Università degli Studi di Brescia – Corso di laurea in Medicina e Chirurgia

Corso integrato di Malattie del Sangue

CASO CLINICO
Sindromi mielodisplastiche

UNIVERSITY OF BRESCIA

Chair of Hematology
Unit of Blood Disease and
Bone Marrow Transplantation

Mirko Farina

Unit of Blood Diseases and Bone Marrow Transplantation
Program of Cell Therapies and Research in Hematology
University of Brescia & ASST Spedali Civili of Brescia
mirko.farina@unibs.it

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

N.D., 72 aa

- 21/2/2023: negli ultimi mesi riferita **astenia**; episodi **febbrili ricorrenti**

Anamnesi patologica remota:

Pregresso infarto del miocardio
Diabete mellito in terapia con Metformina
Tumore alla prostata 3 anni fa (chirurgia + chemio)

Anamnesi famigliare:

Non significativa

EO:

Pz lucido, collaborante, eupnoico.

Petecchie Arti inferiori

Non epato/splenomegalia

Non linfoadenopatie superficiali

Emocromo

Esame	*Risultato*	*Valori riferimento*
Globuli bianchi	1.800	4.000-10.000/mmc
Neutrofili	*700*	*2000-7000/mmc*
Linfociti	*650*	*1100-4000/mmc*
Monociti	*400*	*250-800/mmc*
Eosinofili	*50*	*0-50/mmc*
Basofili	*0*	*0-50/mmc*
Globuli rossi	3.900.000	3.800.000-4.800.000/mmc
Emoglobina	8.5	12-16 g/dL
MCV	104	82-99 fL
MCH	31	27-31 pg
RDW	13%	12-17%
Piastrine	**27.000**	150-400.000/mmc

Esame	*Risultato*	*Valori riferimento*
Globuli bianchi	2.700	4.000-10.000/mmc
Globuli rossi	3.900.000	3.800.000-4.800.000/mmc
Emoglobina	8.5	12-16 g/dL
MCV	104	82-99 fL

Che tipo di anemia?

1) ACUTA

2) CRONICA

1) Lieve

2) Moderata

3) Severa

1) Microcitica

2) Normocitica

3) Macrocitica

Chiedereste altri esami per inquadrare il tipo di anemia?

Reticolociti: 50.000 mU/ml ⬇

Eritropoietina: 200 mU/ml ⬆

Esame	*Risultato*	*Valori riferimento*
Globuli bianchi	1.800	4.000-10.000/mmc
Neutrofili	*700*	*2000-7000/mmc*
Globuli rossi	3.900.000	3.800.000-4.800.000/mmc
Emoglobina	8.5	12-16 g/dL
MCV	104	82-99 fL
MCH	31	27-31 pg
RDW	13%	12-17%
Piastrine	**27.000**	150-400.000/mmc

