**Medical Coverage Policy**

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### Stem-Cell Transplantation for Multiple Myeloma, POEMS Syndrome and Amyloidosis

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#### Related Coverage Resources

- Donor Leukocyte Infusion
- Transplantation Donor Charges
- Umbilical Cord Blood Banking

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### Coverage Policy

#### Multiple Myeloma

An autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of active (i.e., symptomatic) multiple myeloma (MM) is considered medically necessary for EITHER of the following indications:

- after response to primary therapy
- refractory to primary therapy in an individual with relapse or progressive disease

A second or tandem autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary following autologous HSCT.

A third autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary in an individual with progressive disease following a previous autologous HSCT.

Allogeneic HSCT from an appropriately-matched human leukocyte antigen (HLA) donor for the treatment of active (i.e., symptomatic) MM is considered medically necessary in an individual with progressive disease following autologous HSCT.
POEMS Syndrome

An autologous HSCT is considered medically necessary for the treatment of POEMS syndrome.

Amyloidosis

Autologous hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of primary systemic (i.e., amyloid light-chain [AL]) amyloidosis when ALL of the following criteria are met:

- Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (i.e., at a minimum, ambulatory and able to perform most, if not all, self-care)
- ≤ two organs significantly involved with amyloid
- asymptomatic or compensated cardiac function (i.e., absence of congestive heart failure, echocardiographic left ventricular ejection fraction > 30%, interventricular septal thickness < 15 mm)
- adequate pulmonary status as noted on pulmonary function testing, oxygen saturation results on room air and a DLCO > 50% predicted
- adequate liver function (i.e., bilirubin < 3.0 mg/dL)
- adequate renal function (i.e., creatinine clearance > 51 ml/min, serum creatinine ≤ 2.0 ml/dL)
- absence of severe or multiple comorbidities that would increase risk of poor result or death

A second autologous HSCT for the treatment of recurrent or refractory AL amyloidosis is considered experimental, investigational or unproven.

The following procedures for the treatment of AL amyloidosis are considered experimental, investigational or unproven:

- tandem autologous HSCT
- allogeneic HSCT

Overview

This Coverage Policy addresses hematopoietic stem-cell transplantation (HSCT) for the treatment of multiple myeloma (MM), POEMS syndrome and primary systemic amyloidosis (AL amyloidosis).

Multiple myeloma is a cancer that begins in a specific type of white blood cell, called a plasma cell. Plasma cells are formed in the bone marrow and produce antibodies to help fight infection. POEMS syndrome is associated with the uncontrolled growth of a single plasma cell, resulting in the accumulation of immunoglobulins in the blood. In primary amyloidosis the amyloid protein builds up in organs and tissues. The cause of primary (systemic) amyloidosis is not known but may occur in an individual with MM.

Hematopoietic stem-cell transplantation (HSCT) involves taking hematopoietic stem cells that can regenerate all the blood cells normally produced in the bone marrow from the bone marrow or blood of a donor and infusing them into the person with the disorder, following medication to suppress the immune system. The donor may be the person who is receiving the stem cells (i.e., autologous HSCT) or another person (i.e., allogeneic HSCT).

General Background

Plasma cell neoplasms are diseases associated with a monoclonal or myeloma protein and include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM) and other plasmacytomas. POEMS syndrome is associated with MGUS, while amyloidosis is associated with MM and other plasma cell neoplasms (National Cancer Institute [NCI], 2017). Primary systemic amyloidosis (i.e., amyloid light-chain [AL]) amyloidosis) can result in severe organ dysfunction especially in the kidney, heart, or peripheral nerves.
**Stem-Cell Transplantation**

Stem-cell transplantation refers to transplantation of hematopoietic stem cells from a donor into a patient. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (i.e., using the patient’s own stem cells) or allogeneic (i.e., using stem cells from a donor).

