Extracorporeal Photochemotherapy (Photopheresis)

Policy

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

I. Aetna considers extracorporeal photochemotherapy (ECP, photopheresis) medically necessary for erythrodermic variants of cutaneous T cell lymphoma (e.g., mycosis fungoides, Sezary syndrome).

II. Aetna considers ECP medically necessary in the treatment of acute cardiac allograft rejection that is refractory to standard immunosuppressive drug treatment (resistant or dependent to high-dose steroids plus refractory to 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, methotrexate, and/or polyclonal and monoclonal antilymphocyte agents (e.g., anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG)).

III. Aetna considers ECP medically necessary in the treatment of rejection (bronchiolitis obliterans) of lung transplants that are refractory to immunosuppressive drug treatment (resistant or dependent to high-dose steroids plus resistant to 2 or more of the following, unless contraindicated:
azathioprine, cyclosporine, tacrolimus, and/or polyclonal and monoclonal anti-lymphocyte agents (e.g., ALG and ATG) or where there is a rapid decline in lung function.

IV. Aetna considers ECP medically necessary as last resort treatment of rejection of other solid organ transplants when the disease is refractory to standard immunosuppressive drug treatment.

V. Aetna considers ECP medically necessary for the treatment of graft-versus-host disease (GVHD) of an allogeneic bone marrow or stem cell transplant when the disease is refractory to standard immunosuppressive drug treatment.

VI. Aetna considers the use of ECP experimental and investigational as a treatment for the following conditions because the effectiveness of this treatment for these diagnoses has not been established:

- Atopic dermatitis
- Autoimmune diseases
- Bronchiolitis obliterans syndrome after allogeneic stem cell transplantation
- Bullous pemphigoid
- Crohn's disease
- Epidermolysis bullosa acquisita
- Morphea (localized scleroderma)
- Multiple sclerosis
- Nephrogenic systemic fibrosis (previously known as nephrogenic fibrosing dermopathy)
- Pemphigus vulgaris
- Pityriasis rubra pilaris
- Prophylaxis (prevention) of graft-versus-host disease following allogeneic hematopoietic cell transplantation
- Prophylactic use to reduce the risk of infective complications following kidney transplantation
- Scleroedema adultorum Buschke
- Stage 0-p bronchiolitis obliterans syndrome
- Systemic sclerosis (scleroderma)
- Type 1 diabetes
- Xanthogranulomas.

**Background**

Photopheresis, also known as extracorporeal photochemotherapy (ECP), is an immunomodulatory technique based on pheresis of light-sensitive cells. Whole blood is removed from patients who have previously ingested the photosensitizing agent 8-methoxypsoralen (8-MOP) followed by leukapheresis and exposure of the 8-MOP containing leukocytes extracorporeally to ultraviolet-A light before their return to the patient. Two hours after an oral dose of photo-activatable drug, the patient undergoes leukopheresis. The lymphocytes are then exposed to UVA light within the photopheresis device and the photo-irradiated cells are re-infused into the patient.

Photopheresis was approved by the Food and Drug Administration (FDA) in 1988 for treatment of cutaneous T-cell lymphoma, and is considered standard therapy for the early to moderately advanced (stage III) erythrodermic variants of cutaneous T-cell lymphoma (e.g., mycosis fungoides, Sézary's syndrome). However, in a recent randomized controlled study, Child et al (2004) concluded that ECP is not effective in the treatment of plaque stage (1B/T2) mycosis fungoides even in patients with molecular evidence of a peripheral blood T-cell clone. This is in agreement with the findings of Zackheim (2003) who stated the results of ECP for early to moderately advanced erythrodermic mycosis fungoides are favorable. However, results in plaque and tumor stage disease are not impressive.


Photopheresis is usually performed on 2 consecutive days at 4-week intervals with clinical evaluation at 6 months to determine response. Those who show clinical improvement are maintained on this treatment schedule until maximum clearing. An additional 6 months of treatment is typically given after which the patient is gradually weaned off therapy.
Photopheresis for the treatment of scleroderma and other autoimmune diseases is under investigation. The safety and efficacy of this treatment for scleroderma has not been established. Photopheresis, alone or in combination with immunosuppressive therapy, has also been used in the treatment of solid organ (e.g., heart, lung, and kidney) transplant rejection, graft-versus-host disease (GVHD), scleroderma, and other autoimmune diseases. This form of photochemotherapy induces a selective inhibition of the host response to foreign histocompatibility antigens and reverses allograft rejection after organ transplantation.

An assessment conducted by the BlueCross BlueShield Association Technology Evaluation Center (2001) concluded that ECP does not meet TEC criteria for autoimmune diseases, including: progressive systemic sclerosis (scleroderma); pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, or other autoimmune bullous (blistering) diseases; systemic lupus erythematosus; multiple sclerosis; psoriatic arthritis or psoriasis vulgaris; rheumatoid arthritis; type I diabetes; and other autoimmune diseases such as atopic dermatitis, juvenile dermatomyositis, or scleromyxedema.

Extracorporeal photopheresis is also being evaluated as a treatment for Crohn’s disease. Available evidence is limited to case reports and small uncontrolled case series (Reinisch et al, 2001; Guariso et al, 2003). An assessment by the National Institute for Health and Clinical Excellence (2009) concluded: "[c]urrent evidence on extracorporeal photopheresis (ECP) for Crohn’s disease is based on reports that include a very small number of patients. These reports describe no major safety issues but they provide little evidence of efficacy. Therefore, this procedure should not be used outside the context of research."

