Clonal hematopoiesis, isolated cytopenias , and differences with MDS

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Roma, Sept 2016

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MDS or not MDS ?

(A Jacobs)

Mankind is divided into 3 categories:

- MDS
- Not quite MDS
- Not yet MDS

MDS or not MDS ?

- MDS
- ICUS: Idiopathic Cytopenias of Undetermined Significance
- IDUS: Idiopathic Dysplasia of Undetermined significance
- CHIP: Clonal Hematopoiesis of Indeterminate Potential

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Consensus report

Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference

Peter Valent[a,*], Hans-Peter Horny[b], John M. Bennett[c], Christa Fonatsch[d], Ulrich Germing[e], Peter Greenberg[f], Torsten Haferlach[g], Detlef Haase[h], Hans-Jochen Kolb[i], Otto Krieger[j], Michael Loken[k], Arjan van de Loosdrecht[l], Kiyoyuki Ogata[m], Alberto Orfao[n], Michael Pfeilstöcker[o], Björn Rüter[p], Wolfgang R. Sperr[a], Reinhard Stauder[q], Denise A. Wells[k]

Table 1
Minimal diagnostic criteria in MDS[a]

(A) Prerequisite criteria
Constant cytopenia in one or more of the following cell lineages: erythroid (hemoglobin <11 g dL^{-1}); neutrophilic (ANC < 1500 μL^{-1}) or megakaryocytic (platelets <100,000 μL^{-1})
Exclusion of all other hematopoietic or non-hematopoietic disorders as primary reason for cytopenia/dysplasia[b]
(B) MDS-related (decisive) criteria
Dysplasia in at least 10% of all cells in one of the following lineages in the bone marrow smear: erythroid; neutrophilic; or megakaryocytic or >15% ringed sideroblasts (iron stain)
5–19% Blast cells in bone marrow smears
Typical chromosomal abnormality (by conventional karyotyping or FISH)[c]
(C) Co-criteria[d] (for patients fulfilling 'A' but not 'B', and otherwise show typical clinical features, e.g. macrocytic transfusion-dependent anemia)
Abnormal phenotype of bone marrow cells clearly indicative of a monoclonal population of erythroid or/and myeloid cells, determined by flow cytometry
Clear molecular signs of a monoclonal cell population in HUMARA assay, gene chip profiling, or point mutation analysis (e.g. *RAS* mutations)
Markedly and persistently reduced colony-formation (±cluster formation) of bone marrow or/and circulating progenitor cells (CFU-assay)

WHO classification of MDS

1)blood cytopenias and exclusion of reactive or other nonhematopoietic causes of those cytopenias

2) one of the following diagnostic features
- excess blasts(>5%) with a myeloid phenotype

-10% dysplastic cells in 1 of the 3 myeloid lineages (erythroid, granulocytic, megakaryocytic)
-15% ring sideroblasts
- evidence of clonality as manifested by an abnormal MDS-associated karyotype.

MDS defined by

Unexplained Cytopenias +/-

- Marrow dysplasia
- Clonal cytogenetic abnormalities
- Somatic mutations
- (immunophenotypic abnormalities)

Are cytopenias with clonal chromosomal abnormalities without dysplasia MDS ?

- Cytopenias without dysplasia + « typical » cytogenetic abnormality (-7, del 5q, etc…) = MDS

- 3 rearrangements considered not be sufficient for diagnosis of MDS ?

  - Loss of Y chromosome

  - Trisomy 8

  - Del 20q

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Leukemia Research 36 (2012) 1–5

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Invited review

Idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of uncertain significance (IDUS), and their distinction from low risk MDS

Peter Valent[a,b,*], Barbara J. Bain[c], John M. Bennett[d], Friedrich Wimazal[a,e], Wolfgang R. Sperr[a,b], Ghulam Mufti[f], Hans-Peter Horny[g]

Table 2
Idiopathic cytopenia of uncertain (undetermined) significance (ICUS)

(A) Definition
- Cytopenia in one or more of the following cell lineages (for ≥ 6 months): erythroid (Hb < 11 g dL^{-1}); neutrophilic (<1500 μL^{-1}); platelet (<100,000 μL^{-1})
- MDS excluded (see 'B' and 'C')
- All other causes of cytopenia also excluded (see 'B' and 'C')

(B) Initial investigations *required* to establish the diagnosis of ICUS
- Detailed case history (toxins, drugs, mutagenic events, etc.)
- Thorough clinical investigations including X-ray and sonography of spleen
- Differential blood count (microscopic) and complete serum chemistry
- Bone marrow histology and immunohistochemistry
- Bone marrow smear including an iron stain
- Flow cytometry of bone marrow and peripheral blood cells
- Chromosome analysis including FISH[a]
- Molecular analysis where appropriate (e.g. T cell receptor rearrangement—neutropenia)
- Exclusion of viral infections (HCV, HIV, CMV, EBV, others)

(C) Recommended investigations in the follow-up
- Blood count and differential count as well as serum chemistry in 1–6 months intervals
- In those in whom suspicion for MDS becomes evident: bone marrow examination

[a] Proposed minimum standard panel: 5q31, CEP7, 7q31, CEP8, 20q, CEPY, p53.

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- exclude dysplasia (10% cut-off) in any of the 3 major lineages
- cytopenia must be substantial and must be

recorded over a time period of at least 6 months

Table 1
Proposed diagnostic cut-off levels for anemia to count as minimal diagnostic criteria for MDS and ICUS: comparison to normal values.

Lower limit: source of criteria (proposed by)	Proposed cut off levels (lower limit)		
	Hb (g/L)	ANC ($\times 10^9$/L)	PLT ($\times 10^9$/L)
Cut off levels defining the normal blood count (WHO definition)	120 (f) 130 (m)	1.8[a]	150
Cut off levels defining MDS (or ICUS); by WHO criteria[b]	100[b]	1.8[b]	100[b]
Cut off levels defining MDS and ICUS proposed by the IWGM-MDS group[c]	100	1.8	100
Cut off levels defining MDS or ICUS; by the 2007 consensus group[d]	110	1.5	100

Unexplained cytopenias (ICUS: idiopathic cytopenias of undetermined significance)

Table 3
Proposed classification of idiopathic cytopenia of uncertain significance (ICUS).

Proposed term	Suggested abbreviation	Definition (ICUS criteria already met[a])
Idiopathic anemia of uncertain significance	ICUS-A	Hb <110 g/L PLT $\geq 100 \times 10^9$/L ANC $\geq 1.0 \times 10^9$/L
Idiopathic neutropenia of uncertain significance	ICUS-N	Hb $\geq$110 g/L PLT $\geq 100 \times 10^9$/L ANC $< 1.0 \times 10^9$/L
Idiopathic thrombocytopenia of uncertain significance	ICUS-T	Hb $\geq$110 g/L PLT $< 100 \times 10^9$/L ANC $\geq 1.0 \times 10^9$/L
Idiopathic bi/pancytopenia of uncertain significance	ICUS-BI/PAN	Hb <110 g/L and/or[b] PLT $< 100 \times 10^9$/L and/or[b] ANC $< 1.0 \times 10^9$/L

[a] ICUS criteria have already been fulfilled: the patient has constant cytopenia for at least 6 months, MDS criteria are not met, and no other reason/underlying disease that could explain cytopenia has been found.
[b] Two or three cytopenias required.

Idiopathic dysplasia of uncertain significance—IDUS

- Dysplasia in >10% in one or more lineages
- No significant cytopenia
- chromosomal defects indicative of MDS may be detectable
- ring sideroblasts sometimes found (diagnosis of RARS is established as soon as diagnostic cytopenia occurs…)

- *… but dysplasia seen in viral infections (eg, HIV infection), alcohol abuse, exposure to cytotoxic agents (eg, azathioprine, methotrexate), or nutritional deficiencies (eg, copper, folate, cobalamin).*

Table 2
Key features discriminating between MDS, ICUS, and IDUS.

Features/findings	MDS	ICUS	IDUS
Peripheral blood:			
Diagnostic cytopenia[a]	+	+	−
Transfusion dependence	+/−	−/+	−
Pseudo-Pelger-Huët Cells	+/−	−	−/+
Circulating blast cells	−/+	−	−
BFU-E markedly reduced	+/−	−/+	−/+
Clonality by HUMARA	+	−/+	n.k.
Bone marrow:			
Ring sideroblasts ≥15%	+/−	−	+/−
Marked bone marrow dysplasia[b]	+	−	+
Blast cell increase ≥5%	+/−	−	−
Marked bone marrow fibrosis	−/+	−	−
MDS-related Karyotype	+/−	−	−/+
Flow cytometry abnormalities	+/−	n.k.	n.k.

MDS, myelodysplastic syndromes; ICUS, idiopathic cytopenia of undetermined significance; IDUS, idiopathic dysplasia of uncertain significance; BFU-E, burst forming unit erythroid progenitor cells; HUMARA, human androgen receptor X-chromosome inactivation assay; n.k., not known.

