

October 12, 2021

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD

RE: A Formal Request for the Reconsideration of the National Coverage Determination for Stem Cell Transplantation (110.23)

Dear Ms. Syrek Jensen:

The American Society of Hematology (ASH), the American Society for Transplantation and Cellular Therapy (ASTCT), the National Marrow Donor Program (NMDP), and the Center for International Blood and Marrow Transplant Research (CIBMTR) submit this letter as a formal request for reconsideration of the National Coverage Determination (NCD) for Stem Cell Transplantation (110.23). Specifically, the above organizations are asking for full coverage of allogeneic hematopoietic stem cell transplantation (HSCT) for individuals with myelodysplastic syndromes (MDS) and the removal of the Coverage with Evidence Development (CED) requirement currently tied to coverage for HSCT for Medicare beneficiaries with MDS.

Allogeneic HSCT remains the only curative therapy for patients with MDS, a group of blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. MDS primarily impacts older adults: the median age at diagnosis is 70 years, making Medicare coverage for HSCT essential for patients to access this life-saving treatment. Because of the importance of maintaining patient access, our organizations ask that the CED for HSCT remain in place until the full coverage policy requested becomes effective.

Background Information and Current Status of Medicare Coverage of HSCT for MDS

In 2009, the organizations listed above joined other medical societies to request a NCD for allogeneic HSCT for MDS for the Medicare population. On August 4, 2010, CMS established coverage for HSCT for MDS through CED. In December 2010, a CIBMTR study comparing outcomes of patients 55-64 vs. 65 and older was approved by CMS for transplant centers to participate in the CED.

The CED has allowed for coverage of HSCT for Medicare patients with MDS. Currently, there are more than 140 U.S. transplant centers providing Medicare covered HSCT and participating in the CED study of HSCT for MDS in patients over 65. Since approval of the CED, the number of allogeneic HSCTs in the U.S. for patients 65 years and older more than quadrupled, demonstrating that insurance coverage in this population is an essential factor in providing access to HSCT.

The NMDP, operated by Be The Match®, runs the federally authorized bone marrow program that matches living unrelated adult donors with patients in need of a life-saving transplant. For over three decades, through a competitively bid contract with the Health Resources and Services Administration (HRSA), NMDP has been entrusted to operate the federal registry designated by Congress as part of the C.W. Bill Young Cell Transplantation Program (Program). The CIBMTR is a research

collaboration between the NMDP/Be The Match® and the Medical College of Wisconsin (MCW). The CIBMTR runs the Stem Cell Therapeutics Outcomes Database (SCTOD) as part of the Program since 2006. The CIBMTR is charged with collecting data on all allogeneic (related and unrelated) HSCTs performed in the U.S. (from approximately 180 transplant centers), and on all HSCTs done with products procured through the Program but performed outside of the U.S.. In sum, the SCTOD collects and uses data about cellular transplants for research that refines transplantation to help more patients live longer, healthier lives.

Both the NMDP and the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT (FACT-JACIE) have established provider and facility standards directly related to providing HSCT for MDS and the other clinical indications covered by Medicare. These established standards will ensure that the appropriately selected Medicare beneficiaries who receive this service will receive care by qualified providers in a safe environment

Formal Request

With the publication of recent studies strong evidence now exists to motivate our organizations to formally request the reconsideration of the NCD 110.23 for HSCT for patients with MDS and seek the removal of the CED requirements and the inclusion of a statement of full coverage, as suggested here:

B. Nationally Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

c) Effective for services performed on or after (effective date), for the treatment of Myelodysplastic Syndrome (MDS), when it is reasonable and necessary. (New language to be inserted in place of the existing language in NCD 110.23, B. I. c.)

Required Information for Reconsideration

Per the Federal Register Notice: Medicare Program; Revised Process for Making National Coverage Determinations, below is the information as requested for a formal reconsideration.

