Prevenzione delle neoplasie ematologiche: è oggi una realtà?

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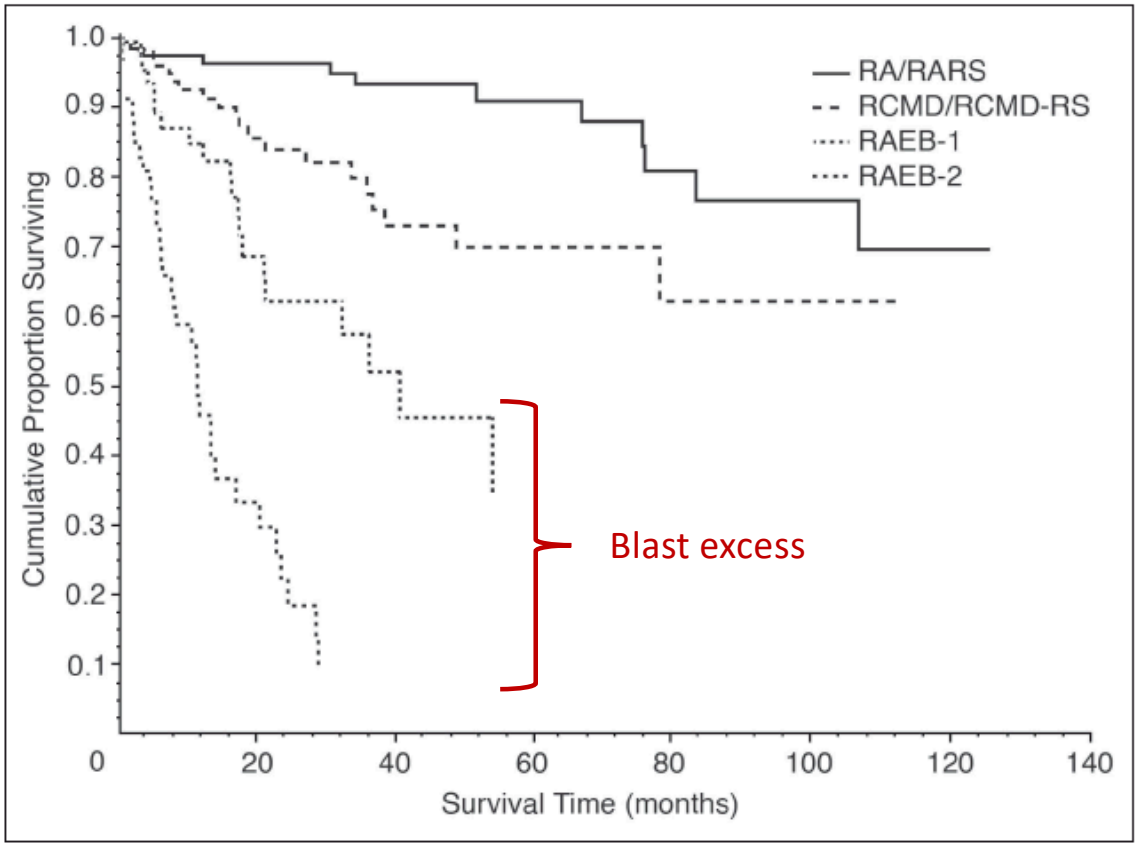
Mario Cazzola

Fondazione IRCCS Policlinico San Matteo & University of Pavia

Outline of presentation

- Predicting progression to AML

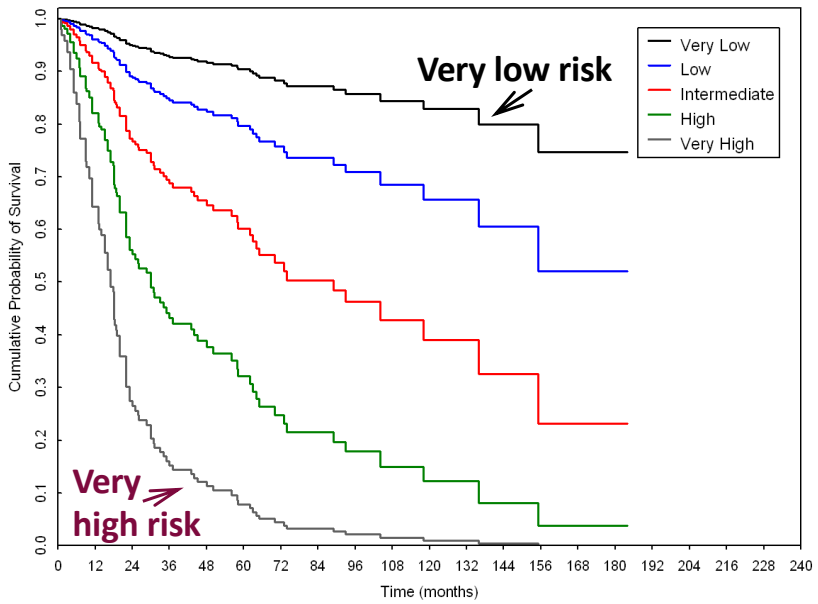
Risk of leukemic evolution according to the WHO subtype



