardiac rejection without increasing the risk of infection. More long-term follow-up is necessary to see the effects of a reduction of acute rejection on long-term graft function, survival of the transplant recipient, and development of graft vasculopathy.

Section Summary: Organ Rejection After Heart Transplant
Evidence for the use of ECP in heart transplant patients relates to 3 indications: acute rejection; recurrent and/or refractory rejection; and prevention of rejection. For acute rejection, a 1992 randomized trial enrolled 16 heart transplant recipients. The use of ECP in combination with immunosuppressive therapy had similar efficacy compared with immunosuppressive therapy alone, with fewer infections in the ECP group. This study was small, and time from transplantation to study entry varied.

The use of ECP for recurrent and/or refractory cardiac allograft rejection has been the focus of most of the research on ECP. Although data are from nonrandomized studies, a comparative study of 343 cardiac transplant recipients in which 36 patients received ECP has been completed. The authors showed that at 3 months, ECP was related to a risk reduction of HC rejection or rejection death (relative risk [RR], 0.29). A reduction in HC rejection or rejection death was observed through 2 years of follow-up. Although results of this trial might be confounded by improvements in immunosuppressive therapy regimens over time, they are consistent with the literature for this indication, which indicates a benefit of ECP in patients with recurrent or refractory cardiac rejection. Thus, the evidence to date, comprising a nonrandomized comparative study, 3 case series, and a case report of 4 patients, provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy.

For prevention of rejection, 1 randomized trial from 12 clinical sites randomized 33 patients to immunosuppressive therapy plus ECP and 27 patients to immunosuppressive therapy alone. Differences between numbers of acute rejection episodes were statistically significant; however, there was no difference in survival at 6 months. Thus, evidence to date is insufficient to permit conclusions concerning the effect of

ECP on net health outcome for the treatment and prevention of acute cardiac rejection. Studies with more patients and longer follow-up are needed.

Lung Transplant

Acute Rejection

In 2000, Villanueva et al reported on a retrospective review of 14 transplant recipients (7 bilateral lung, 6 single lung, 1 heart-lung) who received ECP for BOS. All patients were refractory to standard immunosuppressive therapy. ECP was administered every 2 weeks for 2 months and then monthly for 2 months (for a total of 6 treatments). Four of 8 patients with baseline grade of 0 or 1 BOS had improvement in BOS or stabilization after treatment. Mean survival after ECP was 14 months. Three of 4 patients received ECP during a concurrent episode of acute rejection; all 3 patients had complete resolution of acute rejection after treatment. Another series published in 1999 by Salerno et al reported on 2 patients with histologic reversal of concurrent acute rejection after treatment with ECP. These 2 studies reported on only 5 cases of ECP used to treat acute rejection. Additional prospective trials are needed to determine the efficacy of ECP to treat acute rejection after lung transplantation.

In 2008, Benden et al published a single-center study of 24 patients treated with ECP, 12 for recurrent acute rejection and 12 for BOS (reviewed in the next section). The primary outcome measure was clinical stabilization of rejection after ECP. Twelve patients had biopsy-confirmed chronic acute rejection, defined as two or more biopsy-proven episodes of acute rejection before ECP. Of 11 patients who had follow-up biopsies during treatment, 2 patients had an episode of biopsy-proven acute rejection. All 12 patients experienced clinical stabilization after 12 ECP cycles; none experienced BOS. Treatment was well-tolerated with no ECP-related adverse events reported. Median patient survival post-ECP treatment was 4.9 years (range, 0.5-8.4); however, these data are not specific to the group being treated for acute rejection.

Chronic Rejection Refractory to Corticosteroid and Refractory BOS

In 2013, Greer et al reported a retrospective analysis of 65 patients treated at a single institution with ECP for chronic lung allograft dysfunction, defined as deteriorating forced expiratory volume in 1 second (FEV_1) due to BOS, as well as reduced total lung capacity and broncho-alveolar lavage neutrophilia. Fifty-one (78%) patients had undergone double lung transplant, 9 (14%) patients had undergone single-lung transplant, and 5 (8%) patients had undergone heart-lung transplant. The median time to chronic lung allograft dysfunction diagnosis was 3 years (interquartile range [IQR], 2-5 years). Patients had progressed (≥10% decline in FEV_1) on first-line azithromycin. At ECP initiation, 35 (54%) patients were graded BOS stage 3; 21 (32%) patients were BOS stage 2; and 9 (14%) patients were BOS stage 1 or 0p (potential BOS). ECP was administered every 2 weeks for 3 months; subsequent treatments were administered not more than 8 weeks apart to maintain stabilized graft function. The median follow-up time was 17 months; 44 patients who continued treatment beyond 3 months received a median of 15 ECP treatments. Eight (12%) patients achieved a 10% or greater improvement in FEV_1, considered treatment response; 27 (42%) patients experienced no change in FEV_1; and 30 (46%) patients experienced a 10% or greater decline in FEV_1, considered progressive disease. Median progression-free survival was 13 months (IQR, 10-19

months) among responders and 4 months (IQR, 3-6 months) among those who did not respond. This study was retrospective and lacked a control group.

Jaksch et al (2012) reported on a prospective series of 194 patients who developed BOS and received standard treatment (n=143) or standard treatment plus ECP (n=51). Patients who did not respond to standard immunosuppressive therapy and showed further decline of lung function received ECP when reaching BOS stage 1 or higher. ECP was administered on 2 successive days every 2 weeks during the first 3 months and then every 4 weeks until the end of therapy. The use of ECP was discontinued after a minimum of 3 months if lung function decreased significantly. If FEV_1 improved or stabilized, ECP was continued for a minimum of 6 months. Change in FEV_1 at 3, 6, and 12 months after ECP initiation was used as a surrogate for treatment response. The primary end point was change in lung function before and after ECP. Eighteen percent of patients receiving ECP experienced an improvement in FEV_1 for more than 1 year after initiation of ECP, and 12% showed improvement for only 3 to 6 months. FEV_1 stabilized in 31% of patients and declined in 39%. Kaplan-Meier method analysis showed a significant difference in responders and nonresponders in survival and the need for transplant. Compared with patients who had BOS and did not receive ECP but were similar in demographics and treatment history, the ECP group had longer survival (p=0.046) and underwent fewer transplantations (18 vs 21; p=0.04). Mean time to transplant also was twice as long in the ECP group (1839 days vs 947 days; p=0.006). No ECP-related adverse events were reported. Although this study was not randomized, a group with similar demographics and treatment history was available for comparison.

