Hematopoietic Cell Transplantation for Autoimmune Diseases

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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.

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.*

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

Patient Selection Criteria

Coverage eligibility will be considered when **all** of the following criteria are met:

- Adult patients <60 years of age; AND
- Maximum duration of condition of 5 years; AND
- Modified Rodnan Scale Scores ≥15; AND
- Internal organ involvement indicated by the following measurements:
    - 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 CT; OR
    - Renal: scleroderma related renal disease; AND
- The individual does not have the following internal organ involvement indicated by the following measurements:
    - Cardiac: left ventricular ejection fraction < 50%; tricuspid annual 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; AND
- History of < 6 months treatment with cyclophosphamide; AND

- 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.

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:***

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

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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 **investigational.***

Background/Overview

Autoimmune Disease Treatment

Immune suppression is a common treatment strategy for many of these diseases, particularly rheumatic diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, 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 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

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients 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.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, 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. 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, 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 GVH disease.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA 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

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

For individuals with multiple sclerosis who receive HCT, the evidence includes 2 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. One RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging 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. 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 3 RCTs and observational studies. The 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, maximum duration of disease of 5 years, with modified Rodnan skin scores >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 clinical outcomes such as modified Rodnan skin scores and forced vital capacity, as well as overall mortality 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 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 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 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 case reports. The 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 the effects of the technology on health outcomes.
For individuals with type 1 diabetes who receive HCT, the evidence includes case series and a meta-analysis of 22 studies. The 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. A meta-analysis further revealed that HCT is more effective in patients with type 1 diabetes compared with type 2 diabetes and when HCT 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 the effects of the technology on health outcomes.

For individuals with other autoimmune diseases (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 1 RCT and small retrospective studies. The 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 the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American Academy of Neurology et al

A review of guidelines from the AAN and the American College of Rheumatology found no mention of stem cell transplantation for multiple sclerosis (MS), lupus, rheumatoid arthritis, or juvenile idiopathic arthritis. The AAN (2016) affirmed the statements in the Myasthenia Gravis Foundation of America's consensus guidelines for the management of myasthenia gravis. The consensus guidelines did not discuss HCT as a therapeutic option. The AAN (2018) published guidelines on the use of disease-modifying medications for patients with MS; the AAN does not discuss HCT as a therapeutic option for MS.

American Society for Blood and Marrow Transplantation

The American Society for Blood and Marrow Transplantation (2015) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial setting. Table 1 lists guidelines for specific indications addressed in this evidence review.

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

Indications for HCT in Pediatric Patients (Generally <18 y)	Allogeneic HCT	Autologous HCT

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	D
Systemic sclerosis	N	D
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn disease	N	D
Polymyositis-dermatomyositis	N	D

D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication.

The American Society for Blood and Marrow Transplantation (2019) position statement on autologous HCT (AHCT) for treatment-refractory relapsing multiple sclerosis "recommends revising the indication for AHCT for MS in 'standard of care, clinical evidence available'" for patients "who have prognostic factors that indicate a high risk of future disability."

European League Against Rheumatism

The European League against Rheumatism (2017) convened a task force to update recommendations for the treatment of systemic sclerosis. The task force consisted of clinical experts from Europe and the United States. In regard to HCT, the task force concluded: "HSCT should be considered for the treatment of selected patients with rapidly progressive systemic sclerosis at risk of organ failure." However, due to the high risk of treatment-related adverse events and mortality, "careful selection of patients with systemic sclerosis for this kind of treatment and the experience of the medical team are of key importance." (Strength of recommendation: A)

American College of Gastroenterology
The American College of Gastroenterology (2018) published clinical guidelines on the management of adults with Crohn's disease. The use of HCT for the treatment of Crohn's disease was not discussed in this guideline.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There are numerous ADs, 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
Allogeneic HCT
"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"
"Effective...2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study"
Autologous HCT
"Effective...1989, [autologous HCT] is considered reasonable and necessary … for the following conditions and is covered under Medicare for patients with:

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Covered and Noncovered Indications
1. Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched; 2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response; 3. Recurrent or refractory neuroblastoma; or, 4. 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

