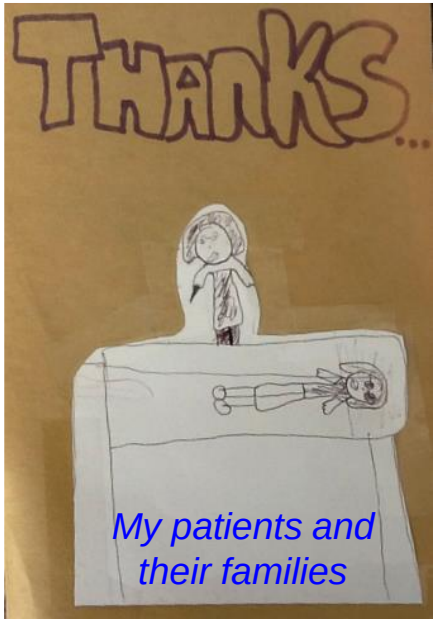
Germline predisposition to hematopoietic malignancies

Lucy A. Godley, M.D., Ph.D.
Hospira Foundation Professor in Oncology
Departments of Medicine and Human Genetics
The University of Chicago

Acknowledgments



Godley Lab

Kristina Bigelow
Lorraine Canham
Yoga Haribabu
Ashwin Koppayi
Sophia Korotev
Courtnee Rodgers
Mancy Shah
Taylor Walker

Soma Das
and the
Genetic Services Lab

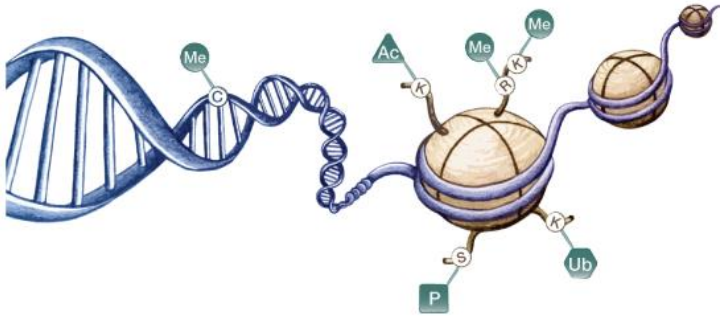
Jeremy Segal
James Vardiman

Funding: NIH, DoD, The Leukemia and Lymphoma Society, Cancer Research Foundation, The Taub Foundation, V Foundation, Edward P. Evans Foundation, RUNX1 Research Program/Mark Foundation for Cancer Research

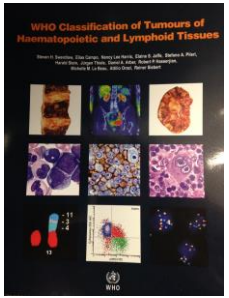
Realizing the goal of precision medicine in oncology

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



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: *J Natl Compr Canc Netw* 20:106-117 (2022).

Myelodysplastic Syndromes, Version 3.2022

Featured Updates to the NCCN Guidelines

Peter L. Greenberg, MD[1,*]; Richard M. Stone, MD[2,*]; Aref Al-Kali, MD[3,*]; John M. Bennett, MD[4]; Uma Borate, MD[5]; Andrew M. Brunner, MD[6]; Wanxing Chai-Ho, MD[7]; Peter Curtin, MD[8]; Carlos M. de Castro, MD[9]; H. Joachim Deeg, MD[10,*]; Amy E. DeZern, MD, MHS[11]; Shira Dinner, MD[12]; Charles Foucar, MD[13]; Karin Gaensler, MD[14]; Guillermo Garcia-Manero, MD[15]; Elizabeth A. Griffiths, MD[16]; David Head, MD[17]; Brian A. Jonas, MD, PhD[18]; Sioban Keel, MD[19]; Yazan Madanat, MD[19]; Lori J. Maness, MD[20]; James Mangan, MD[21]; Shannon McCurdy, MD[22]; Christine McMahon, MD[23]; Bhumika Patel, MD[24]; Vishnu V. Reddy, MD[25,*]; David A. Sallman, MD[26]; Rory Shallis, MD[27,*]; Paul J. Shami, MD[28]; Swapna Thota, MD[29]; Asya Nina Varshavsky-Yanovsky, MD, PhD[30]; Peter Westervelt, MD, PhD[31]; Elizabeth Hollinger, BSN, RN[32,*]; Dorothy A. Shead, MS[32,*]; and Cindy Hochstetler, PhD[32,*]

ICC classification includes germline predisposition: Blood 140: 1200-1228 (2022).

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

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,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli 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: *Blood* 140: 1345-1377 (2022).

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*

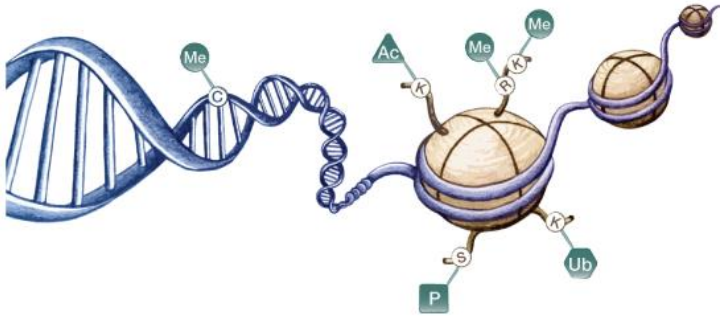
* DKC, dyskeratosis congenita; FA, Fanconi anemia; HBOC, hereditary breast and ovarian cancer; LS, Lynch syndrome

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

Realizing the goal of precision medicine in oncology

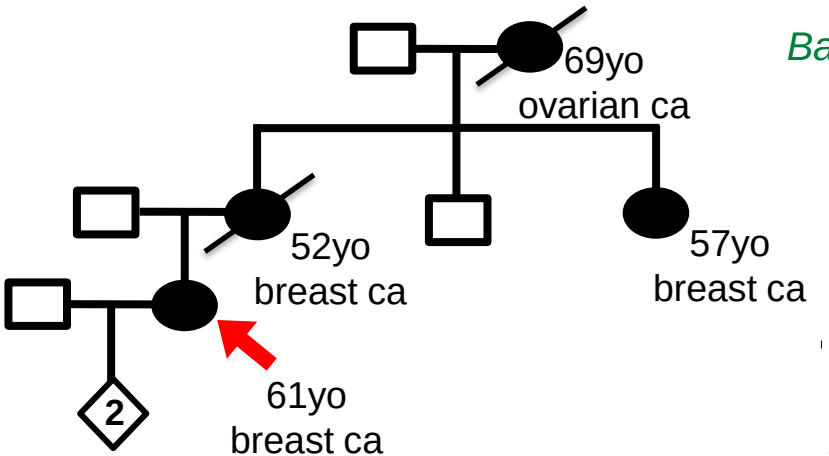
DEFINE:
Baseline genetics/epigenetics
[germline]
Acquired genetics/epigenetics in the HSC
[clonal hematopoiesis]
Acquired genetics/epigenetics in the tumor
[tumor profiling]
Microbiome/Immunotype

to devise an effective treatment strategy for a particular patient



Precision oncology from my perspective today

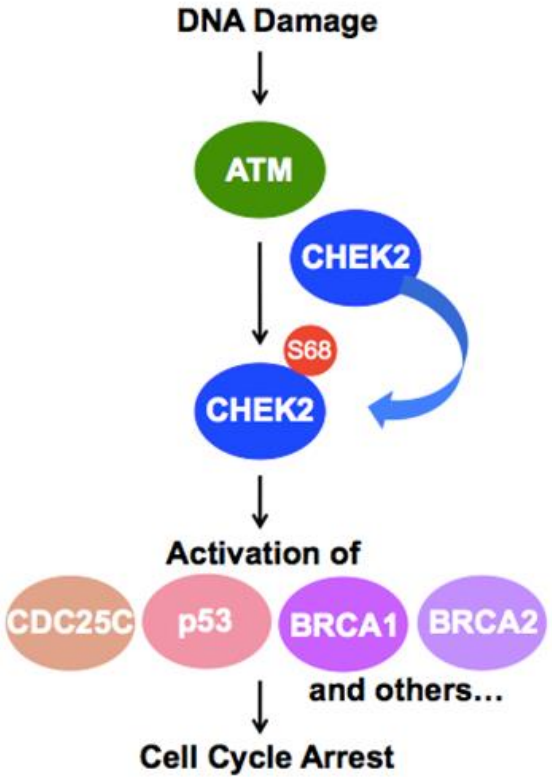
One of our oncology nurses was diagnosed with breast cancer…

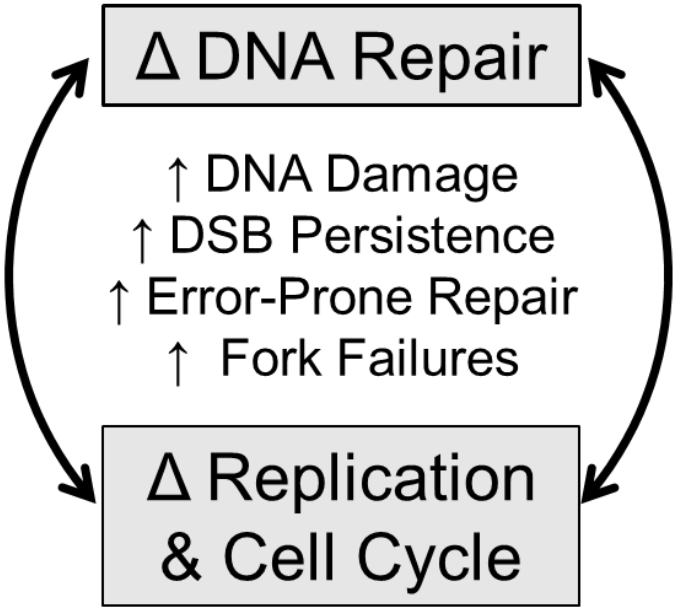


Based on her personal and family history of cancer, she underwent germline genetic testing

The CHEK2 *I200T (I157T) allele was identified*

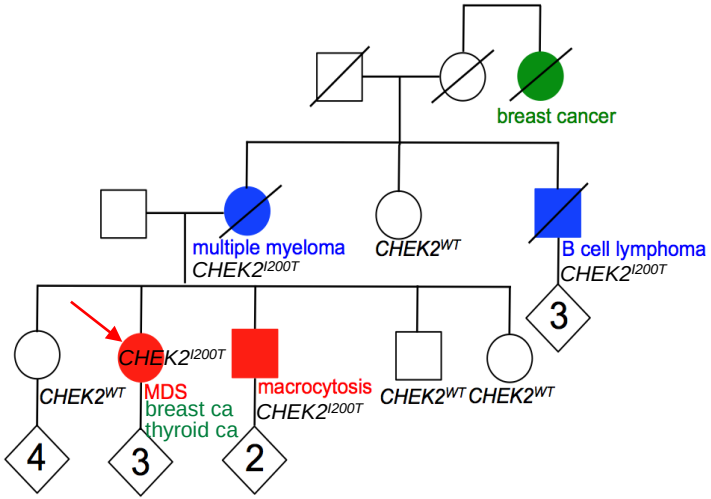
The molecular impact of HR DNA repair pathway deficiencies on DNA integrity within hematopoietic cells



