American Society of Hematology

Carrier Advisory Committee (CAC) Meeting

June 23, 2023

Annual Meeting
ASH Headquarters
Washington, DC
8:00 a.m. – 3:00 p.m. ET
https://hematology.zoom.us/j/91560945949

American Society of Hematology

Helping hematologists conquer blood diseases worldwide

Carrier Advisory Committee (CAC) Networking Meeting

June 23, 2023

Agenda

8:00 a.m.	BREAKFAST		
8:30 a.m.	Welcome and Introductions	Dianna Howard, MD	
	• Attendee List		3
	• Speaker List		5
	• ASH Staff List		8
	• CMD List		9
	• Jurisdiction Map		11
8:45 a.m.	Molecular Profiling of Hematopoietic Malignancies	Lucy Godley, MD, PhD	12
10:30 a.m.	BREAK		
10:45 a.m.	Chemotherapy Infusion Codes	Janet Lawrence, MD, MS Larry Clark, MD	46
11:15 a.m.	Life Cycle of an Local Coverage Determination	Meredith Loveless, MD	53
12:00 a.m.	LUNCH and NETWORKING		
1:00 p.m.	Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome	Corey Cutler, MD, MPH Doug Rizzo, MD, MS	64
1:30 p.m.	Minimum Residual Disease Testing	Amar Kelkar, MD	84
2:30 p.m.	What's going on in your Jurisdiction?	All	
	• Open discussion on Coverage or Reimbursement Issues		
2:50 p.m.	Closing Remarks and Reference Materials	Dianna Howard, MD	
	• CMS Resources		94
	• ASH Practice Resources		95
	• Meeting Reimbursement Policy		97
	• Meeting Reimbursement Form		100
3:00 p.m.	ADJOURN		

In-Person Attendee List

As of June 15, 2023

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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 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.

Lucy Godley, MD, PhD

Lucy Godley, MD, PhD is an expert in the care and treatment of patients with diseases of the bone marrow, including leukemias, lymphomas, and multiple myeloma. She also cares for patients undergoing stem cell transplantation and patients with benign hematologic conditions.

Dr. Godley has a special interest in the molecular basis of bone marrow malignancies and is an active researcher in the field. In her laboratory, Dr. Godley studies the basis for cancer cells' abnormal patterns of DNA methylation, as well as inherited forms of bone marrow cancers.

She has received numerous awards for her research, including the Howard Hughes Medical Institute Physician Postdoctoral Award, the Cancer and Leukemia Group B (CALGB) Foundation Clinical Research Award, the American Society of Clinical Oncology Young Investigator Award, the Cancer Research Foundation Young Investigator Award, the Schweppe Foundation Career Development Award and the Kimmel Scholar Award. She was inducted into the American Society of Clinical Investigation in 2012.

Dr. Godley's goal is to improve health through a deeper understanding and appreciation of science by integrating knowledge about fundamental networks within cancer cells and by bringing novel insights into the pathophysiology of her patients' diseases while offering them new treatment options.

Janet I. Lawrence, MD, MS, FACP

Janet Lawrence, MD, MS, FACP, joined Noridian Healthcare Solutions as a Contractor Medical Director in October 2018. She is a physician with18 years of medical review experience dating all the way back to the old Health Care Financing Administration (now known as CMS). Her experience includes serving as the U.S. Army deputy command surgeon in Birmingham, AL. She also spent five years at the Qualified Independent Contractor for Medicare DME. Prior to that, she was at National Government Services as a MAC contractor medical director. Dr. Lawrence is a board-certified internal medicine physician with an M.S. in strategic studies from the U.S. Army War College.

Larry Clark, MD, FACP
Larry Clark, MD, FACP, joined Noridian as a Contractor Medical Director in spring 2019. Dr. Clark is a graduate of the Georgetown University School of Medicine. He completed his Internal Medicine training as an intern with the S.U.N.Y. Stony Brook program, and residency with the Georgetown University- Washington Veterans Administration Medical Center program. During his 34 years of internal medicine practice in Alexandria, VA, he served as the President of the Medical Staff of Mount Vernon Hospital, as the President of the Virginia Society of Internal Medicine, and on the Governor's Council of the VA chapter of the American College of Physicians.

He served as the Internal Medicine alternate for VA on the inaugural Medicare Carrier Advisory Committee for the DC Metro Area. Eventually, he became the co-chair of the Committee, and then stepped down to serve as a regional consultant for TrailBlazer Medicare. He served as a Medicare Medical Director for TrailBlazer in the Mid-Atlantic region for almost a decade, and subsequently served in the same role for Highmark, while also continuing in clinical practice. This was followed by seven years with NGS, as medical director for New York and New England. Dr. Clark continues to practice clinical medicine as the volunteer medical director of the Carpenters Shelter clinic, a homeless shelter in the City of Alexandria. His interests remain in medical policy development and clinical outcomes.

Meredith Loveless, MD
Meredith Loveless, MD is a Chief Medical Officer for CGS Administrators J15 Part A/B and focuses on policy. She was a teaching physician in OB/GYN at Johns Hopkins and University of Louisville prior to transitioning to Medicare. She has multiple academic papers and presentations, chaired several committees for the American College of Ob/Gyn and is an enthusiastic supporter of evidence-based medicine.

Corey Cutler, MD, MPH, FRCPC
Corey Cutler, MD, MPH, FRCPC received his MD from McGill University, Montreal, Canada. He subsequently received his MPH from the Harvard school of Public Health. He completed postgraduate training in Internal Medicine at Royal Victoria Hospital, Montreal, followed by a fellowship in Hematology/Oncology at Dana-Farber Cancer Institute (DFCI). In 2002, he joined DFCI, where he currently is a member of the Hematologic Malignancies staff.

J. Douglas Rizzo MD, MS
J. Douglas Rizzo, MD, MS Associate Director of Clinical Operations, Senior Scientific Director, Center of International Bone Marrow Transplant Research (CIBMTR), Professor, Medicine/Hematology and Oncology, Project Director Stem Cell Therapeutic Outcomes Database. The Associate Director of Clinical Operations (ADCO) for the Medical College of Wisconsin (MCW) Cancer Center provides direction for cancer clinical operations while overseeing the multidisciplinary clinics and Cancer Service Line. Dr. Rizzo fosters a climate of multidisciplinary cancer care with a visible emphasis on research-driven patient care. He works closely with Froedtert administrative leadership and Medical College clinical leadership to ensure that MCW clinicians deliver top quality cancer care and create an environment that is structured for and supports clinical research. He assists with implementation of community engagement strategies, and integration of care across all Cancer Network locations. He is responsible for design and implementation of value-based care strategies – including CMS' Oncology Care Model. Dr. Rizzo coordinates with counterparts at Children's Hospital of Wisconsin to share knowledge and apply research-driven cancer care best practices. He is also the Project Director of the Stem Cell Therapeutic Outcomes Database (SCTOD), one component of the CW Bill Young Cell Transplantation Program. As such he has responsibility for all aspects of collection and use of data to fulfill CIBMTR's contractual obligations. Dr. Rizzo has more than 20 years' experience collecting, managing and analyzing HCT data, and has been integrally involved in CIBMTR initiatives studying late effects and quality of life, regimen intensity and toxicity, and health economics and access disparities. He has participated in numerous quality of care initiatives within and beyond the HCT community. He has international recognition and plays an important part of CIBMTR's collaborative international presence. Dr. Rizzo has been a key contributor to both screening and practice guideline efforts for HCT survivors from the CIBMTR. Elective Paragraph: Dr. Rizzo received his bachelor of science degree from the Virginia Polytechnic Institute and State University in Blacksburg, VA., in 1986, and he earned his medical degree from Johns Hopkins University in Baltimore, MD., in 1990. He was a Clinical Fellow in Oncology and Hematology from 1994-1998 and completed the Robert Wood Johnson Clinical Scholars Program

from 1996-1998 at Johns Hopkins University. He joined the MCW faculty in 1998. He received his master of science in epidemiology from MCW in 2005.

Amar Kelkar, MD

Amar Kelkar, MD is a Stem Cell Transplantation Physician at the Dana-Farber Cancer Institute and an Instructor in Medicine at Harvard Medical School. He is a member of the Abel Laboratory with research interests in hematology, care delivery, cost-effectiveness, medical ethics, and health policy. He is also completing a Master of Public Health degree at the Harvard T.H. Chan School of Public Health. His background is in molecular biology and genetics with a degree from Cornell University in Biological Sciences, where he worked for 3 years as a member of the Andrew Clark Laboratory focused on population genetics. He completed postgraduate medical training at the University of Illinois College of Medicine at Peoria, the University of Florida College of Medicine, and the Dana-Farber Cancer Institute. He has interests in health policy and medical advocacy and serves on the American Society of Hematology Committee on Practice and Subcommittee on Reimbursement, the American Society for Transplantation and Cellular Therapy Value and Health Economics Special Interest Group, and the Massachusetts Medical Society (MMS) Committee on Publications that oversees the NEJM Group. He previously served on the MMS Board of Trustees, the American Medical Association Council on Legislation.

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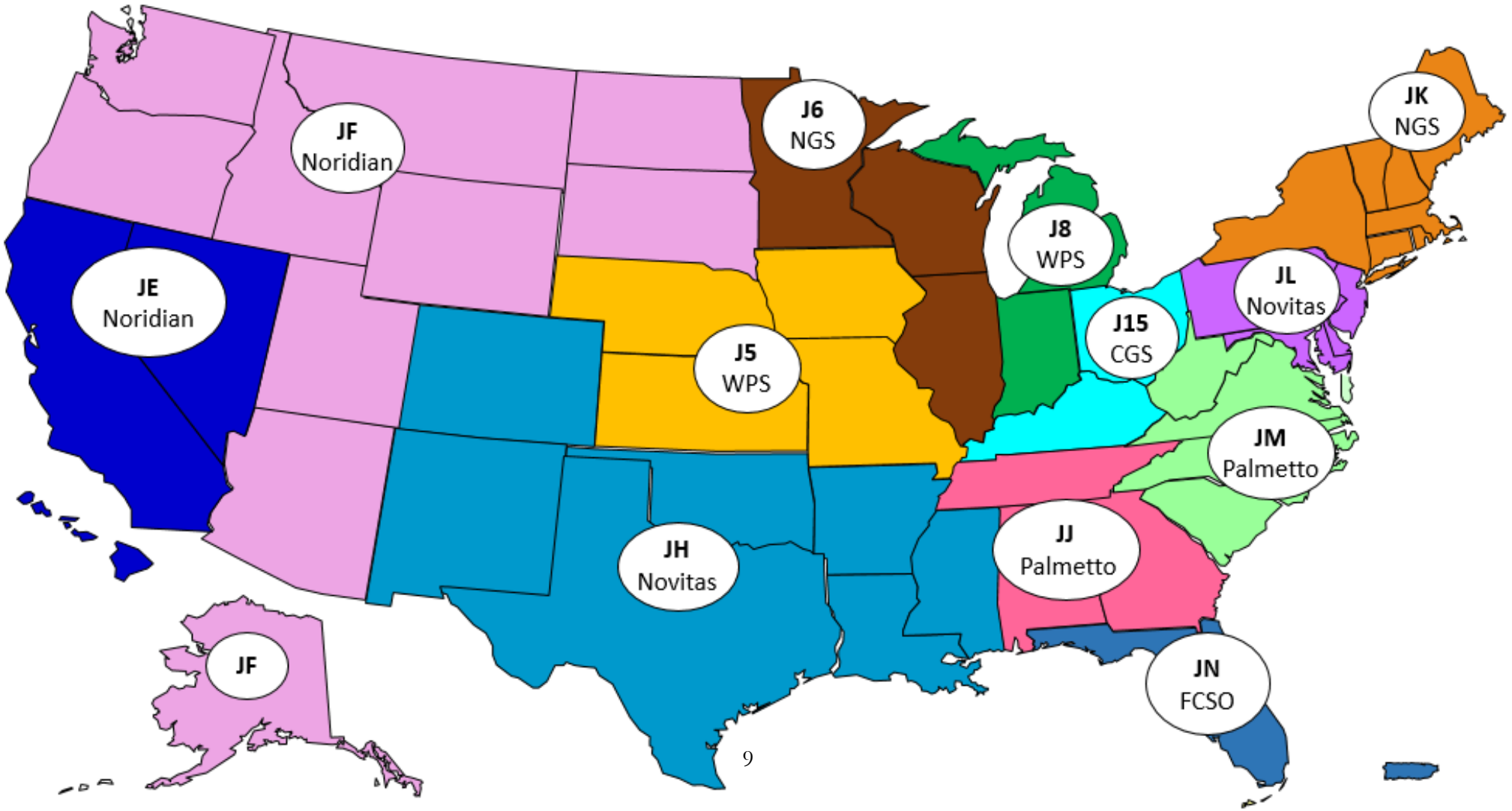
as of June 2019



Molecular profiling of hematopoietic malignancies

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Northwestern University

1

Realizing the goal of precision medicine in oncology

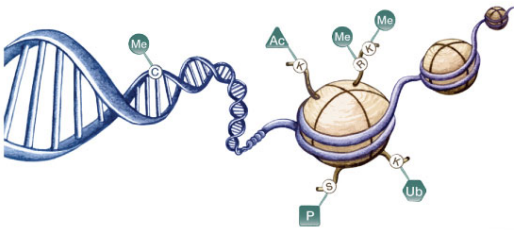
DEFINE:
Baseline genetics/epigenetics
[germline]

Acquired genetics/epigenetics in the HSC
[clonal hematopoiesis]

Acquired genetics/epigenetics in the tumor
[tumor profiling]

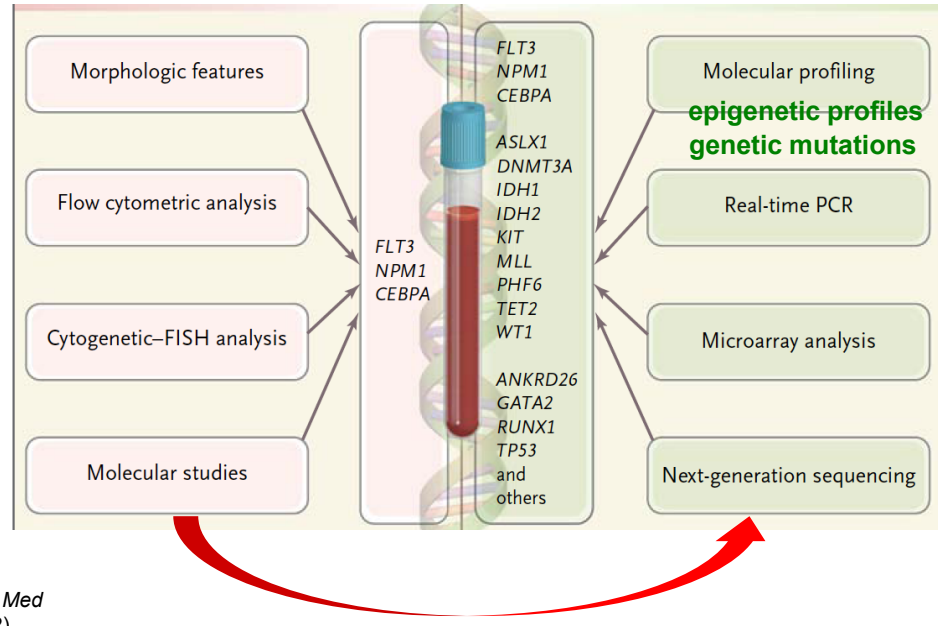
Microbiome/Immunotype

to devise an effective treatment strategy for a particular patient



2

Realizing the goal of precision medicine in oncology



Godley, L.A. *N Engl J Med* 366: 1152-1153 (2012)

3

Molecular profiling informs clinical decisions

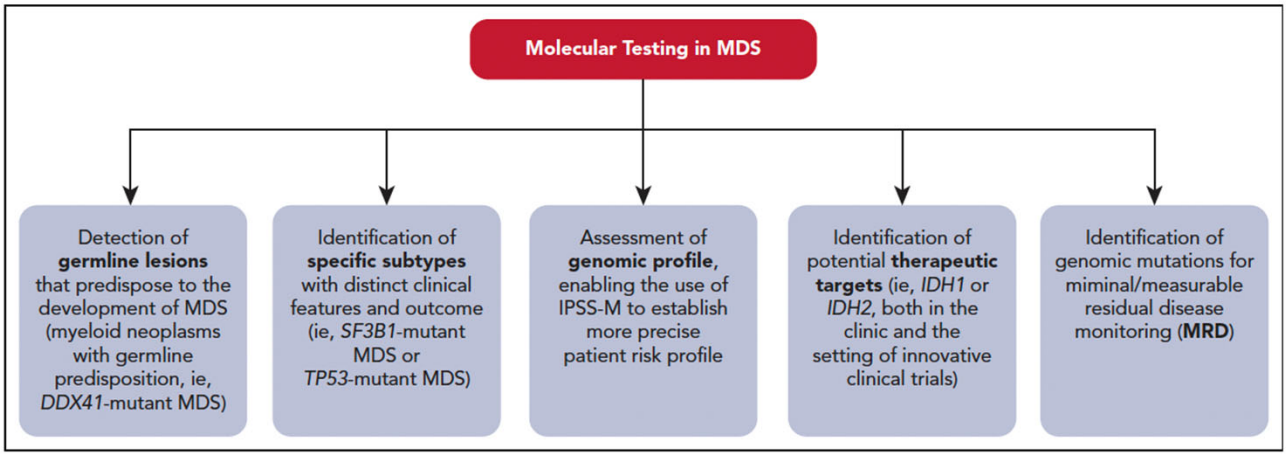


Figure 1. How molecular profiling can inform clinical decision making in MDS. IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndrome; MRD, minimal/measurable residual disease. Professional illustration by Patrick Lane, ScEYEnce Studios.

Duncavage, E.J. *et al. Blood* 140: 2228-2247 (2022)

4

Realizing the goal of precision medicine in oncology

DEFINE:
Baseline genetics/epigenetics
[germline]

Acquired genetics/epigenetics in the HSC
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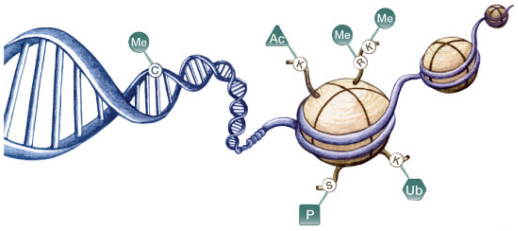
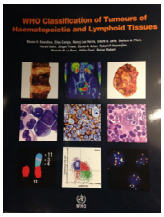


5

Germline predisposition to myeloid malignancies is now widely recognized

WHO classification includes germline predisposition to myeloid malignancies



NCCN MDS guidelines urge testing for germline predisposition

Greenberg, P.L. *et al. J Natl Compr Canc Netw* 20: 106-117 (2022)

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Arber, D.A. *et al. Blood* 140: 1200-1228 (2022)

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[25] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.C. Loh,[26] Bob Löwenberg,[27] Elizabeth Macintyre,[28] Luca Malcovati,[29] Charles G. Mullighan,[30] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Eli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN

Hartmut Döhner,[1] Andrew H. Wei,[2] Frederick R. Appelbaum,[3] Charles Craddock,[4] Courtney D. DiNardo,[5] Hervé Dombret,[6] Benjamin L. Ebert,[7] Pierre Fenaux,[8] Lucy A. Godley,[9] Robert P. Hasserjian,[10] Richard A. Larson,[11] Ross L. Levine,[12] Yasushi Miyazaki,[13] Dietger Niederwieser,[14] Gert Ossenkoppele,[15] Christoph Röllig,[16] Jorge Sierra,[17] Eytan M. Stein,[18] Martin S. Tallman,[18] Hwei-Fang Tien,[19] Jianxiang Wang,[20] Agnieszka Wierzbowska,[21] and Bob Löwenberg[22]

European LeukemiaNet guidelines also include testing for predisposition mutations

Döhner, H. *et al. Blood* Blood 140: 1345-1377 (2022)

6

Germline hematopoietic malignancy risk genes

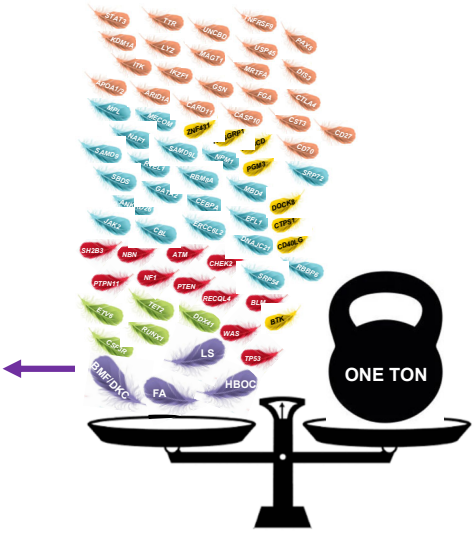
Risk for myeloid malignancies	Risk for lymphoid malignancies or immunodeficiency	Risk for hematopoietic malignancies	Risk for hematopoietic and non-hematopoietic malignancies
ANKRD26, CBL, CEBPA, DNAJC21, EFL1, ERCC6L2, GATA2, JAK2, MECOM/EVI1, MPL, NAF1, NPM1, RBBP6, RBM8A, RTEL1, SAMD9, SAMD9L, SBDS, SRP72	*APOA1, APOA2, ARID1A, BTK, CARD11, CASP10, CD27, CD40LG, CD70, CST3, CTLA4, CTPS1, DIS3, DOCK8, FGA, GSN, IKZF1, ITK, KDM1A, LYZ, MAGT1, MALT1, MRTFA, NPAT, PAX5, PGM3, PIK3CDG, RASGRP1, STAT3, TTR, UNC13D, USP45 TNFRSF9, ZNF431*	*CSF3R, DDX41, ETV6, RUNX1, TET2, trisomy 21*	*ATM, BLM, BRCA1, BRCA2, CHEK2, MBD4, NBN, NF1, POT1, PTEN, PTPN11, RECQL4, SH2B3, TP53, WAS,* BMF/DKC*, FA*, HBOC*, LS*

* DKC, dyskeratosis congenita; FA, Fanconi anemia; HBOC, hereditary breast and ovarian cancer; LS, Lynch syndrome

7

8

ACD, ADH5/ALDH2, ALAS2, BRCA1/2, BRIP1, CECR1, CSF3R, CTC1, CXCR4, DCLRE1B, DDX41, DKC1, DNAJC21, DPP9, EFTUD1, ELANE, ERCC4, ERCC6L2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, G6PC3, GATA1, GFI1, HAX1, LIG4, MAD2L2, MDM4, MECOM, MPL, NAF1, NHP2, NOP10, NPM1, PALB2, PARN, POT1, RAD51, RAD51C, RBM8A, RFWD3, RPL5, RPL11, RPL15, RPL18, RPL23, RPL26, RPL27, RPL31, RPL35, RPL35A, RPL36, RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, RTEL1, RUNX1, SAMD9, SAMD9L, SBDS, SLX4, SRP54, SRP72, TERC, TERT, TINF2, TP53, UBE2T, USB1, VPS45, WAS, WRAP53, XRCC2



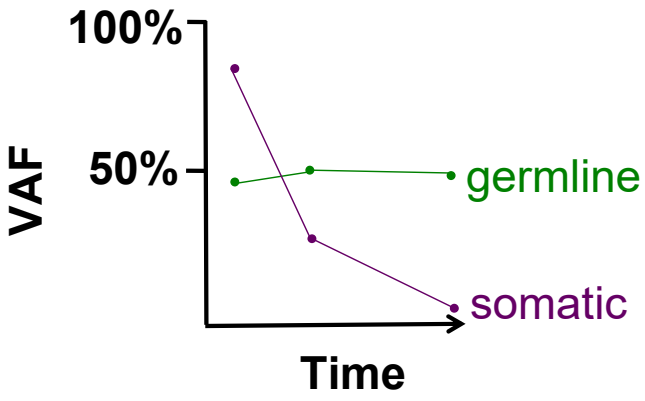
9

Why does it matter to identify germline predisposition?

