American Society of Hematology

Carrier Advisory Committee (CAC) Meeting

June 28, 2024

Annual Meeting

ASH Headquarters
2021 L St. NW
Washington, DC
8:00 a.m. – 3:00 p.m. ET
https://hematology.zoom.us/j/98784329033?pwd=a2LT0bGuyqpvqJAVA0Oayfk4RB2P7q.1

Agenda

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

American Society of Hematology
Carrier Advisory Committee (CAC) Network Meeting
Friday, June 28, 2024
8:00 a.m. – 3:00 p.m. ET

AGENDA

8:00 a.m.	BREAKFAST		
8:30 a.m.	Welcome and Introductions	Dianna Howard, MD	
	• In-Person Attendee List		4
	• Speaker List and Bios		6
	• ASH Staff List		9
	• CMD List and Jurisdiction Map		10
9:00 a.m.	Coverage and Payment Updates	Panel	13
	• Local Coverage Determination for HSCT for Lymphoma (letter)	Dr. Howard	14
	• Duffy Null ICD-10 Coding Update	Kay Moyer, MS	
	• National Coverage Determination for Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome (letters)	Corey Cutler, MD	17
10:00 a.m.	NETWORKING BREAK		
10:30 a.m.	Next Generation Sequencing (NGS)	Jonathan Gerber, MD Annette Kim, MD, PhD	38
11:15 a.m.	Inclusion of Dental Services Pre-transplant	Nectarios Pavlakos, DDS	53
12:00 p.m.	LUNCH		
1:00 p.m.	What's going on in your Jurisdiction?	All	
	• Open discussion on any coverage or reimbursement issues		
1:30 p.m.	Cell and Gene Therapy	Alexis Thompson, MD, MPH Claire White, MSN, RN	54
	• Treatment journey for a patient electing gene therapy for Sickle Cell Disease		
	• Administrative considerations and challenges		
2:30 p.m.	Closing Remarks and Reference Materials	Dr. Howard	
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3:00 p.m.	ADJOURN		

CAC 101

The Carrier Advisory Committee is established by a Medicare Administrative Contractor (MAC) to share valuable clinical insight to inform coverage decisions across the 13 MAC Jurisdictions. MACs are private health insurers contracted with the Centers for Medicare and Medicaid Services (CMS) to process Medicare claims for a specific geographic region.

CAC members include physicians (limited to one per specialty or provider type), a beneficiary representative, and representatives of other medical organizations. CAC members are a valuable asset to policy development and serve as a mechanism for physicians to be made aware of and participate in the development of new Local Coverage Determinations (LCD), to discuss and amend administrative policies, and to serve as a link between Medicare and the local provider community. Often, MACs include a summary of the CAC members' recommendations with the final Local Coverage Determinations (LCDs).

ASH sponsors the Hematology CAC Network Meeting as an opportunity for CAC representatives to meet, network, and strengthen relationships with the Medical Directors from the MAC and provide input on trending topics, as well as receive information which may help members understand Medicare policy and reimbursement. The meeting allows participants to discuss Medicare-related coverage and policy issues, draft policies, and the relationship between Medicare and the provider community. This diverse group of stakeholders also has an opportunity to discuss possible solutions to real-world issues. ASH hosts the Hematology CAC Network Meeting annually at ASH Headquarters in Washington, DC.

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Speaker List

Dianna Howard, MD

Dianna Howard, MD has been the director of a bone marrow transplant (BMT) program for 15 years, first at the University of Kentucky, and now at Wake Forest. Both programs provide care to a swath of the Appalachian region and a subset of patients for whom barriers to access either because of co-morbidities, distance, or delay in referral remain a challenge. Dr. Howard has a special interest in the adolescent and young adult (AYA) population as she is trained in both pediatric and internal medicine. When Dr. Howard joined Wake Forest, her priorities included improving data management and quality reporting to Center for International Blood and Marrow Transplant Research (CIBMTR); transitioning autologous transplant care to outpatient; starting a transplant survivorship program; and positioning Wake as a center of excellence with insurers so patients would have access to transplant without having to travel. BMT programs are evaluated on volume and outcomes - accomplishing both at the same time is an imperative with greater challenges in modest sized transplant programs. Dr. Howard has been involved in efforts focused on expanding regional access for patients who need transplant. Her team was awarded an ASHP Best Practice Award in 2017 for our Autologous SCT outpatient program, recognizing our inclusion of clinical practice pharmacists. Consistent with her interest in patient access to health care, she has participated in advocacy campaigns with LLS, ACP, ASH and ASTCT.

Dr. Howard completed the ASH Advocacy Leadership Institute and serves on ASH Committee of Government Affairs. Dr. Howard also serves on ASTCT Outcomes Committee, as faculty for the inaugural ASTCT Leadership Course, Co-Chair the ASTCT Leadership course for 2020, Chair ASTCT Government Relations Committee, and represents ASTCT on the ASH Committee on Practice and ACP Council of Subspecialists, where she has co-chaired a health policy subcommittee. Through this level of committee engagement Dr. Howard has been able to work with colleagues to advocate for access to transplant and cell therapy - advancing health policy that impacts patient barriers. At Wake Forest she has worked with the government policy office to respond to the call for comments to CMS on issues important to our transplant program and led a regional effort to influence insurer policy with regard to transplant reimbursement practices.

Kay Moyer, MS

Kay Moyer leads CRD Associates' team of experts in analyzing regulations promulgated by the Centers for Medicaid & Medicaid Services, the Food and Drug Administration, National Institutes of Health and other healthcare-oriented government agencies. If there is a federal regulation of importance to CRD clients, Kay and the team will track it down and provide guidance and insight on how to respond. Kay has extensive experience with physician payment policy that includes a keen understanding the Medicare Physician Fee Schedule, the AMA CPT code process and the AMA Relative Value System Update Committee (the RUC) process. Kay is a certified professional coder certified under the Association of Academy Professional Coders.

Prior to joining CRD Associates, Kay honed her skills on payment policy issues working at the Infectious Diseases Society of America (IDSA), monitoring Federal regulations including the Medicare Physician Fee Schedule, Outpatient Prospective Payment System and other regulations that may have impacted infectious diseases physicians. As the staff liaison to the IDSA Clinical Affairs Committee, Kay was integral in developing and authoring regulatory comment letters, as well as leading the committee in creating a CPT coding manual for evaluation and management services. Recently, Kay assisted with projects to highlight the value of infectious diseases (ID) physicians within the healthcare system and has advocated for improved reimbursement for their work.

Corey Cutler, MD, MPH

Corey Cutler, MD, MPH, FRCP(C) graduated from McGill University's Faculty of Medicine, completed a residency in Internal Medicine at the McGill University Health Science Center, and completed fellowship training in hematology, medical oncology, and stem cell transplantation at the Dana-Farber Cancer Institute. Dr. Cutler earned an MPH degree at the Harvard School of Public Health. Dr. Cutler's research is in the prevention and treatment of acute and chronic graft-vs.-host disease. Dr. Cutler also studies the role and timing of transplantation for the myelodysplastic syndromes and is a contributing author on more than 300 peer-reviewed publications.

Dr. Cutler is the Director of the Stem Cell Transplantation Program at the Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School. Dr. Cutler is also currently the President of the American Society for Transplantation and Cellular Therapy.

Johnathan Gerber, MD
Effective July 1, 2024, Jonathan M. Gerber, MD will be joining NYU Langone Health as the Chief Clinical Officer of the Perlmutter Cancer Center.

Dr. Gerber received his BA in Biology (Phi Beta Kappa) and MD (Alpha Omega Alpha), as well as Internal Medicine residency and Hematology Fellowship training at Johns Hopkins. Upon completion of his training, he served on the faculty of the Johns Hopkins School of Medicine and Johns Hopkins Hospital for 5 years, in the Division of Hematology. Dr. Gerber then joined the newly created Levine Cancer Institute (LCI), where he was the founding Director of the Leukemia Division, the founding Medical Director of Hematology, and the Associate Director of LCI Operations. He also helped launch the BMT Program, performing the first allogeneic BMT in an adult in the city of Charlotte, NC in March of 2014. He was a clinical faculty member at the University of North Carolina School of Medicine at Chapel Hill during his time in Charlotte. Dr. Gerber was then recruited to the University of Massachusetts (UMass) Chan Medical School and UMass Memorial Health in 2018 , where he served as the Director of the Cancer Center, Medical Director of the Cancer Service Line, and Chief of Hematology & Oncology. He was a Professor of Medicine and Molecular, Cell, & Cancer Biology; and from 2018-2024, he held the Eleanor Eustis Farrington Chair in Cancer Research at UMass.

Dr. Gerber's clinical interests include leukemia and related hematologic conditions, as well as BMT. He is a translational laboratory researcher and an early phase clinical trial investigator. His research focuses on improving the identification and targeting of the stem cells at the root of leukemia and other clonal hematologic diseases, with the goal of personalizing therapy and developing better treatments that are more effective and less toxic. He has published numerous articles in his field, presented his research findings at national & international meetings, and served as a reviewer for the National Institutes of Health and prominent journals. He is a member of the editorial board and an Associate Editor for *HemOnc Today*, overseeing hematology content.

Dr. Gerber has also received many grants and awards for his research, which has resulted in 3 U.S. patents and has been translated into clinical trials. During the COVID-19 pandemic, his research also branched into plasma-based therapies for COVID, including collaborations with Johns Hopkins that were published in the *New England Journal of Medicine* and were named a *2023 Top 10 Clinical Research Achievement* by the Clinical Research Forum. More recently, he has served as an investigator on cutting edge protocols utilizing cellular therapy for autoimmune diseases, such as systemic lupus erythematosus.

Dr. Gerber is a member of the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO). He currently is a member of the ASH Committee on Practice and the liaison to the ASH Subcommittee on Precision Medicine, as a well as a member of the ASH Continuing Certification Working Group. He previously served on the ASCO Cancer Research and Education committees. In addition, he was a member of the Massachusetts Department of Public Health's Diagnosis & Treatment Working Group for the 2024-2029 State Cancer Plan. Dr. Gerber has also served on the boards of the Charlotte and the New England chapters of the Leukemia & Lymphoma Society.

Annette Kim, MD, PhD
Annette S. Kim, MD, PhD is the Henry Clay Bryant Professor and Division Head of Diagnostic Genetics and Genomics at the University of Michigan. Annette S. Kim received her MD, PhD from Harvard in 1998. After a postdoc at Memorial Sloan Kettering Institute and several years at Merck, Dr. Kim completed residency and fellowship in Hematopathology at the University of Pennsylvania in 2008. Dr. Kim has been the Medical Director at Cooper University Hospital (2008-2009) and hematopathologist and molecular pathologist at Vanderbilt University (2009-2015) and Brigham and Women's Hospital (2015-2023). Dr. Kim's research program has focused on the study

of hematolymphoid malignancies, including miRNAs in myelodysplastic syndromes, myeloid and lymphoid mutational patterns, and test utilization management. At the Brigham and Women's Hospital, Dr. Kim has served as the Laboratory Director of the Heme Molecular Lab and the Translational Biomarker Core of the Center for Advanced Molecular Diagnostics. She was Co-Director of the Interpretive Genomics Program at the Dana Farber Cancer Institute, the Director of the BH3 Profiling Laboratory, and the PI of the molecular core for the Leukemia SPORE program. She has served on several national pathology committees including the College of American Pathologists Molecular Oncology and Personalized Health Care Committees, the latter as current Vice-Chair, and the Association of Molecular Pathology Board and Executive Committee as well as chairing the Hematopathology Subdivision and the Training and Education Committees. In addition, she is the Vice-Chair of the ASH Precision Medicine committee and served on the Somatic Working Group committee. She also serves on a number of other national biomarker and pathology committees. She has been awarded several teaching awards and was awarded the CAP Public Service Award in 2019.

Nectarios Pavlakos, DDS

Nectarios Pavlakos RDH DDS, joined Noridian Healthcare Solutions in January 2024, as a Contractor Medical Director. Dr. Pavlakos completed his Doctor of Dental Surgery degree at the University of Missouri Kansas City and completed a residency in Advanced Education in General Dentistry at the University of New Mexico. Dr. Pavlakos brings 8 years of experience, specifically in the private practice sector and as a faculty member at the University of New Mexico Department of Dental Medicine. He then joined the VA hospital system and served as a staff dentist for the veteran population before joining Noridian. During his tenure, he provided dental care in restorative/prosthodontic dentistry, implant dentistry, oral surgery and advanced hospital-based dentistry. He also has 7 years of experience with Medicaid/Medicare treatment plan review, pre-authorization review and dental policy during his time in the hospital settings. He continues to practice dentistry part time in private practice, in addition to volunteering his time lecturing to dental residents and dental hygiene students at the University of New Mexico.

Alexis Thompson, MD, MPH

Dr. Alexis Thompson is Chief, Division of Hematology at the Children's Hospital of Philadelphia. She is also Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine and holds the Elias Schwartz MD Endowed Chair in Hematology. Her research interests include hemoglobinopathies (thalassemia and sickle cell disease), and stem cell transplantation in pediatric patients, including gene therapy. Her most significant scientific contributions are clinical and translational studies to better understand and treat hemoglobinopathies. She has served on regional and national on advisory committees for governmental agencies as well as non-profit organizations focused on improving healthcare access, increasing workforce diversity and reducing health disparities. As a leader of the American Society of Hematology (ASH), including ASH President in 2018, Dr. Thompson helped to develop a comprehensive report on the current state of clinical care for SCD in an effort to identify unmet medical needs, launch a national sickle cell data collection platform and create a sickle cell learning community to improve outcomes. She is also leading efforts to implement newborn screening and early intervention efforts in sub-Saharan Africa, where the burden of SCD is profound. Dr. Thompson received the ASH Award for Leadership in Promoting Diversity in 2023.

Claire White, MSN, RN

Claire White, MSN, RN is the administrative manager for the Cancer Immunotherapy Program in the Cell Therapy and Transplant Section at The Children's Hospital of Philadelphia. In this role, she supports access operations and health policy work for the Cell Therapy program with a focus on equitable and timely patient access to cell & gene therapy treatments offered both commercially and on clinical trials. Claire joined The Children's Hospital of Philadelphia as a staff nurse in the Pediatric Oncology Clinic in 2012 and later joined the Cancer Immunotherapy Program as a Nurse Navigator in 2015. Claire serves on various access, health equity, and payor relations committees. She is passionate about health system innovation to support access to and sustainability of novel cellular and gene therapies.

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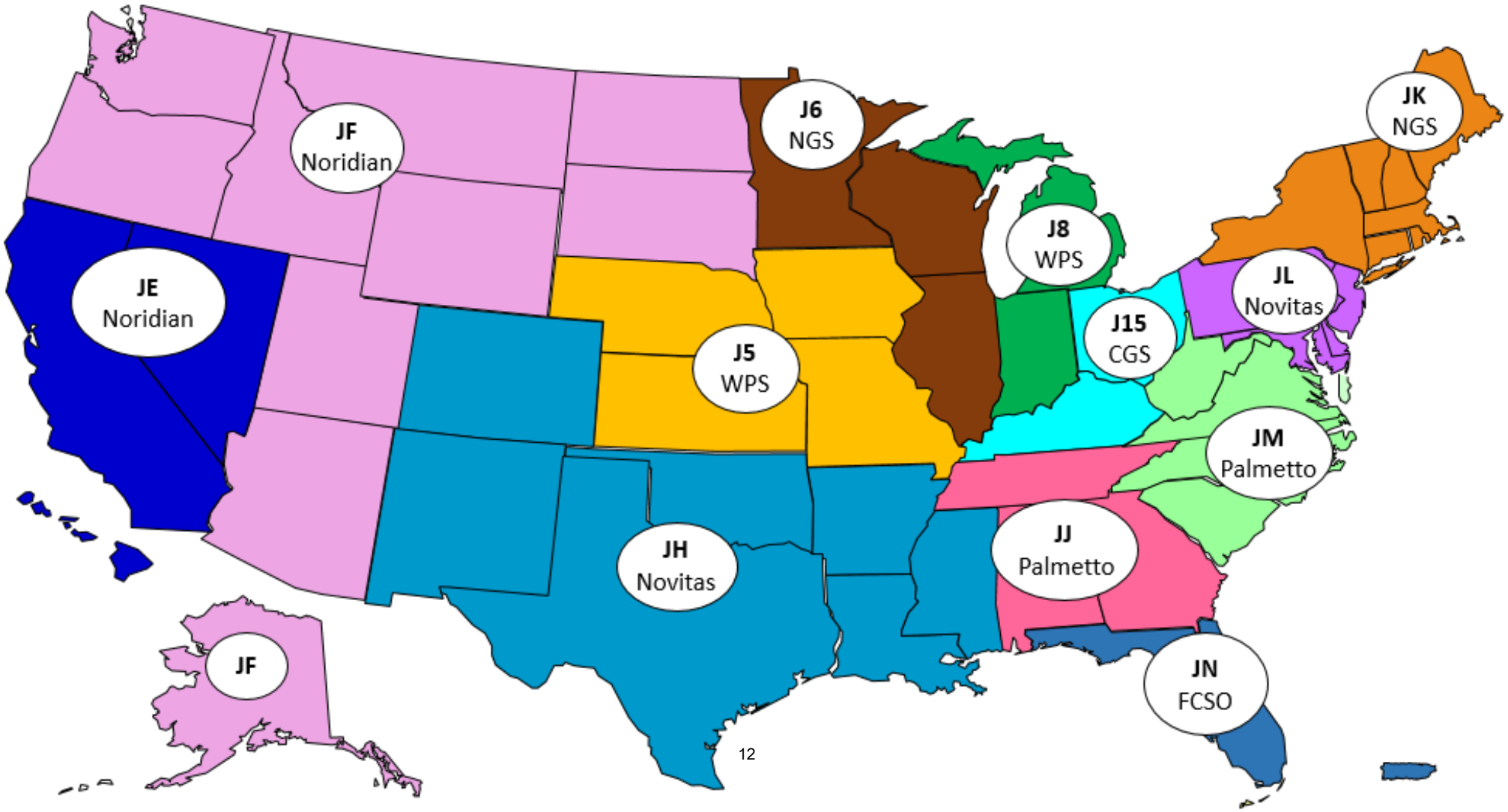


Coverage and Payment Updates

Local Coverage Determination for HSCT for Lymphoma

As raised during previous ASH CAC annual meetings, ASH has been working with all Medicare Administrative Contractors (MACs) to propose local coverage determinations (LCD) that would expand coverage for allogeneic stem cell transplants (HSCT) for Medicare beneficiaries with primary refractory or relapsed Hodgkin and non-Hodgkin lymphomas with B- or T-cell origin. The current Medicare National Coverage Determination for Allogeneic Stem Cell Transplantation does not specifically include lymphoma as a covered indication, which leaves Medicare beneficiaries with lymphoma without nationally consistent access to this potentially curative treatment and creates a different standard of care under Medicare than what is afforded to patients with commercial insurance. ASH, with the support of the American Society for Transplantation and Cellular Therapy, has sent letters (p. 14) to all MACs to encourage the adoption of the new LCDs. Please refer to the map on p. 16 for a status of all LCDs on HSCT for lymphoma across the country.

