FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
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Studio TITAN per la classificazione delle neoplasie mieloidi

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Disclosures of Alessia Campagna

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Genomics Impacts Classification and Clinical Management of Myeloid Neoplasms

- Classification efforts and routine clinical practice are shifting towards increasing adoption of actionable information from somatic targeted DNA sequencing. Whole exome sequencing and RNA sequencing are next in line.

- Genomic profiling allows categorization in distinct subgroups, discovery of biomarkers for disease monitoring and detection of germ line predisposition.

The Challenge:
how do we handle and act upon increasingly vast and complex information to improve and personalize care in myeloid neoplasms?

Arber et al., Blood 2022, PMID 35767897
Khoury et al., Leukemia 2022, PMID: 35732831

Aims of the Study

- Utilize Explainable Artificial Intelligence to define a comprehensive classification of myeloid neoplasms based on genomic, morphological and histological features starting from a large real-world patient population
- Define the hierarchical importance of genomic versus morphological features in determining disease entities
- Specifically address areas of overlap among different myeloid neoplasms

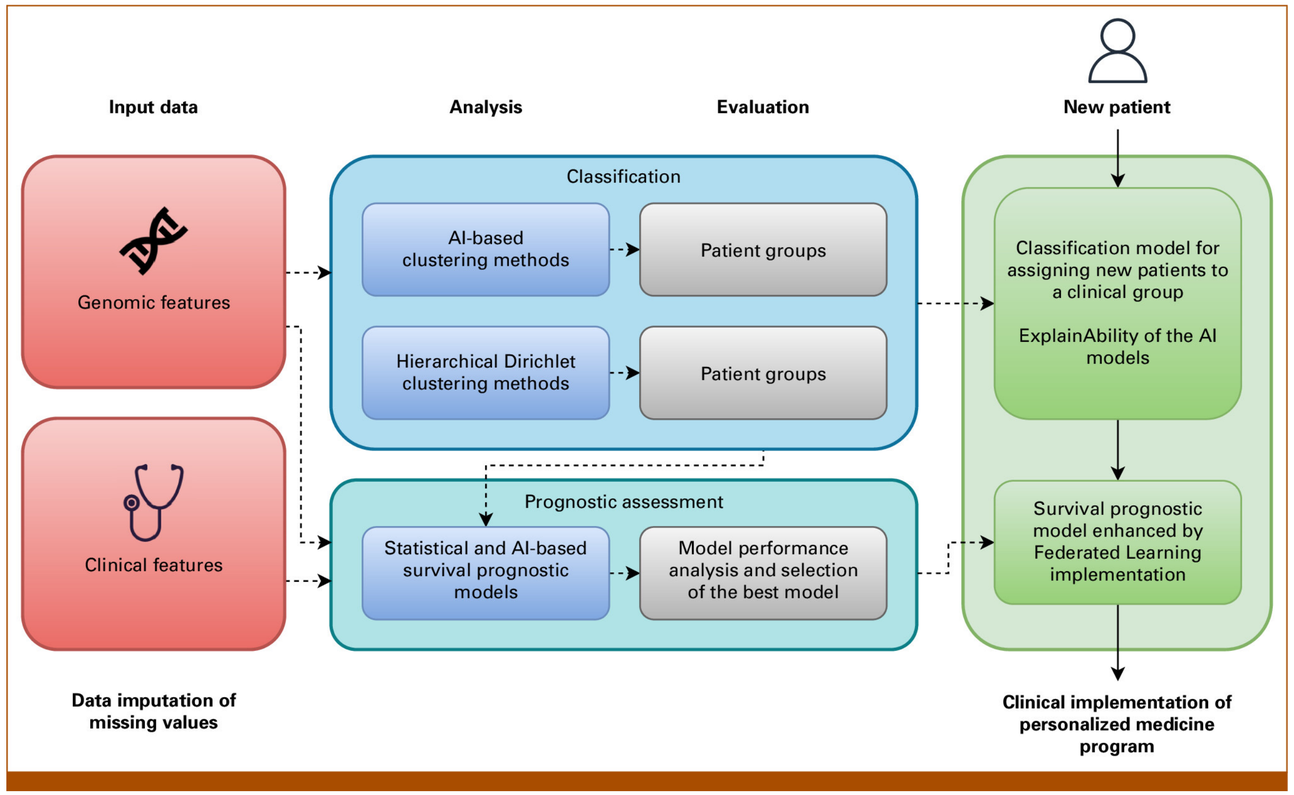
The TITAN Study

- A collaborative, world-wide effort to collect and analyze clinical and genomic information from real-world patients affected by myeloid neoplasms.

- 103 Hospitals and Cancer Centers
- 20,012 retrospective patients with clinical and genomic information from local sequencing facilities:
  - **6,311 AML**
  - **8,378 MDS**
  - **2,720 MDS/MPN**
  - **1,597 MPN (Myelofibrosis)**

- 1,482 patients with matched RNAseq information from bone marrow progenitors for correlative analyses

MOSAIC
An AI-based Framework for Multi-Modal Analysis in Rare Cancers



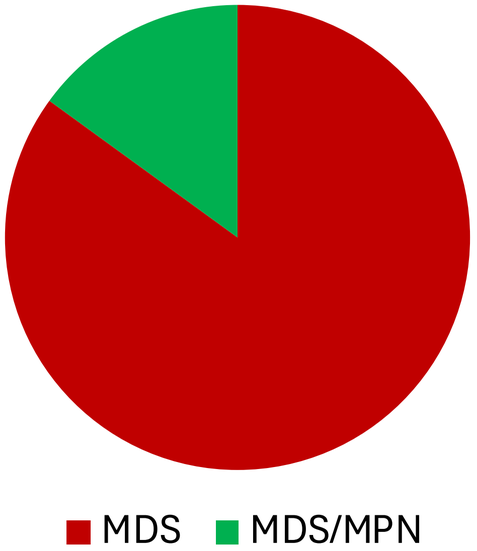
Information for unsupervised clustering:

- Morphology
  - Cellularity
  - Fibrosis
  - Dysplasia (including Ring Sideroblasts)
  - Blasts
- Annotated chromosomal abnormalities from conventional karyotypes
- Mutational status for 35 recurrently mutated genes in Myeloid Neoplasms

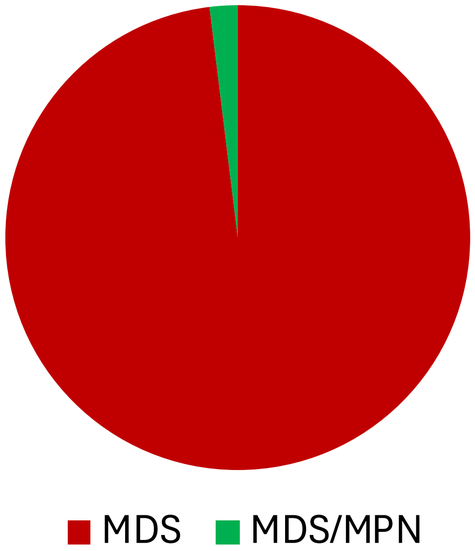
D'Amico et al., JCO-CCI 2024, PMID 38875514

Model Explainability – AI Methods are Reliable and Clinically Informative

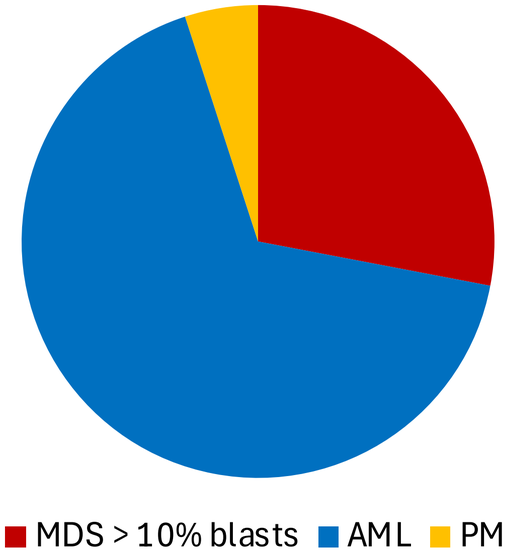
Classification of MN patients with SF3B1 mutations (n=1991)