- Influences treatment regimens
- Influences decision about using an allogeneic hematopoietic stem cell transplant
- Influences decision about who the donor should be
- Influences cancer surveillance of organs outside the bone marrow/blood compartment
- Allows cascade testing and better cancer/health surveillance for additional family members

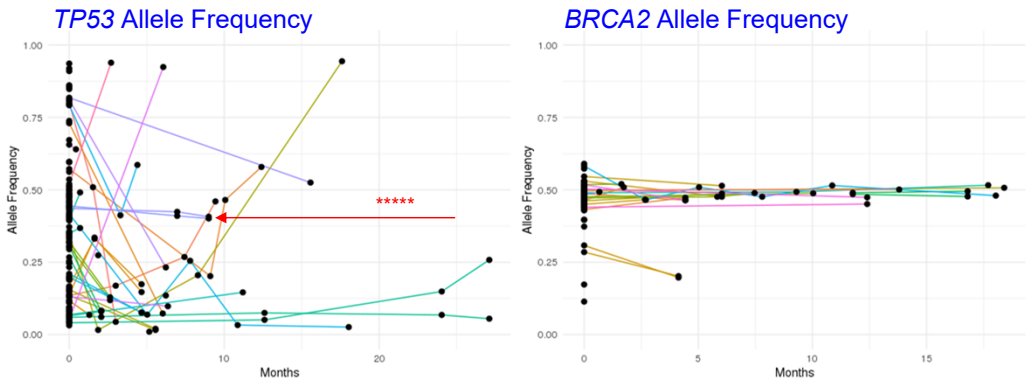
10

The power of sequential testing



11

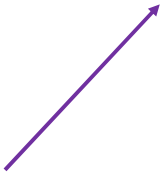
The power of sequential testing



12

Realizing the goal of precision medicine in oncology

DEFINE:
Baseline genetics/epigenetics
[germline]



assumption about germline mutations causing cancer exclusively in the young is wrong (at least for hematopoietic malignancies)!

13

Disease mechanisms– What does age tell us?

14

Age of presentation (of MDS) is a surrogate for the biological pathway

AVERAGE age of diagnosis: 68yo!!

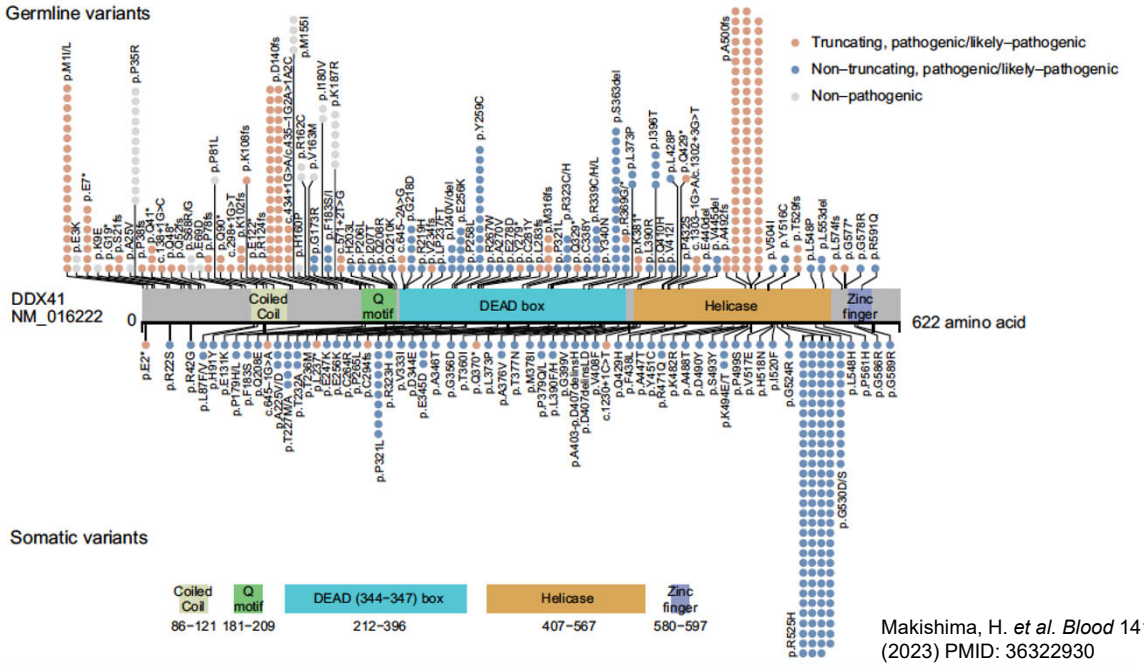
Feurstein, S. *et al. Leukemia* **35:** 2439-2444 (2021)

15

Disease mechanisms– DDX41 and its unique biology

16

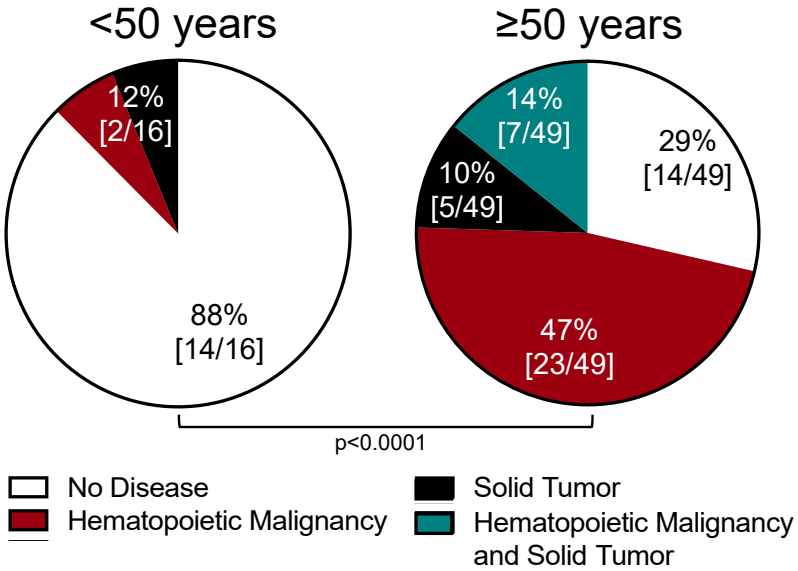
DDX41 on 5q35.3 encodes a DEAD/H-Box helicase



Makishima, H. *et al. Blood* 141: 534-549 (2023) PMID: 36322930

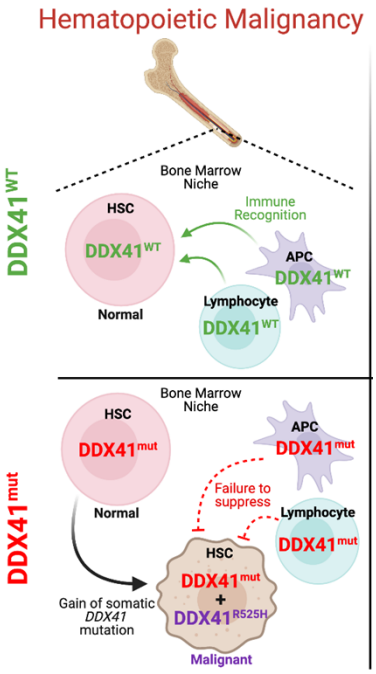
17

Germline *DDX41*^{mut} predispose to late-onset malignancies



18

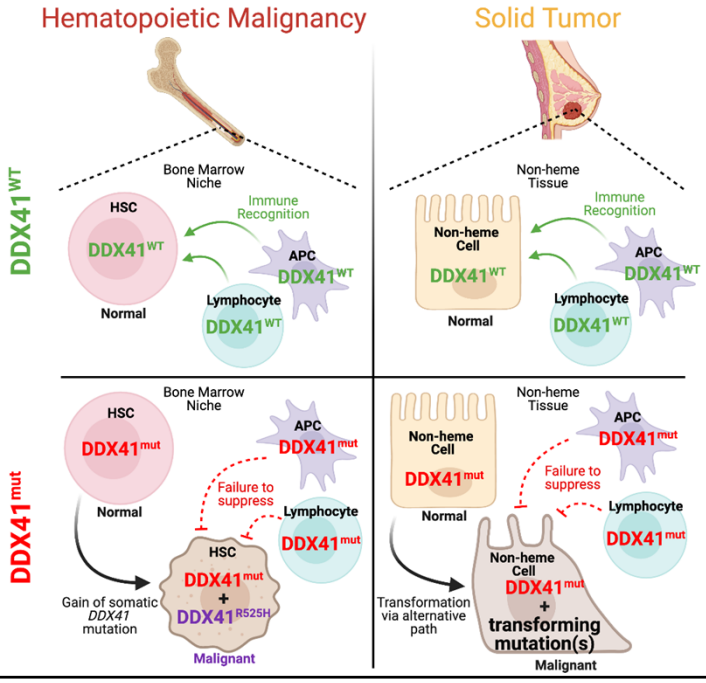
Mechanistic model for *DDX41*^{mut}-mediated tumorigenesis



↑ inflammation?

19

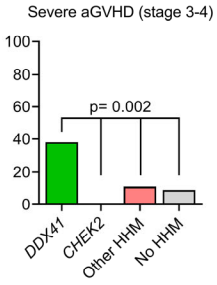
Mechanistic model for *DDX41*^{mut}-mediated tumorigenesis



↑ inflammation?

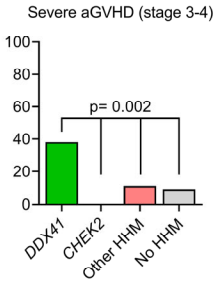
20

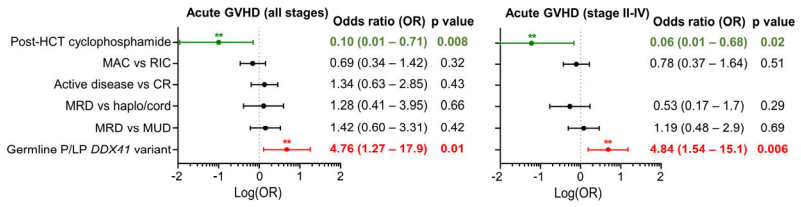
People with deleterious germline *DDX41*^{mut} develop more GVHD post-transplant (with WT donors)



Saygin, C. *et al. Blood Advances* 7: 549-554 (2023)
PMID: 36001442

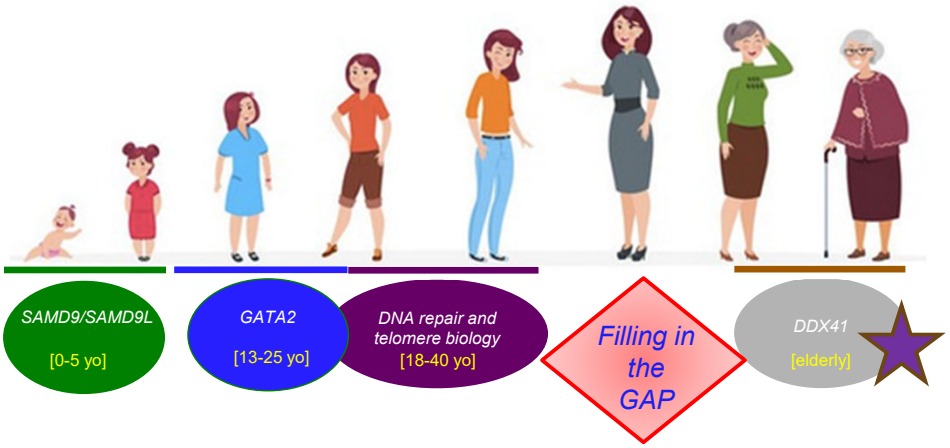
People with deleterious germline *DDX41*^{mut} develop more GVHD post-transplant (with WT donors)





Saygin, C. *et al. Blood Advances* 7: 549-554 (2023)
PMID: 36001442

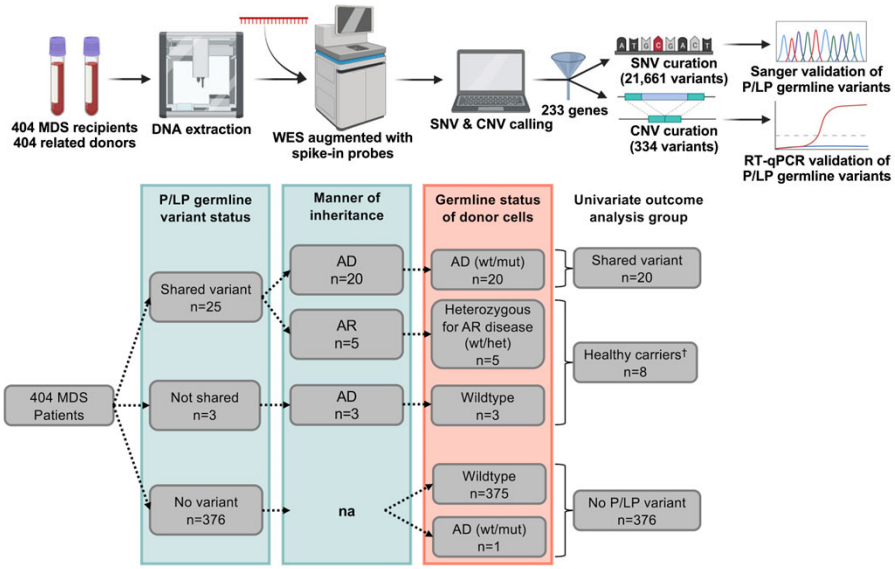
Age of presentation (of MDS) is a surrogate for the biological pathway



Feurstein, S. *et al. Leukemia* **35:** 2439-2444 (2021)

23

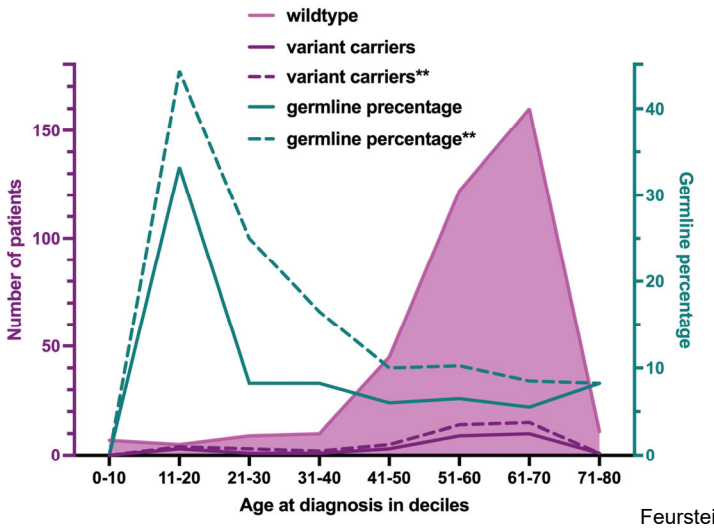
Determining the frequency of deleterious germline variants in MDS across the age spectrum (CIBMTR cohort)



Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

24

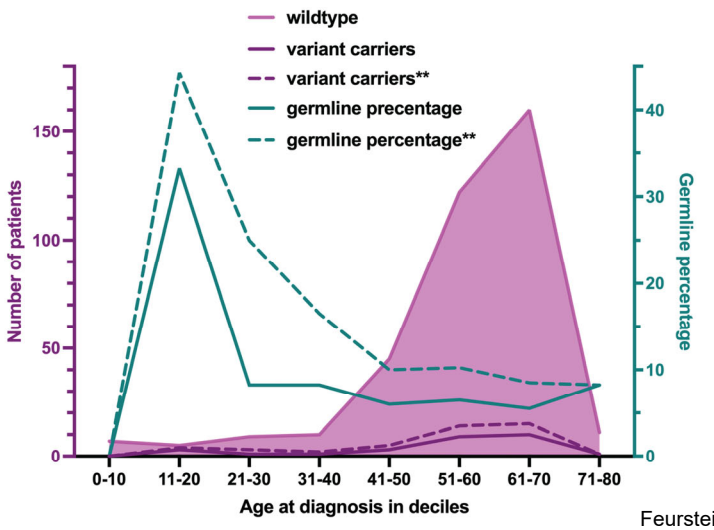
Frequency of deleterious germline variants in MDS across the age spectrum: 7% (>5% in all age deciles)

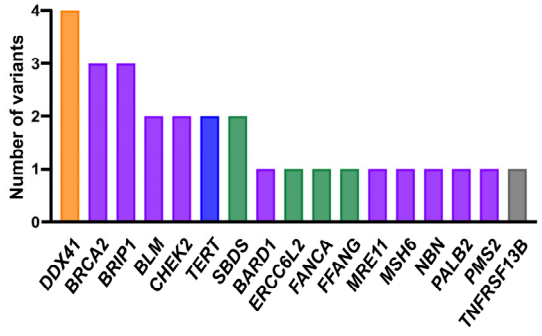


Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

25

Frequency of deleterious germline variants in MDS across the age spectrum: 7% (>5% in all age deciles)