[a] Diagnostic cytopenia: neutrophils $<1.0 \times 10^9$/L or/and hemoglobin <110 g/L or/and platelets $<100 \times 10^9$/L.

[b] Erythroid dysplasia >10% or/and granulocyte dysplasia >10% or/and megakaryocyte dysplasia >10%. +, seen in all patients; +/−, seen in a majority of patients; −/+, seen in a minority of patients; −, not seen.

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MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance

Brian Kwok, Jeff M. Hall, John S. Witte, Yin Xu, Prashanti Reddy, Keming Lin, Rachel Flamholz, Bashar Dabbas, Aine Yung, Jenan Al-Hafidh, Emily Balmert, Christine Vaupel, Carlos El Hader, Matthew J. McGinniss, Shareef A. Nahas, Julie Kines and Rafael Bejar

- 144 patients with unexplained cytopenias. 17% MDS, 15% ICUS and some evidence of dysplasia, and 69% with ICUS and no dysplasia
- Somatic mutations : 71% of MDS , 62% ICUS and some dysplasia, 20% of ICUS patients and no dysplasia.
- 35% of ICUS patients carried a somatic mutation or chromosomal abnormality

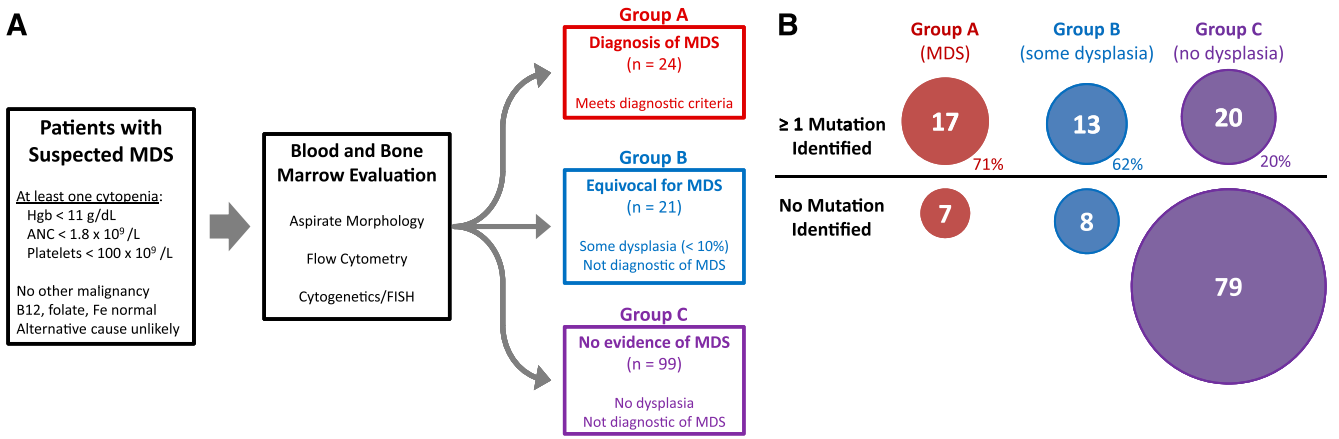

Figure 1. Prospective trial schema and diagnostic groups. (A) Schema showing how patients were screened and selected for entry. Patients were placed into 1 of 3 groups based on their bone marrow findings. (B) Proportions of patients with and without mutations in each diagnostic group are shown after DNA sequencing 22 genes associated with myeloid neoplasms.

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- spectrum of mutated genes similar between the 3 groups except SF3B1 rarely mutated in patients without dysplasia
- Variant allele fractions, mean age and blood counts. comparable between clonal ICUS and MDS
- Clonal ICUS (CCUS) is a more frequent diagnosis than MDS in cytopenic patients.

Clonal ICUS (CCUS)

Table 2. Proposed criteria for CCUS

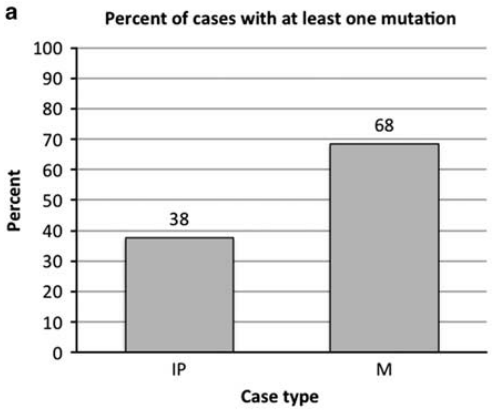
Peripheral blood findings	Bone marrow findings	Genetic findings
1 or more of the following:	None of the following:	1 or more of the following:
Hemoglobin, $<$11 g/dL	$\geq$10% dysplasia in the granulocytic, erythroid, or megakaryocytic lineage	An acquired chromosomal abnormality not diagnostic of a heme malignancy
ANC $<$1500/μL, 1.5 $\times$ 10^9/L	Myeloblasts comprise $\geq$5% of total cellularity	Presence of a somatic mutation with a VAF $\geq$2% in a heme malignancy–associated gene in the peripheral blood or bone marrow
Platelet count $<$100 000/μL, 100 $\times$ 10^9/L	An acquired chromosomal abnormality specific for MDS/AML	
Additional criteria: No other likely cause of cytopenias or evidence of another hematologic disorder.		

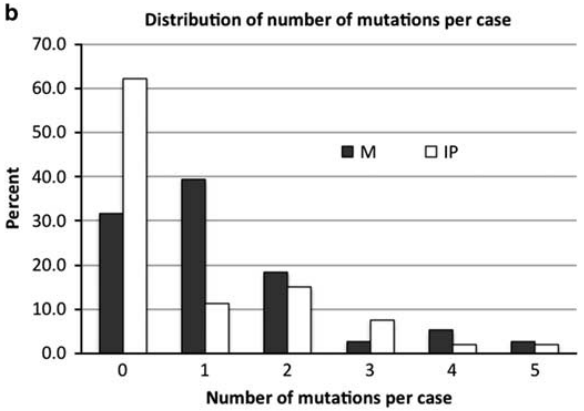
Modern Pathology (2016) 29, 996–1003

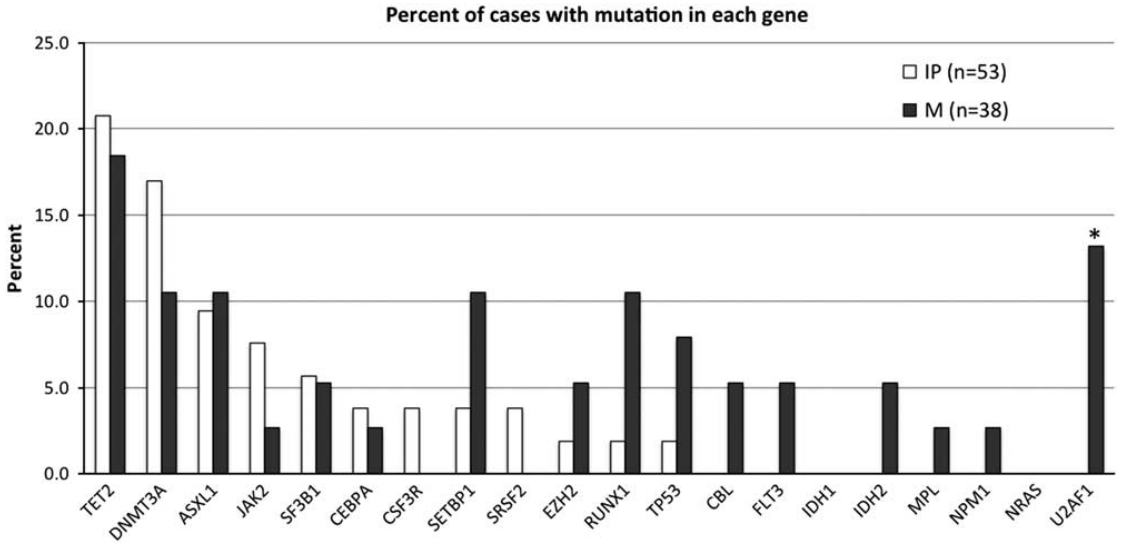
Significance of myelodysplastic syndrome-associated somatic variants in the evaluation of patients with pancytopenia and idiopathic cytopenias of undetermined significance

Sebastian Fernandez-Pol, Lisa Ma, Robert S Ohgami and Daniel A Arber

Idiopathic pancytopenia		
ICUS	28 (31%)	50 (25)
Aplastic anemia	13 (14%)	35 (15)
Liver disease	4 (4%)	59 (12)
Autoimmune disease	4 (4%)	27 (7)
Drug effect	4 (4%)	54 (12)
Non-neoplastic total	53 (58%)	46 (22)[a] Med = 49
Malignant		
MDS and MDS/MPN	21 (23%)	69 (30)
AML	17 (19%)	62 (25)
Malignant total	38 (42%)	66 (16)[a] Med = 70







