

Precision Oncology in Myeloid Malignancies

Incorporating computational risk models into the clinic

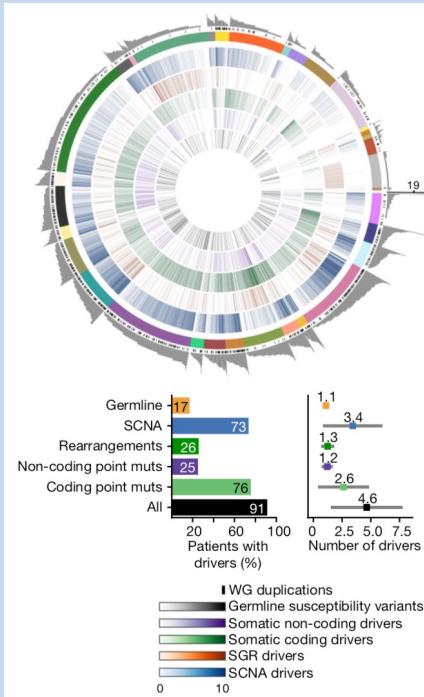
Elsa Bernard, PhD

Team Leader Computational Oncology

Gustave Roussy

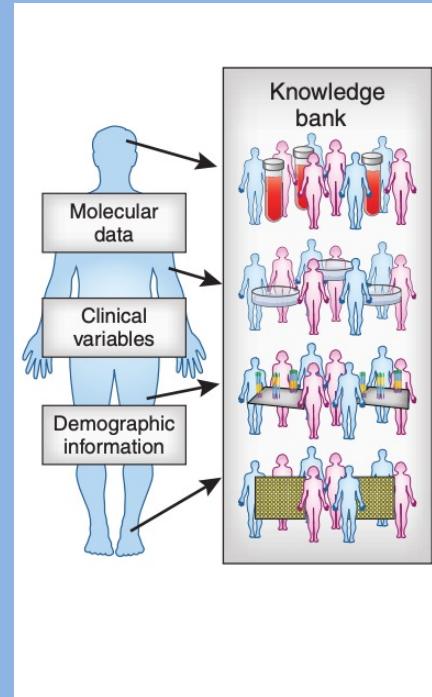


Cancer genomes



Campbell et al Nature 2020

Knowledge banks



Gerstung et al Nat Gen 2017 | Biankin 2017

Clinical implementation

Calculator [About](#) [References](#)

CMML CPSS-Mol
Estimate risk of progression to AML in those with CMML using molecular genetics data

Questions

1. Cytogenetics
2. ASXL1
3. NRAS
4. RUNX1
5. SETBP1
6. BM blasts
7. WBC
8. Transfusions

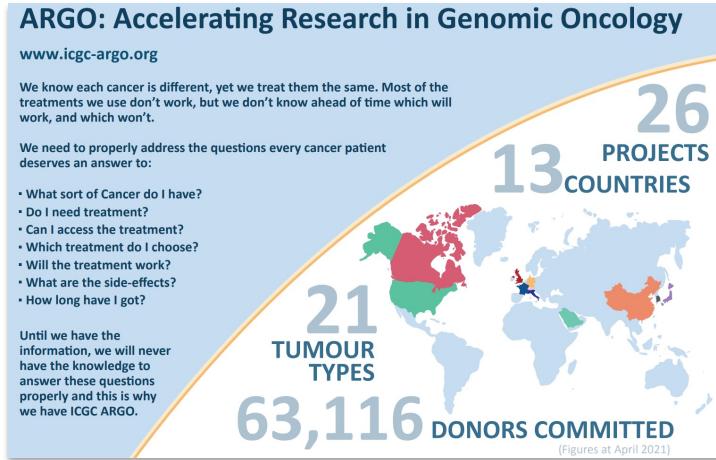
About
The CPSS-Mol is a new CMML-specific prognostic scoring system (CPSS) that incorporates molecular genetic data resulting in a 4-level integrated clinical/pathological/genetic risk stratification tool. This tool was derived from a cohort of European patients, 93% of whom possessed 1 or 38 somatic mutations. Based on multivariable Cox regression analyses, cytogenetic abnormalities and mutations in RUNX1, NRAS, SETBP1, and ASXL1 were independently associated with overall survival (OS). The CPSS-Mol fully retained its ability to risk stratify survival in an independent validation cohort of CMML patients.

References
Elena C, Galli A, Such E, et al. [Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia](#). Blood 2016;128(10):1408-1417.
The [CMML CPSS-Mol](#) calculator is created by QxMD.

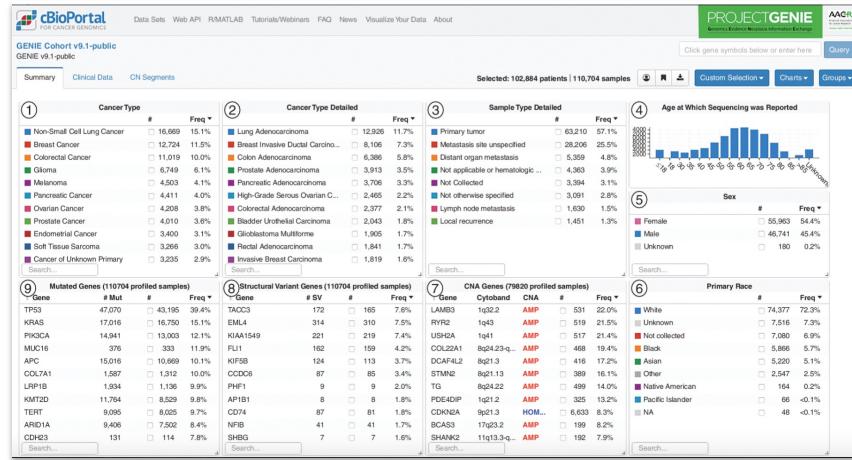
Elena et al Blood 2016

Large scale clinical cancer genomics initiatives

ICGC ARGO



AACR Project GENIE



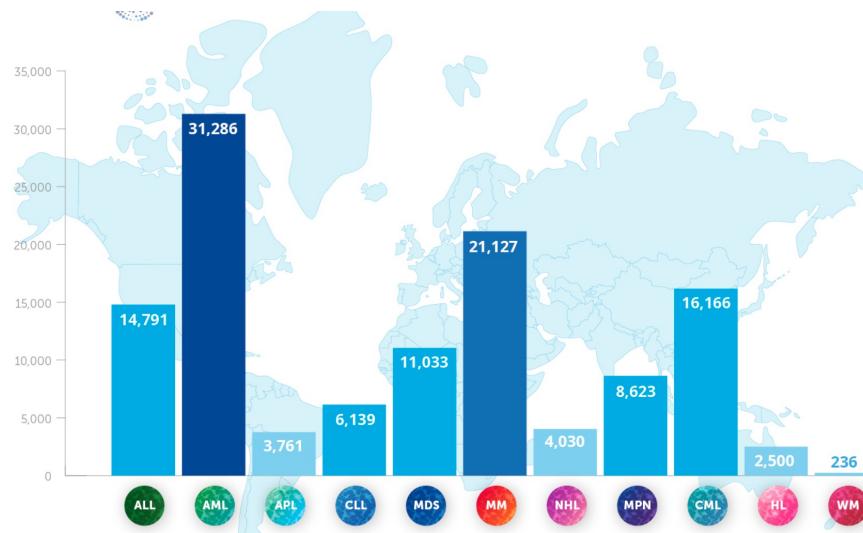
... Genomics England 100000 Genomes Project, Hartwig Medical Database, Harmony Alliance ...

Sources: icgc-argo.org | genie.cbiportal.org | genomicsengland.co.uk | hartwigmedicalfoundation.nl | harmony-alliance.eu

Large scale clinical cancer genomics initiatives



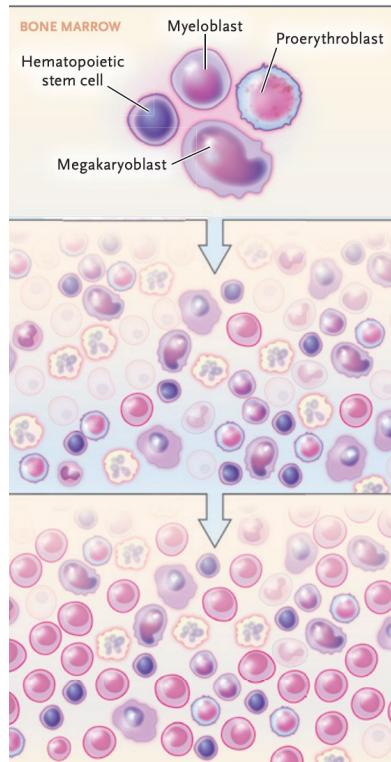
Harmony Alliance *big data for blood cancers*



... Genomics England 100000 Genomes Project, Hartwig Medical Database, Harmony Alliance ...

