

# Precision Oncology in Myeloid Malignancies

*Incorporating computational risk models into the clinic*

Elsa Bernard, PhD

Team Leader Computational Clinical Oncology

Gustave Roussy



computational clinical oncology  
[elsabernardlab.com](http://elsabernardlab.com)

# Precision Oncology in Myeloid Malignancies

*How to build a prognostic score?*

Elsa Bernard, PhD

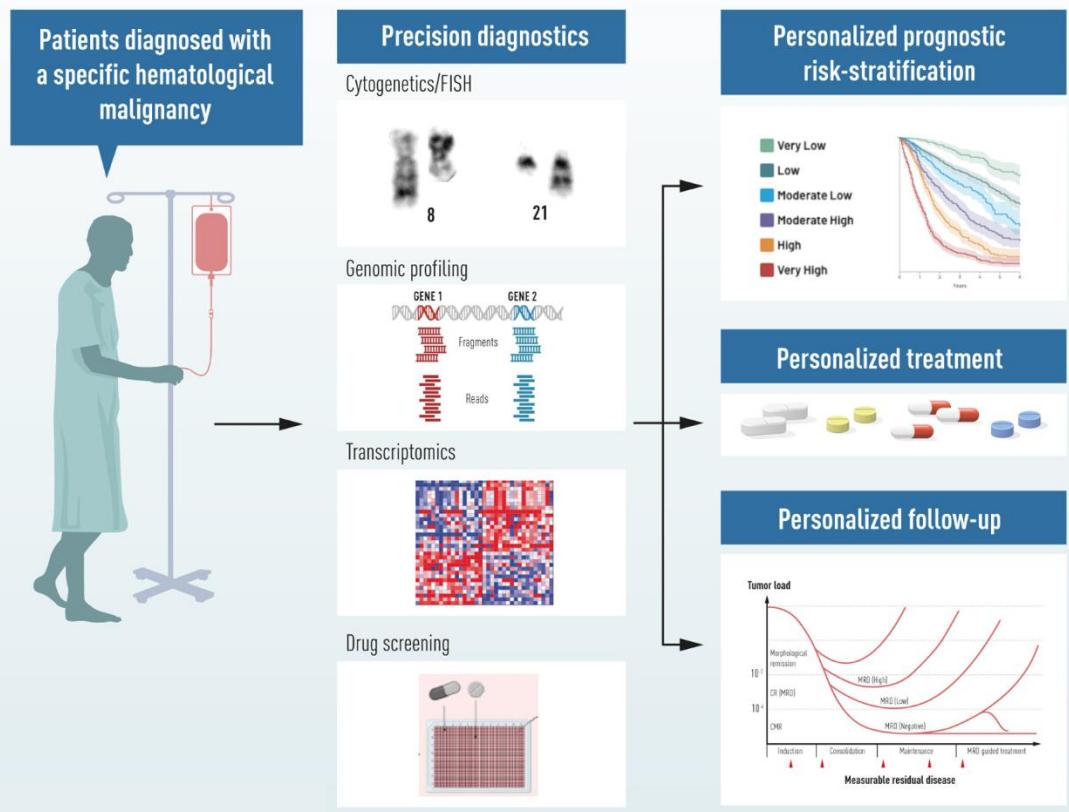
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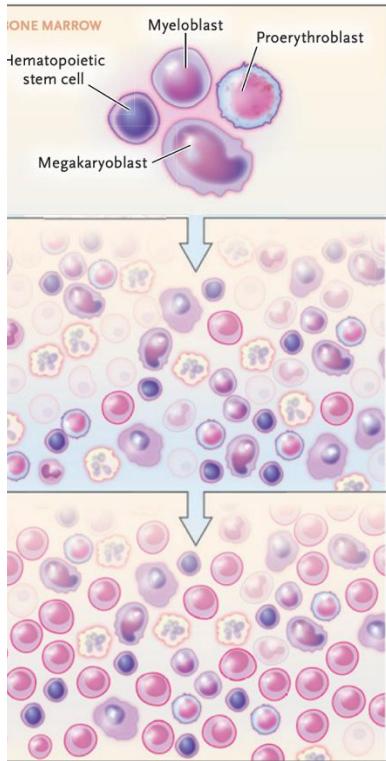
# Risk stratification in hematological malignancies



- Optimized follow-up and monitoring
- Tailored treatment decision
- Improved patient counselling
- Clinical trial eligibility

# Myeloid malignancies

MDS



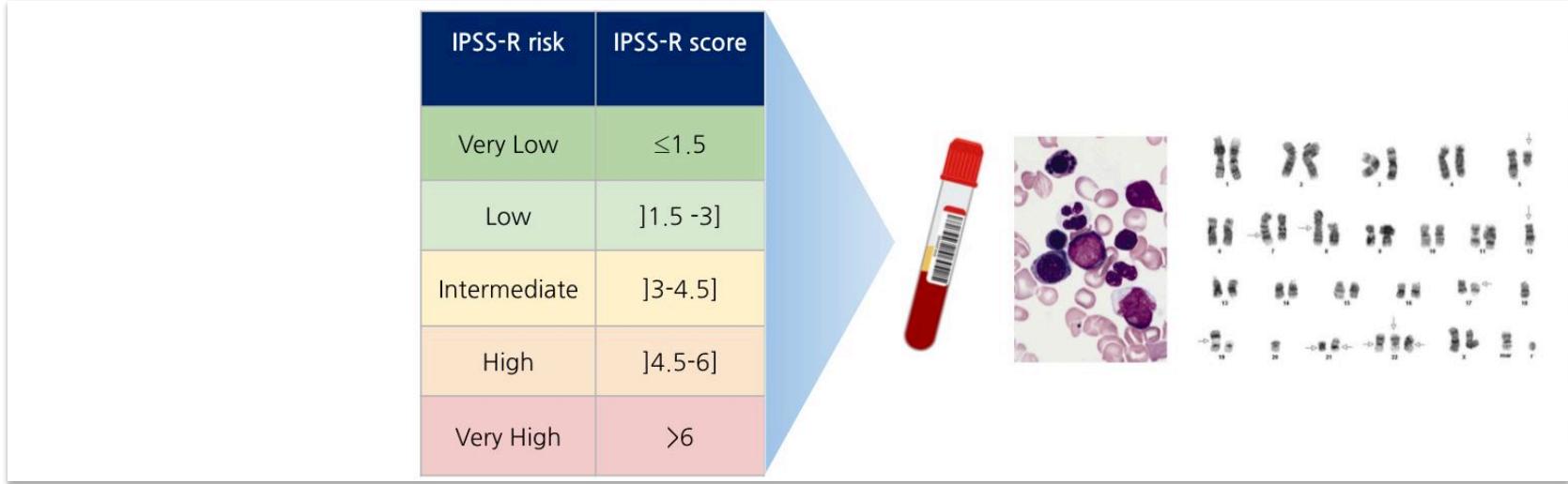
- **Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML)**
- **Mutations in hematopoietic stem cells**
- **Ineffective hematopoiesis, morphologic dysplasia, immature blood cells (blasts)**
- **Limited treatment options**
- **< 1 year survival for high-risk patient**

# Risk stratification guides treatment decision for myeloid malignancies

	IPSS-R risk	IPSS-R score	Median OS, yrs	Median time to 25% AML-t, yrs	
Fatigue	Very Low	$\leq 1.5$	8.8	NR	Supportive care
Bleeding	Low	$]1.5 - 3]$	5.3	10.8	Improving blood counts
Infection	Intermediate	$]3-4.5]$	3.0	3.2	Transfusions
Progression to AML	High	$]4.5-6]$	1.6	1.4	Limit AML-t, Improve OS
	Very High	$>6$	0.8	0.7	Disease modifying agents Stem cell transplantation

Revised International Prognostic Scoring System IPSS-R

# Risk stratification guides treatment decision for myeloid malignancies



Revised International Prognostic Scoring System IPSS-R

# Need for a molecular prognostic risk score in myeloid malignancies

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-2 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		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 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).

