January 5, 2024

Tamara Syrek Jensen, JD
Director, Coverage & Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: Proposed Decision Memo for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS) CAG-00415R

Dear Ms. Syrek Jensen:

On behalf of the American Society of Hematology (ASH), the American Society for Transplantation and Cellular Therapy (ASTCT), the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the Center for International Blood and Marrow Transplantation (CIBMTR), and the National Marrow Donor Program (NMDP), thank you for this opportunity to comment on the proposed decision memo for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS). We are pleased that the Centers for Medicare & Medicaid Services (CMS) has proposed to remove the coverage with evidence development (CED) criteria for HSCT for patients with Myelodysplastic Syndromes (MDS), but note that important modifications are needed to the proposed decision memo to support appropriate medical indications and equitable access to care.

Allogeneic HSCT is 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 most patients to have access to this life-saving treatment.

The patients we care for have greatly benefited from the CED policy established more than 10 years ago. The availability of HSCT through the CIBMTR and BMT CTN CED studies dramatically increased access among Medicare beneficiaries to levels that reflect the clinically appropriate need in the patient population, as demonstrated by the growth in annual volume from fewer than one hundred patients per year before 2010 and to more than seven hundred per year in 2022. We appreciate the Agency's work on this issue and appreciate the commitment to appropriate patient care.

The proposed decision memo requests comments on the nationally covered indications for allogenic HSCT under section 110.23 – Stem Cell Transplantation (Formerly 110.81) of the Medicare National Coverage Determinations Manual. The proposed modifications to the nationally covered indications are as follows: c) *Effective for services performed on or after xx/xx/xx, allogeneic HSCT using only bone marrow or peripheral blood stem cell products for Medicare patients with myelodysplastic syndromes (MDS) designated as high-risk or very high-risk with a score of ≥ 4.5 points according to criteria specified by the International Prognostic Scoring System-Revised (IPSS-R).*

We respectfully submit the following proposed changes in the bolded text and proposed removal of text indicated by strikethroughs. The revised text would therefore read as follows:

c) Effective for services performed on or after xx/xx/xx, allogeneic HSCT ***hematopoietic stem cell sources*** ~~*peripheral blood stem cell products*~~ *for Medicare patients with myelodysplastic syndromes (MDS) designated as*

intermediate or high-risk ~~or very high-risk with a score of ≥ 4.5 points~~ according to criteria specified ~~the International Prognostic Scoring System-Revised (IPSS-R)~~ ***by a current validated scoring system, as recognized by authoritative clinical bodies such as the World Health Organization or National Comprehensive Cancer Network (NCCN).***

The following comments support our requested changes to the text.

Exclusion of Cord Blood as a Donor Source:

The specific exclusion of cord blood as a graft source will limit the availability of curative transplantations for some Medicare patients, particularly those from certain racial and ethnic populations. Many Medicare beneficiaries, particularly those who are not of Caucasian descent, will have difficulty identifying a suitably matched allogenic adult donor and cord blood may be the only HSCT option. Cord blood provides an additional option for any patient, no matter their racial or ethnic status, and has been shown to be an effective hematopoietic stem cell source in numerous studies over the past twenty years. It has the advantage of being rapidly available, an asset for patients with very high-risk disease. We believe that the physician must be able to choose the best available graft source for their patients, based on the patient's unique disease characteristics, acuity, and the degree of Human Leukocyte Antigens (HLA) match and availability of the stem cell product. Data from the CIBMTR indicate that cord blood provides access to HSCT for a small, but meaningful number of patients annually. It should be noted that cord blood is included as a stem cell source under the current CIBMTR CED study and accounted for about sixty patients in the 2020 JAMA Oncology paper resulting from that CED (Atallah, E. et.al); in multivariate analyses of HSCT outcomes in that study, results were like other unrelated donor graft sources.

