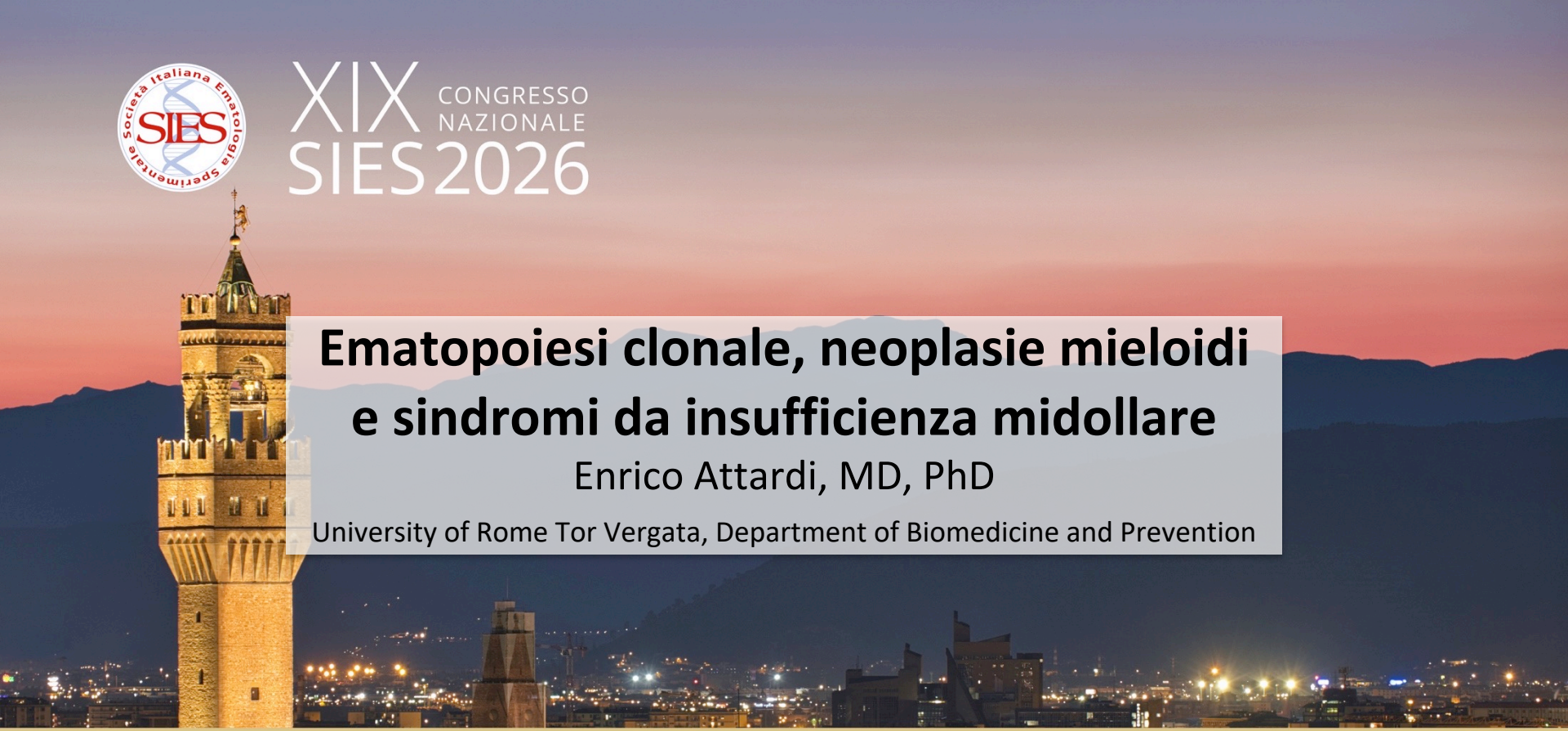


XIX CONGRESSO NAZIONALE SIES 2026

Ematopoiesi clonale, neoplasie mieloidi e sindromi da insufficienza midollare

Enrico Attardi, MD, PhD

University of Rome Tor Vergata, Department of Biomedicine and Prevention

Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Enrico Attardi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

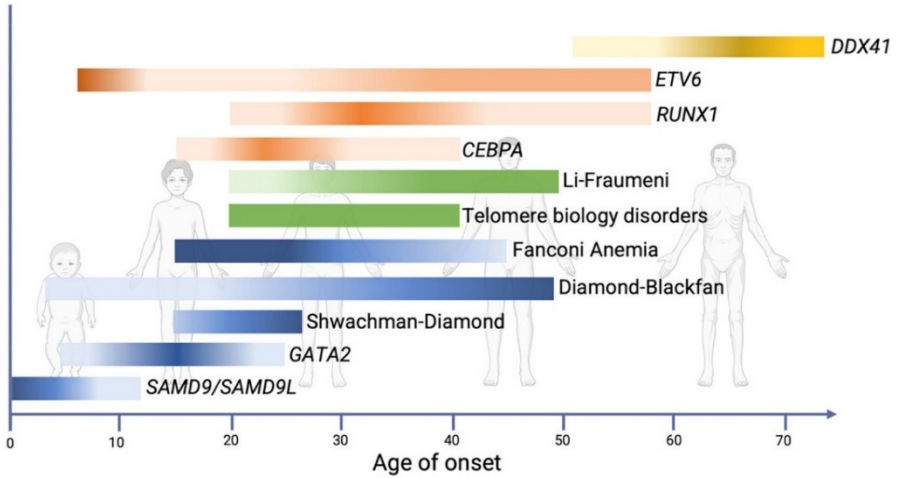
none

Bone Marrow Failure (BMF) and Leukemia Predisposition Syndromes (LPS)

WHO22	ICC
Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction	**Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems**
Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)	Myeloid neoplasms with germline *CEBPA* mutation
Germline *DDX41* P/LP variant *(myeloid and lymphoid neoplasms)*	Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Germline *TP53* P/LP variant (Li–Fraumeni syndrome) *(myeloid and lymphoid neoplasms)*	Myeloid or lymphoid neoplasms with germline *TP53* mutation
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder	**Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder**
Germline *RUNX1* P/LP variant (familial platelet disorder with associated myeloid malignancy, FPD-MM) *(myeloid and lymphoid neoplasms)*	Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Germline *ANKRD26* P/LP variant (thrombocytopenia 2) *(myeloid and lymphoid neoplasms)*	Myeloid neoplasms with germline *ANKRD26* mutation
Germline *ETV6* P/LP variant (thrombocytopenia 5) *(myeloid and lymphoid neoplasms)*	Myeloid or lymphoid neoplasms with germline *ETV6* mutation
Myeloid neoplasms with germline predisposition and potential organ dysfunction	**Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems**
Germline *GATA2* P/LP variant (GATA2-deficiency)	Myeloid neoplasms with germline *GATA2* mutation
Germline *SAMD9* P/LP variant (MIRAGE syndrome)	Myeloid neoplasms with germline *SAMD9* mutation
Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia-Pancytopenia syndrome	Myeloid neoplasms with germline *SAMD9L* mutation
Bone marrow failure syndromes	Myeloid neoplasms associated with bone marrow failure syndromes
Severe congenital neutropenia (SCN)	Severe congenital neutropenia
Fanconi anemia (FA)	Fanconi anemia
Shwachman–Diamond syndrome (SDS)	Shwachman–Diamond syndrome
Telomere biology disorders	Telomere biology disorders including dyskeratosis congenita
	Diamond–Blackfan anemia
RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan-like disorders) *(myeloid and lymphoid neoplasms)*	JMML associated with neurofibromatosis JMML associated with Noonan syndrome-like disorder (CBL syndrome)
Down syndrome	Myeloid or lymphoid neoplasms associated with Down syndrome
Biallelic germline *BLM* P/LP variant (Bloom syndrome)	

