Myelodysplastic Syndromes
Diagnosis and Prognostic scoring systems

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Netherlands

Belangenverklaring

In overeenstemming met de regels van de Inspectie van de Gezondheidszorg (IGZ)

Naam: *prof.dr. A.A. van de Loosdrecht*

Organisatie: Amsterdam UMC, location VU University Medical Center]

Ik heb geen 'potentiële' belangenverstrengeling

.

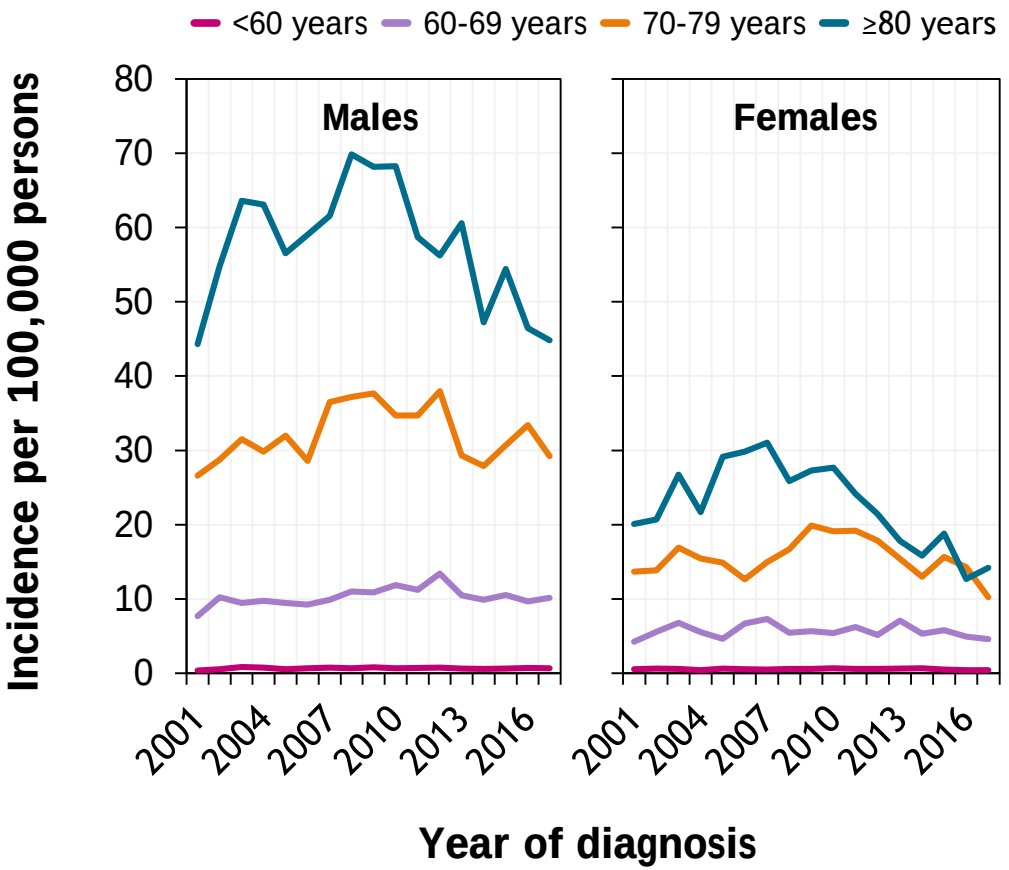
Type van verstrengeling / financieel belang	Naam van commercieel bedrijf
Ontvangst van subsidie(s)/research ondersteuning:	Celgene, Alexion
Ontvangst van honoraria of adviseursfee:	-
Lid van een commercieel gesponsord ‘speakersbureau’:	-
Financiële belangen in een bedrijf (aandelen of opties):	-
Andere ondersteuning (gelieve te specificeren):	-
Wetenschappelijke adviesraad:	Novartis, Celgene, Amgen, Pfizer, Takeda, Helsinn

Myelodysplastic Syndromes

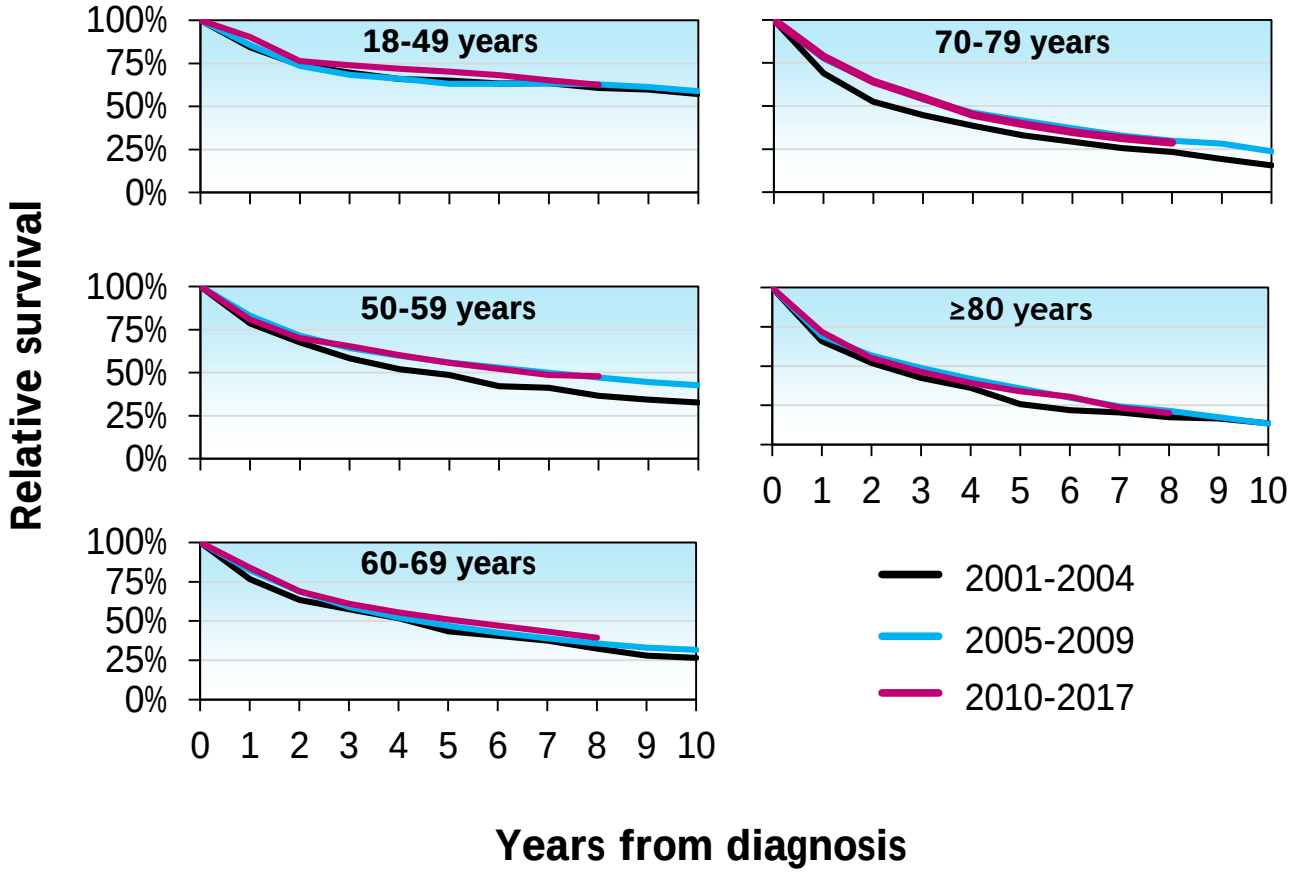
- **Heterogeneous**
  - → ***MD-Syndrome***
  - → Part of: *bone marrow failure syndromes*
  - → *stem cell disease*
  - → ***Anemia*** *is presenting symptom in >80% of cases*
- **Heterogeneous:**
  - → ***Morphology/FlowCytometry/Cytogenetics/Molecular***
- **Heterogeneous:**
  - → ***clinical course***

The burden of MDS in the Netherlands

Annual age-specific incidence according sex



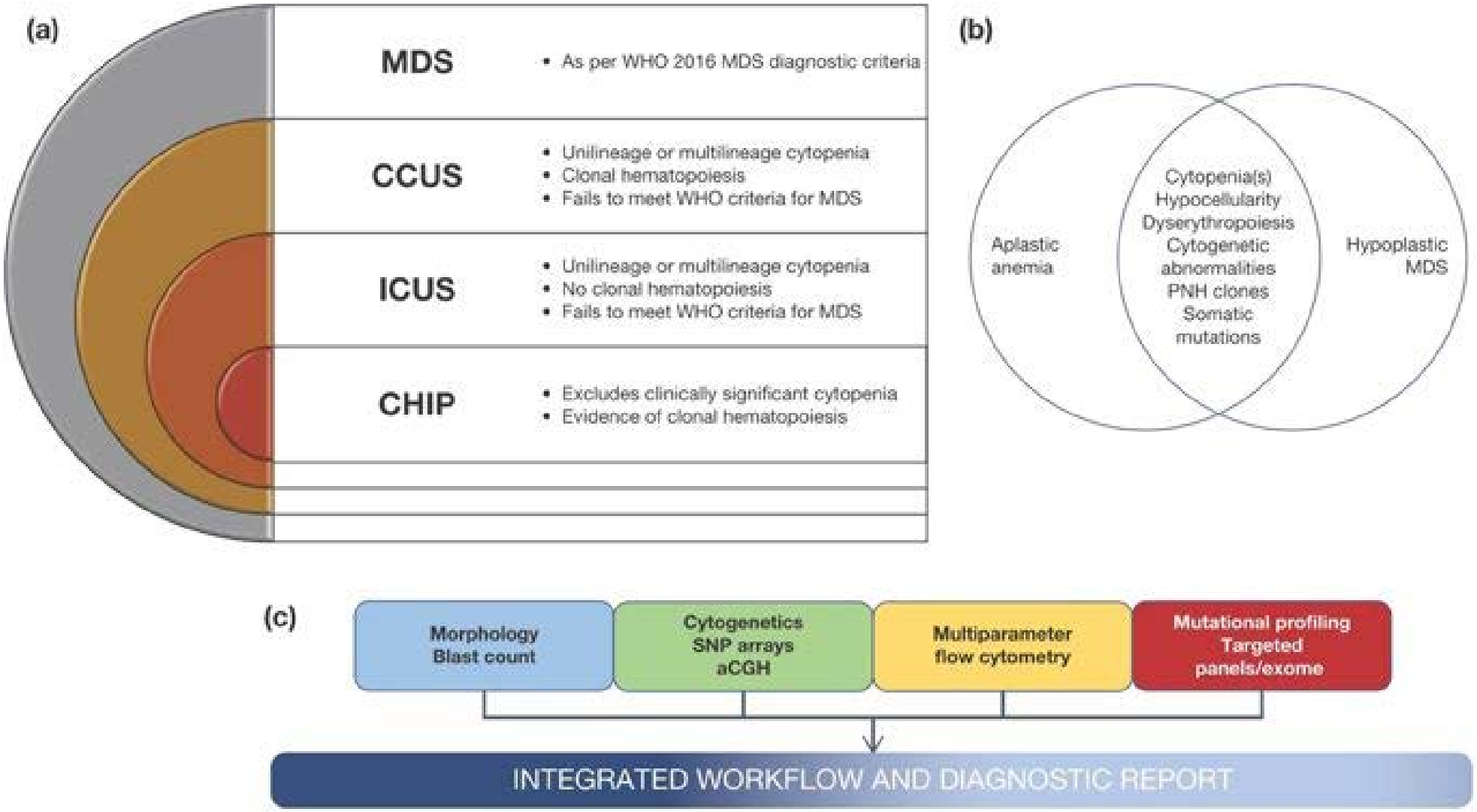
Relative survival according age at diagnosis and period of diagnosis