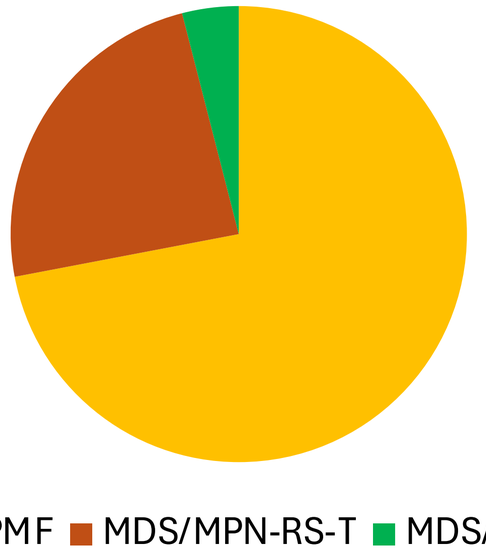
Isolated *SF3B1*
± *DNMT3A/TET2*
n = 1350



SF3B1 and low blasts
+ *RUNX1 or CK*
n = 145



SF3B1 and excess blasts
+ adverse genomics*
n = 358

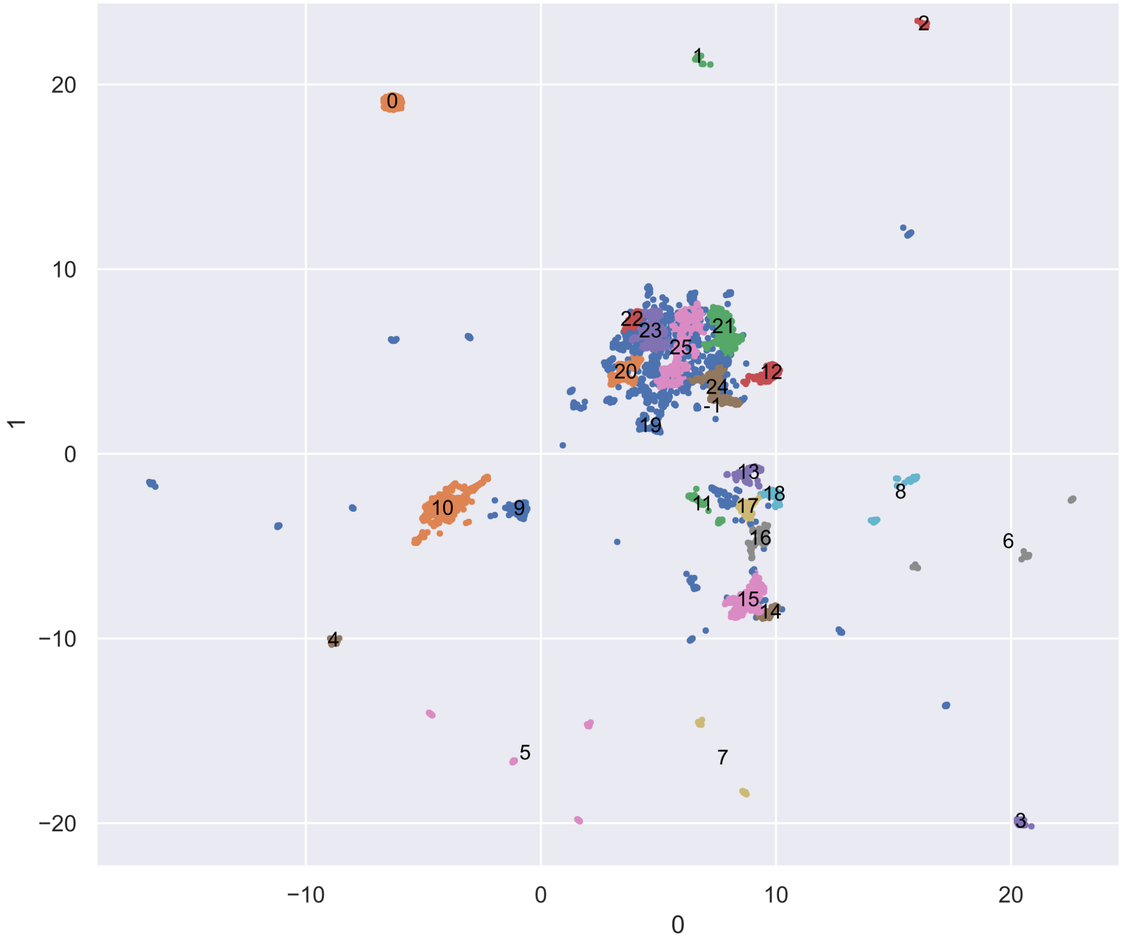


SF3B1
+ *JAK/STAT* mutations
n = 138

* MDS/AML related gene mutations (ASXL1, BCOR, EZH2, RUNX1, STAG2) or complex karyotype

Results 1 – Unsupervised Clustering

UMAP + HDBSCAN Clusters