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« Median and mean clinical follow-up for the idiopathic pancytopenia group available for 444 and 739 days, respectively. Over this time frame, none of the idiopathic pancytopenia patients was diagnosed with MDS or AML »

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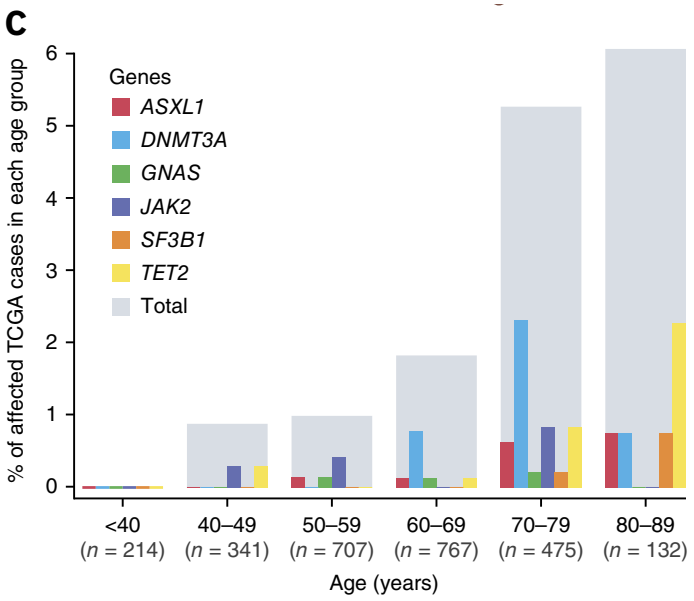
Age-related mutations associated with clonal hematopoietic expansion and malignancies

Mingchao Xie[1,2,7], Charles Lu[1,7], Jiayin Wang[1,2,7], Michael D McLellan[1], Kimberly J Johnson[3], Michael C Wendl[1,4,5], Joshua F McMichael[1], Heather K Schmidt[1], Venkata Yellapantula[1,2], Christopher A Miller[1], Bradley A Ozenberger[1,2], John S Welch[2,6], Daniel C Link[2,6], Matthew J Walter[2,6], Elaine R Mardis[1,2,4,6], John F Dipersio[2,6], Feng Chen[2,6], Richard K Wilson[1,2,4,6], Timothy J Ley[1,2,4,6] & Li Ding[1,2,4,6]

Nature Medecine, 2014

- N=2718
- blood cells of more than 2% of individuals (5–6% of people older than 70 years) show a somatic mutation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

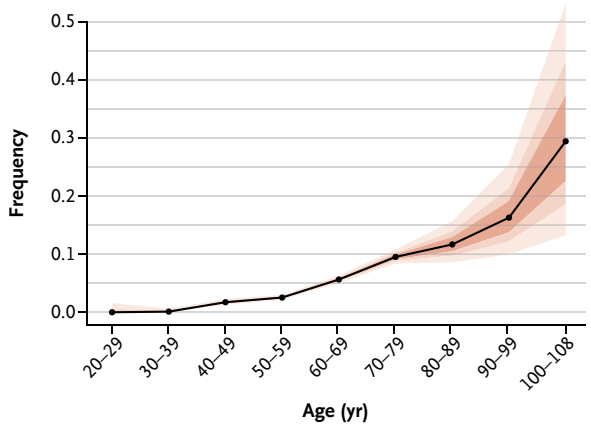
Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D., Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D., R. Coleman Lindsley, M.D., Ph.D., Craig H. Mermel, M.D., Ph.D., Noel Burtt, B.S., Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Moltchanov, Ph.D., Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D., Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Claes Ladenvall, Ph.D., Gad Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin F. Banahan, Ph.D., Stacey Gabriel, Ph.D., Sekar Kathiresan, M.D., Heather M. Stringham, Ph.D., Mark I. McCarthy, M.D.,* Michael Boehnke, Ph.D.,* Jaakko Tuomilehto, M.D., Ph.D., Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., Gil Atzmon, Ph.D., James G. Wilson, M.D., Donna Neuberg, Sc.D., David Altshuler, M.D., Ph.D.,* and Benjamin L. Ebert, M.D., Ph.D.†

17,182 individuals

Mutations, predominantly of DNMT3A, TET2, and *ASXL1 genes in normal subject*

- 70 to 79 years of age, 9.5%
- 80 to 89 years : 11.7%
- 90 to 108 years :18.4%

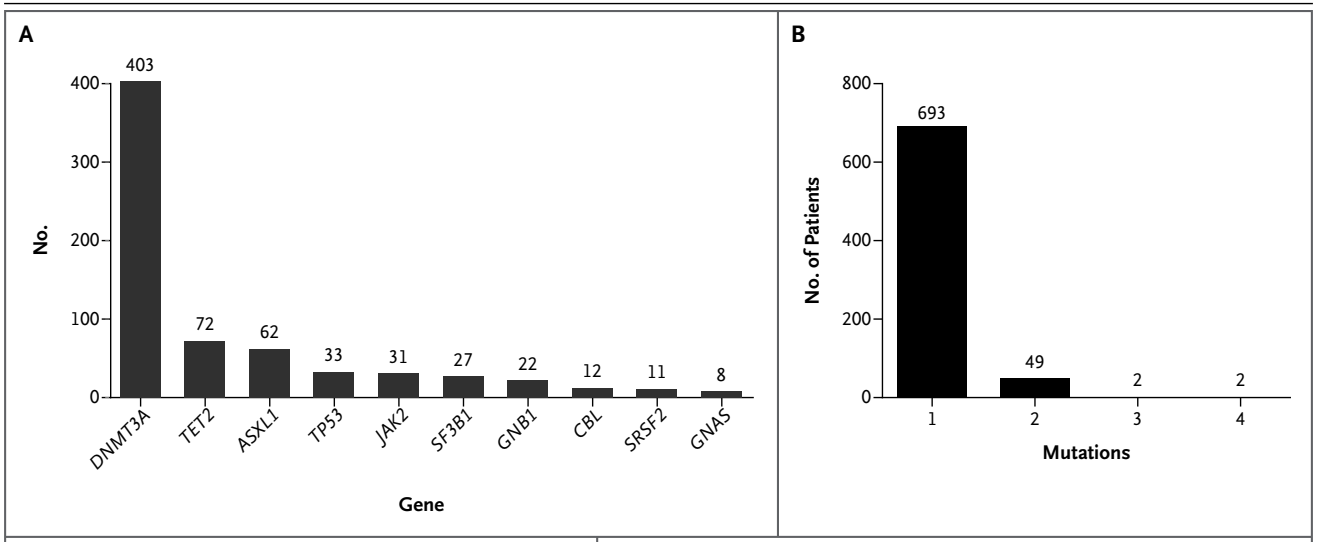
somatic mutation associated with increased risk of developing hematologic malignancy (HR 11), increased all-cause mortality (HR 1.4), and increased risk of incident coronary heart disease (HR 2.0) and ischemic stroke (HR 2.6).



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.

Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

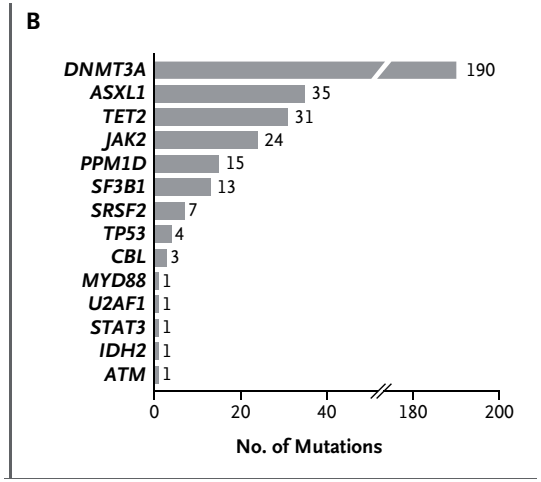


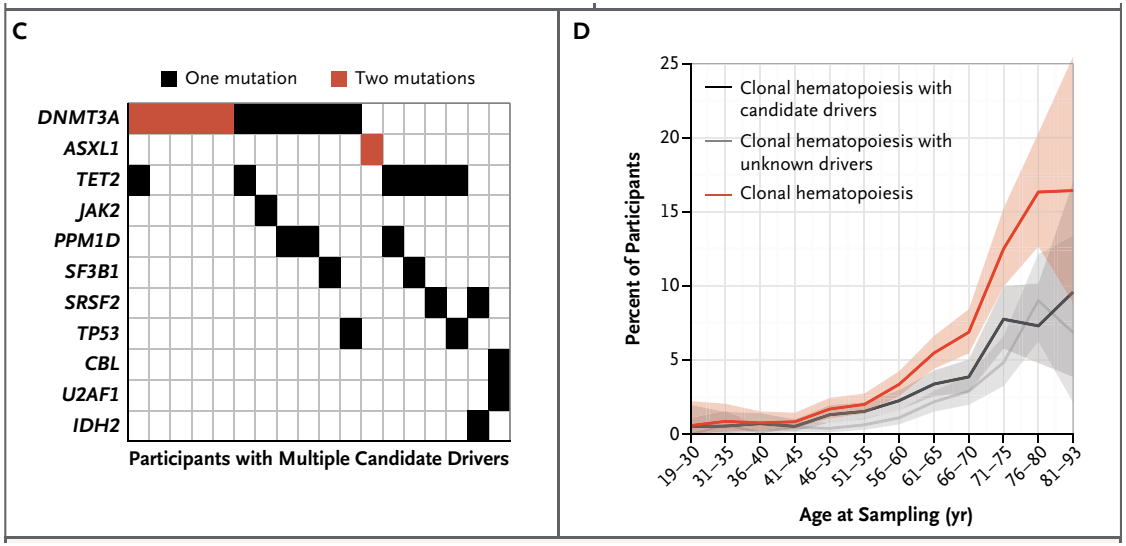
ORIGINAL ARTICLE

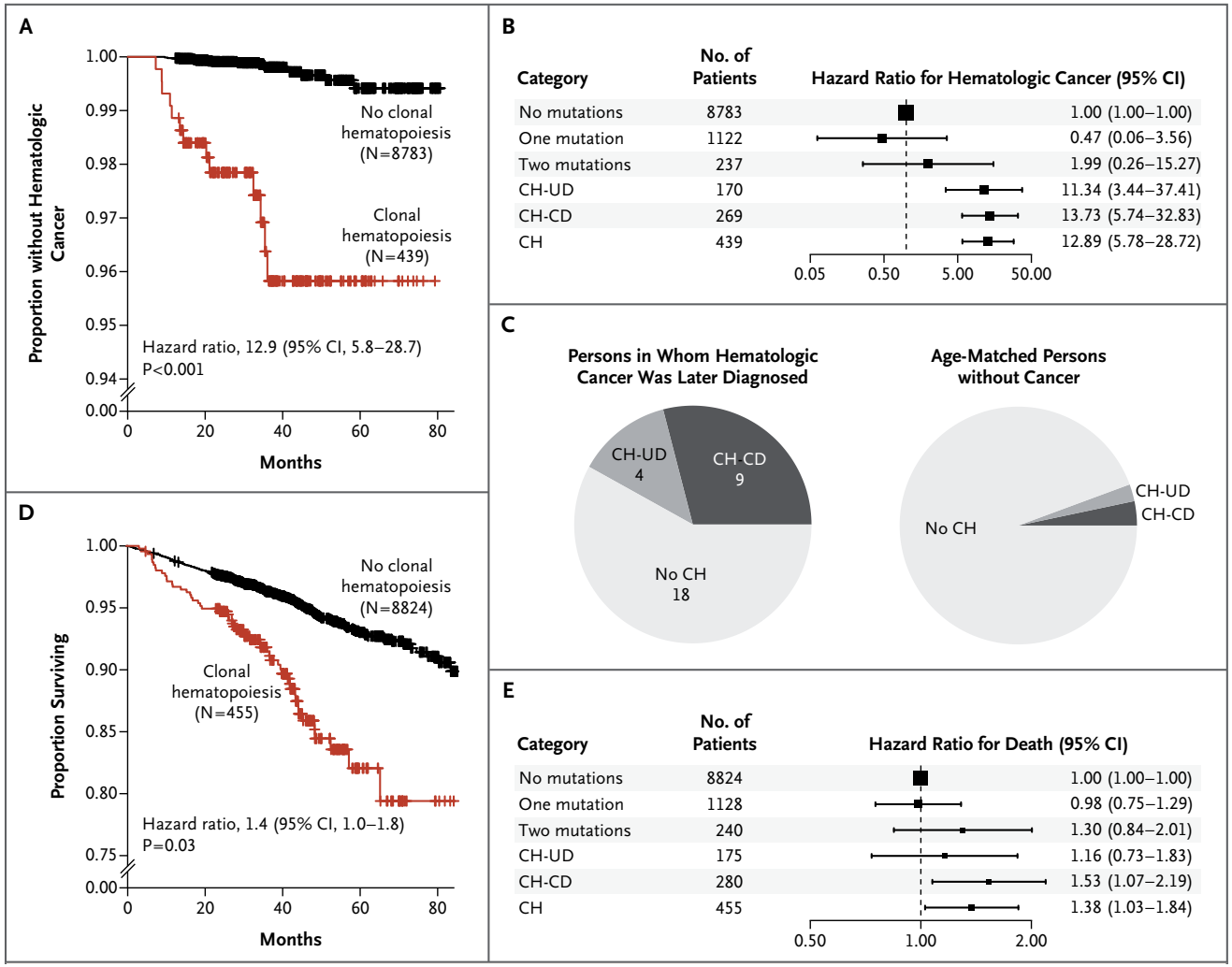
Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhoum, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svantesson, M.S., Mikael Landén, Ph.D., Martin Höglund, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.

- 12,380 persons
- 10% persons > 65 years of age but in only 1% < 50 years .
- most frequently involved somatic mutations in three genes (*DNMT3A*, *ASXL1*, and *TET2*)
- Clonal hematopoiesis strong risk factor for subsequent hematologic cancer (hazard ratio, 12.9).


B
DNMT3A
ASXL1
TET2
JAK2
PPM1D
SF3B1
SRSF2
TP53
CBL
MYD88
U2AF1
STAT3
IDH2
ATM
190
35
31
24
15
13
7
4
3
1
1
1
1
1
0
20
40
180
200
No. of Mutations


C
One mutation
Two mutations
DNMT3A
ASXL1
TET2
JAK2
PPM1D
SF3B1
SRSF2
TP53
CBL
U2AF1
IDH2
Participants with Multiple Candidate Drivers
D
Clonal hematopoiesis with candidate drivers
Clonal hematopoiesis with unknown drivers
Clonal hematopoiesis
Percent of Participants
0
5
10
15
20
25
19–30
31–35
36–40
41–45
46–50
51–55
56–60
61–65
66–70
71–75
76–80
81–93
Age at Sampling (yr)


A
Proportion without Hematologic Cancer
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.00
No clonal hematopoiesis (N=8783)
Clonal hematopoiesis (N=439)
Hazard ratio, 12.9 (95% CI, 5.8–28.7)
P<0.001
0
20
40
60
80
Months
B
Category
No. of Patients
Hazard Ratio for Hematologic Cancer (95% CI)
No mutations 8783 1.00 (1.00–1.00)
One mutation 1122 0.47 (0.06–3.56)
Two mutations 237 1.99 (0.26–15.27)
CH-UD 170 11.34 (3.44–37.41)
CH-CD 269 13.73 (5.74–32.83)
CH 439 12.89 (5.78–28.72)
0.05
0.50
5.00
50.00
C
Persons in Whom Hematologic Cancer Was Later Diagnosed
CH-UD 4
CH-CD 9
No CH 18
Age-Matched Persons without Cancer
No CH
CH-UD
CH-CD
D
Proportion Surviving
1.00
0.95
0.90
0.85
0.80
0.75
0.00
No clonal hematopoiesis (N=8824)
Clonal hematopoiesis (N=455)
Hazard ratio, 1.4 (95% CI, 1.0–1.8)
P=0.03
0
20
40
60
80
Months
E
Category
No. of Patients
Hazard Ratio for Death (95% CI)
No mutations 8824 1.00 (1.00–1.00)
One mutation 1128 0.98 (0.75–1.29)
Two mutations 240 1.30 (0.84–2.01)
CH-UD 175 1.16 (0.73–1.83)
CH-CD 280 1.53 (1.07–2.19)
CH 455 1.38 (1.03–1.84)
0.50
1.00
2.00