Around 700 MDS cases annually in the Netherlands

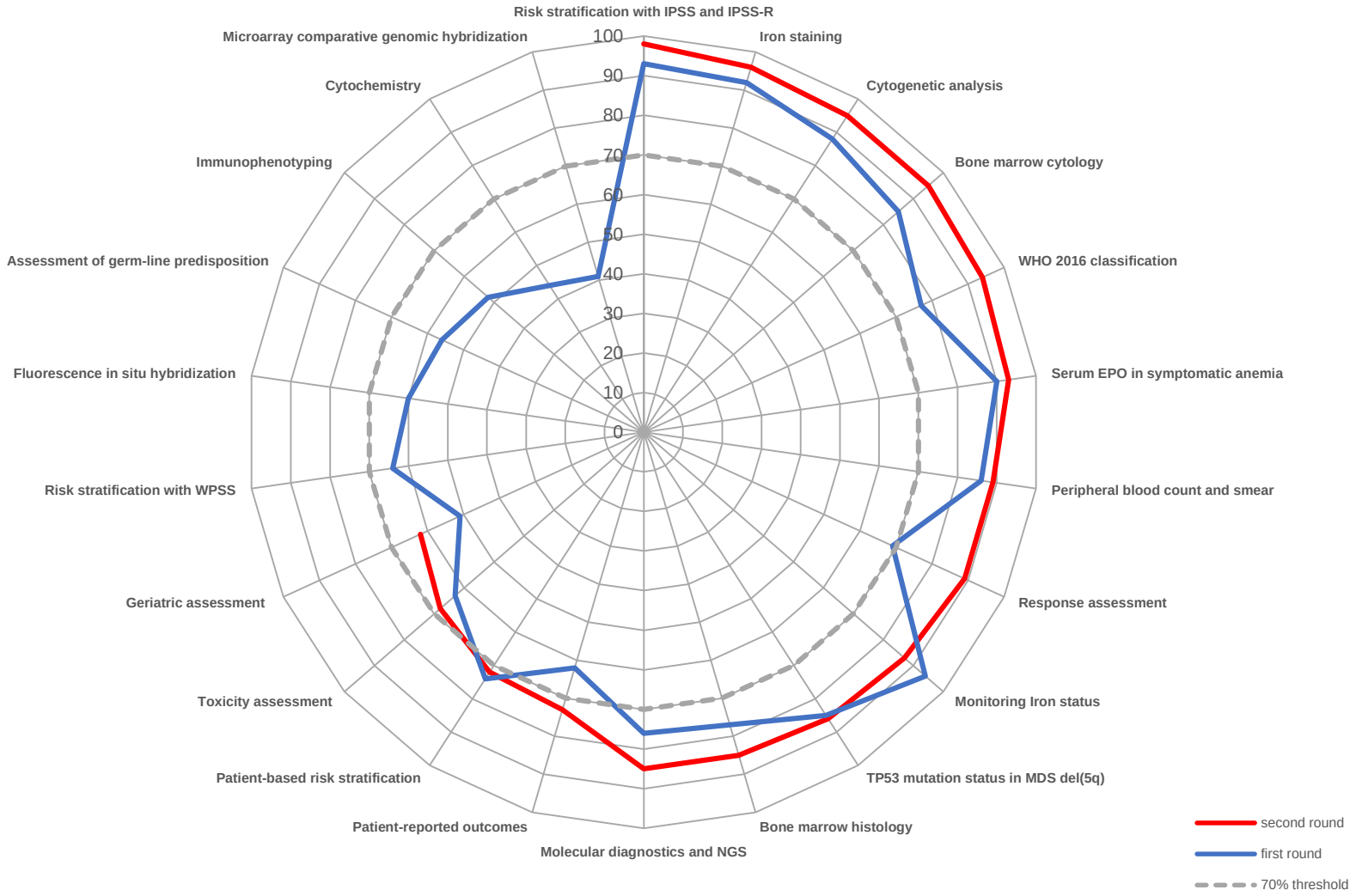
Data published in part in Dinmohamed AG et al. *Eur J Cancer*. 2014;50(5):1004-12
Source: The nationwide Netherlands Cancer Registry, 2001-2017 *(unpublished)*

Integrated diagnostics 2020



Mufti GJ, et al., Leukemia 2018;32;1679-1696; Malcovati L, et al., ELN guidelines. Blood 2013;122:2943-64;

Guideline Based Indicators: *Diagnosis* (DELPHI rating rounds)

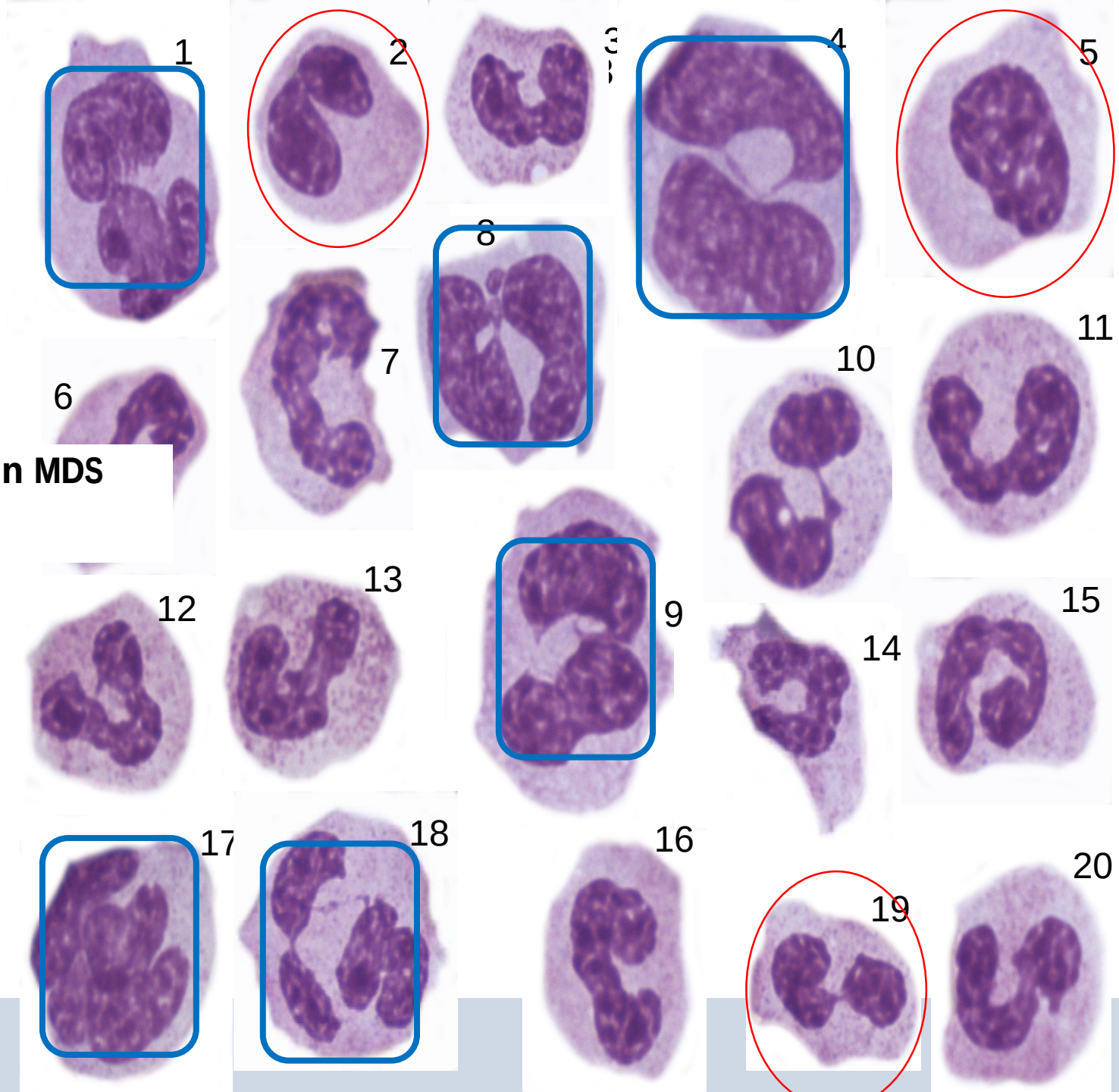


Stojkov K, Bonadies N., et al., 2020 (submitted)

