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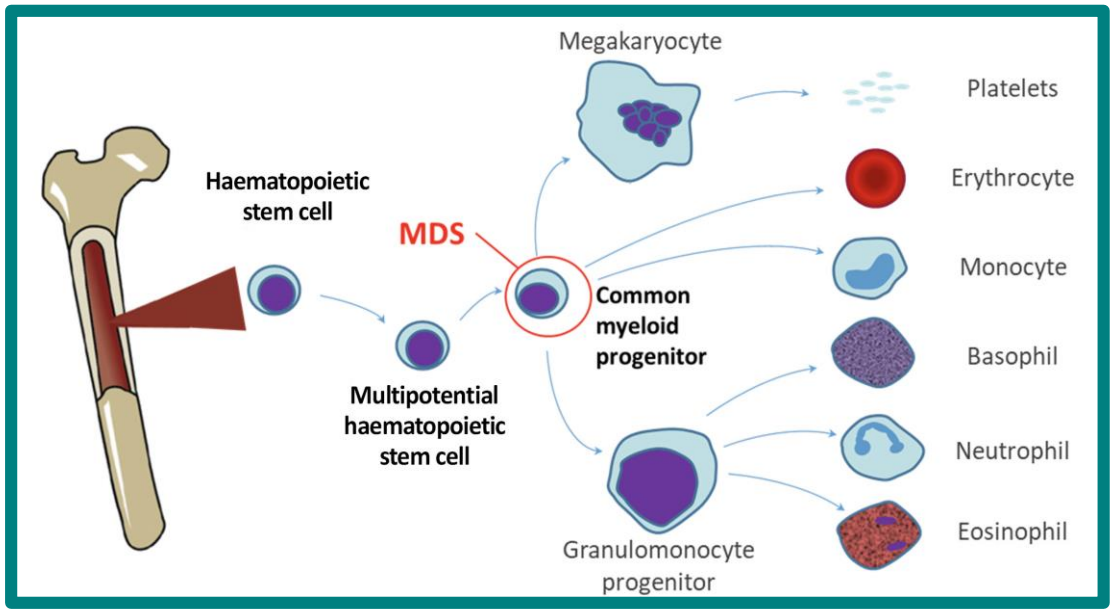
Artificial Intelligence to improve clinical management of MDS

MATTEO DELLA PORTA, MD
Humanitas Research Hospital, Milan Italy

C.A.L.R.

HU HUMANITAS UNIVERSITY

Myelodysplastic Syndromes (MDS)



- Myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic disorders characterized by peripheral blood cytopenia and increased risk of evolution into acute myeloid leukemia (AML).

- MDS range from indolent conditions to cases rapidly progressing into AML, and therefore a risk-adapted strategy is needed

GENOMDE4ALL: Genomics and Personalized Medicine for all through AI in Rare Hematological Diseases

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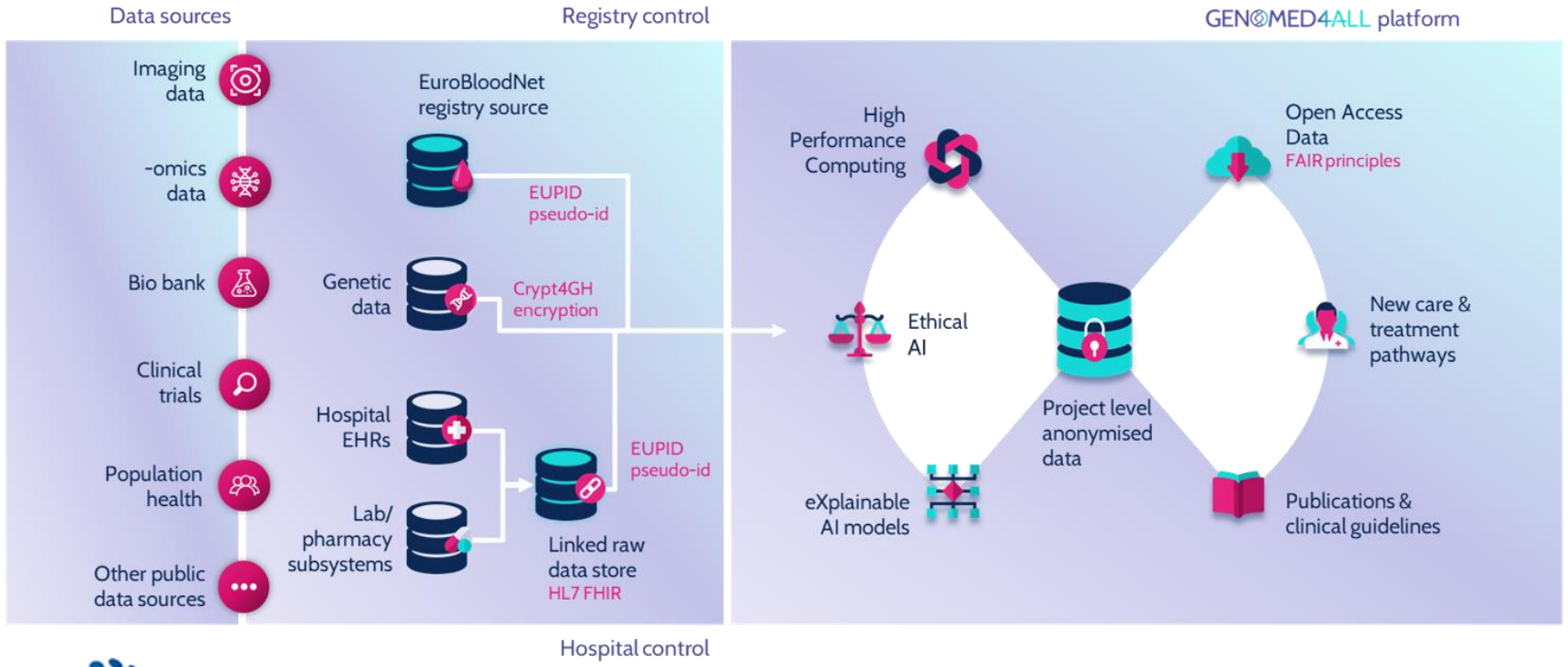

EuroBloodNet

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Artificial Intelligenece (AI) for precision medicine

1- Machine Learning

2- Generative AI

2021 WHO guidance on ethics and governance of AI for health

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

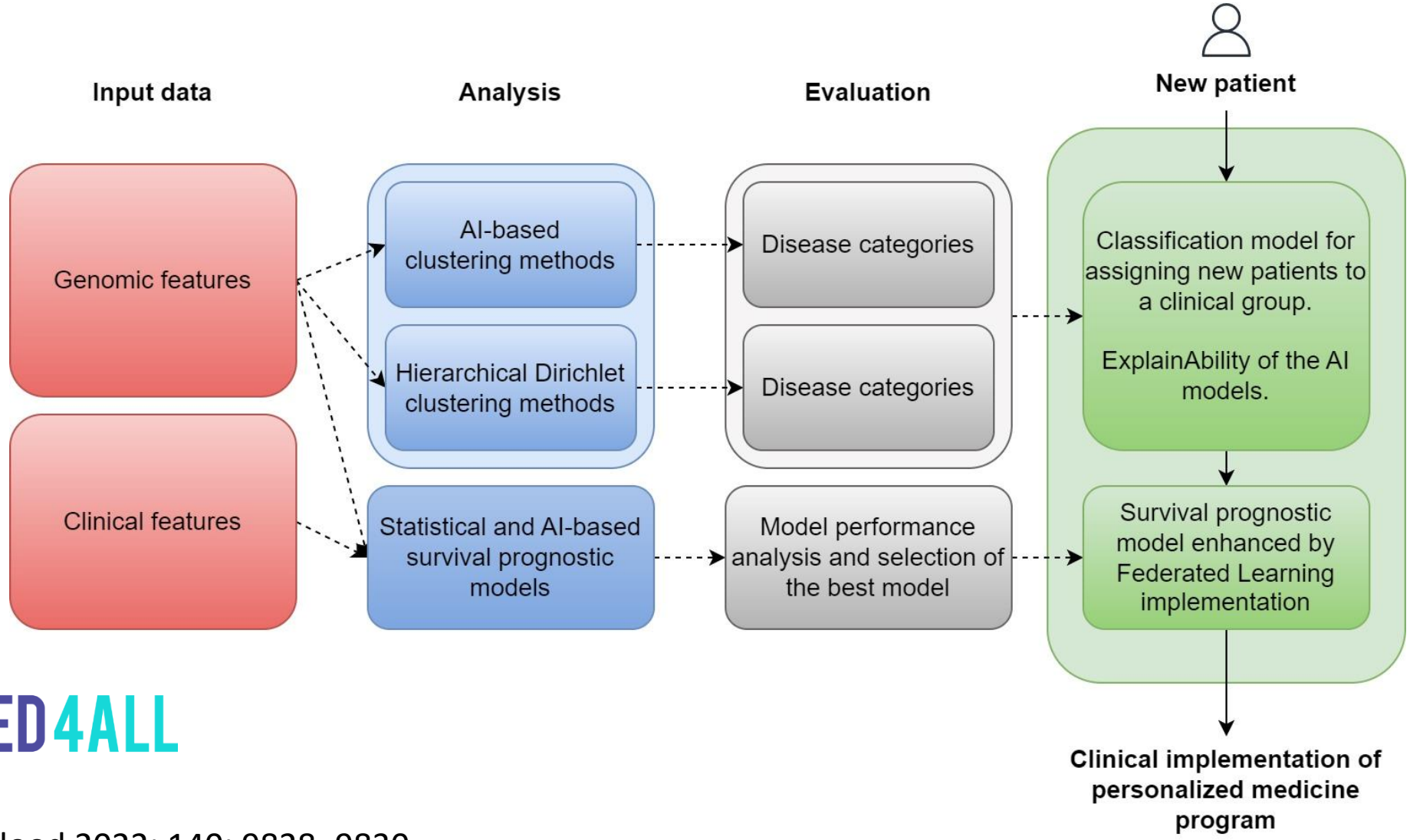
- **Transparency of models.** We have to provide a good understanding of the models (interpretability and explainability)

- **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

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

MOSAIC - Multi-Modal Analysis and Federated Learning Approach for Classification and Prognostic Assessment in Rare Cancers



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D'Amico et al, Blood 2022: 140: 9828–9830

2022 WHO/ICC classification of MDS

Table 1. Comparison of MDS subtype definitions in WHO 2016, WHO 2022, and ICC classification of MDS.

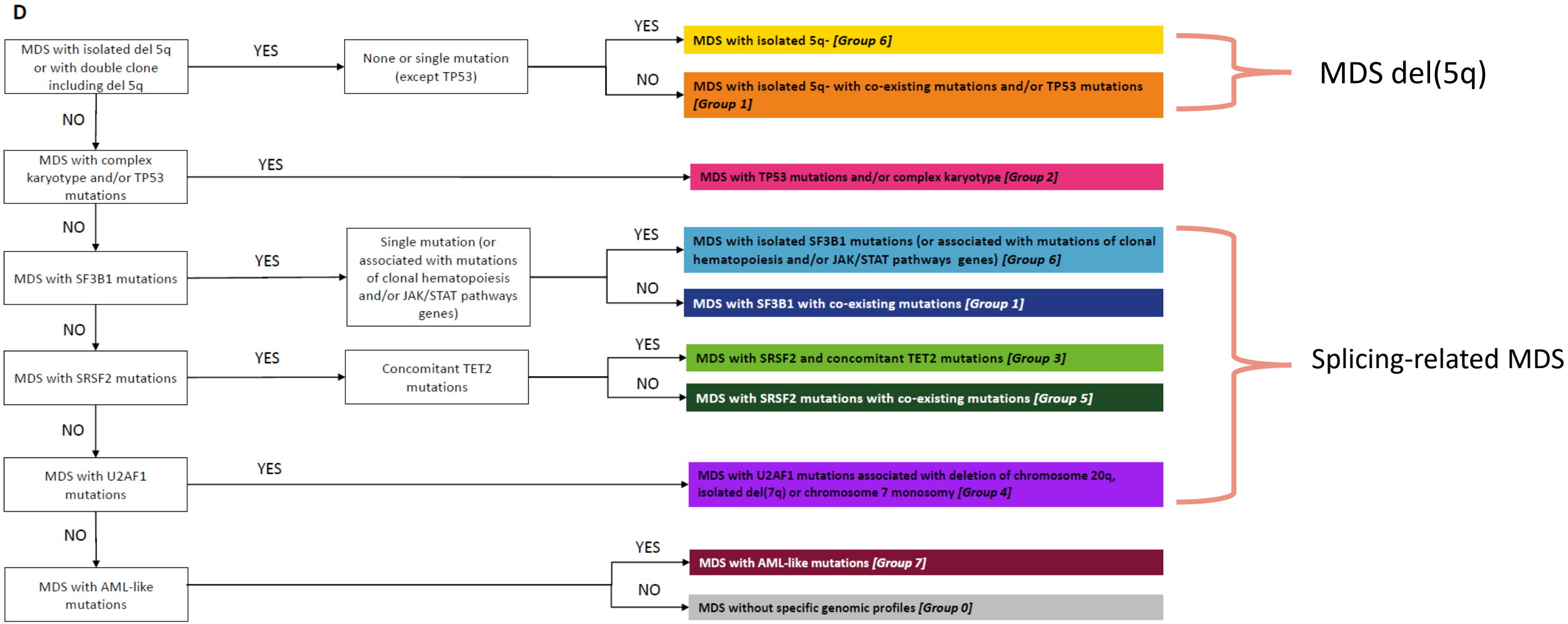
WHO 2016 [1]	WHO 2022 [3]	ICC [5]
MDS with single lineage dysplasia (MDS-SLD)	Not included MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
MDS with multi-lineage dysplasia (MDS-MLD)	MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
MDS with ring sideroblasts • With single lineage dysplasia (MDS-RS-SLD) • With multi-lineage dysplasia (MDS-RS-MLD)	MDS with low blasts and mutated *SF3B1* or MDS with ring sideroblasts (if ≥ 15% RS and *SF3B1* wild-type)	MDS with mutated *SF3B1*
MDS with isolated del(5q)	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)
MDS unclassifiable	Not included	Not included
Not included	Not included	MDS, not otherwise specified without dysplasia (e.g., monosomy 7/del(7q))[a]
MDS excess blasts-1 (MDS-EB1; 5–9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1; 5–9% bone marrow and/or 2–4% peripheral blood blasts)	MDS excess blasts (5–9% bone marrow and/or 2–9% peripheral blood blasts)
MDS excess blasts-2 (MDS-EB2; 10–19% bone marrow or peripheral blood blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2; 10–19% bone marrow or 5–19% peripheral blood blasts or Auer rods)	MDS/AML (10–19% bone marrow or peripheral blood blasts)
AML-defining genetics[b]	AML-defining genetics independent of bone marrow and peripheral blood blast count	AML-defining genetics with ≥10% bone marrow and peripheral blood blasts
AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)
Not included	MDS with biallelic *TP53* inactivation (Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH)	MDS with mutated *TP53* (Multi-hit *TP53* mutation, or *TP53* mutation (VAF > 10%) and loss of 17p) and MDS/AML with mutated *TP53* (Any somatic TP53 mutation (VAF > 10%)
Not included	MDS, hypoplastic (MDS-h)	Not included
Not included	MDS with fibrosis (MDS-f)	Not included
Not included	Clonal hematopoiesis (CHIP, CCUS)[c]	Pre-malignant clonal cytopenias and CCUS[c]

Open issues:

- Increasing the number of clinical entities defined according to biological features
- ICC/WHO harmonization

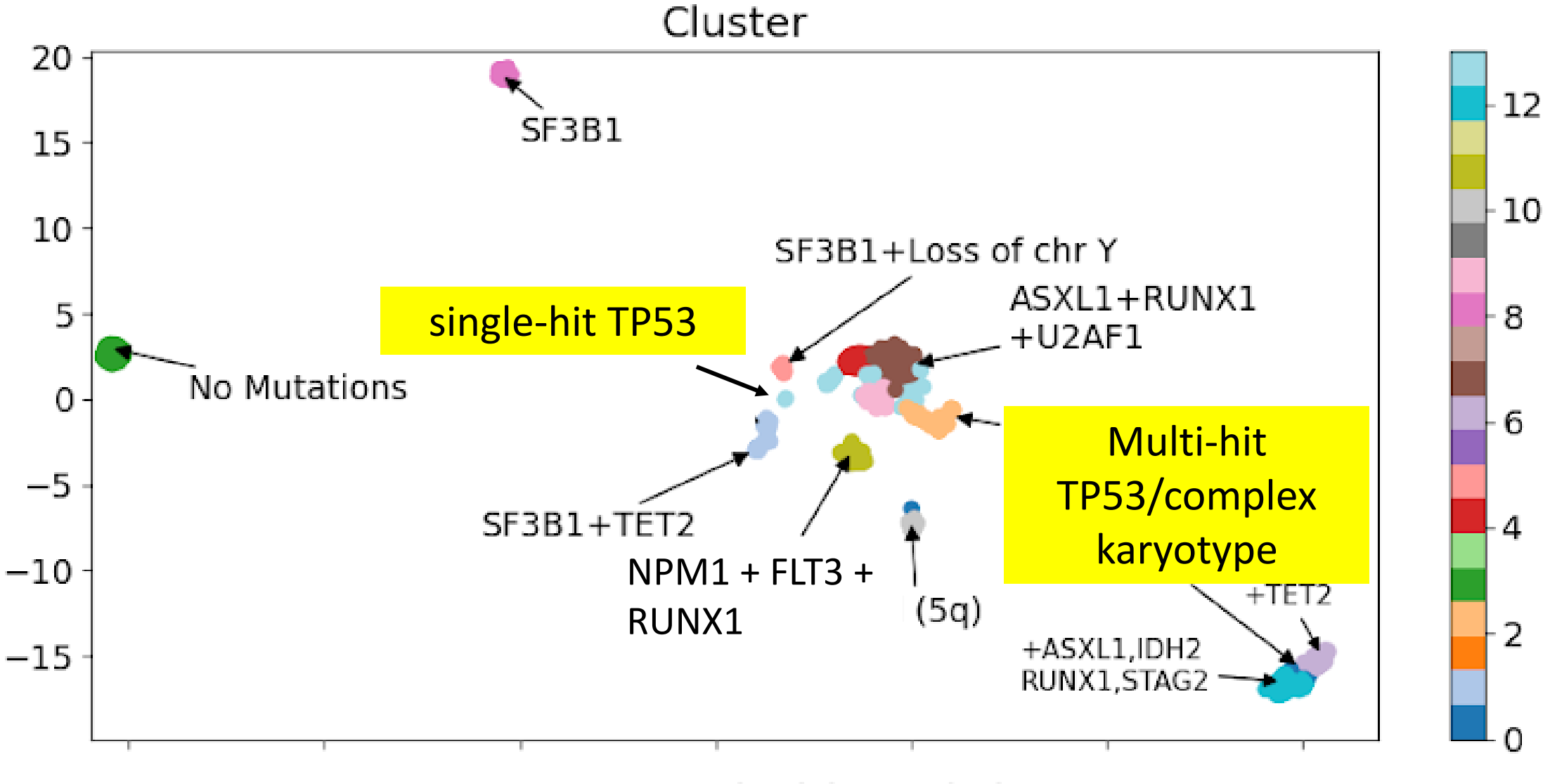
Zeidan A et al, Leukemia. 2022;36:2939-2946