Lucid et al (2011) published a review of 9 patients treated with ECP between 2008 and 2009. Median follow-up was 23 months posttransplant (range, 9-93 months), and the median age was 38 years (range, 21-54 years). The primary indication for ECP was symptomatic progressive BOS that failed previous therapy. Patients were treated weekly with 2 sessions of ECP for 3 to 4 weeks. Treatment frequency then decreased to every 2 to 3 weeks, with the goal of reducing treatment to every 4 weeks. Clinical response was defined as symptomatic improvement, decreased dependency on supplemental oxygen, and improved pulmonary function tests. Six (67%) of 9 patients responded to ECP after a median of 25 days. No ECP-related complications occurred in this series. As in several previous studies, this report has no control group for comparison.

Morrell et al (2010) published a retrospective case series of all lung transplant recipients (n=60) who received ECP for progressive BOS at a university-based hospital. Ninety-five percent of patients had received a bilateral lung transplant, and 58% had grade 3 BOS. The indication for ECP was progressive decline in lung function that was refractory to standard immunosuppressive therapy. The primary end point was the rate of change in lung function before and after the initiation of ECP. ECP was delivered as 2 cycles on days 1, 2, 5, 6, 10, 11, 17, 18, 27, and 28 during the first month (10 treatments); biweekly for the next 2 months (8 treatments); and then monthly for the following 3 months (6 treatments), for a total of 24 treatments. Sixty patients were followed from the time of lung transplantation to death or the end of the study (July 2008). Median follow-up was 5.4 years (range, 1.0-16.6 years). At the end of the study, 33 patients were still alive; 4 deaths occurred early in the study. Most deaths were due to the progression of respiratory failure, except for one due to sepsis and another to graft failure. In the 6 months before ECP, the

mean rate of decline in FEV_1 was -116.0 mL/mo; after ECP, the mean rate of decline was -28.9 mL/mo (mean difference, 87.1 mL; 95% confidence interval [CI], 57.3 to 116.9 mL). The rate of decline in lung function decreased in 44 (79%) patients, and lung function improved (increase in FEV_1 above pretreatment values) in 14 (25%) patients. Through 12 months of follow-up, mean improvement in FEV_1 was 145.2 mL. Ten (17%) of 60 patients experienced adverse events. Eight were hospitalized for catheter-related bacteremia; 1 case resulted in death. All cases resulted from indwelling pheresis catheters. The authors concluded that ECP was associated with a significant reduction in the rate of decline in lung function. This reduction was sustained through 12 months of follow-up. The major limitations of this study were its retrospective nature and lack of a control group. Most patients had grade 3 BOS and, therefore, may differ from patients with other grades. Statistical analyses were robust.

As mentioned, Benden et al (2008) published a single-center study of 24 patients treated with ECP (12 for BOS and 12 for recurrent acute rejection). ECP was delivered when BOS grade worsened despite standard therapy. At the start of therapy, 5 patients had BOS grade 1; 2 patients had BOS grade 2; and 5 patients had BOS grade 3. Before ECP, the rate of decline in FEV_1 was 112 mL/mo compared with 12 mL/mo after ECP (mean difference, 100 mL/mo; range, 28-171 mL/mo). However, ECP did not seem to affect absolute FEV_1. Treatment was well-tolerated, with no ECP-related adverse events reported. Median patient survival was 7.0 years (range, 3.0-13.6 years); median patient survival post-ECP was 4.9 years (range, 0.5-8.4 years). However, results were pooled and not specific to the 12 patients with BOS.

Also as noted, Villanueva et al (2000) retrospectively reviewed outcomes of 14 transplant recipients (7 bilateral lung, 6 single lung, 1 heart-lung) who received ECP for BOS. All patients were refractory to standard immunosuppressive therapy. ECP was administered every 2 weeks for 2 months and then once monthly for 2 months (for a total of 6 treatments). In 4 of 8 patients with grade 0 or 1 BOS, BOS improved or stabilized after treatment. Mean survival after ECP was 14 months. Six patients with initial BOS grade 2 or higher suffered progression of their BOS after ECP. Mean survival after ECP was 14 months. Four of these patients died of chronic rejection, and one died of lung cancer. The remaining patient survived to retransplantation. Two of the 14 patients developed line-related sepsis, which cleared with antibiotic therapy and catheter removal.

In 1999, O'Hagan et al published a case series of 6 patients who received ECP for BOS refractory to standard immunosuppressive therapy and various other strategies including antithymocyte globulin, methotrexate, monomurine anti-C3 antibody, and tacrolimus. ECP was performed on 2 consecutive days twice a month until FEV_1 stabilization. Treatment was then repeated every 4 to 6 weeks. Four of the 6 patients had temporary stabilization of their airflow obstruction with minimal adverse events. BOS grade was not reported. The study lacked a control group. Larger prospective randomized trials are necessary to examine the comparative effects of ECP for patients with BOS stratified by BOS grade.

Prevention of BOS and/or Transplant Rejection
There are no studies addressing the prophylactic effects of ECP for lung transplant recipients.

Section Summary: Organ Rejection After Lung Transplant
Evidence on the use of ECP in lung transplant recipients relates to 2 indications: acute rejection and chronic rejection refractory to corticosteroids or refractory BOS. Data for acute rejection are very limited and do not permit any conclusions. Data derive from subgroups of larger studies that received ECP during periods of acute rejection. Use of ECP in this population needs a prospective, randomized trial focused specifically on the treatment for acute rejection.

The bulk of the evidence for ECP in lung transplantation focuses on treatment of refractory BOS. The primary limitations of these data are that they derive from nonrandomized and uncontrolled studies. Further, the evidence is inconsistent, with some studies reporting ECP to be beneficial in those with early refractory BOS but not in those with grade 2 or higher BOS, which contrasts with a retrospective series of 60 patients who responded well to ECP (nearly 60% of these patients were BOS grade 3). Prospective, RCTs are necessary, and analyses should be stratified by BOS grade, because there is some evidence that ECP efficacy may vary by BOS grade at the start of therapy.

Liver
The published evidence on the use of ECP in liver recipients is from a group in Italy. Urbani et al (2004-2008) published a series of articles on various potential applications of ECP for liver transplant recipients. The first, from 2004, retrospectively reviewed 5 patients who received liver transplantation and ECP for biopsy-proven allograft rejection. Indications for ECP were recalcitrant ductopenic rejection with hepatitis C virus recurrence; corticosteroid-resistant acute rejection (2 patients); severe acute rejection in a major ABO-incompatible liver graft; and severe acute rejection in a patient with a proven corticosteroid allergy. ECP was performed twice weekly for 4 weeks, then every 2 weeks for 2 months, and then once monthly. ECP was discontinued when indicated by biopsy-proven reversal of rejection or the absence of clinically evident rejection relapse. Liver function tests improved to baseline in all but 1 patient, and no procedure-related complications were reported. At a median follow-up of 7.9 months, 3 patients were off ECP treatment with normal liver function tests and low-level immunosuppressive therapy, and 2 patients continued ECP treatments with full-dose immunosuppressive therapy.

