Intelligenza artificiale in ematologia: luci e ombre

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SITE
SOCIETA' ITALIANA TALASSEMIE ED EMOGLOBINOPATIE

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Disclosures of Matteo Della Porta

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

A technological ecosystem to support MDS patients management

GENOMED4ALL

SYNTHEMA

synthia

Realise

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

NTT DATA

FISA

Digital Twin

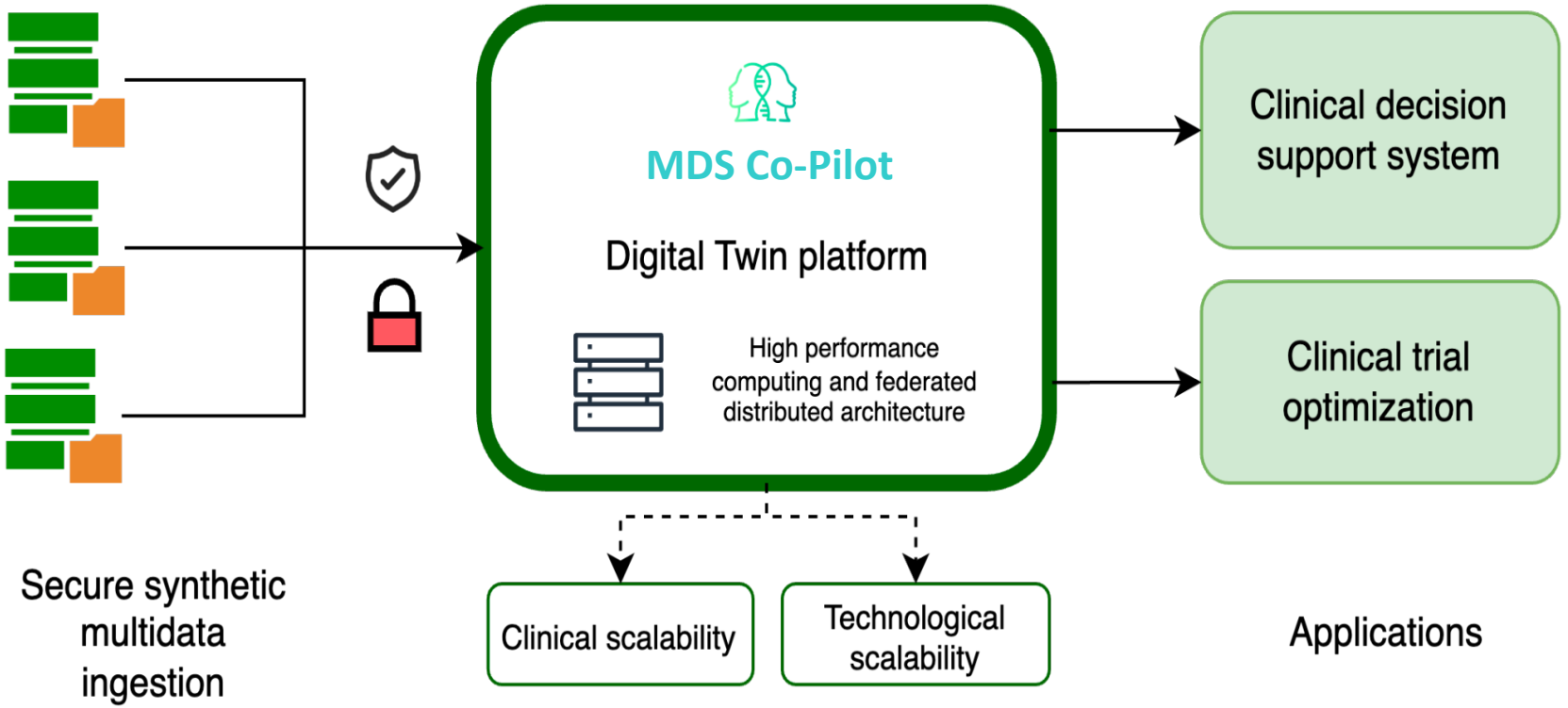
- Digital twins are **replicas of real-world objects or systems created through high-resolution models** from **real-world data** to better understand how the system works and to see what would happen in **simulation scenarios**.

- Applied to medicine, this concept involves modeling a specific disease to **generate new clinical evidence and support more efficient and dynamic clinical decision-making** within the framework of personalized medicine.

Katsoulakis E. et al. NPI Digit. Med. 2024;7,77

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

2021 WHO guidance on ethics & governance of AI for health

We have to address three important topics for a **right deployment of AI in hematology**:

- **Transparency of models.** We have to provide a good understanding of the models (interpretability and explainability)
- **Reliability of models.** The main vulnerabilities of AI models are related to lack of generalizability. Therefore, extensive, independent validation of generated AI-models is required.
- **Protection of data and data sharing**. Innovative technologies such as federated learning procedures for data collection and analysis (without moving sensitive medical data from their original locations) are required to facilitate clinical implementability of AI solutions

The World Health Organization. 2021 WHO guidance on ethics and governance of artificial intelligence for health. https://www.who.int/publications/i/item/9789240029200

The MDS Co-Pilot Project – Data Source

N=7,117

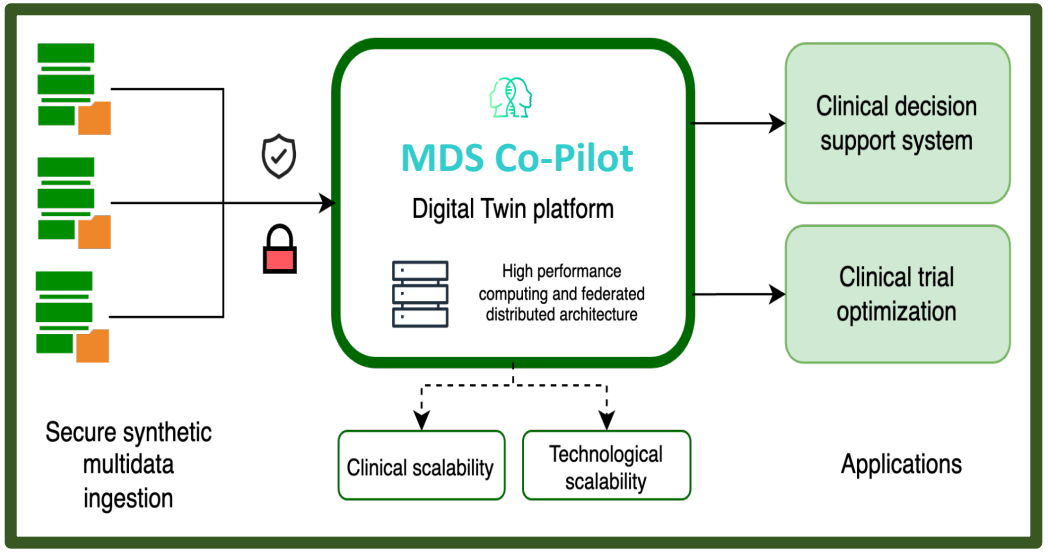
N>2, 000

Including QoL

MDS- CAN

Canadian MDS registry N>1,500

Including frailty, comorbidity



VALIDATE dataset

N=2,135

N=8, 050

Lombardia region

EHR from >10 M people

The MDS Co-Pilot Project – Data Source

Disease-related

- Clinical features
- Genomics
- Treatments
- Clinical outcomes

Patient-related

- Comorbidity
- Frailty
- QoL
- Patients Reported Outcomes

Patients Reported Outcomes in MDS

- **Prognostic Value**: independent predictors of survival and treatment response
- **Personalized Care**: tailored treatment plans by considering individual patient preferences and experiences.
- **Symptom Management**: early detection and management of symptoms, reducing hospitalizations /improving well-being.
- **Quality of Life Assessment**: insights into the impact of disease and treatment on patients' daily lives, facilitating interventions to enhance QoL.
- **Healthcare Decision-Making**: inform health economic evaluations and policy decisions, ensuring patient-centered approaches in oncology care