# Integrate gene mutations into routine risk stratification

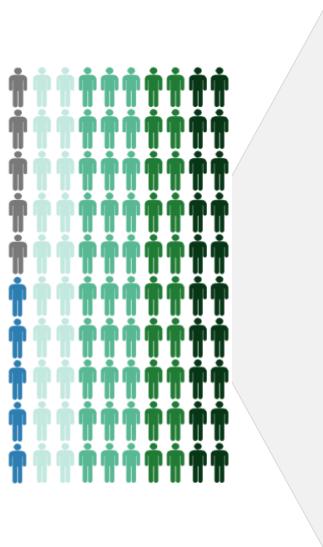
Large **discovery** and **validation** cohorts



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 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, Papaemmanuil Elli

# Comprehensive molecular annotation in myeloid malignancies

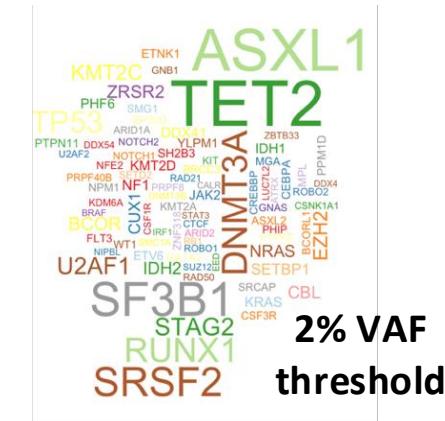
n=2,957



## 3,186 cytogenetic alterations 41% of patients



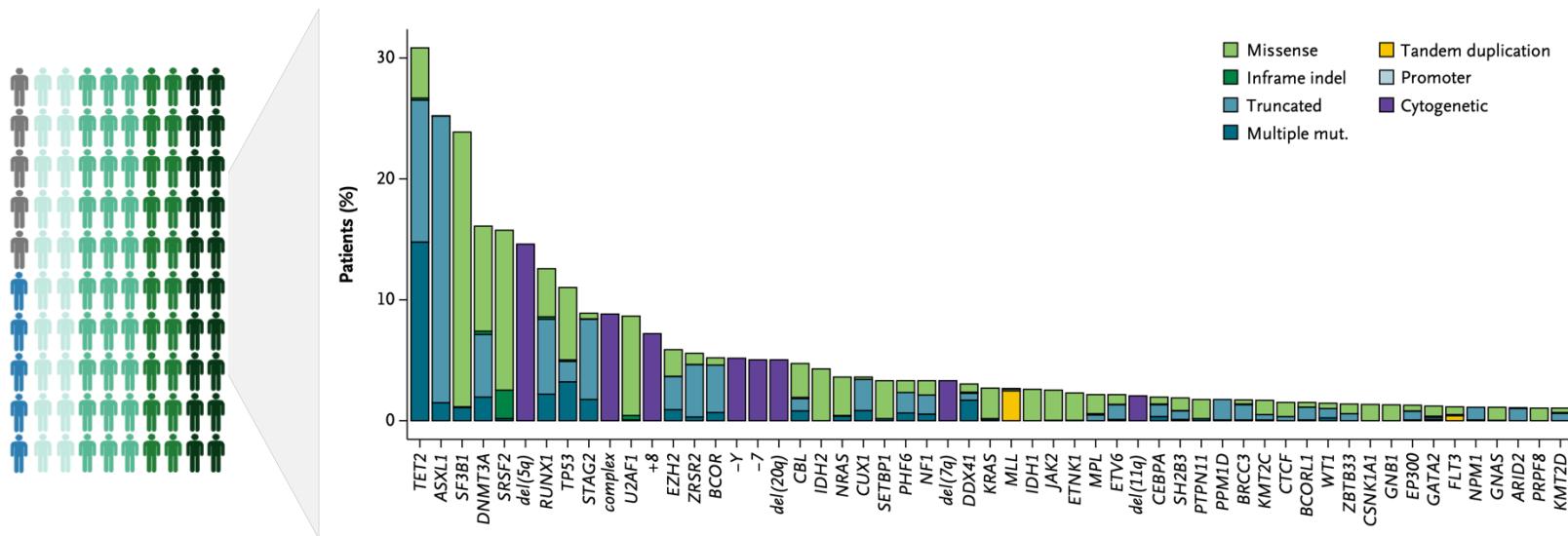
# 9,254 mutations in 121 genes 90% of patients



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

# Comprehensive molecular annotation in myeloid malignancies

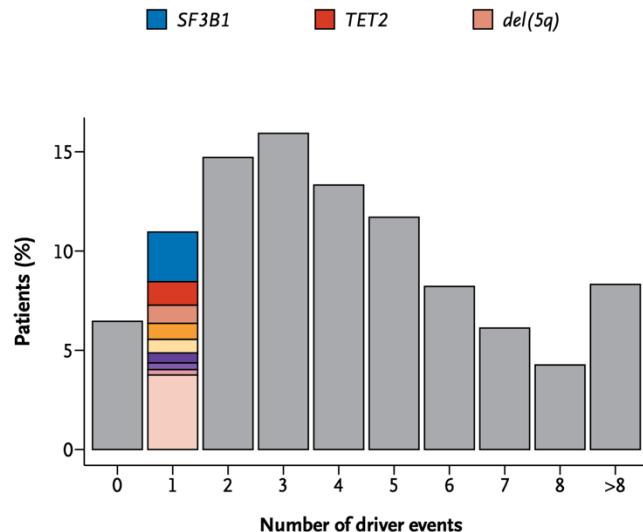
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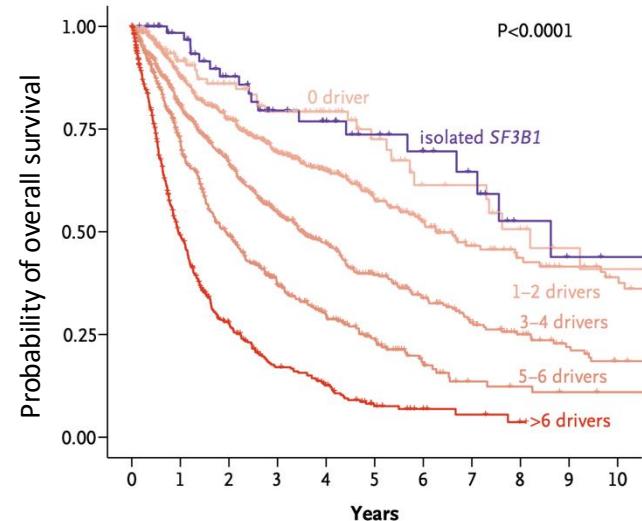
- 48 genes mutated in >1% of patients.
- Median 4 lesions per patient (range 0-20).

# 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

**1. Features definition**

**2. Model development (a personalized risk system)**

**3. Clinical implementation (web tools)**

**1. Features definition**

**2. Model development (a personalized risk system)**

**3. Clinical implementation (web tools)**

# 1. Features definition

Type of mutations

Allelic state

Clonality (VAF)

