Plasma Exchange

Plasma exchange (PE) is considered medically necessary for the conditions listed below:

**Autoimmune**
- Severe multiple manifestations of mixed cryoglobulinemia (MC) such as cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis in combination with immunosuppressive treatment;
- Catastrophic antiphospholipid syndrome

**Hematologic**
- ABO incompatible hematopoietic progenitor cell transplantation;
- Hyperviscosity syndromes associated with multiple myeloma or Waldenstrom macroglobulinemia;
- Idiopathic thrombocytopenic purpura in emergency situations;
- Thrombotic thrombocytopenic purpura (TTP);
- Atypical hemolytic-uremic syndrome;
- Post-transfusion purpura;
- HELLP syndrome of pregnancy (a severe form of preeclampsia, characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts);
- Myeloma with acute renal failure

**Neurologic**
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome [GBS]; severity grade 1–2 within 2 weeks of onset; severity grade 3–5 within 4 weeks of onset; and children younger than 10 years -old with severe GBS);
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP);
- Multiple sclerosis (MS); with acute fulminant central nervous system (CNS) demyelination
- Myasthenia gravis in crisis or as part of preoperative preparation;
- Paraproteinemia polyneuropathy; IgA, IgG
Renal
- Anti-glomerular basement membrane disease (Goodpasture syndrome);
- ANCA [antineutrophil cytoplasmic antibody]-associated vasculitis [e.g., Wegener's granulomatosis also known as granulomatosis with polyangiitis (GPA)] with associated renal failure;
- Dense deposit disease with factor H deficiency and/or elevated C3 Nephritic factor.

Transplantation
- ABO incompatible solid organ transplantation;
  - Kidney;
  - Heart (infants);
- Renal transplantation: antibody mediated rejection; HLA [human leukocyte antigen] desensitization;
- Focal segmental glomerulosclerosis after renal transplant.

Plasma exchange (PE) is considered investigational in all other conditions, including, but not limited, to the following:
- ABO-incompatible solid organ transplant; liver;
- Acute disseminated encephalomyelitis;
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) in children younger than 10 years old with mild or moderate forms;
- Acute liver failure;
- Amyotrophic lateral sclerosis;
- ANCA [antineutrophil cytoplasmic antibody]-associated rapidly progressive glomerulonephritis (Wegener granulomatosis or GPA without renal failure);
- Aplastic anemia;
- Asthma;
- Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia; cold agglutinin disease;
- Chronic fatigue syndrome;
- Coagulation factor inhibitors;
- Cryoglobulinemia; except for severe mixed cryoglobulinemia, as noted above;
- Dermatomyositis and polymyositis;
- Focal segmental glomerulosclerosis (other than after renal transplant);
- Heart transplant rejection treatment;
- Hemolytic uremic syndrome (HUS); typical (diarrheal-related);
- Idiopathic thrombocytopenic purpura; refractory or nonrefractory;
- Inclusion body myositis;
- Lambert-Eaton myasthenic syndrome;
- Multiple sclerosis; with chronic progressive or relapsing remitting course;
- Neuromyelitis optica (NMO);
- Mushroom poisoning;
- Myasthenia gravis with anti-MuSK antibodies;
- Overdose and poisoning (other than mushroom poisoning);
- Paraneoplastic syndromes;
- Paraproteinemia polynephropathy; IgM
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS);
- Pemphigus vulgaris;
- Phytic acid storage disease (Refsum disease);
- POEMS (polynephropathy, organomegaly, endocrinopathy, M protein, skin changes);
- Psoriasis;
- Red blood cell alloimmunization in pregnancy;
- Rheumatoid arthritis;
- Sepsis;
- Scleroderma (systemic sclerosis);
- Stiff person syndrome;
- Sydenham chorea (SC);
- Systemic lupus erythematosus (including SLE [systemic lupus erythematosus] nephritis);
Thyrotoxicosis;
Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom macroglobulinemia)

Related Policies

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Policy Guidelines

This policy only addresses plasma exchange (PE) as a therapeutic apheresis procedure.

Patients receiving PE as a treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) should meet the diagnostic criteria for CIDP that are included in the Appendix.

Patients receiving PE as a treatment of acute inflammatory demyelinating polynuropathy, also known as Guillain-Barré syndrome (GBS), should meet the criteria of diagnostic severity that are included in the Appendix.

The use of PE in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis (RA) and SLE, may need to be considered on an individual basis. An example of such a situation would be the development of a severe vasculitis, in which it is hoped that the use of PE can acutely lower the level of serum autoantibodies until an alternate long-term treatment strategy can be implemented. However, in these situations, the treatment goals and duration of treatment with PE need to be clearly established before its initiation; without such treatment goals, the use of an acute short-term course of PE may insidiously evolve to a chronic use of PE with uncertain benefit.

Coding

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<td>36514</td>
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Description

Plasma exchange (PE) is a procedure in which the plasma is isolated, then discarded and replaced with a substitution fluid such as albumin. PE is a nonspecific therapy, because the entire plasma is discarded. PE has been used in a wide variety of acute and chronic conditions, as well as in the setting of solid organ transplantation.

Background

The terms therapeutic apheresis, plasmapheresis, and PE are often used interchangeably, but when properly used denote different procedures. The American Society for Apheresis (ASFA) definitions for these procedures are as follows:

Apheresis: A procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment.
or replacement of the separated component.

**Plasmapheresis:** A procedure in which blood of a patient or the donor is passed through a medical device which separates out plasma from the other components of blood and the plasma is removed (i.e., <15% of total plasma volume) without the use of replacement solution.

**Plasma exchange:** A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.

The rationale for PE is based on the fact that circulating substances, such as toxins or autoantibodies, can accumulate in the plasma. Also, it is hypothesized that removal of these factors can be therapeutic in certain situations. PE is essentially a symptomatic therapy, because it does not remove the source of the pathogenic factors. Therefore the success of PE will depend on whether the pathogenic substances are accessible through the circulation and whether their rate of production and transfer to the plasma component can be adequately addressed by PE. For example, PE can rapidly reduce levels of serum autoantibodies; however, through a feedback mechanism, this rapid reduction may lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to render the replicating pathogenic clone of lymphocytes more vulnerable to cytotoxic drugs; therefore, PE is sometimes used in conjunction with cyclophosphamide.

Applications of PE can be broadly subdivided into 2 general categories: (1) acute self-limited diseases, in which PE is used to acutely lower the circulating pathogenic substance; and (2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. Because PE does not address underlying pathology, and, due to the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

In addition, plasmapheresis has been used in the setting of solid organ transplantation. It has been used as a technique to desensitize high-risk patients before transplant and also as a treatment of antibody-mediated rejection (AMR) reaction occurring after transplant. Before transplant, plasmapheresis has been most commonly used to desensitize patients receiving an ABO mismatched kidney, often in combination with a splenectomy. As a treatment of AMR, plasmapheresis is often used in combination with intravenous immunoglobulin (IVIg) or anti-CD20 therapy (i.e., rituximab).

**Regulatory Status**

FDA has a compliance program to ensure that source plasma, source leukocytes, and therapeutic exchange plasma for further manufacture into products for human use are safe, pure, potent, and appropriately labeled. The compliance program covers products intended for use both in injectable drug products (e.g., immune globulin, albumin) and noninjectable products (e.g., in vitro devices such as blood bank reagents).


