Nuove prospettive nella stratificazione delle MDS

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Disclosures

NA

Inclusion of molecular screening in clinical decision-making process for MDS

- Molecular prognostication in MDS *Bersanelli JCO 2021*
- Clinical relevance of TP53 in MDS *Bernard Nat Med 2021*
- IPSS-M scoring system *Bernard NEJM Evid 2022*
- IPSS-M in transplantation (HSCT) *Sauta JCO 2023*
- Clinical decision support system HSCT *Tentori JCO 2024*
- MDS taxonomy *Bernard Blood 2024*
- Personalized medicine for HSCT *Gurnari Blood 2025*
- P53 dysfunction in MDS *Zampini JCO 2025*
- Molecular ecosystem for CMML *Lanino JCO 2026*

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Clinical Decision Support System (CDSS)

- **Clinical Decision Support Systems** are AI-based tools that assist clinicians in making decisions by providing them with real-time, patient-specific information and recommendations

- **Benefits:**

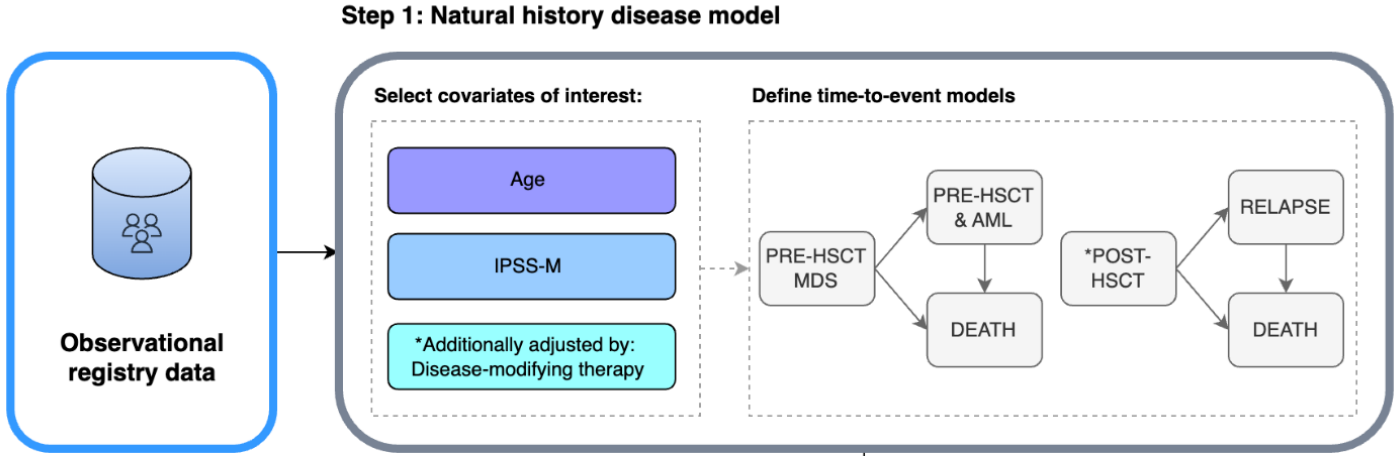
✓ Improve quality and efficiency of care
✓ Increase patient safety (potential drug interactions, dosing errors, etc.)
✓ Update clinicians about latest guidelines and research
✓ Reduce costs and optimize expenses

Vasey B et al. Nat Med 28:924-933, 2022

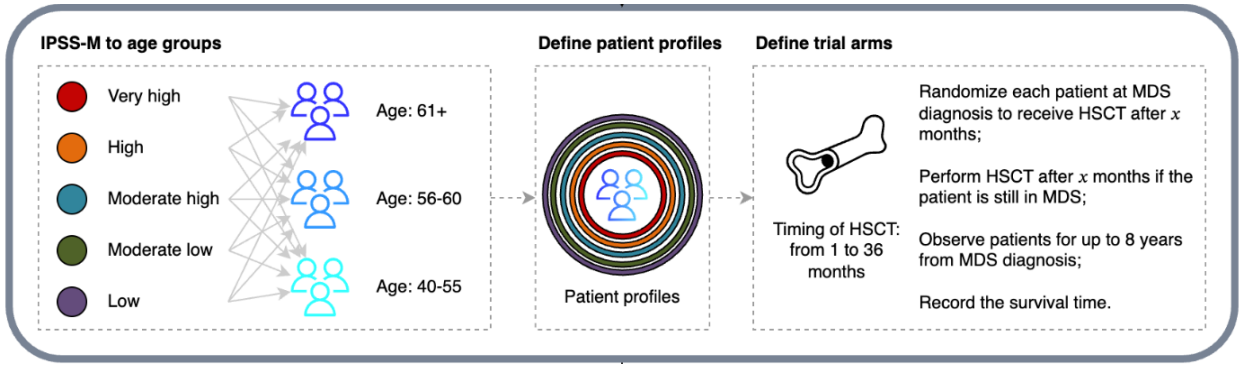
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Development of a Decision Support System by AI

