Germline predisposition to hematologic cancer

MB&C course

February 9, 2024

Jolien De Bie

Germline *CHEK2* and *ATM* Variants in Myeloid and Other Hematopoietic Malignancies

Germline Predisposition

Volume 17, pages 94–10

Prognostic impact of DDX41 **germline** mutations in intensively treated **acute**

Germ line DDX41 mutations define a unique subtype of myeloid neoplasms.

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Makishima H, Saiki R, Nannya Y, Korotev S, Gurnari C, Takeda J, Momozawa Y, Best S, Krishnamurthy P, Yoshizato T, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, Shiraishi Y, Nagata Y, Kakiuchi N, Onizuka M, Chiba K, Tanaka H, Kon A, Ochi Y, Nakagawa MM, Okuda R, Mori T, Yoda A, Itonaga H, Miyazaki Y, Sanada M, Ishikawa T, Chiba S, Tsurumi H, Kasahara S, Müller-Tidow C, Takaori-Kondo A, Ohyashiki K, Kiguchi T, Matsuda F, Jansen JH, Polprasert C, Blombery P, Kamatani Y, Miyano S, Malcovati L, Haferlach T, Kubo M, Cazzola M, Kulasekararaj AG, **Godley LA**, Maciejewski JP, Ogawa S

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PMID: 3632293

LBA-6 ERG Is a New Malignancy

Program: General Sessions
Session: Late-Breaking Abstracts Session
Hematology Disease Topics & Pathways: Bleeding and Clotting, Acute Myeloid Maligr
Syndromes, Genetic Disorders, Diseases, th

Tuesday, December 12, 2023, 9:00 AM-10

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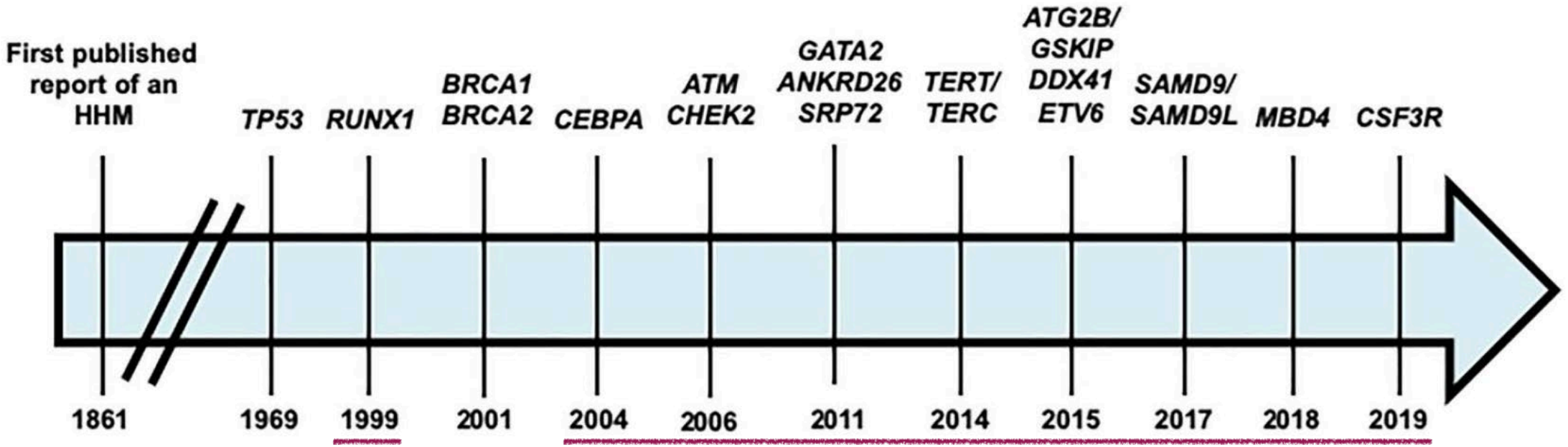
Germ line predisposition variants occur in myelodysplastic syndrome patients of all ages

ver [1],

Simone Feurstein [1 2], Amy M Trottier [1 3], Noel Estrada-Merly [4], Matthew Pozsgai [1],