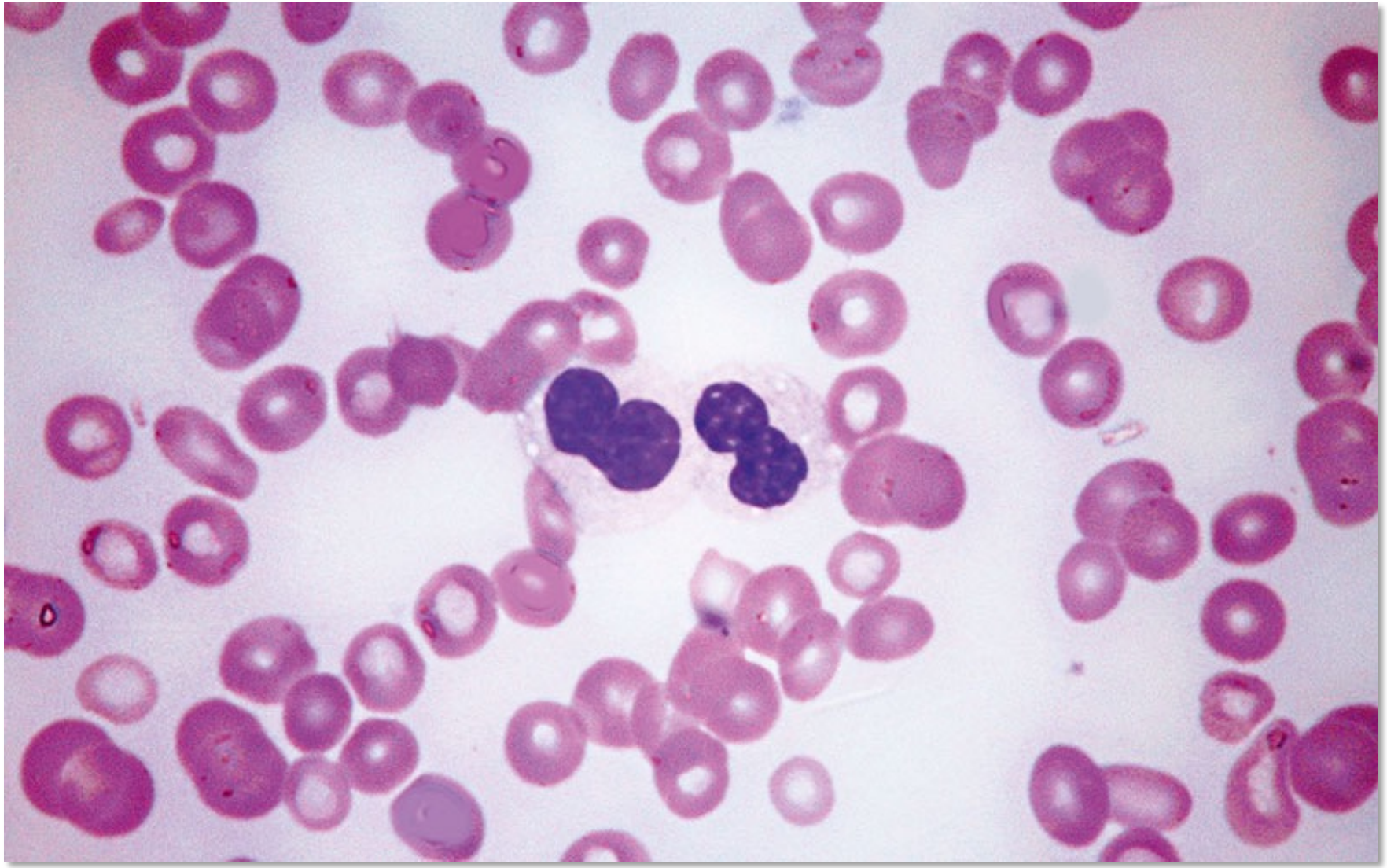
Che tipo di piastrinopenia?

1) Lieve 2) Moderata **3) Severa**

Che tipo di neutropenia?

1) Lieve **2) Moderata** 3) Severa

Chiedereste altri esami?

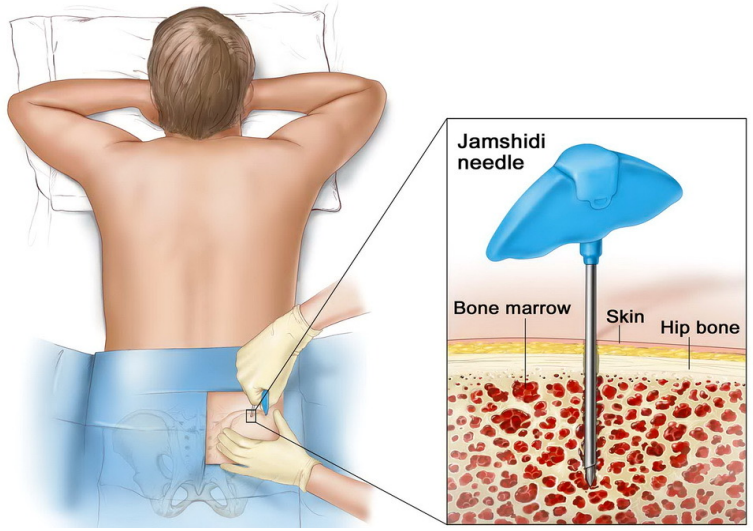


- Neutrofili iposegmentati
- Aniso-poichilocitosi
- Ovalociti
- Piastrinopenia
- NO BLASTI