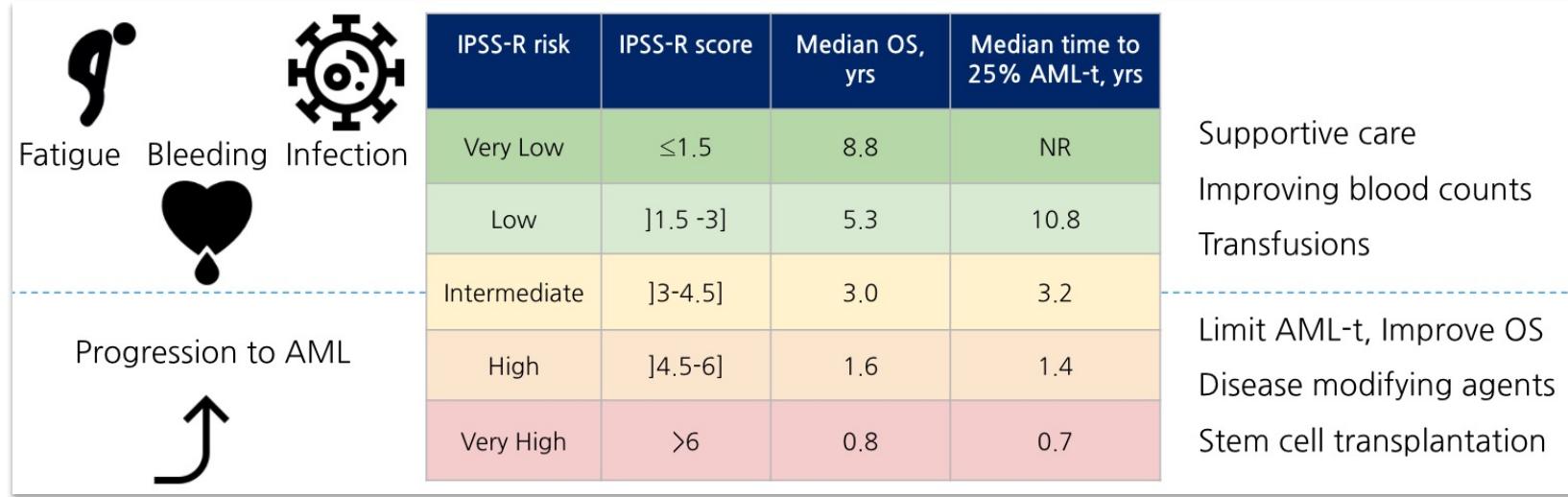
Myelodysplastic Syndromes ([MDS](#))

MDS



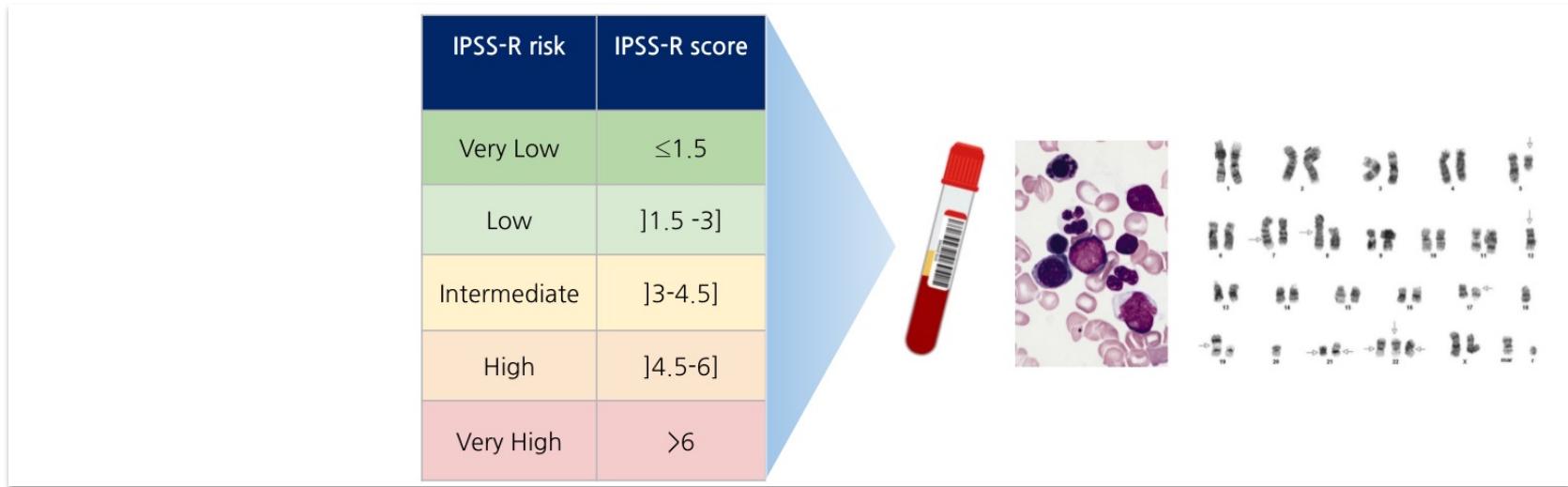
- Clonal stem cell myeloid neoplasms
- Mutation in hematopoietic stem cell | Differentiation block
- Age related incidence >60 years
- Ineffective hematopoiesis, morphologic dysplasia
- ~30% progress to AML ([acute myeloid leukemia](#))
- Limited treatment options
- < 1 year survival for high-risk patient

Risk stratification guides treatment decision in MDS



Revised International Prognostic Scoring System IPSS-R

Risk stratification guides treatment decision in MDS



Revised International Prognostic Scoring System IPSS-R

Prognostic value of gene mutations in MDS

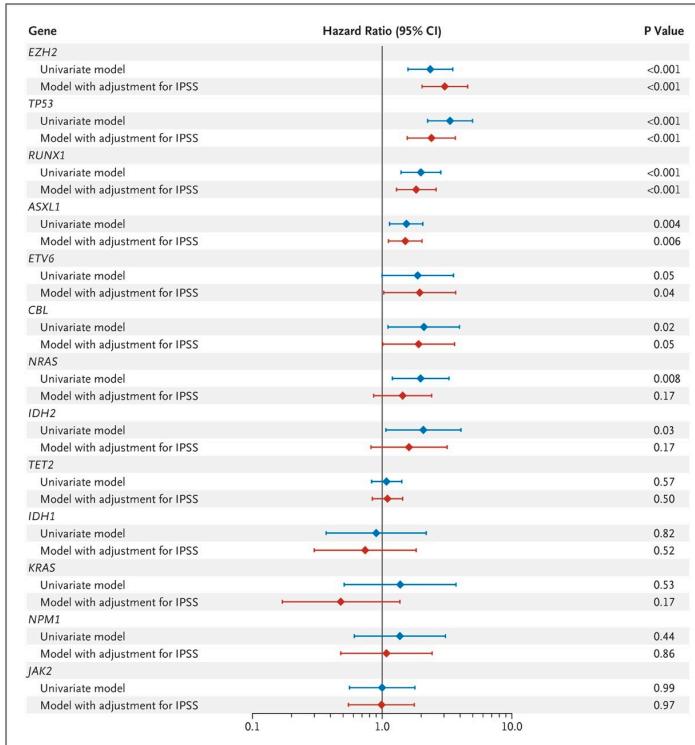


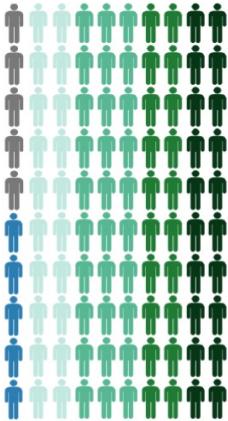
Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
<i>TP53</i> mutation present vs. absent	2.48 (1.60–3.84)	<0.001
<i>EZH2</i> mutation present vs. absent	2.13 (1.36–3.33)	<0.001
<i>ETV6</i> mutation present vs. absent	2.04 (1.08–3.86)	0.03
<i>RUNX1</i> mutation present vs. absent	1.47 (1.01–2.15)	0.047
<i>ASXL1</i> mutation present vs. absent	1.38 (1.00–1.89)	0.049

* The model was generated from a stepwise Cox regression model that included the International Prognostic Scoring System (IPSS) risk category (based on the percentage of blasts in bone marrow, the karyotype, and the number of cytopenias [see Table 2 in the Supplementary Appendix]), age, sex, and mutation status for genes that were mutated in 1% or more of the 428 samples for which the IPSS classification was recalculated. Age was included in the analysis as a categorical variable on the basis of a best-split algorithm showing a significant difference in overall survival between patients less than 55 years of age and those 55 years of age or older (see Table 8 in the Supplementary Appendix).

