I. POLICY

Autologous or allogeneic hematopoietic stem-cell transplantation is considered investigational as a treatment of autoimmune diseases, including, but not limited to the following:

1. multiple sclerosis
2. juvenile idiopathic and rheumatoid arthritis
3. systemic lupus erythematosus
4. systemic sclerosis/scleroderma
5. type 1 diabetes mellitus
6. chronic inflammatory demyelinating polyneuropathy.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross reference:

MP-9.038 Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
MP-9.039 Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
MP-9.040 Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
MP-9.041 Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
MP-9.042 Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
MP-9.043 Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
MP-9.044 Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
MP-9.045 Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) 110.8.1, Stem Cell Transplantation.

**The Federal Employee Program (FEP) may include specific conditions in which autologous and nonmyeloablative (reduced-intensity conditioning or RIC) allogeneic blood or marrow stem cell transplants may be considered eligible for coverage. Refer to the Service Plan Benefit Brochure for covered indications.

III. DESCRIPTION/BACKGROUND

Most patients with autoimmune disorders respond to conventional therapies. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic stem-cell transplantation (HSCT).

Autoimmune Diseases
Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma, and chronic immune demyelinating polyneuropathy (CIDP). The National Institutes of Health (NIH) estimates that 5–8% of Americans have an autoimmune disorder.

The pathogenesis of autoimmune diseases is not well-understood but appears to involve underlying genetic susceptibility and environmental factors that lead to loss of self-tolerance, culminating in tissue damage by the patient’s own immune system (T cells).

Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., RA, SLE, and scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressant, and immunomodulating drugs. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic stem-cell transplantation (HSCT). HSCT in autoimmune disorders raises the question of whether ablating and “resetting” the immune system can alter the disease process and sustain remission and possibly lead to cure.¹

**Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in MP-9.001.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Autologous Stem-Cell Transplantation for Autoimmune Diseases**

The goal of autologous HSCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new self-tolerant lymphocytes.² This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HSCT for hematologic malignancies.² However, there is
currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and myeloablative regimens are used. The efficacy of the different conditioning regimens has not been compared in clinical trials.

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the GVHD associated with allogeneic transplant, and the need to administer post-transplant immunosuppression after an allogeneic transplant.

Allogeneic Stem-Cell Transplantation for Autoimmune Diseases

The experience of using allogeneic HSCT for autoimmune diseases is currently limited but has two potential advantages over autologous transplant. First, the use of donor cells from a genetically different individual could possibly eliminate genetic susceptibility to the autoimmune disease and potentially result in a cure. Second, there exists a possible graft-versus-autoimmune effect, in which the donor T cells attack the transplant recipient’s autoreactive immune cells.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

IV. RATIONALE

The most recent literature review was completed through December 10, 2015.

Recent reviews summarize the research to date using hematopoietic stem cell transplantation (HSCT) to treat a number of autoimmune diseases.

In March 2009, patients with an autoimmune disease registered in the European Group for Blood and Marrow Transplantation/European League Against Rheumatism (EBMT/EULAR) database who had undergone HSCT included 1031 with the clinical indications of multiple sclerosis (MS; n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE; n=92), rheumatoid arthritis (RA; n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn disease (n=23).

Multiple Sclerosis

Only 1 randomized controlled trial (RCT) evaluating HSCT for treatment of MS has been published, but this trial did not report clinical outcomes. No controlled trials with contemporaneous control groups were identified that reported clinical end points such as overall survival (OS), progression-free survival (PFS), or disability status as their primary outcomes.
The 2015 RCT by Mancardi et al was originally designed as a phase 3 study reporting on disability progression. However, due to low patient enrollment, the protocol was amended as a phase 2 study with the primary outcome of cumulative number of new T2 magnetic resonance imaging (MRI) lesions in the 4 years after treatment. Eligibility for the trial was secondary progressive or relapsing-remitting MS, a documented worsening during the last year, and lack of response to conventional therapy. A total of 21 patients were randomized to autologous HSCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were not available on 4 patients; missing data was imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HSCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval, 0.10 to 0.48, p<0.001). Among secondary outcomes, the annualized relapse rate was significantly lower in the HSCT group (0.19) than in the conventional therapy group (0.6), but there was no statistically significant difference between groups in the rate of disease progression or change in disability status.