Efficace F et al. Hemasphere. 2024; 8(5):e69

The need

1) **Improving access to and sharing** of real-world clinical and omics data to generate new insights and advance knowledge.

2) Supporting **prospective (longitudinal)** initiatives aimed at validating the generated knowledge and enabling the clinical implementation of next-generation tools for decision-making.

3) Shifting the focus from the natural history of the disease **to patient-centered treatment approaches to improve outcomes**.

4) **Leveraging advanced technologies, particularly AI** to extract greater scientific and clinical value from data and to accelerate research timelines.

Clinical relevance of prospective/longitudinal data: the example of p53 dysfunction in MDS

Data collected at diagnosis

- *TP53* multi-hit state predicted high risk of death and leukemic transformation
- Monoallelic patients did not differ from *TP53* wild-type patients in outcomes and response to therapy

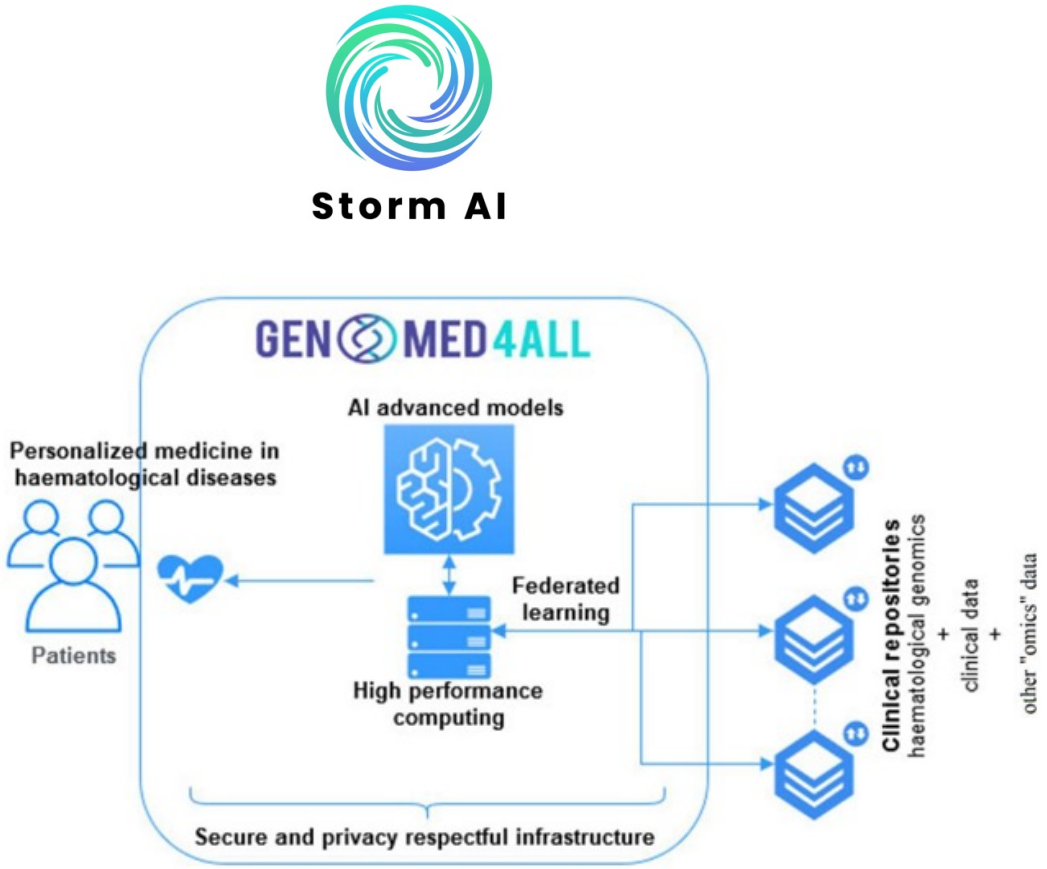
Longitudinal data

- Monoallelic and biallelic inactivation represent disease stages occurring as a multi-hit process in MDS with *TP53* mutations
- A distinct immunosuppressive profile is associated with disease progression in MDS with *TP53* mutations, which may provide the groundwork for innovative immunotherapies.
- Non-mutational p53 dysfunction identifies MDS with poor outcomes (5% of patients).

Bernard E, Nat Med. 2020;26:1549-155

Zampini M et al. JCO 2025 doi: 10.1200/JCO-24-02394

The solution - STORM_AI: Supporting innovaTion in MyelOdyspastic Syndromes by Reliable and Multimodal AI