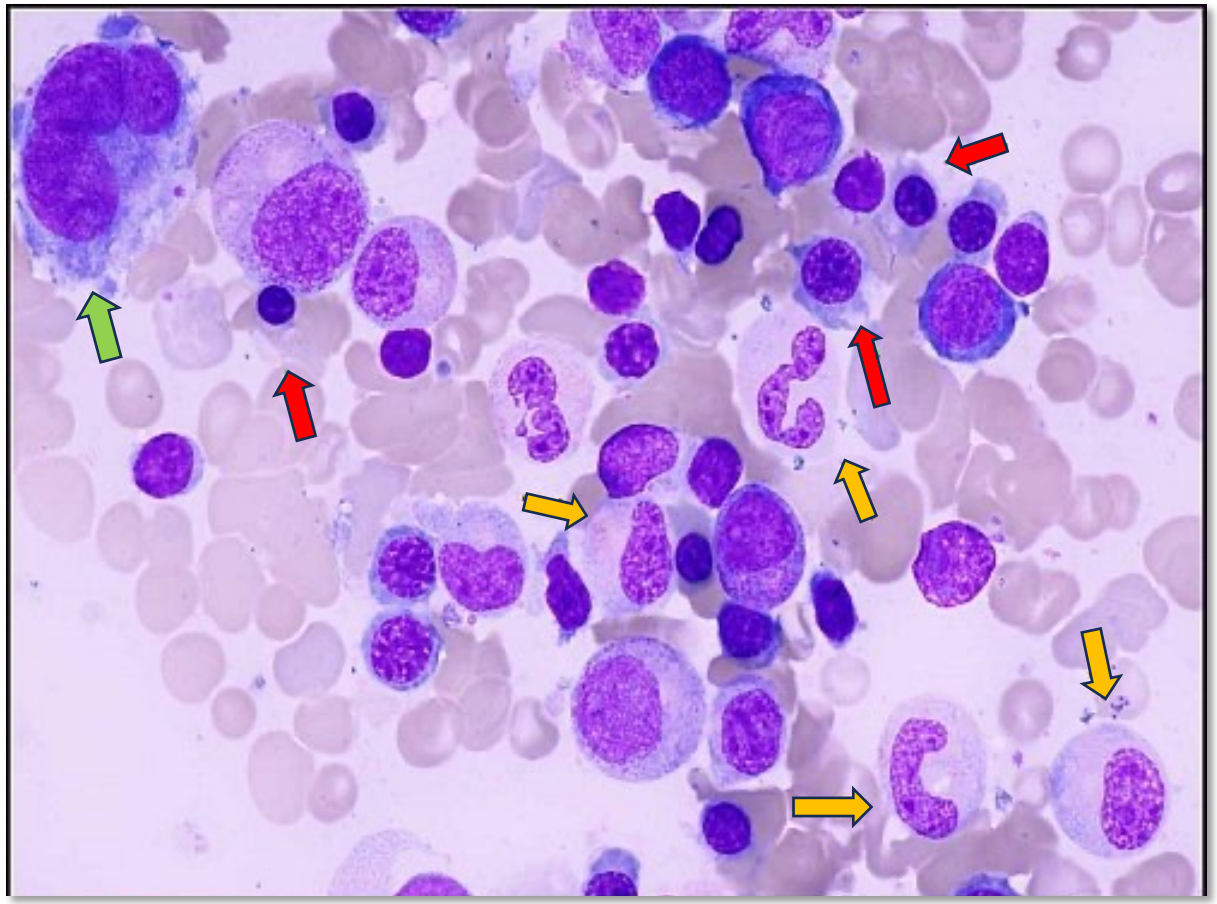
Che cosa sospettate?