The remaining published literature consists of case series. In 2010, Pasquini et al published data on more than 350 consecutive cases included in the EBMT database. Most patients who underwent autologous HSCT for MS in the early years had secondary progressive MS, and relatively fewer had relapsing-remitting disease, with Kurtzke Expanded Disability Status Scale (EDSS) scores of 3.0 to 9.5 at the time of HSCT. Improvements in supportive care and patient selection have contributed to improved outcomes, with a significant reduction in treatment-related mortality to 1.3% seen during 2001 to 2007. Thinking at the time was that administering HSCT relatively early in the course of the disease to reduce inflammation before irreversible neuronal damage occurs was important. More recent studies have targeted MS patients with active disease and worsening disability, as evidenced clinically by relapse, change in EDSS score, and/or inflammatory activity seen on MRI and who have failed at least 1 approved first-line immunomodulatory MS therapy before enrollment.

A 2011 systematic review published evaluated the safety and efficacy of autologous HSCT in patients with progressive MS refractory to conventional medical treatment. Eight case series met the inclusion criteria for the primary outcome of PFS, with a median follow-up of at least 2 years. An additional 6 studies were included for a summary of mortality and morbidity. For the 8 case series, there was substantial heterogeneity across studies. Most patients (77%) had secondary progressive MS, although studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. Numbers of patients across studies ranged between 14 and 26. The studies differed in the types and intensities of conditioning regimens used prior to HSCT, with 5 studies using an intermediate-intensity regimen and 3 using high-intensity regimens. All studies were rated as moderate quality. The estimated rate of long-term PFS of patients receiving intermediate-intensity conditioning regimen was 79.4% (95% CI, 69.9% to 86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6% (95% CI, 26.5% to 64.5%) at a median follow-up of 24 months. Of the 14 studies that reported on adverse events, 13 were case series; from these, 7 treatment-related deaths were recorded; 6 non-treatment-related deaths occurred, 5 associated with disease progression.
A 2012 study by Shevchenko et al reported the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HSCT with reduced-intensity conditioning regimen in 95 patients with different types of MS. Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality-of-life (QOL) outcomes. No transplantation-related deaths were observed. All patients, except 1, responded to treatment. At long-term follow-up (mean, 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS at 5 years was 92% in the group after early transplant and 73% in the group after conventional/salvage transplant (p=0.01). No active, new, or enlarging lesions on MRI were found in patients without disease progression. All patients who did not have disease progression were off therapy throughout the posttransplantation period. HSCT was accompanied by a significant improvement in QOL, with statistically significant changes in most QOL parameters (p<0.05). A 2015 subsequent publication reported on 64 patients participating in this trial who had at least 36 months of follow-up (median, 62 months). (Another 35 patients had shorter follow-up and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved at least 0.5 point on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable and 5 (7%) experienced worsening disease.

In 2012, Mancardi et al reported on 74 consecutive patients with MS treated using autologous HSCT with an intermediate-intensity conditioning regimen in the period from 1996 to 2008. Thirty-six patients had secondary progressive disease and 25 had relapsing-remitting MS. Clinical and MRI outcomes were reported. Median follow-up was 48.3 months (range, 0.8-126 months). Two patients (2.7%) died from transplant-related causes. After 5 years, 66% of patients remained stable or improved. Among patients with a follow-up longer than 1 year, 8 (31%) of 25 subjects with a relapsing-remitting course had a 6- to 12-month confirmed EDSS score improvement greater than 1 point after HSCT compared with 1 (3%) of 36 patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up longer than 7 years, 8 (44%) remained stable or had a sustained improvement, while 10 (56%), after an initial period of stabilization or improvement (median duration, 3.5 years), showed a slow disability progression.

