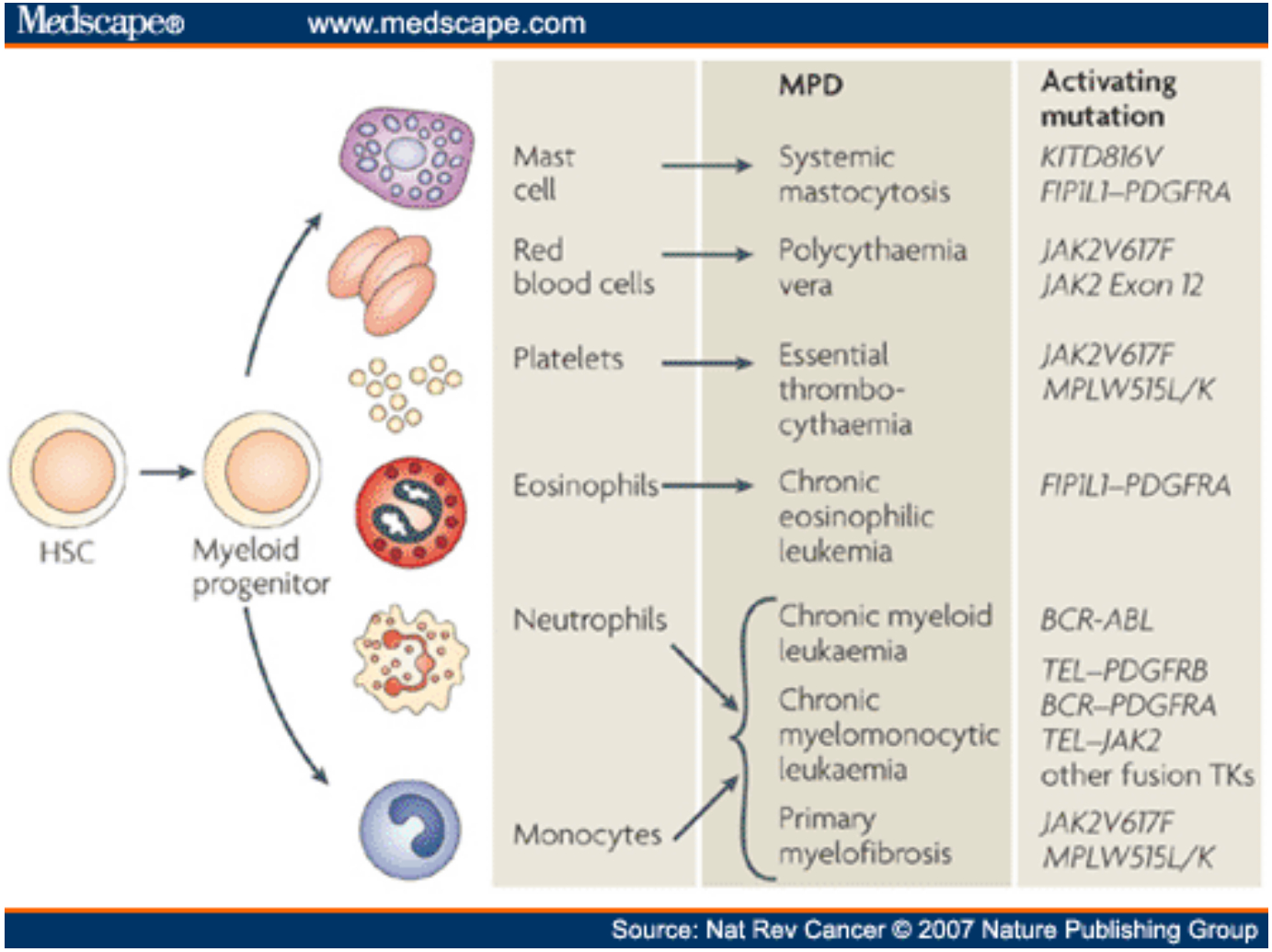
Chronic myelomonocytic leukemia

Lymphoma Tumor Board

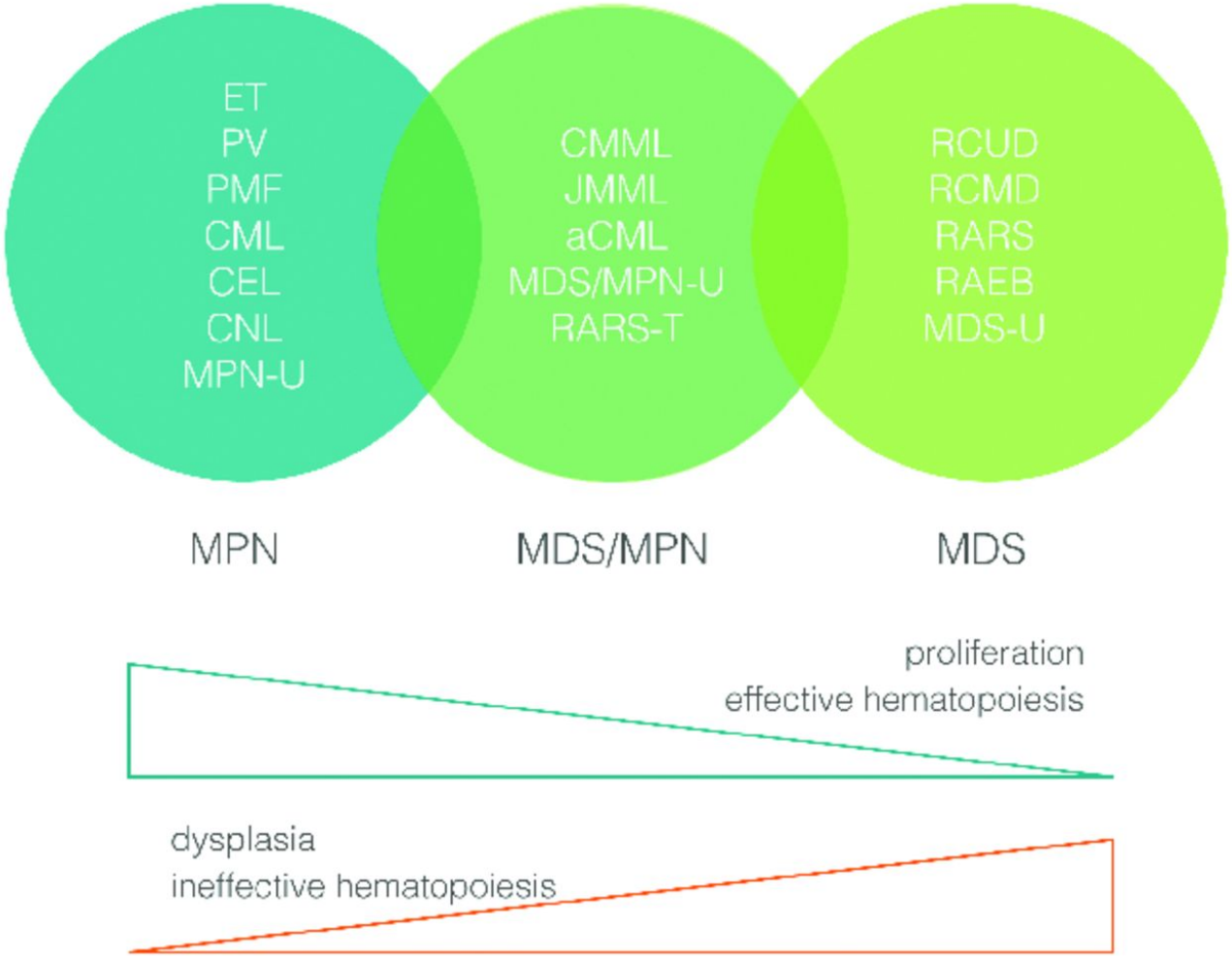
May 26, 2017

Myeloproliferative Neoplasms



CMML has an estimated incidence of less than 1 per 100,000 persons per year

Myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) define a spectrum of pathology