Genetic context  
Inform features through  
clustering analysis

Continuous variables  
Study the functional risk  
form of clinical variables

# Encoding of mutational status



1

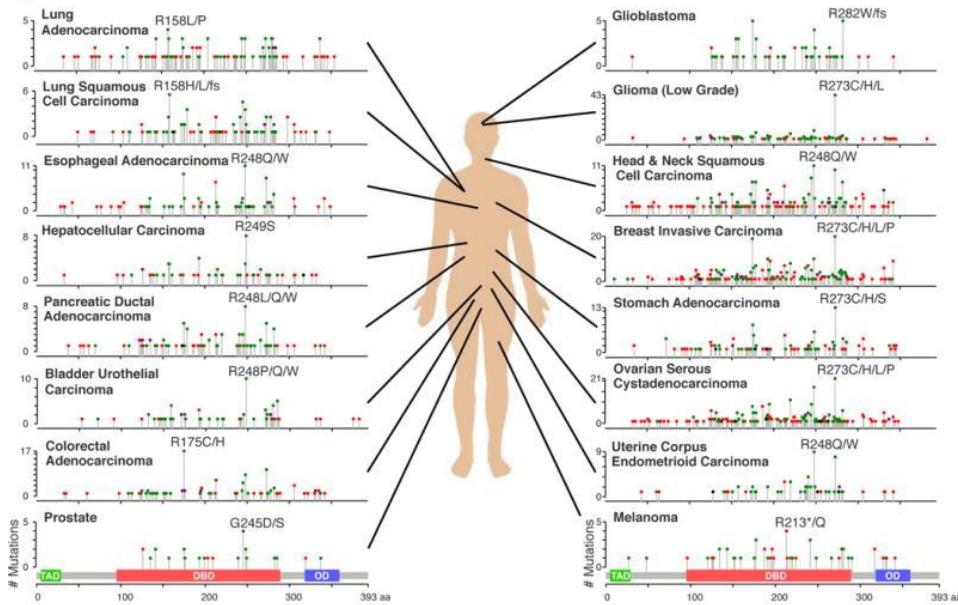
Mutated

0

Wild type

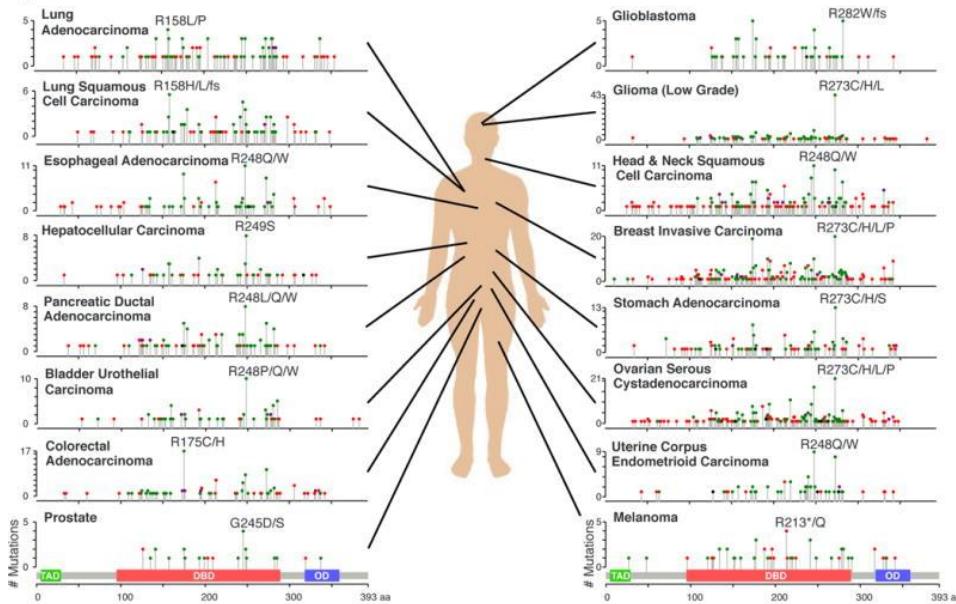
# TP53 mutations in cancer

A

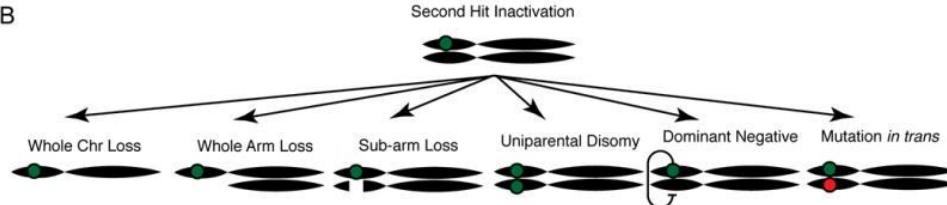


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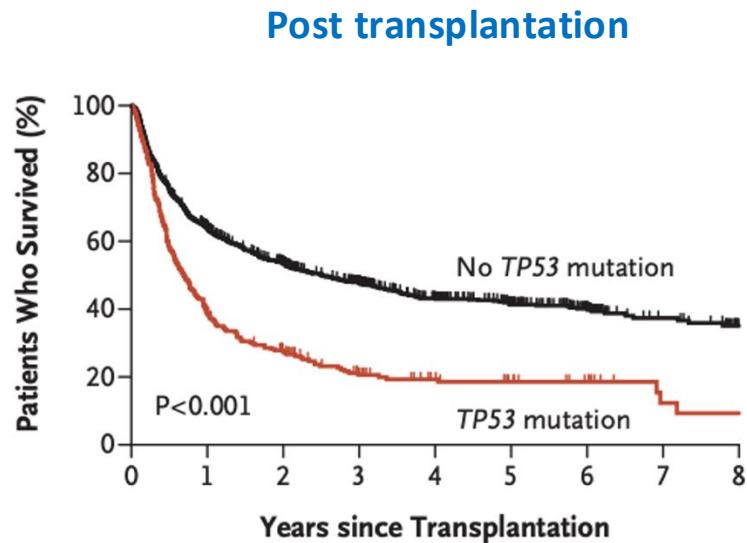
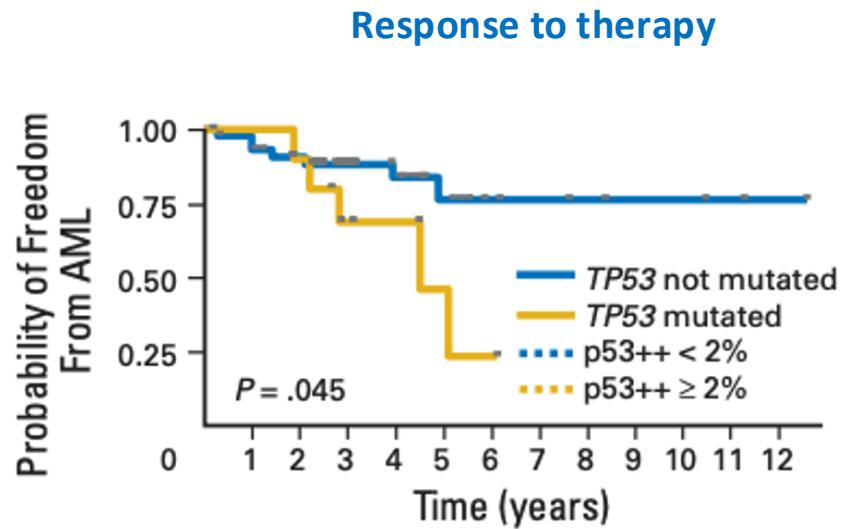
A



B



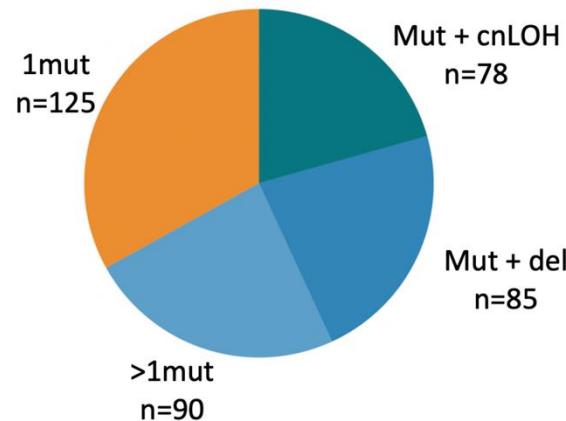
# *TP53* mutations in myeloid neoplasms



*TP53* mutations are associated with resistance to therapy and poor prognosis

# ***TP53* allelic state is a critical biomarker in myeloid neoplasms**

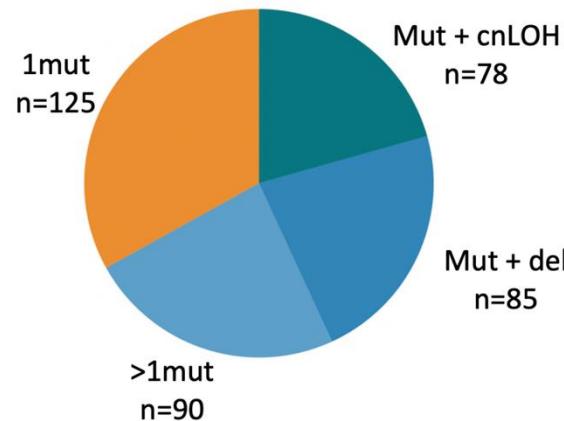
**1/3 patients have mono-allelic  
*TP53* mutations**