A 2015 single-center case series by Burt et al reported on 151 patients, 123 with relapsing-remitting MS and 28 with secondary progressive MS. Patients were treated with nonmyeloablative HSCT between 2003 and 2014. Six patients were not included in the outcome analysis. The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). There were no treatment-related deaths. The primary outcome was change in the EDSS score. A decrease of at least 1.0 point was considered significant improvement and an increase of at least 1.0 point was considered significant progression. There was statistically significant improvement in EDSS score for the group as a whole compared with the pretransplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at 3, 4, and 5 years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS score were those with relapsing-remitting MS, with duration of disease of 10 years or less, and those without sustained fever during HSCT.
Several studies have focused on patients with aggressive MS. In 2011, Fassas et al reported the long-term results of a single-center study that investigated the effect of HSCT in the treatment of MS. The authors reported, after a median follow-up period of 11 years (range, 2-15 years), on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HSCT. Disease PFS at 15 years was 44% for patients with active central nervous system disease and 10% for those without (p=0.01); median time to progression was 11 years (range, 0-22 years) and 2 years (range, 0-6 years), respectively. Improvements by 0.5 to 5.5 (median, 1) EDSS points were observed in 16 cases, lasting for a median of 2 years. In 9 of these patients, EDSS scores did not progress above baseline scores. Two patients died, at 2 months and 2.5 years, from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HSCT.

A 2014 multicenter case series by Burman et al reported on 48 patients with aggressive relapsing-remitting MS, defined as disease with high relapse frequency, and who failed conventional therapy. Patients underwent autologous HSCT. At the 5-year follow-up, relapse-free survival was 87% and the EDSS score PFS (EDSS deterioration of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%.

Systemic Sclerosis/Scleroderma

A recent review summarized the clinical studies performed using conventional therapy, as well as those using autologous HSCT in the treatment of systemic sclerosis. Ongoing randomized trials are also discussed.

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014. ASTIS was a phase 3, randomized controlled trial (RCT) conducted in 10 countries at 29 centers with access to an EBMT-registered transplant facility. A total of 156 patients were recruited between March 2001 and October 2009. Individual patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria, with maximum duration of 4 years; minimum modified Rodnan Skin Score (mRSS) of 15 (range, 0-51; higher scores indicate more severe skin thickening); and involvement of heart, lungs, or kidneys. Patients were randomly allocated to receive high-dose chemotherapy (intravenous cyclophosphamide 200 mL/kg over 4 consecutive days and intravenous rabbit antithymocyte globulin 7.5 mg/kg total dose over 3 consecutive days) followed by CD34+ selected autologous HSCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m²). Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in mRSS, organ function, body weight, and QOL scores. The internal validity (risk of bias) of ASTIS was assessed according to the U.S. Preventive Services Task Force criteria for randomized trials. The study was rated as “poor” quality according to this.
framework because it has 2 fatal flaws: outcome assessment was not masked to patients or assessors, and 18 (24%) of 75 of the control group discontinued intervention because of death, major organ failure, adverse events, or nonadherence. Furthermore, the trial design permitted crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors reported that the use of unspecified concomitant medications or other supportive care measures were allowed at the discretion of the investigators, adding further uncertainty to the results.

A total of 53 primary end point events were recorded: 22 in the HSCT group (19 deaths, 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 in the control group (23 deaths, 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data show patients treated with HSCT experienced more events in the first year but appeared to have better long-term event-free survival than the controls, because the Kaplan-Meier curves for OS crossed at about 2 years after treatment with OS at that time estimated at 85%. According to data from the Kaplan-Meier curves, at 5 years, OS was an estimated 66% in the control group and about 80% the HSCT group (p value unknown). Time-varying hazard ratios (modeled with treatment by time interaction) for event-free survival were 0.35 (95% CI, 0.15 to 0.74) at 2 years and 0.34 (95% CI, 0.16 to 0.74) at 4 years, supporting a benefit of HSCT versus pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HSCT group and 30 (37% by intention-to-treat, p=0.002) of the control group.