Similarity / Overlap between the WHO (2022) and ICC (2022) classifications

- Very strong overlap or Identical categories
- Slight differences between the two classification systems *(differences are highlighted in orange)*
- Considerable difference between the two classification systems *(differences are highlighted in red)*



Godley LA et al. Sem in Hem. 2025

Agenda

1. When to consider germline predisposition to BMF/Leukemia

2. Utility of clonal hematopoiesis in predisposed individuals (CH-IPI)

Algorithm of the Hematology-Genetics outpatient clinic (Progetto GEMMA) - Policlinico Tor Vergata

Prof Maria Teresa Voso
UOSD Diagnostica avanzata oncoematologica
Prof Federica Carla Sangiuolo
Unit Genetica Medica

Proposal for II opinion
- Physicians refer cases with suspected BMF/LPS
- Elegibility evaluation (using a check-list)

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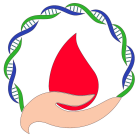
1ª Hematology visit (+ Genetic counselor)
- Clinical evaluation and genogram
- Informed consent
- Germline tissue (skin punch, mesenchimal cells from bone marrow) + Somatic tissue (bone marrow or peripheral bloosd)

Analysis
- clinical exome sequencing on germline tissue
- targeted NGS (myeloid panel) on bone marrow or peripheral blood cells



Germline variant of clinical relevance?

Yes

Implications
- Treatment strategies
- Personalised surveillance
- Rare Disease Registries
- Consequences on family members at risk

No

Storage for future examinations
- Considering whole exome sequencing
- Pathogenicity reassessment of variants of uncertain significance based on functional studies

Multidisciplinary team

2ª Hematology visit (+ Genetic counselor)
- Report and discussion with the patient and family members

Follow-up visits

Checklist adopted for BMF/LPS patient selection

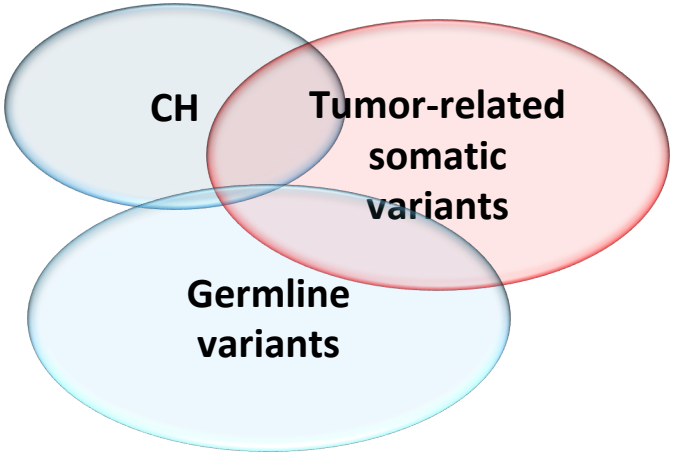
The patient presents with:

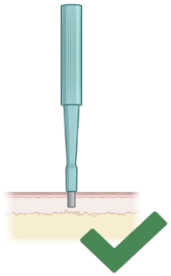
	Eligibility criteria (at least one is required)	YES	NO
Familial history	Family history of at least one first- or second-degree relative** affected by BMF/ICUS (or CCUS)/myeloid neoplasm (MN)		
	Family history of at least 2 first- or second-degree relatives affected by an oncologic/hematologic condition (including solid tumors)		
	Family history of at least 3 relatives (regardless of degree) affected by an oncologic/hematologic condition (including solid tumors)		
Personal history	Personal history of at least two cancers, one of which is a myeloid neoplasm		
	Extra-hematological signs/symptoms suggestive of a syndromic condition If yes, specify		
Disease characteristics	MDS with age at onset <50 years		
	ICUS/CCUS with age at onset <50 years and bone marrow biopsy showing <30% cellularity (or age-adjusted hypocellularity)		
	Therapy-related myeloid neoplasm or history of prolonged cytopenia following exposure to chemo/radiotherapy for another oncologic/hematologic condition		

* For myeloid neoplasm (MN), refer to one of the following: MDS, AML, MPN, CML, or CMML.

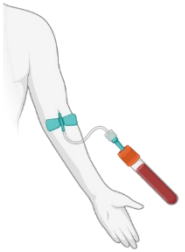
** First-degree relatives: children and parents (direct line). Second-degree relatives: siblings (collateral line), grandchildren and grandparents (direct line).

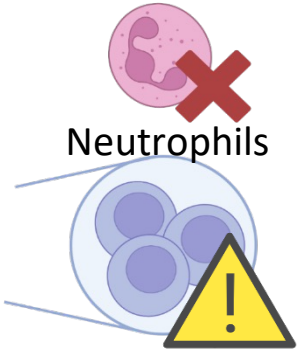
The importance of tissue selection





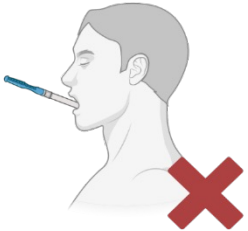
Skin biopsy (fibroblasts)





Nails: ok if the application is confined to Sanger sequencing analysis. They can be used for confirmation OR exclusion of the germline nature.

Nails



Saliva

Our experience: we mostly excluded ***CEBPA*** and ***TP53*** mutations as germline **(Dott.ssa N. Lelli, C034)**