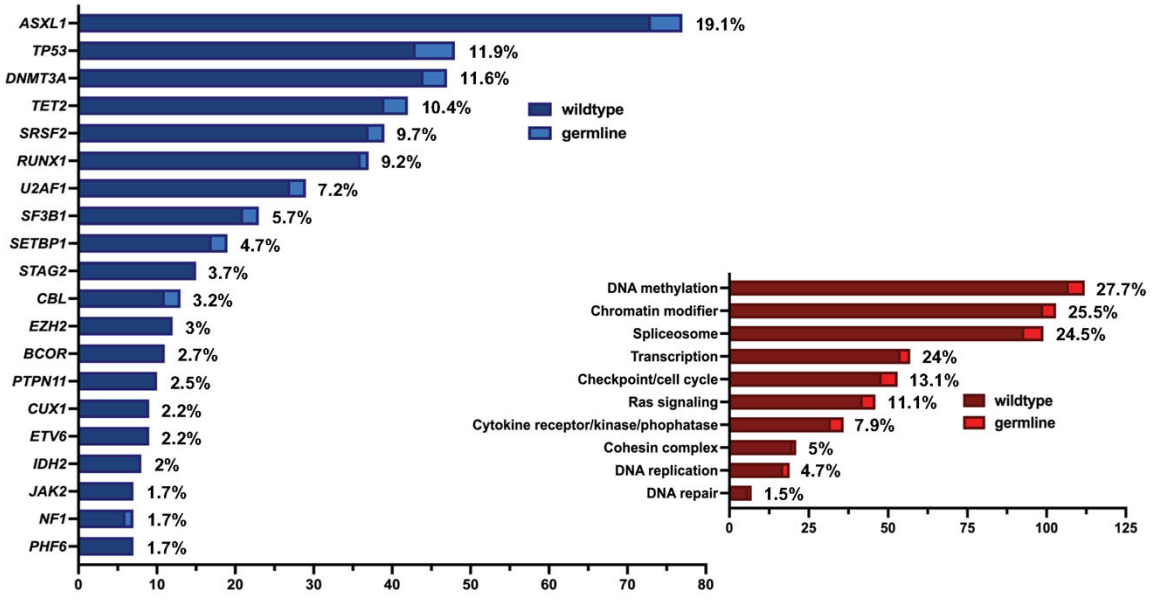




Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

26

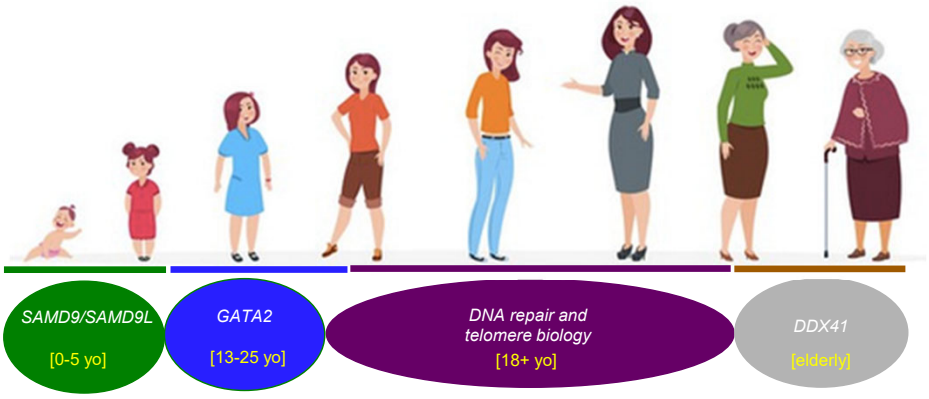
Somatic mutation spectrum = that of *de novo* MDS



Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

27

Age of presentation (of MDS) is a surrogate for the biological pathway



Feurstein, S. *et al. Leukemia* **35:** 2439-2444 (2021)

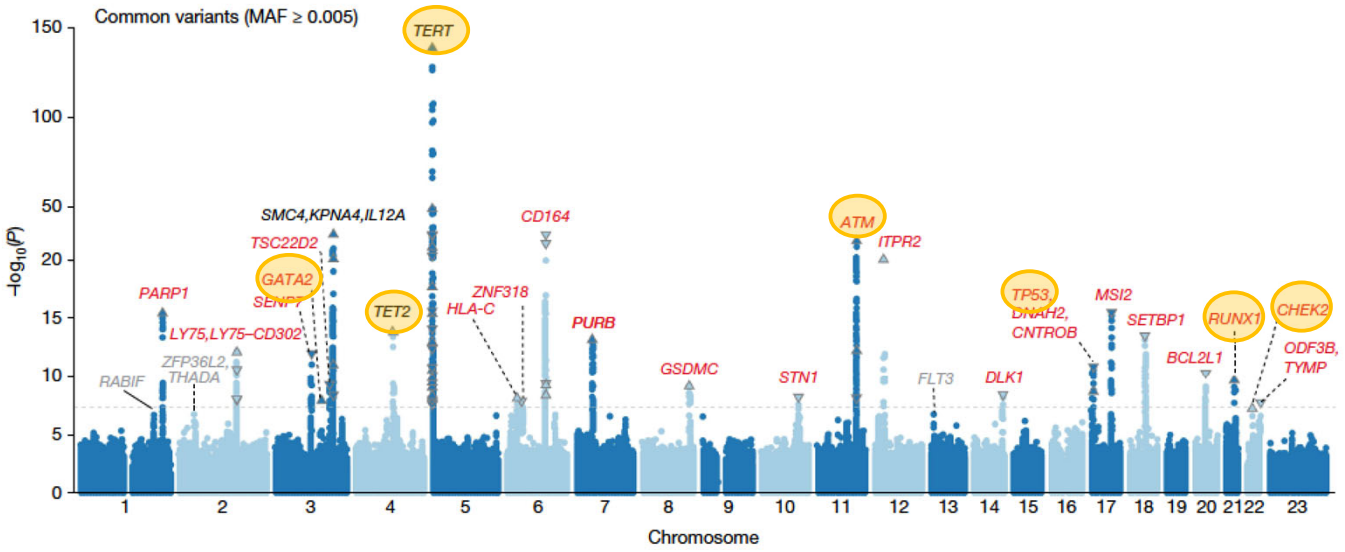
Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

28

Disease mechanisms–
How does transformation happen?

29

GWAS for genes that confer risk for CH

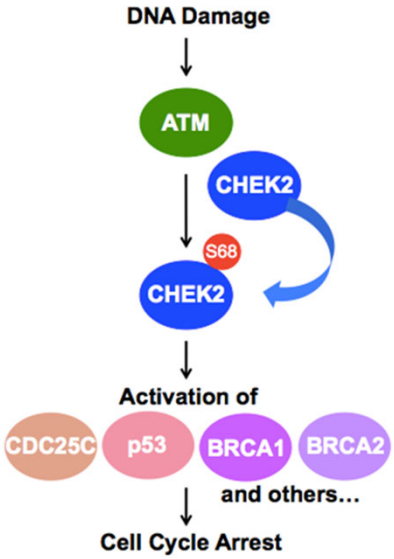


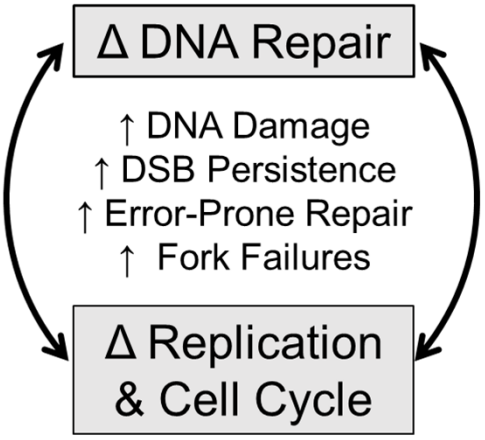
Many of these genes are germline susceptibility genes for HMs→
Is the mechanism development of CH first, then HM?

Kessler, M.D. *et al.* (2022) *Nature* **612:** 301-309.

30

The molecular impact of HR DNA repair pathway deficiencies on DNA integrity within hematopoietic cells

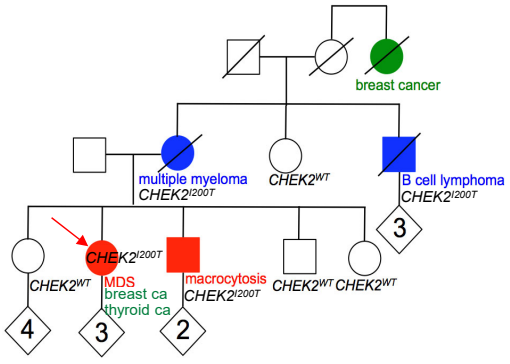




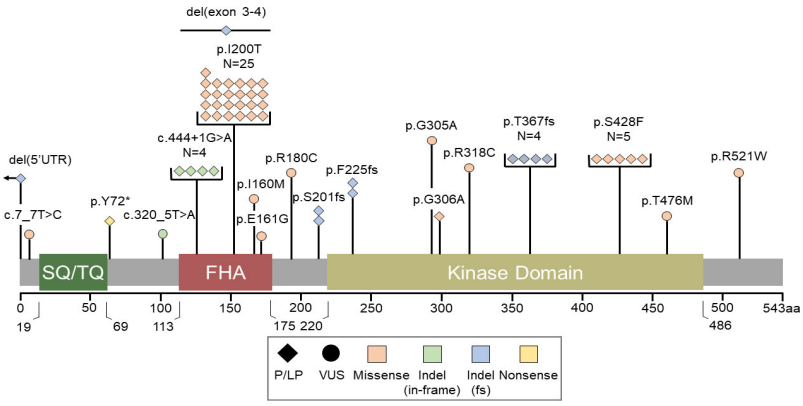
31

Germline *CHEK2* mutations and hematopoietic malignancies

representative pedigree



Godley Lab Cohort



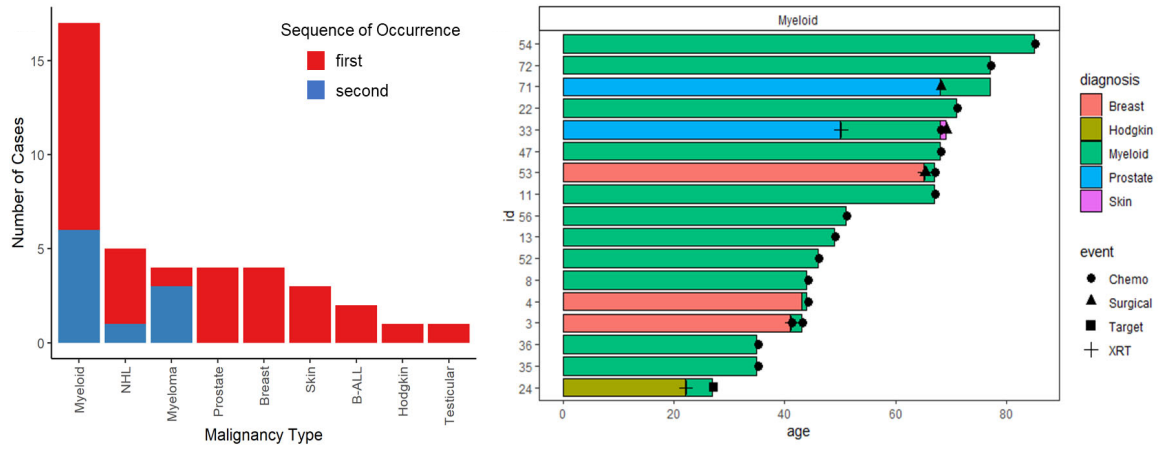
32

Germline *CHEK2* mutations and hematopoietic malignancies

Hematologic Malignancy Patients with *CHEK2* Variant (n = 33)			Non-cancer ExAc Control Population (gnomAD)		Hematologic Malignancy vs gnomAD cohort	Significance
Variant	Proportion of Individuals with the Mutation	Variant Frequenecy	ExAc Allele Number (excluding homozygous)	Allele Frequency	OR (95% CI)	*p*
p.I200T (c.470T>C)	14 variant 544 total tests	0.026	691 variants 141,208 total alleles	0.00489	5.37 (3.14 to 9.18)	$p < 0.0001$
p.S428P (c.1283C>T)	3 variant 544 total tests	0.006	19 variants 76,097 total alleles	0.00025	22.20 (6.55 to 75.25)	$p < 0.0001$
p.T367fs (c.1100delC)	1 variant 544 total tests	0.002	131 variants 76,103 total alleles	0.00172	2.14 (0.53 to 8.65)	$p = 0.2877$
Total *CHEK2*	33 *CHEK2* 544 total tests	0.061				

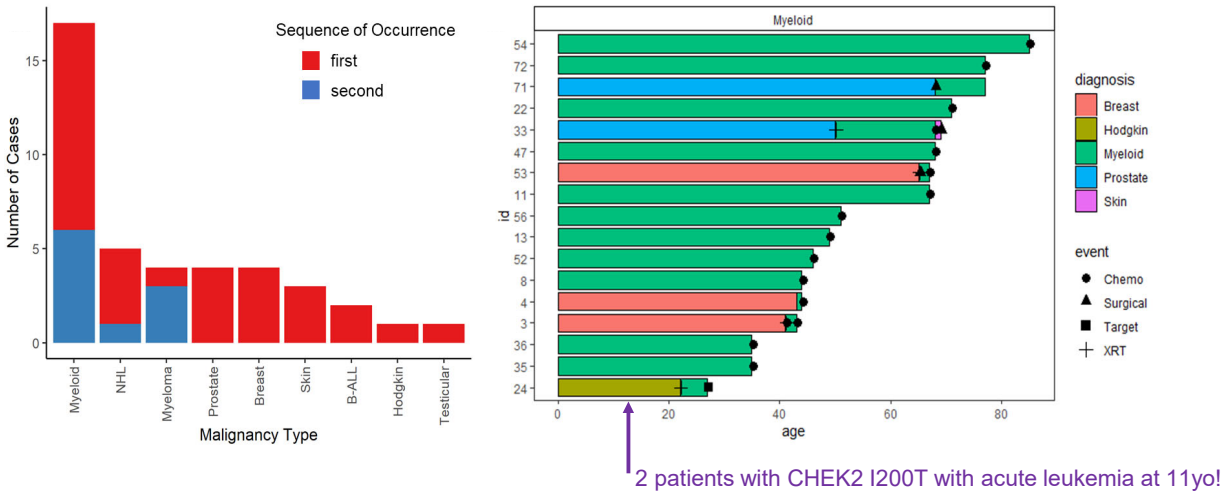
33

Germline *CHEK2* mutations and hematopoietic malignancies



34

Germline *CHEK2* mutations and hematopoietic malignancies

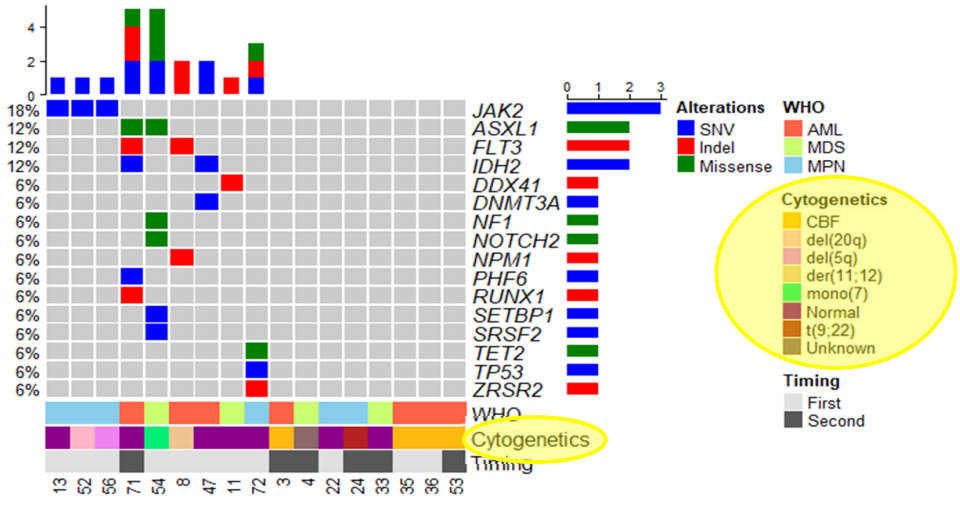


2 patients with CHEK2 I200T with acute leukemia at 11yo!

35

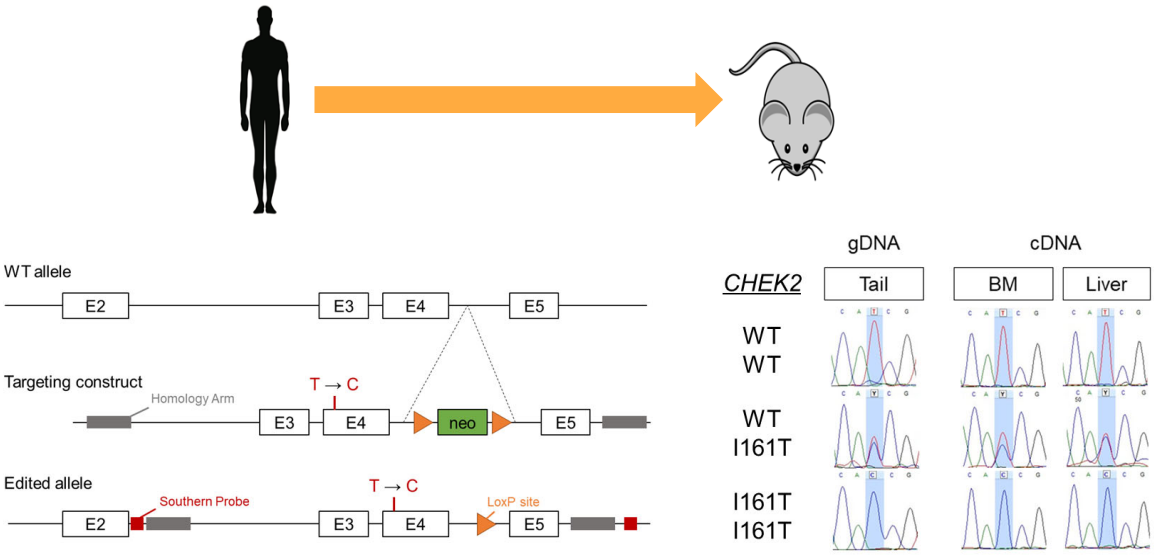
Germline *CHEK2* mutations and hematopoietic malignancies

mutational spectrum in myeloid malignancies



36

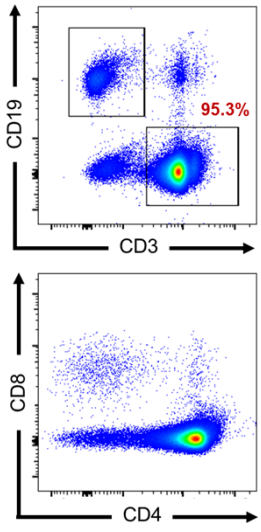
Germline *CHEK2* mutations and hematopoietic malignancies



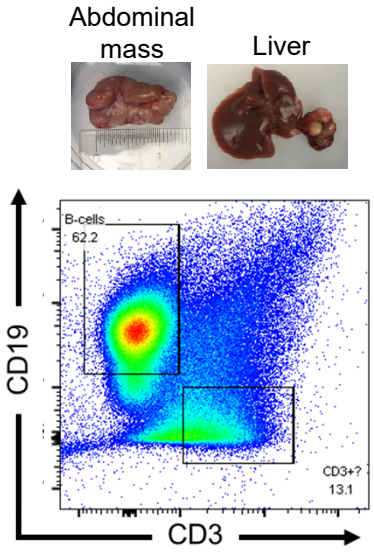
37

Germline *CHEK2* mutations and hematopoietic malignancies

T-helper cell Leukemia (18 mo)

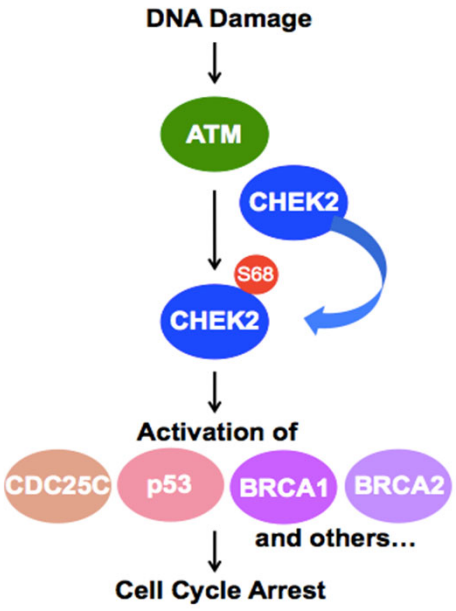


Lymphoma (24 mo)



38

The molecular impact of HR DNA repair pathway deficiencies on DNA integrity within hematopoietic cells



39

The molecular impact of HR DNA repair pathway deficiencies on DNA integrity within hematopoietic cells

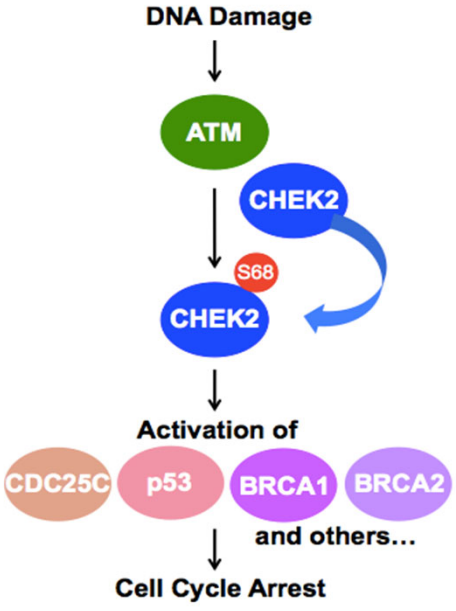


Table 2. Allele burden calculation for loss of function *BRCA1/2* variants and occurrence of primary *de novo* hematologic malignancy

Probands with P/LoF† germline *BRCA* mutations with clinical panel testing for a first HM diagnosis		P/LoF† germline BRCA variants in non-cancer gnomAD control population (v3.1.2)	Allele burden calculation		
BRCA1	7 total variants‡	112 total variants	OR: 8.61	95% CI: 4.00, 18.51	*P*<0.0001
	1074 total tests	147,895 total alleles*			
BRCA2	8 total variants	237 total variants¶	OR: 4.65	95% CI: 2.29, 9.43	*P*<0.0001
	1074 total tests	147,870 total alleles*			
Total	19 total variants				
	1074 total tests				

Abbreviations used: CI, confidence interval; LoF, loss of function; OR, odds ratio; P, pathogenic

† Pathogenicity was assessed per ClinVar deposit, conflicting reports included if majority deposits were pathogenic or likely pathogenic; if no ClinVar deposition, clear loss of function (LoF) protein damaging insertions or deletions were included

† N=1 patient excluded due to non-proband status, N=1 patient excluded as testing was initiated on a research basis

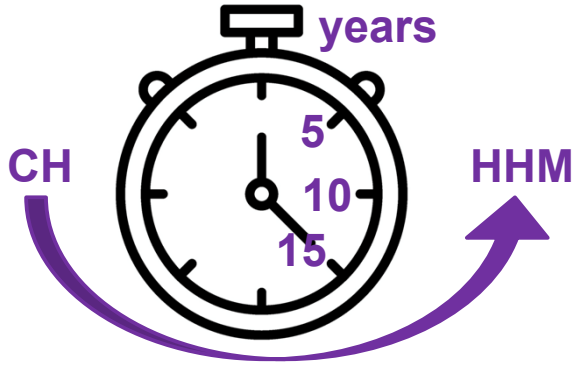
‡ Excludes the BRCA2 p.Lys3326Ter variant reported as benign in ClinVar

* Represents the average of total allele numbers reported per variant

Stubbins, R. *et al.* Germline loss of function *BRCA1* and *BRCA2* mutations and risk of *de novo* hematopoietic malignancies. *Haematologica, in press.*

40

Disease mechanisms–
Is clonal hematopoiesis a universal predictor of HHMs?



