PROGNOSTIC OF CYTOGENETIC AND MOLECULAR ALTERATIONS IN MYELODYSPLASTIC SYNDROMES (MDS)

Institut de Recerca
CONTRA LA LEUCÈMIA
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Coordinator MDS Group

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PROGNOSTIC OF CYTOGENETIC AND MOLECULAR ALTERATIONS IN MYELODYSPLASTIC NEOPLASMS (MDS)

NEW WHO 2022

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- **¿Debemos incorporar los estudios moleculares en pacientes con sospecha o diagnóstico de SMD?**

- **A) no deben realizarse**
- **B) son recomendables**
- **C) son obligatorios**

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- Technical and methodological aspects
- Prognostic value of cytogenetic findings: IPSS-R
- Cytogenetic/genetic changes and IPSS-M
- CONCLUSIONS

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- **CONCLUSIONS**

WHO (2017)

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THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9]

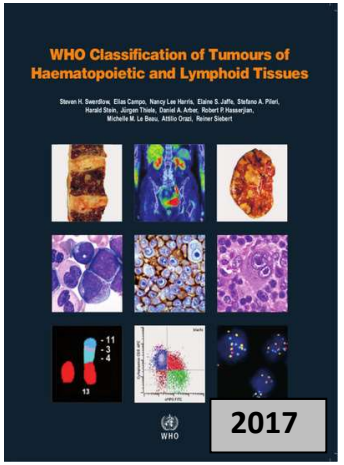

Table 15. PB and BM findings and cytogenetics of MDS

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10^9/L

†If *SF3B1* mutation is present

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

NGS

CG

Arber *et al.* Blood (2016)

New WHO (2022)

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Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

Khoury *et al.* Leukemia (2022)

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MYELODYSPLASTIC NEOPLASMS (MDS) NEW

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
NEW MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
NEW MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
NEW MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
NEW MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

GEN

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New ICC (2022)

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blood®
Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Arber *et al.* Blood (2022)

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Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

NEW

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b,***]	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS - without dysplasia	0	≥1	0	<5% BM <2% PB[d]	-7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥10% VAF)
MDS, NOS - with single lineage dysplasia	1	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS - with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*

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MDS with excess blasts (MDS-EB)	Typically ≥1[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

[a]Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

[b]*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

[c]Although dysplasia is typically present in these entities, it is not required.

[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confimed on two separate occasions also qualifies for MDS-EB.

[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.

[f]AML-defining cytogenetics are listed in the AML section.

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Table 21. Myeloid neoplasms with mutated *TP53*

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Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF >10%)

[a]Defined as two distinct *TP53* mutations (each VAF >10%) OR a single *TP53* mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus.

[b]If *TP53* locus LOH information is not available

Arber *et al.* Blood (2022)

WHO vs ICC (2022)

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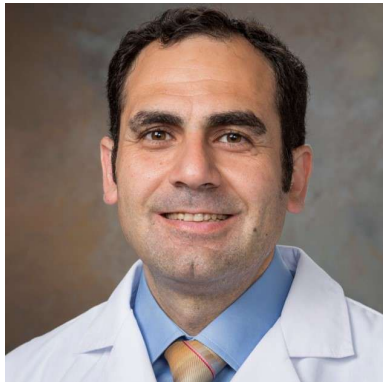
Leukemia

www.nature.com/leu



Check for updates

CORRESPONDENCE

MYELODYSPLASTIC NEOPLASM

Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the International Workshop for Myelodysplastic Syndromes

WHO vs ICC (2022)

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Leukemia www.nature.com/leu

CORRESPONDENCE

MYELODYSPLASTIC NEOPLASM

Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the International Workshop for Myelodysplastic Syndromes

Table 1. Comparison of MDS subtype definitions in WHO 2016, WHO 2022, and ICC classification of MDS.

WHO 2016 [1]	WHO 2022 [3]	ICC [5]
MDS with single lineage dysplasia (MDS-SLD)	Not included MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
MDS with multi-lineage dysplasia (MDS-MLD)	MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
MDS with ring sideroblasts • With single lineage dysplasia (MDS-RS-SLD) • With multi-lineage dysplasia (MDS-RS-MLD)	MDS with low blasts and mutated *SF3B1* or MDS with ring sideroblasts (if ≥ 15% RS and *SF3B1* wild-type)	MDS with mutated *SF3B1*
MDS with isolated del(5q)	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)
MDS unclassifiable	Not included	Not included
Not included	Not included	MDS, not otherwise specified without dysplasia (e.g., monosomy 7/del(7q))[a]
MDS excess blasts-1 (MDS-EB1; 5–9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1; 5–9% bone marrow and/or 2–4% peripheral blood blasts)	MDS excess blasts (5–9% bone marrow and/or 2–9% peripheral blood blasts)
MDS excess blasts-2 (MDS-EB2; 10–19% bone marrow or peripheral blood blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2; 10–19% bone marrow or 5–19% peripheral blood blasts or Auer rods)	MDS/AML (10–19% bone marrow or peripheral blood blasts)
AML-defining genetics[b]	AML-defining genetics independent of bone marrow and peripheral blood blast count	AML-defining genetics with ≥10% bone marrow and peripheral blood blasts
AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)
Not included	MDS with biallelic *TP53* inactivation (Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH)	MDS with mutated *TP53* (Multi-hit *TP53* mutation, or *TP53* mutation (VAF > 10%) and loss of 17p) and MDS/AML with mutated *TP53* (Any somatic TP53 mutation (VAF > 10%)
Not included	MDS, hypoplastic (MDS-h)	Not included
Not included	MDS with fibrosis (MDS-f)	Not included
Not included	Clonal hematopoiesis (CHIP, CCUS)[c]	Pre-malignant clonal cytopenias and CCUS[c]

[a]This would have been classified as MDS-unclassifiable (MDS-U) in the WHO 2016 classification.
[b]AML-defining genetic abnormalities: Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML::RARA*; APL with other *RARA* rearrangements; AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*; AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*; AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*; AML with other *KMT2A* rearrangements; AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*; AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)*; AML with other *MECOM* rearrangements; AML with other rare recurring translocations; AML with mutated *NPM1*; AML with in-frame bZIP *CEBPA* mutations (ICC only); AML with *RBM15::MRTFA* fusion (WHO only); AML with *NUP98*-rearrangement (WHO only).
[c]cytopenias are defined as follows: hemoglobin <13 g/dL in males and <12 g/dL in females for anemia, absolute neutrophil count $<1.8 \times 10^9$/L for leukopenia, and platelets $<150 \times 10^9$/L for thrombocytopenia.

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IPSS. Blasts, Cytogenetics and Cytopenias in MDS