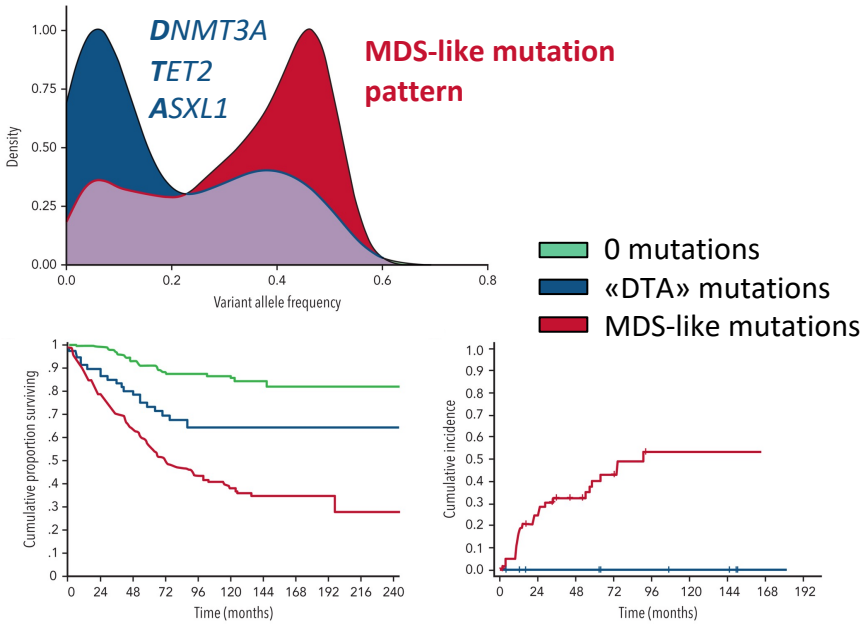
Agenda

1. When to consider germline predisposition to BMF/Leukemia

2. Utility of clonal hematopoiesis in predisposed individuals (CH-IPI)

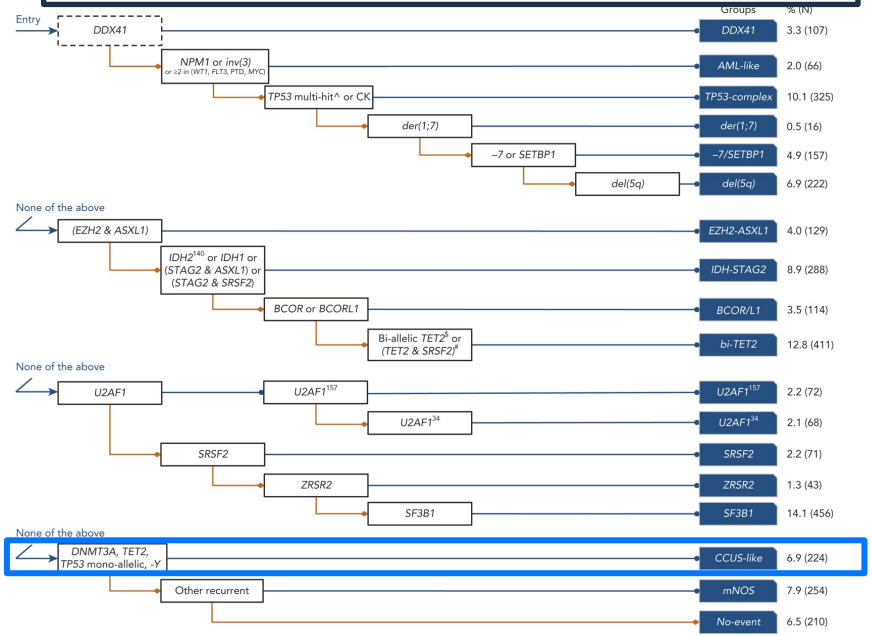
“La marcia clonale”: from CHIP to LR-MDS

MDS-like CCUS



Gallì A et al, Blood 2021

CCUS-like MDS



Bernard E et al, Blood 2024

Stressors in clonal hematopoiesis

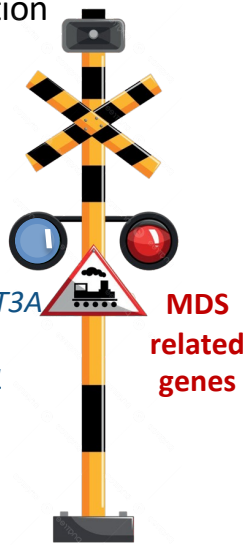
clonal hematopoiesis of indetermined potential (CHIP)