An open-label, randomized, controlled phase 2 trial (ASSIST) assessed the safety and efficacy of autologous nonmyeloablative HSCT compared with the standard of care cyclophosphamide. Nineteen consecutively enrolled patients who were younger than 60 years of age with diffuse systemic sclerosis, mRSS of more than 14, and internal organ involvement or restricted skin involvement (mRSS, <14) but coexistent pulmonary involvement were randomly allocated 1:1 using a computer-generated sequence to receive HSCT, intravenous cyclophosphamide 200 mg/kg, and rabbit antithymocyte globulin or to intravenous cyclophosphamide 1.0 g/m² once per month for 6 months. The primary outcome was improvement at 12-month follow-up, defined as a decrease in mRSS (<25% for those with initial mRSS >14) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HSCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HSCT (n=10) improved at or before 12-month follow-up compared with none of the 9 allocated to cyclophosphamide (p<0.001). Treatment failure (ie, disease progression without interval improvement), occurred in 8 of 9 controls, but did not occur in any of the 10 patients treated by HSCT (p<0.001). After long-term follow-up (mean, 2.6 years) of patients allocated to HSCT, all but 2 patients had sustained improvement in mRSS and forced vital capacity, with a longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HSCT without complication, and all improved after
HSCT. Four of these patients, followed for at least 1 year, had a mean (SD) decrease in mRSS from 27 (SD=15.5) to 15 (SD=7.4), an increase in forced vital capacity from 65% (20.6%) to 76% (26.5%), and an increase in total lung capacity from 81% (14.0%) to 88% (13.9%). Data for 11 patients with follow-up to 2 years after HSCT suggested that the improvements in mRSS (p<0.001) and forced vital capacity (p<0.03) persisted.

Vonk et al reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HSCT from 1998 to 2004. There was 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1-7.5 years), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with an mRSS, and a significant (ie, >25%) decrease (ie, improvement) was achieved in 19 of 26 patients after 1 year and in 15 of 16 after 5 years. At inclusion into the study, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5- and 7-year follow-up. Analyzing World Health Organization Performance Status, which reflects the effect of HSCT on the combination of functional status, skin, lung, heart, and kidney involvement, the percentage of patients with a Performance Status score of 0 increased to 56% from 4% at baseline. Estimated survival at 5 years was 96.2% (95% CI, 89% to 100%) and at 7 years was 84.8% (95% CI, 70.2% to 100%); and event-free survival (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI, 47.9% to 86%) at 5 years and 57.1% (95% CI, 39.3% to 83%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40%.

Nash et al reported the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HSCT. Of the 34 patients, 79% survived 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Seventeen of the 27 (63%) evaluable patients had sustained responses at a median follow-up of 4 years (range, 1-8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline (p<0.001) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients using the Disability Index of the modified Health Assessment Questionnaire showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of 8 of 27 patients. Estimated OS and PFS were both 64% at 5 years.

Henes et al reported on 26 consecutive patients with systemic sclerosis scheduled for autologous HSCT between 1997 and 2009. The major outcome variable was response to treatment (reduction of mRSS by 25%) at 6 months. Secondary end points were TRM and PFS. At 6 months, significant skin and lung function improvement of the mRSS was achieved in 78.3% of patients. Overall response rate was 91%, and some patients improved even after month 6. Three patients died between mobilization and conditioning treatment, 2 due to severe disease progression and 1 whose death was considered treatment-related. Seven patients relapsed during
the 4.4 years of follow-up. PFS was 74%. Four patients died during follow-up, and the most frequent causes of death were pulmonary and cardiac complications of systemic sclerosis.