Sindrome mielodisplastica

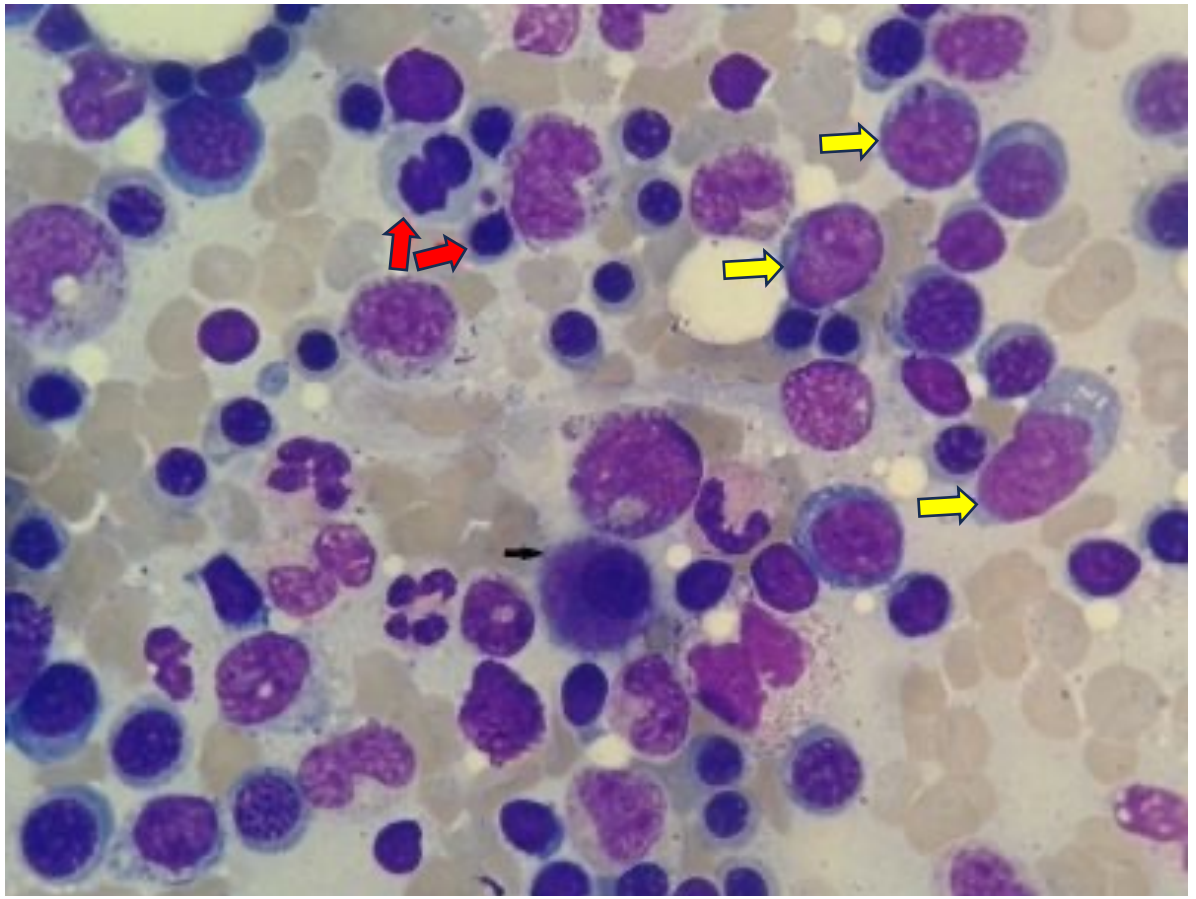
Chiedereste altri esami?



Valutazione midollare



- Mitosi anormali e ponti internucleari fra eritroblasti
- Blasti
- Granulociti con citoplasma ipogranulato
- Promegacariocito