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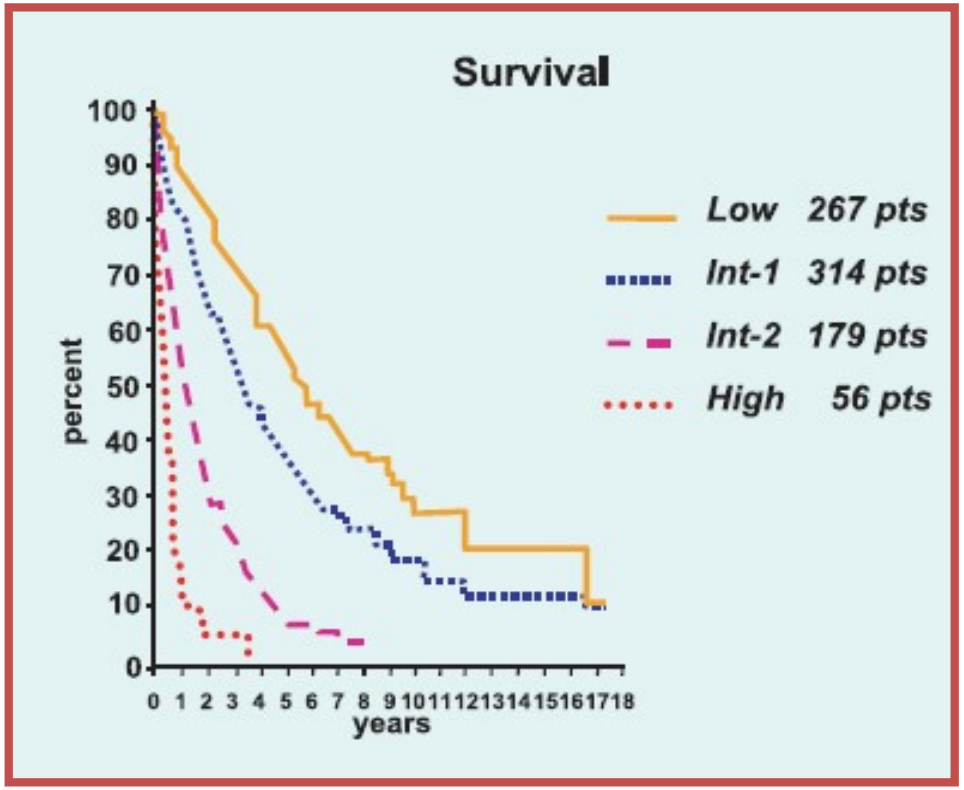
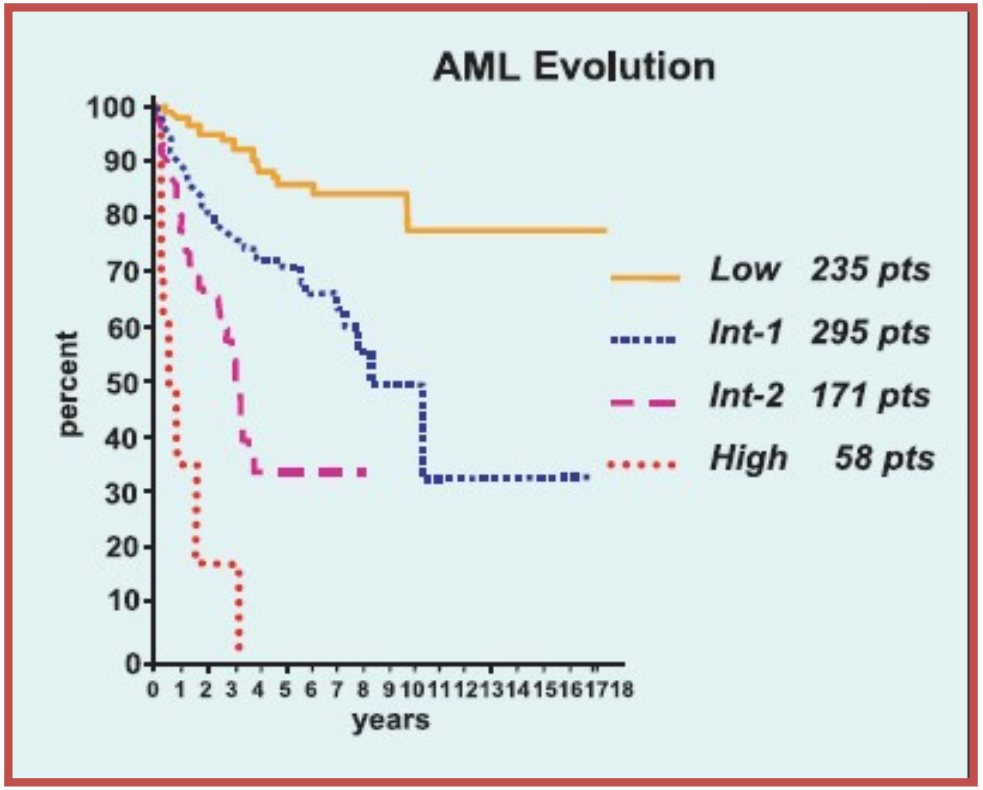
International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

By Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti, and John Bennett

N= 816

Blood, Vol 89, No 6 (March 15), 1997: pp 2079-2088





IPSS. Cytogenetics

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ALTERATIONS WITH **GOOD** PROGNOSIS	del(5q) del(20q) loss of Y chromosome normal karyotype
ALTERATIONS WITH **INTERMEDIATE** PROGNOSIS	other alterations 
ALTERATIONS WITH **POOR** PROGNOSIS	alterations of chr. 7 complex karyotype (≥3 alterations)

Only 4 different cytogenetic alterations considered!!!!

Greenberg *et al.* (1997)

IPSS. Cytogenetics

Institut de Recerca CONTRA LA LEUCÈMIA Josep Carreras

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Greenberg *et al.* (1997)

IPSS. Cytogenetics. New Proposal

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- **Patients obtained from registries:**
  - ***IPSS*** **(IMRAW)**
  - **German-Austrian Group**
  - **GCECGH (Spain)**
  - **International Working Group on MDS Cytogenetics from the MDS Foundation**

N= 2902

IPSS. Cytogenetics. New Proposal

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

N= 2902

New Comprehensive Cytogenetic Scoring System for Primary Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia After MDS Derived From an International Database Merge

Julie Schanz, Heinz Tüchler, Francesc Solé, Mar Mallo, Elisa Luño, José Cervera, Isabel Granada, Barbara Hildebrandt, Marilyn L. Slovak, Kazuma Ohyashiki, Christian Steidl, Christa Fonatsch, Michael Pfeilstöcker, Thomas Nösslinger, Peter Valent, Aristoteles Giagounidis, Carlo Aul, Michael Lübbert, Reinhard Stauder, Otto Krieger, Guillermo Garcia-Manero, Stefan Faderl, Sherry Pierce, Michelle M. Le Beau, John M. Bennett, Peter Greenberg, Ulrich Germing, and Detlef Haase

Schanz *et al*., JCO (2012)

IPSS. Cytogenetics. New Proposal

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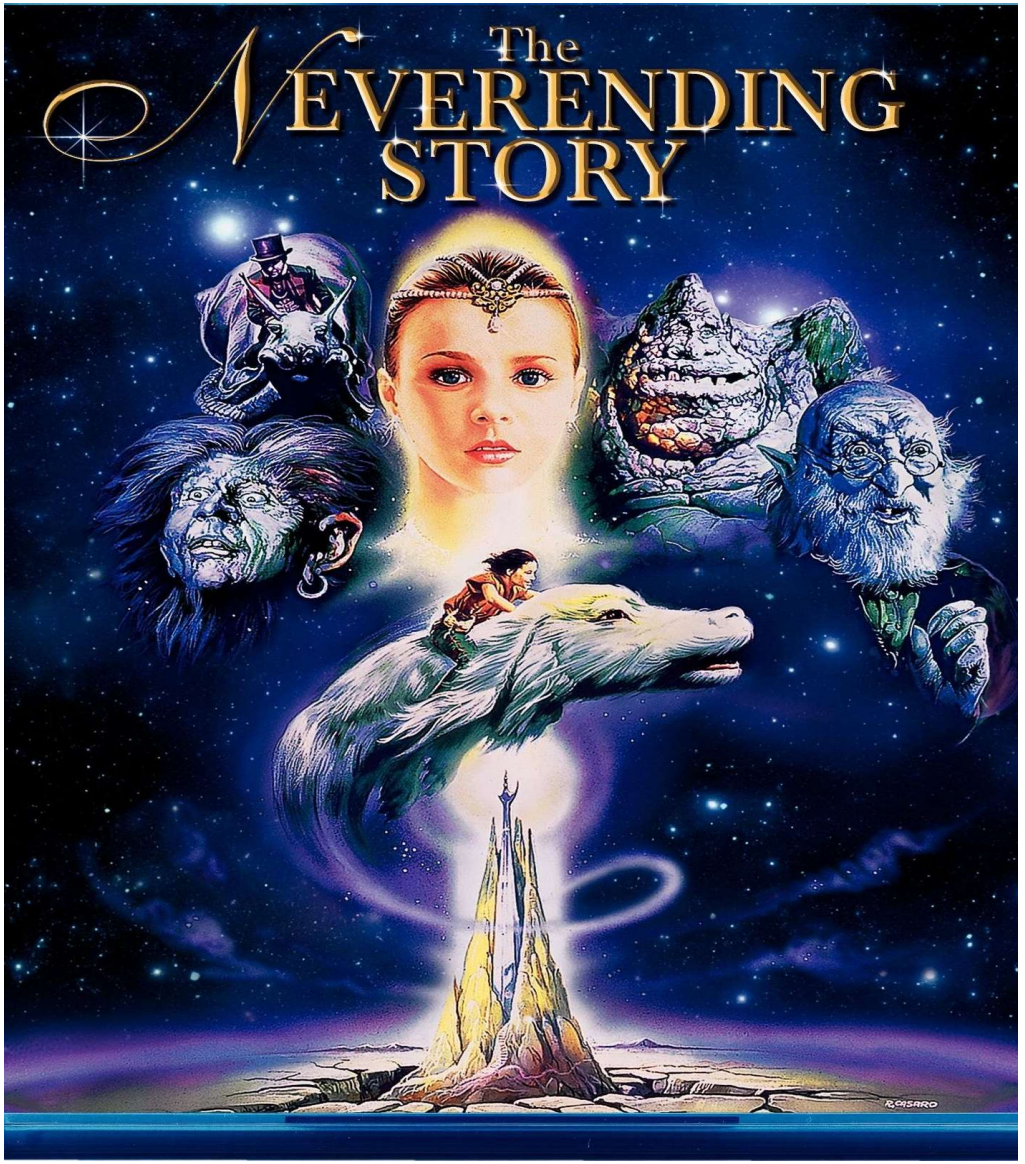
VERY GOOD	GOOD	INT.	POOR	VERY POOR
Single: del(11q) -Y	Normal Single: der(1;7) del(5q) del(12p) del(20q)	Single: 7q- +8 i(17q) +19 +21 Other singles unrelated	Single: der(3)(q21q26) -7	Complex>3 alt.
	Double with 5q-	Other doubles	Complex 3 alt.	
			Double with -7/7q-	
OS 60.8m HR 0.47 (0.3-0.7)	**OS 48.5m** HR 1 (0.8-1.3)	**OS 25.0 m** HR 1.59 (1.4-1.9)	**OS 15.0 m** HR 2.83 (2.2-3.7)	**OS 5.7 m** HR 4.37 (3.5-5.5)