The second study, from 2007, was a nonrandomized comparative assessment of 36 patients (18 treatment, 18 historical matched controls) who received ECP to delay the introduction of calcineurin inhibitors (CNI) to avoid CNI toxicity. Patients were included if they were at risk of postliver transplant renal impairment and neurologic complications, defined as having at least one of the following risk factors: a calculated glomerular filtration rate of 50 mL/min or less at transplantation; severe ascites; history of more than 1 hospitalization for encephalopathy within 1 year of transplant and/or 1 hospitalization within 1 month of transplantation; or age 65 years or older. Outcome measures were treatment success rate, defined as the ratio of patients with full CNI-sparing or delayed immunosuppression; interval from liver transplantation to CNI introduction; safety of ECP; and need for biopsy. ECP was initiated during the first week posttransplant; 2 different systems (Therakos, PIT) for photopheresis were used, and treatment was given as scheduled for the system used. All 18 patients tolerated and completed ECP therapy. For 17 patients, CNI was introduced at a mean of 8 days; 1 patient remained CNI-free for 22 months. Acute rejection occurred in 5 (28%) of 18 patients in the ECP group and in 3 (17%) of 18 historical controls. One-, 6-, and 12-month survival was

94.4%, 88.1%, and 88.1%, respectively, for ECP recipients vs 94.4%, 77.7%, and 72.2%, respectively, for controls. The authors concluded that the addition of ECP improved management of liver transplant patients in the early transplant phase, delayed CNI introduction, and lower CNI-related mortality. This study was not randomized and had a small number of patients.

The third (2008) reported on three fields of interest for ECP as prophylaxis of allograft rejection in liver transplant patients:

- Use of ECP to delay CNI among high-risk liver transplant recipients to avoid toxicity (previously discussed);
- Use of ECP for prophylaxis of acute cellular rejection among ABO-incompatible liver transplant recipients (11 consecutive patients received ECP plus immunosuppressive therapy with no evidence of acute rejection through 568 days of follow-up); and
- Use of ECP in hepatitis C virus–positive patients (use of ECP for the prevention of hepatitis C virus recurrence is beyond the scope of this policy).

Except for the first area, these studies were small and lacked comparison groups; RCTs are needed for the proper assessment of outcomes.

Section Summary: Organ Rejection After Liver Transplant
In liver transplantation, evidence for the use of ECP is limited, and research to date has been generated by a group in Italy. Although there is a comparative (nonrandomized) study, it involved only 18 cases and 18 historical controls. The focus in liver transplantation has been on prevention of rejection with ECP; this would be best addressed by a RCT comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. The evidence to date is insufficient to permit conclusions concerning the effect of ECP on the net health outcome for liver transplant patients.

Kidney Transplant

Recurrent and/or Refractory Rejection
The largest reported group of renal patients to receive ECP was at a hospital in Australia. In 2009, Jardine et al published a prospective case series of 10 patients treated with ECP for recurrent and/or refractory rejection after renal transplantation. ECP was delivered weekly for 4 weeks, then every 2 weeks. Total treatment range was 2 to 12 treatments for more than 5 to 20 weeks. Median follow-up was 66.7 months after transplant and 65.0 months from initiation of ECP. Indication for ECP was acute resistant or recurrent rejection in 9 patients and the need to avoid high-dose corticosteroids in another. Refractory rejection resolved in all patients through the stabilization of renal function. The authors concluded that ECP might have a role as an adjunct to current therapies in patients with refractory rejection. Although this is the largest series of renal patients, it was still a small one, and lacked a comparison group. Renal biopsies were not used to document therapeutic response.

The remainder of the evidence in renal transplant recipients comes from case reports on 32 patients. Twenty-six of these patients had refractory rejection. After ECP, renal function improved in 19 (73%) of 26

patients, 3 patients were stable, and 4 patients returned to dialysis because of deteriorating function. Reports of long-term outcomes varied. Among 22 patients who showed initial improvement and/or stabilization of renal function, five had improved function at 1 year, one was stable at 25 months, 5 were stable at 1 year, seven were rejection-free at 2 to 5 years, and one graft was lost. Long-term outcomes were not reported for 3 patients.

Section Summary: Organ Rejection After Kidney Transplant

For renal transplant recipients, evidence for the use of ECP is sparse. Forty-two ECP-treated patients have been reported in the literature. Studies have consistently reported evidence of benefit from ECP for those with refractory rejection. However, there are no comparative studies, and current numbers are too small to permit conclusions. A prospective, randomized trial, with histologic confirmation of treatment response is needed. This trial would randomize patients to immunosuppressive therapy or immunosuppressive therapy with ECP to address whether there is an additional benefit from ECP for patients with refractory rejection after renal transplantation.

GRAFT-VERSUS-HOST DISEASE

ECP for the treatment of acute and chronic GVHD was addressed in a 2001 Technology Evaluation Center (TEC) Assessment that offered the following observations and conclusions: For acute GVHD or chronic GVHD in previously untreated patients or in those responding to conventional therapy, no studies met selection criteria and reported results of ECP, alone or in combination with other therapies. Therefore, ECP failed to meet TEC criteria for these indications. Studies focusing on patients with chronic GVHD unresponsive to other therapies reported resolution or marked improvement of lesions in approximately 50% of patients. Finally, studies of patients with acute GVHD also reported successful outcomes in 67% to 84% of patients with grade 3 disease, but patients with grade 4 disease rarely responded.

Treatment in Pediatrics

Acute and Chronic GVHD

A 2010 retrospective review assessed 73 pediatric patients (age, <18 years) with acute or chronic GVHD after an allogeneic cell transplant unresponsive to 1 week of steroid treatment. Patients received ECP for a minimum of 10 treatments. ECP was administered 2 to 3 times weekly on alternating days until clinical improvement. Treatment was then reduced to 2 procedures per week for 2 weeks, then 2 procedures every other week for 3 weeks, ending with 2 procedures per month until maximum response as clinically indicated. ECP was discontinued if no improvement ($\geq$50% clinical and laboratory response) was seen after 4 weeks. Of 47 patients with acute GVHD, 39 (83%) patients with skin involvement improved, and 7 (87.5%) of 8 patients with mucosal involvement improved. Among patients with chronic GVHD, all 4 (100%) patients with liver involvement improved, and 22 (95.6%) of 23 patients with skin involvement improved.

