Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

Policy Number: 8.01.42  Last Review: 6/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem-cell transplantation for primary amyloidosis when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Autologous stem-cell transplantation may be considered medically necessary to treat primary systemic amyloidosis.

When Policy Topic is not covered
Allogeneic stem-cell transplantation is considered investigational to treat primary systemic amyloidosis.

Considerations
In 2003, CPT centralized codes describing allogeneic and autologous hematopoietic cell transplantation services to the hematology section (38204-38242). Not all codes are applicable for each stem cell transplant procedure. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207-38215).

CPT 38208 and 38209 describe thawing and washing of cryopreserved cells
CPT 38210-38214 describe certain cell types being depleted
CPT 38215 describes plasma cell concentration.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
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<tr>
<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 primary amyloidosis</td>
<td>• Autologous hematopoietic cell transplantation</td>
<td>• Chemotherapy</td>
<td>• Overall survival</td>
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<td>• Disease-specific survival</td>
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<td>• Change in disease status</td>
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<td>• Treatment-related</td>
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</table>
Hematopoietic cell transplantation (HCT) refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT).

For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse and shows high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input and national and international clinical guidelines support the use of autologous HCT as a treatment of amyloidosis. For primary amyloidosis, allogeneic HCT is not recommended. Thus, autologous HCT may be considered medically necessary for primary amyloidosis and allogeneic HCT for primary amyloidosis is considered investigational.
**Background**

**Primary Amyloidosis**
The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified by the type of amyloidogenic protein involved and by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas in localized disease, the amyloid light chain protein is produced at the site of deposition. Primary or amyloid light chain amyloidosis, the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is 60 years. The amyloidogenic protein in primary amyloidosis is an immunoglobulin light chain or light chain fragment produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in primary amyloidosis is typically low, ranging from 5% to 10%, this disease also may occur in association with multiple myeloma in 10% to 15% of patients. Deposition of primary amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

**Treatment**
Historically, this disease has had a poor prognosis, with a median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous hematopoietic cell transplantation (HCT). Emerging approaches include the use of immunomodulating drugs (eg, thalidomide, lenalidomide) and the proteasome inhibitor bortezomib. Regardless of the approach, treatment of primary amyloidosis aims at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

**Hematopoietic Cell Transplantation**
HCT refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. The use of cord blood is discussed in a separate policy.

**Autologous HCT**
Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. The success of autologous HCT is
predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete response. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**Allogeneic HCT**

Immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility to opportunistic infections.

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains variable with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual
malignant cells. For this evidence review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**Regulatory Status**
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**Rationale**
This evidence review was created in October 2003 and has been updated regularly with searches of the MEDLINE and EMBASE databases. The most recent literature update was performed through November 1, 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, 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. The following is a summary of key literature to date.

**Primary Amyloidosis**
Chemotherapy for the treatment of light chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone. This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies. Survival after oral melphalan with prednisone (typically 12-18 months) is longer than for untreated patients or those given older therapies (10-14 months), but more effective regimens have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone, a well-established regimen for
myeloma, has been investigated.\textsuperscript{1,2} However, because of its toxicity, vincristine, doxorubicin, and dexamethasone therapy are usually limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis.

Because conventional regimens rarely cure systemic amyloidosis, and because of the close biologic similarity to multiple myeloma, myeloablative chemotherapy with autologous hematopoietic stem transplantation (HCT) is being investigated for this disease.

**Hematopoietic Cell Transplantation**

**Clinical Context and Therapy Purpose**
The purpose of HCT, autologous or allogeneic, in patients who have primary amyloidosis, 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 (autologous or allogeneic) improve the net health outcomes in patients with primary amyloidosis compared with chemotherapy alone?

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

**Patients**
The relevant population of interest are patients with primary amyloidosis.

**Interventions**
The therapy being considered is HCT, either autologous or allogeneic. HCT refers to in the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy.

In autologous HCT, stem cells are harvested from the patient’s own bone marrow or peripheral blood. Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete response (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

In allo-HCT, stem cells are harvested from a donor’s bone marrow, peripheral blood, or umbilical cord blood. Immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HCT.
Compatibility is established by typing human leukocyte antigen using cellular, serologic, or molecular techniques. First, cytotoxic agents are administered with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. Immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility to opportunistic infections.

**Comparator**

The comparator to autologous HCT is chemotherapy alone. Treatment of primary amyloidosis aims at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. Emerging approaches include the use of immunomodulating drugs (eg, thalidomide, lenalidomide) and the proteasome inhibitor bortezomib.