Molecular classification of MDS by statistical learning methods



Bersanelli M et al. Journal of Clinical Oncology 2021; 11:1223-1233

Molecular classification of MDS by machine learning methods (AI)



Bersanelli et al. J Clin Oncol 2021; D'Amico et al, J Clin Oncol CCI 2023, in press

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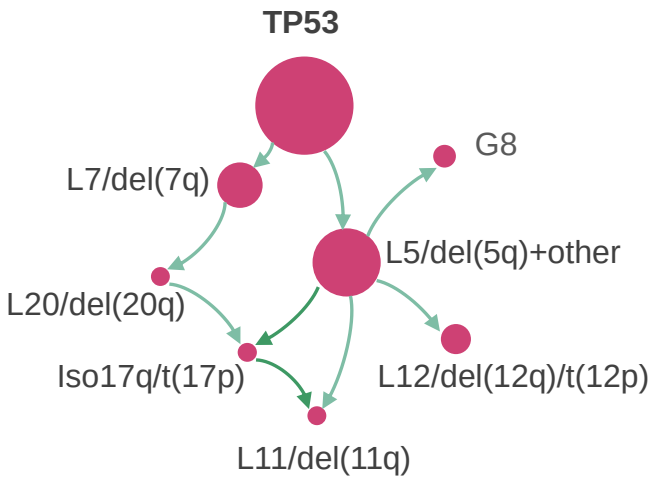
A new category of high-risk MDS is defined according to p53 dysfunction

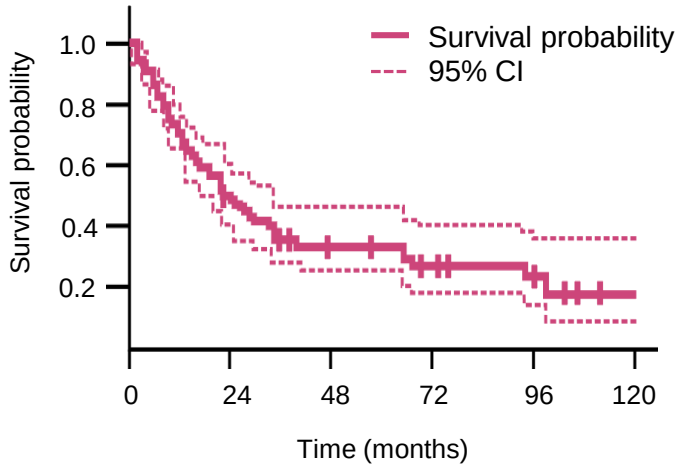
MDS with TP53 mutations and/or complex karyotype is a distinct disease category

Group 2 (n=188)

MDS with TP53 mutations and/or complex karyotype

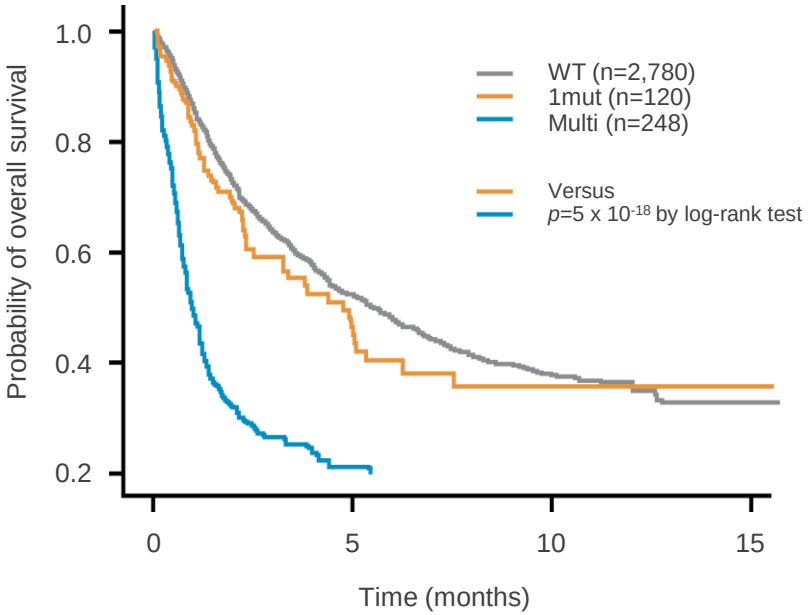
PB: two or more cytopenias with transfusion-dependency
BM: excess of blasts





J Clin Oncol 2021;39:1223–1233

Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in MDS



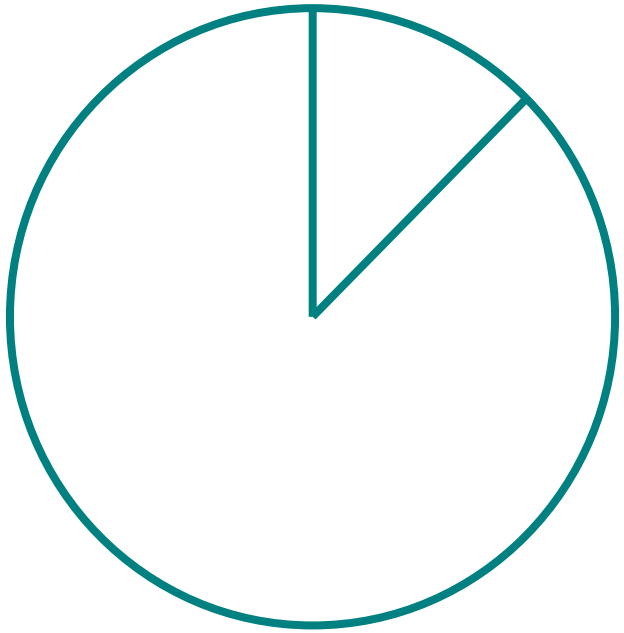
Nat Med 2020;26:1549–1556

A new category of high-risk MDS is defined according to p53 dysfunction

SHAP (Shapley_Additive_Explanations) was used to explain the classification model by computing the contribution of each feature

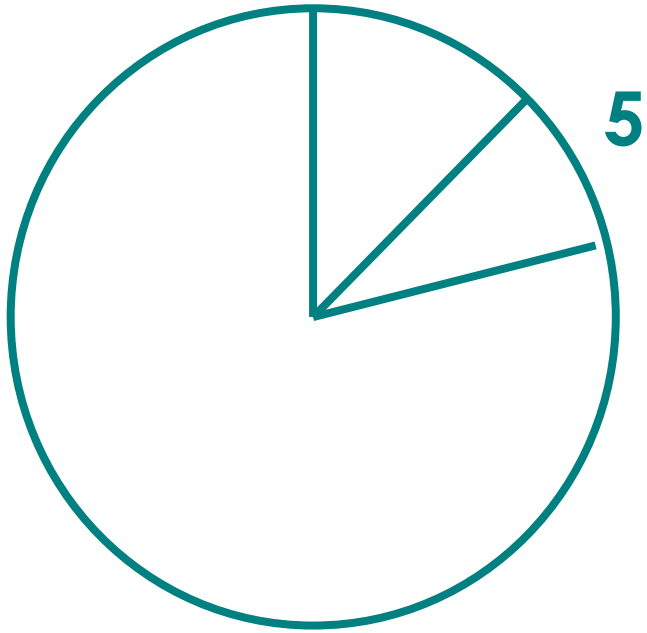
MDS with TP53-mutations

10-12%

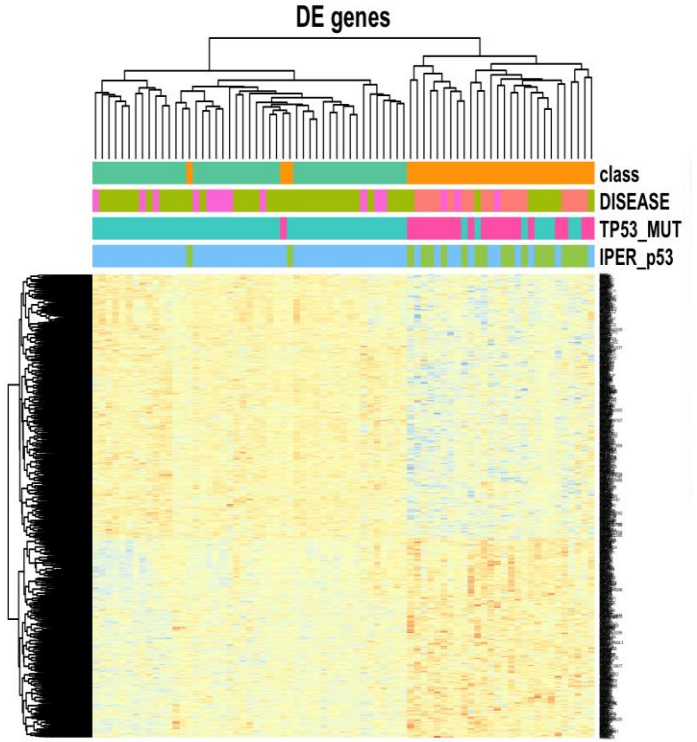


MDS with p53 dysfunction without TP53 mutations

5-7%



RNA sequencing



Bersanelli et al. J Clin Oncol 2021
Riva et al. Blood 2022;140:4001–4; Zampini et al, manuscript in preparation

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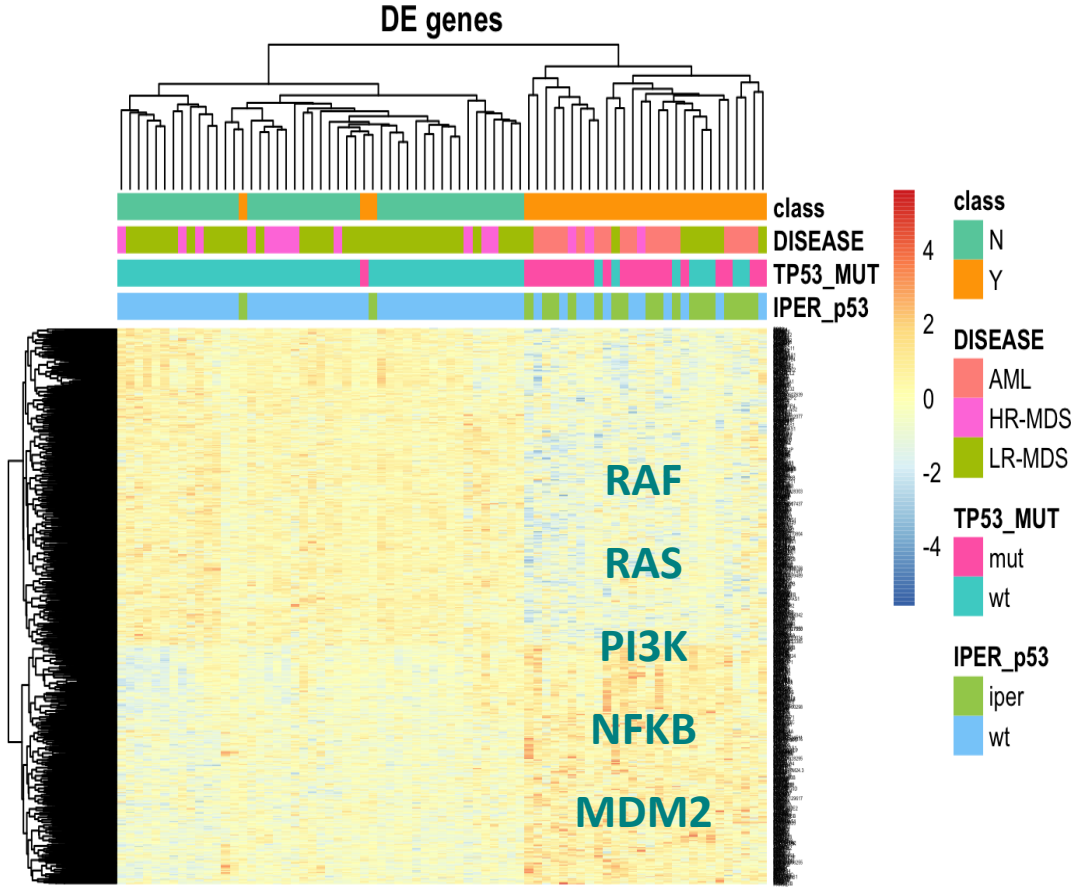
A new category of high-risk MDS is defined according to p53 dysfunction

RNA sequencing of CD34+ progenitor cells form 236 MDS patients



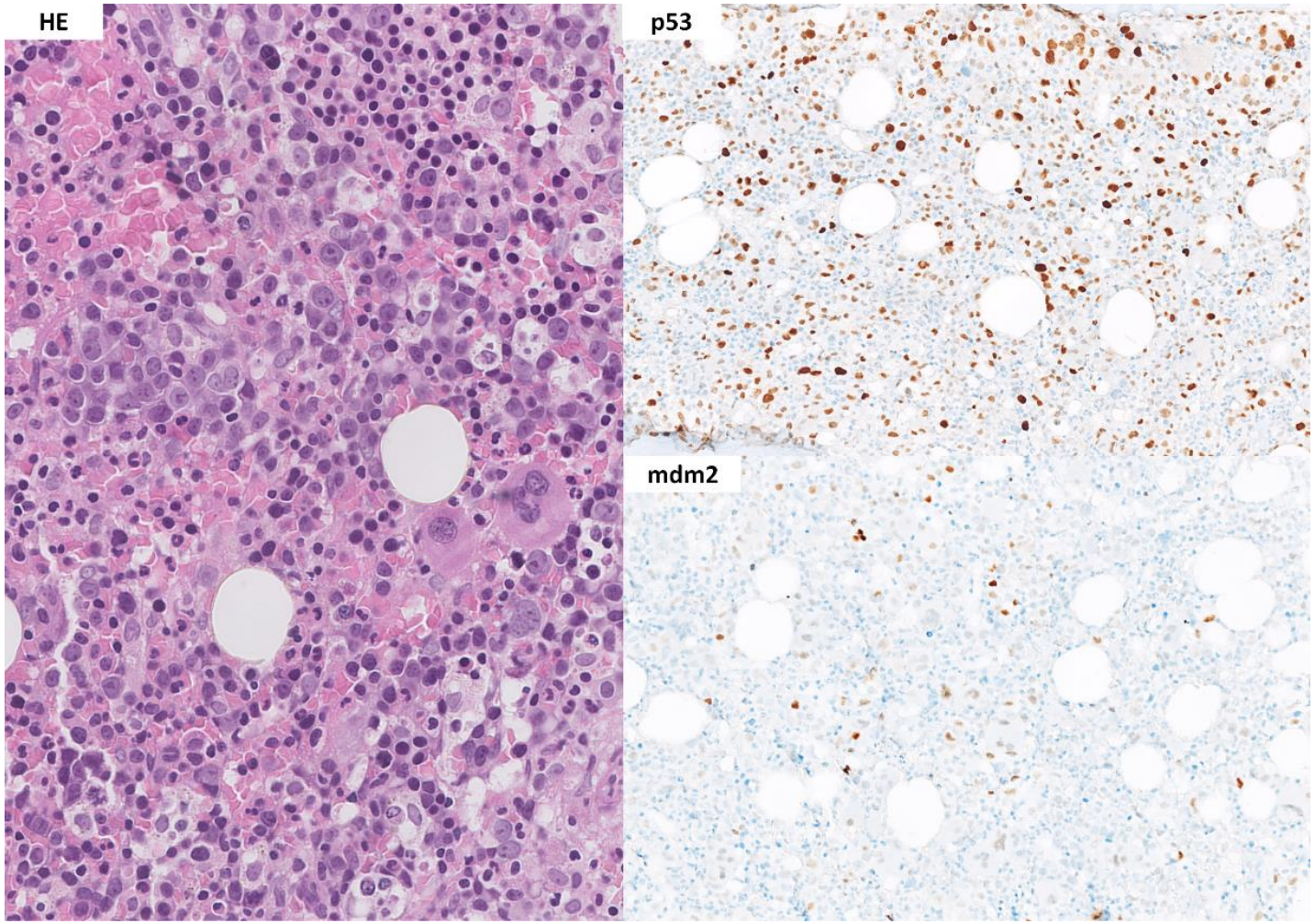
Evidence of impaired T cell and NK maturation and function in MDS with p53 dysfunction

- Immune checkpoint overexpression (PD-L1) at the stem cell level
- Reduced numbers of cytotoxic T cells
- Expansion of myeloid-derived suppressor cells (MDSCs)
- Expansion of regulatory T cells (Tregs).
- Impaired NK maturation and function

Sallman DA Blood (2020) 136 (24): 2812–2823

Riva et al. Blood 2022;140:4001–4; Zampini et al, manuscript in preparation

A new category of high-risk MDS is defined according to p53 dysfunction



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Riva et al. Blood 2022;140:4001–4; Zampini et al, manuscript in preparation

2022 WHO/ICC harmonization: an international project by GenoMed4all and icMDS

Aim

To create a hierarchical and harmonized classification of MDS based on a large comprehensive patient dataset using advanced statistical and machine leraning methods of inference

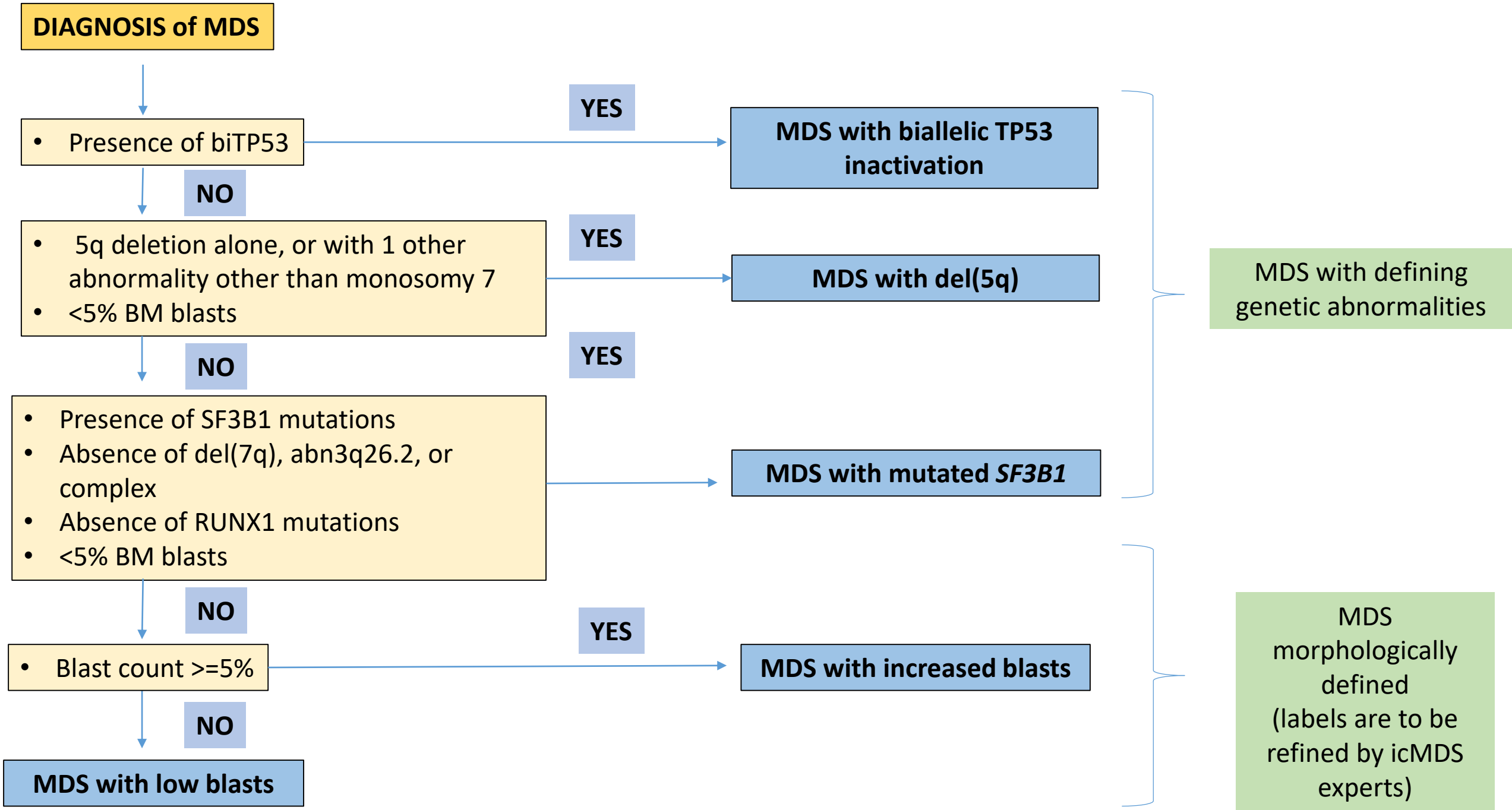
Methods

- MCC/Genomed4all merged cohorts (n=7117)
- Hierarchical Dirichlet processes applied to define clusters capturing broad dependencies among gene mutations and cytogenetic abnormalities
- Patients are classified by neural networks
- SHAP was then used to explain the classification model by computing the contribution of each feature

