

Subject: Hematopoietic Stem Cell Transplantation for Autoimmune Disease and Miscellaneous Solid Tumors

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Description/Scope

This document addresses hematopoietic stem cell transplantation in the treatment of the following conditions:

- Autoimmune Diseases
- Epithelial Ovarian Cancer
- Breast Cancer
- Malignant Astrocytomas and Gliomas
- Miscellaneous Solid Tumors in Adults

Note: For additional stem cell transplant information and criteria, see the applicable document(s):

- [TRANS.00027 Hematopoietic Stem Cell Transplantation for Pediatric Solid Tumors](#)
- [TRANS.00030 Hematopoietic Stem Cell Transplantation for Germ Cell Tumors](#)

Position Statement

Autoimmune Diseases

Medically Necessary:

A *single* autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation is considered **medically necessary** for individuals with *multiple sclerosis* when **all** of the following criteria are met:

- A. The transplant is used to treat *relapsing-remitting multiple sclerosis*; **and**
- B. The individual is between 18 and 45 years of age with disease duration less than 10 years; **and**
- C. The individual is disabled in at least one functional system but able to ambulate for 100 meters without aid or rest (expanded disability status scale [EDSS] score from 2.0 to 5.5); **and**
- D. The individual has highly active and treatment resistant disease meeting criteria **1 and 2** below:
 1. Highly active disease as seen by 1.a **or** 1.b below:
 - a. Two or more clinical relapses at separate times but within the previous 12 months; **or**
 - b. One clinical relapse and one or more magnetic resonance imaging (MRI) lesions typical for MS (gadolinium-enhancing or T2-hyperintense lesion), with the MRI lesion occurring at a separate time than the clinical relapse but both occurring within the previous 12 months; **and**
 2. Treatment resistant disease as seen by the disease activity meeting criteria D1 above occurring despite disease-modifying treatment (DMT) meeting **all** of the following requirements:
 - a. Each relapse or episode of new MRI lesion(s) must occur after at least 3 months of treatment with a U.S. Food and Drug Administration-approved DMT; **and**
 - b. At least 1 episode must be a clinical relapse, and MRI evidence of activity must include at least 2 unique or active lesions in the brain or spinal cord; **and**
 - c. At least 1 of those episodes must occur after treatment with a DMT considered to be highly efficacious (natalizumab, ocrelizumab, rituximab, or alemtuzumab).

Investigational and Not Medically Necessary:

A *single* autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplant is considered **investigational and not medically necessary** as a treatment of multiple sclerosis when the above criteria are not met, including for primary progressive or secondary progressive forms of multiple sclerosis.

A *repeat* autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplant is considered **investigational and not medically necessary** as a treatment of relapsing-remitting multiple sclerosis.

An allogeneic (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, or planned tandem is considered **investigational and not medically necessary** as a treatment of multiple sclerosis.

An *autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem* is considered **investigational and not medically necessary** as a treatment of all other autoimmune diseases including, but not limited to:

- juvenile idiopathic arthritis;
- rheumatoid arthritis;
- systemic lupus erythematosus;
- systemic sclerosis

Epithelial Ovarian Cancer

Investigational and Not Medically Necessary:

An *autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem* is considered **investigational and not medically necessary** as a treatment of epithelial ovarian cancer.

Breast Cancer

Investigational and Not Medically Necessary:

An autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem is considered **investigational and not medically necessary** as a treatment of breast cancer.

Malignant Astrocytomas and Gliomas

Investigational and Not Medically Necessary:

An autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem is considered **investigational and not medically necessary** as a treatment of malignant astrocytomas and gliomas, including both glioblastoma multiforme and oligodendroglioma.

Other Miscellaneous Solid Tumors in Adults

Investigational and Not Medically Necessary:

An autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem is considered **investigational and not medically necessary** as a treatment of adult miscellaneous solid tumors, including but not limited to the following:

- Cancer of the bile duct;
- Cancer of the fallopian tubes;
- Cervical cancer;
- Colon cancer;
- Esophageal cancer;
- Gallbladder cancer;
- Lung cancer, any histology;
- Malignant melanoma;
- Neuroendocrine tumors;
- Nasopharyngeal cancer;
- Pancreas cancer;
- Paranasal sinus cancer;
- Prostate cancer;
- Rectal cancer;
- Renal cell cancer;
- Soft tissue sarcoma;
- Stomach cancer;
- Thyroid tumors;
- Tumors of the thymus;
- Uterine cancer;
- Undifferentiated tumors and tumors of unknown primary origin.