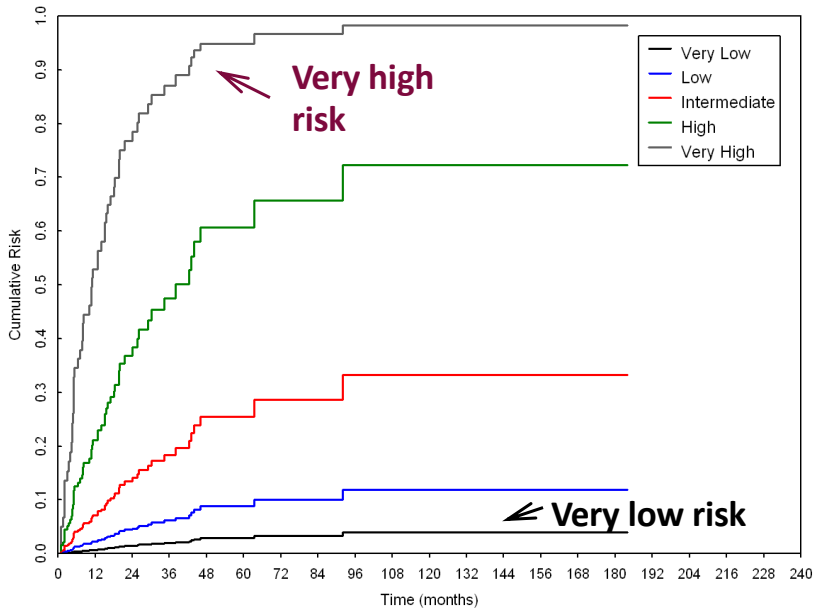
Malcovati et al. J Clin Oncol. 2005 Oct 20;23(30):7594-603

Time-dependent WPSS

Overall survival
(P<.001)

