Anthem FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE

Medical Policy

Subject:	~~Mesenchymal~~ Non-Hematopoietic Adult Stem Cell Therapy ~~for the Treatment of Joint and Ligament Disorders, Autoimmune, Inflammatory and Degenerative Diseases~~		
Document#:	TRANS.00035	**Publish Date:**	09/25/2019~~04/24/2019~~
Status:	Revise~~d~~ed~~wed~~	**Last Review Date:**	0~~8~~3/2~~2~~1~~1~~/2019

Description/Scope

This document addresses the use of ~~mesenchymal~~ non-hematopoietic adult stem cell ~~(MSC)~~ therapy for the prevention and treatment of health conditions, including but not limited to, ~~of joint and ligament disorders~~orthopedic, ~~due to injury or degeneration, as well as~~ autoimmune, inflammatory, and degenerative ~~diseases~~conditions. Stem cell therapy involves the use of stem cells (usually in the form of an injection or infusion) to repair damaged cells and body tissues. Examples of non-hematopoietic adult stem cells (also called somatic stem cells or tissue-specific stem cells) include, but are not limited to, mesenchymal (also called stromal stem cells), neural, epithelial, epidermal, and follicular. Extraction sources of non-hematopoietic adult stem cells include, but are not limited to, blood, bone marrow, adipose tissue, umbilical cords, placentas, and amniotic fluid.

~~MSC therapy refers to the procurement (through autologous or cadaveric allogeneic harvest) of MSCs, processing (such as, concentration and/or expansion of cells) and subsequent infusion or implantation of the MSCs into various anatomic areas to promote healing or regeneration of damaged tissue and bone.~~

Notes:

- This document does *not* address hematopoietic adult stem cell therapy.
- This document does *not* address mesenchymal stem cells ~~MSC~~ therapy for cardiac conditions (please refer to MED.00117 Autologous Cell Therapy for the Treatment of Damaged Myocardium) or mesenchymal stem cells ~~MSC~~ as an adjunct to spinal fusion or surgical procedures involving bone.
- For additional information on related topics, please see the following ~~related documents~~:
  - MED.00110 Growth Factors, Silver-based Products and Autologous Tissues for Wound Treatment, ~~and~~ Soft Tissue Grafting, and Regenerative Therapy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- SURG.00011 Allogeneic, Xenographic, Synthetic and Composite Products for Wound Healing and Soft Tissue Grafting
- TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation
- TRANS.00036 Stem Cell Therapy for Peripheral Vascular Disease

Position Statement

Investigational and Not Medically Necessary:

~~Mesenchymal~~ Non-hematopoietic adult stem cell therapy including but not limited to mesenchymal stem cell therapy is considered **investigational and not medically necessary** for the prevention and treatment of all conditions including but not limited to orthopedic, autoimmune, inflammatory and degenerative conditions.~~joint and ligament disorders caused by injury or degeneration as well as autoimmune, inflammatory and degenerative diseases.~~

Rationale

Mesenchymal Stem Cell (MSC) Therapy

~~***Mesenchymal Stem Cells***~~

~~*Stem cells are specialized cells that are capable of renewing themselves through cell division and differentiating into multi-lineage cells. These cells are categorized as embryonic stem cells, induced pluripotent stem cells and adult stem cells.*~~

~~*Mesenchymal stem cells (MSCs), also known as multipotent mesenchymal stromal cells, are adult stem cells that can be isolated from animal and human sources. Human MSCs (hMSCs) are non-hematopoietic, multipotent stem cells that can differentiate into a variety of cell types. The four major cell types are osteocytes (bone), myocytes (muscle), adipocytes (fat) and chondrocytes (cartilage). MSCs have immunomodulatory properties and secrete cytokines. MSCs remain in a quiescent (non-proliferative) state during most of their lifetime, pending stimulation by the signals triggered by tissue renewal, damage and remodeling processes. Because of their multi-lineage*~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~*potential, immunomodulatory properties and ability to secrete anti-inflammatory molecules, MSCs may have the potential to treat various chronic autoimmune, inflammatory and degenerative diseases (Ullah, 2015).*~~

~~*MSCs have been isolated from various sites, including dermis, amniotic fluid, adipose tissue, endometrium, dental tissue, synovial fluid and umbilical cord tissue. Additionally, researchers have been able to culture hMSCs in specific media.*~~

~~*The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271.*~~

Orthopedic Conditions

Surgical repair of tendon, ligament, cartilage and bone defects has been the standard therapy, which may be augmented by autologous grafts, cadaveric allografts or synthetic grafts. However, there have been several limitations to the use of grafts in orthopedic therapy. For instance, autologous graft sources may be hampered by comorbid conditions, limited sites suitable for harvesting, and the potential of graft failure. Alternative regenerative technologies, which could minimize or avoid these issues while regenerating damaged tissue~~,~~ are being actively investigated.

Various agents and techniques to procure and expand mesenchymal stem cells (MSCs) to achieve sufficient numbers for infusion or implantation are being studied and implemented in proprietary processes for diverse orthopedic indications. The processing of cadaveric allogeneic donor MSCs typically involves proprietary techniques and a combination of MSCs with various transport mediums. In addition, it is not clear that MSCs procured from different tissue sources are functionally equivalent. There is a paucity of randomized controlled trials in humans to support the safety and efficacy of using MSC therapy for orthopedic indications, including cartilage and ligament repair and bone regeneration.

At this time, the medical evidence supporting the use of MSCs for orthopedic indications involving the cartilage or ligaments is limited to pre-clinical studies, case series and small, randomized controlled trials. The efficacy and safety of these novel therapies have not been established in well-designed, large randomized controlled trials with long-term follow-up.

Several preclinical studies have been conducted to evaluate the effectiveness of MSCs in tissue regeneration. Caudwell and colleagues (2014) conducted a systematic review of preclinical studies using MSC and scaffolds in the treatment of knee ligament regeneration. The authors concluded, based on their investigation of 21 articles, that preclinical evidence of ligamentous regeneration with MSC and scaffold use was established, but limited clinical evidence exists to support recently developed scaffolds. Furthermore, no consensus has been reached on the nature of scaffold material that is most suitable.

A systematic review of preclinical studies published by Haddad and colleagues (2013) reviewed 19 articles that had used cell-based approaches to tissue-engineered menisci; cell types used included MSCs amongst others. The authors stated that, "The diversity of studies made it impossible to adhere to full guidelines or perform a meta-analysis," but concluded that overall superior tissue integration and favorable biochemical properties were observed in regenerated tissues when compared to acellular techniques.

In 2011, Wakitani reported long-term follow-up of 45 articular cartilage repairs utilizing autologous bone marrow-derived MSCs (BMSCs) in 41 individuals. With a mean follow-up of 75 months (5 to 137 months), the authors reported no tumors or infections observed in the individuals who were treated between 1998 and November 2008. Although considered a low risk, the authors concluded that, "The possibility that the cells transplanted in joints move and injure other parts of the body remains unresolved" (Wakitani, 2011)

A pilot study was conducted by Wakitani and colleagues (2004) using autologous bone MSC therapy to repair nine full-thickness cartilage defects in the patello-femoral joints of 3 individuals. The assessment of clinical symptoms were rated with the International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC score), with 0 being the worst and 100 being the best rating. IKDC scores improved for all 3 individuals during the follow-up period ranging from 7 to 20 months after receiving mesenchymal therapy. In all 3 cases, the investigators were unable to confirm the material covering the defects was in fact hyaline cartilage resulting from mesenchymal cell therapy.