Based upon an evidence review, the Centers for Medicare and Medicaid Services (CMS, 2006) concluded that ECP is reasonable and necessary for persons with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment. Centers for Medicare and Medicaid Services also concluded that ECP is reasonable and necessary for persons with chronic GVHD whose disease is refractory to standard immunosuppressive drug treatment. There is evidence that photopheresis is effective in the treatment of heart, bone marrow and stem cell transplant rejection. Photopheresis has been reported to be as effective as conventional immunosuppressive agents in reducing rejection episodes in heart transplant recipients. It has also been demonstrated to
be effective in treating steroid-resistant chronic GVHD following bone marrow or stem cell transplantation (Foss et al, 2005; Couriel et al, 2006; Bisaccia et al, 2006). By contrast, there is limited scientific evidence to determine the effectiveness of photopheresis in treating rejection of lung or kidney transplants.

Morrell et al (2010) reported that ECP is associated with a reduction in the rate of decline in lung function associated with progressive bronchiolitis obliterans syndrome (BOS). The authors retrospectively analyzed the efficacy and safety of ECP in 60 lung transplant recipients treated for progressive BOS at a single institution between 2000 and 2007. They reported that during the 6-month period before the initiation of ECP, the average rate of decline in forced expiratory volume in 1 second (FEV(1)) was -116.0 ml/month, but the slope decreased to -28.9 ml/month during the 6-month period after the initiation of ECP, and the mean difference in the rate of decline was 87.1 ml/month (95% confidence interval [CI]: 57.3 to 116.9; p < 0.0001). The authors noted that FEV(1) improved in 25.0% of patients after the initiation of ECP with a mean increase of 20.1 ml/month.

Haenssle and colleagues (2004) noted that pityriasis rubra pilaris (PRP) is a rare papulosquamous skin disease of unknown etiology that has been categorized into 5 clinical types based on age at onset, cutaneous features and prognosis. These investigators presented a patient with chronic exanthematic type II atypical adult PRP, whose skin status was significantly improved with monthly ECP. Various therapeutic regimens including narrow-band UV-B, bath psoralen plus ultraviolet A (PUVA) therapy, systemic fumaric acid esters and systemic cyclosporin had failed. Oral retinoids could not be administered due to a type IIa hyperlipoproteinemia with profound hepatic steatosis and elevated liver transaminases. The observed clinical benefit may encourage future clinical studies analyzing the clinical value of ECP in otherwise unresponsive cases of type II PRP.

Dall'Amico and Messina (2002) stated that ECP is a new type of photochemotherapy used for the treatment of oncological and autoimmune diseases. Additionally, recent reports indicated that this therapy is promising in both pediatric and adult patients who develop GVHD resistant to conventional protocols after bone marrow transplantation. These researchers reviewed 31 studies where ECP was used in the treatment of acute and chronic GVHD. A total of 76 (32% female) acute GVHD patients have been considered in 11 series; 59 patients presented with skin involvement; 47 had liver involvement, and 28 had gastro-intestinal manifestations. Treatment duration ranged from 1 to 24 months.
A regression of skin manifestations was observed in 83 % of the patients with a complete response in 67 %. A complete regression of liver and gut manifestations was reported in 38 % and 54 % of the patients, respectively. The overall patient survival was 53 %. Of the 43 patients alive, 8 developed chronic GVHD manifestations. The immunosuppressive therapy was discontinued in 28 % of cases and reduced in 46 %. A total of 204 (45 % female) chronic GVHD patients treated with ECP 1 to 110 months from transplantation have been considered in 20 series. A total of 128 patients presented with skin involvement; 84 with liver, 31 with lung, and 59 with oral manifestations. Treatment duration ranged from 3 to 40 months. A regression of skin manifestations was observed in 76 % of patients with a complete response in 38 %. An improvement of liver and lung involvement was reported in 48 % and 39 % of the patients, respectively. Of the 59 patients with oral manifestations, an improvement was obtained in 63 % of cases. The overall patient survival was 79 %. Extracorporeal photopheresis is a non-aggressive treatment that may benefit patients with both acute and chronic GVHD who do not respond to standard immunosuppressive therapy.

Perfetti and associates (2008) examined the effects of ECP for the treatment of steroid refractory acute GVHD. Extracorporeal photopheresis was given to 23 patients with steroid-refractory acute GVHD (aGVHD, grade II (n = 10), III (n = 7) or IV (n = 6)). The median duration of ECP was 7 months (1 to 33) and the median number of ECP cycles in each patient was 10. Twelve patients (52 %) had complete responses. Eleven patients (48 %) survived and 12 died, 10 of GVHD with or without infections and 2 of leukemia relapse. The average grade of GVHD was reduced from 2.8 (on the first day of ECP) to 1.4 (on day +90 from ECP) (p = 0.08), and the average dose of intravenous methylprednisolone from 2.17 to 0.2 mg/kg/day (p = 0.004). Complete responses were obtained in 70, 42 and 0 % of patients, respectively, with grades II, III and IV aGVHD; complete responses in the skin, liver and gut were 66, 27 and 40 %. Patients treated within 35 days from onset of aGVHD had higher responses (83 versus 47 %; p = 0.1). A trend for improved survival was seen in grade III-IV aGVHD treated with ECP as compared to matched controls (38 versus 16 %; p = 0.08). The authors concluded that ECP is a treatment option for patients with steroid refractory aGVHD and should be considered early in the course of the disease. Moreover, the authors stated that "[t] he good results in patients receiving ECP, within 1 month from the onset of GVHD and when the severity does not exceed grade II-III may warrant a prospective trial to explore the role of photochemotherapy as upfront treatment of aGVHD".
A decision memorandum from the CMS concluded that there is insufficient evidence to support the use of ECP in pemphigus vulgaris and bullous pemphigoid (CMS, 2006).