The rationale to exclude cord blood under the proposed NCD is unclear, would be inconsistent with current policy regarding allogeneic HSCT under the CED and for other indications, and would exclude a donor source that may be the best source available to certain populations. Therefore, we strongly encourage CMS to rephrase the covered indications to state ***hematopoietic stem cell sources*** as opposed to limiting language to "*bone marrow or peripheral blood stem cell products"* to allow the physician to have the decision-making power to determine the most appropriate donor source.

In the proposed decision memo, CMS states the following: "In this national coverage analysis, the sources of stem cells included bone marrow as well as peripheral blood. As mentioned in the background section, other sources of stem cells may include the placenta, amniotic fluid, as well as cord blood. None of the included studies used these other sources for stem cells. There is no study evidence that other sources for stem cell transplantation in Medicare patients with MDS have similar benefits and harms treatment profiles. Therefore, we propose that national coverage will be restricted to the sources of stem cells used in the studies reviewed as part of this analysis (bone marrow and peripheral blood)." Placenta and amniotic fluid are not currently validated sources for stem cells capable of hematologic and immunologic reconstitution and should not be compared to peripheral blood stem cells, bone marrow or cord blood, where there is more than 20-year history of comparable results in diverse indications.

CMS' claims processing manual specifically focuses on the three stem cell sources utilized for HSCT, and as outlined in the Further Consolidated Appropriations Act of 2020:

"90.3 - Stem Cell Transplantation (Rev. 11113; Issued: 11-16-21; Effective: 12-17-21; Implementation: 12-17-21) A. General Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Effective for cost reporting periods beginning on or after October 1, 2020, for subsection (d) hospitals (that is, hospitals paid under the IPPS) furnishing an allogeneic hematopoietic stem cell transplant, such transplant is defined, in accordance with Section 108 of the Further Consolidated Appropriations Act, 2020 (Pub. L. 116-94), as the intravenous infusion of hematopoietic cells derived from bone marrow, peripheral blood stem cells, or cord blood, but not including embryonic stem cells, of a donor to an individual that are or may be used to restore hematopoietic function in such individual having an inherited or acquired deficiency or defect."

Use of the International Prognostic Scoring System-Revised (IPSS-R):

We strongly encourage the agency to not require adherence to a specific scoring system. Instead, we suggest the agency allow use of the most current validated scoring system as recognized by authoritative clinical bodies such as the World Health Organization and the NCCN. Use of a specific scoring system locks the coverage language to a particular point in time, whereas such scoring systems are not static but evolve with scientific advances in diagnosis and prognosis. Risk stratification systems for MDS are rapidly evolving. For example, while the BMT CTN trial was based on the original IPSS, the agency proposed a decision memo based on the IPSS-R. However, currently, IPSS-R is being replaced as the clinical standard by the IPSS-M (Bernard et al, NEJM 2022). This scoring system incorporates important molecular mutations in the prognostic model and is dynamic to account for changes in patients across time and treatments. Importantly, it is not always possible to crosswalk a score from a current scoring system to an outdated system due to new factors implemented as the systems evolve – thus it may not be simple nor practical for a physician to score a patient using whatever the current system is and score the same patient via IPSS-R for purposes of Medicare coverage.

More importantly, as new prognostic factors such as molecular mutations are incorporated into scoring systems, patients' prognostic classification may substantially change compared to historic systems, with some patients historically classified as lower risk now recognized to be higher risk based on molecular or other criteria. We point this out to note the need for flexibility in CMS' coverage language so clinicians can treat the most appropriate candidates going forward. The NCCN clinical guidelines, for example, are reviewed annually, are almost universally referenced by payers in the United States and are regularly updated to reflect the most current and validated scoring system.

In addition to the IPSS, there are other risk stratification models including personalized prediction models, and the EuroMDS. These models provide important prognostic information and have improved risk prediction guidance for clinicians, yet under the NCD, would be excluded from use. Prognostic models will continue to evolve alongside our understanding of risk prediction, and we therefore believe the use of a specific risk model, as indicated in the proposed decision memo, does not allow flexibility for providers and patients when choosing treatment options.

