Cancer predisposing syndromes nei bambini con MDS/LMA

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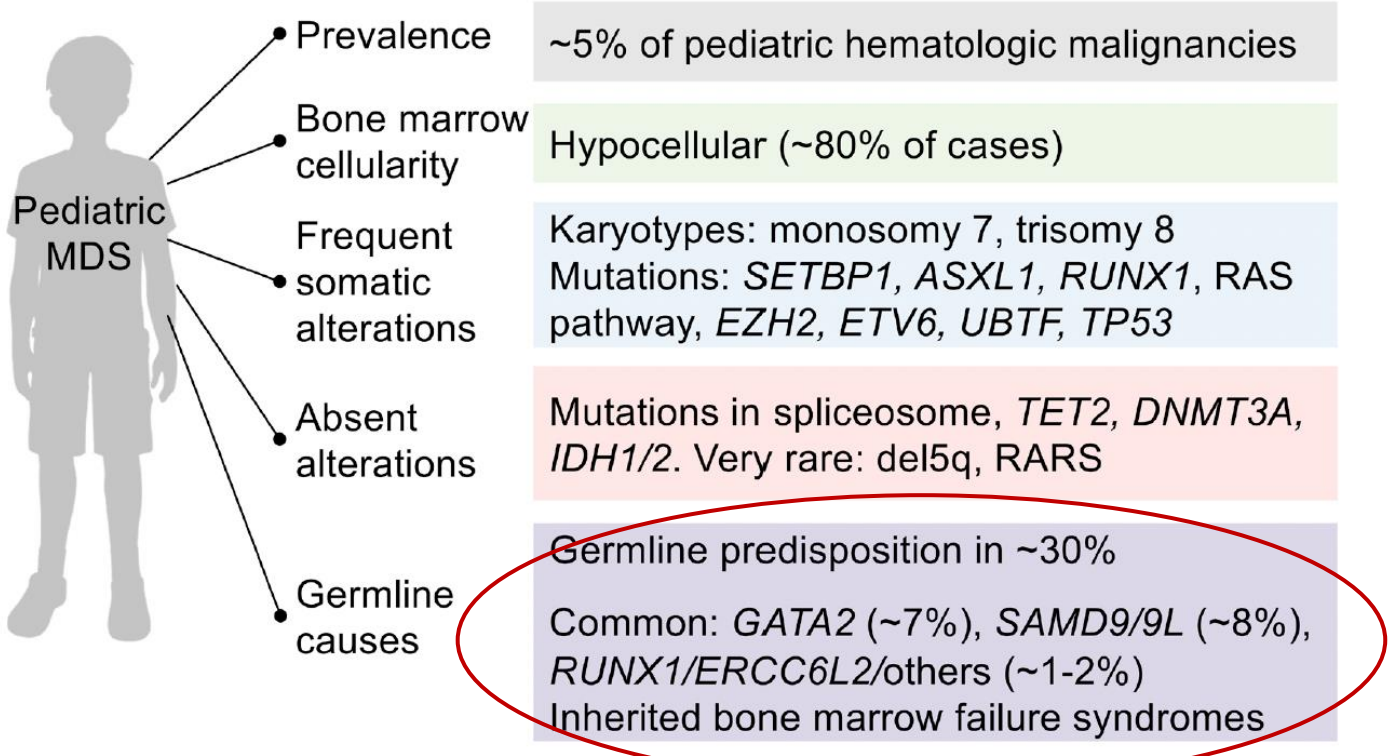
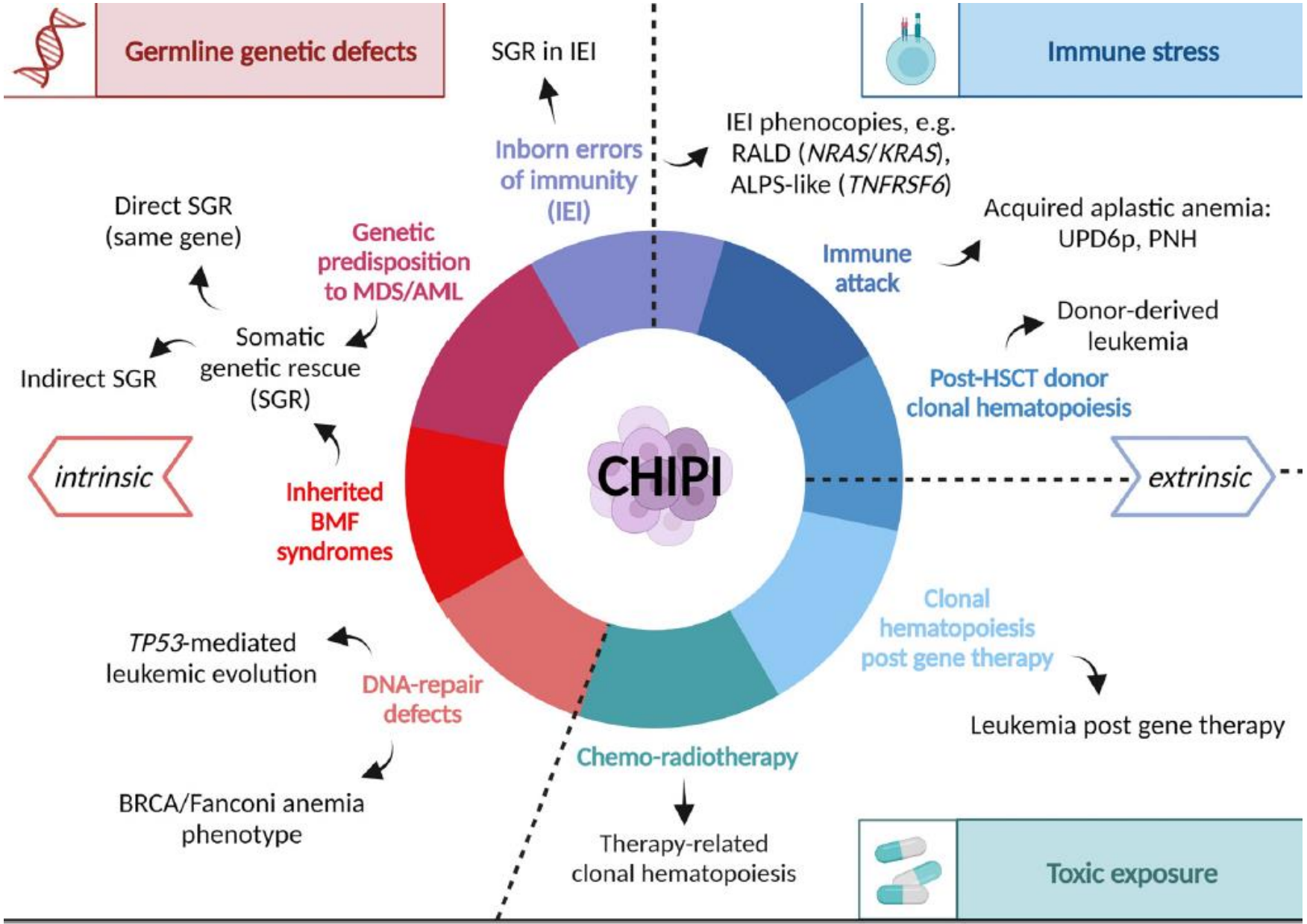
Pediatric MDS with predisposition: old and novel concepts



- Predisposition/exposition
- Clonality/progression and plasticity
- Gentoype-phenotype correlation

Stressors that can initiate CH in predisposed individuals (CHIPI).



Myeloid neoplasms with predisposition

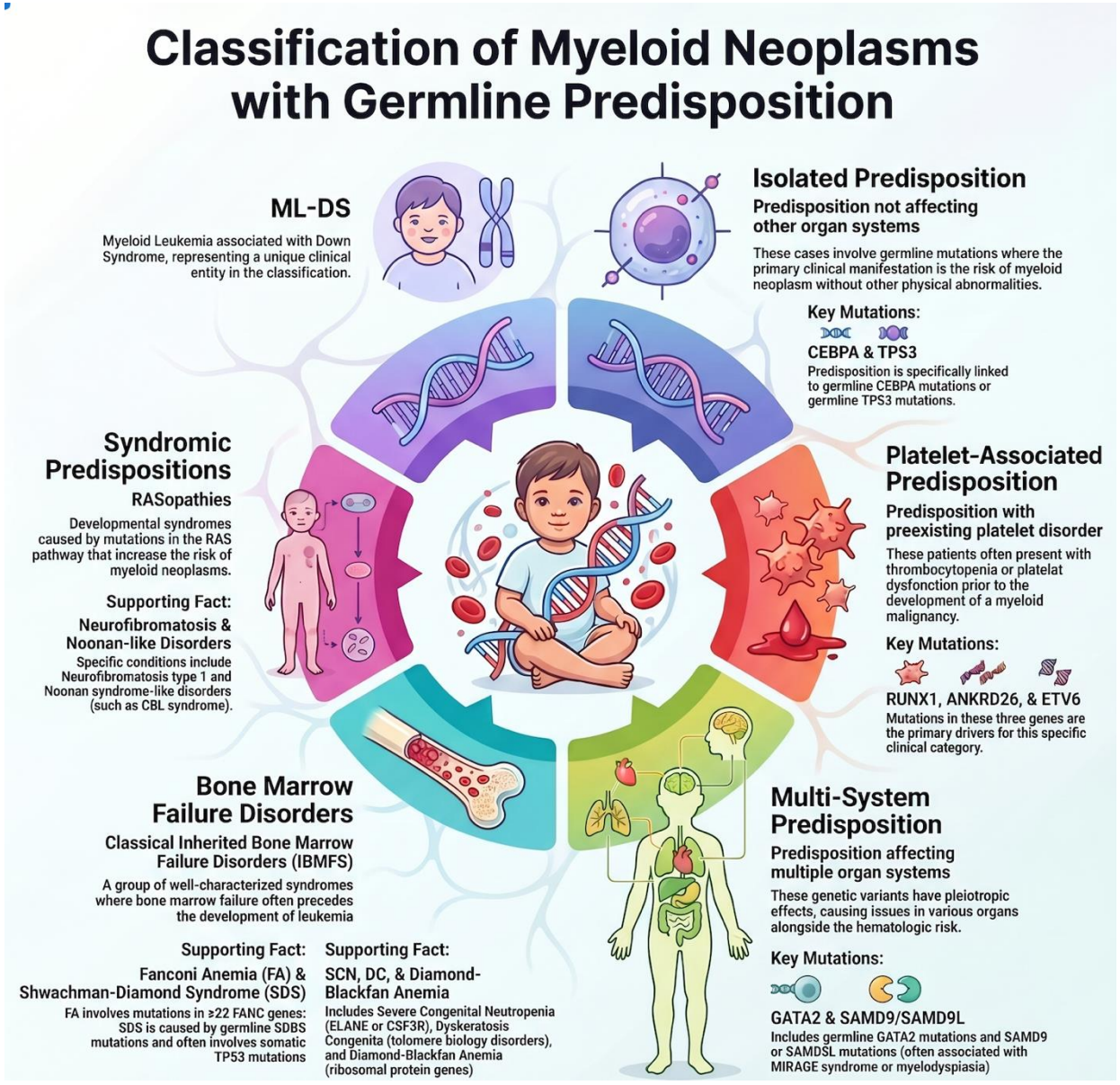
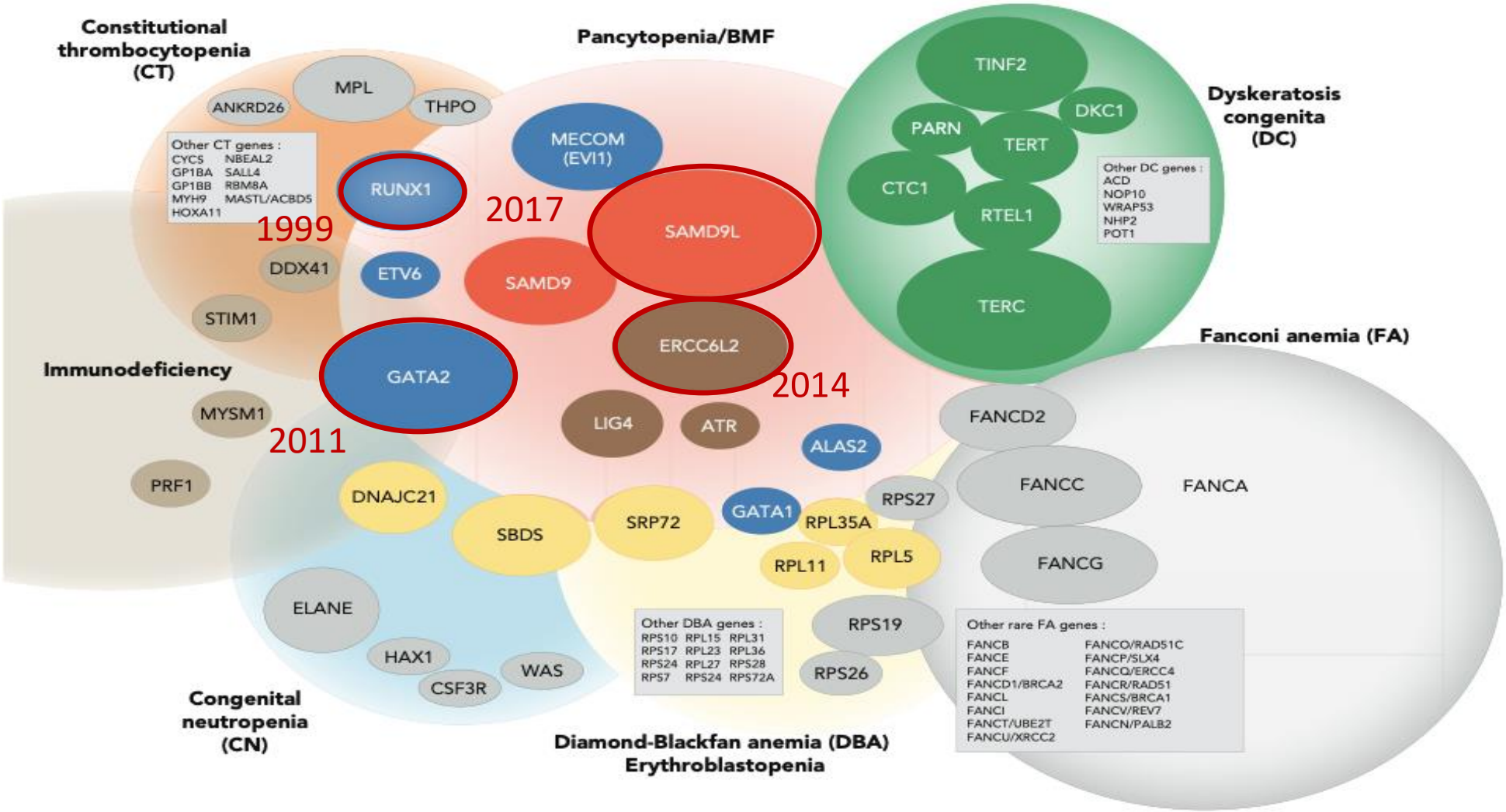