In a systematic review by Longo and colleagues (2011), authors state that the use of MSC therapy for repair of tendon injuries is "At an early stage of development. Although these emerging technologies may develop into substantial clinical treatment options, their full impact needs to be critically evaluated in a scientific fashion."

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

In 2012, Lee and colleagues conducted a prospective, short-term comparative study to determine if knees with symptomatic cartilage defects treated with outpatient injections of MSCs and hyaluronic acid (HA; n=35) had better outcomes than an open-air implantation of MSCs (n=35). The outcome of interest was the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package and MRI results 1 year post-procedure. No adverse events ~~was~~ were reported and significant improvement was seen across several domains of the ICRS evaluation package at final follow-up (mean 24 months). Although MRI results were promising, authors acknowledge that the sensitivity of MRIs in lesion identification was only estimated at 45%. A shortcoming of this study, aside from the small sample size and short-term data, is the inability to distinguish the MSC effect on outcomes from the HA effect since the control group received neither.

In 2013, Wong and colleagues conducted a randomized controlled trial (RCT) evaluating 56 participants with unicompartmental, osteoarthritic, varus knees enrolled in either the stem cell recipient group (n=28) or the control group (n=28). The treatment group received intra-articular injections of MSCs and HA 3 weeks post-surgical intervention and the control group received HA only. Participants were re-evaluated at 6-, 12- and 24-month follow-up. The treatment group showed significantly better scores than the control group in Tegner (p=0.021), Lysholm (p=0.016), and IKDC (p=0.01) scores. MRI scans at 1 year follow-up showed significantly better Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores (p<0.001). Authors concluded that the investigated intervention demonstrated efficacy in short-term clinical and MOCART outcomes. However, data was insufficient to demonstrate clinical improvement and long-term efficacy and safety data.

In 2014, Vangsness and colleagues performed the first randomized, double-blind controlled clinical trial investigating the efficacy and safety of MSCs in the treatment of an orthopedic indication. A total of 55 participants from seven institutions who were eligible for a partial medial meniscectomy were enrolled and randomized into one of three treatment groups: Group A (n=17) received an injection of $50x10^6$ allogeneic MSCs; Group B (n=18), received $150x10^6$ MSCs; and the control group (n=19) received an HA injection only. Outcomes of interest at intervals over the 2-year follow-up period included safety, meniscus regeneration, overall knee joint condition and clinical outcomes. No adverse events occurred and investigators found a significant increase in meniscal volume (p=0.022; determined by MRI) in both Groups A and B; no participants met the threshold for increased volume (15%) in the control group. Furthermore, both groups A and B reported a significant reduction in pain compared to the control group. Results of this small, Phase I/II clinical trial are promising for use of MSCs in knee-tissue regeneration. Data from larger trials are needed to confirm the early results.

Vega and colleagues (2015) conducted a small, randomized, controlled trial comparing intra-articular injections of allogeneic bone marrow MSCs and HA in individuals with knee osteoarthritis (n=30). Each participant received either one injection of MSC or HA and were followed for 1 year. Assessed outcomes included evaluations of pain, disability, quality of life and articular cartilage quality as determined by MRI. The MSC group reported a medium to large treatment effect (effect size, 0.58-1.12) while the HA group reported a small treatment effect (effect size, 0.19-0.48). While the MSC group reported improved results over the HA group, it is noted that this is the first study to demonstrate the feasibility, safety and efficacy of the use of allogeneic MSCs in treating osteoarthritis. The authors note that further research is needed on how MSCs "relieve pain, promote regeneration, and become immune evasive."

Jo and colleagues (2017) reported the results of a 2-year follow-up study that evaluated the safety and effectiveness of intra-articular injections of adipose tissue-derived MCSs (AD-MCSs) for the treatment of osteoarthritis of the knee. A total of 18 subjects with osteoarthritis of the knee were enrolled (15 female; 3 male; mean age, 61.8 ± 6.6 years [range, 52-72 years]). Participants in the low-, medium-, and high-dose groups received an intra-articular injection of 1.0×10^7, 5.0×10^7, and 1.0×10^8 AD MSCs into the knee, respectively. Clinical and structural evaluations were conducted using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and measurements of the size and depth of the cartilage defect, signal intensity of regenerated cartilage, and cartilage volume MRI. No treatment-related adverse events were reported during the 2-year period. An intra-articular injection of autologous AD MSCs enhanced knee function, as measured with the WOMAC, Knee Society clinical rating system (KSS), and Knee injury and Osteoarthritis Outcome Score (KOOS), and decreased knee pain, as measured with the visual analog scale (VAS), for up to 2 years regardless of the cell dosage. However, statistical significance was seen primarily in the high-dose group. Clinical outcomes tended to decline after 1 year in the low- and medium-dose groups, whereas those in the high-dose group remained level until 2 years. The structural outcomes gauged with MRI also showed similar trends. The authors concluded that this study demonstrated the safety and efficacy of the intra-articular injection of AD-MSCs into the osteoarthritic knee over 2 years. The authors acknowledged that this study highlighted potential concerns about the durability of clinical and structural outcomes and encouraged larger randomized clinical trials.

In a randomized controlled trial, Centeno and colleagues (2018) compared a protocol of bone marrow concentrate (BMC) combined with platelet products to exercise therapy for moderate (grade II or III) knee osteoarthritis. A total of 48 participants were randomized to either receive image-guided injections of BMC containing mesenchymal stem cells and platelet products (n=26) or a home exercise therapy program (n=22). Outcome measurements included vital signs, physical exam and self-reporting. Those in the exercise group were allowed to cross over to

BMC injection therapy after 3 months. Participants in the injection and crossover groups received a pre-treatment injection, bone marrow aspiration, BMC with platelet injection, and a post-treatment injection. No serious adverse events were reported, and the most common complaint after treatment was pain (recurrent knee pain was treated with plasma injections at the discretion of the physician). At 3-months, the injection group (n=24) showed significant improvement over the exercise group (n=22) for lower extremity activity scale (LEAS) and KSS-knee scores, but there were no differences for visual analog scale (VAS) pain, KSS-function, SF-12, or range of motion. At 3 months, all participants in the exercise group crossed over to the injection therapy group; however, after 3 months, 4 withdrew voluntarily, 7 were withdrawn by the investigator, and 3 were withdrawn to have a total knee replacement. Outcome scores, except for SF-12 mental health, remained significantly improved in the injection and crossover participants at 2 years compared to baseline. The study was limited by its small size and limited follow-up with a crossover at 3 months.

