**Medical Policy Reference Manual**
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# 7.03.006 Nonmyeloablative Allogeneic Hemopoietic Stem Cell Transplantation for Hematologic Malignancies

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## Description

Transplantation of hematopoietic stem cells (HSCT) in conjunction with myeloablative chemotherapy is an established treatment for various hematological malignancies such as lymphomas and leukemias. The treatment effect is the result of the combination of chemotherapeutic ablation of malignant cells and an immune-mediated graft-versus-tumor (GVT) effect from the donor stem cells. HSCT with myeloablative conditioning is associated with serious complications such as organ failure, severe infections, and graft-versus-host disease (GVHD). Thus, the treatment is generally used on younger patients who are more medically fit, without comorbidities, and who would be more tolerant of the toxic effects of the treatment.

Non-myeloablative (NMA) transplantation, also known as "mini" bone marrow transplant (BMT) / "mini" stem cell transplant or reduced-intensity transplant, involves the use of a milder conditioning regimen prior to the stem cell infusion, and depends more on a GVT effect than anticancer drugs to destroy the malignant cells. NMA transplantation is being considered as an alternative for patients who generally are older, heavily pre-treated, and less medically fit, who would otherwise be poor candidates for surviving myeloablative conditioning with HSCT.

**NOTE**: This medical policy does not address nonmyeloablative hematopoietic stem cell transplantation for conditions other than hematologic malignancies.

## Policy

**NOTE: Certain contracts contain specific wording with regard to coverage of this service. Benefits provided by the member's contract supersede the statements of Medical Policy. Therefore, one should refer to the contract language to be certain of limitations of coverage prior to quoting benefits, adjudicating claims, preauthorizing or performing treatment.**

Nonmyeloablative hemopoietic stem cell transplantation for hematologic malignancies is considered **medically necessary** for patients who would otherwise be candidates for stem cell transplantation with myeloablative conditioning.

Nonmyeloablative hemopoietic stem cell transplantation for hematologic malignancies is considered **experimental / investigational** for patients who do not meet selection criteria for stem cell transplantation with myeloablative conditioning, as it does not meet TEC criteria # 2 - 5.

## Policy Guidelines

Rationale:

1. The technology must have final approval from the appropriate government regulatory bodies:

NMA transplantation itself is a procedure not subject to FDA approval. Chemotherapeutic agents or radiation therapy delivery used in conditioning prior to transplant are subject to FDA regulation, however.

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

The published evidence for NMA transplantation derives primarily from retrospective studies and relatively small, uncontrolled series. A retrospective analysis by Sorror and colleagues (2007) has attempted to assess the appropriateness of NMA vs. MA pre-transplant conditioning based on adjustments for comorbidities, in planning for the design of prospective trials. In this analysis, patients with comorbidity index values of 0-2 and either low or high disease risks had probabilities of overall 2-year survival of 70% and 57% after NMA conditioning compared with 78% and 50% after myeloablative conditioning. Patients with scores of 3 and either low or high disease risks had probabilities of overall survival of 41% and 29% with NMA compared with 45% and 24% with myeloablative regimens. The authors concluded that patients with low comorbidity scores could be candidates for prospective randomized trials comparing NMA and MA conditioning regardless of disease status. To date, there have been no prospective, randomized trials directly comparing NMA transplantation with MA transplantation, as patients who received NMA transplantation were not eligible for standard myeloablative conditioning, so randomization was not possible in these differing populations.

There is evidence from retrospective studies that NMA transplantation is feasible and may be beneficial in terms of remission and disease-free survival to patients with hematologic malignancies who are otherwise ineligible for conventional HSCT with myeloablative conditioning, due to advanced age, high risk disease, or comorbidities. Such patients may be able to tolerate a reduced-intensity preparation and demonstrate a satisfactory GVT effect. However, serious and potentially life-threatening complications such as graft rejection, GVHD, and opportunistic infections are seen in these populations, particularly those with acute disease processes. The retrospective nature of the studies recorded to date limit the ability to draw conclusions, and most experts agree that prospective study designs are needed to establish patient selection criteria and NMA conditioning regimens. At the present time, HSCT with NMA conditioning is employed on high-risk, heavily pretreated patients for whom no other treatment alternatives are available.

3. The technology must improve the net health outcome:

NMA transplantation is under active investigation for treatment of several types of hematologic malignancies such as chronic and acute lymphocytic and myelocytic leukemias, multiple myeloma, and non-Hodgkin's lymphoma. There is no standardized NMA regimen, and treatment protocols are variable. These treatment approaches are generally reserved for older, heavily pretreated patients who are medically unfit for conventional HSCT with MA conditioning and who have no other treatment alternatives. The evidence that the technology improves net health outcomes is limited.