Red: Pelger

Blue: dysmorphic

Dysgranulopoiesis in MDS



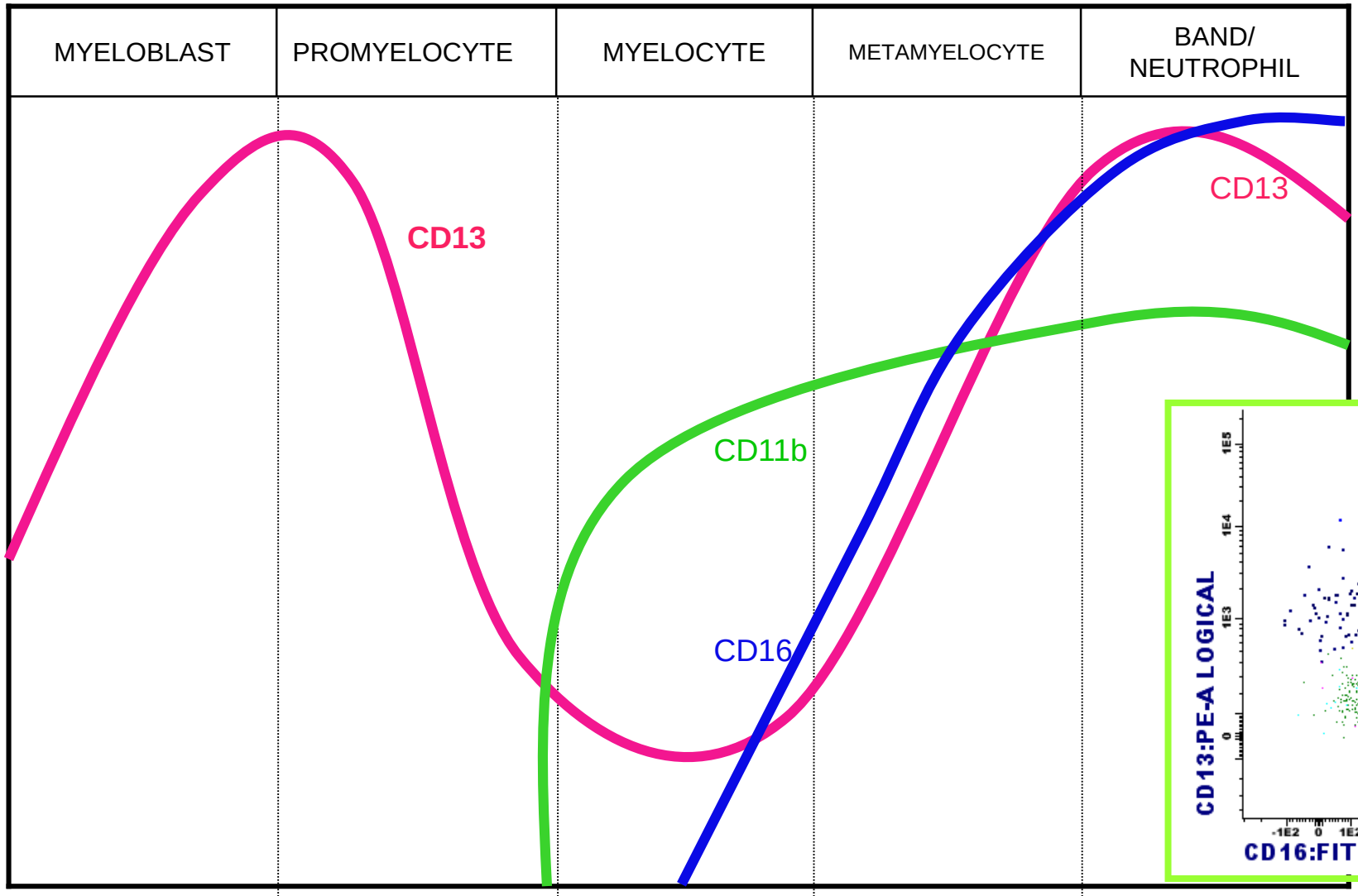
Kindly provided by Bennett J (Vancouver BC, 2019)

WHO2016 vs WHO2008
classifying MDS: comments on criteria/techniques

- Morphology:
  - no changes
  - dysplasia cut-off levels remains 10% in all lineages
  - **blast cell counts by cytology: *not* by FCM**
  - due to IPSS-R push towards counts of <2% vs 2-5% (500 cells)
- Cytogenetics:
  - no changes
- **Flow cytometry:**
  - in suspected MDS if performed according to recommended panels
  - as part of an integrated report

Arber DA and Hasserjian RP. Hematology 2015;294-298
Porwit A, et al., Leukemia 2014:28:1793-98
Arber DA, et al., Blood 2016;127:2391-2405

Antigen expression during neutrophil differentiation: *the concept*



Adapted from: A Orfao, ELNet Flow MDS 2008-2018, Amsterdam

Van de Loosdrecht AA, et al., Haematologica 2009; 94:1124-34
Westers TM, et al., Leukemia 2012;36:422-30; Porwit A, et al., Leukemia 2014:28:1793-98

Statements in: **WHO-2016 guidelines on FC in MDS**

- **Percentages myeloid progenitor cells** are informative
  but cannot replace differential blast counts on smears
  (fibrosis, hemodilution)

- **Abnormal phenotypes of CD34^{+}** may be additional evidence of dysplasia

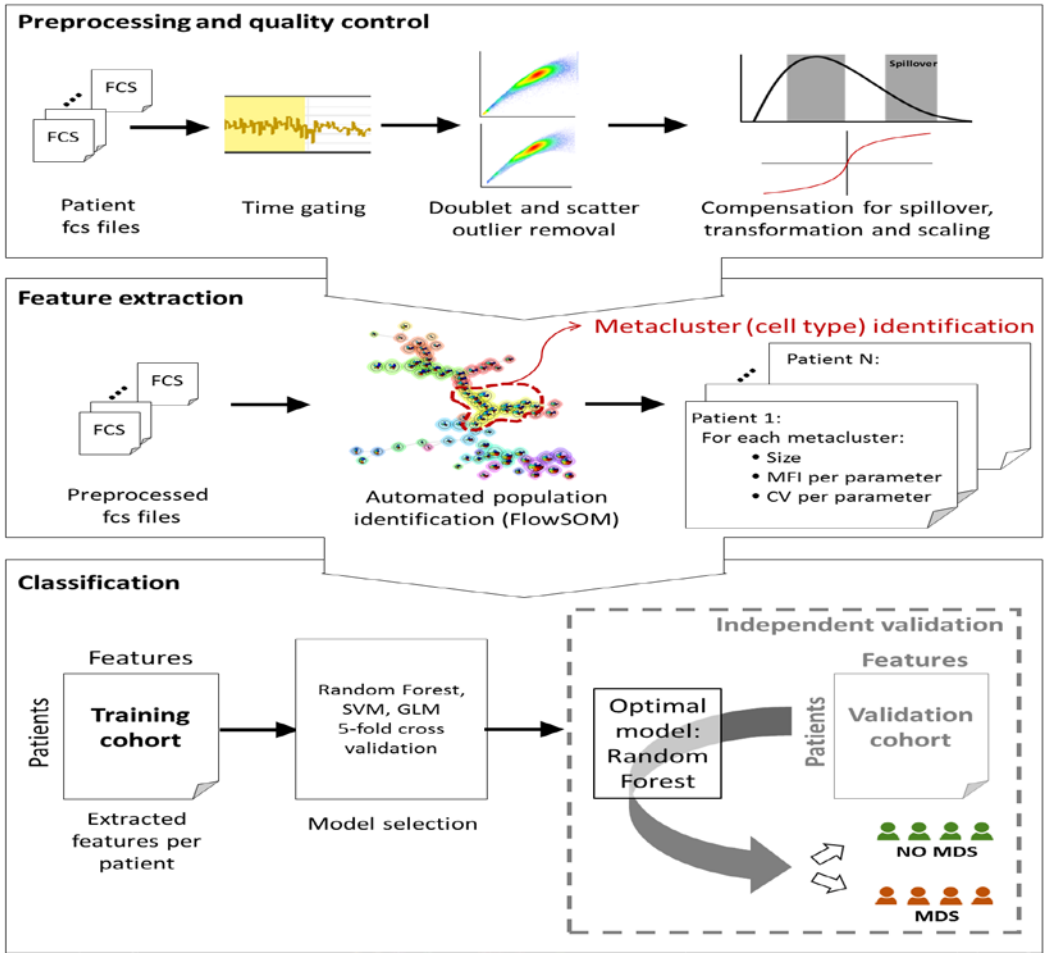
- **Aberrant differentiation patterns** (myeloid and erythroid) can indicate dysplasia

- Aberrant findings in **at least three tested features** (not specified) and at least two cell compartments are highly associated with MDS or MDS/MPN

- Yet, **FC is not diagnostic** in the *absence* of *conclusive morphological and/or cytogenetic criteria*,
  follow-up with repeated BM studies is recommended

Arber D, et al., Blood 2016, 127(20); 2391-2405

Computational Analysis/Artificial Intelligence in MDS diagnostics



	Single-tube workflow	
	Sensitivity	**Specificity**
AI analysis	97%	95%
iFS	80%	86%

Time needed for analysis: 60 to 90 minutes → **30 seconds**
Amount of bone-marrow and materials needed → Seven fold decrease **(from 6 to 1 tube)**

Duetz C, et al. Pathobiol 2019;86:14-23
Duetz C, et al. 2020 (submitted)
Duetz C, et al. Curr Opin Oncol. 2019 Dec 23. [Epub ahead of print]

WHO2016: Classifying Myelodysplastic Syndromes

- MDS with multilineage dysplasia (MDS-MLD)

- MDS with single lineage dyplasia and RS **(MDS-RS-SLD)**
- MDS with multilineage dysplasia and RS **(MDS-RS-MLD)**

- MDS with excess blasts-1 (MDS-EB1)
- MDS with excess blasts-2 (MDS-EB2)
- MDS-U

- **MDS (isolated) del(5q)**
- **Familial myeloid neoplasms with germ line mutations**

Arber DA and Hasserjian RP. Hematology 2015;294-298
Arber DA et al., Blood 2016;127:2391-2405

WHO2016: Classifying Myelodysplastic Syndromes *comments*

Additional new concepts:

- **Add:** ***SF3B1*** mutation and **RS (5-15%)** (MDS-RS-SLD / MDS-RS-MLD)
- **Add:** ***MDS del(5q)***: isolated or with one add. chrom abnormality
  - excl. monosomy 7
- **Delete:** blast cell count corrected for % of erythroid nucleated cells
- **Add:** Familial myeloid neoplasms with germ line mutations (TERT, RUNX1, GATA2)

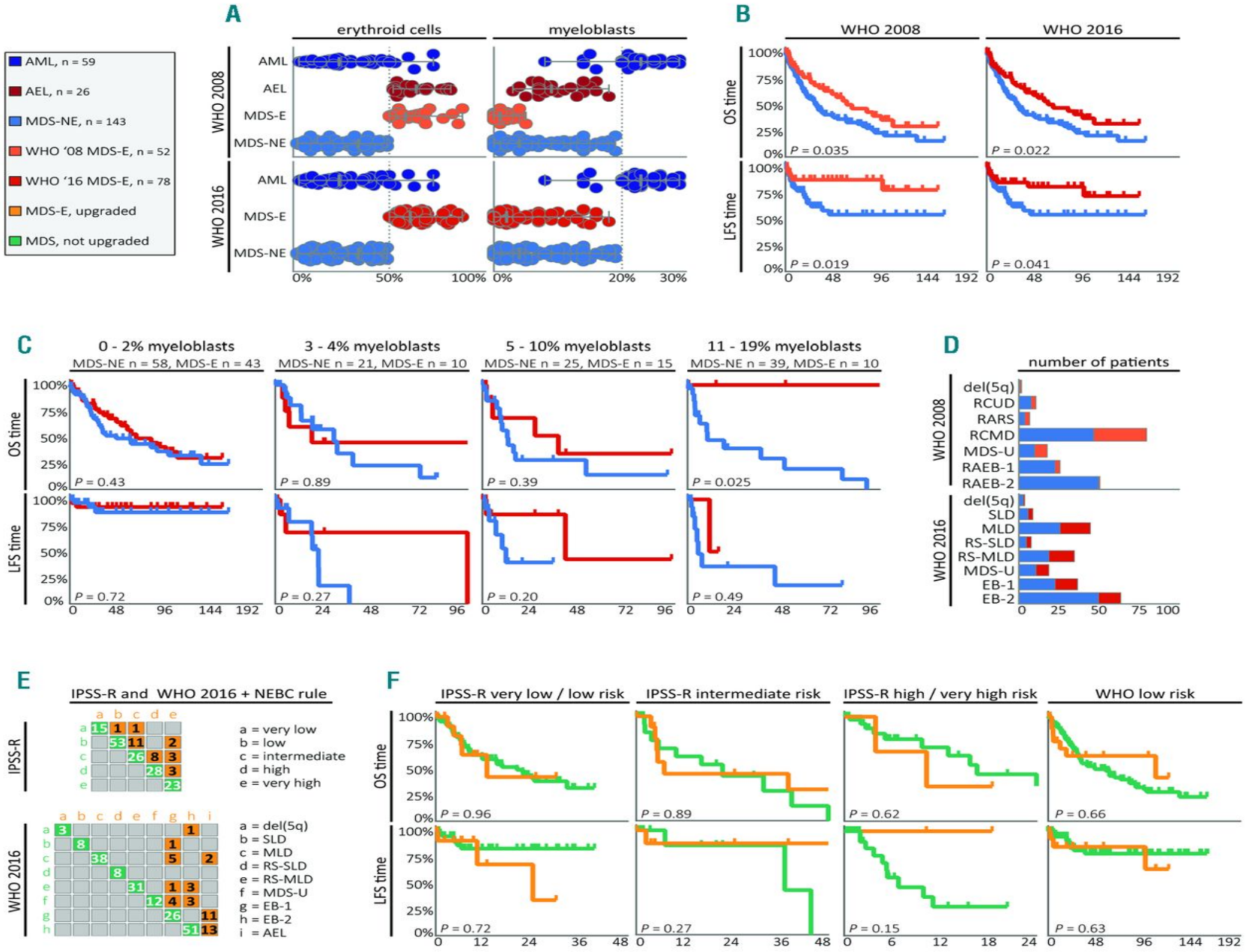
Arber DA and Hasserjian RP. Hematology 2015;294-298; educational session
Van Spronsen MF, et al. Haematologica 2019 Dec;104(12):e547-e550