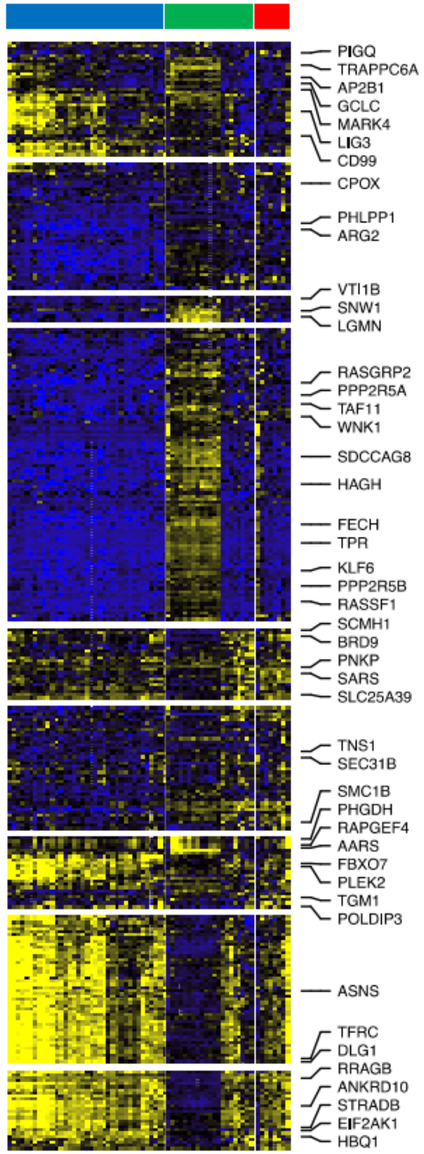


- We identified 34 clusters characterized by homogeneous profiles
- According to SHAP analysis, genomic features often outweighed morphological information for cluster assignment
- Fibrosis and blast count retained an important role in identifying clusters
- 10 clusters were characterized by different disease entities as defined by WHO/ICC 2022 criteria (38% of entire population)