**Not all *TP53* mutations are equal**

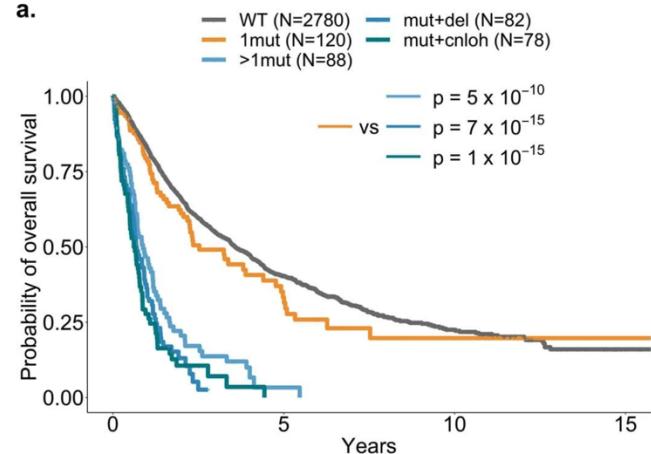
# ***TP53* allelic state is a critical biomarker in myeloid neoplasms**

**1/3 patients have mono-allelic  
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***TP53* allelic state (mono-allelic/multi-hit)  
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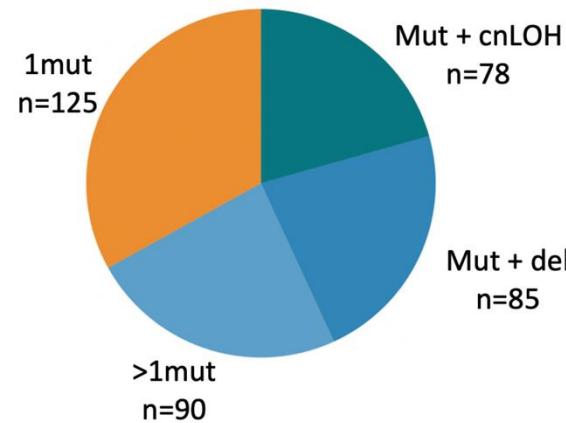
a.



**Not all *TP53* mutations are equal**

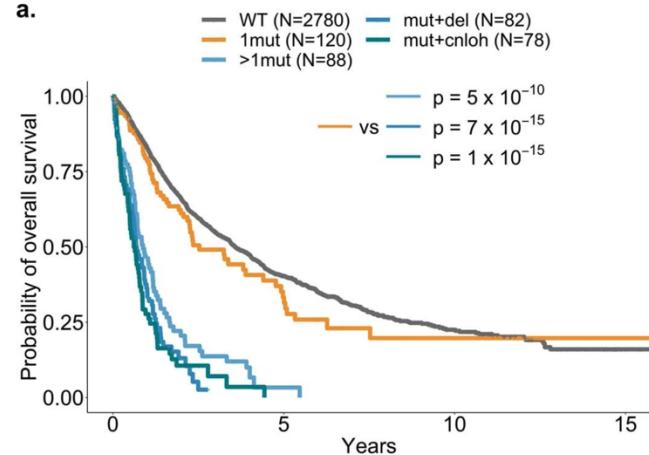
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**1/3 patients have mono-allelic  
*TP53* mutations**



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

a.



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

# **TP53 allelic state is a critical biomarker in myeloid neoplasms**

## **WHO 2022 Classification of myelodysplastic neoplasms**

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

	<b>Blasts</b>	<b>Cytogenetics</b>	<b>Mutations</b>
<b>MDS with defining genetic abnormalities</b>			
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 <sup>a</sup> (MDS-SF3B1)		Absence of 5q deletion, monosomy 7, or complex karyotype	<i>SF3B1</i>
MDS with biallelic <i>TP53</i> inactivation (MDS-biTP53)	<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
<b>MDS, morphologically defined</b>			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic <sup>b</sup> (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		

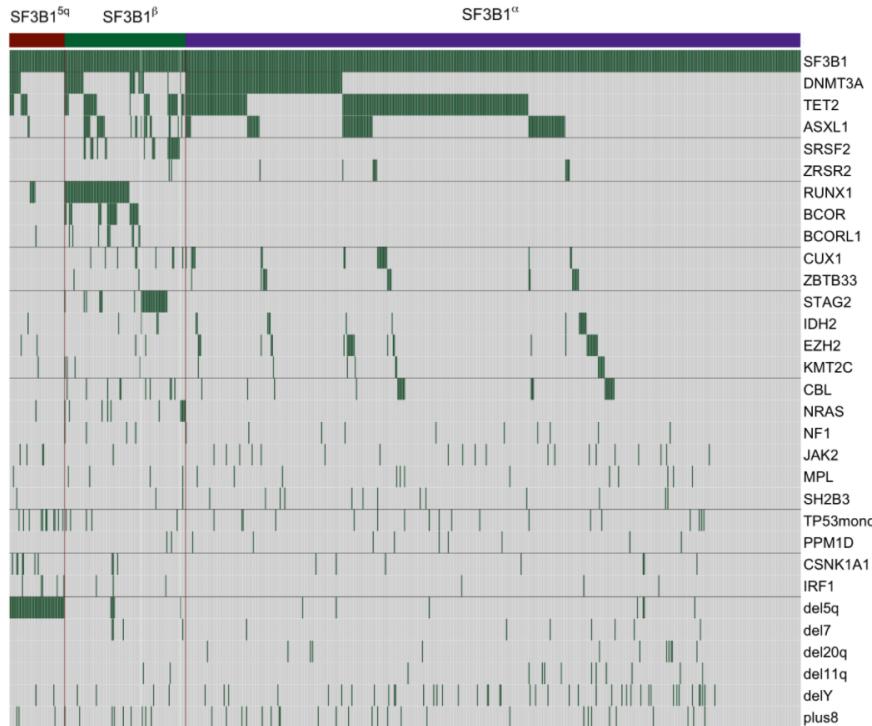
<sup>a</sup>Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

<sup>b</sup>By 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**

# Genetic context matters: *SF3B1*-mutant disease



Subsets of mutant-*SF3B1* based on patterns of co-mutations:

## 1. *SF3B1*<sup>5q</sup> (7%, n=49)

Concomitant isolated del(5q)

## 2. *SF3B1*<sup>β</sup> (15%, n=108)

Co-occurrence of mutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*

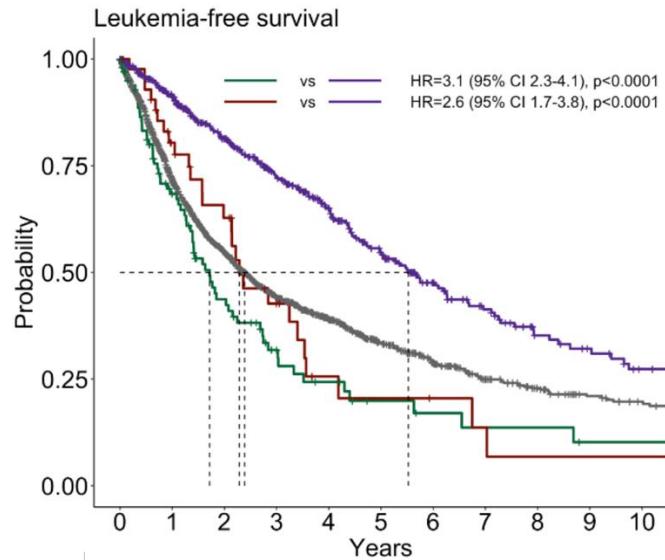
## 3. *SF3B1*<sup>α</sup> (78%, n=549)

Any other *SF3B1* mutations.

# Genetic context matters: *SF3B1*-mutant disease

Strong modulation of the favorable outcome associated with *SF3B1* mutations with co-mutations

Favorable outcome confined to *SF3B1<sup>α</sup>*



Subsets of mutant-*SF3B1* based on patterns of co-mutations:

1. *SF3B1<sup>5q</sup>* (7%, n=49)

Concomitant isolated del(5q)

2. *SF3B1<sup>β</sup>* (15%, n=108)