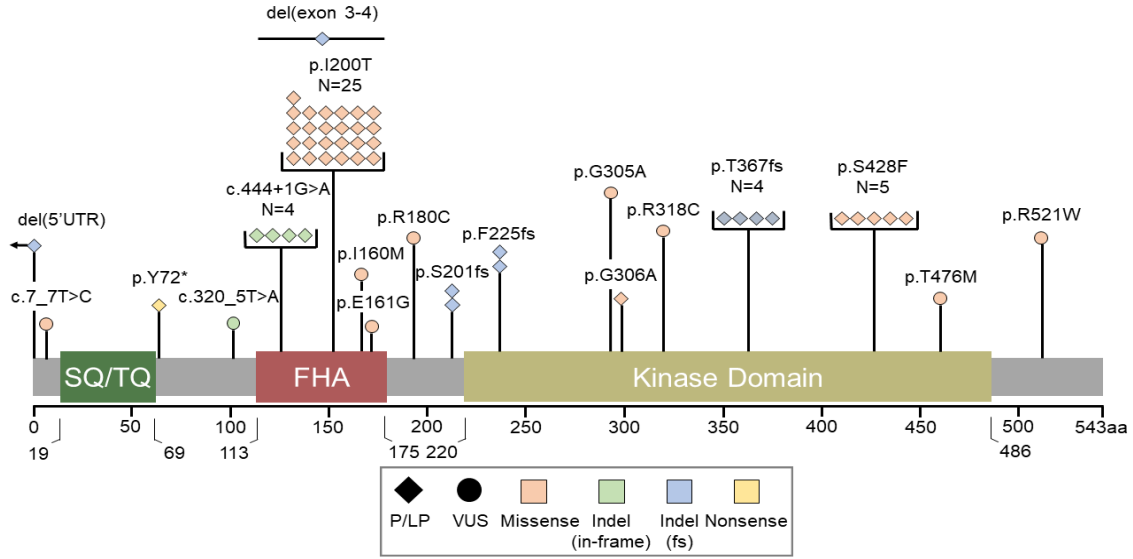


Germline *CHEK2* mutations and hematopoietic malignancies

representative pedigree



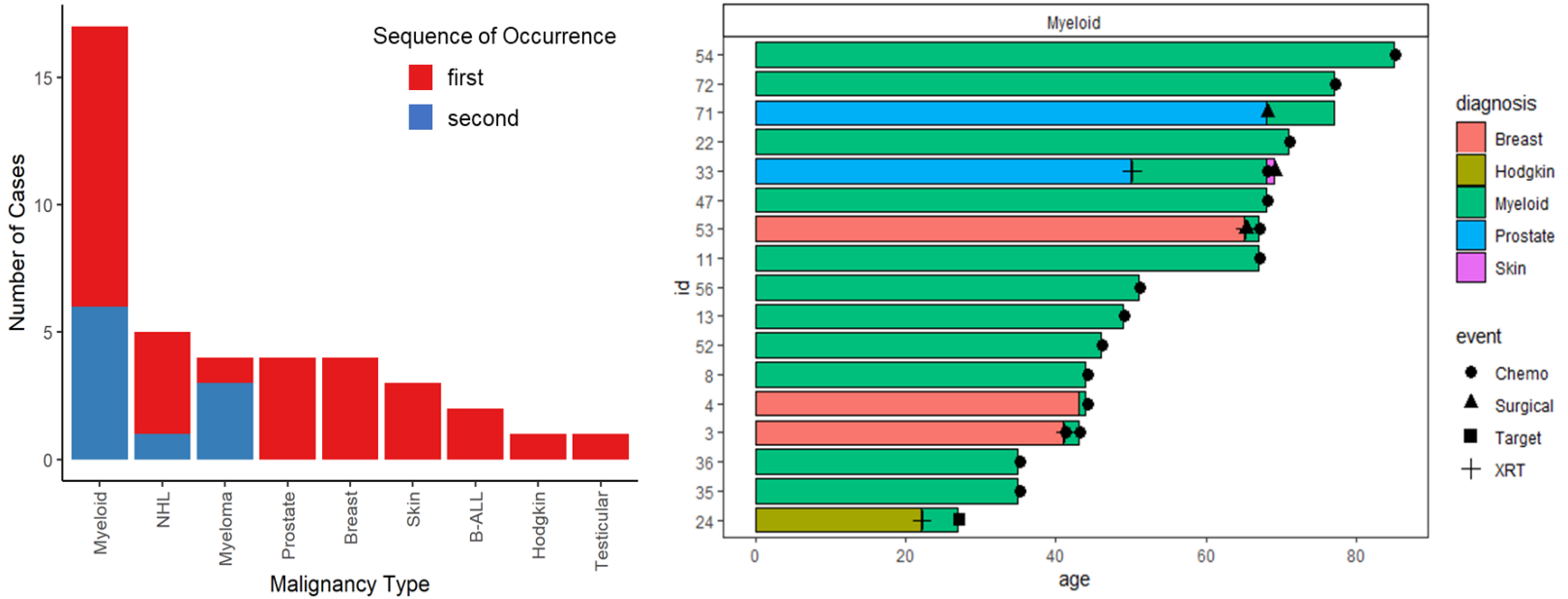
Godley Lab Cohort



Germline *CHEK2* mutations and hematopoietic malignancies

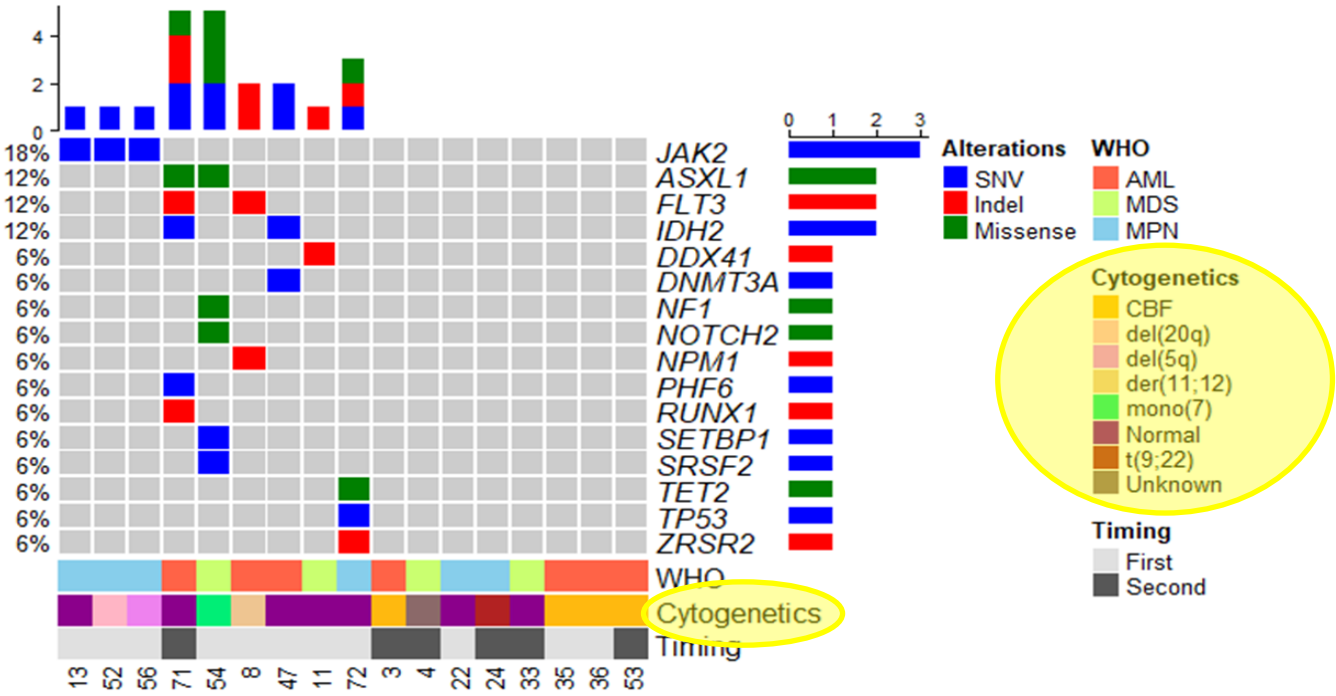
Hematologic Malignancy Patients with *CHEK2* Variant (n = 33)			Non-cancer ExAc Control Population (gnomAD)		Hematologic Malignancy vs gnomAD cohort	Significance
Variant	Proportion of Individuals with the Mutation	Variant Frequenecy	ExAc Allele Number (excluding homozygous)	Allele Frequency	OR (95% CI)	*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				

Germline *CHEK2* mutations and hematopoietic malignancies



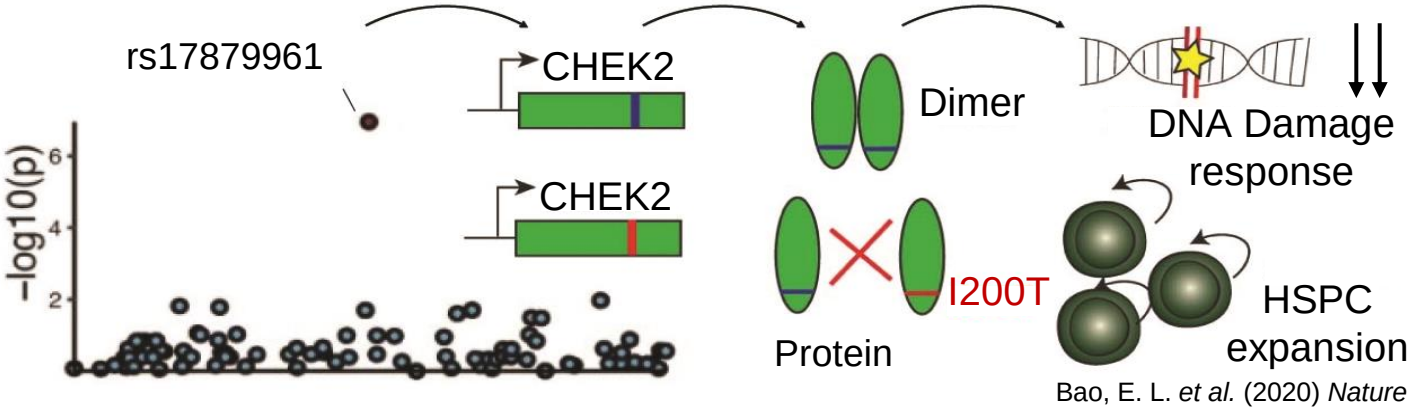
Germline *CHEK2* mutations and hematopoietic malignancies

mutational spectrum in myeloid malignancies



Germline *CHEK2* mutations and hematopoietic malignancies

The CHEK2 I200T variant predisposes to clonal hematopoiesis



Bao, E. L. *et al.* (2020) *Nature*

Human Disease

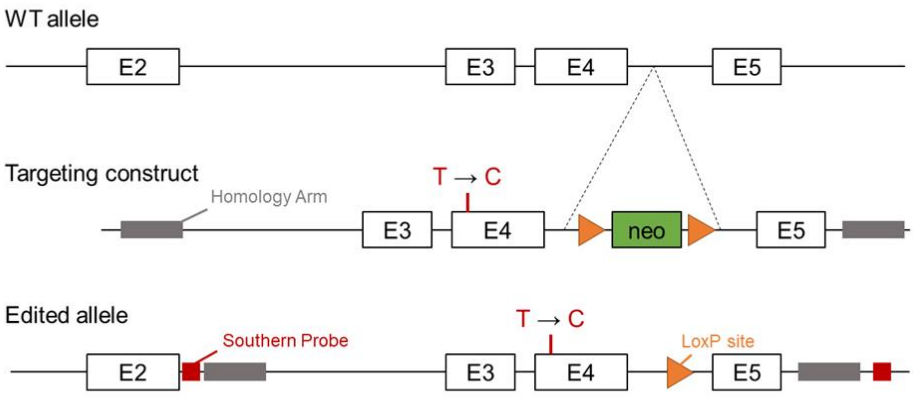
Colon, prostate, breast

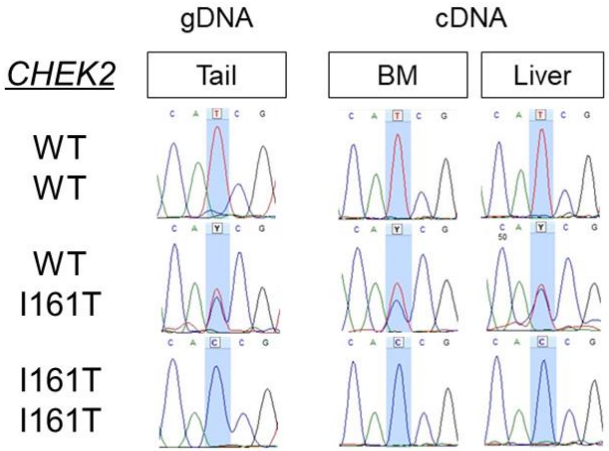
Myeloid malignancies, CLL

Clonal Hematopoiesis

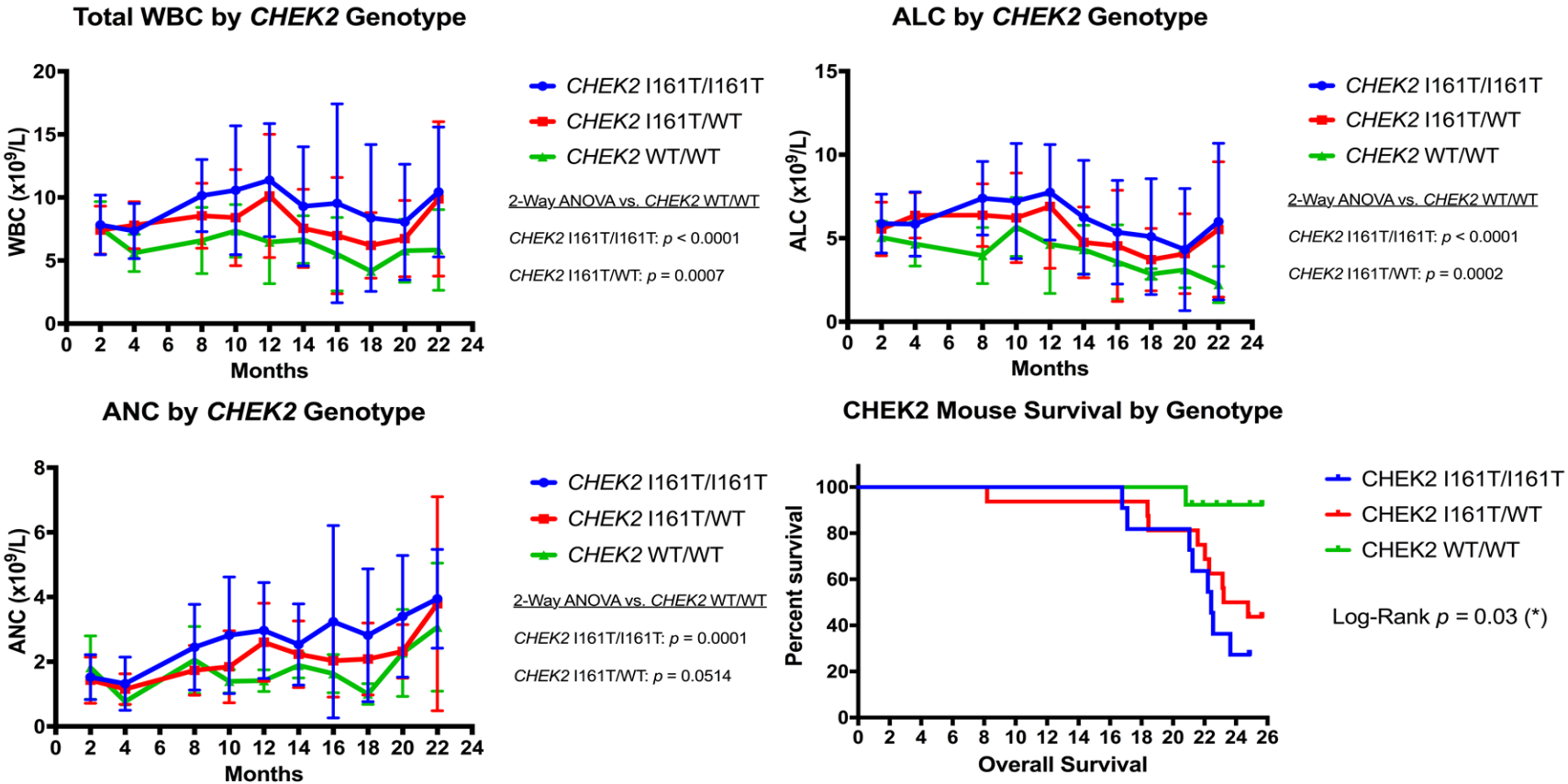
Smith, J., *et al.* (2010) *Adv Cancer Res*
Liu, C., *et al.* (2012) *Asian Pac J Cancer Prev*
Wang, Y., Dai, B. & Ye, D. (2015) *Int J Clin Exp Med*
Filippini, S. E. & Vega, A. (2013). *Front Biosci*
Liu, C., *et al.* (2012). *Asian Pac J Cancer Prev*
Janiszewska, H., *et al.* (2018) *Leuk Res*
Bick, A. G., *et al.* (2020) *Nature*

Germline *CHEK2* mutations and hematopoietic malignancies





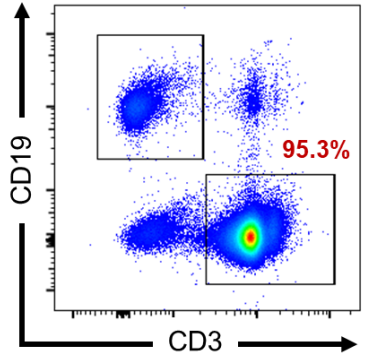
Germline *CHEK2* mutations and hematopoietic malignancies

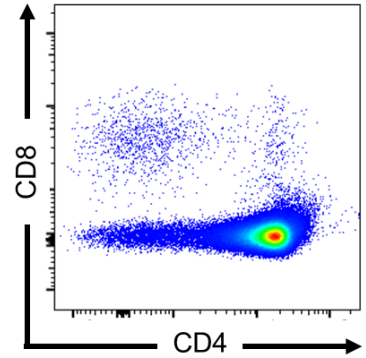


Do the knock-in *Chek2*^{I161T}-mutant mice develop clonal hematopoiesis?