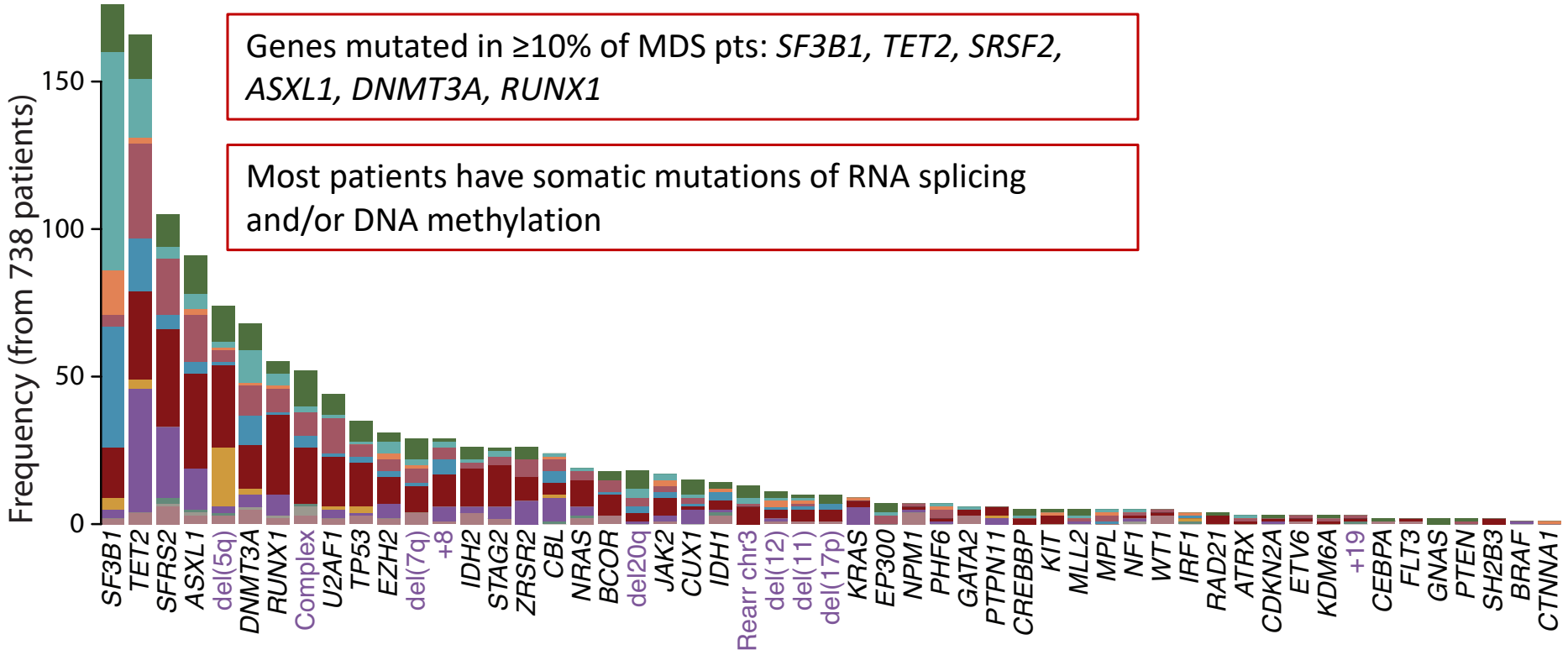


Risk of leukemic evolution
(P<.001)



Malcovati et al. J Clin Oncol 2007 Aug 10;25(23):3503-10

Genetic lesions in patients with MDS



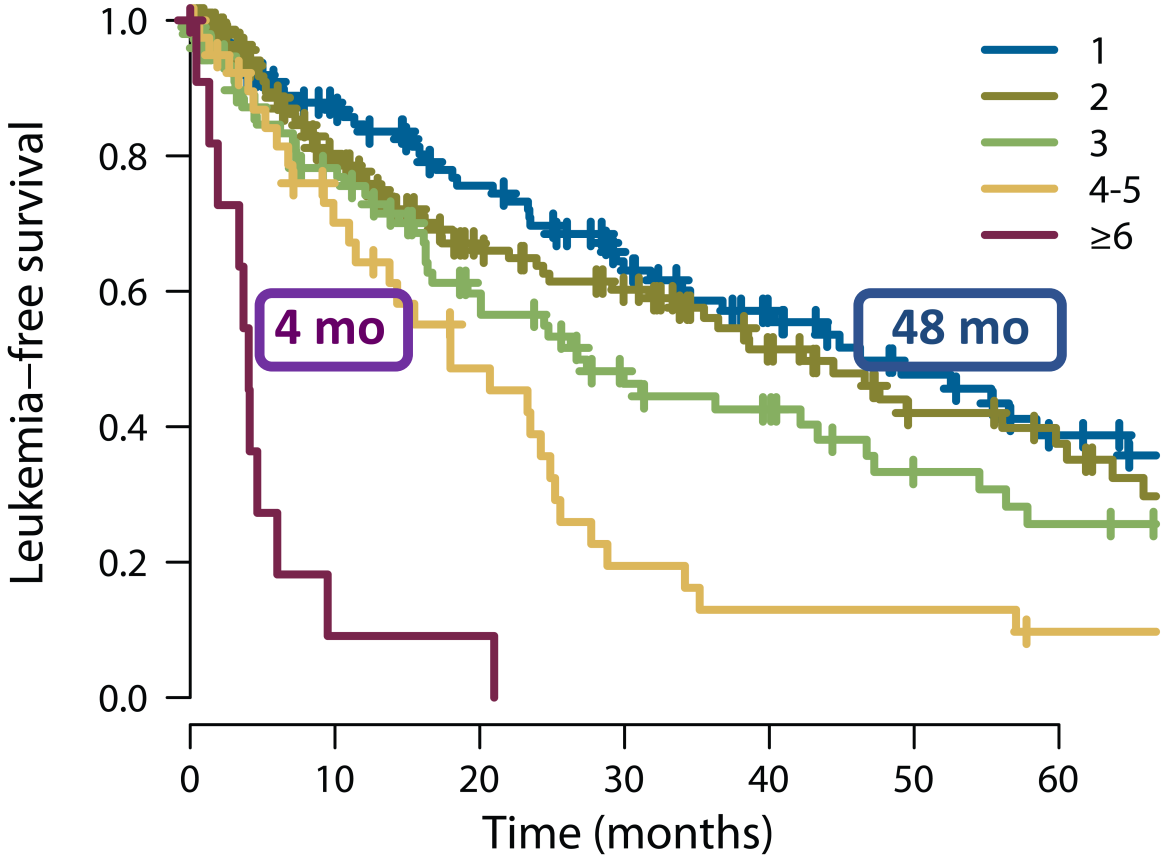
Genes mutated in ≥10% of MDS pts: *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1*