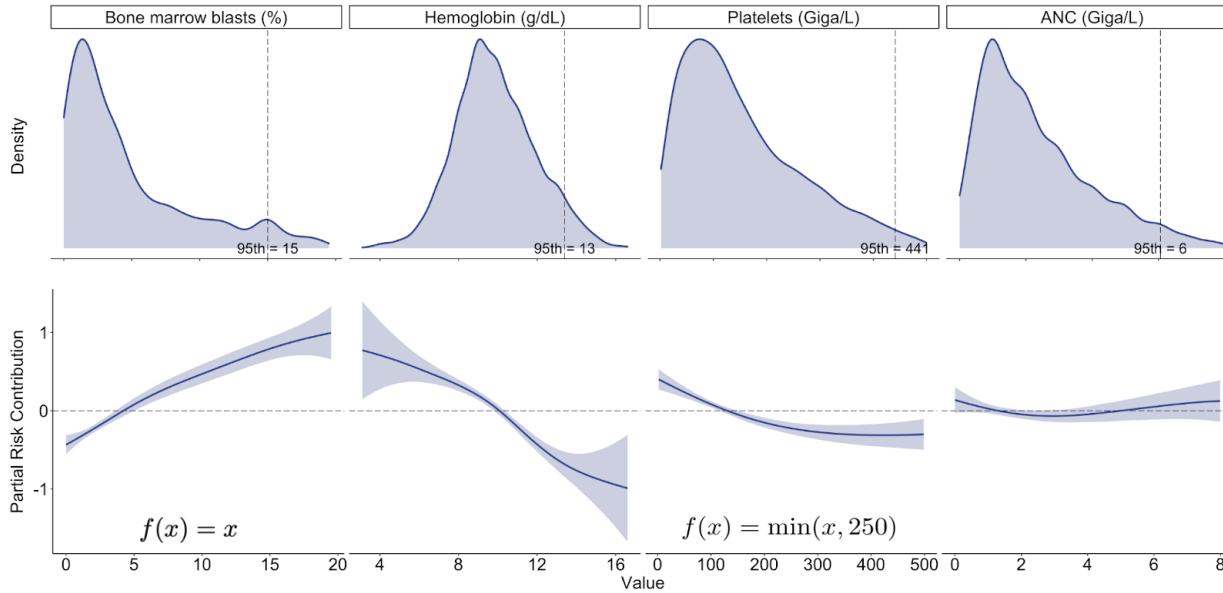
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3. *SF3B1<sup>α</sup>* (78%, n=549)

Any other *SF3B1* mutations.

# Clinical variables: functional risk forms

Density distribution  
Fitted function to capture relation with risk



- Clinical variables were encoded continuously
- Linear functions for BM blasts and hemoglobin
- Platelet values capped at  $250 \times 10^9 / L$
- ANC not included

# 1. Features definition

Type of mutations	Genetic context	Continuous variables
Allelic state	Inform features through clustering analysis	Study the functional risk form of clinical variables
Clonality (VAF)		
<b><i>TP53</i></b> allelic state	<b><i>SF3B1</i></b> subsets (co-mutations)	Linear or capped functions ..

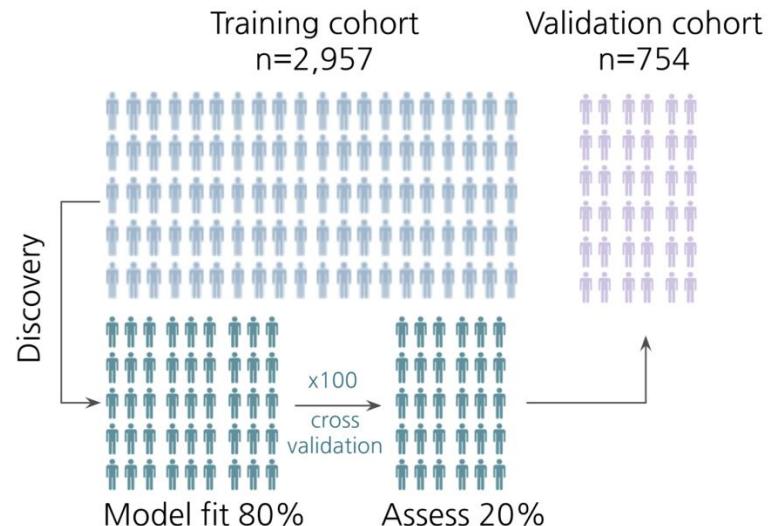
1. Features definition (e.g. *TP53* allelic state)
2. Model development (a personalized risk system)
3. Clinical implementation (web tools)

# Model development

## Molecular International Prognostic Scoring System (IPSS-M)

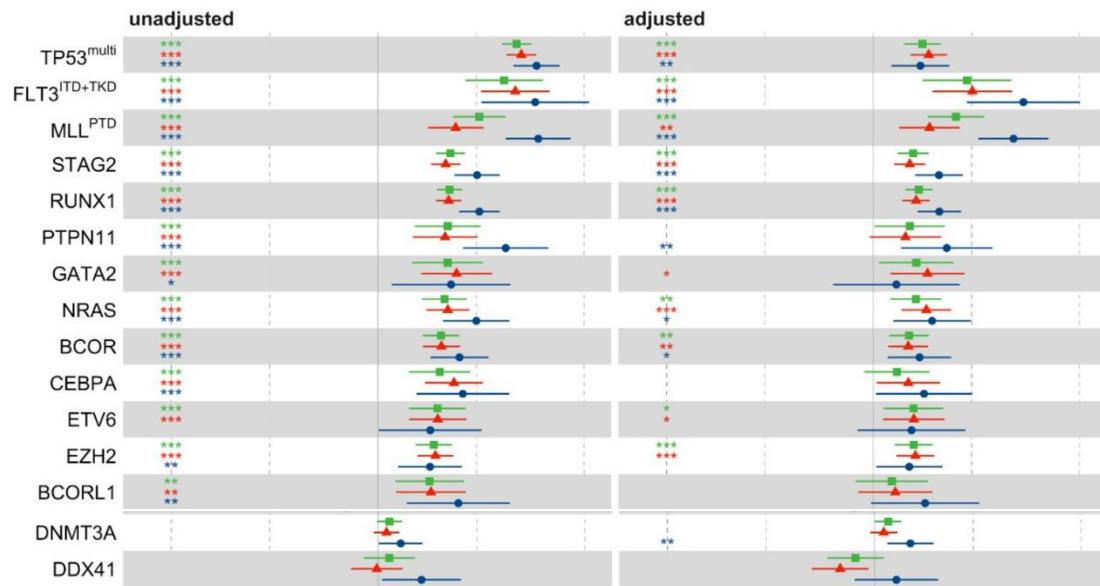
Leukemia-free survival (LFS) primary endpoint