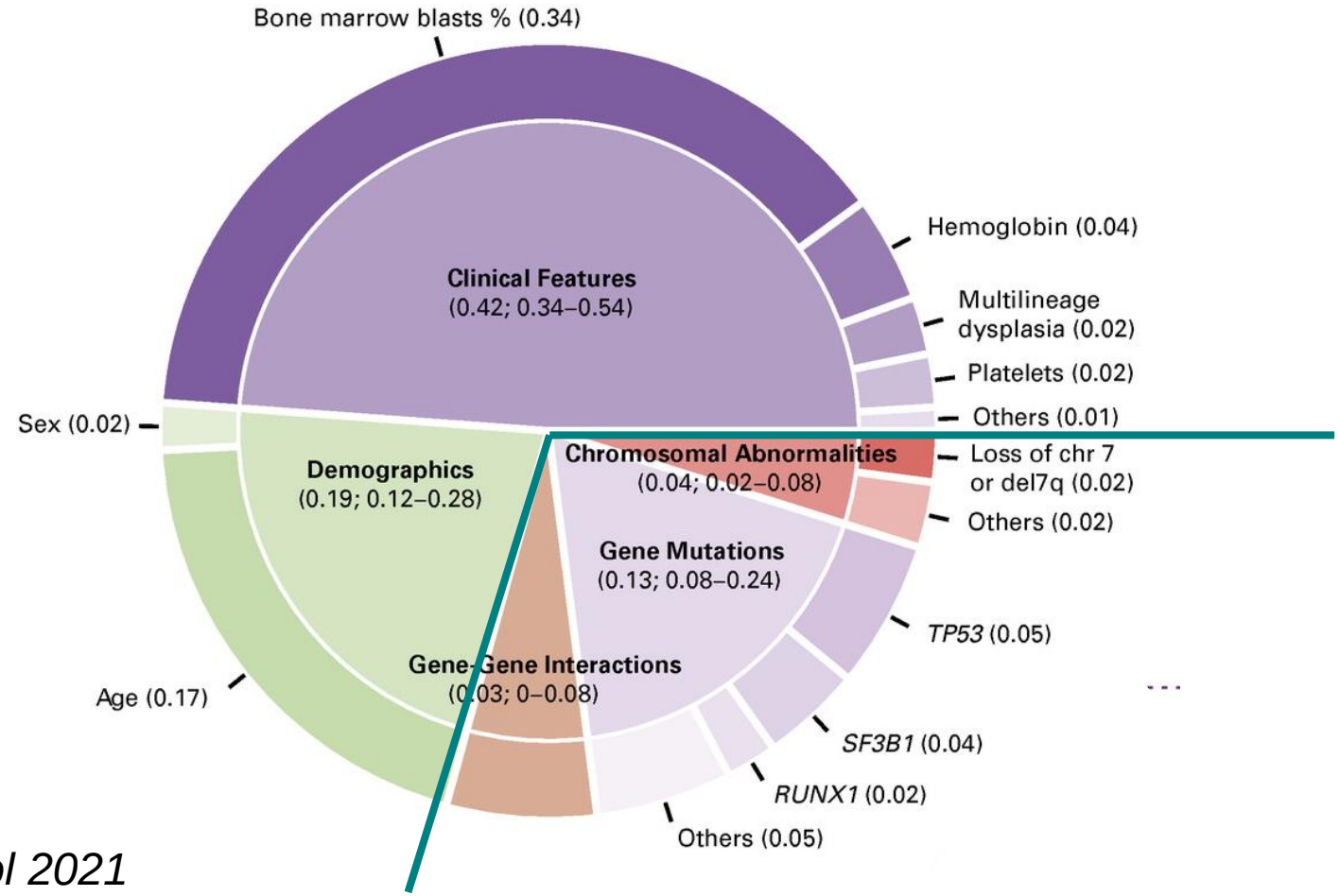
↓

Consensus Phase (panel of international experts - icMDS)

WHO – ICC harmonization proposal


DIAGNOSIS of MDS
• Presence of biTP53
YES
MDS with biallelic TP53 inactivation
NO
• 5q deletion alone, or with 1 other abnormality other than monosomy 7
• <5% BM blasts
YES
MDS with del(5q)
NO
• Presence of SF3B1 mutations
• Absence of del(7q), abn3q26.2, or complex
• Absence of RUNX1 mutations
• <5% BM blasts
YES
MDS with mutated SF3B1
NO
• Blast count >=5%
YES
MDS with increased blasts
NO
MDS with low blasts
MDS with defining genetic abnormalities
MDS morphologically defined (labels are to be refined by icMDS experts)

Contribution of molecular information to the prognostic assessment of MDS



Bersanelli et al. J Clin Oncol 2021
Maggioni et al. Lancet Haematol 2022
Sauta et al. J Clin Oncol 2023

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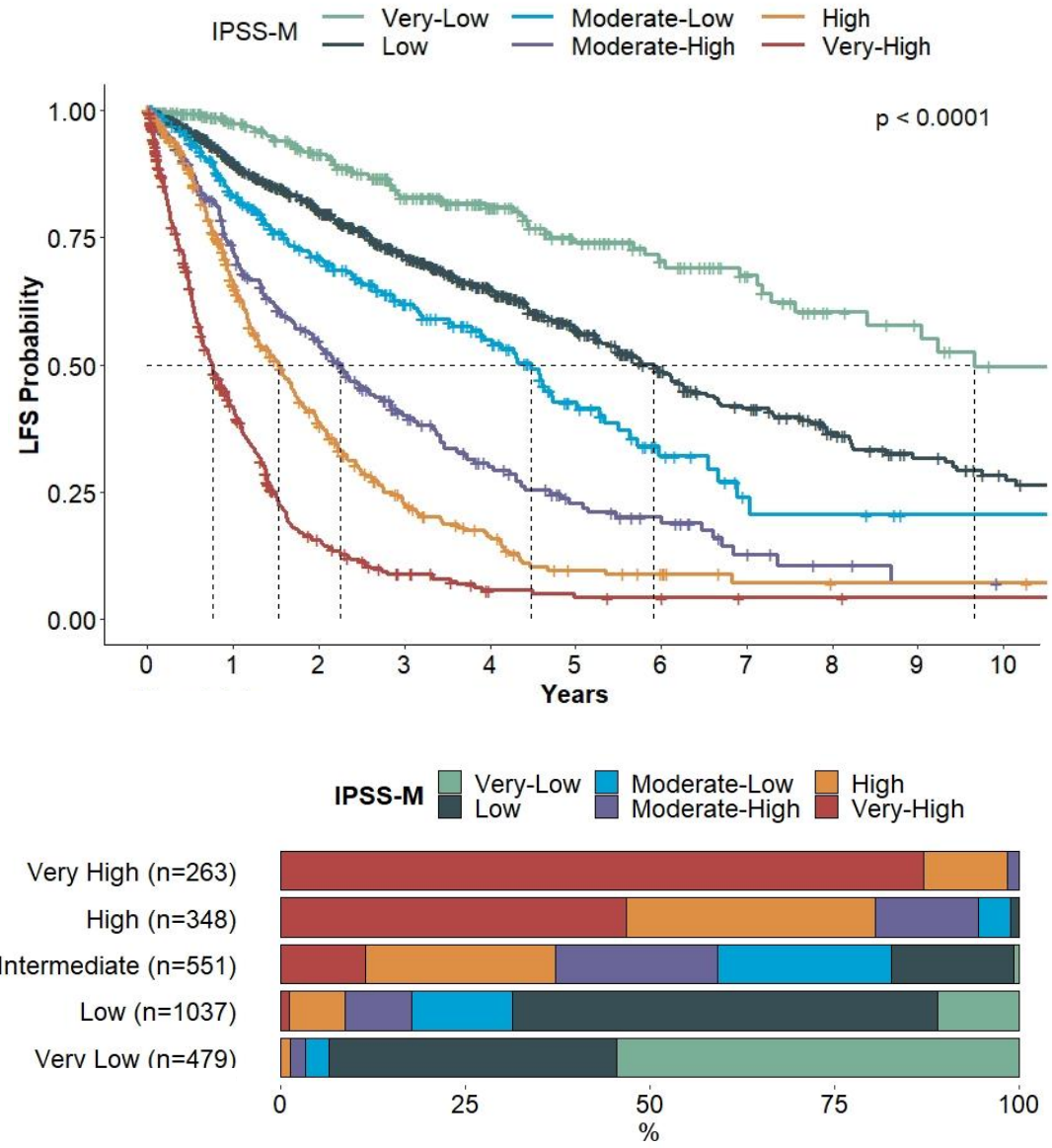
Molecular IPSS (IPSS-M)

A new MDS prognostic model (**IPSS-M**) has been proposed by Bernard E et al*, expanding the original IPSS-R based on:

- Hematological parameters (hemoglobin, bone marrow blasts and platelets)
- Cytogenetic features

by including:

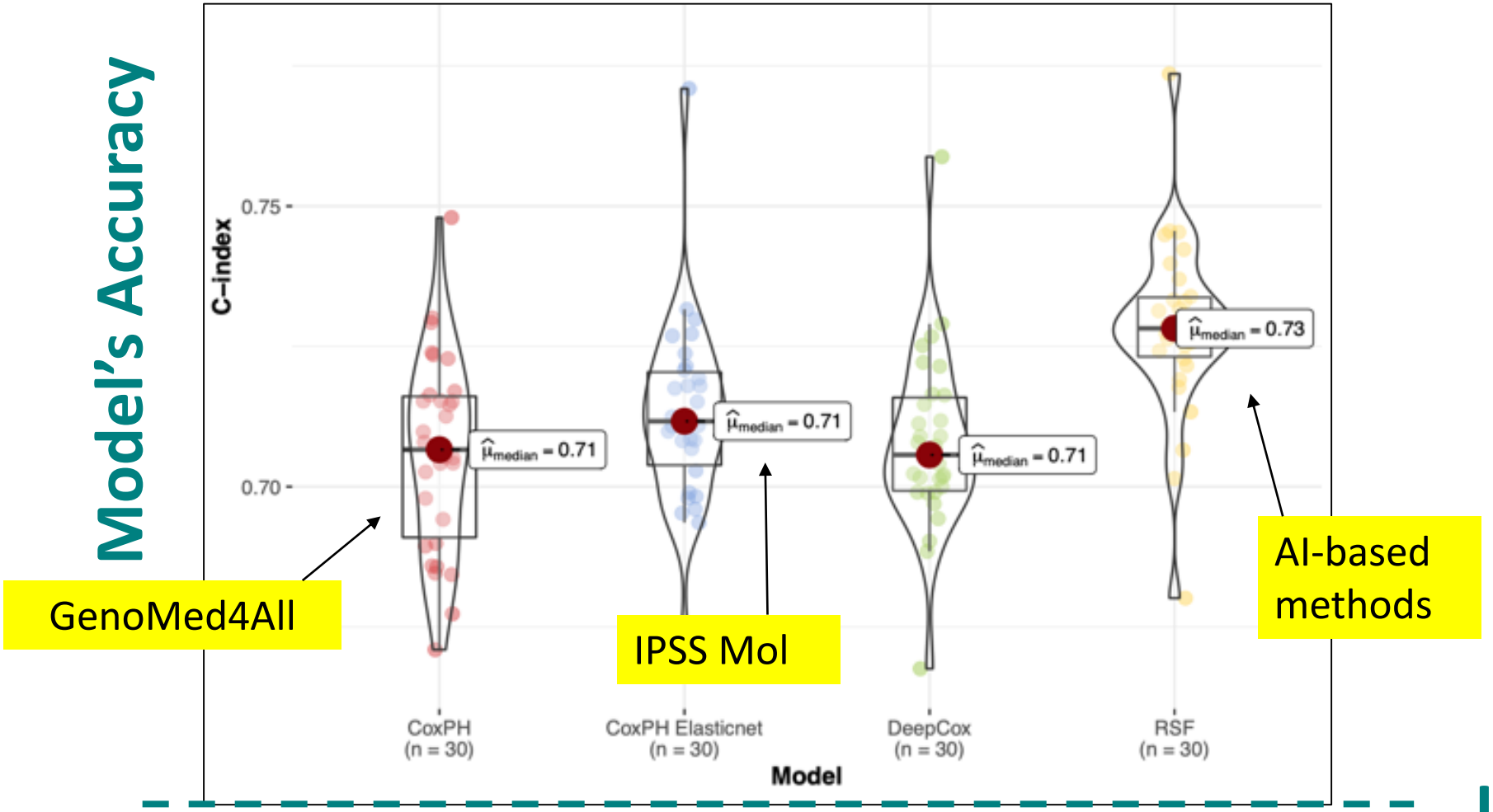
- **Somatic mutations on 31 genes (16 "Main Effect" genes and 15 "Residual Genes"),** weighting their impact on prognosis and clinical outcomes



*Bernard E et al. NEJM Evid 2022

Sauta E et al. J Clin Oncol. 2023 Mar 17:JCO2201784. doi:10.1200/JCO.22.01784.

Personalized prediction of overall survival in MDS. Statistical learning vs. Machine Learning methods



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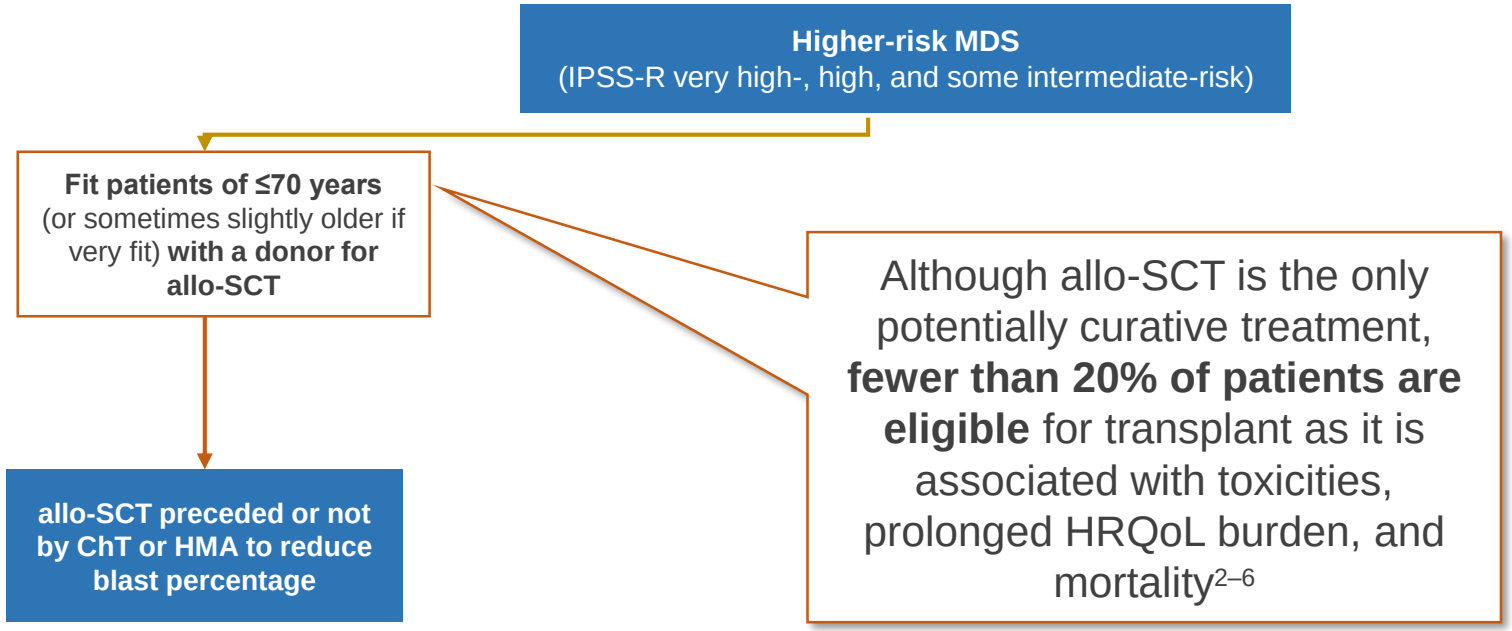
1- Machine Learning

2- Generative AI

Current treatment options in high-risk MDS include HSCT and Hypomethylating agents (HMAs)

Higher-risk MDS carries a major risk of progression to AML and short survival; treatment should aim to modify the disease course, with options including allo-SCT and HMAs*[1]

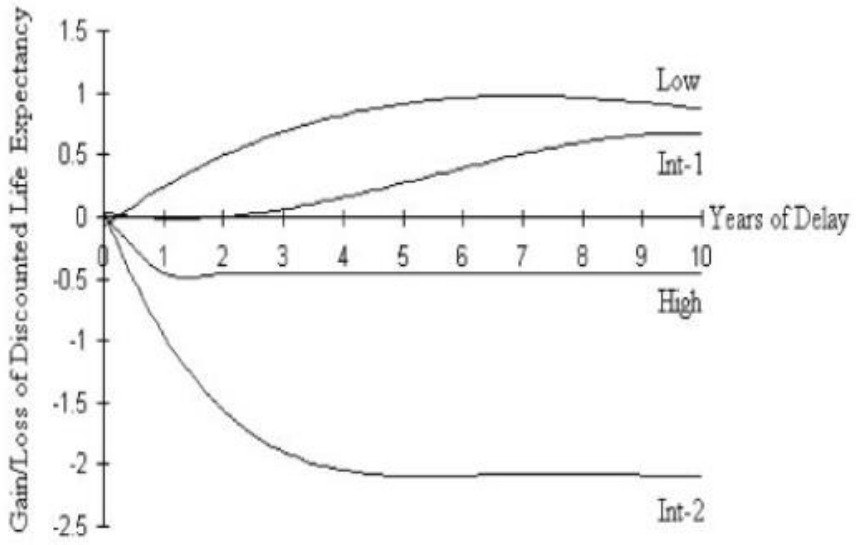


***According to ESMO Clinical Practice Guidelines**

1. Fenaux P, et al. Ann Oncol 2021;32:142–156; 2. Karoopongse E, et al. Expert Rev Clin Immunol 2012;8:373–381; 3. Della Porta MG, et al. Blood 2014;123:2333–2342; 4. Malcovati L, et al. Blood 2013;122:2943–2964; 5. Sekeres MA, et al. J Natl Cancer Inst 2008;100:1542–1551; 6. Bhatt VR & Steensma DP. J Oncol Pract 2016;12:786–792

