

Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Systemic sclerosis/scleroderma

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) as a treatment of systemic sclerosis/scleroderma if **ALL** of the following conditions are met to be **eligible for coverage**:**

- Adult individuals less than 60 years of age with diagnosis of systemic sclerosis/scleroderma; **AND**
- Documented maximum duration of condition of 5 years; **AND**
- Documented modified Rodnan Scale Scores greater than or equal to 15; **AND**
- Medical records support internal organ involvement indicated by **ANY** of the following findings:
 - Pulmonary:
 - Diffusing capacity of carbon monoxide (DLCo) less than 80% of predicted value; **OR**
 - Decline of forced vital capacity (FVC) of greater than or equal to 10% in last 12 months; **OR**
 - Pulmonary fibrosis; ground glass appearance on high resolution chest CT; **OR**
 - Renal: scleroderma related renal disease; **AND**
- None of the following exclusion criteria are documented in the medical record (individuals with internal organ involvement demonstrated by **ANY** of the following measurements should not be considered for autologous HCT):
 - Cardiac:
 - Left ventricular ejection fraction less than 50%; **OR**
 - Tricuspid annular plane systolic excursion less than 1.8 cm; **OR**
 - Pulmonary artery systolic pressure greater than 40 mm Hg; **OR**

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- Mean pulmonary artery pressure greater than 25 mm Hg; **OR**
- Pulmonary:
 - DLCo less than 40% of predicted value; **OR**
 - FVC less than 45% of predicted value; **OR**
- Renal: creatinine clearance less than 40 ml/minute; **AND**
- History of less than 6 months treatment with cyclophosphamide; **AND**
- No documented active gastric antral vascular ectasia; **AND**
- Documented progression of disease despite treatment with immunosuppressive therapies like mycophenolate mofetil

Notes

- *Medical records will need to be provided, including but not limited to history of disease and previous treatment, recent Modified Rodnan Scale Score, pulmonary function testing (PFT) including diffusing capacity of carbon monoxide (DLCo) and serial forced vital capacity (FVC) measurements, high resolution chest CT report, renal function and heart testing reports.*
- *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.*
- *Modified Rodnan Scale Score: This score consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, (right and left separately), fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. These individual values are added and the sum is defined as the total skin score.*

Multiple sclerosis

Based on review of available data, the Company may consider autologous HCT (aHCT) for the treatment of multiple sclerosis when **ALL** of the following criteria are met to be **eligible for coverage:****

- Request is for a single aHCT for treatment-refractory relapsing-remitting multiple sclerosis (RRMS) with substantial breakthrough disease activity; **AND**
- The individual is between 18 to 45 years old; **AND**
- Disease duration is less than or equal to 10 years; **AND**
- The individual has a functional status with EDSS score between 2.0 (minimal disability in one functional system) to 5.5 (ambulatory without aid or rest for approximately 100 meters); **AND**
- Documented disease progression or continued activity despite treatment with disease-modifying therapy (DMT), evidenced by **BOTH** of the following:
 - Highly active disease evidenced by **ANY** of the following:

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- Two or more clinical relapses at separate times but within the previous 12 months; **OR**
- One clinical relapse and one or more magnetic resonance imaging (MRI) lesions typical for MS (T2-hyperintense or gadolinium-enhancing), with new MRI lesion occurring at a separate time than the clinical relapse but both occurring within the previous 12 months; **AND**
- Treatment failure evidenced by ALL of the following:
 - 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 disease-modifying therapy (DMT); **AND**
 - 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**
 - At least 1 of those episodes must occur after treatment with a high-efficacy disease-modifying therapy (DMT) (e.g., Alemtuzumab, Natalizumab, Cladribine, Ofatumumab, Ocrelizumab); **AND**
- The individual does not have medical comorbidities that would increase the risk of the procedure.