Germline *CHEK2* mutations and hematopoietic malignancies

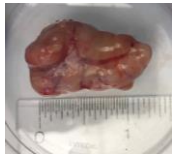
T-helper cell Leukemia (18 mo)



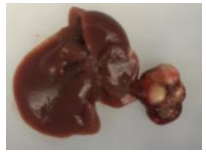


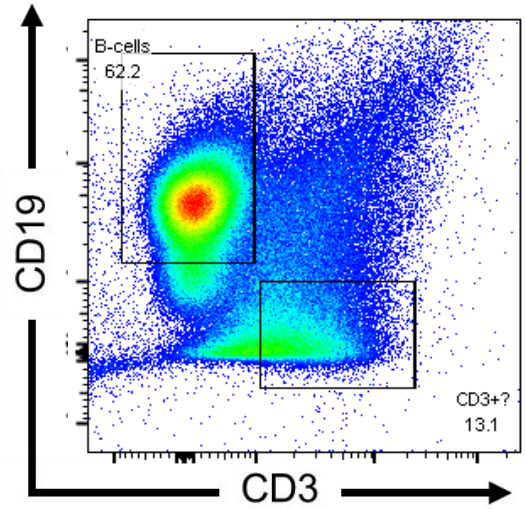
Lymphoma (24 mo)

Abdominal mass

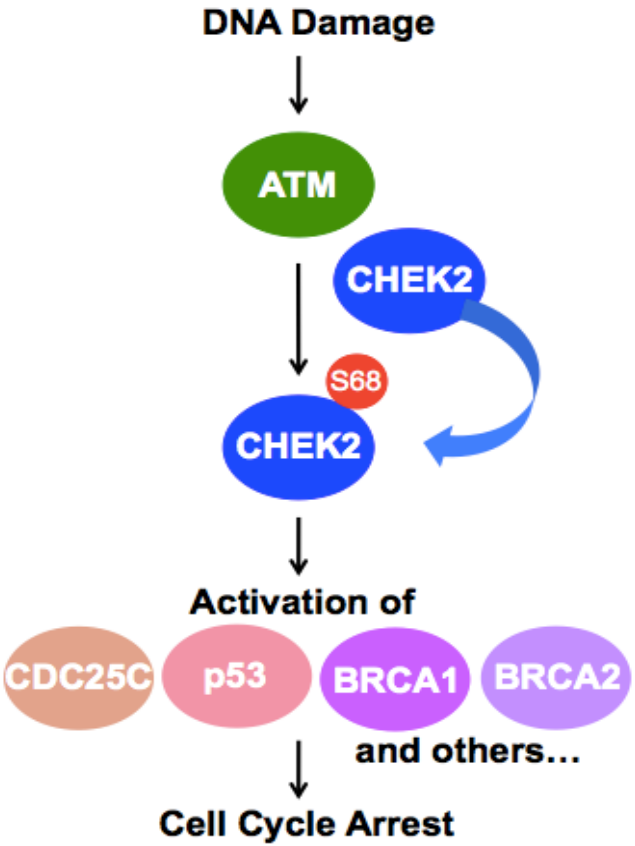


Liver

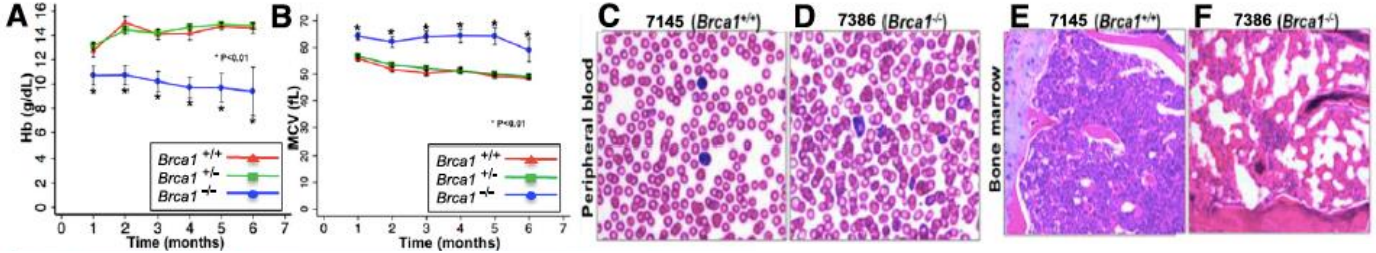




The molecular impact of HR DNA repair pathway deficiencies on DNA integrity within hematopoietic cells

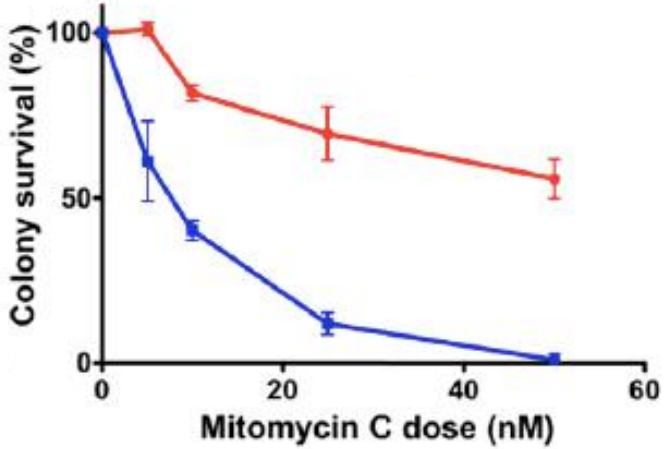


Brca1 is a Fanconi gene (*FANCS*)



***Brca1* +/+**
***Brca1* +/-**
***Brca1* -/-**

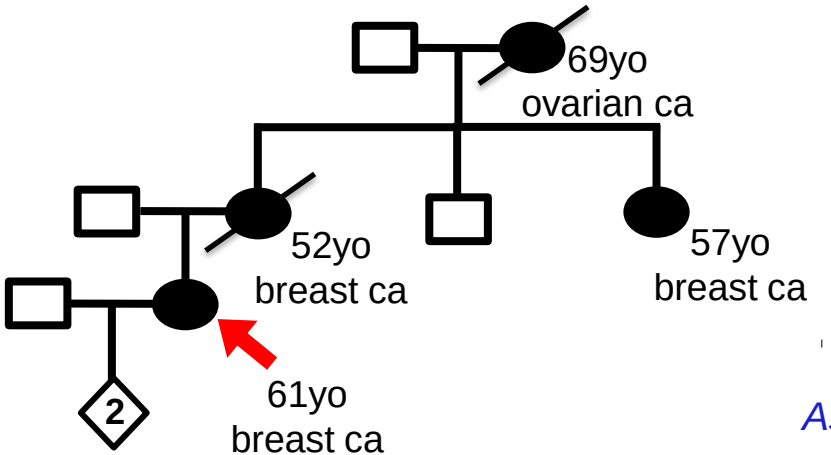
Cytogenetic abnormalities
40,XX[13]
40,XX,chrb(4)(C2)[1]
40,XX,chtb(2)(H1),chtg(6)(B1)[1]
40,XX,chtb(1)(H5),chrg(5)(D)[1]
40,XX,chrg(2)(E2)[1]
39,XX,chtb(2)(B),chrb(3)(F1),chrg(13)(C3),chrg(15)(E),-16,chtb(17)(B)[1]
40,XX,chte(2;5)(F1;C2),chte(9;12)(F1;E),pcd(16)(A)[1]
40,XX,t(1;17)(H4;A2)[1]



Vasanthakumar, A *et al.* *Blood* 127: 310-313 (2016)

Precision oncology from my perspective today

So what did we do for my colleague?



Assessed for clonal hematopoiesis

↓

It was not there →

Surgical treatment for her breast cancer [she opted for bilateral mastectomy]

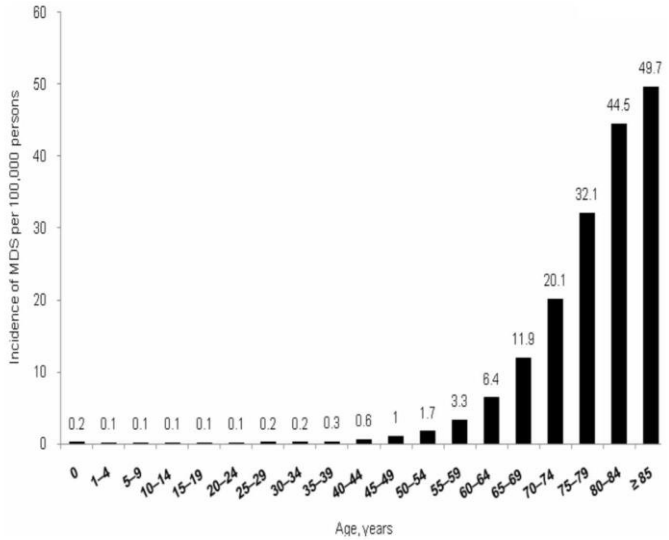
Cytotoxic chemotherapy

Disease mechanisms–
What does age tell us?

Germline mutations in young MDS/t-MDS/AA patients

Rationale

MDS is a disease of the elderly,
with a median age of diagnosis of 76 years in the US



Ma, Am J Med, 2012

Germline mutations in young MDS/t-MDS/AA patients

Inclusion criteria ⇢

Confirmed diagnosis of
- MDS
- Secondary AML (sAML) with myelodysplasia
- Therapy-related MDS (t-MDS)
- Aplastic anemia (AA)

AND
Age at diagnosis: 18-40yo

AND
Sufficient germline DNA available

Irrespective of family history

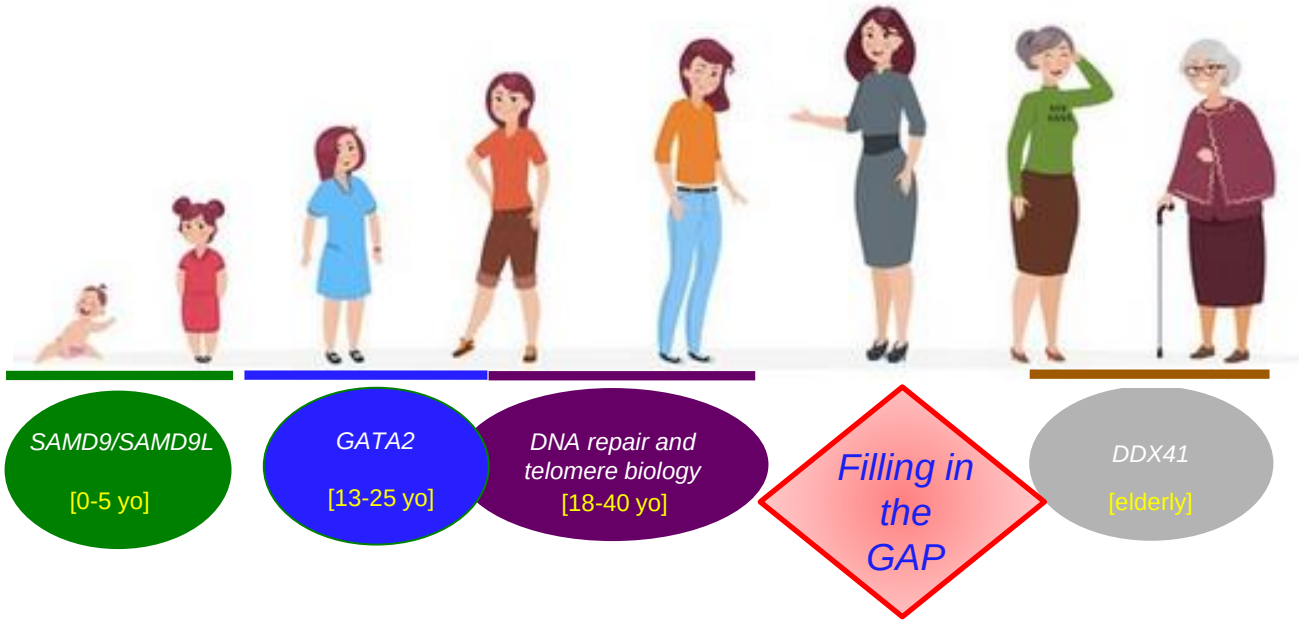
cohort sequenced:
n=121

MDS	75
t-MDS	9
AA	33
sAML	2
Cytopenia/BM dysplasia	2

Overall percentage of likely/known pathogenic variants:
in MDS- **19%**
in AA- **15%**

Simone Feurstein, Jane E. Churpek, Tom Walsh, Sioban Keel, Marja Hakkarainen, Thomas Schroeder, Ulrich Germing, Stefanie Geyh, Michael Heuser, Felicitas Thol, Christian Pohlkamp, Torsten Haferlach, Juehua Gao, Carolyn Owen, Gudrun Goehring, Brigitte Schlegelberger, Divij Verma, Daniela S. Krause, Guimin Gao, Tara Cronin, Suleyman Gulsuner, Ming Lee, Colin C. Pritchard, Hari Prasanna Subramanian, Daniela del Gaudio, Zejuan Li, Soma Das, Outi Kilpivaara, Ulla Wartiovaara-Kautto, Eunice S. Wang, Elizabeth A. Griffiths, Konstanze Döhner, Hartmut Döhner, Mary-Claire King. *Leukemia* **35:** 2439-2444 (2021)