Need for a molecular prognostic risk score in MDS

Heterogeneous presentation & outcome



Cytogenetic abnormalities



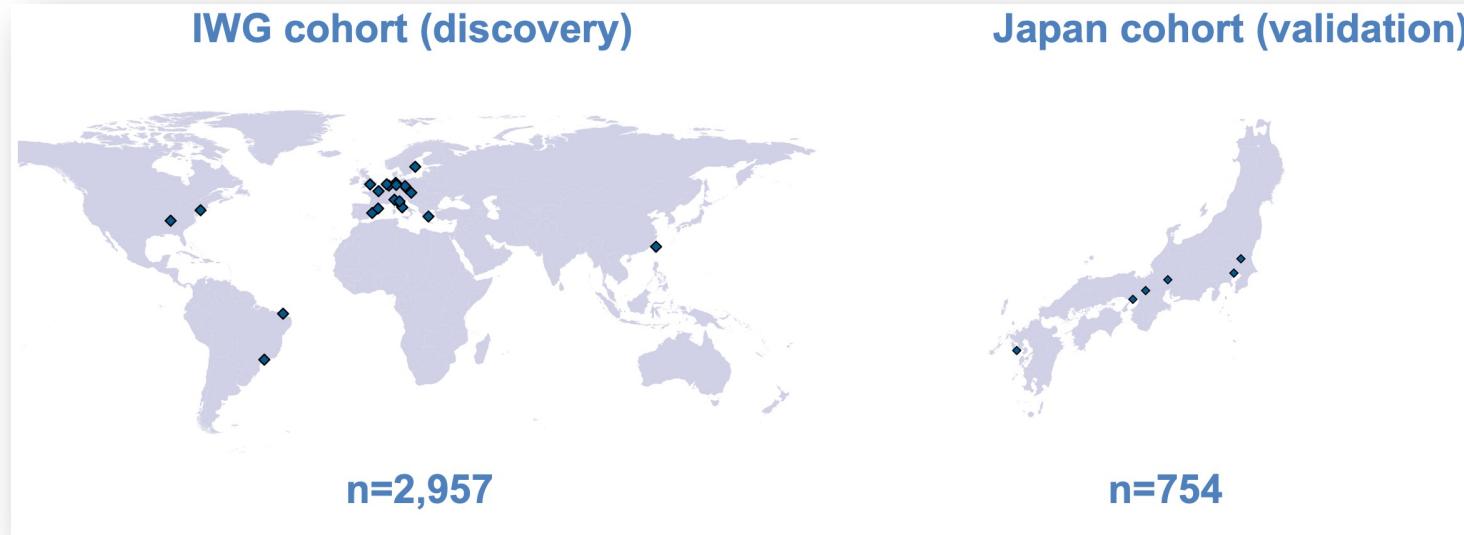
Prognostic value of gene mutations

Table 2. Hazard Ratios for Death in a Multivariable Model.*		
Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
<i>TP53</i> mutation present vs. absent	2.48 (1.60–3.84)	<0.001
<i>EZH2</i> mutation present vs. absent	2.13 (1.36–3.33)	<0.001
<i>ETV6</i> mutation present vs. absent	2.04 (1.08–3.86)	0.03
<i>RUNX1</i> mutation present vs. absent	1.47 (1.01–2.15)	0.047
<i>ASXL1</i> mutation present vs. absent	1.38 (1.00–1.89)	0.049

* The model was generated from a stepwise Cox regression model that included the International Prognostic Scoring System (IPSS) risk category (based on the percentage of blasts in bone marrow, the karyotype, and the number of cytogenetic anomalies [see Table 2 in the Supplementary Appendix]), sex, and mutation status for genes that were mutated in 1% or more of the 428 samples for which the IPSS classification was recalculated. Age was included in the analysis as a categorical variable on the basis of a best-split algorithm showing a significant difference in overall survival between patients less than 55 years of age and those 55 years of age or older (see Table 8 in the Supplementary Appendix).

Integrate gene mutations into routine MDS risk stratification

An international effort by the International Working Group (IWG) for the Prognosis of MDS



Heinz Tuechler, Peter L. Greenberg, Robert P. Hasserjian, Juan E. Arango Ossa, Yasuhito Nannya, Sean M. Devlin, Maria Creignou, Philippe Pinel, Lily Monnier, Juan S. Medina-Martinez, Yesenia Werner, Martin Jädersten, Ulrich Germing, Guillermo Sanz, Arjan A. van de Loosdrecht, Olivier Kosmider, Matilde Y. Follo, Felicitas Thol, Lurdes Zamora, Ronald F. Pinheiro, Andrea Pellagatti, Harold K. Elias, Detlef Haase, Christina Ganster, Lionel Ades, Magnus Tobiasson, Matteo Giovanni Della Porta, Akifumi-Kondo Takaori, Takayuki Ishikawa, Shigeru Chiba, Senji Kasahara, Yasushi Miyazaki, Pierre Fenaux, Monika Belickova, Michael R. Savona, Virginia M. Klimek, Fabio P. S. Santos, Jacqueline Boulwood, Ioannis Kotsianidis, Valeria Santini, Francesc Solé, Uwe Platzbecker, Michael Heuser, Peter Valent, Kazuma Ohyashiki, Carlo Finelli, Maria Teresa Voso, Lee-Yung Shih, Michaela Fontenay, Joop H. Jansen, José Cervera, Norbert Gattermann, Benjamin L. Ebert, Rafael Bejar, Luca Malcovati, Mario Cazzola, Seishi Ogawa, Eva Hellström-Lindberg, Papaemmanuil Elli

A representative multi-center diagnostic MDS cohort

n=2,957



Inclusion criteria:

Diagnostic treatment naive samples

Blast < 20% | White blood cell count < $13 \times 10^9/L$

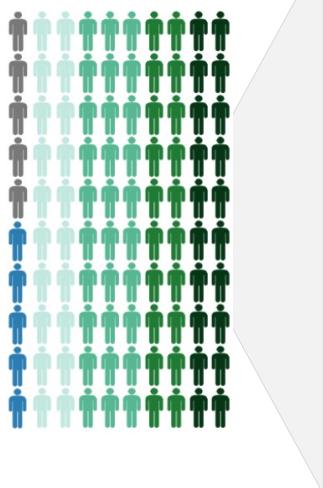
- Median Age 72y (39-88)
- Blasts 3% (0-16) | Hb 10g/dL (6-14) | Plt $130 \times 10^9/L$ (13-542)
- Representative of all IPSS-R risk categories and WHO subtypes.
- Clinical outcomes for 95% of patients.
- Median follow-up 3.8 years.

Comprehensive molecular annotation in MDS

n=2,957

3,186 cytogenetic alterations 41% of patients

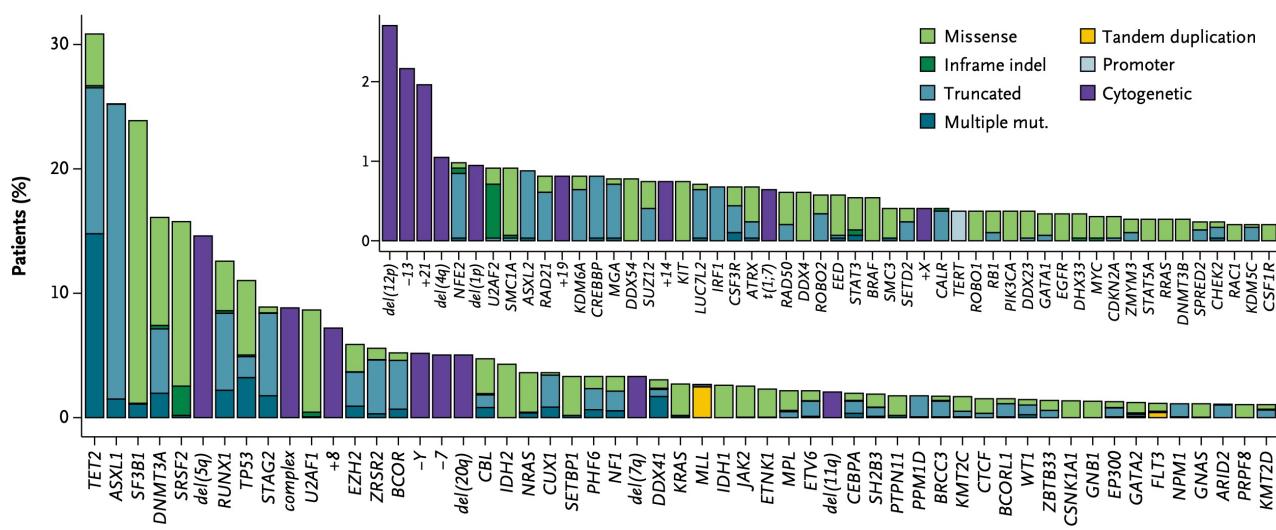
9,254 mutations in 121 genes
90% of patients



- 94% of patients had at least one oncogenic lesion
- 53% gene mutations only | 4% cytogenetic alterations only | 37% both

Comprehensive molecular annotation in MDS

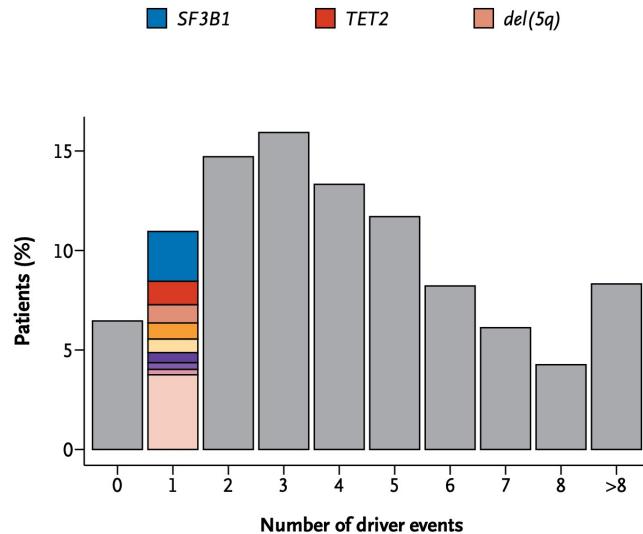
n=2,957



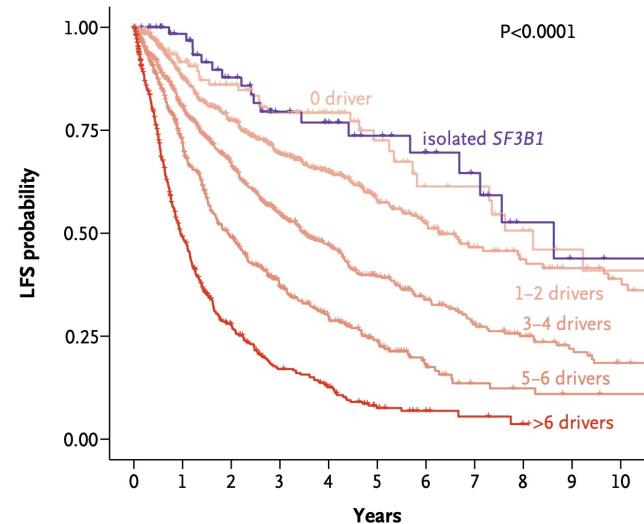
- 48 genes mutated in >1% of patients.
- Median 4 lesions per patient (range 0-20).