The literature also includes some small studies that have focused on ECP for treatment of GVHD in children and a larger retrospective case series. This 2007case series reported results of ECP for steroid-resistant GVHD in pediatric patients (age, 6-18 years) who had undergone hematopoietic cell transplantation for a variety of cancers. Patients had acute GVHD (n=15, stages 2-4) or chronic GVHD (n=10, 7 deemed

extensive) that had not responded to at least 7 days of methylprednisolone therapy. Patients received ECP on 2 consecutive days at weekly intervals for the first month, every 2 weeks for 2 months, and then monthly for 3 months. The use of ECP was progressively tapered and discontinued based on individual patient response. Response to ECP was assessed 3 months after ECP ended or after 6 months if the ECP protocol was prolonged. Among patients with acute GVHD, complete response (CR) occurred in all 7 (100%) patients with grade 2 and 2 (50%) of 4 patients with grade 3 disease; none of 4 patients with grade 4 disease responded to ECP. In the group with chronic GVHD, CR occurred in all 3 (100%) patients with limited disease and 1 (14%) of 7 patients with extensive disease. Five (71%) of 7 patients with extensive chronic GVHD had no response to ECP. Adverse events of ECP were generally mild in all cases. These results are similar to those summarized in the 2001 TEC Assessment (previously discussed).

One of the 2 smaller studies reported on 8 children (age, 5-15 years) with refractory chronic GVHD who received ECP and either oral 8-MOP or infusion of an 8-MOP solution into the pheresed lymphocytes. Cutaneous status reportedly improved in 7 patients. Five patients stopped treatment; 3 patients decreased doses of immunosuppressive therapy. In addition, gut involvement resolved in all patients, and liver involvement resolved in 4 of 6 patients. Two years after discontinuation of ECP, 5 patients remained in remission without immunosuppressive therapy. Salvaneschi et al (2001) reported on ECP in refractory GVHD in 23 pediatric patients (age, 5.4-11.2 years). Seven (78%) of 9 patients with acute GVHD experienced either partial response (PR) or CR. Nine (64%) of 14 patients with chronic GVHD experienced PR or CR.

In 2014, Cochrane published 2 systematic reviews, one on acute GVHD and the other on chronic GVHD in pediatric patients. Literature searches were performed in September 2012, and no RCTs were found. Reviewers cited the need for RCTs but stated that “performing RCTs in this patient population will be challenging because of the limited number of patients, the variable disease presentation, and the lack of well-defined response criteria.”

Treatment in Adults

Acute GVHD

In 2015, Zhang et al in China reported a systematic review of prospective studies of ECP for acute GVHD. Literature was searched through September 2014, and 7 cohort studies were included (total N=121 patients). In meta-analyses, pooled overall and CR rates were both 71%. Statistical heterogeneity was considered not high for both results (I^2<50%). The response rate was highest for cutaneous disease (86%), although a funnel plot indicated the presence of publication bias.

Greinix et al (2006) reported findings from a phase 2 (nonrandomized) study of intensified ECP as second-line therapy in 59 patients with poststem cell transplant, steroid-refractory, acute GVHD (grade 2-4). ECP was initially administered on 2 consecutive days (1 cycle) at 1- to 2-week intervals until improvement was noted and thereafter every 2 to 4 weeks until maximal response. At the start of ECP, all patients had been receiving immunosuppressive therapy with prednisone and cyclosporine A. Complete resolution of GVHD was documented in 82% of patients with cutaneous manifestations, 61% with hepatic involvement, and 61%

with gut involvement. Further, CR occurred in 87% and 62% of patients with exclusively skin or skin and liver involvement, respectively; only 25% with GVHD of skin, liver, and gut involvement and 40% with skin and gut involvement obtained a CR of GVHD with ECP therapy. The probability of survival was 59% among patients with CR to ECP, compared with 11% of those who did not achieve CR. Although these results would suggest ECP may be beneficial in the treatment of acute GVHD, the small sample size, few study details in the report, and lack of a standard treatment comparator group limit inferences as to the clinical efficacy of ECP for acute GVHD.

In 2008, Perfetti et al reported on a retrospective review of 23 patients with corticosteroid-refractory acute GVHD (n=10 grade 2; n=7 grade 3; and n=6 grade 4). The median duration of ECP was 7 months (range, 1-33 months) and the median number of cycles per patient was 10. Moreover, CRs were seen in 70%, 42%, and 0% of patients with GVHD grades 2, 3, and 4, respectively. Eleven (48%) patients survived, and 12 (52%) died (10 of GVHD, 2 of relapse of leukemia); 83% of patients treated within 35 days from onset of GVHD responded compared with 47% of patients treated after 35 days (p=0.1). Although these findings would suggest that ECP may provide benefit for patients with refractory acute GVHD, they are limited by a small sample size and the noncomparative study design.

Shaughnessy et al (2010) studied ECP to prevent acute GVHD in patients undergoing standard myeloablative conditioning and allogeneic transplant. ECP was administered before a standard conditioning regimen. Results were compared with historical controls from the Center for International Blood and Marrow Transplant Research database. Multivariate analysis indicated a lower incidence of grade 2, 3, or 4 acute GVHD among patients who received ECP. Adjusted overall survival at 1 year was 83% in the ECP group and 67% among historical controls (RR=0.44; 95% CI, 0.24 to 0.80).

Jagasia et al (2013) reported an international, retrospective comparative analysis of nonconcurrent cohorts who received ECP (n=57) or anticytokine therapy (inolimomab or etanercept; n=41) for steroid-refractory acute GVHD (grade 2 or higher). ECP was initiated at 2 to 3 treatments weekly or biweekly until maximal response and then discontinued (European sites) or tapered (U.S. sites). More patients in the ECP group than in the anticytokine group experienced overall response (CR plus PR; 66% vs 32%, p=0.001) and CR (54% vs 20%, p=0.001). The 2-year overall survival rate was 59% in the ECP group and 12% in the anticytokine group (p not reported).

Rubegni et al (2013) reported on a cohort of 9 patients with grade 2 or 3 steroid-refractory acute GVHD at a single institution in Italy. ECP was administered on 2 consecutive days weekly until improvement and then every 2 weeks; treatment was then tapered as tolerated. At 3 months, the mean dose of methylprednisolone decreased from 2.22 mg/kg to 0.27 mg/kg, and mean dose of cyclosporine decreased from 2.46 mg/kg to 0.77 mg/kg. Six (67%) patients showed a complete skin response. Five (83%) of 6 patients with liver and gastrointestinal tract involvement had CRs. All patients developed chronic GVHD, 7 (78%) while still receiving ECP.