Most patients have somatic mutations of RNA splicing and/or DNA methylation

Papaemmanuil et al. Blood. 2013 Nov 21;122(22):3616-27

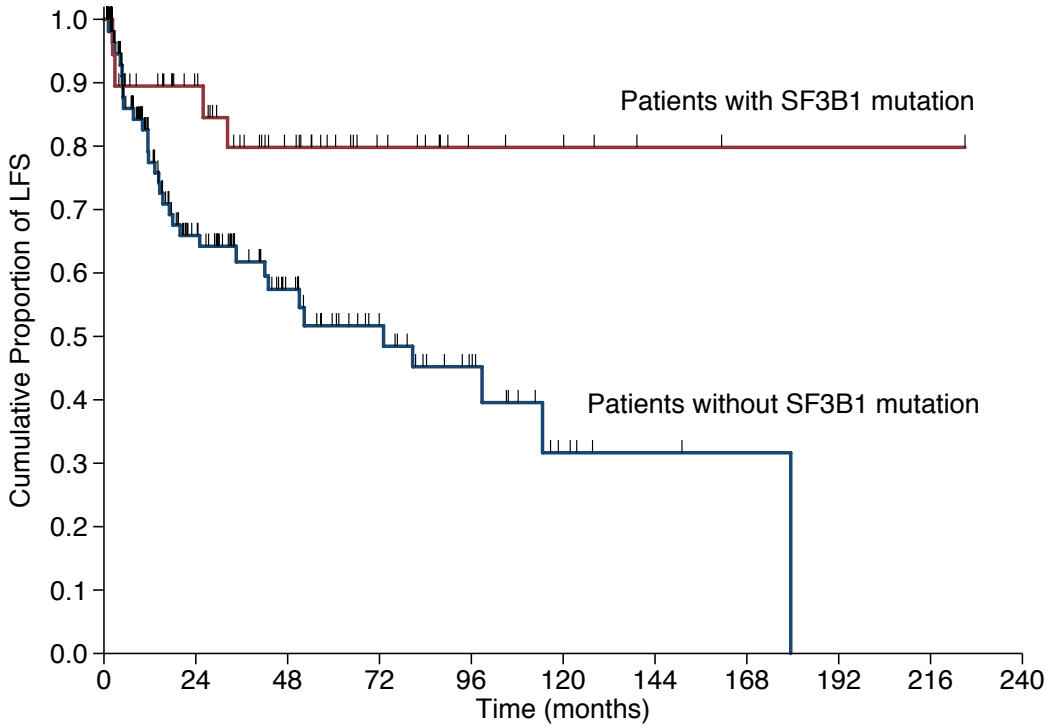
Haferlach et al. Leukemia. 2014 Feb;28(2):241-7

