Cigna Medical Coverage Policy

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

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Coverage Policy

Multiple Myeloma

Cigna covers an autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of active (i.e., symptomatic) multiple myeloma (MM) as 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

Cigna covers a second or tandem autologous HSCT for the treatment of active (i.e., symptomatic) MM as medically necessary following autologous HSCT.

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

Cigna covers allogeneic HSCT from an appropriately-matched human leukocyte antigen (HLA) donor for the treatment of active (i.e., symptomatic) MM as medically necessary in an individual with progressive disease following autologous HSCT.

POEMS Syndrome

Cigna covers an autologous HSCT as medically necessary for the treatment of POEMS syndrome.

Amyloidosis

Cigna covers autologous hematopoietic stem-cell transplantation (HSCT) as 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

Cigna does not cover second autologous HSCT for the treatment of recurrent or refractory AL amyloidosis because it is considered experimental, investigational or unproven.

Cigna does not cover the following procedures for the treatment of AL amyloidosis because they are considered experimental, investigational or unproven (this list may not be all-inclusive):

- tandem autologous HSCT
- 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], 2014). Primary systemic amyloidosis (i.e., amyloid light-chain [AL]) amyloidosis) can result in severe organ dysfunction especially in the kidney, heart, or peripheral nerves. Hematopoietic stem-cell transplantation (HSCT) has been proposed for the treatment of selected individuals with MM, POEMS syndrome and AL amyloidosis.

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 an 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; Rajikumar, 2008; Gono, 2004). 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], 2014, National Comprehensive Cancer Network® [NCCN®], 2013). Treatable, but rarely curable, this disease is usually progressive and is characterized by renal failure, lytic bone lesions, anemia and hypercalcemia (National Cancer Network [NCI], 2014).

Patients may be initially classified as having smoldering (asymptomatic) or active (symptomatic) disease. Primary therapy for individuals with smoldering (asymptomatic) MM may include observation and follow-up surveillance until progression to symptomatic myeloma (NCCN, 2013).

Active myeloma is characterized by the NCCN (2013) as having one or more of the following: “calcium elevation (>11.5m g/dL), renal insufficiency (creatinine >2g/L, anemia (hemoglobin <10 g/dL or 2 g/dL < normal), or lytic or osteopenic bone disease.” Patients are further staged according to the Durie-Salmon staging system, which is based on the amount of abnormal monoclonal immunoglobulin in the blood or urine; blood calcium levels; the amount of bone damage shown by x-ray; and blood hemoglobin levels, and the International Staging System which relies on the levels of albumin and beta-2-microglobulin in the blood (NCI, 2014; Reece, 2005). According to the NCI (2014), 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
Autologous HSCT
Initial Hematopoietic Stem-Cell Transplantation (HSCT): According to consensus guidelines published by the British Committee for Standards in Haematology ([BCSH], 2010) there is currently no evidence to support deferral of the first autologous HSCT until the time of first relapse, although prospective studies are underway to

explore this possibility further. HSCT has become the first line standard of care in selected patients who are biologically fit enough for this option mainly because of the low transplant-related mortality (TRM) and prolongation of EFS resulting in improved quality of life (BCSH, 2010). For individuals with multiple myeloma (MM), high-dose chemotherapy (HDC) with autologous HSCT is the treatment associated with the highest complete remission rate (Giralt, 2009). NCCN Guidelines™ (2013) note for 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; Rajkumar, 2008; Barlogie, 2006 [a-c]; Lenhoff, 2006; Child, 2003; Attal, 1996). 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 (2013), advanced age is not a contraindication to transplantation.

Summary for Initial Autologous 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], 2014; National Comprehensive Cancer Network [NCCN], 2013; Bensinger, 2006).

Second or Tandem HSCT: 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 (Munshi, 2008). 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 (Rajkumar, 2008; 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 OS may exist for use of tandem HSCT in patient subgroups.

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.

Summary for Second or Tandem Autologous 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], 2013).

Allogeneic HSCT
Myeloablative Allogeneic HSCT: Allogeneic HSCT may include the use of a myeloablative or non-myeloablative 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% (Rajkumar, 2008; 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 (Rajkumar, 2008; 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, 2014; 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).