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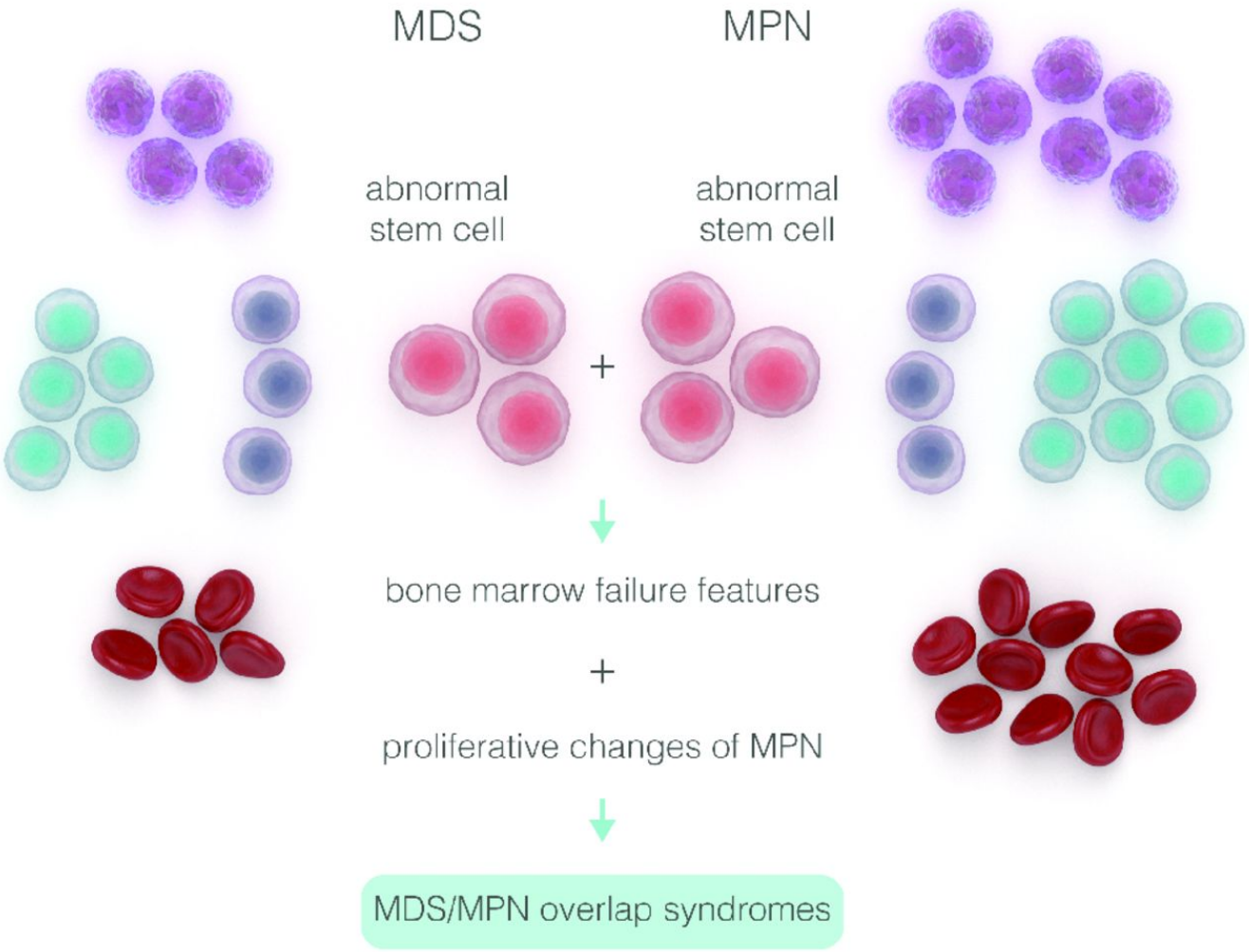
Overlap syndromes with features of both MDS and MPN are common



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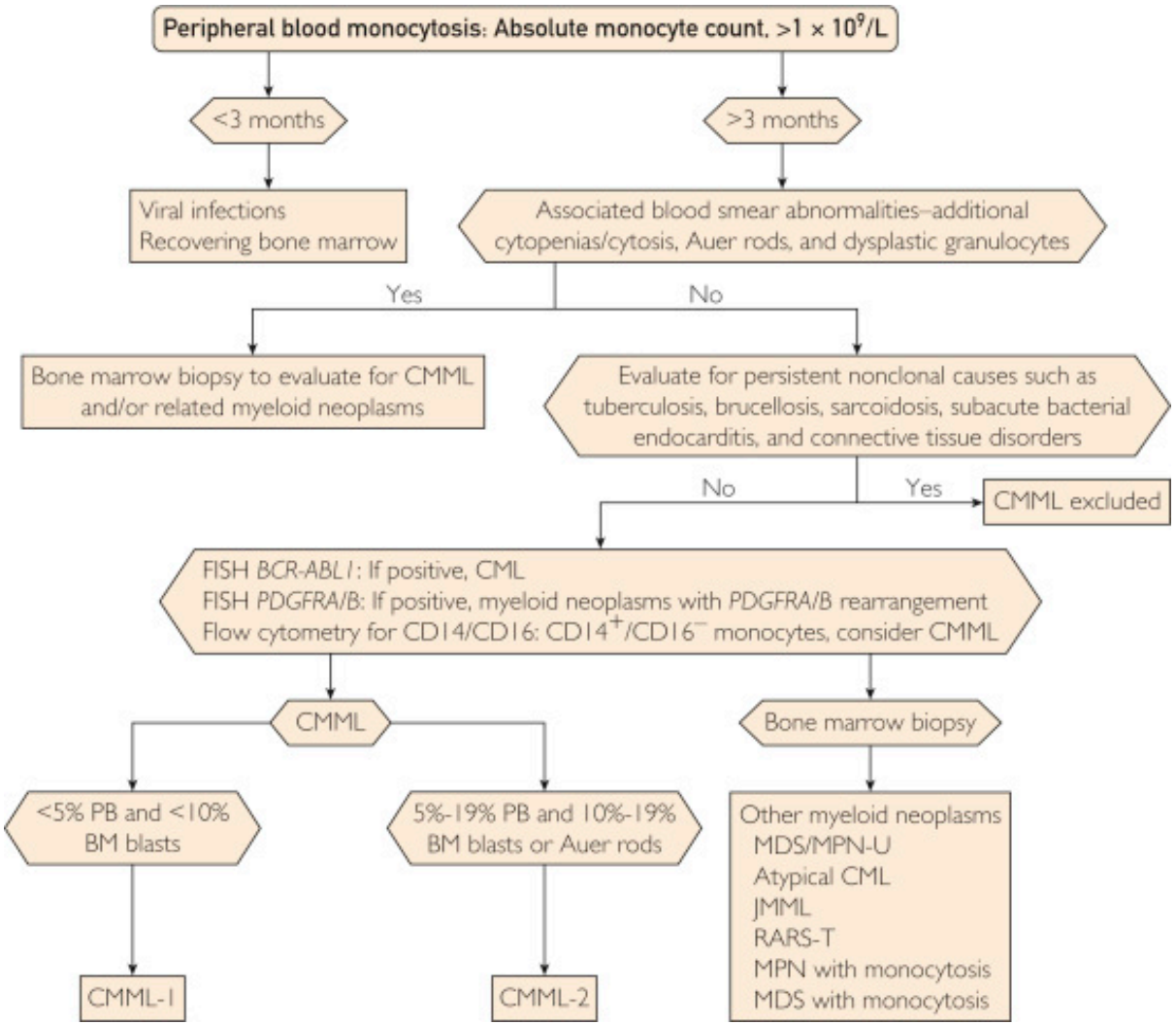
Chronic myelomonocytic leukemia (CMML)

- Increased numbers of monocytes and immature blood cells (blasts) in the peripheral blood and bone marrow
- Abnormal looking cells (dysplasia)
- Shows characteristics of myelodysplastic syndrome (MDS) and myeloproliferative disorder (MPD)
- Splenomegaly is quite common
- Other symptoms include:
  - Anemia
  - Fever
  - Weight loss
  - Night sweats
  - Infection
  - Bleeding
  - Synovitis
  - Lymphadenopathy
  - Pleural effusion, pericardial effusion, and/or peritoneal effusion
- Diagnosis (WHO): Persistent (> 3 months) blood monocytosis (>1,000/µL)
- No Philadelphia chromosome or mutations in *PDGFRA* or *PDGFRB*
- Blast count must be <20% and dysplasia of at least one lineage of myeloid blood cell should be present

Diagnostic algorithm for peripheral blood monocytosis



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Potential diagnostic approach for patients suspected to have a MDS/MPN overlap syndrome

	CMML	aCML	MDS/MPN-U
Mean age	72	72	72
Sex ratio	2/1	2/1	2/1
Mean OS	~3 years	~1 year	~2 years
Incidence	1/100000	1/100 CML	Unknown
Criteria	Monocytosis > 1 G/L at least 3 months +/- bone marrow cell dysplasia	Persistent leukocytosis > 13 G/L + immature circulating myeloid precursors > 10% of leukocytes + Marked dysgranulopoiesis, and - Absent/minimal monocytosis (<1 G/L and <10% of leukocytes) - Absent/minimal basophilia (<2%)	Heterogeneous group of rare myeloid neoplasms with myeloproliferative features & myelodysplastic features that cannot be classified as JMML, CMML, RARS-T, and aCML

A definitive diagnosis of MDS/MPN requires the exclusion of: AML: BM blast cells < 20%; CML: lack of BCR-ABL; MLN-Eo: lack of PDGFR/FGFR fusion & eosinophilia. CMML: chronic myelomonocytic leukemia; aCML: acute chronic myeloid leukemia; MDS: myelodysplastic syndromes; MPN-U: myeloproliferative neoplasms-Unknown; AML: acute myeloid leukemia; myeloproliferative neoplasms; BM: bone marrow.