Systemic Lupus Erythematosus
Burt et al published the results of the largest single-center series using HSCT in SLE in the United States. Between April 1997 through January 2005, they enrolled 50 patients (mean age, 30 years, SD=10.9; 43 women, 7 men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg/d of prednisone or its equivalent despite use of cyclophosphamide. Patients underwent autologous HSCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a treatment-related mortality of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), 5-year OS was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity (described in the 2001 TEC Assessment) improved, including renal function, SLE Disease Activity Index score, antinuclear antibody, anti-ds DNA, complement, and carbon monoxide diffusion lung capacity. The investigators suggested these results justified a randomized trial comparing immunosuppression plus autologous HSCT and continued standard of care.

Song et al reported on the efficacy and toxicity of autologous HSCT for 17 patients with SLE after 7 years follow-up. The probabilities of OS and PFS were used to assess the efficacy and toxicities of the treatment. Median follow-up time was 89 months (range, 33-110 months). The probabilities of 7-year OS and PFS were 82.4%±9.2% and 64.7%±11.6%, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggested that autologous HSCT was beneficial for SLE patients.

Juvenile Idiopathic Arthritis
A 2008 review article by Saccardi et al summarized the experience with juvenile idiopathic arthritis and RA as follows: More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used 1 conditioning regimen and, thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. The frequency of HSCT for RA has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HSCT have had persistence or relapse of disease activity within 6 months of transplant.

Chronic Inflammatory Demyelinating Polyneuropathy
Several review articles have summarized experience with HSCT in treatment of chronic inflammatory demyelinating polyneuropathy. In general, evidence comprises a few case reports describing outcomes of autologous HSCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange.
Type 1 Diabetes Mellitus

Several case series were identified evaluating autologous HSCT in patients with new-onset type 1 diabetes; there were no published comparative studies. In the series, although a substantial proportion of patients tended to become insulin-free after HSCT, remission rates were high. In 2015, Xiang et al published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than 6 weeks before study enrollment.\(^\text{26}\) After a mean follow-up of 28.5 months (range, 15-38 months), 71 patients (55%) were considered to be insulin-free. These patients had a mean remission period of 14.2 months (SD=6.1 months). The other 57 patients (45%) were insulin-dependent. The latter group includes 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (1 patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HSCT were younger age at onset of diabetes, lower tumor necrosis factor α, and higher fasting C peptide.

A 2015 case series by Snarski et al reported on 24 patients with a diagnosis of type 1 diabetes within 6 weeks of enrollment who underwent autologous HSCT.\(^\text{27}\) Patients had a mean age of 26.5 years (range, 18-34 years). After treatment, 20 of 23 patients (87%) went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. Median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at 2 and 3 years, but the insulin doses returned to pre-HSCT levels at years 4 and 5. Among patients (n=20) remaining in follow-up at the time of data analysis for publication, 4 (20%) remained insulin-free. Adverse events include neutropenic fever in 12 patients (50%). There were 4 cases of sepsis, including a fatal case of *Pseudomonas aeruginosa* sepsis. There was also 1 case of pulmonary emphysema after insertion of a central venous catheter.

In 2009, Couri et al reported the results of a prospective case series evaluating autologous HSCT in 23 patients with type 1 diabetes mellitus (age range, 13-31 years) diagnosed in the 6 weeks before transplant by clinical findings including hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies.\(^\text{28}\) At a mean follow-up of 29.8 months (range, 7-58 months) after autologous nonmyeloablative HSCT, C-peptide levels increased significantly (C peptide measures islet cell mass, and an increase after HSCT indicates preservation of islet cells), and most patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14-52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, hemoglobin A\(_{1c}\) levels were less than 7.0%. There was no transplant-related mortality.
Other Autoimmune Diseases

Phase 2/3 protocols are being developed for Crohn disease. For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others), sample sizes are too small to draw conclusions.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