Rationale

Autoimmune Diseases

Multiple Sclerosis

Burt and colleagues (2009) reported a retrospective case series of 21 subjects with relapsing-remitting multiple sclerosis who had not previously responded to conventional treatment with interferon beta and received autologous non-myeloablative hematopoietic stem cell transplantation (HSCT) following conditioning with cyclophosphamide and either alemtuzumab or antithymocyte globulin. Initial study results 3 years post-transplantation reported progression-free survival (PFS) and reversal of neurologic disability. Of the 21 subjects transplanted, 17 (81%) increased their score by at least one point on the Kurtzke EDSS. Relapse was reported in 5 individuals (24%), but after further immunosuppressive therapy remission was achieved. The author reported a mean follow-up of 37 months (range 24-48 months) at which time all participants were free from progression (no deterioration in EDSS score) and 16 were free of relapse. Significant improvements were noted in neurological disability scores ($p < 0.0001$) and quality of life as measured with the short form-36 (SF-36) questionnaire.

Shevchenko (2008) reported a prospective, multi-center Russian case series of 50 subjects who received high-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (auto-HSCT) as a treatment alternative for various forms (secondary progressive [n=27], primary progressive [n=11], relapsing-remitting [n=11], and progressive relapsing [n=1]) of multiple sclerosis. Median disease duration prior to the trial was 7.5 years. Study participants were conditioned with BCNU, etoposide, cytarabine, and melphalan (BEAM) followed by stem cell transplantation. In vivo T-cell depletion was achieved through infusion of anti-thymocyte globulin. The results were pooled for three different strategies of HDIT + auto-HSCT: "early" transplantation (n=6; EDSS 1.5-3.0), "conventional" transplantation (n=37; EDSS 3.5-6.5) and "salvage/late" transplantation (n=4; EDSS 7.0-8.0).

Results were reported for 45 individuals. Twenty-eight subjects achieved an objective improvement in neurologic symptoms, defined as at least a 0.5 point decrease in the EDSS score from baseline at 6 months. Estimated progression-free survival at 6 years was 72% and no active, new, or enlarging lesions were seen on brain MRI in individuals without disease progression. One participant died of acute promyelocytic leukemia 3 years after HDIT + auto-HSCT. This study was limited by the lack of an active comparator group and a heterogeneous population mix. In addition, the number of subjects in groups with different treatment strategies was quite small and mean follow-up was only 19 months with less than half of the participants observed for more than 3 years. Although early clinical studies are promising, a randomized, comparative trial is needed to establish the efficacy and safety of HDIT with auto-HSCT in the treatment of multiple sclerosis.

A systematic review published by Reston and colleagues (2011) evaluated the safety and efficacy of autologous HSCT in participants with progressive MS refractive to conventional treatment. A total of 10 full-text articles were reviewed, and 8 case series with 161 enrolled participants and median 2 year follow-up were included, meeting the inclusion criteria for primary outcome of progression-free survival. An additional 6 studies were included for a summary of mortality and morbidity. Analysis from the 8 case series found there was substantial heterogeneity across studies. Secondary progressive MS was reported in 77% of participants, but studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. The studies used varied conditioning regimens prior to HSCT. Five of the studies used intermediate-intensity regimens and the remaining 3 used high-intensity regimens. All studies were rated as moderate quality. Among a total of 14 studies, 13 were case series; in which 7 treatment-related deaths were reported. Six non-treatment related deaths were reported, and 5 of these were associated with disease progression:

The estimated rate of long-term progressive-free survival of patients receiving intermediate-intensity conditioning regimens

was 79.4% (95% confidence interval [CI]: 69.9-86.5%) with a median follow-up of 39 months, while the estimate for the patients receiving high-intensity regimens was 44.6% (95% CI: 26.5-64.5%) at a median follow-up at 24 months.

Muraro and colleagues (2017) reported long term results (median 6.6 years) from a multicenter, observational retrospective cohort study. Data was obtained for 281 participants with predominantly progressive forms of MS (n=218; 78%), with median EDSS score of 6.5 (range 1.5-9) treated with autologous HSCT (aHSCT). Within the first 100 days of AHSCT there were 8 (2.8%; 95% CI, 1.0%-4.9%) deaths reported and considered transplant-related mortality. "The 5-year probability of progression-free survival as assessed by the EDSS score was 46 (95% CI, 42%-54%), and overall survival was 93% (95% CI, 89%-96%) at 5 years." The summary the authors conclude:

In this observational study of patients with MS treated with AHSCT, almost half of them remained free from neurological progression for 5 years after transplant. Younger age, relapsing form of MS, fewer prior immunotherapies, and lower baseline Expanded Disability Status Scale EDSS score were factors associated with better outcomes. The results support the rationale for further randomized clinical trial of AHSCT for the treatment of MS.