Richmond and colleagues (2007) stated that nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an idiopathic condition observed in patients with renal disease that is characterized by cutaneous sclerosis that can often result in contractures, pain, functional disability, and systemic complications. Recent reports have suggested a possible link with exposure to gadolinium. No current therapy has clearly demonstrated effectiveness for NSF, although case reports suggested that ECP may be of benefit. These researchers explored the plausibility of a gadolinium linkage with NSF and evaluated the effectiveness of ECP in the treatment of a cohort of patients with NSF (n = 8). Of the 8 patients, 6 had a history of arterial or venous thrombotic disease, and 7 had a documented exposure to gadolinium within 1 week to several months before onset of NSF. Specifically, all patients were exposed to gadodiamide. These investigators treated 5 of the patients with ECP. After a mean number of 34 treatment sessions over a mean of 8.5 months, 3 patients experienced a mild improvement in skin tightening, range of motion, and/or functional capacity. The authors concluded that their findings support the hypothesis that exposure to gadolinium, perhaps specifically gadodiamide, plays a role in the pathogenesis of NSF. They noted that larger epidemiologic studies will be needed to confirm this association. Furthermore, their experience suggest that, if used for extended periods, ECP might have some mild benefit for patients with NSF. They stated that larger, randomized, placebo-controlled trials of ECP should be performed to more specifically assess the benefit of ECP in the treatment of NSF.

Regarding the appropriate duration of ECP, an article from eMedicine recommends ECP weekly for 2 consecutive days each week, tapering to every other week until rejection resolves (Introcaso et al, 2007). A systematic review (Dall’Amico and Messina, 2002) assessed 31 studies of ECP for GVHD, and noted that treatment duration ranged from 3 to 40 months.

Shaughnessy et al (2010) stated that GVHD is partly mediated by host antigen-presenting cells (APCs) that activate donor T cells. Extracorporeal photopheresis can modulate APC function and benefit some patients with GVHD. These investigators reported the results of a study using ECP administered before a standard myeloablative preparative regimen intended to prevent GVHD. Grades II
to IV acute GVHD developed in 9 (30 %) of 30 recipients of HLA-matched related transplants and 13 (41 %) of 32 recipients of HLA-matched unrelated or HLA-mismatched related donor transplants. Actuarial estimates of overall survival (OS) at day 100 and 1-year post transplant were 89 % (95 % CI: 78 to 94 %) and 77 % (95 % CI: 64 to 86 %), respectively. There were no unexpected adverse effects of ECP. Historical controls receiving similar conditioning and GVHD prophylaxis regimens but no ECP were identified from the database of the Center for International Blood and Marrow Transplant Research and multi-variate analysis indicated a lower risk of grades II to IV acute GVHD in patients receiving ECP (p = 0.04). Adjusted OS at 1 year was 83 % in the ECP study group and 67 % in the historical control group (relative risk 0.44; 95 % CI: 0.24 to 0.80) (p = 0.007). The authors concluded that these preliminary findings may indicate a potential survival advantage with ECP for transplant recipients undergoing standard myeloablative hematopoietic cell transplantation. Moreover, they stated that longer follow-up, larger sample sizes, and randomized comparisons to standard approaches are needed.

Kusztal et al (2011) stated that ECP is considered a promising immunomodulatory therapy of acute allograft rejection in organ transplantation and GVHD. These researchers investigated the biological responses of 10 patients who underwent kidney transplantation with ECP as prophylactic treatment. They received conventional immunosuppressive therapy plus ECP immediately after transplantation: 12 to 16 applications over the course of 2.5 months. ECP procedures were performed using an automated system for leukocyte separation and photo-activation with methoxsalen. All recipients were followed by estimated glomerular filtration rate (eGFR) and peripheral T, B, natural killer, T-regulatory (Treg) and dendritic cells (DC) counts and phenotypes. An acute rejection episode appeared in one control group recipient. The ECP group showed a positive trend to an higher GFR at months 3 (53 ± 11 versus 47.1 ± 9; p = 0.17) and 6 (67.5 ± 10 versus 53.6 ± 3; p = 0.03, Wilcoxon test). An increased percentage of Treg (CD3+ CD4+ CD25+) among the total CD3 cell count (4.9 % ± 1 % to 9.4 % ± 15 %) as well as inducible Treg (CD3+ CD8+ CD28-) was observed among CD3 cells (3.3 % ± 3 % to 11.8 % ± 8 %, p = 0.025) within 3 months of ECP treatment. A significant difference in the percentage of Treg was noted at month 3 (completed ECP) between the ECP and the control groups (9.4 % ± 15 % versus 3 % ± 1 %; p = 0.01). Addition of ECP to standard immunosuppression was associated with a significantly higher GFR at 6 months and with a significant increase in natural Treg among CD3 cells. The authors stated that these preliminary results are promising.
Gurcan and Ahmed (2011) noted that long-term remission in epidermolysis bullosa acquisita (EBA) patients is difficult to achieve. Patients who are resistant or develop side effects to conventional immunosuppressive therapy (CIST) have been treated with several other agents. These researchers reviewed the clinical outcome in patients treated with a single drug or combination, and determined if long-term remission can be induced. Data on 71 patients were analyzed. There are no controlled trials. The regimens used included dapsone, colchicine, mesalazine, cyclosporine, mycophenolic acid, intravenous immunoglobulin, rituximab, daclizumab, extracorporeal photochemotherapy, and plasmapheresis. The use of CIST, especially in wide spread and recalcitrant patients, usually does not produce a prolonged clinical remission and can have hazardous side effects. Intravenous immunoglobulin, rituximab and immunoadsorption have been successfully used in some, but the benefits from their use may require additional studies.