Ha and colleagues (2019) conducted a systematic review assessing the efficacy of intra-articular MSCs in terms of clinical outcomes including pain and function and cartilage repair in individuals with osteoarthritis of the knee. Clinical outcomes were evaluated using clinical scores, and cartilage repair was assessed using magnetic resonance imaging and second-look arthroscopy findings. A total of 17 studies met the inclusion criteria: 6 randomized controlled trials; 8 prospective observational studies; and 3 retrospective case-control studies. Of the 17 studies, 1 used umbilical cord blood-derived MSCs, 2 used adipose tissue-derived MSCs, 6 used adipose tissue-derived stromal vascular fraction and 8 studies used bone marrow-derived MSCs. All studies except for 2 reported improved clinical outcomes at final follow-up or significantly better clinical outcomes in the MSC group. With regard to cartilage repair, 9 of 11 studies reported an improvement in the state of the cartilage on magnetic resonance imaging. A total of 6 of 7 studies reported the presence of repaired tissue on second-look arthroscopy. The authors concluded that in many cases, intra-articular MSCs improve pain and function in knee osteoarthritis at short-term follow-up (< 28 months), however, the evidence of efficacy of intra-articular MSCs on both cartilage repair and clinical outcomes remains limited.

~~In 2014, Vangsness and colleagues performed the first randomized, double-blind controlled clinical trial investigating the efficacy and safety of MSCs in the treatment of an orthopedic indication. A total of 55 participants from seven institutions who were eligible for a partial medial meniscectomy were enrolled and randomized into one of three treatment groups: Group A (n=17) received an injection of $50x10^6$ allogeneic MSCs; Group B (n=18), received $150x10^6$ MSCs; and the control group (n=19) received an HA injection only. Outcomes of interest at~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~intervals over the 2-year follow-up period included safety, meniscus regeneration, overall knee joint condition and clinical outcomes. No adverse events occurred and investigators found a significant increase in meniscal volume (p=0.022; determined by MRI) in both Groups A and B; no participants met the threshold for increased volume (15%) in the control group. Furthermore, both groups A and B reported a significant reduction in pain compared to the control group. Results of this small, Phase I/II clinical trial are promising for use of MSCs in knee tissue regeneration. Data from larger trials are needed to confirm the early results.~~

~~In a systematic review by Longo and colleagues (2011), authors state that the use of MSC therapy for repair of tendon injuries is "At an early stage of development. Although these emerging technologies may develop into substantial clinical treatment options, their full impact needs to be critically evaluated in a scientific fashion."~~

Although preclinical studies, case series, and small~~,~~ randomized trials suggest that MSC therapy may improve regeneration of bone or tissue in orthopedic indications, the lack of validated, comparable scoring, robust sample sizes and long-term follow-up data~~,~~ preclude definitive conclusions regarding the net health benefit of MSC therapy~~.~~ in the treatment of orthopedic conditions.

Neurodegenerative Diseases

Alzheimer's Disease

Kim and colleagues (2015) conducted a phase I clinical trial in individuals (n=9) with mild-to-moderate Alzheimer's disease to evaluate the safety and dose-limiting toxicity of stereotactic brain injection of human umbilical cord blood-derived MSCs (hUCB-MSCs). The low- (n=3) and high-dose (n=6) cohorts received a total of 3.0×10^6 cells/60 µL and 6.0×10^6 cells/60 µL, respectively, into the bilateral hippocampi and right precuneus. None of the study participants demonstrated serious adverse reactions during the 24-month follow-up period. During the 12-week follow-up period, the most frequent acute adverse event was wound pain from the surgical procedure (n=9), followed by headache (n=4), dizziness (n=3), and postoperative delirium (n=3). No dose-limiting toxicity was reported. The authors concluded that the administration of hUCB-MSCs into the hippocampus and precuneus by stereotactic injection was feasible, safe, and well tolerated but additional trials are warranted to determine treatment efficacy.

Amylotrophic lateral sclerosis (ALS)

Mazzini and colleagues (2003) evaluated the feasibility and safety of a method of intraspinal cord implantation of autologous MSCs in 7 participants (4 females and 3 males; range: 23–74 years, mean age 46.6 ± 16.8 years) with ALS. The group had severe functional impairment of the lower limbs and mild functional impairment of the upper limbs without signs of respiratory failure. Participants were monitored by clinical evaluation which included the Norris score, ALS-FRS scale, bulbar score, and MRC strength scale. Respiratory assessment included clinical evaluation, arterial blood gas analysis, pulmonary function tests and nocturnal cardio-respiratory monitoring. The neurophysiological assessments consisted of somatosensory evoked potentials (SEP) and EMG. The neuro-radiological assessment included MRI of the spinal cord and brain before and after gadolinium DTA infusion. A clinical psychologist conducted a psychological evaluation. None of the participants experienced severe adverse events such as death, respiratory failure or permanent post-surgical neurological deficits. Minor adverse events included intercostal pain (n=4) which was reversible after a mean period of 3 days (range: 1–6) after surgery, and leg sensory dysesthesia (n=5) which resolved after a mean period of 6 weeks (range: 1–8) following surgery. None of the participants manifested bladder and bowel dysfunction, or leg motor deficit. There were no anesthetic complications. MRI with gadolinium DTA infusion carried out at 3 and 6 months post implantation demonstrated no evidence of structural changes of the spinal cord or signs of abnormal cell proliferation when compared with the baseline. SEPs from tibial nerve stimulation demonstrated a mild delay of the central conduction time 3 days after surgery but this normalized within 1 month following transplantation. All of the participants showed a good acceptance of the procedure and no significant modifications of the quality of life or the psychological status were observed. In all of the participants, muscular strength (MRC scale) declined during the 6 months before transplantation. However, at the third month post stem cell implantation a trend towards a slowing down of the linear decline of muscular strength was evident in 4 participants in the proximal muscle groups of the lower limbs, while a mild increase in strength was observed in the same muscle groups of 2 participants. While the authors concluded that the study seemed to demonstrate MSC transplantation into the spinal cord of humans is safe and well tolerated by individuals with ALS, the authors stated that additional controlled studies are needed to evaluate the efficacy of stem cell therapy in the treatment of ALS.

Parkinson's Disease

Research exploring the feasibility of MSC transplantation as a treatment of Parkinson's disease is ongoing. In one study (NCT00976430), researchers investigated the safety and efficacy of autologous MSCs in treating advanced Parkinson's disease by harvesting and processing the stem cells from bone marrow and transplanting them via stereotactic techniques into the striatum of the subject. However, the study was terminated because an adequate number of participants could not be recruited in the set timeframe. Other studies exploring the use of MSCs as a

treatment of Parkinson's disease are ongoing but not yet completed or published. Information regarding these studies is available on the clinicaltrials.gov web site.

At this time, there is insufficient evidence from well-designed clinical trials to evaluate the clinical utility of MSC therapy in individuals with neurodegenerative diseases.

Autoimmune Diseases

Celiac Disease

Ciccocioppo and colleagues (2016) reported the results of a study that investigated the feasibility, safety, and efficacy of serial infusions of autologous bone marrow-derived MSCs in a 51-year-old woman with type II refractory celiac disease. MSCs were separated, expanded, and characterized according to standard protocols. The researchers monitored the participant's malabsorption indexes, mucosal architecture, and percentage of aberrant intraepithelial lymphocytes during study enrollment, at each infusion, and 6 months post treatment. Mucosal expression of interleukin (IL)-15 and its receptor was also monitored. The subject underwent 4 systemic infusions of 2×10^6 MSCs/kg body weight 4 months apart~~,~~ without adverse effects. During the treatment period, the participant experienced gradual and durable amelioration of her general condition, with normalization of stool frequency, body mass index, laboratory test results, and mucosal architecture. The expression of IL-15 and its receptor practically disappeared. At this time, there is insufficient evidence from well-designed clinical trials to evaluate the clinical utility of MSC therapy in individuals with celiac disease.