The selection of an appropriately-matched allogeneic donor source is dependent on several variables including the availability of a human leukocyte antigen (HLA)-identical sibling donor, and stage of disease. It is preferable for donors to have an HLA type that is identical to the recipient due to the potential for increased complications such as graft rejection and graft-versus-host disease; however, only about one-third of individuals who might otherwise be eligible for allogeneic HSCT have an HLA-matched sibling donor. Especially for individuals with high-risk disease, additional appropriate donor sources may include HLA-matched unrelated and HLA partially-matched related donors.

**Contraindications to Transplantation**

Many factors affect the outcome of a tissue transplant; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplantation. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Although improved responses have been reported in the peer-reviewed scientific literature, autologous HSCT is not considered an appropriate therapy for every individual with AL amyloidosis. Strict patient selection criteria are required to increase the chances for success (Gertz, 2008; Rajkumar, 2008). Individuals are highly selected on the basis of age, performance status, the number of organs involved with amyloidosis, absence of severe cardiomyopathy, and the presence of preserved renal function.

Several risk factors predicting outcome have been identified. The significant visceral organ dysfunction that occurs with amyloidosis puts patients at high risk for complications. The number of organs affected at the time of transplantation is an important predictor of outcome (Gertz, 2008). Persons with two affected organs have a median survival of 55 months while those with three or more affected organs have a median survival of 25.5 months. Cardiac involvement (i.e., congestive heart failure, left ventricular ejection fracture <30%, interventricular septal thickness >15 mm), poor renal function (i.e., reduced glomerular filtration rate, creatinine clearance < 51ml.min, serum creatinine >2.0 ml/dL, high-proteinuria), advanced age, poor Eastern Cooperative Oncology Group (ECOG) performance status, multiorgan involvement and elevated liver function tests (i.e., bilirubin >3.0mg/dL) are considered risk factors for poor outcome (Gertz, 2008; Bird, 2006). Poorer outcomes are also seen in individuals who are already dialysis-dependent (Comenzo, 2002).

Causes of treatment-related mortality in AL include gastrointestinal tract bleeding, cardiac rhythm disturbances, and multiorgan failure (Gertz, 2008). Despite stringent patient-selection criteria; treatment-related mortality can range from 12% to 43% in certain subsets of patients (Leung, 2005; Dispenzieri, 2004).

**Multiple Myeloma**

Multiple myeloma (MM) is a systemic malignancy of plasma cells, resulting in the accumulation of these cells in the bone marrow, destruction of bone, and marrow failure (National Cancer Institute ([NCI], 2017, National Comprehensive Cancer Network® [NCCN®], 2016).

Active multiple myeloma (MM) is characterized as having one or more of the following: calcium elevation, renal insufficiency, anemia, or lytic or osteopenic bone disease. Patients are further staged according to the Durie-
Salmon staging system and the International Staging System (NCCN, 2016; NCI, 2017; Reece, 2005). The stage of the disease at presentation is a strong determinant of survival, but it has little influence on the choice of therapy since almost all patients have generalized disease. Treatment selection is influenced by the age and general health of the patient, prior therapy, and the presence of complications of the disease. The failure of conventional therapy to cure active (symptomatic) MM has led to the study of dose intensification, with stem-cell support.

**Literature Review**

**Initial Autologous Hematopoietic Stem-Cell Transplantation (HSCT):** Despite conflicting evidence regarding the benefit of autologous hematopoietic stem-cell transplantation (HSCT) in various patient subgroups, an initial autologous HSCT is considered a standard treatment option for individuals with multiple myeloma (MM) (National Cancer Institute [NCI], 2017; National Comprehensive Cancer Network [NCCN], 2016).

According to consensus guidelines published by the NCCN (2016) regarding individuals with active (symptomatic) MM, autologous stem-cell transplant results in high response rates and remains the standard of care following primary therapy for eligible patients.