Results 2 – Splicing Mutations Are Shared Across Multiple Entities

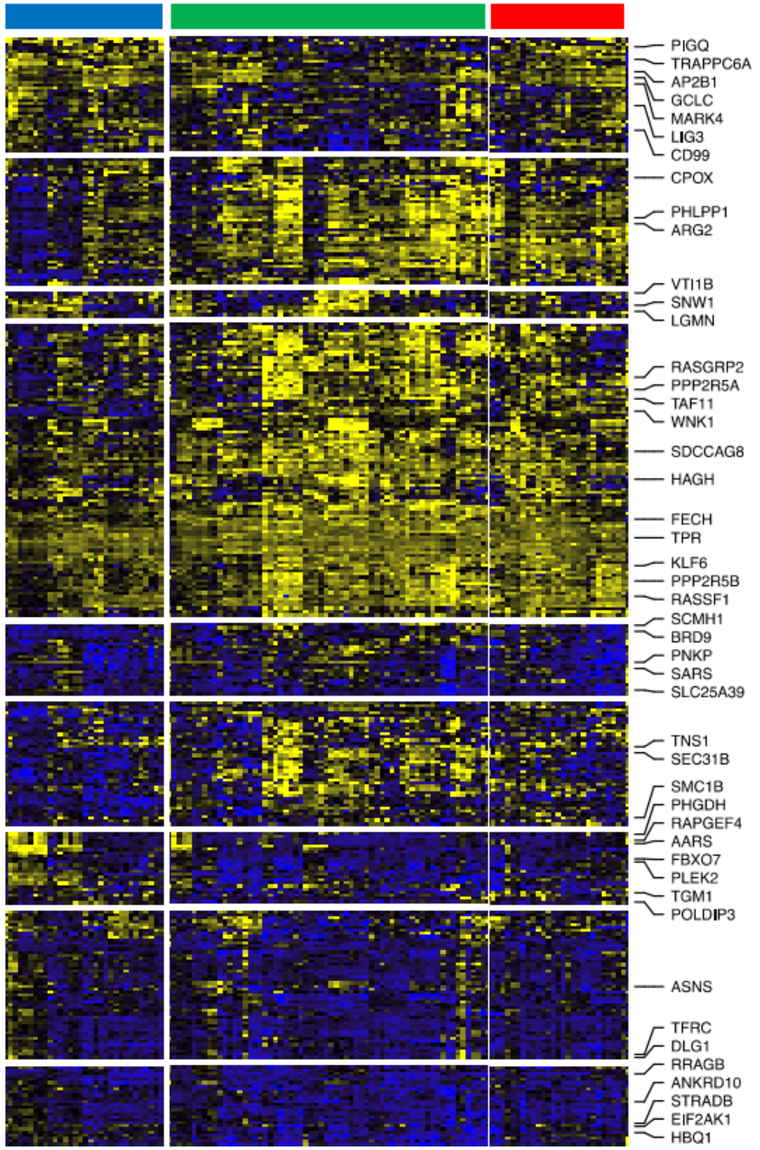
Disease Entity	Early Disease: - Absence of High-Risk Features - No Excess Blasts	High-Risk Features: - RUNX1/ASXL1 mutations - del(7)/-7, abn(3q) or CK Advanced Disease: - Excess Blasts
MN with ***SF3B1*** mutation (n=1991)	MDS: 88.1% MDS/MPN: 11.9%	MDS: 40.8% MDS/MPN: 8.4% AML: 50.8%
MN with ***SRSF2*** mutation (± *TET2*) (n=1447)	MDS: 54.5% MDS/MPN: 45.5%	MDS: 25.6% MDS/MPN: 22.2% AML: 52.1%
MN with ***U2AF1*** mutation (n=1118)	MDS: 87.5% MDS/MPN: 12.5%	MDS: 34.8% MDS/MPN: 4.6% AML: 60.6%