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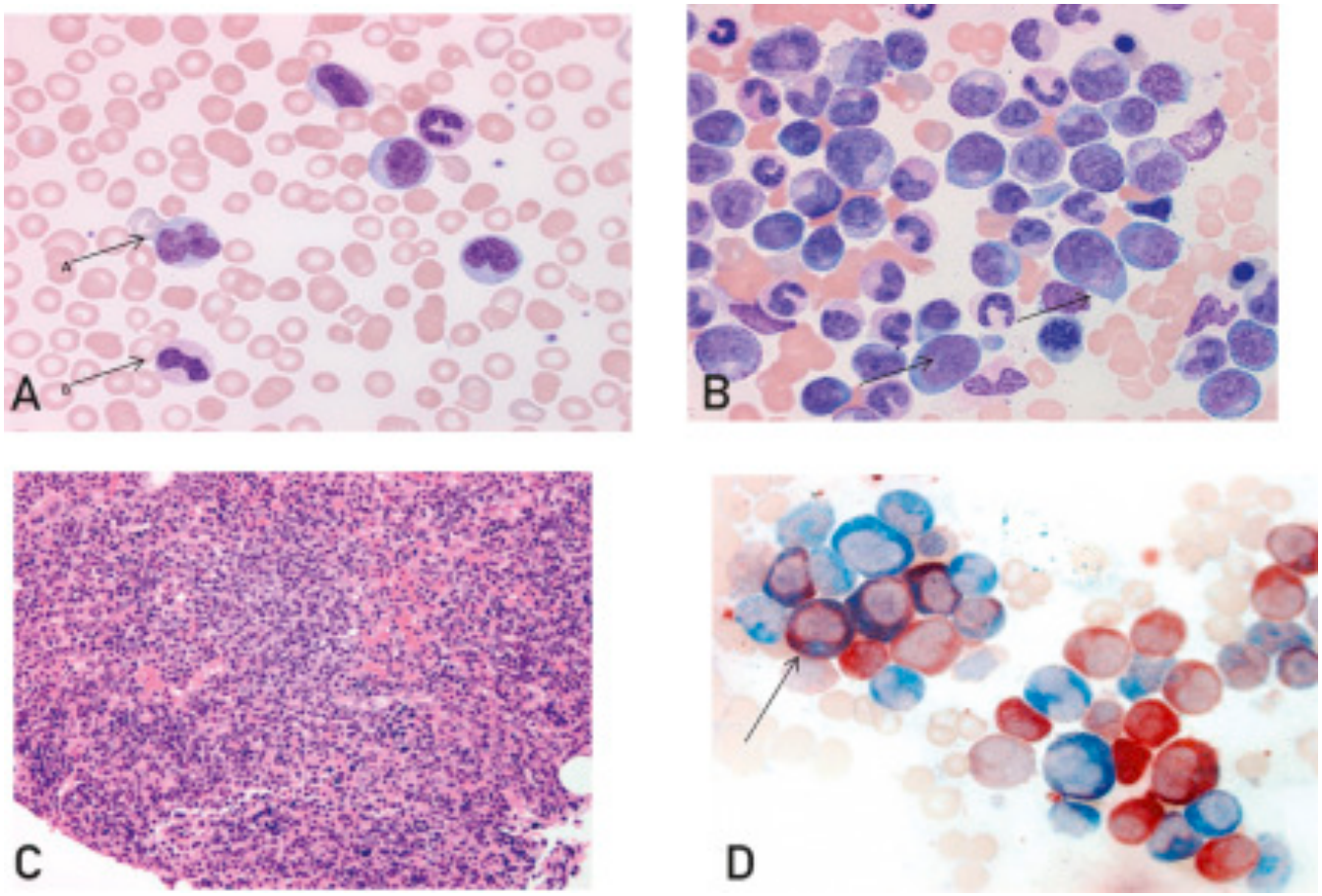
Peripheral blood and bone marrow findings in CMML



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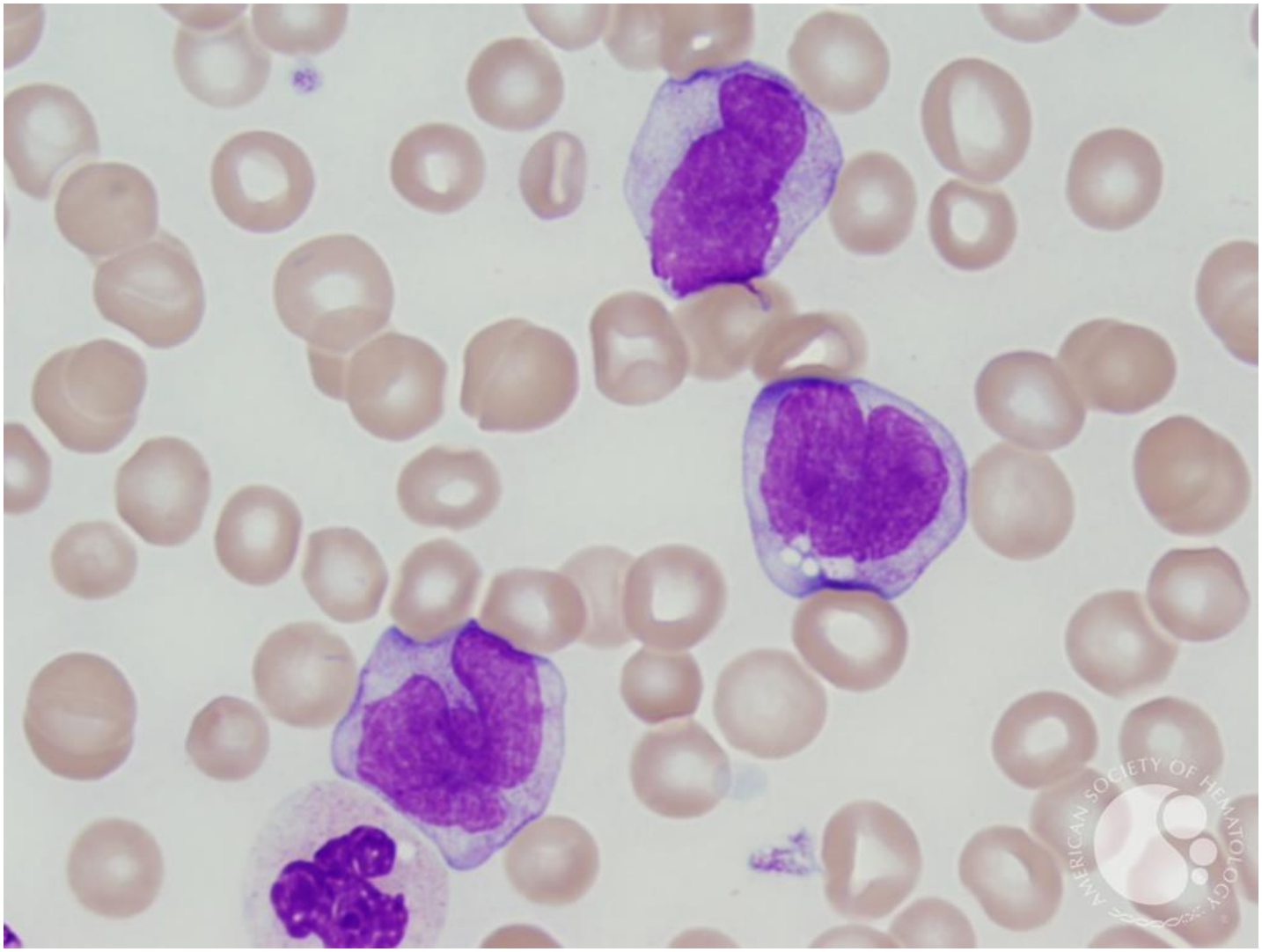
Chronic myelomonocytic leukemia-1 (CMML-1) 1



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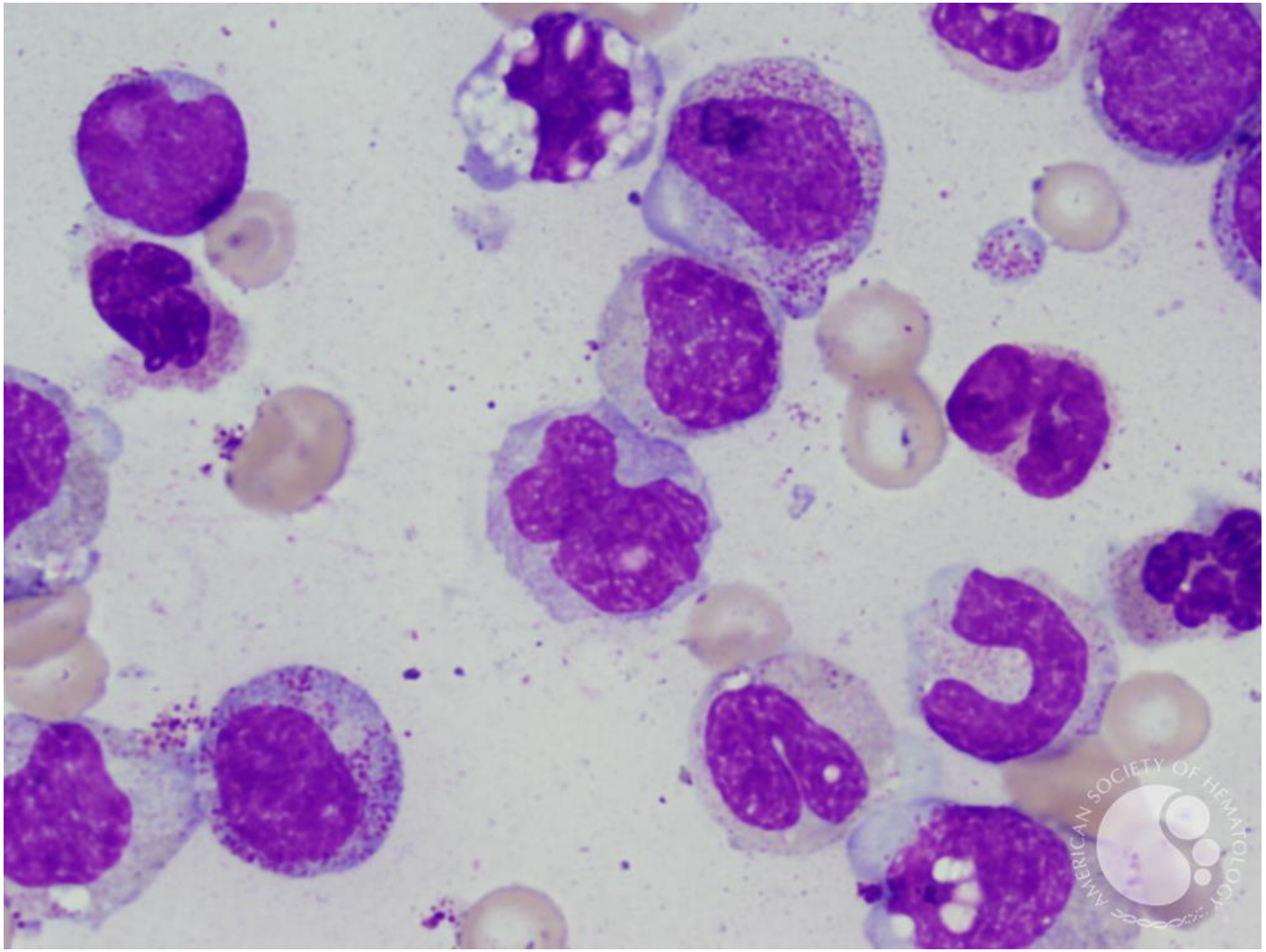
Chronic myelomonocytic leukemia-1 (CMML-1) 3