Transplantation strategy according to IPSS or IPSS-R

IPSS



Cutler CS et al. Blood 2004;104(2):579-85

IPSS-R

	delay time (months)	***40***	***50-55***	***>60***
Years of life expectancy under policy 1: IPSS-R Low	***0***	16.4	16.1	15.1
	12	17.3	16.8	15.4
	24	17.9	17.3	15.6
	48	18.5	17.7	15.7
	60	18.7	17.9	15.7
Years of life expectancy under policy 2: IPSS-R intermediate	***0***	19.3	18.1	15.9
	12	17.9	17.1	14.9
	24	17.1	16.4	14.5
	48	16.3	15.7	14.2
	60	16.0	15.5	13.9

Della Porta MG et al Leukemia. 2017;312449-57

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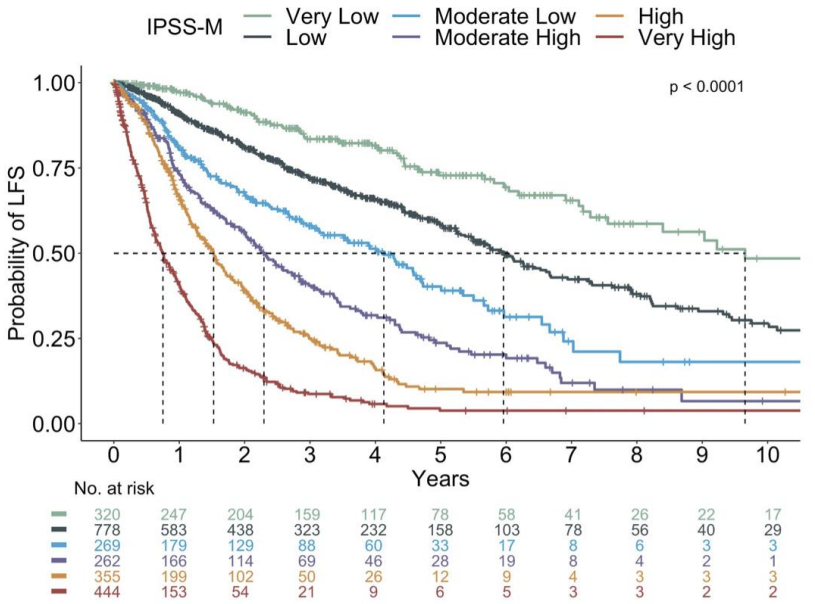
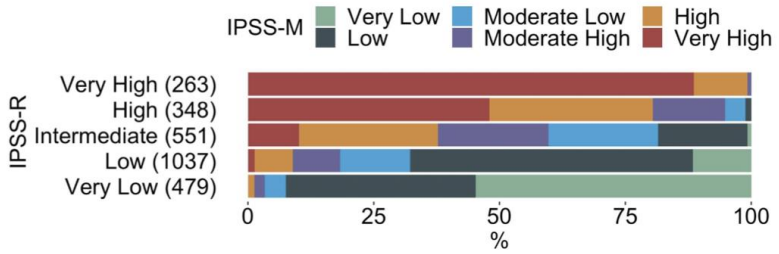
IPSS-M

- Study Population: 2,957 patients (validation on 718)
- The IPSS-M risk score consisted of:
  - hemoglobin, platelets and bone marrow blasts
  - IPSS-R cytogenetic category
  - 31 mutated genes
- No information on patients receiving disease modifying treatments



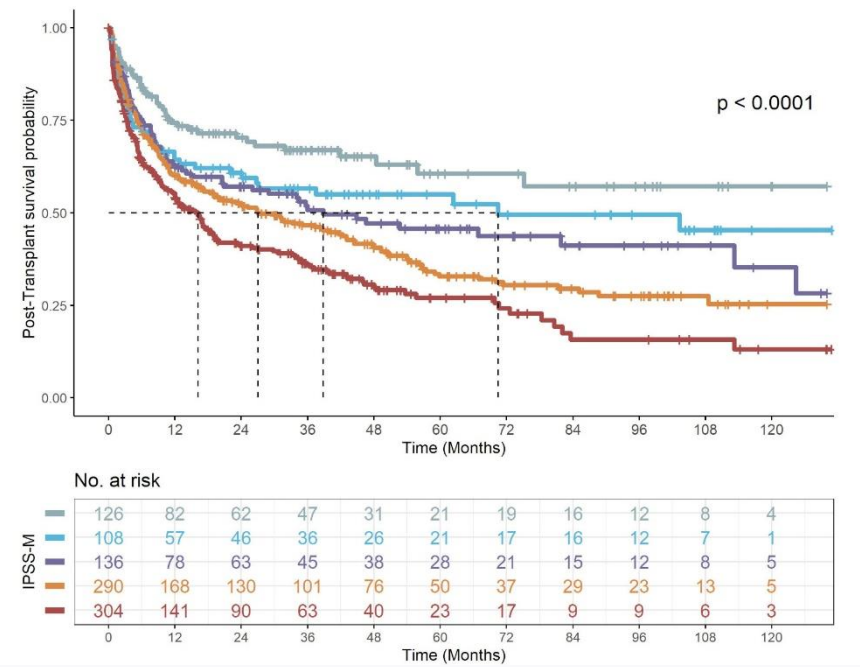


Bernard E at al. NEJM Evid 2022; 1 (7) DOI:https://doi.org/10.1056/EVIDoa2200008

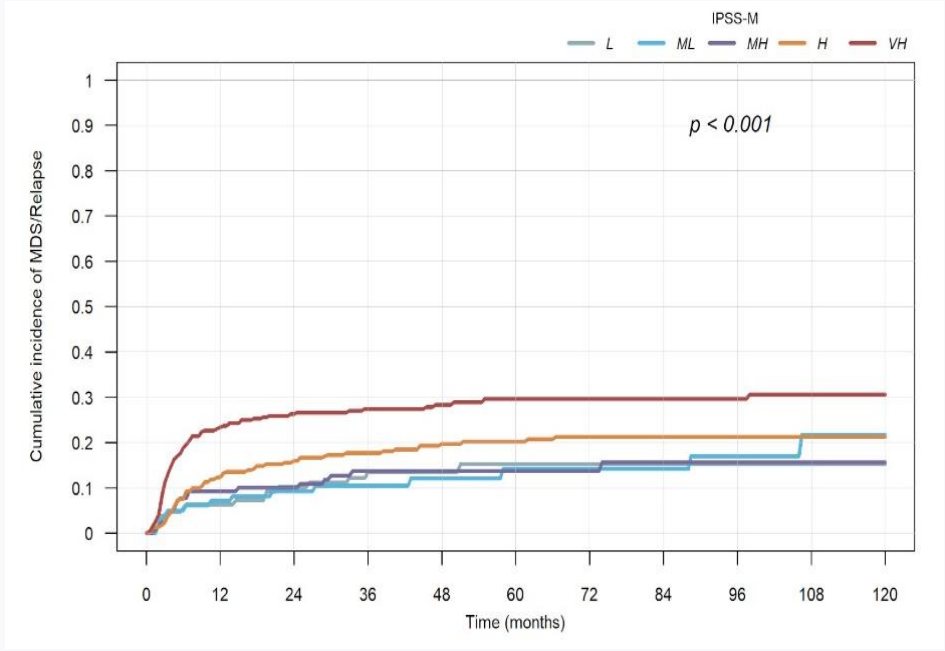
Molecular International Prognostic Scoring System for MDS (IPSS-M): Real World Validation by GENOMED4ALL (n=2,876)

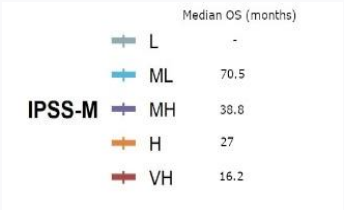
IPSS-M on 964 patients who underwent allo-HSCT

Probability of overall survival



Probability of relapse





Sauta E at al. J Clin Oncol. 2023;41:2827-2842

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Controversy: Is the new IPSS-M helpful for decision making regarding allo HSCT?

- Mutation screening provides relevant prognostic information at individual patient level
- The implementation of IPSS-M is expected to result in a more effective selection of patients with early disease stage who are candidate to allo-HSCT
- Mutation screening may affect clinical decision making in transplantation (specific mutations are associated to a high probability of disease relapse)
- The definition of a minimum set of relevant genes may facilitate the clinical implementation of the score

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

- Here, we aimed to develop and validate a Decision Support System to define the optimal timing of HSCT for MDS patients based on clinical and genomic information as provided by the IPSS-M.

- Patients and methods: retrospective population of 7118 patients, stratified into training and validation cohorts.

- A decision-strategy was built to estimate the average survival over an 8-year time horizon (Restricted_Mean_Survival_Time, RMST) for each combination of clinical and genomic covariates, and to determine the optimal transplantation policy by comparing different strategies.

Tentori C et at, submitted

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

Gregorio C et at, submitted

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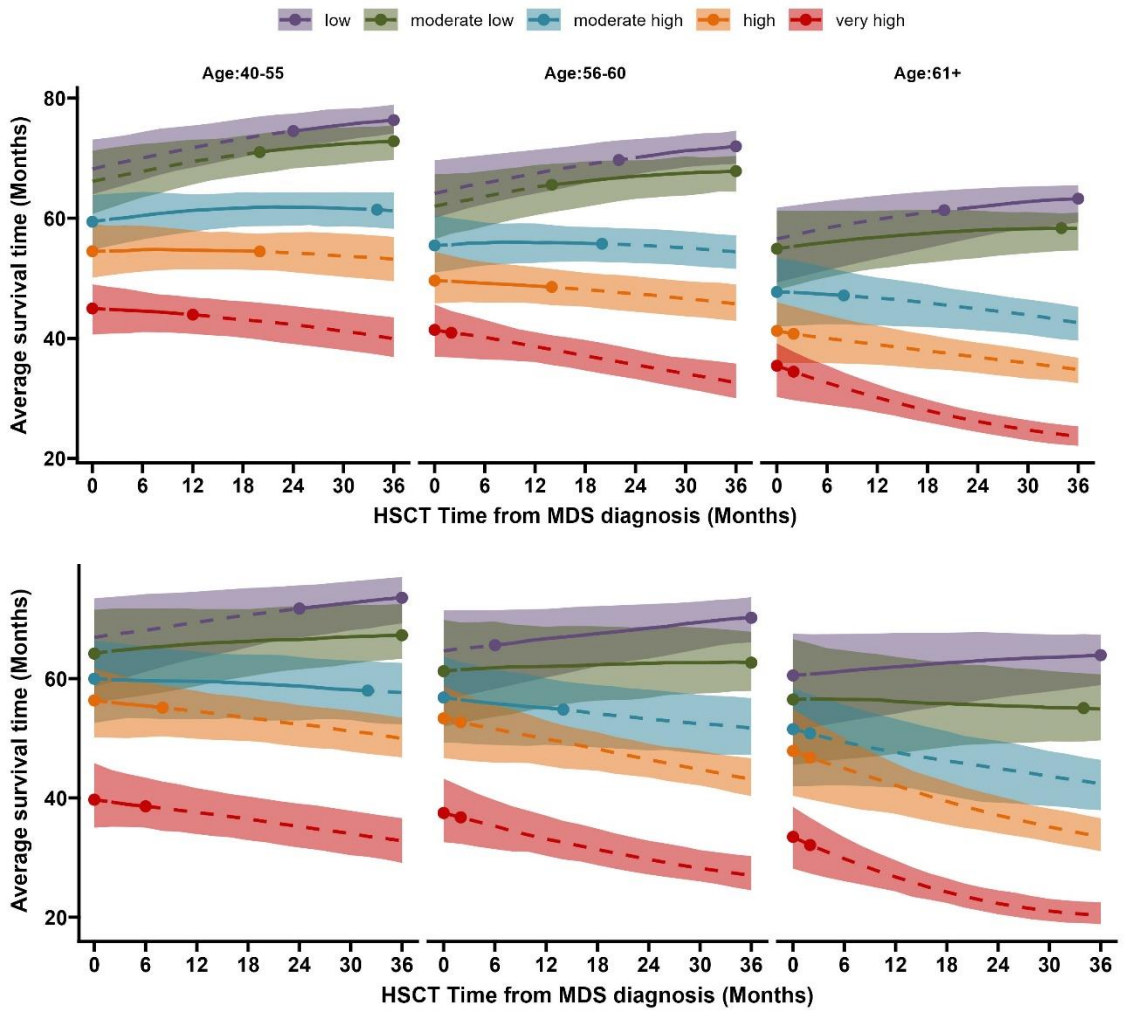
IPSS-M based transplantation strategy



TRAINING
n=3854

VALIDATION
n=2075

Tentori C et at, submitted

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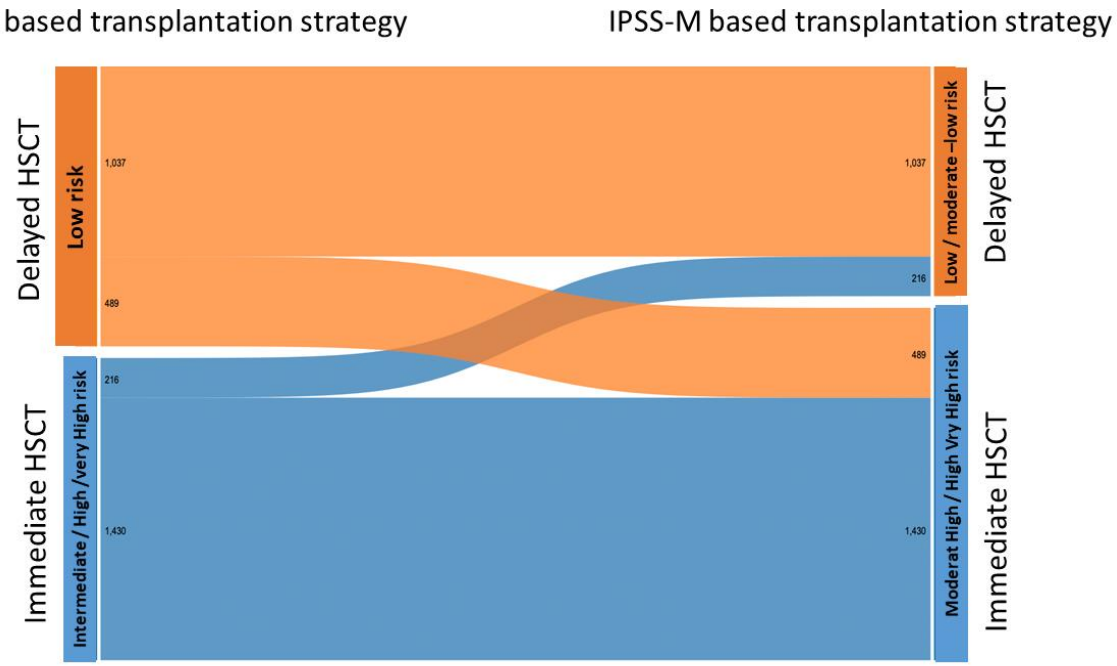
IPSS-M vs. IPSS-R based transplantation strategy



- 13% of candidates to be immediately transplanted under an IPSS-R based policy would benefit from a delayed strategy under an IPSS-M based policy, while 32% of candidates to delayed transplantation by IPSS-R, would benefit from immediate HSCT by IPSS.
- The comparison of the average conditional survival time for the optimal transplantation policies obtained using different scoring systems (IPSS-R/IPSS-M) resulted in a significant gain of live expectancy under an IPSS-M based policy across all age groups (P=0.002)

Tentori C et at, submitted

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IPSS-M vs. IPSS-R based transplantation strategy

- Under an IPSS-M based policy, patients with either low and moderate-low risk benefit 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.

- Modelling decision analysis on IPSS-M vs. conventional IPSS-revised (IPSS-R) changed transplantation policy in a significant proportion of patients (45%)

- The grate majority of these patients would benefit for earlier transplantation under a IPSS-M vs. IPSS-R based policy, resulting in a significant gain-in-life expectancy under an IPSS-M based policy.

- These results provide evidence for the clinical relevance of including genomic features into the transplantation decision making process, allowing personalizing the hazards and effectiveness of HSCT in patients with MDS.

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2- Generative AI

C.A.L.R.