When Services Are Considered Not Medically Necessary

The use of autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma when patient selection criteria are not met is considered to be **not medically necessary**.**

The use of autologous hematopoietic cell transplantation (aHCT) as a treatment of multiple sclerosis when patient selection criteria are not met, including primary progressive or secondary progressive forms of multiple sclerosis and repeat aHCT, is considered to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous or allogeneic hematopoietic cell transplantation as a treatment of autoimmune diseases, including, but not limited to, the following to be **investigational**:*

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

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma and multiple sclerosis to be **investigational**.*

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Policy Guidelines

Kurtzke's Expanded Disability Status Scale (EDSS)

0 Normal neurologic exam

1.0 No disability, minimal signs in one functional system

2.0 Minimal disability in one functional system

2.5 Minimal disability in two functional systems

3.0 Moderate disability in one functional system, or mild disability in three or four functional systems though fully ambulatory

3.5 Fully ambulatory but with moderate disability in three or four functional systems

4.0 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability. Able to walk without aid or rest some 500 meters

4.5 Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability. Able to walk without aid or rest for some 300 meters

5.0 Ambulatory without aid or rest for about 200 meters; disability severe enough to preclude full daily activities (e.g. to work full day without special provisions)

5.5 Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities

6.0 Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting

6.5 Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting

Background/Overview

Autoimmune Disease Treatment

Immune suppression is a common treatment strategy for many autoimmune diseases, particularly rheumatic diseases (eg, rheumatoid arthritis [RA], systemic lupus erythematosus [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 a severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT). The primary concept underlying the use of HCT for these diseases is this: ablating and “resetting” the immune system can alter the disease process by inducing a sustained remission that possibly leads to cure.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation 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.

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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 6. 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 (eg, 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. Reduced-intensity conditioning 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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Most individuals with autoimmune disorders respond to conventional drug therapies; however, conventional drug therapies are not curative and a proportion of individuals suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is in this group of individuals with a severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

Summary of Evidence

For individuals with multiple sclerosis who receive hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs), systematic reviews, a network meta-analysis, and several nonrandomized studies. 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. A network meta-analysis comparing AHSCT with other stem cell-based and non-stem cell therapies found AHSCT favored for EDSS change, although the analysis was limited by mixed stem cell types, small transplant arms, and indirect comparisons. A prospective phase II trial using a modern conditioning regimen reported event-free survival of 60% at 3 years and no treatment-related mortality. 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, although TRM rates have declined with the use of modern conditioning regimens. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes systematic reviews, 3 RCTs, and observational studies. Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. All 3 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 5 years, modified Rodnan skin score (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 (4 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 2 of the 3 RCTs, statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with systemic lupus erythematosus (SLE) who receive HCT, the evidence includes a systematic review and case series. 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 5-year survival rate of 84% and the probability of disease-free survival (DFS) was 50%. 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 juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data and a case series. 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 that the technology results in an improvement in the net health outcome.

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

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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 (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 2 RCTs and small retrospective studies and case series. Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. The RCT was conducted on patients with Crohn disease. At 1-year follow-up, 1 patient in the control group and 2 patients in the HCT group achieved remission. Data are needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

2026 Clinical Input

Clinical input was sought to help determine whether the use of autologous hematopoietic cell transplantation for individuals with multiple sclerosis would provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice in selected patients. In response to requests, clinical input was received from 3 physician-level respondents, all identified by the American Academy of Neurology.

For individuals with relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis with ongoing inflammatory disease activity who receive autologous hematopoietic cell transplantation, clinical input unanimously supports that this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected individuals. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy (formerly the American Society for Blood and Marrow Transplantation) published consensus guidelines on the use of hematopoietic cell transplantation (HCT) to treat specific conditions in and out of the clinical trial setting. Table 1 summarizes recommendations for specific indications addressed in this guideline.