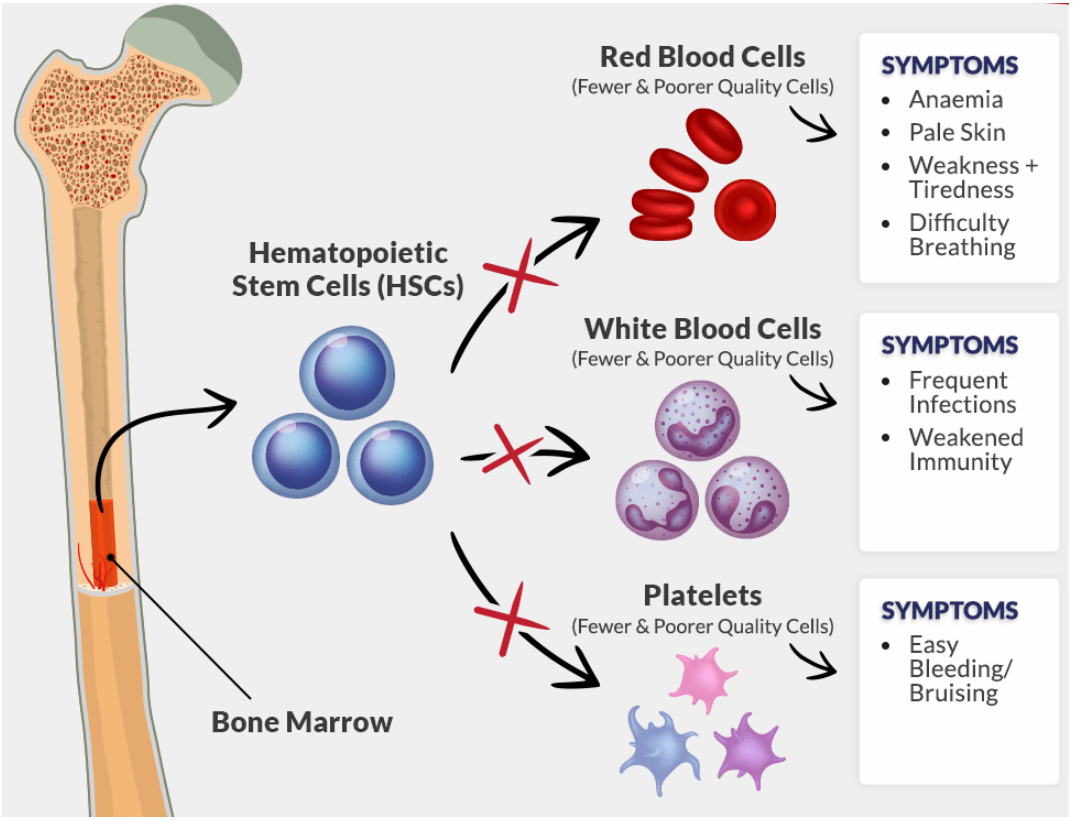
- Cellularità aumentata
- **8% BLASTI**

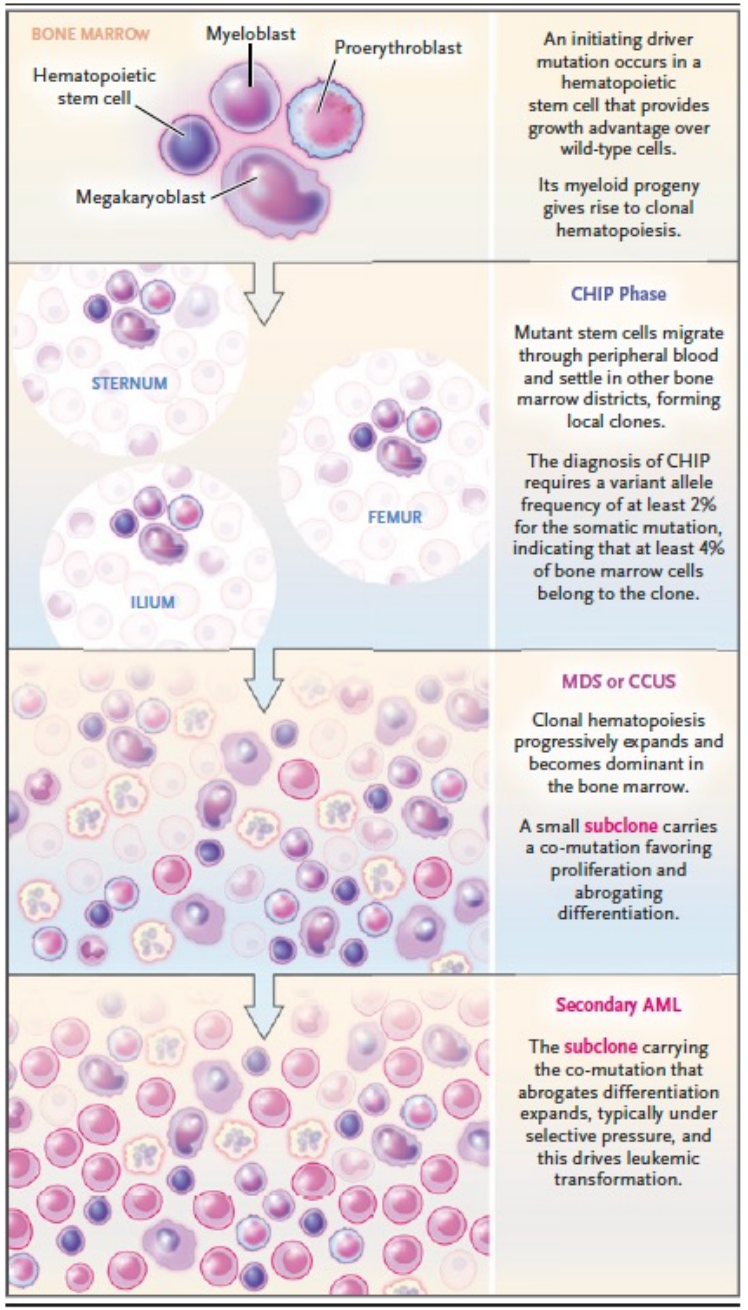
MDS

1) **citopenia** periferica

2) **dismielopoiesi**, con midollo più spesso normo-ipercellulato, più raramente ipocellulato, con o senza incremento della quota blastica (comunque < 20%)