A number of randomized controlled trials (RCT), prospective nonrandomized comparisons and systematic reviews have examined outcomes for individuals who received HDC followed by an initial autologous HSCT compared with standard dose chemotherapy options. Improved overall survival (OS) and/or progression-free survival (PFS) has been demonstrated following complete or partial response to primary therapy, in those who are refractory to primary therapy, and in the setting of progressive disease. Although autologous HSCT is not curative, studies demonstrate an improvement in complete response rates and prolongation of median overall survival (OS) by approximately 12 months (Giralt, 2009; Barlogie, 2006 [a-c]; Lenhoff, 2006). However, other studies have demonstrated variable benefit to high-dose therapy including two meta-analyses of over 3000 persons (Koreth, 2007; Fermand, 2005, Levy, 2005, Seregren, 2003).

In addition, several studies have compared outcomes achieved with high-dose chemotherapy (HDC) and autologous hematopoietic stem-cell transplantation (HSCT) for individuals who are older versus younger than age 65 and determined that there is no difference in the time to progression or overall survival (Kumar, 2008; Jantunen, 2006) or progression-free survival (Jantunen, 2006) between these groups. According to the NCCN Guidelines (2016), advanced age is not a contraindication to transplantation.

**Second or Tandem HSCT:** Despite conflicting results regarding safety and effectiveness, the use of a second or tandem autologous HSCT is considered an appropriate therapy for the treatment of selected individuals with MM following prior autologous HSCT as noted by consensus recommendations from the National Comprehensive Cancer Network ([NCCN], 2016).

Multi-institutional trials demonstrating that initial hematopoietic stem-cell transplantation (HSCT) prolongs remission duration and survival but is not curative has led to the exploration of whether a second HSCT should be used early after diagnosis (i.e., tandem, generally within six-months after initial transplantation therapy) or its use delayed as a treatment for relapsed or progressive myeloma. Evidence regarding the effectiveness of tandem autologous HSCT versus a single HSCT is conflicting. As a result, the timing of second transplantation is somewhat controversial (Kumar, 2009; Rajikumar, 2008).

Several randomized controlled trials (RCTs) have demonstrated improved response rates (47% versus 33%, respectively) and overall survival (OS) rates (42% versus 21%, respectively) with the use of tandem compared with single autologous transplantation (Kumar, 2009; Bruno, 2007; Cavo, 2007; Attal, 2003). In some studies, the benefit of a second autologous HSCT was restricted to patients who failed to achieve a complete, or very good partial response (e.g., >90% reduction in M protein level) with the first procedure (Attal, 2007). In other studies OS- and event-free survival (EFS) rates were not improved (Kumar, 2009; Abdelkelfi, 2008; Rosinol, 2008; Garbon, 2006). In the study by Kumar, the authors noted that none of these studies stratified patients according to biologic and genomic risk factors that have been proposed to affect prognosis of patients with multiple myeloma (MM); therefore, it is not known whether a benefit in overall survival (OS) may exist for use of tandem hematopoietic stem-cell transplantation (HSCT) in selected patient subgroups.
Cook et al. (2016) reported final results of the BSBMT/UKMF Myeloma X multicenter, phase III, open-label, randomized trial. Eligible patients with multiple myeloma relapsing after a prior autologous HSCT were randomized to high-dose melphalan and salvage autologous HSCT (n=89) or weekly oral cyclophosphamide (for 12 weeks) (n=85). The primary endpoint was time to disease progression. Secondary endpoints were overall survival (OS), response rate, progression-free survival, toxicity and safety, pain and quality of life. Median follow-up was 52 months. The median OS was superior in the salvage autologous HSCT group compared with weekly cyclophosphamide group (67 months versus 52 months, respectively; p=0.0169). An updated analysis of time to disease progression and progression-free survival showed the superiority of salvage autologous HSCT over weekly cyclophosphamide (67 months versus 35 months, respectively; p<0.0001).