Genetic complexity and risk of leukemic evolution



Papaemmanuil et al. Blood. 2013 Nov 21;122(22):3616-27

Risk of leukemic evolution according to *SF3B1* mutational status

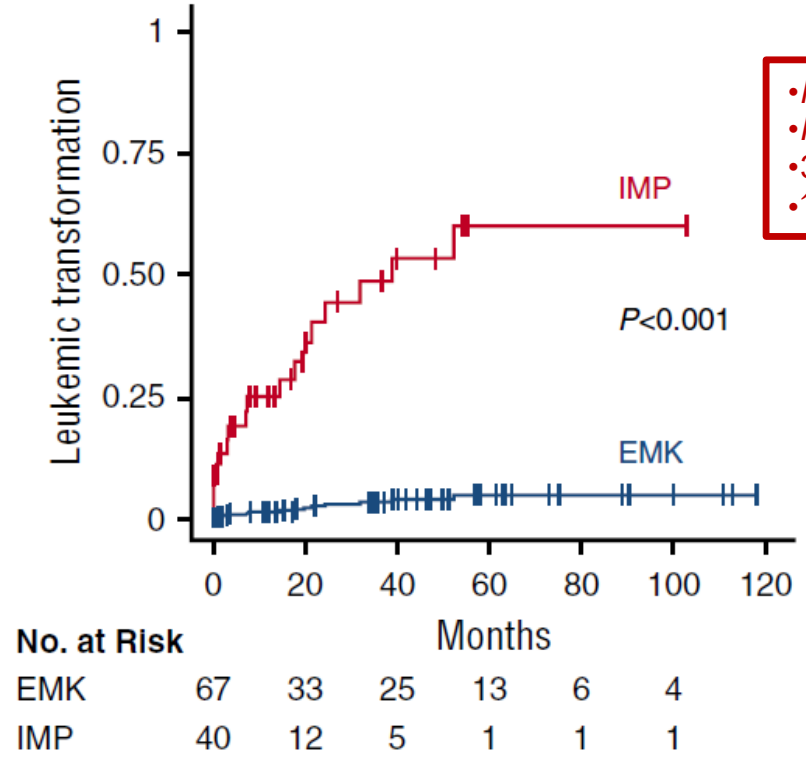


Malcovati et al. Blood. 2011 Dec 8;118(24):6239-46

Gene expression and risk of leukemic transformation in MDS

- Erythroid/megakaryocytic (EMK) signature

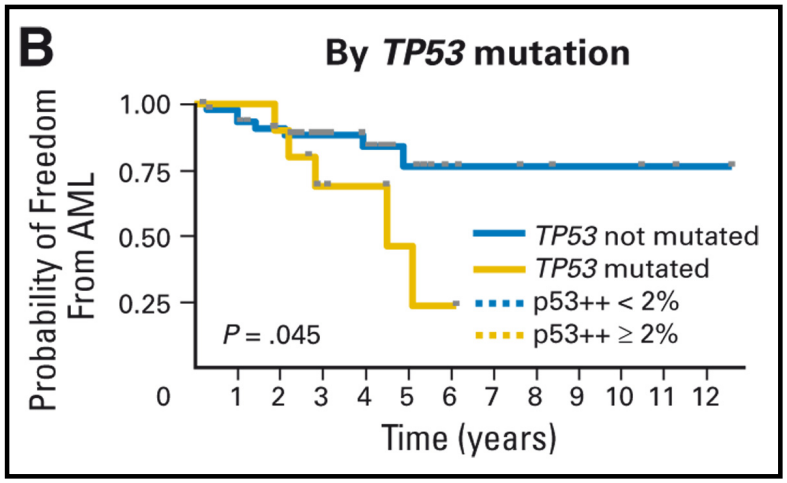
- Immature progenitor (IMP) signature

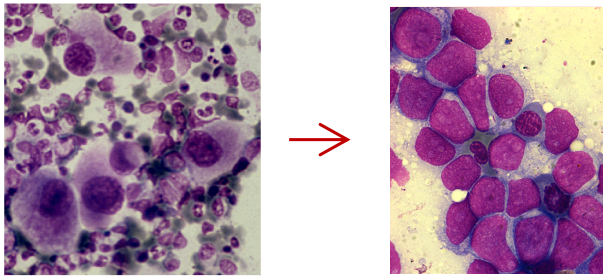


- *NRIP1-EVI1*
- *RUNX1-EVI1*
- 3q26 abnormality
- ↑ *EVI1* expression

Shiozawa et al. Blood. 2017 Dec 14;130(24):2642-2653

TP53 mutation and risk of progression to AML in MDS with del(5q)