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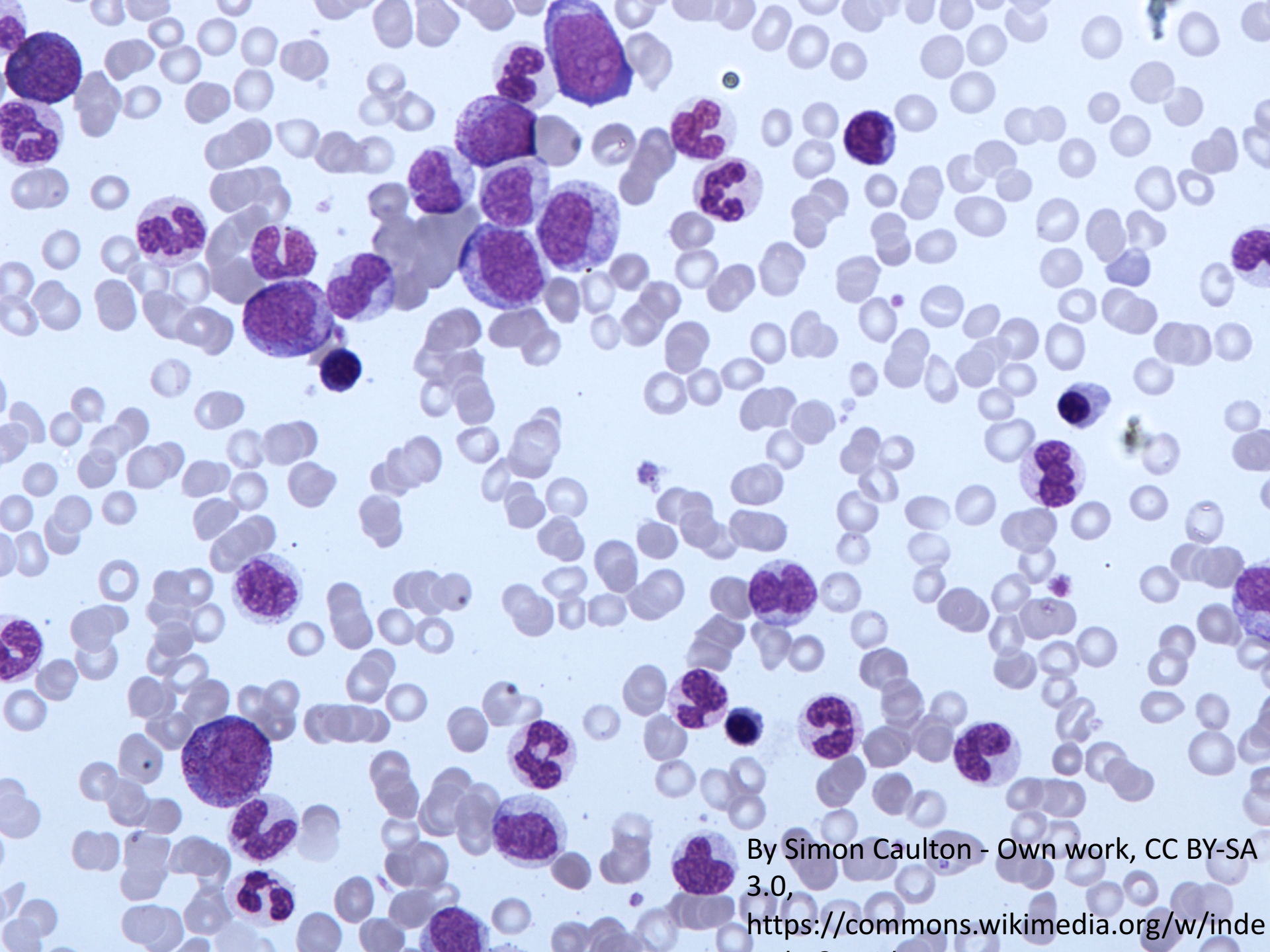

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Features of MDS vs. CMML

Table 1. Clinically Significant Features of MDS vs CMML

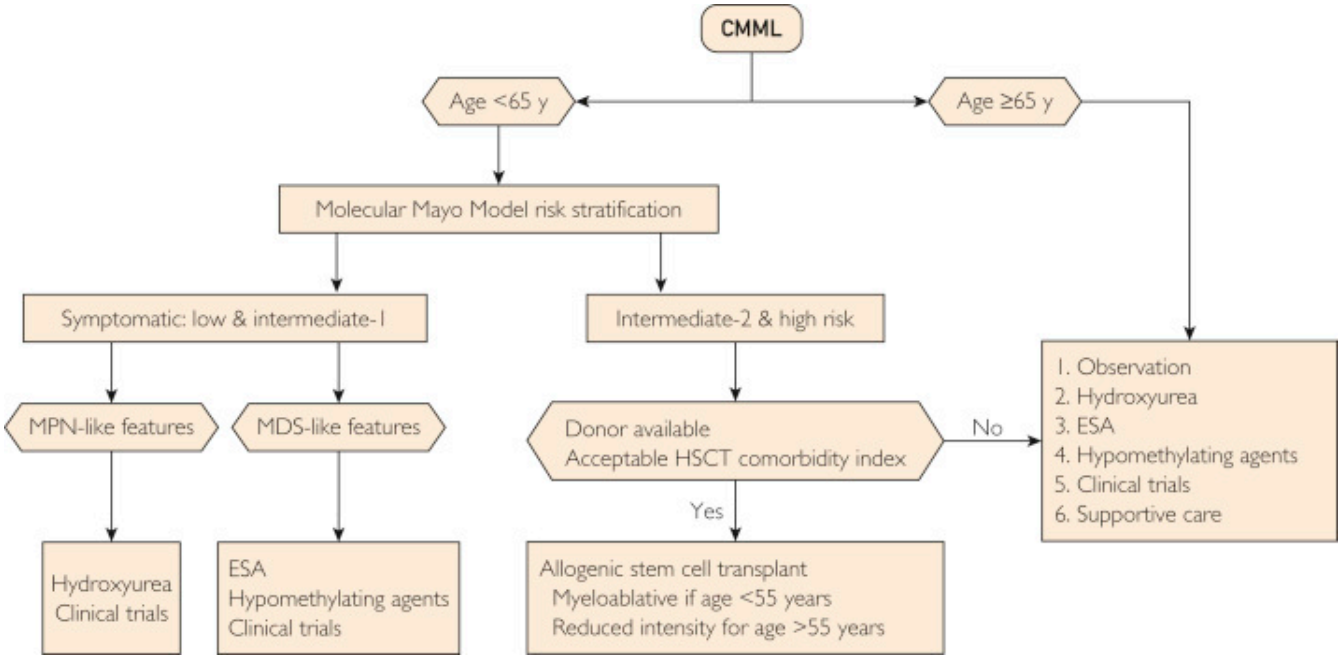
	MDS	CMML
Cytopenias present	Yes	Yes
Splenomegaly present	No	Yes (50% of cases)
Constitutional symptoms	Rare	Yes (frequency unknown)
AML transformation rate	30% of cases	30% of cases
Median survival	30 months	12-19 months
Preferred prognostic tool	IPSS/IPSS-R	Unknown
Treatment options --Hematologic improvement --Splenomegaly --Disease modification	 HMA, lenalidomide NA Azacitidine	 HMA Hydroxyurea, topotecan None
Stem cell transplant options	Allogeneic	Allogeneic

CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; NA, not applicable.