Proposed use of service

HSCT is a procedure in which stem cells are taken from a person's bone marrow or blood and then administered to the patient by intravenous infusion. When the stem cells come from a donor, the procedure is called an allogeneic HSCT. The only treatment providing or leading to or yielding long-term, progression-free survival for MDS is allogeneic HSCT.

Target Medicare population & Medical indications

Medicare beneficiaries with a diagnosis of MDS regardless of age should have access to HSCT. The services provided to Medicare beneficiaries diagnosed with MDS, and who require a transplant, include, but are not limited to, the statutorily defined benefit categories of inpatient hospital services and the physician services benefit categories (1861(b) and 1861(q), respectively).

MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and chromosome analysis. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow. Patients may die as a result of complications of cytopenias, or after progression to Acute Myelogenous Leukemia. Please see Appendix A for a list of the diagnosis codes for MDS.

Relevance, usefulness, or the medical benefits of the service to the Medicare population

Allogeneic HSCT remains the only curative therapy for patients with MDS. The recent studies summarized below met CMS' criteria for its CED and further substantiate the effectiveness of allogeneic HSCT for MDS among Medicare aged beneficiaries and provide the full response to the request for this information.

Summary of Recent Scientific Evidence to Justify the Request

Summary of Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

Nakamura R, Saber W, Martens MJ, et al. Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome. J Clin Onc 2021, online ahead of print.

Allogeneic HSCT, widely used in younger MDS patients, is the only curative therapy for MDS. While transplantation outcomes among selected older patients with MDS are similar to younger patients with MDS, early transplantation for older patients is infrequently offered since the relative benefits of HSCT over non-HSCT therapy have not been well defined in this patient group. The goal of this multi-center, biologic assignment study in older individuals with high-risk MDS was to define the benefit of HSCT over non-HSCT therapy. Specifically, the study compared allogeneic HSCT with DNA hypomethylating therapy or best supportive care in individuals aged 50-75 years with advanced MDS.

To summarize, the study found that overall survival and leukemia-free survival was significantly improved for individuals who had a suitably matched donor in comparison with those who did not have a donor. Nearly half of subjects with a donor were alive 3 years after trial entry when compared with only one quarter when a donor was unavailable.

Biologic assignment was to the donor or no donor group based on the identification of a suitable, HLA-matched related or unrelated donor within 90 days of trial entry. Subjects with an identified donor were expected to undergo transplantation within 6 months, while those without a suitable donor were expected to receive DNA hypomethylating therapy or best supportive care. The primary endpoint of the study was a point comparison of adjusted overall survival at 3 years from study registration. Secondary endpoints included disease-free survival at 3 years from study registration, quality of life measured at 6 timepoints, and a cost-effectiveness comparison. Additionally, pre-specified as-treated analyses were performed, analyzing only subjects who received their biologically-assigned therapy.

384 subjects in total were accrued at 34 participating centers, with enrollment ending at the end of 2018, when sufficient subjects had been accrued to the no donor arm. Of the 384 subjects, a suitable donor was identified in 260 while no donor was found for 124. Seven subjects died during the 90-day search window and were included in the no donor arm. The donor and no donor arms were well balanced for age, gender, duration of MDS, disease risk and response to prior DNA hypomethylating therapy.

At three years from trial enrollment, overall survival was significantly higher in the donor vs. no donor group, with an absolute improvement of 21.3% (47.9% vs. 26.6%, $p=0.0001$). In a sensitivity analysis, excluding subjects who died or withdrew prior to the end of the search window, no effect on outcomes was noted (48.0% vs. 28.1%, $p=0.0004$). **The effect of age on the primary outcome was specifically analyzed, with no difference in the odds ratio for outcomes when stratified by Medicare age eligibility (age < 65 [OR for survival with donor vs no donor, 2.44] vs age > 65 [OR for survival, 2.962]).** Similar to overall survival, 3-year leukemia-free survival was significantly better in the donor arm (35.8% vs. 20.6%, $p=0.003$), without a measurable difference in the sensitivity analyses (35.9% vs. 21.8%, $p=0.0074$). **Moreover, no effect of age was noted when stratified by Medicare age eligibility (OR for leukemia-free survival, 2.396 vs 2.206).**

In as-treated analyses, only subjects who underwent matched donor transplantation were included in the donor arm, and only those subjects who did not undergo transplantation in the no donor arm. The differences in outcome in this analysis were greater for both 3-year overall survival (47.4 % vs 16%, $p<0.0001$) and 3-year leukemia-free survival (39.3% vs 10.9%, $p<0.0001$).