Duffy Null ICD-10 Coding Update

On April 11, the Centers for Medicare & Medicaid Services (CMS) released its FY2025 Inpatient Prospective Payment System Rule which included a provision for new Z codes to appropriately code for Duffy Null status. This is a win for ASH in that the Society submitted a proposal to the National Center for Health Statistics' ICD-10 Coordination and Maintenance Committee in May, 2023, requesting the creation of new Z codes that would be used to indicate Duffy phenotype status in medical documentation and claims submissions. The application was a part of a broader, ASH-led Duffy Status Health Equity Project to ensure that the people who have lower absolute neutrophil count (ANC) due to Duffy phenotype are accurately documented within the medical record and are not considered to have "abnormal" ANC levels. In conjunction with that application, ASH member Maureen M. Achebe, MD presented to the ICD-10-CM Coordination and Maintenance Committee in September 2023 on the need for the new codes as well the significance of accurate documentation of Duffy status. The new codes will be effective on October 1, 2024, after the final IPPS rule is issued.

National Coverage Determination for Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome

On March 6, CMS released a final decision memo on the national coverage determination (NCD) for Allogenic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes (MDS), effective immediately. ASH, along with the American Society for Transplantation and Cellular Therapy (ASTCT), the Blood and Marrow Transplant Clinical Trials Network, the Center for International Blood and Marrow Transplantation, and the National Marrow Donor Program (NMDP), submitted comments after the proposed decision memo was released in December 2023. The comment letter (p. 17)1 included supporting evidence for the use of cord blood stem cell products as a donor source and the use of additional recognized scoring systems and risk designations. CMS had originally proposed that cord blood be excluded as a donor source and proposed that only the International Prognostic Scoring System-Revised could be used to determine when a patient qualified for a stem cell transplant. The final decision memo outlined the inclusion of cord blood as a donor source and CMS will allow the use of other recognized risk scoring systems. ASH views this as an important win for Medicare patients with MDS, who will now have greater access to this treatment option. Click here for an analysis of the decision.

Following the announcement of the NCD, ASH, ASTCT and NMDP sent a letter (p. 23) to all Medicare Administrator Contractor (MAC) medical directors to alert them of a potential influx of HSCT cases that were previously covered under the prior policy. The NCD removed the coverage with evidence development criteria and created revised coverage indications for MDS. While all organizations appreciated the changes outlined in the NCD, the policy was effective immediately which has the potential of causing gaps in coverage for current transplant patients. The letter strongly encouraged MAC medical directors to use their discretion and approve coverage for HSCT for these individuals.

March 15, 2023

Contractor Medical Directors
National Government Services, Inc.
P.O. Box 7108
Indianapolis, IN 46207-7108

RE: (DL39513) Allogeneic Hematopoietic Cell Transplantation for Primary Refractory or Relapsed Hodgkin's and Non-Hodgkin's Lymphoma with B-cell or T-cell Origin

Dear Contractor Medical Directors,

The American Society of Hematology (ASH) and the American Society for Transplantation and Cellular Therapy (ASTCT) support the National Government Services (NGS) proposed draft local coverage determination (LCD), DL39513, Allogeneic Hematopoietic Cell Transplantation (allo-HCT) for Primary Refractory or Relapsed Hodgkin's and Non-Hodgkin's Lymphoma with B-cell or T-cell Origin. We appreciate this important step to provide coverage for this life-saving treatment to the Medicare beneficiaries that our members treat.

The Medicare National Coverage Determination (NCD) for Allogeneic Stem Cell Transplantation (110.23) does not specifically include lymphoma as a covered indication for stem cell transplantation which leaves Medicare beneficiaries who have lymphoma without access to this potentially curative treatment. The lack of Medicare coverage at the national level creates a different standard of care than what is afforded to patients with commercial insurance. For the subset of lymphoma patients who are prime candidates for this procedure, allo-HCT is their only option for curative intent therapy, making the proposed LCD critically important to their recovery and survival.

We have reviewed NGS's draft LCD and appreciate that the language mirrors the language in Palmetto GBA's L39270 and CGS Government Administrators DL39434 LCDs that cover allo-HCT for the covered indications as previously noted. ASH and ASTCT believe uniform language across Medicare contractors will provide the same standard of care for all Medicare beneficiaries and will help to avoid regional differences in interpretation.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

The ASTCT is a professional membership association of more than 3,000 physicians, scientists and other health care professionals promoting blood and marrow transplantation and cellular therapy

through research, education, scholarly publication, and clinical standards. The clinical teams in our society have been instrumental in developing and implementing clinical care standards and advancing cellular therapy science, including participation in trials that led to current FDA approvals for chimeric antigen receptor T-cell (CAR-T) therapy.

Thank you for proposing to expand coverage for allo-HCT to individuals living with lymphoma as this treatment may be their only option. If you have questions or need additional information, please contact ASH's Chief Policy Officer Suzanne Leous at sleous@hematology.org or ASTCT's Director of Government Relations, Alycia Maloney at amaloney@astct.org.

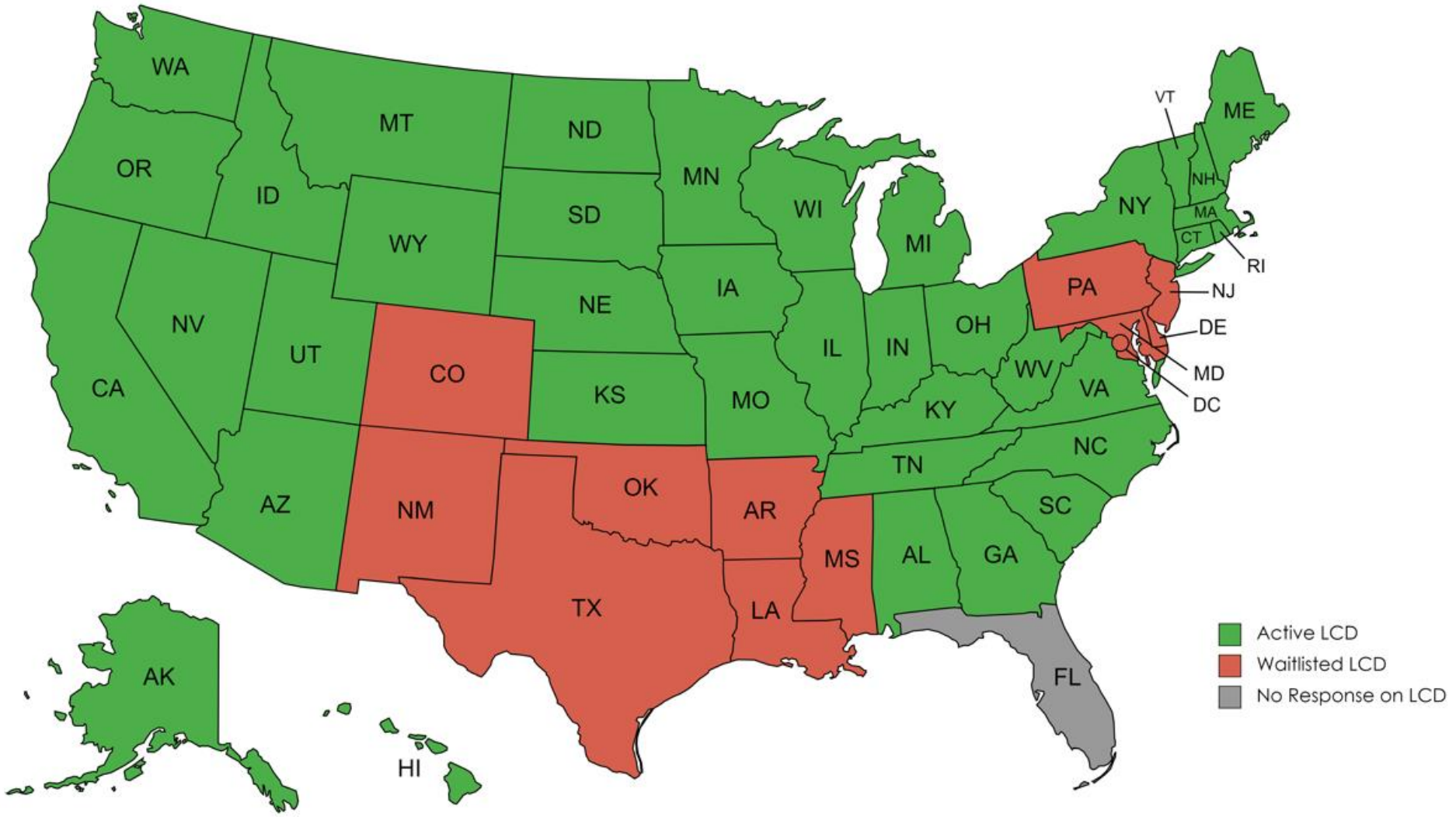
Sincerely,

Robert A. Brodsky, MD
ASH President
The Johns Hopkins Family Professor of Medicine and Oncology
Director, Division of Hematology

Miguel-Angel Perales, MD
ASTCT President
Chief, Adult Bone Marrow Transplantation Service
Attending Physician and Member
Division of Hematologic Malignancies, Department of Medicine
Professor of Medicine, Weill Cornell Medical College

Local Coverage Determinations

Medicare beneficiaries to receive **allogeneic hematopoietic cell transplantation** for primary refractory or relapsed Hodgkin's and Non-Hodgkin's Lymphoma with B-cell or T-cell origin for whom there are no other curative options



Agenda

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,

Mohandas Narla, DSc
2024 President, ASH

Robert A. Brodsky, MD
2023 President, ASH

Miguel Perales, MD
President, ASTCT

Corey Cutler, MD
President-Elect, ASTCT, and BMT CTN 1102 Co-Principal Investigator

Mary M. Horowitz, MD, MS, MACP
Principal Investigator, BMT CTN Data and Coordinating Center, Medical College of Wisconsin

J. Douglas Rizzo, MD, MS
Senior Scientific Director and Principal Investigator, Stem Cell Therapeutic Outcomes Database, CIBMTR-Medical College of Wisconsin

Bronwen Shaw, MD, PhD
Chief Scientific Director, CIBMTR-Medical College of Wisconsin

Jeffery J. Auletta, MD
Senior Vice President, NMDP
Chief Scientific Director, CIBMTR-NMDP

Steven Devine, MD
Chief Medical Officer, NMDP/Be the Match

cc: Kimberly Long, Lead Analyst
James Rollins, M.D., Lead Medical Officer

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.

March 29, 2024

On behalf of the American Society of Hematology (ASH) and the American Society for Transplantation and Cellular Therapy (ASTCT), and the National Marrow Donor Program (NMDP) we are writing regarding the revised National Coverage Determination (NCD) for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS), which was finalized by the Centers for Medicare & Medicaid Services (CMS) on March 6, 2024. We extend our thanks to CMS for removing the coverage with evidence development (CED) criteria and for creating revised coverage indications for MDS. While we appreciate the agency's work, these revisions, which were effective upon publication, have implications for local coverage of HSCT for MDS of which we want you to be aware.

The NCD expands coverage for "allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes." Coverage under the NCD is dependent on prognostic risk scores outlined in the policy. Prior to the release of the NCD, coverage for allogeneic stem cell transplant for MDS patients was provided under the less stringent CED policy. However, the elimination of the CED creates a potential coverage gap during the transition period, which could affect many patients within your jurisdiction.

We want to alert you that your area of jurisdiction may be experiencing an influx of HSCT cases that were previously covered under the CED, and that the MACs have the discretion to cover these cases. The NCD specifically states that "coverage of all other indications for stem cell transplantation not otherwise specified above as covered or non-covered will be made by local Medicare Administrative Contractors under section 1862(a)(1)(A)." Our organizations respectfully request that you review these cases expeditiously to ensure that appropriate cases are covered at the local level. This will allow patients and providers to proceed with treatment as centers adjust their practices to meet the NCD's requirements.

HSCT is typically planned at least six to eight weeks in advance to schedule acquisition of cells from the donor, arrange inpatient admission, and otherwise coordinate complex care. An overnight change in coverage is particularly problematic since some centers already scheduled transplants prior to March 6. Caregivers, and donors may have already made the difficult arrangements for time off from work, travel, accommodations, and other pertinent logistical arrangements. Depending on the patients' clinical status and risk scores, some patients already scheduled for HSCT before March 6 had their coverage based on the CED may now experience a coverage shift and could be left without coverage which would have been determined at the federal level and will now be left for adjudication locally.

Thank you for consideration. We would like to offer our societies as resources to you and would be happy to identify subject matter experts or provide the names of hematology Carrier Advisory

Committee representatives, should you need their assistance. We also have resources available that can be provided to you during this period of transition. If you have questions or would like to discuss the revised NCD and other coverage issues, please use Suzanne Leous, ASH Chief Policy Officer (sleous@hematology.org; 202-292-0258), as your point of contact.

Sincerely,

Mohandas Narla, DSc
ASH President

Corey Cutler, MD, MPH
ASTCT President

Amy Ronneberg
NMDP Chief Executive Officer

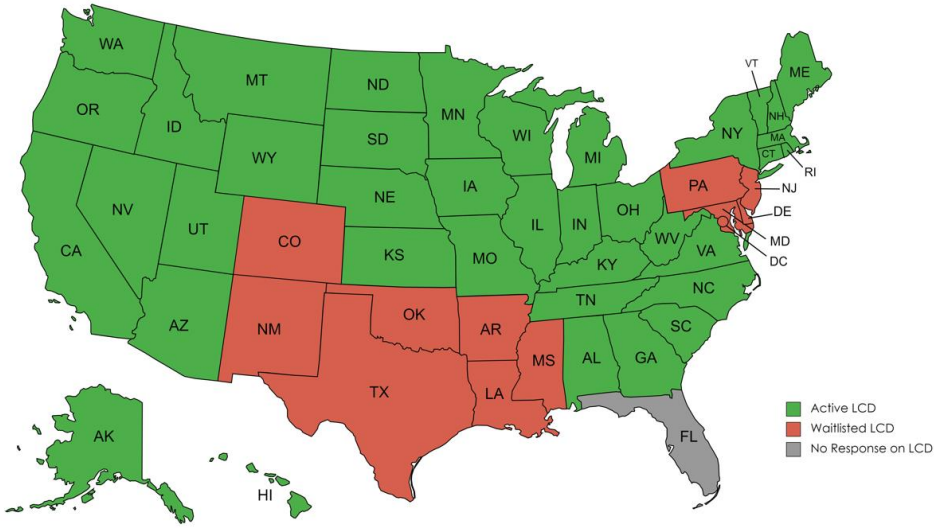
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

Local Coverage Determination
HSCT for Lymphoma

1

Local Coverage Determinations

Medicare beneficiaries to receive **allogeneic hematopoietic cell transplantation** for primary refractory or relapsed Hodgkin's and Non-Hodgkin's Lymphoma with B-cell or T-cell origin for whom there are no other curative options



American Society *of* Hematology

2

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

New ICD-10-CM Z Codes
Duffy Phenotype

3

Creation of ICD-10-CM Z Codes for Duffy-null Phenotype

- ASH requested creation of Z codes to properly document the Duffy status for individuals in the summer of 2023.
- ASH stated that specific codes will ensure:
  - Accurate documentation of the ANC reference range, and inclusion in the electronic health record.
  - Appropriate clinical care and management.
  - Augmented ability to conduct research.
  - The Duffy status can now be captured in a consistent and longitudinal manner.

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Duffy-null Phenotype ICD-10-CM Z Codes

- **Approved and Effective October 1, 2024**
  - The new codes were approved by the National Center for Health Statistics – the entity that oversees the ICD-10-CM code set.
  - Code Structure
    - Z67.A1: Duffy Null
    - Z67.A2: Duffy a positive
    - Z67.A3: Duffy b positive
    - Z67.A4: Duffy a and b positive

5

Why Were the Codes Needed?

Patients

- Anxiety to patient/family
- Referral to Hematology
- Extensive work-up, > once
- Impact on patient/family

Physicians

- Concern of primary care providers
- Unnecessary specialist referral
- Workforce burn-out
- Impact on healthcare system

Impacts on Treatment

- Premature discontinuation of meds
- Exclusion from medication use
- Chemotherapy dose-reductions – worse outcomes

Impacts on Clinical trials

- Exclusion from clinical trials
- Slower recruitment – longer trials
- Lack of diversity & generalizability of results

6

National Coverage Determination for Stem Cell Transplantation (110.23) for the Myelodysplastic Syndromes

Corey Cutler, MD MPH
Director, Stem Cell Transplant Program, Dana-Farber Cancer Institute
President, American Society for Transplantation and Cellular Therapy

Hematology Carrier Advisory Committee Meeting
June 2024

7

Background – CED for MDS

- Allogeneic hematopoietic stem cell transplantation (HCT) remains the only curative therapy for patients with MDS.
- Historically, patients 65 and older with Medicare did not have coverage for HCT.
- On August 4th 2010 the Centers for Medicare and Medicaid services (CMS) established coverage for HCT for MDS through coverage with evidence development (CED).

8

8

Response to the CED

CIBMTR study comparing outcomes of patients age 55-64 vs. ≥65 (CMS approval, 12/10)

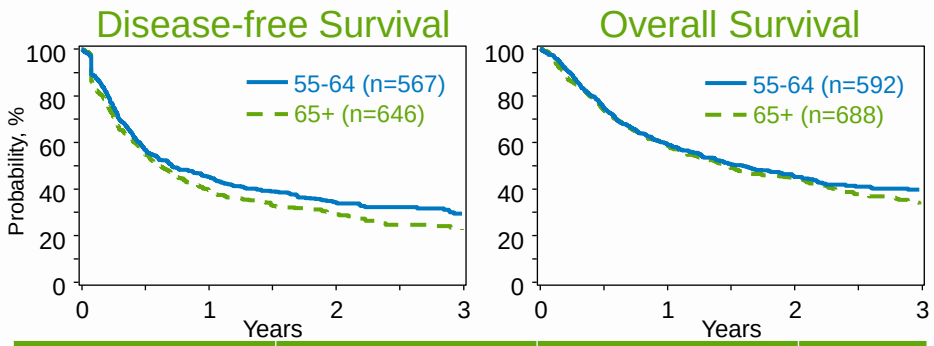
Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do IPSS score, patient age, cytopenias and comorbidities predict outcomes?

Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in outcomes?

BMT CTN Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic HCT to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced MDS (CMS approval, 12/13)

Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes?