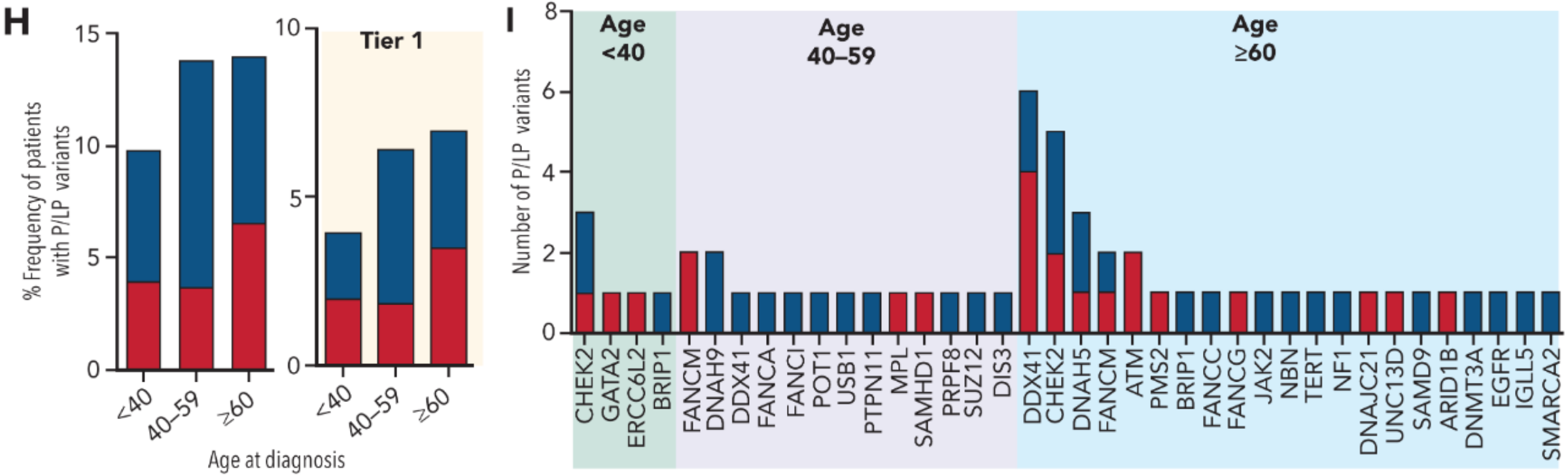


- 1861: first publication
- 1947/1975: large familial investigations (8% probands with familial history of leukemia)
- 1960's: Li-Fraumeni, Lynch…
- 1999: first Hereditary Hematologic Malignancy (HHM) syndrome < *RUNX1*

1. Incidence of germline variants in hematologic cancers

8-10% of children with cancer (hemato + solid) confirmed germline syndrome + 6% with LP germline variant

5% of adults with AML carries germline predisposition allele + 10% with LP variant



1. Incidence of germline variants in hematologic cancers

Children and AYAs (<45y) with MDS/AA or considered for HSCT:

5-13% of all AA cases have germline P/LP variant

13-19% of all MDS cases have germline P/LP variant

mostly genes involved in DNA repair or telomere biology

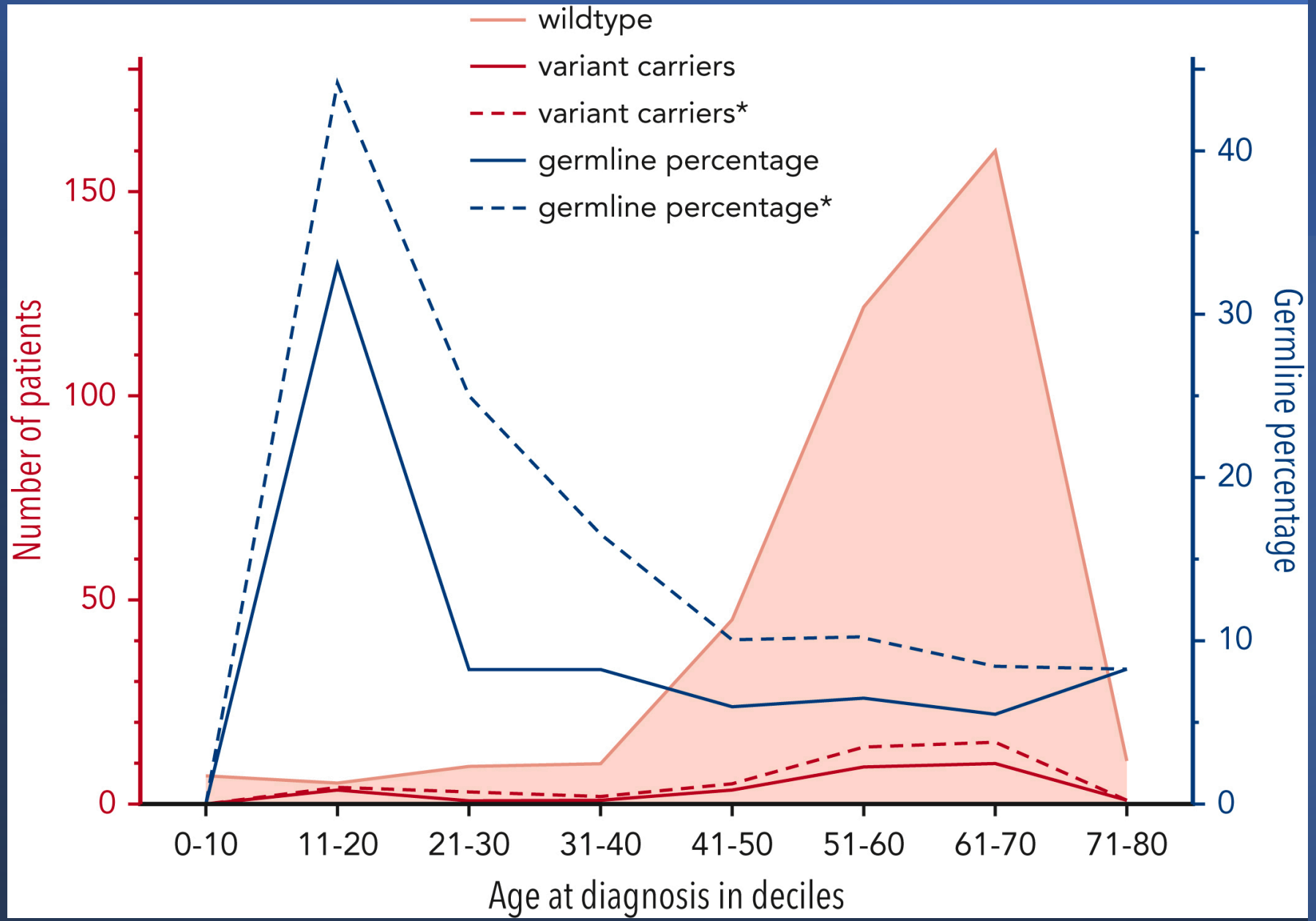
MDS < 18y:

17% with P/LP variant in *SAMD9/SAMD9L*

7% with P/LP variant in *GATA2*

Clinical suspicion of bone marrow failure (BMF) or familial history of MDS or leukemia:

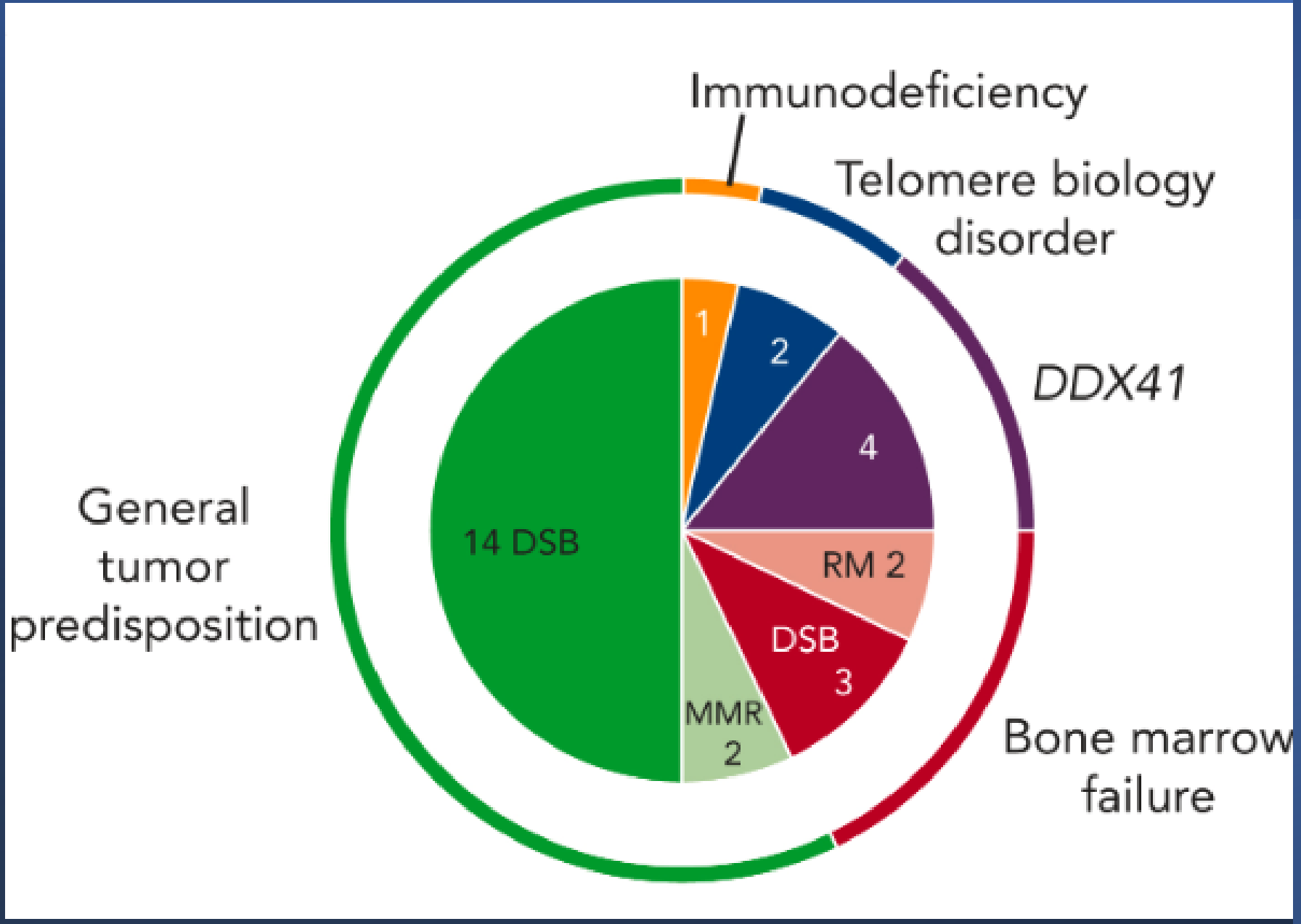
18-48% with germline variants reported



7% of MDS patients carries a P/LP germline variant

- 33% pts <20y with confirmed variant
- still 6% for pts 40-70y

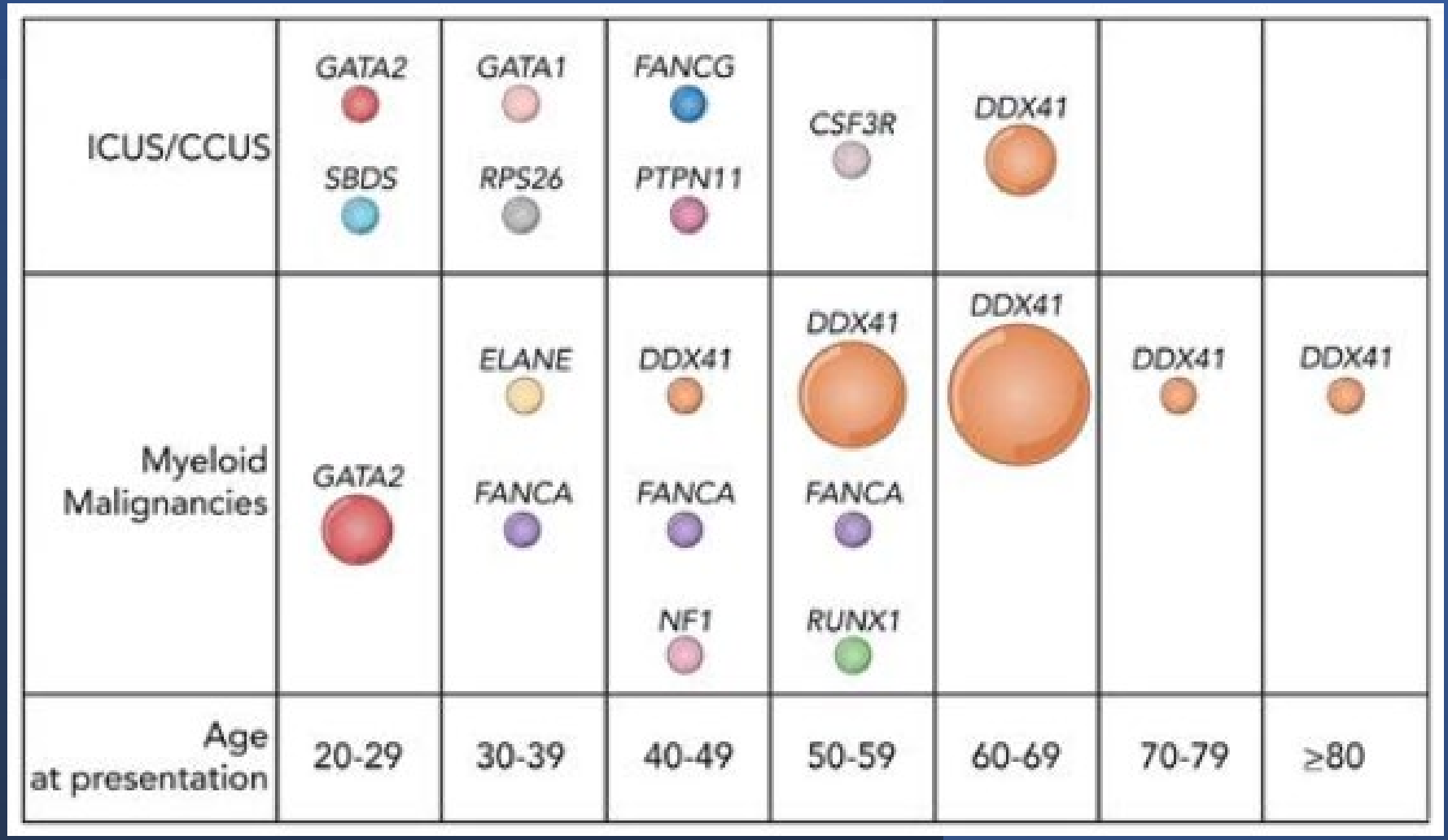
Deleterious germline variants in MDS



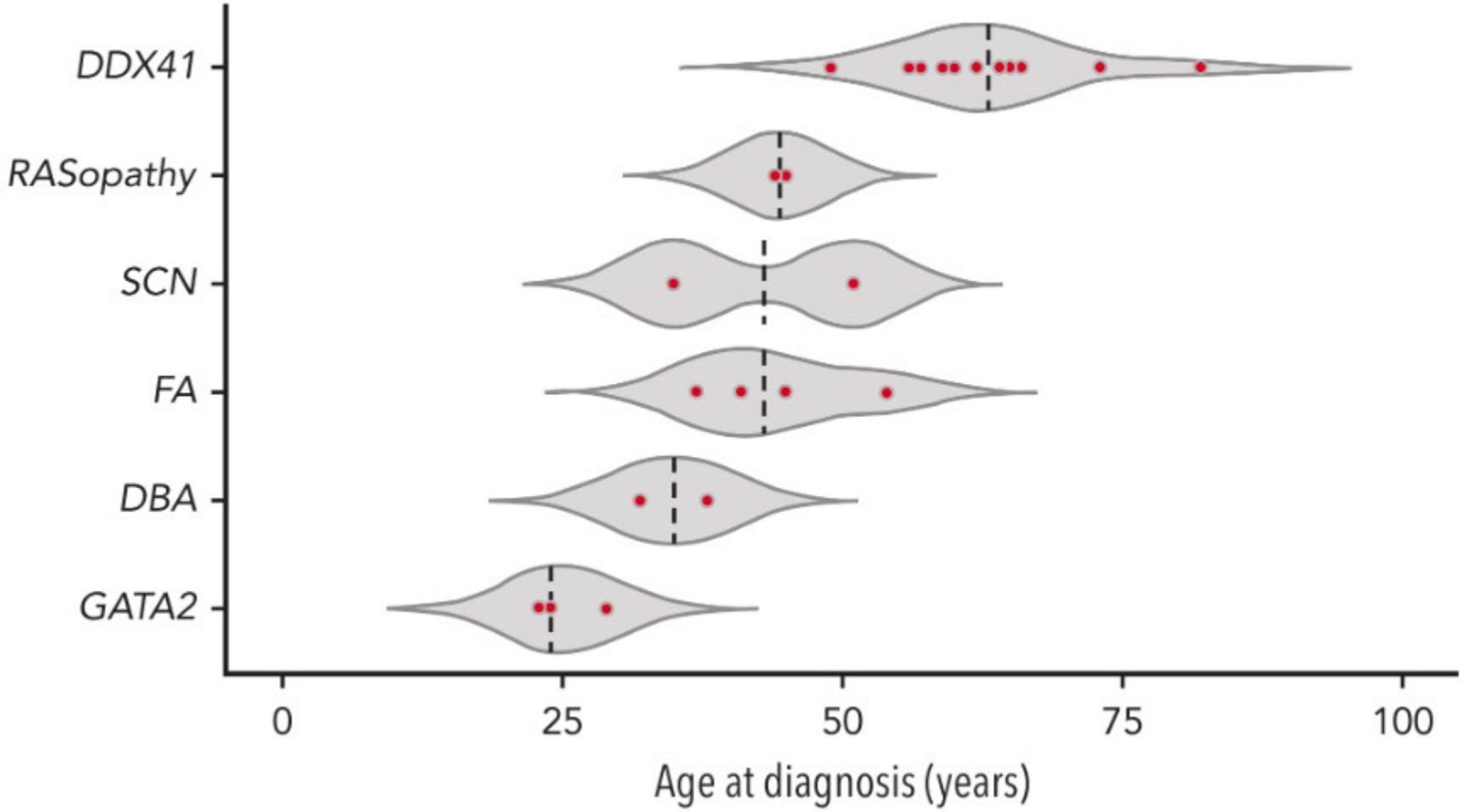
1. Incidence of germline variants in hematologic cancers

6% to 7% deleterious germ line alleles in adults with unexplained cytopenias and hypocellular bone marrows

GWAS studies have shown that germline variants predispose to Clonal Hematopoiesis (SNVs, indels, CAs): loci located close to *GATA2, SMC4, PARP1*,…



1. Incidence of germline variants in hematologic cancers



1. Incidence of germline variants in hematologic cancers

Monozygotic twins

Hodgkin Lymphoma: risk x100

Non-Hodgkin Lymphoma: risk x23

Dizygotic twins

Non-Hodgkin Lymphoma: risk x14

First-degree relatives

NHL: 1.8 fold risk

HL: 1.2-7 fold risk

DLBCL: 9.8 fold risk

FL: 4 fold risk

2. Importance of germline screening in hematologic cancers

Treatment options

selection of optimal treatment and conditioning regimens

donor selection for hematopoietic stem cell transplantation (HSCT)

Genetic counseling

prevention, familial screening, (pre-natal counseling)

3. Detection of germline variants in hematologic cancers

Presentation?

Syndrome

- Specific requests
- High detection rates

Suspicion

- Broad screens
- Lower detection rates

Incidental findings

- Specific requests
- Lower detection rates

3. Detection of germline variants in hematologic cancers

Presentation?