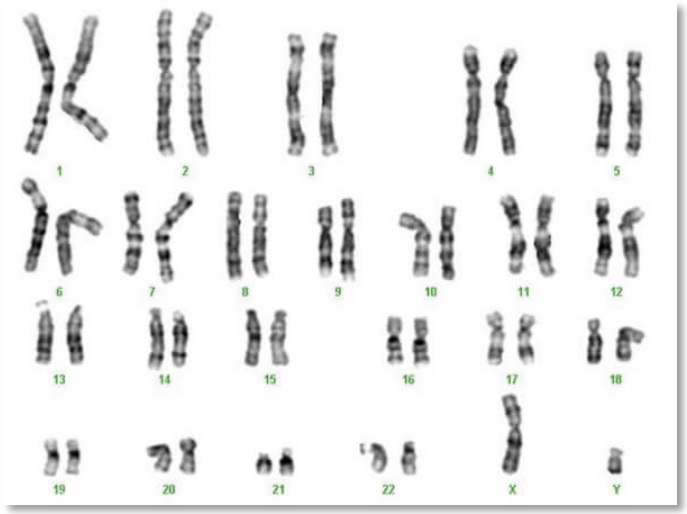
3) **aumentato rischio di evoluzione in leucemia acuta mieloide (AML)**



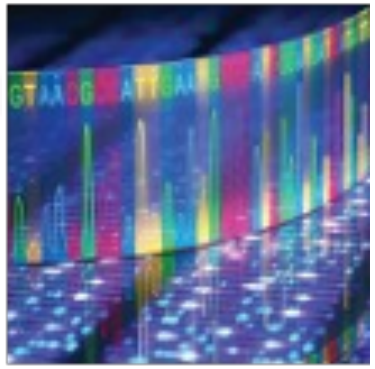


Cazzola, NEJM 2020

Valutazione midollare: quali altri test?



Cariotipo: 46 XY



NGS: ASXL1 & TET2 mutations

Analisi citofluorimetrica

TABLE 6 Integrated MDS-MFC score (iFS) (modified from Cremers et al., 2017)

Diagnostic score	<2 abnormalities								≥2 abnormalities							
Aberrant myeloid progenitors	−	−	−	−	+	+	+	+	−	−	−	−	+	+	+	+
Aberrant neutrophils (SSC or ≥2 other aberrancies) Aberrant monocytes (CD56/≥2 aberrancies)	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+	+
Aberrant erythroid (≥2 aberrancies)	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+
iFS[a]	A	B	B	C	B	C	C	C	A/B	C	C	C	C	C	C	C

Note: The four-parameter diagnostic score is as described by Della Porta et al., 2006. Abnormal features in progenitors, granulocytes, monocytes, and erythropoiesis as depicted in Tables 1–4.

[a]*i*FS Category A: no MDS-related features; B: limited number of changes associated with MDS, or C: features consistent with MDS. Choice for A or B and B or C depends on the kind and number of aberrancies that are encountered. Note that patients with ≥2 points in the four-parameter score can still be concluded as not consistent with MDS by the *i*FS when there are no other abnormalities.

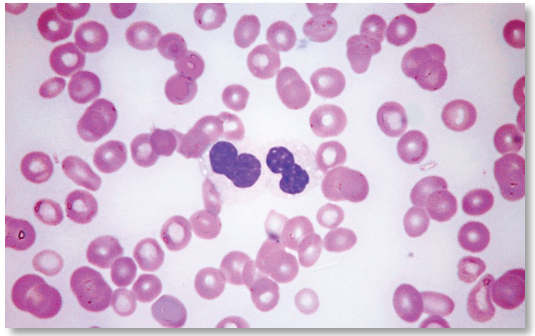
IF: CD34+CD33+CD45dimCD117+: 7%

- Maschio, 72 anni
- Astenia ed episodi infettivi ricorrenti all'esordio

Pancytopenia

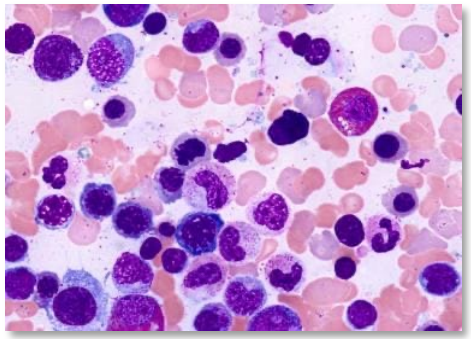
- Hb: 8.5 g/dL
- PLT: 26 x10^9/L
- GB: 2.7 x10^9/L