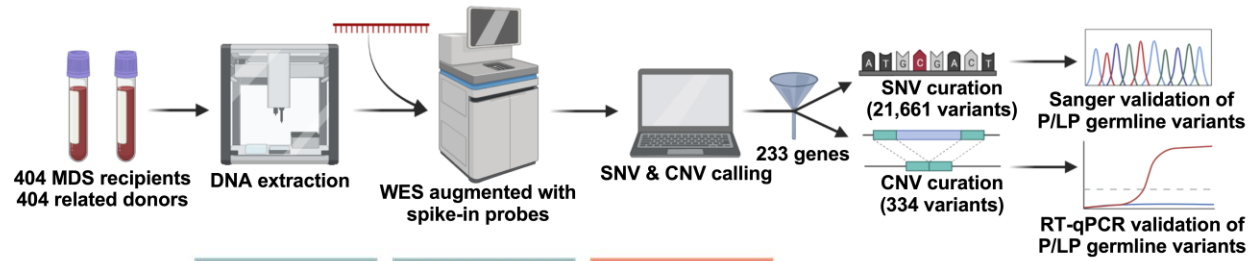
Age of presentation (of MDS) is a surrogate for the biological pathway

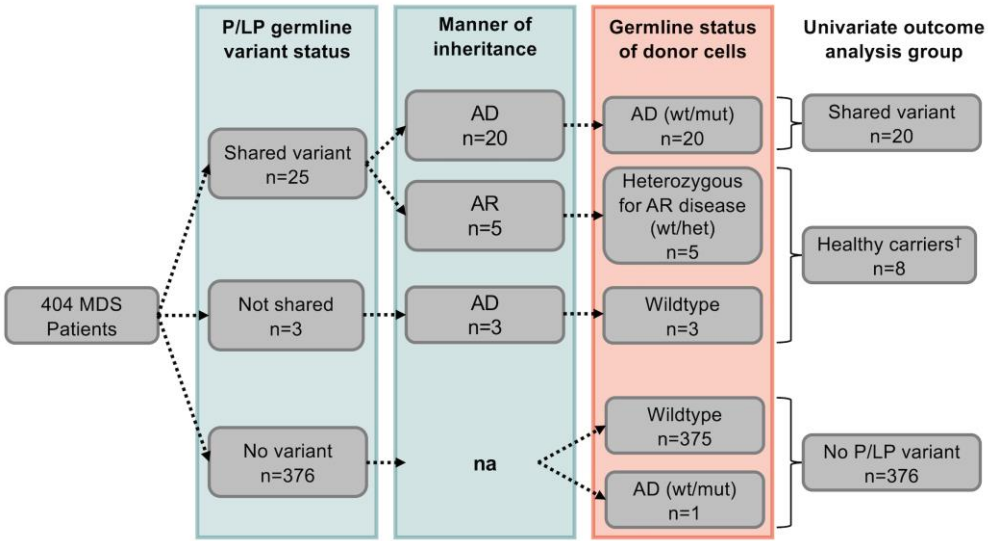


Private Information

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

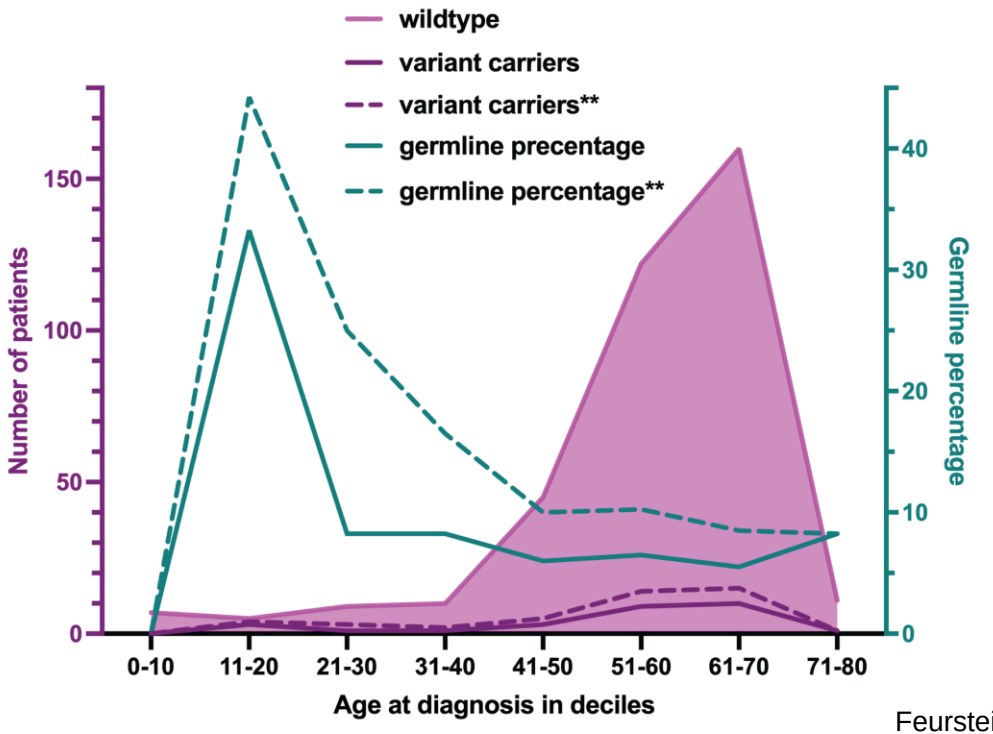
Determining the frequency of deleterious germline variants in MDS across the age spectrum (CIBMTR cohort)





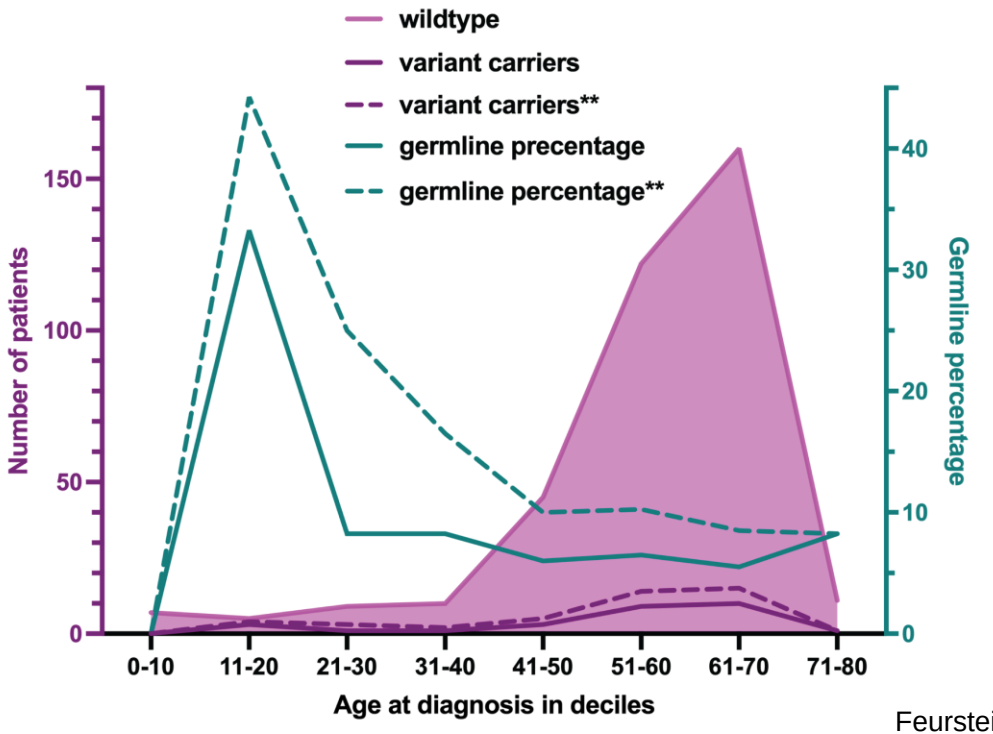
Feurstein, S. *et al. Blood* **140:** 2533-2548 (2022)

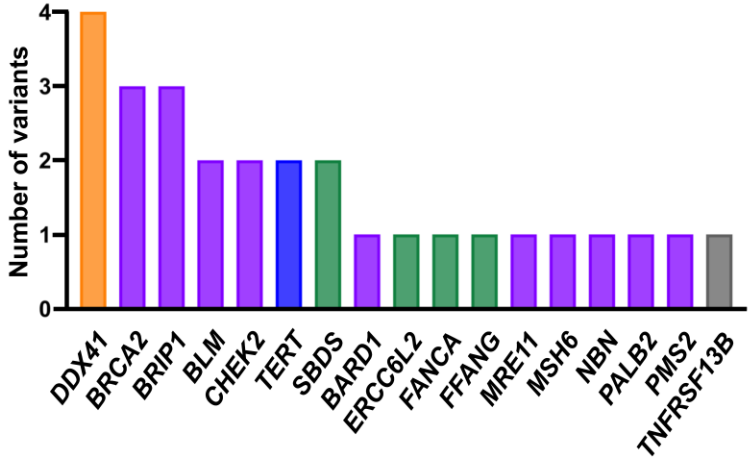
Frequency of deleterious germline variants in MDS across the age spectrum: 7% (>5% in all age deciles)



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

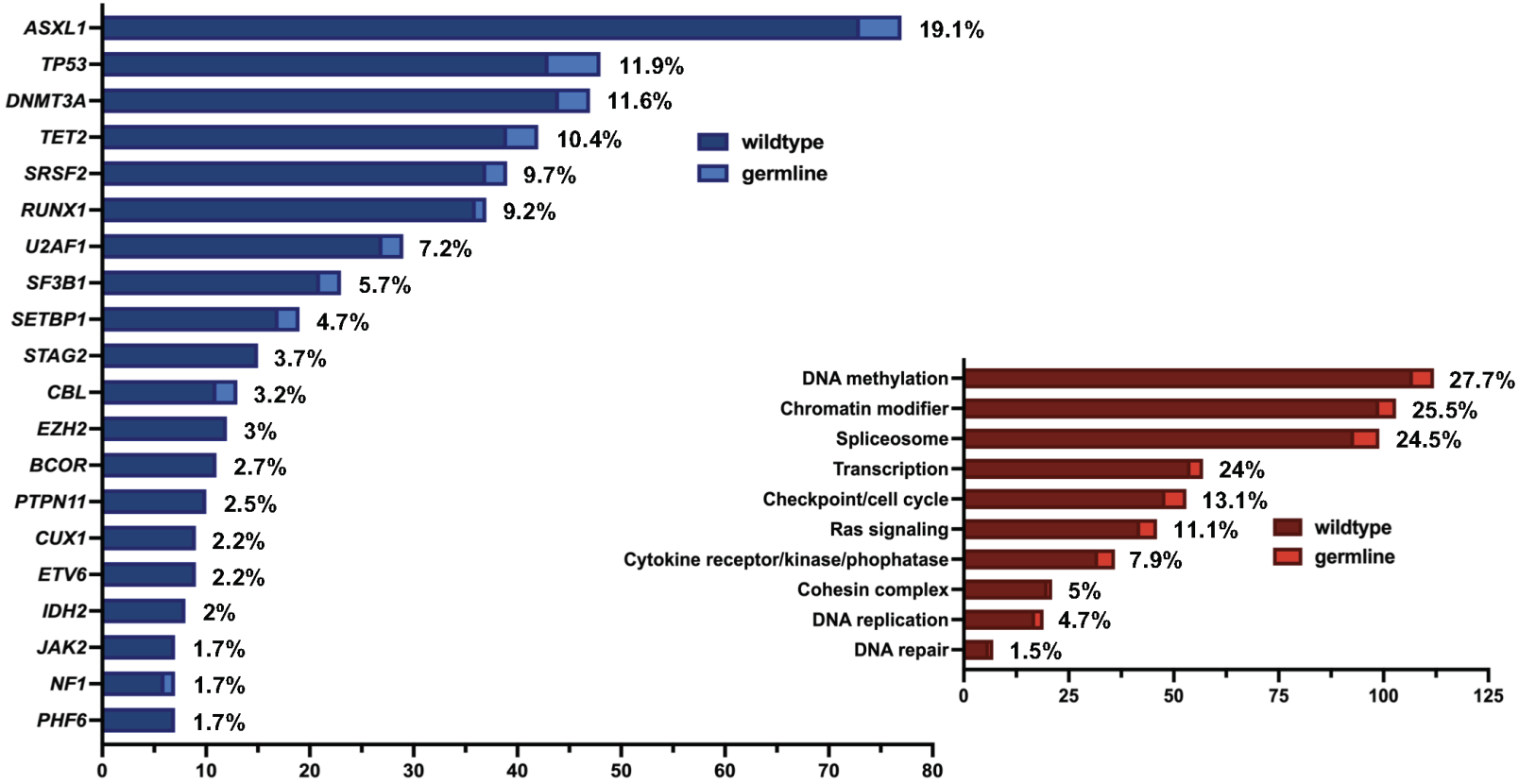
Frequency of deleterious germline variants in MDS across the age spectrum: 7% (>5% in all age deciles)





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

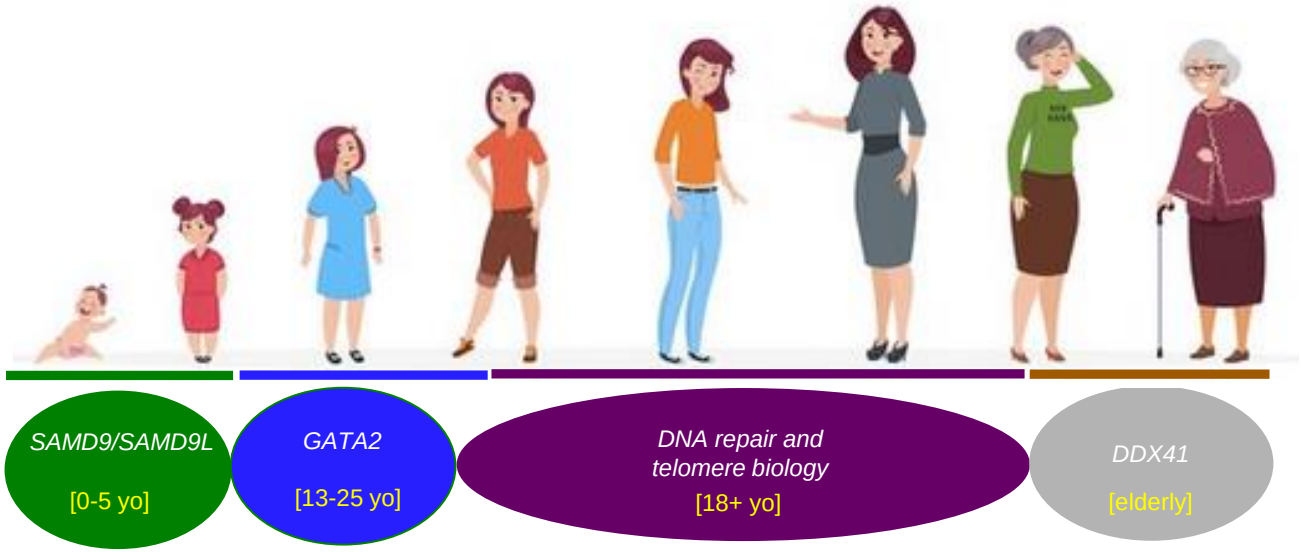
Somatic mutation spectrum = that of *de novo* MDS



