LEUKEMIA2020-2021

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ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Relevance of molecular characterization in prognostic stratification and choice of therapy

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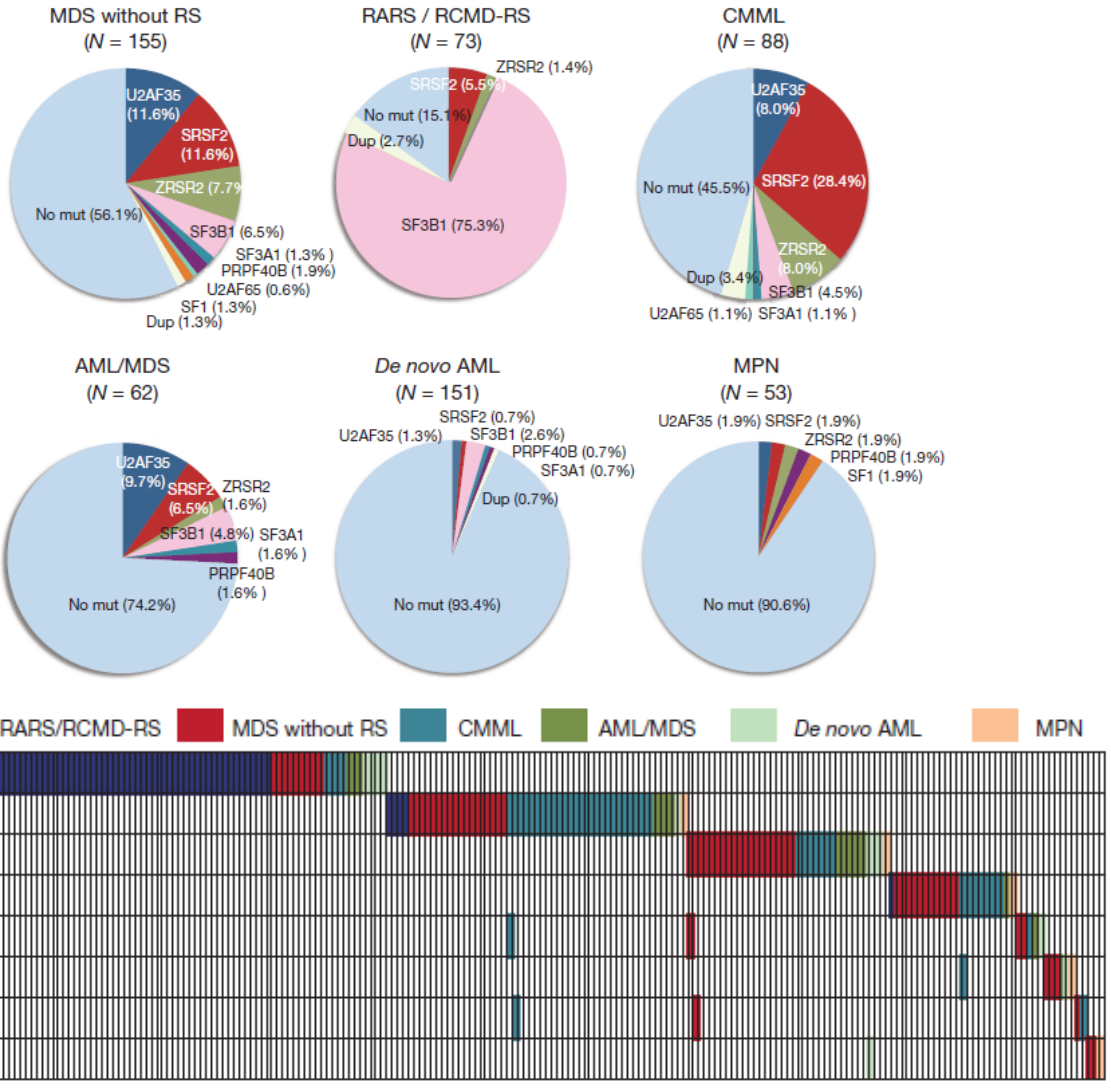
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIES Società Italiana Ematologia Sperimentale