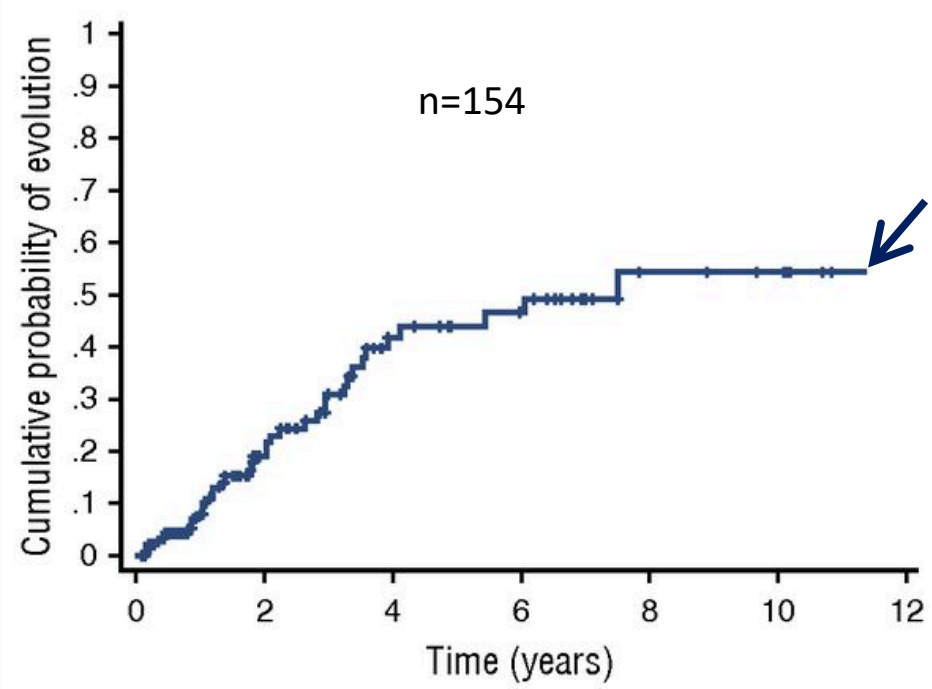


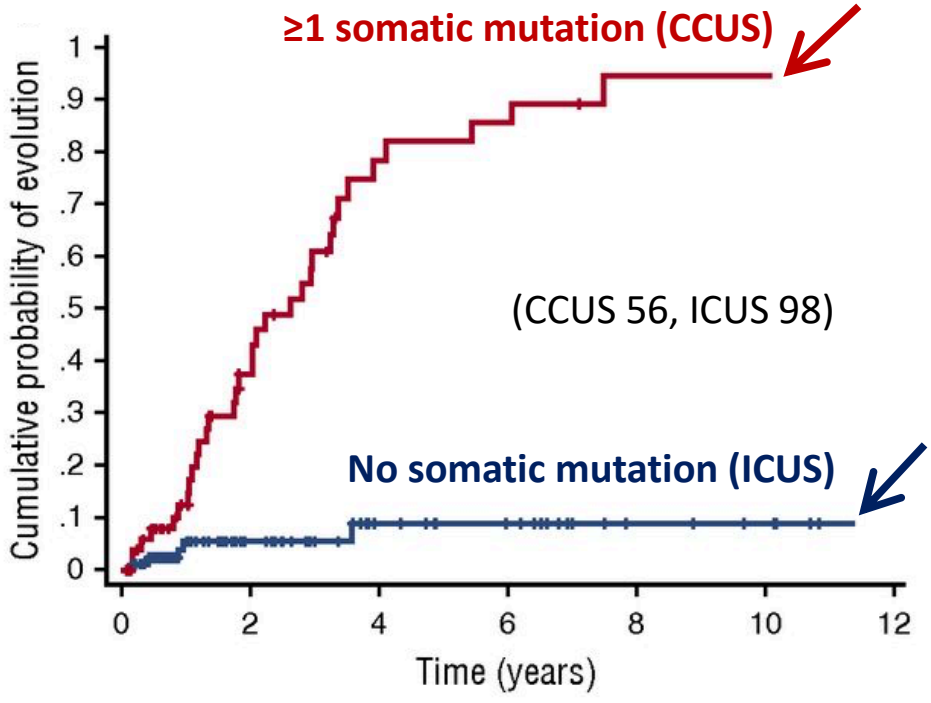
Jädersten et al. J Clin Oncol. 2011 May 20;29(15):1971-9

Clonal cytopenia of undetermined significance (CCUS)

- Persistent unexplained cytopenia (≥4 months)
- Insufficient criteria for diagnosis of MDS (dysplasia <10%, blast count <5%)
- Presence of a somatic mutation with a VAF ≥2% in a hematologic malignancy-associated gene (eg, *TET2*, *ASXL1*, or *DNMT3A*) in the peripheral blood or bone marrow

Diagnostic value of mutation status in patients with cytopenia of undetermined significance





Malcovati et al. Blood. 2017 Jun 22;129(25):3371-3378

Somatic mutations precede acute myeloid leukemia years before diagnosis