9

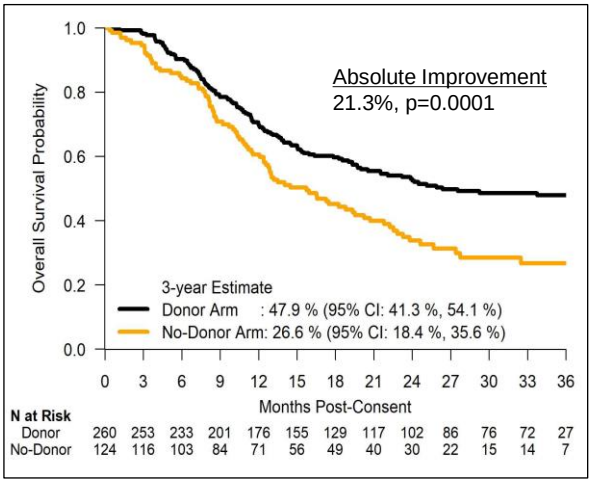


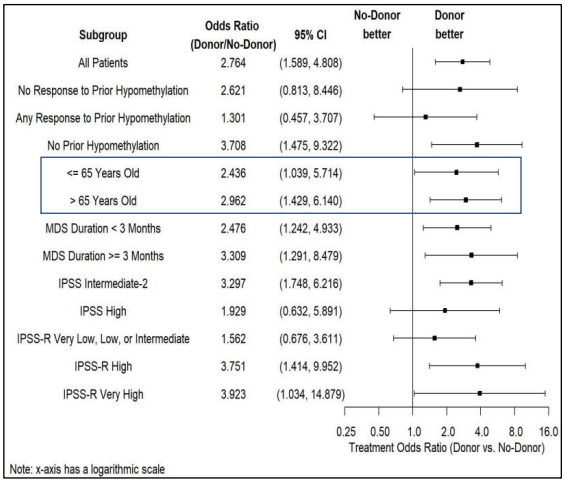
Outcomes	65+ (n=688) N Eval	65+ (n=688) (95% CI)	55-64 (n=592) N Eval	55-64 (n=592) (95% CI)	P-value
Disease-free Survival	646		567		
@ 100-days		68 (65-72)%		73 (69-77)%	0.0590
@ 1-year		40 (36-44)%		45 (41-49)%	0.0564
@ 2-years		29 (25-33)%		34 (30-39)%	0.0780
Overall Survival	688		592		
@ 100-days		85 (23-87)%		87 (84-89)%	0.2468
@ 1-year		58 (54-62)%		59 (55-63)%	0.7518
@ 2-years		44 (40-48)%		44 (40-49)%	0.8355

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Atallah *et al*, JAMA Onc 2020 10

Significant Overall Survival Advantage in the Donor arm





Survival difference persisted after excluding 7 pts who died during donor search or with starting "clock" at 90 days

BMT CTN Blood & Marrow Transplant Clinical Trials Network

Nakamura *et al*, J Clin Onc 2021 11

11

DATE: March 6, 2024

National Coverage Analysis (NCA)	Decision Memo

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

Final Decision: We are expanding Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes who have prognostic risk scores of:

- ≥ 1.5 (Intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or
- ≥ 4.5 (high or very high) using the International Prognostic Scoring System - Revised (IPSS-R), or
- ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M).

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Initial Reaction to Decision Memo

- ASTCT/ASH/CIBMTR/NMDP submitted commentary, and as a result:
  - Cord Blood added as a stem cell source for transplantation
  - Placental/Amniotic stem cells removed as a source for transplantation
  - Exclude secondary MDS in the Decision Memo – was never studied

- Asked that specific risk criteria NOT be included in the NCD
  - Studies used much older IPSS risk scoring system –but it is outdated

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IPSS

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
Percent of blast cells in bone marrow ○ Less than 5 = 0 points ○ 5 to 10 = 0.5 points ○ 11 to 20 = 1.5 points ○ 21 to 30 = 2 points	○ 0 points = Low ○ 0.5 to 1 point = Intermediate-1 ○ 1.5 to 2 points = Intermediate-2 ○ 2.5 or more points = High
Cytogenetics (chromosome changes) ○ None, del(5q), del(20q) = 0 points ○ 3 or more abnormalities, abnormal chromosome 7 = 1 point ○ Other abnormalities = 0.5 points	
Number of cytopenias (anemia, neutropenia or thrombocytopenia) ○ None or 1 = 0 points ○ 2 or 3 = 0.5 points	

IPSS-Revised

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
Percent of blast cells in bone marrow ○ Less than or equal to 2 = 0 points ○ Greater than 2 to less than 5 = 1 point ○ 5 to 10 = 2 points ○ Greater than 10 = 3 points	○ 1.5 or less points = Very Low ○ 2 to 3 points = Low ○ 3.5 to 4.5 points = Intermediate ○ 5 to 6 points = High ○ 6.5 or more points = Very High
Cytogenetics (chromosome changes) ○ –Y, del(11q) = 0 points ○ Normal, del(5q), del(12p), del(20q), double including del(5q)* = 1 point ○ del(7q), +8, +19, i(17q), any other single or double independent clone** = 2 points ○ –7, inv(3), +(3q), del(3q), double including –7/del(7q), complex: 3 abnormalities = 3 points ○ More than 3 abnormalities = 4 points	
Hemoglobin concentration (g/dL) ○ Equal to or greater than 10 = 0 points ○ 8 to less than 10 = 1 point ○ Less than 8 = 1.5 points	
Platelet count (x 10^9/L of blood) ○ Equal to or greater than 100 = 0 points ○ 50 to less than 100 = 0.5 points ○ Less than 50 = 1 point	
Absolute neutrophil count ([ANC] x 10^9/L of blood) ○ Equal to or greater than 0.8 = 0 points ○ Less than 0.8 = 0.5 points	

IPSS-Molecular (2022)

- More Refined Cytogenetics
- Mutation data
  - Emphasis on TP53
- 6 Risk Groups defined

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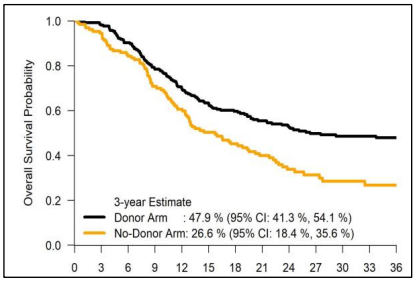
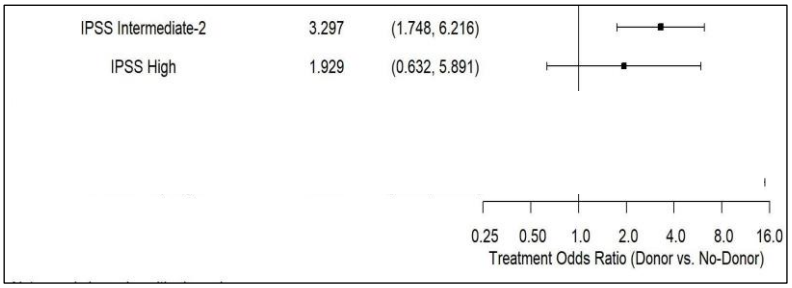
- ≥ 1.5 (Intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or
- ≥ 4.5 (high or very high) using the International Prognostic Scoring System - Revised (IPSS-R), or
- ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M).



CTN 1102 – IPSS Int-2 or High



CTN 1102 NOT DESIGNED to test individual IPSS-R groups

15

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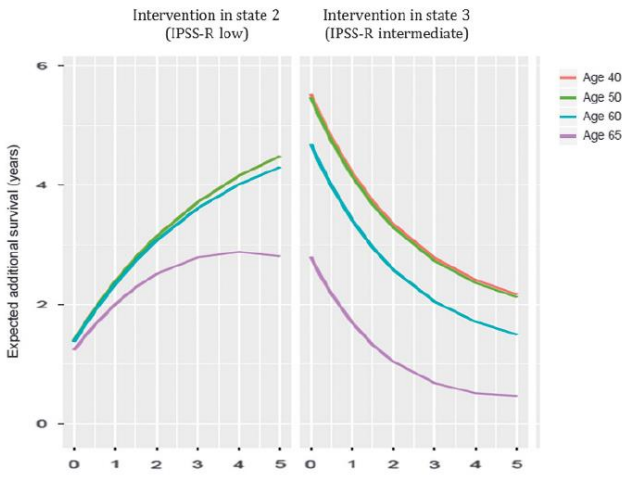

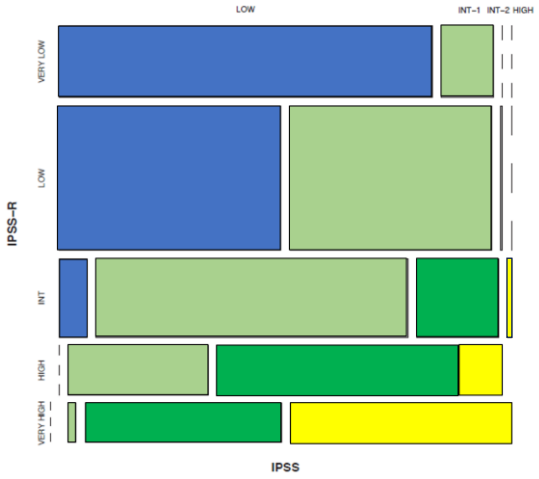

CTN 1102 NOT DESIGNED to test individual IPSS-R groups
IPSS-R groups DO NOT correspond perfectly to IPSS
IPSS-R is BETTER than IPSS at predicting BMT and nonBMT outcomes
IPSS-R Decision Analyses suggest INTERMEDIATE Risk is optimal timing for BMT *(Della Porta, Leukemia 2017)*

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Final Decision: We are expanding Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes who have prognostic risk scores of:

- ≥ 4.5 (high or very high) using the International Prognostic Scoring System - Revised (IPSS-R), or

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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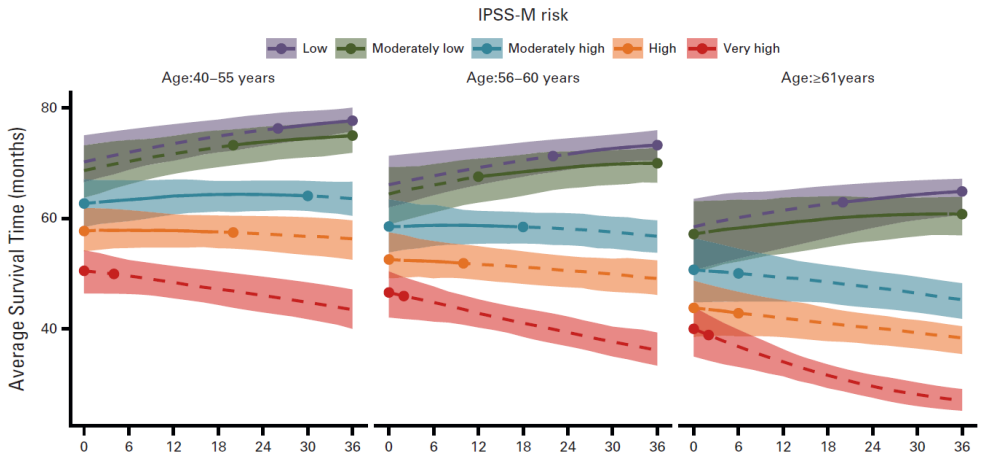

Tentori, J Clin Onc 2024 (in press)

- ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M).

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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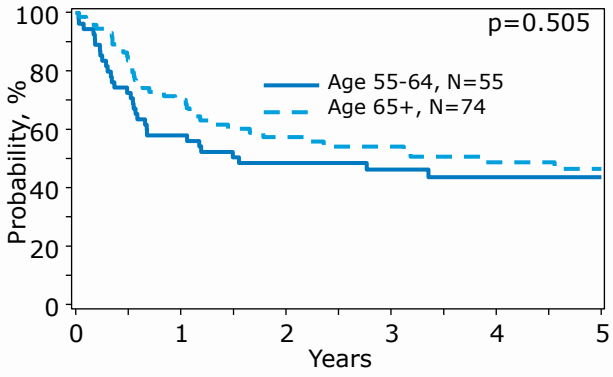
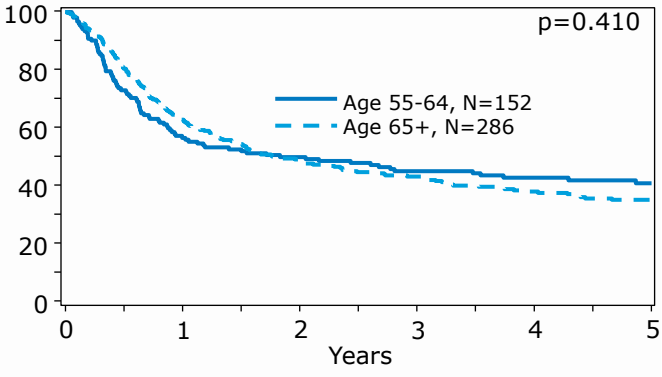
Rarer MDS subtypes not addressed by IPSS-M

Overall Survival after Allogeneic HCT for **MDS/MPN** 2012-2021



Overall Survival after Allogeneic HCT for **CMML** 2012-2021



CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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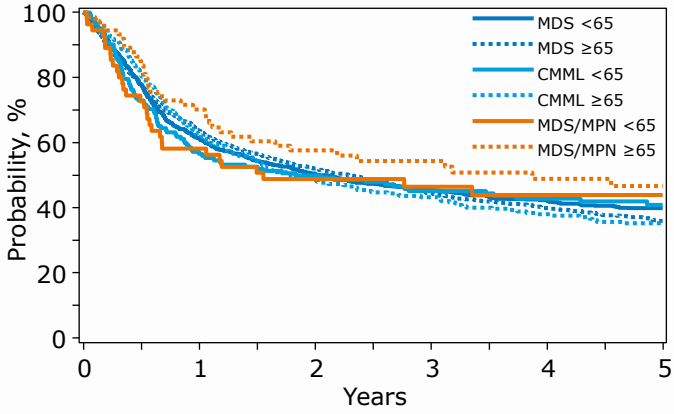
Rarer MDS subtypes not addressed by IPSS-M

Overall Survival after Allogeneic HCT by Age and Disease Subtype 2012-2021



CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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Other Scenarios NOT Addressed by Decision Memo

- Secondary MDS
- MDS after failure of Hypomethylating Therapy
- Transfusion-dependent MDS (Abel, Leukemia 2021)

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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Implementation

Effective Date: March 6, 2024
Date from which ***providers have to follow the new decision/language***

Implementation Date: October 7, 2024
Date by which ***MACs have to have their systems updated*** for the new claims processing requirements.
CMS did require MACs to stop requiring the CED clinical trial number edit as of March 5, 2024

? some claims will have to be reprocessed/appealed by centers depending on the timing of when MAC updated their systems.

In addition, coverage of all other indications for stem cell transplantation not otherwise specified will be made by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

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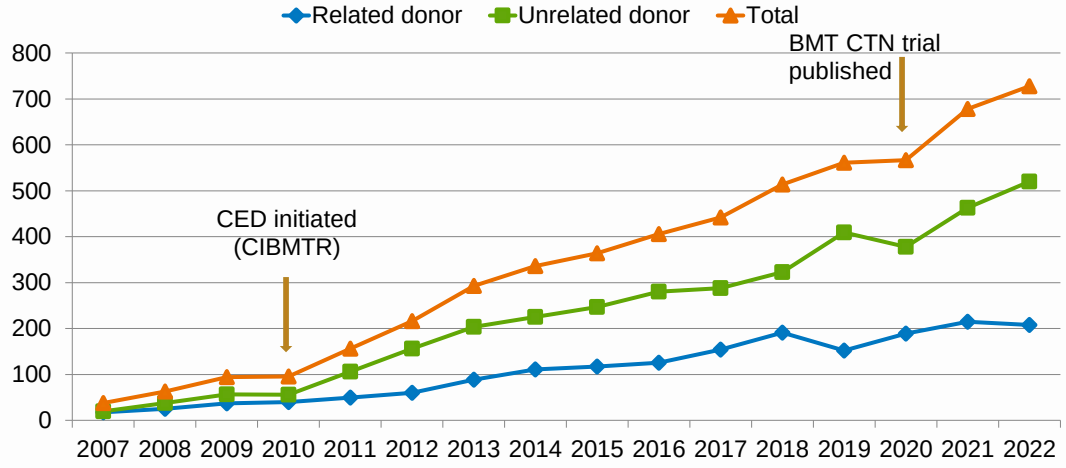
US Allogeneic Transplants for MDS in Patients Older than 65 y, 2007-2022 – What if barriers are removed?



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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Recommendations:

- Use discretion to allow HSCT in Medicare beneficiaries who do not meet current CMS guidelines
  - Application of the 'Top Two Tiers' from IPSS to IPSS-M is <u>not</u> justified
  - We, as an academic community, cannot re-perform the prospective clinical trial as equipoise has been lost
  - MDS subtypes not addressed by Decision Memo have inferior prognosis but transplant outcomes mirror standard MDS subtypes

- Leniency during transition period
  - Patients with previously planned HSCT dates right after Decision Memo published
  - Patients undergoing HSCT between Decision Memo and Implementation phase

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Credit and Appreciation to:

- Doug Rizzo, Wael Saber, Mary Horowitz, CIBMTR
- Ryotaro Nakamura, BMT CTN
- Suzanne Leous, ASH
- Ellie Beaver, Jessica Knudson, NMDP
- Alycia Maloney, ASTCT
- Stephanie Farnia, Nimitt

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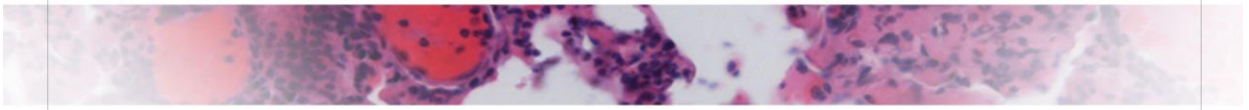
Next Generation Sequencing

Many diseases in classical and malignant hematology are caused by germline or somatic mutations. Therefore, accurate diagnosis now often relies on genetic testing results in patients presenting with a particular phenotype. Our understanding of the genetic basis of hematologic malignancies has expanded in the past decade with the use of next-generation sequencing (NGS) technology. The utility of NGS in the diagnosis, prognosis, treatment, and monitoring of hematologic malignancies is evident by the incorporation of germline and somatic gene mutation testing in recommendations from national and international guideline committees, including the World Health Organization (WHO), The National Comprehensive Cancer Network (NCCN), the European LeukemiaNet (ELN, a not-for-profit alliance of 33 leading cancer centers devoted to patient care, research, and education), and the new International Consensus Classification (ICC) group, among others. However, despite evidence in the literature supporting the impact of NGS on the diagnosis, treatment, and outcomes of patients with hematologic malignancies, there remains inconsistent reimbursement for testing of patients across national centers. Therefore, the ASH Subcommittee on Precision Medicine has organized an initiative to summarize the existing evidence to support the use and reimbursement of NGS testing for patients suspected of harboring germline mutations that predispose them to hematologic malignancies or patients suspected of having a myeloid or lymphoid malignancy. We are currently assembling a comprehensive set of published studies that address the impact of NGS on patient diagnosis, management, prognosis, and outcomes, with a prioritization of those studies showing the potential of NGS to reduce the time and cost of patient evaluation both at diagnosis and in disease monitoring.

