Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

**Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in the Cord Blood as a Source of Stem Cells medical policy.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II 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 (with the exception of umbilical cord blood).

**Conventional Preparative Conditioning for HSCT**

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophoshamide, 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 (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM 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 effects 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 HSCT, immune suppressant drugs...
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are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

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, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT 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 the purposes of this policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

Multiple Myeloma

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. At the time of diagnosis most patients have generalized disease, and, the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease.

The disease is staged by estimating tumor mass, based on various clinical parameters such as hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed “monoclonal gammopathy of undetermined significance” or MGUS). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage. In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized, and referred to as smoldering multiple myeloma. The overall risk of disease progression from smoldering to symptomatic multiple myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.

POEMS Syndrome

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma-cell dyscrasia. This complex, multiorgan disease was first described in 1938, but the acronym POEMS was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. No single test establishes the presence of POEMS
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POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by imbalance of proinflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved. However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the Table. Both major criteria and at least one of the minor criteria are necessary for diagnosis.

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Monoclonal plasmoproliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td></td>
<td>Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diathesis</td>
</tr>
<tr>
<td></td>
<td>Edema (edema, pleural effusion, or ascites)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)</td>
<td></td>
<td>Low vitamin B12 values</td>
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<tr>
<td></td>
<td>Papilledema</td>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000. Other large series have been described in the United States and in India. In general, patients with POEMS have a superior overall survival compared with that of MM, nearly 14 years in a large series from the Mayo Clinic. However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported. Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HSCT support. Optimal treatment involves eliminating the plasma cell clone, for example, by surgical excision or local radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.
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If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias is covered

**Multiple Myeloma**

1. A single or second (salvage) autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat multiple myeloma.
2. Tandem autologous-autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in tandem sequence. (For definitions of near-complete response and very good partial response, see Policy Guidelines).
3. Tandem transplantation with an initial round of autologous hematopoietic stem-cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem-cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered medically necessary to treat newly diagnosed multiple myeloma patients.

**POEMS syndrome**

1. Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome. (see Policy Guidelines)

When Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias is not covered

1. When the medical criteria listed above are not met.
2. Allogeneic hematopoietic stem-cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational.
3. Allogeneic and tandem hematopoietic stem-cell transplantation are considered investigational to treat POEMS syndrome.

Policy Guidelines

Refer to the individual member’s benefit booklet for prior review requirements.

**Multiple Myeloma**

The evidence for autologous hematopoietic stem cell transplantation (HSCT) for upfront treatment in patients who have newly diagnosed multiple myeloma includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy with
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autologous HSCT. Relevant outcomes include overall survival (OS) and treatment-associated morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome. The evidence for autologous HSCT for treatment of relapsed MM following autologous HSCT or refractory disease includes 1 RCT and a systematic review that summarized data from 4 clinical series of patients who relapsed after a first autologous HSCT. Relevant outcomes include OS and treatment-related morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT in patients who have MM who fail to achieve at least a near complete or very good partial response after the first transplant in the tandem sequence (ie, refractory disease) includes 3 RCTs. Relevant outcomes include OS and treatment-related morbidity. The evidence shows tandem autologous HSCT improves OS rates in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT followed by reduced-intensity conditioning (RIC) allogeneic HSCT in patients who have newly diagnosed MM includes several RCTs comparing RIC-allogeneic HSCT following a first autologous HSCT with autologous transplants, single or in tandem (these studies were based on “genetic randomization,” ie, patients with an HLA-identical sibling were offered an RIC-allogeneic HSCT following the autologous HSCT, whereas the other patients underwent either 1 or 2 autologous transplants). Relevant outcomes include OS and treatment-related morbidity. Although the body of evidence shows inconsistencies in terms of OS and DFS rates, some studies have shown a survival benefit with tandem autologous-RIC allogeneic HSCT, although at a cost of higher transplant related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs; nonuniform preparative regimens; different patient characteristics (including risk stratification); and, criteria for advancing to a second transplant. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for allogeneic HSCT with myeloablative or nonmyeloablative conditioning for upfront or salvage treatment in patients who have MM includes nonrandomized studies. Relevant outcomes include OS and treatment-related morbidity. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allogeneic HSCT improves survival compared with autologous HSCT. The evidence is insufficient to determine the effects of the technology on health outcomes.
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**POEMS Syndrome**

The evidence for HSCT of any type in patients who have POEMS syndrome includes case reports and series. Relevant outcomes include OS and treatment-related morbidity. No RCTs of HSCT of any type have been performed in patients with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous with respect to treatment approaches and peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of indirect evidence and contextual factors related to the disease and MM, suggests improvement in health outcomes with autologous HSCT. The evidence is sufficient to determine qualitatively that autologous HSCT results in a meaningful improvement in the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**

**Bone Marrow Transplant for Multiple Myeloma and Primary Amyloidosis**


BCBSA TEC Evaluation, May 1998; Tab 8


BCBSA TEC Evaluation, March 1999; Tab 26


Lemoli R, et.al. Engraftment, clinical and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy. Blood, Volume 95, No. 7, April 1, 2000.


BCBSA Medical Policy Reference Manual, 11/20/01; 8.01.17


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Senior Medical Director – 9/2013


**Policy Implementation/Update Information**

**Bone Marrow Transplant for Multiple Myeloma and Primary Amyloidosis**


2/01 Original policy issued.

1/02 Policy named changed from Bone Marrow Transplant for Multiple Myeloma. Policy statement revised to include Primary Amyloidosis as investigational.
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2/03 Specialty Matched Consultant Advisory Panel meeting 11/2002. Revised the Policy statement to include the statement that, "Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions." Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.

1/04 Benefits Application and Billing/Coding sections updated for consistency.