Federated Learning by AI

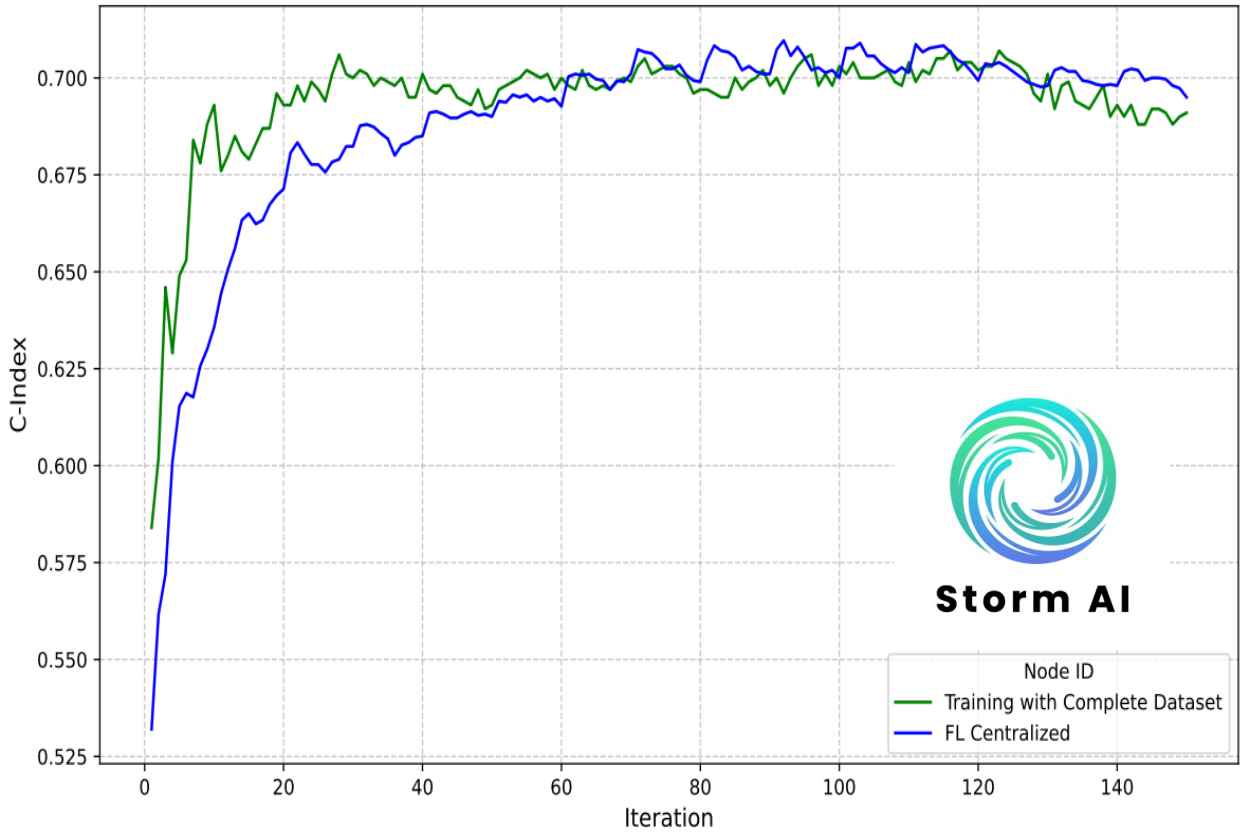
- Innovative technologies for data collection and analysis to preserve data privacy are required for implementing personalized medicine
- Federated learning addresses privacy concerns by collaboratively training algorithms without sharing data.

Under discussion with M Mittelman and MDS Foundation MSAB

Storm AI Platform - federated IPSS-M from 5 centers in EU

IPSS-M C-index progression

Centralized dataset vs. Federated model



Storm AI Platform: advantages

- **Opensource design -** built entirely using opensource components
- **Scalability and flexibility -** the platform adopts a modular approach, making it highly configurable and adaptable to changing functional requirements;
- **Standardization -** it employs internationally recognized and approved standards for data harmonization and homogenization

- Federated model performs comparably with centralized one, without moving patient data beyond the firewalls of the institutions in which they reside

Asti G, et al. Blood 2024; 144: 4989.

MDS Co-Pilot as a platform to improve diagnosis and prognosis

Digital Pathology For Personalized Medicine In Myeloid Neoplasms

Patients Cohort Characteristics	All Patients (n = 1,688 *)
Age (y), median (range)	67 (20-96)
Gender (Male/Female), %	1003/685, 60% ; 40%
Patient Diagnosis	
AML (%)	363 (22%)
MDS (%)	640 (38%)
MDS/MPN (%)	107 (6%)
MPN (%)	578 (34%)

*: MMG, H&E, Gomori, IHC stainings collected at diagnosis and multiple timepoints during follow-up.

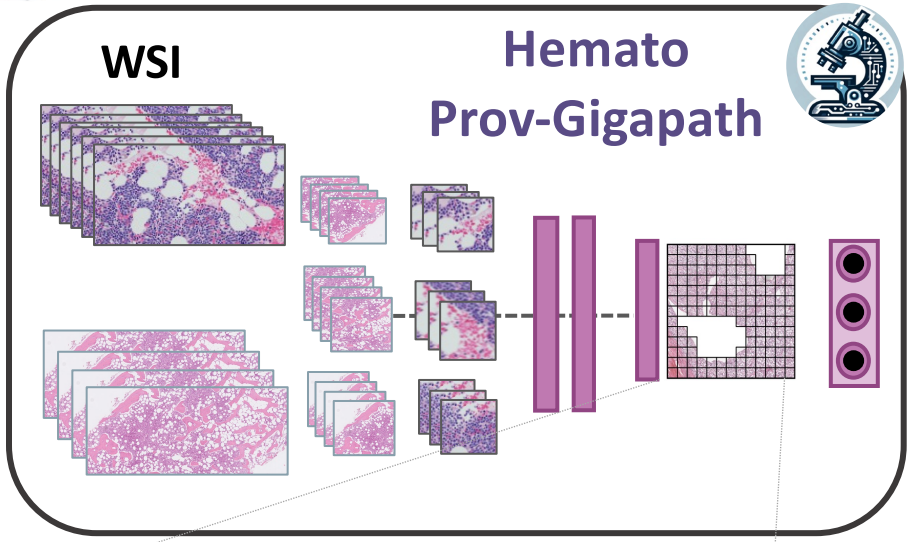
AIMS:

1. To develop an AI-based diagnostic system for Myeloid Neoplasms (MDS)
2. To predict genomic profiles based on morphological features
3. To define innovative personalized prognostic/predictive models based on computational pathology