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Realizing the goal of precision medicine in oncology

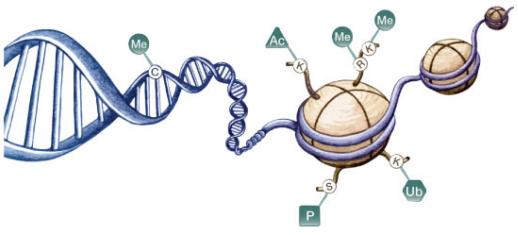
DEFINE:
Baseline genetics/epigenetics
[germline]

Acquired genetics/epigenetics in the HSC
[clonal hematopoiesis]

Acquired genetics/epigenetics in the tumor
[tumor profiling]

Microbiome/Immunotype

to devise an effective treatment strategy for a particular patient



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Clonal hematopoiesis = Somatic mosaicism within the hematopoietic system

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Clonal hematopoiesis = Somatic mosaicism within the hematopoietic system

Example: PNH = acquired mutation of the *PIGA* gene→ causes a clinical phenotype of hemolytic anemia

PNH is rare, but you detect it.
CH is common but you can't see it.

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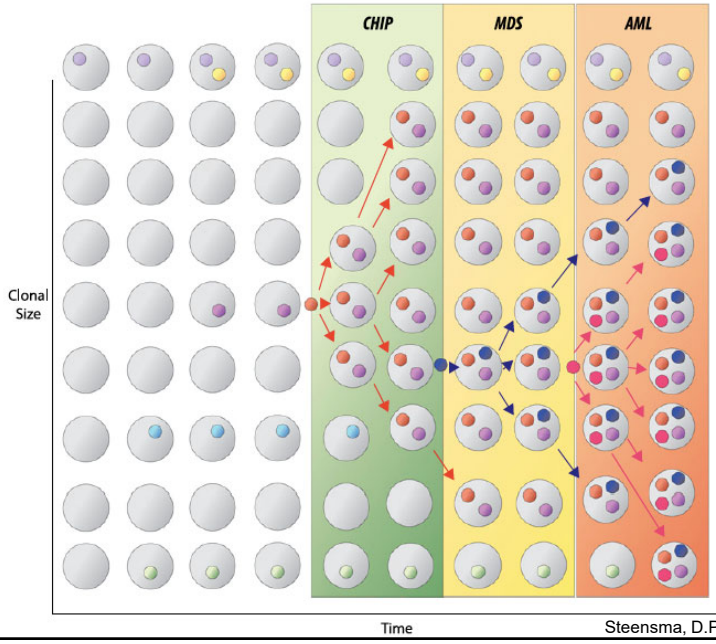
This expansion of myeloid cells is called clonal hematopoiesis



Steensma, D.P. *et al. Blood* 126: 9-16, 2015

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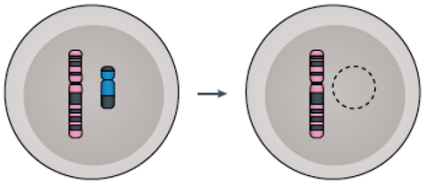
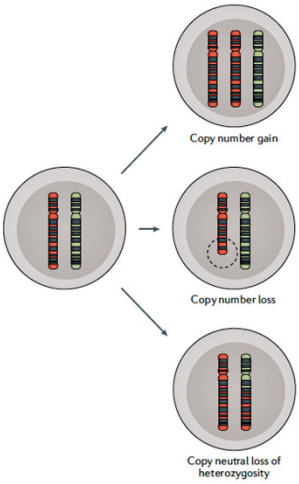
Clonal hematopoiesis is comprised of many types of genetic lesions

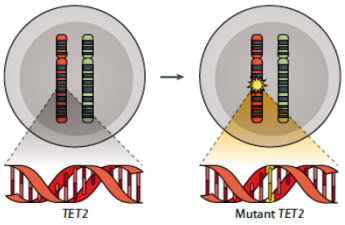
Most common:
Loss of Y-chromosome in men



Copy number gains/losses



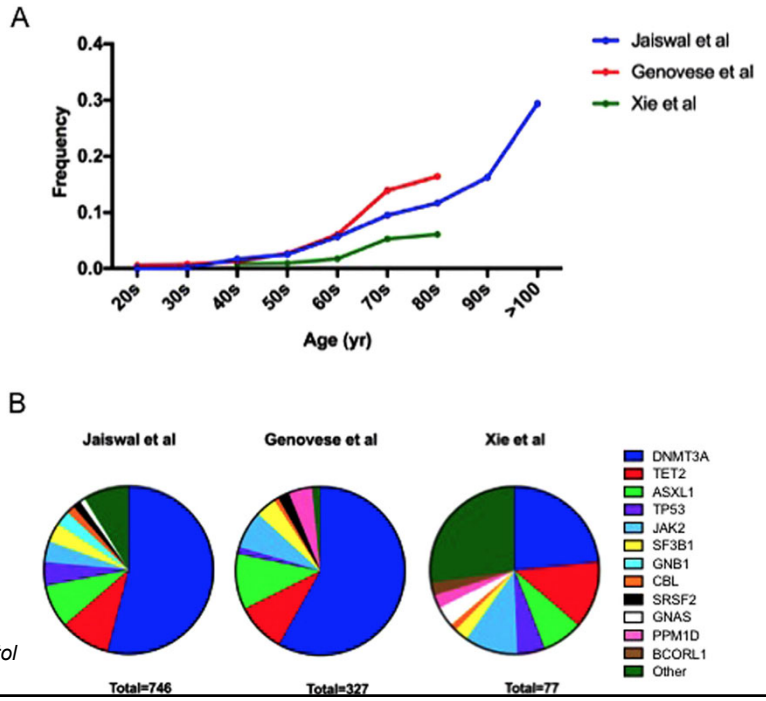
Single nucleotide variants (often 5-mC→T)



Silver, A.J., Bick, A.G., and Savona, M.R. (2021) *Nature Rev Genet* **22:** 603-617.

46

Clonal hematopoiesis is common (universal)



Jan, M. *et al.* (2017) *Sem Hematol* **54:** 43–50.

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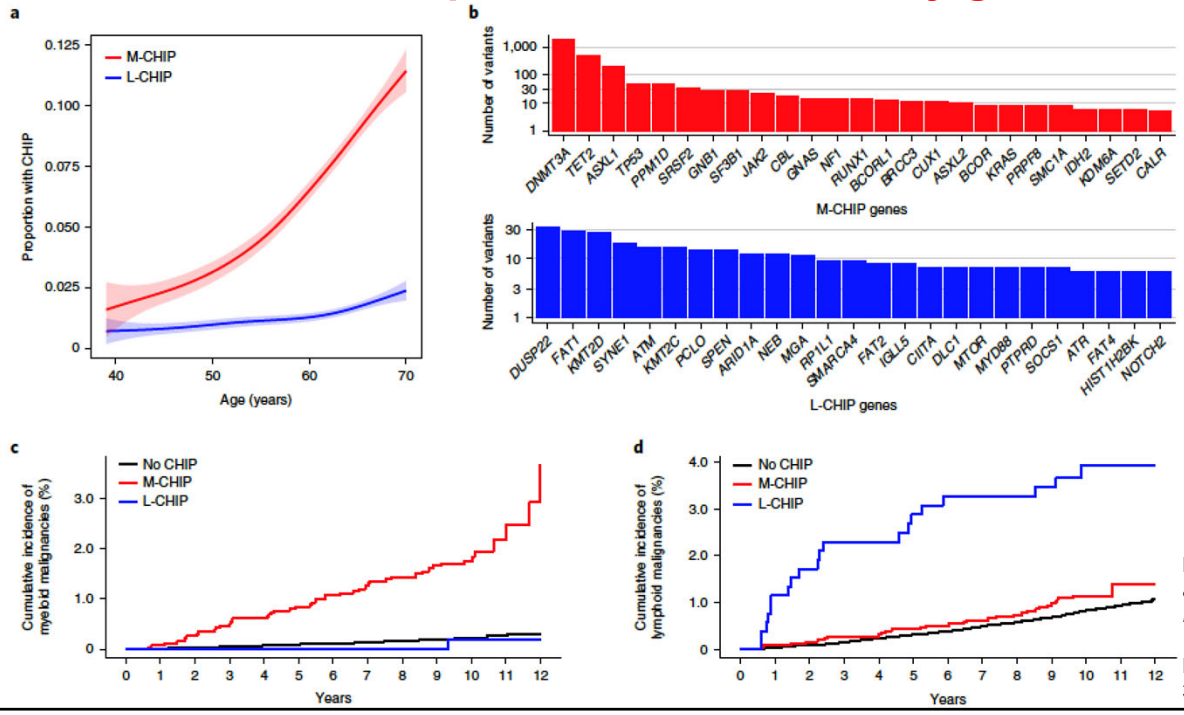
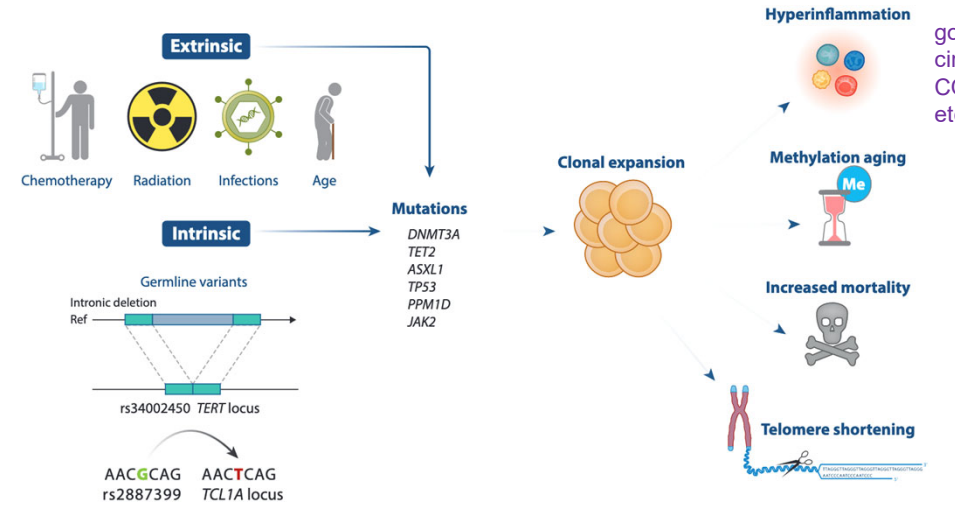
Clonal hematopoiesis occurs in many genes



Niroula A *et al.* (2021) *Nat Med.* **27** 1921-1927. PMID: 34663986

48

Clonal hematopoiesis is a risk factor for many diseases



gout
cirrhosis
COPD
etc.

Figure 1

Extrinsic and intrinsic risk factors synergize with somatic mutations in CHIP driver genes to facilitate clonal expansion, leading to pathological aging outcomes such as hyperinflammation and increased mortality.

Ahmad, H., Jahn, N., and Jaiswal, S.. (2023) *Annu. Rev. Med. 2023. 74:249–60*

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Clonal hematopoiesis is a risk factor for many diseases

Table 1 CHIP has a systemic effect on aging that increases the risk of diseases ranging from cancer to heart disease even in otherwise healthy individuals

Disease/condition	Associations with CHIP	References
Hematological malignancies	Approximately three- to tenfold increased risk of myeloid neoplasia, though the risk varies considerably with driver mutations and size of the clone Modest increase in risk of lymphoid malignancy. Features of CHIP that confer a higher risk of transformation include mutations in *TP53*, *SF3B1*, *SRSF2*, *U2AF1*, VAF >10%, presence of multiple mutations, and coexistence of mosaic chromosomal alterations	1, 5, 12, 15–17, 25, 26, 78
Solid tumors	Increased prevalence of clones with mutations in DNA damage response genes (*TP53*, *PPM1D*) in patients with exposure to cytotoxic vaccine Associated with risk of progression, recurrence, and all-cause mortality in those with solid tumors	17–19
CAD	1.1–2-fold increased risk of incident CAD in human observational studies. Risk is greater in those with VAF >10%	1, 22, 24, 25
Ischemic heart failure	*DNMT3A* and *TET2* mutations associated with worsened survival and increased hospitalization due to ischemic HF	32, 33
Stroke	1.1–2-fold increased risk of hemorrhagic and ischemic stroke. Mutations in *TET2* show the strongest association	1, 23
Methylation aging	Increased epigenetic age acceleration as measured by multiple methylation clocks Patients with CHIP and age acceleration have the greatest risk of mortality and CAD, while patients with CHIP and no acceleration have no increased risk of mortality and CAD	69, 70
Other aging diseases	1.6-fold increased risk of COPD 1.4-fold increased risk of osteoporosis 35% decreased risk of Alzheimer's dementia	38–40

Abbreviations: CAD, coronary artery disease; CHIP, clonal hematopoiesis of indeterminate potential; COPD, chronic obstructive pulmonary disease; HF, heart failure; VAF, variant allele fraction.

Ahmad, H., Jahn, N., and Jaiswal, S.. (2023) *Annu. Rev. Med. 2023. 74:249–60*

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Clonal hematopoiesis is a risk factor for many diseases

Table 1 CHIP has a systemic effect on aging that increases the risk of diseases ranging from cancer to heart disease even in otherwise healthy individuals

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Ahmad, H., Jahn, N., and Jaiswal, S.. (2023) *Annu. Rev. Med. 2023. 74:249–60*

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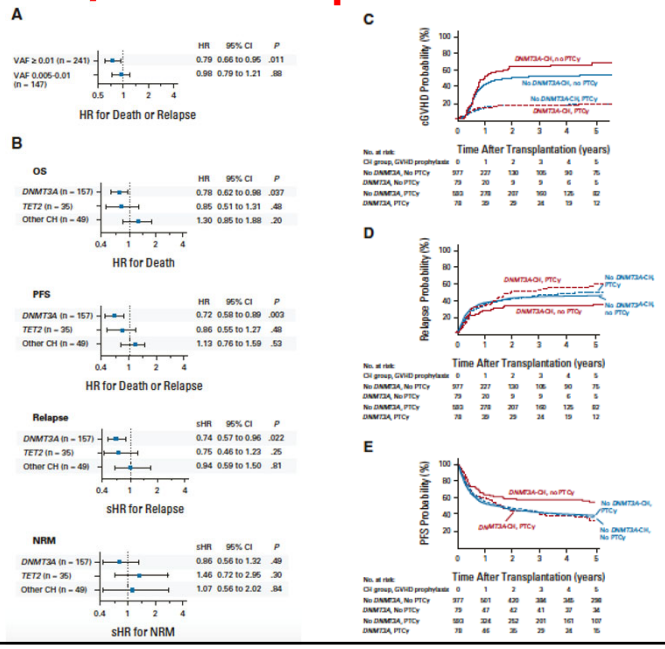
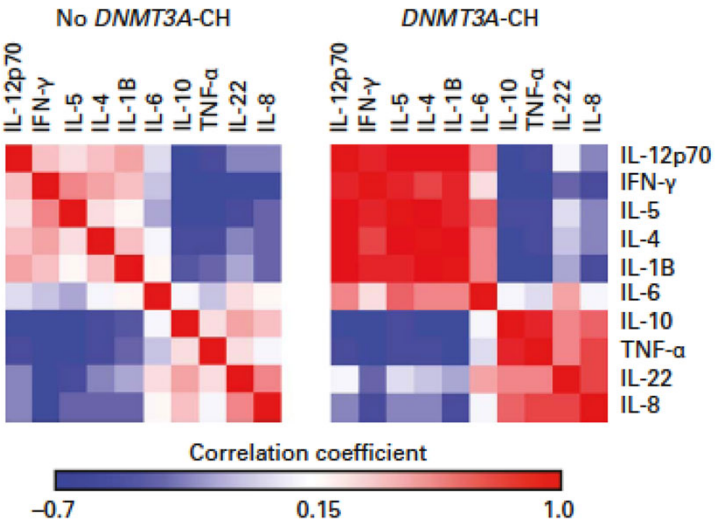
Clonal hematopoiesis in donor hematopoietic stem cells impacts transplant outcomes



Gibson CJ *et al.* (2022) *J Clin Oncol.* **40:**189-201. PMID: 34793200

52

Clonal hematopoiesis in donor hematopoietic stem cells impacts transplant outcomes



Gibson CJ *et al.* (2022) *J Clin Oncol.* **40:**189-201. PMID: 34793200

53

Clinical trials now aim to slow the progression from clonal hematopoiesis to myeloid malignancies

Trial Name	Trial Title	Population	Intervention	Phase	Location	Trial Status
NCT 03418038	Ascorbic Acid for the Treatment of CCUS	*TET2* mutant-CCUS	High dose of ascorbic acid 1g/kg 3 times a week for 12 weeks	2	US single center [Mayo Clinic]	Recruiting
NCT 03682029	Epigenetics, Oral Vitamin C, and Abnormal Blood Cell Formation - Vitamin C in CCUS and LR MDS	CCUS, CMML, and Low-Risk MDS	Vitamin C 1000 mg daily versus placebo for 12 months	2	Denmark multi-center	Recruiting
NCT 05102370	A Study of Enasidenib in People with CCUS and Mutations in IDH2	*IDH2*-mutant CCUS	Enasidenib 100 mg daily for 18 months	1	US multi-center	Recruiting
NCT 04741945	Repurposing Metformin as a Leukemia-preventive Drug in CCUS and LR-MDS	CCUS and LR-MDS	Metformin 2000 mg daily for 12 months	2	Denmark multi-center	Recruiting
NCT 05030441	Ivosidenib for Patients with CCUS and Mutations in IDH1	*IDH1*-mutant CCUS	Ivosidenib 500 mg daily for 17 months	2	US multi-center	Recruiting
NCT 05483010	Statins in Patients With CCUS and MDS	CCUS and MDS	CCUS: Atorvastatin starting at 80 mg daily for 12 months MDS: Rosuvastatin 40 mg daily for 12 months	2	US single center [Washington University]	Not yet recruiting Estimated start date: 10/31/2022
Canakinumab	Canakinumab in CCUS	high risk CCUS	Canakinumab q2m for 2 years	2	US multi-center	Not yet recruiting

Abbreviations used: CCUS, clonal cytopenia of undetermined significance; CMML, chronic myelomonocytic leukemia; LR, low risk; MDS, myelodysplastic syndrome

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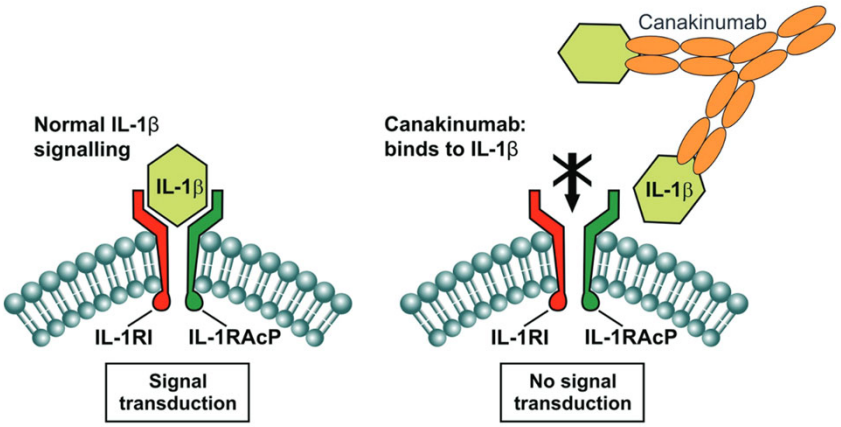
Inflammation modification by canakinumab to prevent leukemic progression of Clonal Cytopenias of Unknown Significance