Inclusion of Intermediate Risk MDS:

We believe the medical evidence demonstrates the benefits of allogeneic HSCT compared to currently available conventional therapy for patients with intermediate risk MDS and supports its inclusion in the indication. Enrollment criteria for BMT CTN 1102 included patients characterized as Intermediate-2 or High according to the IPSS criteria available when the study was designed. Overall results from the study for all patients show a survival advantage with allogeneic HSCT. We acknowledge mapping from IPSS to IPSS-R is challenging, and a recently published study from the EBMT has shown that retrospective application of the IPSS-R criteria to patients who received HSCT for MDS resulted in up-classification to higher risk in 76% of patients compared to the IPSS criteria (Robin et al). Retrospective application of IPSS-R criteria of high risk or very high risk to the population of patients included in BMT CTN 1102 based on IPSS criteria would eliminate approximately one third of eligible patients demonstrated to benefit from allogeneic HSCT in the BMT CTN study. The authors of that study presented a subgroup analysis that shows overall survival benefit in the donor arm (allogeneic HSCT) for patients with IPSS intermediate risk. The odds ratio for retrospectively applied IPSS-R risk groups also demonstrated overall survivor benefit for the patients who met IPSS-R intermediate risk (including six patients categorized as very low or low) in the donor arm. There was not a statistically significant interaction between risk score and treatment effect, indicating similar benefit in all risk strata included in the study, including the one third of patients with intermediate risk disease.

The French Biologic Assignment trial and Vidazaallo also demonstrate survival benefit of allogeneic HSCT in intermediate risk MDS. We also note NCCN guidelines characterize IPSS-R intermediate as higher risk MDS.

Additionally, the proposed restriction does not address the issue of secondary MDS (MDS that arises because of prior chemoradiotherapy). Patients with secondary MDS have a uniformly worse prognosis than primary MDS, and, while these patients are excluded from all prognostic scoring systems, these patients are universally accepted as very high risk. Allogeneic HSCT is the only accepted therapy for secondary MDS, and we encourage CMS to cover allogeneic HSCT for all Medicare beneficiaries with secondary MDS.

Lastly, we note a minor correction to the decision memo, which states that the CED study BMT CTN 1102 was funded by industry (Helocyte, Miyarisan Pharmaceutical). This study was conducted by the BMT CTN which is an NIH-funded network supported by the National Heart, Lung and Blood Institute and the National Cancer Institute and this study was fully funded by NIH grants U10HL069294 and U24HL138660.

Thank you for your consideration of our comments. If beneficial to the decision-making process, we are available to meet with you and your colleagues to discuss our proposed changes. Should you have any questions or require more information, please contact Suzanne Leous, American Society of Hematology's Chief Policy Officer, at sleous@hematology.org or 202-292-0258.

Sincerely,

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cc: Kimberly Long, Lead Analyst
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Appendix A: Literature outlining clinical evidence which supports eliminating the CED requirement

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.

Cusatis R, Martens MJ, Nakamura R, et al. Health-Related Quality of Life in Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: BMT CTN 1102. *Am J Hematol, 2021.*

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.

DeFillip Z, Ciurea SO, Cutler C et al. Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. TCT 29; 71-81, 2023.

Greenberg PL, Stone RL, Al-Kali A, et al. NCCN Clinical Practice Guidelines in Oncology for Myelodysplastic Syndromes Version 1.2023. National Comprehensive Cancer Network, Inc. 2023. All rights reserved. www.nccn.org. Accessed June 26, 2023.

Bernard E, Tuechler H, Greenberg PL et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndrome; NEJM Evid 2022.

Nazha A, Komrokji R, Meggendorfer M, et al. Personalized Prediction Model to Risk Stratify Patients with Myelodysplastic Syndromes. J Clin Oncology 2021; 39:3737.

Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. J Clin Oncol 2021; 39:1223.

Auletta, J, Kou J, Chen, M et al. Real-World Data Showing Trends and Outcomes by Race and Ethnicity in Allogeneic Hematopoietic Cell Transplantation: A Report from the Center for International Blood and Marrow Transplant Research. Transplant Cell Ther 2023.