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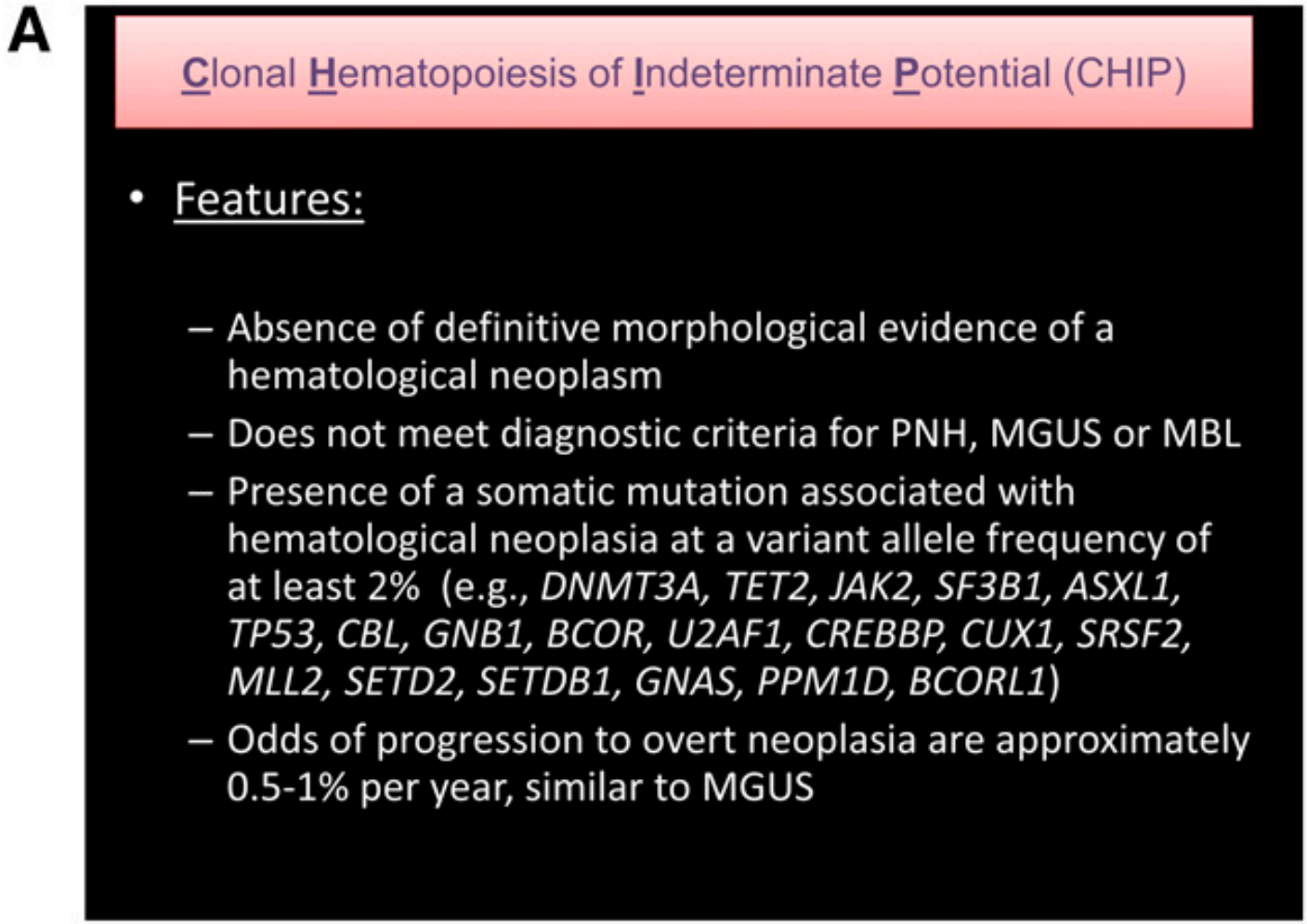
Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes

David P. Steensma, Rafael Bejar, Siddhartha Jaiswal, R. Coleman Lindsley, Mikkael A. Sekeres, Robert P. Hasserjian and Benjamin L. Ebert



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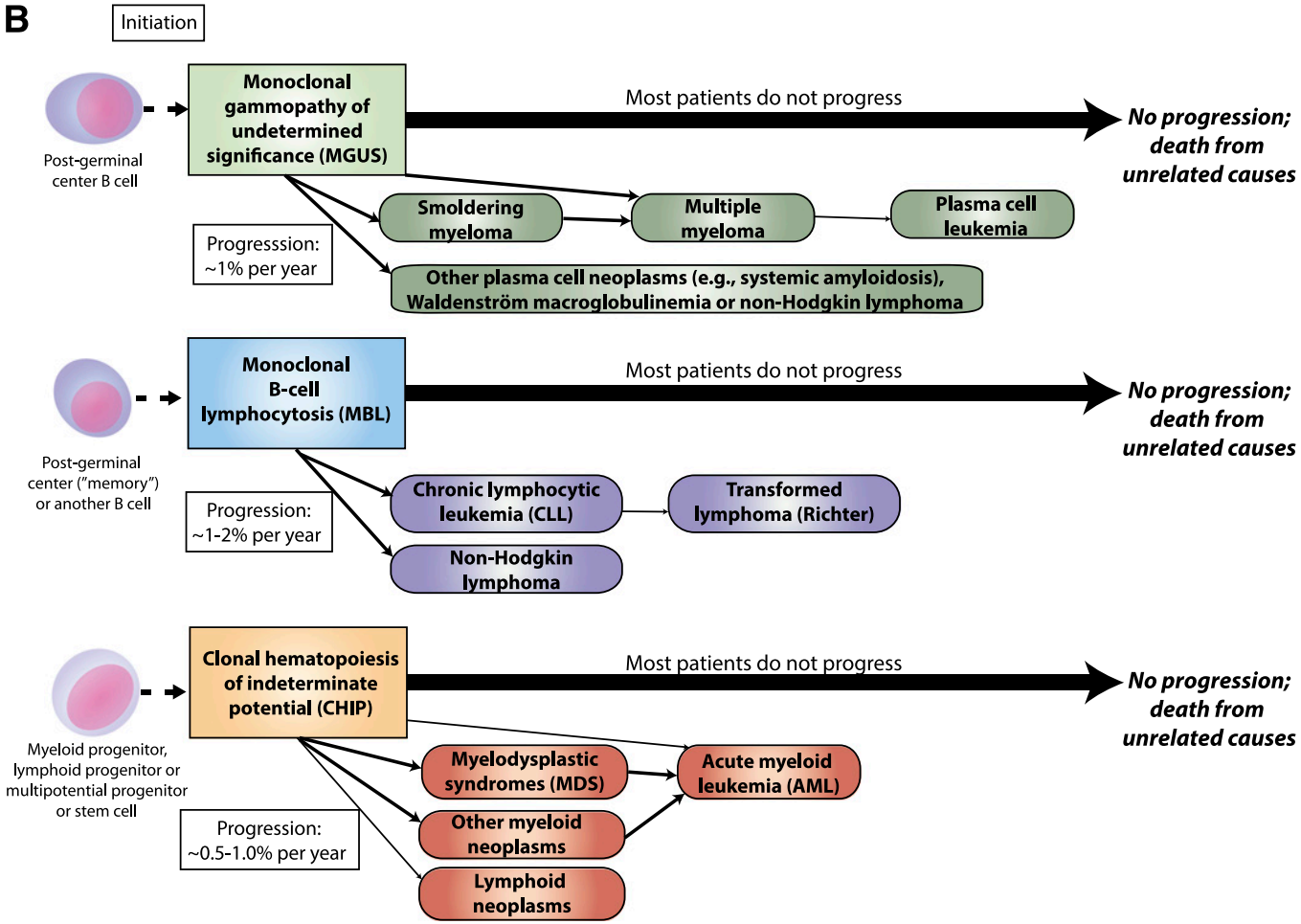
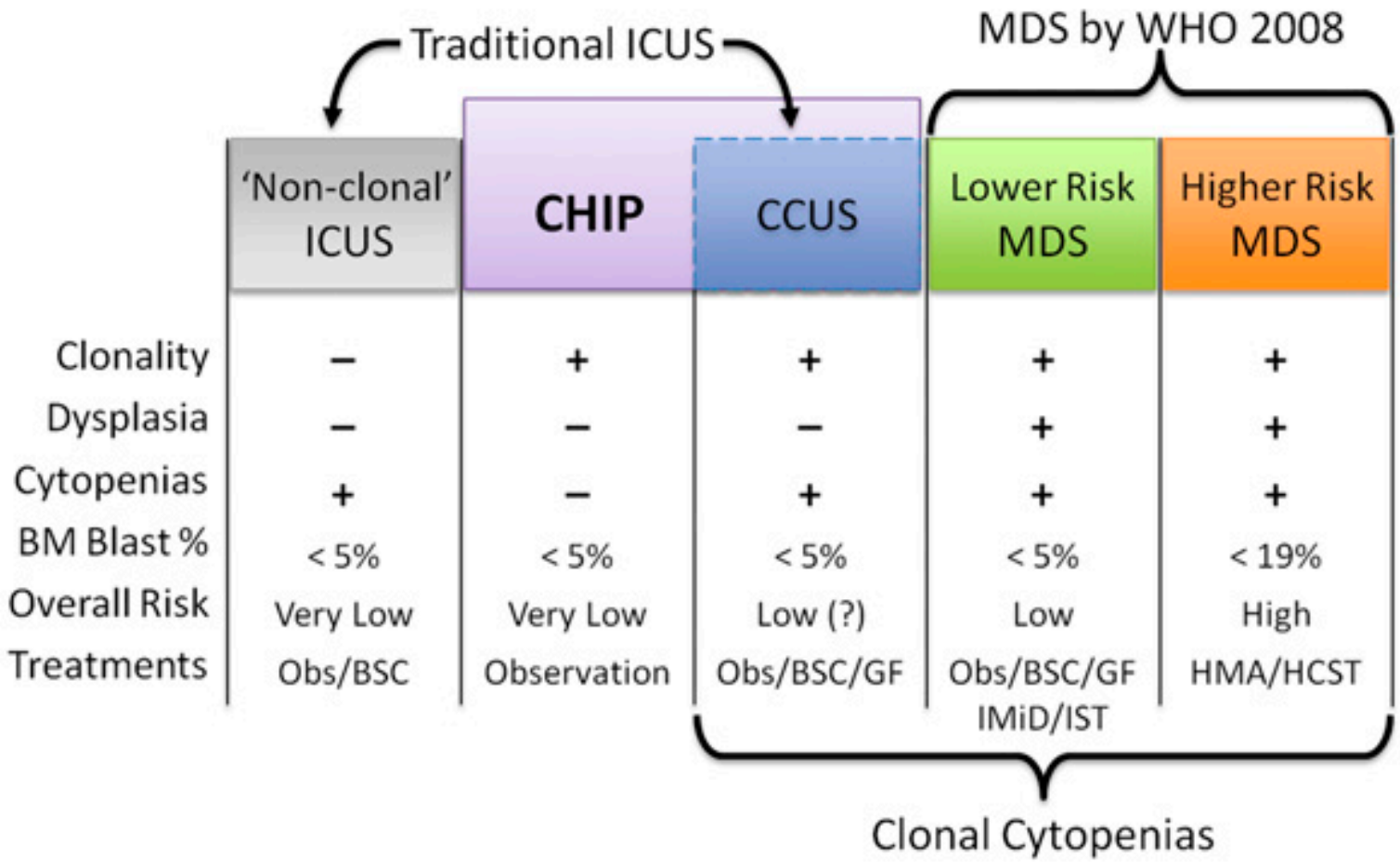


