

Corporate Medical Policy

Extracorporeal Photopheresis

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Origination: 9/2010
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Last Review: 8/2018

Description of Procedure or Service

Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory procedure that involves the following steps:

1. Patient blood is collected into a centrifuge system that separates the leukocyte-rich portion (buffy coat) from the rest of the blood.
2. The photosensitizer agent 8-methoxypsoralen (8-MOP) is added to the lymphocyte fraction, which is then exposed to ultraviolet (UV) A (320-400 nm wavelength) light at a dose of 1-2 J per square cm.
3. The light-sensitized lymphocytes are reinfused into the patient.

ECP has been investigated for the treatment of patients with a variety of autoimmune diseases, graft-versus-host disease (GVHD), and T-cell lymphoma (TCL), treatment for and prevention of organ rejection after solid-organ transplant and other miscellaneous conditions.

Treatment for and Prevention of Organ Rejection 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 are also affected. This can, in turn, lead to serious infections, including opportunistic infections.

While first approved for the treatment of cutaneous T-cell lymphoma (CTCL), ECP has more recently been used as a supplement to conventional therapies in the area of 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, while 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 immunosuppressant drugs.

Treatment of Graft-versus-Host Disease (GVHD)

ECP as a treatment of GVHD after a prior allogeneic stem-cell transplant is based on the fact that GVHD is an immunologically mediated disease. GVHD can be categorized into acute disease, occurring within the first 100 days after infusion of allogeneic cells, or chronic disease, which

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develops sometime after 100 days. Acute GVHD is commonly graded from I–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, while 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, peripheral nerves, as well as the skin, liver, or gut—the usual sites of acute GVHD.

Treatment of 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 UV light in the presence of 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 antibodies, it is not certain how these antibodies are related to the pathogenesis of the disease, and, as discussed in this policy, photopheresis is not associated with consistent changes in autoantibody levels.

T-Cell Lymphoma

Treatment of Cutaneous T-Cell Lymphoma (CTCL)

According to the National Cancer Institute (NCI), cutaneous T-cell lymphoma (CTCL) is a neoplasia of malignant T-lymphocytes that initially present as skin involvement. CTCL is extremely rare, with an estimated incidence of about 0.4 per 100,000 annually but, because most are low-grade malignancies with long survival, the overall prevalence is much higher. Two CTCL variants, mycosis fungoides and the Sezary syndrome, account for about 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, adult T-cell leukemia/lymphoma (usually with systemic involvement), or subcutaneous panniculitic T-cell lymphoma. In addition, a number of benign or very indolent conditions can be confused with mycosis fungoides, further complicating diagnosis. See the Policy Guidelines for the current staging classification of CTCL using the TNM (tumor, node, metastases) classification system.

Mycosis fungoides typically progress from an eczematous patch/plaque stage covering less than 10% of the body surface (T1) to plaque stage covering 10% or more of the body surface (T2), and finally to tumors (T3) that frequently undergo necrotic ulceration. Sezary 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 a 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, an average of 2 to 10 years, as waxing and waning cutaneous eruptions prior to biopsy confirmation. The prognosis of patients with mycosis fungoides/Sezary syndrome is based on the extent of disease at presentation and its stage. Lymphadenopathy and involvement of peripheral

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blood and viscera increase in likelihood with worsening cutaneous involvement and define poor prognostic groups. The median survival following diagnosis varies according to stage. Patients with stage IA disease have a median survival of 20 or more years, with the majority of deaths for this group typically unrelated to mycosis fungoides. In contrast, more than 50% of patients with stage III through stage IV disease die of their disease, with a median survival of less than 5 years.

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, possibly excepting ones in the earliest stages, is not curable. Thus, systemic cytotoxic chemotherapy is avoided except for advanced-stage cases. Partial or complete remission is achievable, although the majority of patients require lifelong treatment and monitoring.

Regulatory Status

The U.S. Food and Drug Administration (FDA) has approved via premarket application for 2 photopheresis systems manufactured by Therakos Inc. Those systems are: UVAR® XTS Photopheresis System and Cellex®. Both systems are approved for use in the ultraviolet-A (UVA) irradiation (in the presence of the photoactive drug 8-MOP, methoxsalen) of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in persons who have not been responsive to other therapy.

8-MOP (UVADEX®) is approved by the FDA for use in conjunction with UVAR XTS Photopheresis System for use in the UVA irradiation in the presence of the photoactive drug methoxsalen of extracorporeally circulating leukocyte-enriched blood in the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other therapy.

