Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

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 “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy No. 7.01.50.

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 of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.
Conventional Preparative Conditioning for HSCT

The conventional ("classical") practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops 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 are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

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 totally 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 (conventional) regimens.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) refer to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into acute myelocytic leukemia (AML). MDS can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40–60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Signs and symptoms of anemia, often complicated by infections or bleeding, are common in MDS; some patients exhibit systemic symptoms or features of autoimmunity that may be indicative of their disease pathogenesis. The vast majority of MDS diagnoses occur in individuals older than age 55–60 years, with an age-adjusted incidence of approximately 62% among individuals older than age 70 years. Patients either succumb to disease
progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

For the past 20 years, the French-American-British (FAB) system has been used to classify MDS into 5 subtypes as follows: 1) refractory anemia (RA); 2) refractory anemia with ringed sideroblasts (RARS); 3) refractory anemia with excess blasts (RAEB); 4) refractory anemia with excess blasts in transformation (RAEBT); and, 5) chronic myelomonocytic leukemia (CMML). However, the FAB system has been supplanted by that of the World Health Organization (WHO), which records the number of lineages in which dysplasia is seen (unilineage vs. multilineage), separates the 5q-syndrome, and reduces the threshold maximum blast percentage for the diagnosis of MDS from 30% to 20% (see Policy Guidelines for WHO classification scheme for myeloid neoplasms).

Several prognostic scoring systems for MDS have been proposed; the most commonly used is the International Prognostic Scoring System (IPSS). The IPSS groups patients into one of four prognostic categories based on the number of cytopenias, cytogenetic profile, and the percentage of blasts in the bone marrow (see Policy Guidelines). This system underweights the clinical importance of severe, life-threatening neutropenia and thrombocytopenia in therapeutic decisions and does not account for the rate of change in critical parameters, such as peripheral blood counts or blast percentage. However, the IPSS has been useful in comparative analysis of clinical trial results and its utility confirmed at many institutions. A second prognostic scoring system incorporates the WHO subgroup classification that accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements. The WHO Classification-based Prognostic scoring system (WPSS) uses a 6-category system, which allows more precise prognostication of overall survival (OS) duration, as well as risk for progression to AML. This system, however, is not yet in widespread use in clinical trials.

Treatment of smoldering or nonprogressing MDS has in the past involved best supportive care including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying therapy (e.g., U.S. Food and Drug Administration-approved hypomethylating agents, nonapproved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic HSCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront, whether it is to improve anemia; thrombocytopenia; or neutropenia, eliminate the need for RBC transfusion, achieve complete remission (CR), or cure the disease. Allogeneic HSCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient’s risk preference, and severity of MDS at presentation.
Chronic Myeloproliferative Neoplasms

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD) with the term myeloproliferative neoplasms (MPN). These are a subdivision of myeloid neoplasms that includes the four classic disorders chronic myeloid leukemia (CML): polycythemia vera (PCV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF); the WHO classification also includes chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES), mast cell disease (MCD), and MPNs unclassifiable (see Policy Guidelines).

The MPNs are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. They share a common stem cell-derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPNs is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis. As a group, approximately 8,400 MPNs are diagnosed annually in the U.S. Like MDS, MPNs primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older. In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Myeloablative allogeneic HSCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse effects of this procedure. However, the use RIC of conditioning regimens for allogeneic HSCT has extended the potential benefits of this procedure to selected individuals with these disorders.

II. Policy

A. Allogeneic HSCT is covered (subject to Limitations/Exclusions and Administrative Guidelines) as a treatment of myelodysplastic syndromes (see guidelines below) or myeloproliferative neoplasms (see guidelines below).

B. Reduced-intensity conditioning (RIC) allogeneic HSCT is covered (subject to Limitations/Exclusions and Administrative Guidelines) as a treatment of myelodysplastic syndromes or myeloproliferative neoplasms in patients who for medical reasons would be unable to tolerate a myeloablative conditioning regimen (see policy guidelines).