**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Rationale

This policy was originally created in 1995 and was updated regularly with searches of the MEDLINE database. The most recent literature review was performed through April 30, 2015. Following is a summary of the key literature to date.

Autoimmune Diseases

One potential type of evidence in support of the clinical effectiveness of plasma exchange (PE) in treating autoimmune diseases is the identification of a pathogenic component of plasma that is reliably eliminated by plasmapheresis. (2) Although many laboratory abnormalities are associated with autoimmune connective tissue diseases, it is unclear which, if any, cause the clinical manifestations of the disease. Furthermore, it is unknown to what extent plasma levels parallel clinical disease. For example, in many of the controlled trials discussed next, PE reliably reduced circulating autoantibodies and immune complexes, but without demonstrable clinical benefit. It may be that the patient had already suffered irreversible damage or that the pathogenesis of the disease was a local process unrelated to circulating factors. Over the past 10 years, randomized trials of PE have been conducted and, in general, have shown a lack of effectiveness as treatment of chronic autoimmune diseases. Clinical results of randomized trials of plasmapheresis for specific chronic autoimmune diseases are discussed here.

Systemic Lupus Erythematosus

Reporting on the results of a randomized controlled trial (RCT), Lewis et al. (1992) concluded that PE had no benefit in patients with systemic lupus and glomerulonephritis compared with a standard therapy regimen of prednisone and cyclophosphamide. (3) Plasmapheresis has also been investigated as a technique to improve the effectiveness of cyclophosphamide therapy. For example, it is thought that the acute lowering of pathogenic autoantibodies with plasmapheresis may result in their rebound production. It is hoped that the pathogenic lymphocytes would be more sensitive to cyclophosphamide at this point. Danieli et al. (2002) reported on a prospective nonrandomized trial of 28 patients with proliferative lupus nephritis; 12 underwent synchronized plasmapheresis and pulse cyclophosphamide therapy, while the remaining 16 underwent cyclophosphamide alone. (4) Although plasmapheresis was associated with a decreased time to remission of renal disease, at the end of the 4-year follow-up, there was no difference in outcome.

Multiple Sclerosis

There have been several RCTs of PE in patients with multiple sclerosis (MS) that have reported inconclusive results. Khatri et al. (1985) studied 54 patients with chronic progressive MS randomized to receive sham or true PE. (5) The degree of improvement in the PE group was greater than that in the control group. Weiner et al. (1989) reported on a study that randomized patients with acute attacks of MS to receive either PE or sham treatments; there was no statistical difference in improvement between groups, although patients receiving PE did have a faster recovery rate from acute attacks. (6) A 1991 Canadian trial randomized 168 patients with progressive MS to receive either PE or immunosuppressive therapy. (7) There were no significant differences in the rates of treatment failures between groups.

Lambert-Eaton Myasthenic Syndrome and Other Paraneoplastic Syndromes

Paraneoplastic neuromuscular syndromes are characterized by the production of tumor antibodies that cross-react with the patient’s nervous system tissues. Lambert-Eaton myasthenic syndrome (LEMS), characterized by proximal muscle weakness of the lower extremities and associated most frequently with small-cell lung cancer, is
the most common paraneoplastic syndrome. The presumed autoimmune nature of LEMS and other paraneoplastic syndromes led to the use of a variety of immunomodulatory therapies, including PE. However, there are minimal data in the published literature and no controlled trials. The largest case series focusing on LEMS was reported by Tim et al. (2000) and included 73 patients with LEMS, 31 of whom were found to have lung cancer. Although detailed treatment strategies are not provided, 19 underwent plasmapheresis, with 27% reporting a moderate to marked response. However, the improvement after plasmapheresis, even when marked was only transient. Patients also received other therapies, for example, various chemotherapy regimens for the underlying lung cancer. In addition, 53 (73%) of the 73 patients received 3,4 diaminopyridine, with 79% reporting marked or moderate responses. In the same year, a small RCT of 3,4 diaminopyridine also reported positive results, confirming other anecdotal reports. Anderson et al. (1988) reported on a case series of 12 patients with paraneoplastic cerebellar degeneration. Although plasmapheresis was associated with an acute drop in the autoantibody titer, only 2 patients (17%) showed a minor improvement in neurologic symptoms. 

Rheumatoid Arthritis
In 1983, Dwosh et al. reported on 26 patients with chronic rheumatoid arthritis randomized in a crossover design to either true or sham PE. The authors concluded that PE did not have any clinical benefit, despite impressive laboratory changes. 

Polymyositis/Dermatomyositis
Miller et al. (1992) conducted a randomized trial of PE in the treatment of 39 patients with polymyositis and dermatomyositis and found that PE was no more effective than sham pheresis. 

Pemphigus
Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. Steroids or other immunosuppressants are the most common forms of treatment, but high doses of steroids can produce significant adverse effects. Guillaume et al. (1988) reported on a study of 40 patients with pemphigus randomized to receive either prednisone alone or prednisone plus plasmapheresis. The goal of the study was to determine whether plasmapheresis could reduce the required dose of steroids, thus limiting its toxicity. Unfortunately, disease control in the 2 groups was the same, and the authors concluded that plasmapheresis in conjunction with low-dose steroids is not effective in treating pemphigus.

Stiff Man (or Stiff Person) Syndrome
Stiff man syndrome is an autoimmune disorder characterized by involuntary stiffness of axial muscles and intermittent painful muscle spasm. Stiff man syndrome may be idiopathic in nature or seen in association with thymoma, Hodgkin disease, and small cell lung; colon; or breast cancer. The mainstay of treatment of stiff man syndrome is diazepam. The published literature regarding plasmapheresis consists of small case series and anecdotal reports. Most of these studies were published in the late 1980s or early 1990s; 1 case series with 9 patients was published in 2014.

Cryoglobulinemia
There are several types of cryoglobulinemia. Type I is associated with hematologic disorders. Types II and III are considered mixed cryoglobulinemias. Mixed cryoglobulinemia is a consequence of immune-complex mediated vasculitis and may be associated with infectious and systemic disorders (e.g., hepatitis C virus). In 2010, Rockx and Clark published a review of studies evaluating PE for treating cryoglobulinemia that included at least 5 patients. They identified 11 studies with a total of 156 patients. The authors concluded, “The quality and variability of the evidence precludes a meta-analysis or even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis.”

