Hematopoietic Cell Transplantation for Autoimmune Diseases

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Next Review: 3/2021

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Hematopoietic Cell Transplantation for Autoimmune Diseases when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Autologous hematopoietic cell transplantation is considered medically necessary as a treatment of systemic sclerosis (scleroderma) if all of the following conditions 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 as noted in Considerations; AND
- history of < 6 months treatment with cyclophosphamide; AND
- no active gastric antral vascular ectasia; AND
- do not have any exclusion criteria as noted in Considerations.

When Policy Topic is not covered
Autologous or allogeneic hematopoietic cell transplant is considered investigational as a treatment of autoimmune diseases, including, but not limited to, the following:

- multiple sclerosis (MS)
- juvenile idiopathic and rheumatoid arthritis (RA)
- systemic lupus erythematosus (SLE)
- type 1 diabetes mellitus
- chronic inflammatory demyelinating polyneuropathy

Autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma not meeting the above criteria is considered investigational.
**Considerations**
Please see the Codes table for details.

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

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

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

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

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

**Description of Procedure or Service**

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<th>Populations</th>
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<th>Outcomes</th>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<tr>
<td>With multiple sclerosis</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy</td>
<td>Overall survival</td>
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<td>Health status measures</td>
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<td>and scleroderma</td>
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<td>Symptoms</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
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<td>With systemic lupus</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy</td>
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<td>erythematosus</td>
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<td>Treatment-related mortality</td>
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<td>Treatment-related morbidity</td>
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</table>
### Hematopoietic Cell Transplantation for Autoimmune Diseases

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With juvenile idiopathic or rheumatoid arthritis</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy, Biologic therapy</td>
<td>Overall survival, Symptoms, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
<tr>
<td>With chronic inflammatory demyelinating polyneuropathy</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy</td>
<td>Overall survival, Symptoms, Health status measures, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
<tr>
<td>With type 1 diabetes</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy</td>
<td>Overall survival, Symptoms, Health status measures, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
<tr>
<td>With other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis)</td>
<td>Hematopoietic cell transplantation</td>
<td>Conventional medication therapy</td>
<td>Overall survival, Symptoms, Health status measures, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
</tbody>
</table>

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 hematopoietic cell transplantation (HCT).

For individuals with multiple sclerosis who receive HCT, the evidence includes a randomized controlled trial (RCT) and several case series. The relevant outcomes are overall survival (OS), health status measures, quality of life (QOL), and treatment-related mortality (TRM) and morbidity. The phase 2 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 findings of the case series revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes 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 one 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 one year follow-up, one patient in the control group and two patients in the HCT group achieved remission. Data are needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

**Autoimmune Disease Treatment**

Immune suppression is a common treatment strategy for many of these diseases, particularly rheumatic diseases (eg, rheumatoid arthritis, systemic lupus erythematous, 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.¹

**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. Cord blood transplantation is discussed in detail in a separate policy.

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.

**Regulatory Status**
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
This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through November 11, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new, self-tolerant lymphocytes. While evidence for the use of allo-HCT for autoimmune diseases is currently limited, the goal is to possibly eliminate genetic susceptibility to the autoimmune disease, potentially resulting in a cure.

Recent reviews have summarized the research to date using HCT to treat a number of autoimmune diseases.2,3.

In March 2009, patients with an autoimmune disease who had undergone HCT were registered in the European Group for Blood and Marrow Transplantation
(EBMT)/European League Against Rheumatism database. The database included 1031 with the clinical indications of multiple sclerosis (MS; n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE; n=92), rheumatoid arthritis (RA; n=88), juvenile idiopathic arthritis (JIA; n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn disease (n=23).3

**Multiple Sclerosis**

**Clinical Context and Therapy Purpose**
The purpose of HCT in patients who have multiple sclerosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with multiple sclerosis compared to conventional medical?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is patients with multiple sclerosis.

**Interventions**
The therapy being considered is HCT. HCT is performed in a tertiary care center by transplant specialist teams.

**Comparators**
Comparators consist of conventional medical therapy. 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.

Primary care practitioners and neurologists manage the care of patients with multiple sclerosis.

**Outcomes**
Outcomes of interest include progression-free survival (PFS), overall survival (OS), improvement in clinical symptoms, adverse events, and treatment-related mortality (TRM).

Follow-up for one year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

An RCT, Autologous Stem Cell Transplantation in Multiple Sclerosis, which compared HCT with mitoxantrone for treatment of MS, was published by Mancardi et al (2015). Due to low patient enrollment, this trial’s protocol, initially designed as a phase 3 study evaluating disability progression, was amended to a phase 2 study with a new primary outcome of disease activity, as measured by the number of new T2 magnetic resonance imaging (MRI) lesions in four years posttreatment. Eligibility for the trial was limited to the following criteria: secondary progressive or relapsing-remitting multiple sclerosis (RRMS), a documented worsening of symptoms during the last year, and lack of response to conventional therapy. Twenty-one patients were randomized to autologous HCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were collected every 6 months for 48 months. Data were not available for four patients; missing data were imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval [CI], 0.10 to 0.48, p<0.001). Among secondary outcomes, the annualized relapse rate was significantly lower in the HCT group (19%) compared with the conventional therapy group (60%; p<0.03). There was no statistically significant difference between groups in the rate of disease progression (defined as increase of >1 point in Expanded Disability Status Scale [EDSS] score if baseline was 3.5 to 5.5 or increase of >0.5 if baseline 5.5 to 6.5) or change in disability status.

Burt et al (2019) reported a randomized controlled trial of nonmyeloablative HCT compared to continued disease-modifying therapy (DMT) on disease progression for patients with relapsing-remitting MS (RRMS). Between 2005 and 2016, with final follow-up in 2018, 110 patients with relapsing remitting multiple sclerosis (RRMS) were randomized to receive HCT plus cyclophosphamide and antithymocyte globulin (n = 55) or DMT of higher efficacy or a different class than DMT taken in the previous year (n = 55). To be eligible, the participants had to have at least 2 relapses with DMT in the prior year and an Expanded Disability Status Score (EDSS) of 2.0 to 6.0 (EDSS score range 0–10, with 10 = worst neurological disability). The primary end point of the study was disease progression, defined as an EDSS score increase of ≥1.0 point (minimally clinically important difference, 0.5) after ≥1 year on 2 evaluations 6 months apart. Three patients in the HCT group and 34 patients in the DMT group experienced disease progression, with a median follow-up of 2 years (mean = 2.8 years). Too few events in the HCT group prevented calculation of time to progression, but it was 24 months (interquartile range = 18–48 months) in the DMT group (hazard ratio [HR] = 0.07; 95% CI: 0.02–0.24). For the HCT group, the proportion of patients...
with disease progression was 1.92% (95% CI: 0.27%–12.9%) at 1 year and 2 years, and by 4 and 5 years it was 9.71% (95% CI: 3.0%–28.8%). Disease progression for the DMT group was 24.5% (95% CI: 14.7%–39.1%) at 1 year, and 75.3% (95% CI: 60.4%–87.8%) by year 5. In the HCT group, the mean EDSS score decreased from a baseline of 3.38 to 2.36 at 1 year. In the DMT group, mean EDSS score increased from 3.31 to 3.98 at one year. Between-group difference in change in scores was -1.7 (95% CI: -2.03 to -1.29; \( p < .001 \)). The results of the study suggest nonmyeloablative HCT is superior to DMT in prolonging time to disease progression in patients with RRMS. Study limitations included sample size, option to cross over from DMT to HCT mid-study and the exclusion of other chemotherapy drugs used in the DMT group.