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: a. Acute leukemia not in remission; b. Chronic granulocytic leukemia; c. Solid tumors (other than neuroblastoma); d. Up to October 1, 2000, multiple myeloma; e. Tandem transplantation (multiple rounds of [autologous HCT]) for patients with multiple myeloma; f. Effective...2000, non primary AL amyloidosis; and, g. 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 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
Ongoing			
NCT00278629	Non-myeloablative Autologous Hematopoietic Stem Cell Transplantation in Patients With Chronic	80	Jul 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Inflammatory Demyelinating Polyneuropathy: A Phase II Trial		
NCT03000296	Autologous Unselected Hematopoietic Stem Cell Transplantation for Refractory Crohn's Disease	50	Mar 2020
NCT03562208[a]	Autologous Bone Marrow Transplant in Chronic Insulin Dependent Diabetic Patients Phase II Clinical Trial	100	Jun 2020
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
NCT02674217	Outpatient Hematopoietic Grafting in Patients with Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: a Feasibility Study	200	Dec 2020
NCT03069170	Safety and Efficacy of Immuno-Modulation and Autologous Bone-Marrow Derived Stem Cell Transplantation for the Treatment of Multiple Sclerosis	50	Jan 2021
NCT01445821	Randomized Study of Different Non-myeloablative Conditioning Regimens with Hematopoietic Stem Cell Support in Patients with Scleroderma (ASSIST-IIb)	160	Sep 2021

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
NCT01895244	High-dose Chemotherapy and Transplantation of 43+ Selected Stem Cells for Progressive Systemic Sclerosis - Modification According to Manifestation	44	Sep 2022
NCT03477500	Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients with Relapsing Remitting Multiple Sclerosis	100	Mar 2024
NCT00273364	Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study	110	Sep 2024
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 2028
Unpublished			
NCT02516124	Autologous Stem Cell Transplantation for Progressive Systemic Sclerosis: a Prospective Non-interventional Approach Across Europe (NISSC) for the Autoimmune Diseases Working Party of the EBMT	82	Jan 2018

NCT: national clinical trial.
[a] denotes industry sponsorship

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Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050
Original Effective Date: 01/28/2002
Current Effective Date: 01/11/2021

Policy History

Original Effective Date: 01/28/2002
Current Effective Date: 01/11/2021

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
05/1820/04	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
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review

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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.
Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 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, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	E08.3211-E08.3299, E08.3311-E08.3399, E08.3411-E08.3499, E08.3511-E08.3599, E08.37X1-E08.37X9, E09.3211-E09.3299, E09.3311-E09.3399, E09.3411-E09.3499, E09.3511-E09.3519, E09.3521-E09.3599, E09.37X1-E09.37X9, E10.10-E10.29, E10.311-E10.319, E10.3211-E10.3299, E10.3311-E10.3399, E10.3411-E10.3499, E10.3511-E10.3599, E10.36-E10.39, E10.37X1-E10.37X9, E10.40-E10.49, E10.51-E10.59, E10.610-E10.649, E10.65-E10.9, E11.00-E11.01, E11.21-E11.29, E11.311-E11.319, E11.3211-E11.3299, E11.3311-E11.3399, E11.3411-E11.3499, E11.3511-E11.3599, E11.36-E11.39, E11.37X1-E11.37X9, E11.40-E11.49, E11.51-E11.59, E11.610-E11.649, E11.65-E11.9 E13.00-E13.29, E13.311-E13.359, E13.3211-E13.3399,

	E13.3411-E13.3499, E13.3511-E13.3599, E13.36-E13.39, E13.37X1-E13.37X9, E13.40-E13.49, E13.51-E13.59, E13.610-E13.618, E13.620-E13.628, E13.630-E13.638, E13.641-E13.649, E13.65-E13.69, E13.8-E13.9, G35, M05.00-M05.079, M05.09-M05.10, M05.111-M05.179, M05.19-M05.20, M05.211-M05.279, M05.29, M05.30, M05.311-M05.379, M05.39, M05.60, M05.611-M05.679, M05.69, M06.1, M06.4, M08.00, M08.011-M08.079, M08.08-M08.09 M08.20, M08.211-M08.279, M08.28-M08.29, M08.3, M08.40, M08.411-M08.479, M08.48, M08.80, M08.811-M08.879, M08.88-M08.90, M08.911-M08.979, M08.98-M08.99, M12.00, M12.011-M12.079, M12.08-M12.09, M32.0, M32.10-M32.19, M32.8-M32.9, M34.0-M34.2, M34.81-M34.89, M34.9 Add the codes eff 10/1/2020: M05.7A, M05.8A, M06.0A, M06.8A, M08.0A, M08.2A, M08.4A, M08.9A

*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 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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.