SF3B1-mutant myelodysplastic syndrome as a distinct disease subtype

Table 4. Proposed diagnostic criteria for the MDS with mutated *SF3B1*.*

Cytopenia (anemia) defined by standard hematologic values
Somatic *SF3B1* mutation
Isolated erythroid or multilineage dysplasia
Any ring sideroblasts percentage
Bone marrow blasts <5% and peripheral blood blasts<1%
Any cytogenetic abnormality other than del(5q); monosomy 7; inv(3) or abn. 3q26,* complex (≥3)
Any additional somatically mutated gene other than *RUNX1*

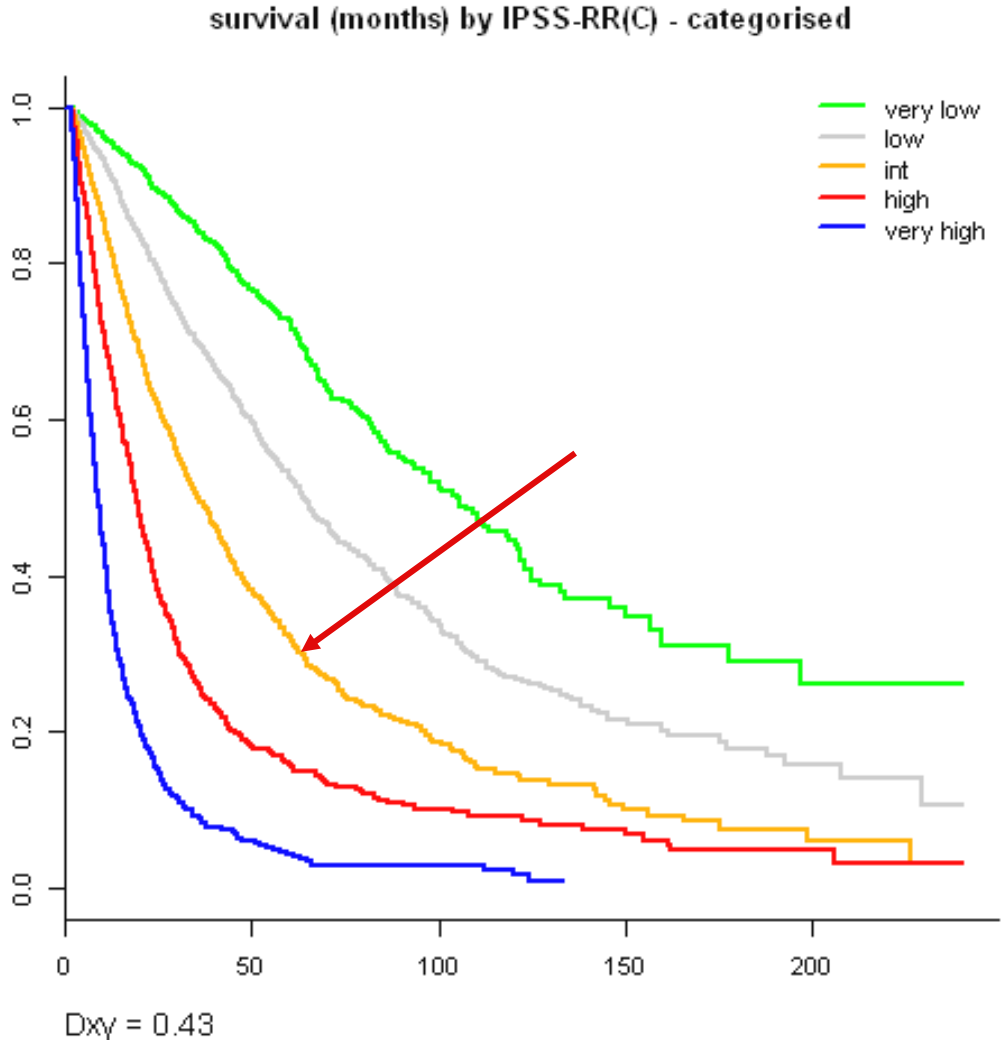
*Rearrangements of 3q26 resulting in aberrant gene fusions and over-expression of *EVI1*.

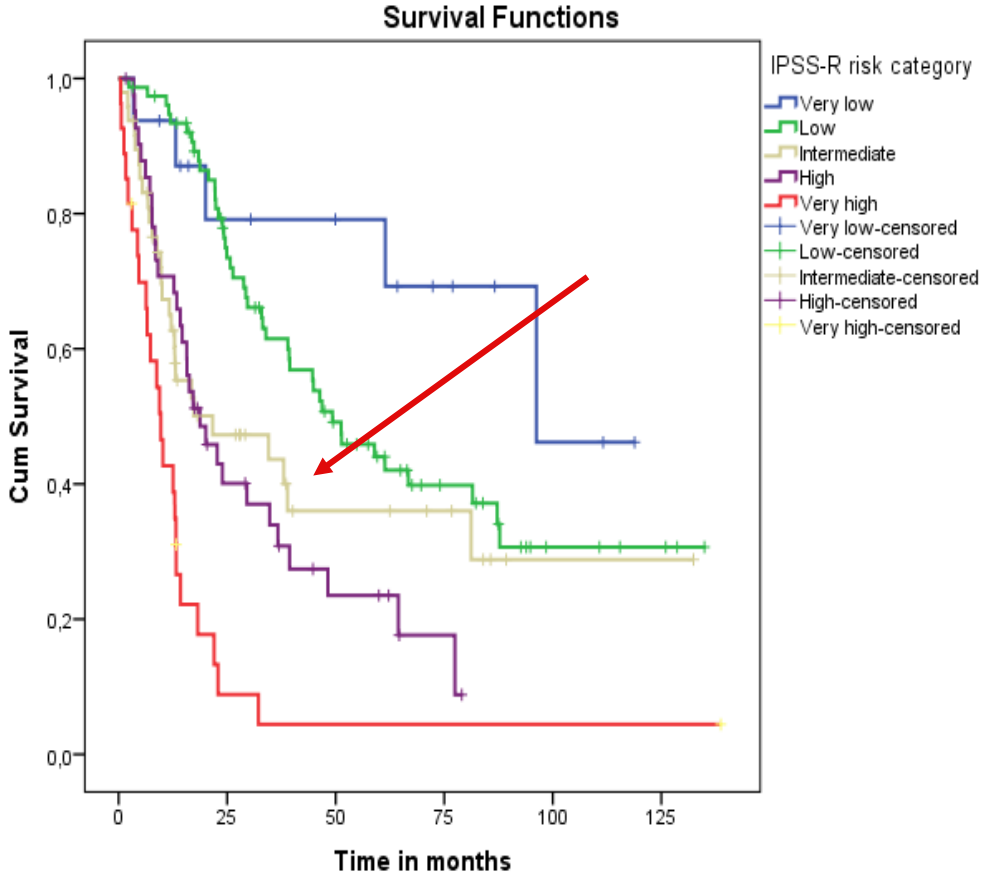


The non-erythroid myeloblast count rule in MDS

Van Spronsen MF, et al., Haematologica 2019 Dec;104(12):547-550

Revised International Prognostic Scoring System (IPSS-Revised) for MDS: *clinical heterogeneity*





Greenberg P, et al., Blood 2012;120:2454-65; Van Spronsen MF, et al., Eur J Cancer 2014;50:3198-3205; Van Spronsen MF, et al., Eur J Cancer 2016;56:10-20

Is there a need for further refinements of prognostic models?