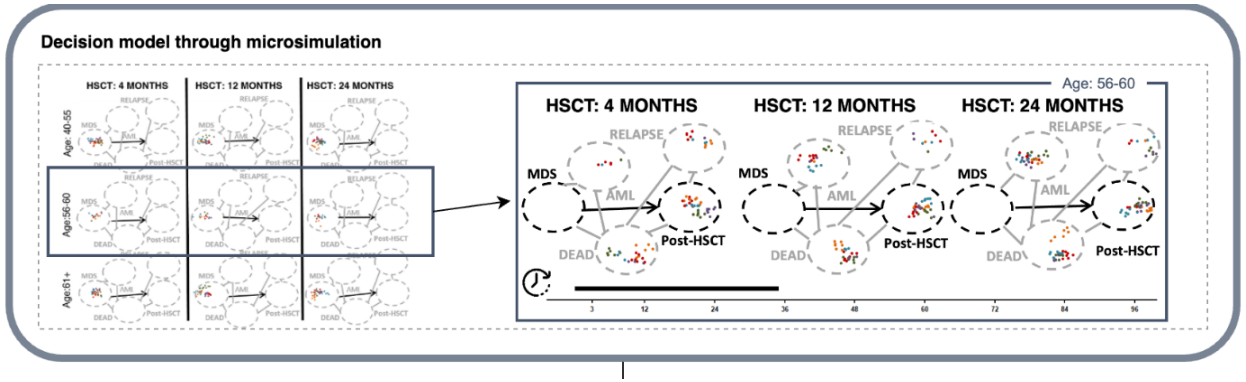
STEP 1 – Model of the disease natural history and the effect of treatment