Hematologic

Thrombotic Thrombocytopenic Purpura and Haemolytic Uraemic Syndrome
Once considered distinct syndromes, thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are now considered different manifestations of the same disease process (i.e., thrombotic
microangiopathy). In 2009, a systematic review evaluated the benefits and harms of different interventions for HUS and TTP (separately). (19) Interventions were compared with placebo or supportive therapy or a comparison of 2 or more interventions. Interventions examined included heparin, aspirin/dipyridamole, prostanooids, ticlopidine, vincristine, fresh frozen plasma (FFP) infusion, plasmapheresis with FFP, systemic corticosteroids, Shiga toxin-binding agents, or immunosuppressive agents. For TTP, 6 RCTs (N=331) were identified evaluating PE with FFP as the control. Interventions tested included antiplatelet therapy plus PE with FFP, FFP transfusion, and PE with cryosupernatant plasma. Two studies compared plasma infusion (PI) to PE with FFP and showed a significant increase in failure of remission at 2 weeks (risk ratio [RR], 1.48) and all-cause mortality (RR=1.91) in the PI group. The authors concluded that PE with FFP is the most effective treatment available for TTP. Seven RCTs included children with HUS. None of the assessed interventions was superior to supportive therapy alone for all-cause mortality, neurologic/extrarenal events, renal biopsy changes, proteinuria, or hypertension at the last follow-up visit. The incidence of bleeding was significantly greater in those receiving anticoagulation therapy compared with supportive therapy alone (risk difference, 0.35). For patients with HUS, supportive therapy including dialysis was the most effective treatment. All studies in HUS have been conducted in the diarrheal form of the disease. There were no RCTs evaluating the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course. A recent review article by Noris and Remuzzi (2009) described data supporting use of PE in the atypical form of this disease, with results showing remission in up to 60% of patients. (20)

All studies in HUS have been conducted with patients with the diarrheal (typical) form of the disease. Because the available evidence for patients with typical HUS shows supportive therapy, including dialysis, to be the most effective treatment, evidence for the use of PE for the treatment of typical HUS is inadequate to draw clinical conclusions. PE for HUS was considered medically necessary in previous updates. PE remains medically necessary for atypical HUS.

**Idiopathic thrombocytopenic purpura**

Idiopathic thrombocytopenic purpura is an acquired disease of either adults or children characterized by the development of autoantibodies to platelets. Management of acute bleeding due to thrombocytopenia typically involves immediate platelet transfusion, occasionally in conjunction with a single infusion of intravenous immunoglobulin (IVIg). PE has been occasionally used in emergency situations.

**Post-transfusion purpura**

Posttransfusion purpura is a rare disorder characterized by an acute severe thrombocytopenia occurring approximately 1 week after a blood transfusion in association with a high titer of antiplatelet alloantibodies. Because of its rapid effect, PE is considered the initial treatment of choice.

**HELLP syndrome of pregnancy**

The HELLP syndrome of pregnancy is a severe form of preeclampsia characterized by hemolysis (H), elevated liver enzymes (EL), and low platelet (LP) counts). The principal form of treatment is delivery of the fetus. However, for patients with severe thrombocytopenia, PE may be indicated if the fetus cannot safely be delivered, or if the maternal thrombocytopenia persists into the postnatal period.

**Neurologic**

**Guillain-Barré Syndrome (GBS)**

GBS is an acute demyelinating neuropathy whose severity is graded on a scale of 1 to 5. In 2012, The Cochrane Collaboration published an updated systematic review of the evidence concerning the efficacy of PE for treating GBS. (21) Six eligible trials (N=649) were identified comparing PE versus supportive treatment alone. No additional trials were published since the 2002 review. The primary outcome measures of the review included time to recover walking with aid and time to onset of motor recovery in mildly affected patients. A pooled analysis of data from 3 trials found that PE significantly increased the proportion of patients who recovered the ability to walk with assistance after 4 weeks (RR=1.60; 95% confidence interval [CI], 1.19 to 2.15). Data on time to onset of motor recovery were not pooled. Pooled analyses found that PE led to significant improvement in secondary outcomes including reduced time to recover walking without aid, increased likelihood of full muscle strength recovery, and reduced likelihood of severe motor sequelae. However, there was a significantly higher risk of relapse in the group that received PE compared with supportive treatment alone (RR=2.89; 95% CI: 1.05 to 7.93;
A 2007 systematic review evaluated the available randomized trials of immunotherapy to treat GBS. (22) In 4 trials with severely affected adult participants (N=585), those treated with PE improved significantly more on the disability scale 4 weeks after randomization than those who were not (weighted mean difference [WMD], -0.89; range, -1.14 to -0.63). In 5 trials (n=582), the improvement on the disability grade scale with IVIg was very similar to that with PE (WMD = -0.02; range, -0.25 to 0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. One trial included patients (n=91) with the mild form of GBS who were able to walk unaided at enrollment. Patients were randomized to receive either 2 sessions of PE in 3 days or supportive care. The number of patients with 1 or more grades of improvement at 1 month was significantly greater, 26 (58%) of 45 in the treated group compared with 13 (29%) of 45 controls. Fewer patients in the PE-treated group had clinical deterioration (4%) compared with the control group (39%) or required ventilation (PE group: 2% vs. controls: 13%). In 1 trial (N=148), administering IVIg after PE did not produce significant extra benefit. Limited evidence from 3 open trials in children suggested that IVIg hastens recovery compared with supportive care alone. None of the treatments significantly reduced mortality. The authors concluded that “since approximately 20% of patients die or have persistent disability despite immunotherapy, more research is needed to identify better treatment regimens and new therapeutic strategies.”

In 2003, a report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN), Practice Parameter: Immunotherapy for Guillain–Barré syndrome, was published. (23) The following are the key findings: (1) treatment with PE or IVIg hastens recovery from GBS; (2) combining the 2 treatments is not beneficial; and (3) steroid treatment given alone is not beneficial. AAN’s recommendations are: (1) PE is recommended for nonambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms (PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms); (2) IVIg is recommended for nonambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms (the effects of PE and IVIg are equivalent); (3) corticosteroids are not recommended for the management of GBS; (4) sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg is not recommended for patients with GBS; and (5) PE and IVIg are treatment options for children with severe GBS.

A 2011 RCT from Iran evaluated PE for treating young children with severe GBS. (24) The study included 41 children with GBS who required mechanical ventilation and had muscle weakness for no more than 14 days. Patients were randomized to receive PE (n=21) or IVIg (n=20). Mean patient age was 96 months in the PE group and 106 months in the IVIg group. Mean (SD) duration of ventilation, the primary outcome, was 11 (1.5) days in the PE group versus 13 (2.1) days in the IVIg group (p=0.037). Duration of stay in the intensive care unit, a secondary outcome, was 15.0 (2.6) days in the PE group and 16.5 (2.1) days in the IVIg group (p=0.94).

**Section Summary**

The available evidence is sufficient regarding PE for the treatment of patients with all severity grades of GBS. This therapy has a beneficial impact on net health outcome for all severity grades. Published studies are insufficient regarding PE for treatment of GBS in the pediatric population. However, based on limited published data, as well as extrapolated data from studies in adults and clinical input, PE may be considered as a treatment option for children younger than 10 years old with severe GBS.

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy**

A 2012 Cochrane review by Mehnidiratta and Hughes identified 2 randomized trials on PE for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). (25) Both trials were considered to be of high quality, but both had small sample sizes. One trial with 29 patients used a parallel design and compared PE with sham treatment. The other study included 15 patients and used a crossover design to compare PE and sham treatment. A pooled analysis of data from the 2 trials found a statistically significantly greater improvement in impairment after 4 weeks with PE versus sham (mean difference in Neuropathy Impairment Score: 31 points, 95% CI: 16 to 45 points). The scale ranges from 0 (normative) to 280 (maximally affected). Data on other outcomes were not suitable for pooled analysis.