In preliminary quality of life analyses, no clinically significant differences were noted between donor and no donor groups at several time points up to 3 years from trial entry using the FACT-G, SF-36 physical, SF-36 mental and EQ-5D scores. In contrast to commonly held beliefs that transplantation is associated with poor quality of life, our analysis suggested that there was no decrement in quality of life in transplant recipients.

Summary of Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study

Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study. *JAMA Oncol.* 2020;6(4):486-493. Doi:10.100/jamaoncol.2019.5140. Published online Dec 12, 2019.

The CIBMTR developed an observational study that met CMS' criteria for CED in response to the August 4, 2010 Decision Memo for Allogeneic HSCT for Myelodysplastic Syndrome (CAG-00415N). This prospective, multicenter observational study compared the outcomes of patients aged 55-64 years with patients 65 years and older who received allogeneic HSCT performed in the United States. The primary outcome was overall survival. Other outcomes included non-relapse mortality, relapse, relapse-free survival, and acute and chronic graft-versus-host disease (GVHD). CIBMTR collected data from all participating HSCT centers and performed the analysis.

From December 2010 to May 2014, 688 patients aged 65 years or older were enrolled in the study, and their outcomes were compared with 592 patients aged 55 to 64 years randomly selected from the population of United States patients treated during the same time period. There was no difference in the outcome of the randomly selected sample of patients included in this study compared with the

rest of patients aged 55 to 64 years treated during the study period. Twenty-four percent of the patients in 65 and older group were 70 years or older. The median follow up was 47 months. Other than age, there were no significant differences in patient and disease characteristics between the two age cohorts. About 50% of patients in both groups had an Hemopoietic Cell Therapy-Comorbidity Index (HCT-CI) score of 3 or greater, about 25% had therapy related MDS; nearly 25% were intermediate risk by the Revised-International Prognostic Scoring System (R-IPSS) and around 30% were high or very high risk by R-IPSS at diagnosis.

Multivariate analysis of overall survival identified high/very high R-IPSS, blasts in bone marrow (bBM) > 11% before HSCT, non-age-adjusted HCT-CI of 4 or greater, and GVHD prophylaxis with calcineurin inhibitor + methotrexate as independently associated with inferior outcome. Age group 65 years or older vs those aged 55 to 64 years had no statistically significant association with mortality with (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.94-1.27; p=0.23) or without (HR, 1.13; 95% CI, 0.98-1.3; p=0.08) adjustment for excess population-based risk of mortality in the older group.

Multivariate analysis of relapse-free survival demonstrated no significant difference between patients in the 65 years and older age group compared to those 55 to 64 years (HR, 1.14; 95% CI, 0.99-1.31; p=0.07). R-IPSS high/very high, in-vivo T depletion, bBM > 11% before HSCT, conditioning regimen, not being in remission before HSCT and HCT-CI of 4 or greater were associated with worse relapse-free survival.

At 3 years, non-relapse mortality was 28% vs 25% for the patients 65 years and older vs. the 55 to 64 years age group. After adjusting for excess risk of mortality in the general older population in multivariate analysis, there was no statistically significant difference in non-relapse mortality between the 65 years or older group compared to 55 to 64 years group (HR, 1.19; 95% CI, 0.93-1.52; p=0.16). There were no differences in the rates of grades II to IV acute GVHD or chronic GVHD between the two groups.