2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.

7/29/04 HCPCS code S2150 added to Billing/Coding section.

Bone Marrow Transplant for Multiple Myeloma

12/23/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. Split policy to remove reference to Primary Amyloidosis and changed name. Created new policy for Primary Amyloidosis/SUR6090.18. Revised Description of Procedure or Service section. Added new indications (bullets 2 and 3) to "When covered section" which states; "A second course of high-dose chemotherapy with autologous stem-cell support may be considered medically necessary to treat responsive multiple myeloma that has relapsed after a durable complete or partial remission following an autologous transplant or" "tandem high-dose chemotherapy with autologous stem-cell support may be considered medically necessary to treat newly diagnosed or responsive multiple myeloma". Added the 3rd and 4th bullet under When not covered which states; "Non-marrow ablative chemotherapy and allogeneic stem cell support following high-dose chemotherapy with autologous stem-cell support is considered investigational as the initial therapy of multiple myeloma." "Monotherapy using high-dose chemotherapy with allogeneic stem-cell support is considered investigational, either as initial therapy or after a prior failed course of high dose chemotherapy and autologous stem cell support." Added additional information regarding "responsive multiple myeloma", "partial remission", and "refractory multiple myeloma" to Policy Guidelines section. Removed reference to tandem autologous bone marrow transplants from the Policy Guidelines section. Added policy number to Policy Key Words. "Hematopoietic" and "Opportunistic" added to Definitions. References added. Notice given 12/23/2004. Effective date 3/3/2005.

11/3/05 Added "including primary refractory myeloma" to first bullet under the "When covered" section. Added explanation of "primary refractory myeloma" to "Policy Guidelines" and to "Policy Key Words" section.

12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/2006. Added the following statement to the "Policy" section; "If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services for Life-Threatening Conditions." No changes to policy statement. References added.

12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. Added "2. HDC and autologous stem cell support may be considered medically necessary in the treatment of multiple myeloma patients with primary progressive disease who are not at high risk." and "5. Tandem transplantation with an initial round of autologous stem cell support followed by a non- marrow-ablative conditioning regimen and allogeneic stem
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cell transplant may be considered medically necessary to treat newly diagnosed multiple myeloma patients with an Human leukocyte antigens (HLA)-identical sibling donor and who are in otherwise reasonably good health." to the "When Covered" section. Removed "Non-marrow ablative chemotherapy and allogeneic stem cell support following high-dose chemotherapy with autologous stem-cell support is considered investigational as the initial therapy of multiple myeloma." from the "When Not Covered" section. Updated "Policy Guidelines" section. References added. (btw)

**Hematopoietic Stem-Cell Transplantation for Multiple Myeloma**

8/31/10 Policy name changed from “Bone Marrow Transplantation for Multiple Myeloma” to Hematopoietic Stem-Cell Transplantation for Multiple Myeloma. The policy has been extensively revised. Policy number removed. “Description” revised. The policy statements have been updated to reflect current practice. Removed the statement in the “Benefit Application” section that indicated “Services for or related to the search for a donor are not covered.” Deleted the following “When Covered” statements: “1. HDC and autologous stem cell support may be considered medically necessary in the treatment of newly diagnosed or responsive multiple myeloma. OR 2.HDC and autologous stem cell support may be considered medically necessary in the treatment of multiple myeloma patients with primary progressive disease who are not at high risk. OR 3.A second course of high-dose chemotherapy with autologous stem-cell support may be considered medically necessary to treat responsive multiple myeloma that has relapsed after a durable complete or partial remission following an autologous transplant. OR 4 .Tandem high-dose chemotherapy with autologous stem-cell support may be considered medically necessary to treat newly diagnosed or responsive multiple myeloma. OR 5.Tandem transplantation with an initial round of autologous stem cell support followed by a non- marrow-ablative conditioning regimen and allogeneic stem cell transplant may be considered medically necessary to treat newly diagnosed multiple myeloma patients with an Human leukocyte antigens (HLA)-identical sibling donor and who are in otherwise reasonably good health.” Removed the following “When Not Covered” statements: “ HDC and autologous stem cell support is considered investigational in the treatment of multiple myeloma in refractory relapse.” and “Monotherapy using high-dose chemotherapy with allogeneic stem-cell support is considered investigational, either as initial therapy or after a prior failed course of high dose chemotherapy and autologous stem cell support.” Policy Guidelines revised. Senior Medical Director review 5/3/10 References added. (btw)


5/24/11 “Description” section revised to show 2010 updated statistics regarding estimated new cases and deaths. Added “in the tandem sequence” to statement “2. Tandem autologous – autologous…”under the When Covered” section Medical Director review 5/12/11. Reference added. (btw)

1/10/12 “Description” section revised. Specialty Matched Consultant Advisory Panel review 11/30/2011. No change to policy intent. (btw)

2/21/12 Added new 2012 CPT code, 38232, to Billing/Coding section. (btw)

6/29/12 Reference added. (btw)

Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

10/1/13  Policy name changed from “Hematopoietic Stem-Cell Transplantation for Multiple Myeloma” to “Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome”. Description section updated to include information regarding POEMS syndrome. Policy section changed from “BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation for Multiple Myeloma when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.” to “BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.” The following statement was added to the When Covered section; “Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome. (see Policy Guidelines)” Added “Allogeneic and tandem hematopoietic stem-cell transplantation are considered investigational to treat POEMS syndrome.” to the When Not Covered. Policy Guidelines section updated. Senior Medical Director review 9/14/2013. Reference added. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. No change to policy intent. (btw)

12/9/14  Changed file name to match title of policy. Reference added. Specialty matched consultant advisory panel review 11/24/2014. No change to policy intent. (lpr)

12/30/15 Updated Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

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