**Systematic Reviews**

A systematic review by Reston et al (2011) evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment (Table 1). Fourteen studies met inclusion criteria, of which eight case series met inclusion criteria for the primary outcome of PFS, with a median follow-up of at least two years. The other six studies were included for a summary of mortality and morbidity rates. The studies differed in the types and intensities of conditioning regimens used before HCT, with five studies using an intermediate-intensity regimen and three using high-intensity regimens. All studies were rated moderate quality. Across the eight case series, there was substantial heterogeneity. Most patients (77%) had secondary progressive MS, although studies also included patients with primary progressive, progressive-relapsing, and RRMS. Results are presented in Table 2.

Sormani et al (2017) conducted a systematic review and meta-analysis on the use of autologous HCT for the treatment of patients with severe treatment-refractory MS (Table 1). The studies differed in types and intensities of conditioning regimens used before HCT: low (n=2), intermediate (n=7), high (n=4), and mixed (n=2). Quality assessment of included studies was not discussed. The rate of progression at two and five years were calculated, as well as treatment-related and overall mortality (Table 2). The pooled proportion of patients with no evidence of disease activity at 2 years was 83% (range 70% to 92%) and at 5 years was 67% (range 59% to 70%).

Ge et al (2019) reported a systematic review and meta-analysis to assess progression-free survival (PFS) and disease activity-free survival, as well as transplant-related mortality (TRM) and overall deaths, after autologous HCT for MS (Table 1). The authors identified 18 eligible studies with a total of 732 participants. Pooled estimated PFS was 75%. Low- and intermediate-intensity treatments had higher PFS than high-intensity treatments (Table 2). In addition, relapsing remitting MS benefited from autologous HCT more than other types of MS subtypes. Patients with gadolinium-enhancing (Gd+) lesions at baseline responded better to autologous HCT. Overall, 9 transplant-related deaths occurred, and estimated TRM was greater with the use of high-intensity treatment regimens and in studies conducted before 2006. Twenty-seven patients died during follow-up; primarily of infection or pneumonia. Several limitations of the
meta-analysis include possible publication bias, a lack of RCTs, and differences in autologous HCT procedures, patient characteristics, and duration of follow-up across studies.

Table 1. Characteristics of Meta-Analyses on the Use of Autologous HCT for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates Through</th>
<th>Studies</th>
<th>Participants</th>
<th>N (range)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reston (2011)</td>
<td>Feb 2009</td>
<td>1 database 13 cohort</td>
<td>Patients with progressive and treatment-refractory multiple sclerosis</td>
<td>428 (5 to 169)</td>
<td>Median: 24 months</td>
</tr>
<tr>
<td>Sormani (2017)</td>
<td>1995 to 2016</td>
<td>1 RCT</td>
<td>14 cohort</td>
<td>Patients with severe and treatment-refractory multiple sclerosis</td>
<td>764 (7 to 178)</td>
</tr>
</tbody>
</table>

HCT: hematopoietic cell transplantation

Table 2. Results of Meta-Analyses on the Use of Autologous HCT for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow-up</th>
<th>PFS, % (95% CI)</th>
<th>Sub-population</th>
<th>N</th>
<th>TRM, N (%)</th>
<th>Non-TRM,N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reston (2011)</td>
<td>39 months</td>
<td>79.4 (69.9 to 86.5)</td>
<td>Cohort studies</td>
<td>259</td>
<td>7 (2.7)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Intermediate-intensity conditioning</td>
<td>39 months</td>
<td>79.4 (69.9 to 86.5)</td>
<td>Cohort studies</td>
<td>259</td>
<td>7 (2.7)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>High-intensity conditioning</td>
<td>24 months</td>
<td>44.6 (26.5 to 64.3)</td>
<td>Database</td>
<td>169</td>
<td>9 (5.3)</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>Ge (2019)</td>
<td>48 months</td>
<td>75 (69 to 81)</td>
<td>61 (53 to 69)</td>
<td>1.34 (0.39 to 2.30)</td>
<td>3.58 (2.30 to 4.86)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>48 months</td>
<td>75 (69 to 81)</td>
<td>61 (53 to 69)</td>
<td>1.34 (0.39 to 2.30)</td>
<td>3.58 (2.30 to 4.86)</td>
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<tr>
<td>Pts with RRMS</td>
<td>85 (77 to 92)</td>
<td>77 (61% to 94%)</td>
<td>47 (33 to 62)</td>
<td>0.97 (-0.05 to 1.98)</td>
<td></td>
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<tr>
<td>Pts with Gd+ lesions</td>
<td>77 (61% to 94%)</td>
<td>47 (33 to 62)</td>
<td>0.97 (-0.05 to 1.98)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pts with Gd− lesions</td>
<td>47 (33 to 62)</td>
<td>0.97 (-0.05 to 1.98)</td>
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<tr>
<td>Low- and Intermediate-intensity conditioning</td>
<td>80 (75 to 85)</td>
<td>0.97 (-0.05 to 1.98)</td>
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<tr>
<td>High-intensity conditioning</td>
<td>58 (40 to 75)</td>
<td>3.13 (1.18 to 5.08)</td>
<td></td>
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<td></td>
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<tr>
<td>Sormani (2017)</td>
<td>2-Year PR, % (95% CI)</td>
<td>17.1 (9.7 to 24.5)</td>
<td>679</td>
<td>23.3 (14.8 to 43.0)</td>
<td>2.1 (1.3 to 3.4)</td>
<td>1.0 (0.7 to 1.5)</td>
</tr>
</tbody>
</table>

CI: confidence interval; DAFS: disease activity–free survival; NR: not reported; OM: overall mortality; PFS: progression free survival; PR: progression rate; Pts: patients; RRMS: relapsing multiple sclerosis; TRM: treatment-related mortality.
remitting multiple sclerosis; TRM: treatment-related mortality.

\[ a \] pooled TRM defined as number of deaths within 100 days of transplant/number of transplants

\[ b \] OM defined as total number deaths/number of patient-years

**Nonrandomized Studies**

Select nonrandomized studies are described below.

Fassas et al (2011) reported on the long-term results of a single-center study that investigated the effect of HCT on the treatment of MS (Table 3).\[^{10}\] PFS and TRM are presented in Table 4. The median time to progression was 11 years (range, 0-22 years) for patients with active central nervous system disease and 2 years for patients without (range, 0-6 years). Improvements by 0.5 to 5.5 (median, 1) EDSS points were observed in 16 cases, lasting for a median of 2 years. In nine of these patients, EDSS scores did not progress above baseline scores. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT.

Shevchenko et al (2012) reported on the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HCT with a reduced-intensity conditioning regimen with different types of MS (Tables 3 and 4).\[^{11}\] Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and QOL outcomes. All patients, except one, responded to treatment. At long-term follow-up (mean, 46 months), the overall clinical response regarding disease improvement or stabilization was 80%. The estimated PFS rate at 5 years was 92% in the group after early transplant and 73% in the group after conventional/salvage transplant (p=0.01). No active, new, or enlarging lesions on were found on MRI without disease progression. All patients who did not have disease progression did not receive therapy during the posttransplantation period. HCT was accompanied by a significant improvement in QOL, with statistically significant changes in most QOL parameters (p<0.05). A subsequent 2015 publication reported on 64 patients participating in this trial who had at least 36 months of follow-up (median, 62 months).\[^{12}\] (Another 35 patients had a shorter follow-up, and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved by at least 0.5 points on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable, and 5 (7%) experienced worsening disease.