IPSS-R



***From 2008 to 2012**

IPSS-R

Institut de Recerca CONTRA LA LEUCÈMIA Josep Carreras

Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Peter L. Greenberg,[1] Heinz Tuechler,[2] Julie Schanz,[3] Guillermo Sanz,[4] Guillermo Garcia-Manero,[5] Francesc Solé,[6] John M. Bennett,[7] David Bowen,[8] Pierre Fenaux,[9] Francois Dreyfus,[10] Hagop Kantarjian,[5] Andrea Kuendgen,[11] Alessandro Levis,[12] Luca Malcovati,[13] Mario Cazzola,[13] Jaroslav Cermak,[14] Christa Fonatsch,[15] Michelle M. Le Beau,[16] Marilyn L. Slovak,[17] Otto Krieger,[18] Michael Luebbert,[19] Jaroslaw Maciejewski,[20] Silvia M. M. Magalhaes,[21] Yasushi Miyazaki,[22] Michael Pfeilstöcker,[2] Mikkael Sekeres,[20] Wolfgang R. Sperr,[15] Reinhard Stauder,[23] Sudhir Tauro,[24] Peter Valent,[15] Teresa Vallespi,[25] Arjan A. van de Loosdrecht,[26] Ulrich Germing,[11] and Detlef Haase[3]

[1]Stanford University Cancer Center, Stanford, CA; [2]Hanusch Hospital, Boltzmann Institute for Leukemia Research, Vienna, Austria; [3]Georg August Universität, Göttingen, Germany; [4]Hospital Universitario La Fe, Valencia, Spain; [5]The University of Texas, MD Anderson Cancer Center, Houston, TX; [6]Hospital del Mar, Barcelona, Spain; [7]James P. Wilmont Cancer Center, University of Rochester Medical Center, Rochester, NY; [8]St James's University Hospital, Leeds, United Kingdom; [9]Hôpital Avicenne, Assistance Publique–Hôpitaux de Paris (AP-HP)/University Paris XIII, Bobigny, France; [10]Hôpital Cochin, AP-HP University of Paris V, Paris, France; [11]Heinrich-Heine University Hospital, Düsseldorf, Germany; [12]Antonio e Biagio e C Arrigo Hospital, Alessandria, Italy; [13]Fondazione Istituti di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo and University of Pavia, Pavia, Italy; [14]Institute of Hematology and Blood Transfusion, Praha, Czech Republic; [15]Medical University of Vienna, Vienna, Austria; [16]University of Chicago Comprehensive Cancer Research Center, Chicago, IL; [17]Quest Diagnostics Nichols Institute, Chantilly, VA; [18]Elisabethinen Hospital, Linz, Austria; [19]University of Freiburg Medical Center, Freiburg, Germany; [20]Cleveland Clinic, Cleveland, OH; [21]Federal University of Ceara, Fortaleza, Brazil; [22]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [23]University Hospital of Innsbruck, Innsbruck, Austria; [24]University of Dundee, Scotland, United Kingdom; [25]Hospital Universitario Vall d'Hebron, Barcelona, Spain; and [26]VU University Medical Center, Amsterdam, The Netherlands

***Greenberg *et al.*, Blood September (2012)**

IPSS-R

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Parameters	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Int.	Poor	Very poor
Blasts MO %	≤2		>2-5%		5-10%	>10%	
Hb	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
Neut.	≥0.8	<0.8					

***Greenberg *et al.*, (2012)**

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- **Cytogenetic/genetic changes and IPSS-M**
- CONCLUSIONS

– Karyotype Features and *TP53*

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-1008-z

Check for updates

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

GESMD

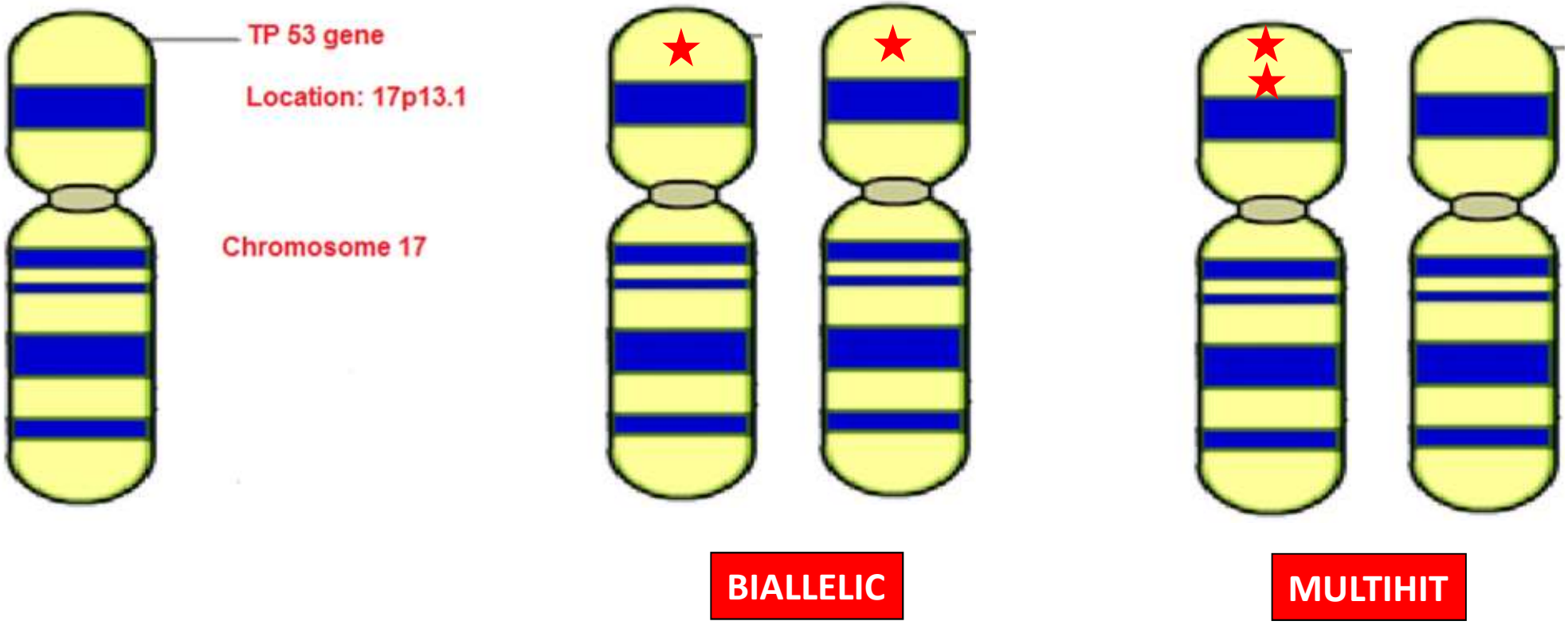
Implications of *TP53* allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes

Elsa Bernard[1,2], Yasuhito Nannya[3], Robert P. Hasserjian[4], Sean M. Devlin[5], Heinz Tuechler[6], Juan S. Medina-Martinez[1,2], Tetsuichi Yoshizato[3], Yusuke Shiozawa[3], Ryunosuke Saiki[3], Luca Malcovati[7,8], Max F. Levine[1,2], Juan E. Arango[1,2], Yangyu Zhou[1,2], Francesc Solé[9], Catherine A. Cargo[10], Detlef Haase[11], Maria Creignou[12], Ulrich Germing[13], Yanming Zhang[14], Gunes Gundem[1], Araxe Sarian[2], Arjan A. van de Loosdrecht[15], Martin Jädersten[12], Magnus Tobiasson[12], Olivier Kosmider[16], Matilde Y. Follo[17], Felicitas Thol[18], Ronald F. Pinheiro[19], Valeria Santini[20], Ioannis Kotsianidis[21], Jacqueline Boultwood[22], Fabio P. S. Santos[23], Julie Schanz[11], Senji Kasahara[24], Takayuki Ishikawa[25], Hisashi Tsurumi[26], Akifumi Takaori-Kondo[27], Toru Kiguchi[28], Chantana Polprasert[29], John M. Bennett[30], Virginia M. Klimek[31], Michael R. Savona[32], Monika Belickova[33], Christina Ganster[11], Laura Palomo[9], Guillermo Sanz[34,35], Lionel Ades[36], Matteo Giovanni Della Porta[37], Alexandra G. Smith[38], Yesenia Werner[1], Minal Patel[2], Agnès Viale[39], Katelynd Vanness[39], Donna S. Neuberg[40], Kristen E. Stevenson[40], Kamal Menghrajani[31], Kelly L. Bolton[31], Pierre Fenaux[36], Andrea Pellagatti[22], Uwe Platzbecker[41], Michael Heuser[18], Peter Valent[42], Shigeru Chiba[43], Yasushi Miyazaki[44], Carlo Finelli[45], Maria Teresa Voso[46], Lee-Yung Shih[47], Michaela Fontenay[16], Joop H. Jansen[48], José Cervera[49], Yoshiko Atsuta[50], Norbert Gattermann[13], Benjamin L. Ebert[51], Rafael Bejar[52], Peter L. Greenberg[53], Mario Cazzola[7,8], Eva Hellström-Lindberg[12], Seishi Ogawa[3,54] and Elli Papaemmanuil[1,2,54] ✉