III. Policy Guidelines

The myeloid neoplasms are categorized according to criteria developed by the World Health Organization. They are risk-stratified according to the International Prognostic Scoring System (IPSS).

A. 2008 WHO Classification Scheme for Myeloid Neoplasms
   1. Acute myeloid leukemia
   2. Myelodysplastic syndromes (MDS)
   3. Myeloproliferative neoplasms (MPN)
a. Chronic myelogenous leukemia
b. Polycythemia vera
c. Essential thrombocytemia
d. Primary myelofibrosis
e. Chronic neutrophilic leukemia
f. Chronic eosinophilic leukemia, not otherwise categorized
g. Hypereosinophilic leukemia
h. Mast cell disease
i. MPNs, unclassifiable

4. MDS/MPN
   a. Chronic myelomonocytic leukemia
   b. Juvenile myelomonocytic leukemia
   c. Atypical chronic myeloid leukemia
   d. MDS/MPN, unclassifiable

5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
   a. Myeloid neoplasms associate with PDGFRA rearrangement
   b. Myeloid neoplasms associate with PDGFRB rearrangement
   c. Myeloid neoplasms associate with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

B. 2008 WHO Classification of MDS
   1. Refractory anemia (RA)
   2. RA with ring sideroblasts (RARS)
   3. Refractory cytopenia with multilineage dysplasia (RCMD)
   4. RCMD with ring sideroblasts
   5. RA with excess blasts 1 and 2 (RAEB 1 and 2)
   6. del 5q syndrome
   7. unclassified MDS

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS. This system was developed after pooling data from 7 previous studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to divide patients into two categories: (1) low risk, and (2) high-risk groups. The low-risk group includes low-risk and Int-1 IPSS groups; the goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group—which includes Int-2 and high-risk IPSS groups—the goals are slowing the progression of disease to AML and improving survival. The IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and beta 2-microglobulin also should be considered after establishing the IPSS. If elevated, the prognostic category becomes worse by one category change.
Given the long natural history of MDS, allogeneic HSCT is typically considered in those with increasing numbers of blasts, signaling a possible transformation to acute myeloid leukemia. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for allogeneic HSCT when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils less 500/mm3, platelets less than 20,000/mm3).

Patients with MPNs may be considered candidates for allogeneic HSCT when there is progression to myelofibrosis or when there is evolution toward acute leukemia. In addition, allogeneic HSCT may be considered in patients with essential thrombocytemia with an associated thrombotic or hemorrhagic disorder. There are no suitable U.S. Food and Drug Administration (FDA)-approved therapies for these patients, only supportive care. The use of allogeneic HSCT should be based on cytopenias, transfusion dependence, increasing blast percentage over 5%, and age.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor (MUD) identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in
haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Clinical input suggests RIC allogeneic HSCT may be considered for patients as follows:

**MDS**
- IPSS intermediate-2 or high risk
- RBC transfusion dependence
- Neutropenia
- Thrombocytopenia
- High risk cytogenetics
- Increasing blast percentage

**MPN**
- Cytopenias
- Transfusion dependence
- Increasing blast percentage over 5%
- Age 60-65 years

**IV. Limitations/Exclusions**

The patient must be an appropriate candidate for transplant. This is defined as:
- A. Adequate cardiopulmonary status
- B. Absence of active infection
- C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
- D. Documentation of patient compliance with medical management

**V. Administrative Guidelines**

Precertification is required for this service as well as for any transplant evaluations. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

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<tr>
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VI. Scientific Background

Myelodysplastic Syndromes (MDS)