Table 1. Recommendations for the Use of HCT to Treat Autoimmune Diseases

Indications for HCT in Pediatric Patients (Generally <18 y)	Allogeneic HCT^a	Autologous HCT^a
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Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other autoimmune and immune dysregulation disorders	R	N
Indications for HCT in Adults >18 y		
Multiple sclerosis	N	C
Systemic sclerosis	N	S
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn disease	N	D
Polymyositis-dermatomyositis	N	D

HCT: hematopoietic cell transplantation.

^a “Standard of care (**S**): This category includes indications that are well defined and are generally supported by evidence in the form of high-quality clinical trials and/or observational studies (e.g., through CIBMTR or EBMT).”

“Standard of care, clinical evidence available (**C**): This category includes indications for which large clinical trials and observational studies are not available. However, HCT/immune effector cell therapy (IECT) has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as ‘Standard of Care’.”

"Standard of care, rare indication (**R**): Indications included in this category are rare diseases for which clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. However, single-center or multicenter or registry studies in relatively small cohorts of patients have shown HCT/IECT to be effective treatment with acceptable risks of morbidity and mortality. For patients with diseases in this category, HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits."

“Developmental; (**D**): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT/IECT to be a promising treatment option. HCT/IECT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as ‘Standard of Care, Clinical Evidence Available’ or ‘Standard of Care’.”

“Not generally recommended (**N**): HCT/IECT is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT/IECT. However, this

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recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial."

European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and International Society for Cell and Gene Therapy (ISCT)

Updated guidelines and recommendations (2019) noted one Grade I recommendation for autologous hematopoietic stem cell transplantation (aHSCT):

- "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 [reasonably well defined and results compare favorably/ or are superior to those of non-transplant], Grade I [evidence from at least one well-executed randomized trial]).

The guidelines indicate that the greatest benefit is observed in individuals who are younger than 45 years, have had disease for less than 10 years, maintain ambulatory function ($EDSS \leq 5.5$), and have evidence of active inflammatory disease. The recommendation is based on evidence from registry studies and a randomized trial, with emphasis on careful patient selection.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There are numerous autoimmune diseases, and the Centers for Medicare & Medicaid Services has not issued a national coverage determination for stem cell transplantation for each disease. A general national coverage determination for stem cell transplantation (110.23; formerly 110.8.1) states as listed in Table 2.

Table 2. Nationally Covered and Noncovered Indications for HCT

Covered and Noncovered Indications
Nationally covered indications
<i>Allogeneic HCT</i>
"Effective...1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary"
"Effective...1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome"

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Covered and Noncovered Indications

"Effective...2024, allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes who have prognostic risk scores of: ≥ 1.5 (intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or ≥ 4.5 (high or very high) using the International Prognostic Scoring System-Revised (IPSS-R), or ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M)"

Autologous HCT

"Effective...1989, [autologous HCT] is considered reasonable and necessary ... for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or,
- Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor."

"Effective...2000, single [autologous HCT] is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function."

"Effective...2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with [autologous HCT] is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%."

Nationally noncovered indications

Allogeneic HCT

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Covered and Noncovered Indications

"Effective...1996, through January 26, 2016, allogeneic [HCT] is not covered as treatment for multiple myeloma."

Autologous HCT

"Insufficient data exist to establish definite conclusions regarding the efficacy of [autologous HCT] for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of [autologous HCT]) for patients with multiple myeloma;
- Effective...2000, non primary AL amyloidosis; and,
- Effective...2000 through March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, [autologous HCT] is not considered reasonable and necessary...and is not covered under Medicare."