**Acute Fulminant Central Nervous System Demyelination**

The policy statement, which suggests that plasmapheresis may be considered medically necessary in patients...
with acute fulminant central nervous system (CNS) demyelination, is based on the results of a 1999 randomized, double-blinded trial, in which 22 patients with MS or other acute idiopathic inflammatory demyelinating diseases of the CNS were enrolled a minimum of 14 days after having failed to respond to at least 5 days of high-dose corticosteroids. (26) Patients were randomized to receive either 7 real or sham PE procedures over a 14-day period. The primary outcome was a targeted neurologic deficit (i.e., aphasia, cognitive dysfunction). Overall, moderate to marked improvement of the targeted outcome was obtained in 42% of the treatment group, compared with only 6% in the placebo group.

Paraproteinemic Polyneuropathies

A 1991 randomized, double-blinded trial compared PE with sham treatment in 39 patients with monoclonal gammopathy of undetermined significance (MGUS)‒associated polyneuropathy. (27) After twice weekly PE for 3 weeks, the treatment group reported improvements in neurologic function in the IgG and IgA groups but not the IgM MGUS groups. In addition, those from the sham group who later crossed over to the PE group also reported improvement.

Myasthenia Gravis

Several RCTs have been published. One of these, a 2011 trial from Germany, included patients with myasthenic crisis. (28) Patients were randomized to treatment with PE (n=10) or immunoadsorption (IA) (n=9). In both groups, 3 apheresis treatments were performed within 7 days; patients could have additional treatments if needed. A total of 16 (84%) of 19 of patients, 8 in each group, completed the study and were included in the efficacy analysis. The mean number of treatments was 3.5 in the PE group versus 3.4 in the IA group (p>0.05). The primary outcome was change in the modified clinical score (maximum of 3 points) on day 14 after the last treatment. The baseline modified clinical score was 2.6 in the PE group and 2.5 in the IA group. At day 14, score improvement was 1.6 points in the PE group and 1.4 points in the IA group (p>0.05). Within 180 days after treatment, 1 patient in the PE group and 3 patients in the IA group experienced another myasthenic crisis; the number of events was too small for meaningful statistical analysis for this outcome. Although there were no statistically significant differences in outcomes in this study, the patient sample was very small and the study was likely underpowered.

Two trials included patients with myasthenia gravis in the absence of myasthenic crisis. Liu et al. (2009) in China randomized 40 patients with late-onset myasthenia gravis to treatment with double-filtration plasmapheresis (n=15), IA (n=10), or intravenous immune globulin (n=15). (29) Treatment was clinically effective, defined as at least a 50% improvement in the relative symptom score, in 12 (80%) of 15 of the plasmapheresis group, 7 (70%) of 10 in the IA group, and 6 (40%) of 15 of the immune globulin group. The clinical efficacy rate was significantly higher in both the plasmapheresis and immunoadsorption groups compared with the immune globulin group (p<0.05). Findings were similar for other outcomes; the study was limited by the small sample size. A 2011 trial by Barth et al in Canada randomized patients with myasthenia gravis to treatment with PE (n=43) or IVIg (n=41). (30) Patients had moderate to severe myasthenia gravis, as defined by a score of at least 10.5 on the Quantitative Myasthenia Gravis Score (QMGS) for disease severity, and worsening weakness requiring a change in treatment. Patients were not experiencing myasthenic crisis. At day 14, there was no statistically significant difference between groups in the change on the QMGS, the primary efficacy outcome. Mean QMGS at day 14 was 4.7 in the PE group versus 3.2 in the IVIg group (p=0.13). Moreover, at day 14, 69% were considered improved on PE versus 65% on IVIg; the difference between groups was not statistically significant (p=0.74). Safety outcomes were published in 2013. (31) Forty-two patients received a total of 203 PE procedures; 40 completed the full course of 5 procedures. Complications occurred in 19 (45%) of 42 patients. Two complications were serious. One patient had hypertension, heart failure, and pneumonia; all of these were unrelated to the procedures. The other patient had a myocardial infarction, which could have been exacerbated by PE.

Results from the few trials evaluating treatment of myasthenia gravis suggest that PE is reasonably safe in patients with moderate to severe myasthenia crisis. There is some evidence on the comparative efficacy of PE versus IVIg, but the trials are small and reported mixed results, and therefore definitive conclusions cannot be made.

Neuromyelitis Optica

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the CNS that predominantly affects the optic nerves and spinal cord. No RCTs evaluating PE for treatment of patients with NMO were identified. Several retrospective nonrandomized studies have evaluated PE as add-on therapy to intravenous (IV) corticosteroids.
In 2015, Abboud et al. reviewed 83 admissions for acute relapse of NMO at a single center in the United States. (32) Relapses could involve the spinal cord, optic nerve, and/or the brain. Patients were initially treated with IV corticosteroids alone for 5 days, and if they did not respond, they were then treated with 5 to 7 sessions of PE in their second week of hospitalization. Eighteen relapses (16 patients) were treated with IV corticosteroid therapy alone, and 65 relapses (43 patients) were treated with IV corticosteroid plus PE. Patients were assessed using the Expanded Disability Status Score (EDSS), which has a possible range of 1 to 10, with higher numbers indicating more disability. The primary endpoint was a return to baseline EDSS (before admission) on discharge. The EDSS scores at baseline and discharge were calculated retrospectively based on available records and without blinding to treatment group.

In the relapses treated with IV corticosteroids only, the median baseline EDSS was 2.5, which increased to 4.5 at presentation and decreased to a median of 4 at discharge. In comparison, among the relapses that were also treated with PE, the median baseline EDSS was 5.75 which increased to 7.75 at presentation and decreased to a median of 6.5 at discharge. At discharge, 3 relapses (17%) in the IV corticosteroid-only group improved to baseline EDSS or lower at discharge compared with 31 relapses in the IV corticosteroid plus PE group (p=0.016). Follow-up data at approximately 1 year (range, 6-18 months) were available on 50 of 65 relapses (77%). At this longer term follow-up point, 6 relapses in the intravenous methylprednisolone (IVMP) only group and 33 in the IVMP group improved to an EDSS equal or below their baseline EDSS (p=0.039).

The study did not directly compare the efficacy of IV corticosteroid treatment alone with IV corticosteroids plus PE because the treatments were applied sequentially. Moreover, the patient populations differed; patients who received PE add-on treatment were older and more disabled at baseline. The finding that a greater proportion of the more severely ill population had resolution of acute relapses suggests that combination IV corticosteroid and PE therapy may be more beneficial than IV corticosteroids alone. However, to draw definitive conclusions, findings would need to be confirmed in randomized trials. Another study limitation was a lack of patient-level analyses and lack of other outcome measures at 1 year measuring disease progression.

Two other studies were conducted at a facility in Martinique, and they compared outcomes in patients treated before and after PE was introduced as a treatment. A 2009 study by Bonnan et al. focused on spinal attacks associated with NMO. (33) The study reported on 43 patients with NMO, 18 of whom received PE as an add-on therapy for at least 1 spinal attack. The study period was 1982 to 2008 and PE was introduced at the facility in 1999. The patients experienced a total of 96 spinal attacks; PE was used in 29 attacks. The PE-treated and corticosteroid-only groups had similar EDSS scores before the spinal attacks, and there was greater reduction in EDSSs following treatment with PE. In the PE group, the mean acute EDSS (SD) was 7.9 (1.3) and the mean EDSS after therapy was 5.1 (2.4), a mean decrease of 2.8 points. In comparison, the mean acute EDSS in the corticosteroid-only group was 8.0 (1.4), and the mean EDSS after treatment was 6.8 (1.9), a mean decrease of 1.2 points. The analysis was done on a per attack basis rather than a per-patient basis.