Table 8. Classification of myeloid neoplasms with germ line predisposition

Myeloid neoplasms with germ line predisposition not affecting other organ systems
Germ line *CEBPA* mutation
Germ line *TP53* mutation
Myeloid neoplasms with germline predisposition with preexisting platelet disorder
Germ line *RUNX1* mutation
Germ line *ANKRD26* mutation
Germ line *ETV6* mutation
Myeloid neoplasms with germ line predisposition affecting multiple organ systems
Germ line *GATA2* mutation
Germ line *SAMD9* or *SAMD9L* mutation
Myeloid neoplasms in classical inherited bone marrow failure disorders
FA (caused by germ line mutations in 1 of ≥22 FANC family genes)
Shwachman-Diamond syndrome (caused by germ line *SDBS* mutation, frequently associated with somatic *TP53* mutation)
Severe congenital neutropenia (most commonly caused by germ line *ELANE* mutation, may also be associated with germ line *CSF3R* and other gene mutations)
Dyskeratosis congenita and other telomere biology disorders (caused by germ line mutations in various genes associated with telomere maintenance)
Diamond-Blackfan anemia (caused by germ line mutations in various ribosomal protein genes)
Myeloid neoplasms in RASopathies
Neurofibromatosis type 1
Noonan syndrome–like disorders (CBL syndrome, rare others)
ML-DS

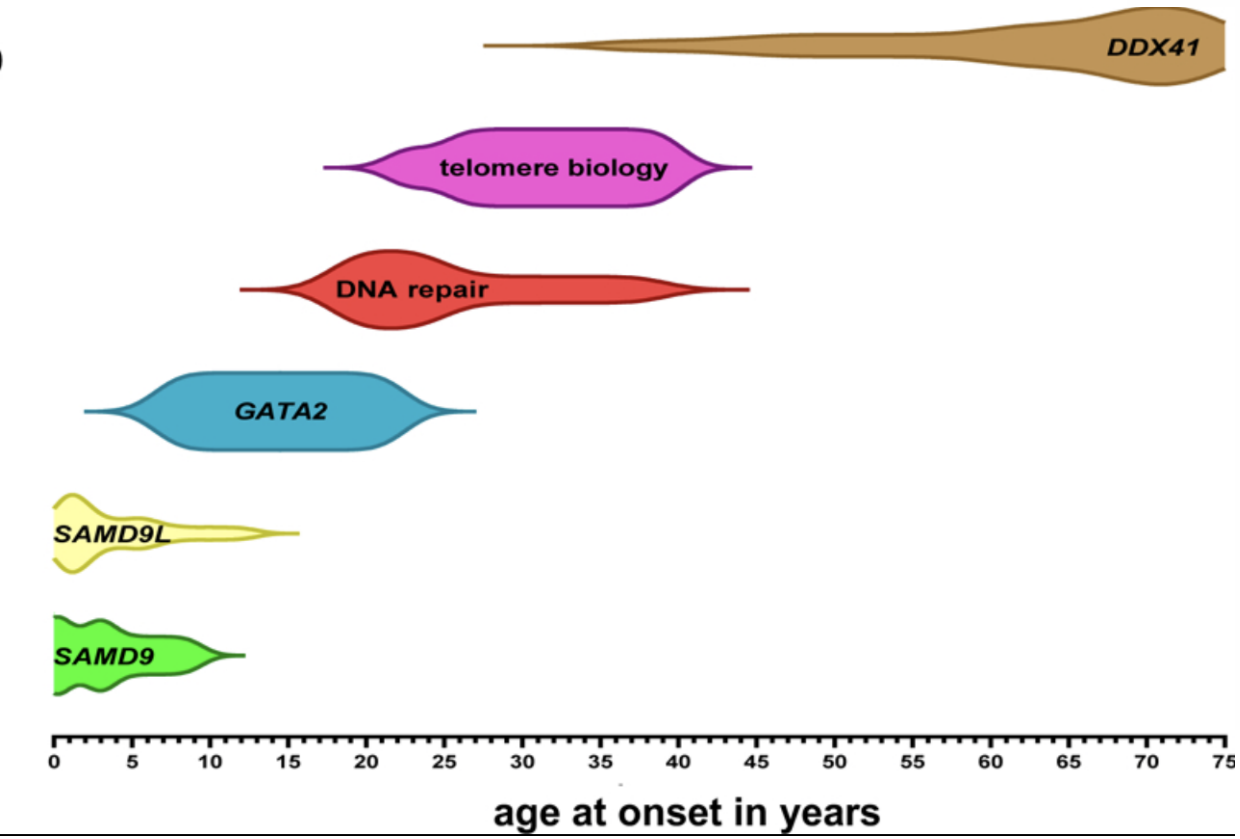
Zwaan CM, et al Blood. 2026 Apr 2;147(14):1532-1561.

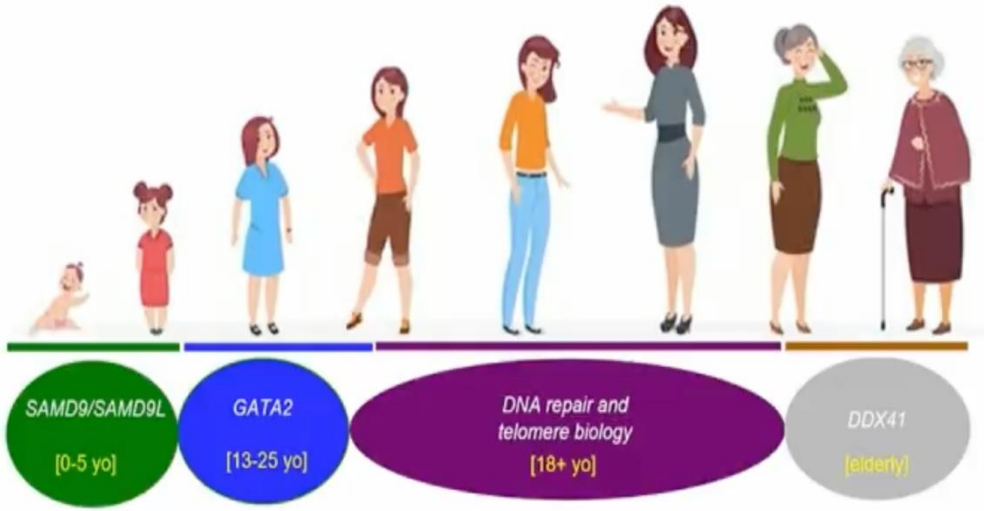
Pediatric MDS predisposition



Bluteau O, et al Blood. 2018 Feb 15;131(7):717-732

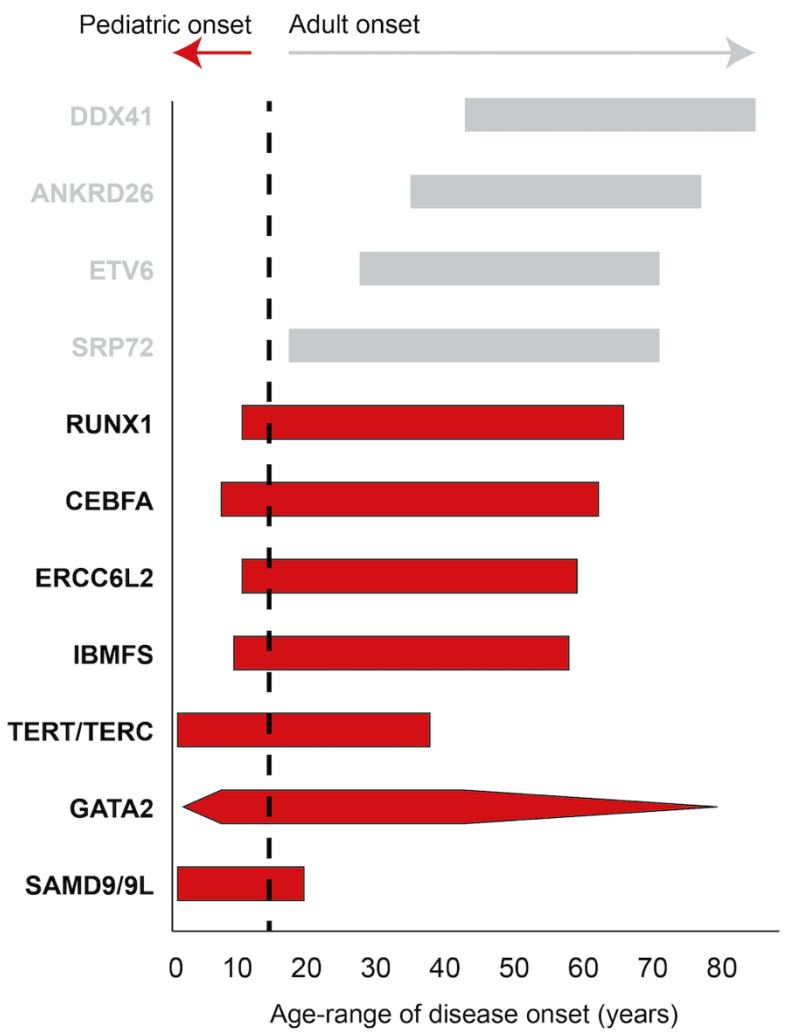
Age of presentation (of MDS) is a surrogate for the biological pathway





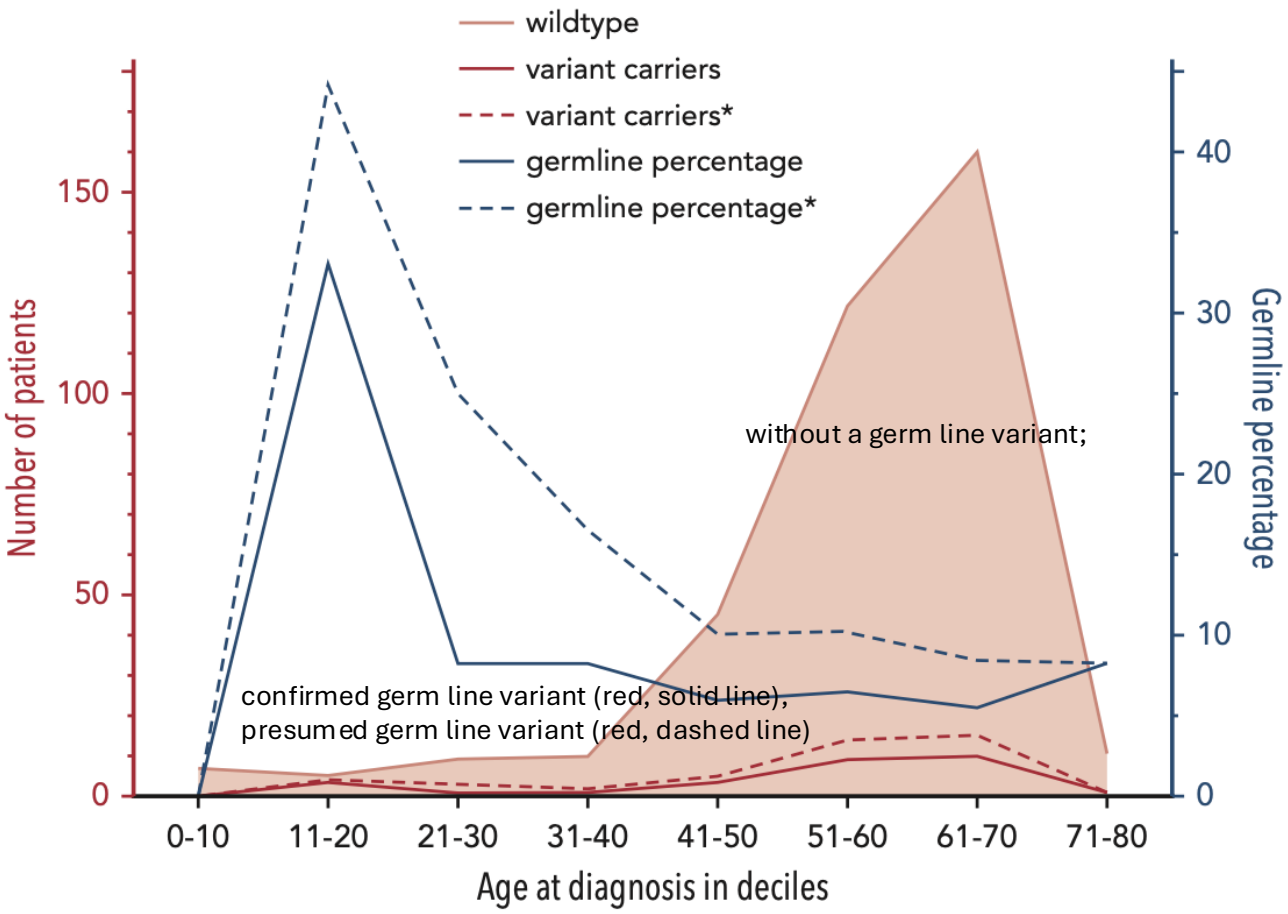
Feurstein S, et al. Leukemia. 2021 Aug;35(8):2439-2444.

Age dependent phenotype of predisposition syndromes



Masetti R, Leardini D et al, submitted

percentage (right y-axis, blue) of confirmed germ line variants (blue, solid line)
presumed germ line variants* (blue, dashed line)

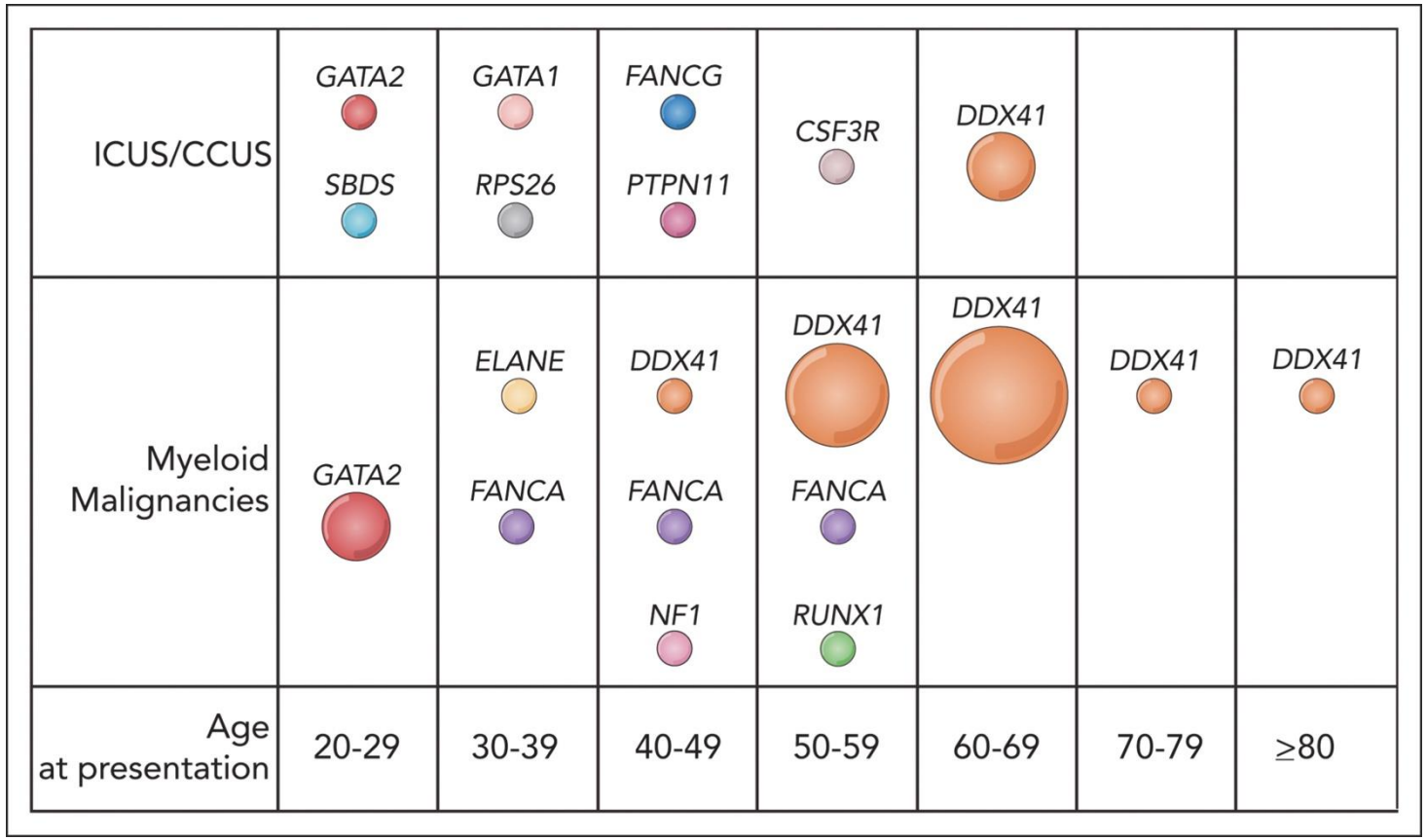


Feurstein S, et al. Blood. 2022 Dec 15;140(24):2533-2548.