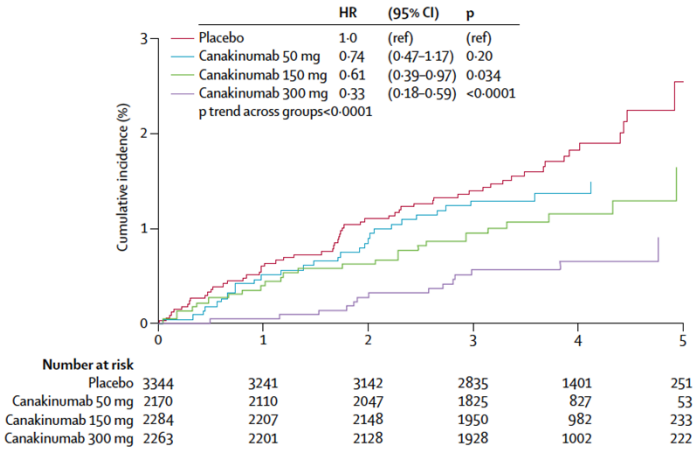
PI: Uma Borate, OSU

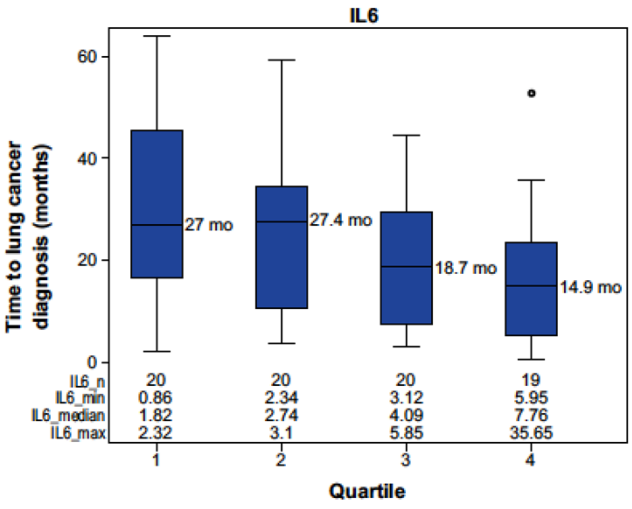


Kuemmerle-Deschner, JB and Haug, I (2013) *Ther Adv Musculoskel Dis* **5:** 315–329

55

Canakinumab to prevent lung cancer





Ridker, PM *et al.* (2017) *Lancet* **390:** 1833-1842. PMID: 28855077

Wong, CC *et al.* (2020) *Cancer Res* **80:** 5597-5605. PMID: 33023946

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Somatic mosaicism within the hematopoietic system is more common than we were taught

57

Clonal hematopoiesis = Somatic mosaicism within the hematopoietic system

Example 1: PNH = acquired mutation of the *PIGA* gene→ causes a clinical phenotype of hemolytic anemia

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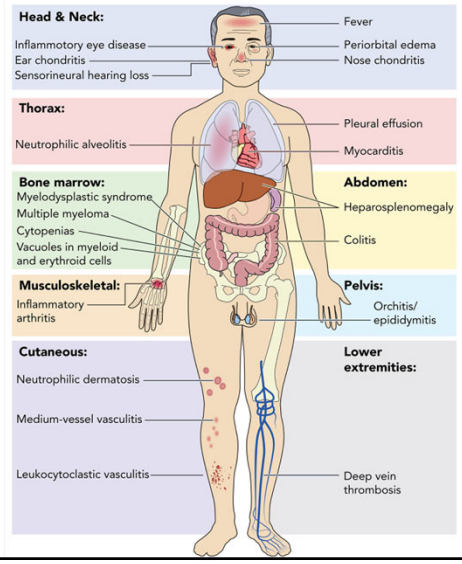
Clonal hematopoiesis = Somatic mosaicism within the hematopoietic system

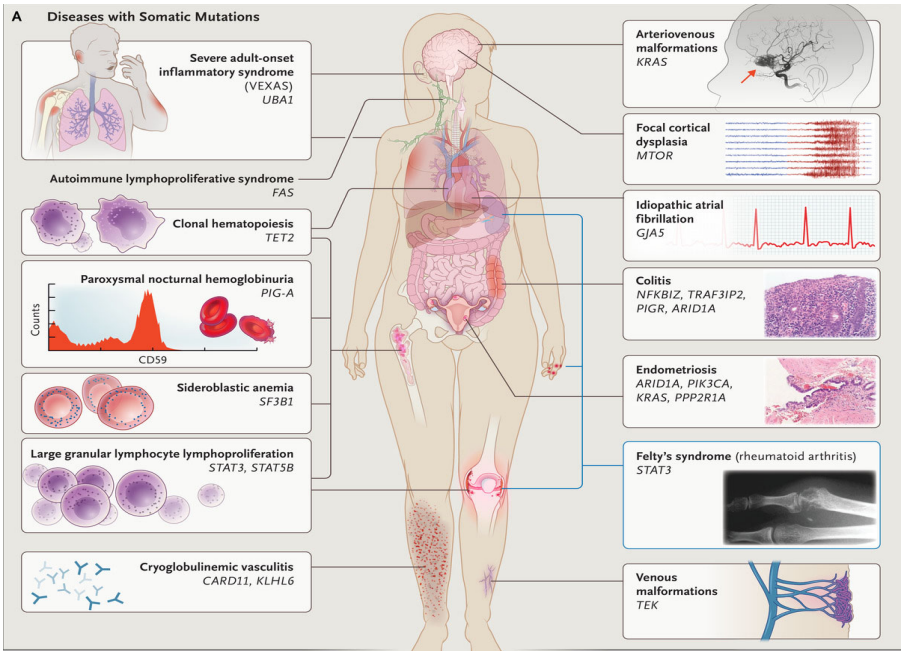
Example 2: VEXUS syndrome = acquired mutation of the *UBA1* gene within myeloid and erythroid cells→ causes many phenotypes



Grayson, PC, Patel, BA, and Young, NS (2021) **137:** 3591-3594. PMID: 33971000

59

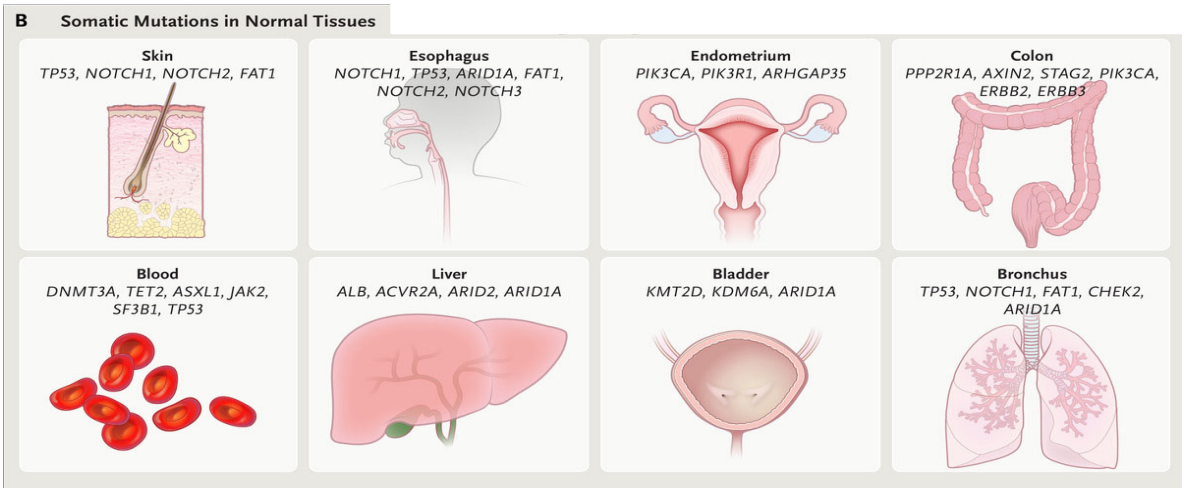
Somatic mosaicism occurs everywhere and causes disease



Mustjoki, S and Young, NS (2021) *N Engl J Med* **384:** 2039-2052. PMID: 34042390

60

Somatic mosaicism occurs everywhere



Mustjoki, S and Young, NS (2021) *N Engl J Med* **384:** 2039-2052. PMID: 34042390

61

Realizing the goal of precision medicine in oncology

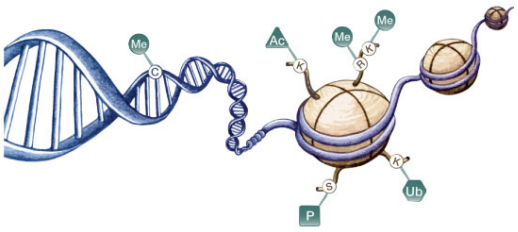
DEFINE:
Baseline genetics/epigenetics
[germline]

Acquired genetics/epigenetics in the HSC
[clonal hematopoiesis]

Acquired genetics/epigenetics in the tumor
[tumor profiling]

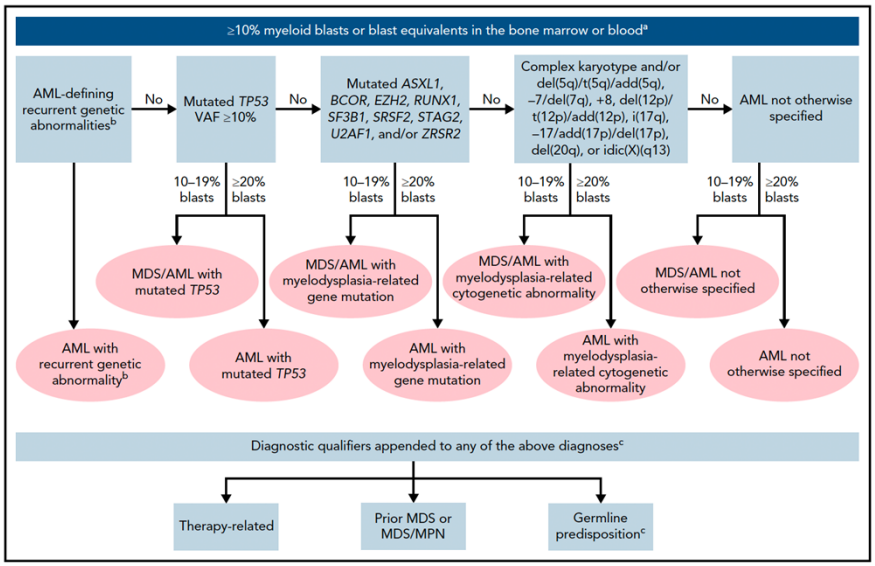
Microbiome/Immunotype

to devise an effective treatment strategy for a particular patient



62

Molecular profiling informs diagnosis



Döhner, H. *et al. Blood* Blood 140: 1345-1377 (2022)

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Molecular profiling informs diagnosis

Table 1. AML and related neoplasms and acute leukemias of ambiguous lineage

AML and related neoplams	
AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)* • APL with t(15;17)(q24.1;q21.2)/*PML::RARA*† • AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*‡ • AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214* • AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*§ • AML with other rare recurring translocations‖ • AML with mutated *NPM1* • AML with in-frame bZIP mutated *CEBPA*¶ • AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1**	**Myeloid sarcoma** **Acute leukemia of ambiguous lineage** • Acute undifferentiated leukemia • MPAL with t(9;22)(q34.1;q11.2)/*BCR::ABL1* • MPAL with t(v;11q23.3)/*KMT2A*-rearranged • MPAL, B/myeloid, not otherwise specified • MPAL, T/myeloid, not otherwise specified
Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB) • AML with mutated *TP53*# • AML with myelodysplasia-related gene mutations Defined by mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2* • AML with myelodysplasia-related cytogenetic abnormalities** • AML not otherwise specified	**Myeloid proliferations related to Down syndrome** • Transient abnormal myelopoiesis associated with Down syndrome • Myeloid leukemia associated with Down syndrome **Blastic plasmacytoid dendritic cell neoplasm**
Diagnostic qualifiers†† Therapy-related‡‡ • Prior chemotherapy, radiotherapy, immune interventions Progressed from MDS • MDS should be confirmed by standard diagnostics and >3 mo prior to AML diagnosis Progressed from MDS/MPN (specify type) • MDS/MPN should be confirmed by standard diagnostics and >3 mo prior to AML diagnosis Germline predisposition (specify type)	

Döhner, H. *et al. Blood* Blood 140: 1345-1377 (2022)

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Molecular profiling informs clinical decisions

Table 2. Gene mutations in myeloid neoplasms and leukemia indicated for clinical testing

Indication	Single gene mutations	Structural variants*
MDS, MDS/MPN, cytopenia	*ASXL1, BCOR, BCORL1, CBL, CEBPA, CSF3R, DDX41, DMNT3A, ETV6, ETNK1, EZH2, FLT3-ITD, FLT3-TKD, GATA2, GNB1, IDH1, IDH2, JAK2, KIT, KRAS, KMT2A-PTD, NF1, NPM1, NRAS, PHF6, PPM1D, PRPF8, PTPN11, RAD21, RUNX1, SAMD9†, SAMD9L†, SETBP1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, UBA1, WT1, ZRSR2*	
MPN and mastocytosis‡	*ASXL1, CALR, CBL, CSF3R, DNMT3A, EZH2, IDH1, IDH2 JAK2§, KIT, KRAS, MPL, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SH2B3, SRSF2, TET2, U2AF1, ZRSR2*	*BCR::ABL1§*
Eosinophilia	*ASXL1, CBL, DNMT3A, EZH2, KRAS, NRAS, RUNX1, SF3B1, SRSF2, STAT5B, TET2, U2AF1*	*BCR::ABL1§, FGFR1::R, FLT3::R, JAK2::R, PDGFRA::R, PDGFRB::R*
AML	**Genes required for diagnosis and risk stratification:** *ASXL1, BCOR, CEBPA, DDX41, EZH2, FLT3-ITD§, FLT3-TKD§, IDH1§, IDH2§, NPM1, RUNX1, SF3B1, SRSF2, STAG2, TP53, U2AF1, ZRSR2* **Additional genes recommended to test for at diagnosis and for use in disease monitoring:** *ANKRD26, BCORL1, BRAF, CBL, CSF3R, DNMT3A, ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPM1D, PTPN11, RAD21, SETBP1, TET2, WT1*	*BCR::ABL1§, CBFB::MYH11, DEK::NUP214 MECOM::R, KMT2A::R, NUP98::R, RUNX1::RUNX1T1, PML::RARA§*
B-ALL	*CREBBP, CRLF2, FLT3, IDH1, IDH2, IKZF1, IL7R, JAK1, JAK2, JAK3, KMT2D, KRAS, NF1, NRAS, PAX5, PTPN11, SETD2, SH2B3, TP53*	*ABL1::R§, ABL2::R, CRLF2::R, CSF1R::R, DUX4::R, EPOR::R, ETV6::R, JAK2::R, KMT2A::R, MEF2D::R, NUTM1::R, PAX5::R, PDGFRA::R, PDGFRB::R, TCF3::R, ZNF384::R*
T-ALL	*DNMT3A, ETV6, EZH2, FBXW7, FLT3, IDH1, IDH2, IL7R, JAK1, JAK3, KRAS, MSH2, NOTCH1, NRAS, PHF6, PTEN, U2AF1, WT1*	*BCL11B::R, LMO2::R, MYB::R, NUP::ABL1, NUP214::R, STIL::R, TAL::R, TLX1::R, TLX3::R*

*Conventional karyotype should be performed on all cases at diagnosis. Specific FISH, RT-PCR, or gene fusion NGS assays (targeted DNA/RNA or WGS) may be included depending on clinical context and results of other clinical studies.

†Pediatric patients.

‡Mast cell disease with suspicion of associated hematologic neoplasm.

§Food and Drug Administration–approved targeted therapy.

Duncavage, E.J. *et al. Blood* 140: 2228-2247 (2022)

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LEUKEMIA & LYMPHOMA SOCIETY*

2017 FDA APPROVALS FOR BLOOD CANCERS

CAR T-Cell Immunotherapy	Acute Myeloid Leukemia	Chronic Myeloid Leukemia	Lymphoma and Hodgkin Lymphoma	Acute Lymphoblastic Leukemia	Graft vs. Host Disease	Erdheim-Chester Disease
tisagenlecleucel* (Kymriah) for acute lymphoblastic leukemia	**midostaurin*** (Rydapt)	**bosutinib†** (Bosulif)	**acalabrutinib*** (Calquence)	**inotuzumab ozogamicin*** (Besponsa)	**ibrutinib†** (Ibruvica)	**vemurafenib†** (Zelboraf)
axicabtagene ciloleucel* (Yescarta) for non-Hodgkin lymphoma	**enasidenib*** (Idhifa)	**dasatinib†** (Sprycel)	**copanlisib*** (Aliqopa)	**blinatumomab†** (Blincyto)		
	daunorubicin and cytarabine† (Vyxeos)		**pembrolizumab†** (Keytruda)			
	gemtuzumab ozogamicin† (Mylotarg)		**rituximab hyaluronidase†** (Rituxan Hycela)			
			brentoximab vedotin† (Adcetris)			
			obinutuzumab† (Gazyva)			

venetoclax
ivosedenib
glasdegib
gilteritinib

Blastic plasmacytoid dendritic cell tumor: tagraxofusp

Multiple myeloma: daratumumab
carfilzomib
elotuzumab

duvelisib

Hairy cell leukemia: moxetumomab

*funded by The Leukemia & Lymphoma Society
†either a new indication or a reformulation of older therapies
*new therapy

66

Realizing the goal of precision medicine in oncology

DEFINE:
Baseline genetics/epigenetics
[germline]

Acquired genetics/epigenetics in the HSC
[clonal hematopoiesis]

Acquired genetics/epigenetics in the tumor
[tumor profiling]

Microbiome/Immunotype

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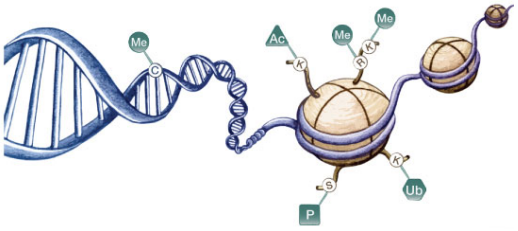

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Molecular profiling informs clinical decisions

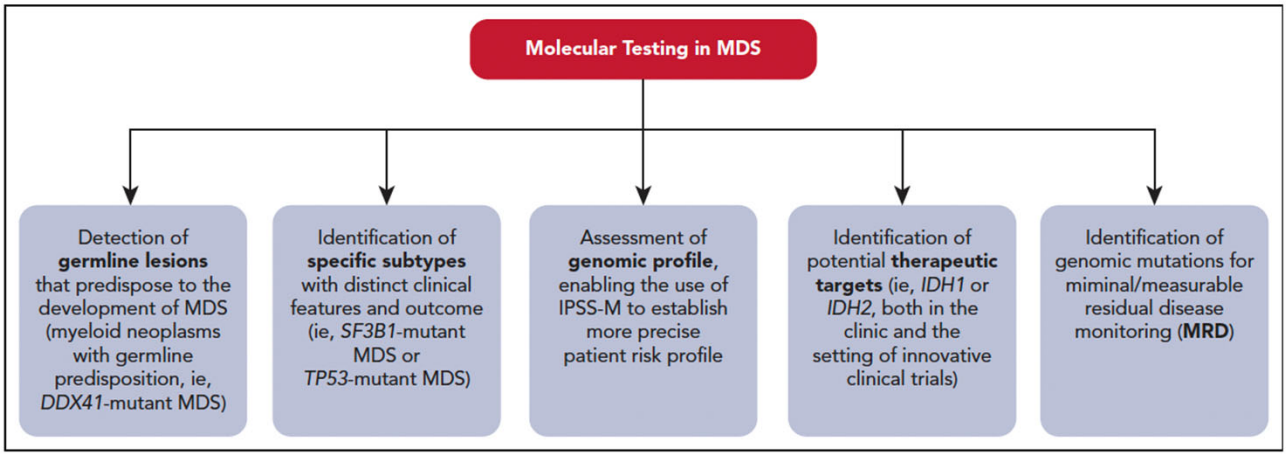

Figure 1. How molecular profiling can inform clinical decision making in MDS. IPSS-M, Molecular International Prognostic Scoring System; MDS, myelodysplastic syndrome; MRD, minimal/measurable residual disease. Professional illustration by Patrick Lane, ScEYEnce Studios.