The 2012 study by Merle et al. evaluated the impact of PE as an add-on therapy on optic outcomes in 32 patients treated for acute optic neuritis between 1996 and 2010. (34) In 2006, PE was added to the treatment protocol and 16 of the 32 patients also received 5 daily consecutive PEs in the intensive care unit. Study outcomes were obtained from an eye examination performed at least 6 months after optic neuritis treatment. At the final follow-up visit, visual acuity was significantly better in the PE group than the corticosteroid-only group (20/400 vs. 20/50, respectively, p=0.04). Visual acuity gain was 20/200 in the corticosteroid group and 20/30 in the PE group (p=0.01). Outcomes could be impacted by confounding factors. For example, longer disease duration was associated with poorer outcomes in univariate analysis and, at baseline, disease duration was significantly longer in the corticosteroid group than the PE group (mean, 10.8 and 5.8 years, respectively, p<0.001).

Limitations of the Bonnan et al. and Merle et al. studies include that patients may have overlapped between studies, and lack of randomization may have led to baseline between-group differences in factors that affected outcomes. In addition, both studies are subject to bias due to use of historical controls, i.e., patients in the latter time period received PE and care could also have improved over time in other ways that led to improved outcomes.

The U.S. National Institute of Neurological Disorders and Stroke (NINDS) has an informational webpage on neuromyelitis optica which states that several treatments are available off-label to reduce symptoms and prevent relapses. (35) These include mycophenolate mofetil, rituximab, and azathioprine. The informational page also states that individuals with frequent relapses have used low-dose steroids for longer periods. PE is mentioned as a potential alternative treatment in patients who are unresponsive to corticosteroid treatment, but is not
specifically recommended. The NINDS website does not cite any evidence in support of any of the treatments for neuromyelitis optica.

In summary, the available nonrandomized retrospective studies have methodologic limitations, and findings need to be confirmed in well-designed and conducted randomized trials.

Renal

**Rapidly Progressive Glomerulonephritis**

Rapidly progressive glomerulonephritis (RPGN) is a general term describing the rapid loss of renal function in conjunction with the finding of glomerular crescents on renal biopsy specimens. There are multiple etiologies of RPGN including vasculitis, the deposition of antiglomerular basement membrane antibodies, as seen in Goodpasture syndrome, or the deposition of immune complexes, as seen in various infectious diseases or connective tissue diseases. PE has long been considered a treatment alternative in immune-mediated RPGN. However, there have been few controlled clinical trials published, and their interpretation is difficult due to the small number of patients, choice of intermediate outcomes (i.e., the reduction in antibody levels as opposed to more direct patient outcomes), and heterogeneity in patient groups. (36) Aside from cases of Goodpasture disease, the rationale for PE in idiopathic RPGN is not strong, because of the lack of an identifiable immune component. Studies of PE in this population have not demonstrated a significant improvement in outcome compared with the use of pulse steroid therapy. (37)

**Antineutrophil Cytoplasmic Antibody-associated Vasculitis**

In 2011, Walsh et al. published a meta-analysis of studies on PE in adults with the diagnosis of either idiopathic renal vasculitis or rapidly progressive glomerulonephritis. (38) A total of 9 trials including 387 patients were identified. Clinical populations in the studies were somewhat ill-defined, but most patients appeared to have antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. In pooled analysis, the risk of end-stage renal disease was significantly lower in patients treated with adjunctive PE compared with standard care alone (RR=0.64; 95% CI: 0.47 to 0.88). The risk of death did not differ statistically between the 2 groups (RR=1.01; 95% CI: 0.71 to 1.40).

In 2007, Jayne et al. published a relatively large RCT, included in the previously mentioned meta-analysis. (39) This was a multicenter trial conducted on behalf of the European Vasculitis Study Group. The study investigated whether the addition of PE was more effective than the addition of intravenous methylprednisolone. Patients (N=137) with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine greater than 5.8 mg/dL were randomly assigned to receive 7 PEs (n=70) or 3000 mg of IVMP (n=67). Both groups received oral cyclophosphamide and oral prednisolone. The primary end point was dialysis independence at 3 months. Secondary end points included renal and patient survival at 1 year and severe adverse event rates. At 3 months, 33 (49%) of 67 were alive and independent of dialysis after IVMP, compared with 48 (69%) of 70 after PE. Compared with IVMP, PE was associated with a reduction in risk for progression to end-stage renal disease (24% at 12 months). At 1 year, patient survival was 51 (76%) of 67 in the IVMP group versus 51 (73%) of 70 in the PE group, and severe adverse events occurred in 48% of the IVMP group versus 50% of the PE group. Compared with IVMP, PE increased the rate of renal recovery in patients with ANCA-associated systemic vasculitis who presented with renal failure. Patient survival and severe adverse event rates were similar in both groups. Long-term outcomes of patients in this trial were published in 2013.40 Median follow-up was 3.95 years. A total of 70 of 136 patients had died, 35 (51%) in the PE group and 35 (51%) in the IVMP group (p=0.75). Similarly, the difference between groups in the proportion of patients with end-stage renal disease (33% in the PE group vs. 49% in the IVMP group, p=0.08) was not statistically significant. According to results of this trial, PE appears to have a short-term benefit on preserving renal function in this population, but long-term efficacy remains uncertain.

Transplantation

**Solid Organ Transplant**

Before 2006, plasmapheresis in the setting of solid organ transplant was not addressed by this policy. However, plasmapheresis has been extensively used in this setting, both as pretransplant prophylaxis (i.e., desensitization) for highly sensitized patients at high risk of antibody-mediated rejection (AMR), and as a treatment of AMR after
transplant. Desensitization protocols vary among transplant centers; 2 commonly used protocols are referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consists of high-dose IVIg (2 g/kg) and is offered to patients awaiting either a deceased or live donor. The Johns Hopkins protocol consists of low-dose IVIg (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD20 (i.e., rituximab). Plasmapheresis is more commonly used in patients receiving a living kidney transplant from an ABO mismatched donor. (41) A variety of protocols have also been developed for the treatment of AMR, often in combination with other therapies, such as IVIg or anti-CD20. (42-45) Most studies of plasmapheresis in the transplant setting are retrospective case series from single institutions. Therefore, it is not possible to compare immunomodulatory regimens to determine their relative efficacy. Nevertheless, in part based on the large volume of literature published on this subject, it appears that plasmapheresis is a component of the standard of care for the management of AMR.