Results 2 – RNAseq analysis of Splicing Mutant Patients



Splicing Mutations without HR Features

- SF3B1 mutation
- SRSF2 mutation
- U2AF1 mutation

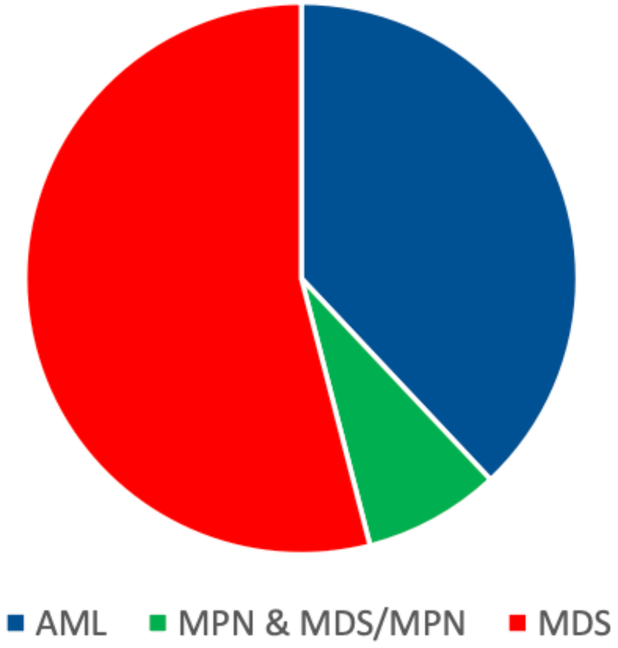


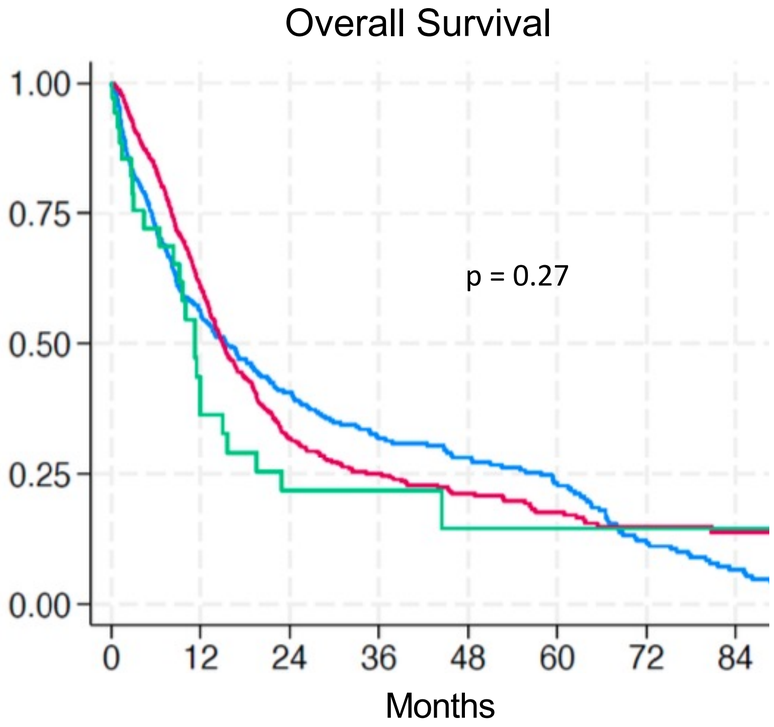
Splicing Mutations with HR Features*:

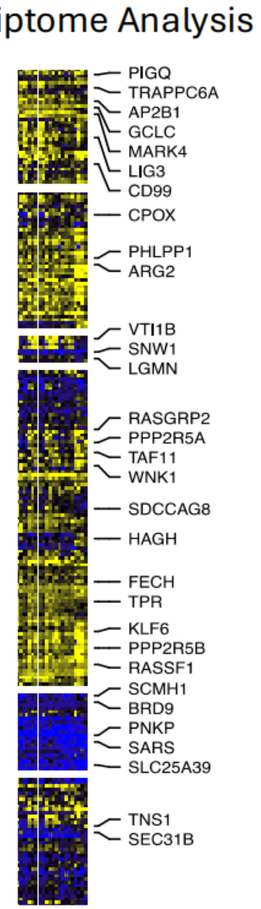
- SF3B1 mutation
- SRSF2 mutation
- U2AF1 mutation

*: $RUNX1^{mut}$, $ASXL1^{mut}$ del(7)/-7, abn(3q), complex karyotype, excess blasts