Treatment of CMML

- Remains challenging as there are few trials investigating CMML as a clinical entity
- Foundation of treatment is supportive care – directed by patients' co-morbidities
- Blood transfusions and ESA administration are used to raise hemoglobin levels in patients with symptomatic anemia
- Hypomethylating agents (HMAs) are a non-transplant treatment option
- Azacitidine is approved by the FDA and European Medicines Agency for treatment of CMML, and indicated for high risk non-proliferative CMML with 10-19% marrow blasts
- Decitabine is also approved by the FDA for CMML and all subtypes of MDS
- Hydroxyurea can be used in the myeloproliferative form of CMML to reduce WBC
- Topotecan, both as single-agent therapy and in combination with cytarabine, was found to have activity in patients with CMML in multiple studies performed at the MD Anderson Cancer Center – enthusiasm for this agent has waned, however
- Some patients can progress rapidly to secondary AML
- Hematopoietic stem cell transplantation is currently the only curative treatment for CMML and secondary AML arising from CMML
    - Often not possible due to late stage disease and co-morbidities

Mayo Clinic risk-adapted algorithm for the management of patients with CMML



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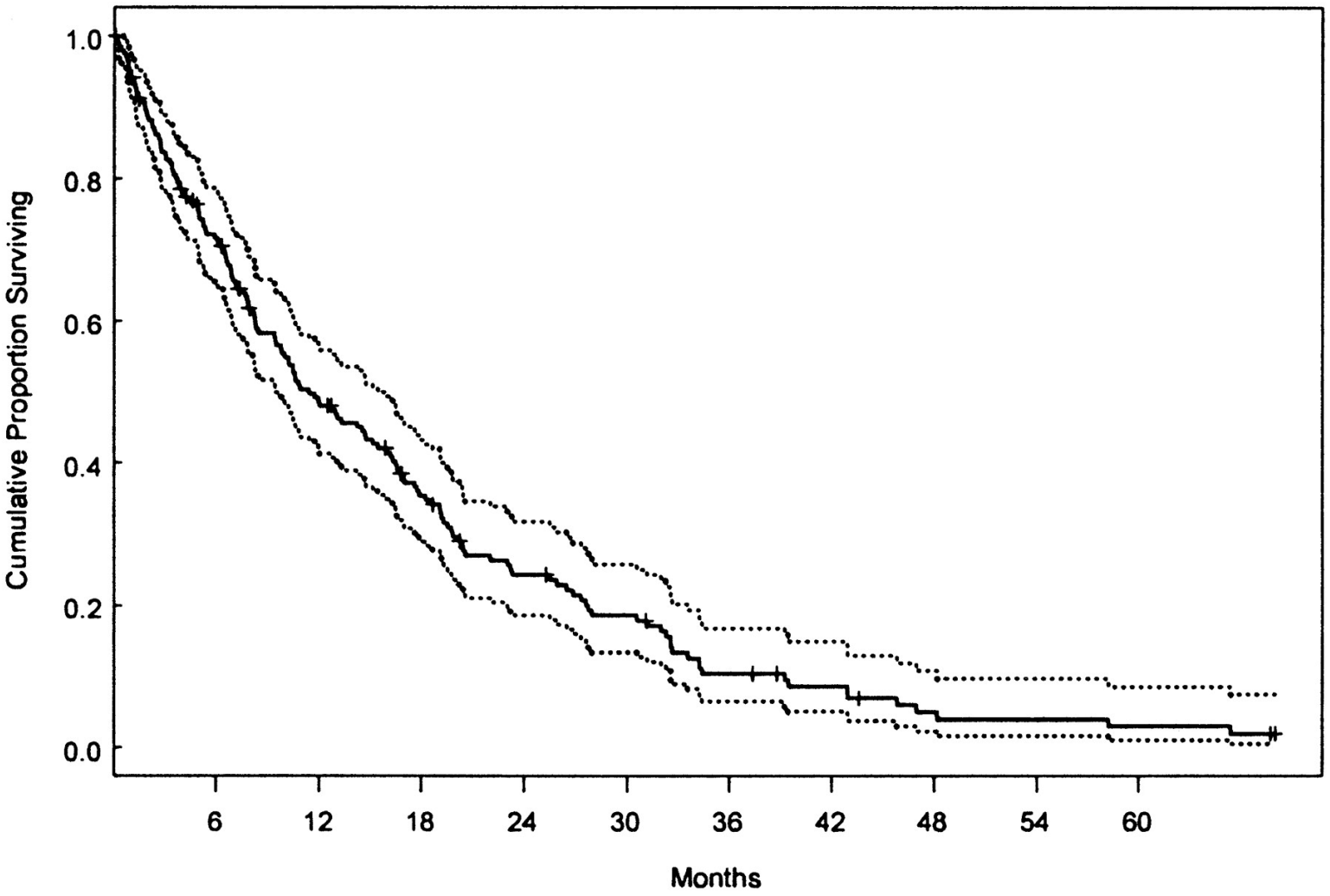
Survival in CMML circa 2002



Francesco Onida et al. Blood 2002;99:840-849

blood

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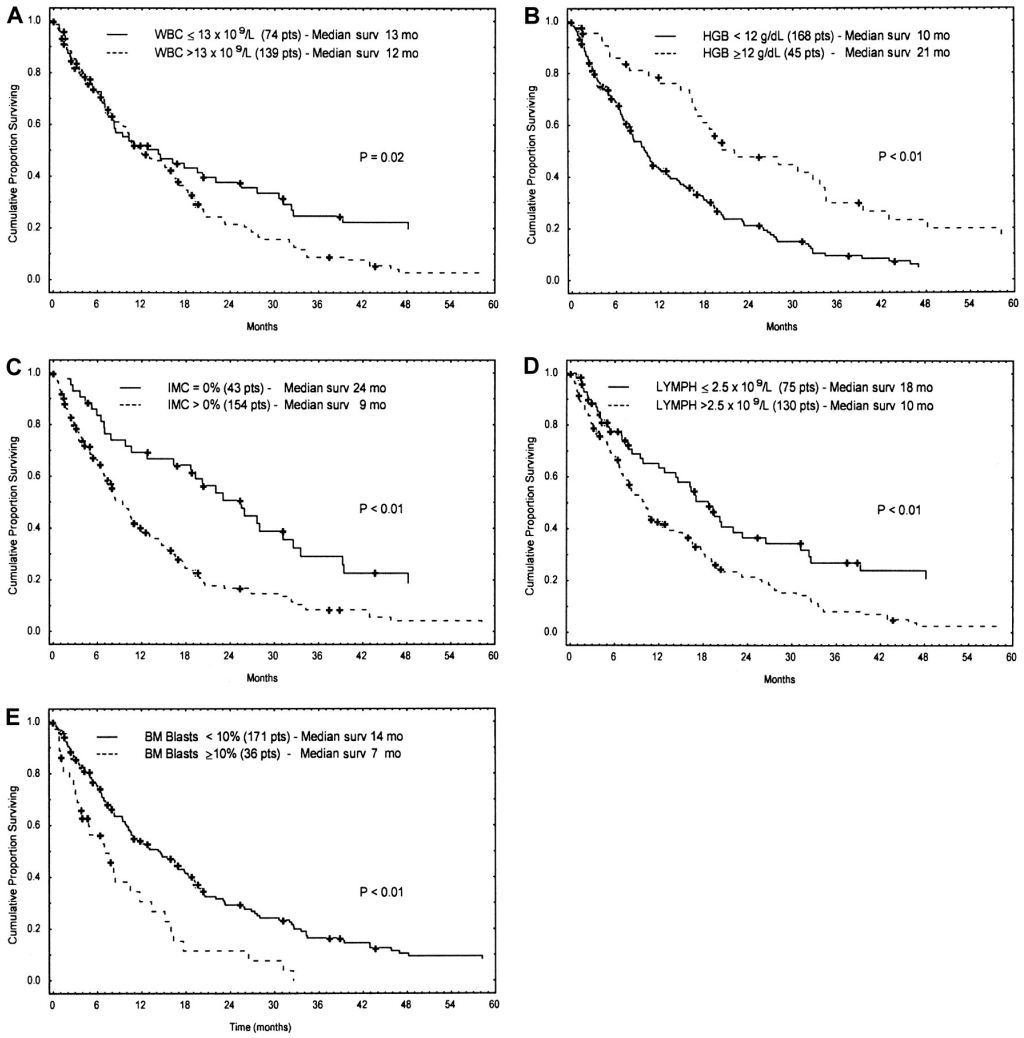
Survival in CMML circa 2002 – association with selected laboratory variables



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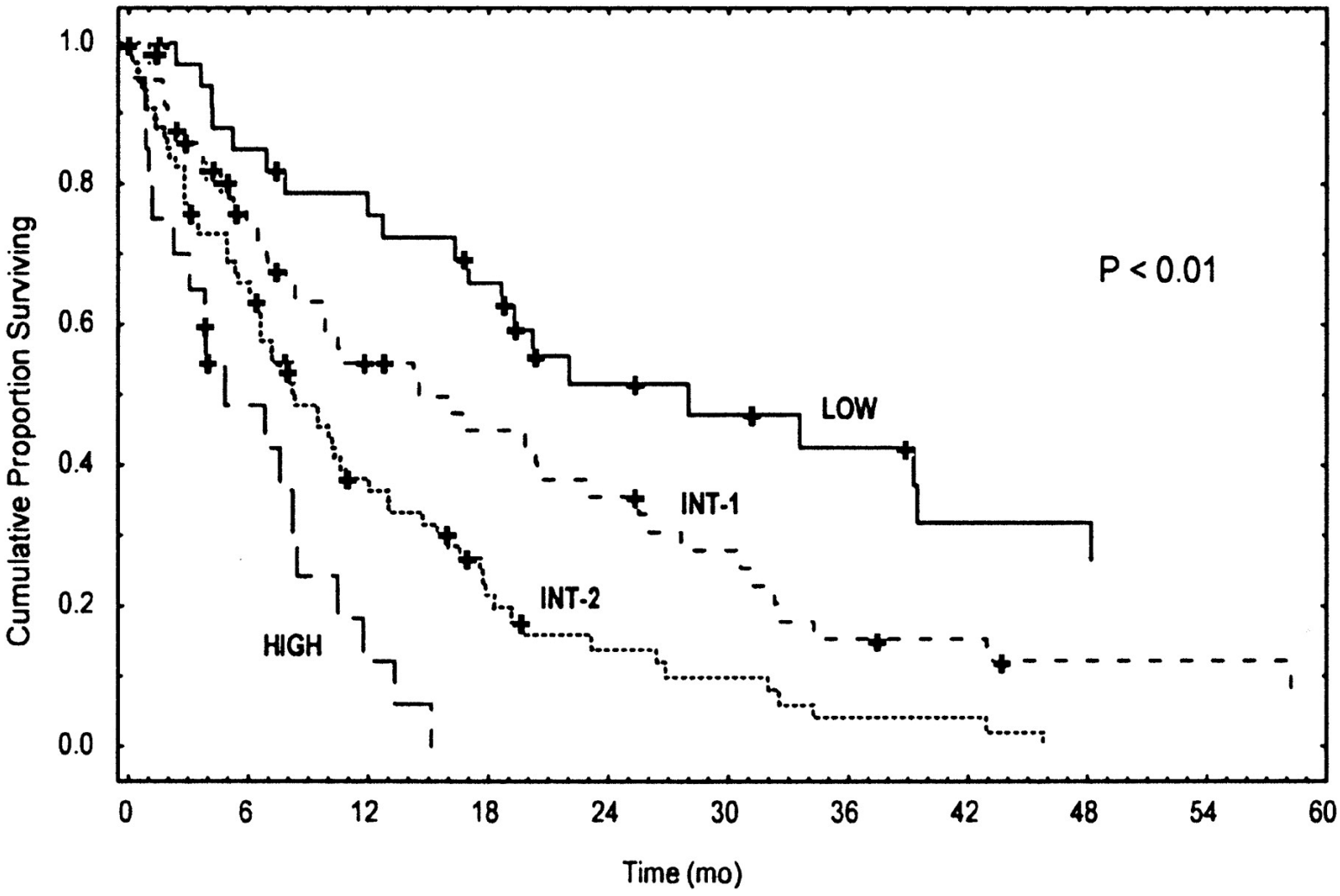
Survival in CMML circa 2002 - association with risk classification