Lucid et al (2011) stated that ECP has been shown to be a promising treatment for chronic GVHD; however, only a few case reports are available that examine the effectiveness of ECP for bronchiolitis obliterans (BO) after allogeneic stem cell transplantation (allo-SCT). Because of the poor response to traditional therapies, ECP has been explored as a possible therapeutic option for severe BO after allo-SCT. A total of 9 patients received ECP between July 2008 and August 2009 after a median follow-up of 23 months (range of 9 to 93 months) post-transplant. The primary indication for ECP was the development of BO in patients who had failed prior multi-drug regimens. The median number of drugs used for BO management before ECP was 5 (range of 2 to 7); this included immunosuppressive therapy. Six of 9 (67%) patients responded to ECP after a median of 25 days (range of 20 to 958 days). No ECP-related complications occurred. ECP seemed to stabilize rapidly declining pulmonary function tests in about 2/3 of patients with severe and heavily pre-treated BO that developed after allo-SCT. The authors concluded that these findings support the need for a larger prospective study to confirm the impact of ECP on BO, and to consider earlier intervention with ECP to improve the outcome of BO after allo-SCT. Limitations of this study included its retrospective nature, small sample size, and short follow-up.

In a prospective study, Wolf and colleagues (2012) examined the effect of a defined 20-week ECP protocol in patients with severe, refractory atopic dermatitis. Patient inclusion criteria included (i) disease duration of at least 1 year, (ii) “SCORing Atopic Dermatitis” (SCORAD; an objective clinical tool for assessing the severity (i.e., extent, intensity) of atopic dermatitis) greater than 45, and (iii) resistance
to first-line therapy, including topical steroids, topical calcineurin inhibitors, and 1 form of phototherapy (ultra-violet A [UVA], ultra-violet B [UVB], or PUVA) or 1 second-line therapy, including systemic steroids or cyclosporine. A total of 10 patients (4 women and 6 men; age range of 29 to 61 years) were enrolled and treated with 2 sessions of standard ECP in 2-week intervals for 12 weeks and 4-week intervals thereafter until week 20. The patients’ clinical status and response was determined by SCORAD at baseline and every 2 weeks, and quality of life was assessed every 4 weeks using SKINDEX, SF-36, and FACT scores. There was a statistically significant (p = 0.015) reduction of the mean SCORAD by 10.3 (95 % CI: 2.5 to 18.0) from 64.8 at baseline to 54.5 (i.e., 15.9 % reduction) at week 20. In a subset of patients (all of female sex), the relative reduction in SCORAD after ECP was more than 25 % at week 20. Improvement in quality of life measured by SKINDEX, SF-36, and FACT did not reach statistical significance. The authors concluded that they detected a small but significant therapeutic effect of ECP in patients with severe, refractory atopic dermatitis. The findings of this small study need to be validated by well-designed studies with larger sample size and longer follow-up.

Stage 0-p BOS (i.e., an average decline in FEV1 of 10 to 19 % of the basal value of 2 measurements at least 3 weeks apart) refers to a decline in lung function that is thought to be predictive of BOS, but does not establish the diagnosis of BOS (Riise et al, 2011).

Russo et al (2012) noted that since 1960, different classes of immunosuppressive drugs have been used in the post-transplant follow-up. Each is assessed for its effectiveness in preventing rejection but also on the basis of the many side effects induced by prolonged treatment. To reduce these side effects, continuous development of knowledge and medical technology to create cutting-edge therapies in the field is necessary. One of these is ECP, which is a useful therapeutic tool for the development of immunomodulation supported by CD8+ clone-specific cytotoxic lymphocytes. The T cells targeted by ECP are modified by photo-activation and seem to develop marked immunogenicity with no suppression of the immune response. Recent studies suggested the possible utility of ECP in the treatment of glomerulonephritis and in countering rejection after transplantation of organs including the kidney.
Lai et al (2012) stated that the fundamental role of antibodies in the development of acute graft rejection has been established recently. Antibody-mediated acute rejection may develop at any time during the post-renal transplant period. Several therapeutic approaches have been proposed in the last decades. However, there is no standardized therapy. These researchers reported the Sapienza University experience of combined plasma treatment and high-dose intravenous immunoglobulin ± ECP. From January 2006 to September 2009, 6 patients were treated at Sapienza University. In 5 cases (83 %) complete regression of the acute rejection was observed, followed by stable renal function (median creatinine value at 1-year follow-up: 1.5 mg/dL). No adverse events were reported. The authors concluded that this approach seems to give good results in terms of graft survival and procedure safety. Moreover, they stated that further studies on a larger number of patients are needed to confirm the validity of these findings. Furthermore, comparison between the authors' protocol and other treatments is necessary.

Benden et al (2012) noted that lung transplantation has evolved as an accepted therapy in selected adults and children with end-stage lung diseases. Outcomes following lung transplantation have improved in the recent era with a 5-year survival of greater than 70 % and an overall good functional status of surviving recipients. Many of the advances have been achieved by the use of modern immunosuppressive agents. To date, multiple strategies exist that may be employed when utilizing immunosuppression. These agents can be used in a variety of roles that may include induction, maintenance or rescue therapy, many of which are illustrated in this review including the current evidence to support their use. Infections in lung transplant recipients remain a significant cause of morbidity and mortality. Special considerations are required with the substantial burden of chronic infection in candidates with cystic fibrosis lung disease before transplantation. Furthermore, recent progress and advances in prevention and treatment of post-transplantation infectious complications were detailed. Chronic lung allograft dysfunction remains to be the burden of lung transplantation in the long-term. Unfortunately, there is no well-established therapy to address it. However, therapy attempts include change/augmentation of immunosuppression, use of neomacrolides and ECP, all of which were reviewed in detail.