**Outcomes**

The general outcomes of interest are organ response, hematologic response, overall survival (OS), treatment-related morbidity, and treatment-related mortality. Organ response may include decreases in urinary protein and stabilization of creatinine clearance (kidney); decreases in interventricular septal thickness and improvements in two New York Heart Association classes (heart); decreases in abnormal alkaline phosphatase or liver size (liver); and improvements in nerve conduction velocity (nerve).

**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.

**Autologous HCT**

Initial results of autologous HCT in uncontrolled patient series were published in 1998.\(^3,4\) Clinical response rates (50%-60%) were near twice those reported for conventional therapy, and 2-year survival ranged from 56% to 68%.\(^5,6\) Kaplan-Meier analysis of a 2004 matched comparison study (63 pairs) showed greater OS for those given autotransplants (71% at 4 years) than for patients who were eligible for transplantation but managed conventionally (41%; \(p=0.004\)).\(^6\) However, procedure-related mortality rates of 15% to 43% were substantially higher than those observed in myeloma patients, usually in cases involving more than 2 organ systems or symptomatic cardiac involvement.\(^3,7,8\)
**Randomized Controlled Trials**

One randomized multicenter trial (2007) from the Myelome Autogreffe and Intergroupe Francophone du Myelome Intergroup compared conventional chemotherapy (melphalan plus dexamethasone, n=50) with myeloablative melphalan followed by autologous HCT (n=50). Randomization was stratified by age (<65 years or ≥65 years) and the affected organ system (cardiac, renal, neurologic, other). Of note, approximately two-thirds of patients had two or more organs affected. Hematopoietic stem cells were obtained from peripheral blood following granulocyte colony-stimulating factor mobilization. According to intention-to-treat analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 partial responses (28%) in the chemotherapy recipients vs 11 CR (22%) and 7 partial responses (14%) in the HCT group (p=0.11). At a median follow-up of 24 months, 20 patients in the chemotherapy group had died vs 31 in the autologous HCT group. Among 65 patients who could be evaluated, the intention-to-treat median survival for patients assigned to chemotherapy was 56.9 months vs 22.2 months in the autologous HCT group (p=0.04). Analysis of patients who survived for at least six months and who received their assigned treatment showed no significant difference in survival rates between treatments.

Although this RCT suggested that autologous HCT may be no more efficacious than conventional chemotherapy in prolonging survival, the results were limited by the proportion of patients not receiving treatment. Among 50 patients assigned to autologous HCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem cell harvest, 10 died before treatment), while 7 (14%) of 50 assigned to chemotherapy did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment).

**Nonrandomized Comparative Studies**

A retrospective comparative analysis from a single treatment center published in 2014 provides long-term evidence for improved survival among patients with amyloid light chain amyloidosis who underwent autologous HCT compared with conventional therapies (CTR). Patients underwent autologous HCT (n=80) or CTR (n=65) following induction therapy. Patients were heterogeneous concerning age, organ involvement, cardiac involvement, renal involvement, and percent of bone marrow blast cells; all were significantly overrepresented in the CTR group compared with the HCT group. Median follow-up was 3 years for the entire cohort, with some survivors followed for up to 14 years postdiagnosis. Median 5-year survival was 63% in the HCT group compared with 38% in the CTR group (p<0.001); median survival at 10 years was 56% in the HCT group and 10% in the CTR group (p<0.001). Among HCT recipients, the transplant-related mortality rate was 7.5% at 100 days and 12.5% within 1 year of transplant.

**Observational Studies**

The evidence has also suggested improvement in symptoms for amyloidosis patients treated with autologous HCT in addition to survival benefits (see Table 1).
### Table 1. Observational Studies on Autologous HCT for Primary Amyloidosis

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>FU</th>
<th>N at FU</th>
<th>CR Rate, %</th>
<th>OS Rate, %</th>
<th>Median Survival</th>
<th>TRM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibeira et al (2011)</td>
<td>421</td>
<td></td>
<td>340</td>
<td>34</td>
<td>6.3 y</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Madan et al (2012)</td>
<td>187</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sanchorawala et al (2007)</td>
<td>80</td>
<td>10 y</td>
<td>63</td>
<td>51</td>
<td>23</td>
<td>57 mo</td>
<td>14</td>
</tr>
<tr>
<td>Parmar et al (2014)</td>
<td>80</td>
<td>10 y</td>
<td></td>
<td></td>
<td>HCT=56 CTR=10</td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>D’Souza et al (2015)</td>
<td>140</td>
<td>5 y</td>
<td></td>
<td>55</td>
<td></td>
<td></td>
<td>20</td>
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<tr>
<td>1995-2000</td>
<td></td>
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<td></td>
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<tr>
<td>2001-2006</td>
<td>596</td>
<td>5 y</td>
<td></td>
<td>61</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>2006-2012</td>
<td>800</td>
<td>5 y</td>
<td></td>
<td>77</td>
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<td>5</td>
</tr>
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</table>

CR: complete response; CTR: conventional therapies; FU: follow-up; HCT: hematopoietic stem transplantation; OS: overall survival; TRM: treatment-related mortality.