CENTER FOR ACCELERATING LEUKEMIA/LYMPHOMA RESEARCH

Artificial Intelligence and real world data analysis to improve patient care and advance medical research in hematology

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HU HUMANITAS UNIVERSITY · Horizon2020 European Union Funding for Research & Innovation · HUMANITAS RESEARCH HOSPITAL

AI people
- Saverio D'Amico
- Elisabetta Sauta
- Gianluca Asti
- Victor Savevski
- Marilena Bicchieri
- Caterina Gregorio
- Marta Spreafico
- Francesca Ieva

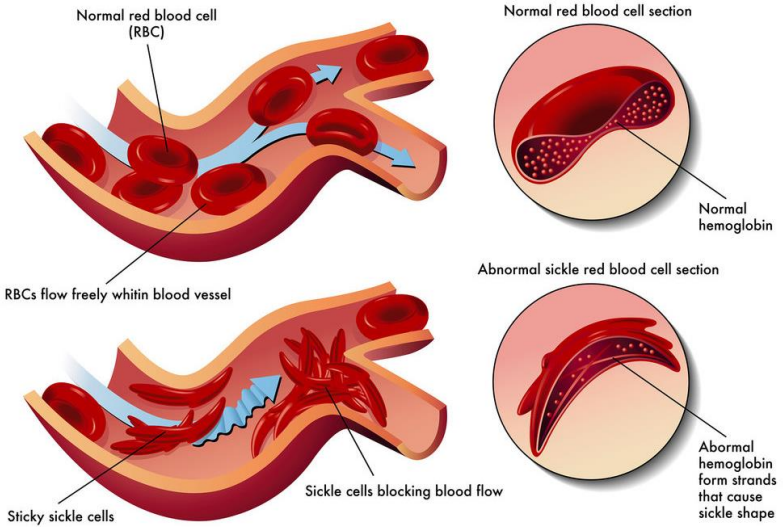
Clinical team
- Luca Lanino
- Giulia Maggioni
- Erica Travaglino
- Alessia Campagna
- Marta Ubezio
- Antonio Russo
- Gabriele Todisco

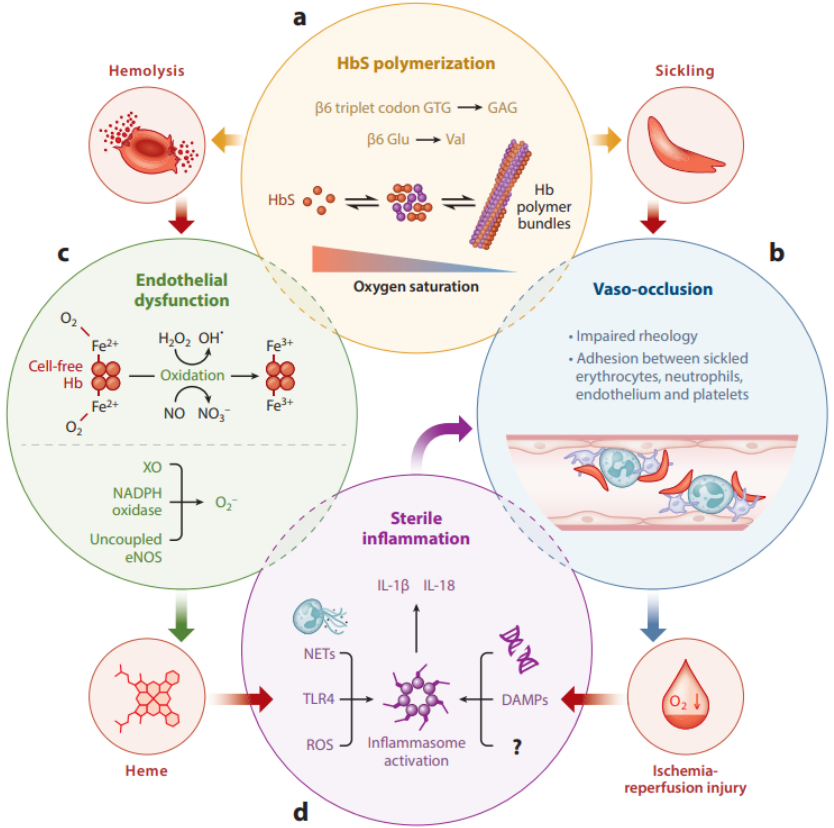
- Gastone Castellani
- Piero Fariselli
- Anders Krogh
- Santiago Zazo
- Claudia Sala
- Lorenzo Dall'Olio
- Daniele Dall'Olio
- Tiziana Sanavia
- Cesare Rollo
- Inigo Prada Luengo
- Patricia Alonso
- Lin-Pierre Zhao
- Pierre Fenaux
- Torsten Haferlach
- Maria Diez-Campelo
- Uwe Platzbecker

Sickle Cell disease (SCD)

María del Mar Mañú Pereira, Raffaella Colombatti

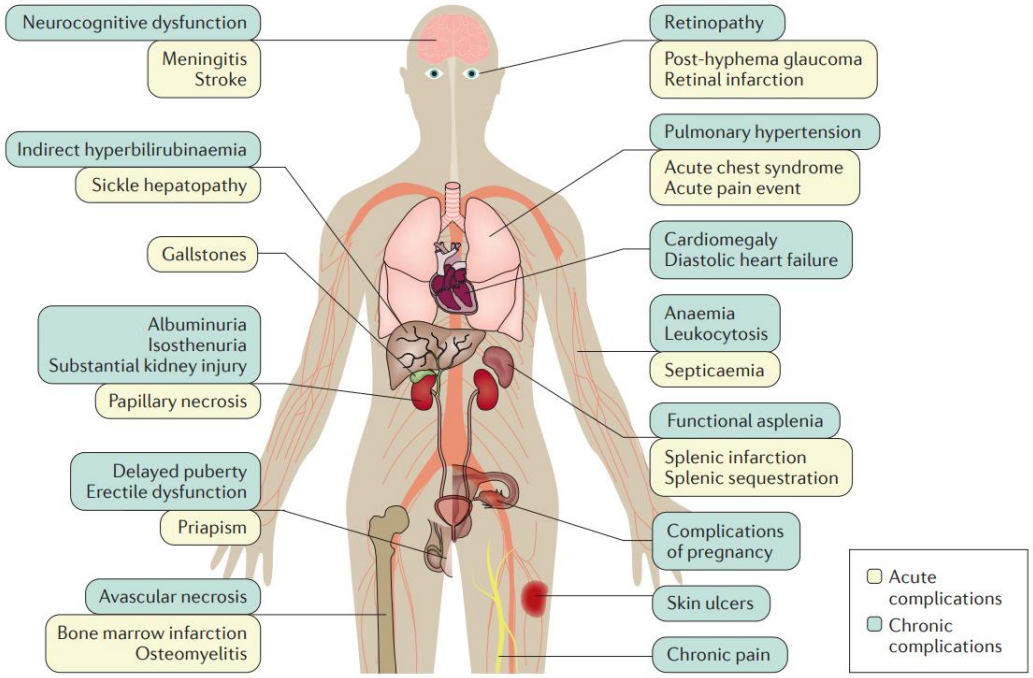
Sickle cell disease





Kato, Gregory J., et al. "Sickle cell disease." Nature Reviews Disease Primers 4.1 (2018): 1-22.

Sickle cell disease



- Chronic disease
- Multi systemic involvement
- Decreased life expectancy
- Low QoL

Kato, Gregory J., et al. "Sickle cell disease." Nature Reviews Disease Primers 4.1 (2018): 1-22.

Sickle cell disease

Silent infarct

- Significant MORBIDITY:
  - affect 25% of children by the age of 6 and 40% by the age of 18 with consequences on cognition, schooling, working capacity and quality of life.
- BARRIERS to screening in the Real World Setting:
  - Screening of neurological complications and chronic organ damage is suboptimal in Europe
  - Not all centers have expert neuroradiologists to identify SCI
- PATHOPHYSIOLOGY, RISK FACTORS, RISK of PROGRESSION are incompletely understood

Disease-modifying and curative therapies

Hematopoietic Stem Cell Transplantation (HSCT)/gene therapy

voxelotor/mitapivat/etavopivat

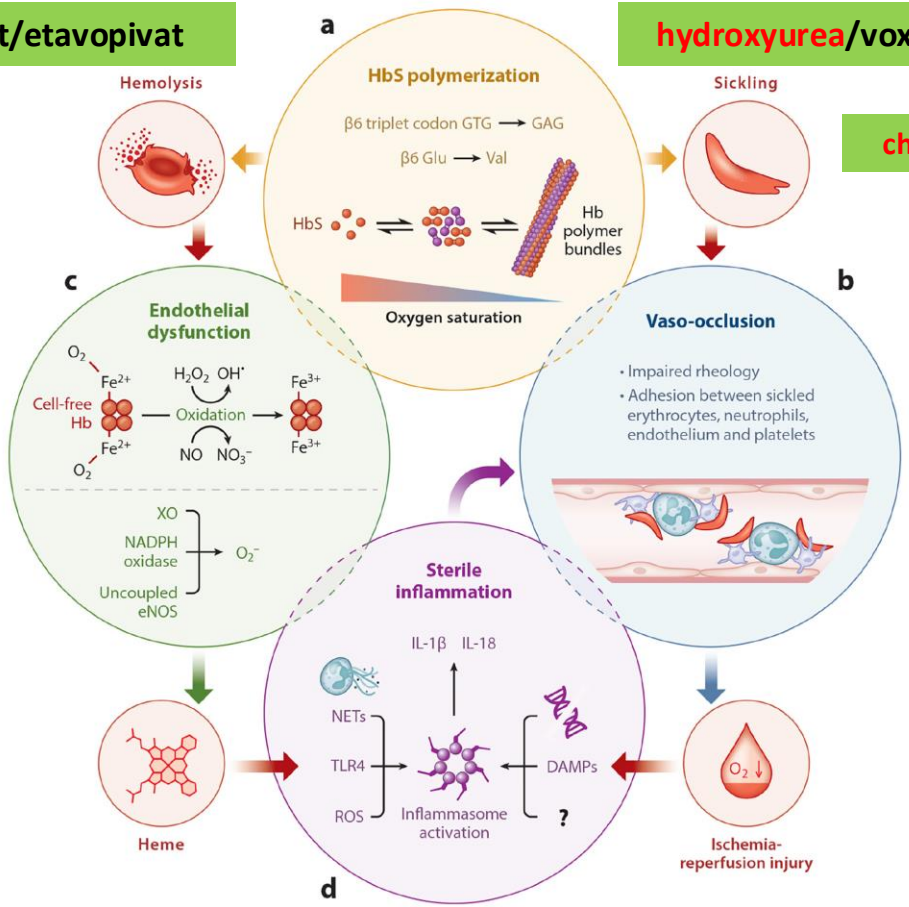
hydroxyurea/voxelotor/mitapivat/etavopivat

chronic transfusion regimen

L-glutamin

hydroxyurea/crizanlizumab /decitabine

canakinumab/haemopexin?



Adapted from *Sundd et al., Annu Rev Pathol , 2019*

Sickle cell disease

Research needs

- Monogenic disorder autosomal recessive BUT different genotypes and many disease modifiers 800+
- Complex and interconnected physio pathological pathways → high heterogeneity of clinical outcomes
- New treatments in the market
- Lack of functional tests for:
  - Disease classification
  - Prognosis
  - Response to treatment

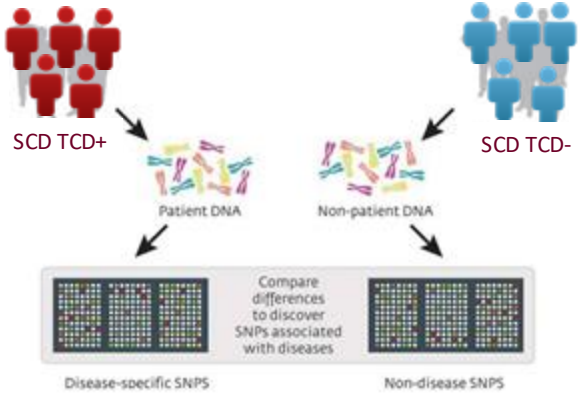
Aim

- Development of AI based scores combining clinical and research data to predict the risk and time of occurrence of severe complications:
  - Recurrent Vaso occlusive crisis
  - Acute chest syndrome
  - Silent infarcts
  - Stroke (hemorrhagic and ischemic)
  - Renal impairment
  - Hepatic failure
  - Retinopathy

Lack of large amount of high quality clinical and research data in SCD

Transcranial doppler (TCD) ultrasound screens for stroke risk

GWAs SCD TCD+ vs SCD TCD-



ERN-EuroBloodNet Survey on TCD

ERN-EuroBloodNet

>70% of SCD are not correctly screened through TCD for stroke risk

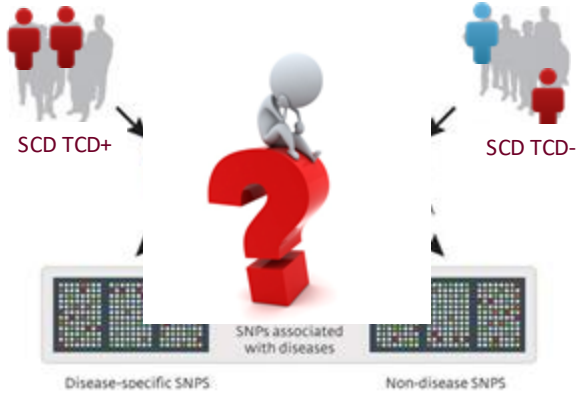
Limited Access to Transcranial Doppler Screening and Stroke Prevention for Children with Sickle Cell Disease in Europe: Results of a Multinational ERN-Eurobloodnet Survey

D Cuzzubbo, V Gutierrez-Valle, M Casale, V Voi, C McMahon, MMañú Pereira, M de Montalembert, B PD Inusa, R Colombatti

Blood (2021) 138 (Supplement 1): 915.

What are the genetic modifiers protecting or increasing the risk for stroke in SCD?

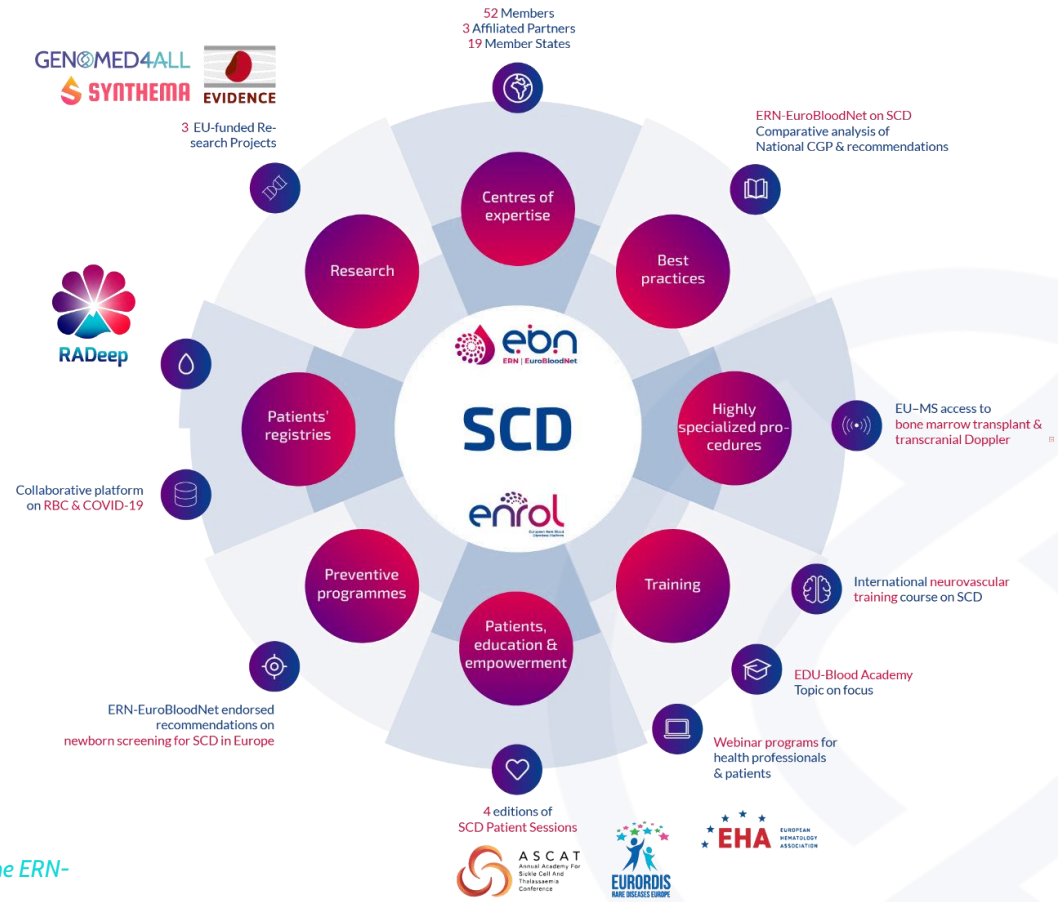
GWAs SCD TCD+ vs SCD TCD-



Sickle cell disease

Landscape and challenges in EU ERN-EuroBloodNet &RADeep

- 12 MS: Belgium, Cyprus, Denmark, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden and The Netherlands .
- Between 28,821-48,928 SCD patients based on experts' opinion (published and available data from existing registries, RADeep and data from national health insurance systems)
- 330 of the 447 million inhabitants of the EU, will be screened for the presence of SCD through national newborn screening (NBS) programmes in 2023. The average birth prevalence is in the order of 1:3000.



Mañú Pereira MDM et al. Sickle cell disease landscape and challenges in the EU: the ERN-EuroBloodNet perspective. Lancet Haematol. 2023 Aug;10(8):e687-e694.

Sickle cell disease

RADeep

- RADeep is an initiative endorsed by ERN-EuroBloodNet for pooling data from patients affected by a Rare anemia disorders (RADs)

RADeep is built in line with the EU Rare Disease Platform recommendations for patients' registries on rare disorders and the European Rare Blood Disorders Platform (ENROL) (an umbrella for both new and already existing registries on rare hematological disorders).

possibility to share and pool data

reach critical numbers

perform clinical trials, research projects

knowledge generation (evidence)

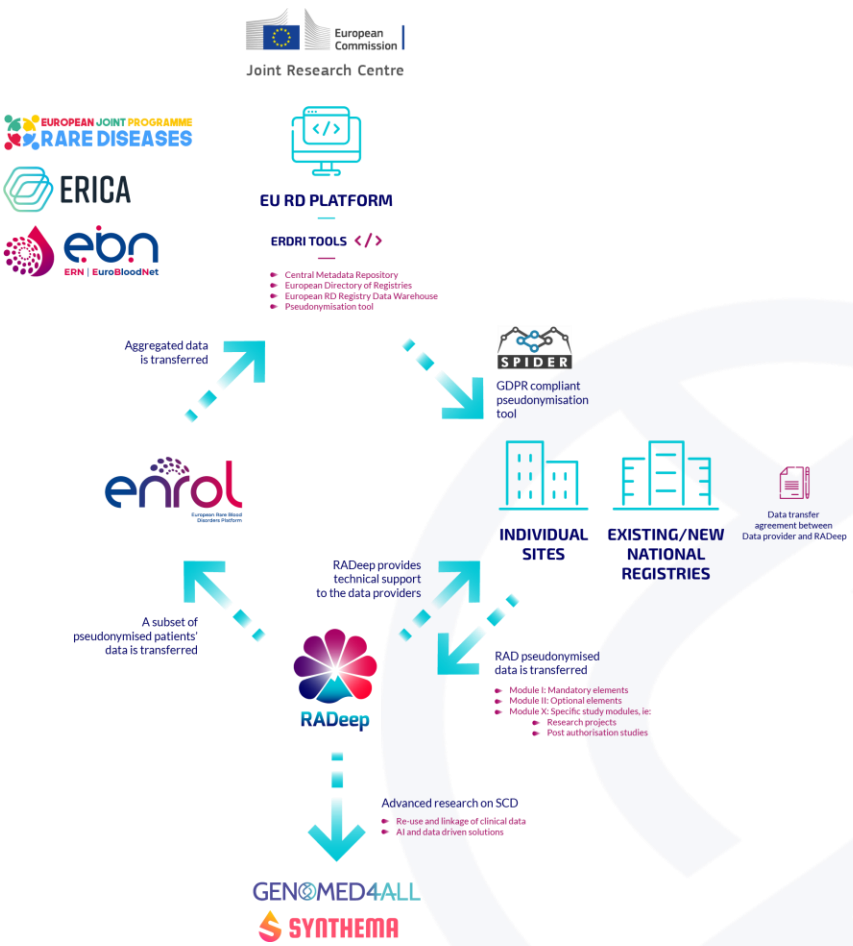
better healthcare for RADs patients

RADeep

Sickle cell disease

Clinical & Lab & Research Data

- Integrated with RADeep
- 400 Parameters
- Different types of data:
  - Demographics
  - Chronic organ damage
  - Organ damage assessment tests
  - Acute complications
  - Treatments
  - Offspring
  - Lab data
  - -omics: radiomics, metabolomics, GWAS
  - Oxygenscan
- Different formats of data = several ontologies (ORPHA, HPO, SCDO, LOINC, ATC…)

