9° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

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Elucidating the role of clonal hematopoiesis in myeloid neoplasms secondary to germline predisposition.

Enrico Attardi, MD PhD

Department of Biomedicine

University of Rome Tor Vergata

Disclosures di Enrico Attardi

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

Surveillance in BMFS and leukemia predisposition

No unique consensus for surveillance of patients with MDS/AML predisposing conditions

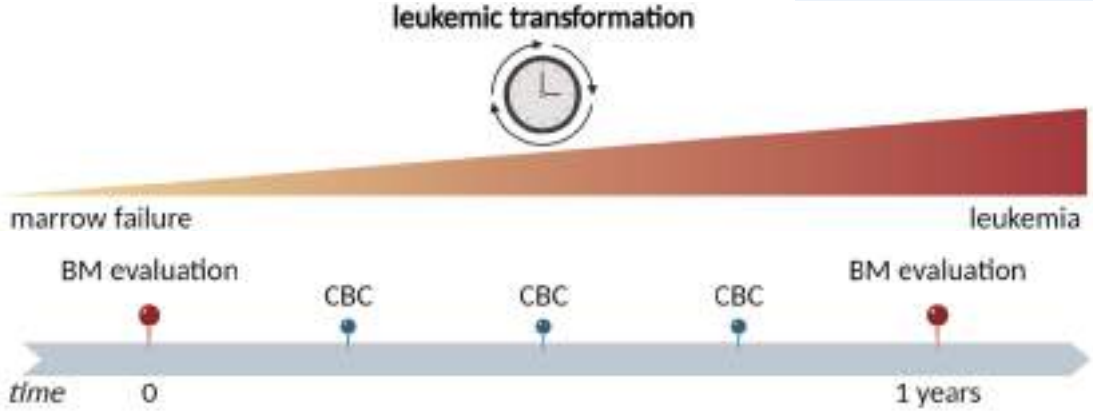
BM evaluation
(cellularity, dysplasia, blast %, cytogenetic alterations)

low risk leukemia predisposition
(TBD, DBA)