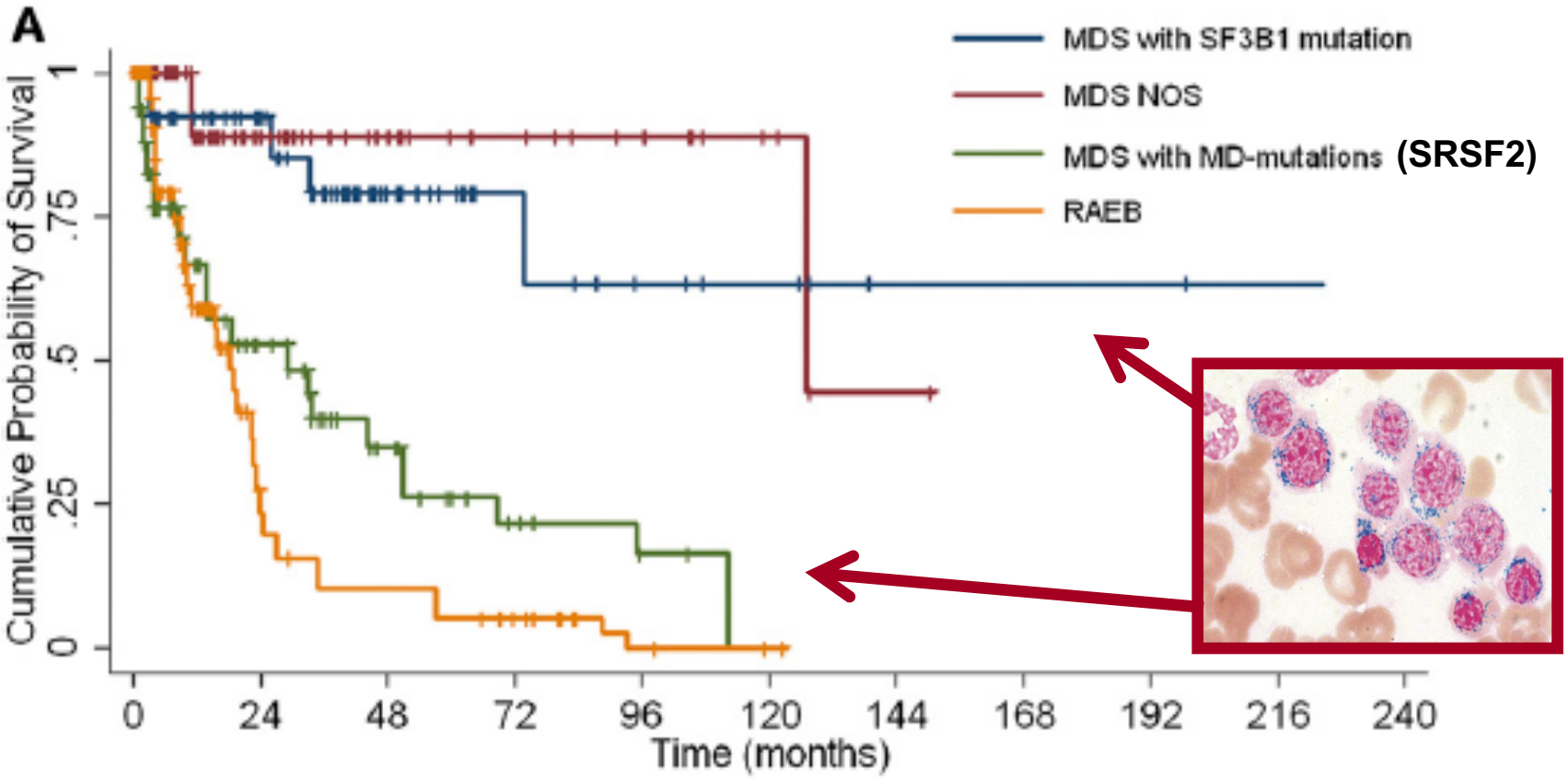
SIE - Società Italiana di Ematologia

Frequent pathway mutations of splicing machinery in myelodysplasia



Nature. 2011 Sep 11;478(7367):64-9

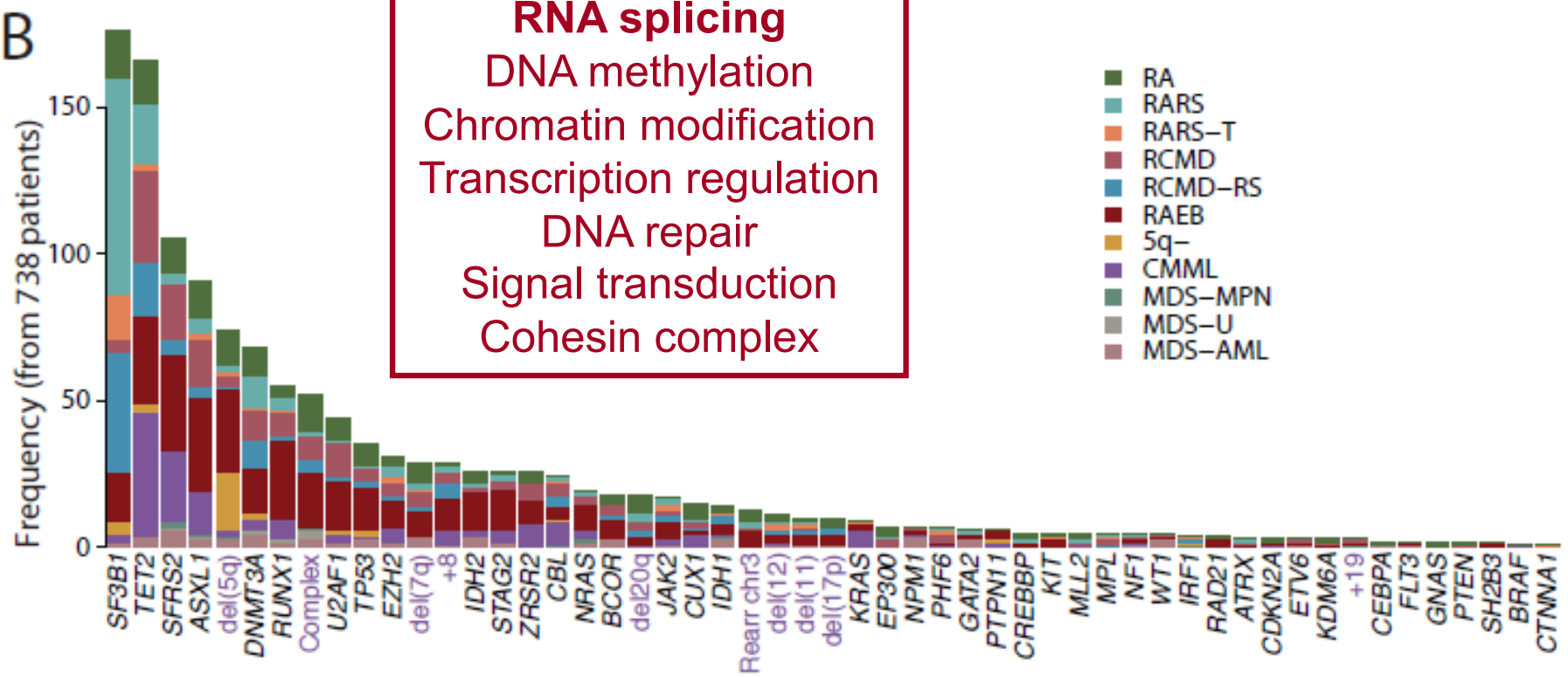
Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia



Malcovati et al. Blood 2014;124:1513-21; Della Porta MG et aL. Leukemia. 2015;29:66-75

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

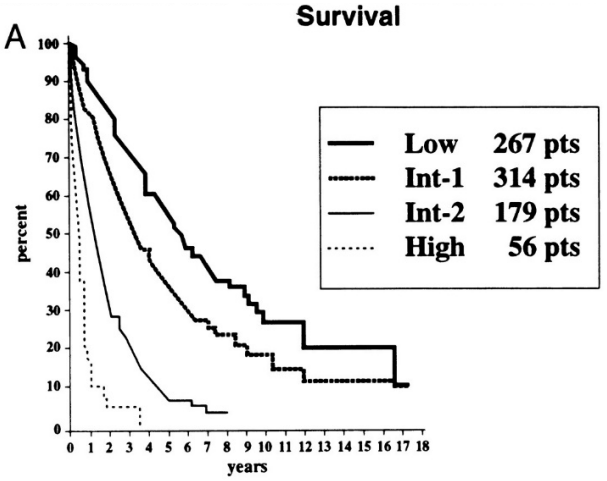
RNA splicing
DNA methylation
Chromatin modification
Transcription regulation
DNA repair
Signal transduction
Cohesin complex

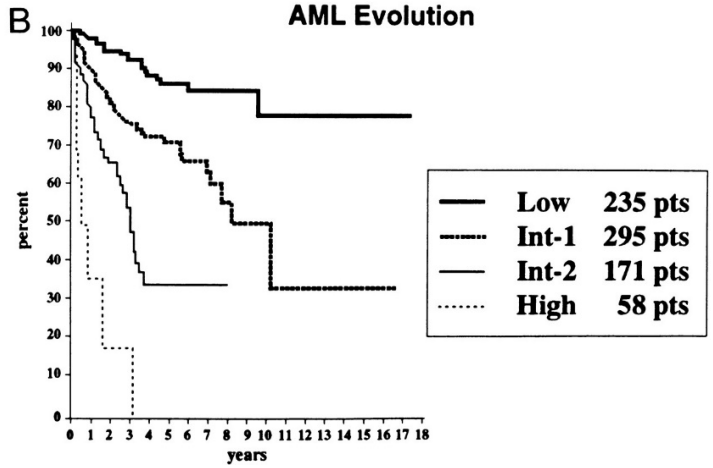


Papaemmanuil E. Blood. 2013;122:3616-27; Cazzola M, Della Porta MG, Malcovati L. Blood 2013;122:4021-34

International Prognostic Scoring System for MDS

Variable	0	0.5	1	1.5	2
BM blasts %	<5	5-10	-	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias°	0/1	2/3			





*_Good_: normal, -Y, del(5q), del(20q); _Poor_: complex, chromosome 7 anomalies; _Intermediate_: other abnormalities.

°Hemoglobin < 10 g/dL, absolute neutrophil count < 1,500/µL, platelet count < 100,000/µL.

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, 2.