Age better than clinical presentation or family hystory?

- *What emerges is the observation that the **age at which MDS is diagnosed is a surrogate for the biological pathway(s)** driving the malignancy, with DNA repair and telomere biology genes dominating in adult age ranges and DDX41 in older patients.*

- *These investigators had **limited ability to predict those with germ line predisposition based on demographic data, clinical presentation, or family history**, demonstrating that it is not obvious a priori who will have germ line risk*



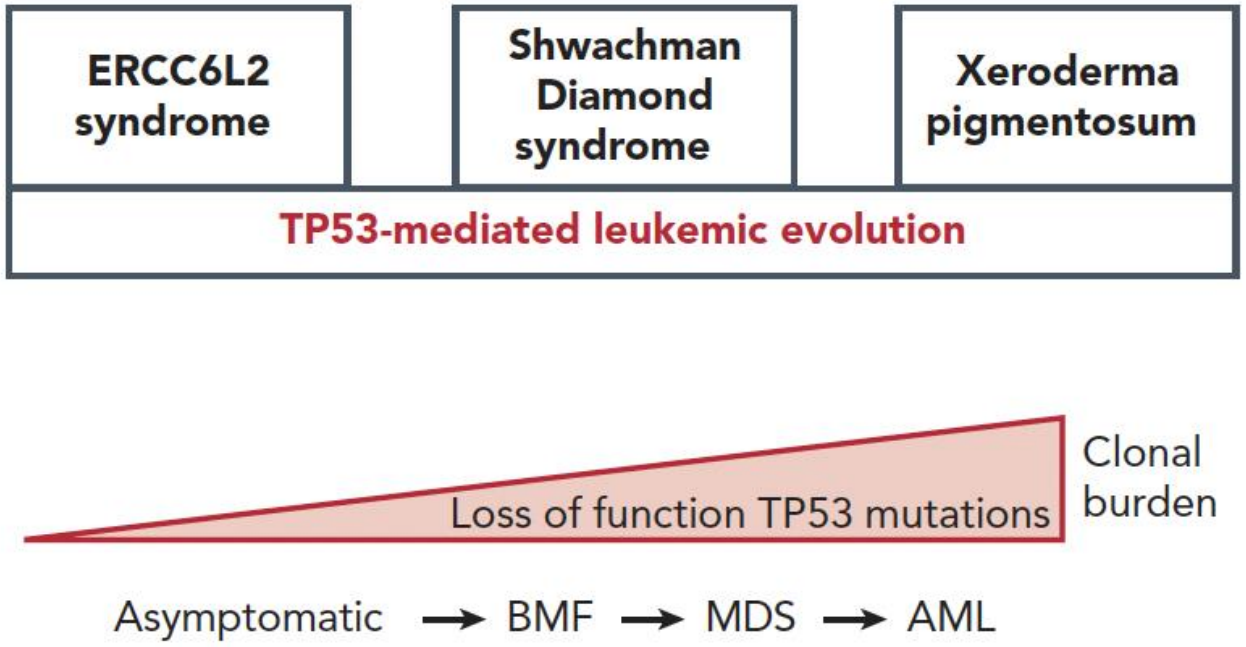
Godley LA. Blood. 2023 Aug 17;142(7):616-617.

Surveillance of a predisposition syndrome

In patients with inherited BMF syndromes, annual bone marrow surveillance is usually conducted to detect leukemic evolution, with complete blood counts (CBCs) performed in between; changes in CBC might suggest AML progression, prompting an earlier bone marrow examination. However, **this strategy is not applicable in some predisposing diseases such as ERCC6L2 disease, Shwachman-Diamond syndrome or XP as CBC abnormalities appear mild despite the presence of TP53-mediated clonal evolution or marrow dysplasia**.

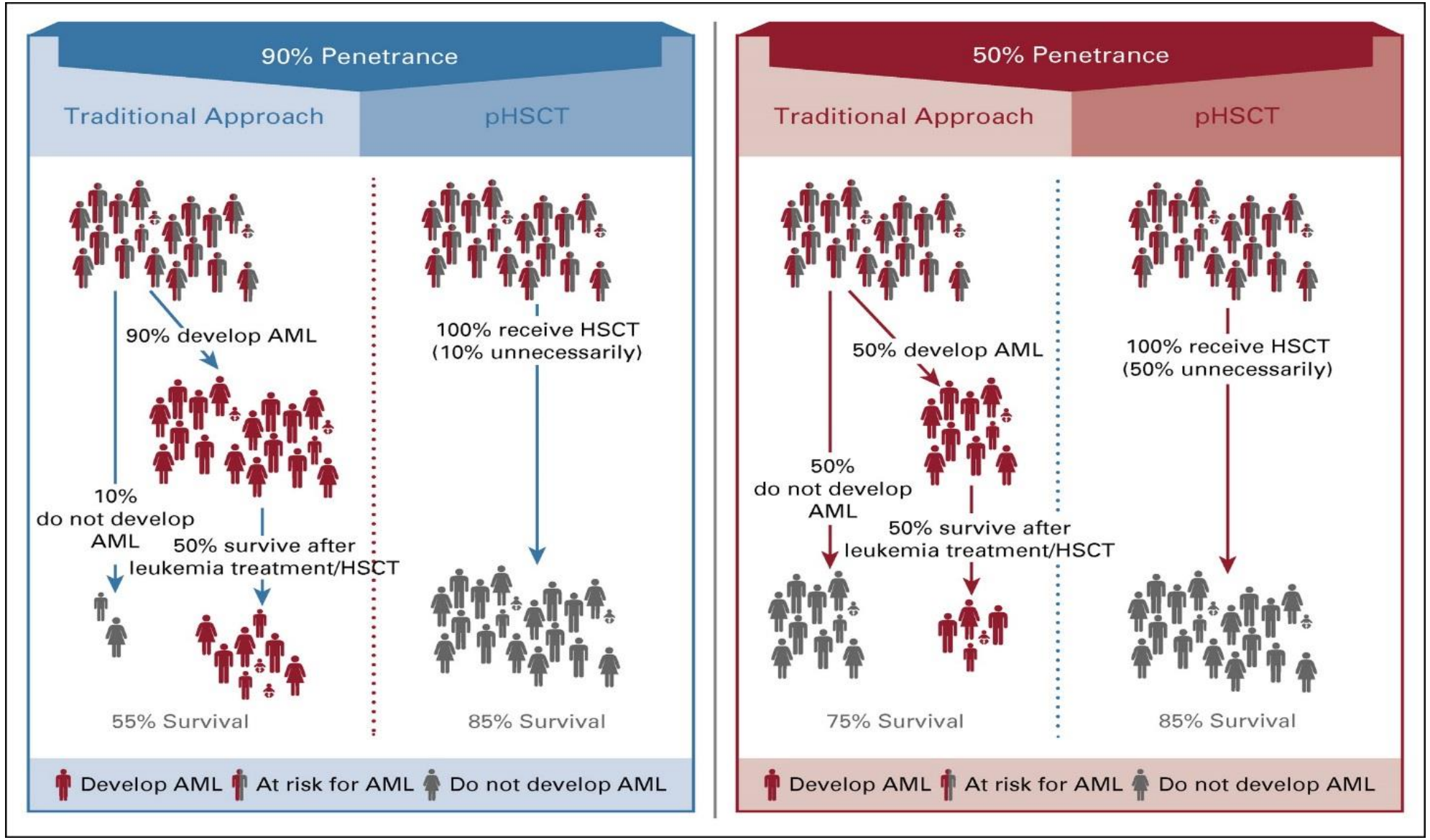
	Gene(s)	HM surveillance test	Frequency[b]
BMF syndromes and predisposition to myeloid neoplasms			
FA	*FANCA*, *FANCB*, *FANCC*, *FANCD1*, and *others*	CBC w/diff & retic	3–4 months[b]
		BMA/Bx	Annual
		Somatic gene panel	Annual
SDS and SDS-like disorders	SDS: *SBDS* and *EFL1*	CBC w/diff & retic	3–4 months
	SDS-like: *DNAJC21* and *SRP54*	BMA/Bx	Annual
		Somatic gene panel	Annual
TBDs including dyskeratosis congenita	*CTC1*, *DKC1*, *RTEL1*, *TERC*, *TERT*, *TINF2*, and *others*	CBC w/diff & retic	6–12 months[b]
		BMA/Bx	1–3 years
		Somatic gene panel	1–3 years
Severe congenital neutropenia	*ELANE*, *CLPB*, *G6PC3*, *HAX1*, *CXCR4*, *CSF3R*, and *GFI1*	CBC w/diff & retic	3–4 months
		BMA/Bx	Annual
		Somatic gene panel	Annual
DBA	*RPS19*, *RPL5*, *RPS24*, *RPS26*, *RPL11*, *RPL35A*, and others	CBC w/diff & retic	4–6 months
		BMA/Bx	As clinically indicate
Emerging predispositions to hematologic malignancies			
USP9X-associated predisposition to lymphoid leukemia	*USP9X*	CBC w/diff & retic	Annual
TYK2-associated predisposition to lymphoid leukemia	*TYK2*	CBC w/diff & retic	Annual
GAB2-associated predisposition to lymphoid malignancy	*GAB2*	CBC w/diff & retic	Annual
SH2B3-associated predisposition to JMML	*SH2B3*	CBC w/diff & retic	As clinically indicated[d]
MBD4-associated predisposition to myeloid malignancy and other tumors	*MBD4*	CBC w/diff & retic	6–12 months[c]
		BMA/Bx	Annual
ERCC6L2-associated predisposition to lymphoid/myeloid malignancy	*ERCC6L2*	CBC w/diff & retic	3–4 months
		BMA/Bx	Annual
		Somatic gene panel	Annual
GATA1-associated predisposition to myeloid malignancy	GATA1s-generating variants	CBC w/diff & retic	3–4 months
		BMA/Bx	Annual
MECOM-associated predisposition to myeloid malignancy	*MECOM*	CBC w/diff & retic	6–12 months
		BMA/Bx	1–3 years
ERG-associated predisposition to myeloid malignancy	*ERG*	CBC w/diff & retic	3–4 months
		BMA/Bx	Annual

Abbreviations: BMA/Bx, BM aspirate and biopsy with morphology and cytogenetic analysis; CBC w/diff & retic, complete blood count with differential ar
reticulocyte count; JMML, juvenile myelomonocytic leukemia; *XPC*, *xeroderma pigmentosum group C*.



Maese LD, et al. Clin Cancer Res. 2024 Oct 1;30(19):4286-4295.

Decision making in predisposition: pre-emptive HSCT



Hamilton KV, et al. Blood. 2023 Jun 29;141(26):3143-3152.

Pre-emptive HSCT

Syndrome-specific factors

- Disease penetrance
- Age of overt leukemia onset
- Risk for therapy-associated toxicities

Patient specific-factors

- Personal preference
- Psychological status
- Family and other support mechanisms

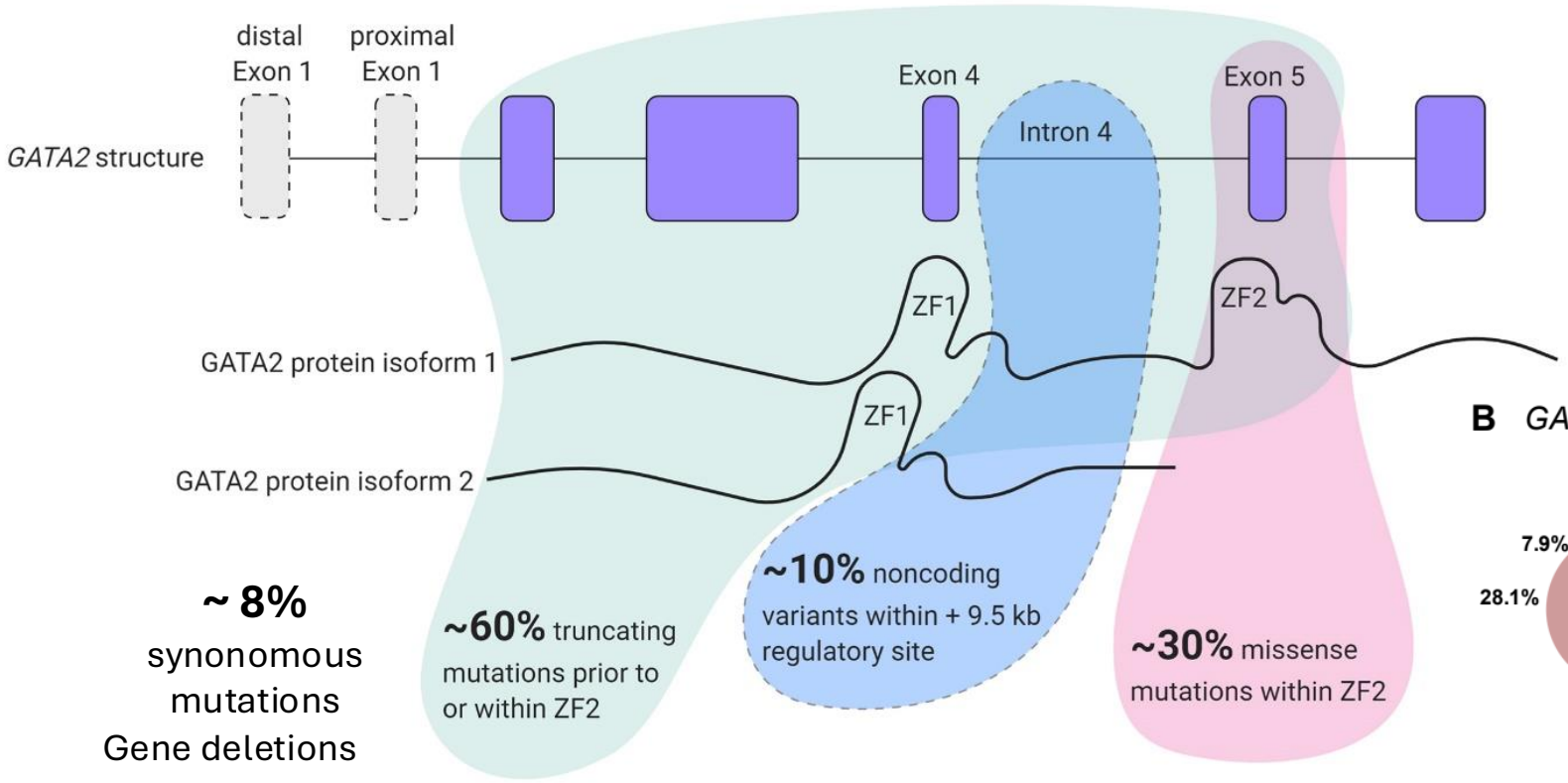
HSCT-related factors

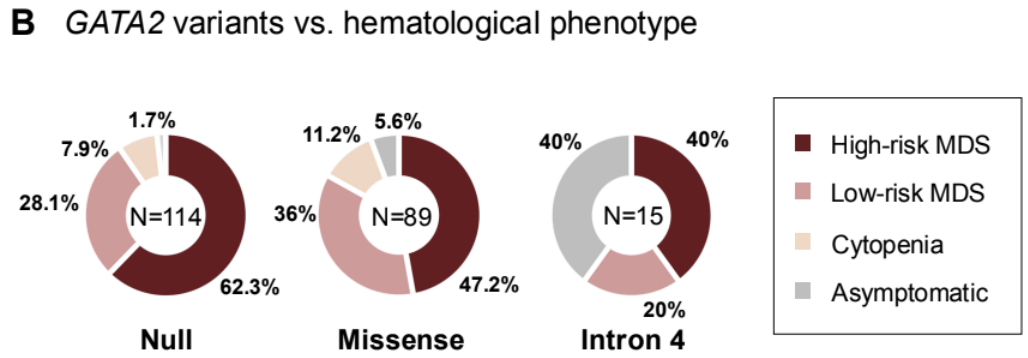
- Age of recipient
- Donor type and availability
- Risk for short and longer-term toxicities

Alex Hall. Relativity. 2013

GATA2 Deficiency Syndrome

Genetic basis: loss of function germline mutations





Adapted from Koyunlar, de Pater; Front Genome Editing 2020

Kotmayer L, et al 2025 Jul 15;15(1):121.