Miscellaneous Potential Applications of PE

Asthma
There has been some research interest in the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, preliminary results do not suggest treatment effectiveness. (46)

Sepsis
In 2014, Rimmer et al. published a systematic review and meta-analysis of literature on PE for treatment of sepsis and septic shock. (47) The authors identified 4 RCTs comparing PE with usual care; the trials included a total of 194 patients. All of the trials were rated as unclear or high risk of bias. In a pooled analysis of data from the 4 trials, PE was not significantly associated with a reduction in mortality risk (RR=0.83; 95% CI: 0.45 to 1.52). Data were insufficient for pooled analyses of other outcomes. The evidence identified in this systematic review is insufficient for drawing conclusions about the impact of PE for treating sepsis on the net health outcome.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and Sydenham Chorea (SC)
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a group A beta-hemolytic streptococcal infection (GABHS). Sydenham chorea (SC) is the neurologic manifestation of acute rheumatic fever. The choreatic symptoms of SC are characterized by involuntary rapid and jerky movements that affect the extremities, trunk, and face. SC is generally a self-limited disorder with symptoms resolving in weeks to months. Perlmutter et al. (1999) conducted an RCT to evaluate the effectiveness of PE and IVIg in reducing the severity of neuropsychiatric symptoms in children diagnosed in the PANDAS subgroup. (48) Children (N=30) with clear evidence of a strep infection as the trigger of their OCD and tics were randomized to receive PE (n=10; 5-6 procedures over 2 weeks), IVIg (n=10; 2 g/kg over 2 days) or placebo (n=10; mimic IVIg). All were severely ill at the time of treatment. At 1 month, both active treatment groups demonstrated symptom improvement, but those in the placebo group were unchanged. The treatment effect was still apparent after 1 year. However, 50% of children were on the same or higher doses of their baseline medications; thus it is not entirely clear that IVIg or PE had a beneficial effect. This study needs to be replicated with a larger number of patients. The authors noted that children in the placebo group (IVIg control group) subsequently received PE in an open trial and had only minor improvements.

Garvey et al. (2005) conducted an RCT designed to determine whether IVIg or PE was superior to prednisone in decreasing the severity of chorea. (49) Children with SC (N=18) were randomized to treatment with PE (n=8; 5-6 procedures over 1-2 weeks), IVIg (n=4; 2 g/kg over 2 days), or prednisone (n=6; 1 mg/kg/d for 10 days followed by taper over next 10 days). The primary outcome was chorea severity at 1 month. The secondary outcome variable was chorea severity at 1 year after treatment. There was no significant difference between the baseline chorea severity scores by treatment group. Chorea severity was assessed at baseline and at 1, 2, 3, 6, and 12 months after treatment. The Chorea Rating Scale scores range from 0 (no chorea) to 18 (severe or paralytic chorea). A score of 9 or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued 1 week before baseline assessment and each follow-up evaluation. Mean chorea severity for the entire group was lower at the 1-month follow-up evaluation (overall 48% improvement). Between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.
**Other Conditions**
Outcome data are inadequate to validate the use of PE in other conditions listed in the Policy as investigational and not otherwise discussed in the Rationale section.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2012. There was consensus or near-consensus that PE for dense deposit disease with factor H deficiency and/or elevated C3 nephritis factor, catastrophic antiphospholipid syndrome, focal segmental glomerulosclerosis after renal transplant, and myeloma with acute renal failure may be considered medically necessary. Clinical input was mixed on the medical necessity of hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström macroglobulinemia). In addition, there was no consensus about an optimal creatinine threshold for instituting PE in patients with renal failure associated with ANCA-associated vasculitis or other diagnoses.

**Summary of Evidence**
Due to data from published studies and/or clinical support, plasma exchange is considered medically necessary for selected conditions. For conditions in which there is a lack of efficacy data and clinical support, plasma exchange is considered investigational.

**Practice Guidelines and Position Statements**

*National Comprehensive Cancer Network (NCCN)*
In the 2014 NCCN guideline on multiple myeloma, the use of plasmapheresis to improve renal function is a category 2B recommendation. Plasmapheresis should also be used as adjunctive therapy for hyperviscosity. (50)

*American Academy of Neurology (AAN)*
In 2011, the AAN (Therapeutics and Technology Assessment Subcommittee) issued an evidence-based guideline on plasmapheresis in the treatment of neurologic disorders. (51) The primary conclusions based on their evidence review are as follows:
- Established effective
  - Acute inflammatory demyelinating polyneuropathy/ Guillain-Barre syndrome
  - Chronic inflammatory demyelinating polyneuropathy, short-term treatment
- Probably effective
  - Relapses in multiple sclerosis
- Possibly effective
  - Fulminant demyelinating CNS disease
- Established ineffective
  - Chronic or secondary progressive multiple sclerosis
- Insufficient evidence
  - Myasthenia gravis
  - Sydenham’s chorea
  - Acute obsessive-compulsive disorder and tics in PANDAS

*American Society for Apheresis (ASFA)*
In 2013, the ASFA released updated guidelines on the use of therapeutic apheresis. (52) Previously, the guidelines had been updated in 2010 and treatment categories were introduced in a 2007 guideline. (53) The following is a description of the ASFA categories (see Table 1) and recommendations in 2007, 2010, and 2013 (see Table 2).
Table 1. American Society for Apheresis Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Category I includes diseases for which TA [therapeutic apheresis] is accepted as first-line treatment, either as the sole treatment or in conjunction with other treatments. Note that this designation need not imply that TA is mandatory in all cases.</td>
</tr>
<tr>
<td>II</td>
<td>Category II denotes diseases for which TA is accepted as second-line treatment, either as the sole treatment or in conjunction with other treatments.</td>
</tr>
<tr>
<td>III</td>
<td>Category III diseases are those for which the optimum role of TE is not established and treatment decisions on an individual basis are recommended.</td>
</tr>
<tr>
<td>IV</td>
<td>Category IV indicates disorders for which published evidence suggests or demonstrates that TE is ineffective or harmful.</td>
</tr>
</tbody>
</table>