Naumann-Winter et al. (2012) performed a systematic review of twenty references representing eight RCTs comparing tandem HSCT with single HSCT as first-line treatment in patients with symptomatic MM. Endpoints included OS, EFS, quality of life (QoL) and treatment- or transplantation-related mortality. Of seven studies completed between 1994 and 2002 comparing tandem and single autologous HSCT, only one RCT resulted in a statistically significant improvement in OS. According to the authors, none of the studies were adequately powered for the analysis of OS; they noted that considerable confounding due to varying access to salvage treatment is likely. Tandem autologous HSCT resulted in improved EFS compared to single HSCT in four of five trials but was statistically significant in only two trials. Treatment- or transplant-related mortality was higher for the tandem autologous HSCT in four of five studies; however, statistical significance was not published. Quality of life was not reported in any of the included studies. Five studies were eligible for meta-analysis; however, the authors observed heterogeneity of treatment and bias between and within the individual studies therefore a formal meta-analysis was not informed. The authors noted that more information is required on the long-term benefit for patients in view of the overall strenuous treatment approach of tandem autologous HSCT.

A systematic review of long term outcomes of several trials of autologous HSCT (Barlogie, 2010), noted that tandem transplantation was superior to both single transplantation and standard therapy.

**Allogeneic HSCT:** Although treatment-related mortality remains high, the published peer-reviewed scientific literature supports the effectiveness of allogeneic HSCT for selected individuals following previous autologous HSCT. This therapy is also supported as an accepted treatment option as salvage therapy in patients with progressive disease following an initial autologous HSCT in published guidelines by the NCCN (2016).

**Myeloablative Allogeneic HSCT:** Allogeneic HSCT may include the use of a myeloablative or nonmyeloablative conditioning regimen. The advantages of allogeneic HSCT include a lack of graft contamination with tumor cells and the presence of a graft-versus-myeloma effect, which may provide long-term disease control and result in a result in a cure rate of 10-20% (Rotta, 2008; Bensinger, 2006). Unfortunately, only a small percentage of individuals are eligible for a fully ablative transplantation due to age, availability of an appropriate donor, and adequate organ function (Rotta, 2008). Additionally, myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) is associated with greater transplant-related mortality (TRM) compared with TRM rates seen with autologous HSCT. Improved patient selection criteria and chemotherapy regimens have resulted in a decrease to approximately 20% (NCI, 2017; Vesole, 2009).

In prospective case series and retrospective studies, two-, five-, and 10-year overall survival (OS) rates were 51%, 41-48%, and 39.9%, respectively, while two- and five-year event-free survival (EFS) rates were 35% and 33.3%, respectively (Kuruvilla, 2007; Kennedy, 2006; Crawley, 2005). Allogeneic HSCT has also been compared with autologous hematopoietic stem-cell transplantation (HSCT) with no significant difference between treatment-related mortality (TRM) at one year for allogeneic and autologous transplantation (p=0.21) or cumulative incidence of relapse at ten years (p=0.10) (Kuruvilla, 2007).

**Nonmyeloablative Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT):** The high treatment-related mortality (TRM) associated with myeloablative allogeneic HSCT has been the impetus for investigation of reduced-intensity or nonmyeloablative conditioning regimens designed to allow engraftment of allogeneic stem cells while limiting complications. A definite graft-versus-myeloma effect has been identified with allogeneic HSCT.
Nonmyeloablative conditioning has been investigated as therapy for individuals who have previously received an initial autologous HSCT. Several studies demonstrate an increase in response rate, and a trend toward improved OS (Vesole, 2009; Rosinol, 2008; Bruno, 2007; Baron, 2006; Garban, 2006, Martino, 2006, Badros, 2002); although relapse rates continue high post allogeneic hematopoietic stem-cell transplantation (HSCT) (Rotta, 2008; Eom, 2006). Long-term disease control, graft-versus-host-disease, and relapse rates remain key issues.

Nonmyeloablative conditioning is infrequently used as first-line therapy. According to National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™], 2016) data do not support nonmyeloablative allografting alone. Although the use of reduced-intensity conditioning compared with myeloablative conditioning is associated with lower nonrelapse mortality, it does not translate into improved overall survival (OS) due to the higher relapse rate associated with reduced-intensity conditioning (Gahrton, 2007).