A case series by Nash and colleagues (2017) reported findings of a phase II clinical trial of high-dose immunosuppression therapy (HDIT) and autologous HCT for participants with relapsing-remitting multiple sclerosis who experienced relapses with disability progression. Of the 25 participants evaluated 24 underwent HDIT/HCT with median follow-up of 62 months. The event free survival was 69.2% (CI 50.2-82.1), "Progression free survival, clinical relapse-free survival and MRI activity-free survival were 91.3% (90% CI 74.7-97.2%), 86.9% (90% CI 69.5%-94.7%), and 86.3% (90% CI 68.1%-94.5%), respectively." There were no neurological treatment-related adverse events reported. There were 3 deaths due to disease progression and no deaths related to transplantation. The authors concluded that research in "prospective clinical trials comparing HDIT/HCT to other approaches are needed."

Burt and colleagues (2019) reported results of analysis of preliminary data from the Multiple Sclerosis International Stem Cell Transplant (MIST) study (NCT00273364), an open-label randomized clinical trial (RCT). The MIST study compared aHSCT using a non-myeloablative regimen (Cy-ATG) versus FDA approved disease-modifying therapy (DMT) on disease progression for relapsing-remitting MS. A total of 110 participants with relapsing remitting MS were randomized to receive HSCT along with cyclophosphamide and antithymocyte globulin (n=55) or DMT (n=55).

Disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group. Median time to progression could not be calculated in the HSCT group because of too few events and was 24 months (interquartile range, 18-48 months) in the DMT group (hazard ratio, 0.07; 95% CI, 0.02-0.24; $P < .001$). During the first year, mean EDSS scores decreased (improved) from 3.38 to 2.36 in the HSCT group and increased (worsened) from 3.31 to 3.98 in the DMT group (between-group mean difference, -1.7; 95%CI, -2.03 to -1.29; $P < .001$).

In the DMT group, those who had treatment failure were allowed to cross over and receive HSCT which limited follow-up data in the DMT group. Researchers concluded "in this preliminary study of patients with highly active relapsing-remitting MS and moderate disability, nonmyeloablative HSCT, compared with DMT, resulted in prolonged time to disease progression. Further research is needed to replicate the findings and to assess long-term outcomes and safety."

In 2020, the European Bone Marrow Transplant (EBMT) Autoimmune Disease Working Party (ADWP) and the Joint Accreditation Committee of the EBMT and ISCT (JACIE) published updated guidelines and recommendations for autologous HSCT and other cellular therapy in MS and immune-mediated neurological disease (Sharrack, 2020). The guidelines included recommendations for aHSCT in individuals with relapsed remitting MS (RRMS):

aHSCT should be offered to patients with RRMS with high clinical and MRI inflammatory disease activity (at least 2 clinical relapses, or one clinical relapse with Gd-enhancing or new T2 MRI lesions at a separate time point, in the previous 12 months) despite the use of one or more lines of approved DMTs. Evidence best supports treatment in patients who are able to ambulate independently (EDSS 5.5 or less), who are younger than 45 years and have disease duration less than 10 years (level Standard of care [S]/ Grade I)

The committee found increasing evidence for effectiveness highest among highly active RRMS where there is growing evidence from large registry studies and a prospective phase III RCT supporting the safe delivery of aHSCT with long-term clinical and MRI remissions observed in a majority of individuals. The Kurtzke EDSS tool was used as a method to assess for disability progression in MS, to validate and generally accept degree of disability.

At this time there is one phase III randomized trial (NCT04047628), designed to compare best available therapy versus of autologous hematopoietic stem cell transplant for multiple sclerosis (BEAT-MS) study in individuals with relapsing forms of MS. Estimated enrollment is 156 participants; the study is active, recruiting participants with an estimated completion date in October 2029 (National Institute of Allergy and Infectious Disease [NIAID], 2022).

Systemic Sclerosis (SSc)

Nash (2007) reported a phase 2 single arm study using high dose immunosuppressive therapy (HDIT) and autologous hematopoietic cell transplant (HCT) to treat 34 individuals with diffuse cutaneous SSc. HDIT included total body irradiation (800 cGy) with lung shielding, cyclophosphamide (120 mg/kg), and equine antithymocyte globulin (90 mg/kg). Seventeen of 27 (63%) evaluable subjects who survived at least 1 year after HDIT had sustained responses at a median follow-up of 4 (range, 1 to 8) years. There was a major improvement in skin (modified Rodnan skin score, -22.08; $p < 0.001$) and overall function (modified Health Assessment Questionnaire Disability Index, -1.03; $p < 0.001$) at final evaluation. Biopsies confirmed a statistically significant decrease of dermal fibrosis compared with baseline ($p < 0.001$). Lung, heart, and kidney function, in general, remained clinically stable. However, there were 12 deaths during the study and 8 of 27 participants had transplant-related mortality. The estimated progression-free survival was 64% at 5 years. The authors concluded that HDIT and autologous HCT for SSc should be evaluated in a randomized clinical trial.