STEP 2 Simulation of the target trial



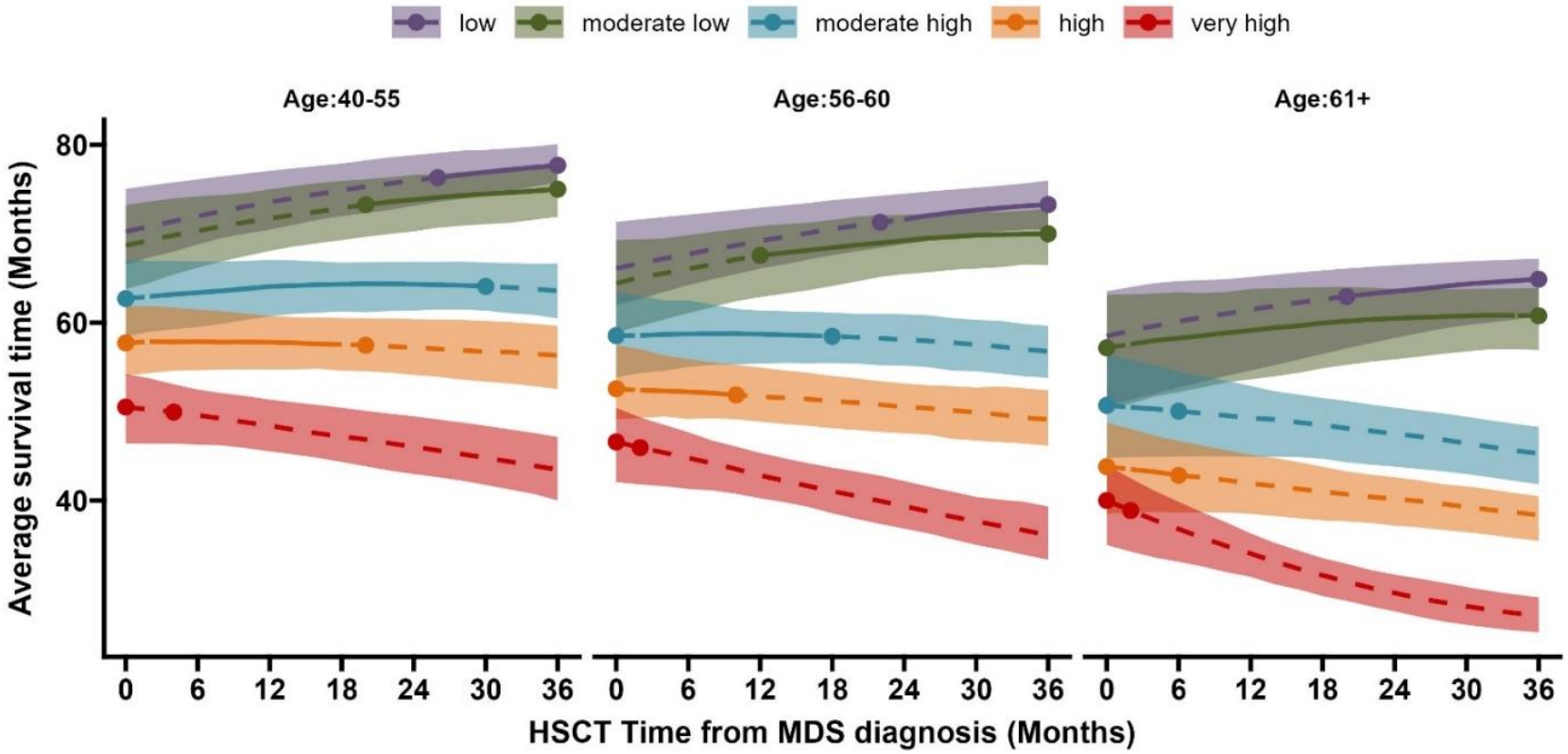
STEP 3 Scenario analysis - microsimulation



Tentori C et al. JCO 2024;42:2873-2886; Gregorio C et al. JCO CCI 2024, May;8:e2300205.

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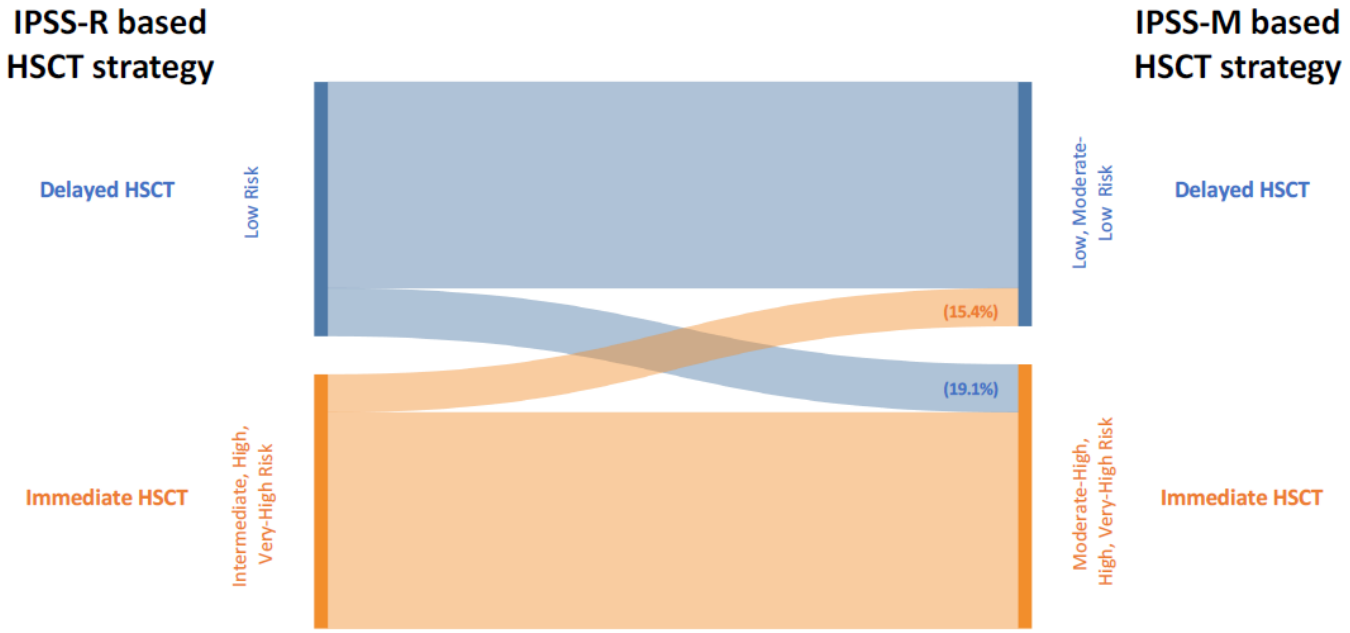
IPSS-M based transplantation policy (n=7118)