Number of mutations impacts outcome

Only 10% of patients with 1 driver alteration



Worse outcome with number of drivers



Single mutations not sufficient to capture risk, need inclusive models for risk stratification

Number of mutations impacts outcome

2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	<ul style="list-style-type: none">t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11†,‡Mutated <i>NPM1</i>†,§ without <i>FLT3</i>-ITDbZIP in-frame mutated <i>CEBPA</i>¶
Intermediate	<ul style="list-style-type: none">Mutated <i>NPM1</i>†,§ with <i>FLT3</i>-ITDWild-type <i>NPM1</i> with <i>FLT3</i>-ITD (without adverse-risk genetic lesions)t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	<ul style="list-style-type: none">t(6;9)(p23.3;q34.1)/DEK::<i>NUP214</i>t(v;11q23.3)/<i>KMT2A</i>-rearranged#t(9;22)(q34.1;q11.2)/<i>BCR</i>::<i>ABL</i>t(8;16)(p11.2;p13.3)/<i>KAT6A</i>::<i>CREBBP</i>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2</i>, <i>MECOM</i>(<i>EVI1</i>)t(3q26.2;v)/<i>MECOM</i>(<i>EVI1</i>)-rearranged-5 or del(5q); -7; -17/abn(17p)Complex karyotype,** monosomal karyotype††Mutated <i>ASXL1</i>, <i>BCOR</i>, <i>EZH2</i>, <i>RUNX1</i>, <i>SF3B1</i>, <i>SRSF2</i>, <i>STAG2</i>, <i>U2AF1</i>, and/or <i>ZRSR2</i>‡‡Mutated <i>TP53</i>³

State-of-the art approaches for risk stratification in myeloid diseases (e.g., AML)
do not consider the additive effect of mutations, but a 1:1 relation gene:risk group.

→ Need for innovation in MDS

Single mutations not sufficient to capture risk, need inclusive models for risk stratification

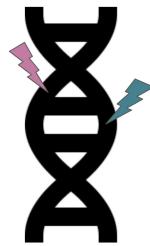
- 1. Features definition (e.g. *TP53* allelic state)**
- 2. Model development (a personalized risk system)**
- 3. Clinical implementation (web tools)**

1. Features definition (e.g. *TP53* allelic state)

2. Model development (a personalized risk system)

3. Clinical implementation (web tools)

Encoding of mutational status



1

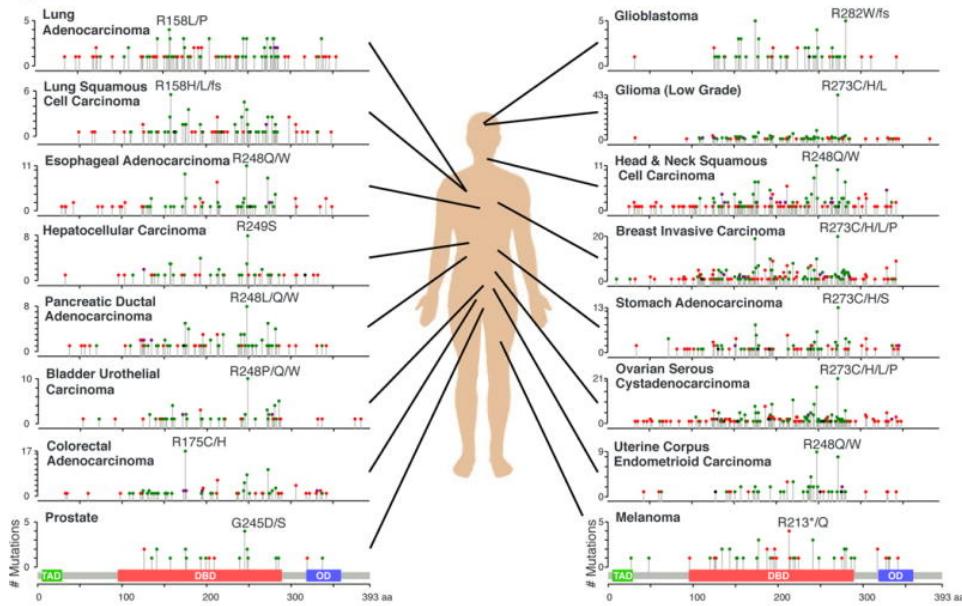
Mutated

0

Wild type

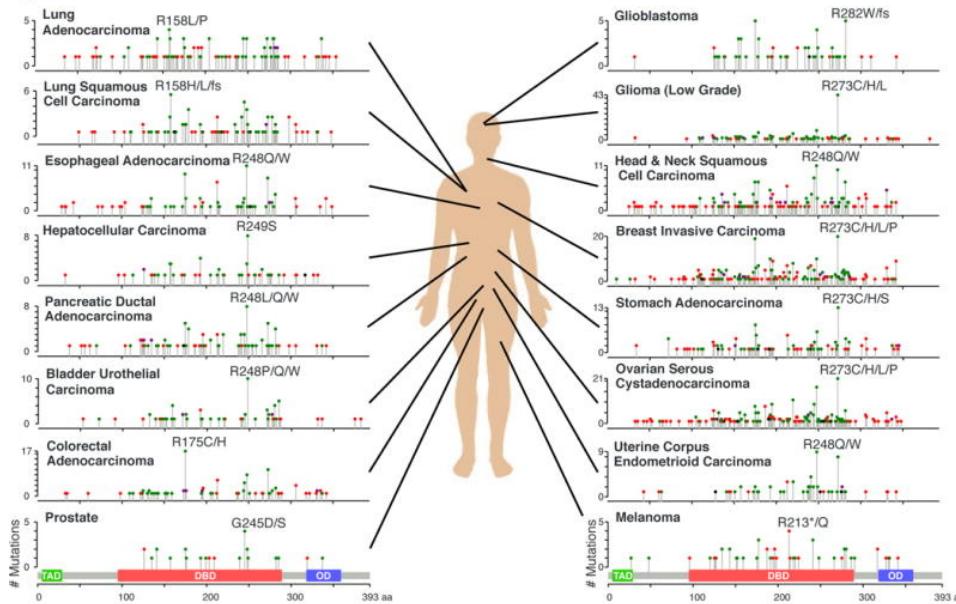
TP53 mutations in cancer

A

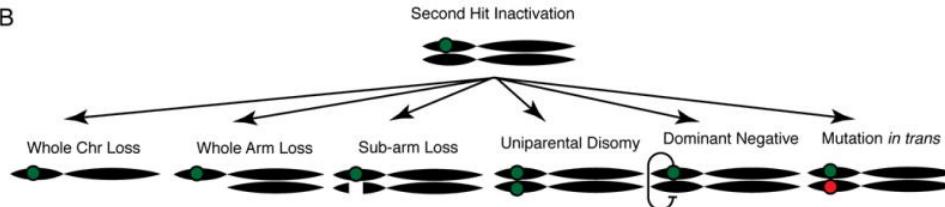


TP53 mutations in cancer

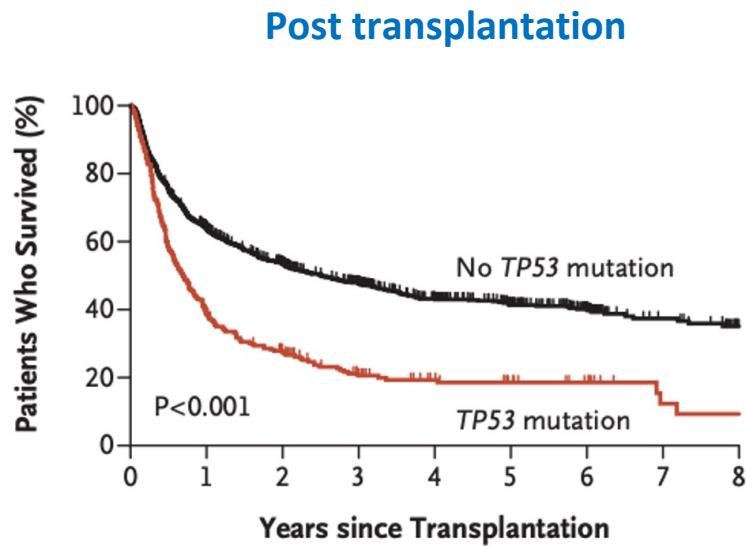
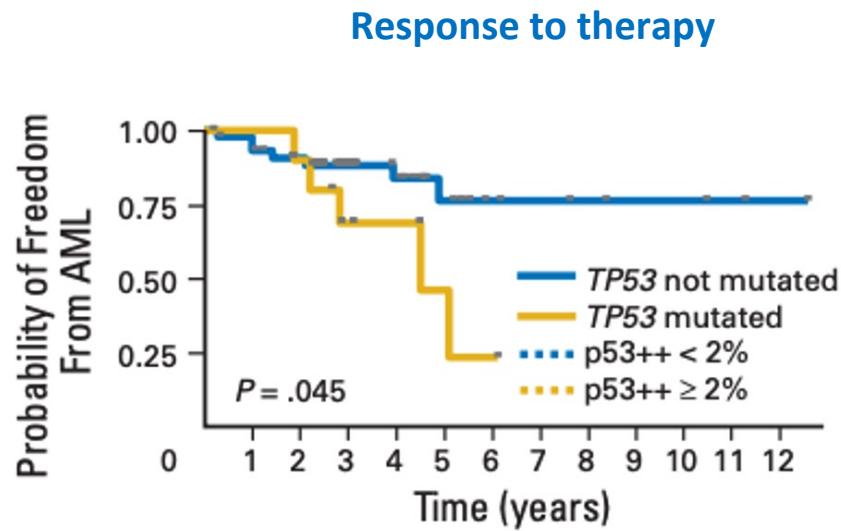
A