Suspicion

- History of multiple cancers
- First- or second-degree relative(s) with hematologic neoplasms or solid tumors
- Immunodeficiency
- Thrombocytopenia or bleeding disorder prior to myeloid neoplasm
- Physical stigmata associated with predisposition syndromes

- ?Age (<45y ⇔ *DDX41, TERT*)

Of note, in case of children: Ripperger or Jongmans questionnaire

3. Detection of germline variants in hematologic cancers

Presentation?

Incidental findings

- Typical genes included in somatic panels: *DDX41, CEBPA, MPL, PTPN11, RUNX1, TP53*,…
- VAF > 30%
- +/- 2nd hit
- Loss of function, hotspots

Caveat: missing genes, only coding regions, confirmation required!

4. Confirmation of germline variants in hematologic cancers

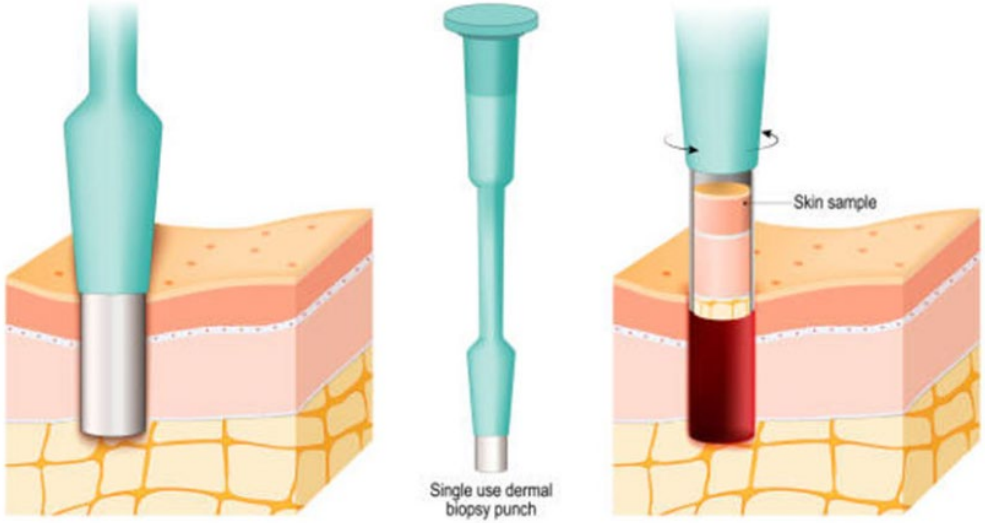
Suspicion

- Large targeted panels or WES
- Bone marrow failure, primary immune deficiency, cancer predisposition,…

Incidental findings

- Specific test on DNA extracted from hair, nails

Gold standard
= fibroblast culture



5. Consequences of germline variants in hematologic cancers

Counseling

patient + family members, including a segregation analysis

Difficulties

penetrance

optimal follow-up strategy largely dependent on detected variant (+ often unknown)

5. Consequences of germline variants in hematologic cancers

Table 3. Recommended clinical assessments for patients with germ line genetic predisposition to hematologic malignancies

	After initial diagnosis of inherited predisposition	At clinical follow-up
Consider expert consultation or referral to specialized center	√	Continued consultation as needed
Genetic counseling with certified genetic counselor trained in inherited hematopoietic malignancies	√	As needed
Update personal/family history	√	√
Physical examination	√	√
CBC with white blood cell differential and microscopy review for dysplasias	√	√
Bone marrow biopsy with cytogenetic/FISH and molecular analysis	√	Consider annually or when abnormalities develop on CBC
HLA typing and referral to allogeneic stem cell transplant center	If significant dysplasia or other indications of malignancy exist at baseline	Increasing dysplasia or other indications of malignancy

CBC, complete blood count; FISH, fluorescence in situ hybridization.