Despite the successes seen with new drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allogeneic hematopoietic stem-cell transplantation (HSCT) is the only treatment capable of complete and permanent eradication of the MDS clone. (1) A review of allogeneic HSCT using myeloablative conditioning for MDS included 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1,378 cases with age range of 32–59 years. (2) A majority of patients (n=885) received matched related donor (MRD) allogeneic HSCT, with other donor types including syngeneic, matched, unrelated donor (MUD), mismatched unrelated donor (URD), and umbilical cord blood. Most studies included de novo and secondary MDS, chronic myelomonocytic leukemia, MPNs, de novo and secondary acute myelocytic leukemia (AML) and transformed AML. Peripheral blood and bone marrow stem-cell grafts were allowed in most studies. The most commonly used conditioning regimens were busulfan plus cyclophosphamide (BU/CY) and CY plus total body irradiation (CY/TBI), with cyclosporine A (CYA) used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from 5 months to approximately 8 years. Grades II-IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at 1 year to 36% at 5 years. Overall survival (OS) ranged from 25% at 2 years to 52% at 4 years, with non-relapse mortality (NRM) ranging from 19% at day 100 to 61% at 5 years.

A growing body of evidence from a number of largely heterogeneous, uncontrolled studies of reduced-intensity conditioning (RIC) with allogeneic HSCT shows long-term remissions (i.e., longer
All autologous or related donor allogeneic stem cell transplantations for myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with myelodysplastic syndromes/acute myelocytic leukemia (MDS/AML) who otherwise would not be candidates for myeloablative conditioning regimens. (2-13) These prospective and retrospective studies included cohorts of 16–215 patients similar to those in the myeloablative allogeneic HSCT studies. The most common conditioning regimens used were fludarabine-based, with CYA and tacrolimus used for GVHD prophylaxis. The reported incidence of grades II–IV GVHD was 9–63%, with relapse risk of 6–61%. The OS rates ranged between 44% at 1 year to 46% at 5 years, with a median follow-up range of 14 months to over 4 years.

In general, these RIC trials showed a low rate of engraftment failure and low non-relapse mortality (NRM) but at the cost of a higher relapse rate than with myeloablative allogeneic HSCT. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HSCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HSCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom myeloablative chemotherapy and allogeneic HSCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, coupled with clinical input (see below), RIC allogeneic HSCT may be considered medically necessary for patients with MDS who could benefit from allogeneic HSCT but who for medical reasons (see Policy Guidelines) would be unable to tolerate a myeloablative conditioning regimen.

The recommendations of a systematic review of the role of allogeneic HSCT in patients with MDS prepared by the American Society for Blood and Marrow Transplantation (ASBMT) are congruent with the present policy statements. (14) Other recent reviews concur with the ASBMT recommendations. (15-17)

Myeloproliferative Neoplasms (MPN)

Data on therapy for MPN remain sparse. (10, 18) As outlined previously in this policy, with the exception of myeloablative chemotherapy and allogeneic HSCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN. However, the significant toxicity of myeloablative conditioning and allogeneic HSCT in MPN has led to study of RIC regimens for these diseases. One recent series included 27 patients (mean age: 59 years) with MPN who underwent allogeneic HSCT using an RIC regimen of low-dose (2 Gy) total body irradiation alone or with the addition of fludarabine. (8) At a median follow-up of 47 months, the 3-year relapse-free survival was 37% and OS was 43%, with a 3-year NRM of 32%. In a second series, 103 patients (median age 55 years, range 32–68 years) with intermediate to high risk (86% of total patients) primary myelofibrosis (PMF) or post-essential thrombocytthemia (PT) and polycythemia vera myelofibrosis (PVM) were included on a prospective multicenter Phase II trial to determine efficacy of a busulfan plus fludarabine-based RIC regimen followed by allogeneic HSCT from related (n=33) or unrelated (n=70) donors. (19) Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. The cumulative incidence of NRM at 1 year in all patients was 16% (95% confidence interval [CI], 9-23%) but reached 38% (95% CI, 15-61%) among those with a mismatched donor versus 12% (95% CI, 5-19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at 3 and 5
years was 22% (95% CI, 13-31%) and 29% (95% CI, 16-42%), respectively. After a median follow-up of 33 months (range, 12-76 months) 5-year estimated disease-free survival (DFS) and OS was 51% (95% CI, 38-64%) and 67% (95% CI, 55-79%), respectively.