Mancardi et al (2012) reported on 74 consecutive patients with MS treated with autologous HCT following an intermediate-intensity conditioning regimen during the period from 1996 to 2008 (Table 3).\[^{13}\] Thirty-six patients had secondary progressive disease and 25 had RRMS. Clinical and MRI outcomes were reported (Table 4). The median follow-up was 48.3 months (range, 0.8-126 months). After 5 years, 66% of patients remained stable or improved. Among patients with follow-up more than 1 year, 8 (31%) of 25 subjects with RRMS had a 6- to 12-month confirmed EDSS score improvement more than 1 point after HCT compared with 1 (3%) of 36 patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up more than 7 years, 8 (44%)
remained stable or had sustained improvement, while 10 (56%), after an initial period of stabilization or improvement (median duration, 3.5 years), showed a slow disability progression.

A single-center case series by Burt et al (2015) reported on 151 patients, 123 with RRMS and 28 with secondary progressive MS (Tables 3 and 4). Patients were treated with nonmyeloablative HCT between 2003 and 2014. Six patients were not included in the outcome analysis (lost to follow-up and nonreproducible neurologic findings). The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). Change in EDSS score was the primary outcome. A decrease of at least 1.0 point was considered a significant improvement and an increase of at least 1.0 point was considered a significant progression. There was a statistically significant improvement in EDSS score for the group as a whole compared with the pretransplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at 3, 4, and 5 years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS scores were those with RRMS, with duration of disease of ten years or less, and those without sustained fever during HCT.

A multicenter case series by Burman et al (2014) reported on 48 patients with aggressive RRMS (defined as a disease with high relapse frequency, and who failed conventional therapy) (Tables 3 and 4). Patients underwent autologous HCT. At the 5-year follow-up, relapse-free survival was 87%, and the EDSS score PFS (defined as a deterioration in EDSS score of <0.5 points) was 77%.

Atkins et al (2016) published a phase 2 trial investigating the use of immunoablation and autologous HCT for the treatment of aggressive MS (Table 3). Inclusion criteria were: poor prognosis, ongoing disease activity, and EDSS score between 3.0 and 6.0. Twenty-four patients enrolled PFS and TRM are presented in Table 4. During the extended follow-up period, without the use of disease-modifying drugs, no signs of central nervous system inflammation were detected clinically or radiologically. Clinical relapses did not occur among the 23 surviving patients in 179 patient-years of follow-up. Moreover, 33% of the patients experienced grade 2 toxic effects and 58% experienced grade 1 transplantation-related toxic effects.

Results from the High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis trial were published by Nash et al (2017) (Tables 3 and 4). The trial evaluated 24 patients with MS who were treated with high-dose immunosuppression and autologous HCT. Outcomes were PFS (91%; 90% CI, 75% to 97%), clinical relapse-free survival (87%; 90% CI, 69% to 95%), and MRI activity-free survival (86%; 90% CI, 68% to 95%). Patients experienced high rates of adverse events: 92% had grade 3, and 100% had grade 4 adverse events. The majority of adverse events occurred between the start of conditioning and day 29 in the trial.

Muraro et al (2017) conducted a retrospective cohort study of patients with MS treated with HCT between 1995-2006 (Table 3). Data was collected from 25
centers in 13 European countries. Results are presented in Table 4. Factors associated with neurological progression included age, progressive versus relapsing MS, and ≥2 previous therapies.

Table 3. Characteristics of Observational Studies of HCT for MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Participants</th>
<th>N</th>
<th>Median years (range) follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassas (2011)</td>
<td>Case series</td>
<td>Greece</td>
<td>Patients with aggressive MS treated with HCT</td>
<td>35</td>
<td>11 (2 to 15)</td>
</tr>
<tr>
<td>Shevchenko (2012)</td>
<td>Case series</td>
<td>Russia</td>
<td>Patients with relapsing/remitting or progressive MS treated with HCT</td>
<td>99</td>
<td>4 (NR)</td>
</tr>
<tr>
<td>Mancardi et al (2012)</td>
<td>Case series</td>
<td>Italy</td>
<td>Patients with severe MS treated with HCT</td>
<td>74</td>
<td>4 (0.8 to 10)</td>
</tr>
<tr>
<td>Burman (2014)</td>
<td>Case series</td>
<td>Sweden</td>
<td>Patients with aggressive MS treated with HCT</td>
<td>41</td>
<td>4 (1 to 9)</td>
</tr>
<tr>
<td>Burman (2014)</td>
<td>Case series</td>
<td>United States</td>
<td>Patients with relapsing/remitting MS treated with HCT</td>
<td>151</td>
<td>2 (0.5 to 5)</td>
</tr>
<tr>
<td>Atkins (2016)</td>
<td>Case series</td>
<td>Canada</td>
<td>Patients with relapsing MS treated with HCT</td>
<td>24</td>
<td>6.7 (4 to 13)</td>
</tr>
<tr>
<td>Nash (2017)</td>
<td>Case series</td>
<td>United States</td>
<td>Patients with relapsing/remitting or progressive MS treated with HCT</td>
<td>24</td>
<td>5.2 (1 to 6)</td>
</tr>
<tr>
<td>Muraro (2017)</td>
<td>Retrospective cohort</td>
<td>Europe (13 countries)</td>
<td>Patients with aggressive treatment-refractory MS treated with HCT</td>
<td>281</td>
<td>6.6 (0.2 to 16)</td>
</tr>
</tbody>
</table>

HCT: hematopoietic cell transplantation; MS: multiple sclerosis.

Table 4. Results of Observational Studies of HCT for MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Followup</th>
<th>PFS, % (95% CI)</th>
<th>TRM, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassas (2011)</td>
<td>15 years</td>
<td>All: 25 (NR) Active MRI lesions: 44 (NR) No active MRI lesions: 10 (NR) 80 (68 to 88)</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Shevchenko (2012)</td>
<td>8 years</td>
<td>92 (85 to 96) 87 (78 to 93)</td>
<td>0</td>
</tr>
<tr>
<td>Mancardi et al (2012)</td>
<td>4 years</td>
<td>70 (47 to 84)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Burman (2014)</td>
<td>5 years</td>
<td>68 (NR)</td>
<td>0</td>
</tr>
<tr>
<td>Burt (2015)</td>
<td>2 years</td>
<td>91 (75 to 97)</td>
<td>0</td>
</tr>
<tr>
<td>Atkins (2016)</td>
<td>3 years</td>
<td>70 (47 to 84)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Nash (2017)</td>
<td>5 years</td>
<td>All: 46 (42 to 54) Relapsing: 73 (57 to 88)</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Muraro (2017)</td>
<td>5 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section Summary: Multiple Sclerosis
Evidence for the use of HCT in patients with MS consists of 2 RCTs, systematic reviews, and many single-arm studies. One RCT compared HCT (n=9) with mitoxantrone (n=12). The primary outcome was the number of new T2 lesions detected by MRI. The HCT group developed statistically fewer new T2 lesions than the mitoxantrone group. The other RCT compared nonmyeloablative HCT results in patients with continued disease-modifying therapy and found a benefit to HCT in prolonging time to disease progression. Outcomes in the single-arm studies included PFS, relapse-free survival, disease activity-free survival, disease stabilization, number of new lesions, and improvements in EDSS scores. While improvements were seen in all outcomes compared with baseline, there were no comparative treatments. Adverse event rates were high, studies reporting treatment-related death rates ranging from 0 to 4%.