Multiple sclerosis

Harris and colleagues (2018) conducted a phase I open-label clinical trial investigating the safety and tolerability of autologous bone marrow MSC-derived neural progenitor cells for the treatment of progressive multiple sclerosis. Of the 20 participants in the study, 16 (80%) had secondary progressive multiple sclerosis. MSC-derived neural progenitor treatment was administered intrathecally in three separate doses of up to 1×10^7 cells per dose, spaced 3 months apart. The primary endpoint was to evaluate the safety and tolerability of the treatment. Expanded disability status scale (EDSS), timed 25-ft walk (T25FW), muscle strength, and urodynamic testing were employed to evaluate treatment response. The MSC-derived neural progenitor treatment was safe and well tolerated. The participants completed all 60 planned treatments without serious adverse effects. Approximately 85% of the participants experienced headaches and transient fever during the first 24 hours post the treatment. Post-treatment

disability score analysis showed improved median EDSS scores, suggesting possible efficacy. Positive trends were identified more frequently in the subset of individuals with secondary progressive multiple sclerosis. Following treatment, 70% of the participants demonstrated improved muscle strength and 50% of the participants had improved bladder function. The disease worsened in 2 participants and the condition of 3 individuals remained the same. The results of this study are limited by its small size and the lack of a sham placebo or active comparator.

In a triple-blind, placebo-controlled study, Fernandez and colleagues (2018), investigated the safety and feasibility of the use of adipose-derived MSCs for the treatment of secondary-progressive multiple sclerosis. The cell samples were obtained from consenting participants by lipectomy and subsequently expanded. Study participants were randomized 1:1:1 to an intravenous infusion of placebo or one of two dose-groups ($1x10^6$ cells/kg or $4x10^6$ cells/kg). The study was triple blinded (the treating physician, study participant and statisticians were unaware of treatment assignment). Participants were followed for 12 months. The researchers monitored safety using laboratory parameters, vital signs and spirometry. EDSS, MRI and other measures of possible treatment effects and adverse events were also recorded. A total of 34 subjects underwent lipectomy for adipose-derived MSC collection, were randomized and 30 were infused (11 placebo, 10 low-dose and 9 high-dose); 4 randomized participants were not infused due to karyotype abnormalities in the cell product. Measures of treatment effect demonstrated an inconclusive trend of efficacy. The mean EDSS score and the individual EDSS did not reflect any significant changes over the course of the study. Baseline MRI data was similar between the three groups. The researchers reported some non-statistically significant differences between the placebo and treatment groups for the evoked potentials parameters after 12 months of treatment. Tibial SEP central conduction time (N22-P39) and the motor evoked potential (MEP) central conduction time for the legs, reflected statistically significant diminishing latencies over time in placebo and the two treatment groups, but these differences were not statistically significant comparing placebo and both treatment groups. Visual evoked potential (VEP) and median nerve SEP (N13-N20) also demonstrated a trend of stabilization or amelioration of latencies over time in treatment groups, however, these differences did not reach statistical significance over the time. There were no significant changes in the cerebral spinal fluid from baseline to the 12-month follow-up. One serious adverse event was reported in the treatment arms (urinary infection, considered not related to study treatment). No other changes in safety parameters were reported. Although the results of the study did not demonstrate treatment efficacy, the authors found infusion of autologous adipose-derived MSCs safe and feasible in individuals with secondary-progressive multiple sclerosis.

Systemic Lupus Erythematosus (SLE)

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Wang and colleagues (2014) conducted a multicenter clinical trial to assess the safety and efficacy of allogeneic umbilical cord MSC transplantation (MSCT) in subjects with active and refractory SLE. Researchers recruited 40 individuals with active SLE from four clinical centers. Allogeneic umbilical cord MSCs were infused intravenously on days 0 and 7. The primary endpoints were safety profiles. The secondary endpoints included major clinical response (MCR), partial clinical response (PCR) and relapse. Each participant was re-assessed at 1, 3, 6, 9 and 12 months post MSC transplantation. Evaluations performed at the follow-up visits included a physical examination, determination of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, British Isles Lupus Assessment Group (BILAG) analysis, serologic studies and evaluation of organ function. A total of 39 subjects (39/40, 97.5%) underwent umbilical cord MSC infusions twice with an interval of 1 week, and 1 participant (1/40, 2.5%) was exempted from the second MSC infusion due to uncontrolled disease progression. The overall survival rate was 92.5% (37 of 40 subjects). Umbilical cord MSCT was well tolerated, and no adverse events related to the transplantation were observed. During the 12 months of follow-up, an MCR was achieved in 13 participants (32.5%) and 11 participants (27.5%) achieved a PCR. Three individuals (12.55%) experienced disease relapse at 9 months and 4 participants (16.7%) experienced disease relapse at 9 months after a prior clinical response. The SLEDAI scores decreased significantly at 3, 6, 9 and 12 months follow-up. Total BILAG scores decreased at 3 months and continued to decrease at subsequent follow-up visits. BILAG scores for hematopoietic, renal and cutaneous systems improved. Among participants with lupus nephritis, 24-hour proteinuria diminished after transplantation, with statistically significant differences at 9 and 12 months. Serum creatinine and urea nitrogen declined to the lowest level at 6 months, but these values slightly increased at 9 and 12 months in 7 relapse cases. Additionally, serum levels of albumin and complement 3 rose after MSCT, peaked at 6 months and then slightly declined by the 9- and 12-month follow-up examinations. Serum antinuclear antibody and anti-double-stranded DNA antibody diminished after MSCT, with statistically significant differences at 3-month follow-up examinations. The authors concluded that the study results demonstrate that umbilical cord MSCT is a safe and effective treatment for individuals with SLE, but a repeated MSC infusion may be necessary after 6 months to avoid disease relapse. The authors also acknowledge that limitations of the study include its lack of a randomized controlled design and the lack of uniformity amongst the condition of the study participants.

In 2015, Wang and colleagues reported the results of a study that investigated whether double transplantations of MSCs is superior to single transplantation. Of the 58 refractory SLE subjects enrolled in the study, 30 were randomly given single MSCT, and the other 28 were given double MSCT. Participants were followed to determine rates of survival, disease remission, and relapse, as well as transplantation-related adverse events. Serologic features and changes in the SLEDAI were monitored. At more than 1 year follow-up, the results demonstrated that no remarkable differences between single and double allogeneic MSCT were found in terms of disease remission

and relapse, amelioration of disease activity and serum indexes. This study demonstrated that single MSC transplantation at the dose of one million MSCs per kilogram of body weight was sufficient to induce disease remission for refractory SLE subjects. Although 95% of the participants had lupus nephritis at the time of enrollment, it is unclear whether MSC therapy can ameliorate renal pathology, aside from the improvements in renal function, because the pathological data on the participants at the time of enrollment was not available.