Duncavage, E.J. *et al. Blood* 140: 2228-2247 (2022)

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Healthcare Solutions
Delivering solutions that put people first.
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DIFFICULTY WITH COMPLEX DRUG AND HIGHLY COMPLEX BIOLOGIC AGENT ADMINISTRATION CODING

American Society of Hematology (ASH)
June 2023
Janet I. Lawrence, MD CMD and Lawrence Clark, MD CMD

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

1

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- Noridian Medicare website
- CMS website

2

AGENDA

- Background
- Codes
- Confusion
- Discussion

3

ADMINISTRATION CODES

- CPT codes 96401-96549 are used to report the parenteral administration of non-radionuclide anti-neoplastic drugs and anti-neoplastic drugs used for non cancer diagnoses as well as for substances such as monoclonal antibodies and other biologic response modulators.
- CPT codes 96365 – 96379 are used to report the parenteral administration of medications (e.g., antibiotics, steroids, antiemetics, narcotics, analgesics)

4

CODING HISTORY

- When these codes were initially developed by CPT, they were used to describe drugs used in the treatment of cancers that required significant additional physician and staff work during administration and/or additional equipment and preparation prior to administration or after for safe handling and disposal.
- These drugs began to used for other nonchemotherapeutic indications and newer classes of drugs or drugs that could be used for similar indications or biosimilars were developed that did not have the associated safety issues as the original drugs did during administration.
- If these drugs were from the same class or biosimilars providers billed for them using the same codes that were originally intended to allow for the additional work and cost associated with the original class even though they did not require the additional work or special handling during administration.

5

CODING GUIDANCE

- The Contractor Medical Directors attempted to provide correct billing and coding guidance with articles that provided instructions as to what drugs required the additional work (frequent monitoring or infusion rate changes during administration, close monitoring with physician or NPP ready to respond to serious reactions during infusion or the need for special preparation and handling of the substance itself)
  - Unfortunately, these instructions were not well received.
- As the variability of reactions, monitoring and risk varies between substances in the same class, the administration instructions were provided based on the risk and work during administration and the peri-administrative period and not those that may occur a day, a week, or longer after administration.

6

SUBSTANCE BILLING

- The work of the handling and administration of these substances should reflect the actual work required and should not be billed just because the drug family has a member that may require the additional handling.
- Also, the correct billing and coding should reflect the work involved in the administration of the substance rather than the diagnosis for which it is prescribed.
- The Contractor medical Directors are attempting to address and clarify how the codes are billed both through CPT which created and "owns" the codes as well as through the AMA RUC which determines and recommends the appropriate billing based on the work, PE and liability associated with the use of these substances.

7

CPT EDITIORIAL PANEL INFORMATION

- The CMD's brought these concerns to both the CPT Editorial panel as well and the AMA RUC to assist with clarifying when Complex drug admin codes should be used verses regular drug infusion codes
- We are presently awaiting a potential CPT Editorial article or vignette to describe the types of drugs that would be expected to be billed using the complex codes.
- This coding would be based on the drug and its safety profile and would be the same regardless of the indication or specialty administering them

8

REFERENCE

- AMA CPT Professional Edition 2023

9

THANK YOU, DR. LAWRENCE

"for this interesting consult"

A response from the other side of the house

10

WHAT DO MACS HAVE TO DO WITH AMA CPT?

- A/B MACs may provide additional guidance as to which drugs may be considered to be chemotherapy drugs under Medicare
- Medicare Claims Processing Manual, Chapter 12, Section 30.5

11

ALSO FROM CHAPTER 12

- Types of injections and infusions
  1) Hydration
  2) Therapeutic, prophylactic and diagnostic injections (just remember T,P,D!)
  3) Chemotherapy administration (if you can define this, you win a prize)

12

BOTH SIDES OF THE HOUSE

- As the CMD rep to AMA CPT Assistant, there is no escape for me
- There needs to be transparent, inclusive, processes in the coding, valuation, and coverage of these services
- As you have seen, parallel processes must move forward in the AMA, on both sides (the valuation and coding process) with CMS and its contractors in the guidance process that was mentioned
- Dr. Lawrence and I will try to summarize these processes and answer your questions as best we can. Thanks for your attention.

Medicare Policy Development Process

Meredith Loveless, MD, FACOG | Chief Medical Officer |
CGS Administrators | A/B MAC Jurisdiction 15

June 23, 2023

1

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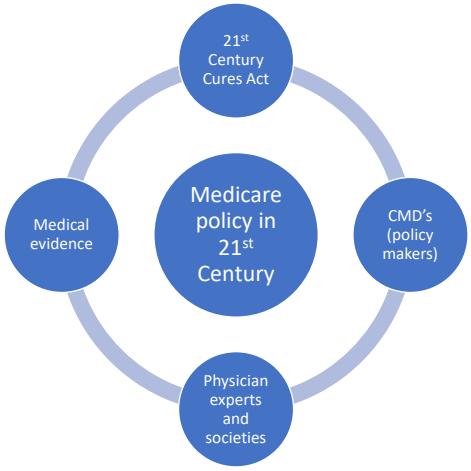
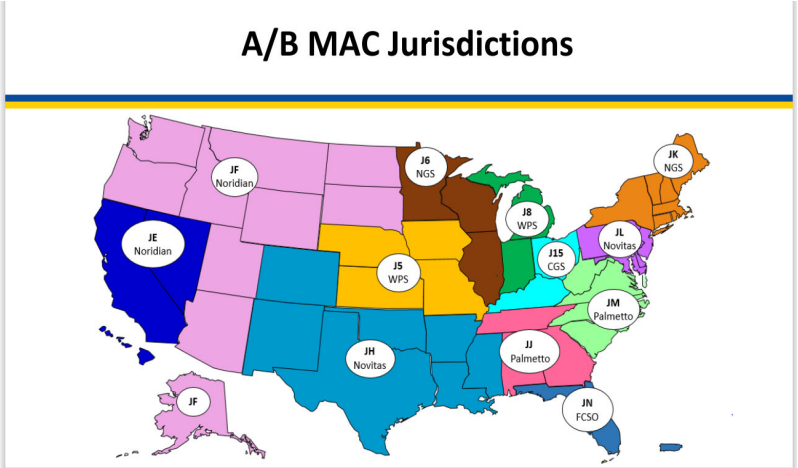
2

Medicare Policy in 21st Century



3

Medicare Administrative Contractors (MACs)



4

Local Coverage Decisions (LCDs)

- LCDs are “local” Medicare Coverage Decisions created by Medicare Contractors in the absence of specific statute, regulation, or national coverage (NCD), or as an adjunct to national coverage.
- LCD defines if a service is covered AND under what specific clinical circumstances a service is “reasonable and necessary.”
- Historically, much quicker process than NCDs
- Services must be ‘R & N’ even in the absence of NCD or LCD for Medicare coverage (SSA 1862(a)(1)(A)).

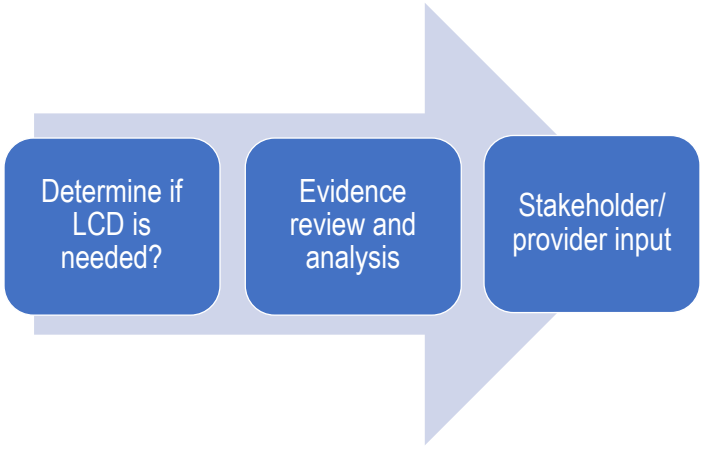
LCD vs. NCD

- LCD – Local Coverage Determination made by the MAC for the jurisdiction
  - May vary between jurisdictions
  - Time to development ranges (6 months to 2 years)
  - Based on clinical evidence
  - Changes at MAC discretion
- NCD – National Coverage Determination made by CMS
  - The same for all jurisdictions
  - Can take years to develop
  - Based on clinical evidence
  - Changes at CMS discretion

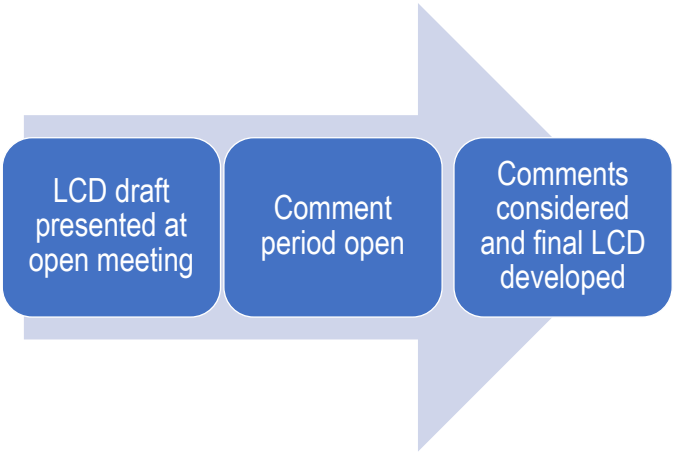
Medically Reasonable and Necessary?

- Safe and effective;
- Not experimental or investigational; and
- Appropriate, including the duration and frequency in terms of whether the service or item is:
  - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the beneficiary's condition or to improve the function of a malformed body member;
  - Furnished in a setting appropriate to the beneficiary's medical needs and condition;
  - Ordered and furnished by qualified personnel; and
  - One that meets, but does not exceed, the beneficiary's medical need.

Lifecycle of LCD



Lifecycle of LCD



LCD Development Process

LCDs will be developed, in keeping with CMS directives:

- A validated widespread problem; (Data, MR, CERT findings);
- A significant risk to the Medicare trust fund (high dollar and/or high-volume services);
- Assuring beneficiary access to care;
- Frequent denials issued or anticipated;
- Multi-state contractor creating uniform LCDs across its jurisdiction.

Multi-MAC Contractor Advisory Meeting

LCDs will be developed, in keeping with CMS directives:

- National experts;
- Geographical representation;
- Academic and clinical practice;
- Various specialties that perform or involved in the procedure;
- Evidence-based review.

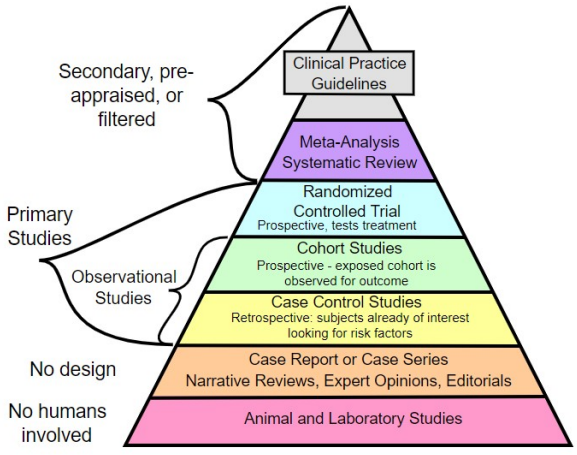
Multi-MAC Contractor Advisory Meeting

- Selecting literature
- Developing questions
- Holding the meeting
- Transparency through the process

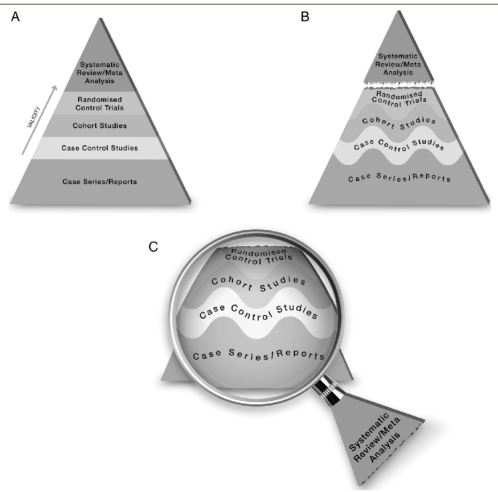
Policy Development

- Evidence review
- CAC input
- Definitions
- Determining coverage criteria
- Rationale

Evidence Review



Updated Hierarchy of Study Design



Determining Coverage

Is the service medically reasonable and necessary?

How is the proper diagnosis made?

Is the treatment supported by evidence to be effective?

What is the acceptable standards of care for this condition?

What is the risk and benefits?

What are the alternatives?

Is it experimental/investigational?

Has this been investigated in Medicare population?

New Policy Roll-Out

- Response to Comments
- Billing and Coding Article
- Education

Update Coverage Decisions to Keep Pace with New Technology

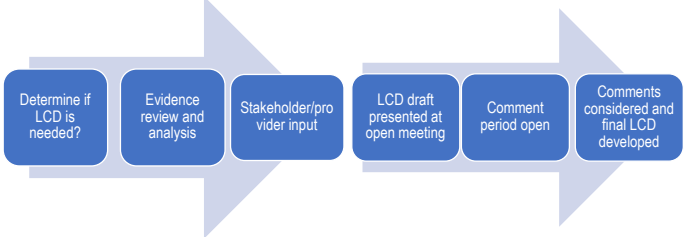
- Informal Meeting – Informal discussion that can help determine best approach for that service.
- If existing policy is in place – LCD reconsideration.
- If no policy in place – LCD request.
- In some cases, education of MACs to help guide case-to-case review is beneficial.
- In all cases peer reviewed supporting literature is critical to process.

Articles: What is What?

- Billing and Coding Article – linked to an LCD to explain how to code for the services in LCD.
- Educational Articles – to provide education.
- Response to Comment Articles – responses to all comments received through the open comment.
- Medical Policy Article "Local Coverage Article" – explains a service that is defined by Medicare and not related to LCD (example Self-Administered Drug Article.)
- In all cases articles do not determine coverage which can only be done through LCD, NCD or rule making.

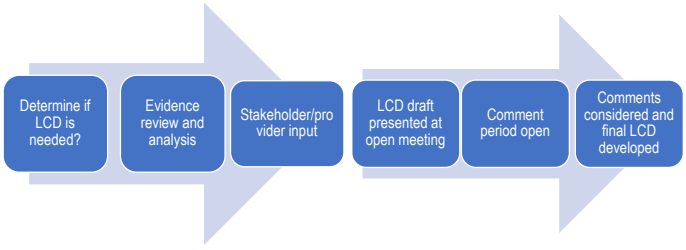
Top 10 Ways Providers Can Engage in the Policy Development Process

1. LCD request/reconsiderations.
2. Research! Producing high quality literature to answer questions in evidence-based way.
3. Sharing pertinent literature with your MAC.
4. Serving as CAC member or as subject matter expert.



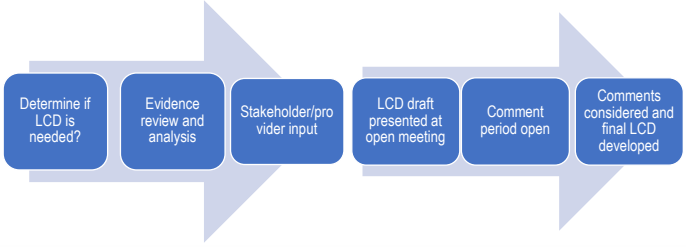
Top 10 Ways Providers Can Engage in the Policy Development Process

5. Participating in societies/ providing input for societies.
6. Societies/panels to produce evidence-based guidelines – encourage use of GRADE or systematic evidence review process.
7. Present at open meetings or submit comments if concerns – back it up with evidence.



Top 10 Ways Providers Can Engage in the Policy Development Process

8. Full disclosure of potential bias.
9. Understand that we are fulfilling requirements determined by law when we follow the policy process.
10. Participate in education.



National Coverage Analysis (NCA) | Tracking Sheet

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS)

CAG-00415R

Submit Public Comment

Issue

Stem cell transplantation is a process that includes mobilization, harvesting, and transplant of stem cells and the administration of high dose chemotherapy and/or radiotherapy prior to the actual transplant. During hematopoietic stem cell transplantation (HSCT), stem cells are harvested from a related or unrelated donor (allogeneic) and subsequently administered by intravenous infusion to the patient.

Myelodysplastic Syndromes (MDS) are a heterogeneous group of hematologic disorders characterized by (1) cytopenia due to bone marrow failure and (2) the potential development of acute myeloid leukemia (AML). In MDS, groups of clonal stem cell disorders are observed, characterized by low blood cell counts, abnormal blood cell development, genetic markers, hypercellular bone marrow, cytopenias, mutations and dysplastic cells.

Currently, CMS has a National Coverage Determination (NCD 110.23) covering allogeneic HSCT for the treatment of leukemia, leukemia in remission, or aplastic anemia; for the treatment of severe combined immunodeficiency disease (SCID); for the treatment of Wiskott-Aldrich syndrome; and for the treatment of MDS only for beneficiaries participating in a Medicare-approved, prospective clinical study through Coverage with Evidence Development (CED).

CMS received a complete, formal request to reconsider the NCD, specifically coverage of allogeneic HSCT for beneficiaires with MDS. This NCA will align with the scope of the request which is for coverage of allogeneic HSCT for beneficiaries with MDS absent a CED requirement. CMS is not reconsidering any other section of the NCD.

CMS is soliciting public comment relevant to the request. We are particularly interested in comments that include scientific evidence and that address the breadth of the request. We are also interested in aspects of health disparities and health equity that should be considered in the review.

National Coverage Determinations

NCD for Stem Cell Transplantation (Formerly 110.8.1) (110.23)

Benefit Category

Incident to a physician's professional Service
Inpatient Hospital Services

Requestor Information

Requestor Name	Requestor Letter
The American Society of Hematology (ASH), the American Society for Transplantation and Cellular Therapy (ASTCT), the National Marrow Donor Program (NMDP), and the Center for International Blood and Marrow Transplant Research (CIBMTR)	View Letter

Important Dates

Formal Request Accepted and Review Initiated
06/07/2023

Expected NCA Completion Date
03/06/2024

Public Comment Period
06/07/2023 - 07/07/2023

Proposed Decision Memo Due Date
12/07/2023

Comments for this NCA
View Public Comments

Contacts

Lead Analysts
Kimberly Long
kimberly.long@cms.hhs.gov
410-786-5702

Lead Medical Officers
James Rollins M.D.

Actions Taken

June 7, 2023

CMS initiates this national coverage analysis for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS). The 30-day public comment period begins with this posting date, and ends after 30 calendar days. CMS considers all public comments, and is particularly interested in clinical studies and other scientific information relevant to the topic under review. We are also interested in aspects of health disparities and health equity that should be considered in the review.

Instructions on submitting comments can be found at: http://www.cms.gov/Medicare/Coverage/InfoExchange/publiccomments.html. To submit a comment, please use the blue "Submit Public Comment" button at the top of the page. Enter comments directly into the form on that page.

October 12, 2021

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

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

Dear Ms. Syrek Jensen:

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

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

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

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

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

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

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

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

Formal Request

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

> B. Nationally Covered Indications
>
> I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
>
> c) Effective for services performed on or after (effective date), for the treatment of Myelodysplastic Syndrome (MDS), when it is reasonable and necessary. (New language to be inserted in place of the existing language in NCD 110.23, B. I. c.)

Required Information for Reconsideration

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

Proposed use of service

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

Target Medicare population & Medical indications

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

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

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

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

Summary of Recent Scientific Evidence to Justify the Request

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

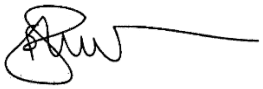
ASH, ASTCT, NMDP, and CIBMTR submit this letter as a formal request for reconsideration of the NCD for Stem Cell Transplantation (110.23). Specifically, the above organizations are asking for full coverage of allogeneic HSCT for individuals with myelodysplastic syndromes and the removal of the CED requirement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

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

Sincerely,

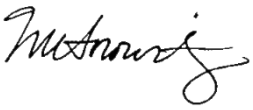
Martin S. Tallman, M.D.
President, ASH

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

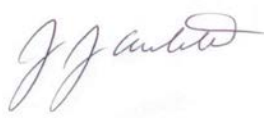


Bronwen Shaw, MD, PhD
Chief Scientific Director, CIBMTR-MCW

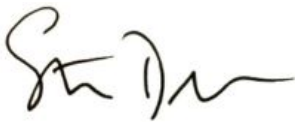
J. Douglas Rizzo, MD, MS
Senior Scientific Director and Principal Investigator, Stem Cell Therapeutic Outcomes Database, CIBMTR-MCW



Mary Horowitz, MD, MS, MACP
Principal Investigator, BMT CTN Data and Coordinating Center, MCW



Jeffery J. Auletta, M.D.
Senior Vice President, Patient Outcomes and Experience, NMDP
Chief Scientific Director, CIBMTR, NMDP



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

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

D46 Myelodysplastic syndromes

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

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

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

D46.1 Refractory anemia with ring sideroblasts
RARS

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

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

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

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

D46.A Refractory cytopenia with multilineage dysplasia

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

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

D46.4 Refractory anemia, unspecified

D46.Z Other myelodysplastic syndromes

Excludes1: chronic myelomonocytic leukemia (C93.1-)

D46.9 Myelodysplastic syndrome, unspecified
Myelodysplasia NOS

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

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

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

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

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

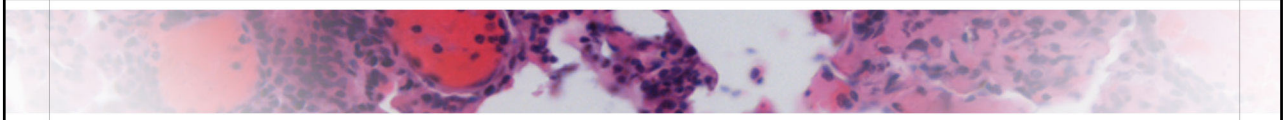
Warlick E, Ustun C, Andreescu, A, et al. Blood and Marrow Transplant Clinical Trials Network Study 1102 Heralds a New Era in Hematopoietic Cell Transplantation in High-Risk Myelodysplastic Syndromes: Challenges and Opportunities in Implementation. *Cancer* 2021.