Systemic Sclerosis (Scleroderma)
Clinical Context and Therapy Purpose
The purpose of HCT in patients who have systemic sclerosis (scleroderma) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with systemic sclerosis (scleroderma) compared to conventional medical therapy?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients with systemic sclerosis or scleroderma.

Interventions
The therapy being considered is HCT. HCT is performed in a tertiary care center by transplant specialist teams.

Comparators
Comparators consist of conventional medical therapy. Most patients with autoimmune disorders such as systemic sclerosis or scleroderma 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.
Primary care practitioners and rheumatologists manage the care of patients with systemic sclerosis.

**Outcomes**
Outcomes of interest include progression-free survival (PFS), overall survival (OS), improvement in clinical symptoms, adverse events, and treatment-related mortality (TRM).

Follow-up for one year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.

**Study Selection Criteria**
Methodologically credible studies were selected using the principles described in the first indication.

**Systematic Reviews**
A review by Milanetti et al (2011) summarized 8, phase 1 and 2 clinical studies using autologous HCT to treat systemic sclerosis.\(^\text{19}\) The number of patients in each study ranged from 6 to 57. The proportion of patients across the studies achieving a 25% decrease in the Rodnan Skin Score (RSS) ranged from 60% to 100%. Pooled analyses were not conducted.

Host et al (2017) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.\(^\text{20}\) The literature search, conducted through March 2016, identified 9 studies (2 RCTs and 7 observational studies) for inclusion. The RCTs reported improvements in progression- and event-free survival (EFS) and all studies reported improvements in modified RSS. However, TRM rates ranged from 0% to 23%, with higher rates found with higher doses of cyclophosphamide or myeloablative conditioning regimens. No pooled analysis was conducted.

Shouval et al (2018) conducted a meta-analysis of 4 studies (3 RCTs and 1 retrospective comparative study) on the use of autologous HCT compared with cyclophosphamide alone for the treatment of systemic sclerosis.\(^\text{21}\) Quality assessment of the 3 RCTs found that 2 of the RCTs had low-risk in the randomization methods and outcome reporting, one RCT was unclear in randomization methods, and all 3 were high-risk since blinding of patients and outcome assessors was not conducted. Meta-analyses of the RCTs showed that all-cause mortality favored HCT (risk ratio 0.6 [95% CI: 0.4 to 0.9]) and TRM favored cyclophosphamide alone (risk ratio 10.8 [95% CI: 1.4 to 85.7]).

**Randomized Controlled Trials**
An open-label, randomized, controlled phase 2 trial (ASSIST; Burt et al [2011]) evaluated the safety and efficacy of autologous nonmyeloablative HCT compared with the standard of care (cyclophosphamide) (Table 5).\(^\text{22}\) The primary outcome was an improvement at 12 months, which was defined as a decrease in modified RSS (<25% for those with initial modified RSS >14) or an increase in forced vital capacity (FVC) of more than 10% (Table 6). Patients in the control
group with disease progression (>25% increase in modified RSS or decrease of >10% in FVC) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. Patients allocated to HCT (n=10) improved at or before the 12-month follow-up compared with none of the 9 patients allocated to cyclophosphamide (p<0.001). Treatment failure (ie, disease progression without interval improvement), occurred in 8 of 9 controls but did not occur in any of the 10 patients treated by HCT (p<0.001). After long-term follow-up (mean, 2.6 years) of patients allocated to HCT, all but 2 patients had sustained improvement in modified RSS and FVC, with the longest follow-up of 60 months. Seven patients allocated to cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HCT without complication; all improved after HCT. Four of these patients, followed for at least 1 year, had a mean (standard deviation [SD]) decrease in modified RSS from 27 (SD=15.5) to 15 (SD=7.4), an increase in FVC from 65% (20.6%) to 76% (26.5%), and an increase in total lung capacity from 81% (14.0%) to 88% (13.9%). Data for 11 patients, with a follow-up of to 2 years after HCT, suggested that the improvements in modified RSS (p<0.001) and FVC (p<0.03) persisted.

Results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published by van Laar et al (2014), (Tables 5 and 6). ASTIS was a phase 3 RCT comparing autologous HCT with cyclophosphamide for the treatment of systemic sclerosis. A total of 156 patients were recruited between March 2001 and October 2009. Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary endpoint was EFS, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary endpoints included TRM, toxicity, and disease-related changes in modified RSS, organ function, body weight, and QOL scores. The internal validity (risk of bias) of ASTIS was assessed according to the U.S. Preventive Services Task Force criteria for randomized trials. The trial was rated as poor-quality according to this framework because of 2 flaws: outcome assessment was not masked to patients or assessors, and 18 (24%) of 75 of the control group discontinued intervention because of death, major organ failure, adverse events, or nonadherence. Furthermore, the trial design permitted crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors reported the use of unspecified concomitant medications or other supportive care measures was allowed at the discretion of the investigators, adding further uncertainty to the results. Of the 53 primary endpoint events recorded, 22 were in the HCT group (19 deaths, 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 were in the control group (23 deaths, 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data showed patients treated with HCT experienced more events in the first year but appeared to have better long-term EFS than the controls, with Kaplan-Meier curves for OS crossing at about 2 years after treatment, with the OS rate at that time estimated at 85%. According to the Kaplan-Meier curves, at 5 years, the OS rate
was estimated at 66% in the control group and estimated at 80% in the HCT group (p-value unknown). Time-varying hazard ratios (modeled with treatment by time interaction) for EFS were 0.35 (95% CI, 0.15 to 0.74) at 2 years and 0.34 (95% CI, 0.16 to 0.74) at 4 years, supporting a benefit of HCT compared with pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HCT group and 30 (37% by intention-to-treat, p=0.002) of the control group.

Sullivan et al (2018) conducted an RCT comparing autologous HCT with cyclophosphamide for the treatment of scleroderma (Table 5).\textsuperscript{24} The trial was originally designed for 226 patients, but due to low accrual, a total of 75 patients participated. Of the 36 patients randomized to receive HCT, 27 completed the trial per protocol (3 died and 6 withdrew prematurely). Of the 39 patients randomized to receive cyclophosphamide alone, 19 completed the trial per protocol (11 died and 9 withdrew prematurely). The primary outcome was a global rank composite score. This score does not measure disease activity or severity but performs a pairwise comparison of the following: death, EFS, FVC, Disability Index of the Health Assessment Questionnaire, and the modified RSS. There were more percent pairwise comparisons favoring HCT over cyclophosphamide alone at 4- and 4.5-years follow-up (Table 6). The following disease progression events were significantly higher among patients receiving cyclophosphamide alone: initiating disease-modifying antirheumatic drugs, congestive heart failure leading to treatment, and pulmonary arterial hypertension. The following disease progression events were not significantly different among the two treatment groups: arrhythmia, pericardial effusion, renal crisis, and myositis. Comparisons in mortality rates are presented in Table 6.

