MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES
POLICY NUMBER	MP 9.053

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	**6/1/2026**

POLICY

Autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** as a treatment of systemic sclerosis/scleroderma if all of the following conditions are met:

- Adult individuals <60 years of age; **and**
- Maximum duration of condition of five (5)-years; **and**
- Modified Rodnan Scale Scores ≥15; **and**
- Internal organ involvement as noted in the Policy Guidelines; **and**
- History of < six (6)-months treatment with cyclophosphamide; **and**
- No active gastric antral vascular ectasia; **and**
- Do not have any exclusion criteria as noted in the Policy Guidelines.

Autologous HCT as a treatment of systemic sclerosis/scleroderma not meeting the above criteria is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Autologous or allogeneic HCT is considered **investigational** as a treatment of autoimmune diseases, including, but not limited to, the following:

- Multiple sclerosis
- Systemic lupus erythematosus
- Juvenile idiopathic or rheumatoid arthritis
- Chronic inflammatory demyelinating polyneuropathy
- Type 1 diabetes.

POLICY GUIDELINES

Autologous HCT should be considered for patients with systemic sclerosis (SSc) only if the condition is rapidly progressing and the prognosis for survival is poor. An important factor influencing the occurrence of treatment-related adverse effects and response to treatment is the level of internal organ involvement. If organ involvement is severe and irreversible, HCT is not recommended. Below are clinical measurements that can be used to guide the determination of organ involvement.

Individuals with internal organ involvement indicated by the following measurements may be considered for autologous HCT:

- Cardiac: abnormal electrocardiogram; **or**
- Pulmonary: diffusing capacity of carbon monoxide (DLCo) <80% of predicted value; decline of forced vital capacity (FVC) of ≥10% in last 12 months; pulmonary fibrosis; ground glass appearance on high resolution chest computed tomography (CT); **or**
- Renal: scleroderma-related renal disease.

Individuals with internal organ involvement indicated by the following measurements should not be considered for autologous HCT:

- Cardiac: left ventricular ejection fraction <50%; tricuspid annular plane systolic excursion <1.8 cm; pulmonary artery systolic pressure >40 mm Hg; mean pulmonary artery pressure >25 mm Hg.
- Pulmonary: DLCo <40% of predicted value; FVC <45% of predicted value.
- Renal: creatinine clearance <40 ml/minute.

Cross-Reference:
MP 4.031 Plasma Exchange (PE)
MP 9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies**.**

DESCRIPTION/BACKGROUND

Autoimmune Diseases

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

Treatment

Immune suppression is a common treatment strategy for many autoimmune diseases, particularly the rheumatic diseases (e.g., RA, SLE, scleroderma). Most patients with

autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of patients suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is for this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT). The primary concept underlying use of HCT for these diseases is that ablating and "resetting" the immune system can alter the disease process by inducing a sustained remission that possibly leads to cure.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in patients with cancer who receive bone marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is discussed in greater detail in policy **MP-9.001**.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. The term HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation.

Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-Intensity Conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

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 title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RATIONALE

Summary of Evidence

For individuals with multiple sclerosis who receive HCT, the evidence includes randomized controlled trials (RCTs), systematic reviews, and several nonrandomized studies. The relevant outcomes are overall survival (OS), health status measures, quality of life (QOL), and treatment-related mortality (TRM) and morbidity. Systematic reviews are primarily comprised of observational data. One RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging [MRI] lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The other RCT compared nonmyeloablative HCT results in patients with continued disease-modifying therapy and found a benefit to HCT in prolonged time to disease progression. The findings of the nonrandomized studies revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes systematic reviews, three RCTs, and observational studies. The relevant outcomes are OS,

symptoms, health status measures, QOL, and TRM, and morbidity. All three RCTs compared cyclophosphamide conditioning plus autologous HCT with cyclophosphamide alone. Patients in the RCTs were adults <60 years of age with a maximum duration of disease of five (5)-years, modified Rodnan skin scores (mRSS) >15, and internal organ involvement. Patients with severe and irreversible organ involvement were excluded from the trials. Short-term results of the RCTs show higher rates of adverse events and TRM among patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, long-term improvements (four years) in overall mortality and clinical outcomes such as mRSS and forced vital capacity (FVC) in patients receiving HCT compared with patients receiving cyclophosphamide alone were consistently reported in all RCTs. Due to sample size limitations in two of the three RCTs, statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals with systemic lupus erythematosus (SLE) who receive HCT, the evidence includes a systematic review and case series. The relevant outcomes are OS, symptoms, QOL, and TRM and morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (n=50) reported an overall five (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.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data and a case series. The relevant outcomes are OS, symptoms, QOL, and TRM and morbidity. The registry included 50 patients with juvenile idiopathic or rheumatoid arthritis. The overall drug-free remission rate was approximately 50% in the registry patients and 69% in the smaller case series. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes a recent observational study and case reports. Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and 2 meta-analyses. Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high. The meta-analyses revealed that HCT may improve hemoglobin A_{1c} and C-peptide levels compared with baseline values and compared with insulin. One meta-analysis found that HCT is more effective in patients with type 1 diabetes compared with type 2 diabetes, and when the treatment is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes; those factors are heterogeneity in the stem cell types, cell number infused, and

infusion methods. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes two RCTs,small retrospective studies, and case series. The relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. The RCT was conducted on patients with Crohn disease. At one year follow-up, one patient in the control group and two patients in the HCT group achieved remission. Data are needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

DEFINITIONS

NA

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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:

Procedure Codes								
38204	38205	38230	38240	S2140	S2142			

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Covered when medically necessary:

Procedure Codes								
38206	38207	38208	38209	38210	38211	38212	38213	38214
38215	38232	38241	S2150					

ICD-10-CM Diagnosis Code	Description
M34.0	Progressive systemic sclerosis
M34.1	CR(E)ST syndrome
M34.2	Systemic sclerosis induced by drug and chemical
M34.81	Systemic sclerosis with lung involvement
M34.82	Systemic sclerosis with myopathy
M34.83	Systemic sclerosis with polyneuropathy
M34.89	Other systemic sclerosis
M34.9	Systemic sclerosis, unspecified

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POLICY HISTORY

MP 9.053	**01/01/2020 Administrative Update.** FEP Variation information updated.
	04/07/2020 Consensus Review. Minor changes to reflect BCBSA Policy. No change to policy statement. References reviewed. No coding changes.
	05/21/2021 Consensus Review. No change to policy statement. References and Coding Reviewed.
	02/16/2022 Consensus Review. No changes to policy statement. References, background, and rationale updated. Coding reviewed.
	02/24/2023 Consensus Review. No changes to policy statement. References updated. Coding reviewed**.**
	03/13/2024 Consensus Review. No changes to policy statement. References updated. Coding reviewed with no coding changes.
	01/23/2025 Consensus Review. No changes to policy statement. References updated. Coding reviewed with no coding changes.
	02/05/2026 Consensus Review. No changes to policy statement. Removed benefit variations. Updated policy formatting, cross-references, product variations, background, rationale, disclaimer, and references. No coding changes.