Private Information

Tefferi, Gerds *et al. Blood* **140:** 2533-2548 (2022)

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

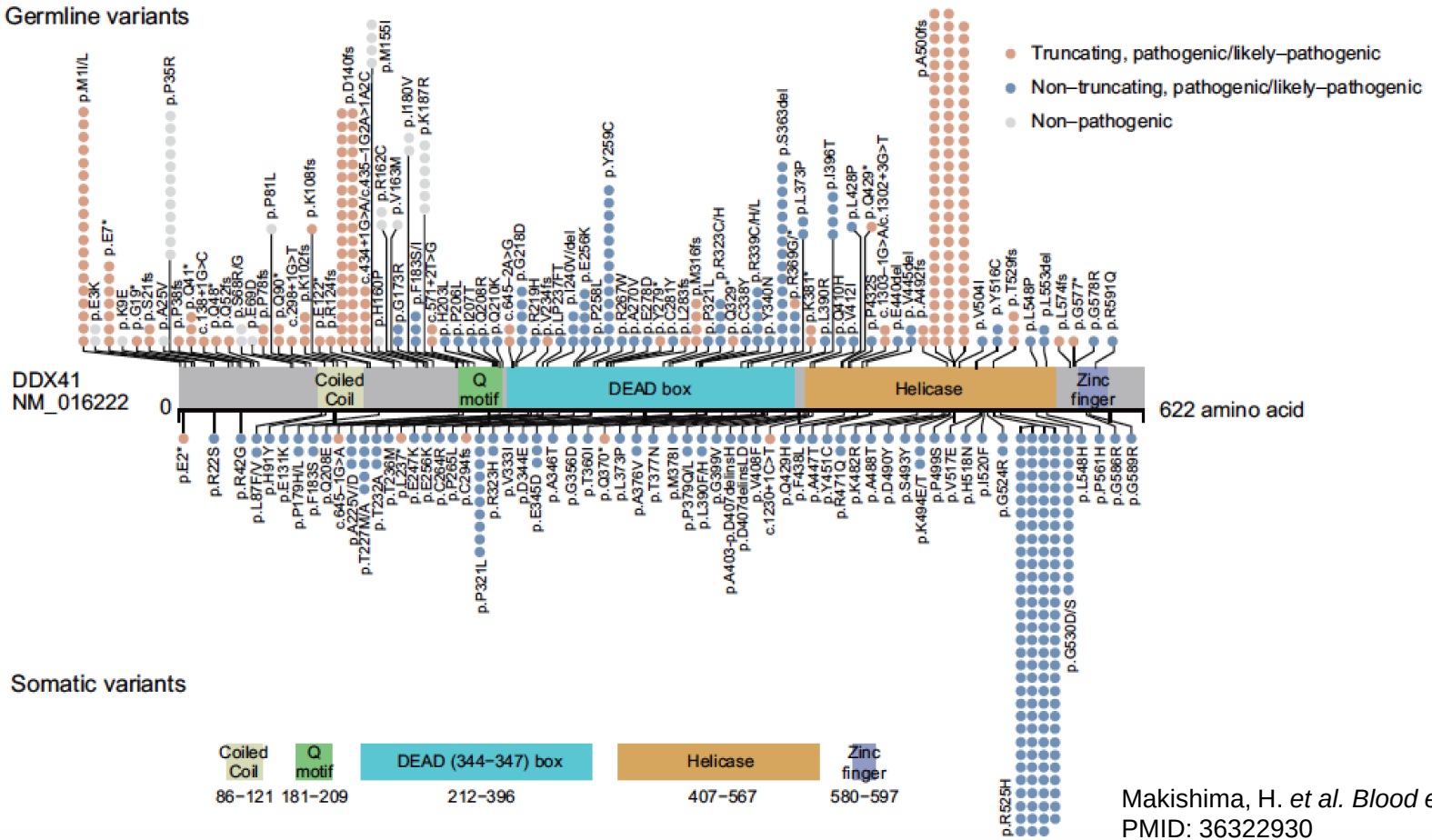


Feurstein, S. *et al. Leukemia* **35:** 2439-2444 (2021)

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

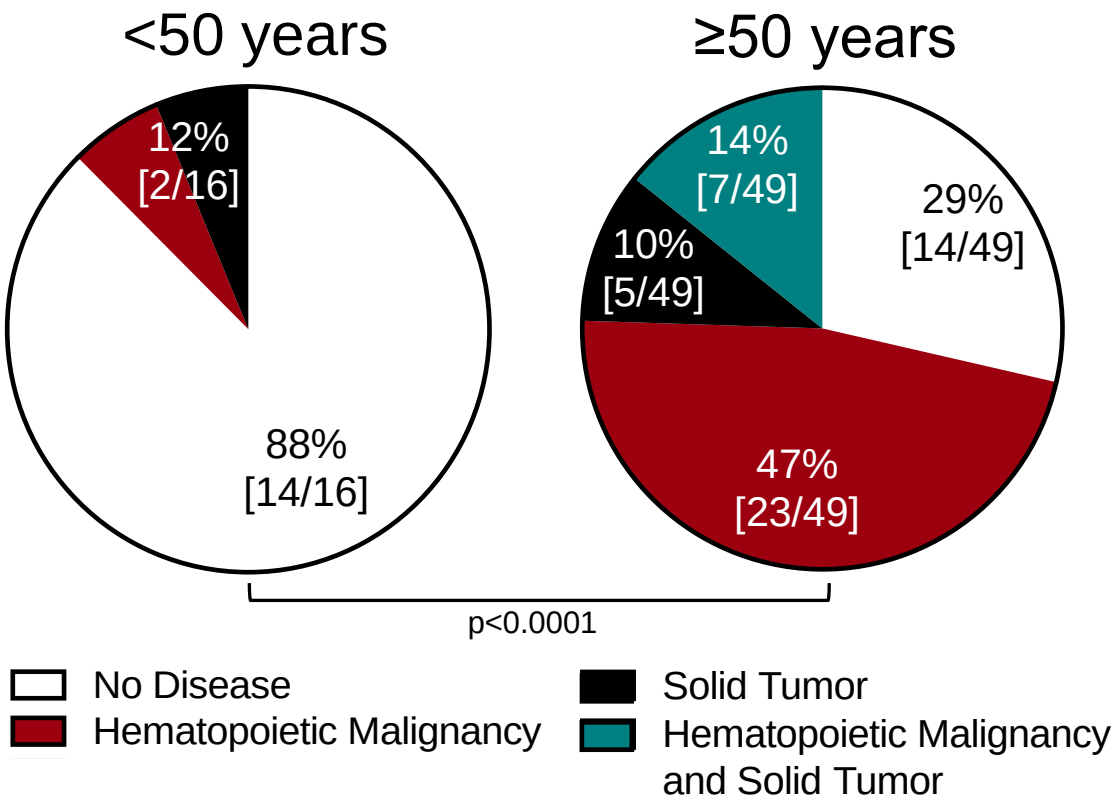
Disease mechanisms–
DDX41 and its unique biology

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

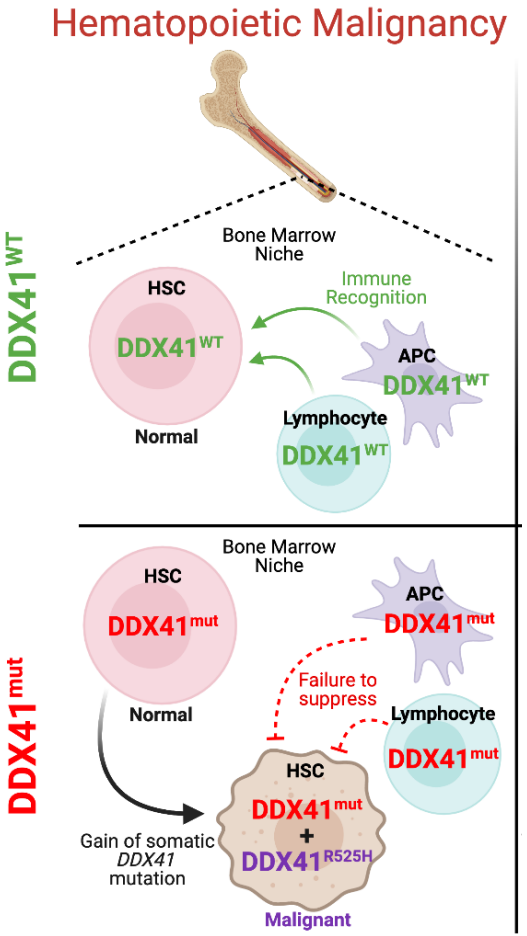


Makishima, H. *et al. Blood epub* (2022)
PMID: 36322930

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

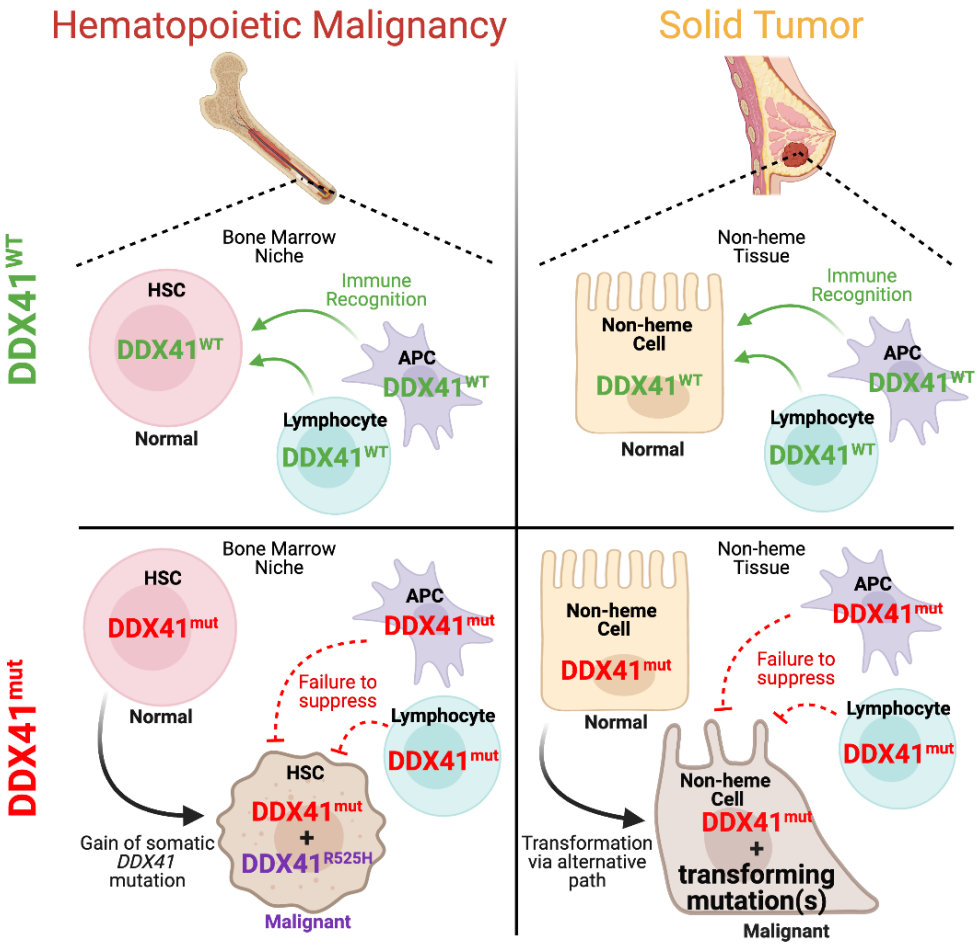


Mechanistic model for *DDX41*^{mut}-mediated tumorigenesis



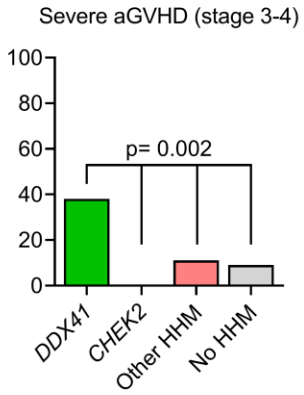
↑ inflammation?

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



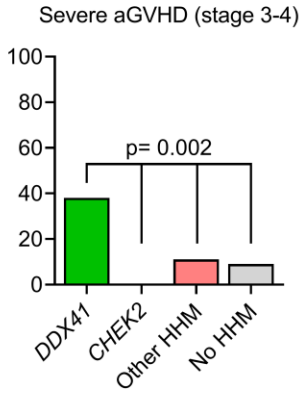
inflammation?

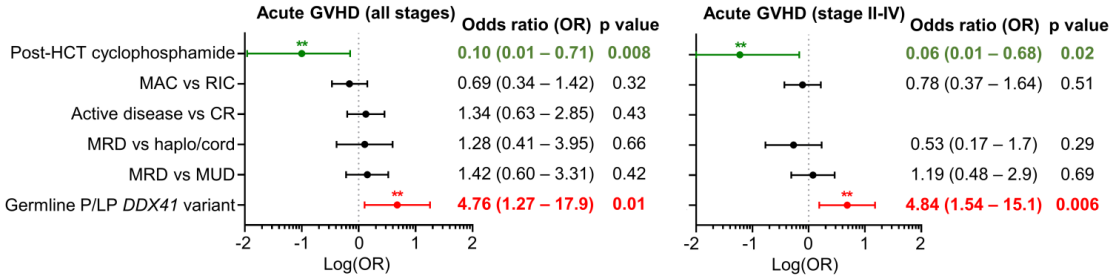
People with deleterious germline *DDX41*^{mut} develop more GVHD post-transplant (with WT donors)



Saygin, C. *et al. Blood Advances epub* (2022) PMID: 36001442

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





Saygin, C. *et al. Blood Advances epub* (2022) PMID: 36001442

The unique biology of deleterious germline *DDX41* variants

- Some variants are more common in particular populations:
  - Asian: A500fs
  - Northern European: M1? and D140fs

- Clonal hematopoiesis does not exist decades before malignancy

- Malignancies develop LATER in life, on average = *de novo*
  - Myeloid > Lymphoid
  - Men > Women

- Severe GVHD develops after allogeneic HSCT unless post-transplant cytoxan is used→ suggesting inflammatory milieu?