→ **Genetic mutations (role of NGS)?**

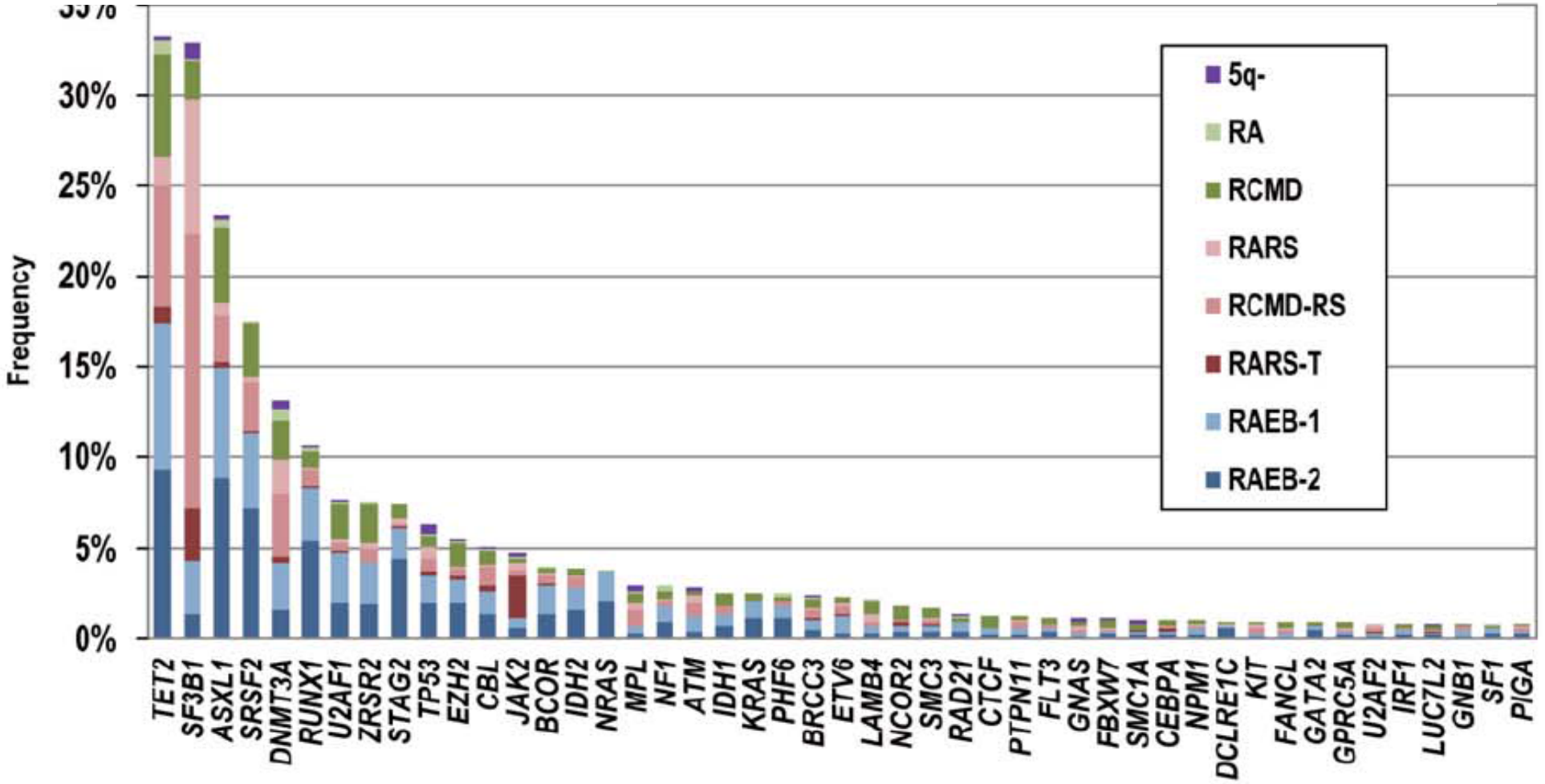
Flowcytometric aberrancies?

→ **Stemcell phenotypes (LAIP)?**

Immuneprofiling?

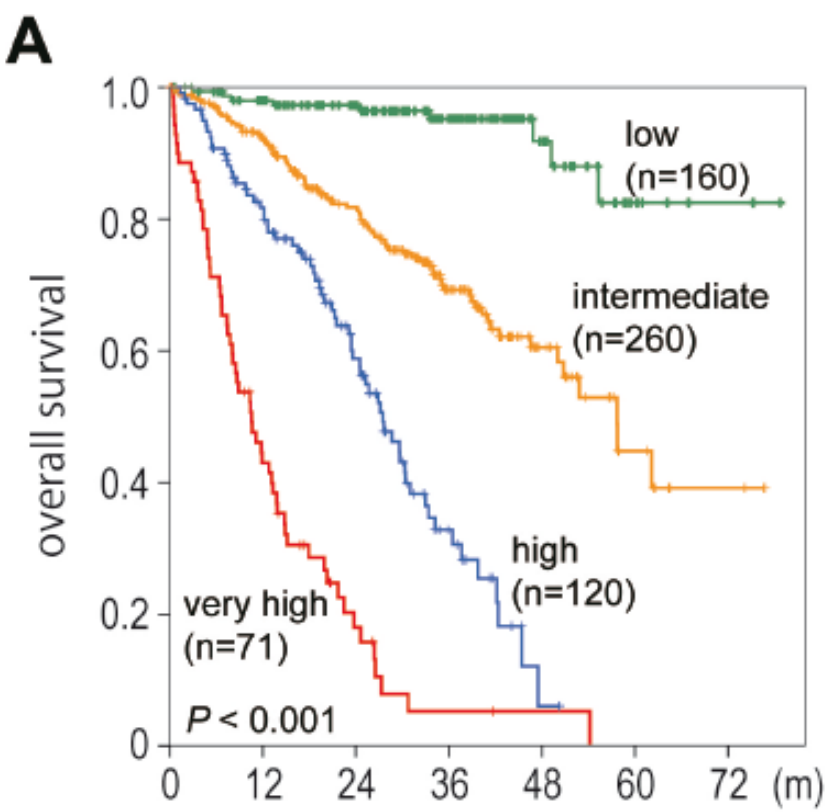
Geriatric Assessment?

The landscape of genetic aberrations in MDS: genomic architecture (targeted deep seq)

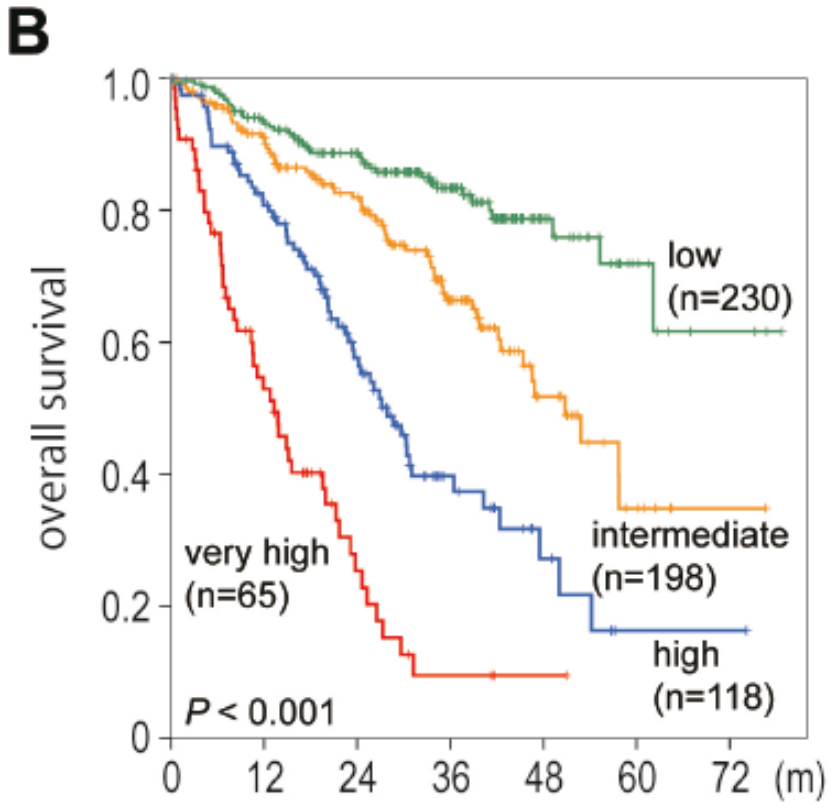


Haferlach T, et al., Leukemia 2014;28:241-7

Prognostic models beyond IPSS-R: genetics incorporated or as an isolated strong prognostic marker? [training cohorts]



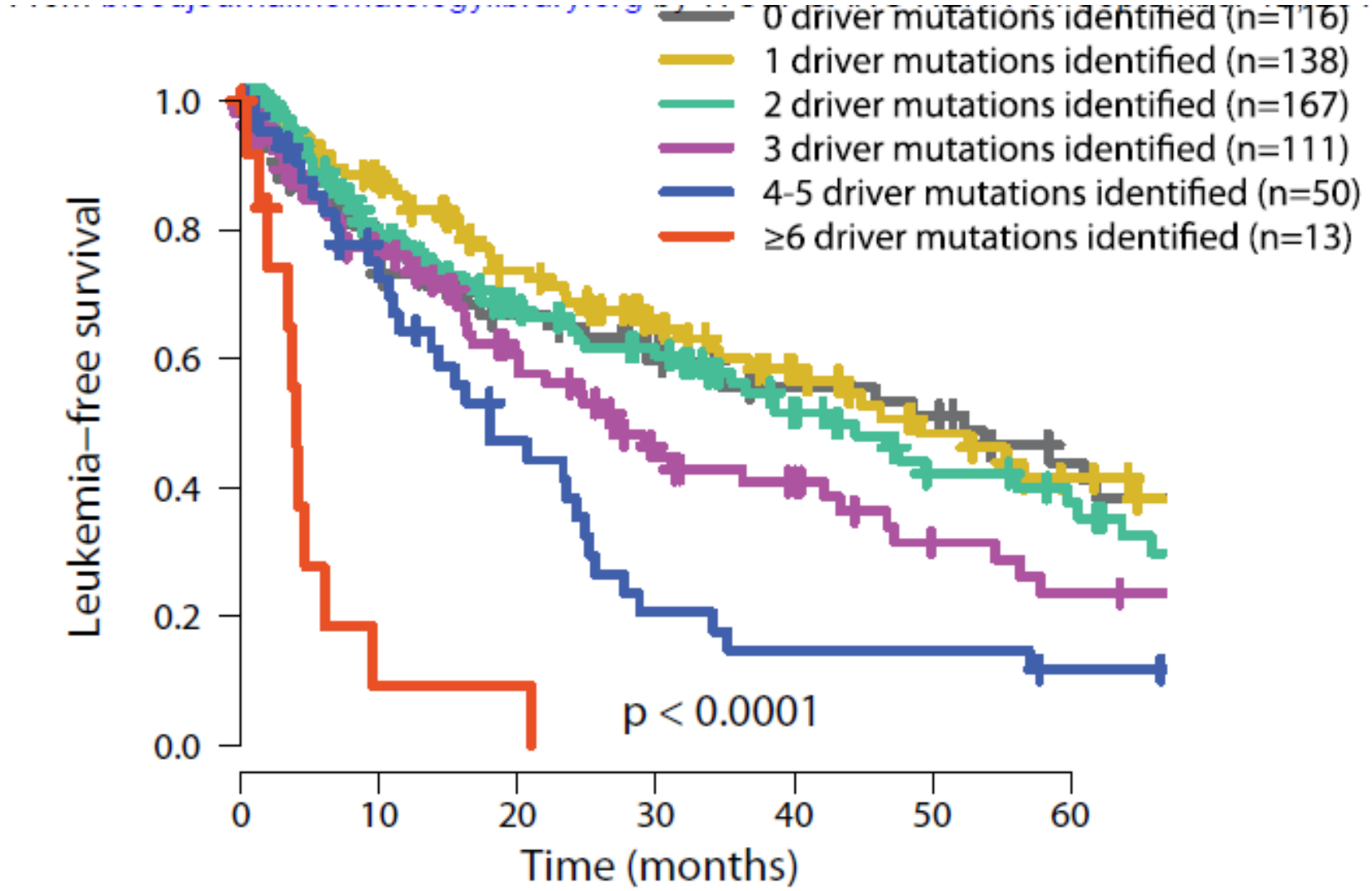
Model 1: 14 genes + age + WBC, Hb, Plt, % blasts, Cytogenetics according IPSS-R [integrated model]