POEMS Syndrome
POEMS syndrome is an extremely rare plasma cell disorder associated with monoclonal gammopathy of undetermined significance; however, the exact etiology is unknown. The term ‘POEMS’ is an acronym of the most common symptoms: polyneuropathy, organomegaly, endocrinopathy, M proteins and skin changes. POEMS syndrome been variously referred to in the literature as osteosclerotic myeloma, Crow-Fukase syndrome, PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy) syndrome, and Takatsuki syndrome (Laurenti, 2008). With only several hundred cases documented it is likely that the incidence is higher because of undiagnosed cases. For patients with widespread osteosclerotic lesions, treatment is similar to that for multiple myeloma. Effective treatment of the underlying plasma cell disorder controls the disease and results in dramatic reversal of symptoms. In eligible patients, autologous HSCT has provided significant responses and have more recently been used to treat this disease (Dispensieri, 2008).

Literature Review
As POEMS syndrome is associated with plasma cell disorders, it may respond to high-dose chemotherapy and autologous HSCT. The syndrome is rare and it is unlikely that randomized controlled trials of sufficient size will become available. In several small case series, slow, but progressive improvement of neurological involvement and performance status was noted after autologous HSCT (Laurenti, 2008; Dispensieri, 2008, Kuwabara, 2006; Dispensieri, 2004; Jaccard, 2002).

Amyloidosis
Amyloidosis is a group of diseases characterized by the deposit of insoluble protein into peripheral nerves and visceral organs such as the kidney, heart, liver, and spleen, and end-organ dysfunction. It is clinically classified as either systemic or localized. Systemic amyloidosis is sub-classified as primary (when associated with a plasma-cell dyscrasia), secondary (when it occurs as a result of a chronic inflammatory condition) or hereditary (familial). Patients with primary systemic amyloidosis (i.e., amyloid light-chain [AL] amyloidosis) present with a hematologic malignancy as well as progressive dysfunction of one or more organs.

Most conventional strategies for AL amyloidosis remain unsatisfactory with conventional chemotherapy yielding only moderate efficacy (Frossard, 2008). Autologous hematopoietic stem-cell transplantation has been proposed for the treatment of primary systemic AL amyloidosis.

Literature Review
Autologous HSCT: Remission of the effects of amyloidosis on organs can be achieved with autologous HSCT in approximately 50%–75% of patients treated with such therapy (Bird, 2006). However, autologous HSCT is associated with risks of higher morbidity and mortality than the use of this therapy for other disorders, with associated treatment-related mortality of approximately 15% (Chee, 2010).

Survival varies greatly depending on the dominant organ that is involved—with cardiac amyloid having the worst outcome—and the number of major organs that are affected (Gertz, 2008). Untreated individuals have a median survival of 10 months to two years (Sanchorawala, 2007; Lebowitz and Morris, 2003). The presence of symptomatic congestive heart failure is associated with a median survival of 4–6 months and is the single most important predictor of poor outcome. One- and two-year overall survival (OS) rates are 69%–89%, and 62%–81%, respectively, for those who undergo autologous HSCT (Afrough, 2015; Gertz, 2011; Perz, 2006; Vesole, 2006; Skinner, 2004, Dispensieri, 2001).
Several prospective case series and retrospective studies have demonstrated higher complete response rates in addition to improved outcomes after high-dose chemotherapy and autologous HSCT, in selected subgroups with AL amyloidosis (Cibeira, 2011; Sanchorawala, 2007; Dispenzieri, 2006; Vesole, 2006; Skinner, 2004). In a large prospective case series (n=421) by Cibeira et al. (2011) utilizing high-dose melphalan and autologous HSCT, patients with complete response had a median event-free survival (EFS) and OS of 8.3 and 13.2 years, respectively. Among the 195 patients who did not achieve complete response, EFS and OS were two and 5.9 years, respectively. However, in a single randomized controlled trial involving 100 individuals (Jaccard, 2007), hematologic complete response rates were not improved with HSCT compared with conventional chemotherapy, and results were not statistically significant (36% versus 52%). OS was higher in the conventional chemotherapy group (56.9 months versus 22.2 months, respectively). The authors noted that one explanation for the relatively poor results using high-dose melphalan was the high mortality rate before and after the intensive treatment. Additionally, the time required to collect stem cells for the transplantation procedure resulted in a delay of treatment of approximately one month for the patients in the transplantation group compared to the non-transplantation arm.