B



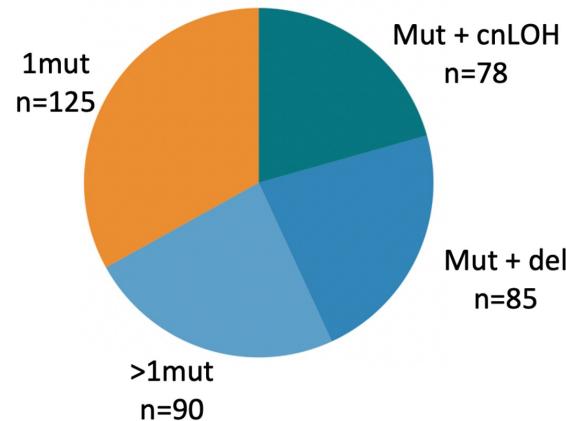
TP53 mutations in myeloid neoplasms



TP53 mutations are associated with resistance to therapy and poor prognosis

***TP53* allelic state is a critical biomarker in MDS**

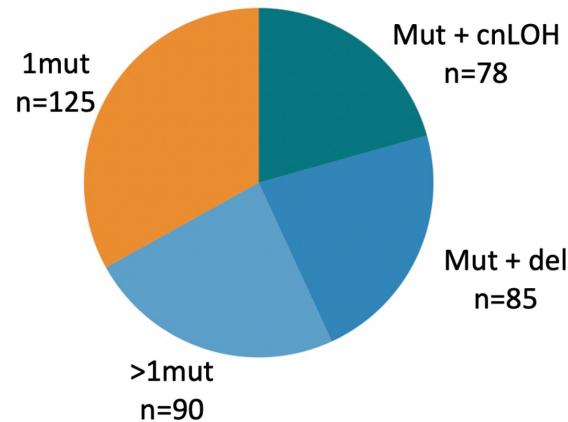
**1/3 patients have mono-allelic
TP53 mutations**



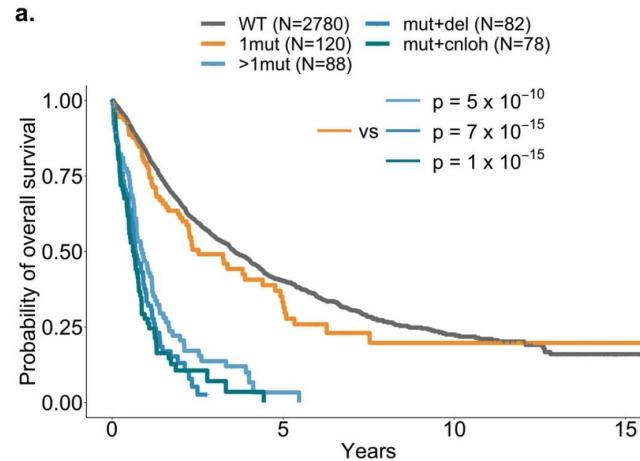
Not all *TP53* mutations are equal

***TP53* allelic state is a critical biomarker in MDS**

**1/3 patients have mono-allelic
TP53 mutations**



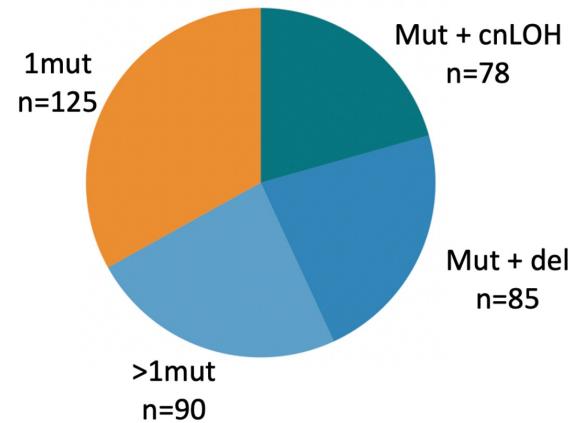
***TP53* allelic state (mono-allelic/multi-hit)
associated with distinct outcomes**



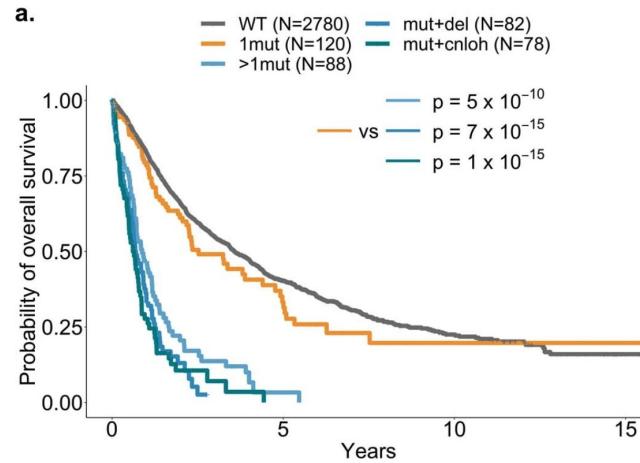
Not all *TP53* mutations are equal

***TP53* allelic state is a critical biomarker in MDS**

**1/3 patients have mono-allelic
TP53 mutations**



***TP53* allelic state (mono-allelic/multi-hit)
associated with distinct outcomes**



Need to map integrate *TP53* mutation, LOH mapping and cytogenetic finding on chr 17

TP53 allelic state is a critical biomarker in MDS

WHO 2022 Classification of MDS

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

MDS with defining genetic abnormalities	Blasts	Cytogenetics	Mutations
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	
MDS with low blasts and <i>SF3B1</i> mutation ^a (MDS- <i>SF3B1</i>)		Absence of 5q deletion, monosomy 7, or complex karyotype	<i>SF3B1</i>
MDS with biallelic <i>TP53</i> inactivation (MDS-bi <i>TP53</i>)	<20% BM and PB	Usually complex	Two or more <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
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		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

^aDetection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

^bBy definition, ≤25% bone marrow cellularity, age adjusted.

BM bone marrow, PB peripheral blood, cnLOH copy neutral loss of heterozygosity.

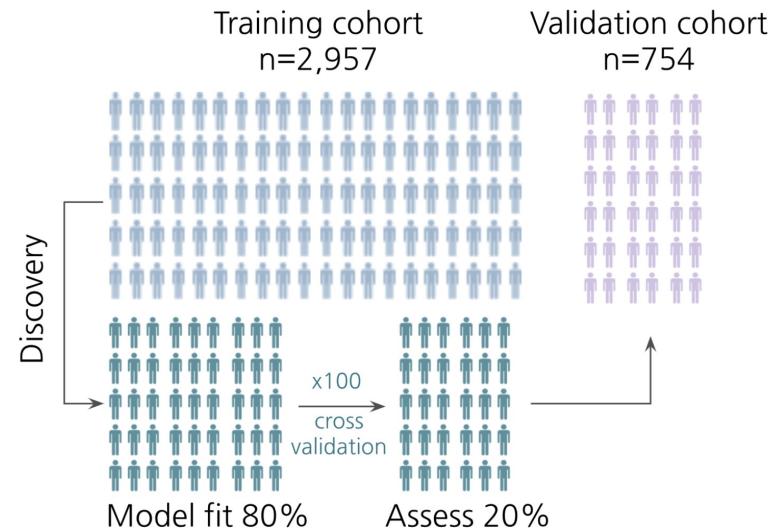
MDS with bi-allelic *TP53* inactivation introduced as a new WHO 2022 diagnostic class

1. Features definition (e.g. *TP53* allelic state)
2. Model development (a personalized risk system)
3. Clinical implementation (web tools)

Molecular International Prognostic Scoring System (IPSS-M)

Leukemia-free survival (LFS) primary endpoint

1. Feature encoding clinical and molecular variables.
2. Feature selection independent prognostic variables.
3. IPSS-M risk score continuous patient-specific score.
4. IPSS-M risk categories discrete risk grouping



The IPSS-M model

Model fit with a robust Cox multivariable regression for LFS adjusted for age, sex, and MDS type