Vonk (2008) reported a case series of 26 subjects with severe, diffuse cutaneous SSc treated with autologous stem cell transplant following HDIT. In this study, peripheral blood stem cells were collected using cyclophosphamide (4 g/m²) and rHu G-CSF (5 to 10 microg/kg/day) and were reinfused after positive CD34+ selection. For conditioning, cyclophosphamide 200 mg/kg was used. After a median follow-up of 5.3 (1-7.5) years, 81% (n=21/26) of the participants demonstrated a clinically beneficial response. The Kaplan-Meier estimated survival at 5 years was 96.2% (95% CI, 89-100%) and at 7 years 84.8% (95% CI, 70.2-100%) and event-free survival, defined as survival without mortality, relapse or progression of SSc resulting in major organ dysfunction was 64.3% (95% CI, 47.9-86%) at 5 years and 57.1% (95% CI, 39.3-83%) at 7 years. The results of this study are promising, but its small size and uncontrolled design limit the conclusions which can be drawn. Further study with larger phase III, randomized controlled trials are needed. Burt and colleagues (2011) reported on a non-randomized phase II study evaluating HSCT effectiveness in the treatment of diffuse SSc. Participants were randomly allocated via computer sequencing, 10 participants to the HSCT (cyclophosphamide 200mg/kg IV in combination with rabbit antithymocyte globulin 6.5mg/kg IV) group and 9 participants to cyclophosphamide group (1.0 g/m² IV once every 6 months). At 1 year the primary outcome was measured as decrease of greater than 25 % in subjects presenting at enrollment with greater than 14 modified Rodnan skin scores (mRSS) or an increase in the forced vital capacity by 10%. The

primary outcome results at 1 year reported with the mean (mRSS) increased in the control group (19 to 22) and a decrease in the transplant group (28 to 15) 1 year post treatment. The vital capacity results at 1 year in subjects "undergoing HSCT compared with controls, the rate of change from pretreatment forced vital capacity was 34% compared with -10% at 6 months ($p=0.002$) and 15% compared with -9% at 12 months ($p=0.006$)." Eight of 9 subjects in the control group with disease progression reported at 1 year were able to switch over to the HSCT protocol for additional treatment. The study provides promising initial findings with use of non-myeloablative autologous HSCT in SSc, although larger studies are needed with long term follow-up to demonstrate the benefits of treatment.

In 2014, van Laar and colleagues published results from the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a phase III, multicenter, randomized (1:1), open-label, parallel-group, clinical trial conducted in Europe. The objective was to compare the efficacy and safety of autologous non-myeloablative selective HSCT versus 12 successive monthly intravenous pulses of cyclophosphamide in treating individuals with early diffuse cutaneous SSc. A total of 79 subjects received HSCT and 77 received cyclophosphamide. In the group that received HSCT, there were 22 deaths and 3 individuals had irreversible organ failure. Among participants in the control group, there were 23 deaths and 8 individuals with irreversible organ failure. HSCT treatment was associated with more serious adverse events in the first year compared to treatment with cyclophosphamide. During the first 2 years of follow-up, there were 51 severe or life-threatening events in the HSCT group compared to 30 events in the cyclophosphamide group ($p=0.002$). The study found a significantly higher treatment-related mortality in the HSCT group, with 8 deaths occurring in the first year after HSCT compared to no deaths in the control group. HSCT was associated with higher rates of long-term survival. After 4 years, there had been 13 deaths (16.5%) in the HSCT group compared to 20 deaths (26.0%) in the cyclophosphamide group. Results may have been confounded by a 20% attrition rate in the cyclophosphamide group due to death, major organ failure, or nonadherence to treatment.

The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial was a randomized, open label, active control trial comparing the efficacy and safety of high-dose immunosuppressive therapy (HDIT) followed by HCT and high-dose pulse IV cyclophosphamide. SCOT was a multi-center study with enrollment originally designed for 226 participants, with event-free survival as the preliminary endpoint. As a result of low accrual, the study was amended to broaden entry criteria, then ultimately to reduce the sample size by changing the primary endpoint to global rank composite, a design with an estimated enrollment of 114 subjects. The study enrolled 75 participants with severe scleroderma including participants with internal organ involvement, 36 to the HCT group and 39 to the cyclophosphamide group.

In 2018, Sullivan and colleagues assessed SCOT trial results at 54 to 72 months in the intent-to-treat population. At that point, 205 subjects had been screened and 73 were randomized. Thirty three of 37 randomized subjects received myeloablative autologous transplant. Thirty two of the 36 subjects randomized to receive 12 months of cyclophosphamide received that treatment. The study used a unique global score as the primary outcome, making comparison to other studies of scleroderma treatment difficult. Sixty seven percent of pairwise comparisons between transplant and cyclophosphamide recipients showed a higher global score for the transplant recipient. There were a total of 21 reported deaths, 7 in the transplant group ($n=3$ did not undergo transplantation; $n=2$ died of treatment-related causes; 2 had prior respiratory, renal or cardiac failure) and 14 in the cyclophosphamide group ($n=3$ received 5 or less doses; $n=7$ had respiratory, renal or cardiac event; none attributed directly to treatment). Estimated event free survival at 72 months, 74% for transplant group and 47 % for cyclophosphamide group and overall survival 86% versus 51% ($P=0.03$ and 0.02 , respectively). In a letter-to-the-editor, Shenoy and Sreenath (2018) note that the event-free survival benefit for the transplanted group in the SCOT trial did not occur until the second year after initiation of treatment, one year after the cyclophosphamide group stopped treatment. The very low transplant-related mortality may not be generalizable to treatment at other transplant centers.