Table 2. American Society for Apheresis Recommendations

<table>
<thead>
<tr>
<th>Disease Group / Name / Condition</th>
<th>AFSA 2007</th>
<th>AFSA 2010</th>
<th>AFSA 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>III</td>
<td>II</td>
<td>II</td>
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<tr>
<td>Cryoglobulinemia</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Pemphigus vulgaris</td>
<td>III</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td><strong>Systemic lupus erythematosus</strong></td>
<td></td>
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<tr>
<td>Manifestations other than nephritis</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Severe</td>
<td>NC</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Nephritis</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
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<tr>
<td>ABO incompatible hematopoietic progenitor cell transplantation</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Pure red blood cell aplasia</td>
<td>II</td>
<td>II</td>
<td>II</td>
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<tr>
<td><strong>Autoimmune hemolytic anemia</strong></td>
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<tr>
<td>Warm autoimmune hemolytic anemia</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Cold agglutinin disease</td>
<td>III</td>
<td>II</td>
<td>II</td>
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<tr>
<td>Coagulation factor inhibitors</td>
<td>III</td>
<td>IV</td>
<td>IV</td>
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<tr>
<td>Hyperviscosity in monoclonal gammopathies</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>I</td>
<td>I</td>
<td>NC</td>
</tr>
<tr>
<td>Refractory immunoadsorption</td>
<td>II</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Refractory or non-refractory</td>
<td>IV</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td><strong>Myeloma and acute renal failure (in 2010 and 2013 myeloma cast nephropathy)</strong></td>
<td></td>
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<tr>
<td>Post-transfusion purpura</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Red blood cell alloimmunization in pregnancy</td>
<td>II</td>
<td>II</td>
<td>III</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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<td>I</td>
<td>I</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td>Acute liver failure</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Sepsis (in 2010 and 2013 sepsis with multiorgan failure)</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Thyrotoxicosis (in 2010, thyroid storm)</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td>Acute disseminated encephalomyelitis</td>
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<td>II</td>
<td>II</td>
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<tr>
<td>Acute inflammatory demyelinating polyneuropathy (Guillian-Barre syndrome)</td>
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<td>I</td>
<td>I</td>
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<tr>
<td>Acute inflammatory demyelinating polyneuropathy. Post IVIG</td>
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<td>NC</td>
<td>III</td>
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<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
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<td>I</td>
<td>I</td>
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<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
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<td>II</td>
<td>II</td>
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<tr>
<td><strong>Multiple Sclerosis</strong></td>
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<tr>
<td>Acute CNS inflammatory demyelinating disease</td>
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<td>II</td>
<td>II</td>
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<tr>
<td>Devic’s syndrome</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>Chronic progressive</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>In 2013, moderate-severe</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>In 2013, pre-thymectomy</td>
<td></td>
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<td>I</td>
</tr>
<tr>
<td>Paraneoplastic neurologic syndromes</td>
<td>III</td>
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<tr>
<td><strong>Paraproteinemic polyneuropathies</strong></td>
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<tr>
<td>IgG/IgA</td>
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<tr>
<td>Condition</td>
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<tr>
<td>IgM</td>
<td>II</td>
<td>I</td>
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<tr>
<td>Multiple Myeloma</td>
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<td>III</td>
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<tr>
<td><strong>Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); Sydenham's chorea (SC)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Severe PANDAS (2010 exacerbations)</td>
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<td>I</td>
<td>I</td>
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<tr>
<td>Severe SC</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Rasmussen's encephalitis</td>
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<td>III</td>
<td>III</td>
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<tr>
<td>Stiff-person syndrome</td>
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<td>IV</td>
<td>III</td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td><strong>ANCA-associated rapidly progressive</strong></td>
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<tr>
<td>Glomerulonephritis (Wegener's granulomatosis)</td>
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<td></td>
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<tr>
<td>Dialysis dependence</td>
<td>NC</td>
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<tr>
<td>Dialysis independence</td>
<td>NC</td>
<td>III</td>
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<tr>
<td><strong>Anti-glomerular basement membrane disease</strong></td>
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<td>Goodpasture's syndrome</td>
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<tr>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>NC</td>
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<tr>
<td>Dialysis dependence and no DAH</td>
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<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>NC</td>
<td>I</td>
<td>I</td>
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<tr>
<td><strong>Focal segmental glomerulosclerosis</strong></td>
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<tr>
<td>Primary</td>
<td>III</td>
<td>NC</td>
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<tr>
<td>Secondary</td>
<td>III</td>
<td>NC</td>
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<tr>
<td>Recurrent</td>
<td>NC</td>
<td>I</td>
<td>I</td>
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<tr>
<td><strong>Hemolytic uremic syndrome (HUS); thrombotic microangiopathy; transplant-associated microangiopathy</strong></td>
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<tr>
<td>Idiopathic HUS</td>
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<td>III</td>
<td>NC</td>
</tr>
<tr>
<td>Transplant-associated microangiopathy</td>
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<td>NC</td>
<td>NC</td>
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<tr>
<td>Diarrhea-associated, pediatric</td>
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<td>NC</td>
<td>NC</td>
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<tr>
<td>Atypical HUS due to autoantibody to factor H</td>
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<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Diarrhea-associated HUS or typical HUS</td>
<td>NC</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>In 2013, Shiga toxin-associated</td>
<td>IV</td>
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<tr>
<td>Streptococcus pneumoniae associated</td>
<td>III</td>
<td></td>
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<tr>
<td><strong>Renal transplantation; antibody mediated rejection; HLA desensitization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody mediated rejection</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>HLA desensitization</td>
<td>II</td>
<td>NC</td>
<td>II</td>
</tr>
<tr>
<td>Desensitization, living donor, positive</td>
<td>NC</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>High PRA: cadaveric donor</td>
<td>NC</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>Rheumatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scleroderma (progressive systemic sclerosis)</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>ABO incompatible solid organ transplantation</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kidney</td>
<td>II</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>In 2013, desensitization, living-donor</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Humeral rejection</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart (infants)</td>
<td>II</td>
<td>II</td>
<td>NC</td>
</tr>
<tr>
<td>Liver (2010 perioperative)</td>
<td>III</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>In 2013, desensitization living-donor</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Desensitization, deceased-donor</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humeral rejection</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart transplant rejection</strong></td>
<td>III</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

ABO: A, B, and O blood types; AIDP: acute inflammatory demyelinating polyneuropathy; ANCA: antineutrophil cytoplasmic antibody; CNS: central nervous system; DAH: diffuse alveolar hemorrhage; HUS: hemolytic uremic syndrome; Ig: immunoglobulin; IVIg: intravenous immunoglobulin; NC: not categorized; PRA: Panel Reactive Antibody.

**U.S. Preventive Services Task Force Recommendations**

Not applicable

**Medicare National Coverage**

The Centers for Medicare and Medicaid Services, Medicare Coverage Database, National Coverage Determination for apheresis (therapeutic pheresis) (48) states:

*For purposes of Medicare coverage, apheresis is defined as an autologous procedure, i.e., blood is
taken from the patient, processed, and returned to the patient as part of a continuous procedure (as distinguished from the procedure in which a patient donates blood preoperatively and is transfused with the donated blood at a later date). Apheresis is covered for the following indications: Plasma exchange for acquired myasthenia gravis; Leukapheresis in the treatment of leukemia; Plasmapheresis in the treatment of primary macroglobulinemia (Waldenstrom); Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia and hyperviscosity syndromes; Plasmapheresis or plasma exchange as a last resort treatment of thrombotic thrombocytopenic purpura (TTP); Plasmapheresis or plasma exchange in the last resort treatment of life threatening rheumatoid vasculitis; Plasma perfusion of charcoal filters for treatment of pruritis of cholestatic liver disease; Plasma exchange in the treatment of Goodpasture’s Syndrome; Plasma exchange in the treatment of glomerulonephritis associated with antiglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage; Treatment of chronic relapsing polynuropathy for patients with severe or life threatening symptoms who have failed to respond to conventional therapy; Treatment of life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy; Treatment of Guillain-Barre Syndrome; and Treatment of last resort for life threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration."

References

Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (Neurology 1991; 41:617-18, PMID 2027473). The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebral spinal fluid (CSF).

- **Clinical:** Mandatory
  - Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than 1 limb or a peripheral nerve nature, developing over at least 2 months.
  - Hypo- or areflexia. This will usually involve all four limbs.

- **Physiologic Studies:** Mandatory

Nerve conduction studies including studies of proximal nerve segments in which the predominant process is
demyelination.