Francesco Onida et al. Blood 2002;99:840-849

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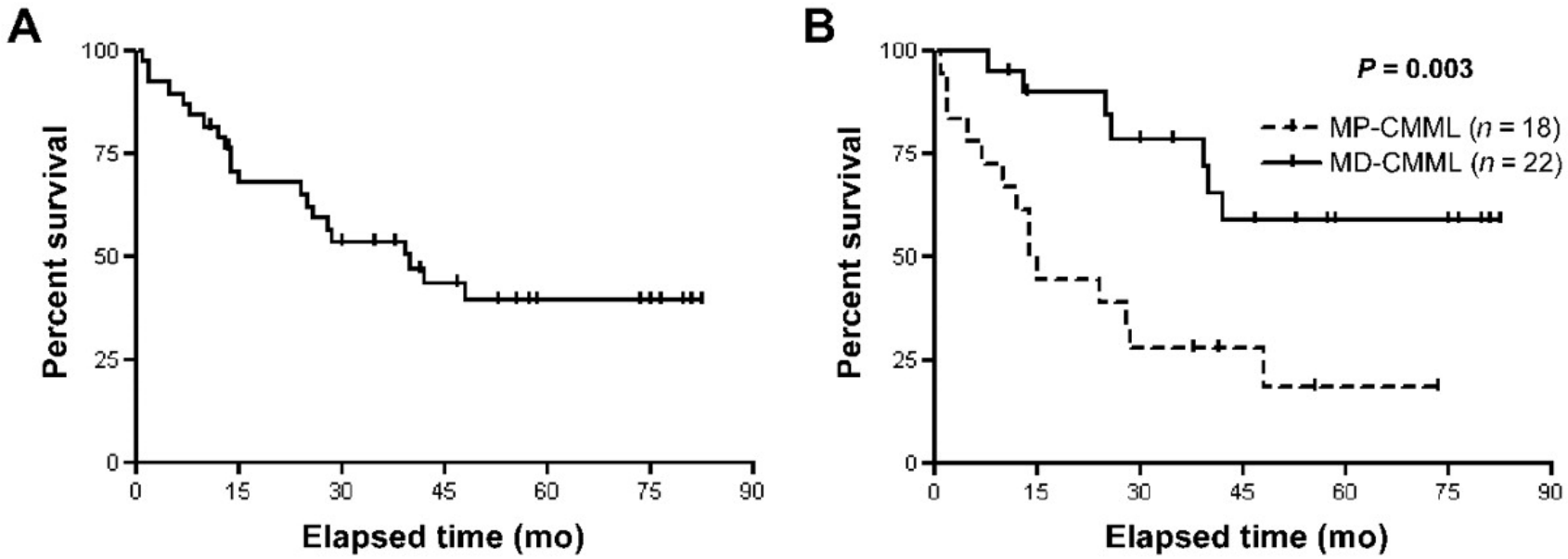
Survival of CMML patients is associated with WBC



MP-CMML: WBC ≥ 13,000/µL

MD-CMML: WBC < 13,000/µL

Clara Ricci et al. Clin Cancer Res 2010;16:2246-2256

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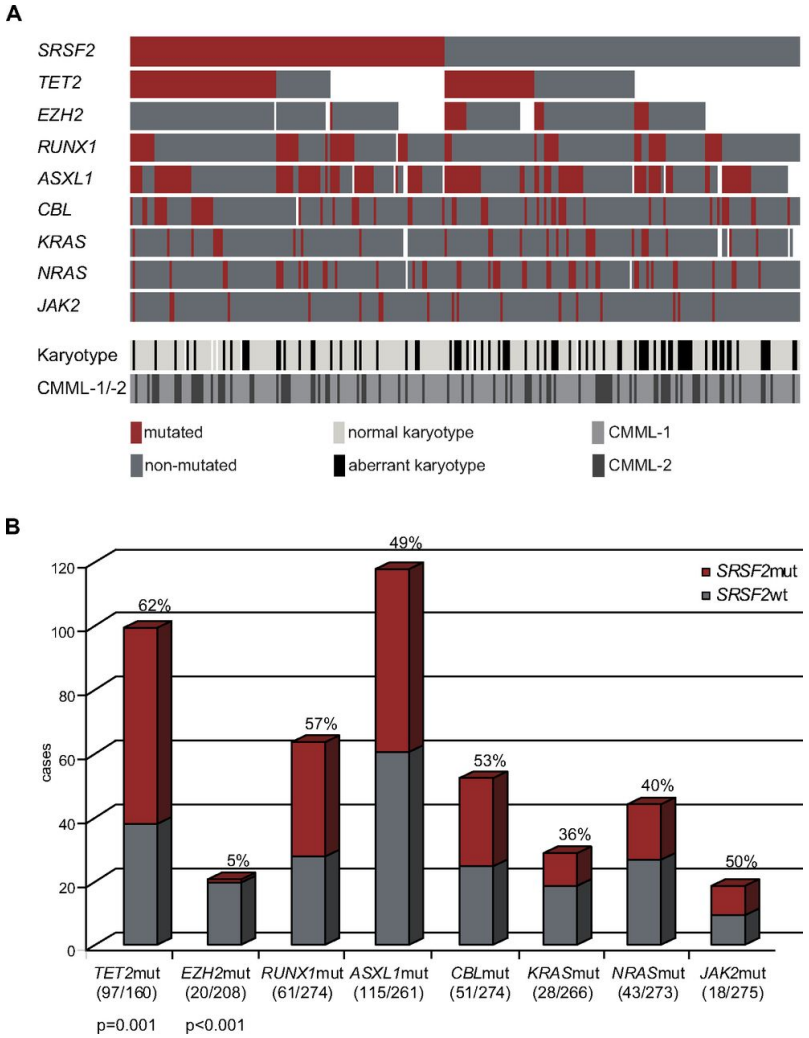
Clinical Cancer Research
AACR American Association for Cancer Research

Alignment of gene mutations, karyotype information, and CMML category for 275 patients



Manja Meggendorfer et al. Blood 2012;120:3080-3088

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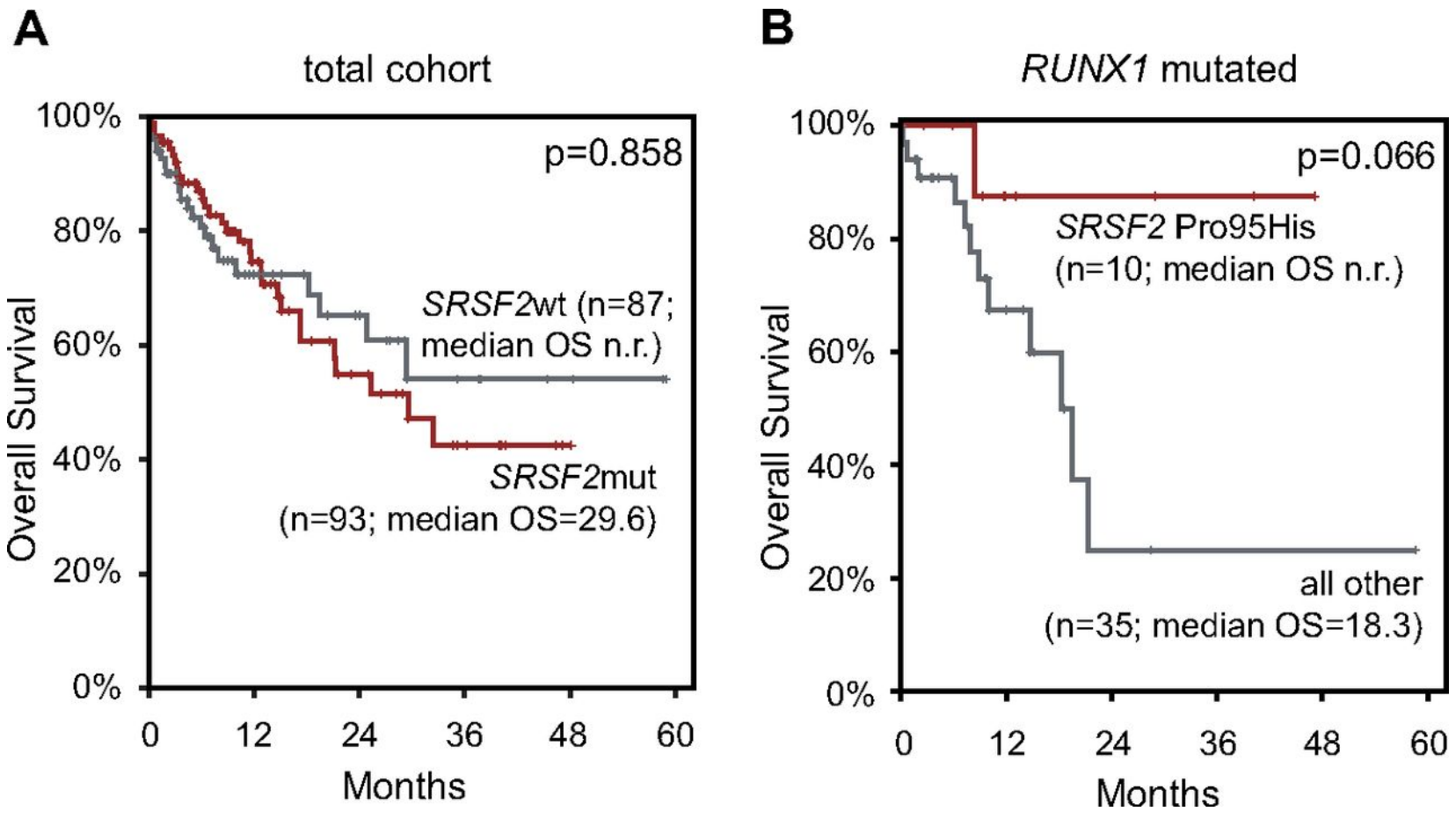
OS of patients with CMML according to *SRSF2* mutations