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) — $\times 10^9/l$	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) [¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{5q}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [#]	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

[▲]residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes

Individual weights attributed to each variable

1 genetic variable from 15 residual genes[▲]

Number of mutated genes (0, 1 or 2)

The IPSS-M model

Model fit with a robust Cox multivariable regression for LFS adjusted for age, sex, and MDS type

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) — $\times 10^9/l$	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) [¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{5q}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [*]	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

[†]residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes

Individual weights attributed to each variable

1 genetic variable from 15 residual genes[^]

Number of mutated genes (0, 1 or 2)

The IPSS-M model

Model fit with a robust Cox multivariable regression for LFS
adjusted for age, sex, and MDS type

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) — $\times 10^9/l$	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) [¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{5q}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [*]	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

[†]residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes

Individual weights attributed to each variable

1 genetic variable from 15 residual genes[^]

Number of mutated genes (0, 1 or 2)

The IPSS-M model

Model fit with a robust Cox multivariable regression for LFS adjusted for age, sex, and MDS type

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) — $\times 10^9/l$	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) [¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{5q}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [#]	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

[▲]residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes

Individual weights attributed to each variable

1 genetic variable from 15 residual genes[▲]

Number of mutated genes (0, 1 or 2)

The IPSS-M model

Model fit with a robust Cox multivariable regression for LFS adjusted for age, sex, and MDS type

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) — $\times 10^9/l$	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) [¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{5q}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [#]	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

[†]residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

Continuous clinical parameters

Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes

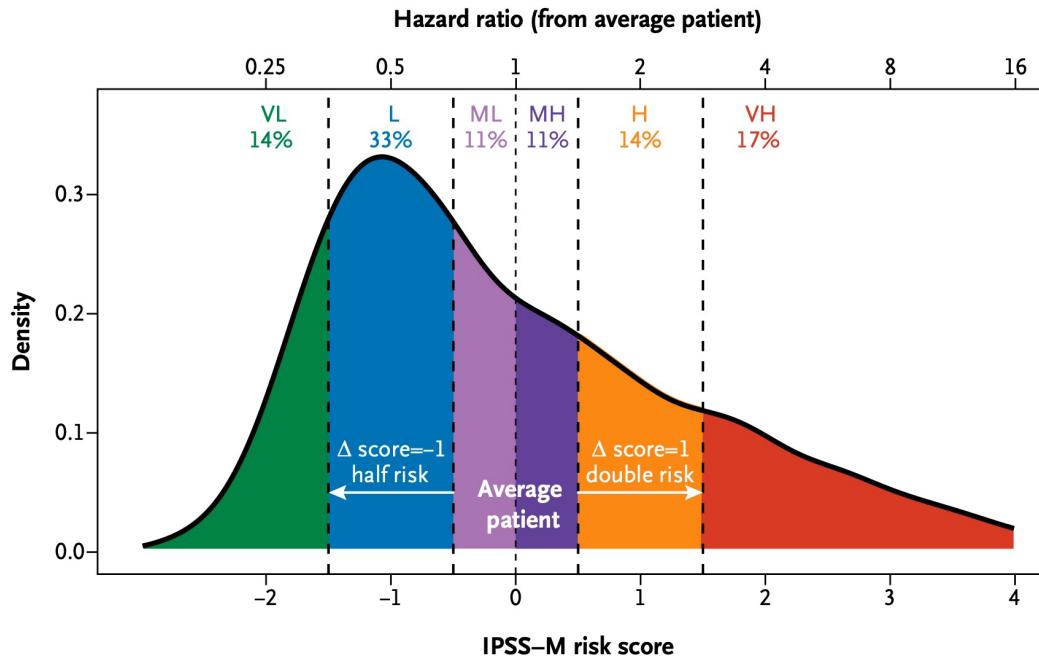
Individual weights attributed to each variable

1 genetic variable from 15 residual genes[^]

Number of mutated genes (0, 1 or 2)

The IPSS-M risk score

A continuous and interpretable risk score *i.e.*, patient-specific

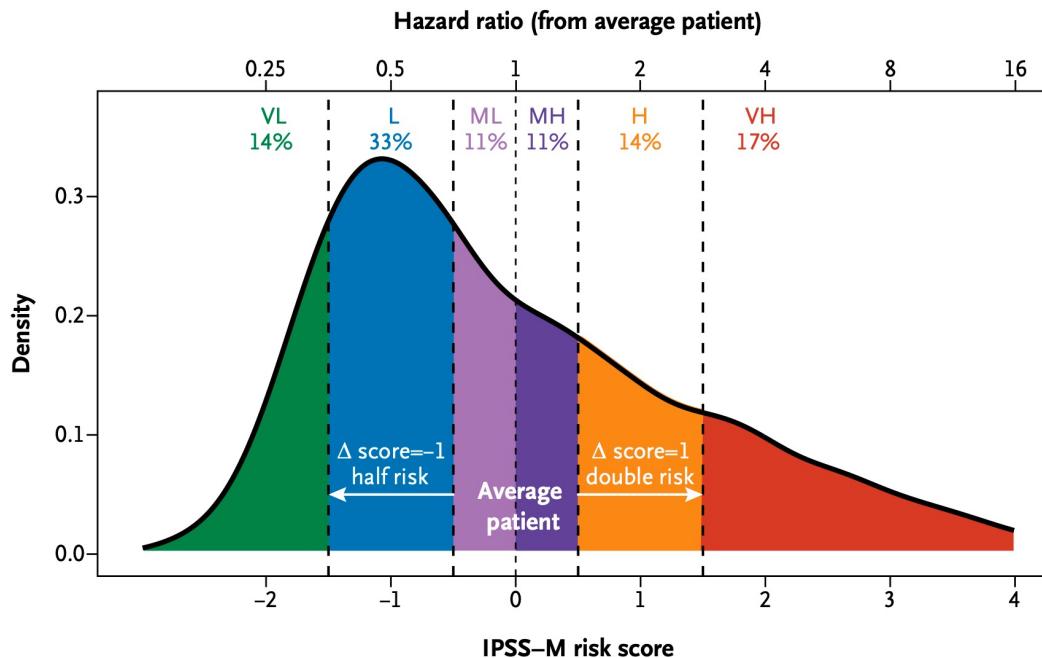


Prominent 0 value for an average patient.

One unit increase/decrease in risk score results in double/half risk.