Non-Myeloablative 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 non-myeloablative conditioning regimens designed to allow engraftment of allogeneic stem cells while limiting complications (Bensinger, 2006). A definite graft-versus-myeloma effect has been identified with allogeneic HSCT.

Non-myeloablative 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.

Non-myeloablative conditioning is infrequently used as first-line therapy. According to National Comprehensive Cancer Network Guidelines™ ([NCCN Guidelines™], 2013) 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).

Summary for 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 (2013).

Professional Societies/Organizations
National Cancer Institute ([NCI], 2014):

- Single autologous HSCT as consolidation: The NCI discusses the results of various clinical trials and notes "While some prospective randomized trials such as the U.S. Intergroup trial (i.e., SWOG-9321), have shown improved survival for patients who received autologous peripheral stem cell or bone marrow transplantation after induction chemotherapy versus chemotherapy alone, 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." "The role of autologous HSCT has also been questioned with the advent of novel induction therapies with high complete-remission rates."
- Tandem autologous HSCT: "Another approach to high-dose therapy has been the use of two sequential episodes of high-dose therapy with stem cell support (i.e., tandem transplant); however, outcomes are mixed with some studies demonstrating no difference in OS or in EFS when compared with single autologous HSCT."
- Allogeneic HSCT: "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." "A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes." "Given the lack of evidence so far that the high-risk patients benefit from allogeneic stem cell transplantation in this era of novel new agents, it remains debatable whether allogeneic stem cell transplantation should be offered in the first-line setting outside the context of a clinical trial."

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™): The published Guideline for Multiple Myeloma (2013) notes "High dose therapy with stem cell support is a critical component in the treatment plan for eligible newly diagnosed MM patients. The types of SCT (stem-cell transplant) may be single autologous SCT, a tandem SCT (a planned second course of high-dose therapy and SCT within six months of the first), or an allogeneic SCT. An allogeneic SCT can be either performed after prior myeloablative therapy or after nonmyeloablative therapy. An allogeneic SCT may also follow an autologous SCT" Regarding the use of autologous HSCT, the Guidelines note that "Autologous HSCT results in high response rates and remains the standard of care following primary therapy for eligible patients Autologous SCT is a category I option for treatment of progressive or refractory disease post primary treatment."." According to the Guideline, "A tandem transplant can be considered for all patients who are candidates for stem cell transplant and is an option for patients who do not achieve at least a very good partial response after the first autologous stem cell transplant." The algorithms also identify three situations where a repeat salvage autologous HSCT may be considered either on or off clinical trial: "In patients initially treated with primary therapy alone, followed by an autologous HSCT when the disease relapsed, who now have progressive disease following a first autologous HSCT; in patients who develop progressive disease after first autologous transplant; and in patients with initial response to single/tandem autologous SCT who then develop progressive disease. The NCCN Panel suggests two-three years as the minimum length of remission for consideration of second autologous transplant as salvage therapy."

According to the Guideline, allogeneic SCT includes either myeloablative or nonmyeloablative (i.e., 'mini' transplant) transplants." "Myeloablative allogeneic SCT is an accepted option, only as part of a clinical trial in patients responding to primary therapy, patients with primary progressive disease, or as salvage therapy in patients with progressive disease following an initial autologous HSCT." In the absence of a clinical trial allogeneic transplantation for patients with MM is considered a category III recommendation.

National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) (2012): Transplantation referral guidelines note that referral for evaluation for HSCT should take place after initiation of therapy and at first progression.

Summary for Multiple Myeloma (MM)
Autologous and allogeneic HSCT are considered accepted treatment options for an individual with MM. Both transplant types demonstrate improved clinical outcomes compared with conventional chemotherapy are supported by published professional society recommendations.

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 (Dispenzieri, 2008; Rajkumar, 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; Dispenzieri, 2008, Kuwabara, 2006; Dispenzieri, 2004; Jaccard, 2002).

Professional Societies/Organizations: The NCI and NCCN do not have published recommendations regarding HSCT for POEMS syndrome.

Summary for POEMS syndrome: Although data are not robust, autologous HSCT has resulted in clinical improvement in individuals with POEMS syndrome, and it is considered a reasonable option for selected patients.