Blood 1997;89:2079-2088

ASH 2018 - Somatic Mutations in MDS Predict Prognosis Independent of the IPSS-R (Analysis by IWG-PM)

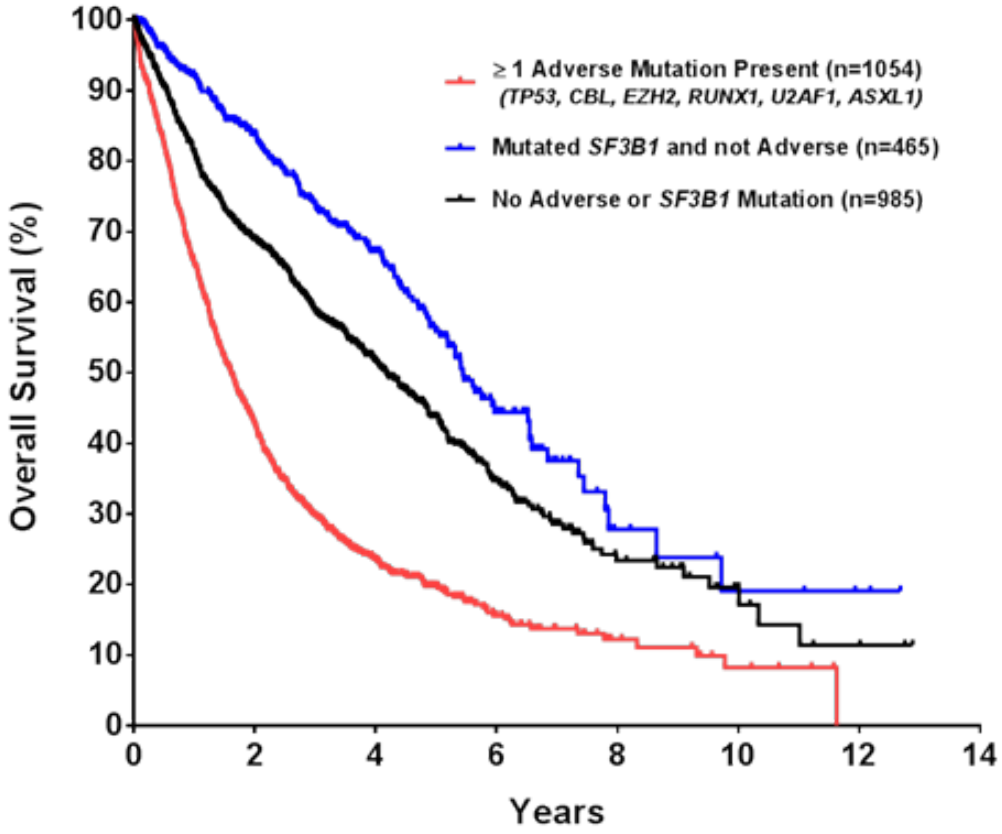
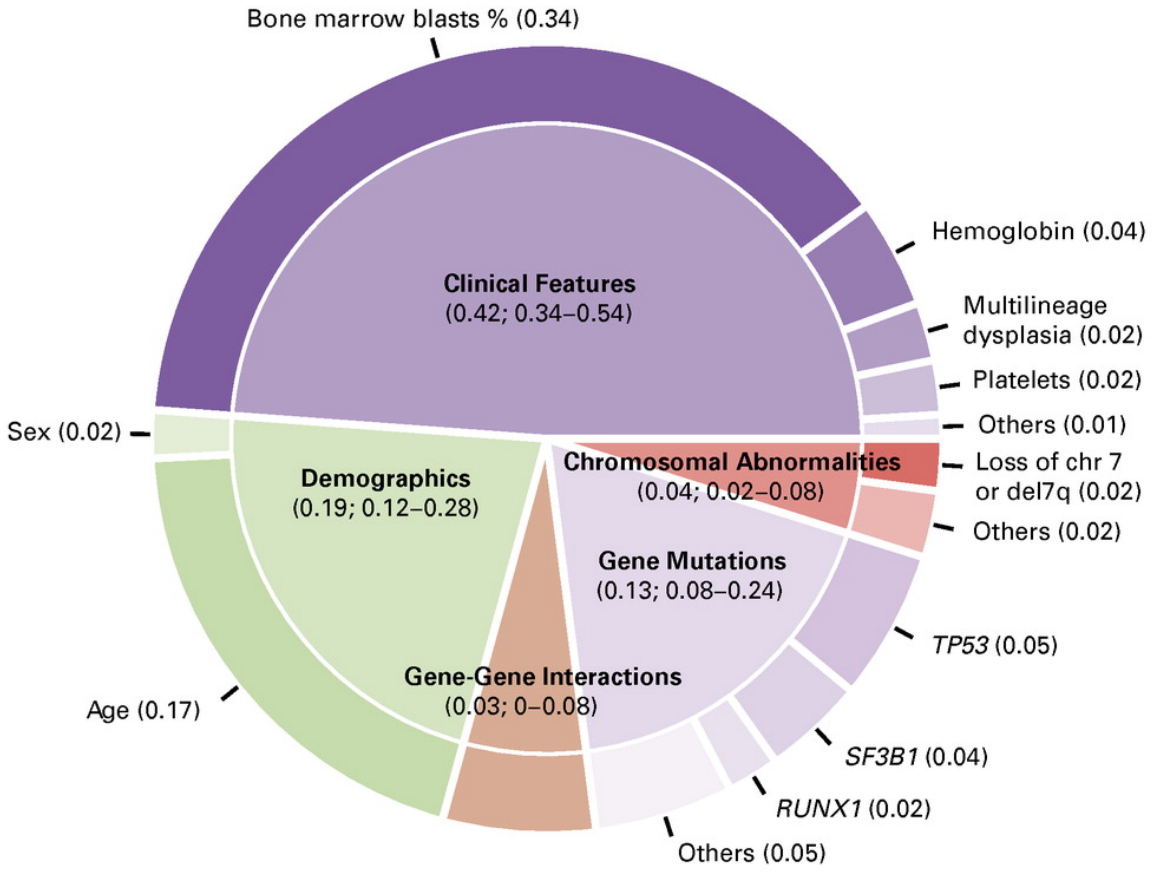


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Fraction of explained variation that was attributable to different prognostic factors for overall survival.