The IPSS-M risk categories

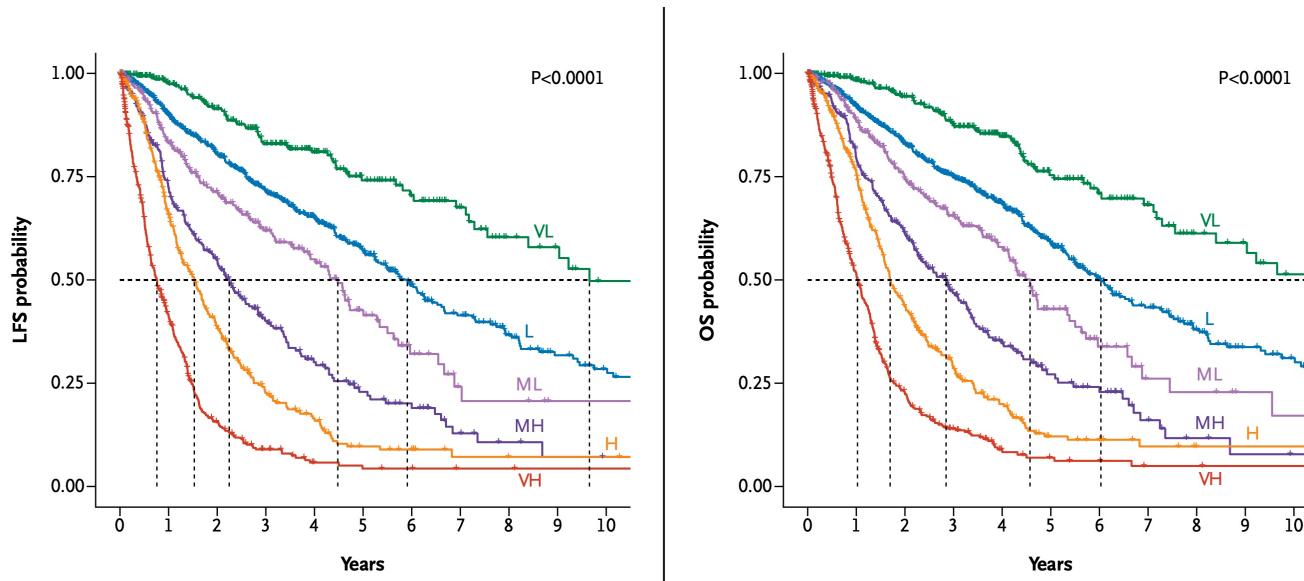
A six-category risk schema



Very Low | Low | Moderate Low | Moderate High | High | Very High

The IPSS-M risk categories

A six-category risk schema



Optimized separation of clinical outcomes with IPSS-M risk groups

The IPSS-M risk categories

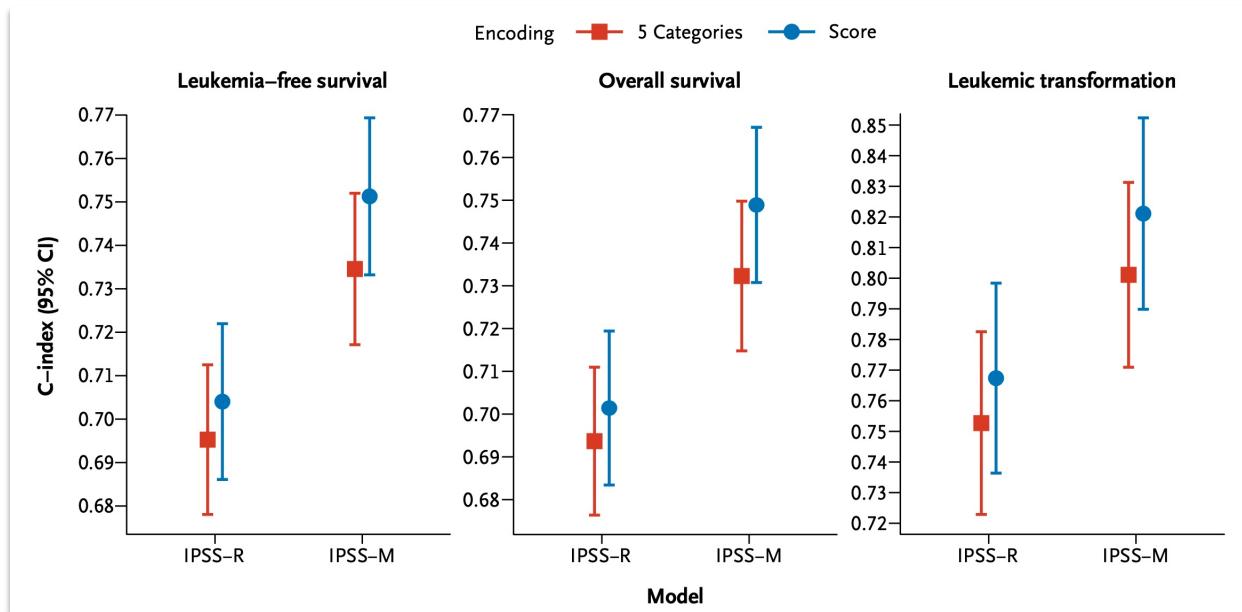
A six-category risk schema

Table 2. Summary of Clinical Outcomes for 2701 Patients by IPSS-M Risk Category.*

Characteristic	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients — No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39–0.67)	1.0 (Reference)	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS (25–75% range) — yr‡	9.7 (5.0–17.4)	5.9 (2.6–12.0)	4.5 (1.6–6.9)	2.3 (0.91–4.7)	1.5 (0.80–2.8)	0.76 (0.33–1.5)
Median OS (25–75% range) — yr	10.6 (5.1–17.4)	6.0 (3.0–12.8)	4.6 (2.0–7.4)	2.8 (1.2–5.5)	1.7 (1.0–3.4)	1.0 (0.5–1.8)
AML-t — %						
By 1 yr	0.0	1.7	4.9	9.5	14.3	28.2
By 2 yr	1.2	3.4	8.8	14.0	21.2	38.6
By 4 yr	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML — %						
By 1 yr	2.2	8.5	12.0	18.0	19.3	30.6
By 2 yr	7.0	16.2	19.8	31.1	39.8	45.6
By 4 yr	15.9	29.5	33.6	51.1	54.2	51.3

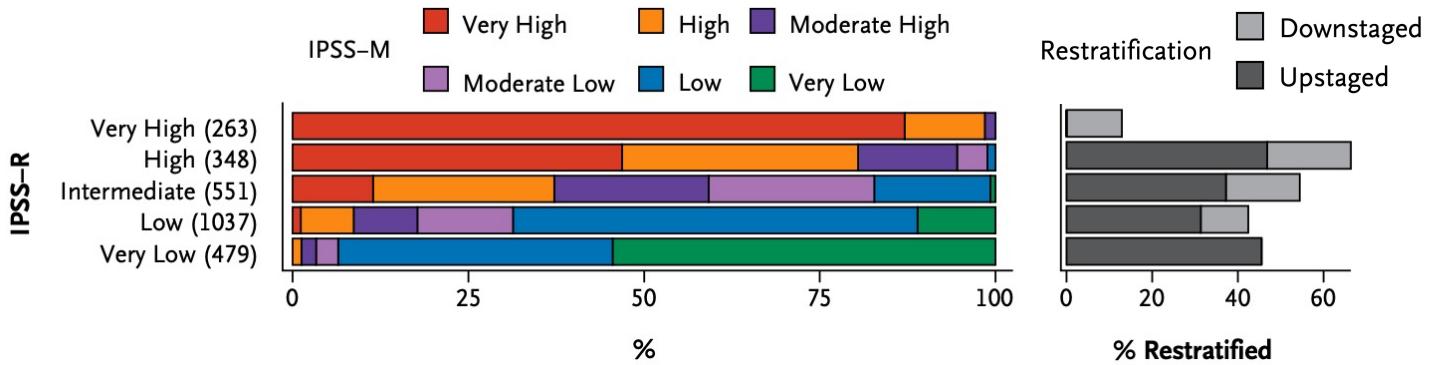
Optimized separation of clinical outcomes with IPSS-M risk groups

Improvement in risk discrimination across clinical endpoints



Five points increase in concordance index from IPSS-R to IPSS-M
across clinical endpoints (LFS, OS, AML-t)

1 in 2 patients with MDS were re-stratified in risk

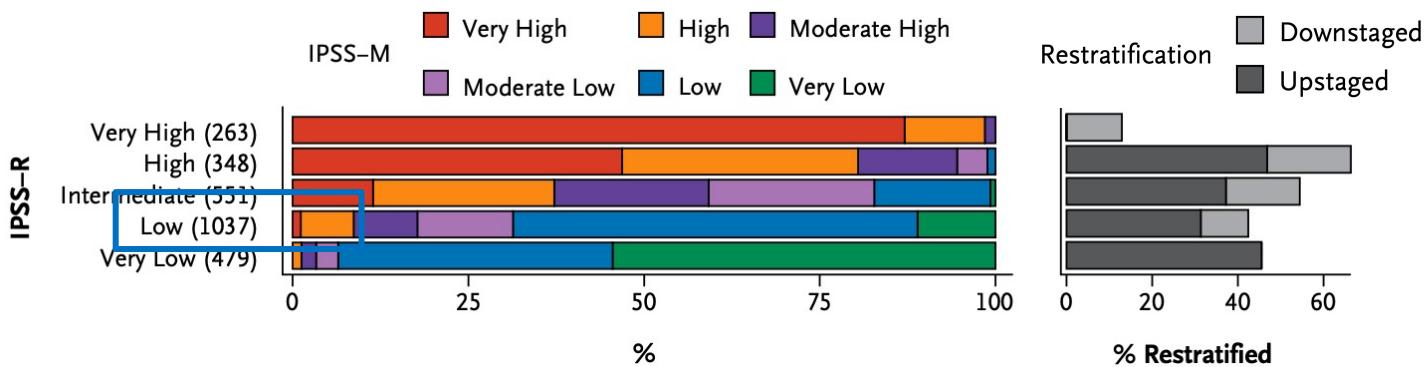


46% (n=1,223) of patients were re-stratified

7% (n=196) of patients were re-stratified by more than one strata

Implications for clinical decision making

1 in 2 patients with MDS were re-stratified in risk



46% (n=1,223) of patients were re-stratified

7% (n=196) of patients were re-stratified by more than one strata

Implications for clinical decision making

1. Features definition (e.g. *TP53* allelic state)
2. Model development (a personalized risk system)
3. Clinical implementation (web tools)

Expedite validation and dissemination of the IPSS-M



1. Data release (cBioPortal)



2. Open source software (R)



3. Web tool and mobile apps



Expedite validation and dissemination of the IPSS-M

Datasheet
with input
variables

<https://github.com/papaemmelab/ipssm>

ipssm

R Package for the Molecular International Prognostic Scoring System (IPSS-M) for Myelodysplastic Syndromes.