Results 3 – TP53 Drives Cluster Assignment Irrespective of Diagnostic Entity

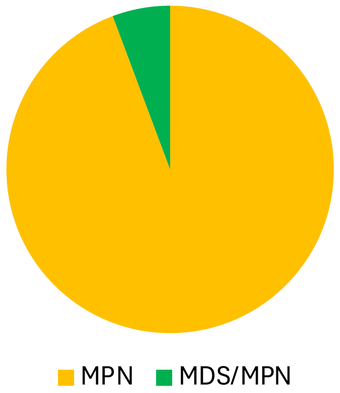




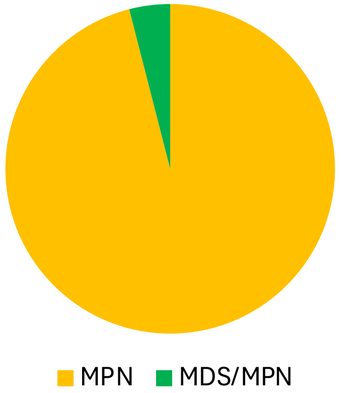


- Dismal survival across disease categories
- Biallelic inactivation was identified in most cases (>65%)
- Monoallelic *TP53* MNs showed progression to biallelic inactivation at leukemic evolution

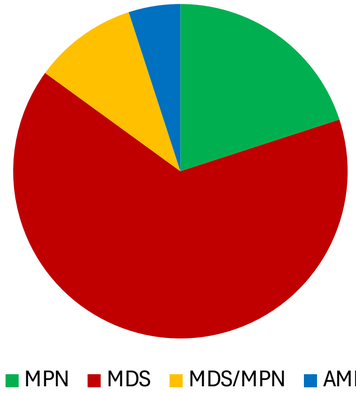
Results 4 - Fibrosis identifies distinct clusters with diverse features and survival



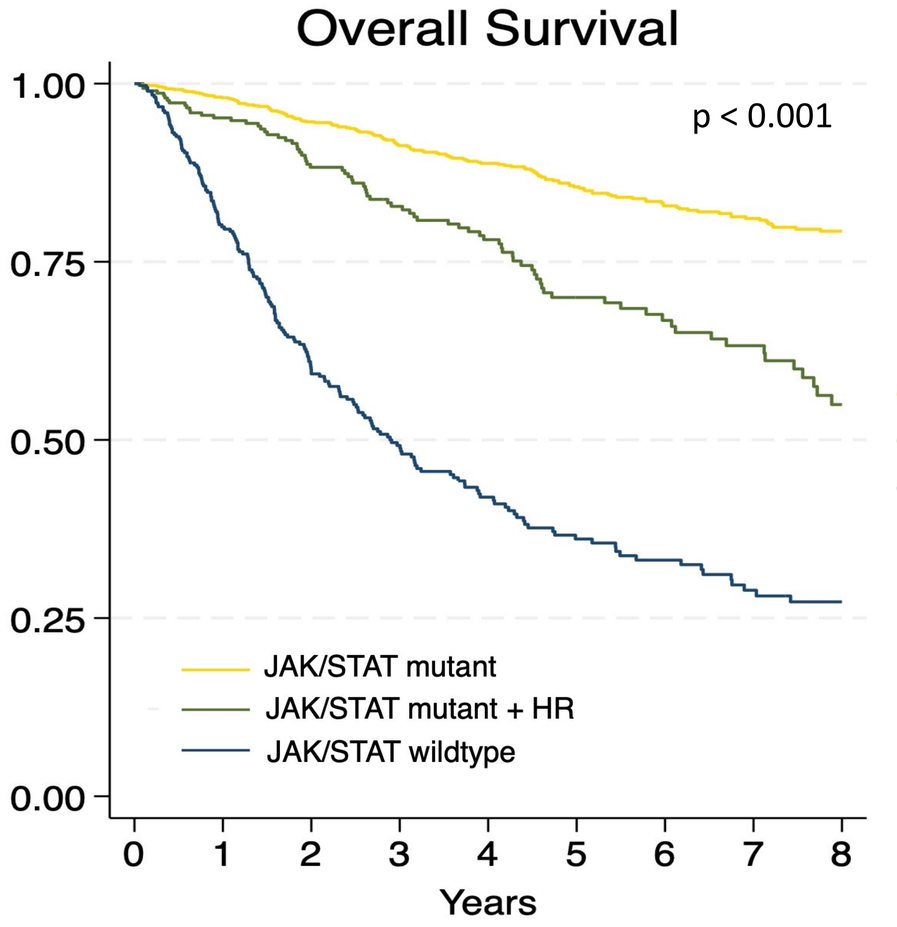
JAK/STAT mutations
No HR Features*
n = 1143