Chronic GVHD

In addition to the 2001 TEC Assessment, several additional publications have reported on the use of ECP to treat GVHD. In 2006, the Ontario Health Technology Advisory Committee (OHTAC) published results of a systematic review of ECP for the treatment of refractory chronic GVHD. OHTAC reported that there was low-quality evidence that ECP improves response rates and survival in patients with chronic GVHD unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory GVHD mostly pertained to study quality and size and heterogeneity in both treatment regimens and diagnostic criteria. OHTAC did, however, recommend a 2-year field evaluation of ECP for chronic GVHD, using standardized inclusion criteria and definitions to measure disease outcomes including response rates, quality of life, and morbidity. There is no current evidence on the OHTAC website of an update.

Malik et al (2014) published a systematic review of ECP for steroid-refractory chronic GVHD. Literature was searched through July 2012 and 18 studies were selected (4 prospective, including 1 RCT [2008], and 14 retrospective; total N=595 patients). In meta-analyses, overall response and CR rates were 64% and 29%, respectively. The pooled response rate was highest for cutaneous disease (74%) and lowest for lung disease (48%). Statistical heterogeneity was high for all results (I^2>60%).

Foss et al (2005) reported on results of a prospective (nonrandomized) study of ECP in 25 patients who had extensive corticosteroid-refractory or corticosteroid-resistant chronic GVHD after allogeneic cell transplantation. ECP was administered for 2 consecutive days every 2 weeks in 17 patients and once weekly in 8 patients until best response or stable disease was achieved. With a 9-month median ECP duration (range, 3-24 months), 20 patients had improvement in cutaneous GVHD, and 6 had oral ulcer healing. 80% of patients reduced or discontinued immunosuppressive therapies. Overall, improvement was reported in 71% of cases with skin and/or visceral GVHD and 61% of those cases deemed to be high-risk patients.

In 2014, Dignan et al reported on a series of 38 consecutive adults who received ECP for chronic GVHD. Median patient age was 47 years (range, 18-73 years). Patients had steroid-refractory or steroid-dependent disease or were intolerant of corticosteroids. Thirty-six (95%) patients were receiving immunosuppressive therapy. ECP was administered on 2 consecutive days every 2 weeks until PR was achieved and was then reduced to monthly treatments. Of note, PR was defined here as minimum 50% improvement from baseline in 1 organ and no evidence of GVHD progression in other organs). Median time from transplant to first ECP was 1.7 years (range, 0.25-7.25 years). Response was assessed after 6 months. Nineteen (50%) patients had a CR (n=2; defined as complete resolution of all signs and symptoms of GVHD) or PR (n=17); all 19 had completed 6 months of ECP. Of 25 patients receiving immunosuppressive therapy who completed 6 months of ECP, 20 (80%) reduced immunosuppressive dose; 5 patients discontinued steroids, and 8 patients had a 50% or greater reduction in steroid dose. Mean improvements in validated quality-of-life measures (Lee Chronic Graft-Versus-Host Disease Symptom Scale and Dermatology Life Quality Index) were clinically and statistically significant in 17 (94%) of 18 patients who completed the questionnaires at 6 months. Five patients developed indwelling catheter-related infections, one had a catheter-related

thrombosis, and another had an increase in red cell transfusion requirements which was attributed to ECP treatments.

Acute GVHD and Chronic GVHD
In 2014, Abu-Dalle et al published a systematic review of prospective studies in patients with steroid-refractory acute or chronic GVHD. Relevant literature was searched through February 2013, and the following items were identified: 1 RCT in patients with chronic GVHD; and 8 cohort studies in patients with acute and/or chronic GVHD (total N=323 patients). In meta-analyses, the overall response rates for acute and chronic GVHD were 69% and 64%, respectively. In both acute GVHD and chronic GVHD, the overall response rates were highest in cutaneous disease (84% and 71%, respectively) followed by gastrointestinal disease (65% and 62%, respectively). Rates of immunosuppression discontinuation were 55% and 23% for acute GVHD and chronic GVHD, respectively. Statistical heterogeneity for most meta-analyses was high (I^2>60%).

Hautmann et al (2013) reported on a cohort of 62 patients with acute GVHD (n=30) or chronic GVHD (n=32) at a single institution in Germany. For acute GVHD, ECP was administered 2 or 3 times weekly on consecutive days until clinical improvement, then 2 treatments on consecutive days biweekly, reducing to monthly, if tolerated. At 3 months, 15 (50%) patients achieved CR or PR (9 [30%] complete). Ten (83%) of 12 patients who continued ECP beyond 3 months and had data available decreased steroid dose by 50% or more. For chronic GVHD, ECP was administered on 2 consecutive days weekly until improvement, then biweekly for 3 to 4 weeks, and then monthly. At 3 months, 14 (44%) patients achieved CR or PR (2 [6%] complete). Five (29%) of 17 patients who continued ECP beyond 3 months had data available and were taking steroids at baseline, decreased steroid dose by 50% or more.

Ussowicz et al (2013) reported on 21 patients with steroid-refractory or steroid-dependent, grade 3 or 4 acute (n=8) or chronic (n=13) GVHD in Poland. For acute GVHD, ECP was administered on 2 consecutive days weekly for up to 4 weeks. Although clinical response was noted in 3 (37.5%) patients, there were no long-term (>18 months after ECP) survivors. For chronic GVHD, ECP was administered on 2 consecutive days every 2 weeks for 14 weeks and then monthly for up to 8 weeks. The 4-year overall survival rate was 67.7%.

Section Summary: Graft-Versus-Host Disease
Evidence for the use of ECP for the treatment of GVHD relates to both acute GVHD and chronic GVHD in pediatric and adult populations. The published literature lacks randomized trials. Evidence comprises retrospective reviews and nonrandomized comparisons. These data have consistently shown improvements in GVHD unresponsive to standard therapy and are consistent with conclusions from a 2001 TEC Assessment. Additionally, there is a lack of other treatment options for these patients; adverse effects of ECP are minimal; and, if there is a response to ECP, patients may be able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents.