Model 2: 14 genes *only*

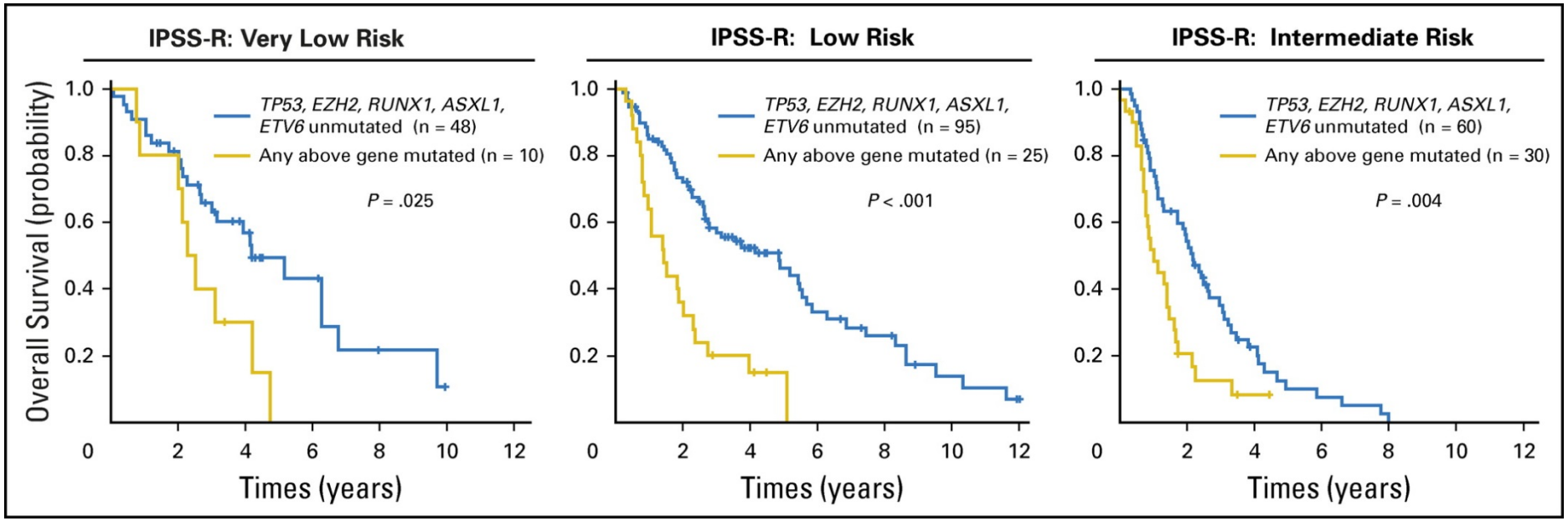
(13/14 from Model 1)

Relationship between number of oncogenic mutations and outcome
[independent of TP53 or SF3B1]



Papaemmanuil E, et al., Blood 2013:122:3616-27

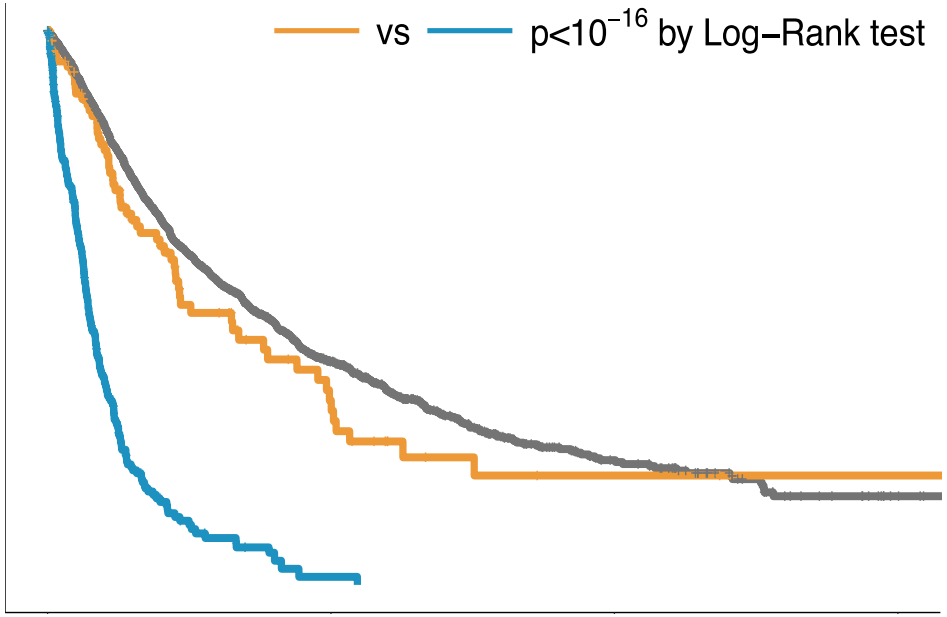
Somatic mutations in any of *TP53*, *EZH2*, *RUNX1*, *ASXL1*, or *ETV6* and prognosis in the IPSS-R lower risk categories



Bejar R, et al., NeJM 2011;364:2496
Kennedy JA, Ebert BL. J Clin Oncol 2017;35:968-74

TP53 allelic state shapes clinical outcomes

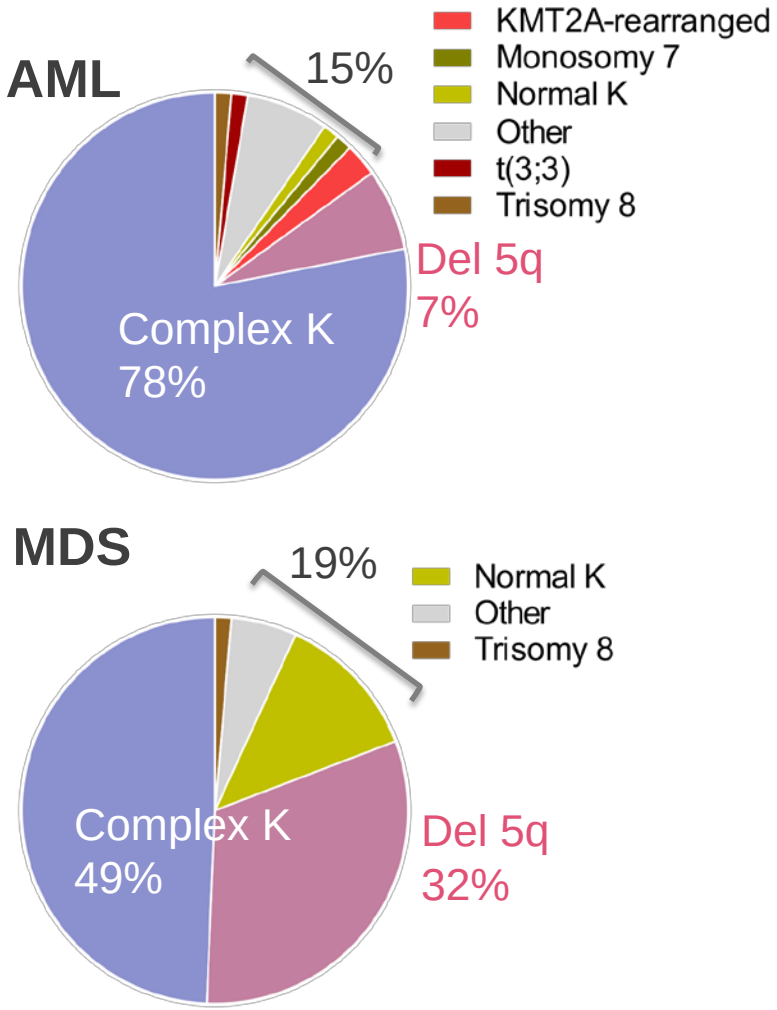
Overall survival

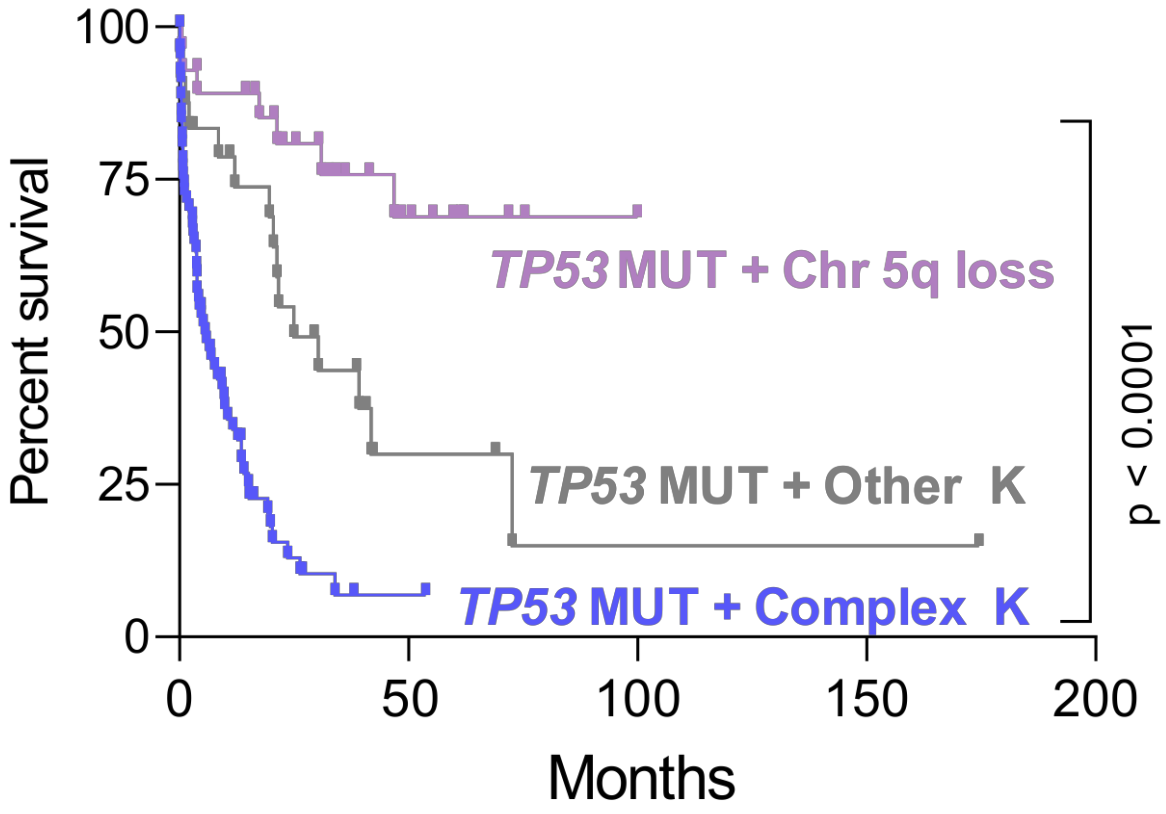


AML transformation

Bernard E, et al. on behalf of the IWG-PM ASH2019 (2020/submitted)