Must have 3 out of 4 of the following criteria in the list of second-level bullets:

- Reduction in conduction velocity (CV) in 2 or more motor nerves
  - < 80% of lower limit of normal (LLN) is amplitude > 80% of LLN
  - < 70% of LLN is amplitude < 80% of LLN
- Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either
  - peroneal nerve between ankle and below fibular head
  - median nerve between wrist and elbow
  - or ulnar nerve between wrist and below elbow.
- Criteria suggestive of partial conduction block: < 15% change in duration between proximal and
  - distal sites and > 20% drop in negative-peak (p) area or peak to peak (p-p) amplitude between
  - proximal and distal sites.
- Criteria for abnormal temporal dispersion and possible conduction block: > 15% change in
  - duration between proximal and distal sites and > 20% drop in p area or p-p amplitude between
  - proximal and distal sites and > 20% drop in p or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals.
- Additional studies, such as stimulation across short segments or recording of individual motor
  - unit potentials, are required for confirmation.
- Prolonged distal latencies in two or more nerves:
  - > 125% of upper limit of normal (LEN) is amplitude > 80% of LLN
  - > 150% of LEN if amplitude < 80% of LLN
- Absent F waves or prolonged minimum:
  - > 120% of ULN if amplitude > 80% of LLN
  - > 150% of ULN if amplitude < 80% of LLN

- Pathologic Features: Mandatory

Nerve biopsy showing unequivocal evidence of demyelination and remyelination.

Demyelination by either electron microscopy (> 5 fibers) or teased fiber studies >12% of 50 fibers, minimum of 4 internodes each, demonstrating demyelination/ remyelination.

- CSF Studies: Mandatory
  - Cell count <10/mm-3 if HIV-seronegative or <50/mm-3 if HIV seropositive
  - Negative VDRL

**Guillain-Barré Syndrome Disability Scale**
The scale appears below as it did in the Hughes et al. 2007 systematic review published in Brain 2007; 130(9):2245-2257. (22)

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2. Able to walk without support of a stick (*5 m across an open space*) but incapable of manual work/running
3. Able to walk with a stick, appliance or support (5m across an open space)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (for any part of the day or night)
6. Death

**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/13/01</td>
<td>Replace Policy - Revised Policy replaces P8.02.100</td>
</tr>
<tr>
<td>08/13/02</td>
<td>Replace Policy - Policy reviewed; new indications added.</td>
</tr>
<tr>
<td>05/13/03</td>
<td>Replace Policy - Update CPT codes only.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy reviewed with literature search; references added. No change in policy statement.</td>
</tr>
</tbody>
</table>
06/14/05  Replace Policy - Policy updated with literature search; no change in policy statement. Reference 22 updated, and comparison between ASA recommendations and policy statement included in the Rationale Section.
02/06/06  Codes updated - No other changes.
05/16/06  Update Scope and Disclaimer - No other changes.
08/08/06  Replace Policy - Policy revised with addition of policy statements and discussion of plasmapheresis in the setting of solid organ transplantation, considered medically necessary; references added.
06/09/09  Replace Policy - Policy updated with literature search. Policy statement updated to include Wegener’s Granulomatosis as a medically necessary indication.
04/13/10  Replace Policy - Policy reviewed with literature search The policy statement has been modified to include: Guillain-Barré syndrome severity grades 1-2 as medically necessary; use in the pediatric population is investigational for mild and moderate forms of GBS and medically necessary for the severe form of GBS; the policy statement has been modified to include severe manifestations of mixed cryoglobulinemia (MC) as medically necessary when used in combination with immunosuppressive therapy; typical- hemolytic uremic syndrome is investigational (considered medically necessary in previous updates) and investigational for treatment of PANDAS, Sydenham Chorea, Refsum’s disease, cryoglobulinemia (except severe MC), myasthenia gravis with anti-MuSk antibodies; additional conditions were added as investigational based on American Society for Apheresis (ASFA) review. Title changed from “Plasma Exchange (Plasmapheresis) to “Plasma Exchange.” References added.
06/08/10  Cross Reference Update - No other changes.
06/13/11  Replace Policy - Policy reviewed with literature search from May 2009 through January 2011. No changes to policy statements. Rationale rewritten. References 16, 24, 31 and 41 added; other references renumbered or removed. ICD-10 codes added to policy.
06/20/12  Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.
07/10/12  Replace policy. Policy statement revised with additional conditions that may be medically necessary myeloma with acute renal failure, catastrophic antiphospholipid syndrome; dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor and focal segmental glomerulosclerosis after renal transplant. The investigational statement on focal segmental glomerulosclerosis was modified to indicate that it applied to situations other than after renal transplant. Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström’s macroglobulinemia) added as investigational. In addition, the serum creatinine threshold was removed from the medically necessary policy statement on ANCA-associated vasculitis. Rationale rewritten. Updated literature review with references 22, 26 and 29 added, other references renumbered or removed.
09/28/12  Update Related Policies – Add 7.03.509; ICD-10 codes are now effective 10/01/2014.
02/11/13  Replace policy. Minor clarification regarding medical necessity of MS for acute and chronic forms. The intent of the policy statement is unchanged.
04/18/13  Update Related Policies. Change title to 8.01.36.
07/24/13  Replace policy. Policy reviewed with literature search through March 21, 2013. Policy statements unchanged. References 19, 23 and 40 added.
08/15/13  Update Related Policies. Change title to 7.03.05.
10/18/13  Update Related Policies. Change title to 8.01.17.
07/31/14  Annual Review. Policy updated with literature review through April 3, 2014. Minor changes to bullet points on multiple sclerosis for clarity only. References 16, 25, 29, 30, 40, 44 and 46 added.
10/22/14  Update Related Policies. Change title to 8.02.04.
07/14/15  Annual Review. Neuromyelitis optica (NMO) added to the list of investigational conditions. CAPS, abbreviation for catastrophic antiphospholipid syndrome, removed from medically necessary policy statement. Policy updated with literature review through April, 2015. References 32-35, 47 added. Retained the criteria for CIDP and Guillain-Barré syndrome in the Appendix. Investigational policy statement updated as noted. ICD-9 diagnosis codes removed; these were listed for informational purposes only. Related Policies updated, the following were removed: 7.03.05, 7.03.509, 7.03.510, 8.01.17, 8.01.25 and 8.01.503.
09/01/15  Update Related Policies. Add 7.03.04.
05/10/16  Annual Review. No change to policy statements. No new literature added.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).
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Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Amharic):
تم تحديد تواصل مع مكتبنا للإعاقة بقلم Premera Blue Cross. في هذه الإعاقة، قد يشمل الحصص المتاحة في هذا الإعاقة، من بينها:
• نصائح للحصول على هذه المعلومات والمساعدة بمثابة ندوة تركز على اللغة العربية. 
• 800-722-1471 (TTY: 800-842-5357), 888 defensively

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaa mabalini nga adda ket naglaon iti napateg nga impormasion maianggpep iti aksapayowo nyo coverage babaen iti Premera Blue Cross. Daytoy ket mabilini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramideng nga addang sakkay dagiti partikular a naituding nga adda lau tapo napat tagaliitadegyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Premera Blue Cross.

Преде all, если у вас есть вопросы или потребуется дополнительная информация, обратитесь по телефону 800-722-1471 (TTY: 800-842-5357).

Russian (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами.

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Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross.

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Iste tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Vietnamese (Vietnamese):