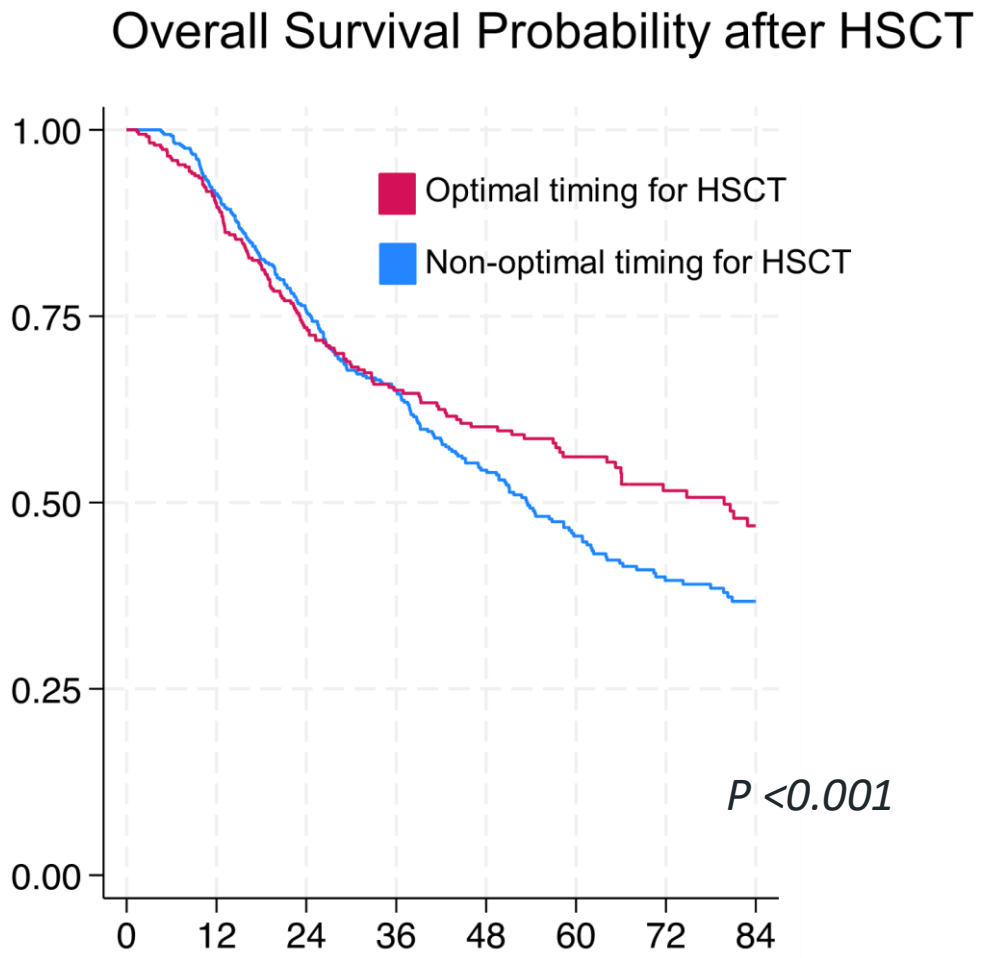


Tentori C et al. JCO 2024;42:2873-2886;
Gregorio C et al. JCO CCI 2024, May;8:e2300205.
Lanino L et al. JCO 2026; in press

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Clinical Utility of CDSS in MDS and CMML