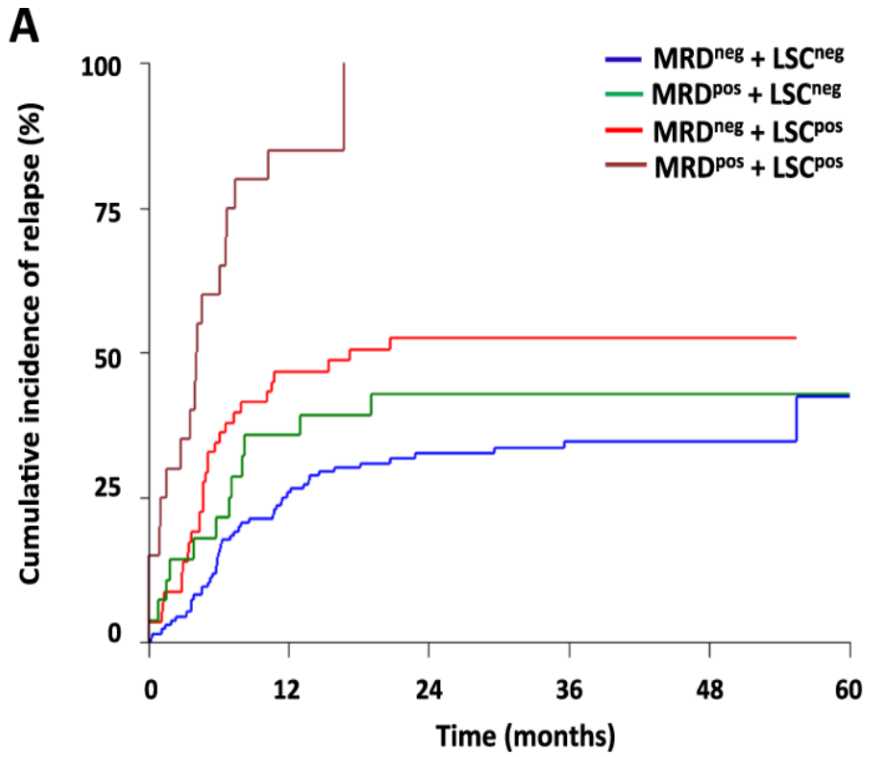
TP53 mutations were associated with complex karyotype in AML and MDS

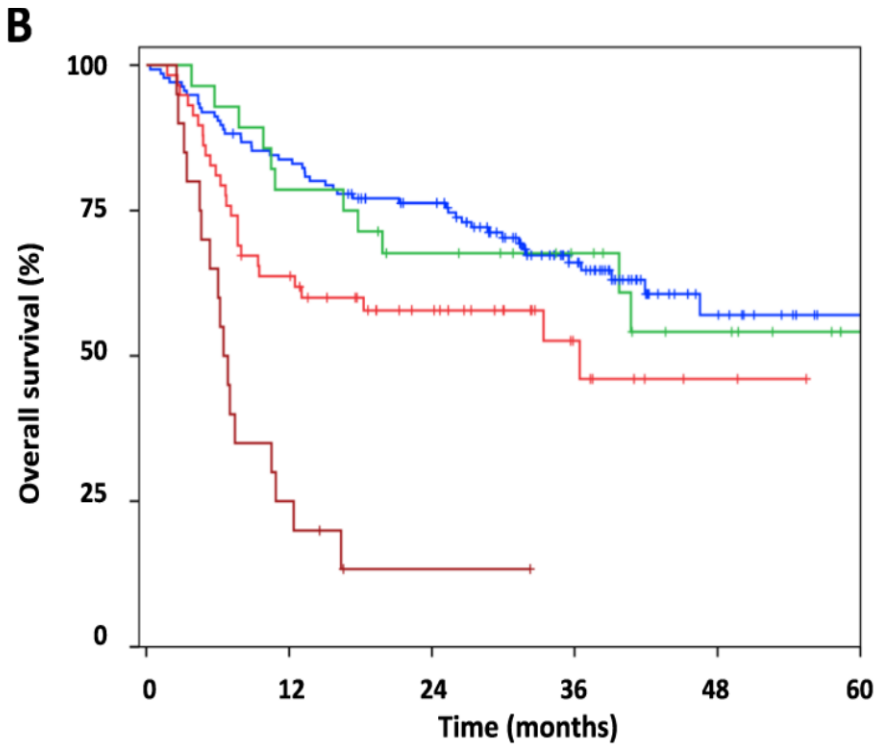




Haferlach T, et al., ASH2019 late breaking abstracts

Prognostic value of MRD/LSC status as defined at follow-up. Cumulative incidence of relapse (CIR) for the four different MRD/LSC patient groups

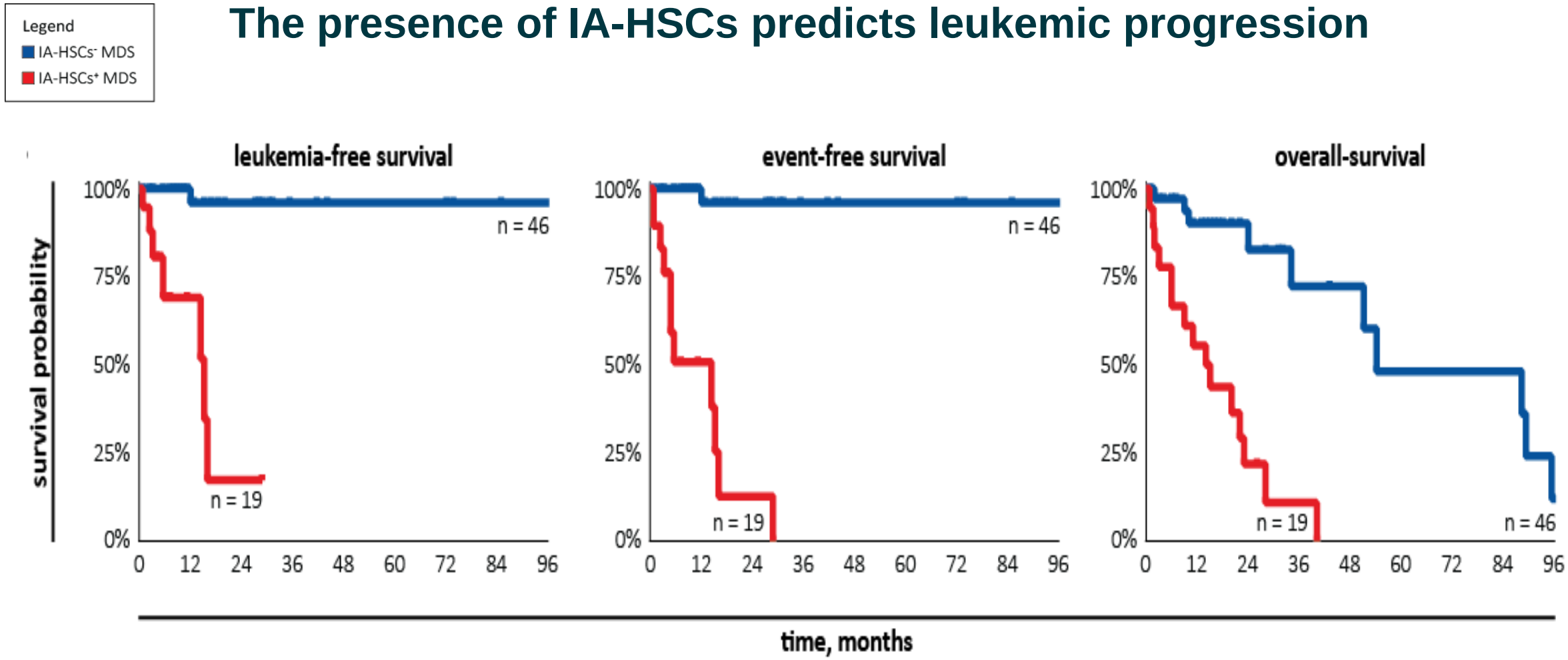




	At risk						3-yr CIR (%)	At risk						3-yr OS (%)	Median OS (months)
MRD^{neg} LSC^{neg}	136	96	77	46	15	5	35 (SE 4)	136	113	95	52	16	6	66 (SE 4)	not reached
MRD^{pos} LSC^{neg}	28	17	13	9	6	1	43 (SE 9)	28	22	17	12	6	1	68 (SE 9)	not reached
MRD^{neg} LSC^{pos}	58	28	20	7	2	0	53 (SE 7)	58	36	22	8	2	0	53 (SE 8)	36.4 (95% CI -)
MRD^{pos} LSC^{pos}	20	3	0	0	0	0	100 (-)	20	5	1	0	0	0	0 (-)	6.5 (95% CI 5.1-7.9)

Zeijlemaker W et al., Leukemia 2019:33:1102-1112

The presence of IA-HSCs predicts leukemic progression



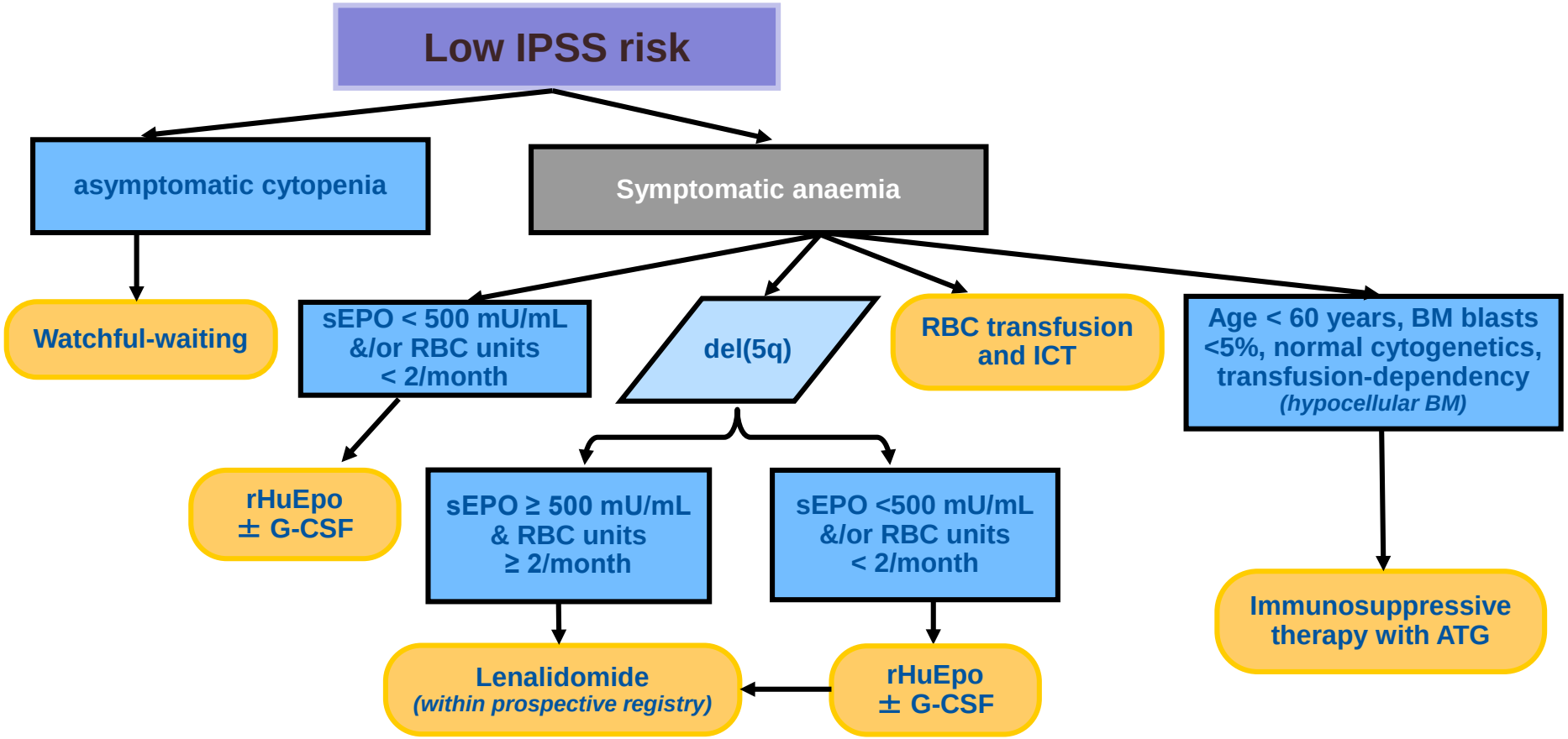
Van Spronsen MF, et al. (2020, submitted)

Why integrated diagnostics including conventional cytogenetics, flow cytometry and NGS?