5. Consequences of germline variants in hematologic cancers

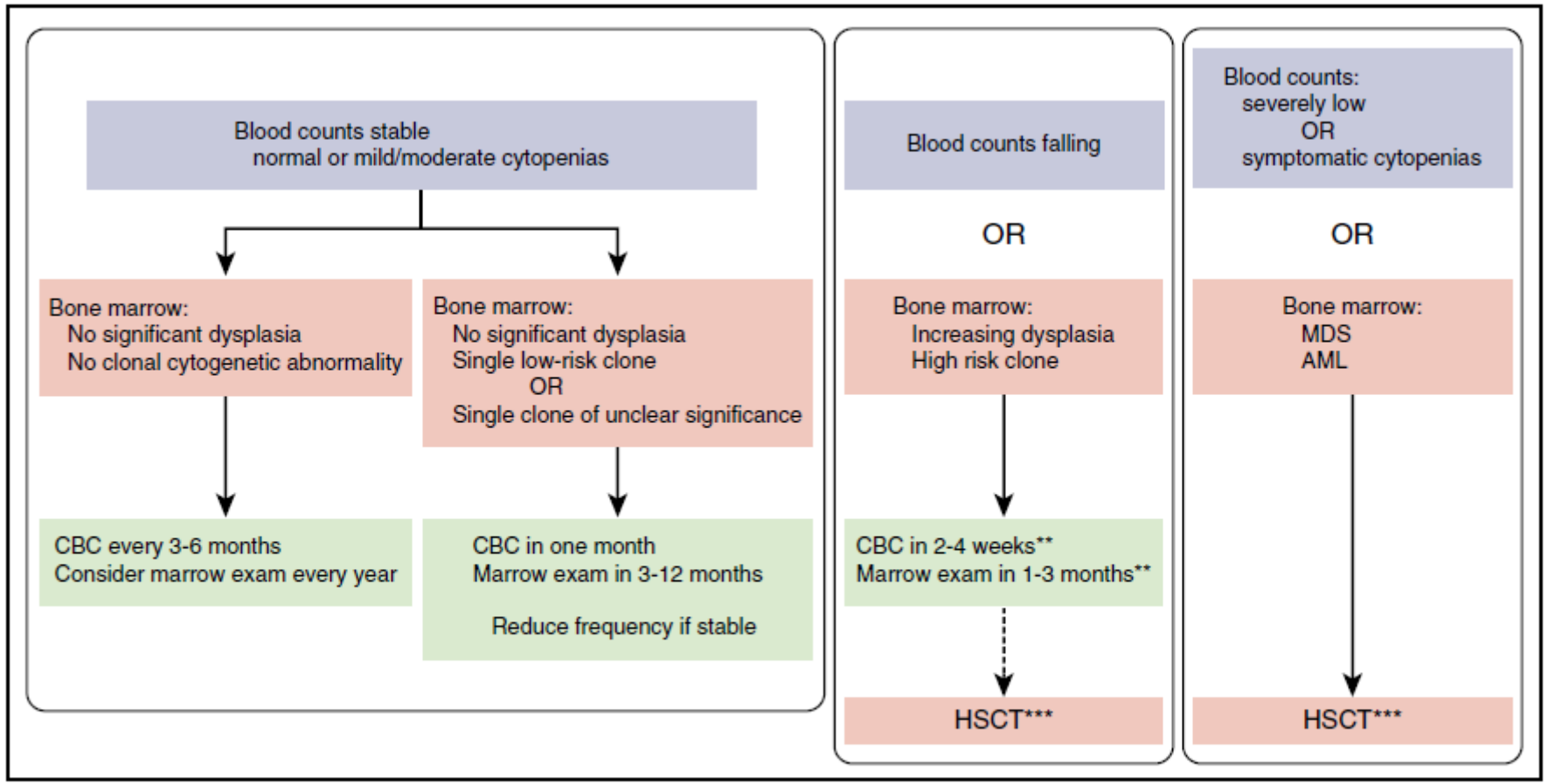


Figure 1. Surveillance for predisposition to MDS/AML. A general approach to surveillance is outlined. A discussion of low-risk clones is provided in the text. HSCT, hematopoietic stem cell transplant. *Excludes baseline dysplasia typically associated with specific disorders. **See text for additional discussion. ***For some disorders, chemotherapy may be considered to treat leukemia.

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction

Germline *CEBPA*

Germline *DDX41*

Germline *TP53*

= ICC 2022 *Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems*

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction

Germline *CEBPA*	10% of patients with biallelic *CEBPA* variants has a germline variant 5’ end mutation: 100% penetrance ⇔ 3’ end mutation favorable (yet increased risk of 2nd AML?)
Germline *DDX41*	1.5%-6.1% of individuals presenting with MDS/AML Adult-onset single- or multiple-lineage cytopenias and/or red blood cell macrocytosis Also reports of lymphoid malignancies and solid tumors, but predominantly MDS/AML Penetrance: 27%-39% have a family history of hematologic malignancies

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition and pre-existing platelet disorder

Germline *RUNX1*	(myeloid >> T-ALL/LBL and B-cell malignancies)
Germline *ANKRD26*	(lowest platelet counts, only myeloid malignancies to date)
Germline *ETV6*	(B-ALL >> myeloid malignancies)

= ICC 2022 *Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder*

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition and potential organ dysfunction

Germline *GATA2*
Bone marrow failure syndromes
Severe congenital neutropenia
Shwachman-Diamond syndrome
Fanconi anemia
Telomere biology disorders

RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan(-like) syndrome)
Down syndrome
Germline *SAMD9*
Germline *SAMD9L*
Bloom syndrome