In a 2004 series of 312 amyloidosis patients eligible for transplant, estimated median survival was 4.6 years. Of 181 evaluable patients (alive and followed-up for ≥1 year), 40% achieved a complete hematologic response, defined as no evidence of plasma cell dyscrasia at 1 year after transplant with functional improvement in at least 1 affected organ.

A 2006 registry analysis evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers. For those with no or 1 organ involved at transplant, survival at 1 year was 72%, while for those with 2 or more organs involved, survival at 1 year was 54%. Treatment-related mortality at 30 days was mostly among patients with cardiac and/or multiple organ involvement.

Patients with primary amyloidosis and cardiac involvement were treated in a 2012 series from a single center. Overall, hematologic and cardiac responses were observed in 66% and 41% of patients, respectively.

A 2011 series of 421 consecutive patients treated with HCT at a single referral center compared outcomes for patients with and without a CR. Eighty-one patients died within the first year after HCT and were not evaluable for hematologic and organ response. Of 340 evaluable patients, 43% achieved CR, and 78% of them experienced an organ response. Thus, treatment of selected amyloid light chain amyloidosis patients with autologous HCT resulted in high organ response and longer OS rates, even for those patients who did not achieve CR. These results are compatible with others previously cited.

Several additional retrospective and prospective series were reported in 2012 and 2013 on the use of autologous HCT in patients with primary amyloidosis. Results from these series are consistent with others that have suggested autologous HCT is feasible and beneficial in selected patients with primary amyloidosis.
Long-term survival and outcomes were evaluated in a 2007 series of 80 patients. Among the 32 patients who achieved CR, median survival had not been reached at the time of reporting. In contrast, the median survival for patients who failed to achieve a CR was 50 months, with a 6% estimated probability of survival at 10 years (p<0.001 vs patients with CR).

A 2015 report from the Center for International Blood and Marrow Transplant Research study identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012. Early mortality and OS were analyzed for 3 time cohorts: 1995 to 2000, 2001 to 2006, and 2007 to 2012. Over this period, OS rates improved from 55% to 77%, while early mortality rates decreased from 20% to 5%. Multivariate analysis showed that cardiac involvement was associated with high mortality and inferior OS. Higher doses of melphalan were associated with a lowered relapse risk.

**Section Summary: Autologous HCT**
The evidence related to use of autologous HCT for the treatment of primary amyloidosis includes an RCT, nonrandomized comparative studies, and large case series. The RCT had a number of limitations, and its results are insufficient to determine the effect of the treatment. A retrospective comparison with ten-year follow-up showed a considerable survival advantage for patients treated with HCT. Although retrospective, with evident interstudy patient heterogeneity, this report suggested autologous HCT may yield long-term survival benefits in patients with this disease. Additional case series have shown a CR rate ranging from 34% to 66%, with a clear survival advantage in patients who receive an HCT. Patients who do not achieve a CR may obtain some benefits in organ function. Treatment-related mortality rates from the Center for International Blood and Marrow Transplant Research study have decreased to 5% in recent years but remain between 11% and 16% in other studies.

**Allogeneic HCT**
Wechalekar et al (2008) state in a review that evidence on the use of allo-HCT to treat primary amyloidosis consists of isolated case reports, with no systematic evaluation in a clinical trial. Concerns about the use of allo-HCT include high TRM (>40%) and morbidity secondary to graft-versus-host disease. In addition, the efficacy of a proposed graft-versus-malignancy effect on low-grade plasma cell dyscrasias remains unknown.

**Section Summary: Allo-HCT**
Evidence on the use of allo-HCT for the treatment of primary amyloidosis consists of isolated case reports. The reports have shown high treatment-related mortality. Currently, allo-HCT for primary amyloidosis has been limited to clinical trials.

**Summary of Evidence**
For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes an RCT, nonrandomized comparative studies, and large case series. The relevant outcomes are OS, disease-specific survival, change in disease
status, and treatment-related morbidity and mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. CR to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who have primary amyloidosis who receive allogeneic (allo-) HCT, the evidence includes case reports. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Evidence on the use of allo-HCT is sparse and has shown high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input and national and international clinical guidelines support the use of autologous HCT as a treatment of amyloidosis. For primary amyloidosis, allo-HCT is not recommended. Thus, autologous HCT may be considered medically necessary for primary amyloidosis, and allo-HCT for primary amyloidosis is considered investigational.