To address this unmet need of consistent NGS reimbursement and provide guidance on NGS testing for ASH members and the community, the Subcommittee on Precision medicine has assembled three working groups to address the impact of NGS for germline and somatic testing. The working groups include individuals with national and international expertise in germline, myeloid, and lymphoid testing. Dr. Lucy Godley presented a discussion on germline testing last year to the Carier Advisory Committee (CAC) Network Meeting. At the upcoming CAC meeting, the Subcommittee on Precision medicine will present an update from the myeloid working group on the utility of NGS testing for patients suspected of having a myeloid malignancy. Drs. Annette Kim and Jonathan Gerber will highlight the importance of multigene NGS testing for the diagnosis, prognosis, management decisions, and monitoring of patients with myeloid malignancies. In parallel, the lymphoid malignancy working group, led by Dr. Caroline Heckman, are assembling the evidence to support the use of NGS in the evaluation, treatment, and monitoring of patients with lymphoid malignancies. Finally, a special report manuscript will be submitted from the three working groups (*e.g.,* germline, myeloid, lymphoid) summarizing our findings that can serve as a resource both for ASH practitioners as well as the various agencies involved in NGS coverage and reimbursement.

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Precision Medicine in Hematology

Annette S. Kim, MD, PhD
Henry Clay Bryant, Professor of Pathology
Director, Division of Diagnostic Genetics and Genomics
University of Michigan

Jonathan M. Gerber, MD
Chief Clinical Officer
Perlmutter Cancer Center
NYU Langone Health

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Definitions

- Germline mutations:
  - DNA sequencing variant occurring in a sperm or egg cell that has ***passed from the parent to the child***
- Somatic mutations:
  - DNA sequencing variant ***acquired after conception*** in cells other than germ cells and therefore cannot be passed on

Either type of variant can cause disease or be benign/passenger.

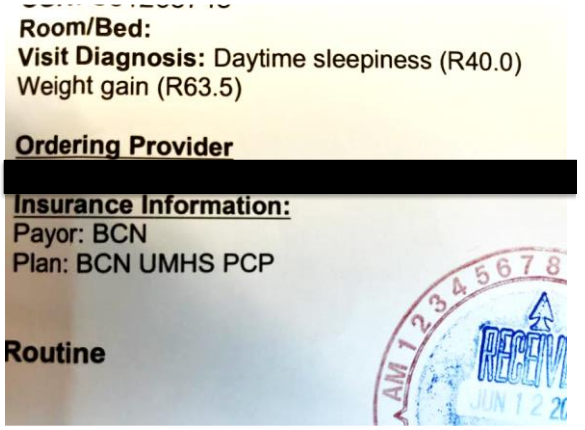
Case #1: Thrombocytopenia presentation

- 65 yo F presents with thrombocytopenia
  - History of T3N1 ER+/PR+/HER2- invasive ductal adenocarcinoma diagnosed 10 years earlier with mastectomy, chest wall radiation, doxorubicin and cyclophosphamide, followed by Taxol. Subsequently maintained on tamoxifen.
  - Chemotherapy was complicated by anemia and thrombocytopenia
  - 4.3 > 12.2 (**100.1**) < **123**; normal differential, no blasts
  - PB NGS requested

Lucas... Kim AS*. Blood Adv. 2020. 4(18):4362-4365.

ICD10 codes that may or may not be helpful…

- **Irrelevant**:
  - Received ICD10s:
  - Other ICDs might be for breast cancer or other conditions unrelated to the clinical concern (for example, of thrombocytopenia)
- **Rule Out**: ICD10s might be for MDS (issues of using a "rule out" ICD10), even if the patient does not end up with a diagnosis of MDS
- **Pre-Diagnostic**: With BM samples, NGS may be ordered before the morphologic diagnosis is rendered (so might be an ICD10 for anemia when the patient has acute myeloid leukemia)



Ancillary testing

- PB Molecular NGS Results

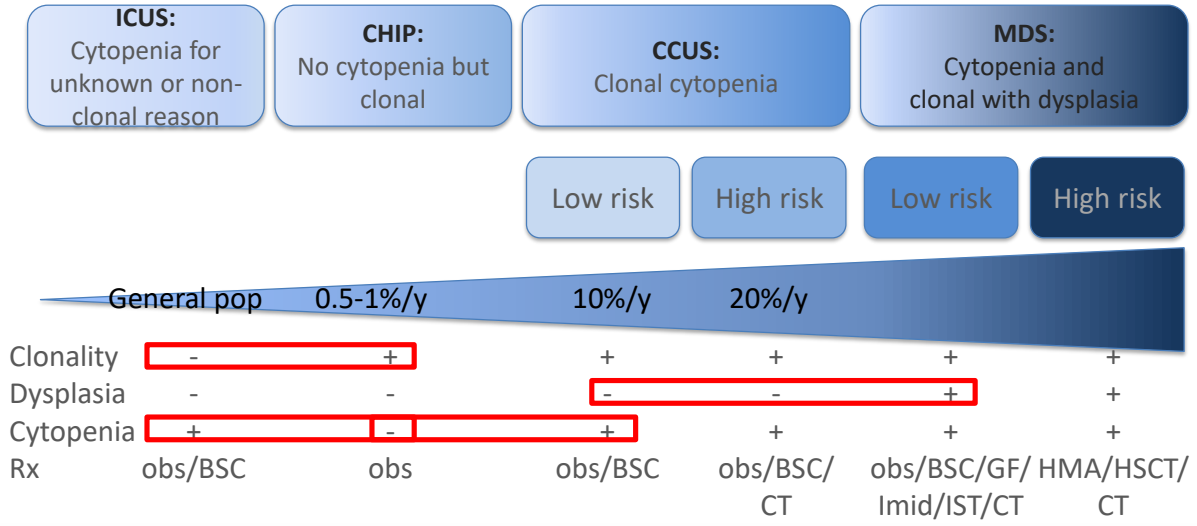
Somatic Variant			Variant allele fraction
Gene	Variant (c.)	Variant (p.)	Dx
DNMT3A	c.2311C>T	p. R771*	8.5%

- Due to the identification of a pathogenic *DNTM3A* mutation, BMBx was performed:
  - Normocellular, no dysplasia
  - Normal karyotype
- Diagnosis: Clonal Cytopenia of Undetermined Significance (CCUS)

If the VAF had been close to 50% in a gene associated with cancer predisposition, a germline variant might be considered, precipitating a constitutional disease workup.

ICUS, UCUS, we all CCUS…

Idiopathic cytopenias of undetermined significance, clonal cytopenias of undetermined significance…



Adapted from Steensma *et al. Blood.* 2015;126: 9-16 and Malcovati et al. *Blood*. 2017;22:3371-3378.

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Using NGS to Diagnose High Risk CCUS

CCUS Progression

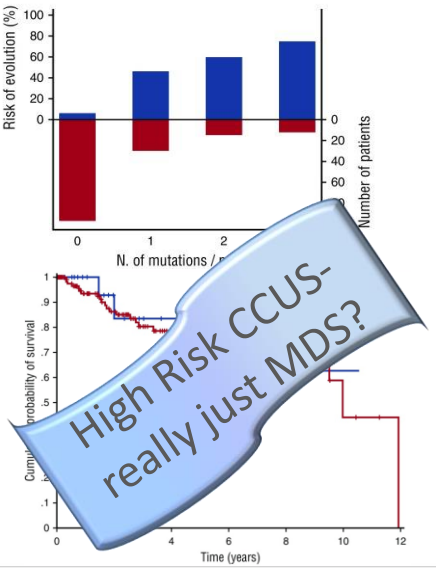
- How many mutations matter

  ≥2 genes PPV 0.88, OR 4.69

- How much of the mutation matters

  ≥ 0.087 VAF PPV 0.86

- Which mutation(s) matters
  - Spliceosome genes, *JAK2*, and *RUNX1* mostly highly a/w MN
  - *DNMT3A, TET2, ASXL1 (DTA genes)* (and *PPM1D**) most often co-occur with other mutations, resulting in high PPV for MN
  - Spliceosome, *DNMT3A, TET2*, and *ASXL1* account for 73% of MNs
  - *SF3B1* alone has OR 4.83 of MN



Malcovati et al. *Blood*. 2017;22:3371-3378.

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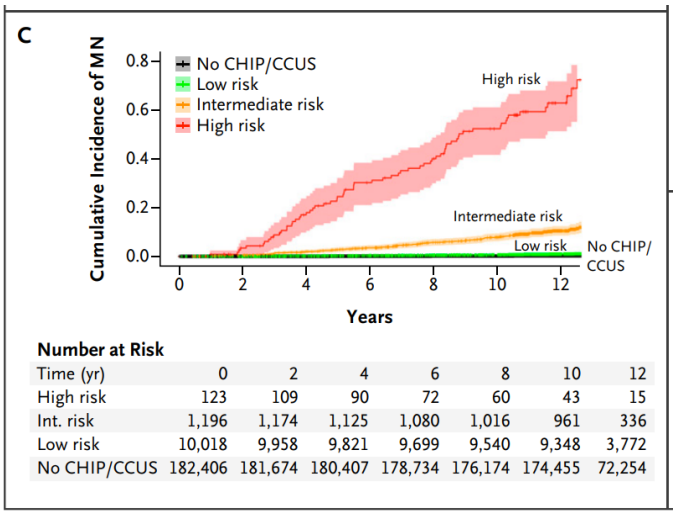
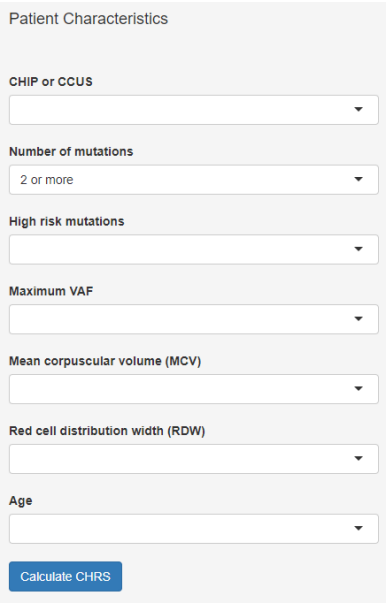
Clonal Hematopoiesis Risk Score



Number at Risk

Time (yr)	0	2	4	6	8	10	12
High risk	123	109	90	72	60	43	15
Int. risk	1,196	1,174	1,125	1,080	1,016	961	336
Low risk	10,018	9,958	9,821	9,699	9,540	9,348	3,772
No CHIP/CCUS	182,406	181,674	180,407	178,734	176,174	174,455	72,254

http://www.chrsapp.com/



Weeks LD, et al. *NEJM Evid* 2023; 2:10.1056.

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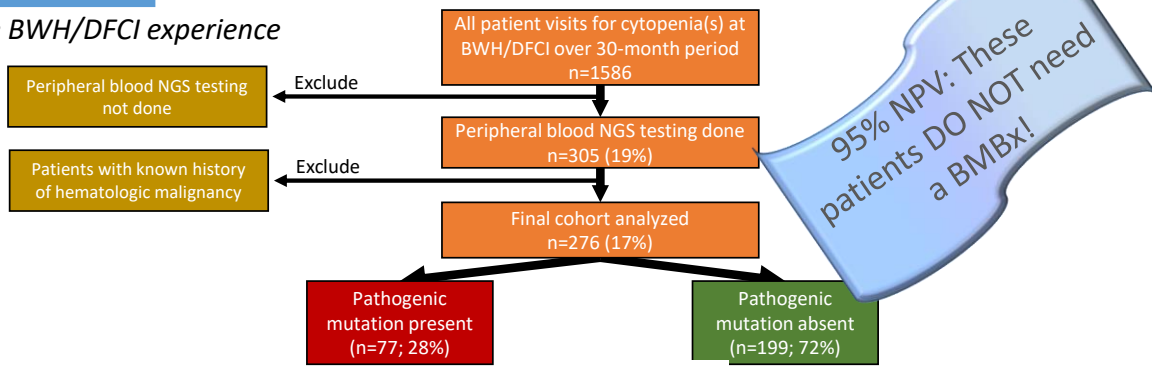
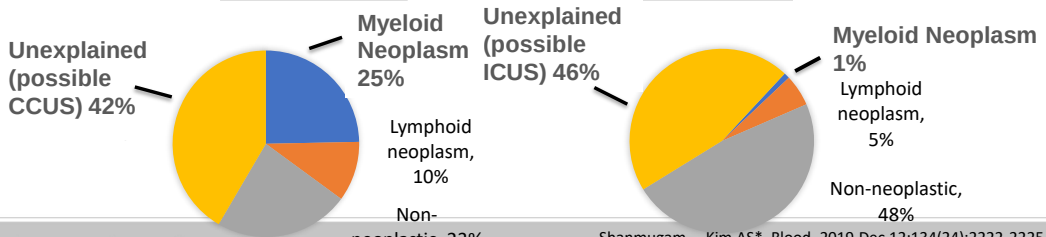
NPV of PB screening by NGS for Cytopenias

The BWH/DFCI experience





Shanmugam … Kim AS*. Blood. 2019 Dec 12;134(24):2222-2225.
Lucas… Kim AS*. Blood Adv. 2020. 4(18):4362-4365.

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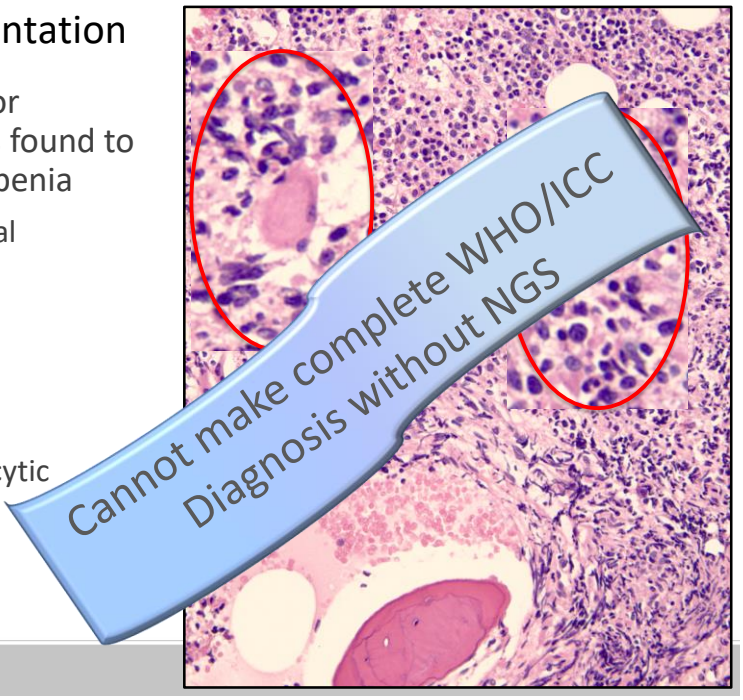
Thrombocytopenia re-presentation

- 6 months later she presents for monitoring of her CCUS and is found to have worsening thrombocytopenia
  - **3.9** > 12.2 (**100.3**) < **70**; normal differential, no blasts
  - BMBx was performed:
    - Hypercellular marrow
    - Erythroid predominant
    - Erythroid and megakaryocytic dysplasia
    - Blasts 5%



Evolution of CCUS to tMDS on serial monitoring

- Molecular NGS Results

Somatic Variant			Variant allele fraction
Gene	Variant (c.)	Variant (p.)	Dx
DNMT3A	c.2311C>T	p. R771*	42%
TP53	c.830G>A	p.C277Y	36%
Loss *CSNK1A1* and *NPM1* on 5q, loss *CUX1*, *BRAF*, *EZH2* on 7q, loss *FLT3* on 13q, CN LOH *TP53* on 17p, and loss *SETBP1* on 18q			

- Karyotype:

  44,XX,del(5)(q12q35),add(7)(p21),-13,-18[4]/46,XX[16]

- Chromosomal Microarray: demonstrates CN-LOH of the TP53 locus

N.B. some NGS platforms can assess CNVs and CN-LOH in the same assay, making these 1-stop shopping for diagnosis of myeloid neoplasms with *TP53.*

Diagnosis

- WHO Classification (5th edition):

  Myelodysplastic neoplasm with biallelic TP53 inactivation, post cytotoxic therapy

  (cytopenia, dysplasia, <20% blasts, <30% proerythroblasts, 2 or more *TP53* mutations or *TP53* mutation with concurrent deletion or CN LOH)

- ICC Classification:

  Myelodysplastic syndrome with mutated *TP53*, therapy-related

  (cytopenia, dysplasia, <10% blasts, 2 or more *TP53* mutations with ≥10% VAF or *TP53* mutation with VAF >50% or *TP53* mutation with ≥10% VAF + CN LOH of *TP53* or *TP53* mutation with VAF 10-49% + complex karyotype and/or 17p deletion)

Somatic Variant			Variant allele fraction
Gene	Variant (c.)	Variant (p.)	Dx
DNMT3A	c.2311C>T	p. R771*	42%
TP53	c.830G>A	p.C277Y	36%
Loss *CSNK1A1* and *NPM1* on 5q, loss *CUX1*, *BRAF*, *EZH2* on 7q, loss *FLT3* on 13q, CN LOH *TP53* on 17p, and loss *SETBP1* on 18q			

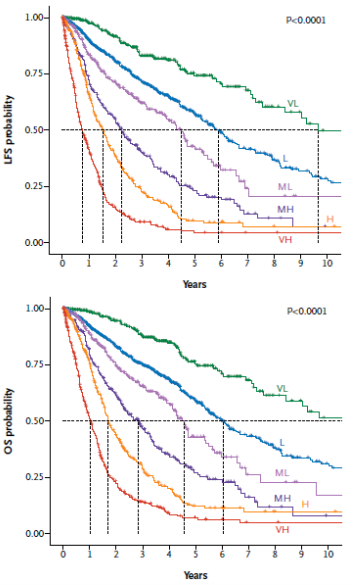
NGS required since mutations can be found throughout the *TP53* gene.
NGS required potentially for CNV and CN-LOH.
NGS required for additional prognostic information

Khoury *et al. Leukemia*. (2022) 36:1703-1719.
Duncavage *et al. Blood*. (2022) 140:2228-2247.
Arber *et al. Blood*. (2022) 140:1200-1228.
Hasserjian *et al. Virchows Archiv*. (2023) 482:39-51.
Orazi *et al. Am J Hematol*. (2023) 98:6-10.