aging

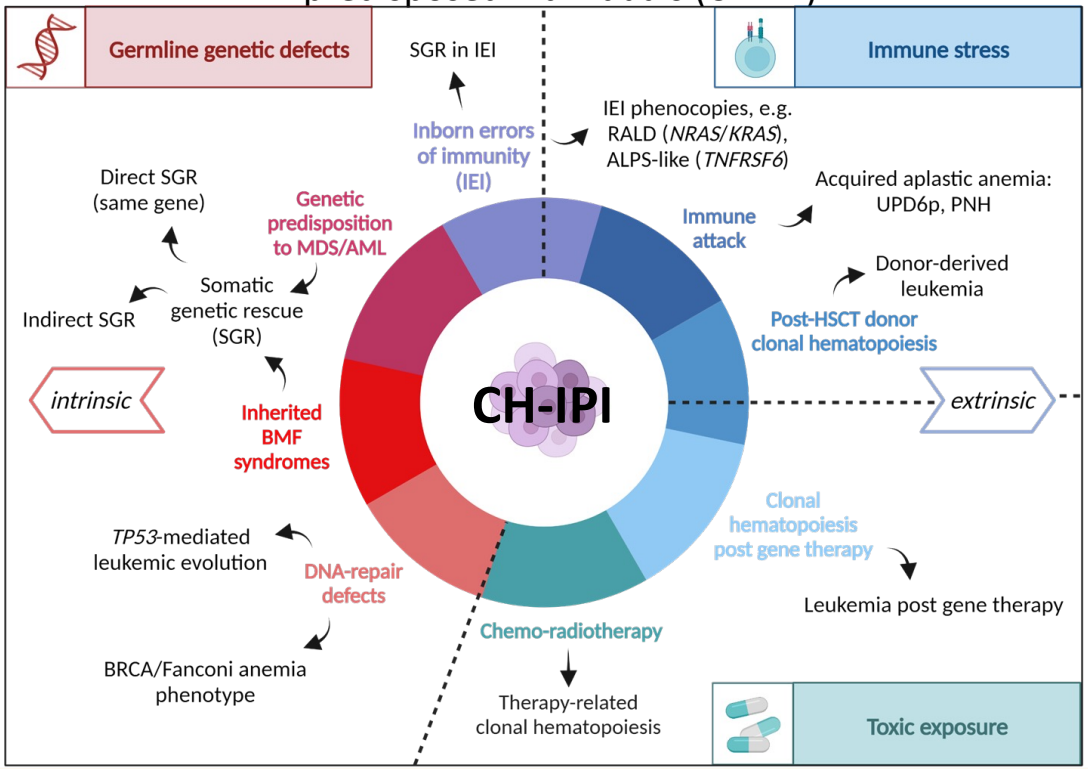
inflammation

CHIP

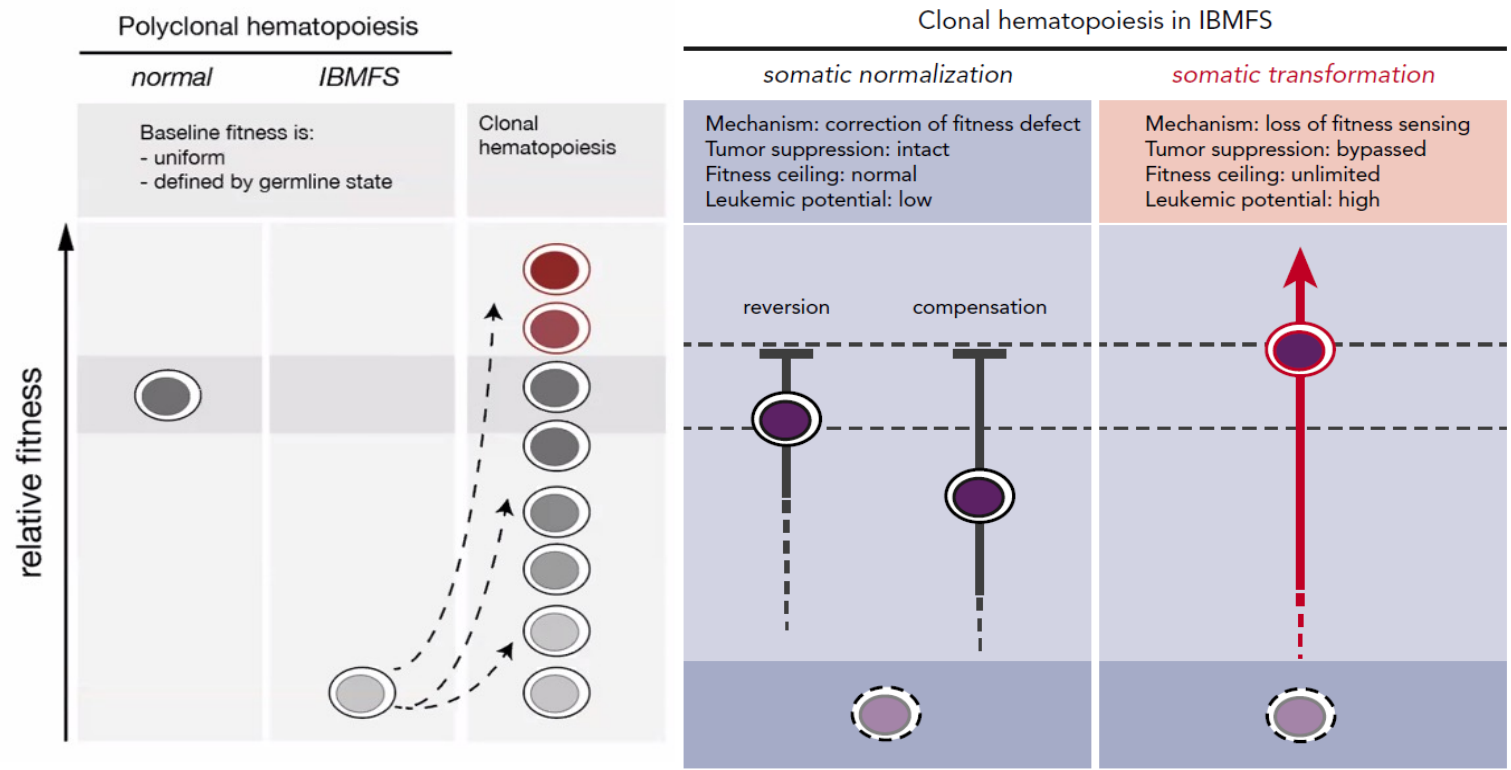
one way (two speeds)



clonal hematopoiesis in predisposed individuals (CH-IPI)



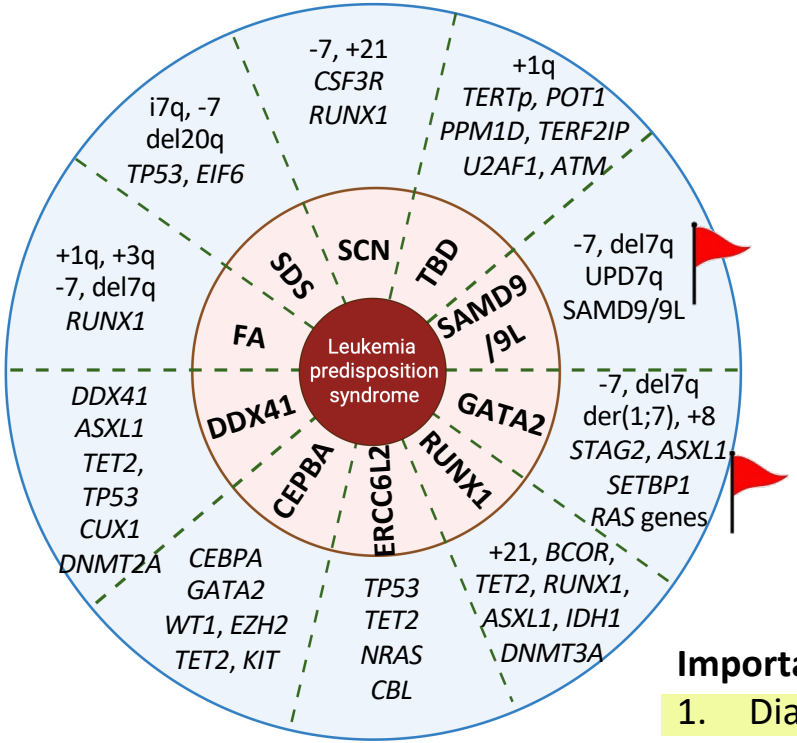
CH-IPI and relative fitness



Adapted from R. Coleman Lindsley

Clonal trajectories in BMFs/leukemia predisposition syndromes (LPS)

CH-IPI:
clonal hematopoiesis in predisposed individuals

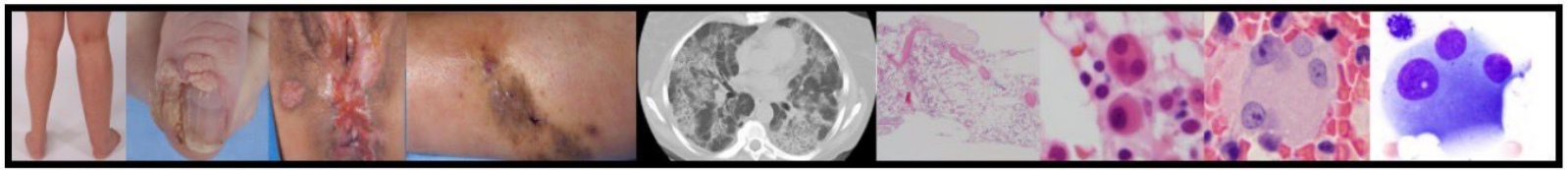


Important for:

1. Diagnosis (red flags)
2. Disease confirmation
3. Disease monitoring (MDS/AML)

GATA2 deficiency

- Different inheritance pattern, AD or arising *de novo* in 80% of cases → caution considering the familial history
- Emberger syndromes – MonoMAC syndrome – Familial MDS/AML → phenotypical spectrum related to the same gene
- 75% of GATA2 mutation carriers develop MN at an estimated median age of 20 years → MDS/AML risk can increase with age