Kaloyannidis and Mallouri (2012) noted that over the last decades significant advances have been made in the field of donor selection, alternative transplant sources, immunosuppressive treatment and supportive care, as well as in the better
understanding of the immunobiology of allogeneic hematopoietic stem cell transplantation (alloTx). Nevertheless, several factors still affect unfavorably the outcome of the procedure. Graft-versus-host disease remains the leading cause of morbidity, non-relapse mortality and treatment failure post alloTx. So far, steroids are the widely used 1st-line treatment for GVHD achieving considerable response rate however, patients who fail to respond to the initial therapy have a dismal prognosis and no standard treatment is well-established for them to date. In recent years, ECP has been proposed as a safe and effective treatment for steroid-refractory GVHD. Overall responses of 75% have been reported in the cutaneous and mucosal involvement and 45 to 65% in other organ manifestations (e.g., lung, liver and intestinal), allowing reduction and even discontinuation of steroids, thus contributing towards a significant reduction of morbidity. Although the mechanism of action of ECP is not fully understood, it seems that it has an immunomodulatory rather than an immunosuppression effect and induces immunotolerance, preserving the beneficial graft-versus-tumor effect. Given these very promising results in steroid-refractory or steroid-dependent GVHD, currently, ECP is being investigated as both first-line and prevention therapy also.

In a review on "Bronchiolitis obliterans after allo-SCT: Clinical criteria and treatment options", Uhling and colleagues (2012) stated that "though several studies have been performed in patients with BO after HSCT and lung transplantation, the studies are difficult to interpret because of the heterogeneity in the treatment schedules, diagnostic criteria and response assessment criteria. A prospective study randomized study of extracorporeal photopheresis treatment performed by Flower et al revealed a significant improvement of cGVHD in the skin, and indicated a steroid sparing effect on cGVHD in general. No effect on lung function parameters was noted .... Solid evidence regarding the efficacy of the various available treatment modalities in BO is still sparse".

On April 30, 2012, a National Coverage Determination (NCD) by the Centers for Medicare & Medicaid Services stated that ECP for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation will be covered only when ECP is provided under a clinical research study that meets criteria. An accompanying decision memorandum (CMS, 2012) stated that the evidence is insufficient to conclude that, in Medicare beneficiaries with BOS developing after lung allograft transplantation refractory to standard immunosuppressive therapy, ECP will improve patient centered health outcomes. However, based on its previously published criteria for considering CED, CMS concluded that evidence of
basic safety, potential for patient-centered health outcome improvement, and demonstrated difficulty of conducting appropriate clinical trials are sufficient in combination to persuade CMS to propose coverage for ECP therapy for BOS after lung allograft transplantation within approved clinical research studies.

Epler (2010) stated that constrictive bronchiolitis is a bronchiolar airway disease that surrounds the lumen with fibrotic concentric narrowing and obliteration. The mosaic pattern seen on the expiratory high-resolution chest CT scan is diagnostic in an individual with shortness of breath, early inspiratory crackles, and irreversible airflow obstruction. Swyer-James-MacLeod syndrome is no longer considered a congenital disorder but as constrictive bronchiolitis detected in young adults who had infectious pneumonia during infancy. For lung transplant recipients, tacrolimus continues to be an important immune suppression medication, extracorporeal photopheresis may improve the decline of pulmonary function, and azithromycin may be effective in some lung transplant recipients for treatment of bronchiolitis obliterans syndrome for prevention of constrictive bronchiolitis.

Also, an UpToDate review on “Bronchiolitis in adults” (King, 2014) does not mention the use of extracorporeal photopheresis as a therapeutic option of constrictive bronchiolitis.

Pileri et al (2014) presented the case of a patient with generalized morphea whose disease completely resolved after combination therapy with ECP and broad-band UVA treatments. This was single case study that used combinational treatments. Furthermore, an UpToDate review on “Treatment of morphea (localized scleroderma) in adults” (Jacobe, 2014) states that “Treatments of morphea with penicillin, penicillamine, colchicine, hydroxychloroquine, mycophenolate mofetil, cyclosporine, bosentan, infliximab, and extracorporeal phototherapy have been reported. There is little evidence to support the efficacies of these treatments”.

Liszewski et al (2014) stated that necrobiotic xanthogranuloma (NXG) is a disease of fibrotic or telangiectatic granulomatous papules and nodules that can ultimately progress into ulcerated plaques. Although the exact cause of NXG is unknown, it most often occurs in patients with paraproteinemia secondary to a hematologic disease. Consequently, therapy for NXG is targeted at treating the underlying hematologic disease, and subsequent paraproteinemia, with alkylating agents, antimetabolites, radiation, and/or immunosuppressive agents. Cases refractory to these therapies often have poor outcomes. These investigators reported the
successful treatment of 2 patients with refractory NXG with 2 different modalities: (i) ECP and (ii) intravenous immunoglobulin (IVIG). The first case showed a patient without paraproteinemia who had success with ECP and IVIG, and the second is a patient with paraproteinemia treated effectively with IVIG. The authors concluded that the beneficial response of these patients to IVIG, as well as ECP, showed that they may be an effective treatment option for refractory NXG. These preliminary findings need to be validated in well-designed studies.

Furthermore, an UpToDate review on “Juvenile xanthogranuloma (JXG)” (Puttgen, 2014) does not mention extracorporeal photopheresis as a therapeutic option.