Crohn's Disease

In a Phase I trial, Duijvestein and colleagues (2010) assessed the safety and feasibility of the use of autologous bone marrow-derived MSC treatment for luminal Crohn's disease refractory to steroids and immunomodulators. A total of 10 adult participants with refractory Crohn's disease underwent bone marrow aspiration under local anesthesia. Bone marrow MSCs were isolated and expanded ex-vivo. MSCs were assessed in- vitro for functionality and phenotype. Nine participants received two doses of $1\text{-}2\times10^6$ cells/kg body weight, intravenously, 7 days apart. During follow-up, the participants were monitored for possible side effects and changes in the Crohn's disease activity index (CDAI). Colonoscopies were conducted at weeks 0 and 6, and mucosal inflammation was assessed using the Crohn's disease endoscopic index of severity. The study demonstrated a decline in CDAI by ≥ 70 from baseline in 3 participants at 6 weeks post treatment; conversely 3 participants required surgery due to worsening Crohn's disease. None of the participants achieved remission. The subjects reported minor allergic reaction (10%), headache (30%), as well as taste and smell disturbances (90%) which were considered related to MSC infusion.

Zhang and colleagues (2018) investigated the efficacy and safety of umbilical MSCs for the treatment of Crohn's disease. The Phase III clinical trial included 82 participants who were diagnosed with Crohn's disease and had received steroid maintenance therapy for more than 6 months. A total of 41 participants were randomly selected to receive four peripheral intravenous infusions of 1×10^6 umbilical cord MSCs/kg, with one infusion per week. Participants were followed for 12 months. Assessment tools included the CDAI and Harvey-Bradshaw index (HBI). Corticosteroid dosage was also assessed. Twelve months post treatment, the CDAI, HBI, and corticosteroid dosage had decreased by 62.5 ± 23.2, 3.4 ± 1.2, and 4.2 ± 0.84 mg/day, respectively, in the umbilical cord-MSC group and by 23.6 ± 12.4, 1.2 ± 0.58, and 1.2 ± 0.35 mg/day, respectively, in the control group ($p<0.01$, $p<0.05$, and $p<0.05$ for UC-MSC vs control, respectively). Fever after the administration of MSC infusion was reported in 4 participants. No serious adverse events were reported. The authors concluded that umbilical cord-MSCs were an effective treatment for Crohn's disease that produced mild side effects. A limitation of this study was that it did not

examine indicators of immune status or intestinal histopathology in the participants. Therefore, the mechanism by which stem cell therapy modifies Crohn's disease remains unclear.

While small, preliminary studies investigating the use of MSC therapy as a treatment for Crohn's disease may show promise, additional well-designed studies with larger populations and longer follow-up periods are needed before conclusions regarding the safety and efficacy of MSC therapy can be made.

Summary

MSCs isolated from bone marrow and other sites, display specific anti-inflammatory and immunomodulation properties and may be a tool for the treatment of various chronic diseases. While the results of some early trials have been promising, a number of questions remain (Goldberg, 2017; Viganò, 2016). The available data have not yet established that MSCs, when infused or transplanted, can regenerate by incorporating themselves into native tissue, survive, differentiate, and promote the preservation of injured tissue. In addition, the optimal source for MSCs has not been clearly identified. Randomized, controlled trials that are adequately powered and include long-term follow-up data are needed before conclusions regarding the safety, efficacy and clinical utility of MSC therapy for the treatment of chronic autoimmune, inflammatory, orthopedic and degenerative diseases can be made.

Other Adult Stem Cell Therapies

The study of other adult stem cell types for stem cell therapy has been limited, with most studies using animal models. Scientists have discovered neuronal stem cells from the brain and spinal cord, and small studies are underway to test olfactory ensheathing glial cells for regenerating spinal cord tissue. Human teratocarcinoma cell line (hNT-)~~hNT~~ cells have shown promise in animal models for treating ALS and stroke. Muscle-derived stem cells are being investigated in rat models for incontinence and cardiac damage. Other possible adult stem cells under investigation include liver stem cells, pancreatic stem cells, corneal limbal stem cells, and mammary stem cells. Stem cells are also being investigated from the salivary glands, skin, and heart. Although small clinical trials are underway, a great deal of research is needed to assess the safety and efficacy of adult stem cell therapies (NIH, 2018).

Background/Overview

Overview

Stem cell therapy, a component of regenerative medicine, involves the insertion (usually an infusion or injection) of stem cells into the body to repair body tissues. Sources of stem cells include a person's own stem cells (such as those extracted from blood and tissues), another person's stem cells, stem cells extracted from embryos, and stem cells extracted from pregnancy remains (amniotic fluid, placentas, umbilical cords or umbilical cord blood).

Stem cells are unspecialized cells that ~~Stem cells~~have the unique ability to self-renew through cell division or differentiate into specialized cells, ~~are specialized cells that are capable of renewing themselves through cell division and differentiating into multi-lineage cells~~such as red blood cells, brain cells, or muscle cells. They form the human body and replace damaged cells throughout a person's lifespan. Stem cells are divided into four main classes: totipotent, pluripotent, multipotent, and unipotent.

Totipotent stem cells can form every cell type in the body, including placental and umbilical cord cells. The first cell of human life, the zygote, is a totipotent stem cell that divides to create more totipotent stem cells. After the first few days of embryonic development, totipotent stem cells cease to exist and give rise to pluripotent stem cells.

Pluripotent stem cells can form every cell type in the body except umbilical and placental cells. They are found in 3 to 5 day old embryos called blastocysts. Additionally, some pluripotent cells are found in fetal tissue after 8 weeks of development. Due to ethical concerns, the use of embryonic stem cells (totipotent and pluripotent) and fetal tissue stem cells for stem cell therapy has been controversial in the United States, with some states banning or limiting research. As an alternative, researchers have been working on the creation of induced pluripotent stem cells (iPSCs), which are specialized adult human cells reprogrammed to act like pluripotent embryonic stem cells. iPSCs are still in the investigative stages, and more research is needed before they can be used for stem cell therapy.

As human development continues, pluripotent cells cease to exist and give rise to multipotent stem cells that stay in the body throughout life. Multipotent stem cells form certain specialized cell types, usually the types needed to repair the tissue or organ where they reside, although some research suggests they may be able to ~~trans~~transdifferentiate into other cell types. Multipotent stem cells can give rise to unipotent stem cells, which differentiate along only one lineage.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Multipotent and unipotent stem cells are referred to as adult stem cells (also called tissue-specific cells or somatic cells) and are found in many areas of the body. They are thought to reside in a specific location in the tissue called the "stem cell niche." Researchers have identified many types of adult stem cells, including neural, epithelial, epidermal, hematopoietic, and mesenchymal. Currently, hematopoietic adult stem cell therapy for transplants is the only established use of stem cells. Researchers are investigating other types of adult stem cells, with the largest focus on mesenchymal stem cells.

Mesenchymal stem cells (MSCs)

~~These cells are categorized as embryonic stem cells, induced pluripotent stem cells and adult stem cells.~~

Mesenchymal stem cells (MSCs) ~~, also known as multipotent mesenchymal stromal cells, are adult stem cells that can be isolated from animal and human sources. Human MSCs (hMSCs)~~ are non-hematopoietic, multipotent stem cells that can differentiate into a variety of cell types. The four major cell types are osteocytes (bone), myocytes (muscle), adipocytes (fat) and chondrocytes (cartilage). MSCs have immunomodulatory properties and secrete cytokines. MSCs remain in a quiescent (non-proliferative) state during most of their lifetime, pending stimulation by the signals triggered by tissue renewal, damage and remodeling processes. Because of their multi-lineage potential, immunomodulatory properties and ability to secrete anti-inflammatory molecules, MSCs may have the potential to treat various chronic autoimmune, inflammatory and degenerative diseases (Ullah, 2015).