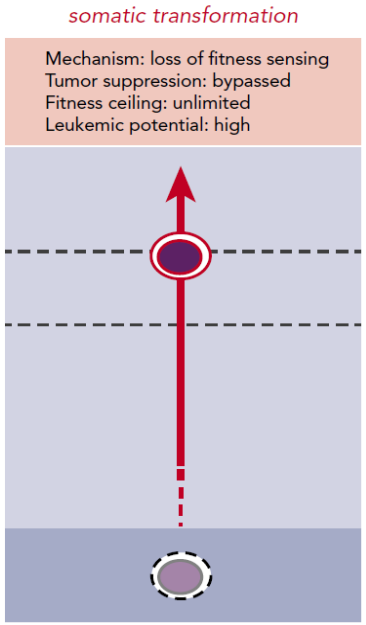


0-15 years	15-20 years	20-30 years	>30 years
Lymphedema (11-20%) Hearing loss (20%)	HPV (60-70%) Nontuberculous mycobacteria (20-50%) EBV, CMV, HSV (10-35%) Invasive fungal infections (4-16%) Other bacterial infections (50%)	Myelodysplastic syndrome (90%) Pulmonary alveolar proteinosis (18%) Autoimmune diseases (panniculitis)(50%) Miscarriage (33%)	Acute myeloid leukemia (AML) (14%) Solid cancers (22%)

monosomy 7 in up to 80% of GATA2-related MDS patients → RED FLAG

Adapted from B. Terrier

Second hit clones in LPS

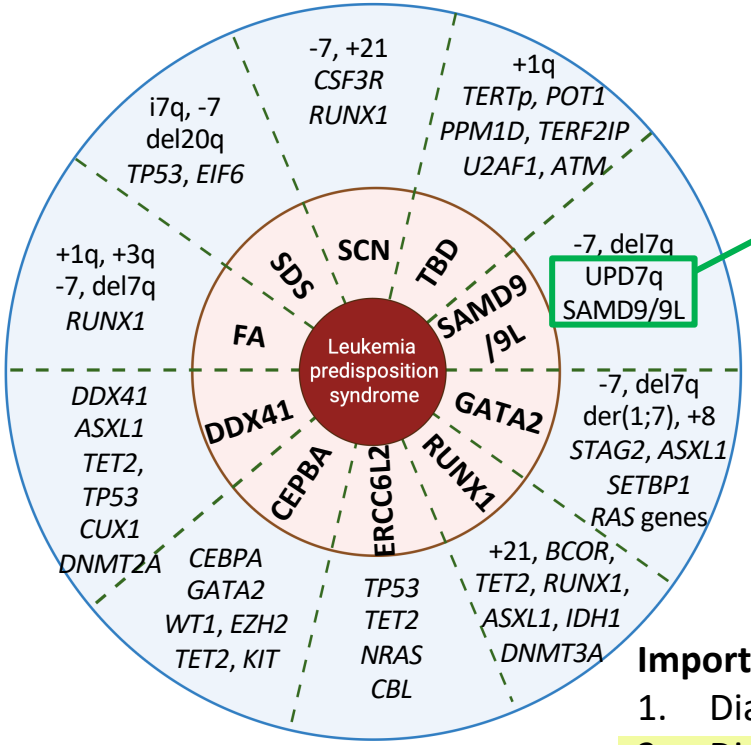


- Germline *CEBPA* → familial AML (median age 25 years)
- 10% of patients with bi-allelic CEBPA-mutant AML have one of those alleles as a germline allele, typically the 5'-end mutation (penetrance ≃ 100%)
- 3'-end acquired mutations are distinct in AML that re-emerge in germline *CEBPA*-mutation carriers, suggesting that they are independent primary AMLs rather than relapses

- Germline *DDX41* → familial MDS/AML (median age 69 years)
- II hit in *DDX41* in around 70% of germline *DDX41* (vs. 0.8% of somatic DDX41 in wt DDX41 MDS/AML).

Makishima H et al. Germ line DDX41 mutations define a unique subtype of myeloid neoplasms. Blood. 2023
Tawana K, et al. Disease evolution and outcomes in familial AML with germline CEBPA mutations. Blood. 2015

Clonal trajectories in BMFs/leukemia predisposition syndromes (LPS)



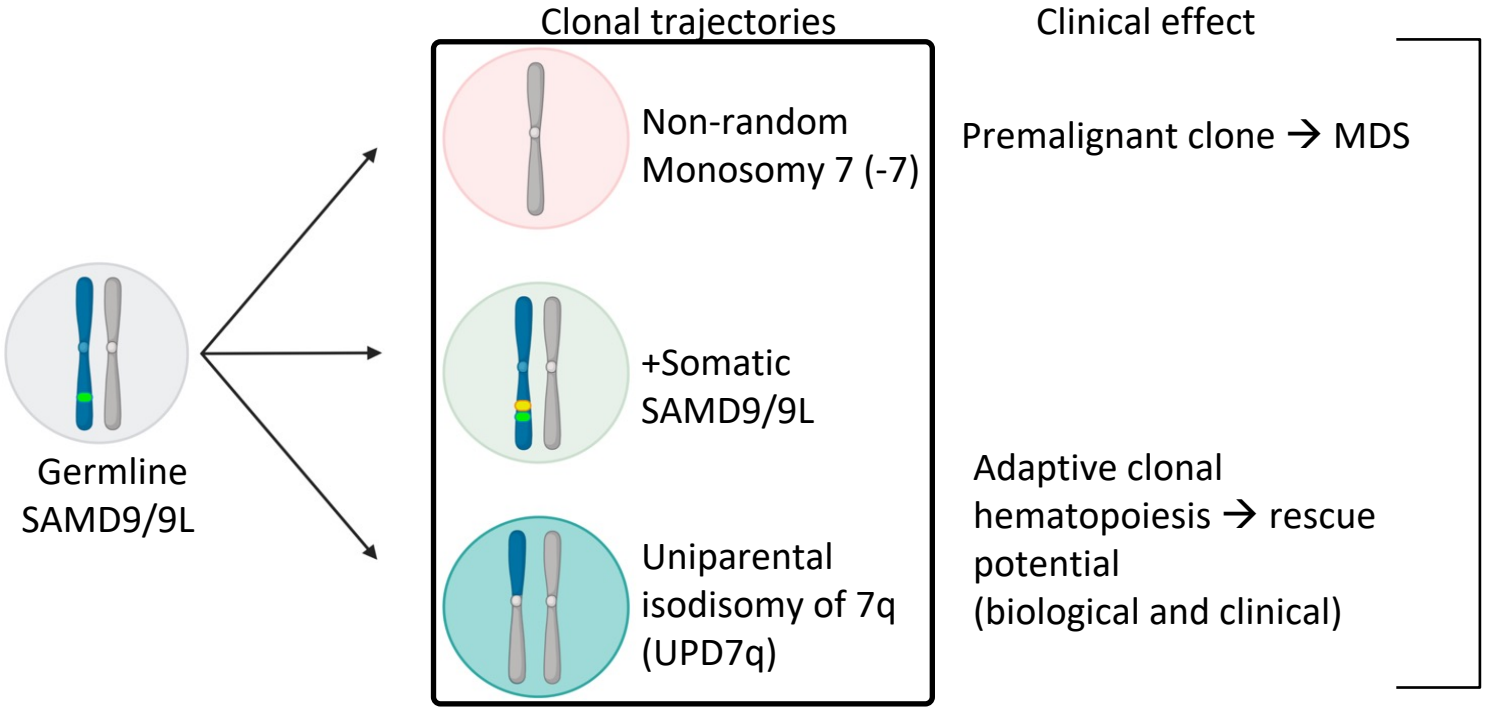
somatic rescue in 64% of SAMD9/9L syndromes

Important for:

1. Diagnosis (red flags)
2. Disease confirmation
3. Disease monitoring (MDS/AML)

Somatic Genetic Rescue in SAMD9/9L Syndromes

Somatic Genetic Rescue: a genetic mechanism to escape disease by modifying or losing the pathogenic mutation

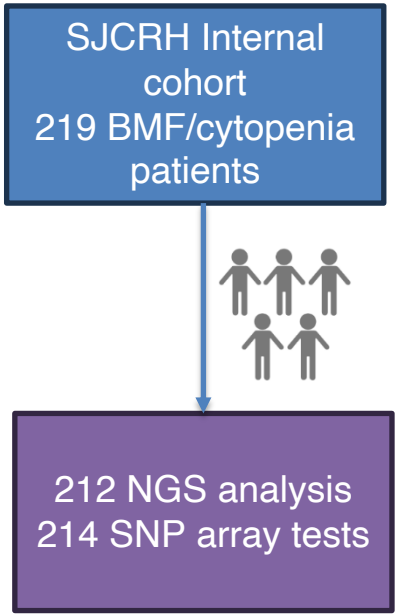


The diagnostic value of rescue CH in SAMD9/9L syndromes

Disease-causing germline *SAMD9/9L* variants are primarily missense GoF with no impact on RNA or protein expression levels.

Poor conservation of both genes complicates interpreting the pathogenic effect of these variants.

Based on our internal experience, we assumed that somatic mutations affecting *SAMD9* and *SAMD9L* are specific for SAMD9/9L syndromes and that UPD7q can be either in SAMD9/9L syndromes and Shwachman-Diamond Syndrome.



The diagnostic value of rescue CH in SAMD9/9L syndromes

In the SJCRH internal cohort CH was found in 23/33 (69.7%) SAMD9/9L syndromes

- Second somatic SAMD9/9L: 21/33 cases (63.6%)
- UPD7q: 5/33 cases (15.1%)
- Monosomy 7: 9/33 cases (27.3%)

somatic	germline SAMD9/9L	other diagnosis
SAMD9/9L pos	21	0
SAMD9/9L neg	11	180

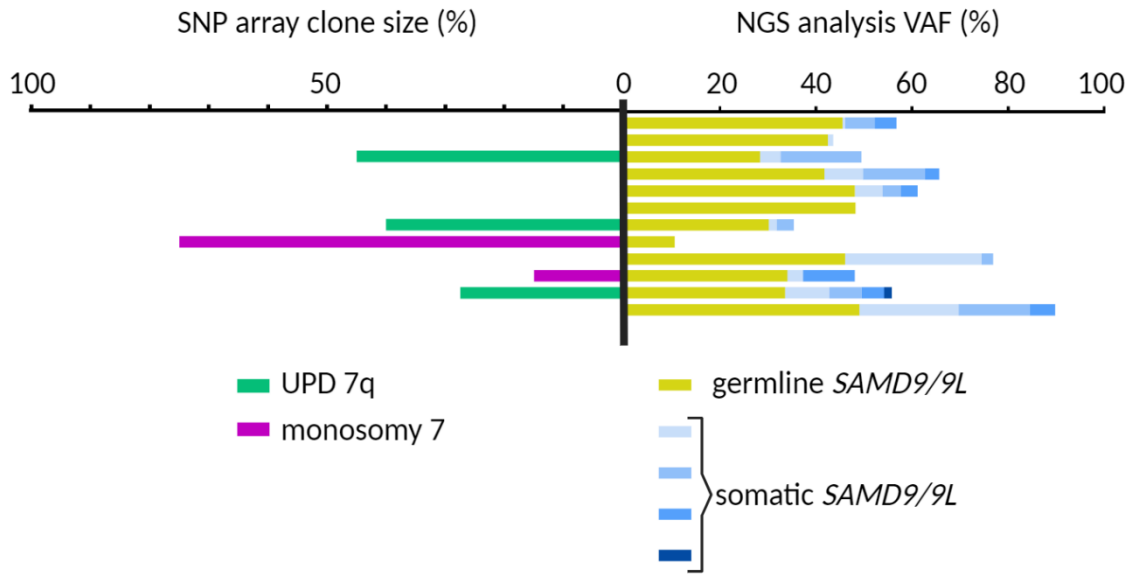
Sensitivity=65.6%
Specificity=100%
Positive predictive value (PPV)=100%
Negative predictive value (NPV)=94.2%

	germline SAMD9/9L	other diagnosis
UPD7q pos	5	1
UPD7q neg	28	180

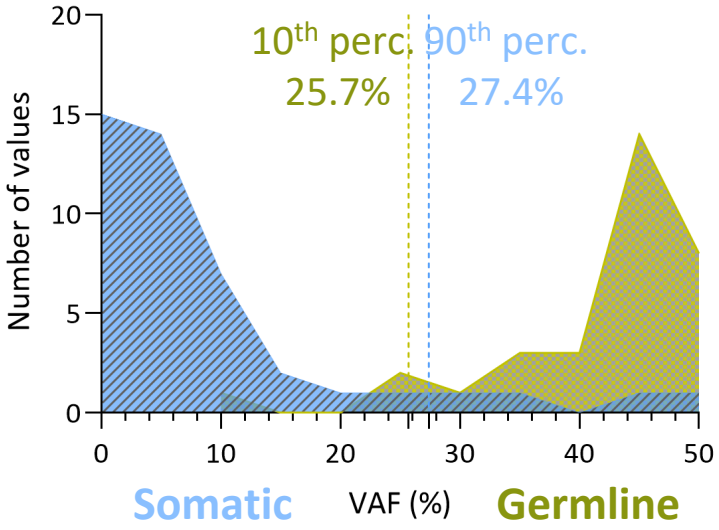
Sensitivity=15.1%
Specificity=99.4%
Positive predictive value (PPV)=83.3%
Negative predictive value (NPV)=86.5%

The diagnostic value of rescue CH in SAMD9/9L syndromes

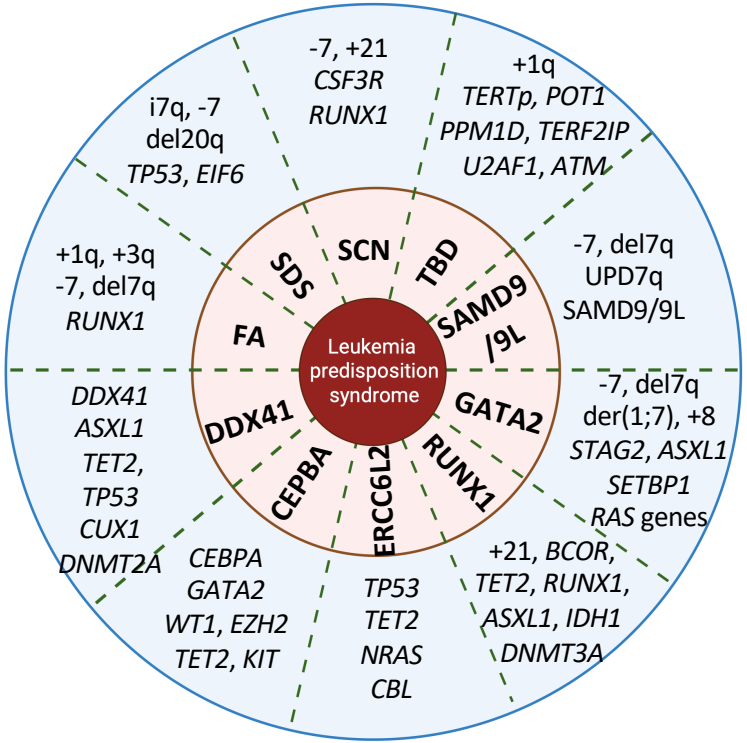
St. Jude Children's Research Hospital
BMF/MDS Program
Bone Marrow Failure and Myelodysplastic Syndromes