Homan et al., Human mutation 2021;42:1399–1421

Kozyra et al., Leukemia 2020

EWOG-MDS

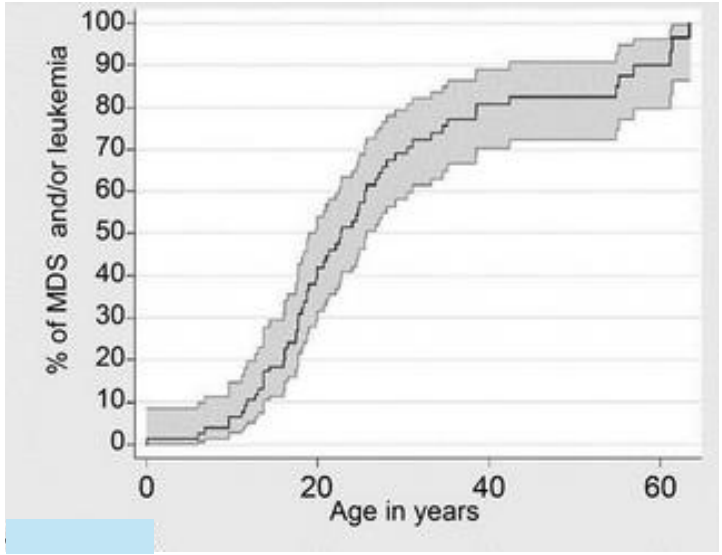
GATA2 Deficiency: Hematological and Non-Hematological Phenotype

Hematological phenotype

Bone marrow failure
- chronic neutropenia

Immunodeficiency
- ↓ B and NK lymphoid cells
- ↓ monocytes

MDS/AML (ALL)



Donadieu et al. Haematologica 2018

Any abnormality 51%

Autism/ADHD 19%

Congenital deafness 9%

Hypothyroidism

Pulmonary alveolar proteinosis

Interstitial lung disease

NTM, bact., viral, fungal infections

Kidney, VUR 12%

Warts

Miscarriage

Hydrocele, Hypospadia

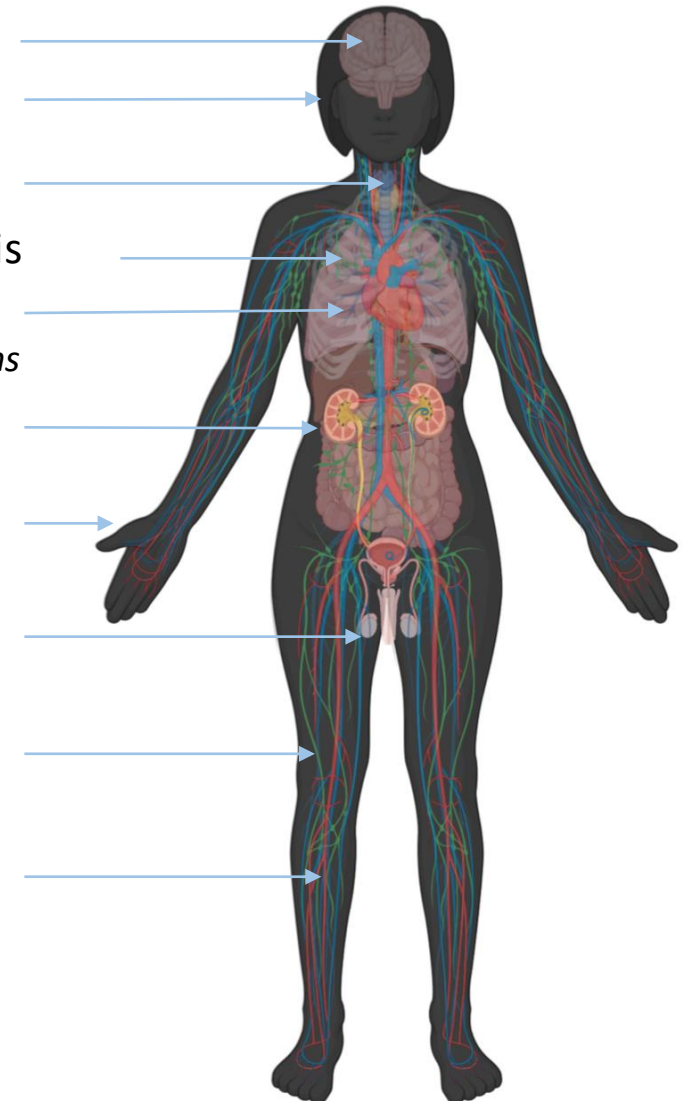
Thrombosis

Lymphedema 23%

Immunodeficiency 39%

Autoimmunity

PHV/EBV cancer



Wlodarski et al., Blood 2016

Sahoo et al. Best Pract Res Clin Haematol 33 (2020) 101197

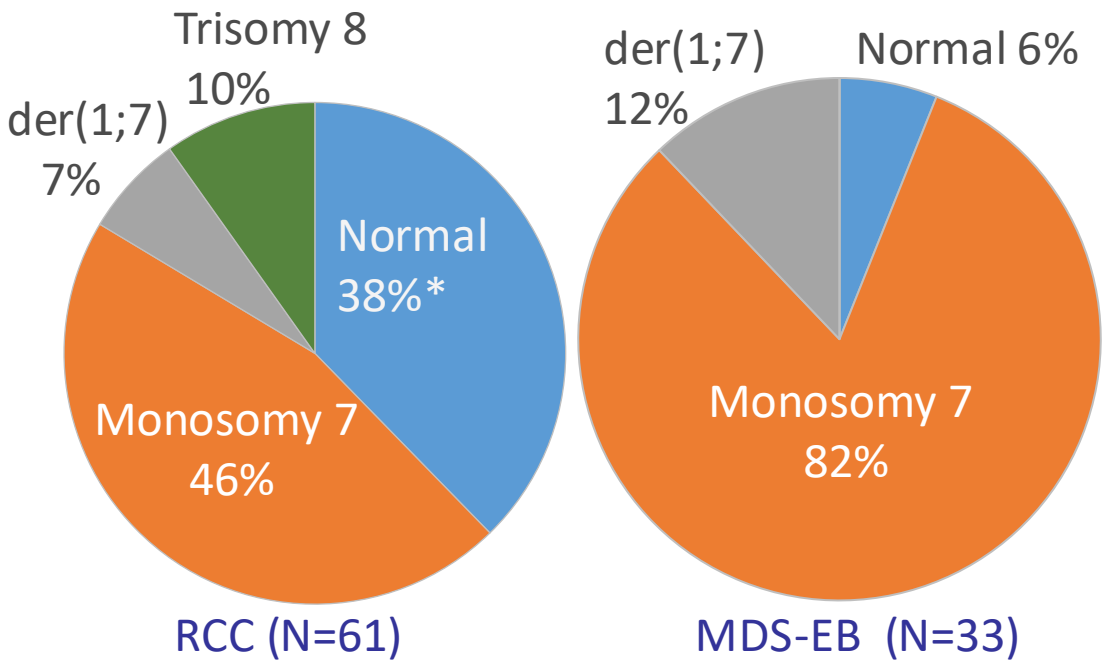
EWOG-MDS

Prevalance and Genetics in GATA2 Deficiency

Consecutively diagnosed cohort (n=426)

Prevalance	RCC	4 %
	MDS-EB	15 %

Cytogenetic abnormalities in GATA2^{mut}



** 1 random abberation included*

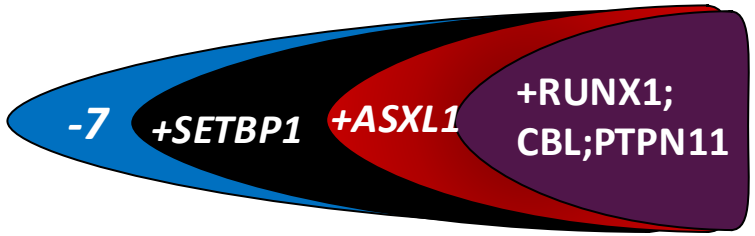
Monosomy 7 in RCC and MDS-EB

- 37% have underlying GATA2 deficiency
- Median age at diagnosis of monosomy 7

  GATA2^{mut}: 12.5 years

  GATA2^{wt} : 4.2 years

Clonal evolution in monosomy 7



Pastor et al.; Leukemia 2018

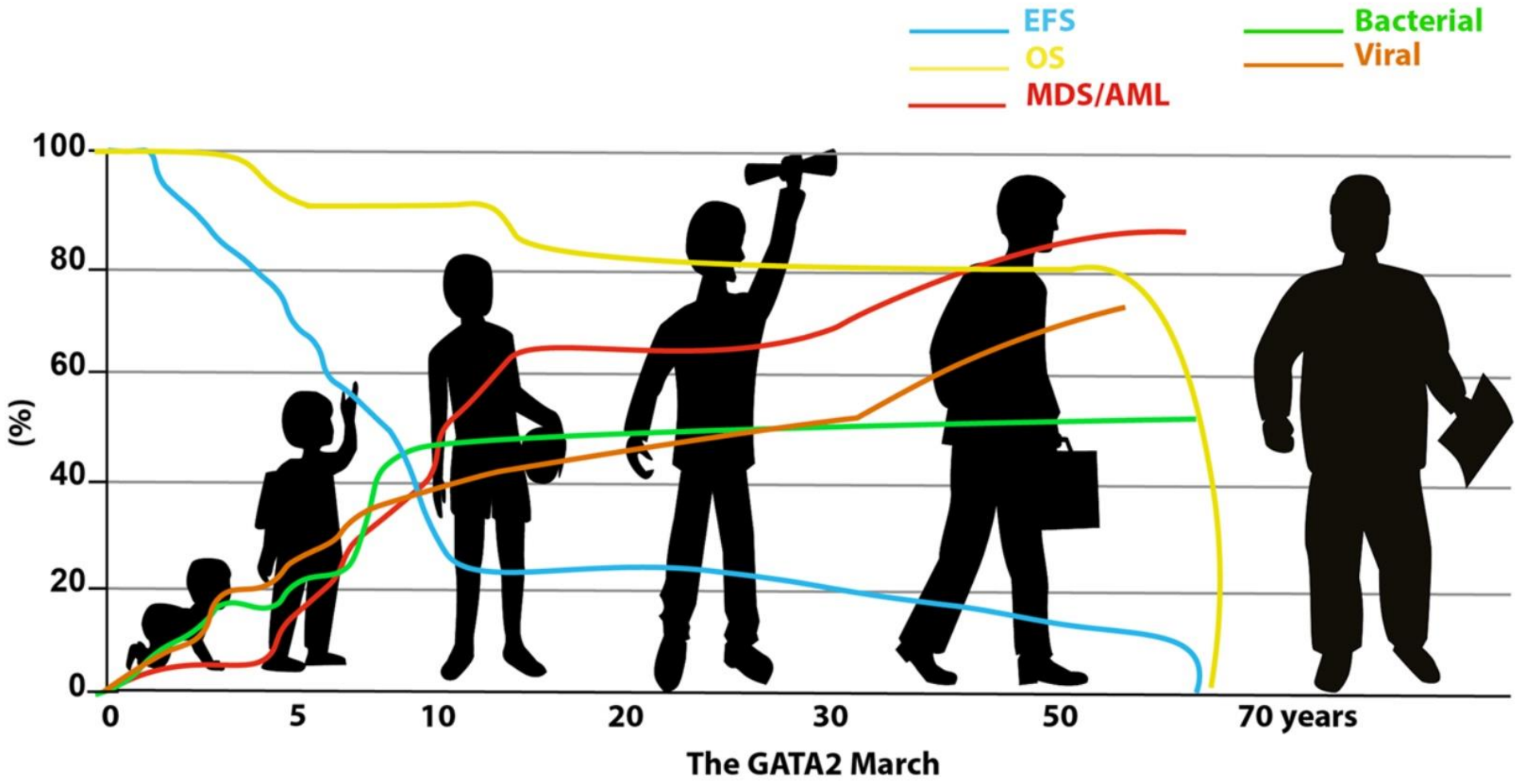
Wlodarski et al.; Blood 2016

Kozyra et al.; Blood 2021

EWOG-MDS, unpublished 2022

EWOG-MDS

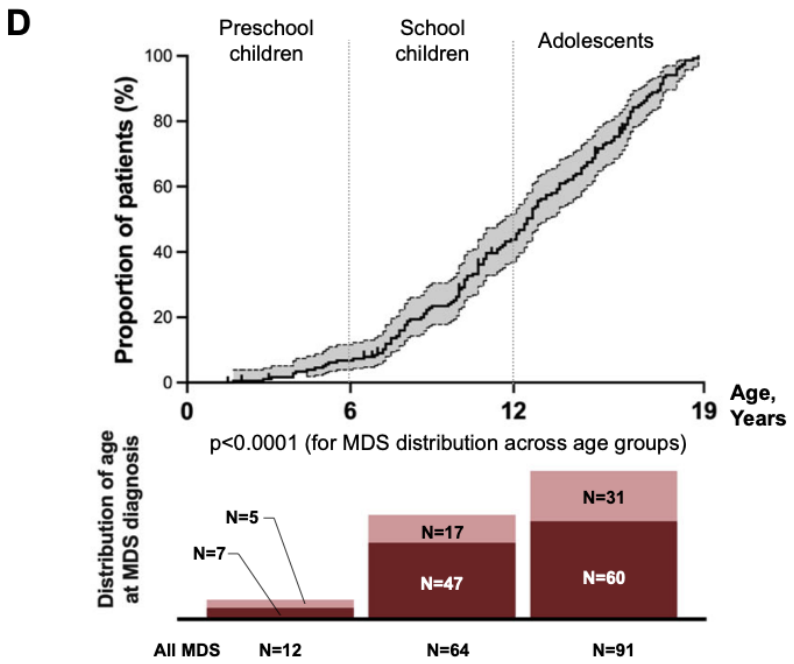
GATA2 Deficiency: progression

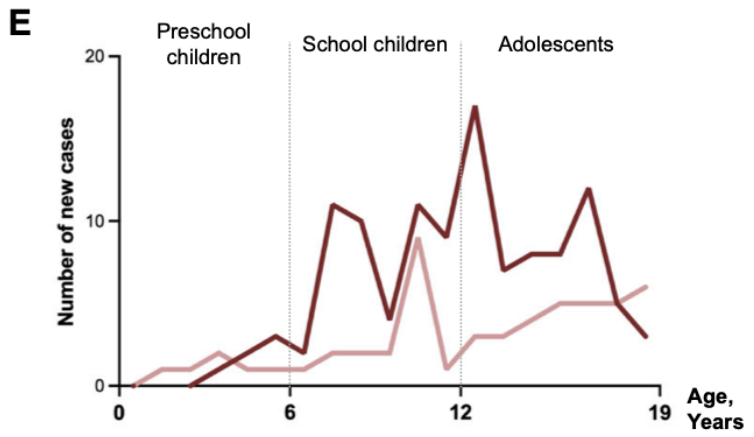


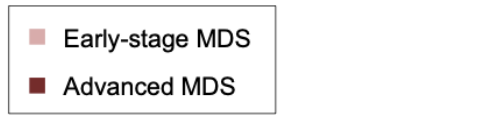
HR-MDS in very young children (below the age of 3 years) is very rare and the rapidly increasing from scholar age to adulthood.