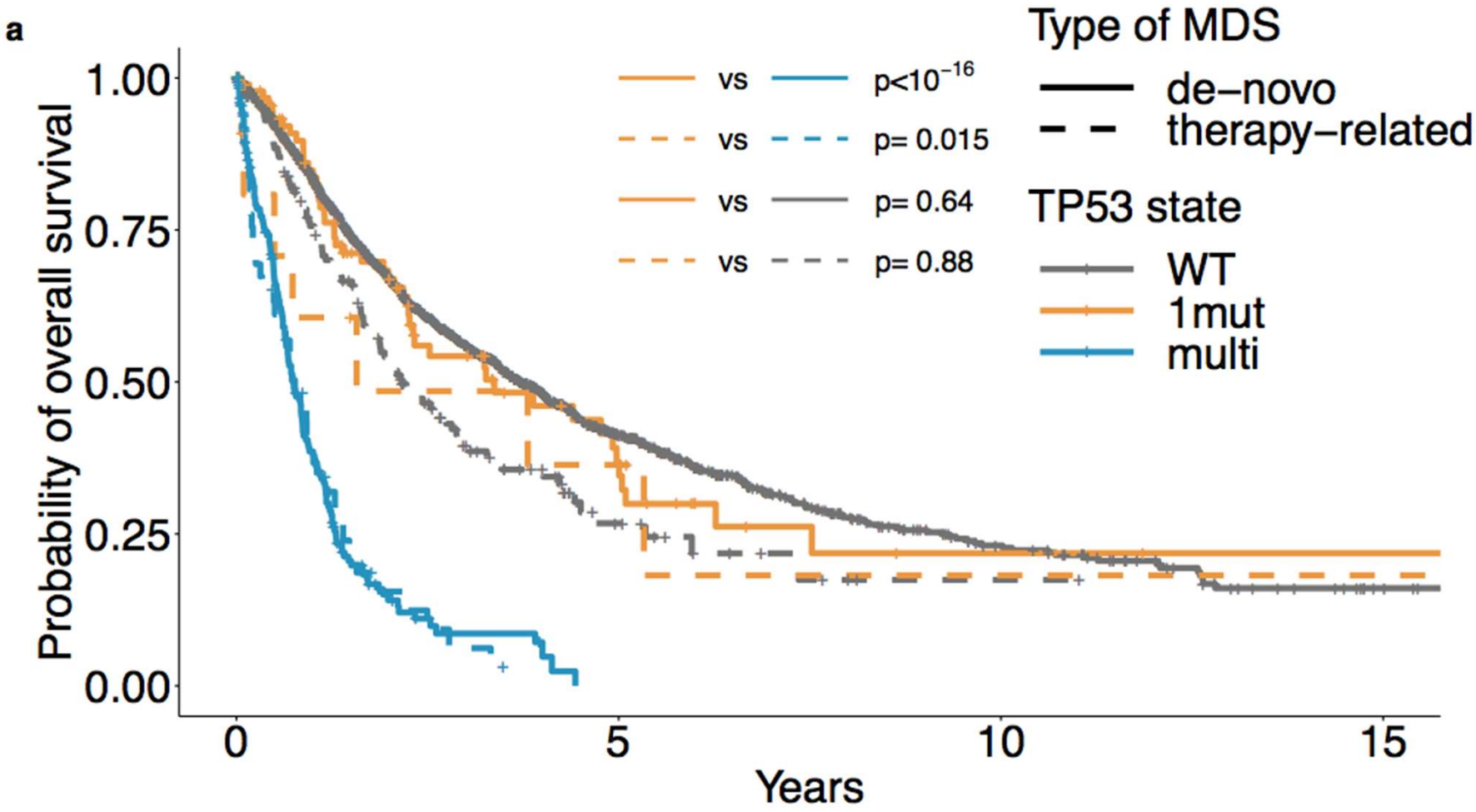
N= 3324

Bernard *et al.* Nat Med (2020)

– Karyotype Features and *TP53*



– Karyotype Features and *TP53*



MULTI HIT: ≥ 2 mutations, 1 mutation + 1 deleted or 1 mutated and LOH

Defined as two distinct TP53 mutations (each VAF >10%) OR a single TP53 mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p TP53 locus.

New Proposal. IPSS-M

***From 2018 to 2022**

New IPSS: IPSS-M

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NEJM Evidence

Published June 12, 2022

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IWG-PM INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

ORIGINAL ARTICLE

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

Elsa Bernard, Ph.D.,[1] Heinz Tuechler, Peter L. Greenberg, M.D.,[2] Robert P. Hasserjian, M.D.,[3] Juan E. Arango Ossa, M.S.,[1] Yasuhito Nannya, M.D., Ph.D.,[4,5] Sean M. Devlin, Ph.D.,[1] Maria Creignou, M.D.,[6] Philippe Pinel, M.S.,[1] Lily Monnier, M.S.,[1] Gunes Gundem, Ph.D.,[1] Juan S. Medina-Martinez, M.S.,[1] Dylan Domenico, B.S.,[1] Martin Jädersten, M.D., Ph.D.,[6] Ulrich Germing, M.D.,[7] Guillermo Sanz, M.D., Ph.D.,[8,9,10] Arjan A. van de Loosdrecht, M.D., Ph.D.,[11] Olivier Kosmider, M.D., Ph.D.,[12] Matilde Y. Follo, Ph.D.,[13] Felicitas Thol, M.D.,[14] Lurdes Zamora, Ph.D.,[15] Ronald F. Pinheiro, Ph.D.,[16] Andrea Pellagatti, Ph.D.,[17] Harold K. Elias, M.D.,[18] Detlef Haase, M.D., Ph.D.,[19] Christina Ganster, Ph.D.,[19] Lionel Ades, M.D., Ph.D.,[20] Magnus Tobiasson, M.D., Ph.D.,[7] Laura Palomo, Ph.D.,[21] Matteo Giovanni Della Porta, M.D.,[22] Akifumi Takaori-Kondo, M.D., Ph.D.,[23] Takayuki Ishikawa, M.D., Ph.D.,[24] Shigeru Chiba, M.D., Ph.D.,[25] Senji Kasahara, M.D., Ph.D.,[26] Yasushi Miyazaki, M.D., Ph.D.,[27] Agnes Viale, Ph.D.,[28] Kety Huberman, B.S.,[28] Pierre Fenaux, M.D., Ph.D.,[20] Monika Belickova, Ph.D.,[29] Michael R. Savona, M.D.,[30] Virginia M. Klimek, M.D.,[18] Fabio P. S. Santos, M.D., Ph.D.,[31] Jacqueline Boultwood, Ph.D.,[17] Ioannis Kotsianidis, M.D., Ph.D.,[32] Valeria Santini, M.D.,[33] Francesc Solé, Ph.D.,[15] Uwe Platzbecker, M.D.,[34] Michael Heuser, M.D.,[14] Peter Valent, M.D.,[35,36] Kazuma Ohyashiki, M.D., Ph.D.,[37] Carlo Finelli, M.D.,[38] Maria Teresa Voso, M.D.,[39] Lee-Yung Shih, M.S.,[40] Michaela Fontenay, M.D., Ph.D.,[12] Joop H. Jansen, Ph.D.,[41] José Cervera, M.D., Ph.D.,[42] Norbert Gattermann, M.D.,[7] Benjamin L. Ebert, M.D., Ph.D.,[43] Rafael Bejar, M.D., Ph.D.,[44] Luca Malcovati, M.D.,[45] Mario Cazzola, M.D.,[45] Seishi Ogawa, M.D., Ph.D.,[4,46,47] Eva Hellström-Lindberg, M.D., Ph.D.,[6] and Elli Papaemmanuil, Ph.D.[1]

Bernard *et al.* NEJM-Evidence (2022)