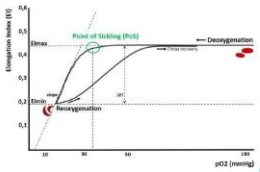


Sickle cell disease

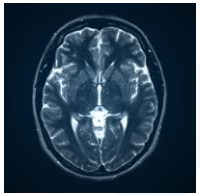
1,000 SCD Patients - Types of data

Genetic modifiers
800+ GWAS

Metabolomics
1900+ metabolites



Functional test
Rheology
LoRRca - Oxygenscan



MRIs

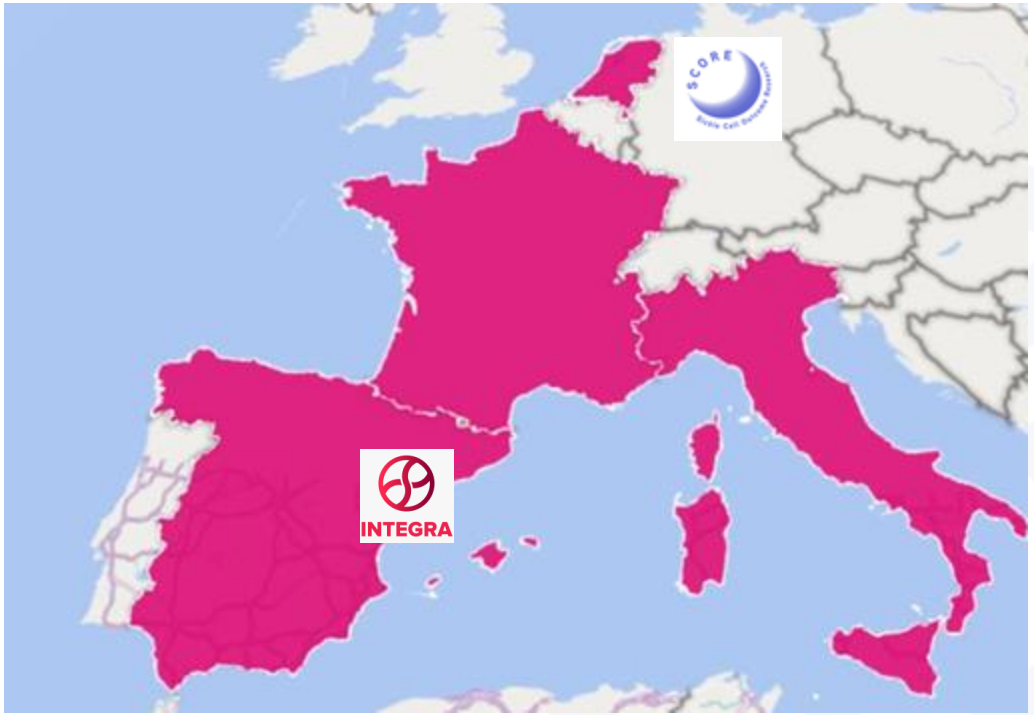
RADeep

Clinical and lab
data

Sickle cell disease

ERN-EuroBloodNet Clinical sites

FR - AP-HP Henri-Mondor Paris – Pablo Bartolucci
Target: 300
FR - AP-HP Necker Paris – Mariane de Montalembert
Target: 150
IT - Università di Padova Padova - Raffaella Colombatti
Target: 150
ES - VHIR-HUVH Barcelona - Mar Mañú Pereira
Target: 250
H Gregorio Marañón - Elena Cela
H Sant Joan de Deu – Anna Ruiz
H Virgen del Rocio – Salvador Payán
NL - UMCU Utrecht, Netherlands - Edward Van Beers
Target: 250
Amsterdan – Bart Biemond
Erasmus MC – Marjon Cnossen
Radboud UMC – Saskia Schols



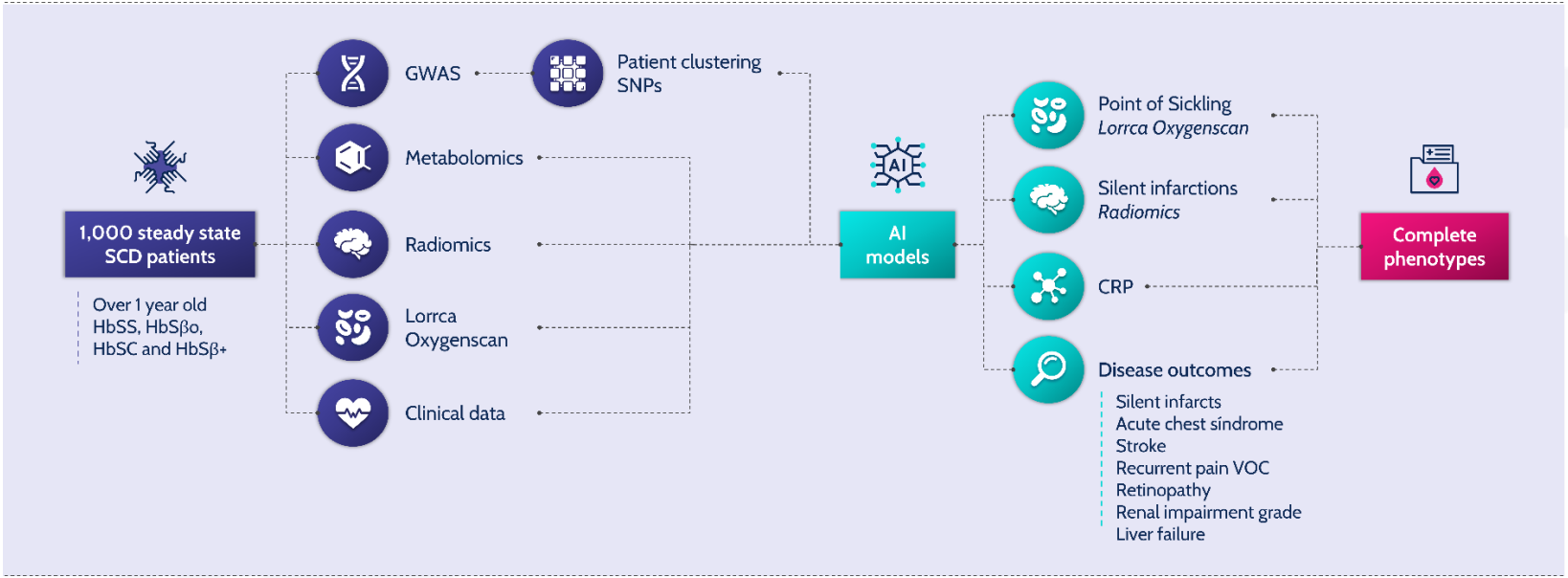
Sickle cell disease

AI Aims in Genomed4All

- Aim 1: To allocate SCD patients in different groups according to their genomic profile and assess correlation with inflammation related markers, point of sickling and phenotype.
- Aim 2: To allocate SCD patients in different groups according to their metabolomic profile and assess correlation with inflammation related markers, point of sickling and phenotype
- Aim 3: Develop a probability score using AI-based brain MRI image analysis (radiomics) to:
  - Diagnose already existing lesions (silent infarcts) that might go undetected due to inter-observer variability or lack of expertise on site.
  - Predict the risk of developing silent infarcts in the future: Correlation between occurrence of silent infarcts and clinical, genomic, metabolomic and functional laboratory features.
- Aim 4: Based on results from objectives 1 to 3, to develop predictive risk scores for the appearance of most prevalent and severe clinical outcomes (e.g., stroke, vaso-occlusive crisis, acute chest syndrome).
- Aim 5: Based on results from objectives 1 to 3, to develop predictive risk scores over time for the appearance of most prevalent and severe clinical outcomes (e.g. stroke, vaso-occlusive crisis, acute chest syndrome).

Sickle cell disease

Study design

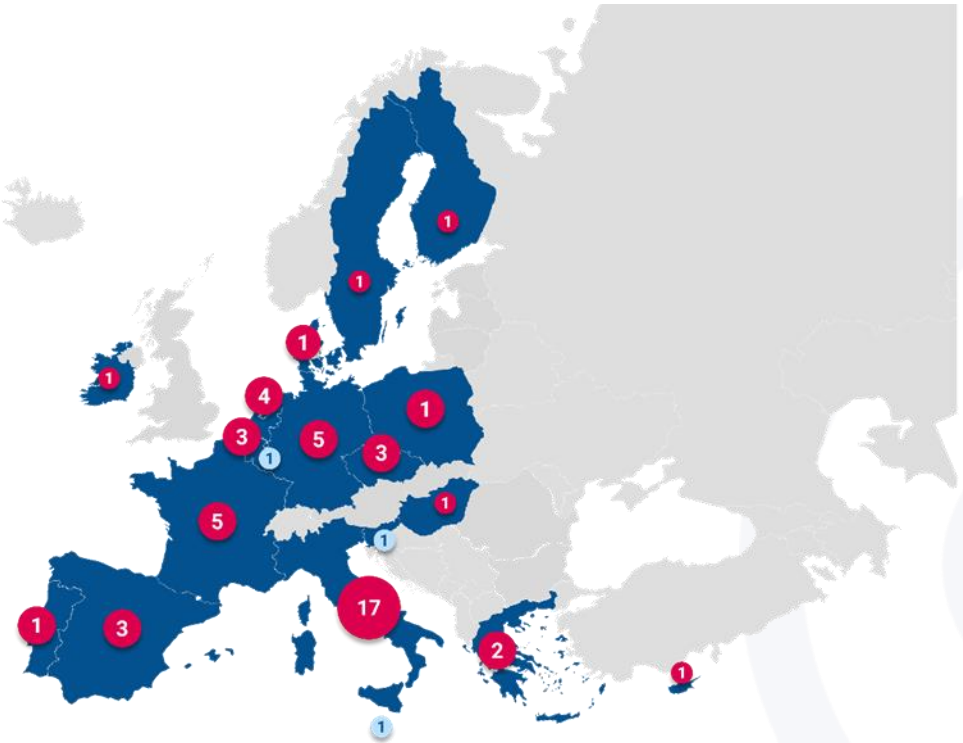


Sickle cell disease

Clinical sites

ERN | EuroBloodNet

RBC subnetwork



Data driven solutions pooling EU standardized clinical data and research data is crucial to advance research in Sickle cell disease

Genomed4all & ERN-EuroBloodNet & RADeep

Thanks!

Any questions?

GenoMed4All & ERN-EuroBloodNet

Educational Program on Artificial Intelligence for public-at-large

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Acknowledgements

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Co-funded by the European Union

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Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

GENOMED4ALL

Funded by the European Union

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GenoMed4All & ERN-EuroBloodNet

Educational Program on Artificial Intelligence for public-at-large

#1

GenoMed4All & ERN EuroBloodNet for precision medicine in hematology

Federico Álvarez

GenoMed4All Coordinator – UPM

Use cases challenges: MDS, SCD and MM

Multiple Myeloma

The need to have information about CLINICS and BIOLOGY

Dr Marina Martello, PhD

DIMEC - Dipartimento di Scienze Mediche e Chirurgiche - Università di Bologna

IRCCS Azienda Ospedaliero-Universitaria di Bologna - Istituto di Ematologia "Seràgnoli"

Multiple Myeloma

The need to have information about CLINICS and BIOLOGY

CLINICS

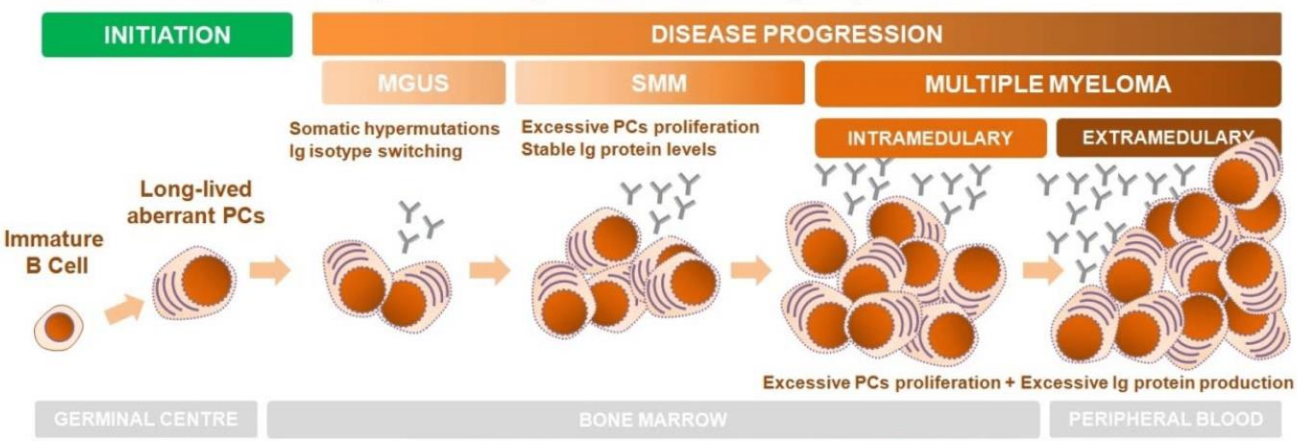
ARTIFICIAL INTELLIGENCE?

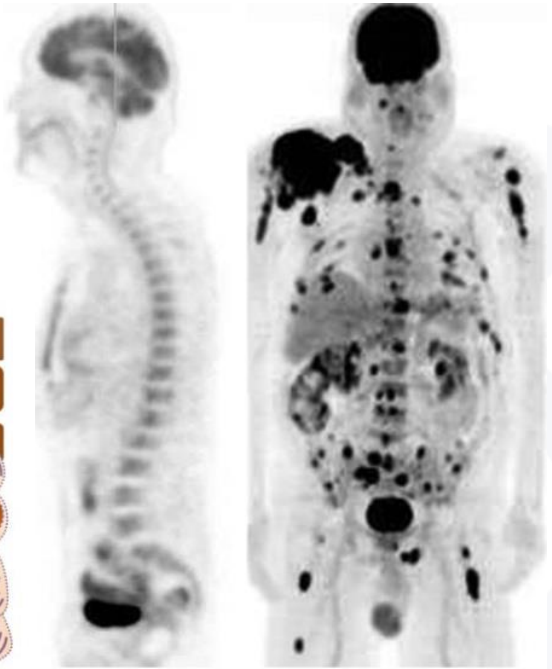
BIOLOGY

Multiple Myeloma(S)

By name and by nature!

- PLASMA CELLS disease: inside bone marrow, but also outside
- MULTI-STEP evolution: from MGUS to MM
- Disease DISTRIBUTION: presence of multiple lytic lesions



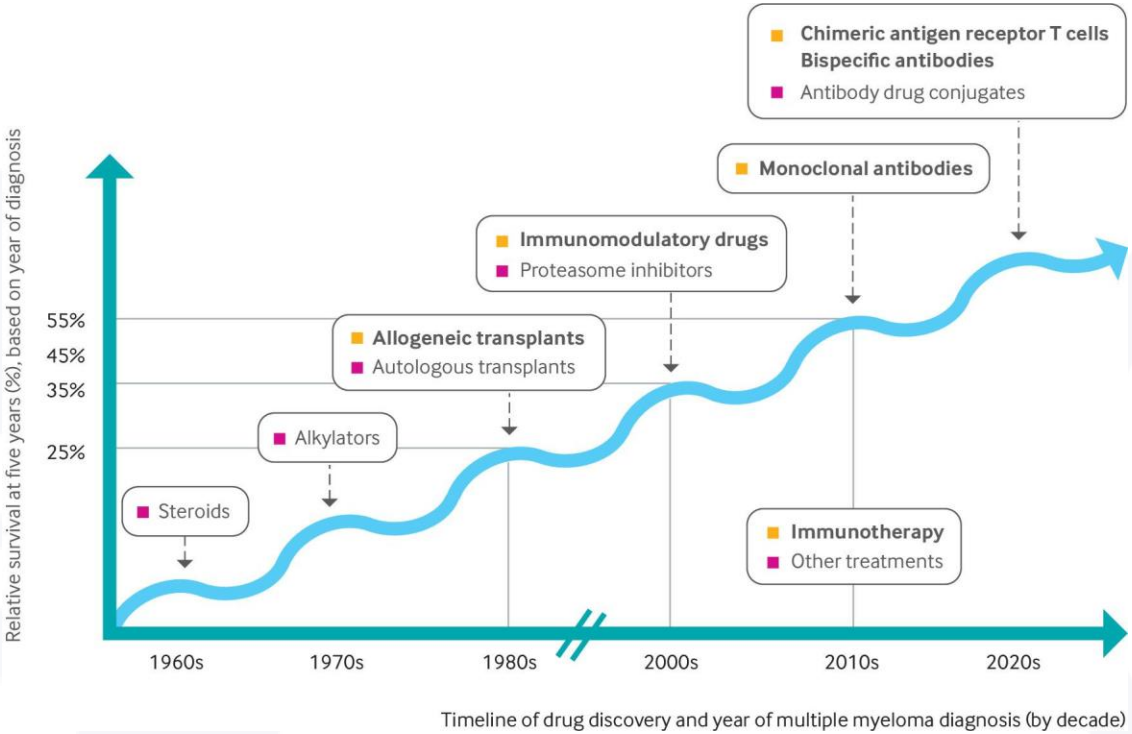


LIQUID BIOPSY

Pinto V et al., Cancers 2020

Multiple Myeloma CLINICS

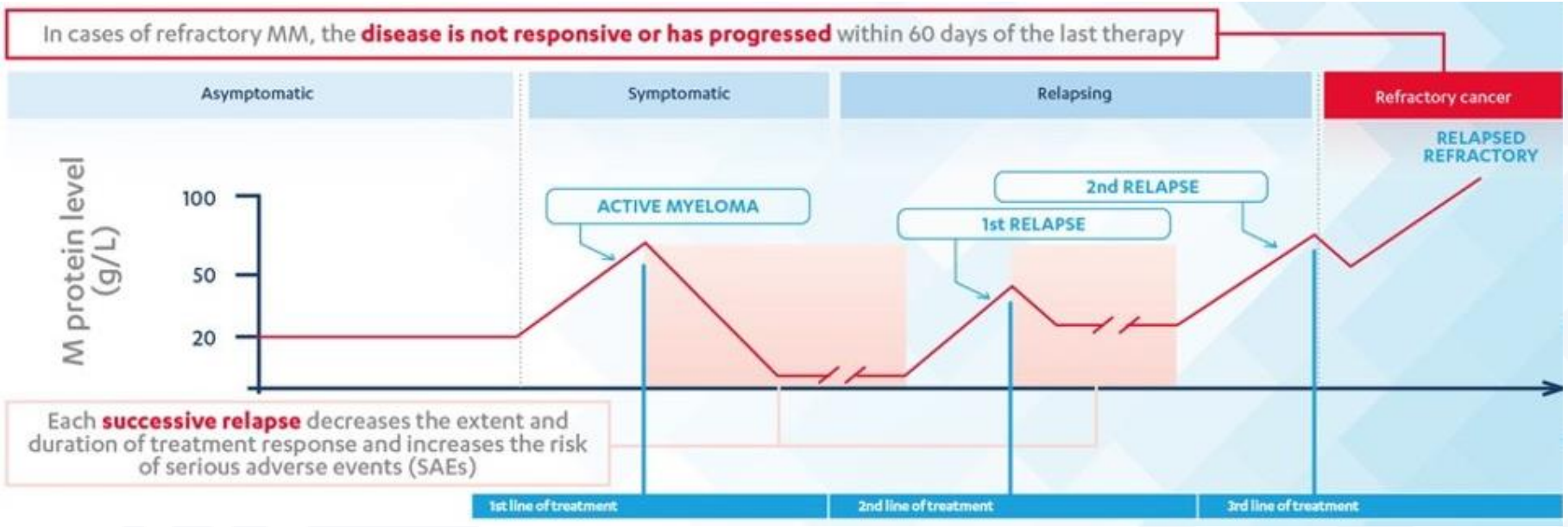
State-of-the-art



Shah U et al., BMJ 2020

Multiple Myeloma CLINICS

Myeloma follows a pattern of alternance of remission and relapse phases

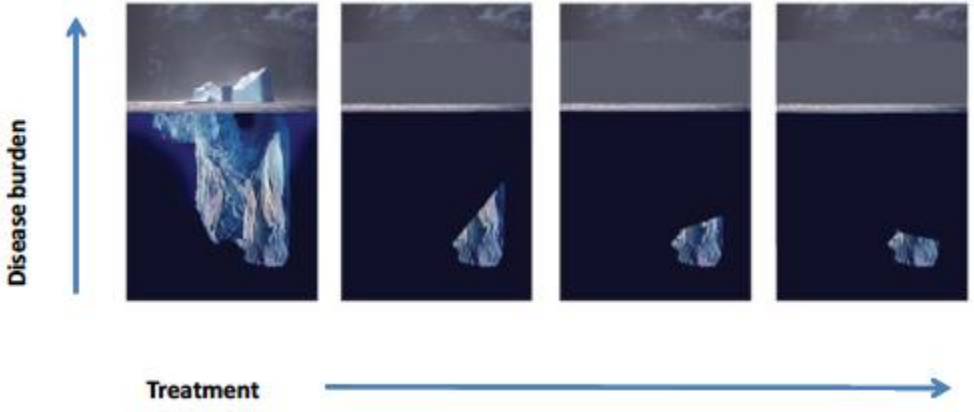


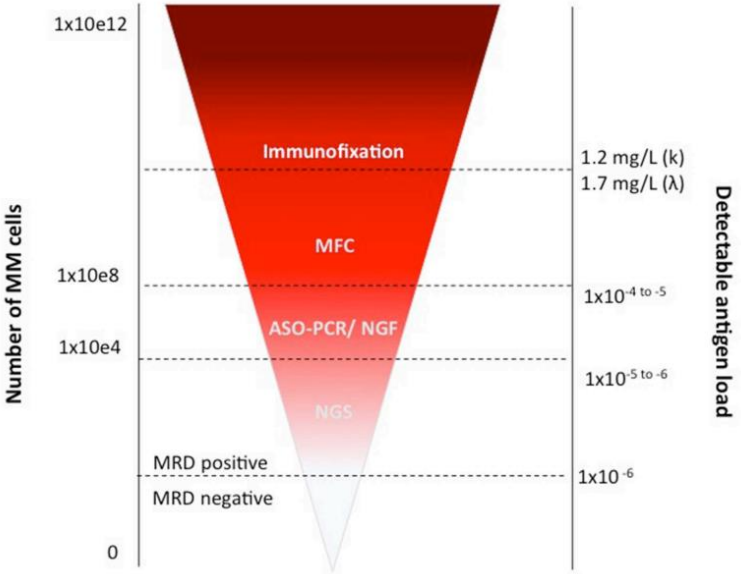
AIM: to reach REMISSION phase and maintain this status