HCT: hematopoietic cell transplantation.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT06228781	Autologous Hematopoietic Stem Cell Transplantation for Refractory Multiple Sclerosis	20	Jan 2029
NCT07284641	Hematopoietic Stem Cell Transplantation (HSCT) for Common Variable Immunodeficiency (CVID) and Other Autoimmune Manifestations of Primary Immune Regulatory Disorders (PIRD)	25	Dec 2031

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02674217	Outpatient Hematopoietic Grafting in Patients with Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: a Feasibility Study	1000	Dec 2025
NCT03477500	Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients with Relapsing Remitting Multiple Sclerosis (RAM-MS)	100	Mar 2028
NCT04047628	A Multicenter Randomized Controlled Trial of Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Treatment-Resistant Relapsing Multiple Sclerosis (ITN077AI)	156	Oct 2029
NCT03219359	Maintenance in Autologous Stem Cell Transplant for Crohn's Disease (MASCT - CD)	50	Oct 2028
NCT00716066	High-Dose Immunosuppressive Therapy Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) + Thymoglobulin Followed by Syngeneic or Autologous Hematopoietic Cell Transplantation for Patients With Autoimmune Neurologic Diseases	53	Jan 2030
NCT05029336	Autologous Stem Cell Transplant (ASCT) for Autoimmune Diseases	20	May 2031
NCT03000296	Autologous Unselected Hematopoietic Stem Cell Transplantation for Refractory Crohn's Disease	50	Dec 2024
NCT04464434	Upfront Autologous Hematopoietic Stem Cell Transplantation Versus Immunosuppressive Medication in Early Diffuse Cutaneous Systemic Sclerosis: an International Multicentre, Open-label, Randomized Con-trolled Trial	50	Oct 2030
<i>Unpublished</i>			
NCT03069170 ^a	Safety and Efficacy of Immuno-Modulation and Autologous Bone-Marrow Derived Stem Cell Transplantation for the Treatment of Multiple Sclerosis	50	Jan 2021

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03113162	Evaluation of the Safety and Efficacy of Reduced-Intensity Immunoablation and Autologous Hematopoietic Stem Cell Transplantation (AHSCT) in Multiple Sclerosis	15	May 2022
NCT00750971	An Open-Label, Phase II Multicenter Cohort Study of Immunoablation with Cyclophosphamide and Antithymocyte-Globulin and Transplantation of Autologous CD34-Enriched Hematopoietic Stem Cells versus Currently Available Immunosuppressive /Immunomodulatory Therapy for Treatment of Refractory Systemic Lupus Erythematosus	30	Aug 2020
NCT01895244	High-dose Chemotherapy and Transplantation of 43+ Selected Stem Cells for Progressive Systemic Sclerosis - Modification According to Manifestation	44	Jun 2024

NCT: national clinical trial.

^a Denotes industry sponsored or co-sponsored trial.

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Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant* **55**, 283–306 (2020). <https://doi.org/10.1038/s41409-019-0684-0>

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12/06/2001	Medical Policy Committee review
01/28/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review
06/28/2004	Managed Care Advisory Council approval. Format revision. No substance change to policy.
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged.
08/06/2008	Medical Director review
08/20/2008	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility. Title changed.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility.
07/07/2011	Medical Policy Committee approval
07/20/2011	Medical Policy Implementation Committee approval. Added indications of juvenile idiopathic arthritis and diabetes mellitus to policy statement as investigational.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding update
08/01/2013	Medical Policy Committee review

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08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Chronic inflammatory demyelinating polyneuropathy added as investigational.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. The word stem removed from title and body of policy.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Policy statement for systemic sclerosis was changed from “investigational” to “eligible for coverage” with criteria.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. No change to coverage.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. No active gastric antral vascular ectasia was added to patient selection criteria statement.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. No change to coverage.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. No change to coverage.
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2025	Medical Policy Committee review
12/10/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2026	Coding update.
08/06/2026	Medical Policy Committee review
08/12/2026	Medical Policy Implementation Committee review
08/20/2026	Medical Quality Management Committee approval. Policy statement for multiple sclerosis was changed from investigational to medically necessary with criteria.

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“The use of autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma when patient selection criteria are not met is considered to be not medically necessary” was changed to not medically necessary from investigational. Added policy guidelines.

Next Scheduled Review Date: 08/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

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whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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.

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NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.