Use of tandem and second autologous HSCT has also been proposed for the treatment of refractory or recurrent AL amyloidosis. These therapies involve performing multiple cycles of chemotherapy and HSCT, either as part of an established protocol of therapy; usually within three to six months of the initial transplantation, or as disease progression or relapse occurs. Data are lacking in the published, peer-reviewed scientific literature regarding the safety and effectiveness of these therapies for primary systemic (amyloid light-chain [AL]) amyloidosis. Although a topic of continuing research, the role of second or tandem autologous hematopoietic stem-cell transplantation (HSCT) has not been established.

Allogeneic HSCT: Data are lacking in the peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for primary (AL) amyloidosis. According to the UK Myeloma Forum AL Amyloidosis Guidelines Working Group (2004) this treatment is appropriate for use in clinical trials only, as it is likely to be associated with extremely high treatment-related mortality. Whether this therapy offers improved outcomes over conventional chemotherapy for patients with AL amyloidosis is unknown. The role for this therapy in the treatment of AL amyloidosis has not yet been established.

Professional Societies/Organizations
American Society of Blood and Marrow Transplantation (ASBMT, 2015): Shah et al. published consensus guidelines regarding the role of HSCT for multiple myeloma. Guidelines note the following recommendations:

- Though prospective evidence is lacking, we recommend consideration of a first auto-HCT for patients with refractory disease (grade C)
- We recommend that age not be used as a selection factor (grade C)
- Based on the conflicting data from the prospective randomized trials there is insufficient evidence to support tandem autologous HSCT as the standard of care for myeloma patients. However, there are cases when this may be considered, based in the IFM data, in patients with less than a very good partial response after a first autologous HSCT (grade D) or as part of a clinical trial
- Upfront myeloablative allogeneic HSCT is not routinely recommended (grade A). It may be appropriate for further study in young patients with very high-risk MM, in the context of a clinical trial.
- Planned RIC-allogeneic HSCT after autologous HSCT has not been found to be superior in the majority of clinical trials and is, therefore, not recommended over auto-HCT (grade A). Its role in high-risk subgroups requires further study.
- Allogeneic HSCT salvage therapy for relapsed MM has not been shown to be superior to salvage autologous HSCT and is not routinely recommended outside of a clinical trial (grade D). For younger patients with a good performance status, allogeneic HSCT can be considered, ideally in the context of a clinical trial
- Second autologous HSCT is a safe and efficacious treatment modality for relapsed MM and should be considered (grade B).
• Patients with longer progression-free interval after first autologous HSCT have better outcomes after salvage second autologous HSCT. It is recommended that the minimum length of remission be at least 12 months for consideration of second autologous HSCT as salvage therapy (grade D).

Grades of Recommendation:
A: At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C: A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D: Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference (2015): Giralt et al. published consensus guidelines regarding use of salvage HSCT with relapsed myeloma. The following recommendations were made:

• In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HSCT, high-dose therapy with autologous HSCT as part of salvage therapy should be considered standard.
• High-dose therapy and autologous HSCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HSCT with initial remission duration of more than 18 months.
• High-dose therapy and autologous HSCT can be used as a bridging strategy to allogeneic HSCT.
• Allogeneic HSCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HSCT or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HSCT.
• Whenever possible, allogeneic HSCT should be performed in the context of a clinical trial.