- In families with solid tumors, second deleterious germline variants often exist→ suggesting permissive role of the *DDX41* variant in solid tumor growth, through inflammatory milieu?

Testing and Management Considerations

Key features that signal patients/families who warrant *PROPER* germline predisposition testing

- Multiple cancers within a single individual (t-MN versus ‘double cancers’)
- Diagnosis of a hematopoietic malignancy at a much younger age than expected from the general population

  BUT… people who present at an “average” age for a particular diagnosis are still potentially deserving of genetic predisposition testing
  (i.e., presentation at an average age does not preclude germline contribution and need for genetic testing).

- Other hematopoietic malignancies or young onset (≤50yo) solid tumors within 2 generations
- Other hematopoietic abnormalities within the family
  (*e.g.,* macrocytosis, bleeding propensity, severe anemia, or anemia in men)
- Identification of a pathogenic DNA variant at a VAF consistent with germline status on tumor-based molecular profiling

Key features that signal patients/families who warrant *PROPER* germline predisposition testing

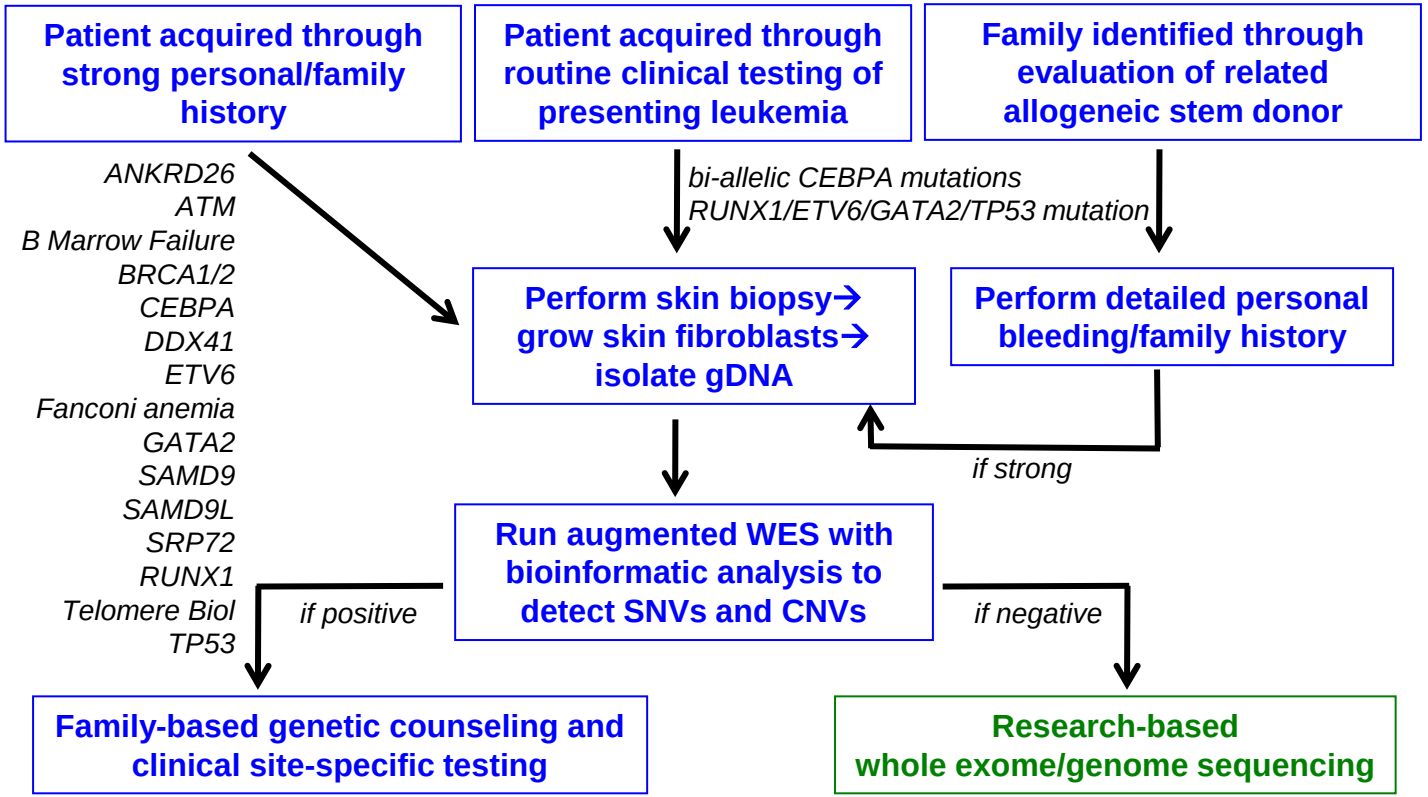
- Multiple cancers within a single individual (t-MN versus ‘double cancers’)
- Diagnosis of a hematopoietic malignancy at a much younger age than expected from the general population

  BUT… people who present at an “average” age for a particular diagnosis are still potentially deserving of genetic predisposition testing
  (i.e., presentation at an average age does not preclude germline contribution and need for genetic testing).

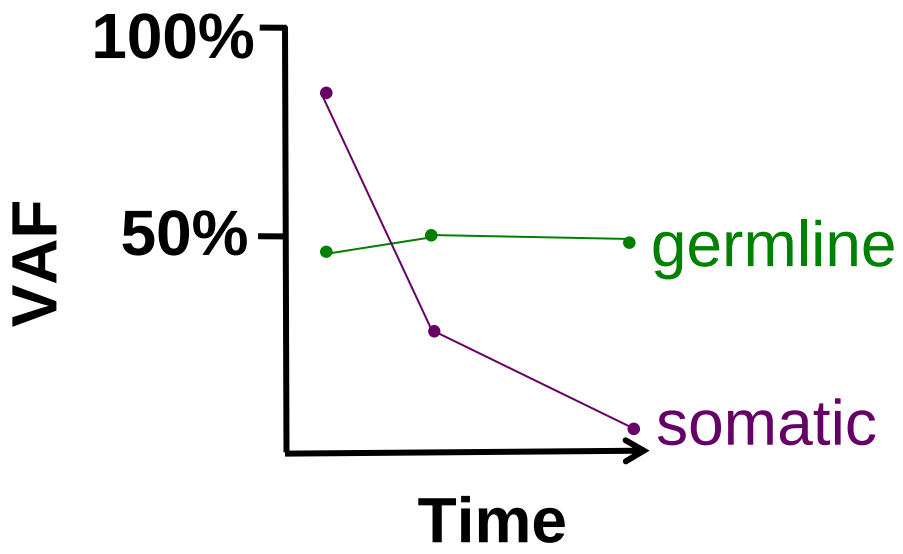
- Other hematopoietic malignancies or young onset (≤50yo) solid tumors within 2 generations
- Other hematopoietic abnormalities within the family
  (*e.g.,* macrocytosis, bleeding propensity, severe anemia, or anemia in men)
- Identification of a pathogenic DNA variant at a VAF consistent with germline status on tumor-based molecular profiling

Soon… all patients diagnosed with a hematopoietic malignancy [and their donors]

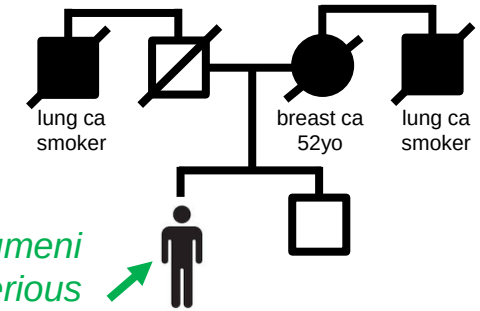
An algorithm for patient work-up



We perform our molecular panel every time a patient with leukemia has a bone marrow biopsy



Sometimes people with germline predisposition do not have strong personal/family histories

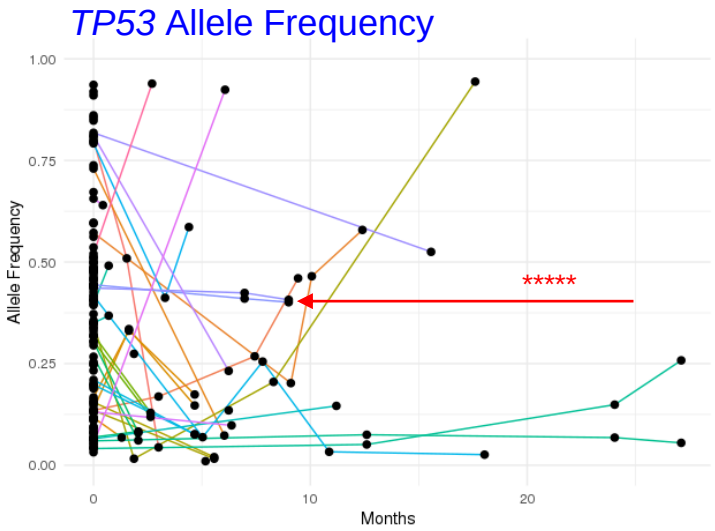


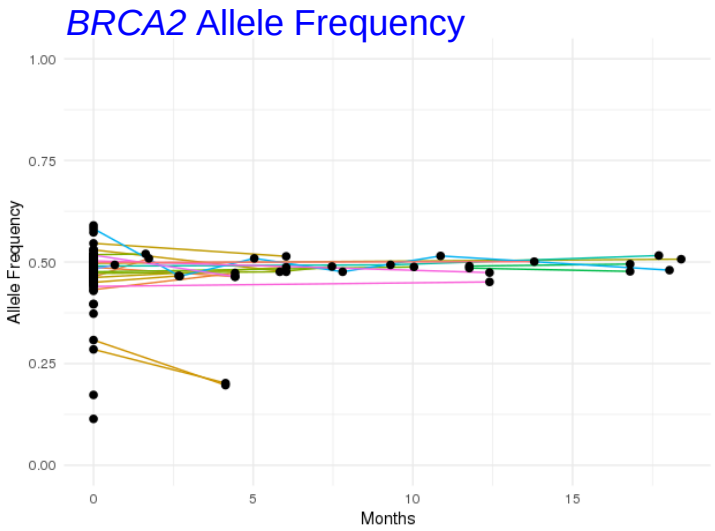
This person has Li-Fraumeni Syndrome-- deleterious germline TP53 variant!

	Diagnosis	Remission
VAFs		
DNMT3A	36%	3%
TP53	64%	45%

Careful interpretation of "somatic" testing can help identify such people

Detecting germline mutations from molecular profiling data over time





Tumor-based versus germline predisposition testing

	Tumor-based Testing	Germline Testing
Sample type	· any sample with hematopoietic tumor cells	· samples LACKING hematopoietic cells *(e.g.,* cultured skin fibroblasts, hair bulbs, and bone marrow-derived mesenchymal stromal cells)

Abbreviations used: CNV, copy number variant; CSF, cerebrospinal fluid; indel, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency

Tumor-based versus germline predisposition testing

	Tumor-based Testing	Germline Testing
Sample type	· any sample with hematopoietic tumor cells	· samples LACKING hematopoietic cells *(e.g.,* cultured skin fibroblasts, hair bulbs, and bone marrow-derived mesenchymal stromal cells)
Benefits	Sample already collected for other tests	Result is equivalent to germline and facilitates cascade testing in families

Abbreviations used: CNV, copy number variant; CSF, cerebrospinal fluid; indel, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency

Tumor-based versus germline predisposition testing

	Tumor-based Testing	Germline Testing
Sample type	· any sample with hematopoietic tumor cells	· samples LACKING hematopoietic cells *(e.g.,* cultured skin fibroblasts, hair bulbs, and bone marrow-derived mesenchymal stromal cells)
Benefits	Sample already collected for other tests	Result is equivalent to germline and facilitates cascade testing in families
Platforms	Cover gene exons Detect SNVs and large CNVs Coverage depth: 100s-1000s to detect small clones	Cover gene exons as well as non-coding regions (*e.g.,* promoters and enhancers) Detect SNVs and CNVs. Require flexibility to accommodate the predisposition genes that continue to be discovered Coverage depth 30-50-fold is sufficient to detect germline-range VAFs.