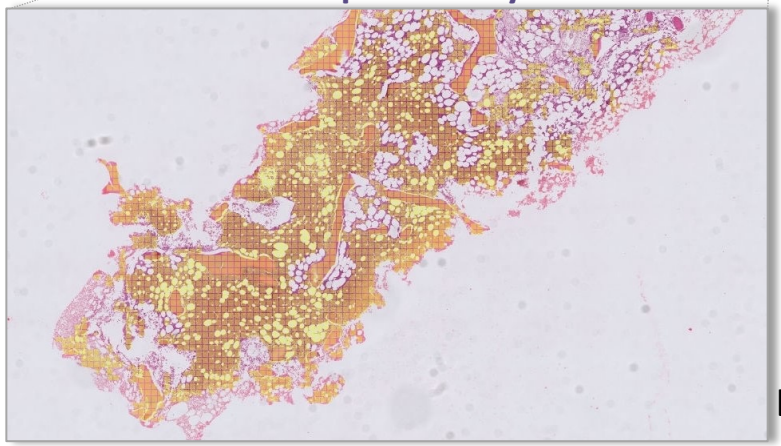
Asti G et al, Blood 2024; 144 : 3598

Digital Pathology For Personalized Medicine In MDS

Histopathological Data



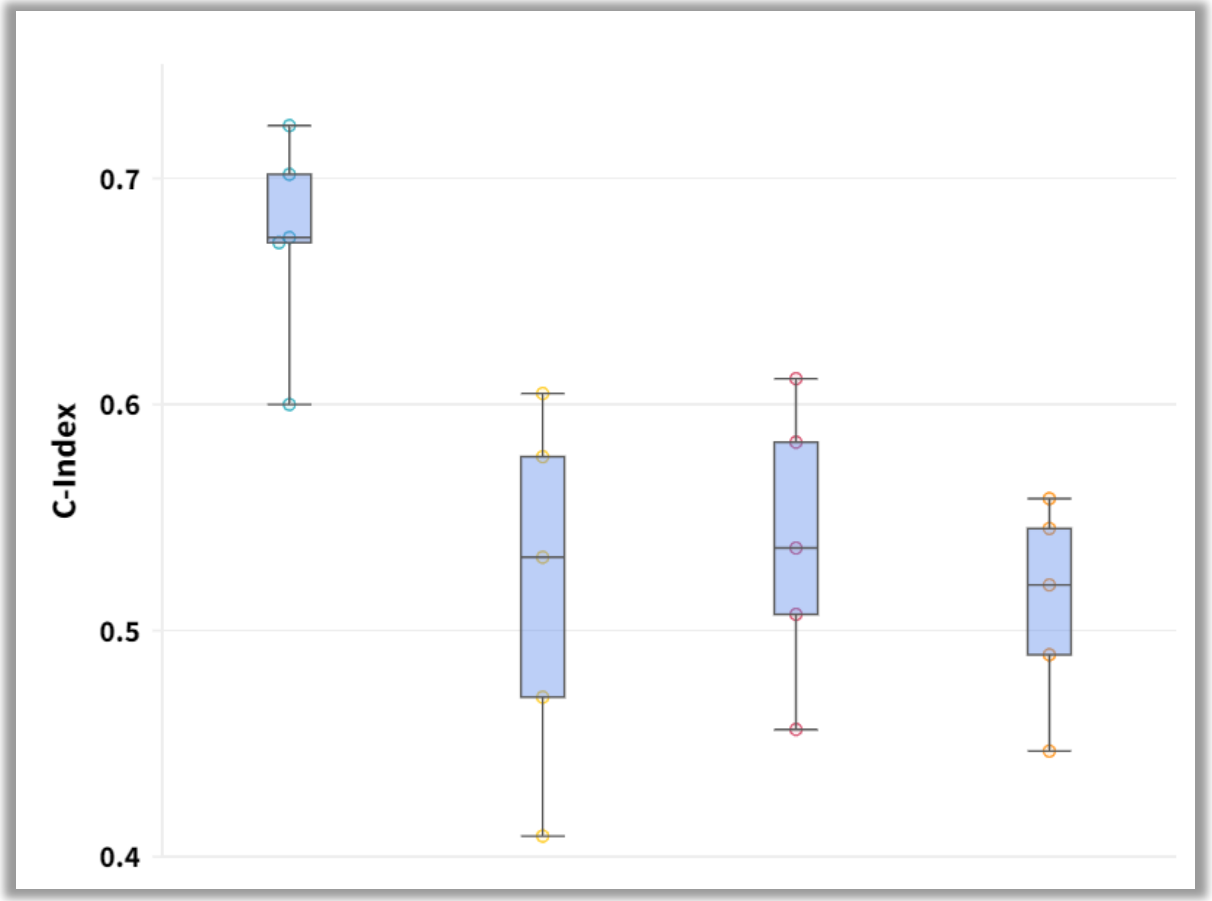
WSI Explainability



Relevance to Prediction

High

Low

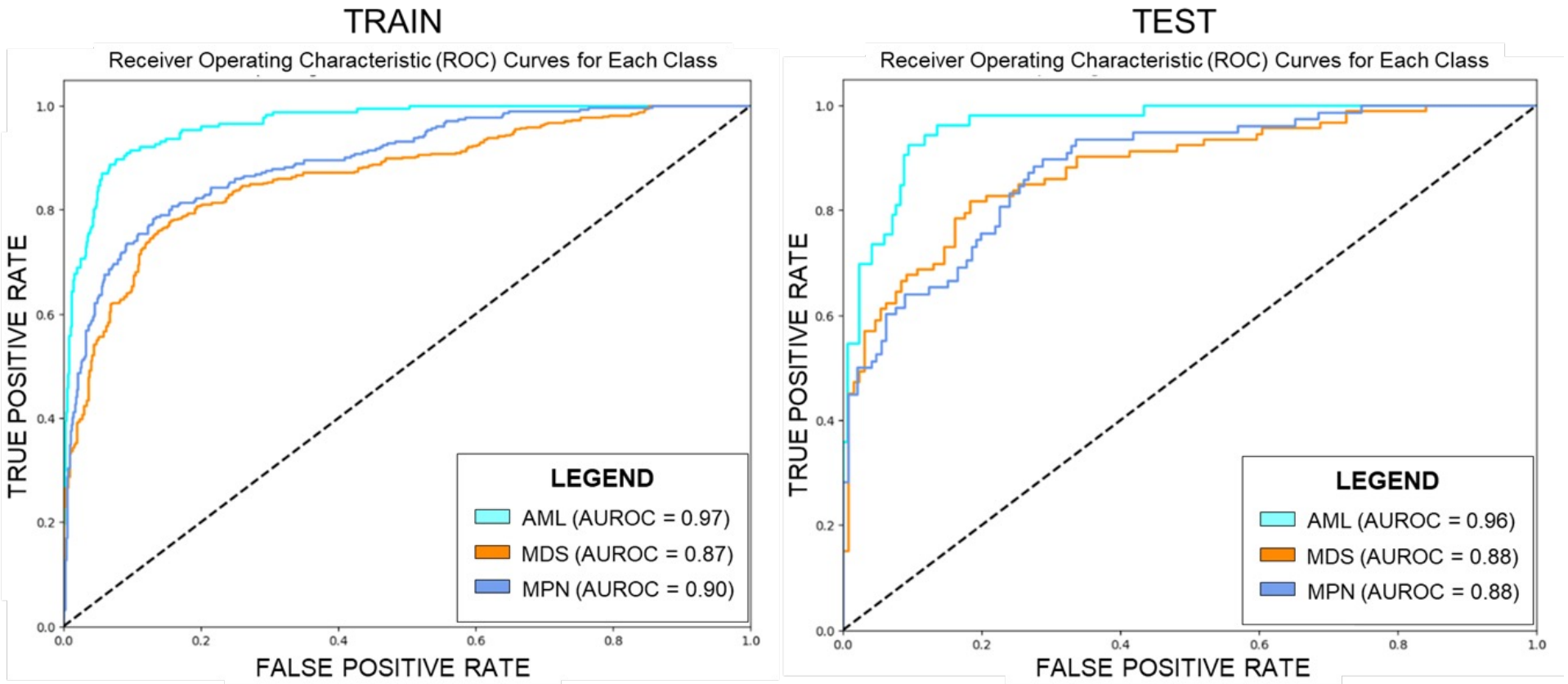


Hematо Prov-Gigapath *DinoBloom* *CLAM* *ResNet50*

Asti G et al, Blood 2024; 144 : 3598

Aim 1 - To develop an AI-based diagnostic system for MN

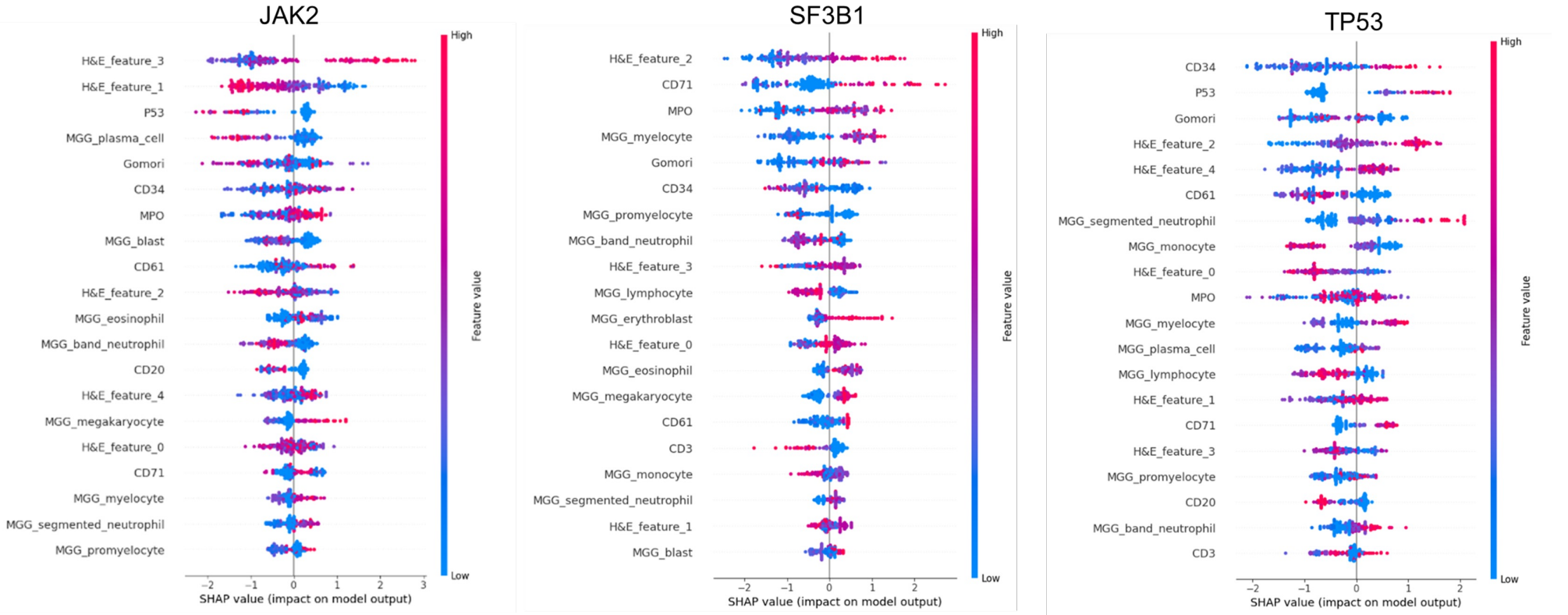
A Deep Learning Model for multiclassification was trained using the WSI features to discriminate specific clinical entities among MN. The models predicted a correct diagnosis with an overall AUROC >0.91, suggesting that extracted features capture clinically relevant information.



Asti G et al, Blood 2024; 144 : 3598

Aim 2 - Predict genomic profiles based on morphological features

We analysed the morphologic and molecular features association. Specific genomic profiles were predicted from WSI features with specialized XGBOOST models with high accuracy, in particular for SF3B1, JAK/STAT, TP53 and RUNX1 mutations (F1 Score > 90%). These findings underline the capability of digital pathology to capture the biological background of MN.



Asti G et al, Blood 2024; 144 : 3598

Aim 3 - define innovative personalized prognostic models

- We integrated morphological features into an innovative prognostic tool for personalized prediction of OS and LFS in MN.