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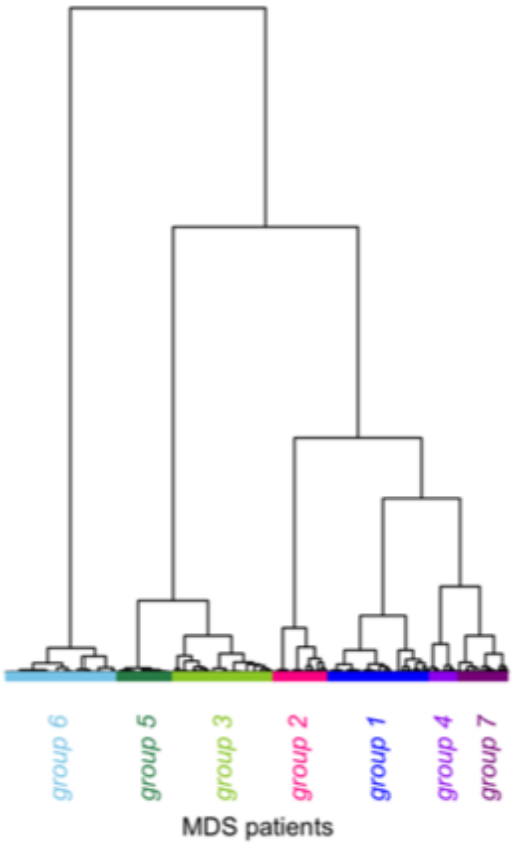
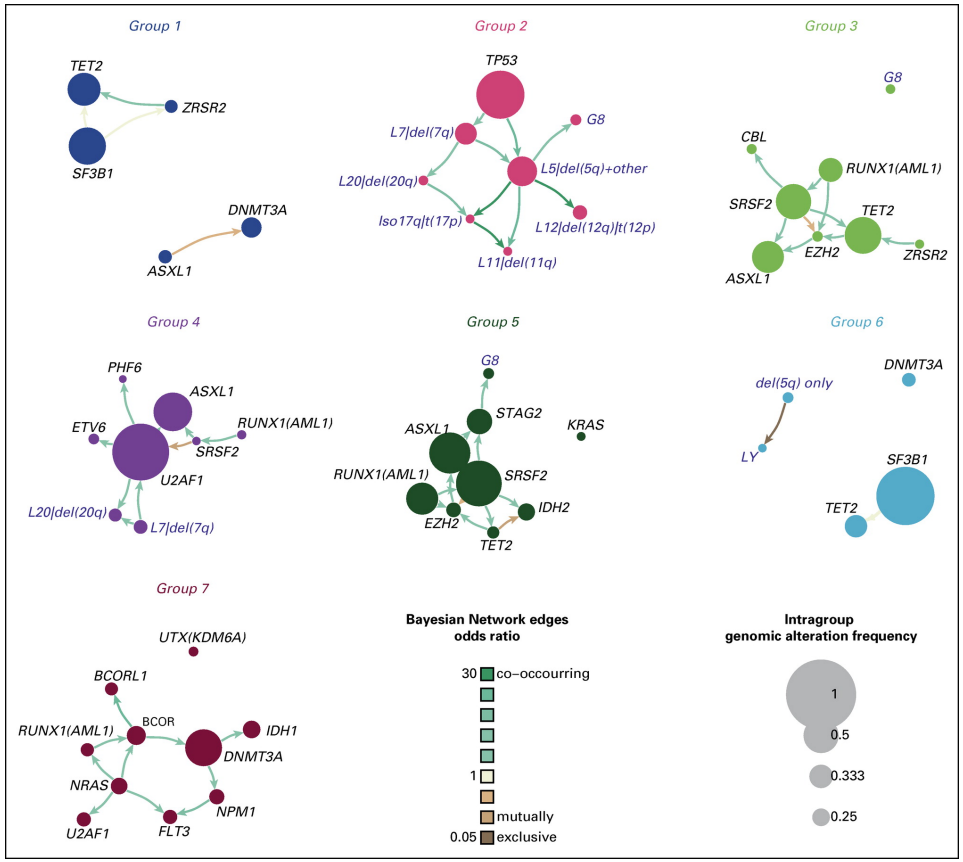
Molecular classification of MDS

Dirichlet Processes (Clustering)



Bayesian Networks (Causality)