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<tr>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>A Phase II Study of High-Dose Immunosuppressive Therapy (HDIT) Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) and Thymoglobulin, and Autologous CD34+ Hematopoietic Stem Cell Transplant (HCT) for the Treatment of Poor Prognosis Multiple Sclerosis. Interim 3 year data reported in 2015; the study is ongoing to 5 years</td>
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<td>A Randomized, Open-Label, Phase II Multicenter Study of High-Dose Immunosuppressive Therapy Using Total Body Irradiation, Cyclophosphamide, ATGAM, and Autologous Transplantation With Auto-CD34+HPC Versus Intravenous Pulse Cyclophosphamide for the Treatment of Severe Systemic Sclerosis (SCSSc-01)</td>
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<td>Hematopoietic Stem Cell Therapy for Patients With lnflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study</td>
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<td>Non-myeloablative Autologous Hematopoietic Stem Cell Transplantation in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: A Phase II Trial</td>
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NCT: national clinical trial.

Summary of Evidence

The evidence for hematopoietic stem cell transplantation (HSCT) in individuals who have multiple sclerosis includes 1 randomized controlled trial (RCT) and case series. Relevant outcomes are overall survival, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The phase 2 RCT reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HSCT developed significantly fewer lesions than the group receiving conventional therapy. Findings of case series report include improvements in clinical parameters following HSCT. Controlled trials that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have juvenile idiopathic and rheumatoid arthritis includes a registry study. Relevant outcomes are symptoms, quality of life, medication use, treatment-related mortality, and treatment-related morbidity. The registry study included 50 patients and the overall drug-free remission rate was approximately 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.
The evidence for HSCT in individuals who have systemic lupus erythematosus includes case series. Relevant outcomes are overall survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity. Several case series have been published. The largest (N=50 patients) found an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have systemic sclerosis/scleroderma includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. The results of the ASTIS trial suggest high-dose chemotherapy with autologous HSCT may improve survival among patients with diffuse cutaneous systemic sclerosis compared with pulsed intravenous cyclophosphamide. However, analysis of the internal validity of the trial using U.S. Preventive Services Task Force criteria showed fatal flaws and a poor study rating due to attrition in the control group that could have skewed the survival curve to show better survival for HSCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in the HSCT group than in the conventional therapy group. Data from these studies are inconclusive; additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have type 1 diabetes mellitus includes case series. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. Several case series evaluated autologous HSCT in patients with new-onset type 1 diabetes; there were no published comparative studies. In the series, although a substantial proportion of patients tended to become insulin free after HSCT, remission rates were high. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have chronic inflammatory demyelinating polyneuropathy includes case reports. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
A review of the guidelines from the American Academy of Neurology (AAN) and the American College of Rheumatology found no mention of stem cell transplantation in guidelines for multiple sclerosis, lupus, rheumatoid arthritis, or juvenile idiopathic arthritis. For example, guidelines from AAN published in 2002 and reaffirmed in 2008 on disease-modifying therapies in multiple sclerosis did not discuss stem cell transplantation.30

U.S. Preventive Services Task Force Recommendations
Not applicable.
**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-9.053</td>
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**Medicare National Coverage**

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services has not issued a national coverage determination (NCD) for stem cell transplantation for each disease. A general NCD (110.8.1) for stem cell transplantation and can be accessed at [https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=AAAAAgAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=AAAAAgAAAAAA%3d%3d&).

V. DEFINITIONS

NA

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered: as a treatment of autoimmune diseases
MEDICAL POLICY

Policy Title: Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
Policy Number: MP-9.053

CPT Codes®

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<td>38205</td>
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HCPCS Code Description

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<th>Code</th>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived 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</td>
</tr>
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</table>

IX. REFERENCES


<table>
<thead>
<tr>
<th>Policy Title</th>
<th>Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases</th>
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Other Sources:


X. POLICY HISTORY

| MP 9.053       | CAC 5/20/14 Minor. Information on HSCT for Autoimmune Diseases was extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. Chronic inflammatory demyelinating polyneuropathy added as an investigational indication. References updated. Rationale section added. Policy coded. |
|               | CAC 6/2/15 Consensus. No change to policy statements. References and rationale updated. Codes reviewed. |
|               | Administrative Update-variation reformatting 1/01/17. |