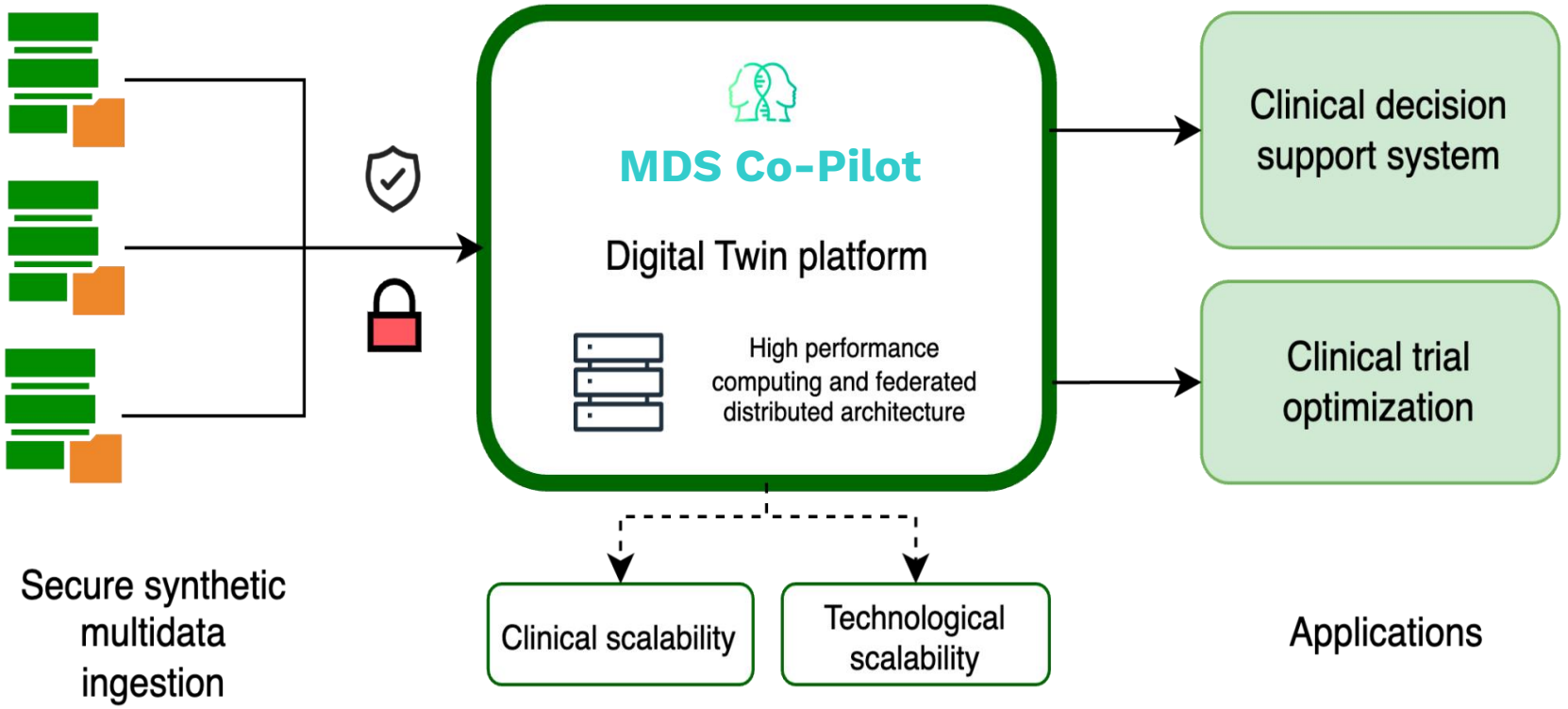


Tentori C et al. JCO 2024;42:2873-2886;
Gregorio C et al. JCO CCI 2024, May;8:e2300205.
Lanino L et al. JCO 2026; 44(17):1608-1623

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The MDS Co-Pilot Project – an overview