MSCs have been isolated from various sites, including dermis, amniotic fluid, adipose tissue, endometrium, dental tissue, synovial fluid, ~~d and~~ placenta and umbilical cord tissue. Additionally, researchers have been able to culture hMSCs in specific media.

~~The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271.~~
~~MSCs are being investigated as a regenerative biologic agent because of their ability to differentiate into multiple tissue types and to self-renew. MSCs can be derived from a variety of sources, including adipose tissue, bone marrow, placenta, and peripheral or umbilical blood.~~ The MSC population in red bone marrow is estimated at 1 per 10^5 nucleated cells. The incidence of MSCs in adults is 1 per 10^3 nucleated cells (Piccirilli, 2017). Counts in cord blood or peripheral blood are lower (Bonab, 2006). These tissue sources differ with respect to MSC cell density and

differentiation capacity. Bone marrow-derived MSCs are considered the preferred source for bone repair and regeneration as there is better chondrogenic differentiation potential (Shao, 2015). Although other sources for MSCs have been identified, the bone marrow is currently the primary source of procurement.

MSC therapy has been proposed as a treatment option for orthopedic indications that include torn cartilage, osteoarthritis, and bone grafting. The proposed benefits of MSC therapy are improved healing and possible avoidance of surgical procedures with protracted recovery times. MSCs are used as a stand-alone therapy in the form of an injection or in combination with scaffolds (Viganò, 2016),

Optimal materials or grafts that promote bone growth and healing require the following properties (Shen, 2005):

- Osteogenic: contains osteoprogenitor cells that can lay down a new bone matrix
- Osteoinductive: provides signals required to induce differentiation of MSCs into mature osteoblasts
- Osteoconductive: passive scaffolding to promote vascular invasion and bone apposition on the surface for new bone formulation

Currently, the risks of MSC therapy for the treatment of chronic, autoimmune, inflammatory and degenerative conditions are unknown. Insufficient data have been reported to allow a proper understanding of how this technology may affect individuals either in the short or long-term. Furthermore, there are known risks related to the various methods utilized to harvest MSCs from the bone marrow, including pain and hemorrhage.

MSC therapy is being investigated as a treatment of many chronic, autoimmune, inflammatory and degenerative conditions, including but not limited to the following diseases:

- Alzheimer's Disease: An irreversible and progressive form of dementia that causes difficulty with memory, thinking and behavior. Symptoms generally develop slowly and worsen over a number of years, eventually becoming severe enough to interfere with tasks. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals are unable to carry on a conversation and respond to their environment. While there is no cure for Alzheimer's disease or a way slow its progression, there are drug and non-drug options that may ameliorate symptoms.
- Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease): A group of rare neurological diseases that primarily involve the nerve cells responsible for controlling voluntary muscle movement. Early symptoms of ALS generally include stiffness or muscle weakness. Gradually all muscles under voluntary control are affected, and the person loses his/her strength and the ability to move, eat, speak and even breathe. The majority of individuals with ALS die from respiratory failure, usually within 3 to 5 years from when the

symptoms first appear. However, approximately 10% of people with ALS survive for 10 years. Currently, there is no cure for this condition and no effective treatment to stop or reverse the progression of the disease.

- Celiac Disease: An autoimmune disease in which the small intestine becomes hypersensitive to gluten, leading to difficulty in digesting food. Currently, the only treatment for celiac disease is lifelong avoidance of foods with gluten in it (for example, wheat, rye and barley).
- Crohn's Disease: A chronic inflammatory condition affecting the lining of the gastrointestinal tract. Crohn's disease can lead to abdominal pain, severe diarrhea, weight loss, fatigue and malnutrition. The inflammation caused by Crohn's disease can involve different areas of the digestive tract in different individuals. People with Crohn's disease may experience severe symptoms followed by periods of no symptoms. There is currently no cure for Crohn's disease. Medical treatment is typically focused on reducing the inflammation that triggers signs and symptoms and improving long-term prognosis by limiting complications.
- Multiple Sclerosis: A chronic and generally progressive, autoimmune disease in which the sheaths of nerve cells in the brain and spinal cord are damaged. The effects of multiple sclerosis varies between affected individuals. Symptoms may include impairment of speech and of muscular coordination, numbness, blurred vision, and severe fatigue. There is no cure for multiple sclerosis. Treatment may focus on slowing the progression of the disease, speeding recovery from attacks, and symptom management.
- Osteoarthritis: A degenerative condition caused by inflammation, breakdown, and eventual loss of cartilage in the joints. Osteoarthritis most commonly affects joints in the knees, hands, hips and spine.
- Parkinson's Disease: A neurodegenerative disorder that affects predominately dopamine-producing neurons in the substantia nigra of the brain. Individuals with Parkinson's disease may experience tremors in a limb (often the fingers or hand). The disorder causes slowness of movement and may also cause stiffness, loss of balance, as well as slurred or slowed speech. There is no cure for Parkinson's disease, but treatments include medications, surgical therapy and lifestyle modifications.
- Systemic Lupus Erythematosus: An inflammatory, disease caused by the immune system attacking its own tissues. Inflammation caused by lupus may affect many different areas of the body including but not limited to the skin, joints, kidneys, brain, blood cells, heart and lungs. Treatment for systemic lupus erythematosus is generally focused on easing the symptoms and will vary depending on how severe the symptoms are and which areas of the body are affected. The goal of treatment is to ease symptoms. Treatment varies depending on the symptoms and the affected areas of the body. Currently, there is no cure for systemic lupus erythematosus.

Other Adult Stem Cell Types

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

In addition to mesenchymal stem cells, researchers have identified other adult stem cell types in the body. Examples include:

- Hematopoietic stem cells – give rise to all types of blood cells.
- Neural stem cells – give rise to nervous system cells, including nerve cells, astrocytes, and oligodendrocytes.
- Epithelial stem cells – give rise to digestive system cells, including absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.
- Epidermal stem cells – give rise to keratinocytes that form the skin's protective barrier.
- Follicular stem cells – give rise to cells that form hair follicles and the epidermis.

Challenges and Risks of Adult Stem Cell Therapy

While the concept of extracting and injecting adult stem cells may seem straightforward, scientists have identified many challenges and risks. Only limited numbers of adult stem cells are found in human tissues. They are difficult to isolate and do not self-renew in the laboratory as easily as embryonic stem cells. In addition, they are unpredictable and do not always differentiate into the desired cell type. Also, the intrinsic nature or external manipulation of stem cells can potentially form malignancies. There have been reports of unregulated stem cell therapy causing infection, blindness, tumor growth, paralysis, and the multiplication of an undesired stem cell type. As stem cell research continues, scientists are working on ways to mitigate these challenges and risks (FDA, 2019; NIH, 2018).