M-IPSS- importance of assessing multiple genes (panel vs single gene assays)

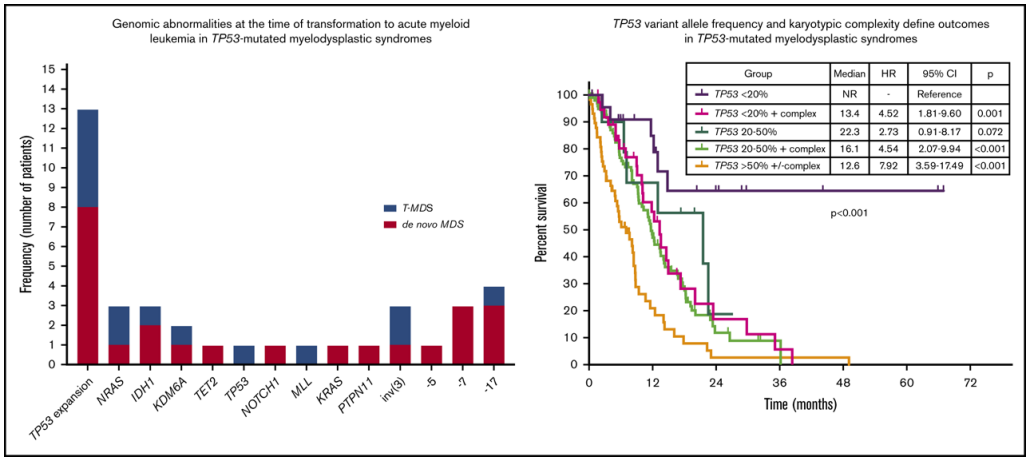
Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multhit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{Sig}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1^{a}	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖	*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, and WT1*	
min(Nres,2)	1.26 (1.12–1.42)	0.231



Bernard *et al. NEJM Evid.* (2022) 1(7).

Genomic context and TP53 allele frequency define clinical outcomes in TP53-mutated myelodysplastic syndromes



Montalban-Bravo G, et al. *Blood Advances* 2020

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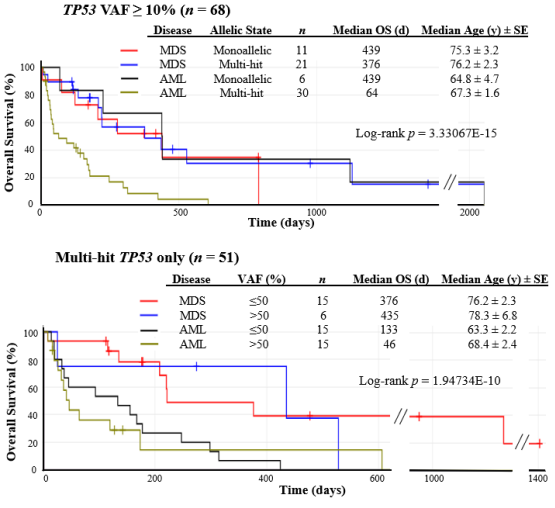
Overall Survival of Subgroups

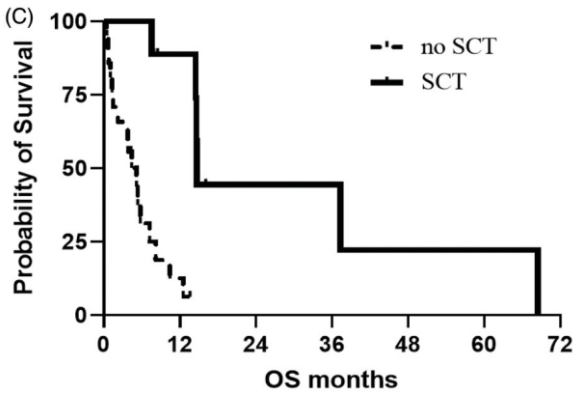


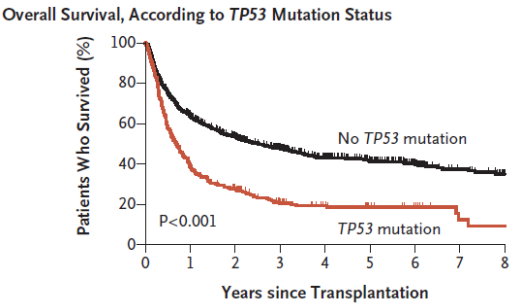
ASH Abstract: *Blood* (2022) 140 (Supplement 1): 6276–6278

Patel SA, et al. *EJHaem* 2023; 4:1059-70

15

Overall Survival with TP53





- *TP53* without SCT has dire prognosis
- *TP53* associated with poor OS after SCT, genomic complexity, and t-MDS.

Patel SA, et al. *Leuk Lymphoma* 2021; 62:3348-3360.
Lindsley et al. NEJM 2017;376:536-547.

16

Case #2: A stitch in time, …

- 68 yo M diagnosed with low risk MDS
  - Refractory anemia with ringed sideroblasts, harboring 5q deletion and SF3B1 mutation
  - Refractory to supplemental erythropoietin
  - Treated with lenalidomide for over 2 years, with suboptimal response
  - Repeat NGS panel revealed acquisition of new mutations, including in TP53, which peaked at 14%

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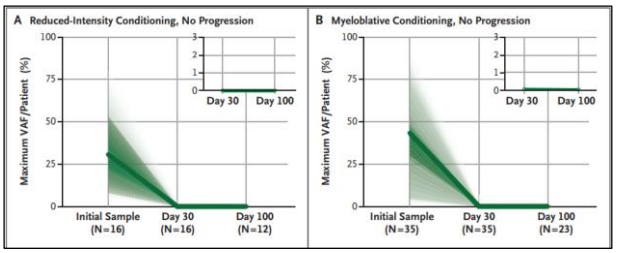
Case #2: A stitch in time, …

- **Evolution from low risk to high risk MDS**
  - Treated with hypomethylating agent-based therapy, followed by reduced intensity haploidentical BMT
  - TP53 (and all other mutations) undetectable at day +30 post BMT assessment
  - However, donor chimerism dropped at day +100 (15% recipient in the CD34+ marrow fraction), with associated drop in blood counts, requiring occasional PRBC and Plt transfusions
  - No mutations detected on repeat NGS panel
  - Given those results, deferred donor lymphocyte infusion and managed just with early withdrawal of immunosuppression (tacrolimus rapidly tapered off)
  - He has remained in a complete remission, without GVHD now for 1.5 years

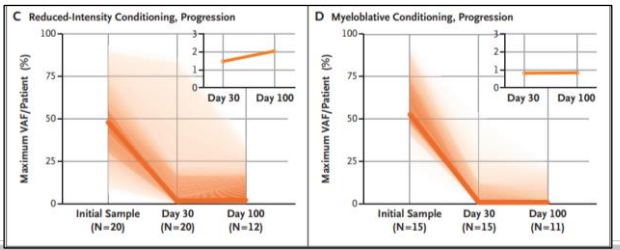
Kuba et al. *Hematopathology*. 2017; 2(2):84-95.
Duncavage et al. *NEJM*.2018;379:1028-1041.
Lindsley et al. *NEJM* 2017;376:536-547.

Implications of MRD after Transplant

No Progression

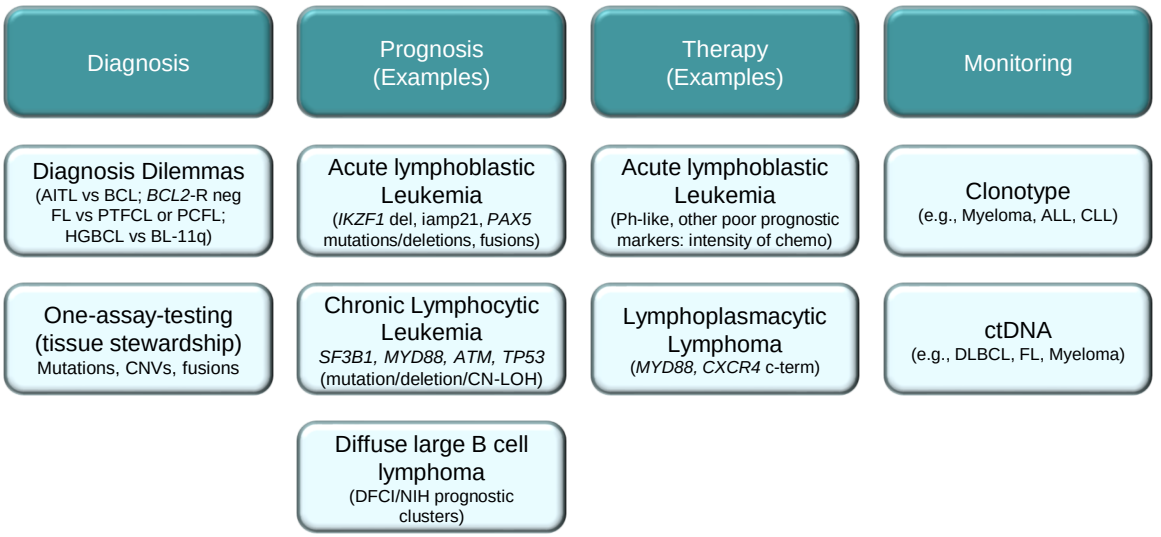


Progression



Duncavage et al. NEJM.2018;379:1028-1041.

Impact of NGS in lymphomas and myeloma



Take-home points

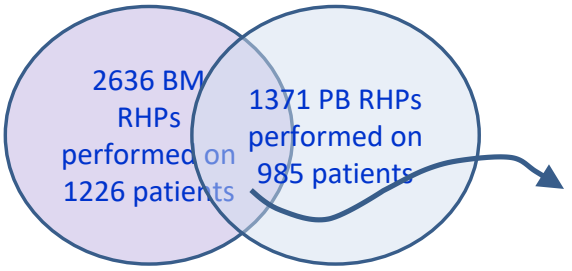
- Issues with timing of ICD10 coding for NGS: need broad range of acceptable codes
  - Beyond the irrelevant codes, there are challenges coding since testing is ordered *BEFORE* the exact diagnosis is known; codes for "rule out" or abnormal blood counts used or "disease of blood and blood-forming organs".
- NGS serial monitoring for CHIP and CCUS
- PB NGS screening for hematopoietic disease – can avoid a costly and invasive BM biopsy
- Inability to make a complete WHO/ICC BM diagnosis without NGS
- NGS superior to single gene assays with regard to cost and nature of targets (many genes are not amenable to single gene assays)
- NGS serial monitoring after diagnosis to adjust therapy and predict relapse, including early intervention post SCT for resurging mutations
- Chimerism not a surrogate for relapse, unlike NGS
- Even VUSes associated with disease (passenger mutations) useful to track disease by NGS
- NGS can identify resistance mutations

Thank You!

Extra Slides

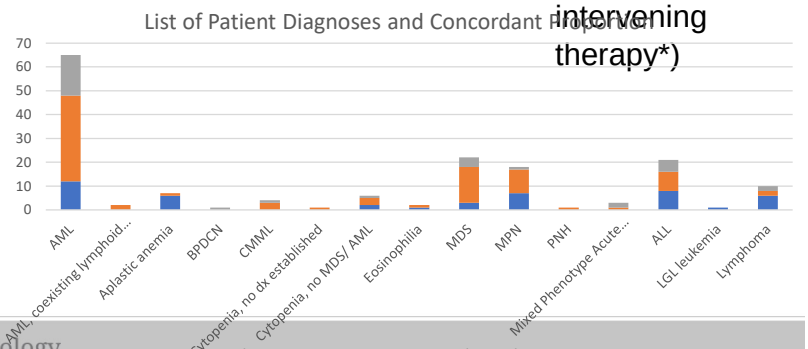
Study 2: PB vs BM

- 38 month time period (9/2014 – 11/2017)



164 patients with paired PB and BM samples within 14 days (no intervening therapy*)

- 46 patients: no pathogenic variants
- 84 patients: concordant pathogenic variants
- 34 patients: discordant pathogenic variants



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Study 2: PB vs BM

- 34 total discordant patient pairs with total of 51 total discordant variants

	Concordant Pairs		Discordant Pairs	
Total Pathogenic Variants (initial report)	**No pathogenic variants**	**Concordant variants**	**Concordant variants**	**Discordant variants**
Total myeloid pathogenic variants	NA	190	54	39
Total MPAL pathogenic variants	NA	4	10	4
Total lymphoid pathogenic variants	NA	13	7	8

- Conc: 98.9%
- Sens (PB): 88.0%
- Spec (PB): 99.7%

		PB		
		POS	**NEG**	**total**
BM	**POS**	278	38	316
	NEG	13	4370	4383
	Total	291	4408	4693

Manual Review
45 SNVs found (low VAF or cov)

- Conc: 99.8%
- Sens (PB): 98.4%
- Spec (PB): 99.9%

		PB		
		POS	**NEG**	**total**
BM	**POS**	314	5	319
	NEG	4	4370	4274
	Total	318	4375	4693

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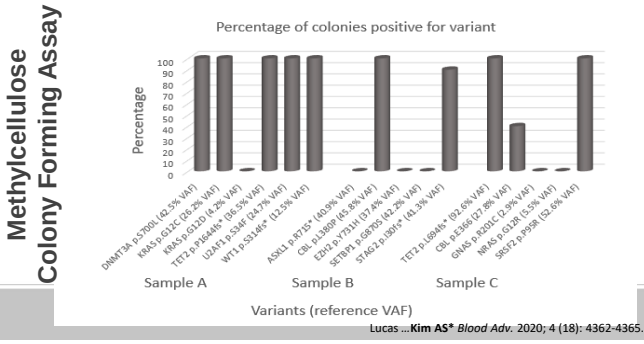
Study 2: BM only, PB only

- BM only:
  - 4/5 variants were *NPM1* or *TP53*
  - 4/5 cases were AML or ALL
  - No AL had circulating blasts, but 1/4 cases had <5% BM blasts as well
  - **BM has greater sensitivity for MRD, even without increased blasts**
  - ***NPM1* and *TP53* with more "stemness" qualities**
- PB only:
  - 3/4 variants were RAS pathway
  - **Are some mutations found preferentially in more mature cells?**

	Variant	VAF BM	VAF PB	Cov BM	Cov PB	pathway
	MYELOID DIAGNOSES					
AML	*NPM1* p.W288fs*>9 (pt 15)	3.8	**ND**	340	230	diverse
AML	*NPM1* p.W288fs*>9 (pt 22)	3.9	**ND**	308	347	diverse
AML	*TP53* p.L194R (pt 18)	35.1	**ND**	282	72	tumor suppressor
	CBL p.I383M (pt 10)	2.2	**ND**	690	540	Signal transduction
	KRAS p.Q61H (pt 6)	**ND**	12.1	318	282	Signal transduction
	KRAS p.G12A (pt 6)	**ND**	8.1	1323	1030	Signal transduction
	KRAS p.G13D	**ND**	6.5	660	536	Signal transduction
	BCORL1 p.T1259fs* (pt 2)	**ND**	71.4	44	14	transcriptional corepressor
	LYMPHOID DIAGNOSES					
B-ALL	*TP53* p.C242fs*5 (pt 35)	4.8	**ND**	379	670	tumor suppressor



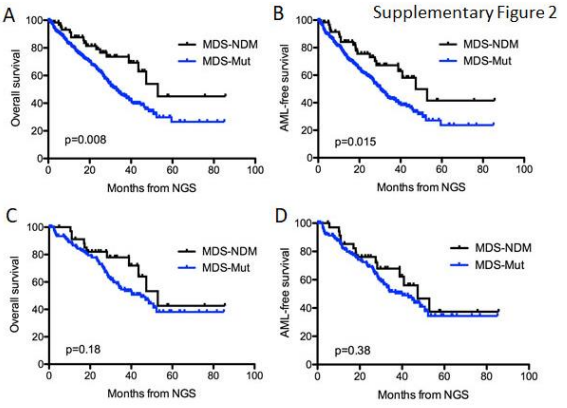
Lucas ...**Kim AS*** *Blood Adv.* 2020; 4 (18): 4362-4365.

26

Study 6: What about MDS without mutations?

- MDS with no detected mutations (NDM) were younger (P<0.001), were more likely to go to SCT, and had better OS and LFS
- So, what do we miss by doing PB-only NGS screening?

Cytopenia: 17,000/100,000 over age of 65
MDS: 75/100,000 over age of 65
MDS-NDM: 7.5/100,000



So, cases missed would be 7.5/17,000 = 0.4% or 99.6% specificity for cytopenic patients

Wang SA... **Kim AS** et al. Am J Hematol. 2021;96(11):E420-E423.
Shanmugam ... **Kim AS***. Blood. 2019 Dec 12;134(24):2222-2225.

27

Expansion of Medicare Dental Services and Implications for Hematology

This presentation discusses the recent expansion of Medicare dental services and its implications, specifically focusing on how these changes intersect with hematological care. It provides an analysis of the statutory exclusions and new guidelines, which now allow for certain dental services to be considered for coverage under Medicare, when linked to medically necessary treatments.

Key Points:

1. **Statutory Exclusion of Dental Services:**
    - **Section 1862 (a)(12) of the Social Security Act:** Historically, dental services related to the care, treatment, filling, removal, or replacement of teeth were excluded from Medicare coverage, with exceptions for payment under Part A for certain inpatient hospital services.
2. **Expansion of Dental Services (2023):**
    - **42 CFR 411.15:** The new regulation includes language stating that dental services which are inextricably linked to and substantially related to the clinical success of a Medicare covered medical service are not excluded from Medicare Parts A and B coverage.
3. **Specific Inclusions Under New Regulations in 2023:**
    - Dental examinations and treatments necessary before medical procedures such as organ transplants, cardiac valve replacements, valvuloplasty, tumor removals, jaw fracture treatments, and preparations for radiation therapy are now considered for coverage if they eliminate oral infections prior to medical treatment.
4. **Changes Effective January 2024:**
    - Medicare will allow payment for dental services linked to the clinical success of cancer treatments, including chemotherapy, CAR-T cell therapy, and high-dose bone-modifying agents, hematopoietic stem cell transplants and bone marrow transplants.
5. **Coordination with Cancer Therapy:**
    - **Dental and Oral Complications:** Highlights the high incidence of oral complications in patients undergoing chemotherapy and stem cell transplants, emphasizing the need for integrated dental care.
6. **Benefits of the New Coverage:**
    - Enhanced patient outcomes by reducing the incidence and severity of oral complications during cancer therapy, resulting in fewer emergency dental treatments and better overall health.

Conclusion:

The expansion of Medicare dental services represents a significant advancement in patient care, particularly for those undergoing critical medical treatments like cancer therapy. By covering necessary dental services, Medicare aims to improve clinical outcomes and quality of life for these patients.

Cell and Gene Therapy

ASH is pleased to host Alexis Thompson, MD, MPH, and Claire White, MSN, RN to discuss their respective experiences in setting up and rolling out a cell and gene therapy program at the Children's Hospital of Philadelphia; discussion will include information about the treatment considerations, coverage, and administrative efforts required at the institutional level to support the delivery of the newly approved therapies.

Advances in gene editing and cellular therapies offer promising new therapeutic options that are poised to revolutionize care for those with hematologic conditions. With the recent approvals for gene editing therapies for sickle cell disease (SCD), there are new considerations for how these new, innovative, and often costly therapies will be administered and covered.