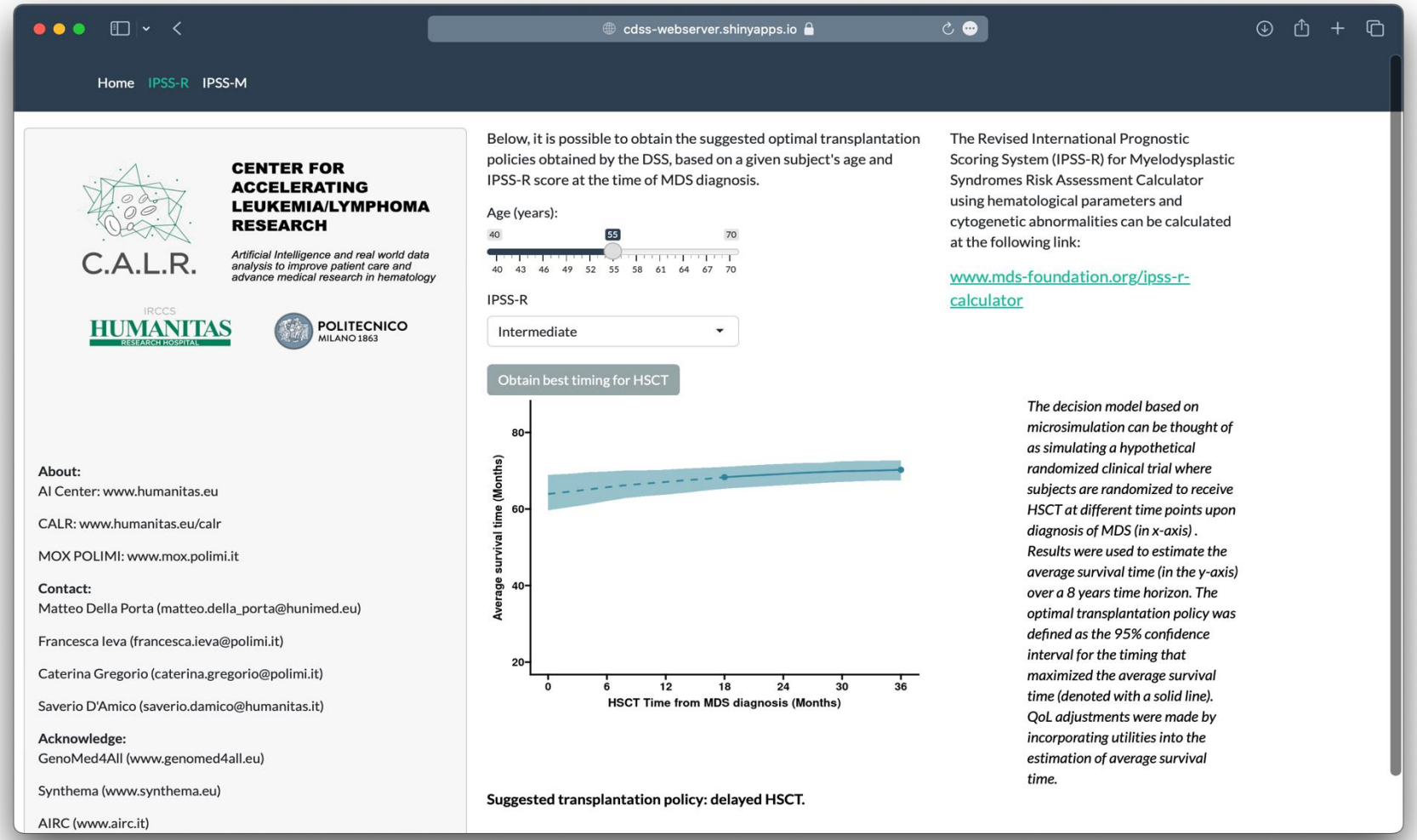
A Digital Twin by generative Artificial Intelligence to boost personalized medicine in Hematology



D'Amico et al. Blood 2024; 144: 2221

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A Digital Twin for MDS - The MDS Co-Pilot Project



MDS Foundation
The Myelodysplastic Syndromes Foundation, Inc.

Tentori C et al. JCO 2024;42:2873-2886; Gregorio C et al. JCO CCI 2024, May;8:e2300205.

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Limitations of currently available prognostic tools in MDS

- We reviewed the cases of the last 50 patients with a diagnosis of low-risk MDS who were eligible for transplant at Humanitas.

- **In 14 of 50 cases (28%), despite guidance from molecular screening, HSCT was performed only after progression to AML, indicating that the optimal transplant window had been missed.**

- MDS are characterized by clonal evolution, while the prognostic scores used in clinical practice incorporate genomic information collected only at the time of diagnosis.