The use of either Therakos Photopheresis System or UVADEX® for other conditions is an off-label use of a FDA-approved device/drug.
FDA product code: LNR.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for extracorporeal photopheresis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Extracorporeal Photopheresis is covered

Organ Rejection after Solid-Organ Transplant

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Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.

Graft-Versus-Host Disease

Extracorporeal photopheresis may be considered medically necessary as a technique to treat acute and chronic graft-versus-host disease that is refractory to medical therapy.

Cutaneous T-cell lymphoma

Extracorporeal photopheresis may be considered medically necessary as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma.

Extracorporeal photopheresis may be considered medically necessary as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies.

When Extracorporeal Photopheresis is not covered

Organ Rejection after Solid-Organ Transplant

Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid-organ transplantation.

Graft-Versus-Host Disease

Extracorporeal photopheresis is considered investigational as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies.

Autoimmune Diseases

Extracorporeal photopheresis is considered investigational 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's disease.

Cutaneous T-cell lymphoma

Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.

Other

Extracorporeal photopheresis is considered investigational for all other indications.

Policy Guidelines

Graft Rejection After Solid Organ Transplant

Heart Transplant

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For individuals who are heart transplant recipients who experience acute graft rejection refractory to immunosuppression who receive ECP, the evidence includes a small randomized controlled trial (RCT). Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small RCT, while suggesting similar outcomes for ECP and corticosteroids, is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are heart transplant recipients who experience recurrent and/or refractory graft rejection who receive ECP, the evidence includes a comparative study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is consistent on the beneficial effect of ECP for cardiac transplant patients with graft rejection refractory to standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are heart transplant recipients who require prophylaxis to prevent graft rejection who receive ECP, the evidence includes a small RCT. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The small randomized trial is insufficient to permit conclusions on the utility of ECP. Studies with more patients and longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lung Transplant

For individuals who are lung transplant recipients who experience acute graft rejection who receive ECP, the evidence includes a small retrospective study and small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence is very limited and any conclusions drawn lack certainty. A prospective, randomized trial is needed specifically evaluating the treatment of patients with acute graft rejection. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are lung transplant recipients with bronchiolitis obliterans syndrome refractory to corticosteroids who receive ECP, the evidence includes a prospective study and numerous retrospective analyses. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Studies have shown inconsistent results across bronchiolitis obliterans syndrome grades. Prospective, RCTs are necessary with analyses stratified by syndrome grade. The evidence is insufficient to determine the effects of the technology on health outcomes.

Liver Transplant

For individuals who are liver transplant recipients who experience graft rejection and receive ECP, the evidence includes a small nonrandomized study, a retrospective study, and a case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the utility of ECP in this population. There is a need for RCTs comparing immunosuppressive therapy alone with immunosuppressive therapy with ECP. The evidence is insufficient to determine the effects of the technology on health outcomes.

Kidney Transplant

For individuals who are kidney transplant recipients who experience recurrent graft rejection who receive ECP, the evidence includes a small prospective study and numerous case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence does not permit conclusions on the effect of ECP on net health outcome. RCTs, comparing immunosuppressive therapy with immunosuppressive therapy using ECP and examining histologic confirmation of treatment response, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Graft-Versus-Host Disease

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For individuals who have acute or chronic graft-versus-host-disease (GVHD) refractory to medical treatment who receive ECP, the evidence includes systematic reviews, retrospective studies, and case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Current evidence has consistently shown that ECP reduces the incidence of GVHD that is unresponsive to standard therapy. Additionally, there is a lack of other treatment options for these patients; adverse events related to 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Autoimmune Disease

For individuals who have autoimmune diseases (eg, 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, and Crohn disease) who receive ECP, the evidence includes isolated RCTs, small prospective and retrospective studies, and case reports. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. The current literature assessing the various autoimmune diseases is not sufficiently robust to support conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have advanced-stage (stage III or IV) cutaneous T-cell lymphoma (CTCL) who receive ECP, the evidence includes a systematic review and numerous small case series. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. Evidence from these small case series has shown a favorable response to ECP treatment and an increase in survival in a proportion of these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory or progressive early-stage (stage I or II) CTCL who receive ECP, the evidence includes a systematic review. Relevant outcomes are overall survival, change in disease status, and treatment-related mortality and morbidity. 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, this therapy is an option for those with refractory or progressive early-stage CTCL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 after standard immunosuppressive therapy.