**Autoimmune Diseases**

Kuzmina et al (2015) noted that systemic autoimmune diseases (AID) have multi-organ, heterogeneous clinical presentations and are characterized by dysregulation of the immune system, immunodeficiency, irreversible organ damage and increased morbidity and mortality. Preventing or decreasing flares of AID correlate with durable disease control, significant reduction of inflammation and prevention of disability or therapy-related toxicity. There is an urgent need for better treatment of severe, therapy-refractory AID. Extracorporeal photopheresis is a cell-based immunomodulatory treatment which has been extensively used in variety of autoimmune disorders for the past 20 years. Prolonged therapy is safe, well-tolerated and allows reduction of systemic immunosuppression in therapy-refractory patients. Both clinical and experimental evidence suggested that ECP mechanism of action is characterized by apoptosis and phagocytosis of activated cells by antigen-presenting cells (APC), secretion of anti-inflammatory cytokines and stimulation of regulatory T cells (Tregs). These investigators reviewed the current evidence of ECP use in the treatment of AID. They summarized the experience of 9 major AID from 65 published reports. The key findings demonstrated substantial evidence of ECP feasibility, safety and in some AID also promising effectiveness. The authors concluded that the role of ECP in AID therapy is not established as most published studies were retrospective with limited number of patients and the trials were small or poorly standardized. They stated that the available data support future investigations of ECP as a therapeutic modality for the treatment of AID in well-designed prospective clinical studies.

**Prophylaxis for Graft-Versus-Host Disease Following Allogeneic Hematopoietic Cell Transplantation**
Kitko and colleagues (2016) stated that reduced-intensity conditioning (RIC) regimens minimize early toxicity after allogeneic hematopoietic cell transplantation (HCT) by placing greater reliance on establishing a graft-versus-leukemia effect (GVL). Because GVHD and GVL are tightly linked, inhibition of T cell populations that cause GVHD may lead to an unintended increased risk of relapse in the RIC setting. Although not completely understood, etanercept and ECP are thought to ameliorate GVHD without direct T cell inhibition. In a prospective, phase II clinical trial, these researchers hypothesized that adding these 2 agents to a standard GVHD prophylaxis regimen of tacrolimus and mycophenolate mofetil (MMF) would improve survival by reducing GVHD-related mortality without increasing relapse rates. They conducted a study that incorporated tacrolimus, MMF, etanercept, and ECP as GVHD prophylaxis in 48 patients undergoing RIC unrelated donor transplantation. The preferred RIC was fludarabine 160 mg/m(2) + busulfan 6.4 mg/kg to 12.8 mg/kg ± total body irradiation (TBI) 200 cGy. Etanercept 0.4 mg/kg (maximum dose of 25 mg) was given subcutaneously twice-weekly for 8 weeks after HCT and ECP was given for 12 treatments, starting weekly on day 28 weekly and tapering off by day 180. The median age of the study patients was 60 (range, of 18 to 71) years. Donors were 7/8 (n = 14, 29 %) or 8/8 (n = 34, 71 %) HLA matched. All patients engrafted neutrophils at a median of 12 days. The cumulative incidence of grades II to IV acute GVHD at day 100 was 46 %, but it was typically sensitive to initial steroid treatment (84 % day 56 complete response/partial response rate). Overall survival at 1 year in this older, frequently mis-matched unrelated donor setting was excellent (73 %) because of low rates of non-relapse mortality (21 %) and relapse (19 %). However, this strategy was not effective at preventing a high incidence of chronic GVHD and late deaths led to a drop in 2-year survival, declining to 56 %, reflecting a high incidence of chronic GVHD.

Treatment of Bronchiolitis Obliterans Syndrome After Allogeneic Stem Cell Transplantation

Chien, et al. (2010) state that current recommendations for BOS therapy after allogeneic stem cell transplantation include: high dose systemic corticosteroids for a protracted course with expected improvements in 8–20%, of which most are likely transient given the poor overall survival. Azithromycin and inhaled steroids have been tested in small clinical trials of patients with BOS after HCT with evidence for some benefit by pulmonary function tests. Anecdotal reports of efficacy for the
stabilization of BOS include: extracorporeal photopheresis, tumor necrosis factor blockade, imatinib. Finally, novel agents such as leukotriene inhibitors and statins have emerged as possible therapies.

Brownback and associates (2016) noted that ECP is a commonly used treatment for severe GVHD. These researchers examined the effects of ECP over a prolonged period on forced expiratory volume in 1 s (FEV1) in patients with severe bronchiolitis obliterans syndrome (BOS) following allogeneic stem cell transplantation (allo-SCT). They identified 8 patients who developed new airflow obstruction following allo-SCT and a substantial decline in FEV1 despite receiving corticosteroids and standard therapy for pulmonary GVHD. Those 8 patients were treated with ECP for a period of 1 year, with a primary end-point of FEV1 change during this treatment period. Over the first 3 months of ECP, there was no further decline in FEV1 in 7 of the 8 patients. However, over the 1-year period, only 2 of the 8 patients had stability in FEV1. The rate of FEV1 decline was substantially less once ECP was initiated, though the median FEV1 continued to decline over 1 year of therapy. All patients survived through the 1st year of ECP therapy. There was a significant decrease in the median dose of prednisone per patient throughout the 12 months of ECP treatment. The authors concluded that ECP showed promise in slowing rate of decline of FEV1 in pulmonary GVHD/severe BOS, though the effects may not be long lived.