timing

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

interval



once per year

CBC, complete blood count

Discrepancy between CBC abnormalities and clonal evolution

Study design and Methods

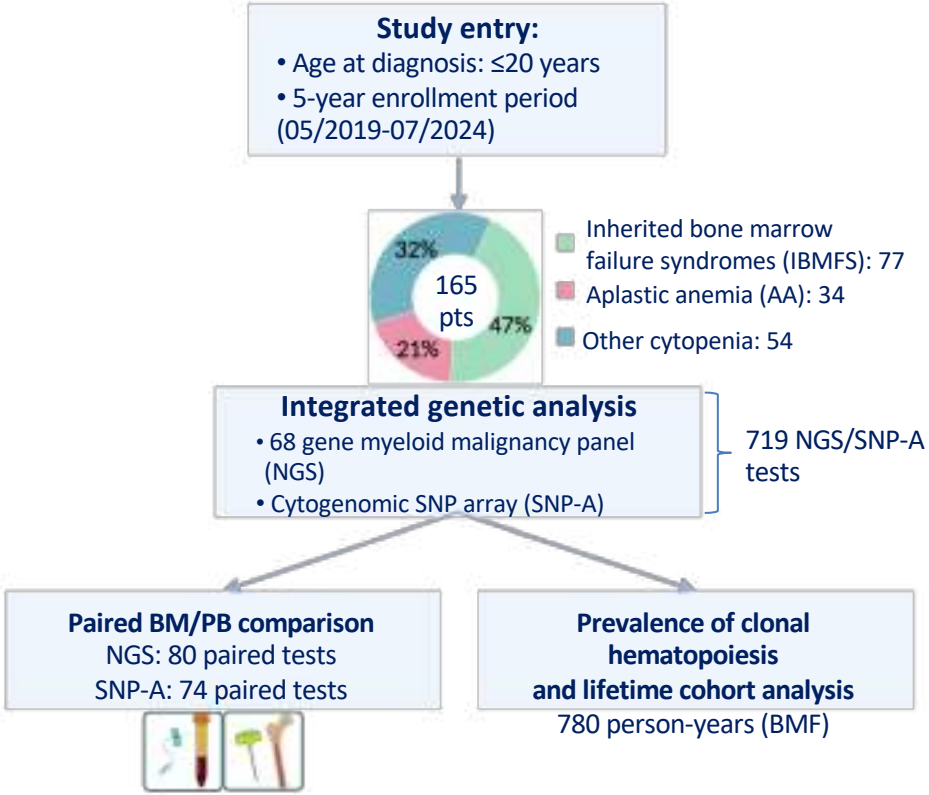
Clinical NGS assay

- Limit of detection: 3% for SNVs and 1% for small insertions or deletions less than 24 base pairs
- 68 gene myeloid malignancy panel

CytoScan(TM) HD Suite (ThermoFisher)

- 2.67 million markers across the genome
- Limit of detection of mosaicism: 20-30%

Patient characteristics	n=165
Male/Female	81/84
Median age at diagnosis (range)	6.2 (0-20.4) years
Median age at first determination (IQR)	10.6 (6.7-16.0) years
Inherited bone marrow failure syndromes (%)	77 (46.7)
Aplastic anemia (%)	34 (20.6)
Other cytopenia (%)	54 (32.7)
Patients with paired BM/PB samples for NGS analysis, n (%)	71 (43.0)
Patients with paired BM/PB samples for SNP-A analysis, n (%)	67 (40.6)



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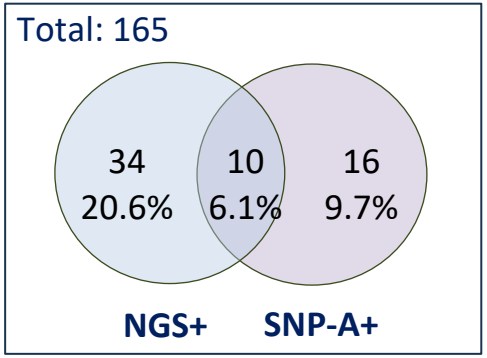
The landscape of clonal events

CH-IPI 36.4%



Functional classification of somatic events in IBMFS/AA patients (n=111)

Clonal hematopoiesis in predisposed individuals (CH-IPI)

Adaptive (somatic genetic rescue): 46.9%
-Compensatory mutations
-Loss of germline predisposing allele by UPD

Maladaptive: 54.1%
-Clonal hematopoiesis of indeterminate significance involving myeloid genes
-Leukemic transformation

-SAMD9/9L syndromes had the highest frequency of somatic alterations (12/14 pts, 85.7%).
-*PIGA*$_{mut}$ and UPD6p had 100% positive predictive value (PPV) for AA diagnosis.

-Novel CH events:
- subclonal UPD2p25 in germline *RPS7*-mutated Diamond Blackfan anemia → somatic rescue
- somatic *CBL*$_{mut}$ in germline *RPL15*-mutated Diamond Blackfan anemia → uncertain significance

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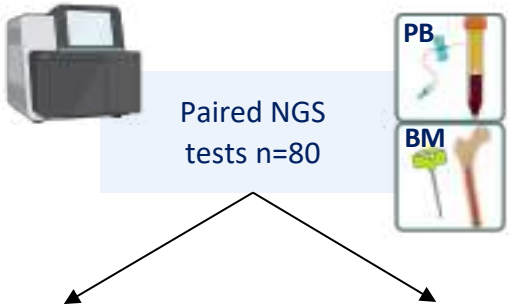
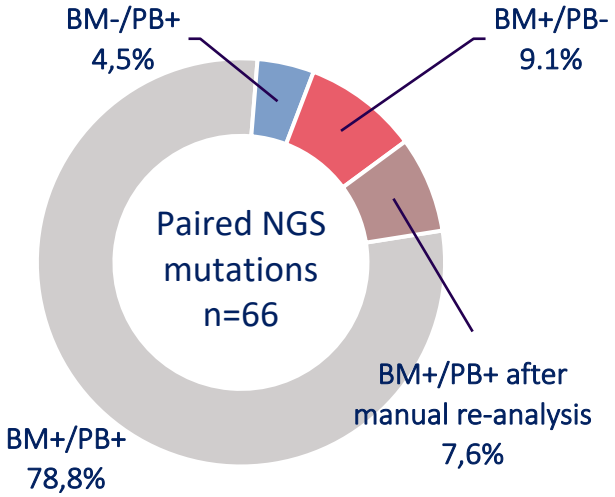
Differences between BM and PB clones by NGS