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Prognostic Score for Myelodysplastic Syndromes Based on Molecular Evolution – The *IPSS-M-Evo*

ProgEvo:

1. **Driver Mutations Ranking**: ProgEvo estimates Cancer Cell Fractions for each mutation and assigns a temporal order among the driver mutations during MDS evolution.
2. **Model of Repeated Evolution**: employing a maximum likelihood approach with Akaike Information Criterion regularization for model selection, ProgEvo identifies the driver mutations presenting temporal relationships, along with their statistical validity in the datasets used, highlighting repeated evolutionary trajectories in the dataset.
3. **IPSS-M Implementation with Evolutionary Signatures (IPSS-M-Evo)**: evolutionary routes and co-occurrences compatible with the evolutionary model associated with leukemia-free survival (LFS) were incorporated into the IPSS-M score, resulting in the IPSS-M-Evo score

Civettini I et al. NEJM Evid 2026, in press

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IPSS-M-Evo

- ProgEvo was trained on **2519** patients in cBioPortal and validated using two external cohorts: Genomed4All (**2043** patients) and a Moffitt Cancer Center cohort (**2157** patients).

- ProgEvo identified **1765** gene co-occurrences aggregated into **45** directional evolutionary routes. Of these, **18** were validated in the Genomed4All cohort and were integrated into IPSS-M to generate IPSS-M-Evo.

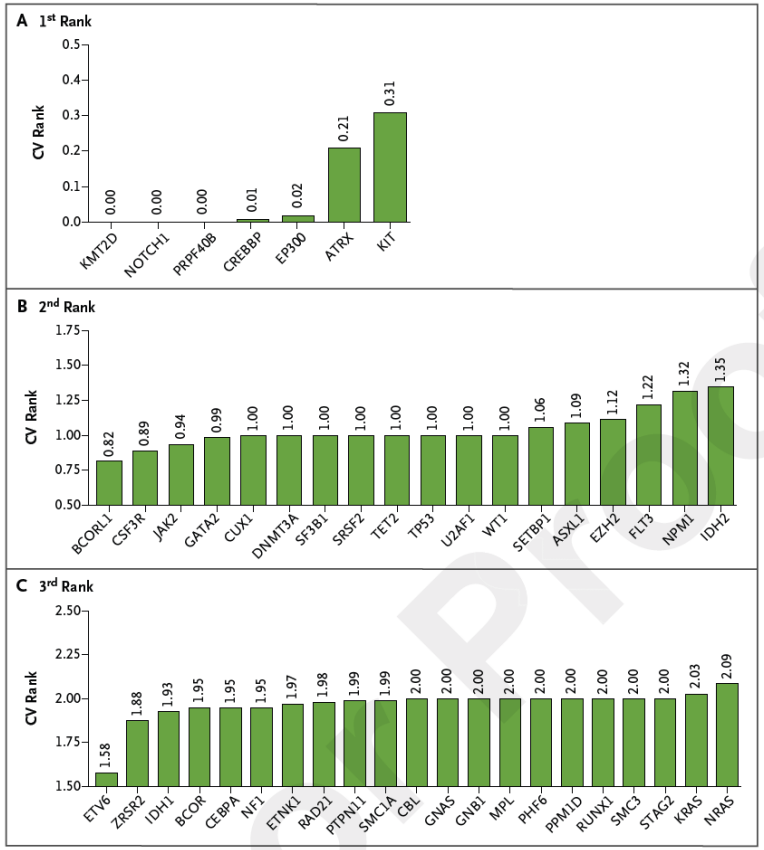
- The model with "-Evo" improved discrimination for both leukemia-free survival and overall survival, with over **40%** of patients restratified in the Genomed4All data. The performance of the model was further confirmed in an external validation cohort of **2157** patients.