National Cancer Institute ([NCI], 2017): The NCI notes the following regarding the use of HSCT for multiple myeloma:

• Single autologous HSCT as consolidation: The NCI discusses the results of various clinical trials and notes that some prospective randomized trials have shown improved survival for patients who received autologous peripheral stem cell or bone marrow transplantation after induction chemotherapy versus chemotherapy alone, while other trials have not shown any survival advantage, including two meta-analyses. The trials suggesting improved survival showed no signs of a slowing in the relapse rate or a plateau to suggest that any of these patients had been cured. With the advent of novel induction therapies with high complete-remission rates, the role of autologous HSCT has been questioned.
• Tandem autologous HSCT: The NCI notes that tandem autologous HSCT, using two sequential episodes of high-dose therapy with stem cell support is another approach. However, outcomes are mixed with some studies demonstrating no difference in OS or in EFS when compared with single autologous HSCT.
• Allogeneic HSCT: The NCI notes that myeloablative allogeneic stem cell transplantation has significant toxic effects (15%—40% mortality), but the possibility of a potent and possibly curative graft-versus-myeloma effect in a minority of patients may offset the high transplant-related mortality. The lower transplant-related mortality from nonmyeloablative approaches has been accompanied by a greater risk of relapse.

Regarding treatment of amyloidosis, the NCI (2017) notes that stem-cell rescue is a treatment option for amyloidosis associated with plasma cell neoplasms.
National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™]): The published Guideline for Multiple Myeloma (2016) notes the following:

- Primary therapy followed by high-dose chemotherapy with stem-cell support is a critical component in the treatment for eligible patients with newly diagnosed MM.
- The types of stem-cell transplantation (SCT) may be single autologous, a tandem SCT (i.e., a planned second course of high-dose therapy and SCT within six months of the first), or an allogeneic SCT. An allogeneic SCT can either be performed after prior myeloablative therapy or after nonmyeloablative therapy. An allogeneic SCT may also follow an autologous SCT.
- Autologous transplantation results in high response rates and remains the standard of care following primary therapy for eligible patients.
- A tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for stem cell transplantation and is an option for patients who do not achieve at least a very good partial response after the first autologous stem cell transplant.
- Repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the previous SCT and documented progression. The NCCN Panel suggests two-three years as the minimum length of remission for consideration of second autologous transplant as for relapsed disease.
- Allogeneic SCT includes either myeloablative or nonmyeloablative (i.e., ‘mini’ transplant) transplants.
- Myeloablative allogeneic SCT is an accepted option in patients responding to primary therapy or as salvage therapy in patients with progressive disease following an initial autologous HSCT. It is suggested that allogenic HSCT is part of a clinical trial.
- Nonmyeloablative allogeneic transplant by itself is not adequate therapy and is usually performed after maximal tumor control through induction therapy or following autologous HSCT.

The NCCN Guideline (2017) for primary treatment of systemic light chain amyloidosis notes the following:

- High-dose melphalan with autologous HSCT is a therapeutic consideration, along with other therapies.
- Patients have to be carefully selected as this treatment modality is associated with significant treatment-related mortality.
- The extent of organ involvement is considered as predictor of outcome.
- The best outcomes are seen in patients who achieve a complete response to high-dose primary chemotherapy including improvement of organ-related disease

National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation ([ASBMT], 2017): Referral guidelines note that referral for evaluation for HSCT should take place at diagnosis and at first progression.

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside of the US

British Committee for Standards in Haematology ([BCSH], 2015): Regarding HSCT and amyloidosis the BSCH (2015) recommends the following:

- Autologous HSCT
  
  - High-dose melphalan (HDM) and autologous HSCT (ASCT) can be considered without prior induction chemotherapy in patients with low level bone marrow plasma cell infiltration.
  - HDM-ASCT is the preferred first line treatment for selected patients up to 65–70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in the bone marrow at the time of transplant and lacking the contraindications mentioned in the next point.
  - HDM-ASCT is not recommended as first line therapy for patients with any of the following: cardiac amyloidosis with NT-proBNP > 590 pmol/l and/or troponin-T > 0·06 ng/ml, severe autonomic neuropathy, significant GI bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions, poor ECOG PS (>2).
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.