- Diagnostics (identifying disease entities)
  - SF3B1
  - Del(5q)
  - FCM: MDS vs ICUS (normal cytogenetics/cytology inappropriate)
- Prognostics
  - Number and type of mutations
  - Specific mutations: TP53
  - → IPSS-R-molecular ASH2020 expected
  - FCM: conventional and leukemic stemcell profiling
- Therapeutic considerations?

Therapeutic options for lower IPSS risk MDS: ELN/Dutch guidelines (2013 → update 2020)

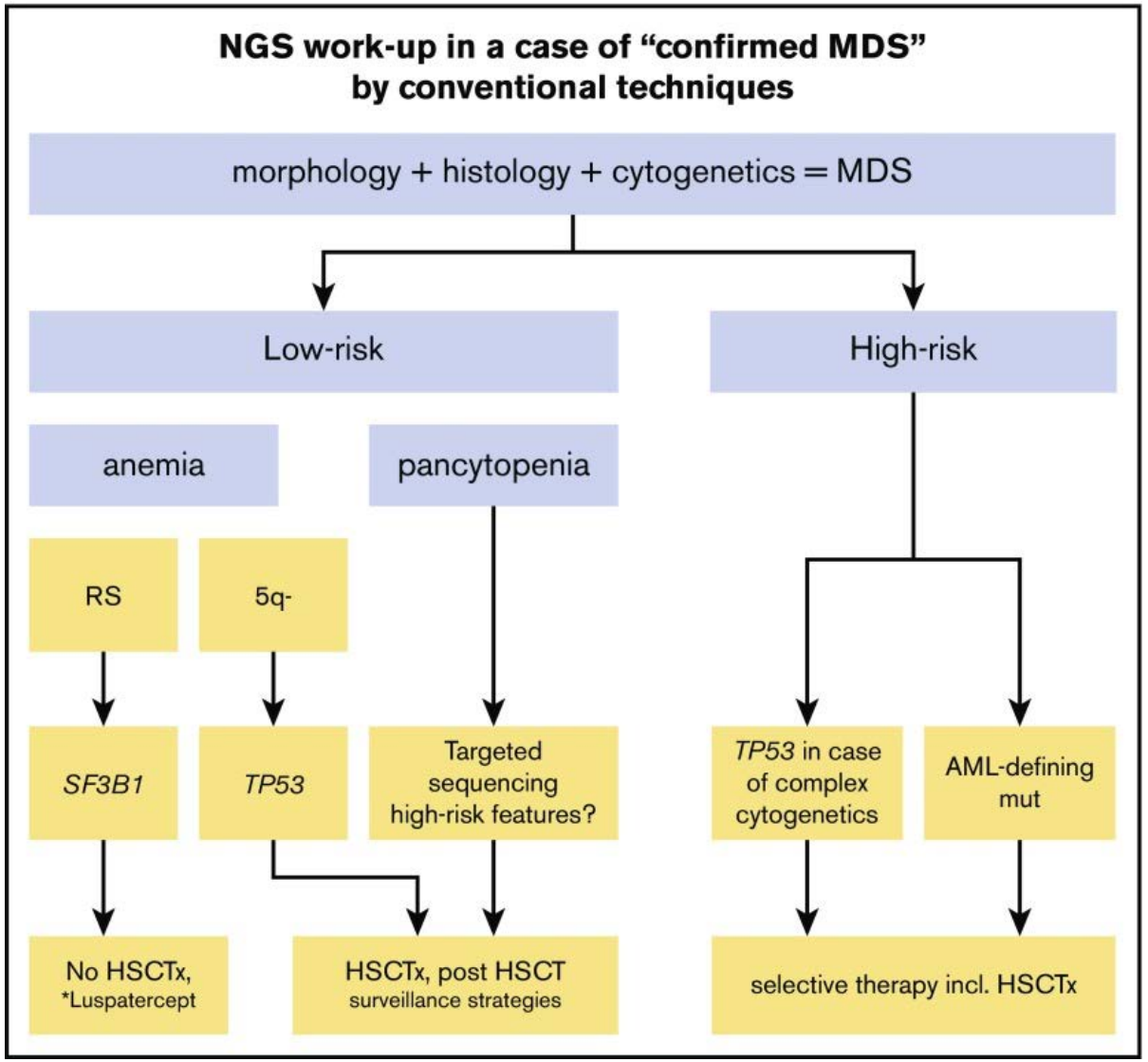
VU medisch centrum



VU Hematologie

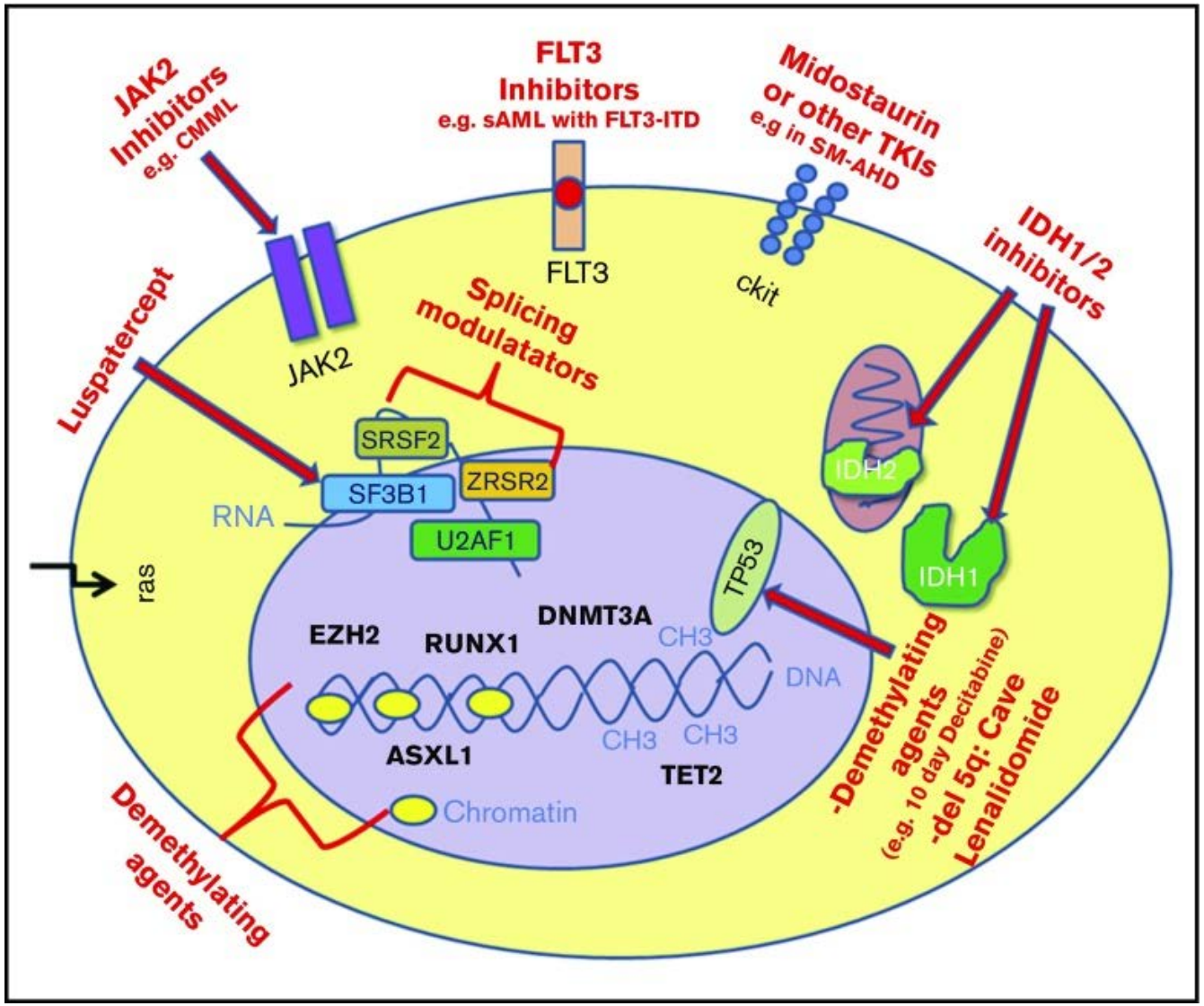
Malcovati L., et al. Blood 2013:122;2943-64; Loosdrecht AA van de, et al., Ned Tijdsch Hematol 2013;10:4-13; Loosdrecht AA van de et al., Ned Tijdsch Hematol 2013;10:43-53

Do next-generation sequencing results drive diagnostic and therapeutic decisions in MDS?



Thol F, Platzbecker U. Blood Adv 2019;3:3449-3453
Fenaux P, et al., New Engl J Med 2020;Jan9 [epub ahead of print]

Do next-generation sequencing results drive diagnostic and therapeutic decisions in MDS?



Thol F, Platzbecker U. Blood Adv 2019;3:3449-3453

Conclusions: DHC 2020 and MDS

- Diagnostics
- Prognostics

- Therapeutic considerations:

  - MDS with SF3B1: luspatercept?
  - MDS with del(5q): lenalidomide
  - Non-del(5q): lenalidomide? (HOVON89)

  - Annotated molecular targeting (IDH1/2i, FLT3-ITDi)
  - Adverse risk mutations: → alloTx
  - Leukemic stemcell profiles: → alloTx

  - non-somatic mutations panel (GATA2/TERT) → genetic counseling and alloTx

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