Frequency distribution of germline and somatic SAMD9/9L



Clonal trajectories in BMFs/leukemia predisposition syndromes (LPS)



portant for:

1. Diagnosis (red flags)
2. Disease confirmation
3. Disease monitoring (MDS/AML)

Surveillance in BMF/LPS

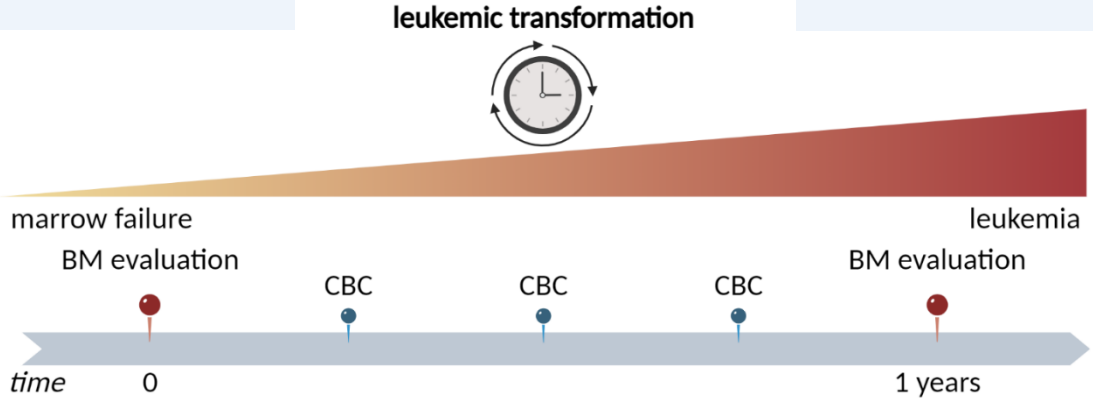
No unique consensus for surveillance of patients with BMFS/leukemia predisposing conditions

BM evaluation
(cellularity, dysplasia, blast %, cytogenetic alterations)

low risk leukemia predisposition
(TBD, DBA)

timing

high risk leukemia predisposition
(FA, SDS, GATA2, RUNX1)

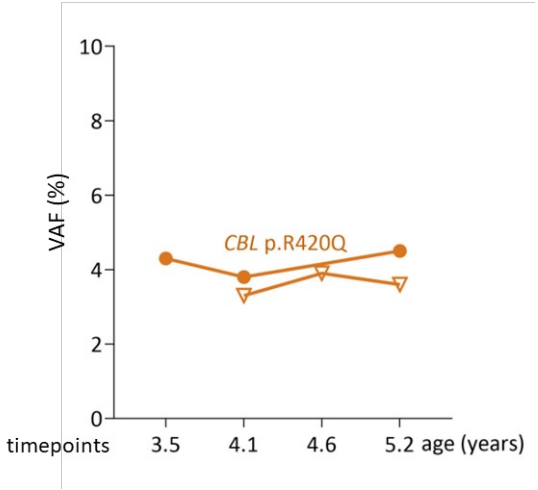


CBC, complete blood count

Discrepancy between CBC abnormalities and clonal evolution

Utility of somatic surveillance for clinical decision-making

ID42 (Diamond Blackfan anemia)



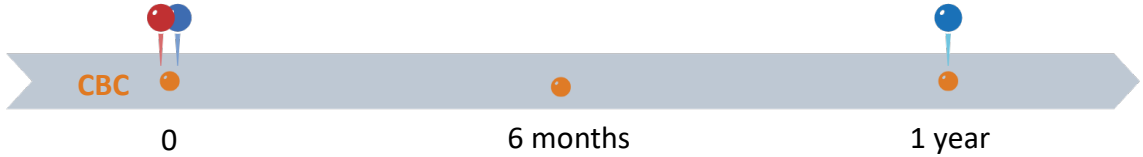
● = Bone marrow

▽ = Peripheral blood

lower risk BMF (TBD, DBA):
no annual BM

BM: karyotype and FISH
BM/PB: NGS and SNP array

PB: NGS and SNP array*
(≥10 yrs), *DBA: Tx independent



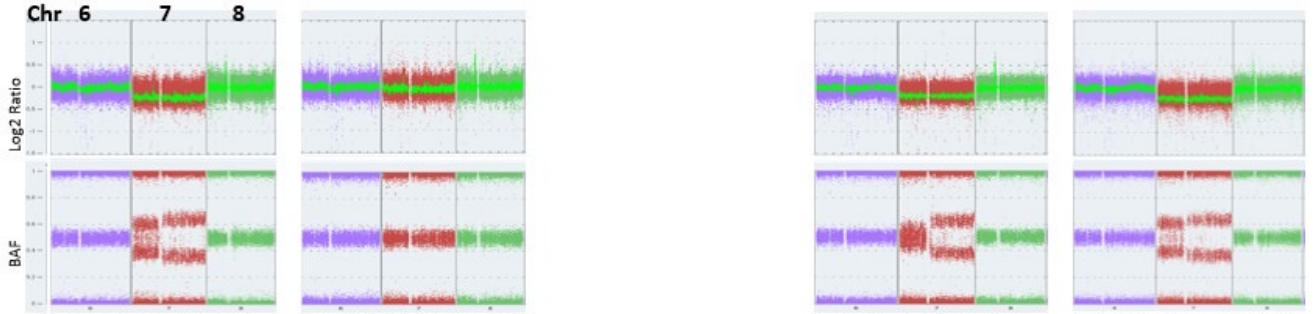
If stable, consider it annually

Serial BM and PB testing using SNP array: comparison with conventional cytogenetics

SAMD9L syndrome case

Age (years) 2.3 2.6 3.0 3.4 3.6

BM



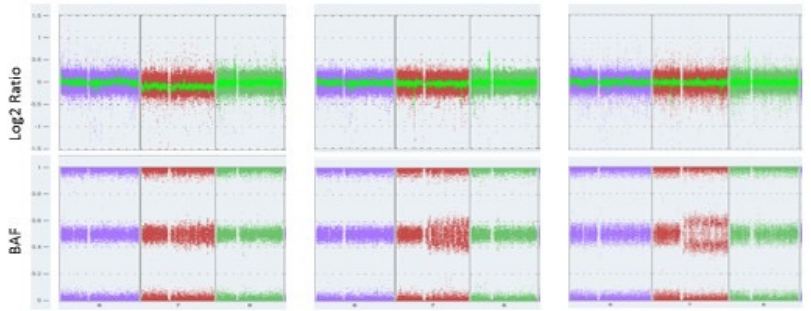
MK: 45,XY,-7[10]/46,XY[10]
FISH: -7: 27.5%
SNP: -7: 31%, UPD7q: 10%

MK: 45,XY,-7[10]/46,XY[10]
FISH: -7: 23.5%
SNP: -7: 7%, UPD7q: N.D.