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

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

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



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

Hematology Carrier Advisory Committee Meeting

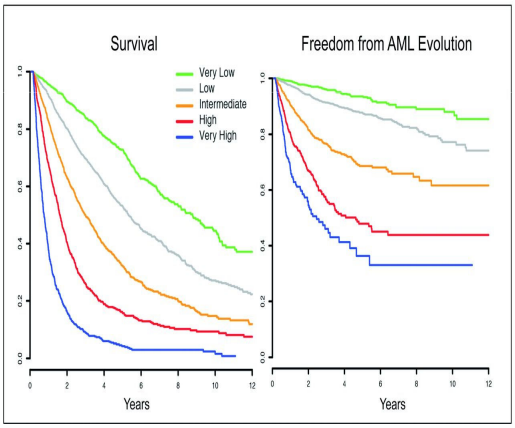
June 2023

1

Myelodysplastic syndrome (MDS)

- Defined by cytopenia, marrow dysplasia and certain karyotypic abnormalities
- Median age at diagnosis is 70 years
- Treatment is based on:
  - Medical fitness
  - Disease risk per IPSS-R* category
- Several treatments, but allogeneic HCT potentially curative, even in older patients using less intensive regimens

IPSS-R prognostic risk-based categories for MDS



Della Porta M. Leukemia. 2015; 29(7):1502-1513

*International Prognostic Scoring System-Revised Greenberg PL et al. Blood; 12:120:2454-2465

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2

2

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).

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MDS CED 2010: 3 Questions to address

- Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes?
  - Non-Relapse Mortality, Progression-free survival, Relapse, Overall Survival
- 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?

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Our 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?

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?

(Non-Relapse Mortality, Progression-free survival, Relapse, Overall Survival)

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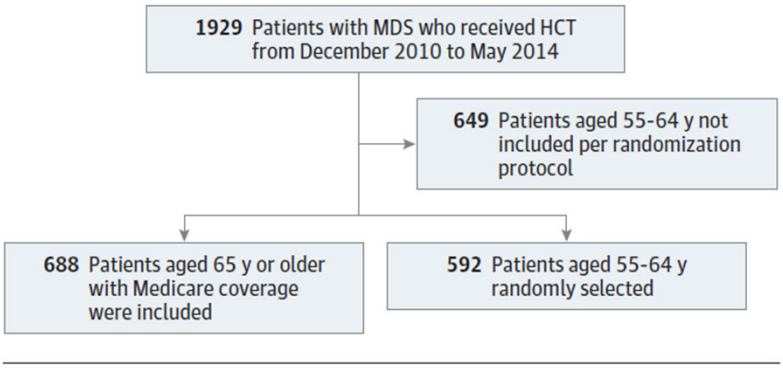
Study Flowchart – Observational study

Figure 1. Study Flowchart



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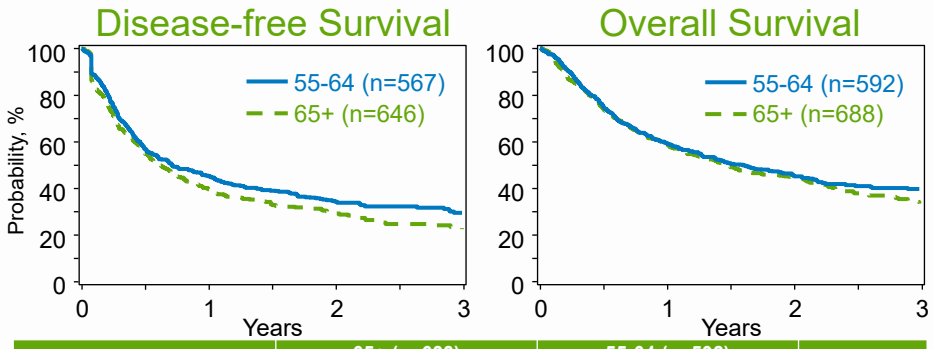
Atallah E, et al. JAMA Oncology. 2020; 6:486-493.



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

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Atallah E, et al. JAMA Oncology. 2020; 6:486-493

Multivariate Analysis

- Logistic regression (100-day mortality) and Cox regression (overall mortality) to examine broad range of patient-, disease- and transplant characteristics on outcomes.
  - Patient factors: Age, sex, race/ethnicity, comorbidity score
  - Disease factors: IPSS, disease status, blasts in BM pre-HCT, secondary MDS, time for diagnosis to HCT, therapy given before HCT
  - Transplant factors: Prior HCT, graft type, donor type/HLA matching, unrelated donor age, donor-recip sex match and CMV status, preparative regimen, GVHD prophylaxis, use of ATG/Campath
  - *Controlled for excess risk of death with age using Esteve method and life tables*
- **Significant variables include comorbidity score, cytogenetic risk, disease status pre-HCT, blasts in BMT pre-HCT, severity of cytopenias pre-HCT**
- **A "center effect" was tested in the multivariate model and not found**
- **No interaction with age – same factors associated with outcome regardless of age**

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BMT CTN 1102

A 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

Co-Chairs: Corey Cutler, MD MPH and Ryotaro Nakamura, MD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

9

BMT CTN 1102 Study Design:
Multicenter, biologic assignment study

Enrollment

Matched related or unrelated donor search for up to 90 days

Donor arm: RIC alloHCT within 6 months

No Donor arm: hypomethylating agent or best available non-HCT care

Inclusion criteria

- Primary MDS, IPSS Intermediate -2 or high risk
- Age: 50-75 years
- Any prior therapy
- No prior unrelated donor search
- Eligible for RIC alloHCT from an 8/8 HLA- matched related or unrelated donor

Primary endpoint:

❖ Overall survival at 3 years

Secondary endpoints:

❖ Leukemia free survival at 3 years
❖ Quality of life (QoL)
❖ Cost effectiveness

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

ClinicalTrials.gov NCT02016781

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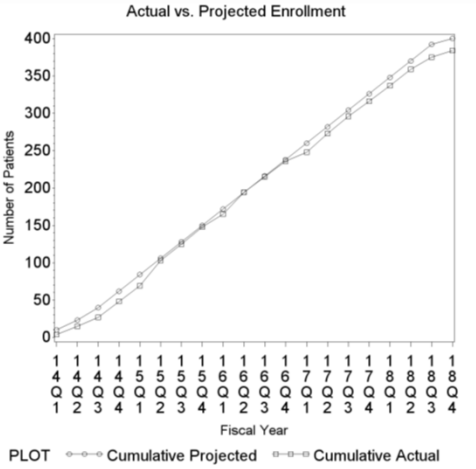
BMT CTN 1102: Subjects and Accrual



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Enrolled + Biologically Assigned: 384

Donor Identified: 260

No Donor Identified: 124
Died During 90-Day Search: 7

Died on Study: 125
Complete 3-year F/U: 62
Alive and on Study: 71
Withdrew: 2

Died on Study: 86
Complete 3-year F/U: 14
Alive and on Study: 23
Withdrew: 1

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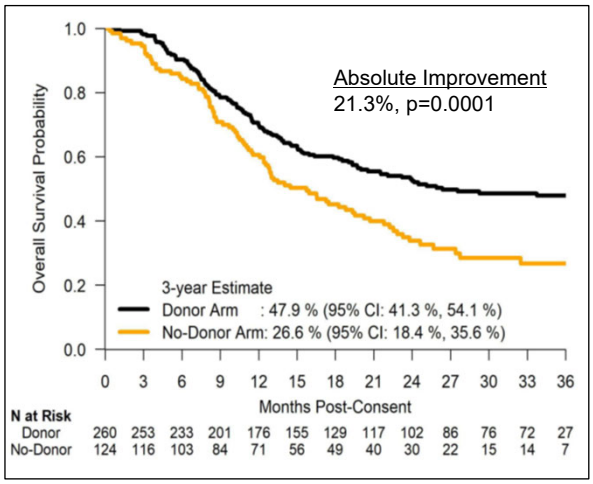
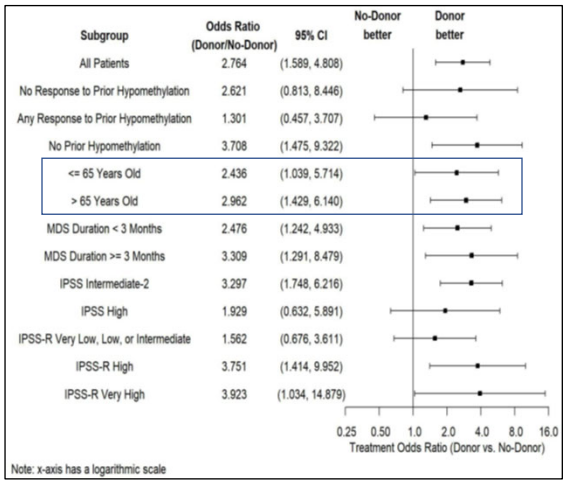
Significant Overall Survival Advantage in the Donor arm





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

Nakamura et al. J Clin Onc 2021

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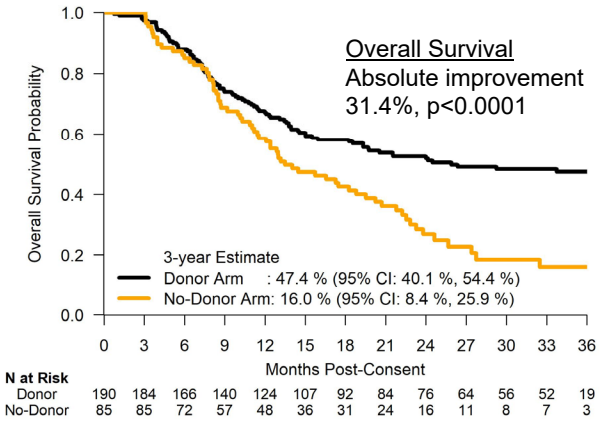
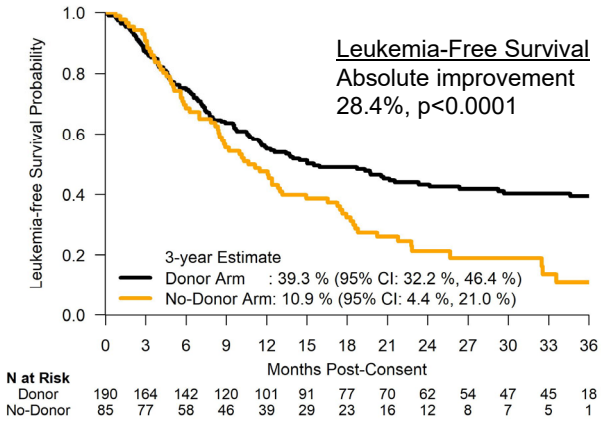
As-Treated Analysis





Nakamura et al. J Clin Onc 2021

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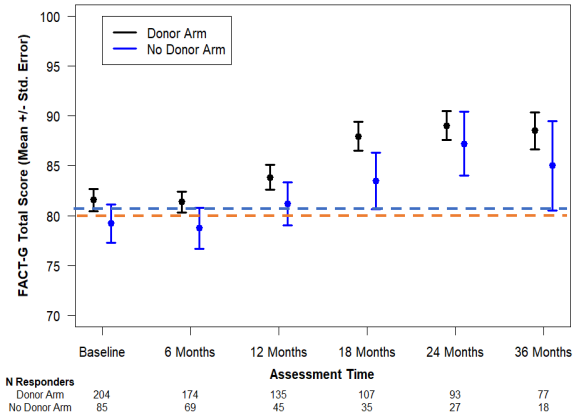
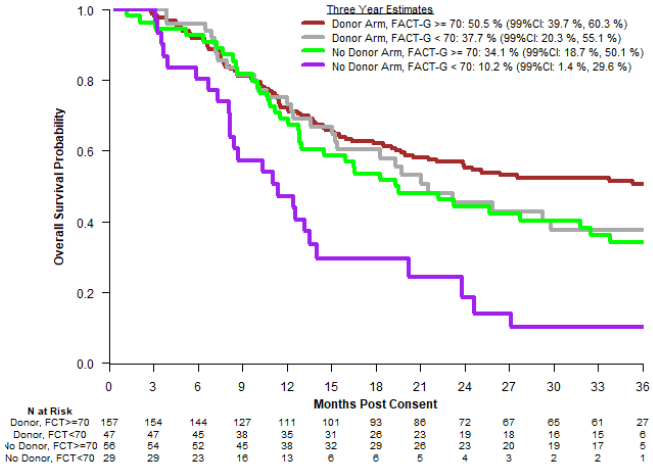
Quality of Life – FACT-G





Cusatis et al. Am J Heme 2022

14

14

What next?

- CMS CED mechanism has provided access for allogeneic HCT for MDS patients 65 and older
  - CIBMTR Observational study remains open and continues to provide access to Medicare beneficiaries
- These studies provide clear evidence of benefit for HCT recipients compared to alternative treatment – reasonable and necessary
- Moving to national coverage will ensure access and relieve administrative burden to CIBMTR for this CED
  - CIBMTR is not a corporate stakeholder – these CED studies are not independently funded nor influenced by profit motive

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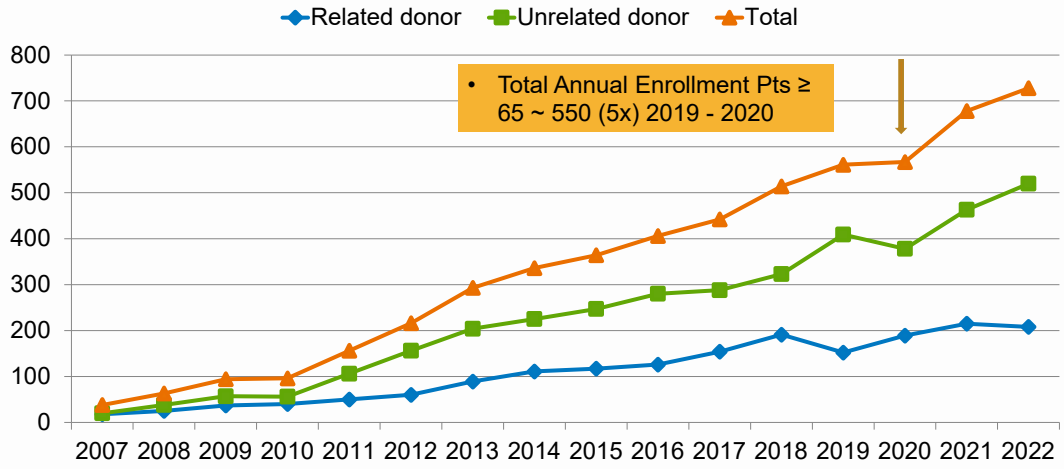
US Allogeneic Transplants for MDS in Patients Older than 65 y, 2007-2022 – What if barriers are removed?



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October 12, 2021

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

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

Dear Ms. Syrek Jensen:

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

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Formal Request Accepted and Review Initiated
06/07/2023

Expected NCA Completion Date
03/06/2024

Public Comment Period
06/07/2023 - 07/07/2023

Proposed Decision Memo Due Date
12/07/2023

Challenges
Changing risk stratification systems
Changing standards of care for donor type
Related, Unrelated, Haploidentical

18

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Minimal Residual Disease Testing in Hematopoietic Cell Transplantation

American Society of Hematology
Carrier Advisory Committee (CAC) Meeting
June 23, 2023

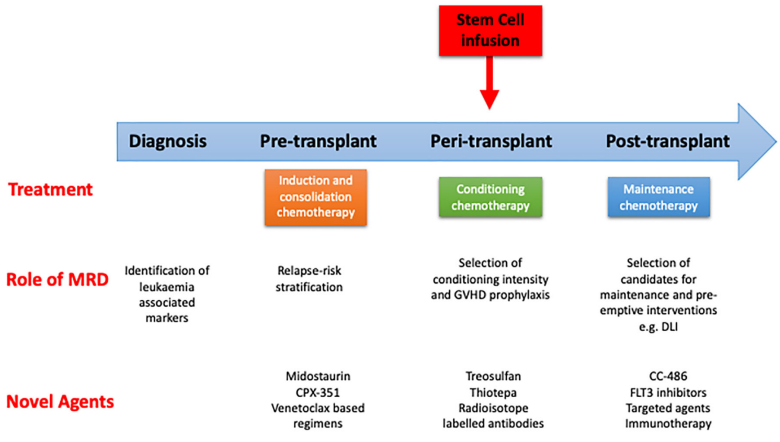
Amar Kelkar, MD, FACP

Dana-Farber Cancer Institute

1

Leukemia Treatment

1. Induction
2. Consolidation
3. Conditioning



Loke J et al, *Front Oncol* 2021

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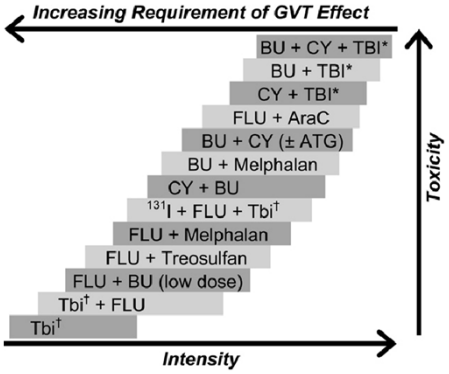
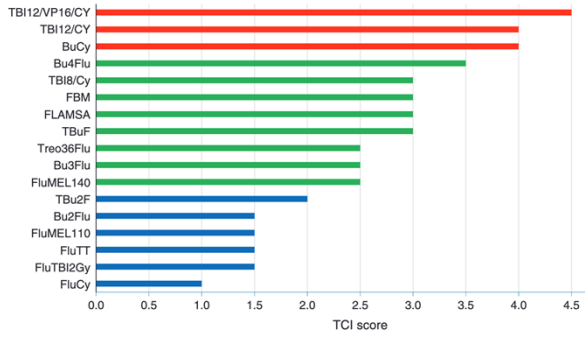
Terminology

- MAC = Myeloablative Conditioning
- RIC = Reduced-intensity Conditioning
- NMA = Non-myeloablative Conditioning





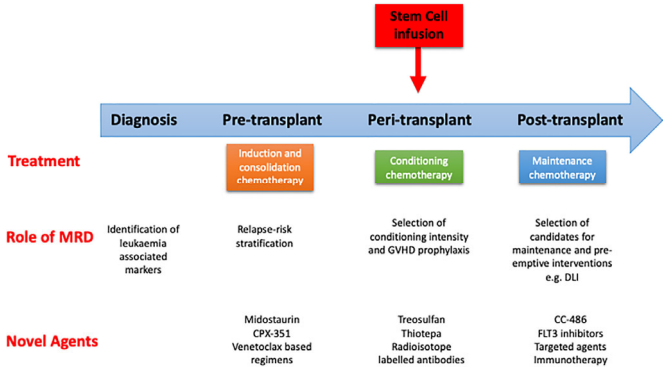
Gyurkocza et al, *Blood* 2014

Spyridonidis et al, *Bone Marrow Transplantation* 2020

3

Leukemia Treatment

1. Induction
2. Consolidation
3. Conditioning
4. Transplant
5. Maintenance
6. Salvage

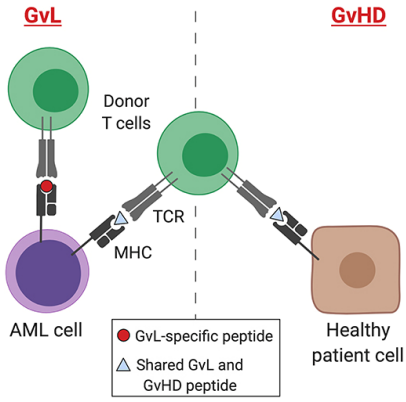


Loke J et al, *Front Oncol* 2021

4

Terminology

- GVL = Graft-versus-Leukemia
- GVHD = Graft-versus-Host Disease

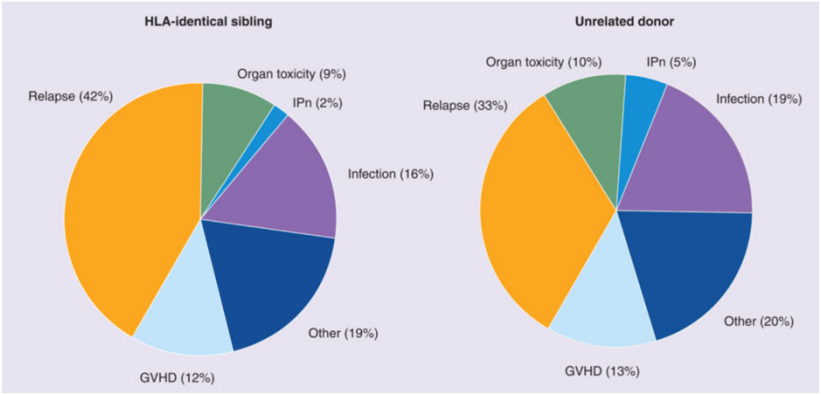


Sweeney C et al, *Front Oncol* 2019

5

Terminology

- OS = Overall Survival
- CIR = Cumulative Incidence of Relapse
- LFS = Leukemia-free Survival
- NRM = Non-relapse Mortality

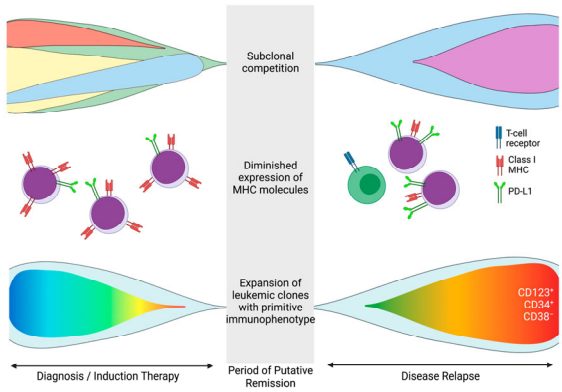


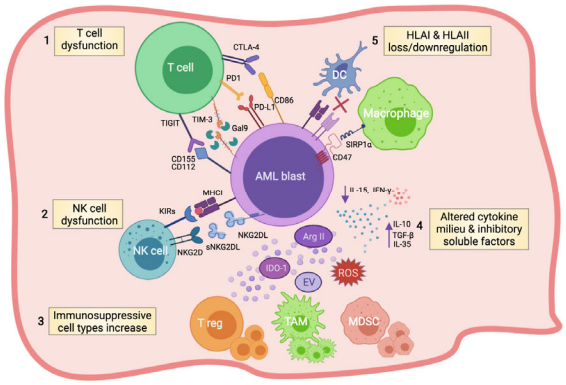
Barrett AJ et al, *Expert Review of Hematology* 2010

6

Why do patients relapse after transplant?