- After the feature selection process (by using a L1-penalized Cox regression) morphological features were included in the model together with demographic, clinical and genomic information. Model discrimination was assessed using CI).

Variables	Overall Survival C-Index	Leukemia Free Survival C-Index
Clinical	0.78	0.68
Clinical + Genomic + Karyotype	0.82	0.80
Clinical + Genomic + Karyotype + Imaging	0.88	0.90

Asti G et al, Blood 2024; 144 : 3598

The PATHroclus project supported by EHA

Specific project's aims:

1) Deploy the *PATHroclus* federated platform
2) Utilize innovative AI algorithms to create next-generation diagnostic and prognostic tools
3) Develop a comprehensive database integrating digital pathology, clinical and genomic information to design next-generation classifications for myeloid and lymphoid malignancies
4) Develop a virtual atlas for hematological malignancies as an educational resource to improve diagnostic standards and reproducibility across Europe

Consortium:

- *M Della Porta - Humanitas*
- *P Harrington – King's UK*
- *A Turki – Essen DE*
- *JM Middeke – Dresden DE*
- *A Mosquera Orgueira - ES*
- *José Cardia – Lisbon PT*
- *M Ponzoni – OSR, IT*

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MDS Co-Pilot as a Clinical Decision Support System (CDSS)

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

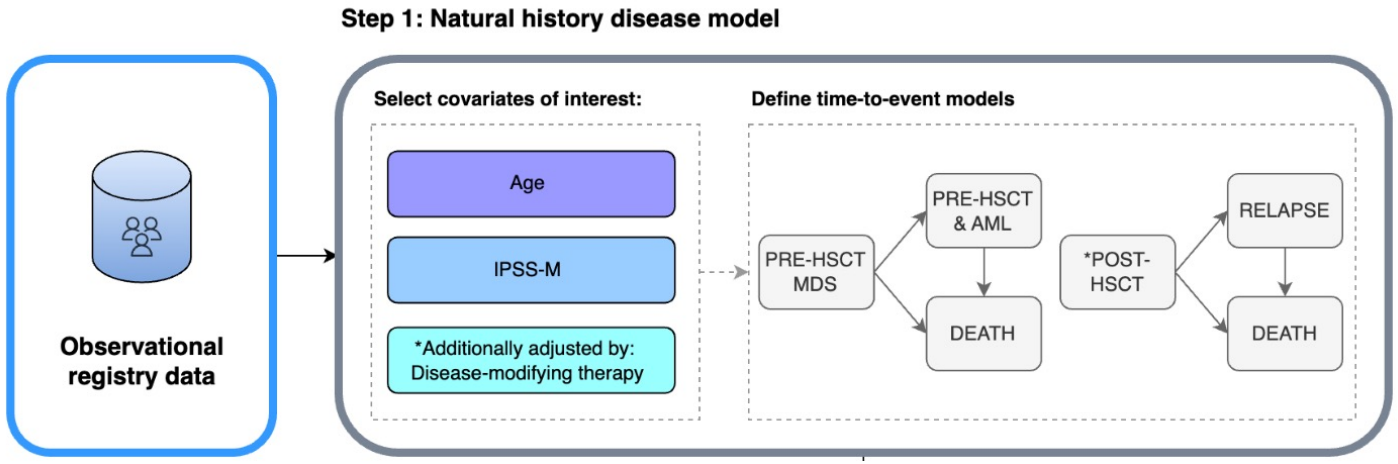
Benefits:

- *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*

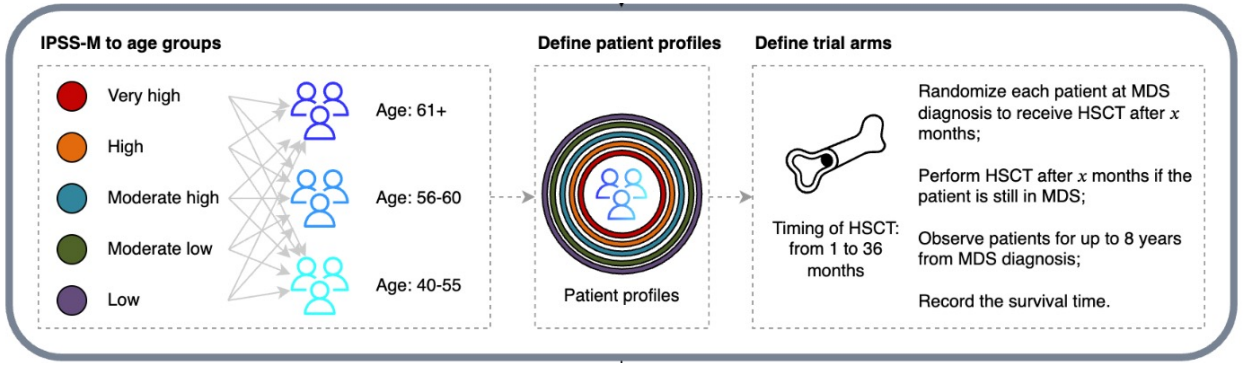
Vasey B et al. Nat Med 28:924-933, 2022

Development of a Decision Support System by AI

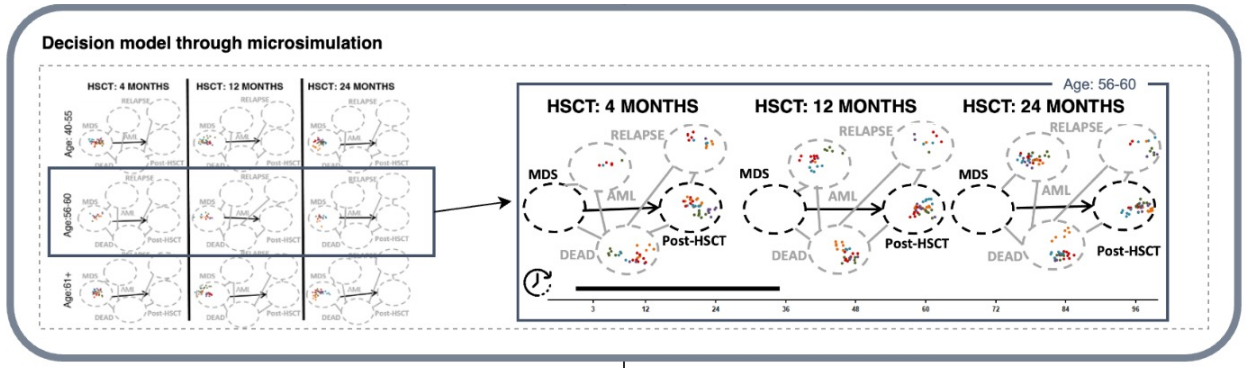
STEP 1 – Model of the disease natural history and the effect of treatment



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.

Clinical and genomic-based Decision Support System to define the optimal timing of HSCT in MDS

- To develop and validate a Decision Support System to define the optimal timing of HSCT in MDS patients based on clinical and genomic information as provided by IPSS-M

- To compare the outcome of transplantation policies based on IPSS-M vs original IPSS-R and to measure the proportion of patients in which the optimal timing for HSCT would change by introducing molecular information in the decision process

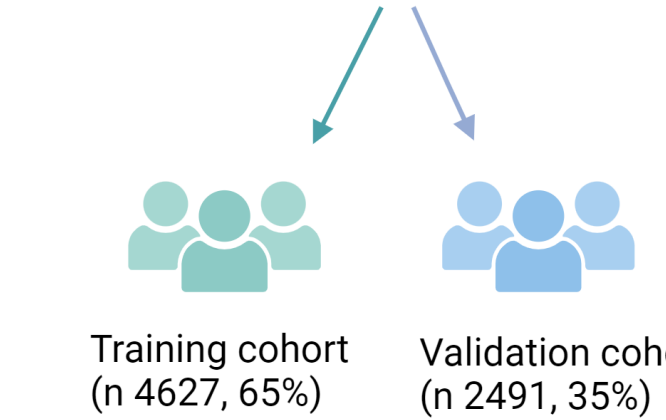
Tentori C et al. JCO 2024;42:2873-2886; Gregorio C et al. JCO CCI 2024, May;8:e2300205.

Study Population

GEN MED 4ALL SYNTHEMA

ebn ERN | EuroBloodNet MDS

7118 patients from 26 institutions



Training cohort
(n 4627, 65%)

Validation cohort
(n 2491, 35%)

Inclusion criteria:

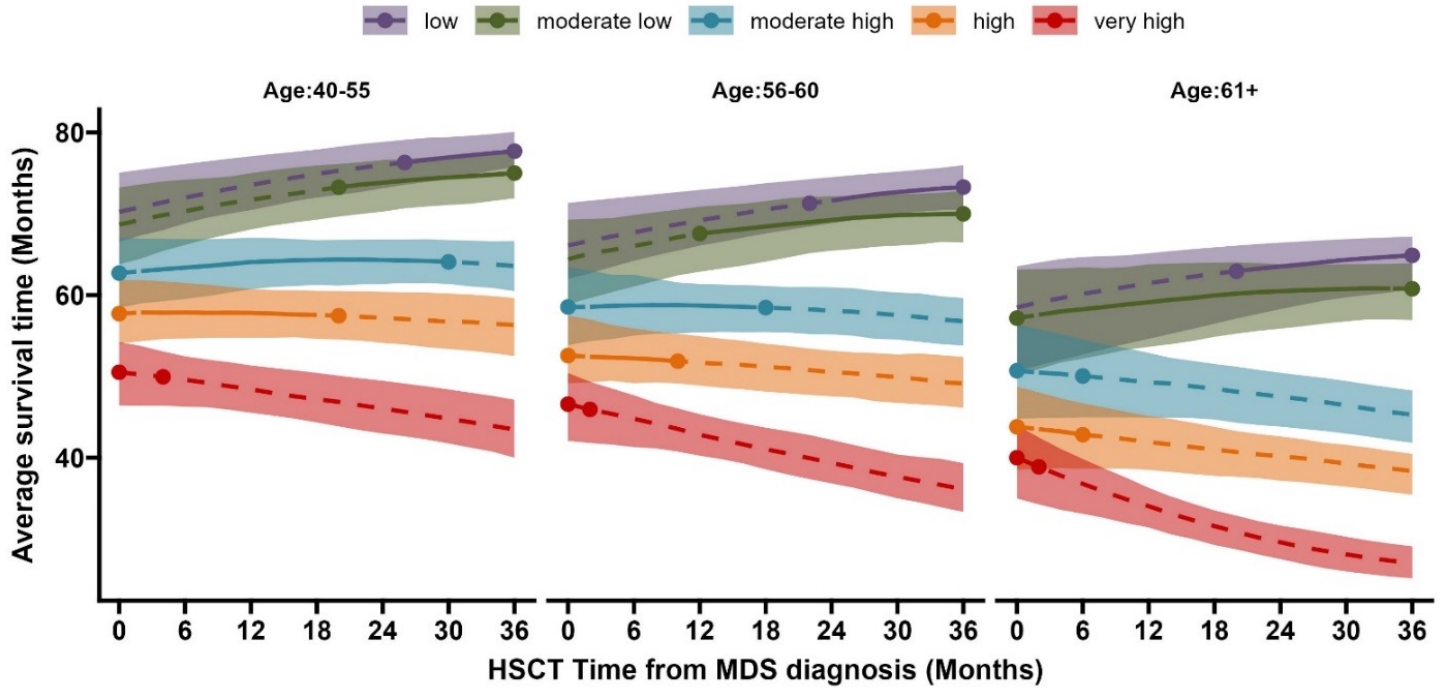
- age ≥18 years
- a diagnosis of primary MDS according to WHO 2016 criteria
- available information on IPSS-M related variables