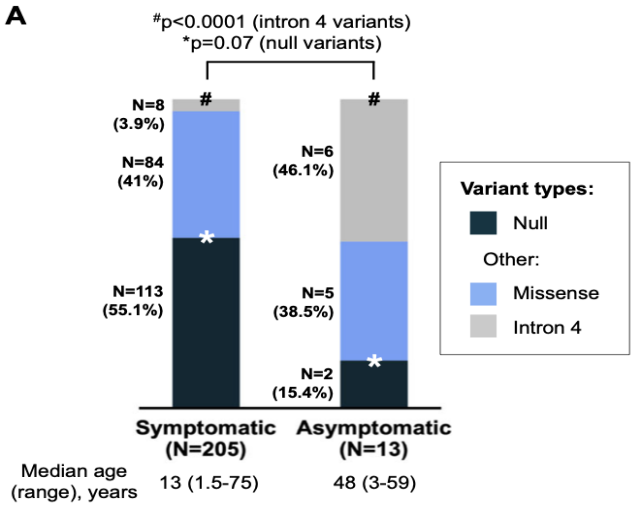
Roncareggi et al., Journal of Clinical Immunology, 2023

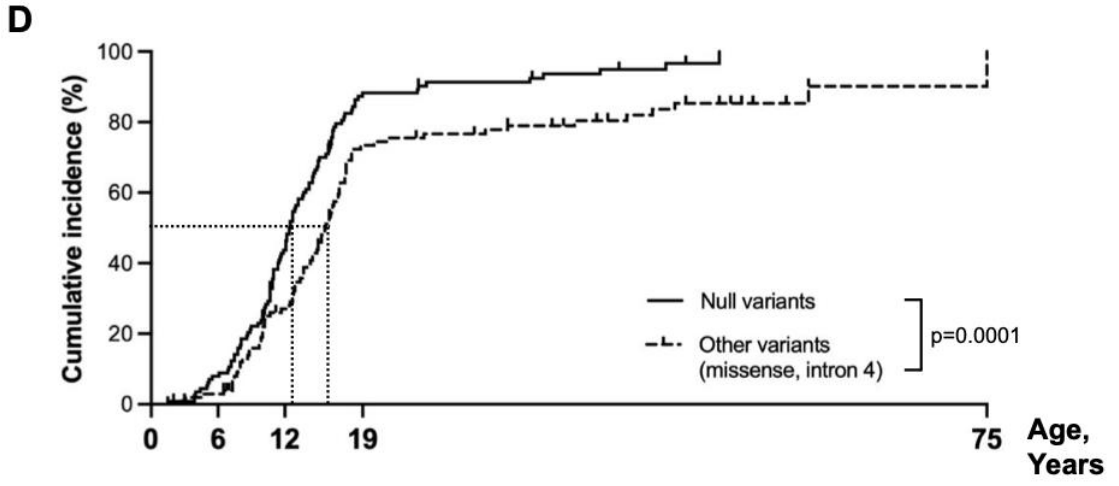
Age-dependent phenotypic evolution of pediatric MDS arising from GATA2 deficiency











Kotmayer L, et al 2025 Jul 15;15(1):121.

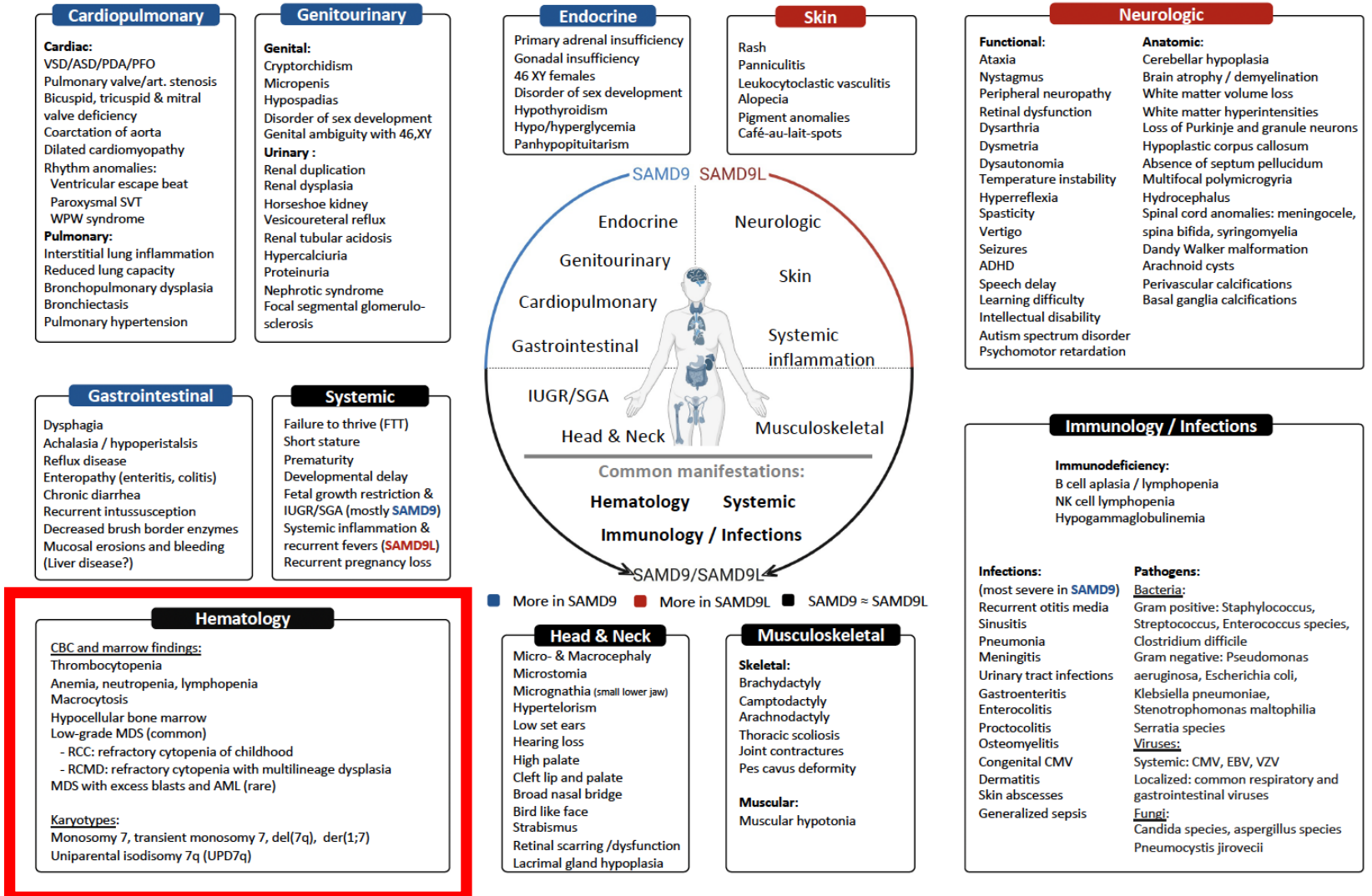
SAMD9/9L Syndrome: Hematological Phenotype

Unlike classical BMF and MDS predisposing conditions where the risk for **BMF/MDS development can increase with age**, SAMD9/9L syndromes are unique in that the associated risk is highest in children but low in adults.

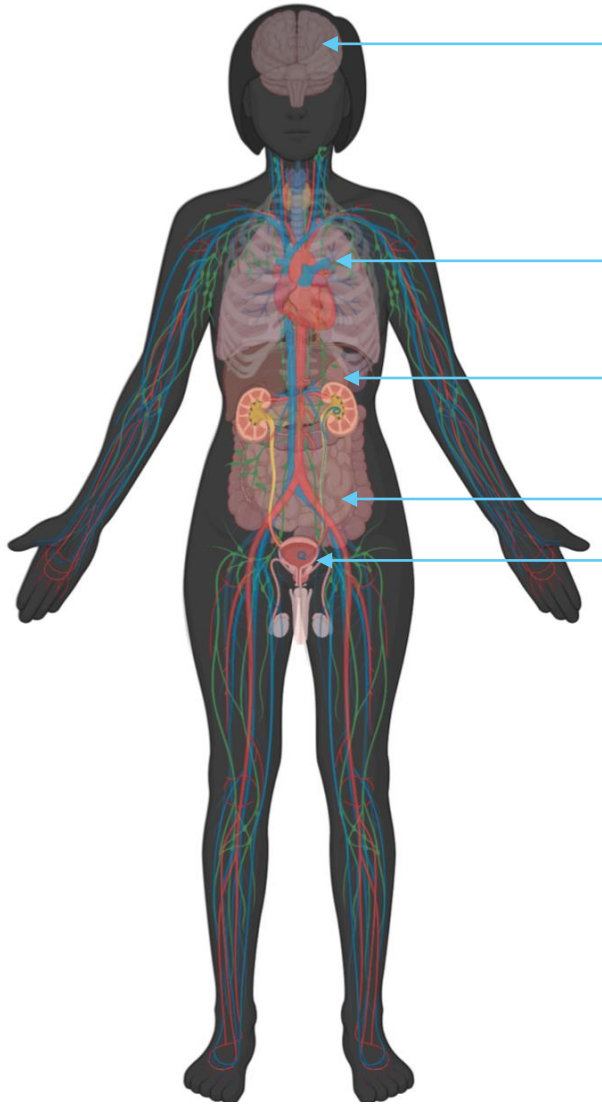
Hematological phenotype

Bone marrow failure
thrombocytopenia
pancytopenia
hypocellular bone marrow

MDS (monosomy 7, del 7q)



SAMD9/9L Syndrome: Non-Hematological Phenotype



Ataxia, cerebellar hypotrophy
Nystagmus, white matter loss
Microcephaly, hydrocephalus
Polyneuropathy, develop. delay

Hypoplastic thymus, achalasia

Adrenal hypoplasia
VUR

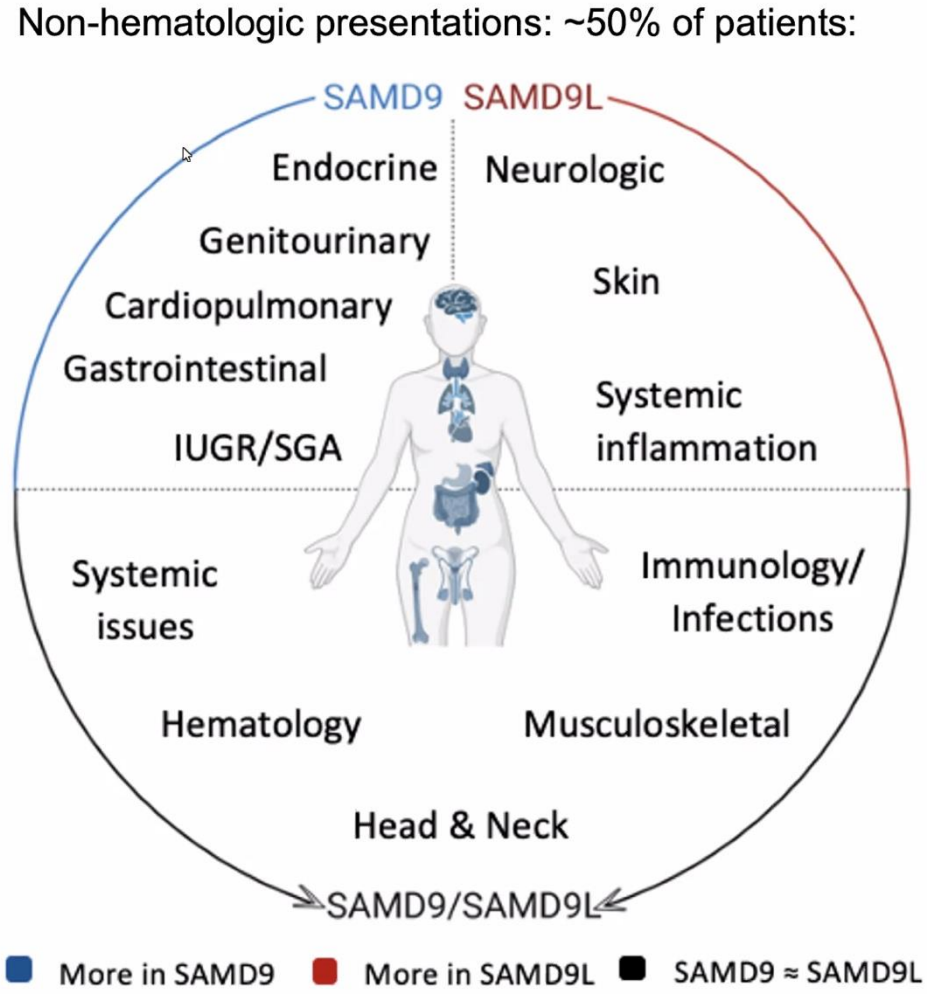
Enteropathy

Disorder of sex development
Cryptorchidism
Micropenis, hypospadia

Intrauterine GF, failure to thrive

Viral and bacterial infections

Any abnormality
SAMD9 59%, SAMD9L 41%



Sahoo et al, Nat Med. 2021 October ; 27(10): 1806–1817

Sahoo et al, Best Pract Res Clin Haematol 33 (2020) 101197

EWOG-MDS

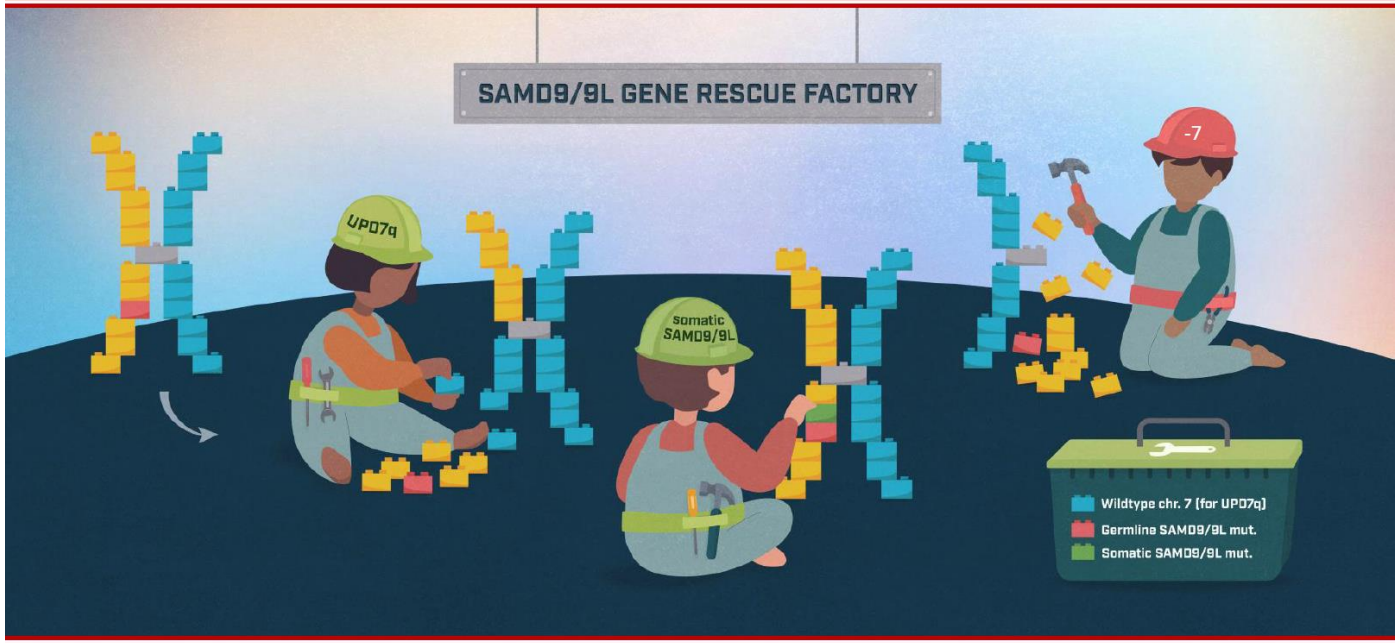
SAMD9 and Hematopoiesis plasticity in children