New IPSS: IPSS-M

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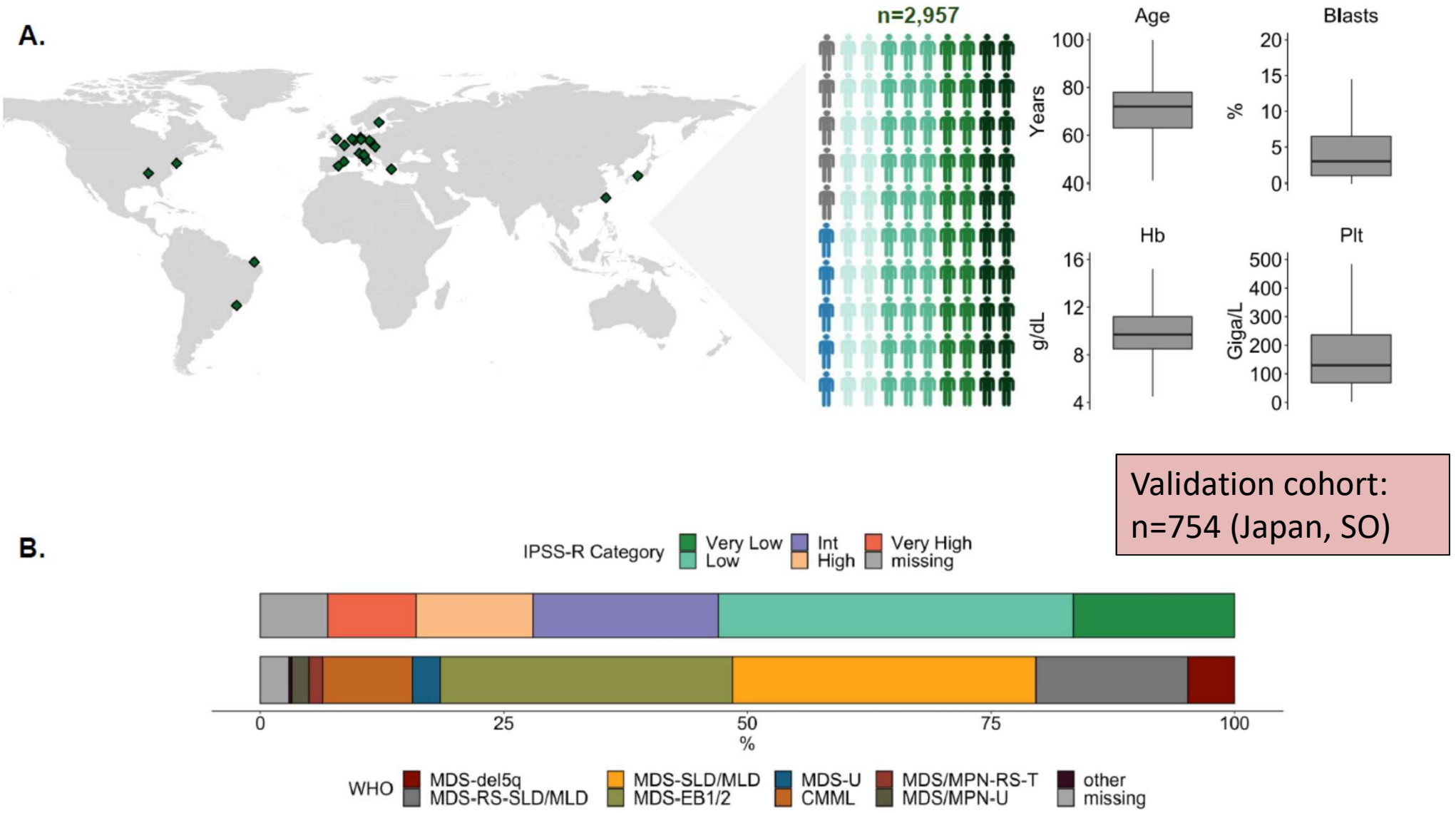
IPSS n = 816 | **IPSS-R n = 7012**



Validation cohort:
n=754 (Japan, SO)

New IPSS: IPSS-M

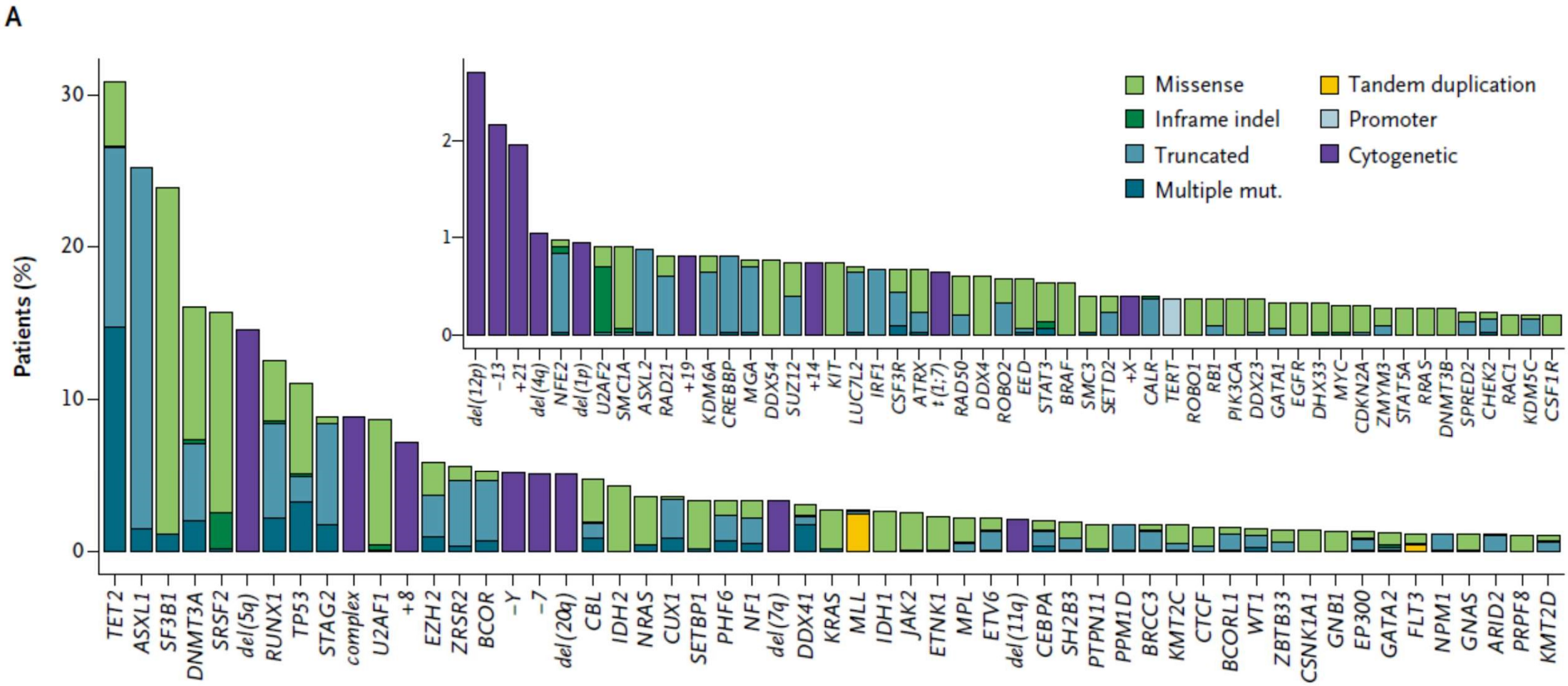


Figure 1 | IWG-PM cohort characteristics.

New IPSS: IPSS-M

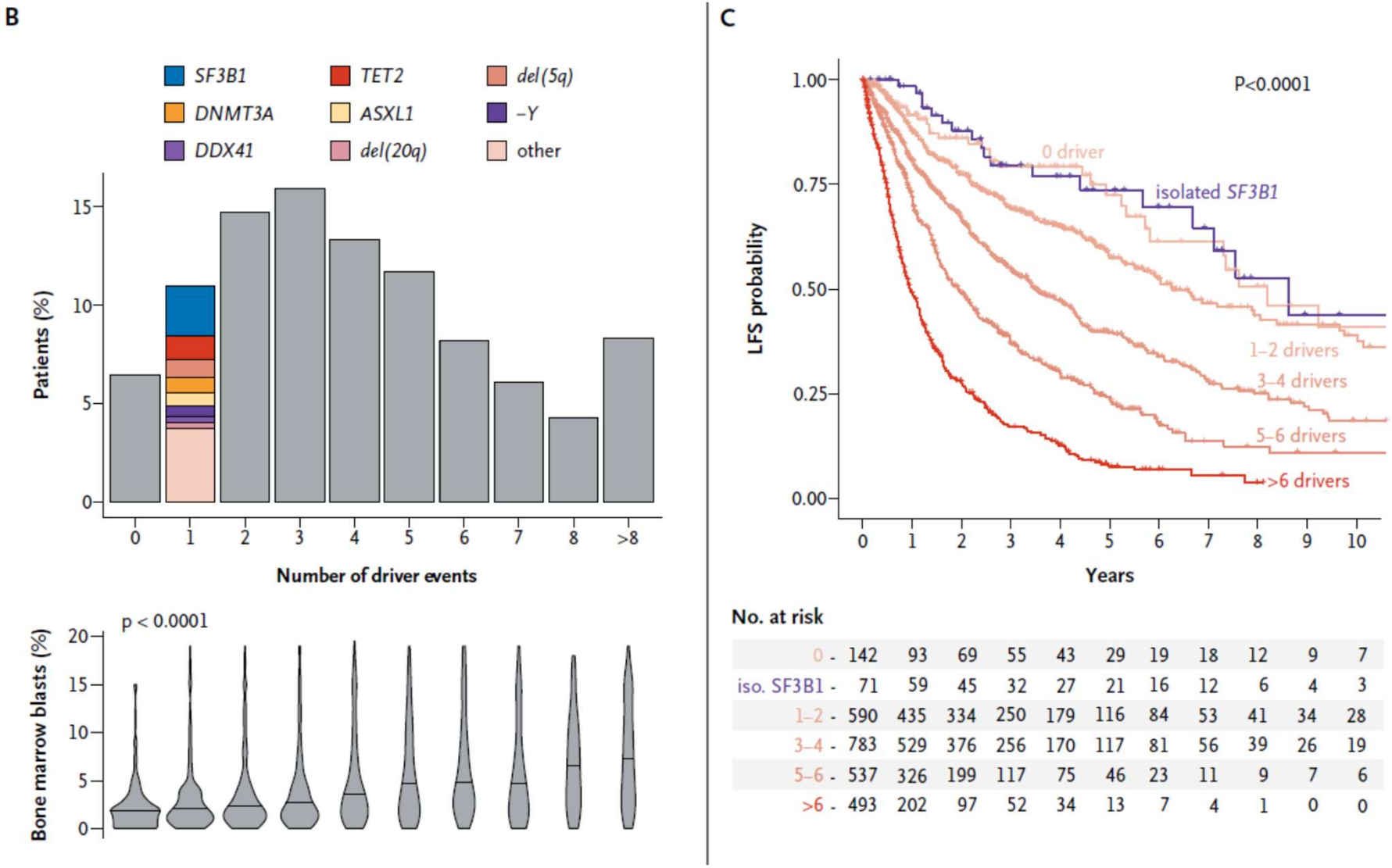


Figure 1 | IWG-PM cohort characteristics.