The largest study of allogeneic HSCT for primary myelofibrosis comes from analysis of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR). (20) The median age was 47 years (range: 18-73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA non-identical family members in 26 patients. Patients were treated with a variety of conditioning regimens and GVHD prophylaxis regimens. Splenectomy was performed in 65 patients prior to transplantation. The 100-day treatment-related mortality was 18% for HLA identical sibling transplants, 35% for unrelated transplants, and 19% for transplants from alternative related donors. Corresponding 5-year OS rates were 37%, 30%, and 40%, respectively. DFS rates were 33%, 27%, and 22%, respectively. DFS for patients receiving reduced-intensity transplants was comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at 3 years. In this large retrospective series, allogeneic transplantation for myelofibrosis resulted in long-term relapse-free survival (RFS) in about one-third of patients.

Data from direct, prospective comparison of outcomes of myeloablative conditioning and allogeneic HSCT versus RIC and allogeneic stem-cell support in MPN are not available. However, a recent retrospective study analyzed the impact of conditioning intensity on outcomes of allogeneic HSCT in patients with myelofibrosis (MF). (21) This multicenter trial included 46 consecutive patients treated at three Canadian and four European transplant centers between 1998 and 2005. Twenty-three patients (median age 47 years, range 31-60 years) underwent myeloablative conditioning, and 23 patients (median age 54 years, range 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate- or high-risk. At a median follow-up of 50 months (range 20-89), there was a trend for better progression-free survival (PFS) at 3 years in RIC patients compared to myeloablative-conditioned patients (58%, range 23-62 vs. 43%, range 35-76, respectively, p=0.11); there was a similar trend in 3-year OS (68%, range 45-84 vs. 48%, range 27-66, respectively, p=0.08). NRM rates at 3 years trended higher in myeloablative conditioned cases than RIC cases (48%, range 31-74 vs. 27%, range 14-55, respectively, p=0.08). The results of this study suggest that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allogeneic HSCT in this population.

Summary

The absence of other curative therapies coupled with clinical data and input permit the conclusion that allogeneic HSCT using either a myeloablative or RIC conditioning regimen is medically necessary in appropriately selected patients with MDS or MPN. Patient selection is guided by age and disease risk factors, as outlined in the Policy Guidelines above.
National Comprehensive Cancer Network Guidelines

The 2011 National Comprehensive Cancer Network (NCCN) treatment guidelines (v.2.2011) for the use of allogeneic HSCT indicate this procedure is preferred at diagnosis in patients who are candidates for high-intensity therapy, have a suitable donor, and have de novo MDS classified as IPSS Int-2 and High, or those who have de novo MDS classified as Int-1 with severe cytopenias unresponsive to standard therapies. Reduced-intensity or myeloablative conditioning may be used based on patient age, performance status, comorbid conditions, psychosocial status, patient preference, and availability of caregiver. MRD cells are preferred, but MUD cells are an option at some centers. The role of pretransplant remission induction using intensive chemotherapy has not been established.

National Cancer Institute (NCI) Clinical Trials Database

A search of the NCI clinical trials database in October 2011 identified 9 active Phase III trials that involve stem-cell support for patients with MDS/AML or MPN. Numerous Phase II trials of various treatments for these diseases are actively recruiting patients. Information on these trials can be accessed via the following link, available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=9718439.

Physician Specialty Society and Academic Medical Center Input

In response to requests, input was received from 2 Academic Medical Center specialists prior to review for May 2009. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted. There was consensus among reviewers that RIC allogeneic HSCT was of value in patients with MDS or MPN who would be medically unable to tolerate a myeloablative HSCT.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with
HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References