Abbreviations used: CNV, copy number variant; CSF, cerebrospinal fluid; indel, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency

Tumor-based versus germline predisposition testing

	Tumor-based Testing	Germline Testing
Sample type	· any sample with hematopoietic tumor cells	· samples LACKING hematopoietic cells (*e.g.,* cultured skin fibroblasts, hair bulbs, and bone marrow-derived mesenchymal stromal cells)
Benefits	Sample already collected for other tests	Result is equivalent to germline and facilitates cascade testing in families
Platforms	Cover gene exons Detect SNVs and large CNVs Coverage depth: 100s-1000s to detect small clones	Cover gene exons as well as non-coding regions (*e.g.,* promoters and enhancers) Detect SNVs and CNVs. Require flexibility to accommodate the predisposition genes that continue to be discovered Coverage depth 30-50-fold is sufficient to detect germline-range VAFs.
Cautions/ caveats	Hematopoietic tissues undergo somatic reversion easily, so the absence of a finding does not give assurance that there is no deleterious germline variant. These assays typically do NOT cover: non-coding gene regions or smaller CNVs	Time to results: up to three months

Abbreviations used: CNV, copy number variant; CSF, cerebrospinal fluid; indel, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency

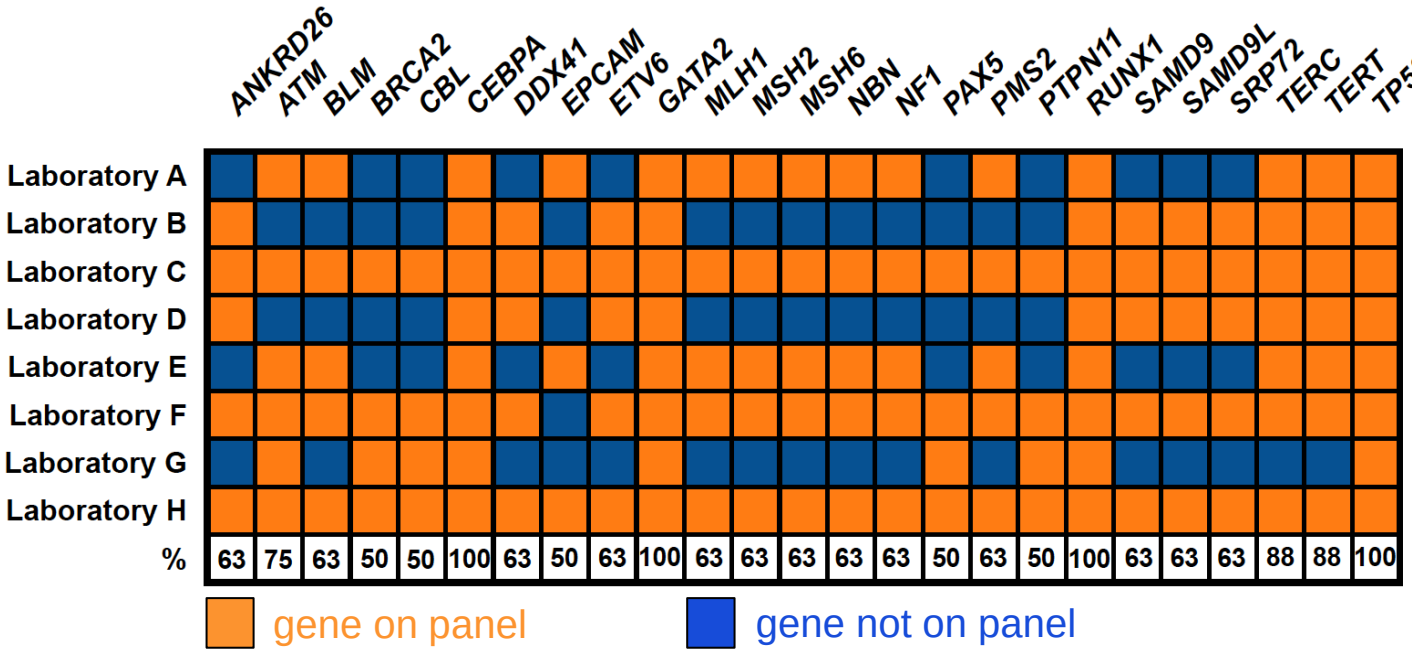
Tumor-based versus germline predisposition testing

	Tumor-based Testing	Germline Testing
Sample type	· any sample with hematopoietic tumor cells	· samples LACKING hematopoietic cells (*e.g.,* cultured skin fibroblasts, hair bulbs, and bone marrow-derived mesenchymal stromal cells)
Benefits	Sample already collected for other tests	Result is equivalent to germline and facilitates cascade testing in families
Platforms	Cover gene exons Detect SNVs and large CNVs Coverage depth: 100s-1000s to detect small clones	Cover gene exons as well as non-coding regions (*e.g.,* promoters and enhancers) Detect SNVs and CNVs. Require flexibility to accommodate the predisposition genes that continue to be discovered Coverage depth 30-50-fold is sufficient to detect germline-range VAFs.
Cautions/ caveats	Hematopoietic tissues undergo somatic reversion easily, so the absence of a finding does not give assurance that there is no deleterious germline variant. These assays typically do NOT cover: non-coding gene regions or smaller CNVs	Time to results: up to three months
Specific alleles	Same allele (*e.g.,* in *TP53* , *RUNX1* , and *CEBPA* , among others) can be somatic or germline	Specific alleles (*e.g.,* in *CHEK2* and *DDX41*) are overwhelmingly likely to be germline

Abbreviations used: CNV, copy number variant; CSF, cerebrospinal fluid; indel, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency

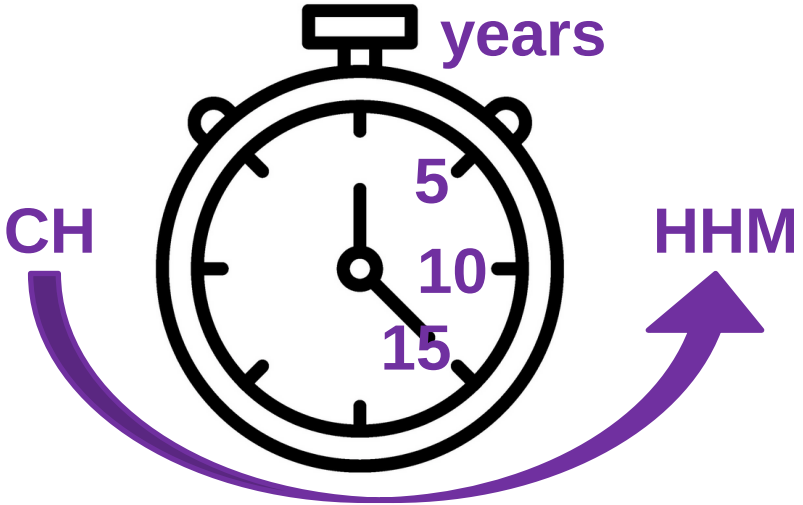
Growing list of germline predisposition genes

Testing platforms/submitted samples are not standardized

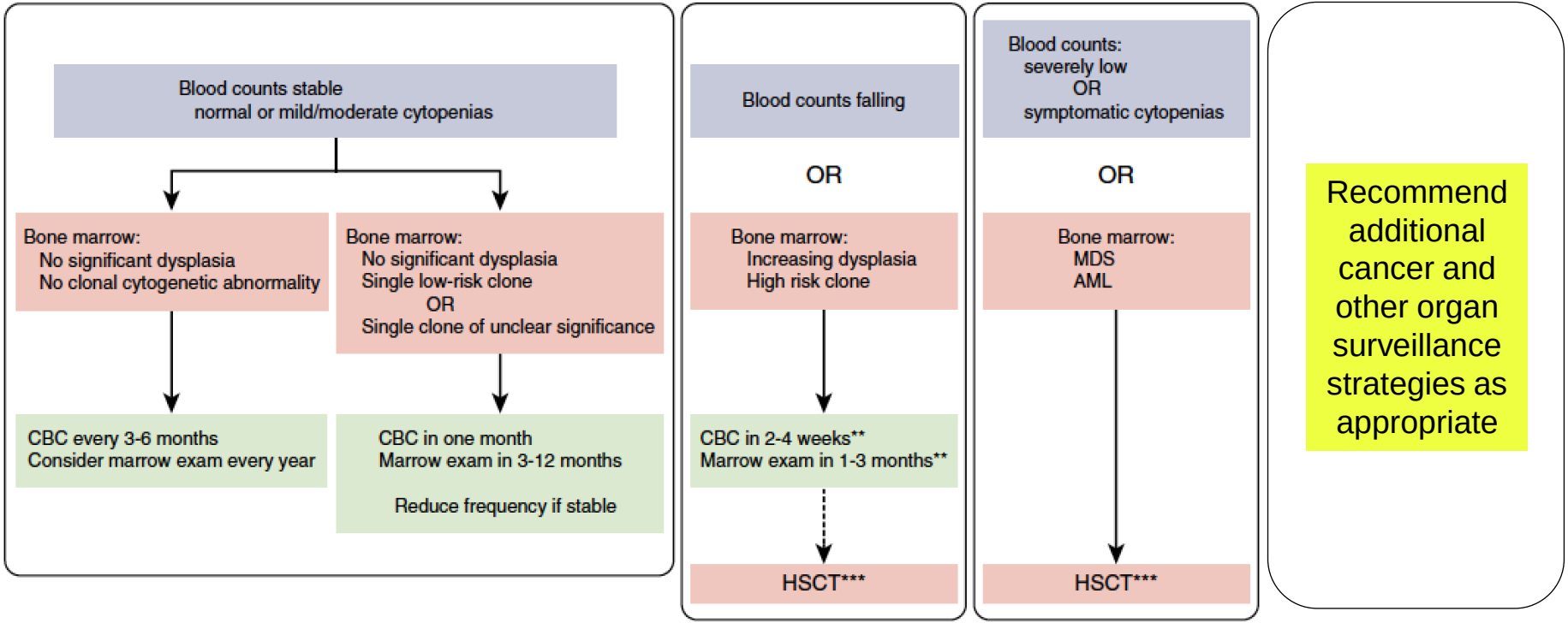


Roloff, G.W. et al. *Genet Med.* 23: 211-214 (2021)

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



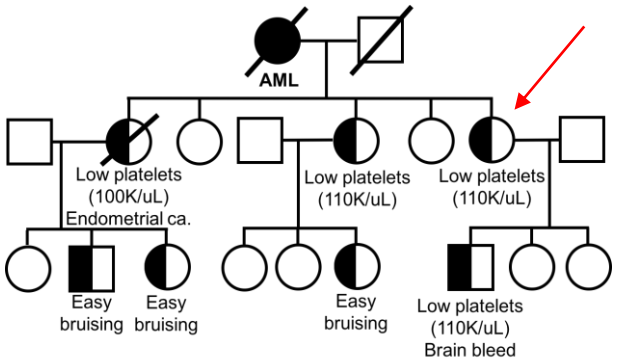
Surveillance recommendations

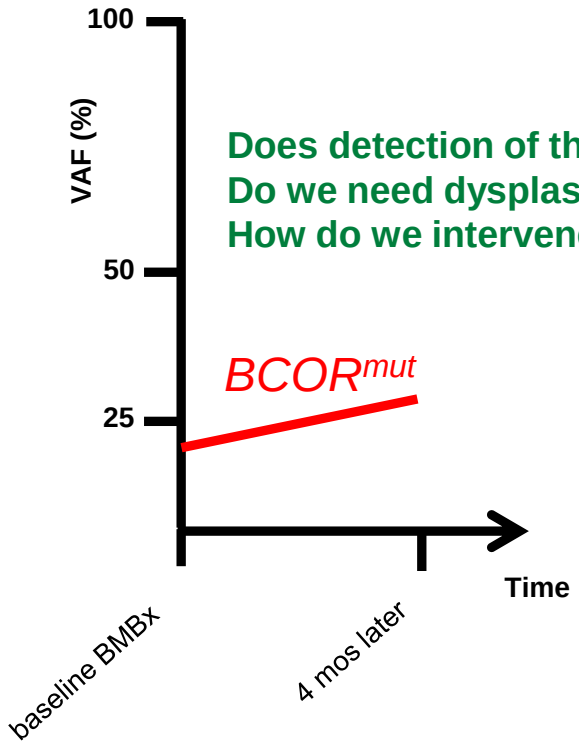


Godley, L. A. and Shimamura, A. *Blood* 130: 424-432 (2017)

Following CH over time

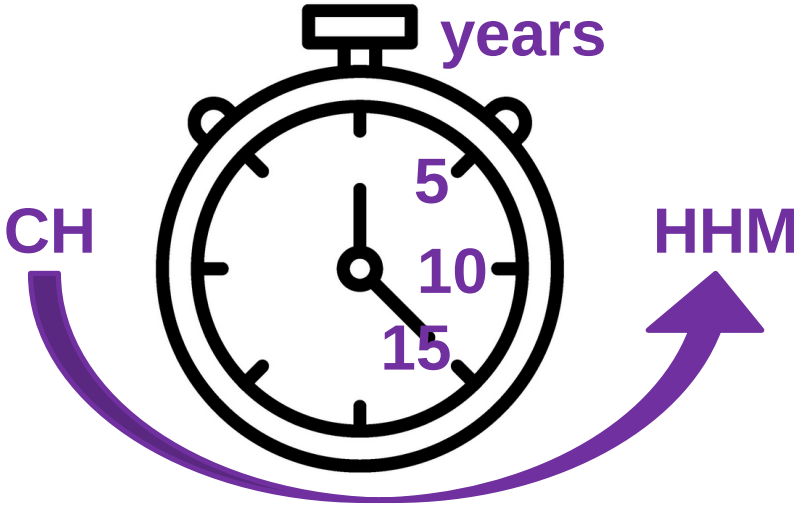
germline *RUNX1*^{mut}





Does detection of this clone constitute molecular MDS?
Do we need dysplastic cells to call MDS?
How do we intervene to slow/stop malignant progression?

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



We need to interpret carefully the molecular data we generate

Allogeneic stem cell donors:
they can have deleterious germline variants too!

Patient with leukemia

Allogeneic stem cell donors:
they can have deleterious germline variants too!

Patient with leukemia

Molecular profiling
of patient leukemia:
DDX41 D140fs (VAF 49%)
DDX41 R525H (VAF 9%)

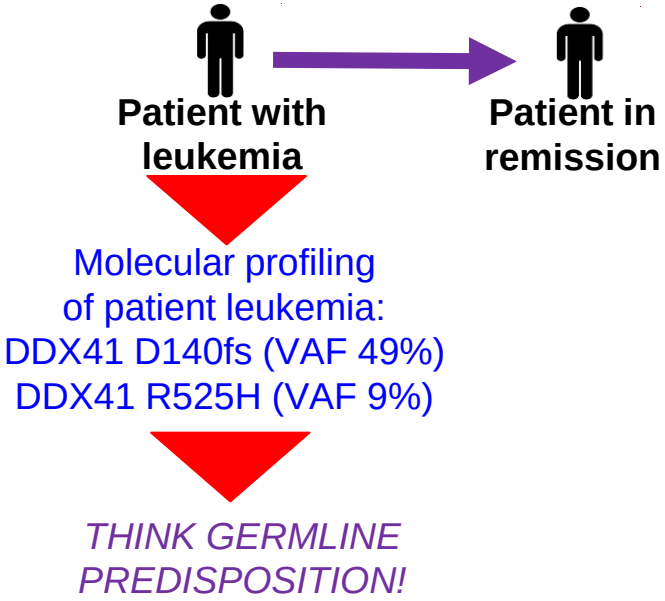
Allogeneic stem cell donors: they can have deleterious germline variants too!