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



# Choice of the primary endpoint (leukemia free survival)

Endpoint    ● AML-t    ↑ OS    ■ LFS

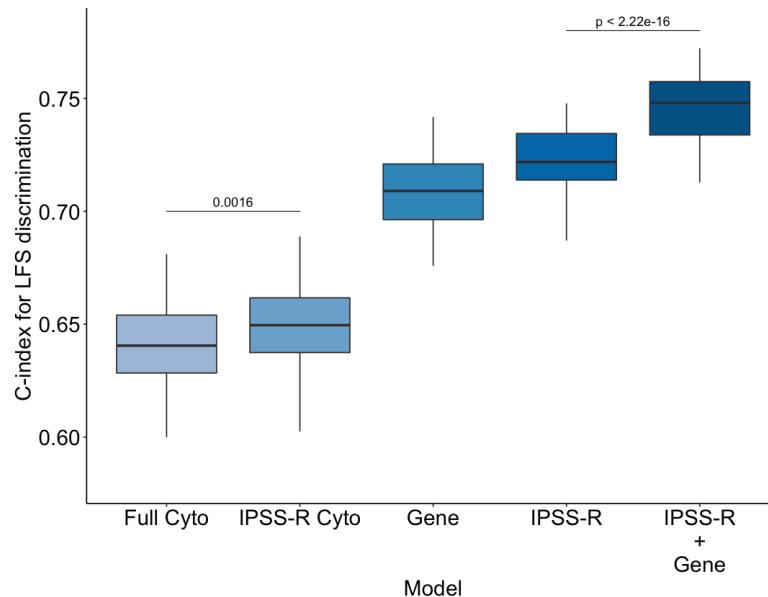


Consistent  
effect/direction  
across endpoints

Exclusion of genes (DDX41)  
with different directions  
across endpoints

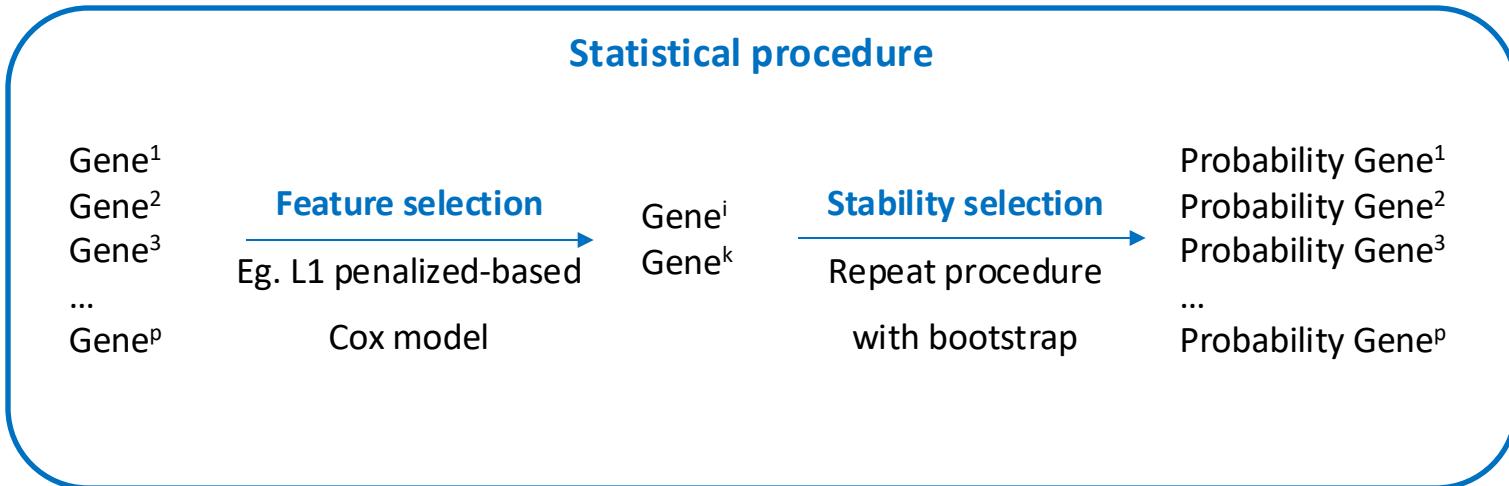
# Selecting the building blocks of discriminative features

Concordance index (c-index) obtained through cross-validation of different prognostic models



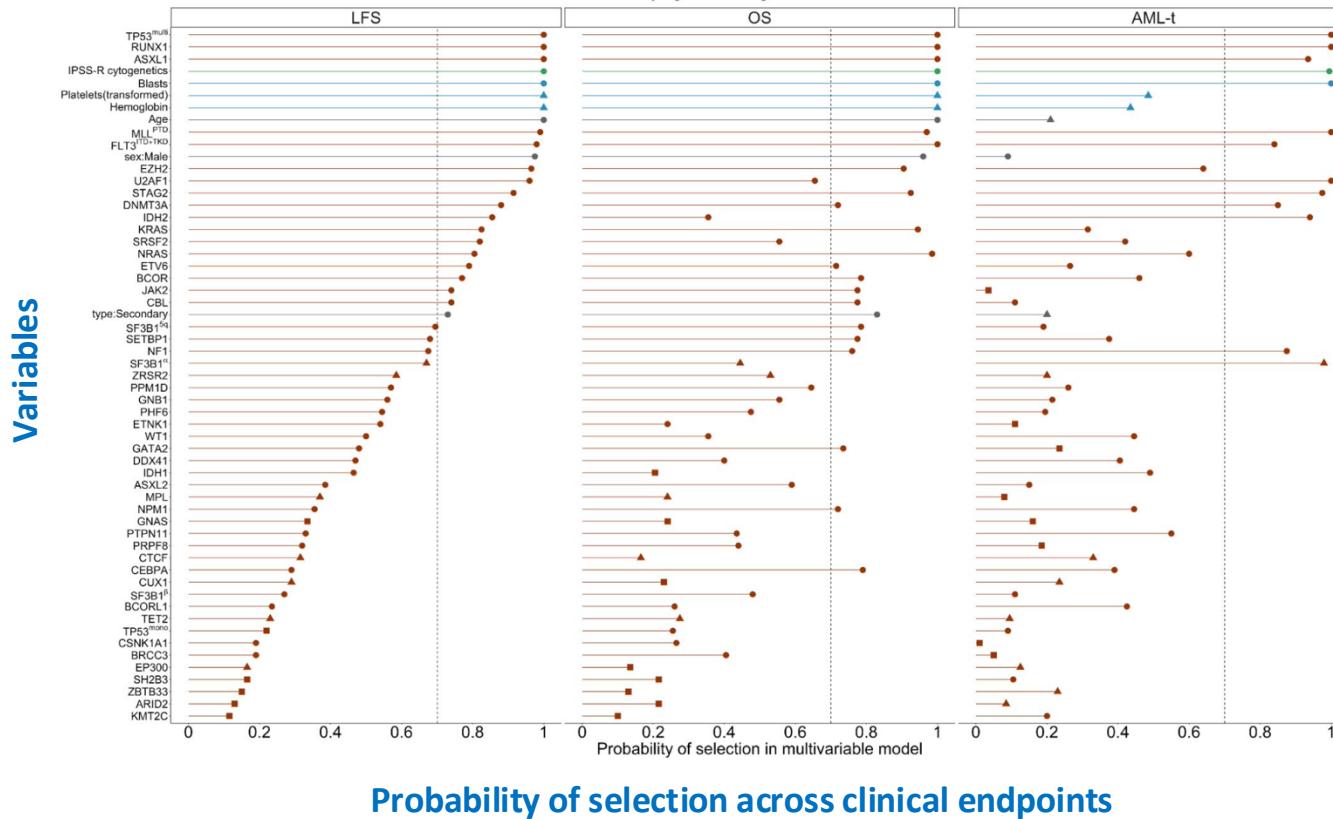
Quantify the added prognostic value of genetic features  
compared to established features

# Robust feature selection



# Robust feature selection

Direction • adverse ▲ favorable ■ unclear



# 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.<sup>†</sup>

Category and Variable	Adjusted Hazard Ratio (95% CI) <sup>‡</sup>	Model Weight <sup>§</sup>
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 <sup>¶</sup>	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes) <sup>¶</sup>		
<i>TP53</i> <sup>multihit</sup>	3.27 (2.38–4.48)	1.18
<i>MLL</i> <sup>PTD</sup>	2.22 (1.49–3.32)	0.798
<i>FLT3</i> <sup>ITD+TKD</sup>	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> <sup>sq</sup>	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> <sup>#</sup>	0.92 (0.74–1.16)	-0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2) <sup>  </sup>		
min(Nres,2)	1.26 (1.12–1.42)	0.231

<sup>†</sup>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<sup>^</sup>  
Number of mutated genes (0, 1 or 2)

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<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
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<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> <sup>#</sup>	0.92 (0.74–1.16)	-0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2) <sup>  </sup>		
min(Nres,2)	1.26 (1.12–1.42)	0.231

<sup>‡</sup>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<sup>^</sup>

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.<sup>‡</sup>

Category and Variable	Adjusted Hazard Ratio (95% CI) <sup>†</sup>	Model Weight <sup>‡</sup>
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 <sup>§</sup>	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes) <sup>¶</sup>		
<i>TP53</i> <sup>multihit</sup>	3.27 (2.38–4.48)	1.18
<i>MLL</i> <sup>PTD</sup>	2.22 (1.49–3.32)	0.798
<i>FLT3</i> <sup>ITD+TKD</sup>	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> <sup>sq</sup>	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
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Continuous clinical parameters  
Marrow blasts, platelets, hemoglobin