www.nature.com/nm / October 2021 Vol.27 No. 10

nature medicine

Hematopoiesis plasticity in children

Germline SAMD9 and SAMD9L Predisposition: High Rates of Somatic Gene Rescue



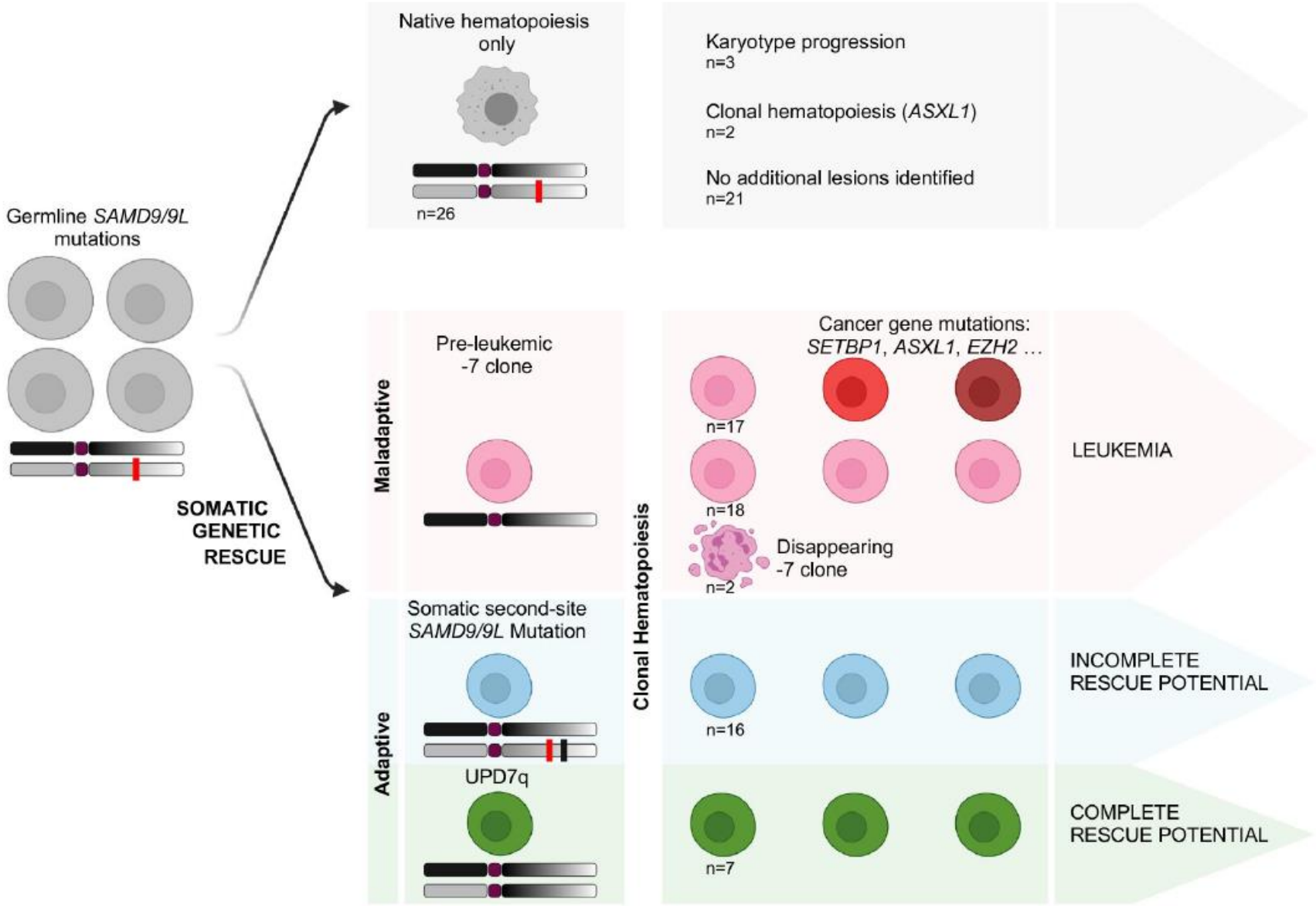
Conclusions: **SAMD9/9L syndromes are caused by germline mutations in *SAMD9* and *SAMD9L* genes, leading to multi-system abnormalities including bone marrow failure, immunodeficiency, and risk for MDS development. Somatic genetic rescue in hematopoietic cells eliminates or suppresses the germline allele. The mechanisms are monosomy 7 which can lead to MDS or disappear, and the adaptive somatic events such as somatic *SAMD9/9L* mutations, or uniparental disomy 7q (UPD7q) both of which can be associated with hematologic remission.**

*Sahoo et al. DOI: 10.xxxx/**blood**.2024xxxxxx*

blood Visual Abstract

Sahoo et al. Nat Med. 2021 October ; 27(10): 1806–1817

SAMD9/9L Syndrome: Somatic Genetic Rescue



A Somatic Genetic Rescue in SAMD9/9L syndromes is highley prevalent (**61%**)

Maladaptive SGR

Benign SGR

Disease	Genes	Type of rescue events	Clinical impact of rescue events	Frequency
SAMD9/9L syndromes	*SAMD9*, *SAMD9L*	Monosomy 7	Negative (MDS/AML)	61%
		Deletion Chr7q	Negative (MDS/AML)	
		Second site truncating/missense mutation	Likely positive (incomplete rescue potential)	
		UPD7q	Positive (complete rescue potential)	

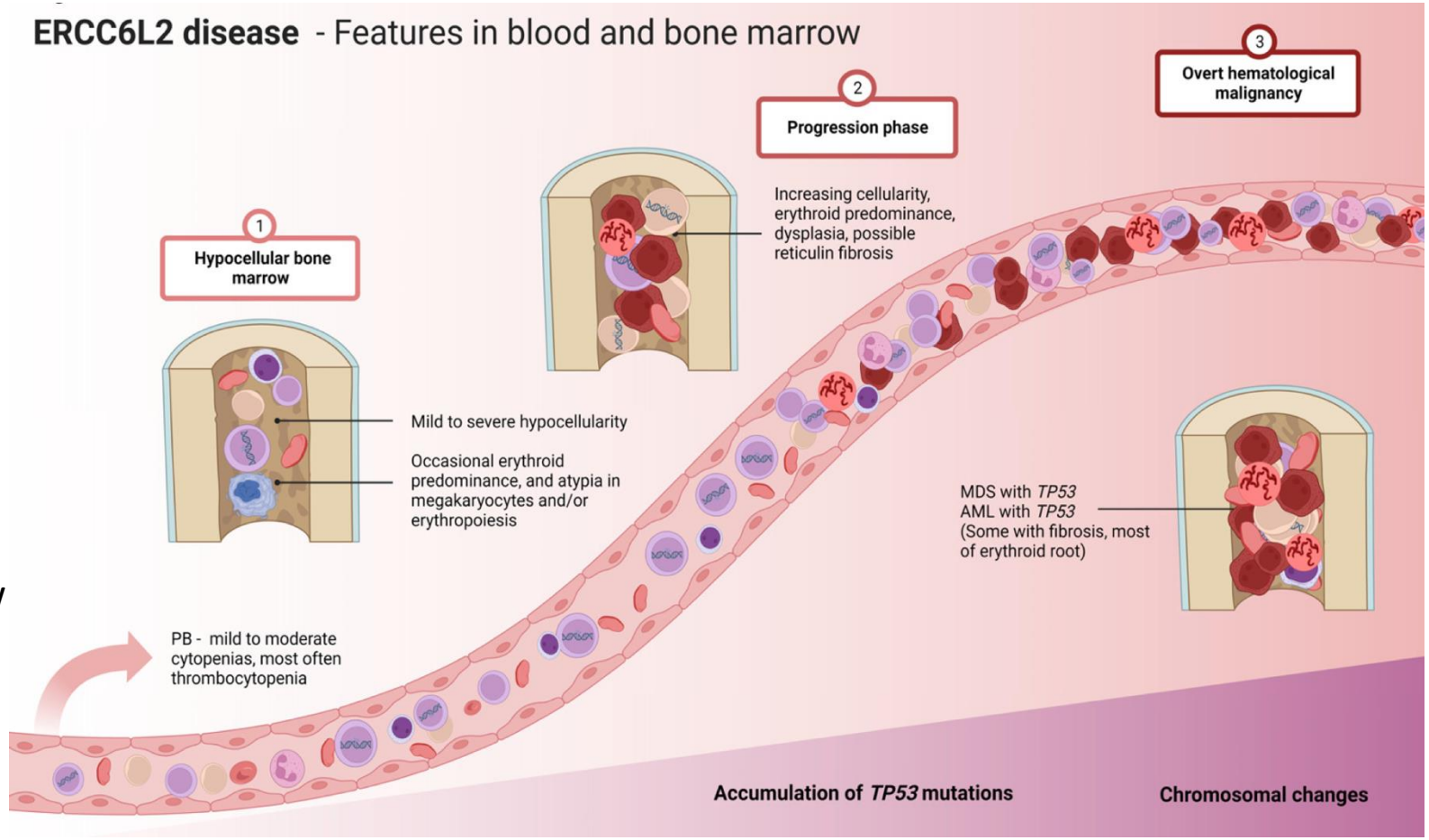
Sahoo et al. Nat Med. 2021 October ; 27(10): 1806–1817

ERCC6L2 germline condition

- ERCC6L2 disease causes bone marrow failure with a **very high-risk of clonal evolution** requiring timely stem cell transplantation before progression.

- Few cases are reported in the literature (**wide age at onset**, regional distribution mainly in Finland)

- **Signs of a progressive disease are**:
  - increasing *TP53* variant allele frequency
  - dysplasia in megakaryocytes and/or erythroid lineage
  - erythroid predominance in bone marrow



Hakkarainen M, et al. Blood. 2023 Mar 23

ERCC6L2 germline variants are associated to BM biallelic TP53 mutations

ERCC6L2 Syndrome

Clinical Phenotypes and Evolution

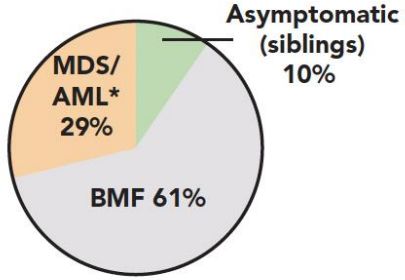
Cohort:

- 52 patients from 35 families
- 9 countries, 11 centers
- 1165 person years

Constitutional features:

- Microcephaly (3/52)
- Neuropsychiatric (4/53)
- Solid tumors (2/52)

Disease at presentation:



* One case with ALL, later progressed to MDS/AML

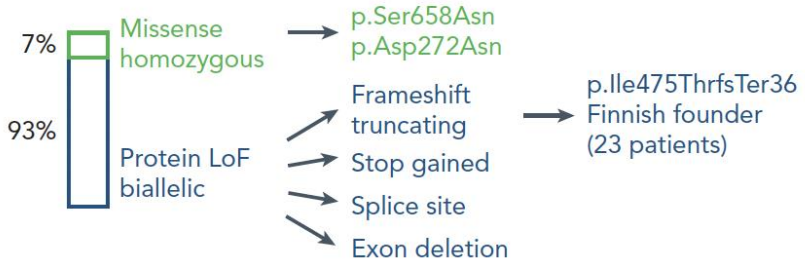
	BMF N = 32	MDS/AML* N = 15
Age at initial diagnosis, years, median (range)	12 (2-57)	29 (12-65)
Hypocellular marrow	96%	36%
TP53 mutations, percent of cases	83%	100%
TP53 median VAF	12%	38%
Overall survival (3 yrs)	95%	19%
Survival after HSCT (3 yrs)	88%	28%

CBC does not predict MDS onset (need for marrow surveillance and TP53 genetics)