4. The technology must be as effective as any established alternatives:

There is evidence that HSCT with NMA conditioning is an established alternative in patients who meet criteria for treatment using myeloablative conditioning, e.g., those for whom establishing a GVT effect is of primary consideration. In patients who because of age, comorbidities, or disease characteristics do not meet criteria for MA conditioning, there are few if any other options available.

5. The improvement must be attainable outside the investigational settings:

At the present time, HSCT with NMA conditioning is being actively pursued in the investigational settings, and a number of clinical trials are in progress. Patient selection criteria and standardization of pre-transplant conditioning regimens have not been fully established; thus, it is not possible to determine whether an improvement in net health outcomes may be expected outside of the investigational settings.

<u>Update 2010:</u>

A search of the peer-reviewed literature was performed from October 2007 through January 2010. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies.

Update 2012:

A search of the peer-reviewed literature was performed for February 2010 through June 2012. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies.

Update 2014:

A search of the peer-reviewed literature was performed from July 2012 through July 2014. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies.

Update 2016:

A search of the peer-reviewed literature was performed from August 2014 through October 2016. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies. Therefore, the policy statement is unchanged.

Update 2018:

A search of the peer-reviewed literature was performed from November 2016 through October 2018. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies. Therefore, the policy statement is unchanged.

Update 2020:

A search of the peer- reviewed literature was performed from the period of November 2018 through November 2020. Findings in the recent literature do not change the conclusions regarding the indications for the use of nonmyeloablative allogeneic hemopoietic stem cell transplantation for hematologic malignancies. Therefore, the policy statement is unchanged.

## Benefit Applications

Certain contracts contain specific wording with regard to coverage of this service. Benefits provided by the member's contract supersede the statements of Medical Policy. Therefore, one should refer to the contract language before treatment.

When the recipient is an eligible subscriber and has been accepted for covered bone marrow transplantation at an approved transplant center, benefits **are provided** for all covered services associated with the harvesting and subsequent infusion.

Benefits are not provided for the storage of stem cells (not associated with active treatment), unless specifically included in the member's contract.

Benefits are usually not provided for donor search services, depending on the contract.

Benefits may be provided for *bone marrow registry,* depending on the contract.

If determined to be experimental / investigational, benefits for bone marrow transplant may be allowed as part of a Clinical Trial. Check member contract and *Clinical Trials, Procedure 10.01.001A*

**Donor Coverage**

There are circumstances where the insured's contract covers donor expenses. See below for various scenarios.

| Donor | Recipient | Coverage |
|---|---|---|
| Uninsured, or insured with contract which does not cover donor expenses | Insured by Plan | Benefits are provided for both donor and recipient under *recipient's* coverage. * |

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|---|---|---|
| | | (Donor utilization of benefits is charged against recipient's contract.) |
| Insured by Plan | Insured by Plan | Benefits are provided for both donor and recipient under their respective coverage. * |
| Insured by other health insurance carrier | Insured by Plan | Benefits for donor services are provided * *only after* other health carrier has made payment for any expenses for which they are liable. |
| Insured by Plan | Uninsured, insured by other health insurance carrier, or insured by Plan with contract which does not cover donor expenses | Benefits are not provided for any/all associated donor services. * |

***** Subject to the terms and to the extent available in the contract(s)

**Non-Approved Transplant**

When a subscriber receives a non-approved bone marrow transplant or receives an approved bone marrow transplant at a non-approved facility, benefits are not provided for any of these services, including the procurement of the bone marrow for transplantation rendered to the recipient or obtained from the donor. Benefits may be provided for subsequent hospital confinement and medical care for the treatment of any related complication(s).

**Other Information**

**NOTE:** For FEP business, check the member's contract for benefits.

**NOTE:** For FEP members, a separate benefit is provided for storage of harvested bone marrow, blood stem cells or cord blood when a covered transplant has already been scheduled.

## Provider Guidelines

Cases involving bone marrow / stem cell transplantation require preauthorization unless otherwise indicated in the contract.

When the recipient is an eligible subscriber and the contract specifically includes a requirement for preauthorization for bone marrow / stem cell transplantation, proper, timely written notice must be received by the Plan prior to surgery. The Plan reserves the right to approve only those covered procedures performed at transplant centers which comply with established criteria and have been designated approved transplant centers.

## Cross References to Related Policies and Procedures

*High Dose Chemotherapy / Radiation Therapy with Allogeneic Stem Cell Support, Policy 7.03.003*
*Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant, Policy 7.03.005*

## References

**The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and**

**conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.**


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