Reduced intensity allogeneic transplantation is not generally recommended as an upfront treatment due to the high treatment-related mortality. However, selected, fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease.

Treatment of AL amyloidosis is based on anti-myeloma therapy. There is no standard treatment and it has to be tailored to the individual.

- Reduced intensity allogeneic HSCT
  - Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes with the treatment goal to achieve a very good partial response or better, if possible.

British Committee for Standards in Haematology and the United Kingdom (UK) Myeloma Forum (2011): On behalf of these professional societies, Bird et al. published guidelines for the diagnosis and management of multiple myeloma (MM). Regarding use of autologous HSCT, the Guidelines note high-dose chemotherapy (HDC) with autologous HSCT should be part of the primary treatment strategy in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function. HDC with autologous hematopoietic stem-cell transplantation (HSCT) should be considered in those >65 years with good performance status. Planned double ('tandem') autologous stem-cell transplantation (ASCT) cannot be recommended on the current evidence. Allogeneic HSCT with human leukocyte antigen-matched sibling donors may also be considered in patients up to the age of 40 years who have achieved at least a partial remission after initial therapy. Reduced-intensity conditioning followed by allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered in patients up to age 70 years with a human leukocyte antigen-matched sibling donor. The procedure would usually follow an initial autologous HSCT, be done early in the disease in individuals with responsive disease, and should always be done as part of a clinical trial.

European Myeloma Network (2014): On behalf of the European Myeloma Network, Engelhardt et al. published recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. The guidelines note novel-agent-based induction and up-front autologous stem cell transplantation in medically fit patients remains the standard of care and that allogeneic stem cell transplantation may be considered for young patients with high-risk disease and preferably in the context of a clinical trial.

International Myeloma Working Group (IMWG) (Sonneveld, 2016): On behalf of the IMWG, Sonneveld et al. published the following consensus guidelines:
- High-dose therapy with autologous HSCT (ASCT) is standard therapy for patients with newly diagnosed MM. It contributes to improved outcome across prognostic groups.
- Double high-dose therapy with ASCT combined with bortezomib may improve progression-free survival in patients with t(4;14) or del(17p), and in those with both abnormalities.
- Although results from stratified randomized trials are not yet available, high-dose therapy plus double ASCT is recommended for patients with high-risk cytogenetics.
- Allogeneic SCT or tandem autologous-allogeneic SCT may improve PFS in patients with t(4;14) or del(17p). Results are better in an early stage of the disease.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Multiple Myeloma
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT®* Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</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>
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<tr>
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<td>38211</td>
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<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<tr>
<td>38213</td>
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</tr>
<tr>
<td>38214</td>
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</tr>
<tr>
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<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<tr>
<td>38230</td>
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</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation, autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<td>Allogeneic lymphocyte infusions</td>
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<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
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<tr>
<td>S2142</td>
<td>Cord blood-derived stem cell transplantation, allogeneic</td>
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<td>S2150</td>
<td>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 of pre-and post-transplant care in the global definition</td>
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**Amyloidosis and POEMS Syndrome**

Considered Medically Necessary when used to report autologous bone marrow or blood-derived stem cell procedures:

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**Experimental/Investigational/Unproven**

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### References


47. Jantunen E, Kuittinen T, Lehtonen P, Mahlamaki E, Nousiainen T. High-dose melphalan (200 mg/m²) supported by autologous stem cell transplantation is safe and effective in elderly (>or=65 years) myeloma patients: comparison with younger patients treated on the same protocol. Bone Marrow Transplant. 2006 May;37(10):917-22.


89. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation. Blood. 2007 (a) Aug 2; [Epub ahead of print]