Exclusion criteria:

- patients affected with therapy-related MDS, acute myeloid leukemia (AML) from MDS
- incomplete information on IPSS-M variables

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

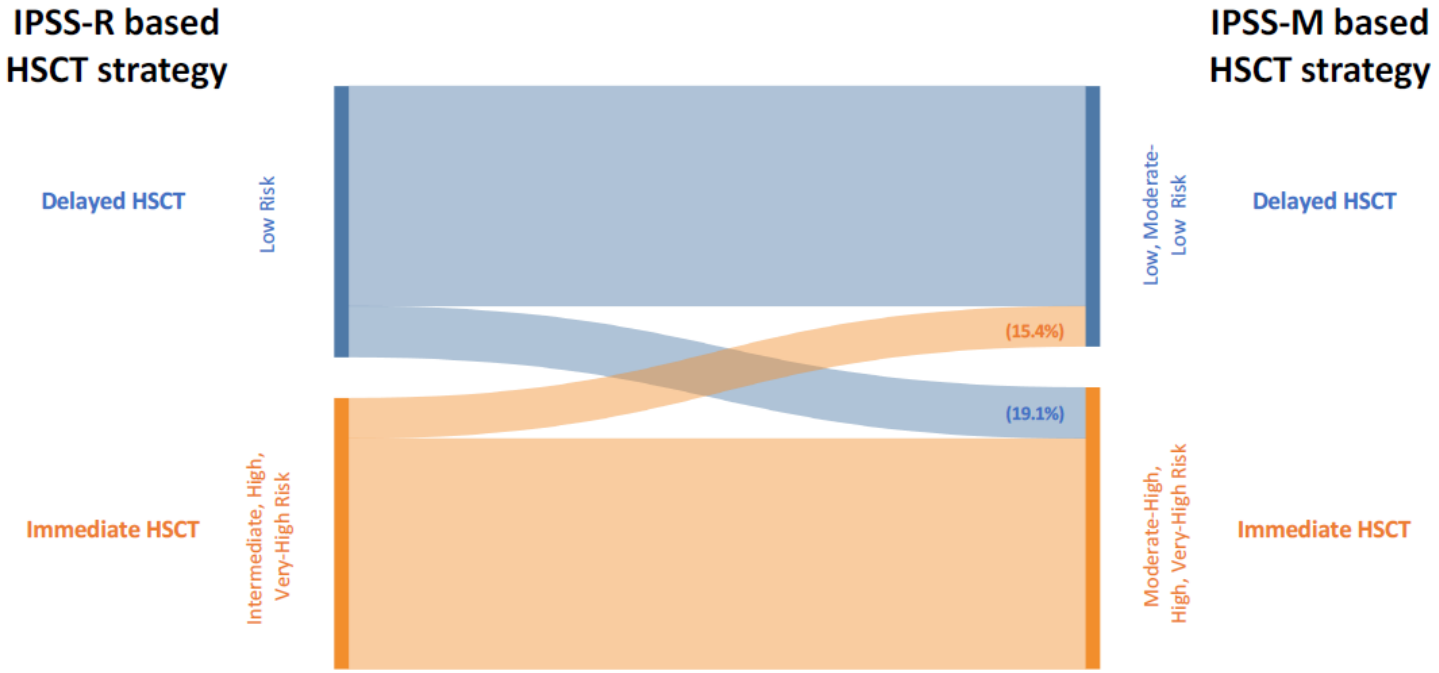
IPSS-M based transplantation policy



- Under an IPSS-M based policy, in patients with either low- and moderate-low risk benefited from a delayed transplantation policy, while in those belonging to moderate-high, high- and very-high risk categories immediate transplantation was associated with a prolonged life expectancy (RMST)

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

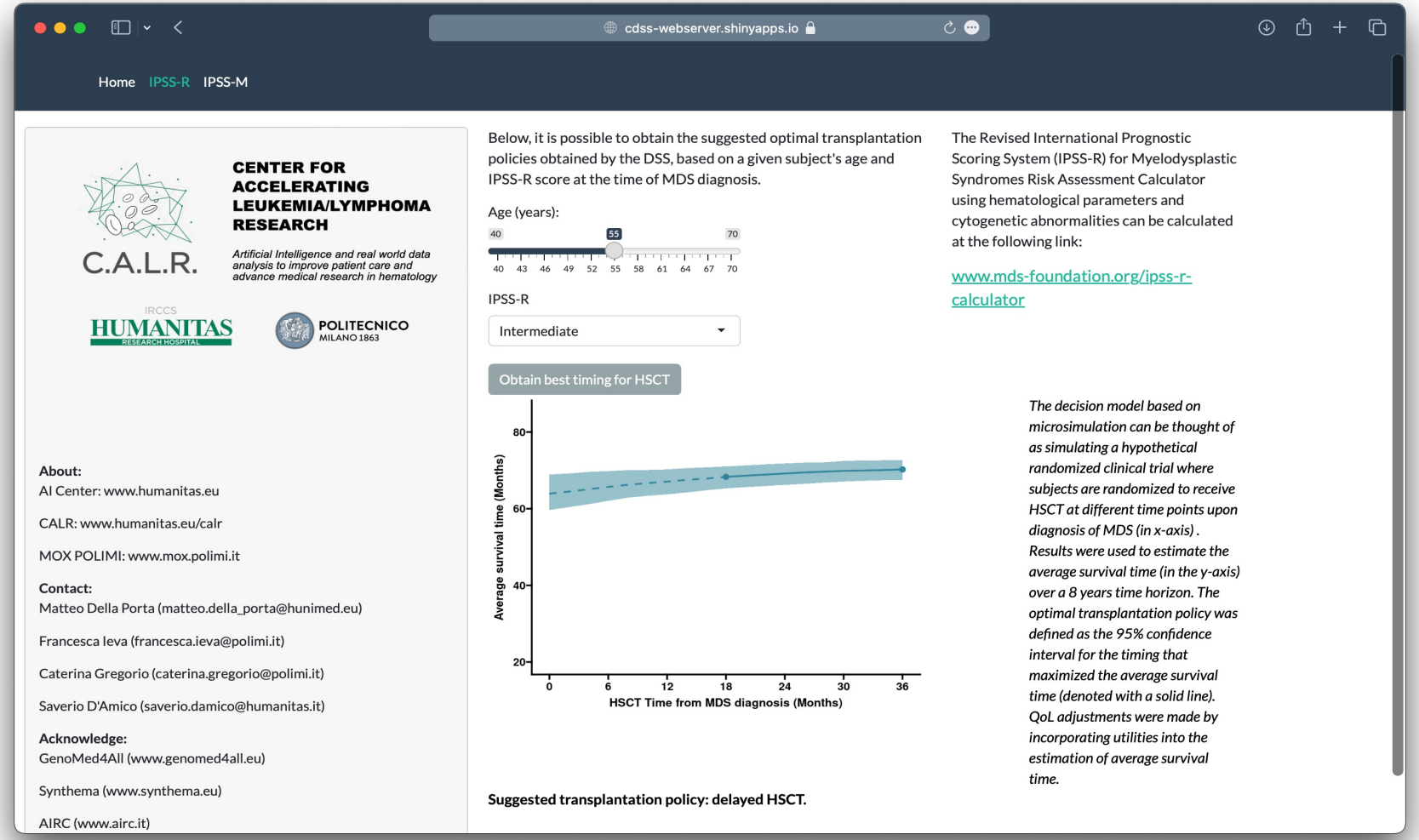
Comparison of IPSS-R vs IPSS-M transplantation policy