Del Fante and Perotti (2017) stated that BOS is the main manifestation of pulmonary GVHD. It has often a dramatic and fast evolution and current treatment (change or increase in immunosuppression, macrolides and inhaled therapy) is poor with high mortality rates. In this scenario, ECP bursts as a new immunomodulatory approach with a different philosophical purpose. In fact, available data show that ECP treatment is intended to delay the inflammatory process and consequently respiratory lung function decline, rather than reverse the damage itself. The authors concluded that preliminary results reported in literature showed that ECP may effectively improve/slow lung function decline in cGVHD patients with BOS after standard treatment failure. Moreover, they stated that further studies are needed to confirm the effectiveness of ECP, evaluate the optimal schedule and consider it for early treatment.

Furthermore, an UpToDate review on “Pulmonary complications after allogeneic hematopoietic cell transplantation” (Kaner and Zappetti, 2016) does not mention ECP as a therapeutic option.

Hefazi and colleagues (2018) performed the first matched retrospective cohort study aimed at studying the safety and efficacy of ECP for BOS after allogeneic HCT. Medical records of 1,325 consecutive adult patients who underwent HCT between 2005 and 2015 were reviewed; 74 patients (median age of 51 years) with a diagnosis of BOS were included in the study. After propensity-score matching for BOS severity, 26 patients who underwent greater than or equal to 3 months of ECP were matched to 26 non-ECP-treated patients, who were assigned an index date corresponding to the ECP start date for their matched pairs. The rate of decline in FEV1 percentage predicted (FEV1PP) decreased after ECP initiation (and after index date in the non-ECP group), with no significant difference between the 2 groups (p = 0.33). On a multi-variable analysis that included baseline transplant and pulmonary function test variables, matched related donor HCT (hazard ratio [HR], 0.1; 95 % CI: 0.03 to 0.5; p = 0.002), ECP (HR, 0.1; 95 % CI: 0.01 to 0.3; p = 0.001), and slower rate of decline in FEV1PP before the ECP/index date (HR, 0.7; 95 % CI: 0.6 to 0.8; p = 0.001) were associated with a better OS. At last follow-up, non-ECP-treated patients were more likely to be on greater than 5 mg daily dose of prednisone (54 % versus 23 %; p = 0.04) and had a greater decline in their Karnofsky performance score (mean difference [MD], -9.5 versus -1.6; p = 0.06) compared with ECP-treated-patients. The authors concluded that compared with other BOS-directed therapies, ECP was found to improve survival in HCT patients with BOS, without significantly impacting measured pulmonary functions. Moreover, they stated that these findings need to be validated in a prospective, larger patient cohort.

**Prophylactic Use to Reduce the Risk of Infective Complications Following Kidney Transplantation**

In an open cohort randomized study, Faenko and colleagues (2018) evaluated the influence of prophylactic use of photopheresis on the risk of long-term infective complications following kidney transplantation. A total of 60 recipients after cadaveric kidney allo-transplantation from 30 donors were assessed. Subjects were randomized into 2 groups (n = 30). All transplants were paired, and 1 kidney was transplanted to patient in intervention group, and the another one was transplanted to patient in control group. In the intervention group all patients received standard immunosuppression therapy (tacrolimus, mycophenolate, prednisone) and 10 to 15 sessions of photopheresis during first 6 months following the transplantation. In the control group only the immunosuppression therapy was given. The follow-up period ranged from 2 to 7 years, an average of 4.5 +/- 2.0
years. The rate infective complications in the both groups gradually decreased as the post-operative period increased exponentially, but it was lower in the intervention group than in the control group. The rate of respiratory infection, asymptomatic bacteriuria and viremia, verified by the genetic amplification was 4, 2 and 1.5 times lower in the intervention group. The risk of clinically meaningful infection was significantly lower in the intervention group than in the control group: incidence rate ratio (IRR) of 0.3888 (95 % CI: 0.2754 to 0.5445; p < 0.0001); 6-year survival in the intervention group was 100 % in comparison to 82.8 % in the control group (95 % CI: 51.6 to 93.16). The authors concluded that the prophylactic use of the photopheresis resulted in a reduction in the risk of infective complications following kidney transplantation. These preliminary findings need to be further investigated.

An UpToDate review on “Overview of care of the adult kidney transplant recipient” (Chandraker and Yeung) does not mention ECP/photopheresis as a management option.

**Treatment of Scleroedema Adulturn Buschke**

Dezoteux and associates (2018) noted that scleredema adulturn (Buschke’s scleredema) is a cutaneous mucinosis of unknown origin, clinically characterized by a diffuse induration of the skin usually involving the neck, shoulders and back, which limits patients’ mobility. These investigators reported a case of a 50-year old woman who presented a chronic sclerodermiform syndrome for 2 years associated with type 1 diabetes. Physical examination revealed an extensive skin induration involving the shoulders, neck and back. Histologic examination confirmed the diagnosis of scleredema adulturn. The patient was treated with extracorporeal photopheresis (EPP) twice-monthly for 2 months. At follow-up, mobility was highly improved after 2 months. Beneficial effect of EPP was maintained on the long-term while sessions were spaced. The authors concluded that EPP is an unconventional treatment of Buschke's scleredema, and may represent a therapeutic option for the treatment of scleredema.