Regulation

The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Currently, the only stem cell products approved by the FDA are hematopoietic progenitor cells from umbilical cord blood. In 2017, the FDA issued a warning to consumers stating some medical providers are using unapproved and unproven stem cell treatments that may be dangerous. They stated that to ensure safety, stem cell treatments should be FDA-approved or have an Investigational New Drug Application (IND), which is a clinical investigation plan the FDA has allowed to proceed. ~~The FDA has issued warnings and lawsuits against noncompliant clinics. In a recent statement, the FDA stated the following:~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~There are many examples of companies deceiving patients with unsubstantiated claims about the potential for stem cell products to prevent, treat or cure serious diseases, and in those cases, we are committed to acting to protect patients. These actors are taking advantage of patients, many in vulnerable positions with chronic or terminal diseases, by leveraging the widespread belief in the eventual promise of these products, flouting the statutes and our regulations. This ultimately puts at risk the very patients that they claim to want to help, by either delaying treatment with legitimate and scientifically sound treatment or, worse, posing harm to patients, such as blindness, infection or possibly death (FDA, 2019).~~

Definitions

Differentiation: The multi-stage process by which an unspecialized stem cell gives rise to specialized cells.

Multipotent: Possessing the ability to produce more than one type of specialized cell of the body, but not all types of cells.

Stem cells: A type of self-renewing cell from which other types of cells develop.

Transdifferentiation: The ability for adult stem cells to give rise to specialized cells other than those expected by the stem cell's lineage.

Coding

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

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

	For the following procedures when specified as harvesting or administration of non-hematopoietic stem cells:
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue ~~[when specified as harvesting of MSCs]~~
20999	Unlisted procedure, musculoskeletal system, general ~~[when specified as harvesting of MSCs or MSC implant]~~
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38999	Unlisted procedure, hemic or lymphatic system ~~[when specified as MSC implant]~~
64999	Unlisted procedure, nervous system ~~[when specified as MSC implant]~~

ICD-10 Procedure

30230AZ	Transfusion of embryonic stem cells into peripheral vein, open approach
30233AZ	Transfusion of embryonic stem cells into peripheral vein, percutaneous approach
30240AZ	Transfusion of embryonic stem cells into central vein, open approach
30243AZ	Transfusion of embryonic stem cells into central vein, percutaneous approach
3E0Q0AZ	Introduction of embryonic stem cells into cranial cavity and brain, open approach
3E0Q3AZ	Introduction of embryonic stem cells into cranial cavity and brain, percutaneous approach
3E0R0AZ	Introduction of embryonic stem cells into spinal canal, open approach
3E0R3AZ	Introduction of embryonic stem cells into spinal canal, percutaneous approach

ICD-10 Diagnosis

	Including, but not limited to, the following:
G12.21	Amyotrophic lateral sclerosis
G20-G21.9	Parkinson's disease, secondary parkinsonism
G30.0-G30.9	Alzheimer's disease
G31	Other degenerative diseases of nervous system, not elsewhere classified
G35	Multiple sclerosis
K50.00-K51.919	Crohn's disease [regional enteritis], ulcerative colitis
K52.3	Indeterminate colitis
K90.0	Celiac disease

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

M04.1-M04.9	Autoinflammatory syndromes
M15.0-M19.93	Osteoarthritis
M21.00-M21.079	Valgus deformity, not elsewhere classified
M21.10-M21.179	Varus deformity, not elsewhere classified
M21.70-M21.769	Unequal limb length (acquired)
M21.80-M21.869	Other specified acquired deformities of limbs
M21.90-M21.969	Unspecified acquired deformity of limb and hand
M23.000-M23.92	Internal derangement of knee
M24.10-M24.176	Other articular cartilage disorders
M24.20-M24.28	Disorder of ligament
M24.60-M24.676	Ankylosis of joint
M24.7	Protrusio acetabuli
M24.80-M24.876	Other specific joint derangements, not elsewhere classified
M24.9	Joint derangement, unspecified
M25.50-M25.579	Pain in joint
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M75.00-M75.92	Shoulder lesions
M84.30XA-M84.9	Disorder of continuity of bone
M87.00-M87.9	Osteonecrosis
M91.0-M94.9	Chondropathies
S43.401A-S43.499S	Sprain of shoulder joint

References

Peer Reviewed Publications:

1. Bonab MM, Alimoghaddam K, Talebian F, et al. Aging of mesenchymal stem cell in vitro. BMC Cell Biol. 2006; 7:14.
2. Buda R, Vannini F, Cavallo M, et al. One-step arthroscopic technique for the treatment of osteochondral lesions of the knee with bone-marrow-derived cells: three year results. Musculoskelet Surg. 2013; 97(2):145-151.
~~2.~~3. Centeno C, Sheinkop M, Dodson E, et al. A specific protocol of autologous bone marrow concentrate and platelet products versus exercise therapy for symptomatic knee osteoarthritis: a randomized controlled trial with 2 year follow-up. J Transl Med. 2018; 16: 355.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~3.~~4. Ciccocioppo R, Gallia A, Avanzini MA, et al. A refractory celiac patient successfully treated with mesenchymal stem cell infusions. Mayo Clin Proc. 2016; 91(6):812-819.
~~4.~~5. Dave M, Mehta K, Luther J, et al. Mesenchymal stem cell therapy for inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2015; 21(11):2696-2707.
~~5.~~6. Duijvestein M, Vos AC, Roelofs H, et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: Results of a phase I study. Gut. 2010; 59(12):1662-1669.
~~6.~~7. Fernández O, Izquierdo G, Fernández V, et al. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. PLoS One. 2018; 13(5):e0195891.
~~7.~~8. Filardo G, Madry H, Jelic M, et al. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. Knee Surg Sports Traumatol Arthrosc. 2013; 21(8):1717-1729.
~~8.~~9. Goldberg A, Mitchell K, Soans J, et al. The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review. J Orthop Surg Res. 2017; 12(1):39.
~~9.~~10. Ha CW, Park YB, Kim SH, Lee HJ. Intra-articular mesenchymal stem cells in osteoarthritis of the knee: a systematic review of clinical outcomes and evidence of cartilage repair. Arthroscopy. 2019; 35(1):277-288.e2.
~~10.~~11. Haddad B, Pakravan AH, Konan S, et al. A systematic review of tissue engineered meniscus: cell-based preclinical models. Curr Stem Cell Res Ther. 2013; 8(3):222-231.
~~11.~~12. Harris VK, Stark J, Vyshkina T, et al. Phase I trial of intrathecal mesenchymal stem cell-derived neural progenitors in progressive multiple sclerosis. EBioMedicine. 2018; 29:23-30.
~~12.~~13. Hogan MV, Kawakami Y, Murawski CD, Fu FH. Tissue engineering of ligaments for reconstructive surgery. Arthroscopy. 2015; 31(5):971-979.
~~13.~~14. Jo CH, Chai JW, Jeong EC, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A 2-Year Follow-up Study. Am J Sports Med. 2017; 45(12):2774-2783.
~~14.~~15. Kan I, Ben-Zur T, Barhum Y, et al. Dopaminergic differentiation of human mesenchymal stem cells--utilization of bioassay for tyrosine hydroxylase expression. Neurosci Lett. 2007; 419(1):28-33.
~~15.~~16. Kim HJ, Seo SW, Chang JW, et al. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. Alzheimers Dement (N Y). 2015; 1(2):95-102.
~~16.~~17. Kitoh H, Kitakoji T, Tsuchiya H, et al. Transplantation of marrow-derived mesenchymal stem cells and platelet-rich plasma during distraction osteogenesis-a preliminary result of three cases. Bone. 2004; 35(4):892-898.