### Table 5. Characteristics of RCTs of HCT for Systemic Sclerosis

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt (2011);\textsuperscript{22} ASSIST</td>
<td>United States</td>
<td>1</td>
<td>2006 to 2009</td>
<td>Adult patients &lt;60 yrs with diffuse SSC; mRSS &gt;15; internal organ involvement</td>
<td>High-dose intravenous cyclophosphamide 200 mg/kg; intravenous rabbit antithymocyte-globulin 6.5 mg/kg total dose; aHCT (n=10)</td>
</tr>
<tr>
<td>Van Laar (2014);\textsuperscript{23} ASTIS</td>
<td>9 European countries and Canada</td>
<td>29</td>
<td>2001 to 2009</td>
<td>Adult patients with diffuse cutaneous SSC; maximum duration 4 years;</td>
<td>High-dose intravenous cyclophosphamide 200 mg/kg; intravenous rabbit antithymocyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 monthly treatments with intravenous pulsed cyclophosphamide (1000 mg/m\textsuperscript{2}) (n=9)</td>
</tr>
</tbody>
</table>
minimum mRSS >15; internal organ involvement

- globulin 7.5 mg/kg total dose; aHCT (n=79)

- Adult patients with scleroderma; maximum duration 5 years; active interstitial lung disease and scleroderma-related renal disease

- Total body irradiation (800 cGy); cyclophosphamide (120 mg/kg); equine antithymocyte globulin (90 mg/kg); aHCT (n=36)

- 12 monthly treatments with intravenous pulsed cyclophosphamide (n=39)

Table 6. Results of RCTs of HCT for Systemic Sclerosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy Outcomes</th>
<th>Adverse Events</th>
<th>TRM n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt (2011);22, ASSIST</td>
<td>mRSS at 1 year mean (SD)</td>
<td>FVC at 1 year Mean % (SD)</td>
<td></td>
</tr>
<tr>
<td>aHCT</td>
<td>15 (7.9)</td>
<td>74 (15.7)</td>
<td>NR</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>22 (14.2)</td>
<td>61 (19.8)</td>
<td>NR</td>
</tr>
<tr>
<td>van Laar (2014);23, ASTIS</td>
<td>Events. 1 yr</td>
<td>Events. 4 yrs</td>
<td>Deaths, 1 yr</td>
</tr>
<tr>
<td>aHCT</td>
<td>13</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>8</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

- Relative Risk (95% CI) 1.6 (0.7 to 4.4) 0.7 (0.4 to 1.3) 1.5 (0.4 to 5.4) 0.6 (0.3 to 1.1)

- Sullivan (2018);24, SCOT | Global Rank Composite Score, at 4 Years | Global Rank Composite Score, at 4.5 Years | >Grade 3 Rate/person-yr | TRM n (%) |
| aHCT | 68% | 67% | 2.0 | 2 (5.5) |
| cyclophosphamide | 32% | 33% | 1.2 | 0 |
| p-value | 0.008 | 0.01 | <0.001 | |

- Death or Respiratory, Renal, or Cardiac Failure, n (%) | Death from any Cause, n (%) |
| aHCT | At 4 years: 10 (28) | At 4.5 years: 6 (17) |
| cyclophosphamide | At 4 years: 20 (51) | At 4.5 years: 11 (28) |
| p-value | 0.06 | 0.28 |

aHCT: autologous hematopoietic cell transplantation; mRSS: modified Rodnan skin scores; RCT: randomized controlled trial; SSc: systematic sclerosis.
Nonrandomized Studies
Vonk et al (2008) reported on the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HCT from 1998 to 2004.\textsuperscript{25} There were 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1-7.5 years), 81\% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified RSS, and a significant (ie, >25\%) decrease (ie, improvement) was achieved in 19 of 26 patients after 1 year and in 15 of 16 after 5 years. At study baseline, 65\% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5- and 7-year follow-ups. Based on the World Health Organization Performance Status, which reflects the effect of HCT on the combination of functional status, skin, lung, heart, and kidney involvement, the percentage of patients with a Performance Status score of 0 increased to 56\% from 4\% at baseline. The estimated survival rate at 5 years was 96.2\% (95\% CI, 89\% to 100\%) and at 7 years was 84.8\% (95\% CI, 70.2\% to 100\%); and the EFS rate (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3\% (95\% CI, 47.9\% to 86\%) at 5 years and 57.1\% (95\% CI, 39.3\% to 83\%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40\%.\textsuperscript{26}

Nash et al (2007) reported on the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HCT.\textsuperscript{27} Of the 34 patients, 27 (79\%) survived 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Of the 27 evaluable patients, 17 (63\%) had sustained responses at a median follow-up of 4 years (range, 1-8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline (p<0.001) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients using the Disability Index of the modified Health Assessment Questionnaire showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of 8 of 27 patients. Estimated OS and PFS rates were both 64\% at 5 years.

Henes et al (2012) reported on 26 consecutive patients with systemic sclerosis scheduled for autologous HCT between 1997 and 2009.\textsuperscript{28} The main outcome variable was a response to treatment (reduction of modified RSS by 25\%) at 6 months. Secondary endpoints were transplant-related mortality and PFS. At 6 months, significant skin and lung function improvement assessed on the modified RSS was achieved in 78.3\% of patients. The overall response rate was 91\%, and some patients even improved after month 6. Three patients died between mobilization and conditioning treatment\textsuperscript{42} were due to severe disease progression and 1 treatment-related. Seven patients relapsed during the 4.4 years of follow-up. The PFS rate was 74\%. Four patients died during follow-up, with the most frequent causes of death being pulmonary and cardiac complications of systemic sclerosis.
Section Summary: Systemic Sclerosis (Scleroderma)
Evidence for the use of HCT in patients with systemic sclerosis/scleroderma consists of 3 RCTs and several nonrandomized studies. All 3 RCTs report long-term improvements in clinical outcomes such as modified RSS and FVC, as well as overall mortality in patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, due to small sample sizes in 2 of the RCTs, only the large RCT shows statistical significance. TRM and adverse events are higher among the patients receiving HCT compared with patients receiving chemotherapy alone.

Systemic Lupus Erythematous

Clinical Context and Therapy Purpose
The purpose of HCT in patients who have SLE is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with SLE compared to conventional medical therapy?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients with SLE.

Interventions
The therapy being considered is HCT. HCT is performed in a tertiary care center by transplant specialist teams.

Comparators
Comparators consist of conventional medical therapy. Most patients with autoimmune disorders such as systemic sclerosis or scleroderma 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.

Primary care practitioners and rheumatologists manage the care of patients with systemic lupus erythematous.

Outcomes
Outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

Follow-up for 1 year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.
Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Systematic Review
Leone et al (2018) conducted a systematic review of clinical and laboratory studies using autologous HCT for patients with SLE.29 The literature search, conducted through 2014, identified 25 studies (n=279 patients): 2 prospective, 10 retrospective, and 13 case reports. Quality assessment of included studies was not discussed in the publication. Heterogeneity between studies was high (I²=87%). The only pooled analysis conducted was on 5 studies reporting deaths, resulting in overall mortality of 8.3% in a mean follow-up of 36 months.

Observational Studies
Select case series from the systematic review and series published after the review are described below.

Burt et al (2006) published results on the largest single-center series using HCT for SLE in the United States.30 Between 1997 through 2005, investigators enrolled 50 patients (mean age, 30 years; 43 women, 7 men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg/d of prednisone or its equivalent, despite the use of cyclophosphamide. Patients underwent autologous HCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a TRM rate of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), the 5-year OS rate was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity improved, including renal function, Systemic Lupus Erythematosus Disease Activity Index score, antinuclear antibody, anti-double-stranded DNA, complement C3, and C4 levels, and carbon monoxide diffusion lung capacity. The investigators suggested these results justified a randomized trial comparing immunosuppression plus autologous HCT with continued standard of care.