In a systematic review on “Treatment of scleroedema adulturn Buschke”, Miguel and colleagues (2018) stated that scleroedema adulturn Buschke (SAB) is a rare skin disease, which can be divided into 3 subtypes: classic type, occurring after respiratory infections; a type lacking association with infections; and a type associated with diabetes; SAB is characterized by thickening and tightening of the
skin, which typically starts at the neck. In 50% of patients, spontaneous remission may occur. Therapeutic options include topical as well as systemic treatments, and physical modalities. These researchers summarized all reported treatments for SAB, based on articles from PubMed database, using the query “sclerodema adultorum Buschke treatment”, English and German, published between 1970 and 2016 and documenting adequate treatments. The results were based mainly on individual case reports, small case series, and retrospective studies often reporting unsuccessful results. They noted that ECP consists of the exposure of 10 to 20% of the body’s leukocytes to photo-activated 8-methoxypsoralen and their re-infusion to the patient. The exact mechanism of ECP is not known. It appeared that the immune system exposure to physically modified T-cell clones may lead to a specific inhibition of T-cell-mediated autoimmunity in diseases where T cells play a major role. A report by Stables et al (2000) showed regression of the skin lesions in a patient with SAB and para-proteinemia after 6 months of ECP treatment. The authors concluded that there is a need for randomized controlled trials (RCTs) and studies on long-term outcomes following treatment.

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>36522</td>
<td>Photopheresis; extracorporeal</td>
</tr>
<tr>
<td>38204 - 38230</td>
<td>Bone marrow or stem cell services and procedures</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>C84.00 - C84.09</td>
<td>Mycosis fungoides</td>
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<tr>
<td>C84.10 - C84.19</td>
<td>Sezary's disease</td>
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<tr>
<td>D89.810</td>
<td>Graft-versus-host disease</td>
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<tr>
<td>D89.813</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>J42</td>
<td>Unspecified chronic bronchitis [only covered for rejection (bronchiolitis obliterans) in lung transplants] [not covered for bronchiolitis obliterans syndrome after allogeneic stem cell transplantation]</td>
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<tr>
<td>T86.00 - T86.09</td>
<td>Complications of bone marrow transplant</td>
</tr>
<tr>
<td>T86.20 - T86.39</td>
<td>Complications of heart and heart-lung transplant</td>
</tr>
<tr>
<td>T86.810 - T86.819</td>
<td>Complications of lung transplant</td>
</tr>
<tr>
<td>Z94.1</td>
<td>Heart transplant status</td>
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<tr>
<td>Z94.81</td>
<td>Bone marrow transplant status</td>
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ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

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<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>D51.0</td>
<td>Vitamin B12 deficiency anemia due to intrinsic factor deficiency [pernicious (congenital) anemia]</td>
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<tr>
<td>D59.0 - D59.1</td>
<td>Acquired autoimmune hemolytic anemia</td>
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<tr>
<td>D69.0</td>
<td>Allergic purpura</td>
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<tr>
<td>D69.3</td>
<td>Immune thrombocytopenic purpura</td>
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<tr>
<td>D76.3</td>
<td>Other histiocytosis syndromes [Xanthogranulomas]</td>
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<tr>
<td>E05.00 - E05.01</td>
<td>Thyrotoxicosis with diffuse goiter</td>
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<td>E06.3</td>
<td>Autoimmune thyroiditis</td>
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<tr>
<td>E10.10 - E11.9</td>
<td>Diabetes mellitus</td>
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<tr>
<td>E13.00 - E13.9</td>
<td>Autoimmune thyroiditis</td>
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<tr>
<td>E27.1 - E27.40</td>
<td>Other disorders of adrenal gland</td>
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<td>G35</td>
<td>Multiple sclerosis</td>
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<tr>
<td>G61.0</td>
<td>Guillain-Barre syndrome</td>
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<td>G70.00 - G70.01</td>
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<td>Crohn's disease [regional enteritis]</td>
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<td>K74.3</td>
<td>Primary biliary cirrhosis</td>
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<td>K75.4</td>
<td>Autoimmune hepatitis</td>
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<td>L12.0 - L12.9</td>
<td>Pemphigoid</td>
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<tr>
<td>L20.0 - L20.9</td>
<td>Atopic dermatitis</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>L44.0</td>
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<td>L63.0 - L63.9</td>
<td>Alopecia areata</td>
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<td>L94.0</td>
<td>Localized scleroderma [morphea]</td>
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<td>M05.00 -</td>
<td>Rheumatoid arthritis and other and unspecified arthropathy</td>
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<td>M06.9, M08.00- M08.99, M12.00 - M12.09</td>
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<td>Polyarteritis nodosa and related conditions</td>
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<td>Other necrotizing vasculopathies</td>
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<td>M33.0 - M33.99</td>
<td>Sicca syndrome [Sjogren]</td>
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<td>M35.00 - M35.09</td>
<td>Other overlap syndromes</td>
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<td>Polymyalgia rheumatica</td>
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<td>M35.3</td>
<td>Diffuse (eosinophilic) fasciitis</td>
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<td>M35.5</td>
<td>Relapsing panniculitis [Weber-Christian]</td>
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<td>M35.6</td>
<td>Hypermobility syndrome</td>
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<td>M35.7</td>
<td>Other specified systemic involvement of connective tissue</td>
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<td>M35.8</td>
<td>Systemic involvement of connective tissue, unspecified</td>
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<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant</td>
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<td>T86.40 - T86.49</td>
<td>Complications of liver transplant</td>
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<td>T86.850 - T86.859</td>
<td>Complication of intestine transplant</td>
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<tr>
<td>T86.890 - T86.899</td>
<td>Complications of other transplanted tissue [transplant failure or rejection of pancreas]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
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<td>Z94.82</td>
<td>Intestine transplant status</td>
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<tr>
<td>Z94.83</td>
<td>Pancreas transplant status</td>
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<tr>
<td>Z94.84</td>
<td>Stem cells transplant status [prophylaxis for graft-versus-host disease following allogeneic hematopoietic cell transplantation]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


92. Puttgen KB. Juvenile xanthogranuloma (JXG). UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2014.


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0241 Extracorporeal Photochemotherapy (Photopheresis)

There are no amendments for Medicaid.