- 212 women from the Women's Health Initiative who were healthy at study baseline, but eventually developed AML during follow-up (median time: 9.6 years)
- Deep sequencing was performed on peripheral blood DNA of these cases and compared to age-matched controls that did not develop AML
- Mutations in *IDH1*, *IDH2*, *TP53*, *DNMT3A*, *TET2* and spliceosome genes significantly increased the odds of developing AML
- All subjects with *TP53* mutations (n = 21 out of 21 patients) and *IDH1* and *IDH2* (n = 15 out of 15 patients) mutations eventually developed AML

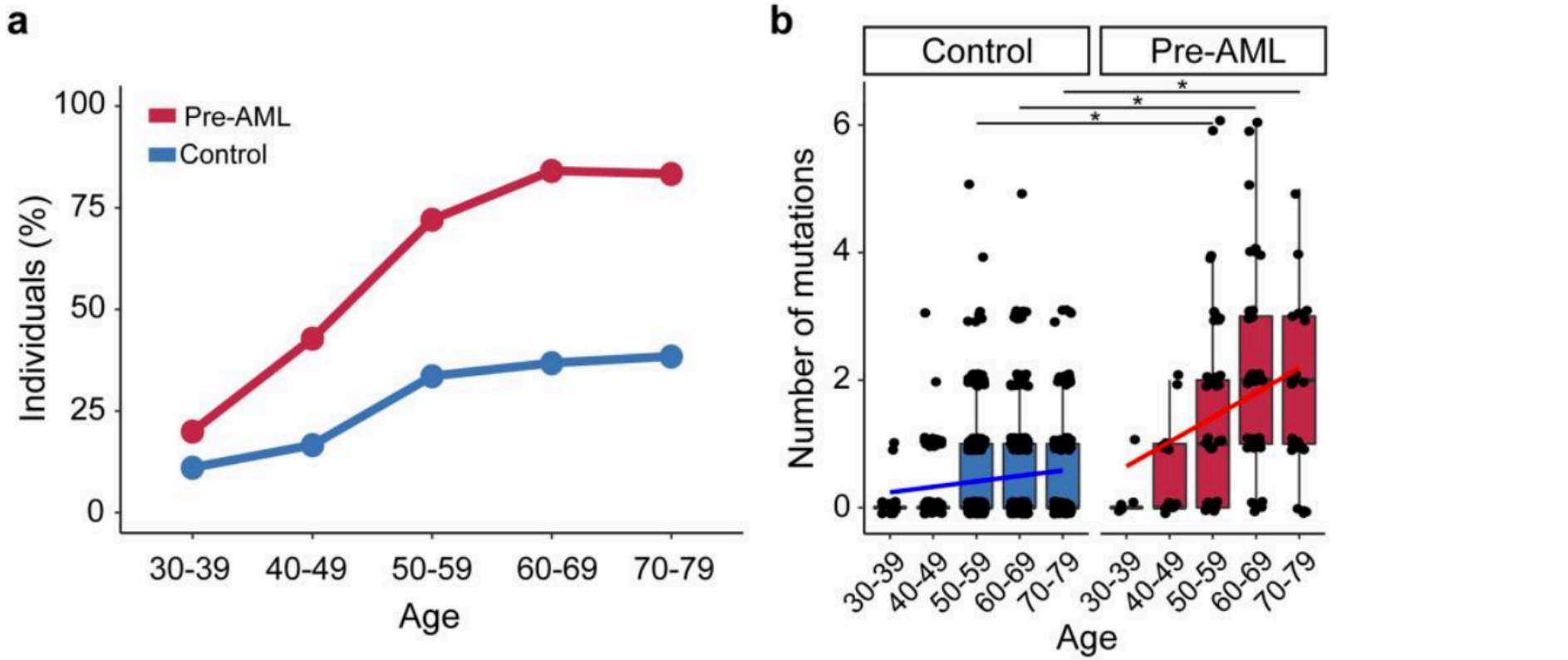
Desai et al. Nat Med. 2018 Jul;24(7):1015-1023