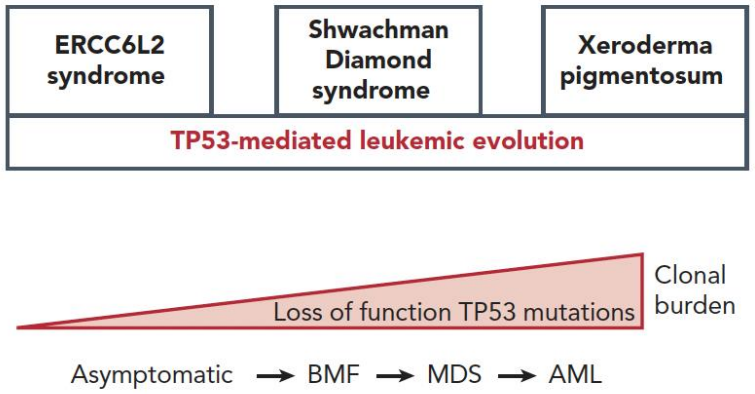
Genetics

All patients have biallelic mutations
34% consanguineous families

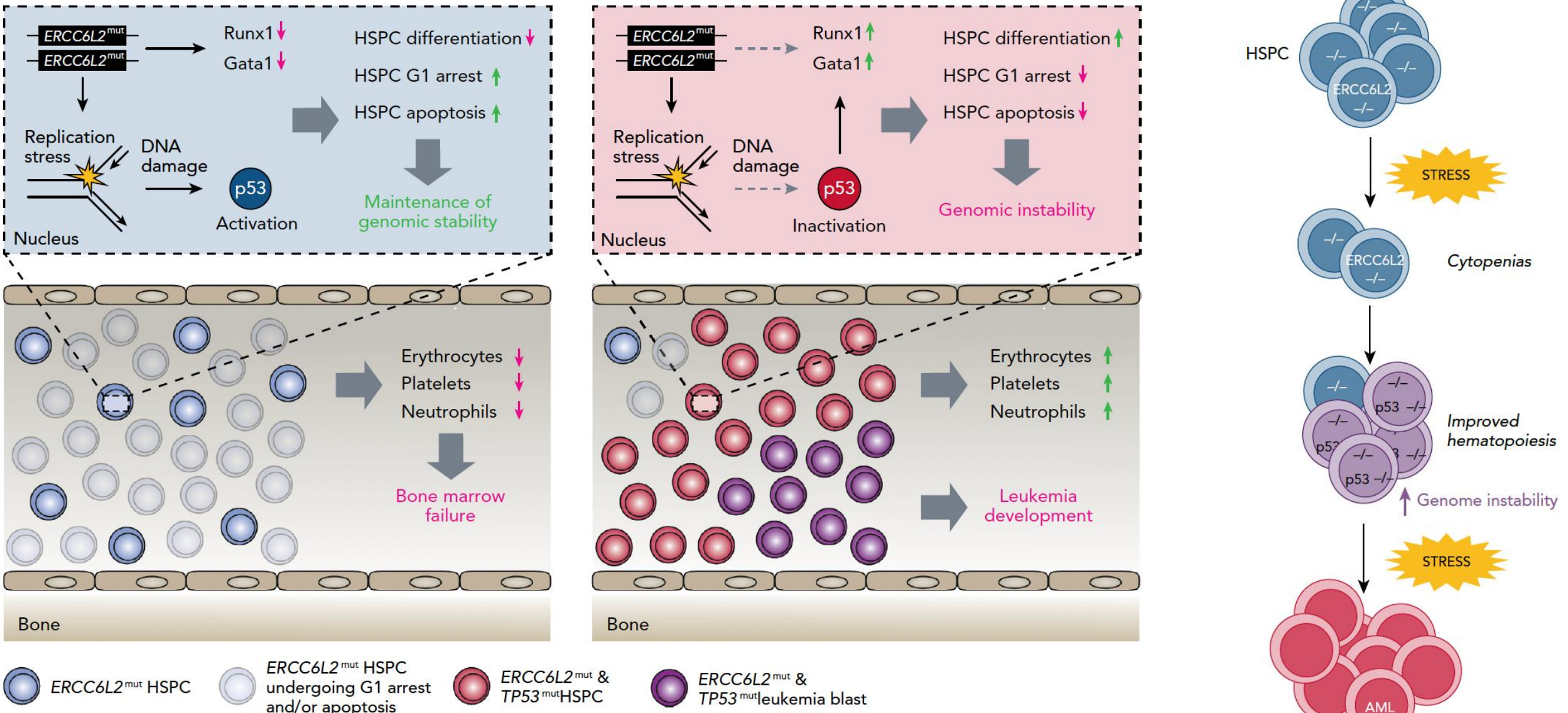
52 patients:



TP53 evolution: ERCC6L2 and beyond



ERCC6L2 and TP53 mutations: rescue gone rogue

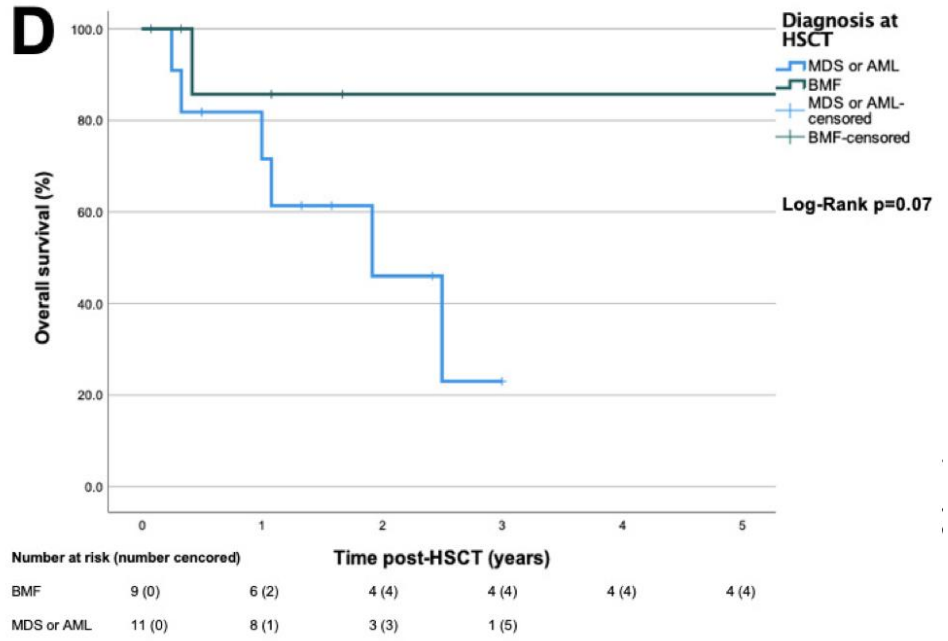


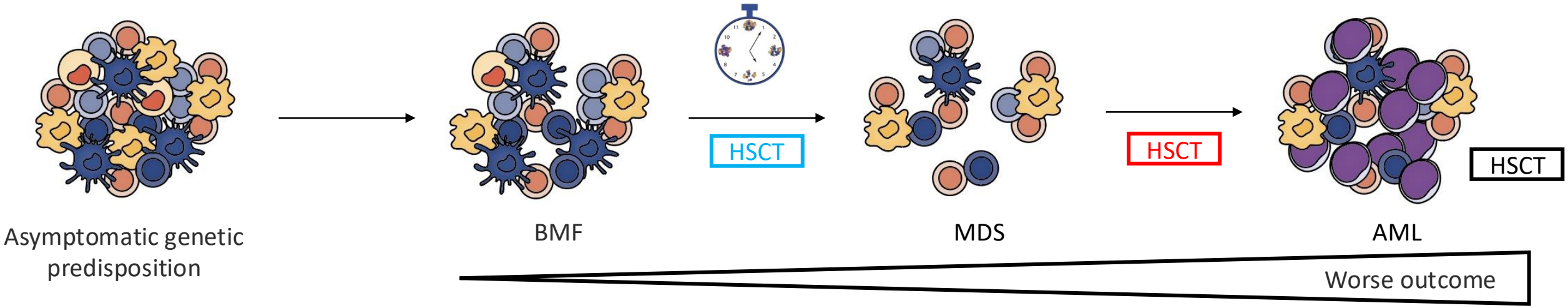
Schimmer RR. Blood. 2026 Apr 9;147(15):1663-1679

ERCC6L2 can progress to an almost incurable disease

Initial condition	n (%)
Sibling with biallelic *ERCC6L2* mutation without diagnosis of BMF, MDS or AML	5 (10)
BMF	32 (62)
MDS	9 (17)
MDS/AML*	2 (4)
AML	3 (6)
Other hematological malignancy (ALL)	1 (2)

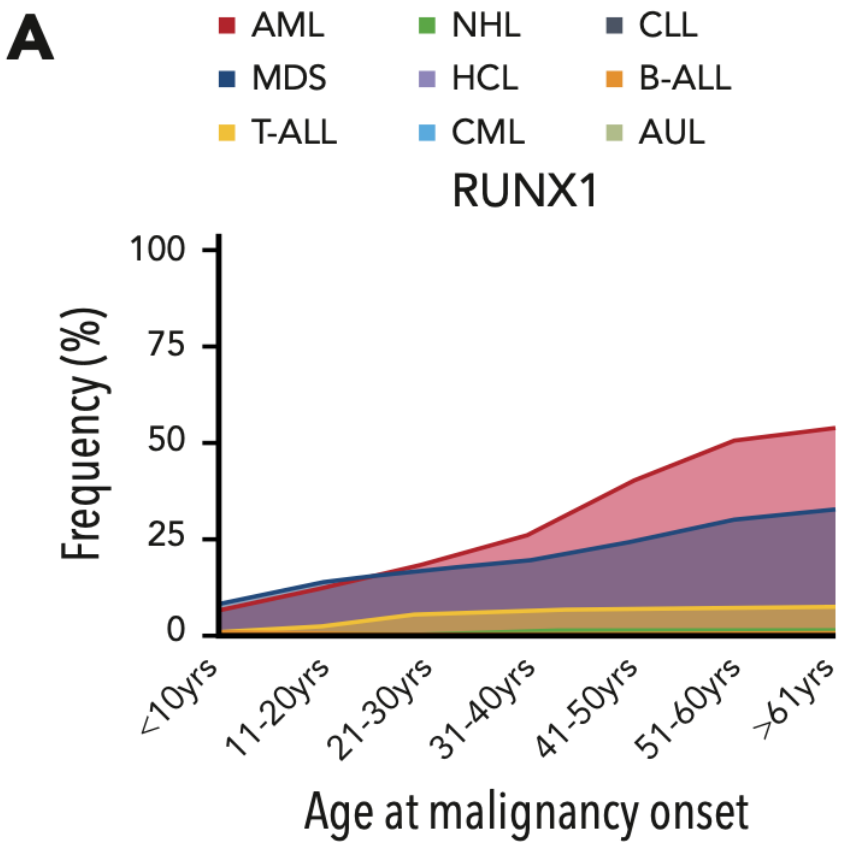
HSCT performed in BMF	9/32 (28.1%)
HSCT performed in MDS or AML	11/15 (73.3%)
Unfavorable outcome (death) in patients who underwent HSCT as BMF	1/9 (11.1%) of TRM
Unfavorable outcome (death) in patients who underwent HSCT as MDS or AML	6/11 (54.5%) of TRM (n =2) and disease progression (n = 4)





Hakkarainen M, et al. Blood. 2023 Mar 23

RUNX1 germline condition



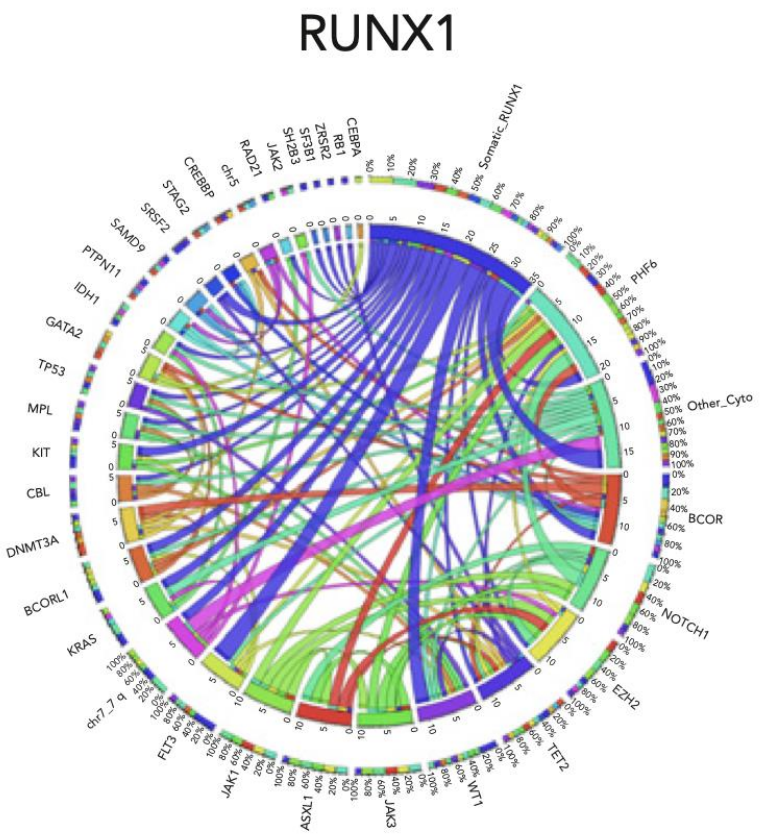
Predisposition of germline RUNX1 carriers

- Germ line RUNX1 variants most frequently predispose to myelodysplastic syndrome (**MDS**)/acute myeloid leukemia (**AML**) and are present in ~12% of families with hereditary MDS and Lymphoid malignancy is seen at lower frequency, most commonly childhood **T-cell ALL** and rarely lymphoma and **B-cell ALL**.
- 43% cummulative incidence of hematological malignancy by the age of 50 years.
- Notwithstanding the time needed to accumulate longitudinal data, current knowledge suggests that **progression to malignancy is less likely to occur in the absence of additional somatic variants**, and the detection of a somatic variant provides another biomarker that can be monitored for changes.

Brown AL, et al. Blood. 2020 Jul 2;136(1):24-35.

Homan CC, et al Blood. 2023 Mar 30;141(13):1533-1543.

RUNX1 germline condition



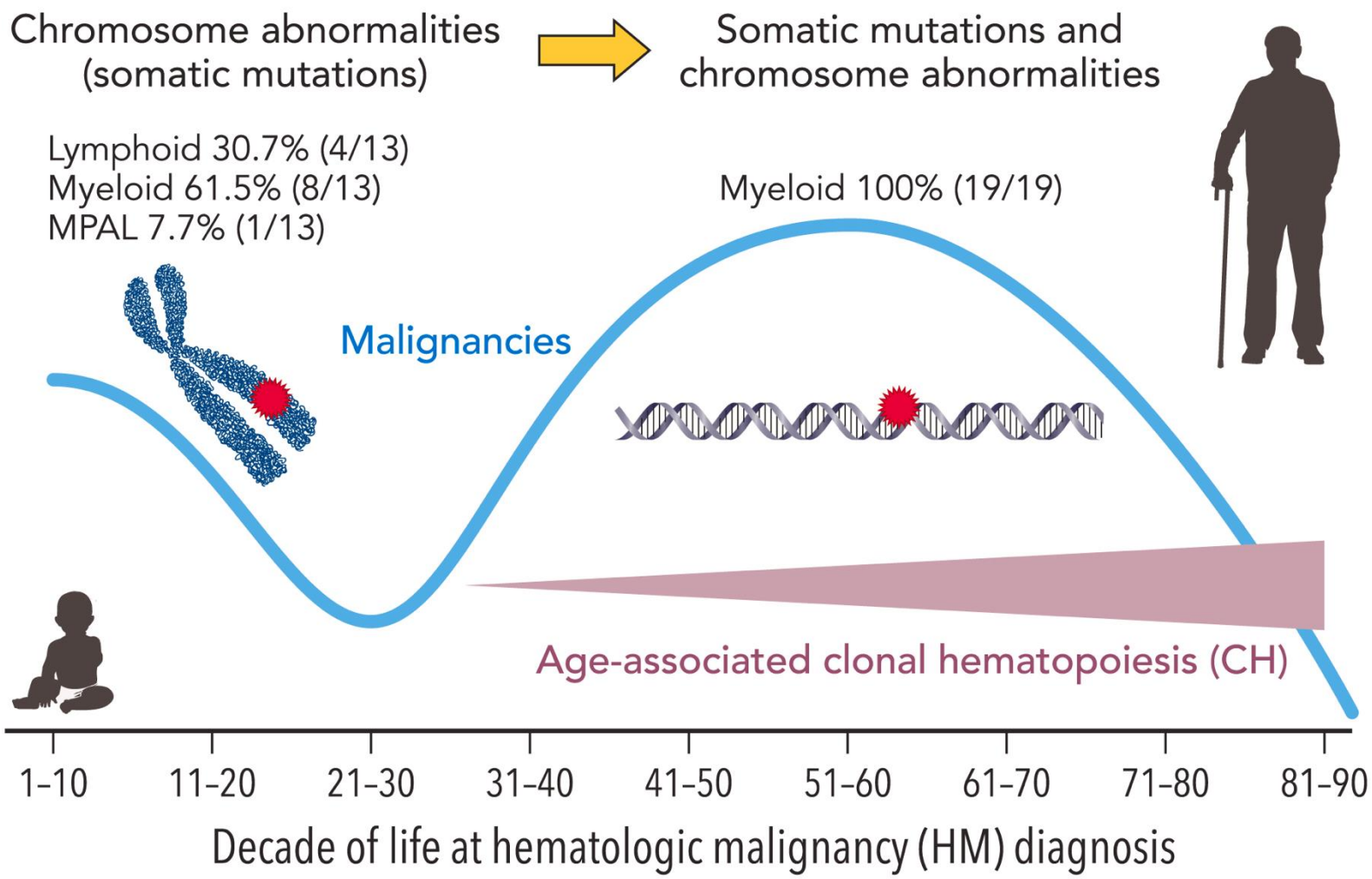
Increased mutagenic processes in germline RUNX1 carriers

- **Somatic mutation of the second RUNX1 allele** is frequently associated with malignancy (including duplication of the germline mutation through trisomy 21 or uniparental disomy).
- Other recurrent somatically mutated genes include **PHF6, BCOR, WT1, and TET2**
- Premalignant somatic variants have been observed and occur frequently in germ-lineRUNX1 carriers, most commonly in BCOR,TET2, DNMT3A, KRAS, and SRSF2, occurring as early-onset clonal hematopoiesis of indeterminate potential (CHIP) in carriers as young as 16 years.