MK: 45,XY,-7[16]/46,XY[4]
FISH: -7: 33.5%
SNP: -7: 25%, UPD7q: 10%

MK: 45,XY,-7[12]/46,XY[8]
FISH: -7: 29%
SNP: -7: 32%, UPD7q: 8%

PB



MK: Metaphase karyotyping
FISH: Fluorescence-in-situ hybridization (chr 7)
SNP: Cytogenomic single nucleotide polymorphism array

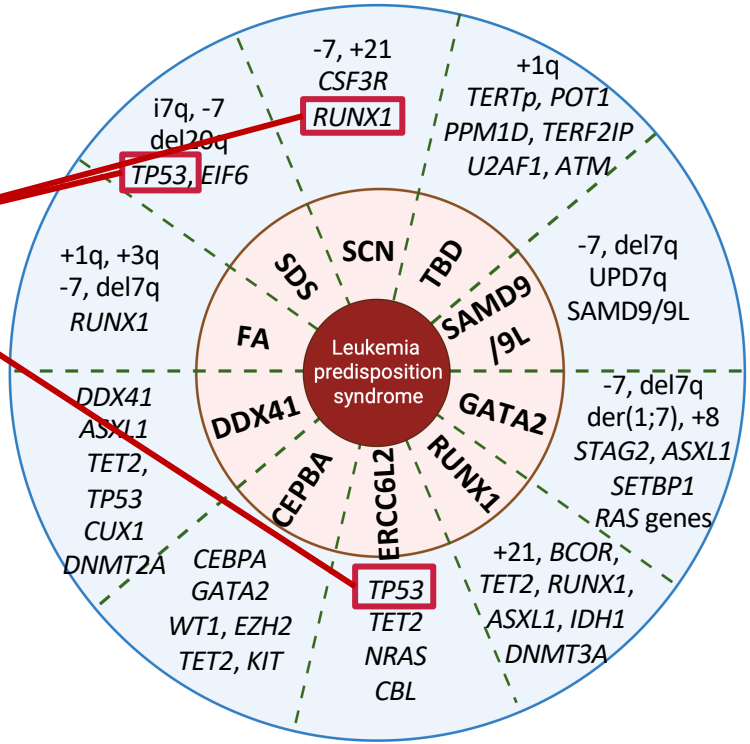
SNP: -7: 13%, UPD7q: <5%

SNP: -7: 3%, UPD7q: 15%

SNP: -7: N.D., UPD7q: 18%

Clonal trajectories in BMFs/leukemia predisposition syndromes (LPS)

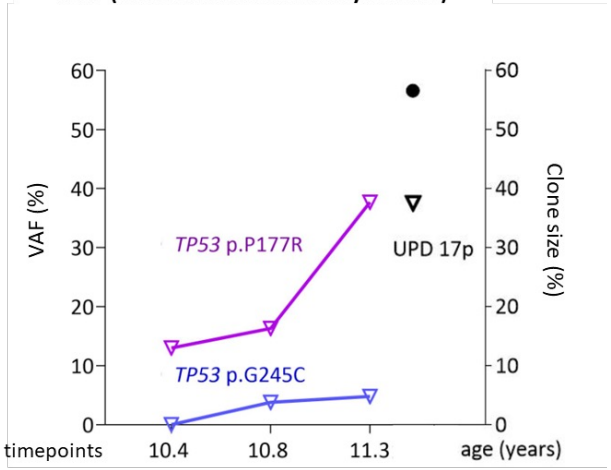
maladaptive clones with high-risk of leukemia transformation



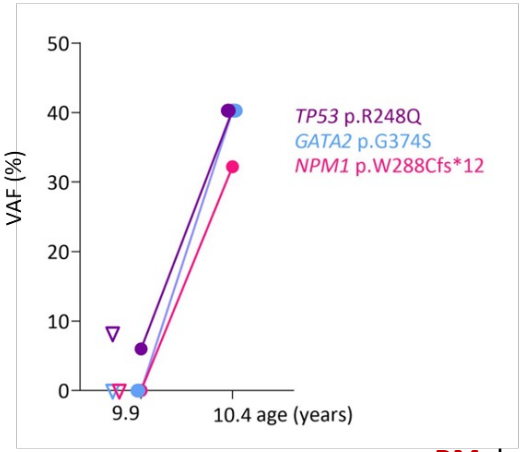
Utility of NGS and SNP-A implementation for clinical decision-making

High risk BMFS: – more intensified FU when clones increase in VAF

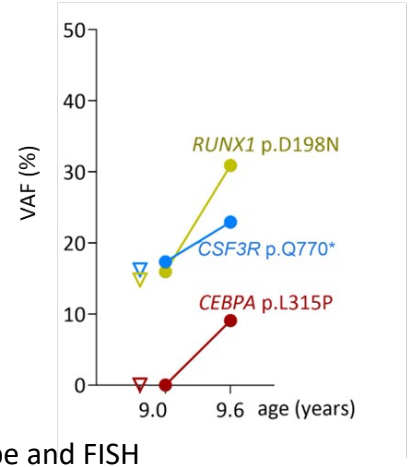
ID19 (Shwachman-Diamond syndrome)



ID3 (ERCC6L2 syndrome)



ID25 (Severe congenital neutropenia)



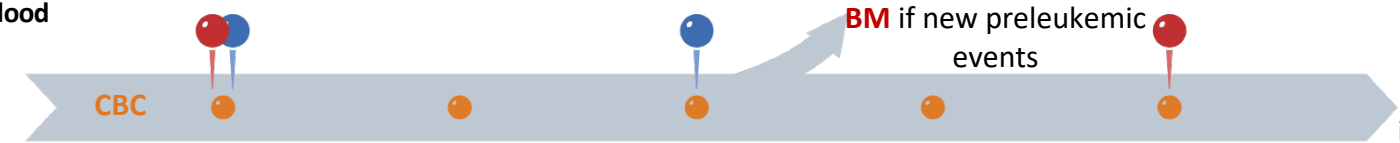
● = Bone marrow

▽ = Peripheral blood

PB: NGS and SNP array

BM: karyotype and FISH
NGS and SNP array

BM if new preleukemic events



*additional testing often required in the interval (case by case decisions)

Implications of genomic profiling for timing of transplantation

	«Too early» unnecessary toxicity	«Right on time» improved outcomes	«Too late» poor outcomes
HSCT:			
Indications:	None	Genomic profiling - Somatic genetics in BM - PB as source for monitoring (interval testing)	Traditional approach - CBC: cytopenia - BM: dysplasia, blast increase, high risk karyotype

Take-home message

Detecting and monitoring clonal hematopoiesis in genetically predisposed individuals is of growing clinical relevance and provides a foundation for the development of standardized, risk-adapted clinical guidelines for BMF/LPS.

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