AUTOIMMUNE DISEASES
The use of ECP for the treatment of autoimmune diseases was addressed by a 2001 TEC Assessment that considered a variety of autoimmune diseases: type 1 diabetes, multiple sclerosis, pemphigoid, systemic sclerosis, severe atopic dermatitis, and Crohn's disease. The Assessment concluded that for all of these indications, available evidence was insufficient to permit conclusions on outcomes. At the time, photopheresis had been most thoroughly studied as a treatment for scleroderma, in a single-blind RCT (1992) and 3 small, uncontrolled series. Although the RCT reported positive outcomes in terms of skin manifestations, a number of methodologic flaws have been discussed in the literature, including inadequate treatment duration and follow-up, excessive dropouts, a midstudy change of primary outcome, and inadequate washout of prior penicillamine therapy. Results reported from other small case series regarding systemic sclerosis conflict with each other and do not resolve the difficulties in interpreting the randomized trial.

Type 1 Diabetes
An RCT on use of ECP to treat diabetes was published by Ludvigsson et al in 2001. This double-blind RCT assessed 49 children with newly diagnosed type 1 diabetes. Forty children (age, 10-18 years) completed the study and were followed for 3 years. All patients received standard treatment with insulin therapy and diet, exercise, and self-management education. Of these patients, 19 received active photopheresis treatment with oral 8-MOP, and 21 received placebo tablets and sham pheresis. Hemoglobin A_{1c} level did not differ statistically between groups.

Multiple Sclerosis
Cavaletti et al (2006) published a small case series of 5 patients with immunorefractory relapsing-remitting multiple sclerosis who received ECP. ECP appeared safe and tolerable in these patients, with some evidence for a reduction in the relapse rate and symptom stabilization. However, data are insufficient to support conclusions on the use of ECP for multiple sclerosis.

Bullous Disorders
In 2010, Sanli et al published a retrospective report on 11 patients with drug-resistant autoimmune bullous diseases. ECP was performed between 2005 and 2010. Patients were treated on 2 consecutive days at 4-week intervals. Of 8 patients with pemphigus vulgaris, 7 (87.5%) experienced CR after 2 to 6 cycles. Of 3 patients with epidermolysis bullosa acquisita, 2 (67%) had CR and 1 (33%) had PR. All patients with pemphigus vulgaris reduced corticosteroid dose. Decrease in the frequency of ECP resulted in progression of lesions for 3 patients with pemphigus vulgaris and 2 patients with epidermolysis bullosa acquisita. No adverse events were observed. RCTs are necessary to adequately assess the efficacy of ECP for patients with drug-resistant autoimmune bullous diseases.

Scleroderma (Systemic Sclerosis)
In addition to the RCT previously discussed, a 2012 cohort study by Papp et al enrolled 16 patients from a single institution in Hungary who had diffuse cutaneous systemic sclerosis. ECP was administered on 2 consecutive days every 6 weeks for 6 cycles. At the end of the treatment period, statistically significant reductions from baseline dermal thickness (by echography) were observed at 4 extensor surfaces (upper

arm, forearm, hand, finger). Lung diffusing capacity did not decrease more than 5% in any of 9 patients with pulmonary fibrosis at baseline.

Severe Atopic Dermatitis
Some patients with atopic dermatitis do not respond to standard treatments and require immunosuppression with traditional (e.g., systemic corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate) or biologic (e.g., alefacept, rituximab, intravenous immunoglobulin, infliximab, omalizumab) agents for chronic disease. In 2013, Rubegni et al reported on 7 patients and summarized previous case series and case reports of patients with varying disease severity who were treated with ECP. Of 81 total patients, 69 (85%) were considered responders to ECP. Wolf et al subsequently published a case series of 10 adults with severe, refractory atopic dermatitis of at least 1-year duration. ECP was administered for 2 consecutive days biweekly for 12 weeks and then monthly for 2 months. Only concomitant topical treatments and antihistamine were allowed. Mean standard deviation (SD) baseline SCORAD (Scoring of Atopic Dermatitis) was 64.8 (18.9) on a 0- to 103-point scale, indicating moderate to severe disease. At week 20, mean (SD) SCORAD was 54.5 (22.8), a statistically significant improvement (p=0.015) of uncertain clinical significance. Improvements in quality-of-life measures were not statistically significant.

Crohn Disease
Patients with steroid-dependent Crohn disease may respond to double immunosuppression with azathioprine and infliximab, but these treatments are associated with significant adverse events, particularly with long-term use. Reinisch et al (2013) assessed the steroid-sparing effect of ECP in 31 patients with steroid-dependent Crohn disease in clinical remission (Crohn Disease Activity Index [CDAI], <150). Other immunosuppressive treatments were tapered and discontinued before ECP initiation and steroid tapering. ECP was administered on 2 consecutive days every 2 weeks for 24 weeks. Steroids were tapered as tolerated during this 24-week period. Nineteen (61%) patients completed 24 weeks of treatment; 7 (23%) patients achieved steroid-free remission at week 24 (the primary end point), and 20 (65%) patients maintained remission with a 50% or greater reduction in steroid dose from baseline. Three (10%) patients maintained steroid-free remission after 48 weeks of ECP (frequency decreased to monthly after week 24), and 3 other patients who discontinued steroids experienced mild disease (CDAI <220) at 48 weeks of ECP. One catheter-related complication was reported.

Section Summary: Autoimmune Disorders
Evidence for the use of ECP for the treatment of autoimmune diseases including multiple sclerosis and cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, autoimmune bullous disorders, severe atopic dermatitis, Crohn disease, and diabetes, is sparse and insufficient to permit conclusions. There are randomized trials for 2 indications: scleroderma and type 1 diabetes. Methodologic flaws in the scleroderma trial limit applicability of the data. In the type 1 diabetes trial, no difference in hemoglobin A_{1c} levels was observed between those treated with and without ECP.

T-CELL LYMPHOMA

Cutaneous T-Cell Lymphoma

Stage III or IV Mycosis Fungoides and Sézary Syndrome
The initial report on the use of ECP as therapy for CTCL was published by Edelson et al in 1987. Twenty-seven (73%) of 37 patients with otherwise resistant CTCL responded, with a mean 64% decrease in cutaneous involvement after a mean of 22 weeks. Responders included 8 (80%) of 10 patients with lymph node involvement, 24 (83%) of 29 with exfoliative erythroderma, and 20 (71%) of 28 whose disease was resistant to standard chemotherapy. Adverse events of standard chemotherapy, such as bone marrow suppression, gastrointestinal erosions, and hair loss, did not occur. In 2012, Knobler et al reanalyzed these data using current response criteria and reported no change in overall response rate. Response was defined as 90% or greater (near CR) or 50% or greater (PR) improvement in skin score for 4 weeks; in the original study, response was defined as 25% or greater improvement for 4 weeks. With 7 years of follow-up, median overall survival was 9 years from diagnosis and 7 years from the start of ECP. (The mean age at study entry was 57 years [range, 24-80 years]). These results showed that ECP is safe and effective in advanced, resistant CTCL.