- Residual disease entering transplant
- Clonal evolution
- Resistant disease
- Immune evasion





Ahmadmehrabi K et al, *Cancers* 2021

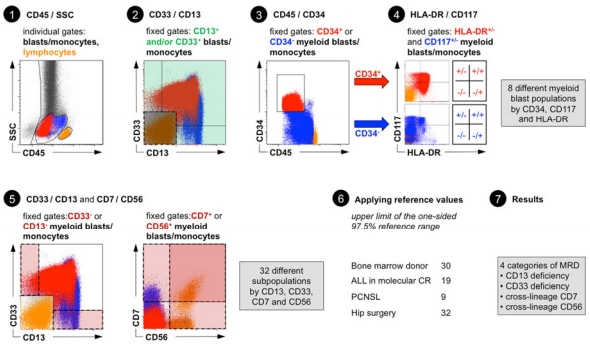
Tettamanti S et al, *Leukemia* 2022

7

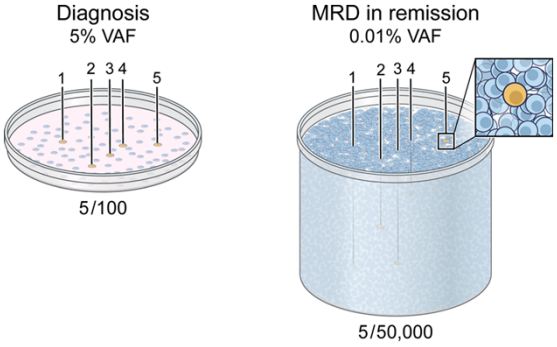
Terminology

- MRD = Minimal Residual Disease

Multiparameter Flow Cytometry



Quantitative Real-Time Polymerase Chain Reaction



Röhnert MA et al, *Leukemia* 2022

Hourigan CS, *Hematology Am Soc Hematol Educ Program* 2022

8

Methods for MRD detection in AML

Method	Sensitivity	Target	Advantages	Disadvantages
Multiparameter Flow Cytometry	0.1-0.01% (4 color) 0.01-0.001% (6-10 color)	"LAIP" (leukemia-associated immunophenotype) *or* "Difference from normal"	Applicable to most AML subtypes Rapid, direct Don't necessarily need prior sample	Not standardized Requires expertise (centralized review) Immunophenotypic shifts
RT-qPCR (NGS-MRD)	0.01-0.001%	Fusion transcript or specific mutation (e.g. NPM1)	High sensitivity Standardized	Time-consuming Not all AML subtypes have somatic mutations suitable for NGS-MRD testing May persist in mature "non-LSCs"
DNA sequencing	Varies by method, as sensitive as 0.0001%	Mutated genes	Applicable to most AML subtypes High sensitivity (e.g., ddPCR) Discovery potential	High cost Time-consuming Not all mutations track with blasts/LSCs (i.e., some mutations are unrelated to AML) Not all mutations persist at relapse

Hourigan CS, *Hematology Am Soc Hematol Educ Program* 2022

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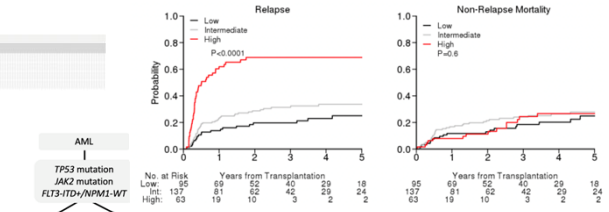
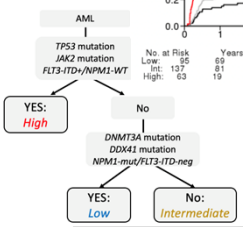
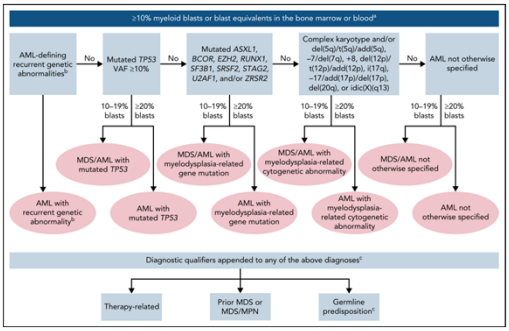
Molecular Risk Model





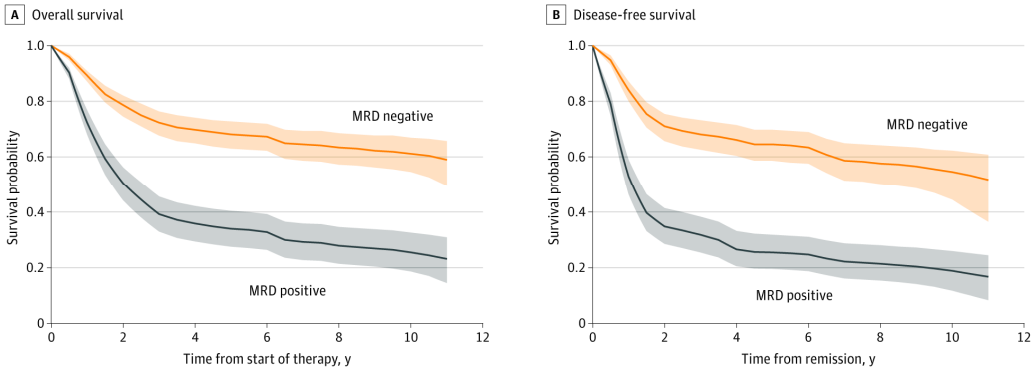


Murdock M et al, *Blood* 2022
Döhner H et al, *Blood* 2022

10

What can pre-transplant MRD testing tell us?

- MRD positivity predicts worse outcomes
- Some still achieve long-term disease-free remission



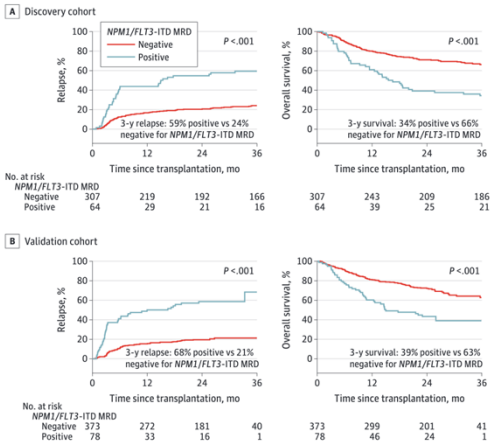
Short NJ et al, *JAMA Oncol* 2020

Przepiorka D et al, *JAMA Oncol 2021*

11

Pre-MEASURE

- >1000 patient study
- Confirmed significance of pre-transplant MRD testing

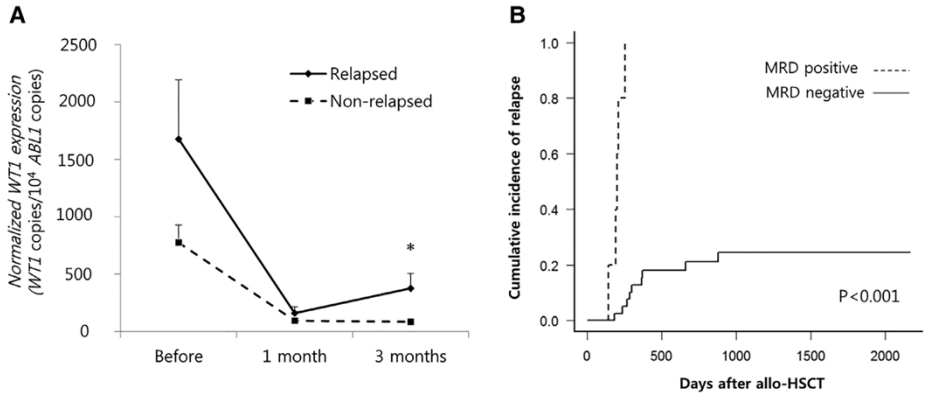


Dillon LW et al, *JAMA* 2023

12

What can we learn from multi-timepoint MRD testing?

- More predictive of transplant outcomes



Cho BS et al, *Biol Blood Marrow Transplant* 2019

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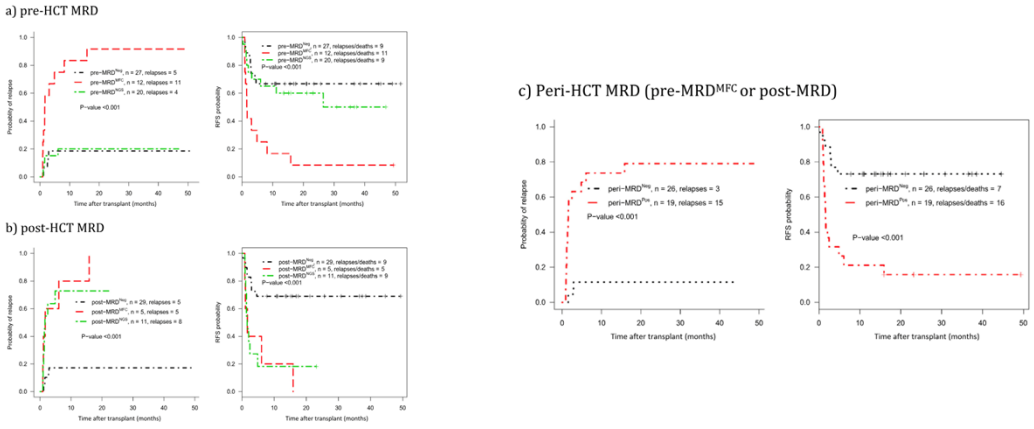
Peri-Transplant MRD Testing

- Pre- and post-transplant MRD+ individually predict relapse
- Combined pre- and post-transplant MRD+ are more predictive of relapse
  - 83% sensitivity



Zhou Y et al, *Biol Blood Marrow Transplant* 2018

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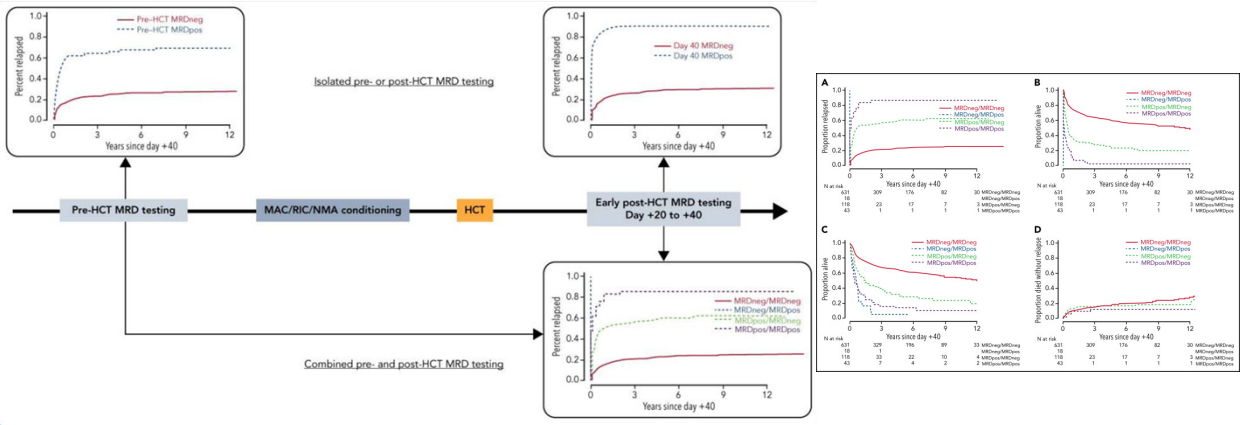
Peri-Transplant MRD Testing

- Conversion of MRD-negative to MRD-positive from pre- to post-transplant had worse outcomes than patients that were MRD-positive at all times



Paras G et al, *Blood* 2022

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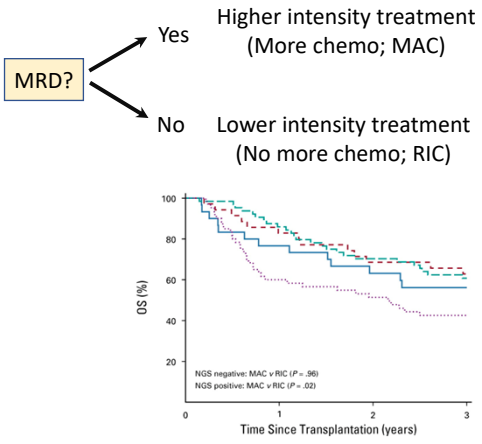
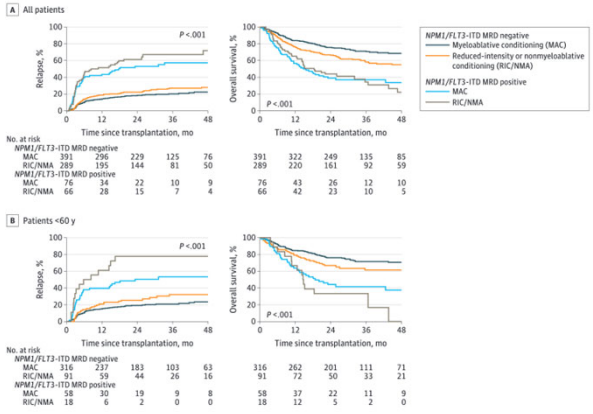
What can we do about pre-transplant MRD+ AML?

- MRD is a modifiable risk factor





Hourigan CS et al, *J Clin Oncol* 2020

Dillon LW et al, *JAMA* 2023

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What do current guidelines recommend?

- There are consensus guidelines for incorporation of MRD in AML management

D22	For patients who are (1) MRD positive by MFC after 2 cycles of intensive chemotherapy, after consolidation chemotherapy, prior to stem cell transplantation, and/or after stem cell transplantation[83,84]; (2) MRD$^+$ by ≥2% *NPM1* mutant copies per *ABL1* copies measured in BM or transcript levels of *NPM1* or CBF fusions failed to reach a 3- to 4-log reduction in the same tissue after completion of consolidation chemotherapy (the ratio of target copies/*ABL1* copies between the sample at diagnosis and the sample after completion of consolidation chemotherapy, measured in the same tissue, preferably BM)[37,71,80,85,86]; and/or (3) demonstrated to have MRD relapse (either molecular or MFC), individualized treatment[83] and/or conditioning regimen strategies should be considered, preferably as part of clinical trials, in an effort to reduce disease relapse.	V	C	100
D26	Pretransplant MRD positivity should not be viewed as a contraindication to stem cell transplantation.	IV	A	100
D27	The panel recommends that patients with detectable MRD before allo-HCT myeloablative conditioning be considered.	II	A	95
D28	All AML clinical trials should monitor molecular and/or MFC-MRD assessments whenever response is assessed in BM.	V	B	100

Heuser M et al, *Blood* 2021

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What's next?

M·E·A·S·U·R·E
MOLECULAR EVALUATION OF AML PATIENTS AFTER STEM CELL TRANSPLANT TO UNDERSTAND RELAPSE EVENTS

- Harmonized, externally validated MRD platforms
- More evidence!
  - What's the right definition of MRD? (Which mutations?)
  - What are the right thresholds for detection?
    - Are there lower limits for clinical impact?
  - Is MRD the same in all patient groups?
    - Older, fit transplant candidate (eligible for MAC) with *de novo* type AML?
    - Younger, fit transplant candidate (eligible for MAC) with secondary type AML?
  - Is treatment intensification always the answer?
- MEASURE will address many of these knowledge gaps

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Why does peri-transplant MRD testing matter?

- Better guidance and informed consent for patients undergoing transplant
- Guiding conditioning chemotherapy decision-making
- Impact on post-transplant therapies
- Guiding clinical trial design to reshape pre- and post-transplant decision-making
- Protecting $400,000 transplant investment

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Thanks to …

- Robert Soiffer, MD & Christopher Gibson, MD
- Medicare Administrative Contractors
- American Society of Hematology
- ASH Staff

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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*)
- Durable Medical Equipment MACs
- Medicare Coverage
- Medicare Coverage Centers
- Patients over Paperwork: 9th Issue - Modernization Update: Local Coverage Determination (LCD)

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 Katherine Stark.

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 monthly e-newsletter reporting on breaking news and activities of interest to the practice community.

- *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

- Meeting on Hematologic Malignancies - The ASH Meeting on Hematologic Malignancies (MHM) features the top experts in the field, comprehensive clinical content, and the opportunity to interact with colleagues in an intimate, small group setting with no competing sessions. The 2023 meeting is scheduled to take place September 8-9, 2023 in Chicago, IL, and on the meeting's virtual platform. Participants will have an opportunity to hear experts present cutting-edge scientific data, provide out-of-the-box treatment approaches, and answer challenging patient care questions during topic-based panel discussions.
- ASH Annual Meeting and Exposition – The 65th ASH Annual Meeting and Exposition is scheduled to take place December 9-12, 2023 in San Diego, CA 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 to provide the highlights of the top presentations from ASH's annual meeting.

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. The sixth edition of the ASH Self- Assessment Program (ASH-SAP) is also available on the ASH Academy on Demand.
- ASH FDA New Drug and Therapy Alerts – ASH partners with the Food and Drug Administration to alert members on newly approved hematologic therapies.
- 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.

If you have any questions on this list or any of the programs, please contact Katherine Stark, Policy and Practice Manager at kstark@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 possible 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.). When the flight is outside of North America AND the total travel time (as indicated on the official flight itinerary) is 10 hours or more, ASH will pay for business class airline tickets. **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 nearby hotel, there are three possible 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 considerably 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 (**65.5 cents per mile as of 1/1/2023, 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.**

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. sky-cap or hotel bellman) and similar expenses are reimbursable up to a maximum of $10 dollars per day.
- Early board fees and onboard airline WiFi 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.*

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 ASH CAC Meeting – June 22-23, 2023

<u>Signature:</u> _____ Date: _____

Itemized Expenses:

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

☐ **I decline some / all of this reimbursement as a donation to the ASH Foundation to benefit the following program(s)**

Greatest Needs Fund $ _____
Career Development and Training Fund $ _____
Clinical Research Training Institute Fund $ _____
COVID-19 Fund $ _____
Global Programs Fund $ _____
Minority Recruitment Initiative Fund $ _____
Quality Care and Education Fund $ _____
Research Awards Fund $ _____
(*ASH Scholar Awards, Global Research Award, Bridge Grant Program, etc.)*
Sickle Cell Disease Initiative Fund $ _____

☐ **I accept this reimbursement**

<u>SUMMARY:</u>

Total of itemized expenses: **$**_____
Total amount declined as a donation to the ASH Foundation per above designation: **$** _____
Total amount to be reimbursed to signatory herein: **$** _____

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 c/o Natalie Bates.