Peripheral blood



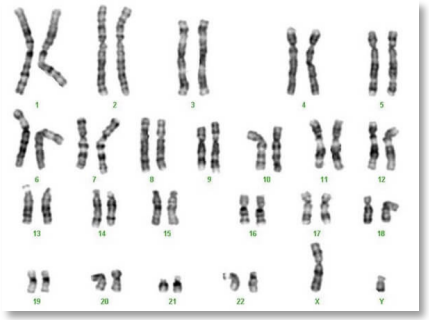
NO blasti circolanti
Neutrofili ipogranulati
IF: CD34+CD117+ 0.5%

Bone Marrow



MDS
8% blasti

Cytogenetics & Molecular Biology



Cariotipo normale

ASXL1 & TET2 mutations

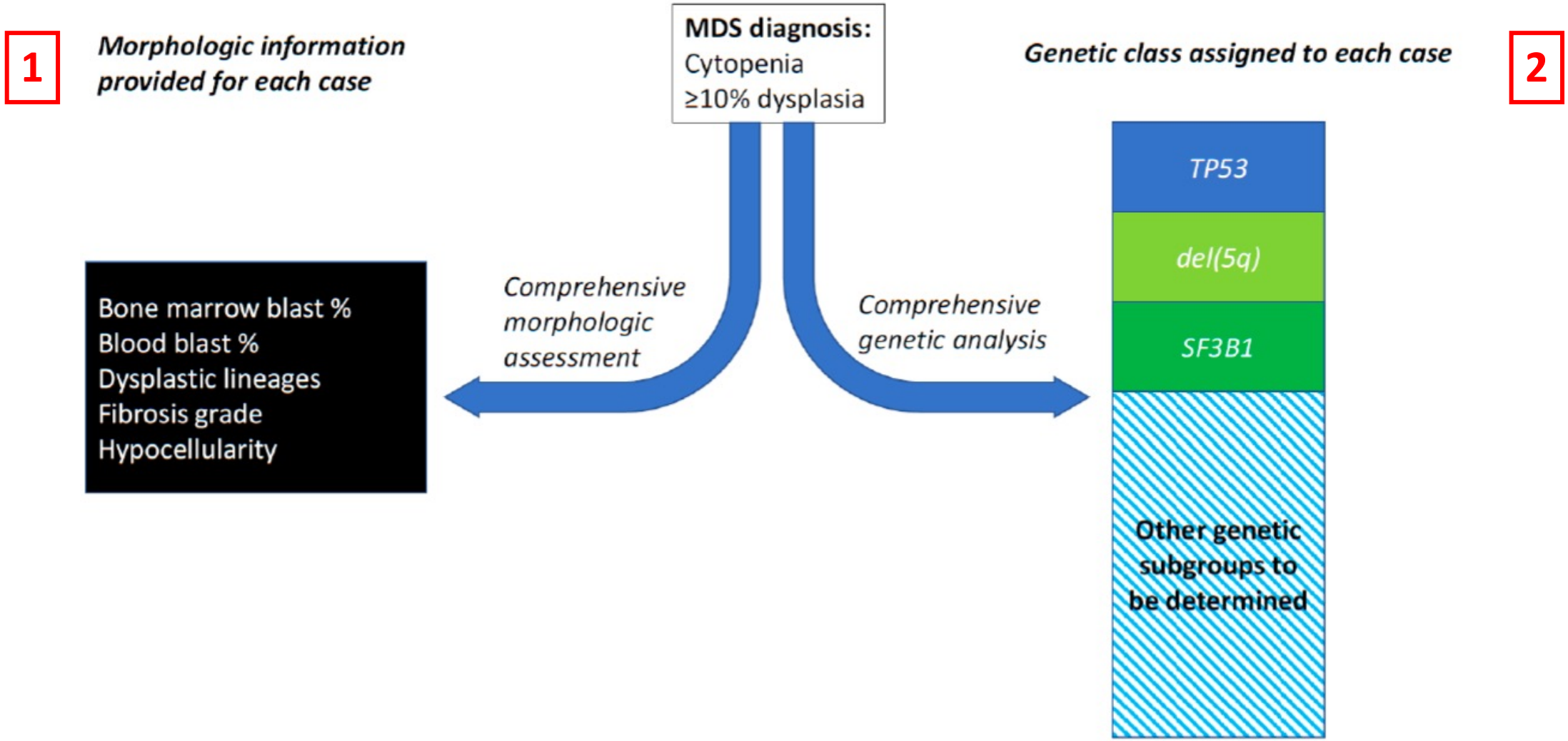
MDS with increased blasts (MDS-IB) type I (WHO 2022)
MDS with excess blasts (MDS-EB) (ICC 2022)