Test agreement



Agreement BM-PB: p<0.0001 (Cohen's Kappa method)

Mutation concordance



PB testing showed a sensitivity of 92.9% and a specificity of 97.9%

NGS-testing on PB is a robust source for detection of clonal hematopoiesis

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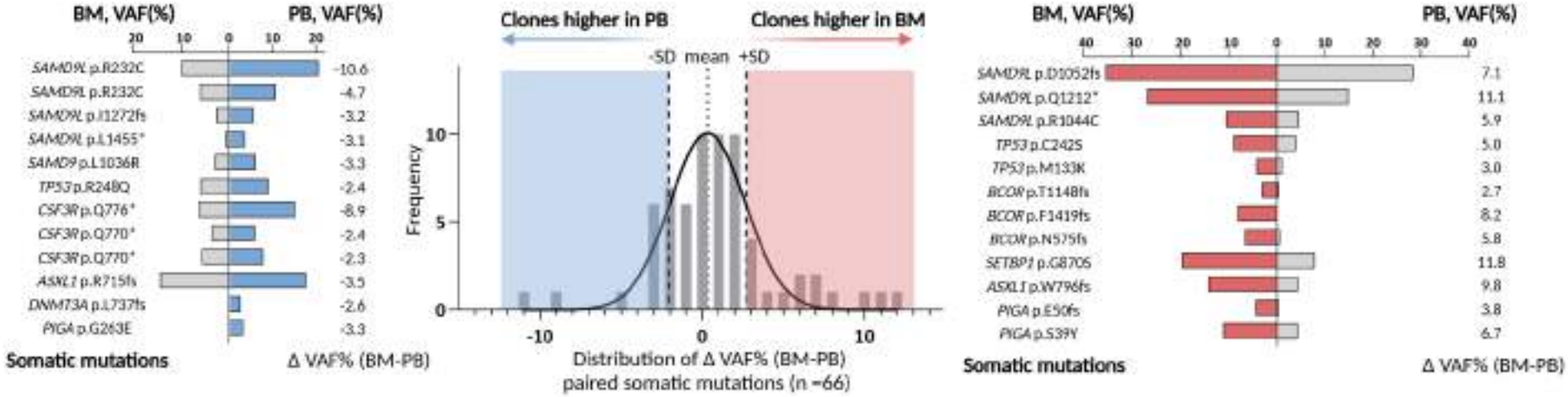
Differences between BM and PB clones by NGS



- *CSF3R*$_{mut}$: VAF ↑ in PB
- *BCOR*$_{mut}$: VAF ↑ in BM
- Major discrepancies involved *SAMD9/9L*$_{mut}$
  (clones can be selectively confined to either the myeloid or lymphoid compartment)

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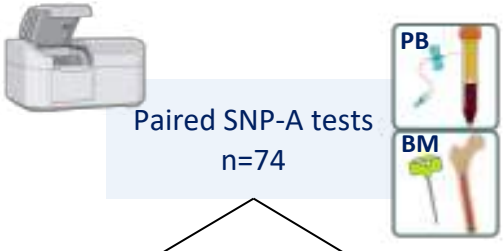
Differences between BM and PB clones by SNP-A

Test agreement

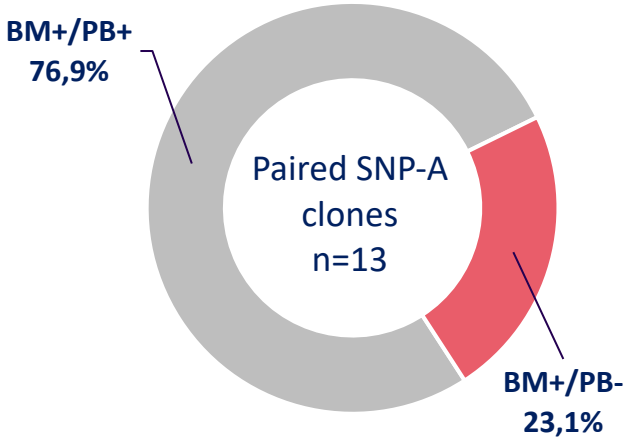


Concordant: 96.0%

Discordant: 4.0%
(clones detected in only 1 compartment)