Figure 2 | IPSS-M score construction.

IPSS-R

IPSS-R Blasts, HB, plat

IPSS-R Cytogenetics

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

*Hazard ratio for the risk of leukemic transformation or death, adjusted for age, sex, and therapy-related versus primary MDS. CI: confidence interval. The Cox regression was performed on 2,428 patients with available covariables and leukemia-free survival data.

^The model weights, derived from the logarithm of the raw hazard ratios up to three significant digits, used to calculated the IPSS-M risk score. The following formula applies: IPSS-M score = 1.15467 + $(\sum_{variables\,j} w_j x_j) / \log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

§0=Very Good; 1=Good; 2=Intermediate; 3=Poor; 4=Very Poor.

‖Nres is defined as the number of mutated genes within the following list:
BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1.
The variable min(Nres,2) can therefore takes the value 0, 1 or 2.

PTD: partial tandem duplication; ITD: internal tandem duplication; TKD: tyrosine kinase domain.

SF3B1^{5q}: *SF3B1* mutation in the presence of isolated del(5q), *i.e.* del(5q) only or with one additional aberration excluding -7/del(7q).

SF3B1$^{\alpha}$: *SF3B1* mutation without co-mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2,* and del(5q).

Figure 2 | IPSS-M score construction.

IPSS-R

IPSS-R Blasts, HB, plat

IPSS-R Cytogenetics

Genes with independent prognostic

Number of mutated genes

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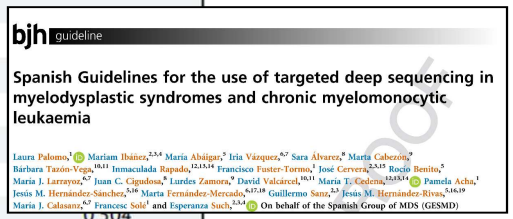
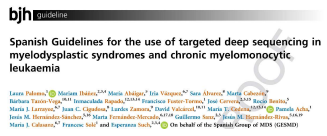

bjh guideline

Spanish Guidelines for the use of targeted deep sequencing in myelodysplastic syndromes and chronic myelomonocytic leukaemia

Laura Palomo,[1] Mariam Ibáñez,[2,3,4] María Abáigar,[5] Iria Vázquez,[6,7] Sara Álvarez,[8] María Cabezón,[9] Bárbara Tazón-Vega,[10,11] Inmaculada Rapado,[12,13,14] Francisco Fuster-Tormo,[1] José Cervera,[2,3,15] Rocío Benito,[5] María J. Larrayoz,[6,7] Juan C. Cigudosa,[8] Lurdes Zamora,[9] David Valcárcel,[10,11] María T. Cedena,[12,13,14] Pamela Acha,[1] Jesús M. Hernández-Sánchez,[3,16] Marta Fernández-Mercado,[6,17,18] Guillermo Sanz,[2,3] Jesús M. Hernández-Rivas,[3,16,19] María J. Calasanz,[6,7] Francesc Solé[1] and Esperanza Such,[2,3,4] On behalf of the Spanish Group of MDS (GESMD)

Application to calculate the IPSS-M

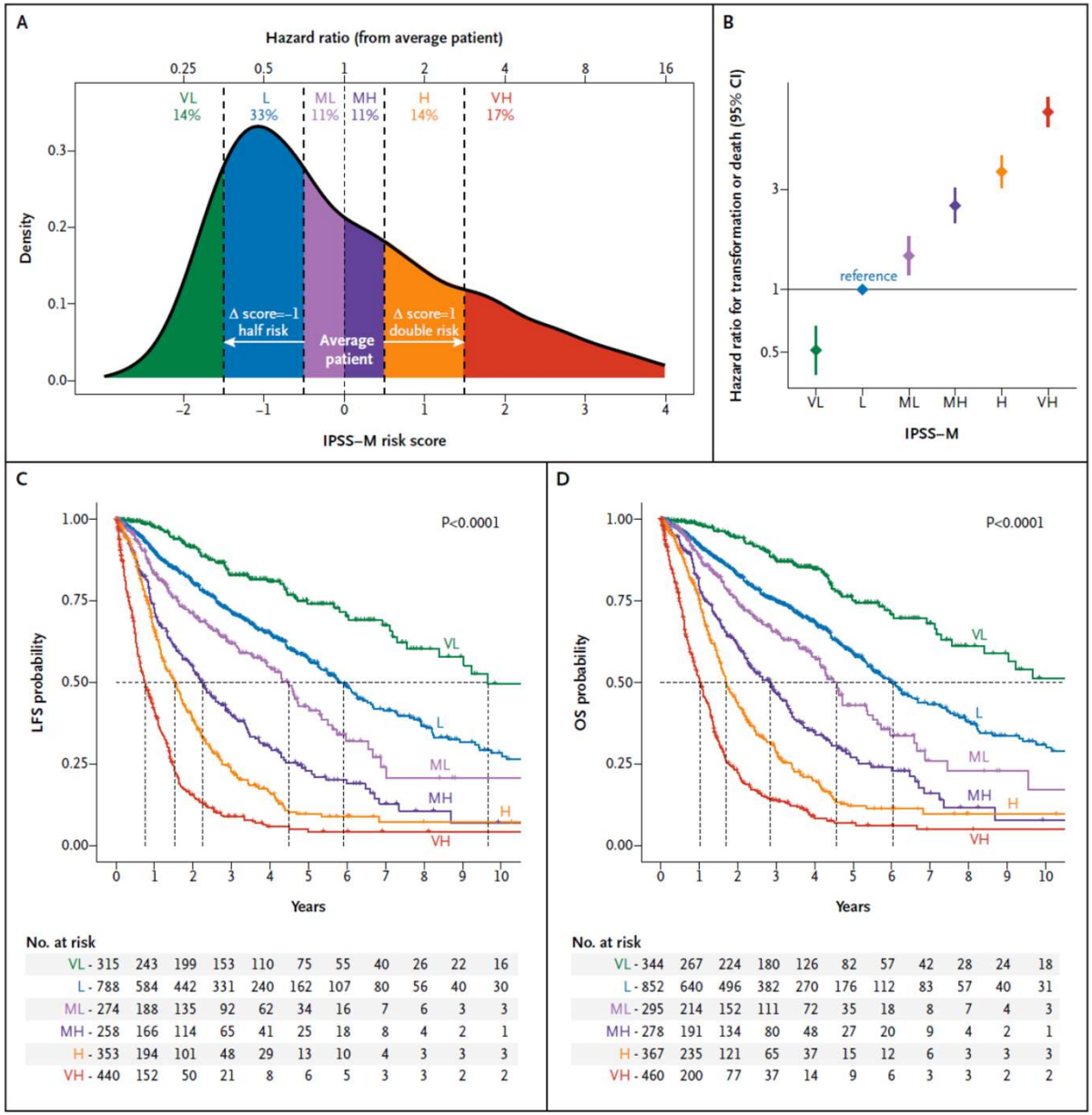

bjh guideline

Spanish Guidelines for the use of targeted deep sequencing in myelodysplastic syndromes and chronic myelomonocytic leukaemia