Song et al (2011) reported on the efficacy and toxicity of autologous HCT for 17 patients with SLE after 7 years follow-up.31 The OS I and PFS rates were used to assess the efficacy and toxicity levels of the treatment. The median follow-up was 89 months (range, 33-110 months). The probabilities of 7-year OS and PFS were 82.4% and 64.7%, respectively. The principal adverse events included allergy, infection, elevated liver enzymes, bone pain, and heart failure. Two patients died, 1 due to severe pneumonia and the other due to heart failure at 33 and 64 months after transplantation, respectively. The authors concluded their 7-year follow-up results suggested that autologous HCT was beneficial for SLE patients.

Leng et al (2017) reported on 24 patients with severe SLE who received high-dose immunosuppressive therapy and HCT.32 Patients were followed for 10 years. One
patient died following treatment. At the 6-month follow-up, 2 patients had achieved partial remission, and 21 patients had achieved remission. At the 10-year follow-up, the OS rate was 86%; 16 patients remained in remission, 4 were lost to follow-up, 2 had died, and 1 had active disease.

Cao et al (2017) reported on 22 patients with SLE who underwent autologous peripheral blood HCT. At 5-year follow-up, PFS was 68% and OS was 95%. At last follow-up, 10 patients had relapsed. Adverse events included infections, secondary autoimmunity, lymphoma, and malignancy. The authors noted difficulty in distinguishing between conditions caused by relapse or by the transplantation.

Burt et al (2018) reported on 30 patients with refractory, chronic, corticosteroid-dependent SLE who underwent autologous HCT. Outcomes were measured at six months and yearly through five years. Disease remission was achieved by 24 patients. The SLE Disease Activity Index and QOL 36-Item Short-Form Health Survey improved significantly at each follow-up compared with baseline. No TRM was reported. Five grade 4 and 60 grade 3 adverse events were reported.

**Section Summary: SLE**
Evidence for the use of autologous HCT to treat patients with SLE consists of a systematic review and numerous case series. The systematic review did not conduct a quality assessment and reported high heterogeneity among the studies. A 4% TRM rate was reported in 2 studies. High rates of remission were reported at various follow-up times and adverse event rates were high. While HCT has shown beneficial effects on patients with SLE, further investigation of more patients is needed.

**Juvenile Idiopathic or Rheumatoid Arthritis**

**Clinical Context and Therapy Purpose**
The purpose of HCT in patients who have JIA or RA is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with JIA or RA compared to conventional medical therapy?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is patients with JIA or RA.

**Interventions**
The therapy being considered is HCT. HCT is performed in a tertiary care center. Primary care practitioners and rheumatologists manage the care of patients with juvenile idiopathic or rheumatoid arthritis.
Comparators
Comparators consist of conventional medication therapy. Most patients with autoimmune disorders such as juvenile idiopathic or rheumatoid arthritis 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.

Primary care practitioners and rheumatologists manage the care of patients with JIA or RA.

Outcomes
Outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

Follow-up for 1 year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

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

Silva et al (2018) reported on 16 patients with JIA refractory to standard therapy or who had failed autologous HCT, who underwent allo-HCT. Patients experienced significant improvements in arthritis and QOL, with 11 children achieving drug-free remission at last follow-up. At a median follow-up of 29 months, 1 patient died of probable sepsis following elective surgery and 1 died of invasive fungal infection, for a TRM rate of 12.5%.

Section Summary: JIA or RA
Evidence for the use of HCT on patients with JIA consists of data from an EBMT Registry (n>50) and a case series. Different conditioning regimens were used among the patients in the registry, with remission rates averaging 50%. However, relapse has been reported within 6 months in many cases, and new biologic therapies that provide improved outcomes are available for these patients. The case series of patients with refractory JIA reported a high rate of drug-free remission (69%), with a TRM rate of 12.5%.
Chronic Inflammatory Demyelinating Polyneuropathy

Clinical Context and Therapy Purpose
The purpose of HCT in patients who have chronic inflammatory demyelinating polyneuropathy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with chronic inflammatory demyelinating polyneuropathy compared to conventional medication therapy?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients with chronic inflammatory demyelinating polyneuropathy.

Interventions
The therapy being considered is HCT. HCT is performed in a tertiary care center with transplant specialist teams.

Comparators
Comparators consist of conventional medication therapy. Most patients with autoimmune disorders such as chronic inflammatory demyelinating polyneuropathy 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.

Primary care practitioners and neurologists manage the care of patients with chronic inflammatory demyelinating polyneuropathy.

Outcomes
Outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

Follow-up for 1 year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Several review articles have summarized experience with HCT in the treatment of chronic inflammatory demyelinating polyneuropathy. In general, the
evidence includes a few case reports describing outcomes for autologous HCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange. While improvements were reported, some with long-term follow-up, the numbers of patients undergoing the procedure are small, and the potential for serious adverse events is a concern.

Section Summary: Chronic Inflammatory Demyelinating Polyneuropathy
Evidence for the use of HCT to treat patients with chronic inflammatory demyelinating polyneuropathy is limited to case reports. Additional investigations are needed due to the toxicity associated with this procedure.

Type 1 Diabetes

Clinical Context and Therapy Purpose
The purpose of HCT in patients who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of HCT improve net health outcomes in patients with type I diabetes compared to conventional medication therapy?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients with type 1 diabetes.

Interventions
The therapy being considered is HCT. HCT is performed in a tertiary care center with transplant specialist teams.

Comparators
Comparators consist of conventional medication therapy. Most patients with autoimmune disorders such as type 1 diabetes 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.

Primary care practitioners and endocrinologists manage the care of patients with type 1 diabetes.

Outcomes
Outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

Follow-up for year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.
Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Systematic Review
El-Badawy and El-Badri (2016) published a meta-analysis on the use of HCT to treat diabetes.\(^40\). The literature search, conducted through August 2015, identified 22 studies for inclusion; study design of included studies was not consistently reported. Fifteen of the studies (n=300 patients) involved patients with type 1 diabetes; 7 studies (n=224 patients) involved patients with type 2 diabetes. The quality of the selected studies was assessed using Cochrane criteria, however, results of the risk of bias assessment were not reported in the publication. The mean follow-up in the studies ranged from 6 to 48 months (median, 12 months). Table 7 presents comparisons of C-peptide levels (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells) and hemoglobin A\(_1c\) levels after 12-month follow-up. Adverse events were reported in 22% of the patients, with no reported mortality. Reviewers concluded that remission of diabetes is possible and safe with stem cell therapy, patients with previously diagnosed ketoacidosis are not good candidates for HCT, and that early-stage patients may benefit more from HCT. Large-scale well-designed randomized studies considering stem cell type, cell number, and infusion method are needed.