Patient with leukemia

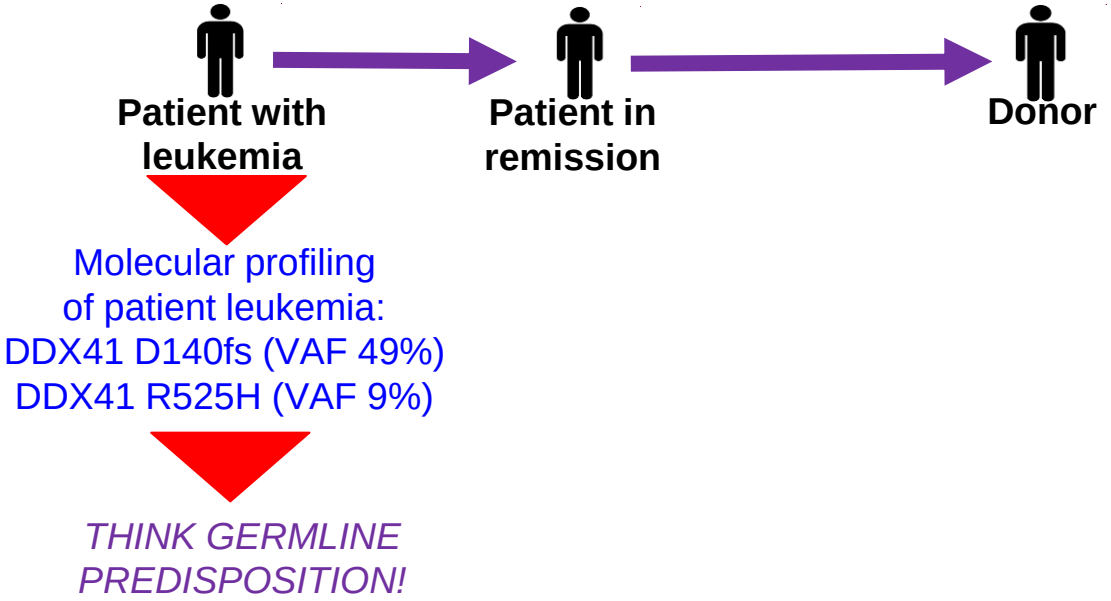
Molecular profiling
of patient leukemia:
DDX41 D140fs (VAF 49%)
DDX41 R525H (VAF 9%)

THINK GERMLINE PREDISPOSITION!

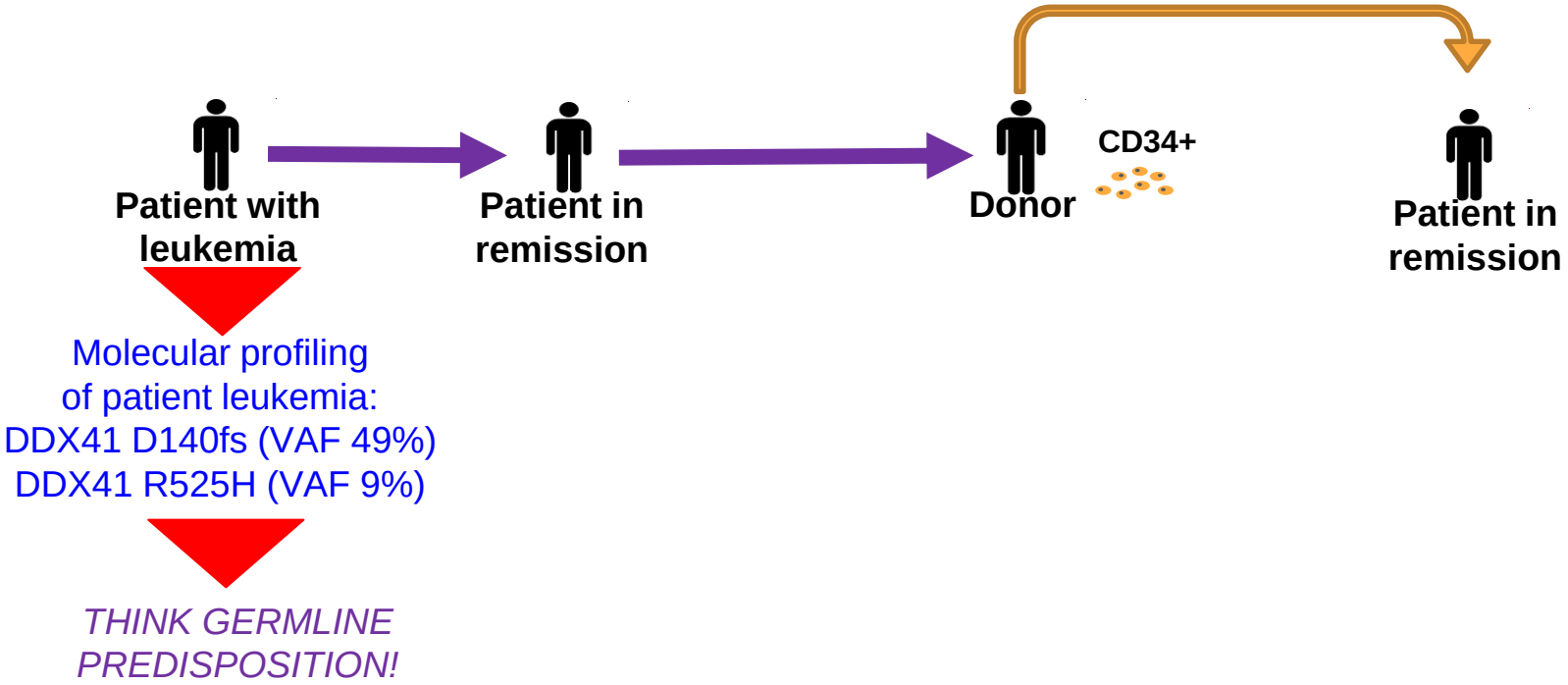
Allogeneic stem cell donors: they can have deleterious germline variants too!



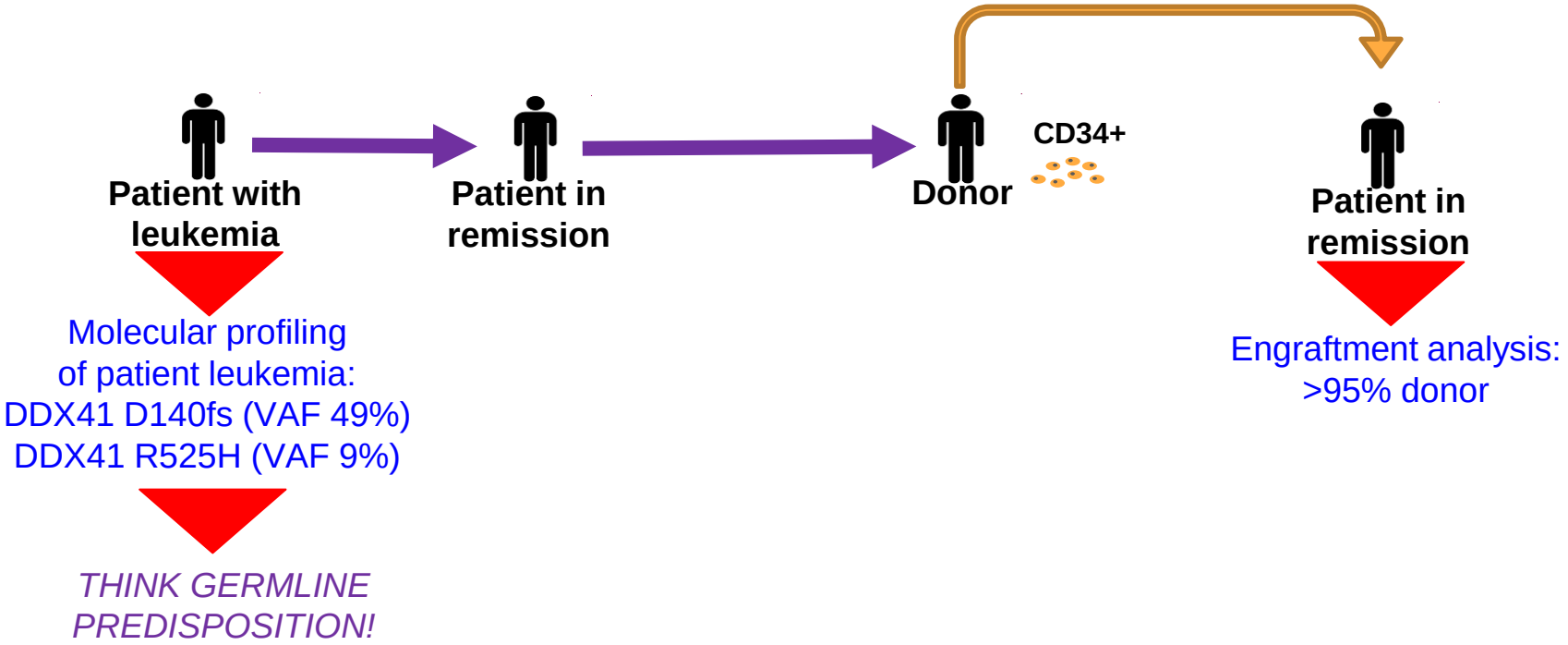
Allogeneic stem cell donors: they can have deleterious germline variants too!



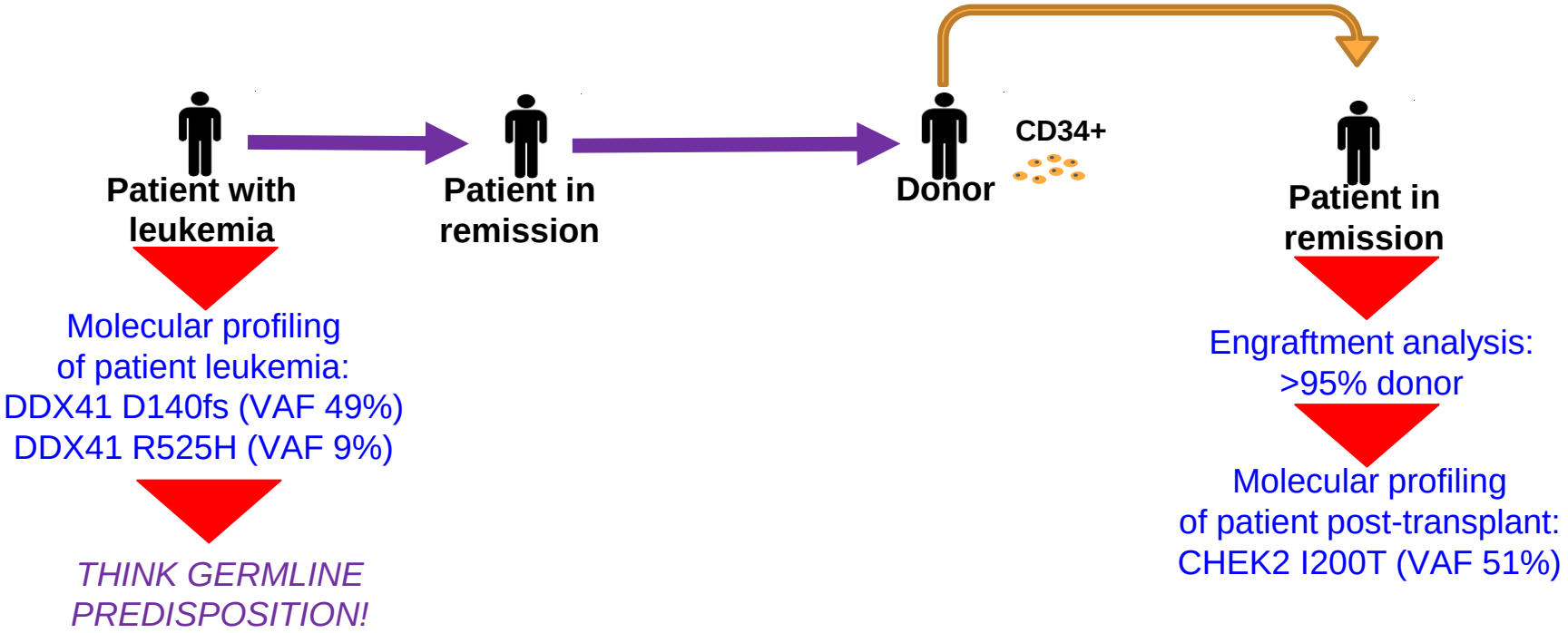
Allogeneic stem cell donors: they can have deleterious germline variants too!



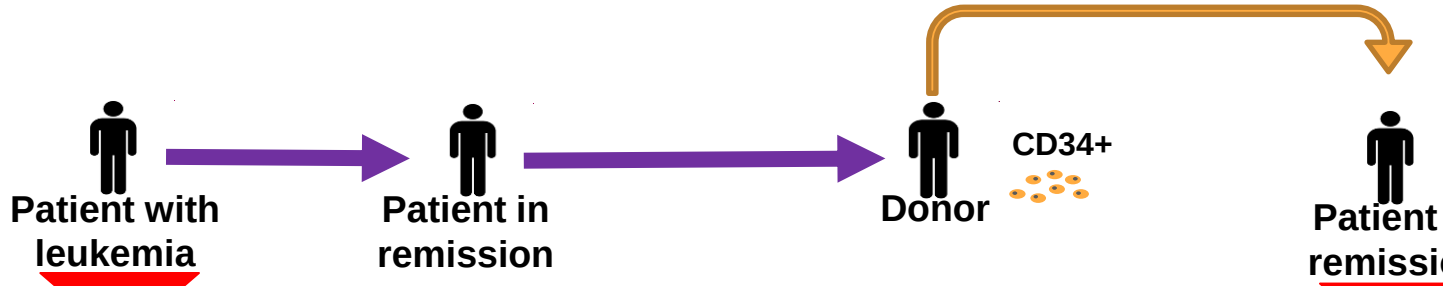
Allogeneic stem cell donors: they can have deleterious germline variants too!



Allogeneic stem cell donors: they can have deleterious germline variants too!



Allogeneic stem cell donors: they can have deleterious germline variants too!



Molecular profiling of patient leukemia:
DDX41 D140fs (VAF 49%)
DDX41 R525H (VAF 9%)

THINK GERMLINE PREDISPOSITION!

Allogeneic stem cell transplantation is ethically compromised–

especially when related donors are used

especially when you perform molecular testing post-transplant with 100% donor chimerism

Engraftment analysis:
>95% donor

Molecular profiling of patient post-transplant:
CHEK2 I200T (VAF 51%)

Inherited predisposition to hematopoietic malignancies: What have we learned?

- Germline predisposition to all cancers is COMMON, and there is significant overlap between ‘solid’ and ‘liquid’ cancer syndromes.
- Testing for risk to hematopoietic malignancies is complicated by high frequency of somatic reversion in hematopoietic tissues and inadequate testing platforms from many laboratories.
- Careful interpretation of tumor profiling data can prioritize patients with likely germline predisposition alleles.
- Post-transplant GVHD prophylaxis should include cytoxan for those with germline *DDX41* mutations

Future:

Standardization of germline testing for some/all patients with hematopoietic malignancies and their donors

Other treatment plans based on susceptibilities conferred by germline variants