JAK/STAT
mutations
+ HR Features*
n = 305



JAK/STAT wildtype
n = 381

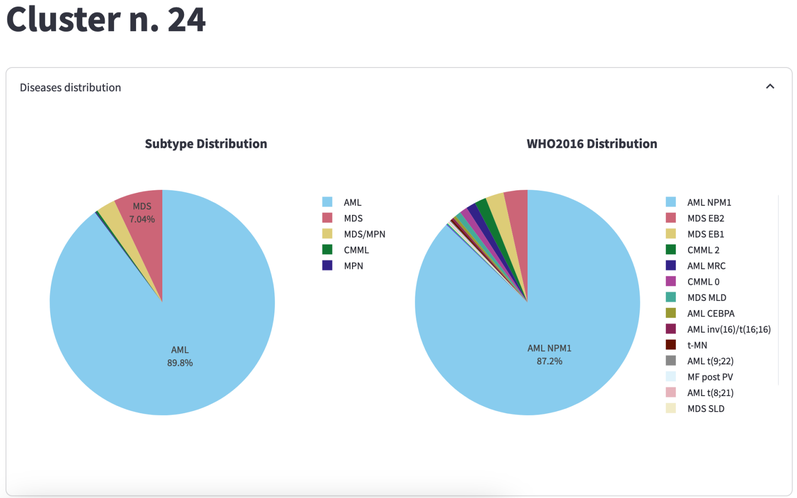


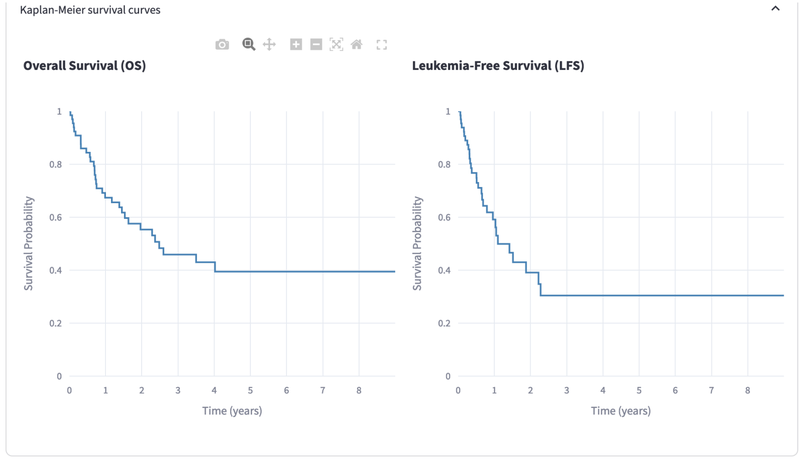
- SHAP analysis identified marrow fibrosis (MF2+) as a relevant features for cluster assignment
- Triple-negative MNs with fibrosis had the worst prognosis and a high prevalence of HR features

*: ASXL1, BCOR, EZH2, RUNX1 mutations
del(7)/-7, complex karyotype

Results 4 - An Interactive Web App for Cluster Assignment

Scan to access
the TITAN
web platform





Conclusions

- The analysis of large, annotated datasets with AI-based inferential techniques is reliable, informative and can handle multiple data layers.
- Genomics is a surrogate of disease biology and often outweighs morphology in cluster assignment.
- Future classification efforts should encourage the adoption of disease entities based on homogeneous mutational profiles, irrespective of minor morphological discrepancies.
- The clinical adoption of next generation classifications of myeloid neoplasms will allow the refinement of treatment strategies and the design of innovative clinical trials.

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