~~17.~~18. Lee K, Wang VT, Chan YH, Hui JH. A novel, minimally-invasive technique of cartilage repair in the human knee using arthroscopic microfracture and injections of mesenchymal stem cells and hyaluronic acid--a prospective comparative study on safety and short-term efficacy. Ann Acad Med Singapore. 2012; 41(11):511-517.
~~18.~~19. Longo UG, Lamberti A, Maffulli N, Denaro V. Tissue engineered biological augmentation for tendon healing: a systematic review. Br Med Bull. 2011; 98:31-59.
~~19.~~20. Mazzini L, Fagioli F, Boccaletti R, et al. Stem cell therapy in amyotrophic lateral sclerosis: a methodological approach in humans. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003; 4(3):158-161.
~~20.~~21. Noth U, Steinert AF, Tuan RS. Technology insight: adult mesenchymal stem cells for osteoarthritis therapy. Nat Clin Pract Rheumatol. 2008; 4(7):371-380.
~~21.~~22. Rai B, Lin JL, Lim ZX, et al. Differences between in vitro viability and differentiation and in vivo bone-forming efficacy of human mesenchymal stem cells cultured on PCL-TCP scaffolds. Biomaterials. 2010; 31(31):7960-7970.
~~22.~~23. Shao J, Zhang W, Yang T. Using mesenchymal stem cells as a therapy for bone regeneration and repairing. Biol Res. 2015; 48:62.
~~23.~~24. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells - current trends and future prospective. Biosci Rep. 2015; 35(2).
~~24.~~25. Vangsness CT, Farr J, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medical meniscectomy: a randomized, double-blind, controlled study. J Bone Joint Surg Am. 2014; 96(2): 90-98.
~~25.~~26. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of Knee Osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation. 2015; 99(8):1681-1690.
~~26.~~27. Viganò M, Sansone V, d'Agostino MC, et al. Mesenchymal stem cells as therapeutic target of biophysical stimulation for the treatment of musculoskeletal disorders. J Orthop Surg Res. 2016; 11(1):163.
~~27.~~28. Wang D, Akiyama K, Zhang H, et al. Double allogenic mesenchymal stem cells transplantations could not enhance therapeutic effect compared with single transplantation in systemic lupus erythematosus. Clin Dev Immunol. 2012; 2012:273291.
~~28.~~29. Wang D, Li J, Zhang Y, et al. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study. Arthritis Res Ther. 2014; 16(2):R79.
~~29.~~30. Wakitani S, Imoto K, Yamamoto T, et al. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis Cartilage. 2002; 10(3):199-206.

~~30.~~31. Wakitani S, Mitsuoka T, Nakamura N, et al. Autologous bone marrow and stromal cell transplantation for repair of full-thickness articular cartilage defects in human patellae: two case reports. Cell Transplant. 2004; 13(5):595-600.
~~31.~~32. Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. J Tissue Eng Regen Med. 2011; 5(2):146-150.
~~32.~~33. Wong KL, Lee KB, Tai BC, et al. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy. 2013; 39(12):2020-2028.
~~33.~~34. Zhang J, Lv S, Liu X, et al. Umbilical cord mesenchymal stem cell treatment for Crohn's disease: a randomized controlled clinical trial. Gut Liver. 2018; 12(1):73-78.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Jaslok Hospital and Research Centre. Autologous Mesenchymal Stem Cell Transplant for Parkinson's Disease. NLM Identifier: NCT00976430. Last updated on August 14, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT00976430?term=NCT00976430&rank=1. Accessed on ~~February 12~~June 26, 2019~~, 2019~~.
2. U.S. Food and Drug Administration (FDA). Regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use guidance for industry and food and drug administration staff. Last updated on May 23, 2019. ~~(Nov 2017)~~ Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf. Accessed on ~~February 12, 2019~~June 26, 2019.
3. U.S. Food and Drug Administration (FDA). FDA warns about stem cell therapies. Last updated November 16, 2017. Available at: https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies. Accessed on June 26, 2019.
4. U.S. Food and Drug Administration (FDA). Approved cellular and gene therapy products. Last updated March 29, 2019. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed on June 26, 2019.
5. U.S. Food and Drug Administration (FDA). Statement on stem cell clinic permanent injunction and FDA's ongoing efforts to protect patients from risks of unapproved products. Last updated June 25, 2019. Available at: https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks. Accessed on June 26, 2019.
~~2.~~

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Websites for Additional Information

1. International Society for Stem Cell Research. Available at: https://www.closerlookatstemcells.org/. Accessed on June 26, 2019.
~~1.~~2. U.S National Institute of Health. Stem Cell Information. Available at: http://stemcells.nih.gov/. Accessed on June 26, 2019~~February 12, 2019~~.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/22/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Title changed to "Non-Hematopoietic Adult Stem Cell Therapy." Position Statement expanded to include non-hematopoietic adult stem cell therapy. Updated the Description/Scope, Rationale, Background/Overview, Definitions, Coding, References and Websites for Additional Information sections. Added Index section.
Reviewed	03/21/2019	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Updated Rationale, Background/Overview, Definitions, References and Websites for Additional Information sections.
Revised	01/24/2019	MPTAC review. Title changed to "Mesenchymal Stem Cell Therapy for the Treatment of Joint and Ligament Disorders, Autoimmune, Inflammatory and Degenerative Diseases". Updated the Description/Scope, Rationale,

		Background/Overview, Definitions, References and Websites for Additional Information sections. Deleted Index section. Updated Coding section to include removing 20930 for spinal surgery no longer addressed.
Reviewed	09/13/2018	MPTAC review Updated Rationale and References sections.
Reviewed	11/02/2017	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, Background, References and Website sections.
	03/06/2017	Revised note in Scope section to clarify that TRANS.00035 addresses bone graft products with added or exogenous MSCs and that bone graft products with endogenous MSCs are addressed in CG-SURG-45.
Reviewed	11/03/2016	MPTAC review. Removed the products Osteocel, Trinity Evolution and Elite and BIO^4 from the rationale. Updated Description, Rationale, References, Website and Index sections.
Reviewed	08/04/2016	MPTAC review. Updated Description, Rationale, Background, References and Websites sections.
	04/01/2016	Updated Coding section with corrected diagnosis code range for spondylosis; also removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated Description/Scope, Rationale, Coding, References, Websites and Index sections.
Reviewed	08/14/2014	MPTAC review. Updated Description/Scope, Rationale, References and Websites sections.
Reviewed	08/08/2013	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	08/09/2012	MPTAC review. Rationale, Background, References and Websites updated.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Reviewed	08/18/2011	MPTAC review. Rationale, Background, References and Websites updated. Updated Coding section with 10/01/2011 ICD-9 changes.
Reviewed	08/19/2010	MPTAC review. Rationale, Background, References and Websites updated.
Reviewed	08/27/2009	MPTAC review. Rationale, websites and references updated.
New	08/28/2008	MPTAC review. Initial document development.