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 (Rajkumar, 2008; Bird, 2006; Gertz, 2004). 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 (Gertz, 1999). One- and two-year overall survival (OS) rates are 69%–89%, and 62%–81%, respectively, for those who undergo autologous HSCT (Gertz, 2011; Perz, 2006; Vesole, 2006; Skinner, 2004, Dispenzieri, 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; Gertz, 2004; 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.

Summary for Amyloidosis
Data in the peer-reviewed scientific literature supporting improved outcomes with autologous stem-cell transplantation are not robust; nonetheless, it is considered to be an accepted treatment option for rescue of myeloablation seen as a result of high-dose chemotherapy for a highly selected subset of individuals with AL amyloidosis as noted in consensus guidelines from the NCCN (2013). The NCI also notes that autologous HSCT is a treatment option for the treatment of primary (AL) amyloidosis. However; data are lacking to demonstrate improved outcomes with tandem or second autologous HSCT, or allogeneic HSCT.

Professional Societies/Organizations
National Cancer Institute (NCI): The NCI (2014) reviews the results of various studies of high-dose chemotherapy followed by autologous HSCT for patients with AL amyloidosis. The NCI notes that stem-cell rescue is a treatment option for amyloidosis associated with plasma cell neoplasms.

National Comprehensive Cancer Network™ (NCCN™): NCCN guidelines (2013) note that there are insufficient data to indicate the optimal treatment of amyloidosis. High-dose melphalan followed by stem cell transplant (SCT) is one therapeutic option; however, 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. Treatment in the context of a clinical trial is strongly encouraged.

Summary for Amyloidosis
Improved outcomes achieved with autologous hematopoietic stem-cell transplantation (HSCT) for primary systemic amyloid light-chain amyloidosis (i.e., AL amyloidosis) appear dependent on the extent of organ involvement. Although data are not robust, single autologous HSCT is an accepted treatment option for a carefully selected subset of individuals with AL amyloidosis. There is insufficient evidence to support the safety and effectiveness of allogeneic HSCT and at this time the role of this therapy has not been established.

Use Outside of the US
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.

International Myeloma Working Group (IMWG) (2009): A consensus statement published by Giralt (2009) notes that high-dose melphalan is still recommended for eligible patients, stem cell collection early in the course of therapy should be attempted in all transplant eligible patients, and that double autologous transplantation has a place in clinical trials, primarily in younger patients. The guidelines also note that allografting should continue to be explored in the context of clinical trials in carefully selected patients as frontline therapy or as salvage therapy.

In an update regarding the role of allogeneic HSCT for the treatment of MM, the IMWG published a consensus statement (2011) which recommends that "Reduced intensity conditioning (RIC) allogeneic transplant should only be performed in the context of clinical trials."

Summary
The published, peer-reviewed medical literature supports the effectiveness of autologous and allogeneic hematopoietic stem-cell transplantation (HSCT) in the treatment of multiple myeloma (MM) for selected individuals. Despite conflicting reports regarding outcomes in various patient subgroups, autologous and allogeneic HSCT are considered a standard of care in the treatment of active (symptomatic) multiple myeloma.

POEMS syndrome is a rare plasma disease which is unlikely to be studied in large, randomized controlled clinical trials. Similar to results seen in MM and resulting in clinical improvement in patients with POEMS syndrome, autologous HSCT is a reasonable treatment option for selected individuals.

HSCT is also considered an accepted treatment for highly selected individuals with amyloidosis, specifically those with good performance status, less than two organs involved with amyloidosis, absence of severe cardiomyopathy, and preserved lung, hepatic, and renal function.

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

Covered when medically necessary:

CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion

38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation, allogeneic
38232	Bone marrow harvesting for transplantation, autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS Codes	**Description**
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem cell transplantation, allogeneic
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 of pre-and post-transplant care in the global definition

Amyloidosis and POEMS Syndrome

Covered when medically necessary when used to report autologous bone marrow or blood-derived stem cell procedures:

CPT®* Codes	**Description**
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS Codes	**Description**
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 of pre-and post-transplant care in the global definition

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic

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