- Modelling decision analysis on IPSS-M vs. original IPSS-R in this population changed transplantation policy in a significant proportion of patients (17%)
- The comparison of life expectancy for the optimal transplantation policies obtained using different scoring systems (IPSS-R/IPSS-M) resulted in a significant gain of RMST under an IPSS-M based policy across all age groups (P=0.001)

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

Clinical Decision Support System for HSCT in MDS - WEB TOOL



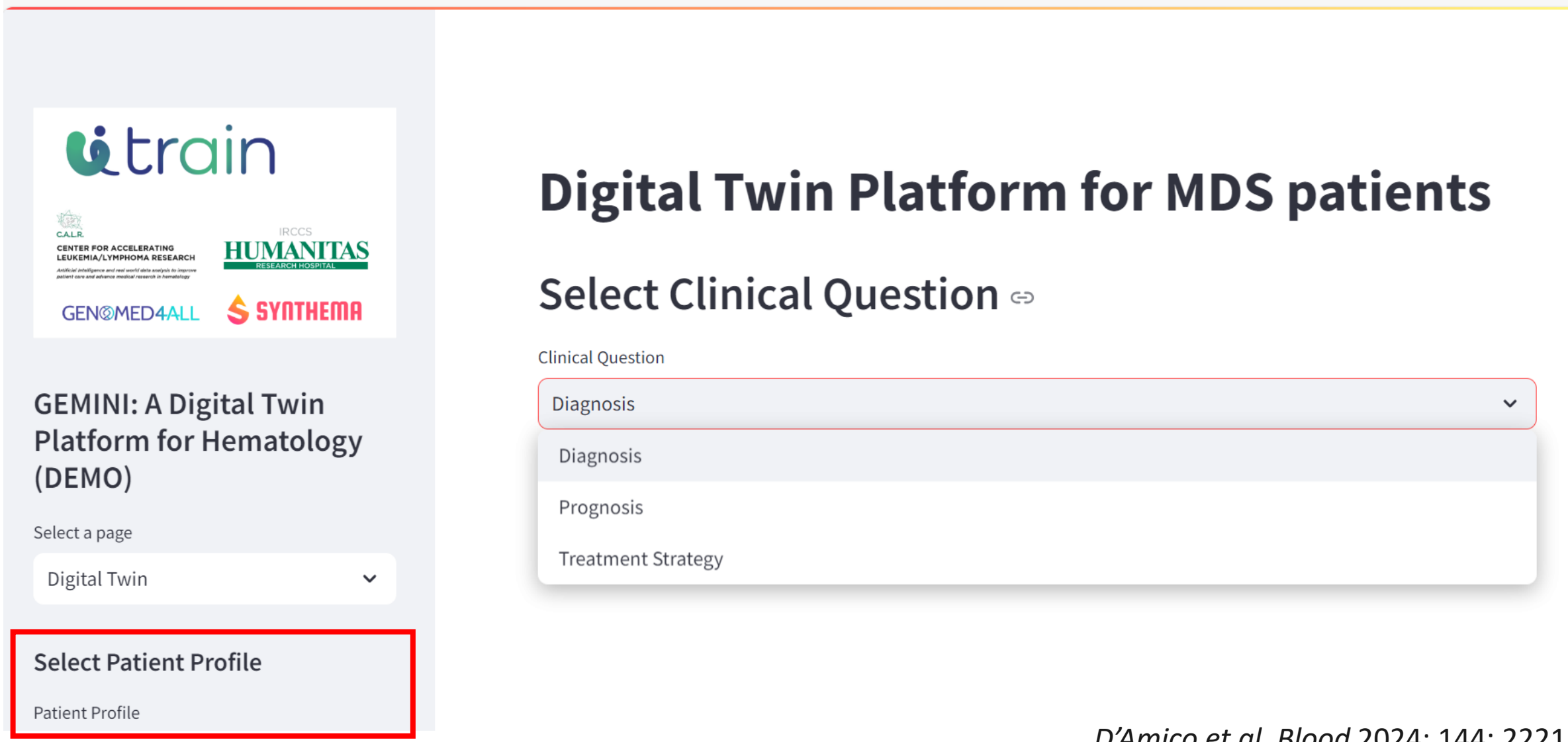
Tentori C et al. JCO 2024;42:2873-2886; Gregorio C et al. JCO CCI 2024, May;8:e2300205.

MDS Co-Pilot as a (Personalised) Decision Support Systems

- Personalized probability of survival and leukemic evolution
- Prediction of response rate to specific treatments (ESA, Luspatercept, HMA)
- Optimal timing of transplantation and prediction of post-transplantation outcome
- Comparison of different treatment policies
- QoL information and prediction according to the natural history of the disease and to specific treatment scenarios

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

MDS Co-Pilot – Web Platform



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

Summary

- Modeling disease- and patient-related characteristics within a **Digital Twin** environment has the potential to significantly improve the management of patients with MDS.
- **MDS Co-Pilot** is the first international initiative aiming to define a Digital Twin for MDS.
- Improved access to **Real-World Data** and the collection of longitudinal data are essential to generate new clinical evidence and support personalized decision-making in MDS.
- **Federated Learning**, a novel AI-driven approach, addresses data privacy concerns by enabling the collaborative training of algorithms without the need to share raw data.
- **Digital pathology** can enhance both the standardization and accuracy of diagnosis, as well as support personalized prognostic assessment.
- **Clinical decision support systems (CDSS)** provide real-time, patient-specific information and recommendations, helping clinicians make more informed decisions.

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