Manja Meggendorfer et al. Blood 2012;120:3080-3088

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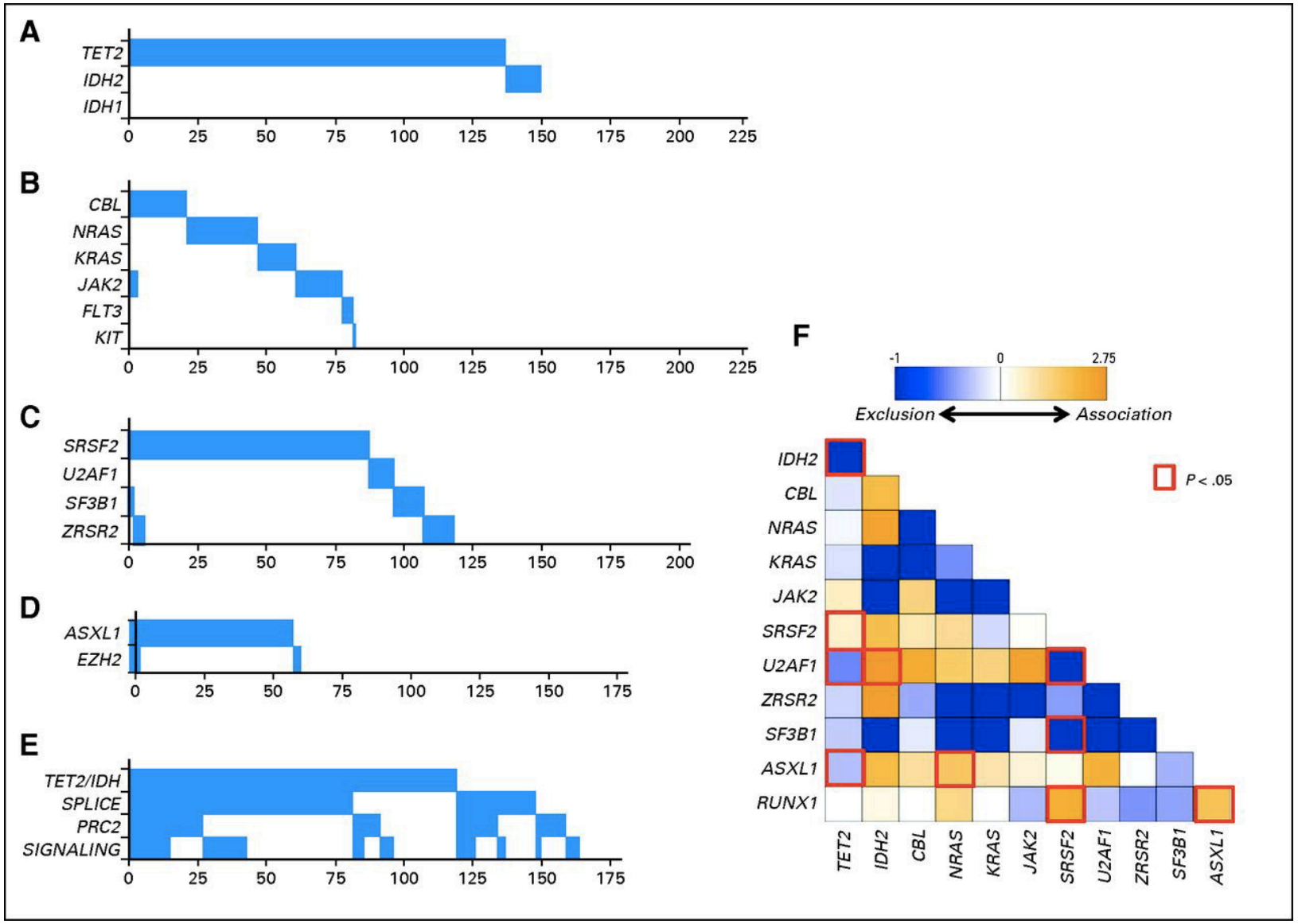
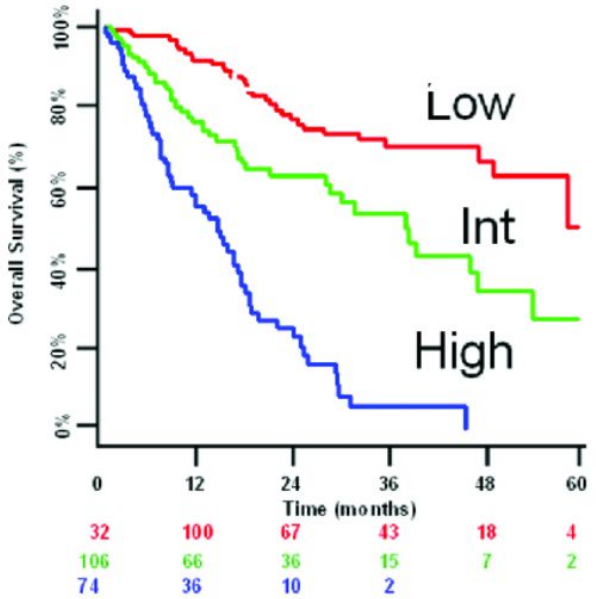
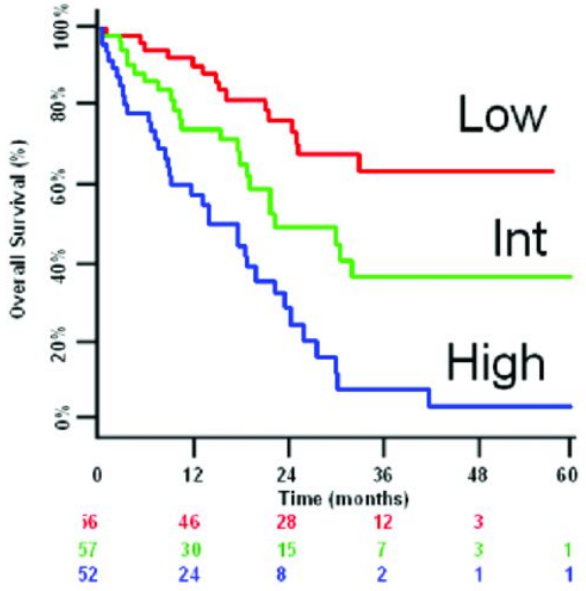
Clusters of gene mutations in CMML



Itzykson et al., J Clin Oncol 2013; 31:2428-2436

A simplified prognostic score for CMML that includes *ASXL1* mutations





	Absence	Presence
Leucocytosis (>15)	0	3
Age (>65)	0	2
Anemia	0	2
Thrombocytopenia (<100)	0	2
ASXL1 mutation	0	2