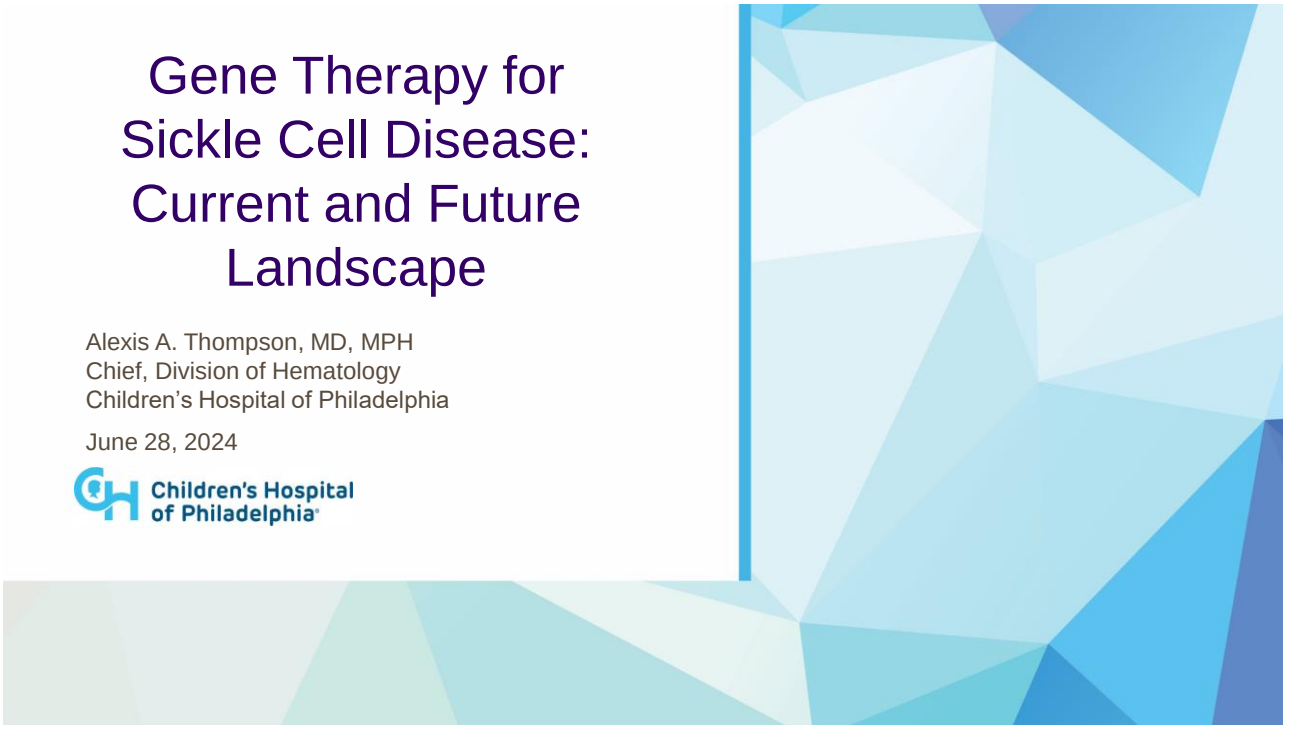
ASH believes that framing these innovative gene therapies in the broader context of comprehensive care is critical for delivering whole-person care not only for individuals with SCD, but for any individual accessing gene therapy. In a comment letter to the Centers for Medicare & Medicaid Services Innovation Center (CMMI) on the Cell and Gene Therapy (CGT) Access Model, ASH shared an inclusive "wishlist" for treatment considerations that are crucial to this model and gene therapy broadly.

Gene Therapy for Sickle Cell Disease: Current and Future Landscape

Alexis A. Thompson, MD, MPH
Chief, Division of Hematology
Children's Hospital of Philadelphia

June 28, 2024

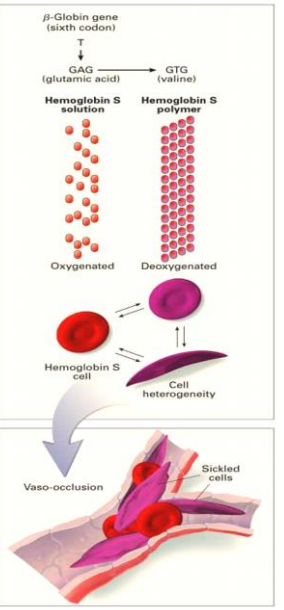
Children's Hospital of Philadelphia



1

SICKLE CELL DISEASE (SCD)

- SCD is caused by a genetic mutation in the ß globin gene that encodes a major component of human hemoglobin.
- It is an autosomal recessive disorder affecting millions worldwide.
- Newborn screening, where available, reduces morbidity and mortality.
- SCD results in severe hemolytic anemia with acute, potentially life-threatening exacerbations, chronic ischemic organ injury, and shortened lifespan.
- Disease manifestations often require urgent attention and/or emergency care and comprehensive medical services.

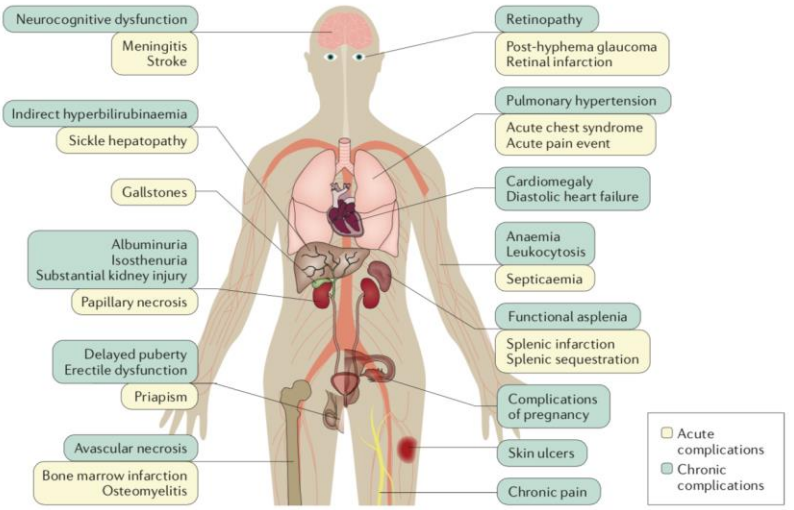


Children's Hospital of Philadelphia

2 Steinberg MH, NEJM 1999; 340:1021-30

2

Acute and Chronic Complications in SCD



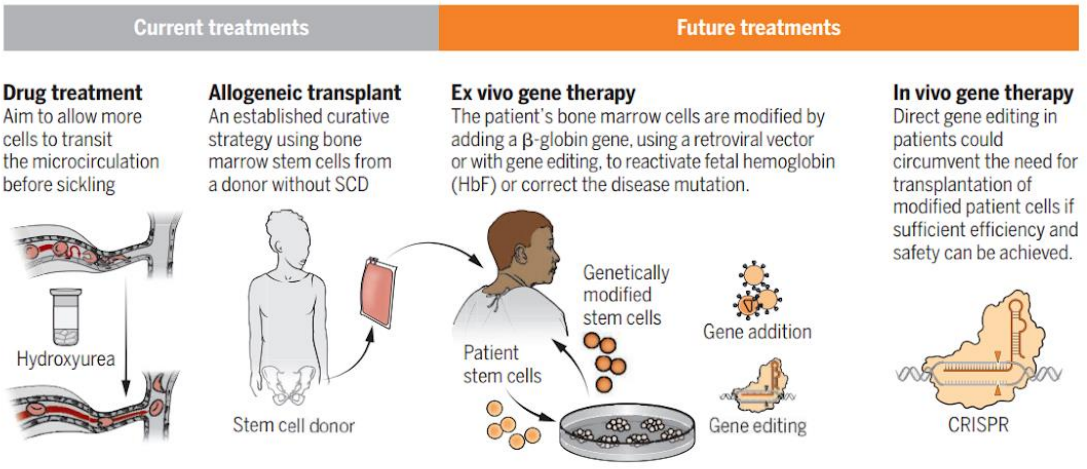
Children's Hospital of Philadelphia

3 Kato GJ et al. Sickle cell disease. Nat Rev Dis Primers. 2018

3

Current and future treatments for sickle cell anemia

Numerous advances in the understanding of sickle cell disease (SCD) have allowed the development of curative therapies through allogenic stem cell transplanation, with the promise of gene therapy–based treatments in the future.



Tisdale JF et al, Science 2020

4

HLA-matched Sibling Donor Transplants: Standard of Care Curative Option for SCD

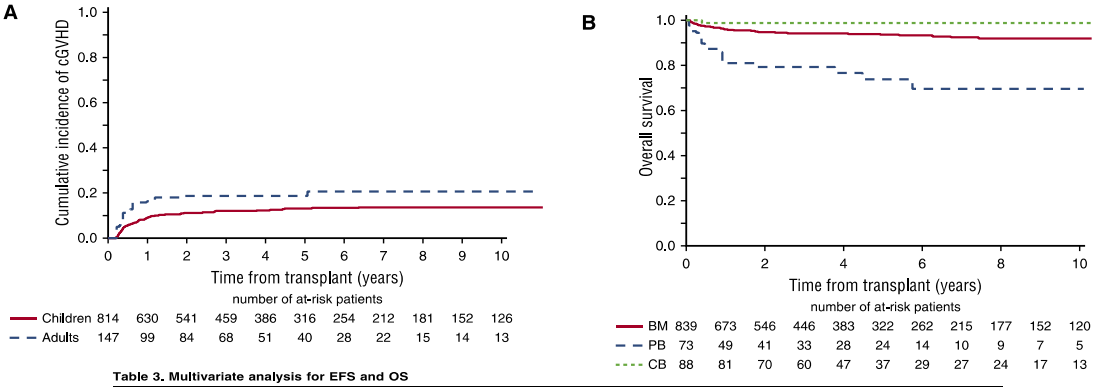


Table 3. Multivariate analysis for EFS and OS

	EFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PB vs BM	1.93 (0.87-4.26)	.104	2.62 (1.17-5.89)	.019
CB vs BM	0.55 (0.13-2.31)	.412	Not applicable*	
Age	1.09 (1.05-1.12)	<.001	1.10 (1.06-1.14)	<.0001
Transplant year, ≥2007 vs ≤2006	0.95 (0.90-0.99)	.013	0.96 (0.91-1.00)	.101
Conditioning regimen, RIC vs MAC	1.13 (0.46-2.81)	.793	0.83 (0.29-2.39)	.735
In vivo T-cell depletion, yes vs no	1.34 (0.63-2.82)	.445	1.10 (0.49-2.48)	.806

The adjusted Cox regression analysis was stratified by registry (EBMT and CIBMTR); age was considered as a continuous variable, and when considering the graft source, PB and CB were compared, separately, with BM (baseline) for the EFS.
*Not evaluable, as there was only 1 event in the CB group; therefore, for OS, the CB transplants were included with BM transplants.

Gluckman E, et al. Blood. 2017;129:1548-1556.

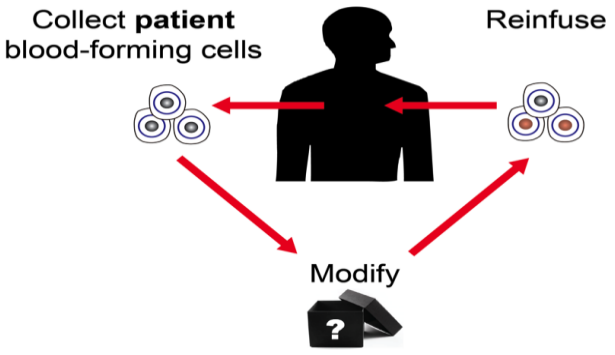
5

Other Considerations

- Most patients with SCD lack a suitable matched related or unrelated stem cell donor
- Open research studies for unrelated with reduced intensity and also haploidentical donors
- Potential complications
  - Nonengraftment/Graft Failure
  - Infections
  - Graft versus Host Disease
  - Infertility
  - Transplant-related Mortality

6

What is Gene Therapy?



- Experimental technique that uses genes/genetic material to treat or prevent disease
- Patient serves as own donor

7

Application of gene therapy strategies for sickle cell disease

- Gene Addition: add a normal β-globin gene
  - "Convert" to HbS trait
- Increase fetal hemoglobin
  - Add a γ-globin (fetal) gene
  - Add a "γ-like" β-globin
  - Alter expression genes that regulate fetal globin
- Direct correction of HbS mutation

8

Autologous Genetic Therapies for Sickle Cell and Thalassemia in Clinical Trials

Strategy	Modality	Lead group	Status	Clinical trial number	No. of participants	Results	References
β-Like globin gene replacement	β^{A-T87Q} LV	bluebird bio	Phase III, marketing approval (Europe)	NCT02140554, NCT02906202	40 SCD, 23 β-thalassemia	25 SCD (group C) participants followed for 3–25 months. Most had near-pancellular expression of HbA^{T87Q} ≥6 months after therapy with 99.5% mean reduction in the annualized VOC+ACS rate overall; 89% of evaluable participants with β-thalassemia are transfusion independent at a median of 19 months follow-up.	55, 210
	Modified γ^{G16D}-globin LV	Cincinnati Children's Hospital Medical Center	Phase I/II	NCT02186418	3	3 SCD participants, follow-up 6–30 months, with clinical improvement (decreased VOEs)	154
	Modified γ^{G16D}-globin LV	CSL Behring	Phase I	NCT04091737	3	No results posted	
	LV expressing the βAS3-globin gene	Assistance Publique–Hôpitaux de Paris	Phase I/II	NCT03964792	10	No results posted	
	βAS3-FB LV	University of California, Los Angeles	Phase I/II	NCT02247843	6	No results posted	
HbF induction	*BCL11A* shRNA LV	Dana-Farber Cancer Institute	Phase I/II	NCT03282656	6	6 SCD participants infused, follow-up 7–29 months. No patient has had a VOC, ACS, or stroke since the gene therapy infusion.	33
	Cas9 NHEJ; disruption of erythroid enhancer in *BCL11A* gene	CRISPR Therapeutics/ Vertex Pharmaceuticals	Phase I/II	NCT03745287	2 SCD, 5 β-thalassemia	2 SCD participants with follow-up of 3 and 12 months have had no SCD-related VOEs since infusion of gene-modified cells; 5 β-thalassemia participants with follow-up of 3–15 months are transfusion independent.	32, 83
	Cas9 NHEJ	Novartis/Intellia	Phase I/II	NCT04443907	Not reported	No results posted	
	ZFN NHEJ; disruption of erythroid enhancer in *BCL11A* gene	Sangamo/Bioverativ/ Sanofi	Phase I/II	NCT03432364	2	2 participants with β-thalassemia infused, follow-up 3–6 months. Both require intermittent transfusions, though requirements are decreased.	211

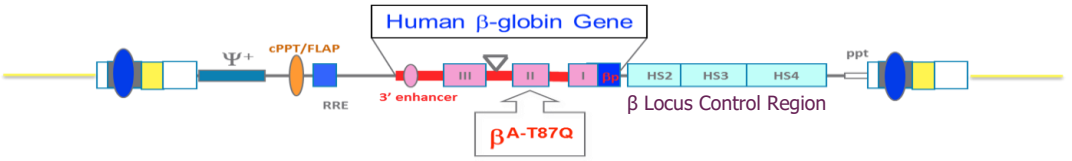
All clinical trials for SCD listed on ClinicalTrials.gov as of January 2021 are shown. Some trials also include patients with β-thalassemia. ACS, acute chest syndrome; NHEJ, non-homologous end joining; VOC, vaso-occlusive crisis; VOE, vaso-occlusive pain event; ZFN, zinc finger nuclease.

Doerfler PA et al, JCI 2021

9

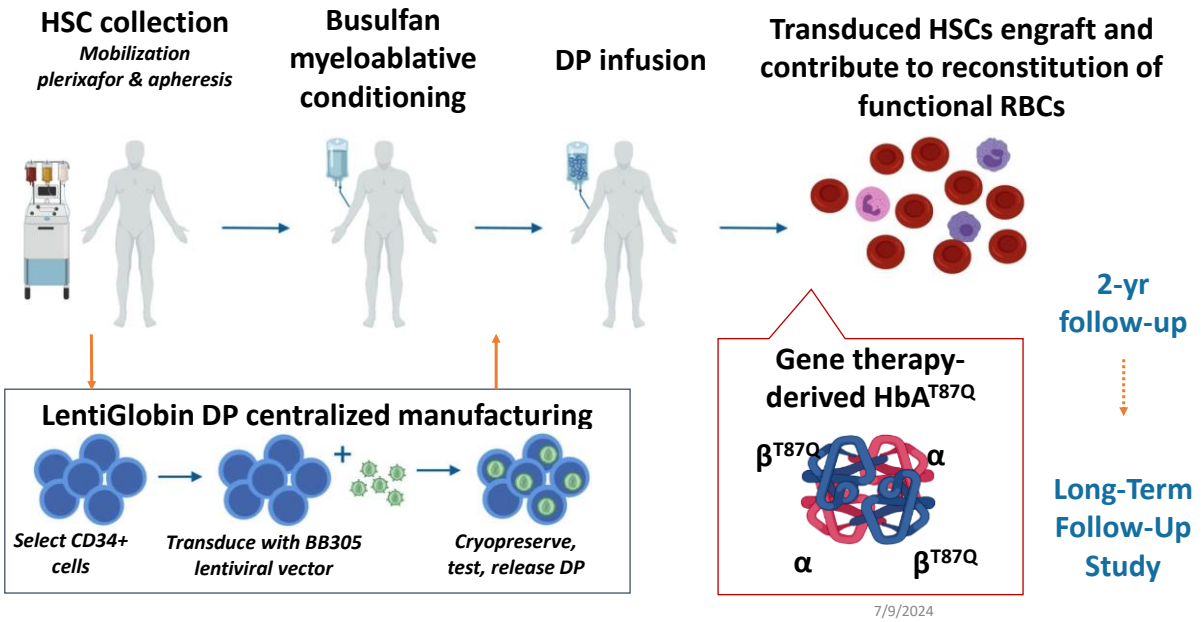
LentiGlobin BB305 Vector

- Replication defective, self-inactivating lentiviral vector, produces βA-T87Q globin using erythroid-specific globin gene regulatory elements
- An amino acid substitution (βA-T87Q) inhibits polymerization, allows for HPLC monitoring of transgene globin levels in the patient's cells



10

Overview of LentiGlobin Gene Therapy

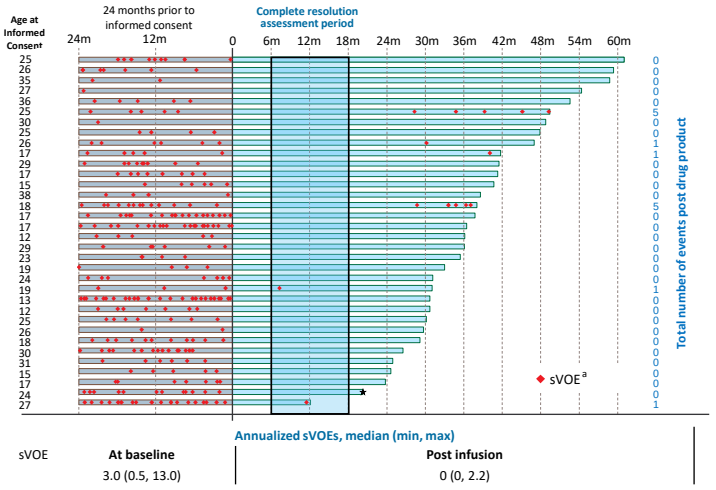


7/9/2024

11

94.1% (32/34) of Patients Achieved Complete Resolution of Severe VOEs (sVOE)

Key Secondary Endpoint (6 – 18 months)



6-18 Month Assessment Period

- **94.1%** (32/34; 95% CI, 80.3-99.3) of patients experienced **complete resolution of sVOEs**[b]

6 Months to Last Follow Up

- **85.3%** (29/34) of patients had no VOE[c]-related hospital admissions from 6 months post infusion to last follow-up (median follow up: 36.3 months).