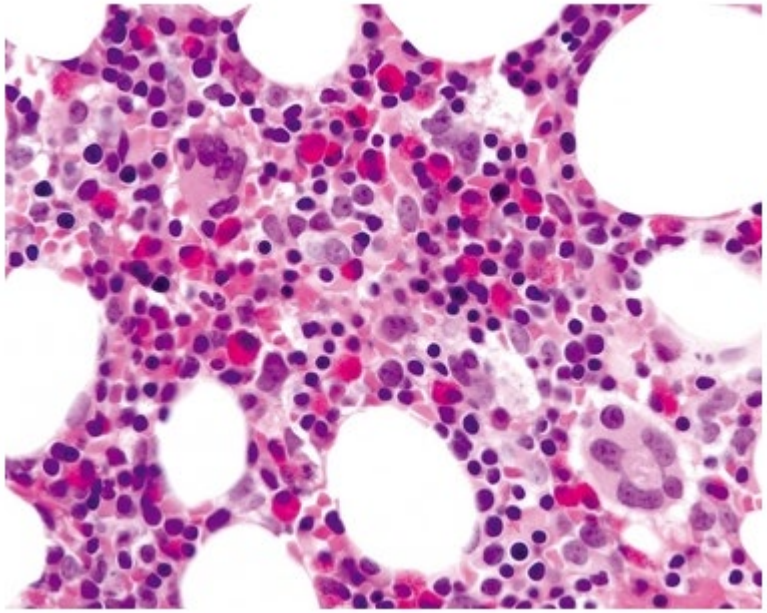
= ICC 2022 *Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems*

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition and potential organ dysfunction

Severe congenital neutropenia



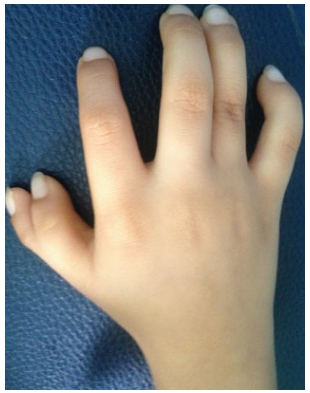
normocellular bone marrow in an 8-year-old child, showing normal erythropoiesis and megakaryopoiesis. Neutrophil maturation is virtually absent. Eosinophils are increased.

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition and potential organ dysfunction

Bone marrow failure syndromes



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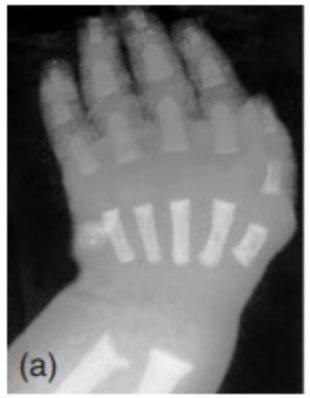
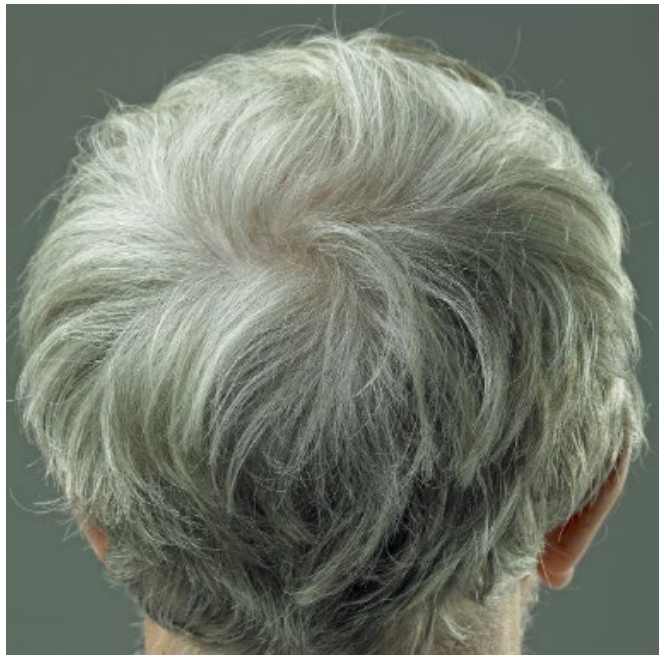


SDS

6. International classification systems

WHO 2022

Myeloid neoplasms with germline predisposition and potential organ dysfunction



Telomere biology disorders

6. International classification systems

WHO 2022

Additional cancer predisposition syndromes that have been associated with myeloid neoplasms

CHEK2, MPL, RECQL4, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, NBN, WAS

WHO 2022

Emerging disorders that require additional research

CSF3R, ERCC6L2, JAK2, MBD4, MECOM, NPM1, RBBP6, SRP72, TET2, GATA1

6. International classification systems

WHO 2022

Inborn error of immunity-associated lymphoid proliferations and lymphomas

Ataxia telangeactasia
Nijmegen Breakage syndrome
Antibody deficiencies, CVID, CD27/CD70 deficiency
Autoimmune lymphoproliferative syndrome (ALPS) with *FAS* mutation

6. International classification systems

ICC 2022

Acute lymphoblastic leukemia with germline predisposition

Germline *PAX5*
Germline *IKZF1*
(Germline *ETV6* and *TP53*)

8. Knowledge gap

Predisposition to MPN

familial MPN ⇔ familial erythrocytosis, familial thrombocytosis, familial neutrophilia

Predisposition to lymphoid cancers

multiple myeloma

(Non-)Hodgkin lymphoma

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