Installation instructions

```
# install devtools if you don't have it already for easy installation
# install.packages("devtools")
library(devtools)
install_github("papaemmelab/ipssm", ref = "main")
```

Usage

The workflow below consists of 4 simple steps, namely 1) Read your input data file and perform some validation on the data, 2) Process the variables in a suitable format for the model, 3) Calculate the IPSS-M risk score and risk category (under the best, mean, and worst scenario to account for missing data if there are some), 4) Annotate the results.

```
# load the ipssm library
library("ipssm")
# path to your input data file
path.file <- system.file("extdata", "IPSSMexample.csv", package = "ipssm")
#path.file <- system.file("extdata", "IPSSMexample.xlsx", package = "ipssm") # equivalent

# 1) Read and Validate File
dd <- IPSSMread(path.file)

# 2) Process User Input Variables into Model Variables
dd.process <- IPSSMprocess(dd)

# 3) Calculate IPSS-M
dd.res <- IPSSMmain(dd.process)

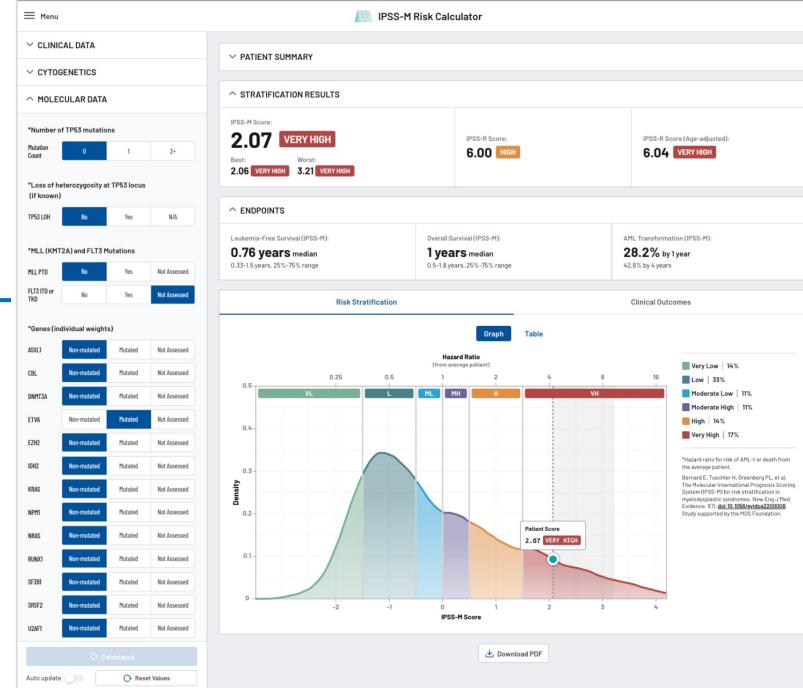
# 4) Annotate Results
dd.annot <- IPSSMannotate(dd.res)
```



IPSS-M
risk score and
category

Expedite validation and dissemination of the IPSS-M

Patient specific
input variables



Patient specific
IPSS-M results
and visualization

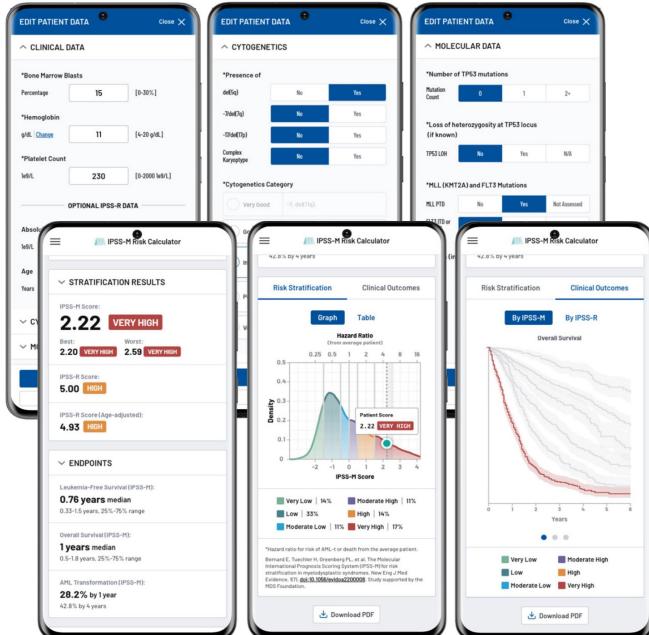


Juan Arango Ossa

Expedite validation and dissemination of the IPSS-M

www.mds-risk-model.com

Input Patient Data and Receive Stratification Results



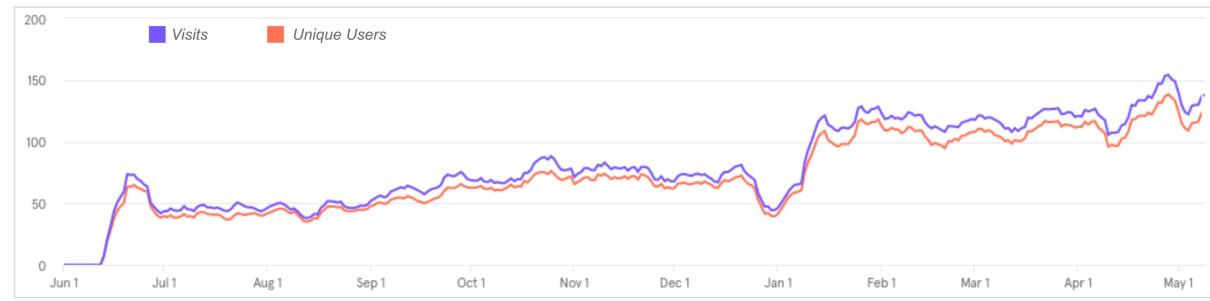
Patient specific
input variables

Patient specific
IPSS-M results
and visualization

Expedite validation and dissemination of the IPSS-M

www.mds-risk-model.com

+90 Countries	+17,5K Accrued Daily Users	+27K Visits
+96K Computed IPSS-M	150 Daily visitors	>90% Start → Compute



Summary: integrate genomic profiling for routine diagnostic and prognostication clinical use in MDS

Biomarker discovery for risk stratification

TP53 allelic state

MLL PTD

SF3B1-mutant MDS

Novel clinico-genomic risk system

IPSS-M

Risk score (personalized)

Risk category (discrete)

Reproducibility & dissemination

cBioPortal

R package

Web calculator & Apps

Validation & Extension

External

Multi-center

Secondary/hypoplastic/SCT

bi-*TP53* WHO 2022 class

NCCN 2023 guidelines

mds-risk-model.com

**Sauta et al JCO 2023
Kewan et al Blood 2023
Baer et al Leukemia 2023
Aguirre et al Leukemia 2023**

Merci

Interested in Computational Oncology?

Elsa Bernard, PhD

Team Computational Oncology

Gustave Roussy

Internship/phd/postdoc positions available

Acknowledgement

KAROLINSKA INSTITUTE
DUSSELDORF MDS REGISTRY
UNIVERSITY OF PAVIA
LA FE UNIVERSITY HOSPITAL
RADBOUDUMC MEDICAL CENTER NIJMEGEN AMSTERDAM UMC/VU UNIVERSITY MEDICAL CENTER
COCHIN HOSPITAL
CHANG GUNG MEMORIAL HOSPITAL
GRUPPO ROMANO LAZIALE MDS
UNIVERSITY OF BOLOGNA
MEDICAL UNIVERSITY OF VIENNA
HANNOVER MEDICAL SCHOOL
UNIVERSITY HOSPITAL DRESDEN
FEDERAL UNIVERSITY OF CEARA
INSTITUT JOSEP CARRERAS
AOU CAREGGI HOSPITAL
DEMOCRITUS UNIVERSITY OF THRACE
UNIVERSITY OF OXFORD
HOSPITAL ISRAELITA ALBERT EINSTEIN
MEMORIAL SLOAN KETTERING CANCER CENTER
VANDERBILT UNIVERSITY
INSTITUTE OF HEMATOLOGY AND BLOOD TRANSFUSION
UNIVERSITY MEDICINE GOTTINGEN
RETE EMATOLOGICA LOMBARDA
SAINT LOUIS HOSPITAL



Heinz Tuechler, Peter L. Greenberg, Robert P. Hasserjian, Juan E. Arango Ossa, Yasuhito Nannya, Sean M. Devlin, Maria Creignou, Philippe Pinel, Lily Monnier, Gunes Gundem, Juan S. Medina-Martinez, Dylan Domenico, Yesenia Werner, Martin Jädersten, Ulrich Germing, Guillermo Sanz, Arjan A. van de Loosdrecht, Olivier Kosmider, Matilde Y. Follo, Felicitas Thol, Lurdes Zamora, Ronald F. Pinheiro, Andrea Pellagatti, Harold K. Elias, Detlef Haase, Christina Ganster, Lionel Ades, Magnus Tobiasson, Laura Palomo, Matteo Giovanni Della Porta, Akifumi-Kondo Takaori, Takayuki Ishikawa, Shigeru Chiba, Senji Kasahara, Yasushi Miyazaki, Agnes Viale, Kety Huberman, Pierre Fenaux, Monika Belickova, Michael R. Savona, Virginia M. Klimek, Fabio P. S. Santos, Jacqueline Boultwood, Ioannis Kotsianidis, Valeria Santini, Francesc Solé, Uwe Platzbecker, Michael Heuser, Peter Valent, Kazuma Ohyashiki, Carlo Finelli, Maria Teresa Voso, Lee-Yung Shih, Michaela Fontenay, Joop H. Jansen, José Cervera, Norbert Gattermann, Benjamin L. Ebert, Rafael Bejar, Luca Malcovati, Mario Cazzola, Seishi Ogawa, Eva Hellström-Lindberg, Elli Papaemmanuil

MDS patients and families



**Memorial Sloan Kettering Cancer Center
Computation Oncology Service**

Papaemmanuil Lab

Elli Papaemmanuil
Dylan Domenico
Maria Sirenko
Gunes Gundem
Joseph McCarter
Genesis Pinada

Sean Devlin

IPSS-M Oversight Committee

Peter Greenberg
Heinz Tuechler
Luca Malcovati
Raf Bejar

MDS Foundation
Tracey Iraca

Juan E. Arango Ossa
Noushin Farnoud
Georgios Asimomitis
Jesus Gutierrez-Abril
Sarun Sereewattanawoot
Charlotte Brierley

Kety Huberman

Eva Hellström-Lindberg
Seishi Ogawa
Mario Cazzola
Ben Ebert

Lea Harrison