Agreement BM-PB: p<0.0001
(Cohen's Kappa method)

Mutation concordance



ID	Dx	Structural alteration	BM clone size %	PB clone size %
43	SAMD9L	monosomy 7	32	nd
49	SAMD9	UPD7q	20	nd
135	SAMD9L	monosomy 7	5-10*	nd

SNP-A on PB may lose essential clonal events detected in BM

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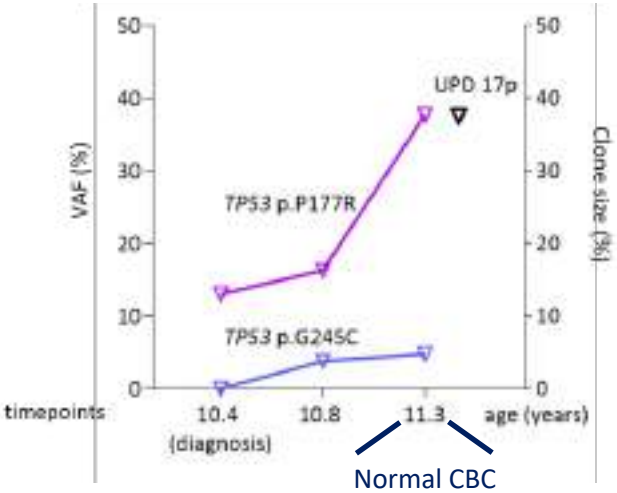
Utility of NGS and SNP-A implementation for clinical decision-making