Prediction of AML risk in healthy individuals

- To distinguish individuals at high risk of developing AML from those with benign ARCH, we undertook deep sequencing of genes recurrently mutated in AML in the peripheral blood cells of 95 individuals sampled on average 6.3 years before AML diagnosis (pre-AML group), together with 414 unselected age- and gender-matched individuals (control group)

Abelson et al. Nature. 2018 Jul;559(7714):400-404

Prediction of AML risk in healthy individuals



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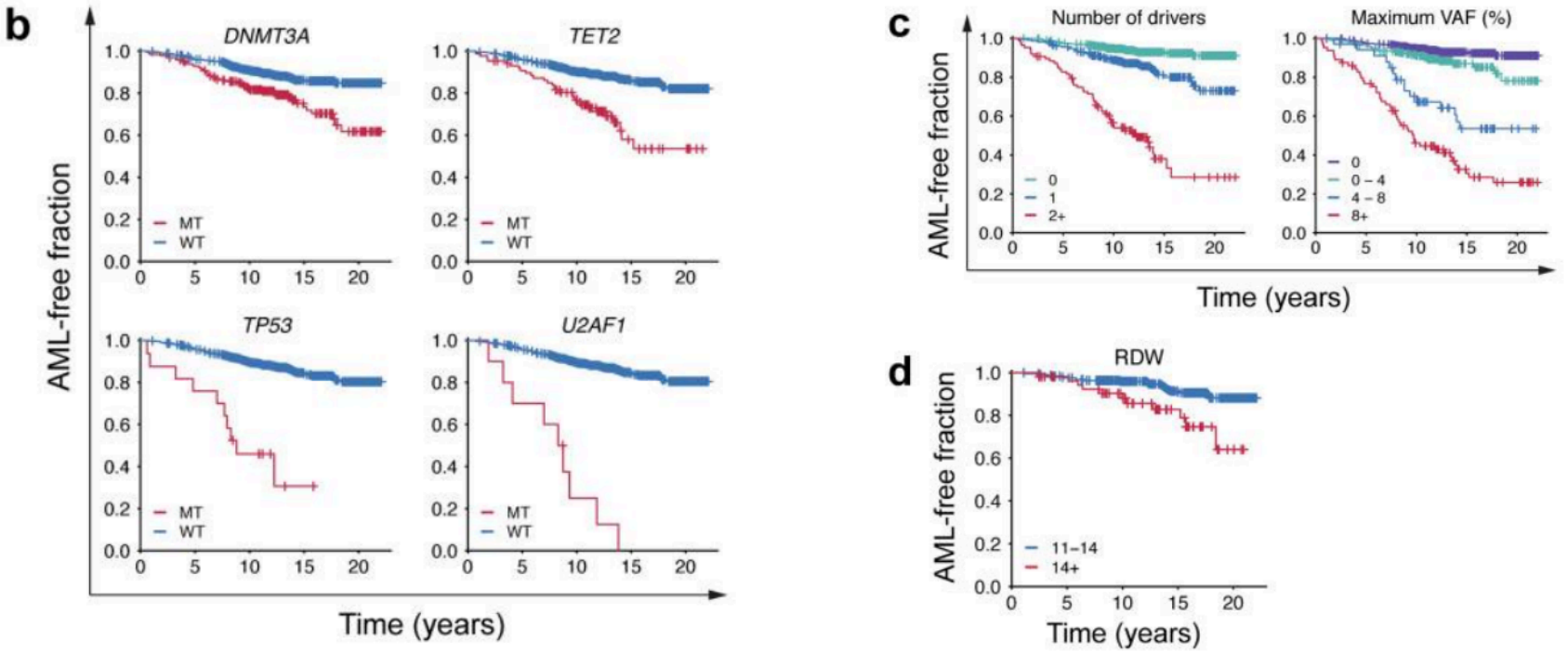
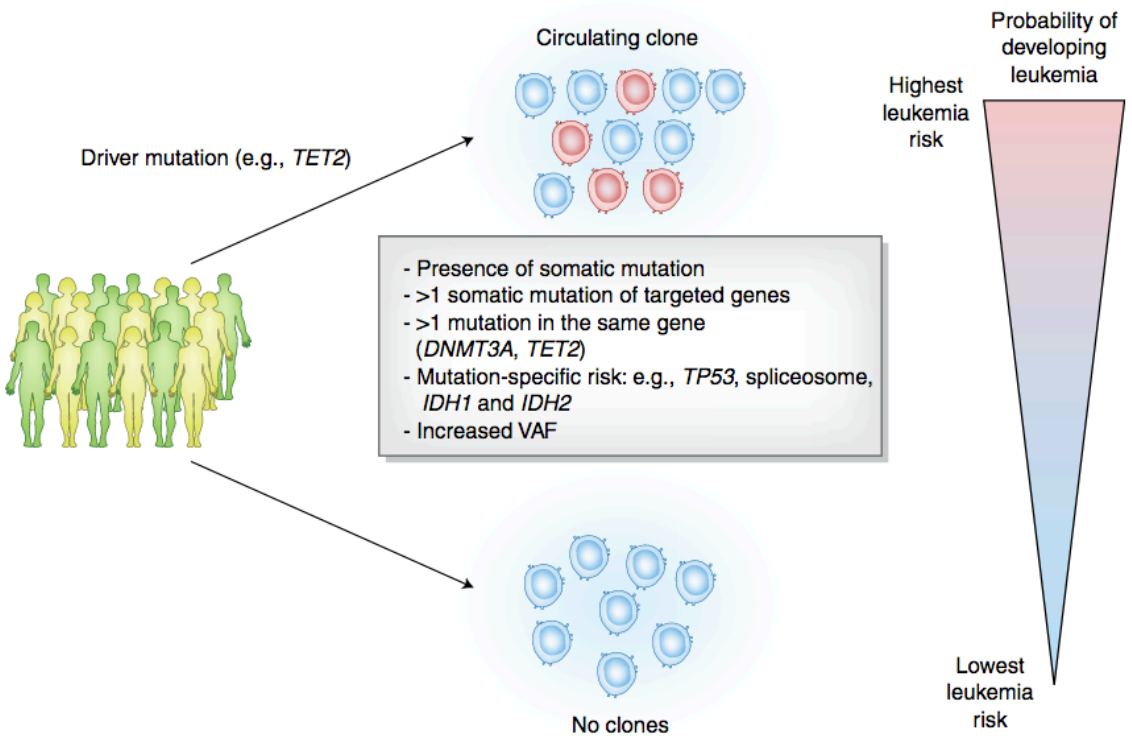


Abelson et al. Nature. 2018 Jul;559(7714):400-404

Predicting progression to AML



Sellar et al. Nat Med. 2018 Jul;24(7):904-906

Germline genetic predisposition to myeloid neoplasms with myelodysplasia

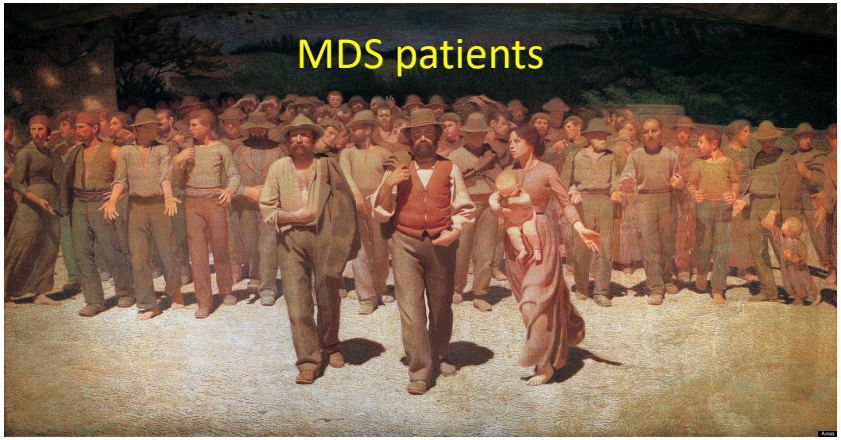
Germ-line predisposition → MDS

Patients under the age of 60 and/or with evidence of familial disease

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or
Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

Arber et al. Blood. 2016 May 19;127(20):2391-405

Acknowledgments



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