Dimopoulous et al., JCO 2013

Multiple Myeloma CLINICS

REMISSION concept evolution over last years until UNDETECTABLE MRD

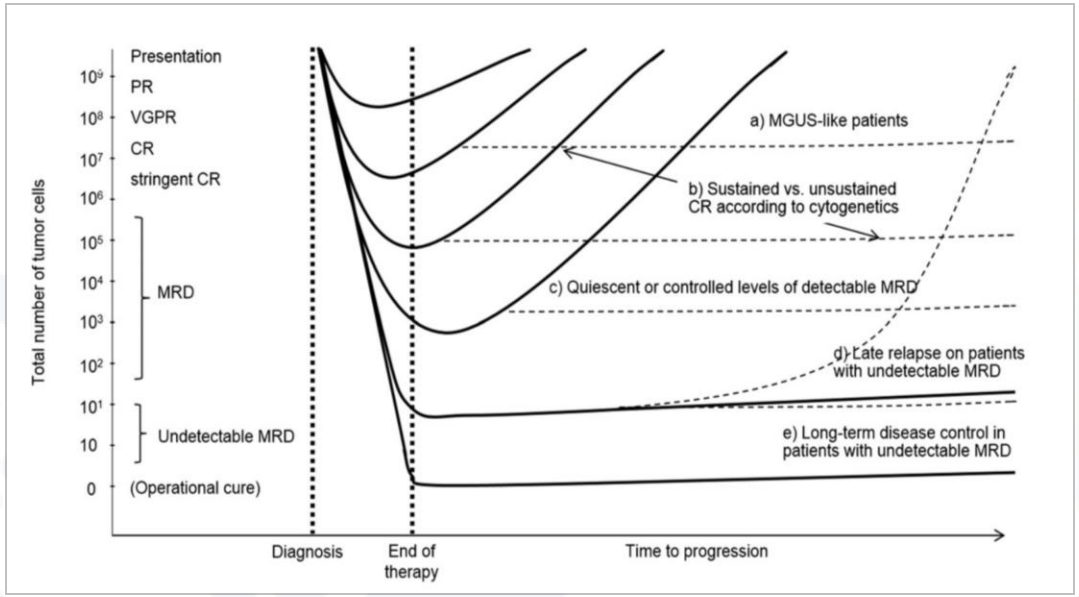




The main goal of current therapies, is to minimize the disease present at diagnosis to MRD, a time when the patient can be defined as being in COMPLETE REMISSION. The deeper and longer this status, the greater the survival

Romano et al., Frontiers Oncology 2019

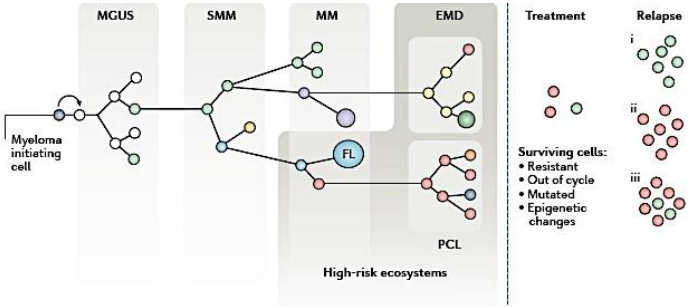
Multiple Myeloma CLINICS?
… also BIOLOGY matters!!

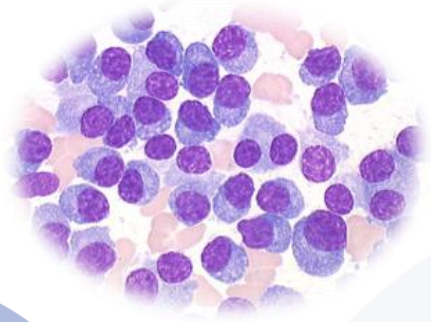


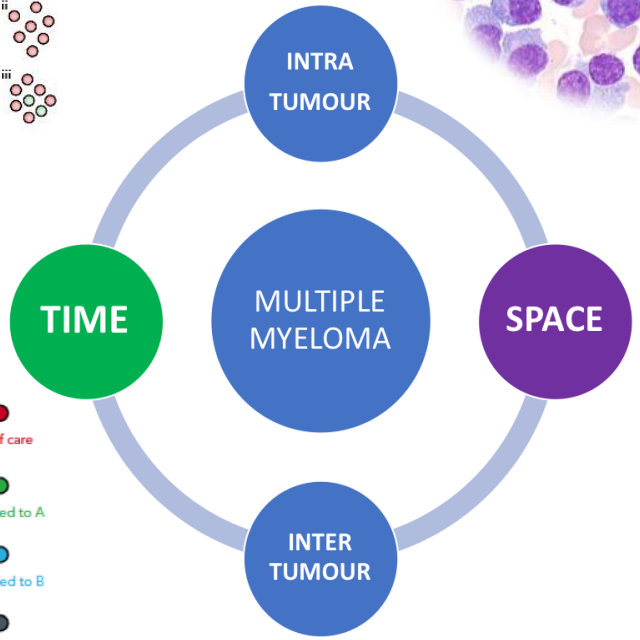
Plesner et al., J Clin Med 2021
Rasche L et al., Leukemia 2019

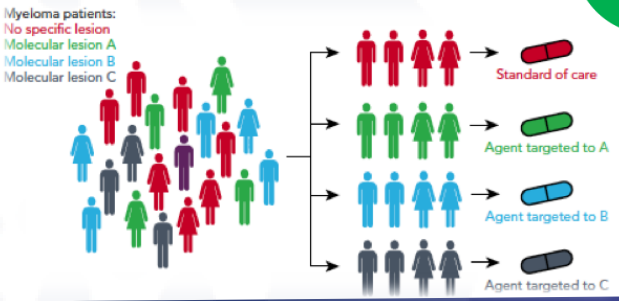
Multiple Myeloma BIOLOGY!

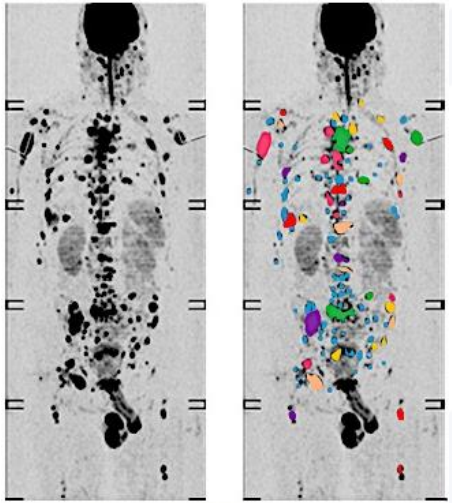
How to face with this multilevel complexity





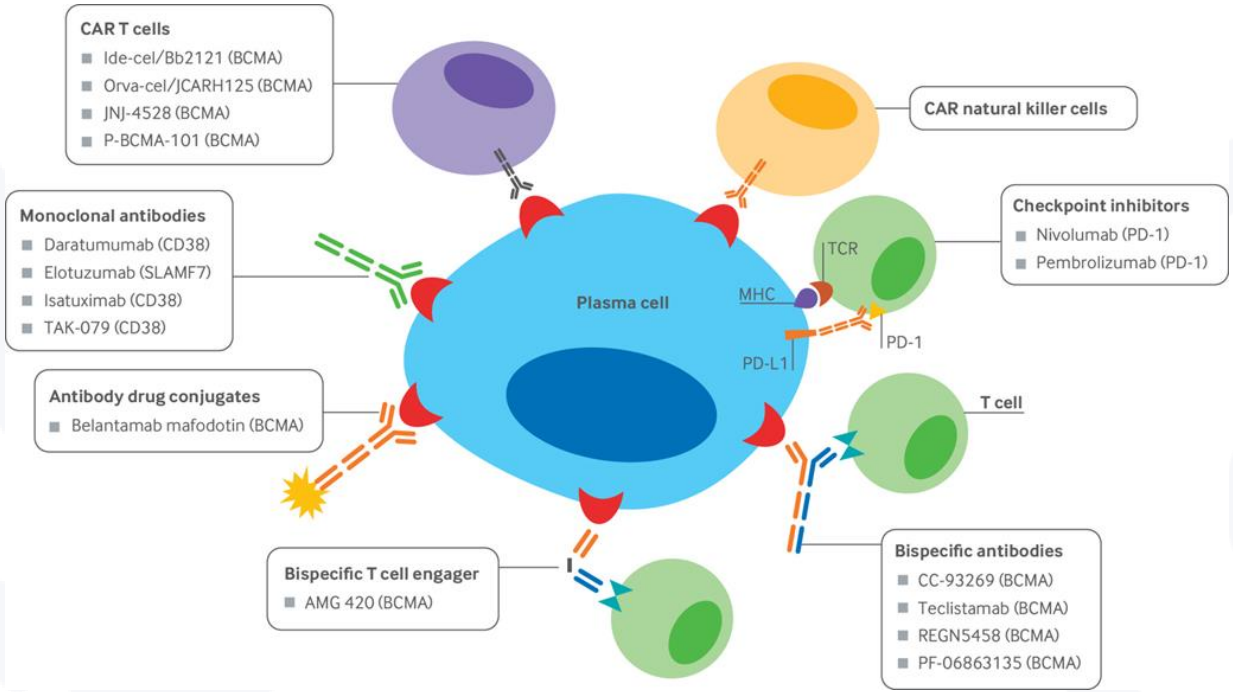






Multiple Myeloma BIOLOGY! ...outside the cells

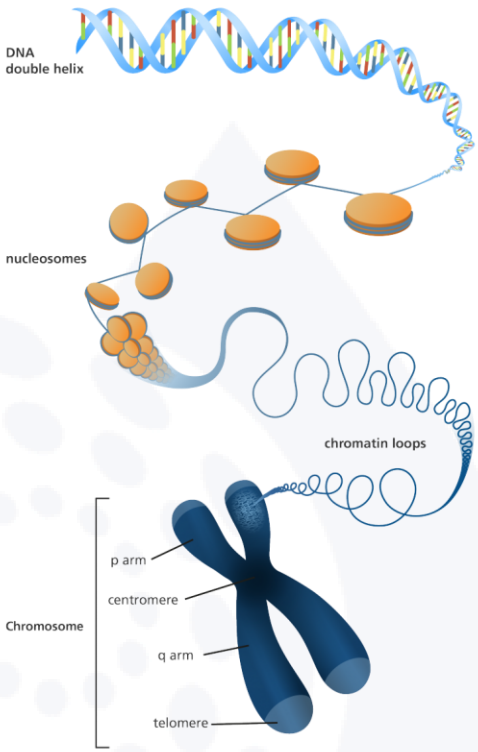
It is essential to know BIOLOGY of the disease, including CLONE and MICROENVIRONMENT



Shah U et al., BMJ 2020

Multiple Myeloma BIOLOGY!... Inside the cells

Genomic abnormalities



Primary abnormalities

Trisomies (~45%)
Odd-numbered chromosomes: 3, 5, 7, 9, 11, 15, 19, and 21

IgH translocations (~55%)
Translocations involving the IgH gene locus at 14q32

Translocation;locus;gene
t(4;14);4p16;*FGFR3–MMSET*
t(14;16);16q23;*MAF*
t(14;20);20q12;*MAFB*
t(8;14);8q24;*MAFA*
t(11;14);11q13;*CCND1*
t(6;14);6p21;*CCND3*

MYC dysregulation

Cyclin dysregulation

Secondary abnormalities

Monosomies
Chromosome 13
Chromosome 17
Chromosome 14

Deletions
Chromosome 17p
Chromosome 1p

Amplification
Chromosome 1q
gain or amplification

Other genomic alterations
miRNA

Recurrent mutations

KRAS
NRAS
TP53
DIS3
FAM46C
BRAF
TRAF3
ROBO1
CYLD
EGR1
SP140
FAT3
CCND1

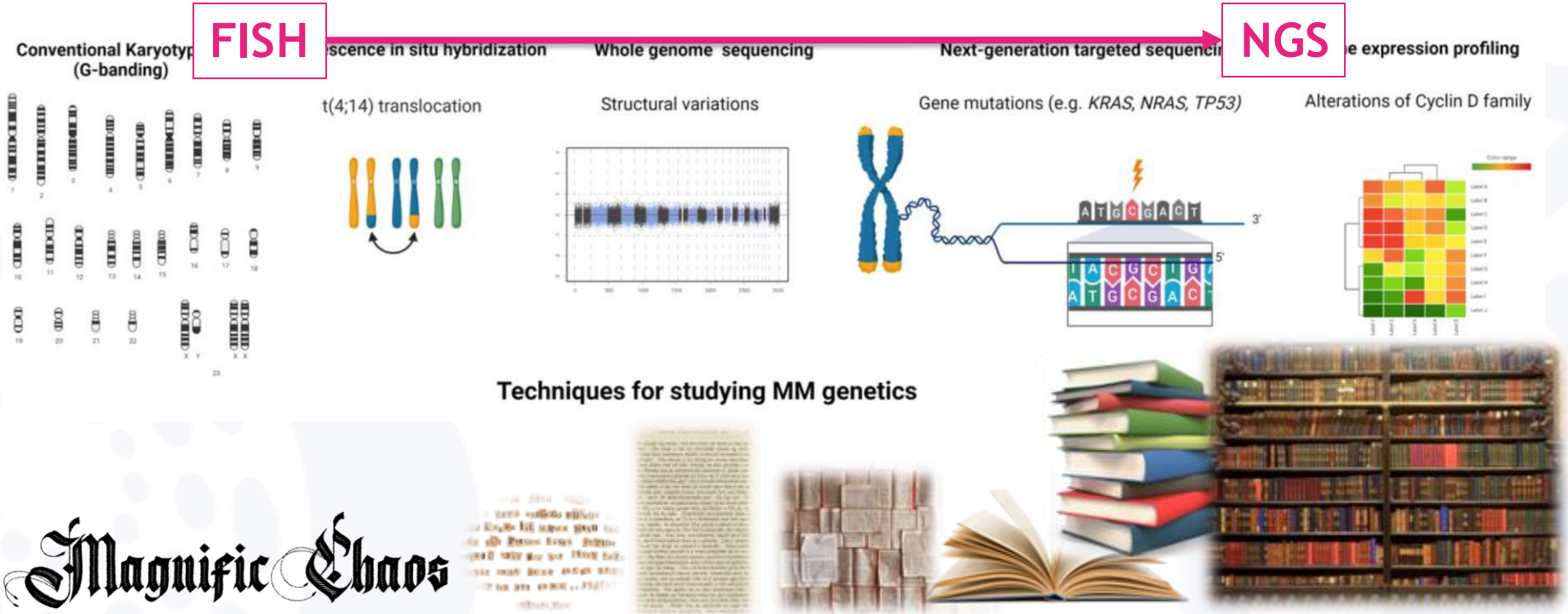
Kumar S et al., Nat Rev Clin Onc 2018

ebn ERN | EuroBloodNet

GENOMED 4ALL

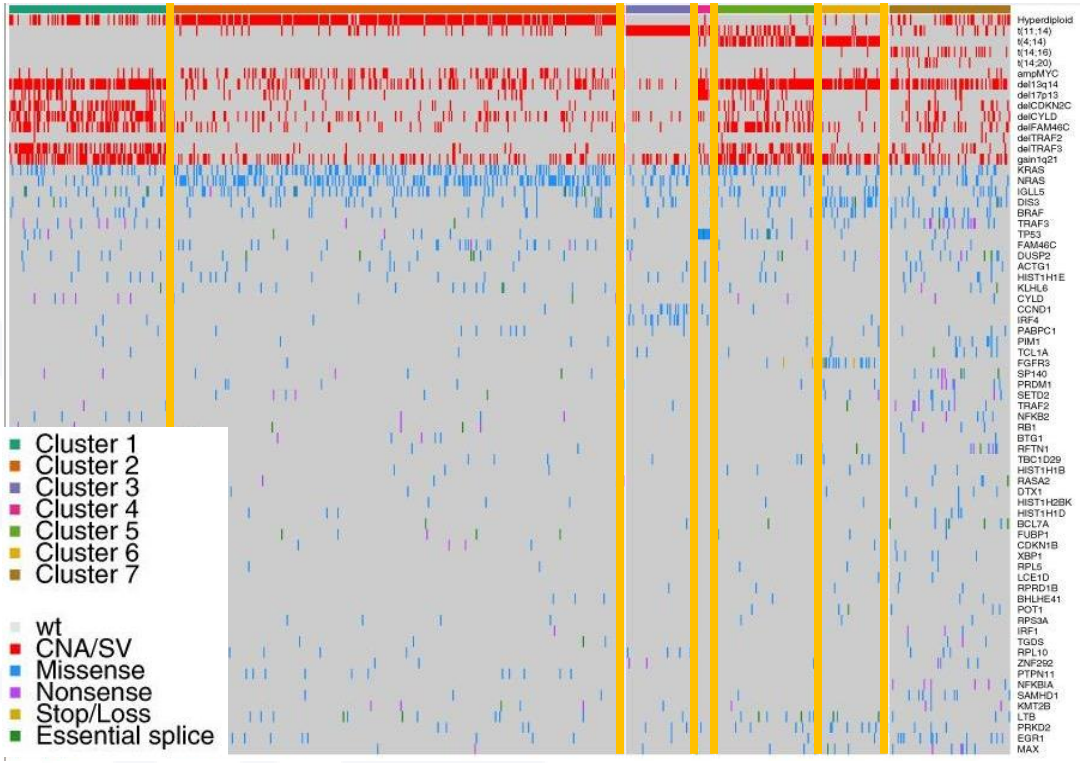
Multiple Myeloma BIOLOGY

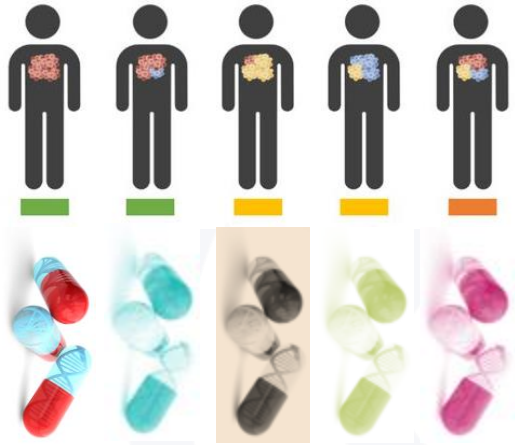
Techniques used for studying the genomics of multiple myeloma