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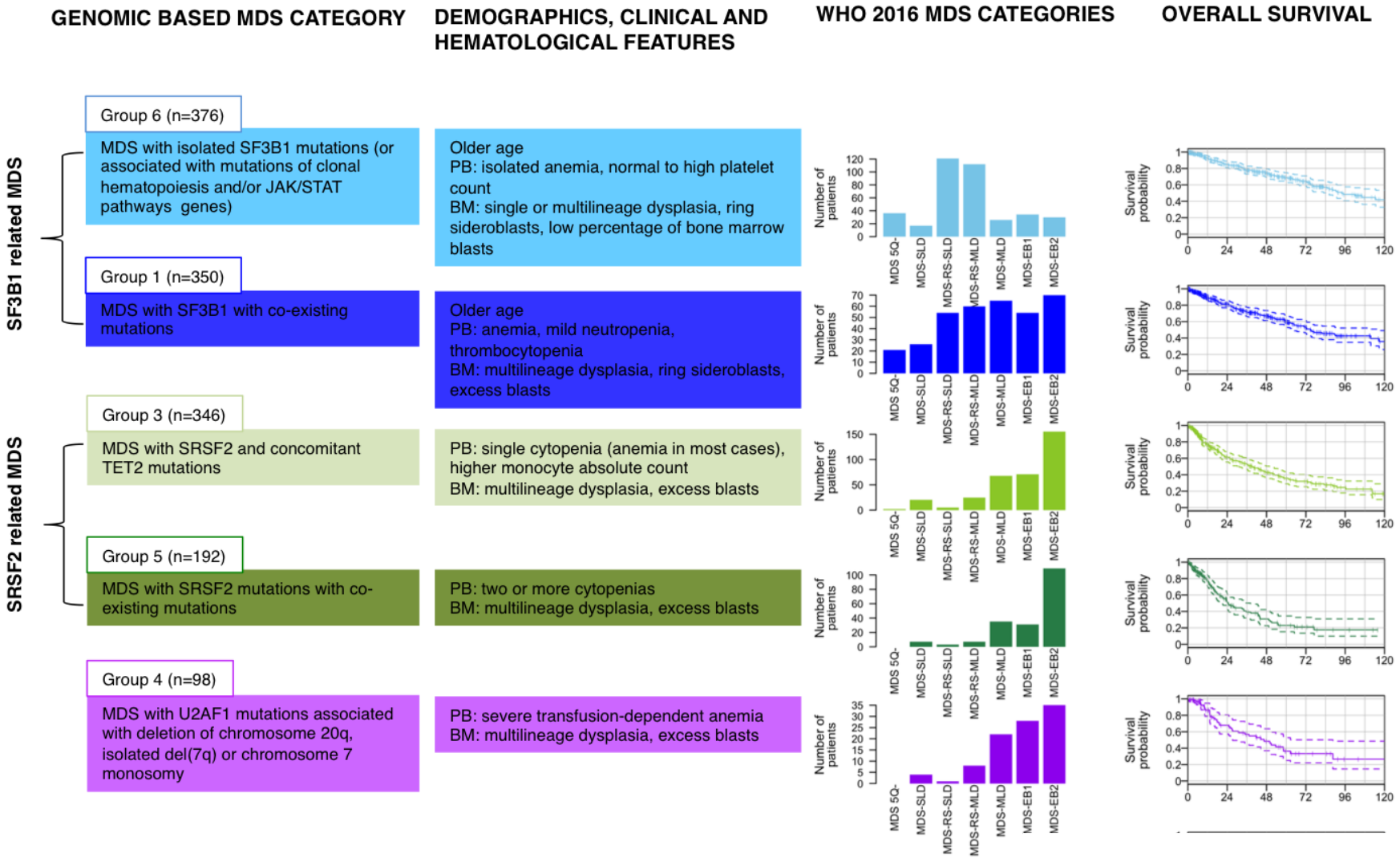
Molecular classification of MDS



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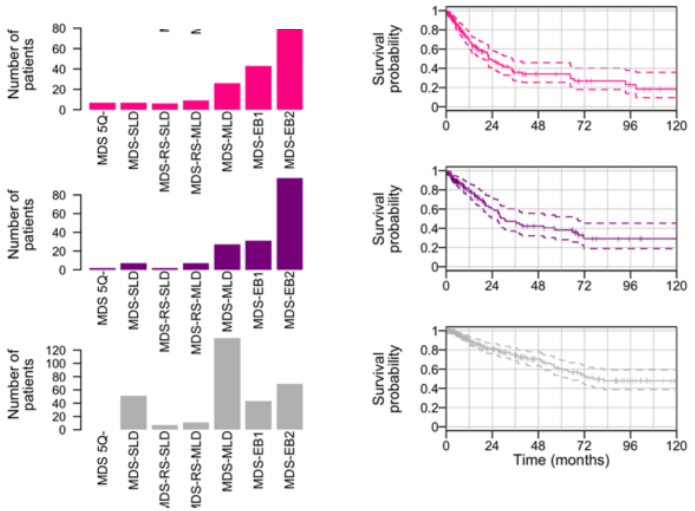
Molecular classification of MDS