Low < 4
Intermediate 4-8
High >8

Adapted, with permission, Itzykson et al. J Clin Oncol, 2013, in press

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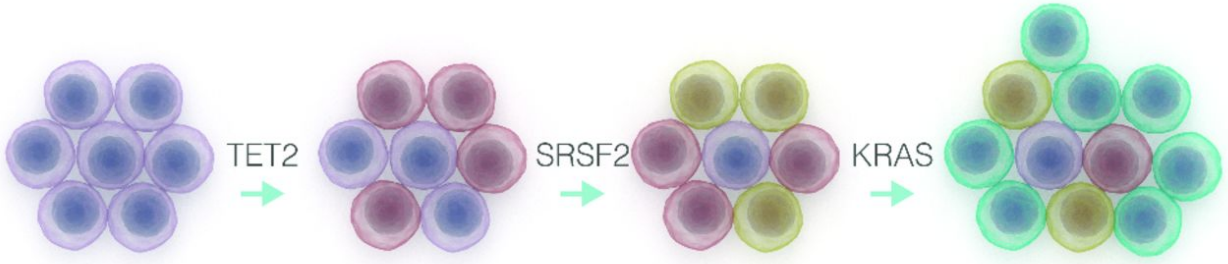
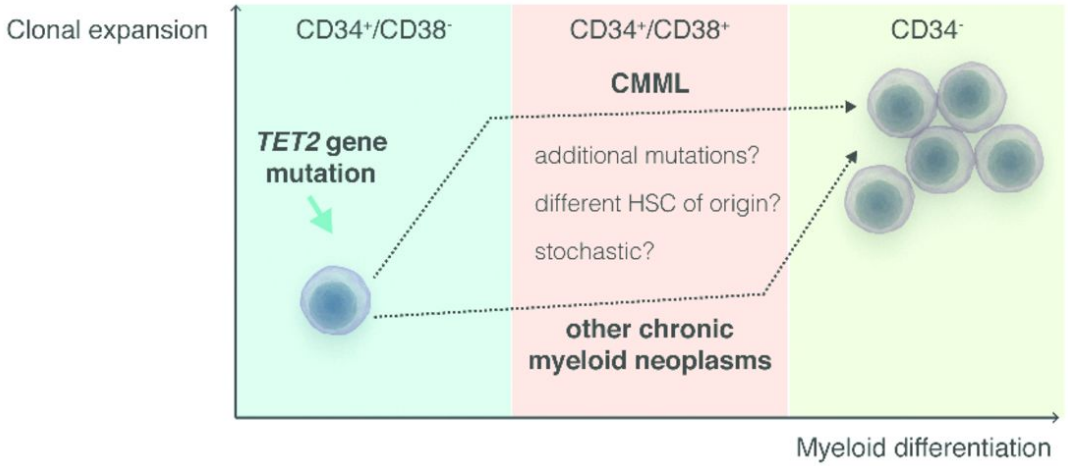
Early clonal dominance (CD34+/CD38−cells) in CMML compared to MPN



- Early clonal dominance in HSC compartment
- Linear acquisition of mutations, starting with epigenetic and splicing genes
- Growth advantage to the more mutated cells with differentiation



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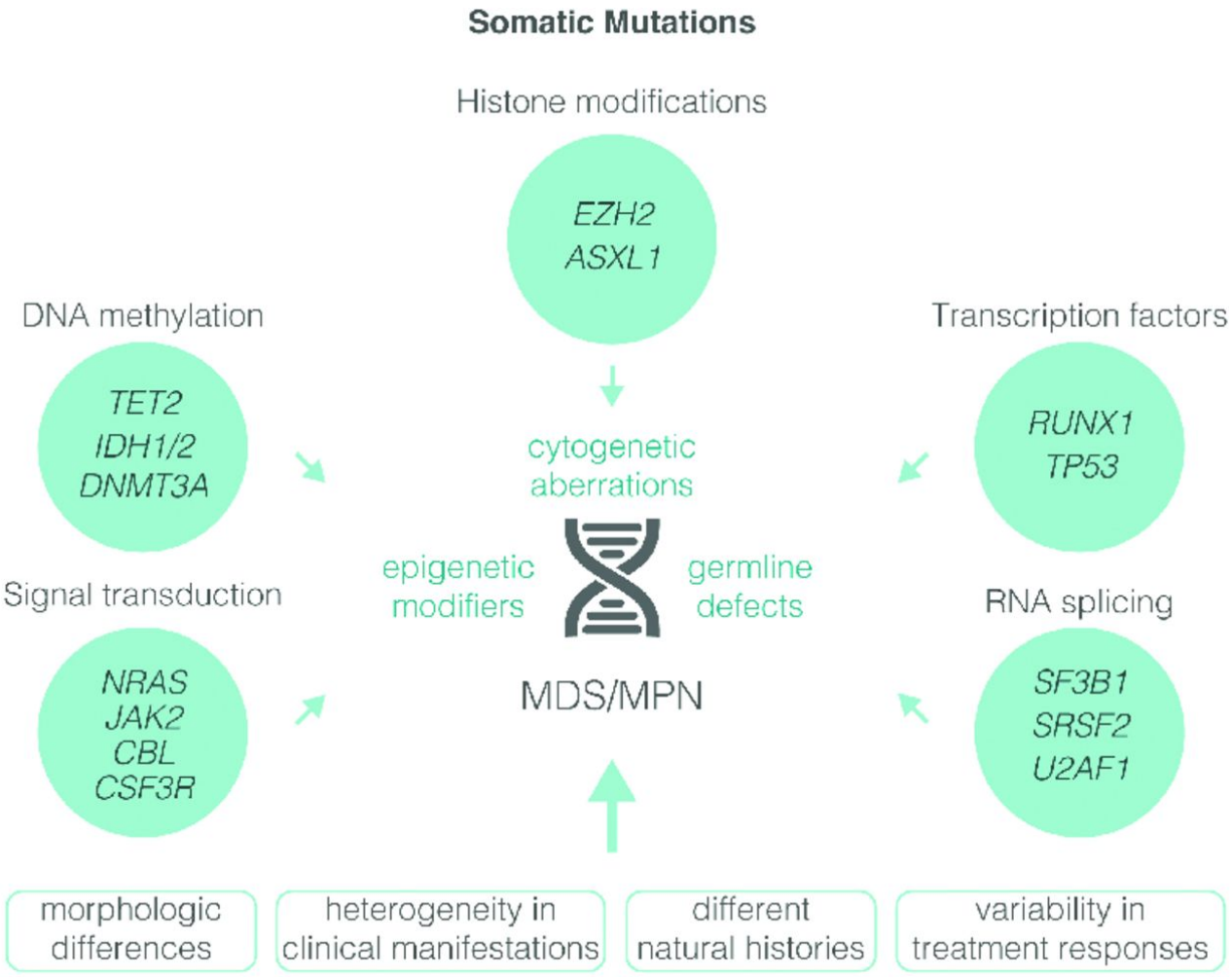
Schematic description of genotypic diversity in patients with MDS and MPN



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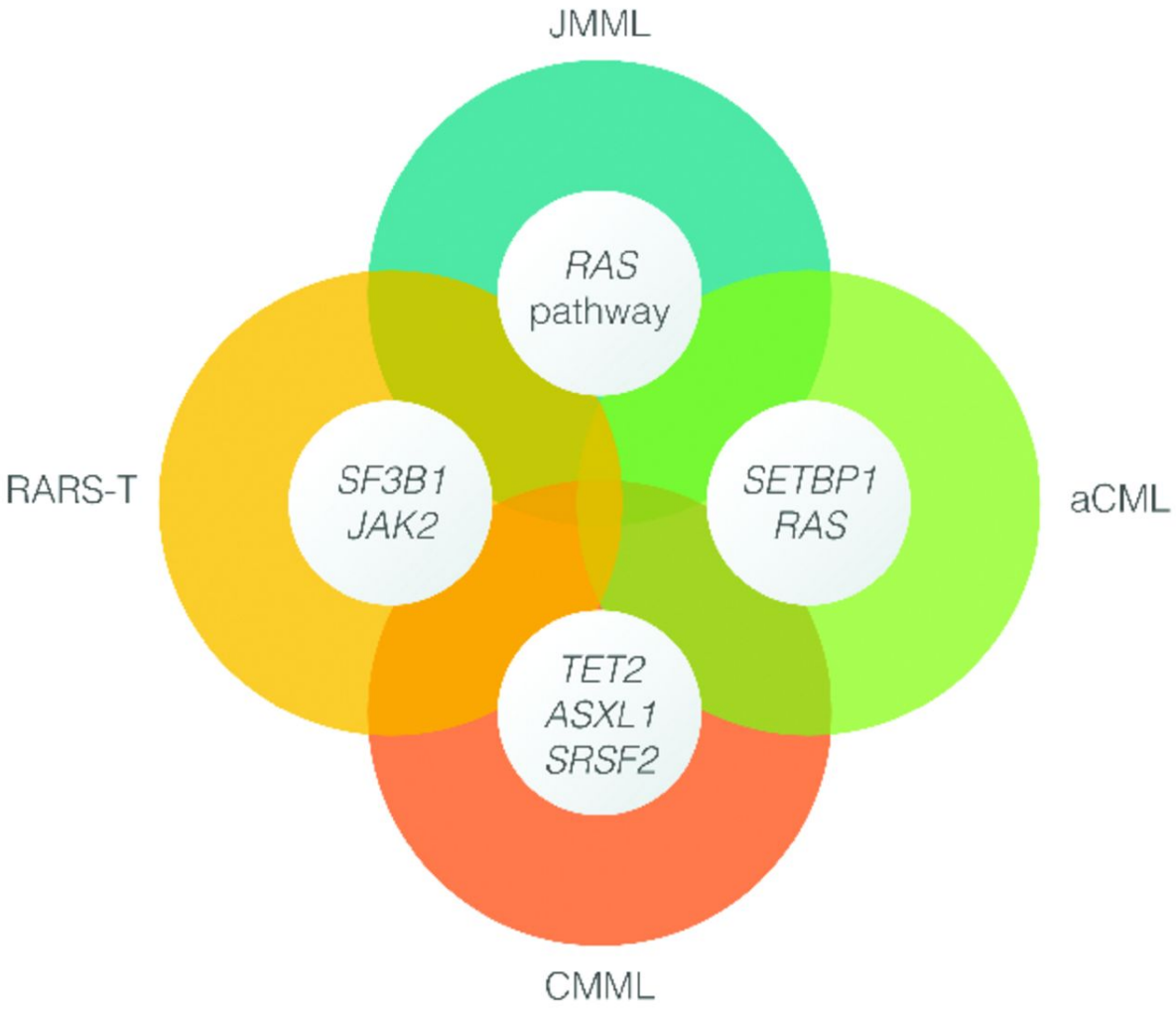
Emerging molecular fingerprints of MDS and MPN



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