Brown AL, et al. Blood. 2020 Jul 2;136(1):24-35.

Homan CC, et al Blood. 2023 Mar 30;141(13):1533-1543.

RUNX1 germline condition

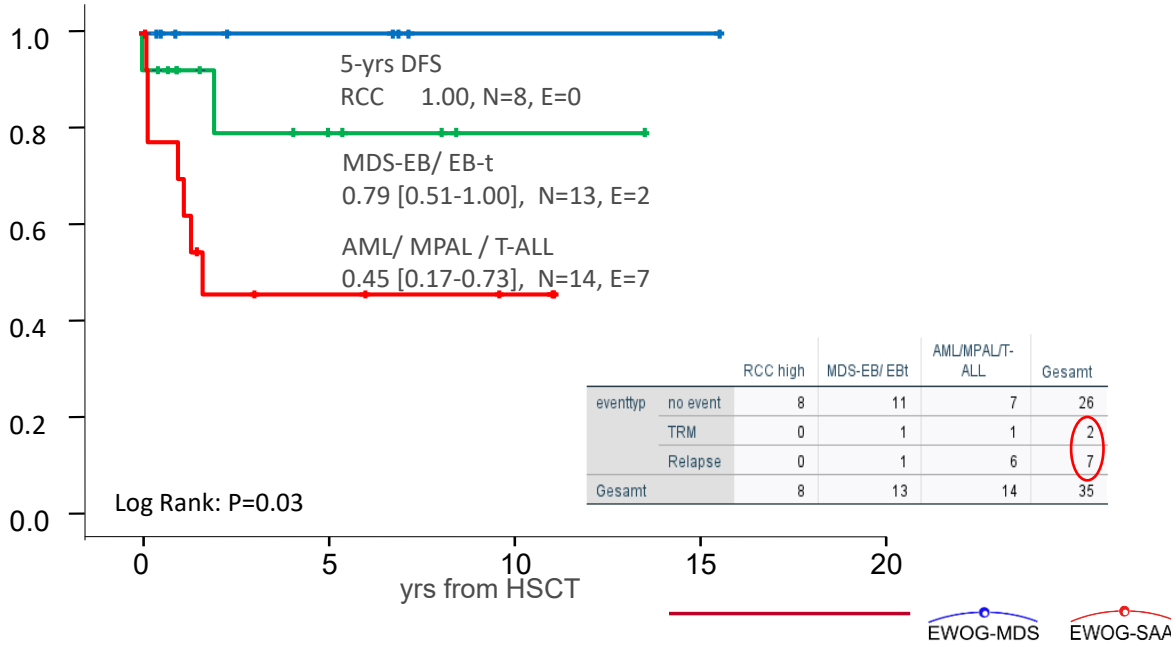


Cantor AB, Shimamura A. Blood Adv. 2026 May 12;10(9):3198-3199.

HSCT in pediatric pts with RUNX1: EBMT PDWP/ EWOG M

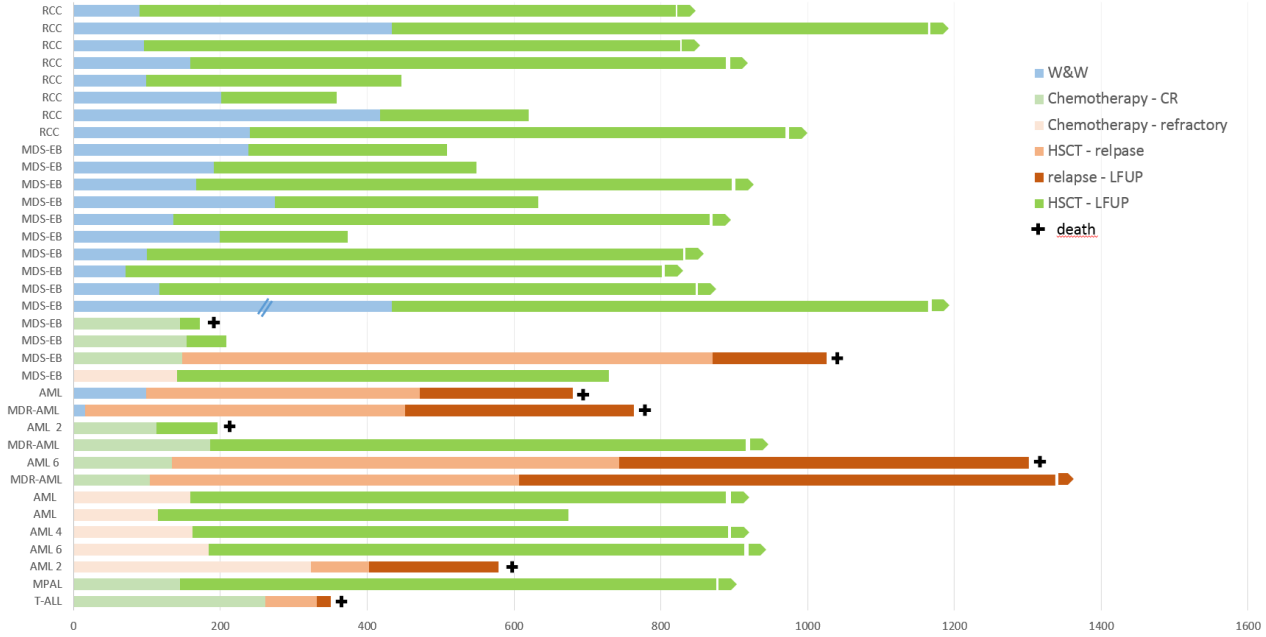
- **Outcome depends on the stage of disease** with significantly better outcome before the development of hematological malignancy.
- RUX1 deficiency is **not associated with a high risk of GvHD or an excess of toxicity**.

Disease stage predicts disease free survival



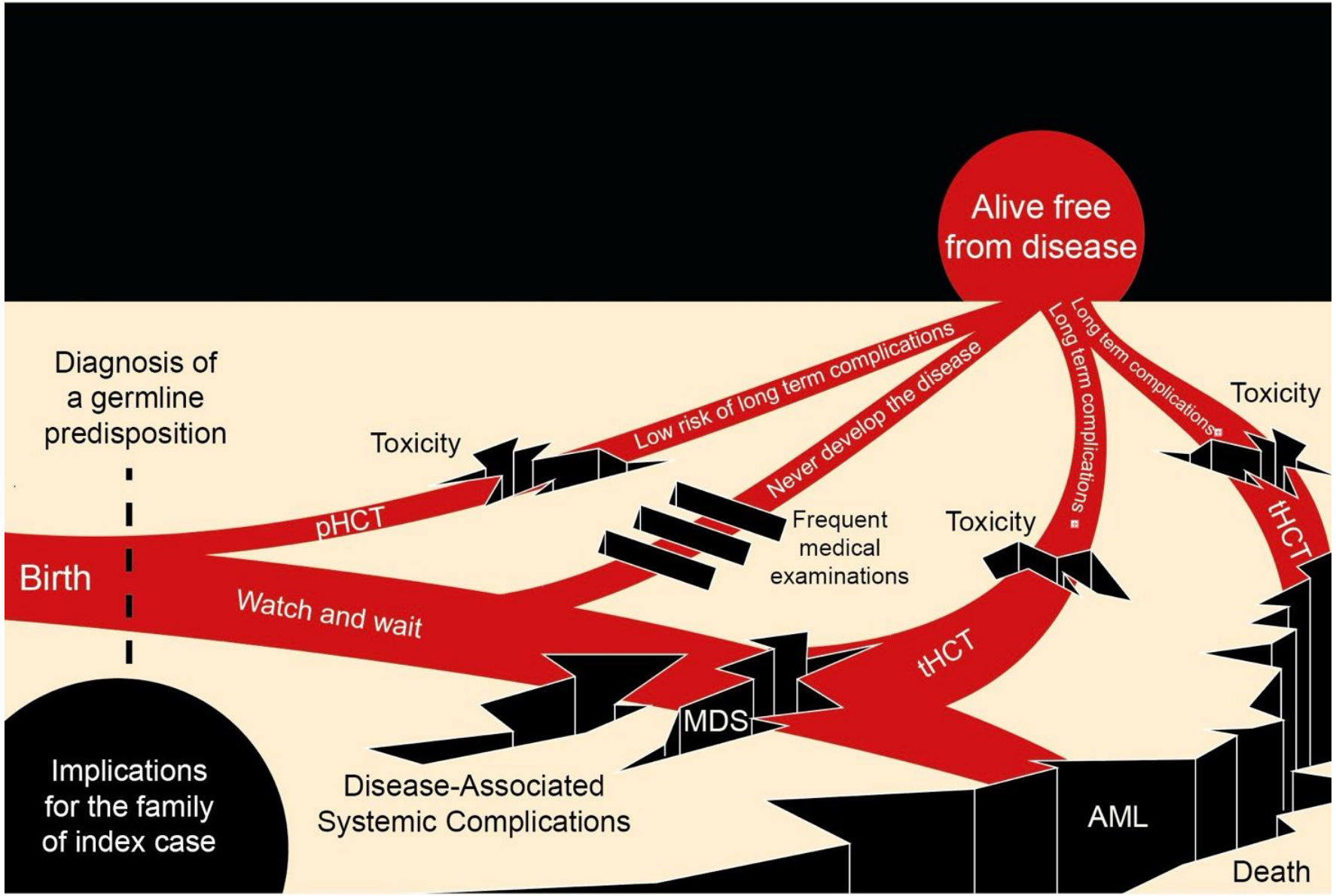
		RCC high	MDS-EB/ EBt	AML/MPAL/T-ALL	Gesamt
eventtyp	no event	8	11	7	26
	TRM	0	1	1	2
	Relapse	0	1	6	7
Gesamt		8	13	14	35

Clinical Course following HSCT for RUNX1 deficiency



Courtesy B. Strahm. Oral Presentation SIOP-Eu 2022

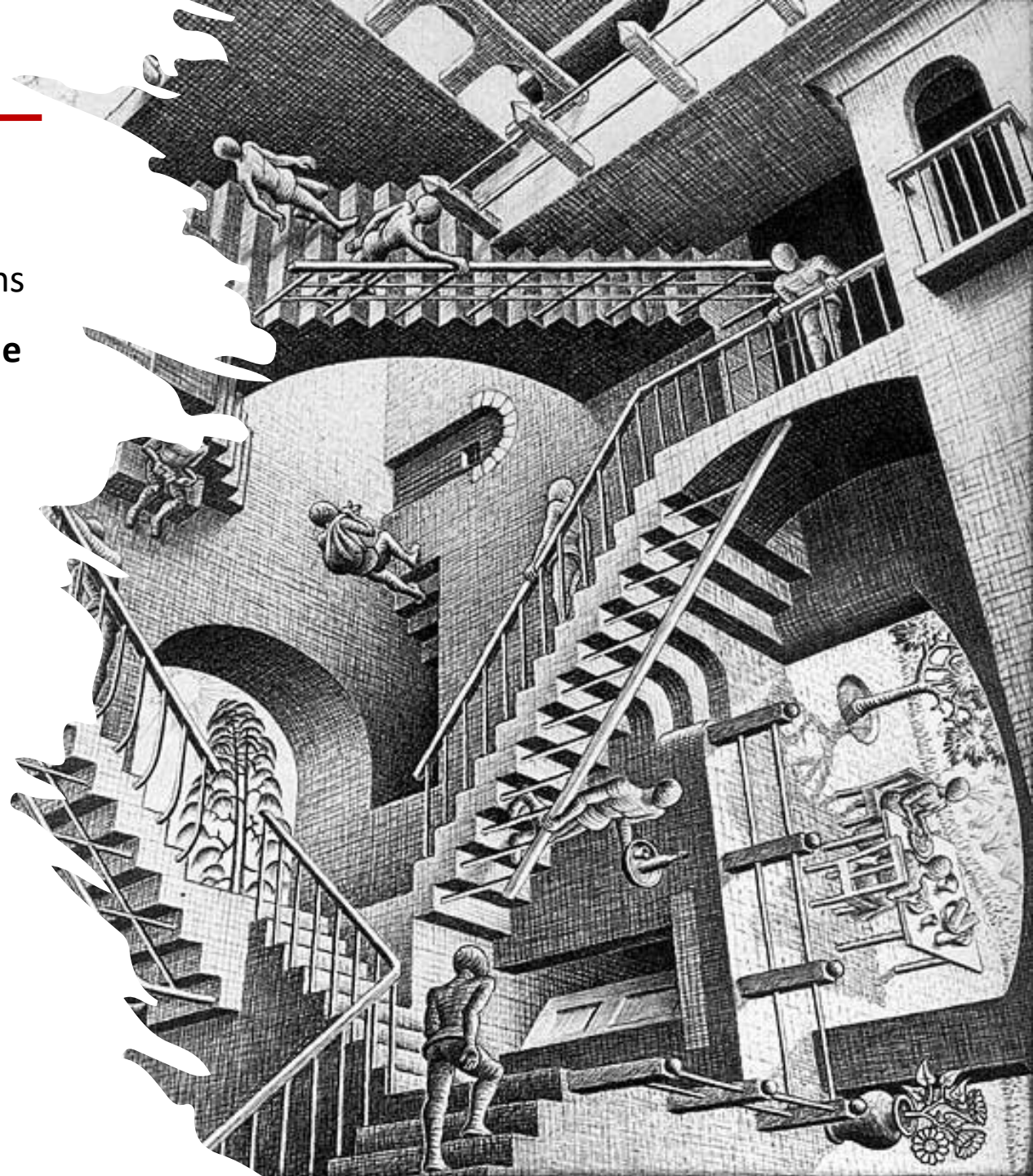
Pathway of a patients with germline predisposition to MDS toward a healthy state



pHCT: pre-emptive hematopoietic cell transplantation, tHCT: therapeutic hematopoietic cell transplantation.

Conclusions

Escher. Relativity. 1953



- Pediatric predispositions to MDS/AML define specific conditions in which the **age of onset of an overt hematological phenotype** is a crucial point to be considered.

- **Decision on timing of HSCT is influenced by a labyrinth of considerations accounting for the diversity of patients (and family background) and heterogeneity of predispositions precluding a prescribed approach.**

- **A strong ethical framework is necessary** to support at-risk individuals and clinicians in making these difficult decisions