● = Bone marrow

▽ = Peripheral blood

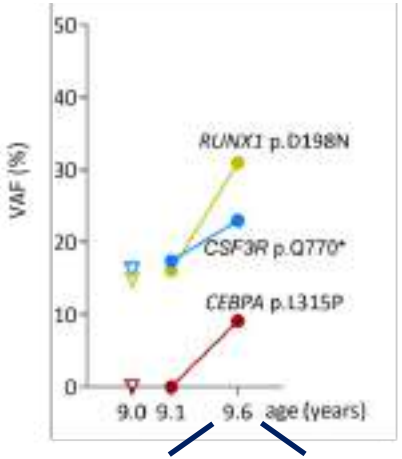
Shwachman-Diamond syndrome



Normal CBC

No PB blasts

Severe congenital neutropenia

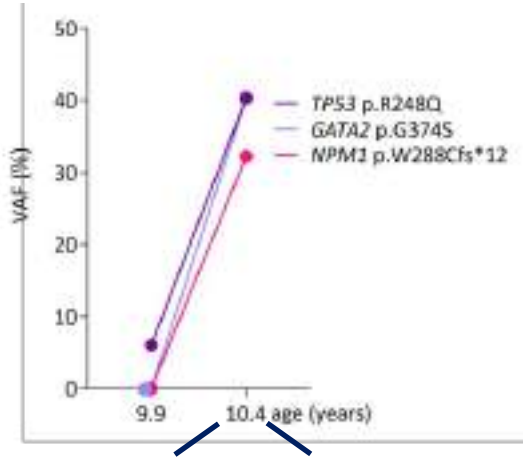


Anemia

Severe neutropenia

PB blasts 8%

ERCC6L2 syndrome



Normal CBC

PB blasts 3.5%

Somatic testing can early predict the leukemic transformation in BMFS

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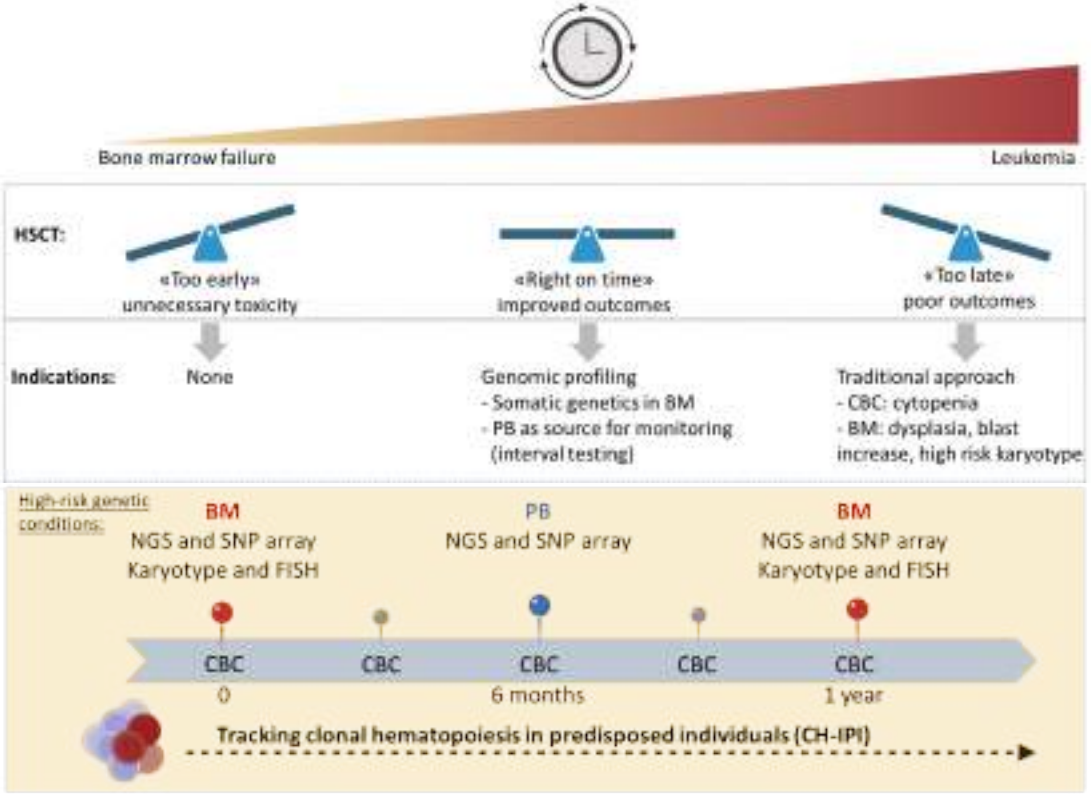
Implications of genomic profiling for surveillance and timing of transplantation

High-risk leukemia predisposing conditions



Somatic testing on PB improve long-term surveillance in BMFS/AA and guide timely clinical interventions

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St. Jude Childrens' Research Hospital

Wlodarski Lab
Marcin W. Wlodarski
Sushree Sahoo
Masanori Yoshida
Damian Krzyzanowski
Swarna Beesetti
Lili Kotmayer

BMF Clinical Team
Nathan Gray
Clifford Takemoto
Rohith Jesudas
Georgios Christakopoulos
Richa Sharma
Senthil Bhoopalan
Sara Lewis
Michelle Boals

Department of Biostatistics
Guolian Kang

ARUP Laboratories
Peng Li
Erica F. Andersen
Jian Zhao
Lucilla Pizzo
Bo Hong

University of Rome Tor Vergata

UOSD Laboratorio di Diagnostica Avanzata Oncoematologica «Francesco Lo Coco»

Maria Teresa Voso
Beatrice Borsellino
Mariadomenica Divona
Emiliano Fabiani
Giulia Falconi
Luca Guarnera
Carmelo Gurnari
Nicole Lelli
Eleonora Lumia
Tiziana Ottone
Eugenia Ricci
Giorgia Silvestrini

Immunologia pediatrica
Caterina Cancrini
Gigliola Di Matteo
Viviana Moschese
Paolo Palma

Genetica medica
Federica Carla Sangiuolo
Enrica Marchionni
Valentina Ferradini