There is no standard schedule for extracorporeal photopheresis (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

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Methylprednisolone is considered first-line treatment of acute graft-versus-host disease (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 (ie, ECP on 2 consecutive days) weekly for acute GVHD and every 2 weeks for chronic GVHD. Treatment duration is based on clinical response (see the Practice Guidelines and Position Statements section); discontinuation is generally recommended for no or minimal response.

Cutaneous T-Cell Lymphoma Staging

Cutaneous T-cell Lymphoma staging is based on the tumor, node, metastases (TNM) classification system.

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 36522

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Extracorporeal Photopheresis for Graft versus Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 12/11/2009

Medical Director Review - 8/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 1/13/2011

Name change - Extracorporeal Photopheresis after Solid Organ Transplant and for Graft versus Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma

Medical Director Review – 3/2011

Specialty Matched Consultant Advisory Panel – 8/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 3/8/2012

Specialty Matched Consultant Advisory Panel – 8/2012

Name change - Extracorporeal Photopheresis

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 2/14/2013

Specialty Matched Consultant Advisory Panel – 8/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 5/22/2014

Specialty Matched Consultant Advisory Panel- 8/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 4/23/2015

Specialty Matched Consultant Advisory Panel- 8/2015

Specialty Matched Consultant Advisory Panel- 8/2016

Specialty Matched Consultant Advisory Panel- 8/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 10/27/2017

Specialty Matched Consultant Advisory Panel- 8/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.36, 10/10/2018

Policy Implementation/Update Information

Extracorporeal Photopheresis for Graft versus Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma

9/28/10 New policy written. “Extracorporeal photopheresis may be considered medically necessary as a technique to treat chronic graft-versus-host disease that is refractory to medical therapy. Extracorporeal photopheresis may be considered medically necessary as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma. Extracorporeal photopheresis may be considered medically necessary as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established

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nonsystemic therapies.” “Extracorporeal photopheresis is considered investigational as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies.

Extracorporeal photopheresis is considered investigational 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, or diabetes. Extracorporeal photopheresis is considered investigational as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.”

Reviewed with Medical Director 8/31/2010. Notification given 9/28/2010. Policy effective date 1/4/2011. (btw)

Name change - Extracorporeal Photopheresis after Solid Organ Transplant and for Graft versus Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma

6/21/11 Added “Solid Organ Transplant to policy name. “Description” section updated to include section regarding use in solid organ transplantation rejection. Added the following statement to the “When Covered” section; “Extracorporeal photopheresis may be considered medically necessary to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment.” Added the following information to the “When Not Covered” section; “Extracorporeal photopheresis is considered investigational in all other situations related to treatment or prevention of rejection in solid-organ transplantation.” Added “autoimmune bullous disorders” to the “Autoimmune Disease” statement as another example of when extracorporeal photopheresis is not covered. Reviewed by Medical Director 3/23/11. References added. (btw)

9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/2011. No change to policy statement. (btw)

5/1/12 Policy Guidelines updated. Reference added. Medical Director review 4/12/12. (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy. (btw)

Name change - Extracorporeal Photopheresis

4/30/13 Name changed from “Extracorporeal Photopheresis after Solid Organ Transplant and for Graft versus Host Disease, Autoimmune Disease, and Cutaneous T-Cell Lymphoma” to “Extracorporeal Photopheresis”. Description section revised to add information regarding Peripheral T-Cell Lymphoma (PTCL). Added the following statement to the When Not Covered section; “Other - Extracorporeal photopheresis is considered investigational for all other indications.” Senior Medical Director review 4/4/2013. Reference added. (btw)

9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)

7/15/14 Under “When Covered” section **Graft-Versus-Host Disease:** added acute GVHD as medically necessary. Under “When Not Covered” section **Autoimmune Diseases:** added severe atopic dermatitis, and Crohn’s disease. Reviewed by Sr. Medical Director. Reference added.(lpr)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

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- 10/1/15 Updated Regulatory Status and Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)
- 9/30/16 Updated Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)
- 9/15/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)
- 11/10/17 Reference added. (lpr)
- 9/28/18 Specialty Matched Consultant Advisory Panel review 8/2018. No change to policy statement. (lpr)
- 11/9/18 Updated Policy Guidelines section. No change to policy statement. Reference added. (lpr)

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