Civettini I et al. NEJM Evid 2026, in press

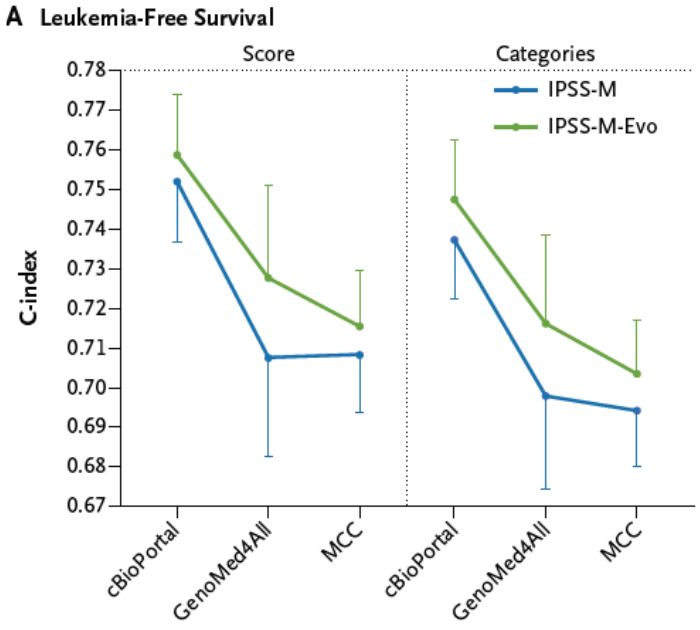
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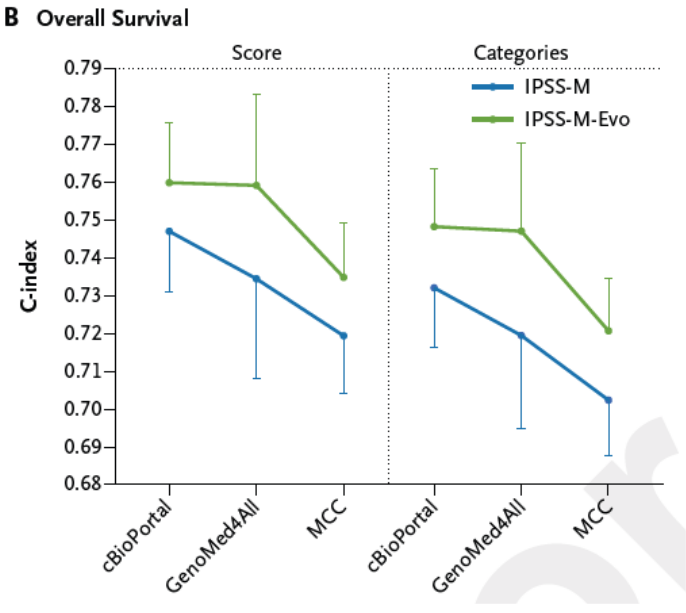
IPSS-M-Evo

Mutations were stratified into three temporal ranks



Integration into IPSS-M-Evo





Civettini I et al. NEJM Evid 2026, in press

A Global Initiative to Transform Personalized Medicine in MDS – *The Precision MDS Project*

Learning Cohort (n > 2,000)

Johns Hopkins University — Amy DeZern

National MDS Natural History Study
ClinicalTrials.gov identifier: NCT02775383.

FISIM Fondazione Italiana Sindromi Mielodisplastiche — FISIM

FISIM Personalized Medicine Program on MDS
ClinicalTrials.gov identifier: NCT04212390

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A Global Initiative to Transform Personalized Medicine in MDS – *The Precision MDS Project*

RWD Validation Cohort (n > 2,000)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Yale University

Cleveland Clinic

MLL

MOFFITT CANCER CENTER

MAYO CLINIC

Guillermo Garcia-Manero
Sanam Loghavi
Jaroslaw Maciejewski
Valeria Visconte
Carmelo Gurnari
Amer Zeidan
Ayalew Tefferi
Rami Komrokji
Torsten Haferlach
Seishi Ogawa

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Summary

- MDS are characterized by clonal evolution, while the prognostic scores used in clinical practice incorporate genomic information collected only at diagnosis
- **Clinical decision support systems** provide real-time, patient-specific information and recommendations, helping clinicians make more informed decisions.
- **MDS Co-Pilot** is the first international initiative aiming to define a Digital Twin for MDS.
- **Cancer cell fraction–based evolutionary modeling** successfully reconstructed temporal mutation sequences and identified specific genes whose clonal expansion independently predicts progression to AML.
- Overall, these findings support the concept that next-generation prognostic tools for MDS should be grounded in the analysis of longitudinal data and the use of advanced technologies to generate new “personalized” clinical evidence.

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