New IPSS: IPSS-M

Institut de Recerca CONTRA LA LEUCÈMIA Josep Carreras

6 CATEGORIES: VL, L, ML, MH, H, and VH



New IPSS: IPSS-M. Calculator

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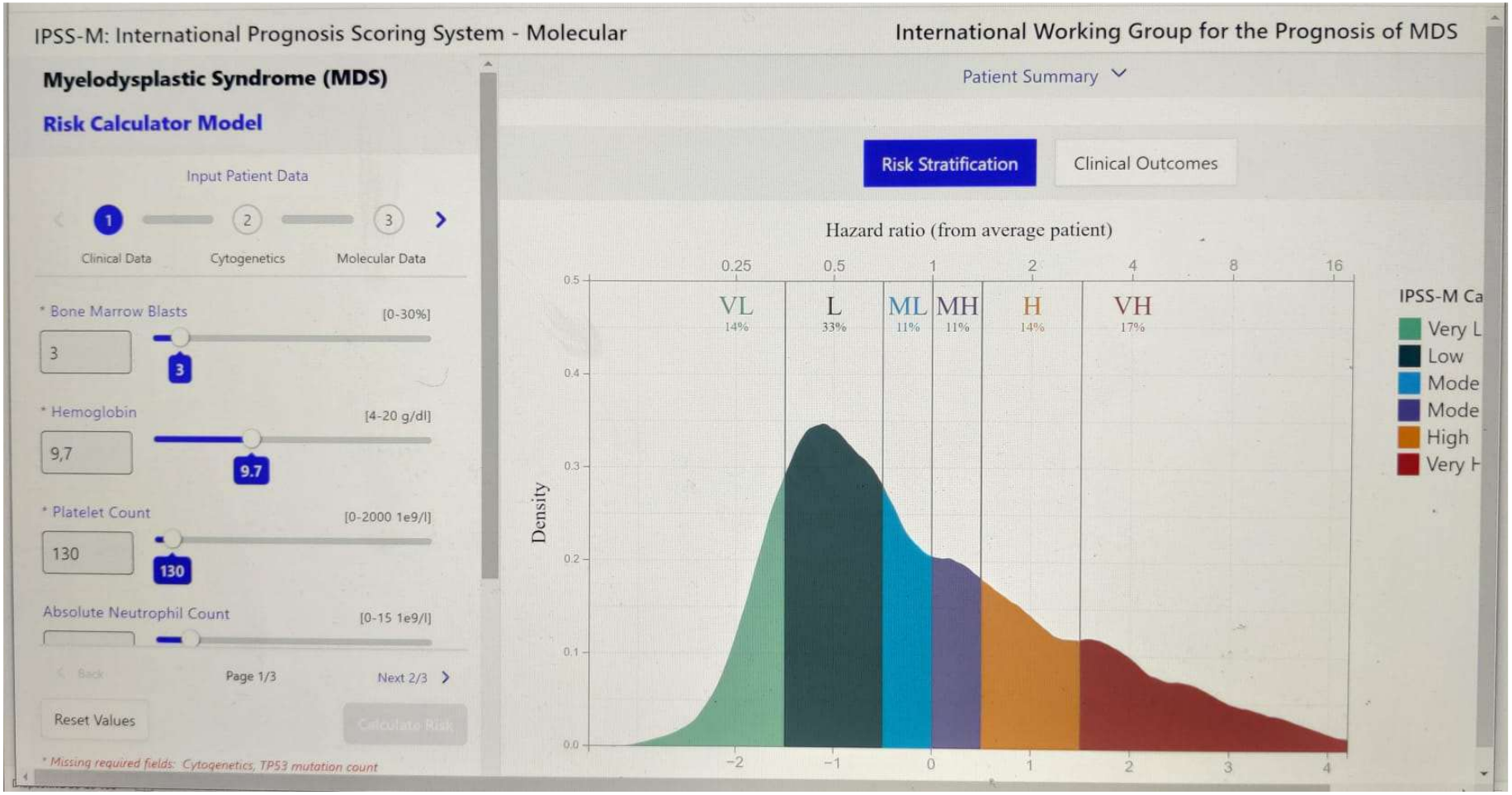

https://mds-risk-model.com/

New IPSS: IPSS-M. Calculator

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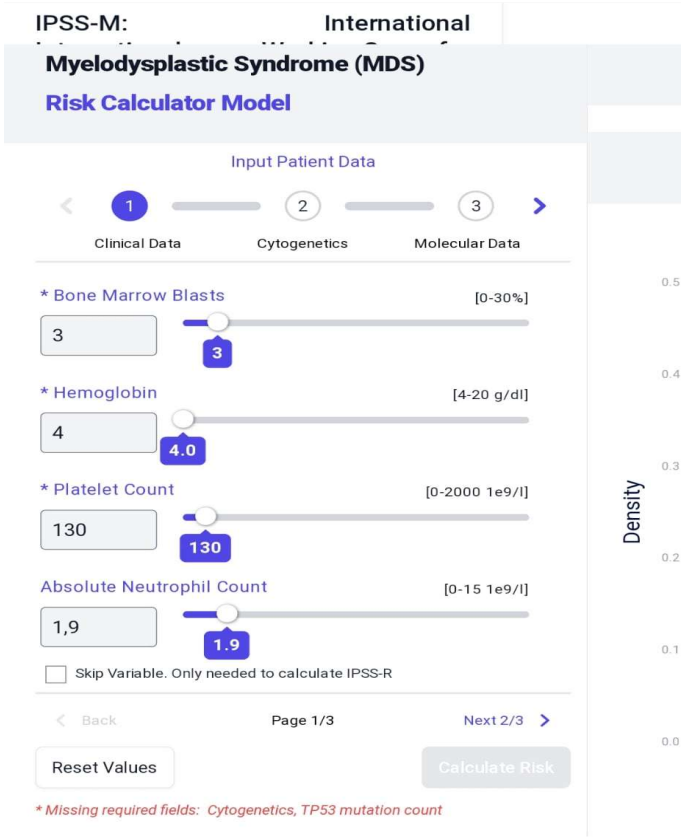
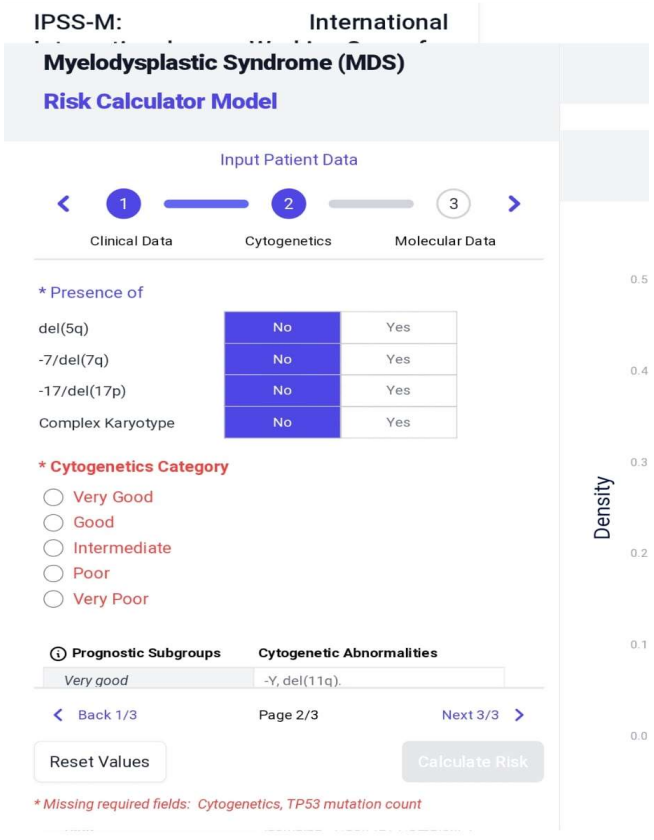
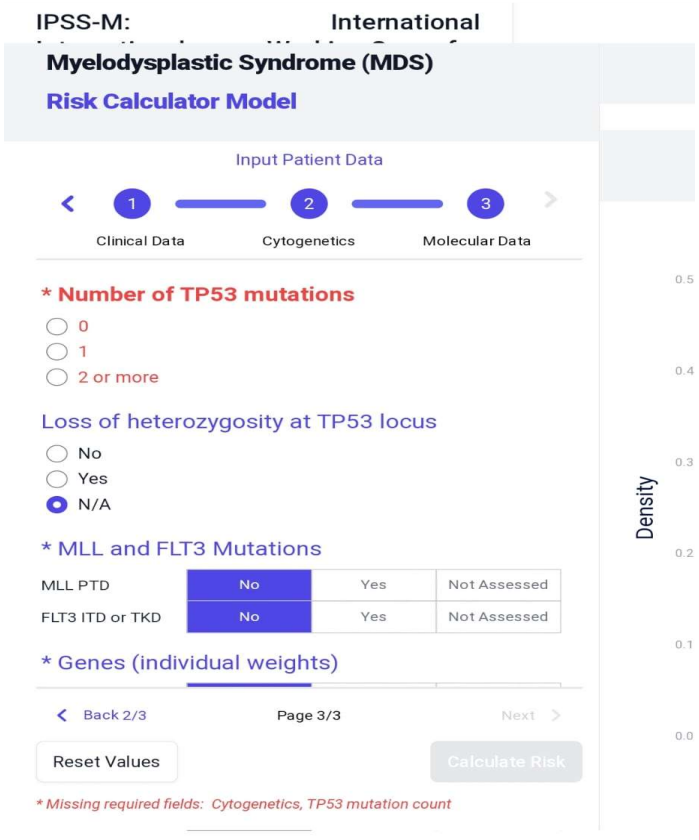
Translated to Spanish, French, German, Japanese…







https://mds-risk-model.com/

New IPSS: IPSS-M

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Tweet, 30 th October, 2022

Elli Papaemmanuil, PhD
@PapaemmanuilLab
4months since publication (https://bit.ly/3aNEU64), >5K unique users from 65 countries have used the IPSS-M model (https://mds-risk-model.com) to compute risk for 42,500 patient profiles.