Group 2 (n=188)
MDS with TP53 mutations and/or complex karyotype
PB: two or more cytopenias with transfusion-dependency BM: excess blasts

Group 7 (n=174)
MDS with AML-like mutations
PB: two or more cytopenias with transfusion-dependency
BM: excess blasts

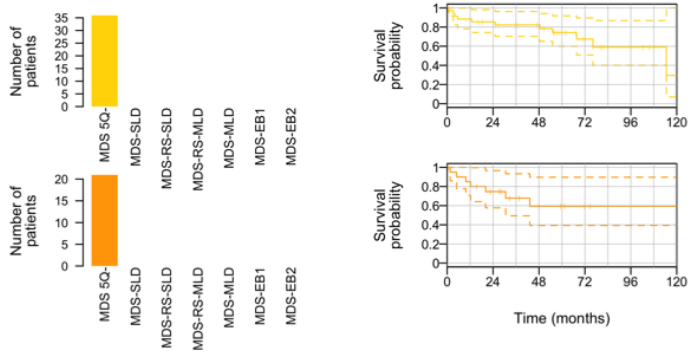
Group 0 (n=319)
MDS without specific genomic profiles
PB: asympotmatic anemia
BM: normal to reduced bone marrow cellularity, no ring sideroblasts, low percentage of marrow blasts



MDS 5q-

Group 6 (n=36)
MDS with isolated 5q-
PB: mild anemia without transfusion-dependency
BM: multilineage dysplasia, low percentage of bone marrow blasts

Group 1 (n=21)
MDS with isolated 5q- with co-existing mutations and/or TP53 mutations
PB: mild anemia
BM: multilineage dysplasia, no excess blast



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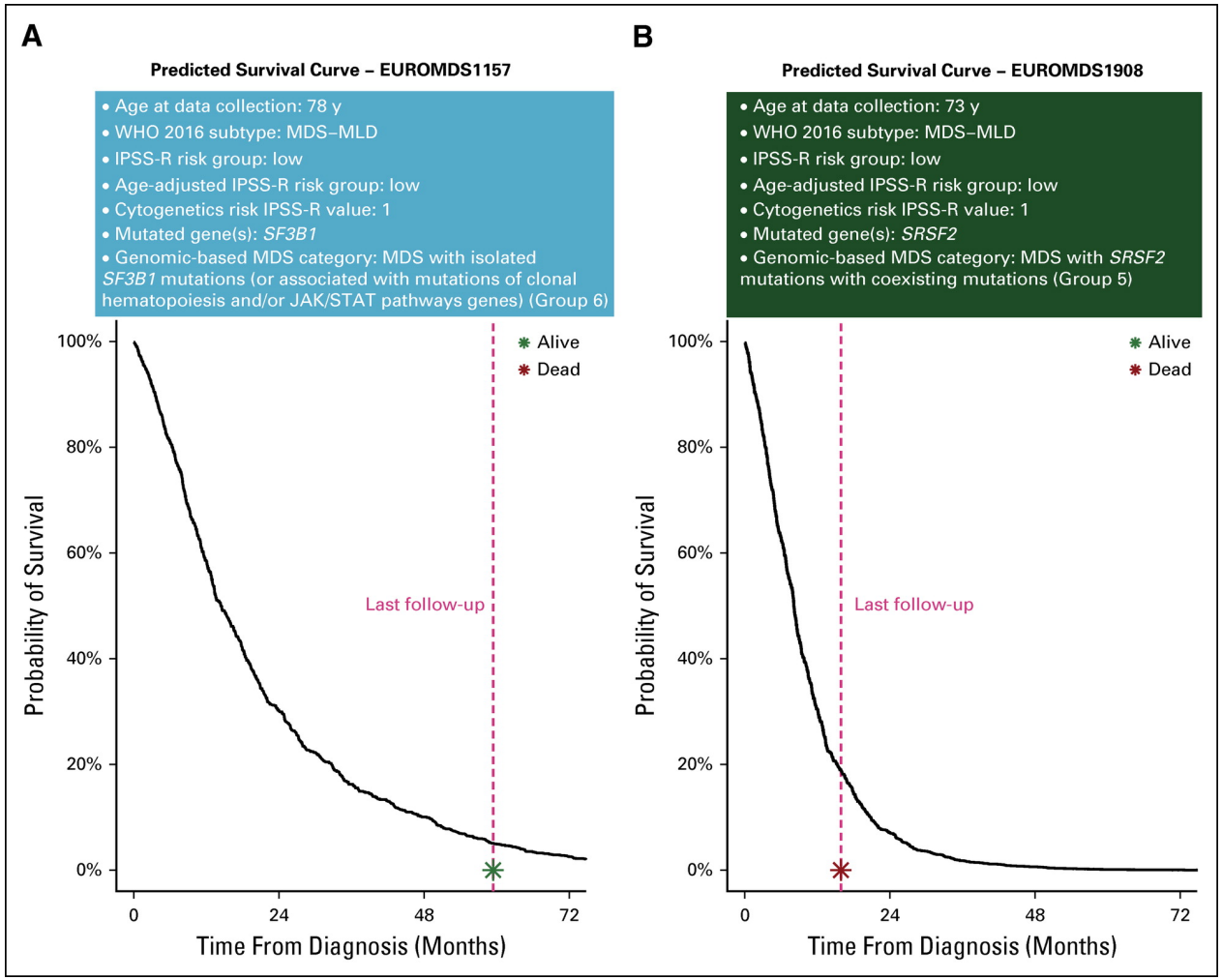
Personalized prediction of overall survival using a multistate prognostic model including clinical and genomic features