In 2023, Keyes-Elstein and colleagues conducted a longitudinal analysis of clinical, laboratory and quality of life assessments of individuals in the SCOT trial. Data from 67 subjects with SSc randomized to either cyclophosphamide treatment ($n=34$) or HSCT ($n=33$) were analyzed. The authors noted that the SCOT trial results were affected by early loss of data due to factors such as organ failure or death. They noted that this early loss was disproportionate for the 2 study arms, but provided no details. In order to account for these missing data, the authors assumed that data were missing at random and used mixed-effects regression models to estimate longitudinal trends when comparing treatment groups. In general, this analysis tended to favor HSCT recipients over cyclophosphamide recipients. However, when subjects were divided into subsets based on baseline gene expression signatures (inflammatory [$n=20$], fibroproliferative [$n=20$] or normal-like [$n=22$]), there was no apparent difference between HSCT and cyclophosphamide treatment in the normal-like group. Missing data were a major limitation of this study and the missing data assumptions cannot be verified. The conclusions of this analysis need confirmation in prospective clinical trials.

Bruera and colleagues (2022) published a Cochrane systemic review of HSCT for systemic sclerosis. Three RCTs that compared HSCT to immunomodulators in the treatment of SSc were included in the review (total of 250 subjects; 125 received HSCT). These included the studies by Burt (2011), van Laar (2014), and Sullivan (2018) described above. No study demonstrated an overall mortality benefit of HSCT when compared to cyclophosphamide. However, myeloablative selective HSCT showed overall survival benefits using Kaplan-Meier curves at 6 years and non-myeloablative selective HSCT at 10 years (moderate certainty of evidence). Event-free survival was improved with non-myeloablative selective HSCT compared to cyclophosphamide at 48 months, but with myeloablative selective HSCT there was no improvement at 54 months. All HSCT modalities showed improvement of mRSS skin thickness scores favoring HSCT over cyclophosphamide. There was also low-certainty evidence that non-myeloablative selective and myeloablative selective HSCT improved physical function. Nevertheless, these HSCT treatment modalities resulted in more serious adverse events than cyclophosphamide. The authors concluded that while HSCT is a promising treatment option for SSc, there is a high risk of early treatment-related mortality and other adverse events. In addition, more research is needed to determine how HSCT compares to other treatment options such as mycophenolate mofetil, as cyclophosphamide is no longer the first-line treatment for SSc.

Higashitani and colleagues (2023) performed a systematic review and meta-analysis of the benefits and risks of systemic sclerosis treatment with HSCT compared to intravenous pulse cyclophosphamide. This review included the 3 RCTs identified by Bruera and described above (Burt [2011], van Laar [2014], and Sullivan [2018]). In addition, 19 observational studies were included in the analysis. Pooled data showed improved all-cause mortality, skin thickness score, and pulmonary function. However, the cumulative treatment-related death rate was significantly higher with HSCT than with cyclophosphamide treatment ($p=0.001$). The most common causes of death were cardiac and respiratory diseases which occurred relatively early after HSCT (< 6 months). The authors noted that the included observational trials were often small in size and used different inclusion criteria and transplant methods. The analysis did not include a comparison to medical treatments other than cyclophosphamide, such as mycophenolate mofetil. The authors concluded that although HSCT can offer an effective treatment for SSc, "more knowledge is needed about the inclusion/exclusion criteria, time of transplantation, regimen optimization, and post-transplant maintenance therapy" in order to optimize use of HSCT and prevent transplant-related deaths.

Chronic Acquired Demyelinated Neuropathy (CADP)

Mahdi-Rodgers (2009) reported results from a small trial of participants with CADP refractory to other treatments who underwent autologous PBSCT. In the study, a total of 6 participants underwent transplantation, 3 with chronic inflammatory demyelinating

polyradiculoneuropathy (CIDP), 2 with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) and 1 with an IgM paraprotein and antibodies to nerve. Four of the 6 participants developed neutropenic septicemia and pneumonia. The authors concluded that "the literature and our limited experience suggest that autologous PBSCT produces improvement in some patients with CADP but carries a risk of serious side effects and relapse after 1 or 2 years."