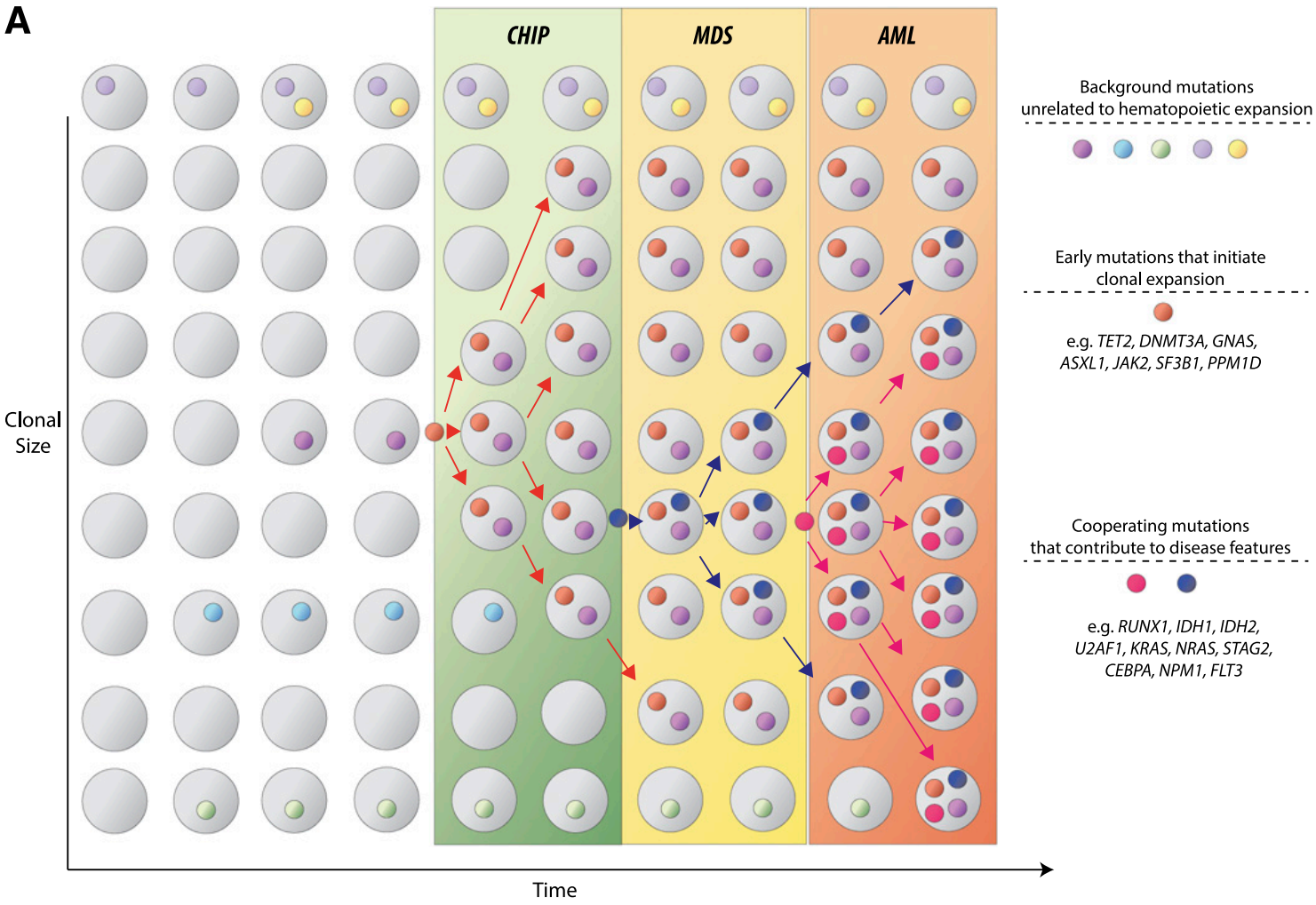
B

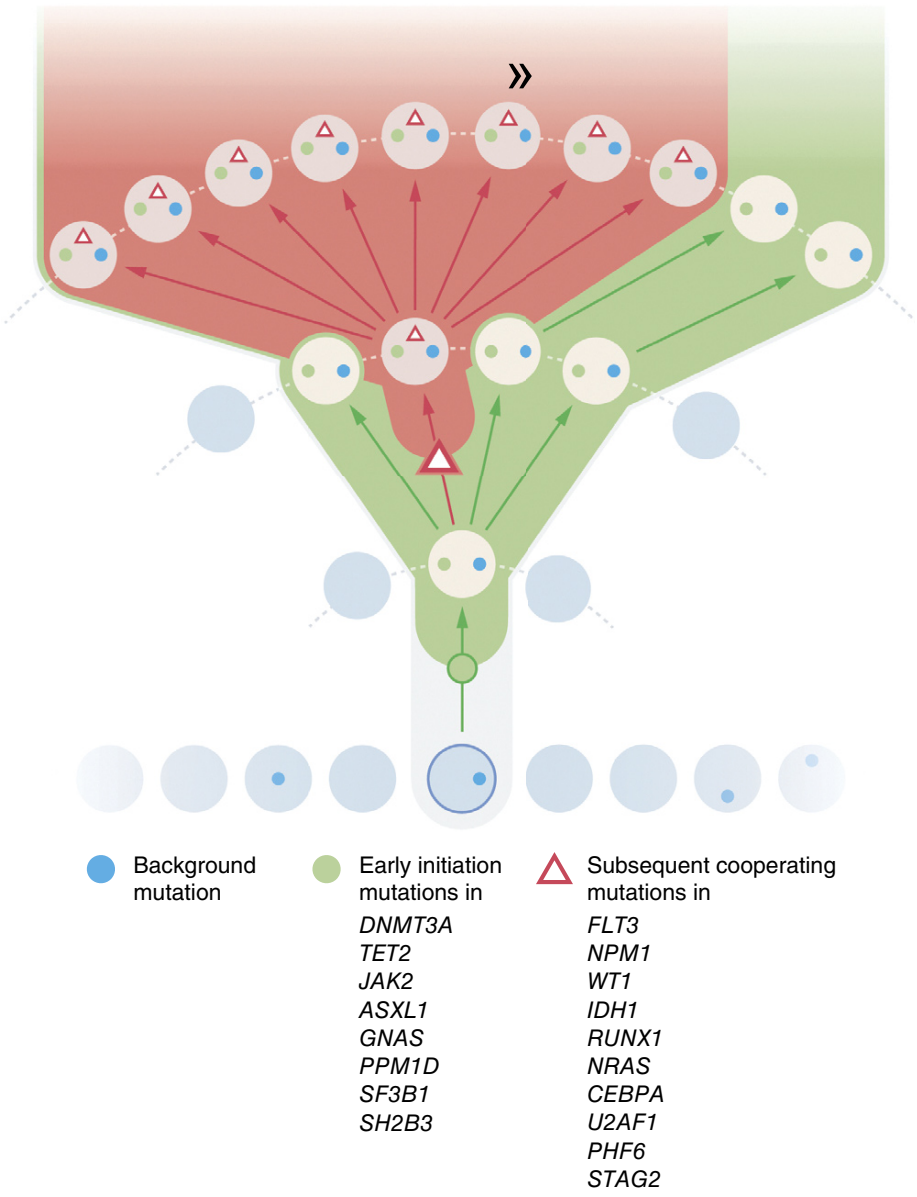

Traditional ICUS
MDS by WHO 2008
'Non-clonal' ICUS
CHIP
CCUS
Lower Risk MDS
Higher Risk MDS
Clonality
Dysplasia
Cytopenias
BM Blast %
Overall Risk
Treatments
– + + + +
– – – + +
+ – + + +
< 5% < 5% < 5% < 5% < 19%
Very Low Very Low Low (?) Low High
Obs/BSC Observation Obs/BSC/GF Obs/BSC/GF IMiD/IST HMA/HCST
Clonal Cytopenias

blood®
2015 126: 9-16
doi:10.1182/blood-2015-03-631747 originally published online April 30, 2015

Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes

David P. Steensma, Rafael Bejar, Siddhartha Jaiswal, R. Coleman Lindsley, Mikkael A. Sekeres, Robert P. Hasserjian and Benjamin L. Ebert





Age-related mutations associated with clonal hematopoietic expansion and malignancies

Mingchao Xie[1,2,7], Charles Lu[1,7], Jiayin Wang[1,2,7], Michael D McLellan[1], Kimberly J Johnson[3], Michael C Wendl[1,4,5], Joshua F McMichael[1], Heather K Schmidt[1], Venkata Yellapantula[1,2], Christopher A Miller[1], Bradley A Ozenberger[1,2], John S Welch[2,6], Daniel C Link[2,6], Matthew J Walter[2,6], Elaine R Mardis[1,2,4,6], John F Dipersio[2,6], Feng Chen[2,6], Richard K Wilson[1,2,4,6], Timothy J Ley[1,2,4,6] & Li Ding[1,2,4,6]

nature medicine 2014

Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia.

Raaijmakers MH Nature 2010

Primary stromal dysfunction can result in secondary neoplastic disease, supporting the concept of niche-induced oncogenesis.

- deletion of Dicer 1 in mouse osteoprogenitors results in MDS having intact Dicer1.
- reduced expression of Sbds (Schwachman-Bodian-Diamond syndrome) protein in osteoprogenitors

LETTER

doi:10.1038/nature12883

Leukaemogenesis induced by an activating β-catenin mutation in osteoblasts

Aruna Kode[1], John S. Manavalan[1], Ioanna Mosialou[1], Govind Bhagat[2], Chozha V. Rathinam[3], Na Luo[1], Hossein Khiabanian[4], Albert Lee[4], Vundavalli V. Murty[5], Richard Friedman[6], Andrea Brum[1,7], David Park[8], Naomi Galili[9], Siddhartha Mukherjee[10], Julie Teruya-Feldstein[8], Azra Raza[9], Raul Rabadan[4], Ellin Berman[11] & Stavroula Kousteni[1,12]

Here we show that an activating mutation of b-catenin in mouse osteoblasts alters the differentiation potential of myeloid and lymphoid progenitors leading to development of acute myeloid leukaemia with common chromosomal aberrations and cell autonomous progression

Research article

Induction of myelodysplasia by myeloid-derived suppressor cells

Xianghong Chen,[1] Erika A. Eksioglu,[1] Junmin Zhou,[1] Ling Zhang,[1] Julie Djeu,[1] Nicole Fortenbery,[1] Pearlie Epling-Burnette,[1] Sandra Van Bijnen,[2] Harry Dolstra,[2] John Cannon,[3] Je-in Youn,[1] Sarah S. Donatelli,[1] Dahui Qin,[1] Theo De Witte,[2] Jianguo Tao,[1] Huaquan Wang,[4] Pingyan Cheng,[1] Dmitry I. Gabrilovich,[1] Alan List,[1] and Sheng Wei[1,4]

[1]H. Lee Moffitt Cancer Center, Tampa, Florida, USA. [2]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. [3]Department of Pediatrics, Children's Research Institute, University of South Florida, Tampa, Florida, USA. [4]Tianjin Medical University Cancer Hospital, Tianjin, China.

-primary bone marrow expansion of MDSC driven by the S100A9/CD33 pathway perturbs hematopoiesis and contributes to the development of MDS

-

ORIGINAL ARTICLE

Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia

T. Yoshizato, B. Dumitriu, K. Hosokawa, H. Makishima, K. Yoshida, D. Townsley, A. Sato-Otsubo, Y. Sato, D. Liu, H. Suzuki, C.O. Wu, Y. Shiraishi, M.J. Clemente, K. Kataoka, Y. Shiozawa, Y. Okuno, K. Chiba, H. Tanaka, Y. Nagata, T. Katagiri, A. Kon, M. Sanada, P. Scheinberg, S. Miyano, J.P. Maciejewski, S. Nakao, N.S. Young, and S. Ogawa