- Among the 8 patients with VOEs post lovo-cel infusion, annualized median (min, max):
  - **Hospital admissions:** reduced from **2.5** (1, 13) to **0.41** (0, 2)
  - **Hospital days:** reduced from **15.75** (3.5, 136.0) to **2.20** (0.0, 25.4)

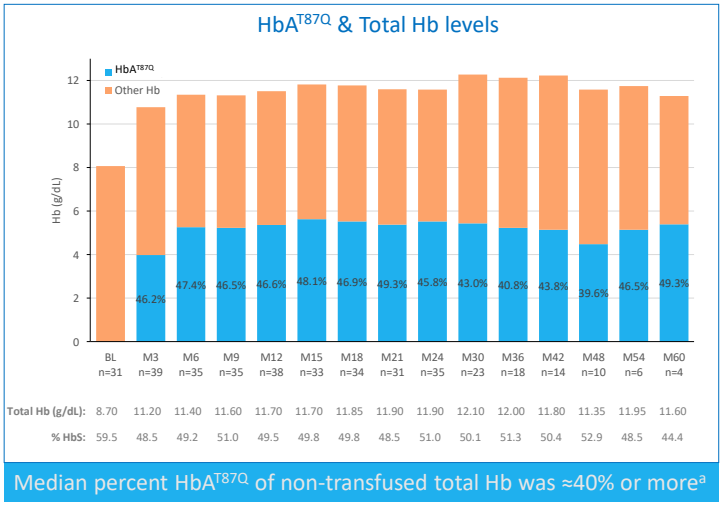
★ Death, due to significant baseline SCD-related cardiopulmonary disease; not considered related to lovo-cel.

An Independent Event Adjudication Committee confirmed VOEs met protocol criteria. [a]Defined as a VOE requiring ≥24-hour hospital or emergency room (ER) observation unit visit or at least 2 visits to a day unit or ER over a 72-hour period, with both visits requiring intravenous treatment; all VOEs of priapism were also considered sVOEs. [b]Maintained for a median (min, max) of 35.8 (20.2, 61.0) months. [c]Any of the following: acute episodes of pain with no medically determined cause other than a vaso-occlusion lasting 2 hours and requiring care at a medical facility; acute chest syndrome requiring oxygen treatment and/or blood transfusion; acute hepatic sequestration; acute splenic sequestration; or acute priapism lasting 2 hours and requiring care at a medical facility.

Hb, hemoglobin; SCD, sickle cell disease; sVOE, severe vaso-occlusive event; VOE, vaso-occlusive event.

Population: VOE evaluable Data as of Feb 13, 2023 12

HbA^{T87Q} Levels and Globin Response Were Maintained Over Time



Median percent HbA^{T87Q} of non-transfused total Hb was ≈40% or more[a]

- All patients maintained stable HbA^{T87Q} levels from 6 months to last follow-up and as far out as month 60

- **86.8%** (33/38) of patients[b] achieved globin response
  (Globin response defined as meeting the following criteria for a continuous period of ≥6 months: weighted average HbA^{T87Q} ≥30% of non-transfused total Hb; AND weighted average increase in non-transfused total Hb of ≥3 g/dL vs baseline total Hb OR weighted average non-transfused total Hb of ≥10 g/dL)

- **100%** (33/33) of patients demonstrated a durable globin response through last follow up[c]

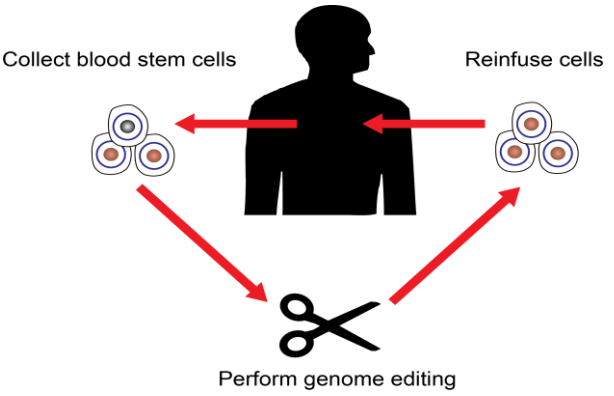
- No patients with a history of stroke experienced a stroke post treatment[d]

Percentages represent the median HbA^{T87Q} fraction as a percentage of non-transfused total Hb. Values below each bar represent the median total Hb or HbS % of non-transfused total Hb at each visit and are not equivalent to the sum of the individual Hb fraction medians. The baseline was an average of 2 qualified, total Hb values (measured in g/dL) during the 24 months before study enrollment. [a]Median (min, max) % HbAT87Q at last visit (n=42) was 44.7 (27.6, 63.2). [b]Assessed in patients who achieved globin response or had ≥18 months follow-up. [c]Three patients achieved globin response but later had transfusions due to an unrelated accident or illness (n=2), or death not related to study drug (n=1). [d]Patients who were receiving chronic transfusions due to a history of overt stroke and maintained globin response, did not require transfusions post engraftment, and have experienced no strokes to the time of the data cut.

BL, baseline; DP, drug product infusion; Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb; HbS, sickle cell hemoglobin; M, month.

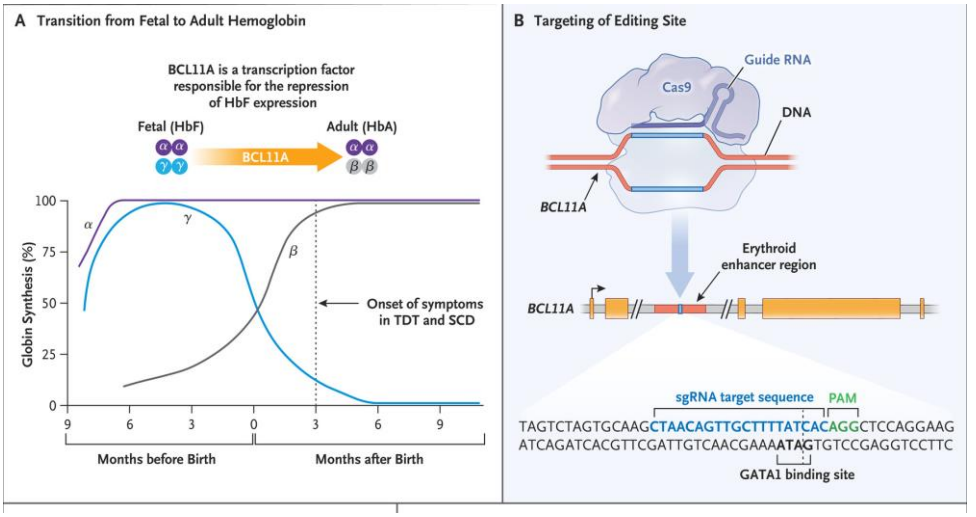
Population: Transplant population Data as of Feb 13, 2023 13

Genome Editing



14

CTX-001 (exac-cel): CRISPR Cas9 targeting BCL11A gene



H Frangoul et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2031054

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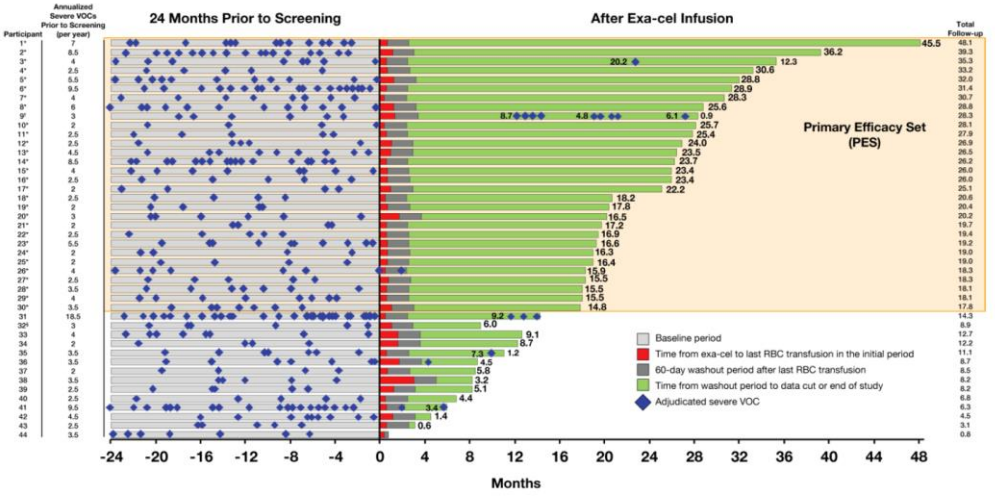
Reduction in Severe VOEs with exa-cel



29 of 30 (96.7%) achieved VF12

VOE-free duration
Median: 22.4 mo
Range: 14.8-45.4 mo

One subject had VOE in setting of parvovirus and VOE-free after

One subject with chronic pain had continued VOE but not requiring hosp.

VF12: no severe VOCs for ≥12 months

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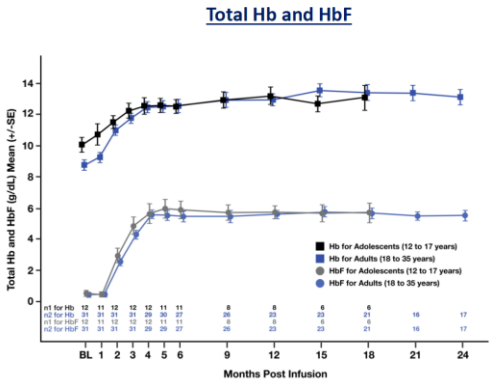
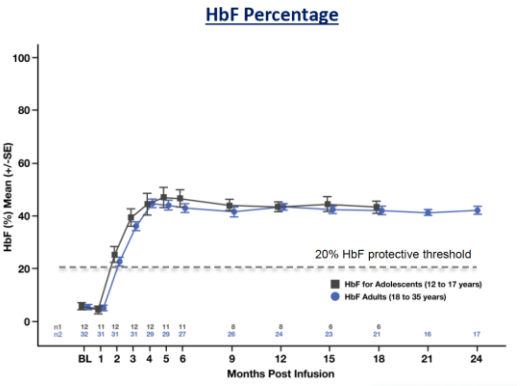
Improvements in total Hb and Fetal Hb were similar between adults and adolescents





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Risks of Gene Therapy

- Conditioning toxicity
  - Mouth sores (mucositis)
  - Hair Loss
  - Liver problems (Transaminitis, Veno-occlusive disease)
- Graft Failure
- Delayed platelet engraftment
- Clonal dominance/insertional oncogenesis
- Off-target gene editing
- Infertility

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FDA approved two curative gene therapies for Sickle Cell Disease in December 2023

Casgevy (exa-cel)
Vertex Gene Therapy

How it Works: In the Vertex gene therapy, patients have their stem cells collected from their blood. These cells from the patient are edited using CRISPR technology to block the expression of a certain gene that causes the cells to become sickle-shaped. The edited cells are infused back into the patient. **This is the first-ever FDA-approved therapy developed using CRISPR gene editing technology.**

Age >12 years
SCD diagnosis:
Primary indication: recurrent admissions for VOE pain

$2.2 million

Lyfgenia (lovo-cel)
Bluebird Gene Therapy

How it Works: In the Bluebird Bio gene therapy, patients have their stem cells collected from their blood. A gene is inserted into the stem cells using a vehicle called a viral vector. As a result, those stem cells, which after they are infused back into the patient with the goal of growing functional red blood cells that produce a new non-sickling form of hemoglobin and reduces or eliminates sickling.

Age >12 years
SCD diagnosis: HbSS and S/beta zero thalassemia
Primary indication: recurrent admissions for VOE pain
Exclusion: Stroke, Moya-moya, severe vasculopathy

$3.1 million

Access and Equity in Curative Therapies

Once new therapies are approved for use, will they be out of reach for some/many?

Children's Hospital of Philadelphia

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Summary

- Results from lovo-cel and exa-cel clinical trials are promising
  - Majority of patients with resolution of VOE
  - Improvements in Hb level, reduction in markers of hemolysis
  - Safety profile largely as expected with autologous transplant
- The first 2 gene therapy products for SCD are now commercially available
- Additional gene therapy approaches are under study in clinical trials
- Fertility Preservation remains an issue primarily due to conditioning
- Individualized approaches to curative therapy (or disease-modifiying therapies) are needed

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QUESTION? THANKS!

Children's Hospital of Philadelphia

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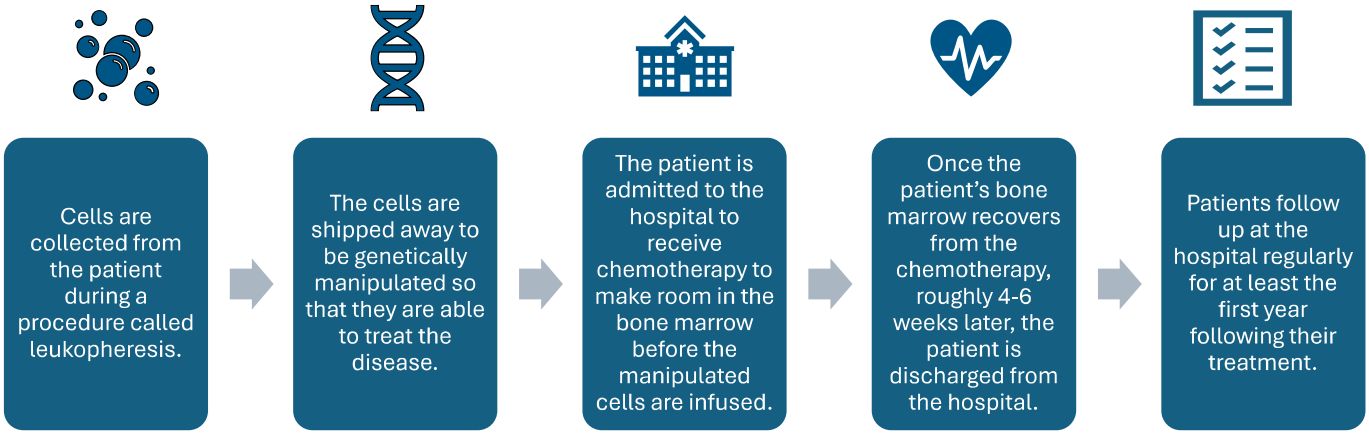
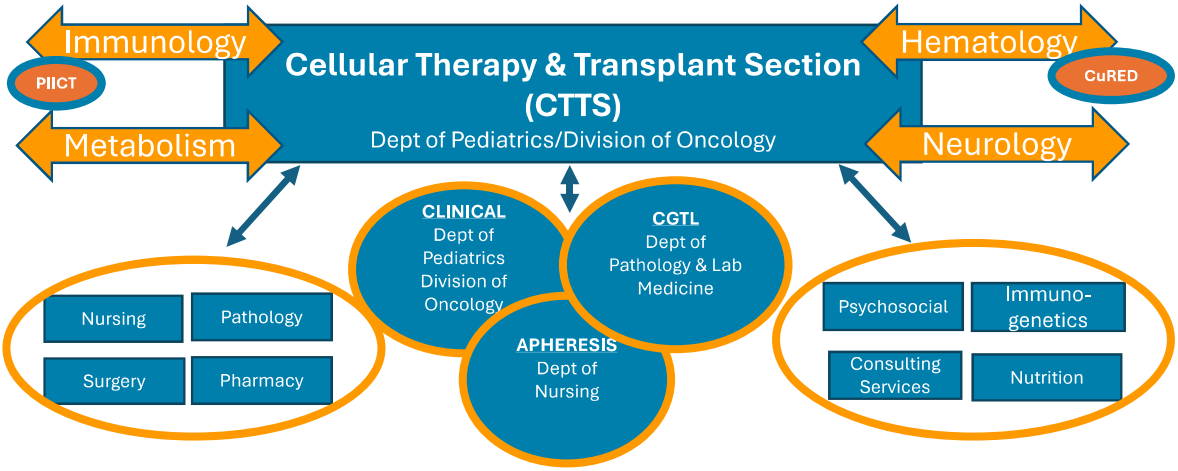
Patient Access and Administrative Considerations in Cell & Gene Therapy: A Provider's Perspective

Annual Hematology Carrier Advisory Committee (CAC) Network Meeting
Friday, June 28, 2024
Presented by:
Claire White MSN, RN
Cell and Gene Therapy Policy Analyst

Treatment Process

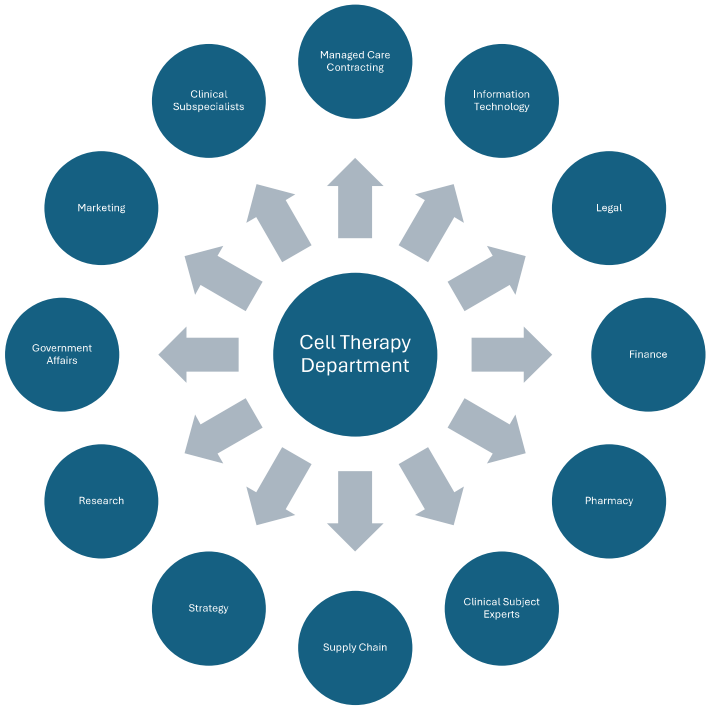


Cell Therapy Requires an "All-Hands on Deck" Approach



Getting Started

- Beyond the Cell Therapy Department, there are many institutional stakeholders that are directly involved in onboarding a new commercialized cellular therapy product.
- Start-up takes time and careful evaluation of:
  - Clinical value for patients, including the alternative treatment landscape
  - Potential patient populations and their geographic spread
  - Existing or upcoming treatment centers
  - Reimbursement realities and potential for financial vulnerability
  - Clinical and administrative resource impact



Contracts, Processes & Quality Assurance

Master Service Agreement	Returns/Refunds Policy	Cancellation Policy	Consent Forms	Confidential Disclosure Agreement	Treatment Plans
HIPAA Compliance	Distributor Relationships	Staff Training	Quality Agreement	Patient Care	Infusion Procedures
Patient Outcome Capture	Patient Specific Product Labels	Lab Manuals	Chain of Custody	Cell Collection Procedures	Managed Care Contracting
Pre-Authorization Procedures	Reimbursement Forecasting and Monitoring	Specialty Pharmacy Relationships	Product Delivery/Acceptance Procedures	Budgeting	Product Portals

What Makes Access to These Therapies So Complicated?