Table 7. Standard Mean Differences from Baseline in C-Peptide and HbA\(_1c\) Levels in Patients with Diabetes Treated with HCT After 12 Months of Follow-Up

<table>
<thead>
<tr>
<th>Diabetes Subgroups</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>SMD (95% CI) C-Peptide</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>SMD (95% CI) HbA(_1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ UCB</td>
<td>4</td>
<td>56</td>
<td>1.07 (0.67 to 1.48)</td>
<td>4</td>
<td>61</td>
<td>0.05 (-0.30 to 0.41)</td>
</tr>
<tr>
<td>▪ UC-MSC</td>
<td>1</td>
<td>15</td>
<td>-0.91 (-1.67 to -0.16)</td>
<td>1</td>
<td>15</td>
<td>1.19 (0.41 to 1.98)</td>
</tr>
<tr>
<td>▪ BM-HSC</td>
<td>4</td>
<td>97</td>
<td>-1.37 (-1.69 to -1.05)</td>
<td>3</td>
<td>96</td>
<td>3.87 (3.29 to 4.44)</td>
</tr>
<tr>
<td>▪ BM-MSC</td>
<td>1</td>
<td>10</td>
<td>-1.18 (-2.15 to -0.22)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>▪ IS-ADSc + BM-HSC</td>
<td>2</td>
<td>21</td>
<td>-1.01 (-1.73 to -0.30)</td>
<td>2</td>
<td>21</td>
<td>0.93 (0.27 to 1.59)</td>
</tr>
<tr>
<td>▪ Total</td>
<td>12</td>
<td>199</td>
<td>-0.57 (-1.73 to -0.35)</td>
<td>10</td>
<td>193</td>
<td>1.09 (0.83 to 1.35)</td>
</tr>
</tbody>
</table>

Adapted from El-Badawy and El-Badri (2016).\(^40\).
BM-HSC: bone marrow hematopoietic stem cells; BM-MNC: bone marrow mononuclear stem cells; BM-MSC: bone marrow mesenchymal stem cells; CI: confidence interval; HbA\(_1c\): hemoglobin A\(_1c\);
Case Series
Several case series have evaluated autologous HCT in patients with new-onset type 1 diabetes; there were no published comparative studies. Although a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high.

Cantu-Rodriguez et al (2016) published a study of 16 patients with type 1 diabetes who received a less toxic conditioning regimen and transplantation. The outpatient procedures were completed without severe complications. At the 6-month follow-up, 3 (19%) were nonresponders, 6 (37%) partially independent from insulin, and 7 (44%) were completely independent of insulin. Hemoglobin A1c levels decreased by a mean of -2.3% in the insulin-independent group.

Xiang et al (2015) published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than 6 weeks before study enrollment. After a mean follow-up of 28.5 months (range, 15-38 months), 71 (55%) patients were considered to be insulin-free. These patients had a mean remission period of 14.2 months. The other 57 (45%) patients were insulin-dependent. The latter group included 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (one patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HCT were of a younger age at onset of diabetes, lower tumor necrosis factor α levels, and higher fasting C-peptide levels.

A case series by Snarski et al (2016) reported on 24 patients with a diagnosis of type 1 diabetes who underwent autologous HCT. Mean age was 26.5 years (range, 18-34 years). After treatment, 20 (87%) of 23 patients went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. The median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at 2 and 3 years, but the insulin doses returned to pre-HCT levels at years 4 and 5. Among 20 patients remaining in follow-up at the time of data analysis for publication, 4 (20%) remained insulin-free. In an update published by Walicka et al (2018), after 6 years of follow-up, 1 patient remained insulin-free. Adverse events include neutropenic fever in 12 (50%) patients. There were 4 cases of sepsis, including a fatal case of *Pseudomonas aeruginosa* sepsis. There was also a case of pulmonary emphysema after insertion of a central venous catheter.

Section Summary: Type 1 Diabetes
Evidence for the use of HCT to treat diabetes consists of several case series and a meta-analysis of 22 studies. The meta-analysis revealed that HCT is more effective...
in patients with type 1 diabetes compared with type 2 diabetes, and when the
treatment is administered soon after the diagnosis. Certain factors limit the
conclusions that can be drawn about the overall effectiveness of HCT to treat
diabetes due to heterogeneity in the stem cell types, cell number infused, and
infusion methods. Case series reported short-term effectiveness in achieving
insulin independence; however, long-term studies showed that a majority of
patients returned to insulin within 4 to 6 years.

Other Autoimmune Diseases

Clinical Context and Therapy Purpose
The purpose of HCT in patients who have other autoimmune diseases is to provide
a treatment option that is an alternative to or an improvement on existing
therapies.

The question addressed in this evidence review is: Does the use of HCT improve
net health outcomes in patients with other autoimmune diseases compared to
conventional medication therapy?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is patients with other autoimmune diseases.

Interventions
The therapy being considered is HCT. HCT is performed in a tertiary care center
with transplant specialist teams.

Comparators
Comparators consist of conventional medication therapy. 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.

Primary care practitioners, rheumatologist sand other subspecialists manage
the care of patients with other autoimmune diseases.

Outcomes
Outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse
events, and TRM.

Follow-up for year is standard to measure treatment-related adverse events and
mortality. Several years of follow-up are necessary to determine the efficacy of
treatment.
Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Crohn Disease
Phase 2/3 protocols are being developed for Crohn disease. Hawkey et al (2015) have conducted the only RCT (ASTIC trial) evaluating the effect of HCT on Crohn disease.\(^4^4\) Patients were randomized to receive either immunoablation and HCT (n=23) or control (HCT deferred for 1 year, n=22). The primary endpoint was remission defined as Crohn Disease Activity Index <150; no use of corticosteroids or immunosuppressive drugs or biologics for 3 months; and no endoscopic or radiologic evidence of active disease. At 1 year follow-up, 2 patients in the treatment group and 1 patient in the control group achieved remission (p=0.6). Adverse events were reported in 76 patients receiving HCT and in 38 controls. One HCT patient died.

Lindsay et al (2017) reported additional analyses on the ASTIC trial participants, combining the treated patients and the control patients who underwent deferred HCT.\(^4^5\) Outcomes were 3 month steroid-free clinical remission at 1 year and degree of endoscopic healing at 1 year. Three-month steroid-free clinical remission was achieved by 13 of 34 (38%; 95% CI, 22% to 55%) patients who had data available. Complete endoscopic healing was seen in 19 of 38 patients (50%; 95% CI, 34% to 66%). However, serious adverse events (76) were experienced in 23 of 40 patients.

Brierley et al (2018) published a review of patients in the EBMT Registry undergoing autologous NCT for Crohn disease (n=82) who had failed a median of 6 lines of drug therapy.\(^4^6\) At a median follow-up of 41 months, 68% achieved either complete remission or significant improvement in symptoms. One patient died of causes relating to the transplant (cytomegalovirus infection, sepsis, and organ failure). At a median of 10 months follow-up, 73% resumed medical therapy for Crohn disease.

Additional Autoimmune Diseases
For the remaining autoimmune diseases (eg, immune cytopenias, relapsing polychondritis), sample sizes are too small to draw conclusions.

A case series of 7 patients with myasthenia gravis was reported by Bryant et al (2016).\(^4^7\) Using the Myasthenia Gravis Foundation of America clinical classification, all patients achieved complete stable remission, with follow-up from 29 to 149 months. The authors concluded that these positive long-term results warranted further investigation of HCT for patients with myasthenia gravis.

Section Summary: Other Autoimmune Diseases
Evidence for the use of HCT to treat Crohn disease consists of an RCT and a retrospective review of registry data. While remission was experienced by some patients receiving HCT, adverse event rates were high, and many patients had a recurrence of symptoms within one year.
Evidence for the use of HCT to treat other autoimmune diseases consists of small retrospective studies. Information from larger prospective studies is needed.