Multiple Myeloma BIOLOGY

Different patients = different myeloma = different subtypes





Maura F et al., Nat Comm 2019

ERN | EuroBloodNet

GENOMED 4ALL

Multiple Myeloma CLINICS&BIOLOGY

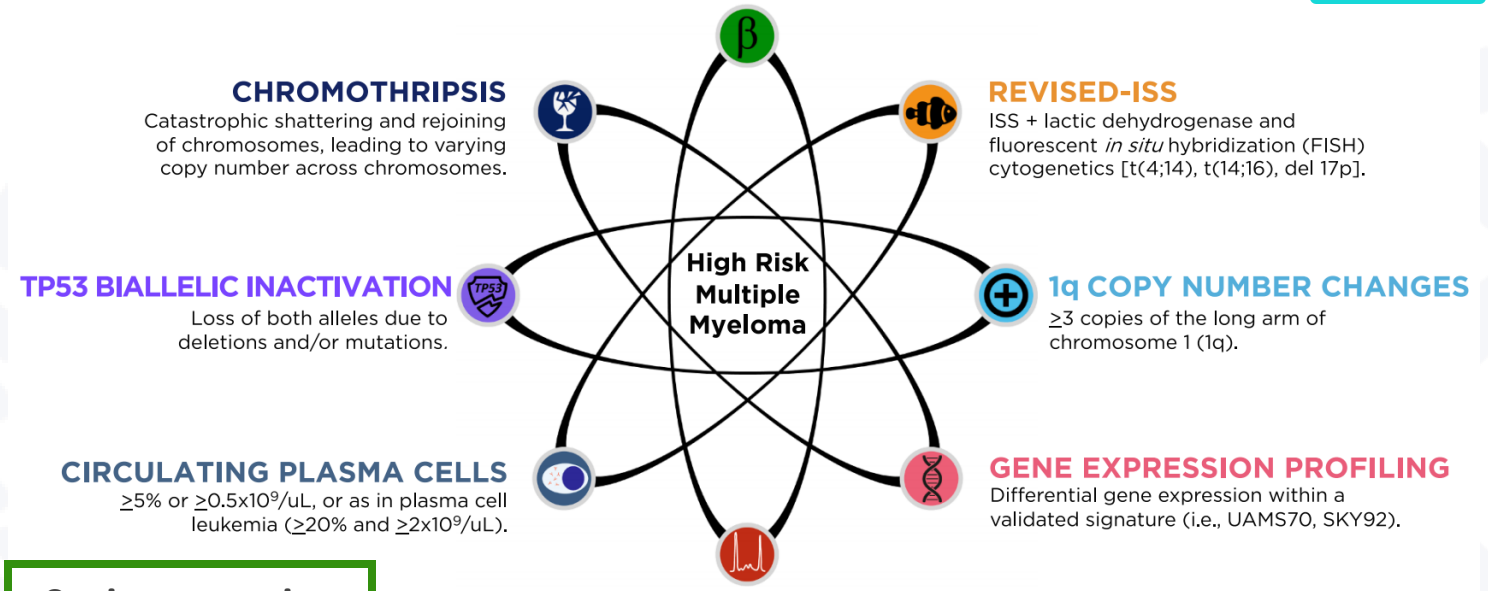
Current MM risk stratification scores are suboptimal

Stage	ISS[3]	R-ISS[4]	IMWG[5]
I Low Risk	β2-microglobulin <3.5 mg/L Albumin ≥3.5 g/dL	ISS Stage I + Standard risk FISH + Normal LDH	ISS I or II Age < 55 No t(4;14), del 17p, 1q gain
II Standard Risk	Not stage I or III	Not stage I or III	Neither low or high risk
III High Risk	β2-microglobulin ≥5.5 mg/L	ISS stage III + t(4;14), t(14;16), or del 17p or LDH > upper limit	ISS 2 or 3 + t(4;14) or del 17p
Median OS	Stage I: 62 months Stage II: 44 months Stage III: 29 months	Stage I: 66 months Stage II: 42 months Stage III: 29 months	Low Risk: >120 months Standard Risk: 84 months High Risk: 24 months

Multiple Myeloma CLINICS&BIOLOGY

Refining the definition of HIGH RISK patients

Frailty



Socioeconomics and access to care

Multiple Myeloma CLINICS&BIOLOGY

The Genomed4All project: Multiple Myeloma use case

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

POLICLINICO DI
SANT'ORSOLA

- 300 newly diagnosed MM patients enrolled by the Institute of Hematology «L. e A. Seràgnoli» - Bologna, Italy
- 995 newly diagnosed MM patients from MMRF CoMMpass Public repository

UNIVERSITÀ
DI TORINO

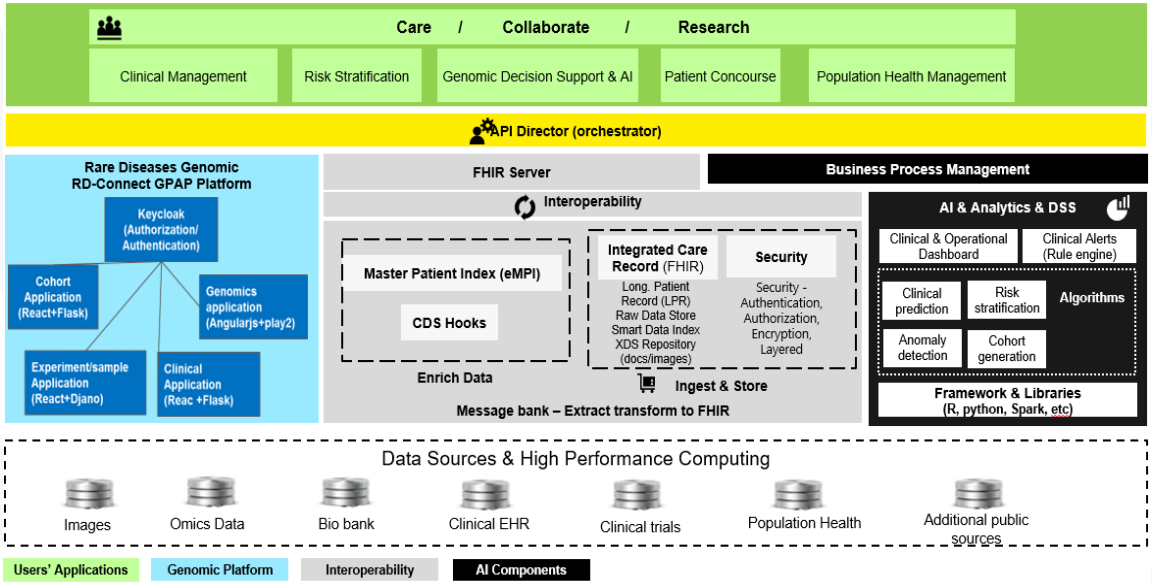
FINAL AIM: to refine the definition of HIGH RISK patients by possibly identifying predictors of EARLY relapse patients (within 18 months) based on the integration of baseline genomic, clinical & imaging data using artificial intelligence

ebn ERN | EuroBloodNet
GENOMED 4ALL

Genomed4All project: AI for MM

Main components of the data sharing platform, data flows and connection to repositories

- Data harmonization
- Data sharing



Multiple Myeloma CLINICS&BIOLOGY

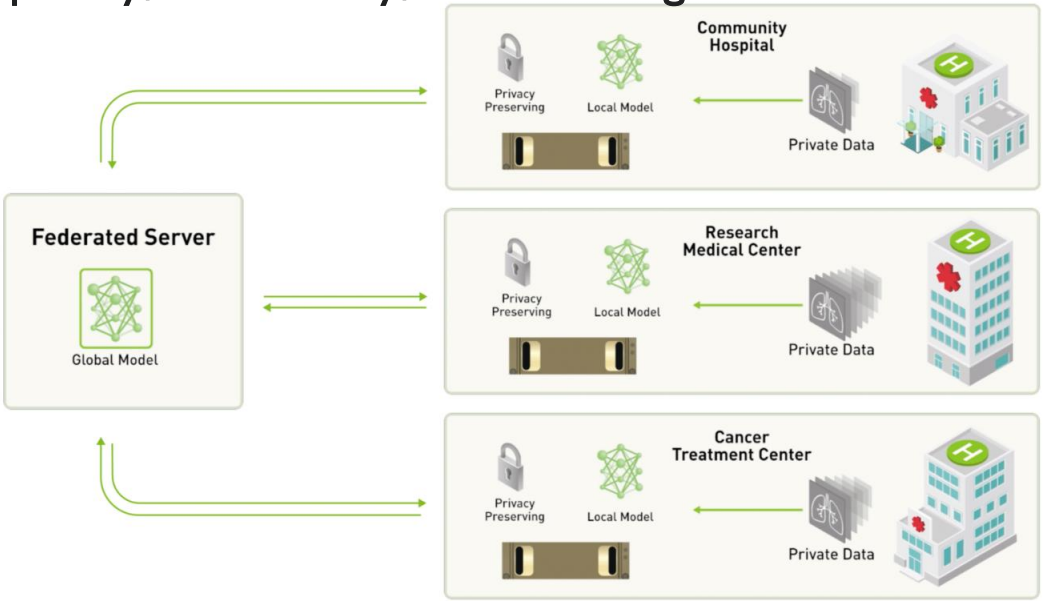
The Genomed4All projects' phases

1. FEDERATED LEARNING – UPM
2. DATA MODELLING and ML TRAINING ALGORYTHMS FOR RISK PREDICTION – UNIBO, UNITO
3. RADIOMICS - UNIBO

Multiple Myeloma CLINICS&BIOLOGY

Federated Learning (also known as *collaborative learning*)

DEF: machine learning technique that trains an algorithm via multiple independent sessions, each using its own dataset without sharing data thus addressing critical issues such as data privacy, data security, data access rights and access to heterogeneous data



DATASET DISCUSSION
FEATURES SELECTION

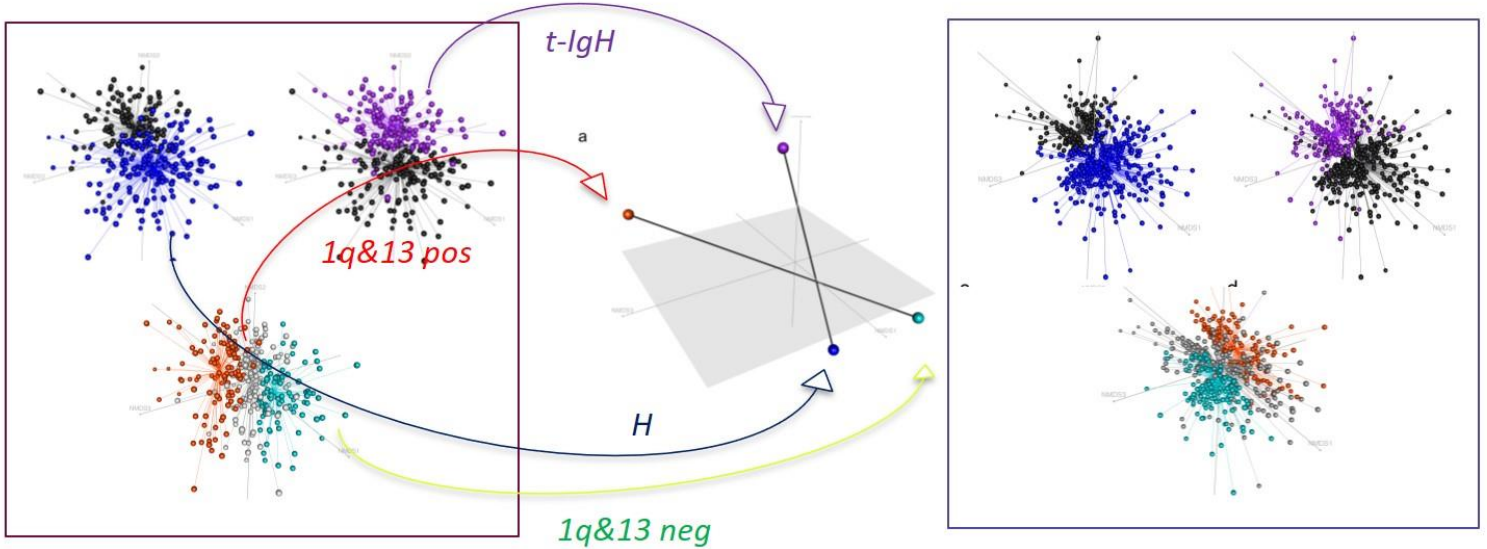
SYNTHETIC DATA GENERATION

SYNTHETIC DATA VALIDATION

Multiple Myeloma CLINICS&BIOLOGY

Data modelling and Machine Learning algorithms

the *organized chaos* of Multiple Myeloma => the major component of MM heterogeneity

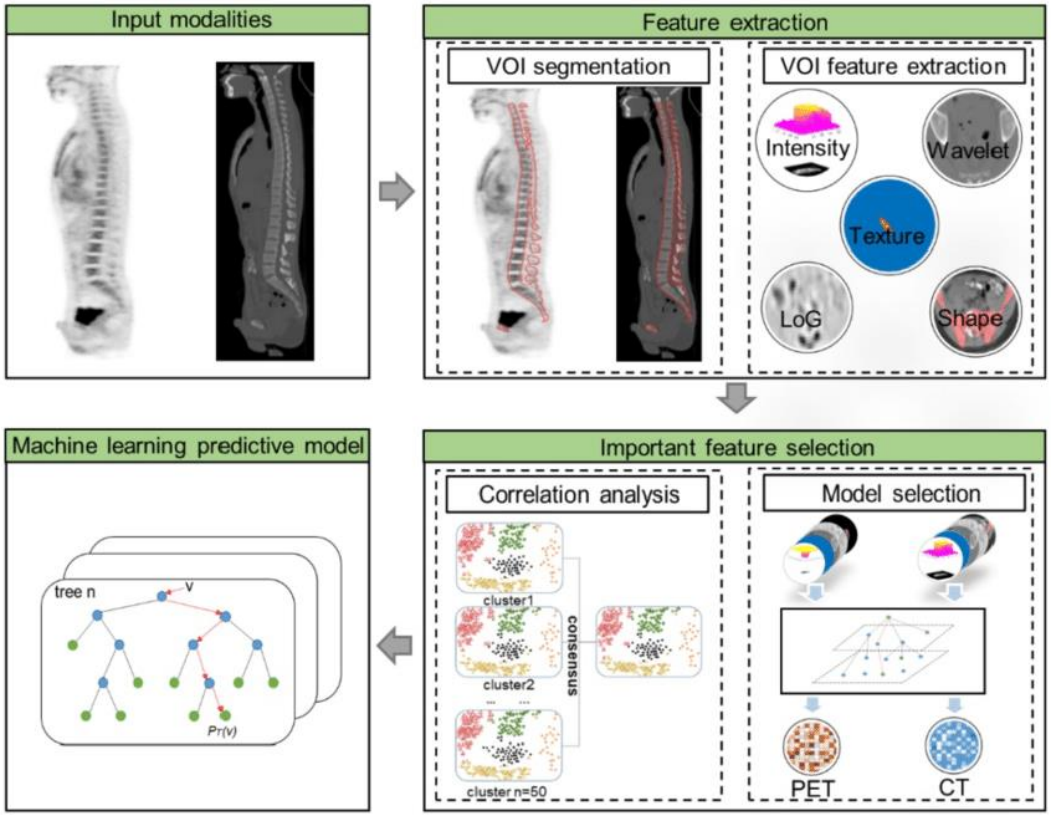


BO dataset

CoMMpass dataset

Multiple Myeloma CLINICS&BIOLOGY

Radiomics



Multiple Myeloma CLINICS&BIOLOGY

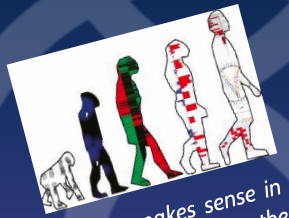
The Genomed4All project: Multiple Myeloma use case WRAP-UP

- Multiple Myeloma is a COMPLEX disease, but it needs a CURE
- Strong need to interconnect CLINICS & BIOLOGY to better predict PATIENTS' RISK
- A precise PREDICTION requires HUGE AMOUNT OF DATA to be statistically significative and clinically meaningful
- ARTIFICIAL INTELLIGENCE can help in data management, interconnection and prediction
- With our partners in the GENOMED4ALL project we aimed at the integration of both CLINICAL, GENOMIC and IMAGING of a large cohort of newly diagnosed MM patients in order to identify PREDICTORS OF EARLY RELAPSE that can refine the definition of high risk patients
- In the FUTURE, these results will contribute to an IMPROVED DESIGN of clinical trials and a BETTER PATIENTS' MANAGEMENT, towards a more PRECISE MEDICINE

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

POLICLINICO DI SANT'ORSOLA

Thanks!



Nothing makes sense in biology expect in the light of evolution
Theodosius Dobzhansky

Multiple Myeloma Research Unit

Prof. Michele Cavo

Gastone Castellani
Santiago Zazo
Piero Fariselli

MOLECULAR BIOLOGY LAB

Carolina Terragna
Marina Martello
Enrica Borsi
Silvia Armuzzi
Ilaria Vigliotta
Barbara Taurisano
Ignazia Pistis

BIOINFO NERDs

Vincenza Solli
Andrea Poletti
Gaia Mazzocchetti
Ajsi Kanapari

CLINICAL RESEARCH UNIT

Elena Zamagni
Paola Tacchetti
Lucia Pantani
Katia Mancuso
Ilaria Rizzello
Emanuele Favero

MULTIPLE MYELOMA Research Foundation

AIL Bologna
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

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Thanks!

Any questions?

GenoMed4All & ERN-EuroBloodNet

Educational Program on Artificial Intelligence for public-at-large

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European Reference Network
for rare or low prevalence complex diseases
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