Summary Autoimmune Diseases:

The use of high dose chemotherapy with autologous stem cell transplantation has demonstrated improved outcomes for specific oncologic indications such as leukemia and lymphoma. Based on the experiences in these historic applications, the use of autologous and allogeneic stem cell transplantations continues to be studied in other oncologic and non-oncologic indications such as autoimmune diseases and miscellaneous solid tumors. However, in a position statement from a National Institute of Allergy and Infectious Diseases and National Cancer Institute-Sponsored International Workshop on the "Feasibility of Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Diseases", the authors concluded that "Although safer allogeneic transplantation strategies have become available, experience is currently insufficient to allow reliable extrapolation of data on safety and risks from patients with malignancies to patients with autoimmune diseases" (Griffith, 2005).

There are multiple ongoing clinical trials using autologous and allogeneic stem cell transplants following high dose immunotherapies for the treatment of autoimmune diseases. Published literature describe lymphoablation or the removal of "autoreactive lymphocytes" through the process of autologous stem cell transplantation to promote the generation of new self-tolerant lymphocytes. Examples of autoimmune disorders being studied in this manner include systemic sclerosis (SSc; that is, scleroderma), rheumatoid arthritis (RA), Crohn's disease and lupus. Further research with randomized controlled trials is needed to verify the benefit and safety of this therapy.

Miscellaneous Solid Tumors

Solid tumors are a heterogeneous group of neoplasms involving many different body systems. These tumors have usually demonstrated chemosensitivity to a variety of antineoplastic agents. Based on the previous responses to standard chemotherapeutic treatment regimens, the use of chemotherapy in higher doses with hematopoietic stem cell transplantation to achieve improved responses was proposed. However, there have not been large randomized trials to demonstrate improved responses and outcomes with the use of high dose chemotherapy with HSC.

At this time, there is not sufficient evidence in the peer-reviewed medical literature, in terms of long-term safety and efficacy, to support the use of bone marrow/stem cell transplantation, for the indications listed as investigational and not medically necessary. The majority of studies performed to date are either case reports, retrospective reviews, or phase II studies with short follow-up, no control groups and heterogeneous populations. There have been no large-scale prospective trials that have demonstrated improved outcomes. There are ongoing clinical trials studying the use, safety and effectiveness of stem cell transplant as a treatment for these investigational indications.

Background/Overview

Hematopoietic stem cell transplantation is a process which includes mobilization, harvesting, and transplant of stem cells after the administration of high dose chemotherapy (HDC) and/or radiotherapy. High-dose chemotherapy involves the administration of cytotoxic or immunosuppressive agents using doses greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (e.g., opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Autologous - Stem cells can be harvested from an individual's own bone marrow or peripheral blood
2. Allogeneic - Stem cells harvested from a histocompatible donor

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease.

The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each individual must balance the risks of graft failure and re-infusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While some hematopoietic stem cell transplant protocols can be administered on an outpatient basis, an inpatient stay may be required.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed "myeloablative." Several less intense conditioning regimens have been developed and rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative," also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This manifests as a stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants also referred to as "mini-transplant, transplant lite or reduced intensity conditioning," are thought to be potentially as effective as conventional HDC followed by an allogeneic stem cell transplantation (AlloBMT), but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for conventional HDC/AlloBMT, conditioning with milder, non-myeloablative regimens (NM-AlloBMT) represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous and/or allogeneic stem cell support is the planned administration of more than one cycle of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved

using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Autoimmune diseases are the result of an inappropriate activation of humoral or cellular immune responses against the individual's own cells or tissues. It is not completely understood why the immune system becomes intolerant to its host. Available evidence implicates a combination of genetic, hormonal, and/or environmental factors. Several common conditions that are believed to involve autoimmunity include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), pemphigus, juvenile RA and systemic sclerosis (scleroderma). In general, these diseases can be controlled with standard anti-inflammatory, anti-malarial, or immunosuppressive medications in conjunction with supportive care. In a small proportion of individuals, the disease is refractory to treatment and can become severe, debilitating, and organ or life threatening. This most commonly occurs with some forms of MS, scleroderma and amyotrophic lateral sclerosis (Lou Gehrig's disease). Individuals with these more severe forms of autoimmune disease or individuals who do not respond to medical treatment have been investigated as potential candidates for high-dose immunosuppressive therapy followed by hematopoietic stem cell transplantation (HSCT).

MS is an autoimmune disease of the central nervous system (CNS). During the MS disease process, inflammation of nervous tissue causes the loss of myelin, a fatty material that acts as a protective insulation for the nerve fibers in the brain and spinal cord. This demyelination leaves multiple areas of hard, scarred tissue (plaques) along the covering of the nerve cells. Another characteristic of MS is the destruction of axons, which are the long filaments that carry electric impulses away from a nerve cell. Demyelination and axon destruction disrupts the ability of the nerves to conduct electrical impulses to and from the brain and produces various symptoms. Common symptoms of the disease include fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, sexual dysfunction, and pain. Classifications of MS are relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive MS (SPMS). Most individuals with MS have a relapsing course, and their first attack may present as a clinically isolated syndrome (CIS). A CIS is a single demyelinating episode with consistent MRI findings (indicating inflammation/demyelination in one site in the CNS). Individuals with CIS are at high risk for developing clinically definite MS.