SUPPLEMENTAL INFORMATION

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an
endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. There was support for the policy statements on hematopoietic stem transplantation in the treatment of amyloidosis.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation
The ASBMT (2015) issued guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (HCT). ASBMT gave the rating of N (not generally recommended; neither evidence nor clinical practice supports the routine use) for the use of allogeneic HCT in the treatment of primary amyloidosis in adults. ASBMT gave a rating of C (standard of care; clinical evidence available) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

British Committee for Standards in Haematology
The British Committee for Standards in Haematology developed guidelines on the management of light chain (primary) amyloidosis. Table 2 summarizes the recommendations from the 2015 guidelines on high-dose melphalan and autologous cell transplantation and allogeneic transplantation as treatments of primary amyloidosis.

Table 2. Recommendations on Use of High-Dose Melphalan, HDM-ASCT, and Allogeneic Transplant to Treat Primary Amyloidosis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOR</th>
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<tr>
<td>HDM-ASCT recommended as “the preferred first line treatment for patients up to 65-70 years of age with estimated glomerular filtration rate (eGFR) &gt;50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in bone marrow at time of transplant and lacking the contraindications….”</td>
<td>1c</td>
</tr>
<tr>
<td>HDM-ASCT recommended with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide &gt;590 pmol/l and/or troponin-T &gt; 0.06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, ... recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status (&gt;2).”</td>
<td>1c</td>
</tr>
<tr>
<td>“HDM-ASCT may be a treatment for selected patients up to 65-70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy.”</td>
<td>1c</td>
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<tr>
<td>“Reduced intensity allogeneic transplantation is generally not recommended as an upfront treatment due to high treatment-related mortality (TRM). However, selected fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease.”</td>
<td>1a</td>
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GOR: grade of recommendation; HDM-ASCT: high dose melphalan autologous stem cell transplantation.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines on systemic light chain amyloidosis (v.1.2019) recommend assessing organ involvement based on
amyloidosis consensus. Next patients should be evaluated for stem cell transplant candidacy. In patients eligible for stem cell transplant, stem cells may be collected, and transplant delayed for a later line of therapy. The dose of melphalan as part of stem cell transplantation can be adjusted based on factors such as age, presence/absence of cardiac involvement, and number of organs involved. In eligible patients, high-dose chemotherapy followed by autologous stem cell transplant has demonstrated higher response rates and improved overall survival compared with chemotherapy alone.

**International Workshops on Waldenström Macroglobulinaemia**  
The International Workshops on Waldenström Macroglobulinaemia (2017) published guidelines on the treatment of several paraproteinaemic neuropathies, one of which is primary, or amyloid light chain, amyloidosis. First-line treatment for eligible patients includes an autologous cell transplant preceded by a high-dose regimen combining rituximab with another agent such as purine analogue, bendamustine, or bortezomib.

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

**Medicare National Coverage**  
The Centers for Medicare & Medicaid Services has determined that the evidence is adequate to conclude that, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan together with autologous stem cell transplantation can provide a net health benefit for Medicare beneficiaries of any age group with primary amyloidosis (110.23, formerly 110.8.1). This technique “is reasonable and necessary or Medicare beneficiaries of any age with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

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

In addition, autologous HCT “must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy ... and/or radiotherapy used to treat various malignancies.”

**Ongoing and Unpublished Clinical Trials**  
A search of ClinicalTrials.gov in December 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**


### Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<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>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow; biopsy, needle or trocar</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 or blood-derived peripheral stem cell transplantation; allogeneic</td>
</tr>
</tbody>
</table>
38241 Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
S2140 Cord blood harvesting for transplantation, allogeneic
S2142 Cord blood-derived stem
S2150 Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days pre- and post-transplant care in the global definition

ICD-10 Codes
E85.0- E85.9 Amyloidosis code range (this policy would exclude E85.3 secondary systemic and E85.4 organ limited as they are not primary systemic)

Additional Policy Key Words
N/A

Policy Implementation/Update Information
12/1/04 New policy. Added to Surgery and Transplant sections
12/1/05 No policy statement change
4/1/06 Considerations section revised to include general criteria.
12/1/06 No policy statement changes.
12/1/07 No policy statement changes.
12/1/08 “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. Allogeneic SCT added to policy statements as investigational; no change in policy statements for auto-SCT.
12/1/09 No policy statement changes.
12/1/10 No policy statement changes.
12/1/11 Waldenstrom macroglobulinemia moved from this policy into a new policy No. 8.01.54. Policy statements unchanged.
6/1/12 No policy statement changes.
6/1/13 No policy statement changes.
6/1/15 No policy statement changes.
6/1/16 No policy statement changes.
6/1/17 No policy statement changes.
6/1/18 No policy statement changes.
6/1/19 No policy statement changes.
6/1/20 No policy statement changes.

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