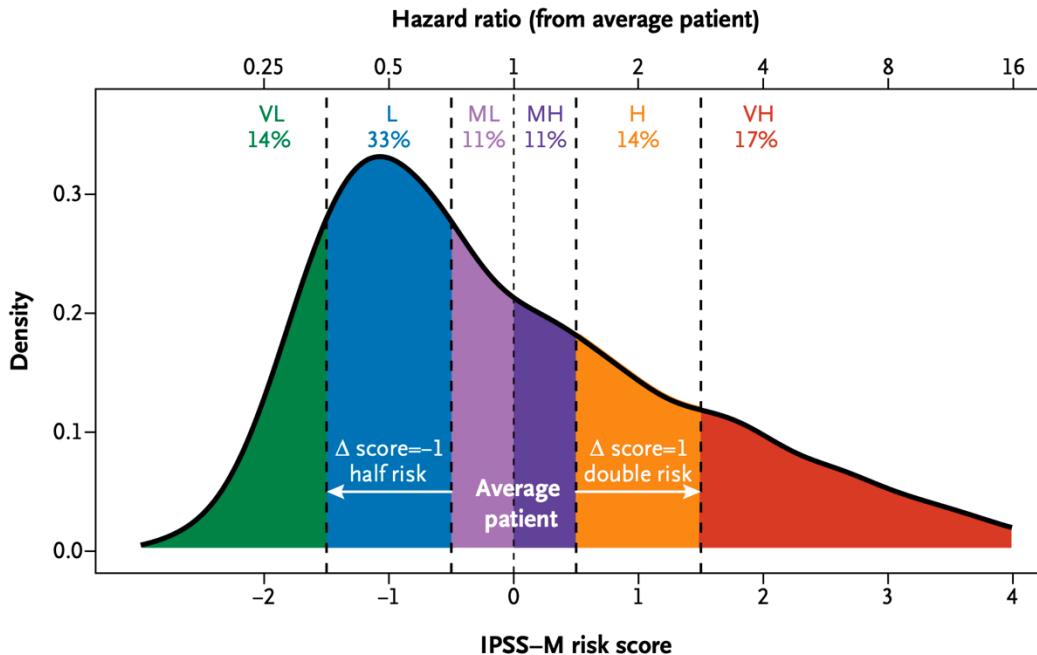
IPSS-R cytogenetic categories

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Individual weights attributed to each variable

1 genetic variable from 15 residual genes<sup>^</sup>  
Number of mutated genes (0, 1 or 2)