Subsequent results from numerous small, nonrandomized studies generally have been consistent with the initial conclusion that ECP treatment can produce clinical improvement and may prolong survival in a substantial proportion of patients with advanced-stage CTCL. These data have informed several evidence-based guidelines and consensus statements on the use of ECP in CTCL, as well as the position of the National Cancer Institute. The National Cancer Institute has consistently recommended ECP as first-line treatment for patients with stage III or IV CTCL.

In 2006, OHTAC published results of a systematic review of ECP for the treatment of erythrodermic CTCL. OHTAC reported that there was low-quality evidence that ECP improves response rates and survival in patients with CTCL unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory erythrodermic CTCL mostly pertained to study quality and size and heterogeneity in both treatment regimens and diagnostic criteria. The committee did, however, recommend a 2-year duration field evaluation of ECP for refractory erythrodermic CTCL, using standardized inclusion criteria and definitions to measure disease outcomes including response rates, quality of life, and morbidity. There is no current evidence on the OHTAC website of an update.

Early-Stage (I or II) CTCL
Between 1987 and 2007, data were reported from at least 16 studies including 124 patients with CTCL in early stages IA, IB, or II who were treated with ECP alone (n=79) or in combination with other agents (e.g., retinoids and interferon-α (n=45). Many of these patients were refractory to numerous other therapies, including topical corticosteroids, interferon-α, or whole skin irradiation. Response rates (PR plus CR) in these studies ranged from 33% to 88% with monotherapy and 50% to 60% with ECP plus adjuvant therapies. Although these findings suggested that ECP may provide benefit in early-stage CTCL, none of the studies was randomized or comparative. Furthermore, many preceded universal acceptance of

standardized elements of classification and diagnosis of CTCL, such as those proposed by the World Health Organization and the World Health Organization–European Organization for Research and Treatment of Cancer. Thus, the actual disease spectrum and burden represented in the available database likely vary between studies, and this complicates conclusions about the efficacy of ECP in this setting. Nonetheless, given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may provide benefit as a treatment for patients with refractory or progressive early-stage CTCL. In contrast, because early-stage CTCL typically responds to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy.

Section Summary: Cutaneous T-Cell Lymphoma
Evidence from small case series has shown a response to ECP in patients with stages III or IV CTCL, as well as prolongation of survival in a proportion of patients.

Given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may be considered as a treatment for patients with refractory or progressive early-stage CTCL.

In contrast, when early-stage CTCL does respond to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy. As a consequence, ECP is not a treatment for patients with stage I or II CTCL that is either previously untreated or is responding to established therapies.

Non-CTCL or Leukemia
Garben et al (2012) used ECP to treat 12 patients with refractory or relapsed disease between 1997 and 2005. Based on the observation that UVA irradiation-induced apoptosis of the malignant T-cell clone may be a mechanism of action of ECP in CTCL, patients were chosen for therapy based on a peripheral clone detected by flow cytometry. One patient had T-lymphoblastic lymphoma. Six patients had PTCL, two with angioimmunoblastic type, four with PTCL-NOS (not otherwise specified). Lastly, 5 patients had large granular lymphocytic leukemia (LGL). At the time of ECP, the median patient age was 49 years (range, 37-82 years). All patients had failed at least 1 line of therapy. Patients were treated according to the Vilbert-Lourmat procedure. Six courses were given over 3 weeks, followed by 1 course per week for 10 weeks. If at least a PR was observed, treatment continued with 1 course per month until progression or CR with the disappearance of the peripheral clone. Response was evaluated after 6 induction courses, then after 10 courses, and then every 3 months until relapse. Of the 12 patients, 6 were in PR after induction (4 PTCL, 2 LGL), and 6 never responded. Of the 6 showing PR after induction, 4 reached CR at 10 courses (2 PTCL, 2 LGL), and 2 patients (with PTCL) had a sustained PR. Although these findings suggest that ECP may provide benefit for patients with non-CTCL and LGL, studies with larger samples are necessary to determine the role of ECP in the treatment of these diseases.

Section Summary: Non-CTCL or Leukemia
Data from a small case series have shown at least a PR to ECP in some patients with refractory noncutaneous T-cell malignancies. More data from larger studies are needed to determine the role of ECP in the treatment of these diseases.

SUMMARY OF EVIDENCE

Organ Rejection After Solid Organ Transplant

Heart Transplant
Evidence for the use of ECP in cardiac transplant recipients relates to 3 indications: acute rejection; recurrent and/or refractory rejection; and prevention of rejection. For acute rejection and for prevention of rejection, 2 small randomized trials have provided insufficient evidence to permit conclusions concerning the effect of ECP on net health outcome. Studies with more patients and longer follow-up are needed. Therefore, ECP is considered investigational for the treatment and prevention of acute rejection in cardiac transplant recipients.

For recurrent and/or refractory cardiac allograft rejection, evidence to date provides consistent evidence for a beneficial effect of ECP for cardiac transplant patients with rejection refractory to standard therapy. Therefore, ECP is considered medically necessary for the treatment of recurrent, multiple and/or refractory cardiac rejection.

Lung Transplant
Evidence for the use of ECP in lung transplant recipients relates to 2 indications: acute rejection and chronic rejection refractory to corticosteroids/refractory BOS. For acute rejection, data are very limited and do not permit any conclusions. This area needs a prospective, randomized, trial focusing specifically on the treatment of patients with acute rejection. For treatment of refractory BOS, nonrandomized and uncontrolled studies have shown inconsistent results across BOS grades. Prospective, RCTs are necessary with analyses stratified by BOS grade. Therefore, ECP is considered investigational when used in lung transplantation.

Liver Transplant
In liver transplantation, evidence to date has focused on prevention of rejection with ECP. This evidence is insufficient to permit conclusions concerning the effect of ECP on net health outcome. There is a need for RCTss comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. Therefore, ECP is considered investigational in liver transplant patients for any indication.

Kidney Transplant
For renal transplant, the evidence includes small case series of patients with refractory rejection. This evidence is insufficient to permit conclusions concerning the effect of ECP on the net health outcome. RCTss comparing immunosuppressive therapy with immunosuppressive therapy using ECP and examining

histologic confirmation of treatment response are needed. Therefore, ECP is considered investigational in renal transplant patients for any indication.