Epithelial ovarian cancer is a clonal disease of unknown cause that arises from a single cell. Epidemiologic studies have not identified any consistent predisposing factors. Caucasian race, nulligravidity, late age of menopause, prolonged intervals of ovulation, and family history are individual characteristics that have been found to be associated with increased risk. Some evidence exists to indicate that ovarian cancers are more prevalent in some families than in the general population. These families also demonstrate a higher prevalence of breast cancer. Familial or hereditary patterns account for less than 5% of epithelial ovarian cancer cases and generally occur in women approximately 10 years earlier than the overall mean age of onset. The precise risk of developing epithelial ovarian cancer in women with a strong family history is undetermined but is believed to be dependent upon the number of first- and/or second-degree relatives affected. In recent years, the option of prophylactic oophorectomy in individuals from families with strong familial histories of ovarian cancer has emerged. This measure, however, does not completely eliminate the possibility of disease since the entire coelomic epithelium is believed to be at risk.

Breast cancer is malignant abnormal cell growth in the breast. Cancer cells may spread to other areas of the body (called metastasis). Fibrocystic changes (for example, formation of cysts, scar tissue) may cause benign (that is, noncancerous) lumps in the breast. It is important for women to become familiar with their breasts and report changes (for example, lump, nipple discharge, and asymmetry) to their health care practitioner. In women, breast cancer is the second most common type of cancer and the second leading cause of cancer-related deaths. One in eight women in the United States will develop breast cancer during her lifetime. According to the National Cancer Institute (NCI) approximately 297,790 women in the United States will be diagnosed with breast cancer in 2023, and 43,170 deaths are expected. The incidence of breast cancer rises after age 40. The highest incidence (approximately 80% of invasive cases) occurs in women over age 50 (CDC, 2023).

Astrocytomas and gliomas arise from the glial cells. Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into three grades of malignancy: grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to the diffuse fibrillary astrocytomas. However, these tumors have generally better prognoses than diffuse astrocytomas with mean survival times of 10 years. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most individuals.

Definitions

Ablative: Very high dose of a treatment, calculated to kill a tumor.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull; this tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals; may be mixed or complete.

Cytotoxic: Destructive to cells.

Graft versus host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to re-populate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Relapsing-remitting MS (RRMS): A clinical course of MS characterized by clearly defined, acute relapses with full or partial recovery; no disease progression or worsening of disability develops between relapses.

Tandem transplant: Planned administration of more than one cycle of high-dose or non-myeloablative chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met for autologous transplantation:

CPT

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [when specified as autologous, includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215]
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS

S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition [when specified as autologous]
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ICD-10 Procedure

	<i>Autologous transplantation</i>
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	<i>Pheresis</i>
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as autologous]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as autologous]

ICD-10 Diagnosis

G35	Multiple sclerosis
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When services are Investigational and Not Medically Necessary for autologous transplantation:

For the procedure and diagnosis codes listed above when criteria are not met, and for the following diagnoses

ICD-10 Diagnosis

C00.0-C80.1	Malignant neoplasms [code range; when not specified as pediatric solid tumors or germ cell tumors]
G61.81	Chronic inflammatory demyelinating polyneuritis
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.0A	Rheumatoid arthritis without rheumatoid factor
M08.00-M08.0A	Unspecified juvenile rheumatoid arthritis
M08.20-M08.2A	Juvenile rheumatoid arthritis with systemic onset
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M34.0-M34.9	Systemic sclerosis (scleroderma)

When services are Investigational and Not Medically Necessary for allogeneic transplantation:

CPT

38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207-38215	Transplant preparation of hematopoietic progenitor cells [when specified as allogeneic, includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215]
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS

S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition [when specified as allogeneic]

ICD-10 Procedure

	<i>Allogeneic transplantation</i>
30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]

6A550ZV
6A551ZV

Pheresis

Pheresis of hematopoietic stem cells, single [when specified as allogeneic]
Pheresis of hematopoietic stem cells, multiple [when specified as allogeneic]

ICD-10 Diagnosis

C00.0-C80.1	Malignant neoplasms [code range; when not specified as pediatric solid tumors or germ cell tumors]
G35	Multiple sclerosis
G61.81	Chronic inflammatory demyelinating polyneuritis
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.0A	Rheumatoid arthritis without rheumatoid factor
M08.00-M08.0A	Unspecified juvenile rheumatoid arthritis
M08.20-M08.2A	Juvenile rheumatoid arthritis with systemic onset
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M34.0-M34.9	Systemic sclerosis (scleroderma)