# The IPSS-M risk score

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

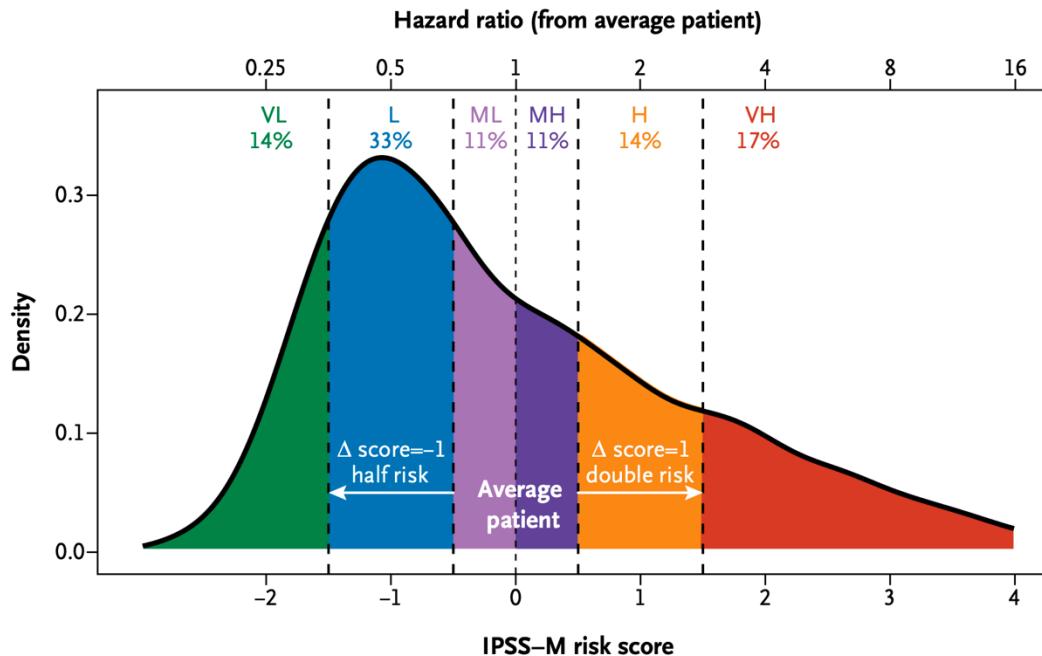


**Prominent 0 value for an average patient.**

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

# The IPSS-M risk categories

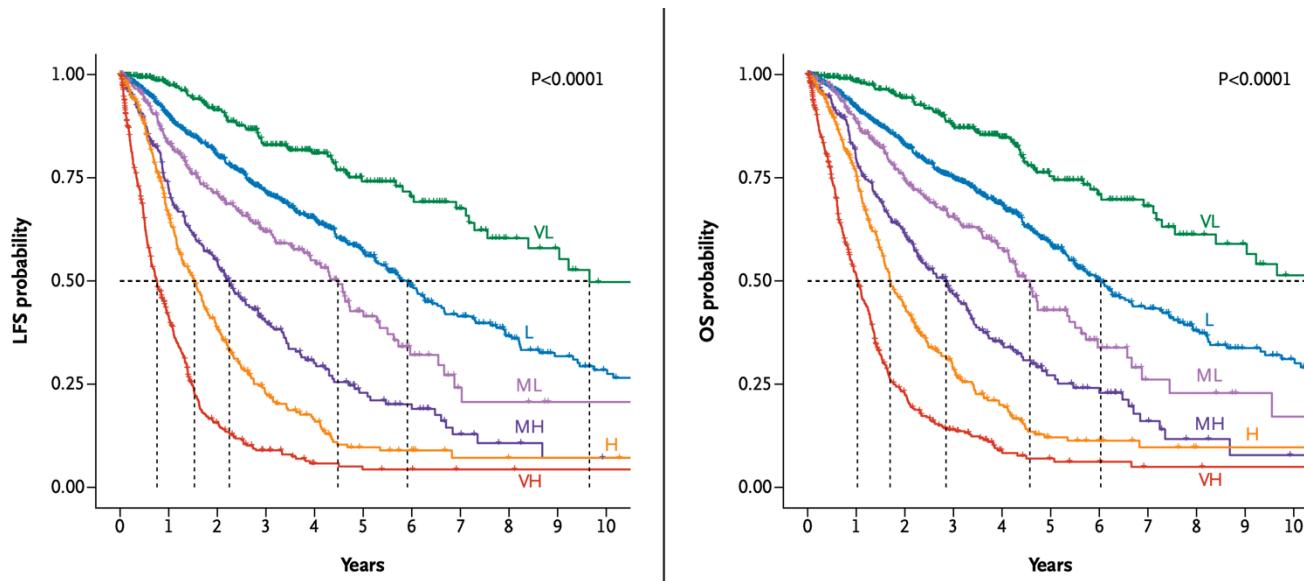
A six-category risk schema



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

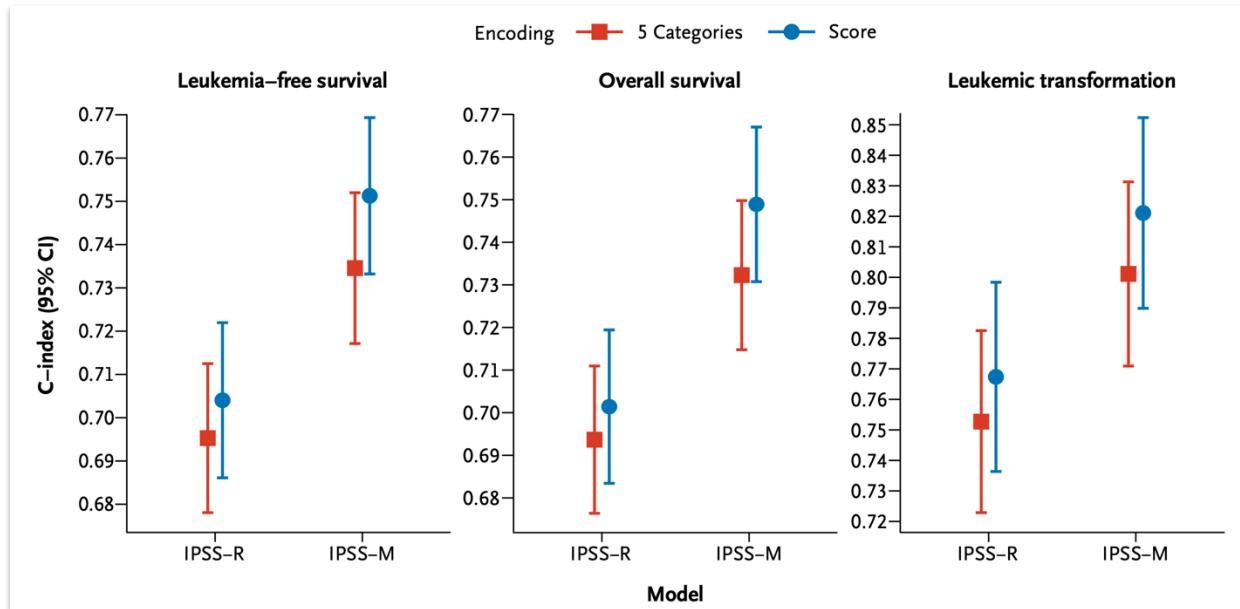
# The IPSS-M risk categories

A six-category risk schema



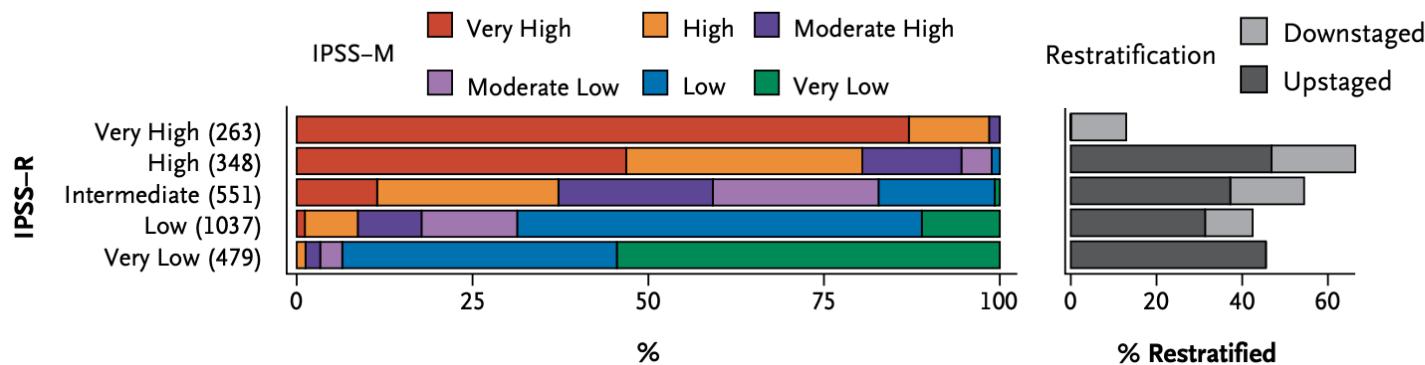
Optimized separation of clinical outcomes with IPSS-M risk groups

# 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

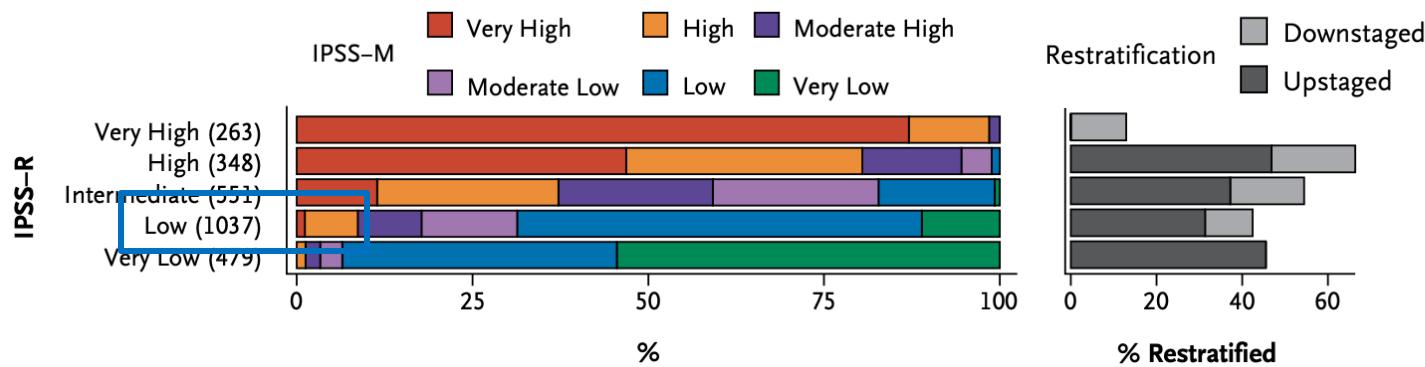


46% (n=1,223) of patients were re-stratified

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

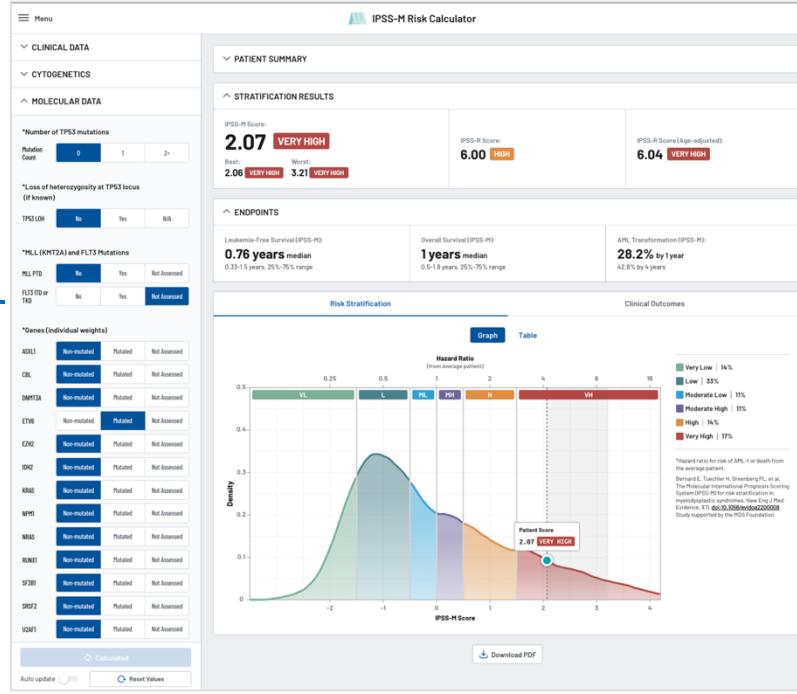
Implications for clinical decision making

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

# Dissemination of the IPSS-M

[www.mds-risk-model.com](http://www.mds-risk-model.com)

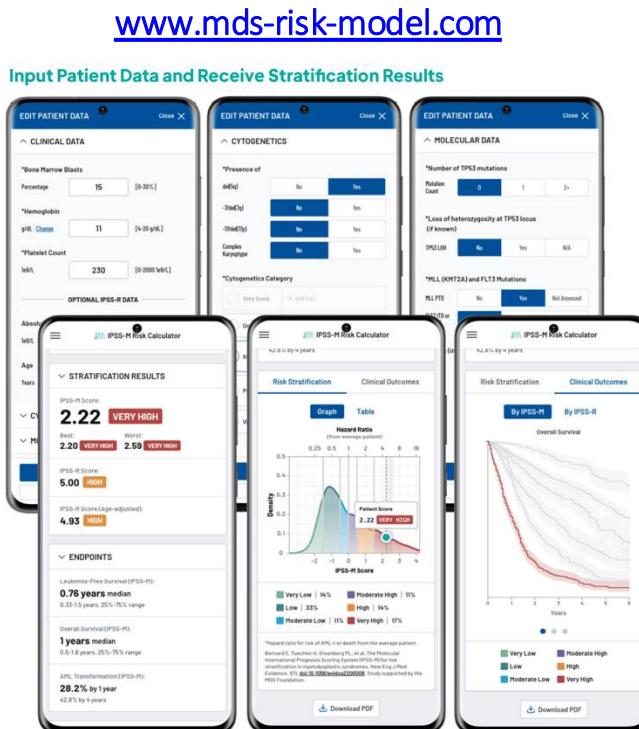
Patient specific  
input variables



Patient specific  
IPSS-M results  
and visualization

# Dissemination of the IPSS-M

Patient specific  
input variables



# **Summary: integrate genomic profiling for clinical diagnostic and prognostication in myeloid malignancies**

## **Biomarker discovery for risk stratification**

*TP53* allelic state

*SF3B1*-mutant disease

## **Clinico-genomic risk system**

Risk score (personalized)

Risk category (discrete)

## **Reproducibility & dissemination**

Web calculator

Mobile app

## **Validation & Extension**

External

Multi-center

Secondary/hypoplastic/SCT

**bi-*TP53* WHO 2022 class**

**NCCN 2023 guidelines**

**[mds-risk-model.com](http://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?*

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