Graft-Versus-Host Disease
Evidence for the use of ECP in the treatment of GVHD relates to both acute GVHD and chronic GVHD in pediatric and adult populations. The evidence includes retrospective reviews and nonrandomized comparisons and has consistently shown improvement in GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events of ECP are minimal; and, if there is a response to ECP, patients may be able to reduce or discontinue treatment with corticosteroids and other immunosuppressive agents. Clinical input supported the use of ECP in patients with refractory acute GVHD. Therefore, treatment of refractory acute or chronic GVHD or chronic GVHD with ECP is considered medically necessary.

For patients with untreated disease or those showing improvements using standard therapy, there is no data to support the use of ECP. Therefore, ECP is considered investigational in these settings.

Autoimmune Disease
Evidence for the use of ECP in the treatment of autoimmune diseases including multiple sclerosis and cutaneous or visceral manifestations of autoimmune diseases, including but not limited to scleroderma, systemic lupus erythematosus, rheumatoid arthritis, pemphigus, psoriasis, autoimmune bullous disorders, severe atopic dermatitis, Crohn disease, and diabetes, is sparse and insufficient to permit conclusions. Therefore, treatment of autoimmune diseases with ECP is considered investigational.

T-Cell Lymphoma

Cutaneous T-Cell Lymphoma
Evidence from small case series has shown a response to ECP in patients with advanced-stage CTCL, as well as prolongation of survival in a proportion of patients. Therefore, ECP may be considered medically necessary as a treatment of patients with stage III or IV CTCL.

Given the unfavorable prognosis for patients with early-stage CTCL that progresses on nonsystemic therapies, the relative lack of adverse events with ECP compared with other systemic treatments, and the good response rates often observed with ECP, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early-stage CTCL.

In contrast, when early-stage CTCL does respond to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience near-normal life expectancy. As a consequence, ECP is considered investigational as a technique for the treatment of patients with stage I or II CTCL that is either previously untreated or is responding to established therapies.

Extracorporeal Photopheresis

Policy # 00099
Original Effective Date: 06/05/2002
Current Effective Date: 03/21/2018

Non-CTCL and Leukemia

Data from a small case series has shown at least a PR to ECP in some patients with refractory noncutaneous T-cell malignancies. More data from larger studies are needed to determine the role of ECP in the treatment of these diseases.

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Extracorporeal Photopheresis

Policy # 00099
Original Effective Date: 06/05/2002
Current Effective Date: 03/21/2018

Policy History

Original Effective Date:	06/05/2002
Current Effective Date:	03/21/2018
05/14/2002	Medical Director review
05/16/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy
06/01/2004	Medical Director review
06/15/2004	Medical Policy Committee review. Format revision. No substance change to policy
06/28/2004	Managed Care Advisory Council approval
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee review. Format revision. No change to policy guidelines.
11/07/2007	Medical Director review
11/15/2007	Medical Policy Committee approval. No change to coverage eligibility.
11/05/2008	Medical Director review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval.
12/16/2009	Medical Policy Implementation Committee approval. Policy title revised to reflect cutaneous T-cell lymphoma (CTCL) indication. Three new policy statements for CTCL added.
12/01/2010	Medical Policy Committee approval.
12/15/2010	Medical Policy Implementation Committee approval. No change to coverage.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Changed title from “Extracorporeal Photopheresis after Solid-Organ Transplant and for Graft-versus-Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma” to “Extracorporeal Photopheresis after Solid-Organ Transplant and for Graft-versus-Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma”. Added coverage statement for extracorporeal photopheresis to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment. Extracorporeal photopheresis in all other situations related to treatment or prevention of rejection in solid-organ transplantation added as investigational. Autoimmune bullous disorders added as investigational. Updated coverage guidelines, Background/Overview, Rationale, and References.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/12/1013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Title changed from “Extracorporeal Photopheresis after Solid-Organ Transplant and for Graft-versus-Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma” to “Extracorporeal Photopheresis”. Statement added that extracorporeal photopheresis is investigational for any other indications.
03/05/2015	Medical Policy Committee review
03/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility updated, added coverage of acute GVHD. Rationale and references updated.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2016	Coding update

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018 Medical Policy Committee review
03/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 03/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	36522			
HCPCS	No codes			
ICD-10 Diagnosis	A00.0	C84.00-C84.09	C84.40-C84.49	D590.-D59.1
	D89.82-D89.89	E06.3	E10.10-E10.11	E10.40-E10.49
	E10.610	E10.641	E10.65	E10.69
	E10.8-E10.9	E11.00-E11.01	E11.40-E11.49	E11.610
	E11.641	E11.65	E11.69	E11.8-E11.9
	E13.00-E13.01	E13.10-E13.11	E13.40-E13.49	E13.610
	E13.641	E13.8-E13.9	E20.0	E20.8-E20.9
	G35	G51.0	G56.00-G56.02	I89.0
	I97.2	K12.1-K12.2	K12.30	K12.39
	L10.0-L10.5	L10.81	L10.89	L10.9
	L11.0	L40.0-L40.9	L85.0-L85.2	L86
	L87.0	L87.2	M05.00	M05.011-M05.079
	M05.09	M05.20	M05.211-M05.279	M05.29-M05.30

	M05.311-M05.379	M05.39-M05.40	M05.411-M05.479	M05.49-M05.50
	M05.511-M05.579	M05.59-M05.60	M05.611-M05.679	M05.69-M05.70
	M05.711-M05.779	M05.79-M05.80	M05.811-M05.879	M05.89-M05.9
	M06.00	M06.011-M06.079	M06.08-M06.09	M06.1
	M06.20	M06.211-M06.279	M06.28-M06.30	M06.311-M06.379
	M06.38-M06.4	M06.80	M06.811-M06.879	M06.88-M06.9
	M08.00	M08.011-M08.079	M08.08-M08.09	M08.20
	M08.211-M08.279	M08.28-M08.29	M08.3	M08.40
	M08.411-M08.479	M08.48	M08.80	M08.811-M08.879
	M08.88-M08.90	M08.911-M08.879	M08.98-M08.99	M24.9
	M25.521-M25.569	M25.711-M25.719	M26.60-M26.69	M26.601-M26.609
	M26.611-M26.619	M26.621-M26.629	M26.631-M26.639	M32.0
	M32.10-M32.19	M32.8-M32.9	M34.0-M34.2	M34.81-M34.89
	M34.9	M35.00-M35.09	M54.5	M72.2
	M75.00-M75.02	M75.30-M75.32	M75.40-M75.42	M75.80-M75.82
	M75.90-M75.92	M77.9	R29.898	T86.00-T86.23
	T86.290	T86.298	T86.30-T86.49	T86.810-T86.819
	T86.90-T86.99			

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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