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Personalized prediction of overall survival using a multistate prognostic model including clinical and genomic features

TABLE 1. (A) Concordance Comparison Between Random-Effects Cox Proportional Hazards Multistate Models (CoxRFX) and IPSS-R on Training-Test Approach. (B) Concordance of CoxRFX Models and Age-Adjusted IPSS-R on Training-Validation Approach

A

	Training (66% of EuroMDS Patients)		Test (33% of EuroMDS Patients)	
Statistical Model and Variable Selection	**Concordance**	**SD**	**Concordance**	**SD**
Cytogenetics IPSS-R risk groups	0.576	0.012	0.567	0.016
Age-adjusted IPSS-R risk groups	0.620	0.015	0.659	0.019
Dirichlet processes	0.649	0.014	0.629	0.020
CoxRFX_Clinical + demographics + Dirichelet processes	0.729	0.015	0.713	0.021
CoxRFX_Clinical + demographics + genomics	0.742	0.015	0.709	0.021

B

	Training (EuroMDS Cohort)		Validation (Humanitas Cohort)	
Statistical Model and Variable Selection	**Concordance**	**SD**	**Concordance**	**SD**
CoxRFX_Clinical + demographics + Dirichlet processes	0.715	0.012	NA	NA
CoxRFX_Clinical + demographics + genomics	0.737	0.012	0.753	0.037

NOTE. For each method, the concordance and its SD are shown for all performed analyses on both training and test sets, where applicable.
Abbreviations: IPSS-R, revised version of International Prognostic Scoring System; NA, not applicable; SD, standard deviation.

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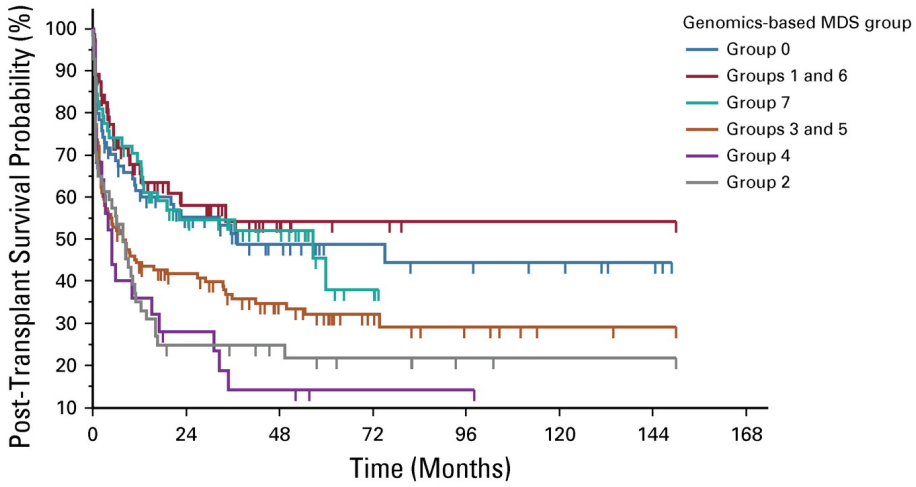
Molecular classification of MDS – effect on post-transplantation outcome

A



B

	Group 0	*Groups 1 and 6*	*Group 2*	*Groups 3 and 5*	*Group 4*	*Group 7*
MDS without specific genomic profiles *(Group 0)*	--	*P* = .49	*P* = .0016	*P* = .0196	*P* = .0019	*P* = .97
SF3B1-related MDS *(Groups 1 and 6)*	*P* = .49	--	*P* = .0003	*P* = .0035	*P* = .0004	*P* = .62
MDS with *TP53* mutations and/or complex karyotype *(Group 2)*	*P* = .0016	*P* = .0003	--	*P* = .24	*P* = .73	*P* = .0019
SRSF2-related MDS *(Groups 3 and 5)*	*P* = .0196	*P* = .0035	*P* = .24	--	*P* = .17	*P* = .0304
MDS with *U2AF1* mutations associated with deletion of chromosome 20q and/or abnormalities of chromosome 7 *(Group 4)*	*P* = .0019	*P* = .0004	*P* = .73	*P* = .17	--	*P* = .0019
MDS with AML-like mutation patterns *(Group 7)*	*P* = .97	*P* = .62	*P* = .0019	*P* = .0304	*P* = .0019	--

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Summary

- A MDS classification based on clinical and morphologic criteria complemented by genomic features better captures clinical-pathological entities with respect to current WHO system.
- Mutation screening provides relevant prognostic information at individual patient level
- Mutation screening may affect clinical decision making (definition of optimal candidate patients to receive allogeneic transplantation)