High IF journal editor said "not ready for prime time". This is my type of impact factor.

New IPSS: IPSS-M

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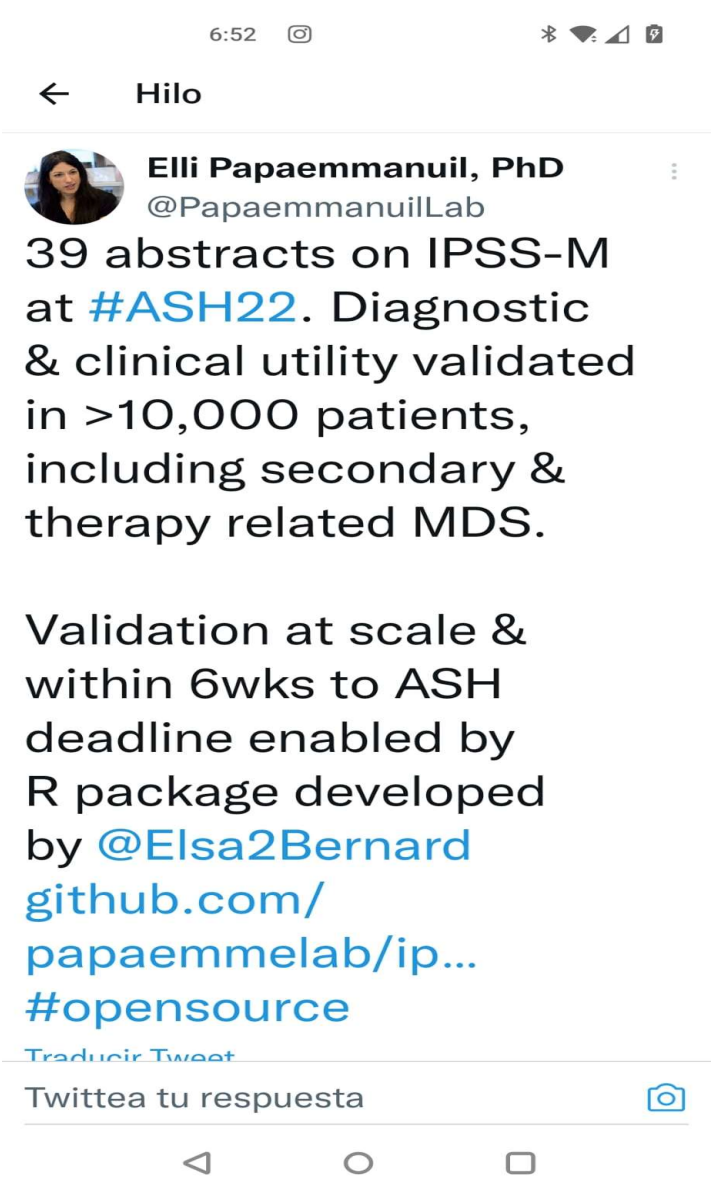
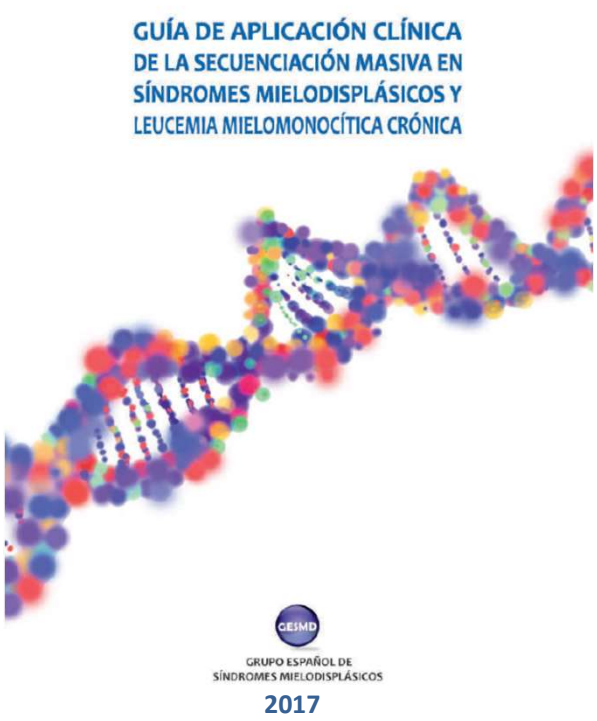
Tweet, 5th November, 2022



GRUPO ESPAÑOL DE SÍNDROMES MIELODISPLÁSICOS



- **¿Debemos incorporar los estudios moleculares en pacientes con sospecha o diagnóstico de SMD?**

- **A) no deben realizarse**
- **B) son recomendables**
- **C) son obligatorios**

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- Technical and methodological aspects
- Prognostic value of cytogenetic findings: IPSS-R
- Cytogenetic/genetic changes and IPSS-M
- **CONCLUSIONS**

To conclude: What should we do?

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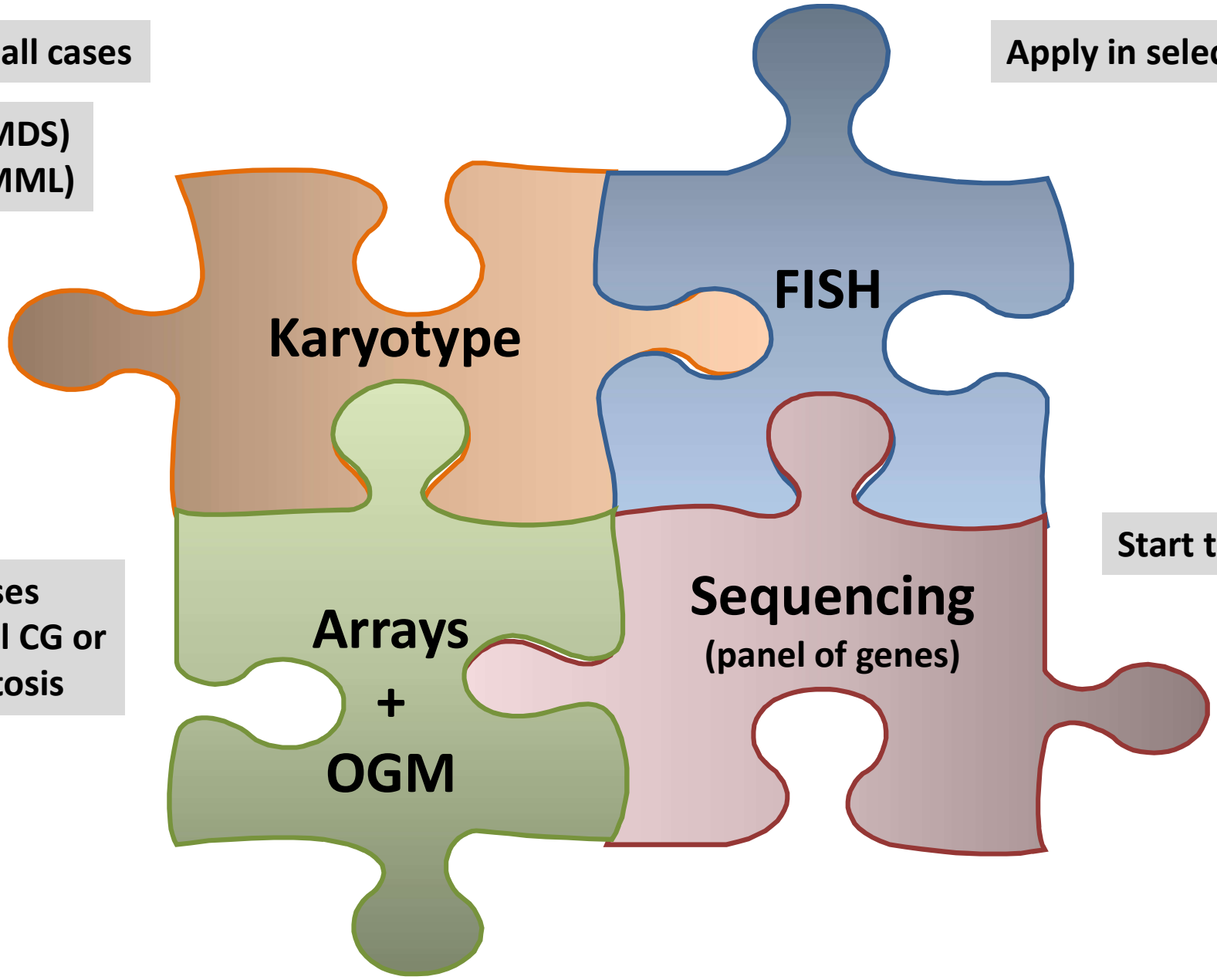
Apply in all cases

IPSS-R (MDS)
CPSS (CMML)



Apply in selected cases

Start to introduce

IPSS-M (MDS)

Apply in cases with normal CG or without mitosis