Summary of Evidence
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. The findings of the case series revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes 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 hematopoietic cell transplantation (HCT) as a therapeutic option. The AAN (2018) published guidelines on the use of disease-modifying medications for
patients with MS\textsuperscript{49,50}; 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.\textsuperscript{51} Table 8 lists guidelines for specific indications addressed in this evidence review.

**Table 8. Recommendations for the Use of HCT to Treat Autoimmune Diseases**

<table>
<thead>
<tr>
<th>Indications for HCT in Pediatric Patients (Generally &lt;18 y)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Juvenile rheumatoid arthritis</td>
<td>D</td>
<td>R</td>
</tr>
<tr>
<td>▪ Systemic sclerosis</td>
<td>D</td>
<td>R</td>
</tr>
<tr>
<td>▪ Other autoimmune and immune dysregulation disorders</td>
<td>R</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications for HCT in Adults &gt;18 y</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Multiple sclerosis</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>▪ Systemic sclerosis</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>▪ Rheumatoid arthritis</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>▪ Systemic lupus erythematosus</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>▪ Crohn disease</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>▪ Polymyositis-dermatomyositis</td>
<td>N</td>
<td>D</td>
</tr>
</tbody>
</table>

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.”\textsuperscript{52}

**European League Against Rheumatism**
The European League against Rheumatism (2017) convened a task force to update recommendations for the treatment of systemic sclerosis.\textsuperscript{53} 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

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 9.

Table 9. Nationally Covered and Noncovered Indications for HCT

<table>
<thead>
<tr>
<th>Covered and Noncovered Indications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nationally covered indications</td>
<td></td>
</tr>
<tr>
<td><strong>Allogeneic HCT</strong></td>
<td></td>
</tr>
<tr>
<td>• “Effective...1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary”</td>
<td></td>
</tr>
<tr>
<td>• “Effective...1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome”</td>
<td></td>
</tr>
<tr>
<td>• “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”</td>
<td></td>
</tr>
<tr>
<td><strong>Autologous HCT</strong></td>
<td></td>
</tr>
<tr>
<td>• ”Effective...1989, [autologous HCT] is considered reasonable and necessary ... for the following conditions and is covered under Medicare for patients with: 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.”</td>
<td></td>
</tr>
<tr>
<td>• ”Effective...2000, single [autologous HCT] is only covered for Durie-Salmon Stage II or III patients that fit the following requirements: 1. 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 2. Adequate cardiac, renal, pulmonary, and hepatic function.”</td>
<td></td>
</tr>
<tr>
<td>• ”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: 1. Amyloid deposition in 2 or fewer organs; and, 2. Cardiac left ventricular ejection fraction (EF) greater than 45%.”</td>
<td></td>
</tr>
</tbody>
</table>

Nationally noncovered indications
Covered and Noncovered Indications

Allogeneic HCT

• "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 10.

Table 10. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00278629</td>
<td>Non-myeloablative Autologous Hematopoietic Stem Cell Transplantation in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: A Phase II Trial</td>
<td>80</td>
<td>Jul 2020</td>
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<tr>
<td>NCT03000296</td>
<td>Autologous Unselected Hematopoietic Stem Cell Transplantation for Refractory Crohn’s Disease</td>
<td>50</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT03562208a</td>
<td>Autologous Bone Marrow Transplant in Chronic Insulin Dependent Diabetic Patients Phase II Clinical Trial</td>
<td>100</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT00750971</td>
<td>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</td>
<td>30</td>
<td>Aug 2020</td>
</tr>
<tr>
<td>NCT02674217</td>
<td>Outpatient Hematopoietic Grafting in Patients with Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: a Feasibility Study</td>
<td>200</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT03069170</td>
<td>Safety and Efficacy of Immuno-Modulation and Autologous Bone-Marrow Derived Stem Cell Transplantation for the Treatment of Multiple Sclerosis</td>
<td>50</td>
<td>Jan 2021</td>
</tr>
<tr>
<td>NCT01445821</td>
<td>Randomized Study of Different Non-myeloablative Conditioning Regimens with Hematopoietic Stem Cell Support in Patients with Scleroderma (ASSIST-IIb)</td>
<td>160</td>
<td>Sep 2021</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>NCT03113162</td>
<td>Evaluation of the Safety and Efficacy of Reduced-Intensity Immunoablation and Autologous Hematopoietic Stem Cell Transplantation (AHSCT) in Multiple Sclerosis</td>
<td>15</td>
<td>May 2022</td>
</tr>
<tr>
<td>NCT01895244</td>
<td>High-dose Chemotherapy and Transplantation of 43+ Selected Stem Cells for Progressive Systemic Sclerosis - Modification According to Manifestation</td>
<td>44</td>
<td>Sep 2022</td>
</tr>
<tr>
<td>NCT03477500</td>
<td>Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients with Relapsing Remitting Multiple Sclerosis</td>
<td>100</td>
<td>Mar 2024</td>
</tr>
<tr>
<td>NCT00273364</td>
<td>Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study</td>
<td>110</td>
<td>Sep 2024</td>
</tr>
<tr>
<td>NCT04047628</td>
<td>A Multicenter Randomized Controlled Trial of Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Treatment-Resistant Relapsing Multiple Sclerosis (ITN077AI)</td>
<td>156</td>
<td>Oct 2028</td>
</tr>
<tr>
<td>NCT02516124</td>
<td>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</td>
<td>82</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a denotes industry sponsorship

REFERENCES


Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow transplantation; autologous</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose</td>
</tr>
</tbody>
</table>
chemotherapy, and 28 days of post-transplant care (including drugs; hospitalization; medical surgical, diagnosis and emergency services)

**ICD10 Codes**

- **E10.10-E10.9**  
  Type 1 diabetes mellitus code range
- **G35**  
  Multiple sclerosis
- **M05.10-M06.9**  
  Rheumatoid arthritis code range
- **M08.00-M08.99**  
  Juvenile arthritis code range
- **M32.0-M32.9**  
  Systemic lupus erythematosus code range
- **M34.0-M34.9**  
  Systemic sclerosis [scleroderma] code range

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- **8/1/02** New policy.
- **8/1/03** No policy statement changes.
- **8/1/04** No policy statement changes.
- **8/1/05** No policy statement changes.
- **8/1/06** No policy statement changes.
- **8/1/07** No policy statement changes.
- **8/1/08** No policy statement changes.
- **8/1/09** Description revised extensively; “high-dose chemotherapy” removed from policy title and policy statements. “Stem-cell transplantation” (SCT) now used instead of “stem-cell support” (SCS) in policy and policy statements. Intent of current policy statements unchanged.
- **8/1/10** “Hematopoietic” included in the policy statement; however, intent remains unchanged.
- **8/1/11** Policy statement revised to add indications of juvenile idiopathic arthritis and diabetes mellitus as investigational.
- **8/1/12** No policy statement changes.
- **8/1/13** No policy statement changes.
- **11/1/13** No policy statement changes.
- **3/1/14** Chronic inflammatory demyelinating polyneuropathy added as an investigational indication. Added cpt codes.
- **3/1/15** No policy statement changes.
- **3/1/16** No policy statement changes.
- **3/1/17** No policy statement changes.
- **3/1/18** “Stem” removed from title and Policy. HSCT changed to HCT. Policy statement unchanged.
- **4/1/19** Policy statement for systemic sclerosis was changed from “investigational” to “medically necessary”. Added investigational.
statement. Main policy intent changed to Medically Necessary.

3/1/20 No policy statement changes.

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