The authors conclude older patients with MDS undergoing allogeneic HSCT have similar overall survival compared with younger patients. The strongest factors associated with survival after allogeneic HSCT were HCT-CI comorbidity score, IPSS-R score and other disease related factors, and GVHD prophylaxis regimen. Chronologic age alone should not be an appropriate selection factor for allogeneic HSCT in patients with MDS.

Please see Appendix B for a list of additional literature outlining new clinical evidence which supports this request.

Conclusion

ASH, ASTCT, NMDP, and CIBMTR submit this letter as a formal request for reconsideration of the NCD for Stem Cell Transplantation (110.23). Specifically, the above organizations are asking for full coverage of allogeneic HSCT for individuals with myelodysplastic syndromes and the removal of the CED requirement currently tied to coverage for HSCT for individuals with MDS. As the agency works to address this reconsideration, the organizations ask that the current CED remains in place to allow for uninterrupted coverage for HSCT for Medicare beneficiaries with MDS.

Thank you for your consideration of this request. For any questions, please contact Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org.

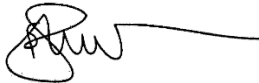
Sincerely,



Martin S. Tallman, M.D.
President, ASH



Stella M. Davies, MBBS, PhD, MRCP
President, ASTCT



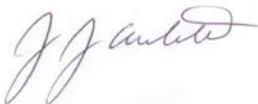
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A handwritten signature in black ink, appearing to read 'Steven Devine', with a stylized flourish at the end.

Steven Devine, M.D.
Chief Medical Officer, NMDP/Be The Match

Appendix A: International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM

D46 Myelodysplastic syndromes

Use additional code for adverse effect, if applicable, to identify drug (T36-T50 with fifth or sixth character 5)

Excludes2: drug-induced aplastic anemia (D61.1)

D46.0 Refractory anemia without ring sideroblasts, so stated
Refractory anemia without sideroblasts, without excess of blasts

D46.1 Refractory anemia with ring sideroblasts
RARS

D46.2 Refractory anemia with excess of blasts [RAEB]

D46.20 Refractory anemia with excess of blasts, unspecified
RAEB NOS

D46.21 Refractory anemia with excess of blasts 1
RAEB 1

D46.22 Refractory anemia with excess of blasts 2
RAEB 2

D46.A Refractory cytopenia with multilineage dysplasia

D46.B Refractory cytopenia with multilineage dysplasia and ring sideroblasts
RCMD RS

D46.C Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
Myelodysplastic syndrome with 5q deletion
5q minus syndrome NOS

D46.4 Refractory anemia, unspecified

D46.Z Other myelodysplastic syndromes

Excludes1: chronic myelomonocytic leukemia (C93.1-)

D46.9 Myelodysplastic syndrome, unspecified
Myelodysplasia NOS

Appendix B: Additional literature outlining new clinical evidence which supports this request

Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study. *JAMA Oncol.* 2020;6(4):486-493. Doi:10.1007/jamaoncol.2019.5140. Published online Dec 12, 2019.

Nakamura R, Saber W, Martens MJ, et al. Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome. *J Clin Onc* 2021, online ahead of print.

Kroger N, Sockel K, Christine W, et al. Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study). *J Clin Onc* 2021.

Gooley T. Two Biologic-Assignment Studies Evaluating the Efficacy of Hematopoietic Cell Transplant Among Older Patients With High-Risk Myelodysplastic Syndrome. *J Clin Onc* 2021.

Warlick E, Ustun C, Andreescu, A, et al. Blood and Marrow Transplant Clinical Trials Network Study 1102 Heralds a New Era in Hematopoietic Cell Transplantation in High-Risk Myelodysplastic Syndromes: Challenges and Opportunities in Implementation. *Cancer* 2021.

Robin M, Porcher R, Ades L, HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM. *Leukemia* (2015) 29, 1496 – 1501.

Abel G, Kim H, Hantel A, et al. Fit Older Adults with Advanced Myelodysplastic Syndromes: Who is Most Likely to Benefit from Transplant? *Leukemia* 2021; 35(4): 1166-1175.