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 Mini Transplant
 Non-Myeloablative Stem Cell Transplant
 Peripheral Blood Stem Cell
 Solid Tumor
 Stem Cell Support (SCS)
 Stem Cell Transplant (SCT)

Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment (MPTAC) review. Updated Rationale, Background, References and Websites for Additional Information sections.
Revised	05/11/2023	MPTAC review. Revised MN statement to correct spelling of ocrelizumab. Updated Rationale, Background, References and Websites for Additional Information sections.
Reviewed	05/12/2022 10/01/2021	MPTAC review. Updated Rationale, Background, References and Websites sections. Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Revised	05/13/2021	MPTAC review. Added MN statement for a <i>single</i> autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation for individuals with RRMS when criteria met. Added INV/NMN statement for a <i>single</i> autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplant for the treatment of MS when criteria above are not met, including primary progressive or secondary progressive forms of MS. Added INV/NMN statement for a <i>repeat</i> autologous (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplant for the treatment of RRMS. Added INV/NMN statement for an allogeneic (ablative or non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation or planned tandem as a treatment of multiple sclerosis. Revised INV/NMN statement for autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) as a treatment of <i>all other</i> autoimmune diseases, removing MS from list of conditions. Updated Rationale, Background, Coding, Definitions, References and Websites sections.
Reviewed	02/11/2021 10/01/2020	MPTAC review. Updated Rationale, Background, References and Websites sections. Updated Coding section; added G61.81. Updated Coding section with 10/01/2020 ICD-10-CM changes; added M06.0A, M08.0A, M08.2A.
Reviewed	02/20/2020 10/01/2019	MPTAC review. Updated Rationale, References and Websites sections. Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Background, References and Websites sections.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date". Updated Rationale, References and Websites sections.
Reviewed	05/04/2017	MPTAC review.
Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Updated Rationale, References and Websites sections.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.
Revised	05/05/2016	MPTAC review.
Revised	05/04/2016	Hematology/Oncology Subcommittee review. Reformatted criteria removing abbreviations from MN position. Updated Rationale, Background, References and Websites sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review.
Reviewed	05/06/2015	Hematology/Oncology Subcommittee review. Updated Rationale, Definitions, References and Websites.
Reviewed	05/15/2014	MPTAC review.
Reviewed	05/14/2014	Hematology/Oncology Subcommittee review. Updated Rationale, References and Websites.
Reviewed	05/09/2013	MPTAC review.
Reviewed	05/08/2013	Hematology/Oncology Subcommittee review. Updated Rationale, References and Websites.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Revised	05/10/2012	MPTAC review.
Revised	05/09/2012	Hematology/Oncology Subcommittee review. Revised investigational and not medically positions to include autologous or allogeneic (ablative and non-myeloablative "[mini-transplant]") hematopoietic stem cell transplantation "single or tandem". Removed redundant investigational and not medically necessary statements for all conditions. Clarified investigational and not medically necessary statements for "adult miscellaneous" solid tumors Reformatted policy. Rationale, Background, References and Websites updated.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Reviewed	05/19/2011	MPTAC review.
Reviewed	05/18/2011	Hematology/Oncology Subcommittee review. Websites, Coding and References updated.
Reviewed	05/13/2010	MPTAC review.
Reviewed	05/12/2010	Hematology/Oncology Subcommittee review. Websites and references updated.
Revised	11/19/2009	MPTAC review.
Revised	11/18/2009	Hematology/Oncology Subcommittee review. Changed title to Hematopoietic Stem Cell Transplantation for Autoimmune Disease and Miscellaneous Solid Tumors. Clarified position statements. Rationale, background, websites and references updated.

Reviewed	05/21/2009	MPTAC review.
Reviewed	05/20/2009	Hematology/Oncology Subcommittee review. Rationale, websites and references updated. No change to position
Reviewed	05/15/2008	MPTAC review.
Reviewed	05/14/2008	Hematology/Oncology Subcommittee review. Rationale, websites and references updated. No change to position.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review.
Reviewed	05/16/2007	Hematology/Oncology Subcommittee review. No change to position. References and coding updated.
Revised	12/07/2006	MPTAC review. References updated. Coding updated.
Revised	12/06/2006	Hematology/Oncology Subcommittee review
Reviewed	12/01/2005	MPTAC review.
Reviewed	11/30/2005	Hematology/Oncology Subcommittee review. Minor formatting changes.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	10/28/2004	TRANS.00002	Stem Cell Transplant following Chemotherapy for Malignant Diseases
	10/28/2004	TRANS.00003	Stem Cell Transplant following Chemotherapy for Non-Malignant Diseases
WellPoint Health Networks, Inc.	12/02/2004	7.11.02	Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies
	12/02/2004	7.11.03	Allogeneic Bone Marrow or Stem Cell Transplantation
	12/02/2004	7.11.05	Mini-Transplants

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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