- Price and cash-flow
- Personalized, complex, high-risk, and multi-step treatment
- Limited treatment sites
- Inconsistent or operationally-complex coverage policies and practices
- Fertility preservation access barriers

SCD Cellular Gene Therapy Coverage and Reimbursement

Medicare	Medicaid	Commercial
• No confirmation of coverage from Medicare • SCT NCD doesn't explicitly included or exclude autologous transplant for SCD • Coverage is left to MAC discretion on a claim-by-claim determination process • Lack of coverage clarity pre-service creates an intolerable financial risk for centers	• Coverage policies are emerging from FFS programs and from MCO plans contracted with the state • These policies do not address the unique challenges that provider enrollment, patient travel, and out-of-network contracting present for patients that do not have local therapy centers	• Coverage policies are emerging from commercial plans • Specialty transplant/cell therapy networks are creating inclusion criteria for centers and for products

All Eyes on Access

- Focus on ensuring that patients appropriate for treatment are informed of their options
- Multi-disciplinary clinic to discuss options, risks, benefits, and supportive care with patients expressing interest
- Navigating interested patients through the care journey
- Obtaining financial clearance on their behalf, pre-service, to ensure that a patient's payer is aligned and in-agreement with the proposed plan of care

What Does the Future Hold?

- Provider-Manufacturer partnership to streamline administrative and operational burden of adopting new therapies
- Shared care models-hub and spoke-CGT at a treatment center and then hand off to community providers
- Payer-provider-manufacturer partnerships to ease financial burden (OBAs, warranty, CMMI model, etc)
- Iterative learning and access process improvement as patients move through treatment
- Cross-center collaboration and access advocacy efforts

Contact Information:
Claire White MSN, RN
Cell Therapy Policy Specialist
Children's Hospital of Philadelphia
whitec3@chop.edu

CMS Resources

- Medicare's Program Integrity Manual, Chapter 13 (*Revised 2/12/19: outlines the local coverage determinations the Carrier Advisory Committee (CAC) and contractor responsibilities surrounding CACs*)
- General Information on CMS' Contracting Reform
- Medicare Administrative Contractors (MAC) Regions and Updates
- Map of Current Jurisdictions
- Map of Consolidated Regions (*what CMS is moving toward*)
- Medicare Coverage
- Medicare Coverage Centers
- Patients over Paperwork: 9th Issue - Modernization Update: Local Coverage Determination (LCD)
- LCD Process Modernization Qs & As

American Society of Hematology Practice-Related Resources

ASH offers a wide range of practice-related resources on its website . Below, please find a list of resources that may be of interest to you.

ASH Carrier Advisory Committee Meeting (CAC) Website

- View resources such as the Medicare Program Integrity Manual, MAC regions, and previous Committee Notebooks.
    - If you are an ASH Member interested in being a subject matter expert, please complete this form.
    - If you are a Medical Director seeking a hematology expert, please download and complete this form, and return via email to ASH at CACnetworkmeeting@hematology.org.

Resources for Clinicians

- ASH Clinicians in Practice – The ASH Clinicians in Practice (formerly the ASH Practice Partnership (APP)) is a group within the Society that was formed to better represent the interests of practicing hematologists. The APP is comprised of practicing hematologists from across the nation; participants must be board-certified in hematology and active members of ASH. Ideal candidates should be interested in malignant and classical hematology.
- Drug Resources - This page provides links to patient assistance programs and sample letters of appeal for high-cost drugs, links to Risk Evaluation and Mitigation Strategies (REMS) resources, an up-to-date list of hematologic drug shortages, resources for physicians dealing with shortages, and links to ASH/FDA webinars featuring an unbiased discussion of newly approved drugs and their uses.
- Consult a Colleague - A member service designed to help facilitate the exchange of information between hematologists and their peers.
- ASH Choosing Wisely List - Evidence-based recommendations about the necessity and potential harm of certain practices developed as part of Choosing Wisely®, an initiative of the ABIM Foundation.
- ASH Clinical Guidelines, ASH Pocket Guides, and Hematology Quality Metrics - Access guidelines on Venous Thromboembolism (VTE), Immune Thrombocytopenia (ITP), von Willebrand Disease, Sickle Cell Disease, Anticoagulation Therapy, and others. Access the full guidelines, along with other tools and resources, including pocket guides, apps, teaching slides, webinars, and podcasts.
- Well-Being and Resilience - Well-being is a critical factor in the strength of the workforce, and the Society is committed to helping hematologists address the myriad factors impacting well-being through interventions such as openly addressing burnout in live meetings and in publications, advocating on behalf of hematologists to streamline administrative work, and sharing approaches to building resilience among hematologists.

Advocacy Resources

- ASH's Advocacy Center houses all of the Society's policy positions, advocacy efforts, and campaigns. Hematologists and their patients can directly influence their representatives through ASH Action Alerts. The Center also displays ASH's official Policy Statements along with Testimony and Correspondence related to federal regulation and private insurance developments.
- ASH's online advocacy toolkit provides members with the information and guidance necessary to communicate with elected officials in support of hematology. The toolkit clearly and concisely explains how members can undertake a number of actions to support ASH's advocacy efforts.

Clinical ASH Publications

- Practice Update – The Practice Update is the Society's bimonthly e-newsletter reporting on breaking news and activities of interest to the practice community.
- ASH Advocacy Blog – Read the latest news and updates on legislation and regulatory matters.

- *ASH Clinical News* – *ASH Clinical News* is a magazine for ASH members and non-members alike – offering news and views for the broader hematology/oncology community.
- *The Hematologist*: ASH News and Reports - An award-winning, bimonthly publication that updates readers about important developments in the field of hematology and highlights what ASH is doing for its members.

Meeting Information for Clinicians

- ASH Annual Meeting and Exposition – The 66th ASH Annual Meeting and Exposition is scheduled to take place December 7-10, 2024 in San Diego, California and as a virtual meeting. The Society's Annual Meeting and Exposition is designed to provide hematologists from around the world a forum for discussing critical issues in the field. Abstracts presented at the meeting also contain the latest and most exciting developments in hematology research.
- Highlights of ASH - This meeting is designed for participants to learn about rapidly evolving developments in hematology-oncology with leading faculty in the field. Discover new treatments for patients and improve overall practice methods.

Other ASH Activities and Resources

- The ASH Academy on Demand – The ASH Academy on Demand provides hematologists with easy-to-use options for knowledge testing (for both MOC and CME purposes), completing practice improvement modules, as well as evaluating ASH meetings you attend and claiming CME credit for participating.
- ASH and the American Medical Association – ASH is an engaged participant and member of the American Medical Association's (AMA) House of Delegates (HOD), AMA Current Procedural Terminology (CPT) Committee, and Relative Value Scale Update Committee (RUC).
- ASH Committee on Practice - The Committee on Practice is concerned with all issues affecting the practice of hematology. The Committee communicates with other organizations that have programs and policies that affect hematology practice. With appropriate review and approval by the Executive Committee, the Committee on Practice responds to practice-related issues by formulating positions on pending federal legislation, regulatory issues, and private insurance developments. The Committee also responds to matters of importance at the regional, state, and local levels, and to Society member requests.
- ASH Reimbursement Subcommittee - The Reimbursement Subcommittee, a subcommittee of the Committee on Practice, ensures that ASH addresses federal legislation and regulation affecting reimbursement for practicing clinical hematologists. The subcommittee focuses on securing appropriate physician reimbursement for cognitive services, such as increasing payment for evaluation and management (E/M) services, as well as expanding educational efforts for ASH members on coding and reimbursement. The subcommittee advises the Committee on Practice on all reimbursement-related issues by formulating positions on pending federal legislation, regulatory, and local Medicare coverage.

If you have any questions on this list or any of the programs, please contact Carina Smith, Manager for Health Care Access Policy at casmith@hematology.org.

AMERICAN SOCIETY OF HEMATOLOGY
Travel Reimbursement Policy

The ASH Travel Reimbursement Policy, as approved by the ASH Executive Committee, is provided to travelers (i.e., committee members, staff, etc.) regarding payment and/or reimbursement for costs incurred to participate in an ASH committee meeting or activity. ***(Special rules apply for speakers at the annual meeting and small meetings* which will be specified in the relevant invitation letters.)*** *It is expected that the policy will be adhered to explicitly. Any exceptions or appeals with a cost impact of $500 or less will be directed to the relevant member of Senior Staff; however, any exceptions or appeals with a cost impact over $500 will be directed to the ASH Treasurer.*

Coverage of allowable and reimbursable expenses begins at the actual start of a trip, whether it is from the traveler's regular place of employment, home, or other location, and terminates when the traveler reaches his/her original destination. Expenses for spouses and/or dependents are personal expenses and are not reimbursable.

Receipts for all expenditures (including E-ticket passenger receipts, taxis, and parking) of **$25.00 or more** should be provided with the ASH Expense Reimbursement Form if reimbursement is to be made. Requests for reimbursement must be submitted within **thirty (30) days** of the meeting or activity for which reimbursable expenses were incurred.

Guiding Principle

It is impossible to delineate every travel scenario in this policy. In general, travelers are asked to consider options that utilize ASH resources most effectively. Unique situations should be reviewed and approved in advance of the travel to avoid misunderstandings when reimbursement is requested after travel has been completed.

Air Travel

Air travel must be booked through the ASH travel agent. ASH will pay for non-stop, coach class (not business or first class) airline tickets when the flight is in North America. When the flight is outside of North America AND at least one segment of the flight is longer than six hours (as indicated on the official flight itinerary), ASH will pay for upgradable coach class airline tickets, or premium seating options within coach class (Economy Plus, aisle seats, etc.). ASH will pay for business class airline tickets when either of the following two travel scenario exists:

1. the flight is between North America and Europe, or
2. the flight is outside of North America AND the total travel time (as indicated on the official flight itinerary) is 10 hours or more.

It is required that tickets be purchased through the ASH travel agent.

Domestic (including Canadian) airline reservations must be made at least 30 days in advance and international airline reservations at least 60 days in advance. **(This requirement has been modified to 30 days for all travelers due to the variety of COVID-19 pandemic re-opening milestones.)** The ASH travel agent will record the coach roundtrip fare for all destinations 30 days (for domestic travel including Canada) or 60 days (for international travel including Mexico) prior to each meeting or activity, and this amount will be the maximum that ASH will pay. If a traveler fails to make reservations at least 30 days (for domestic travel including Canada) or 60 days (for international travel including Mexico) in advance, ASH will pay the allowable

amount and the ASH travel agent will charge the traveler (via his/her own credit card) for any amount that exceeds the allowable amount.

ASH will pay the most economical non-refundable coach fares available on a major airline carrier (American, Delta, Southwest, United, U.S. Airways, etc.). When a significantly less expensive option is available, reservations made at the request of the traveler with a particular carrier to benefit the traveler will not be paid in full; rather, the amount paid will equal the amount of the equivalent ticket on the most economical carrier. ASH will not reimburse a traveler with cash for tickets that were obtained using frequent flier points.

If an approved traveler wants to bring a guest, they must provide the ASH travel agent with a personal credit card for the guest's travel.

When flying into Washington, DC to attend a meeting at ASH Headquarters or a nearby hotel, there are three airports (Baltimore-Washington International, Dulles International, and Reagan Washington National) to consider. Sometimes a flight into Baltimore-Washington International (BWI) airport is less expensive, but ground transportation can be more expensive and time-consuming. In this case, the traveler may select the airport that is more reasonable. If a traveler does not want to use taxi or shuttle service from BWI, arrangements can be made by the ASH Meetings department for other ground transportation. Also, in some instances, staying over a Saturday night will result in a fare that is less than the hotel night and meals; if a traveler is willing to stay for the extra night, ASH will reimburse him/her for those associated costs.

Train Travel

Train travel must be booked through the ASH travel agent. ASH will pay for business class seats on Amtrak regional trains. Where Amtrak's Acela Express trains are available, ASH will pay for business class seats since this is the most economical option on Acela Express. **It is required that tickets be purchased through the ASH travel agent.**

Train reservations must be made at least 30 days in advance. The ASH travel agent will record the fare for all destinations 30 days prior to each meeting or activity, and this amount will be the maximum that ASH will reimburse. If a traveler fails to make reservations at least 30 days in advance, ASH will pay the allowable amount and the ASH travel agent will charge the traveler (via his/her own credit card) for any amount that exceeds the allowable amount.

If an approved traveler wants to bring a guest, he/she must provide the ASH travel agent with a personal credit card for the guest's travel.

Ground Transportation

ASH encourages use of the most economical ground transportation to and from the airport or train station and will reimburse such expenses. Examples of acceptable options include taxis, airport shuttle services, and ride-sharing services (i.e., Uber and Lyft) provided that the most economical option of these services (i.e., UberX or UberXL or equivalent) is utilized. Upgraded options called Uber Black, Uber Select, Lyft Plus, and Lyft Premier are not reimbursable. Travelers should be aware of any surge pricing that is in effect with these services and select more economical options during these peak demand periods.

Use of a personal or university vehicle will be reimbursed at the mileage rate consistent with IRS rules and regulations (**67 cents per mile as of 1/1/2024, a rate that considers the cost of gasoline**) plus toll and parking charges. (ASH will reimburse parking charges and mileage if this amount is not greater than the cost of roundtrip taxi or shuttle service.)

Use of a rental car must be approved in advance and should represent the most economical ground transportation option. If ASH approves the use of a rental car, limits will be set and communicated to the traveler by the appropriate ASH representative. The maximum rates set by ASH consider the cost of the rental, mileage, gasoline, parking, tolls, and any other expenses related to the use of the rental to attend the meeting.

Local attendees who wish to drive to ASH Headquarters can do so and park in the garage located next to the 2021 L Street building; parking charges will be reimbursed.

Hotel

The traveler is responsible for requesting a hotel room via the ASH registration system by the deadline indicated. If an attendee wishes to extend his/her reservation before or after the ASH meeting or activity, he/she must indicate this when registering and present his/her own credit card at check-in to pay for the nights not covered by ASH.

For safety and risk reasons, travelers are not permitted to stay in home-sharing type accommodations (i.e., Airbnb, HomeAway, VRBO, etc.) even if the rate is lower than available hotels.

Meals

ASH will reimburse reasonable actual expenses of the traveler's meals plus tips up to $100 per day; however, receipts must be provided. **When ASH schedules a meal for which it must guarantee a number of attendees and for which it assumes the cost, meals taken elsewhere are not reimbursable.**

ASH offers to reimburse members and staff for a meal if they attend a virtual committee meeting that exceeds three hours and is held during mealtime. Attendees can use their preferred meal provider (e.g., Uber Eats, Door Dash, etc.) and can be reimbursed for up to $50 per meal, not to exceed one meal per day; the reimbursement could be declined and instead donated to the ASH Foundation. In either case, a completed ASH Expense Reimbursement Form along with a receipt must be submitted within 30 days of the meeting.

Cancellations and Changes

When a traveler needs to change or cancel an airline reservation, he/she must contact the issuing agent and notify the appropriate ASH representative **immediately.** The traveler is responsible for all penalty fees and any other charges incurred due to such changes or cancellations more than $150. If the traveler does not inform the travel agency or airline of the cancellation prior to the scheduled departure time, and ticket is thereby rendered unusable for future travel, then the traveler will be held responsible for the cost of the original ticket.

If a traveler needs to change or cancel a hotel reservation, he/she must contact the appropriate ASH representative at least 72 hours prior to his/her originally scheduled arrival. The traveler is responsible for reimbursing ASH for expenses incurred due to last-minute changes, cancellations, no-shows, and early departures.

Miscellaneous Expenses

- Airline baggage fees are reimbursable with receipts.
- Baggage service (e.g., skycap or hotel bellman) and similar expenses are reimbursable up to a maximum of $10 dollars per day.
- Early board fees and onboard airline Wi-Fi access fees are reimbursable with receipts.
- Tips not included with meals or cab fare should be listed separately on the ASH Expense Reimbursement Form.
- ASH will reimburse reasonable phone and Internet usage.

- When a trip involves traveling for both ASH and other purposes, the traveler must reasonably allocate the costs between ASH and other activity.

If a traveler has any questions concerning any other reimbursable expenses, he/she should contact the appropriate ASH representative in advance of travel.

**Highlights of ASH; Clinical Research Training Institute; Translational Research Training in Hematology; ASH Meeting on Lymphoma Biology; ASH Meeting on Hematologic Malignancies, or any other meeting designated by ASH.*

This is a payable invoice eligible for Concur processing.

ASH EXPENSE REIMBURSEMENT FORM

Please fill out the information below and attach <u>original receipts</u> to the following receipt pages.

Make reimbursement payable to: _____

Address: _____

Meeting(s) Attended _____

<u>Signature:</u>* _____ Date: _____
***Form will not be processed Without a Signature**

Itemized Expenses:

Date	Description of Expense	Account (*internal use only*)	Amount
_____	_____	_____ - _____ - _____ - _____ -____	$ _____
_____	_____	_____ - _____ - _____ - _____ -____	$ _____
_____	_____	_____ - _____ - _____ - _____ -____	$ _____
_____	_____	_____ - _____ - _____ - _____ -____	$ _____
_____	_____	_____ - _____ - _____ - _____ -____	$ _____

☐ **I decline $_____ of this reimbursement as a Pledge Payment towards my Pledge with the ASH Foundation.**

☐ **I decline some or all of this reimbursement as a one-time donation to the ASH Foundation to benefit the following program(s):**

Greatest Needs Fund $ _____
Career Development and Training Fund $ _____
Clinical Research Training Institute Fund $ _____
Global Programs Fund $ _____
Minority Recruitment Initiative Fund $ _____
Quality Care and Education Fund $ _____
Research Awards Fund $ _____
(ASH Scholar Awards, Global Research Award, etc.)
Sickle Cell Disease Initiative Fund $ _____

☐ **I accept this reimbursement.**

<u>SUMMARY:</u>
Total of itemized expenses: **$**_____
Total amount declined as a donation/pledge payment to the ASH Foundation per above designation: **$** _____
Total amount to be reimbursed to signatory herein: **$** _____

For more information about any of these ASH programs, please refer to the ASH website at *www.hematology.org/foundation/supported-programs*.
Under U.S. Internal Revenue Service guidelines, the estimated value of benefits you have received, if any, in consideration for your gift, is not substantial and will not affect the deductibility of your gift as a charitable contribution.
Please return this completed form to ASH at invoices@hematology.org or via fax at: 888-783-2183.

<u>Revision Date: 2/16/2023</u>