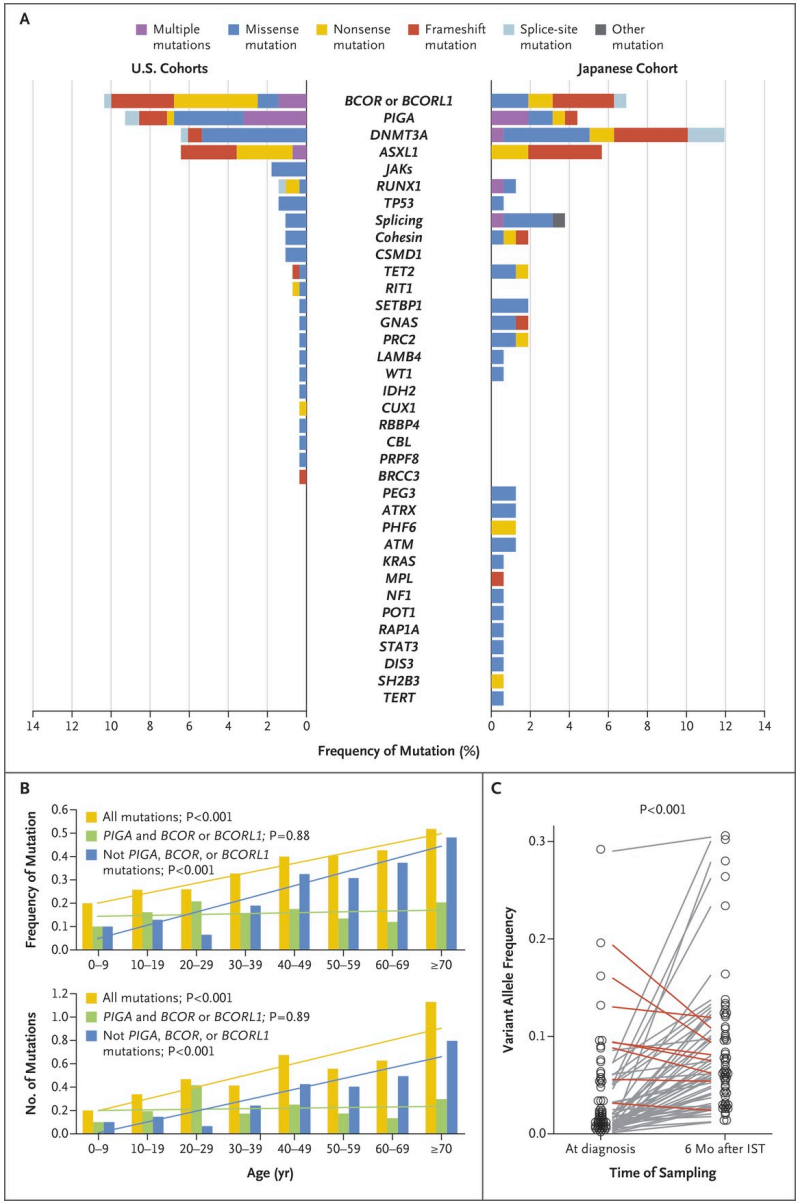
N= 82

Clonal hematopoiesis in 47% patients,

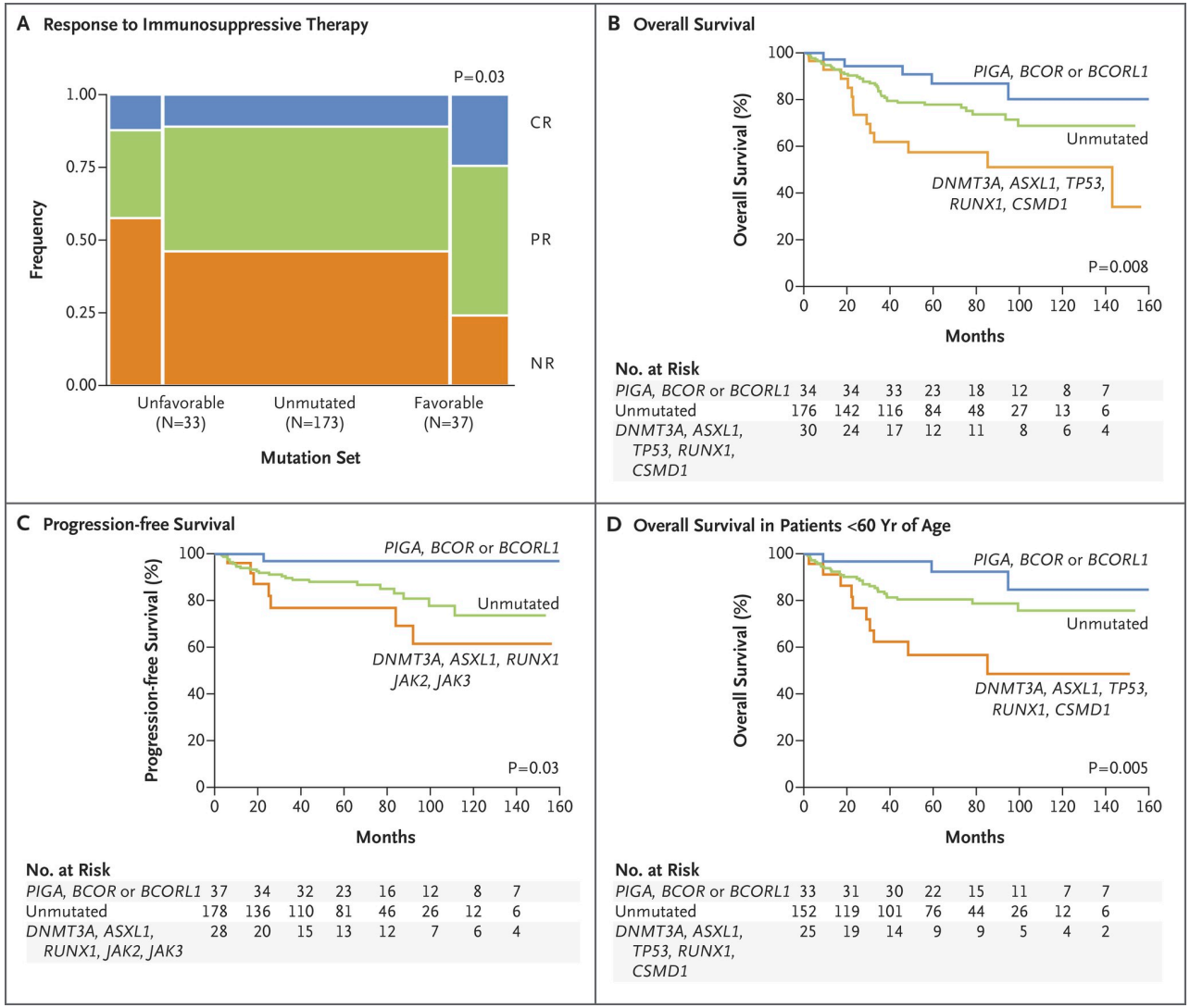
DNMT3A-mutated and *ASXL1*-mutated clones increased over time; *BCOR*- and *BCORL1*-mutated and *PIGA*-mutated clones decreased or remained stable

.Mutations in *PIGA* and *BCOR* and *BCORL1* correlated with a better response to immunosuppressive therapy

mutations in *DNMT3A* and *ASXL1* were associated with worse outcomes.



The NEW ENGLAND JOURNAL of MEDICINE



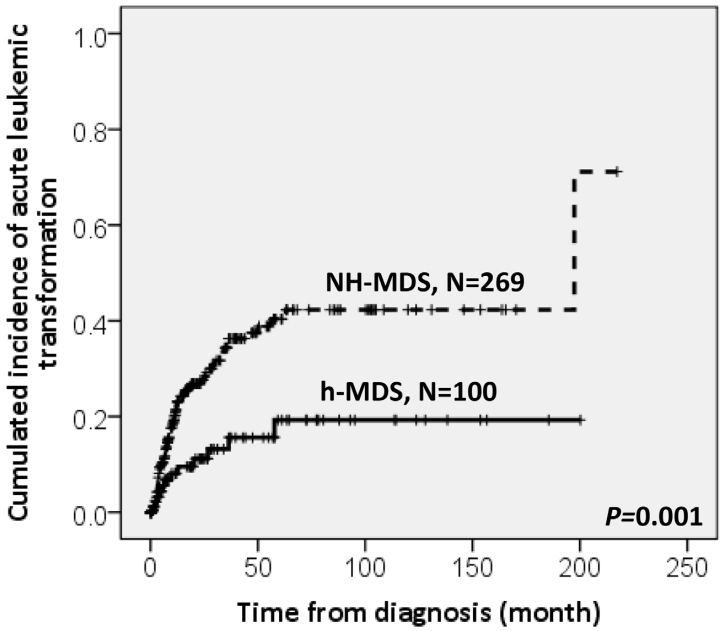
The NEW ENGLAND JOURNAL of MEDICINE

Distinct mutation profile and prognostic relevance in patients with hypoplastic myelodysplastic syndromes (h-MDS)

Chi-Yuan Yao[1,*], Hsin-An Hou[1,*], Tzung-Yi Lin[1], Chien-Chin Lin[1,2], Wen-Chien Chou[1,2], Mei-Hsuan Tseng[1], Ying-Chieh Chiang[1], Ming-Chih Liu[3], Chia-Wen Liu[3], Yuan-Yeh Kuo[4], Shang-Ju Wu[1], Xiu-Wen Liao[5], Chien-Ting Lin[1,5], Bor-Shen Ko[1], Chien-Yuan Chen[1], Szu-Chun Hsu[2], Chi-Cheng Li[5], Shang-Yi Huang[1], Ming Yao[1], Jih-Luh Tang[1,5], Woei Tsay[1], Chieh-Yu Liu[6], Hwei-Fang Tien[1]

Table 2: Comparison of genetic alterations between patients with h-MDS and NH-MDS

Variables	Number examined	Total cohort (%)	h-MDS (%)	NH-MDS (%)	*P* value
		Mutated	Mutated	Mutated	
FLT3/ ITD	366	1.1%	1.0%	1.1%	>0.999
NRAS	369	2.2%	1.0%	2.6%	0.688
KRAS	367	1.1%	0%	1.5%	0.578
JAK2	368	0.8%	1.0%	0.7%	>0.999
RUNX1	367	11.4%	4.0%	14.2%	0.005*
MLL/ PTD	352	0.6%	0%	0.8%	>0.999
IDH1	368	0.5%	1.0%	0.4%	0.470
IDH2	366	2.2%	0%	3.0%	0.113
ASXL1	366	17.8%	7.1%	21.7%	0.001*
TET2	282	12.4%	11.4%	12.7%	>0.999
DNMT3A	369	10.0%	3.0%	12.6%	0.006*
TP53	369	8.7%	3.0%	10.8%	0.020*
SETBP1	369	2.4%	1.0%	3.0%	0.454
EZH2	369	3.8%	0%	5.2%	0.014*
SF3B1	369	11.4%	12.0%	11.2%	0.854
U2AF1	369	7.9%	5.0%	8.9%	0.278
SRSF2	369	10.8%	6.0%	12.6%	0.089



« clinical » conclusions

- Presence of somatic mutations is not diagnostic of MDS in the absence of unexplained cytopenias
- Is CCUS MDS ?
- Is AA with MDS type mutations MDS ?
- Should CCUS be treated like MDS ? … just treat cytopenias

« clinical » conclusion

While discovery of somatic mutations may help in the diagnosis and prognosis of definite MDS or cytopenias, somatic mutations per se currently rarely have an impact on MDS treatment:

- SF3B1 mutation without ringed sideroblasts (luspatercept) ?
- TP53 mutation in lower risk MDS with del 5q?

MDS without significant cytopenias rarely (never?) requires treatment

tMDS/AML or not ?

- MDS post AML with NPM1 mutation
- MDS /AML post APL

Groupe
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Myélodysplasies

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CORRESPONDENCE

Assessment of Minimal Residual Disease in Standard-Risk AML

Morin S el al

Groupe Francophone des Myélodysplasies

- 32 AML (median age, 55 years) with *NPM1* without *FLT3*-ITD in CR after chemotherapy

- 44% relapse (with *NPM1* mutation), 38% remained in CR, 6 (19%) MDS
- In the 6 patients, a preleukemic clone with at least one mutation in *TET2*, *JAK2*, *ASXL1*, *IDH2*, or spliceosome gene was found at AML diagnosis and MDS diagnosis

Molecular analysis of MDS and AML occurring after treatment for APL Ph Attias, A Renneville (ASH 2016)

- 10 cases (1.2%) of MDS/AML during follow up of APL
- Mutations at APL diagnosis: 4 cases of FLT3 ITD or mutation
- *Mutations at MDS/AML:TP 53 (4 pts) ASXL1* (1/10 pts), *CBL* (1/10 pts), *DNMT3A* (1/10 pts), *EZH2* (1/10 pts), *GATA2* (1/10 pts), *KRAS* (1/10 pts), *PTPN11* (1/10 pts), *RUNX1* (1/10 pts), and *TET2* (1/10 pts).

Groupe Francophone des Myélodysplasies

Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS (35 centers in France and Belgium + Switzerland, Tunisia)
- Website: www. gfmgroup.org
- Online registry of French MDS cases
- Close cooperation with:
  - a patient support group
  - the International MDS Foundation
  - the European Leukemia Net

Groupe Francophone des Myélodysplasies