2022-WHO classification of Myelodysplastic Syndromes

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
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 *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (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		

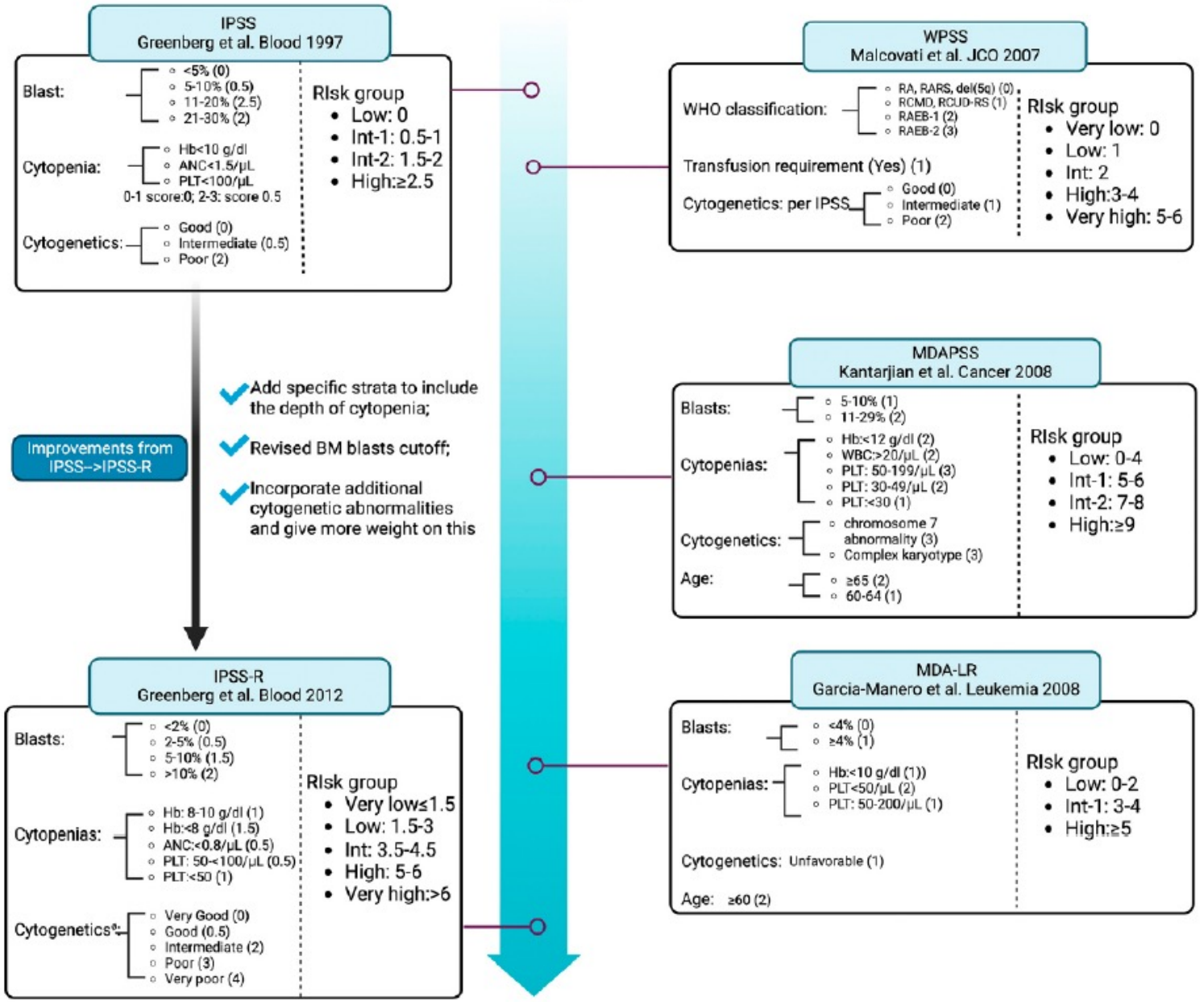
[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

2022-WHO classification of Myelodysplastic Syndromes



Hasserjian R, Germing U, Malcovati L. Blood 2023

Prognosi



Risk Stratification through the IPSS-R

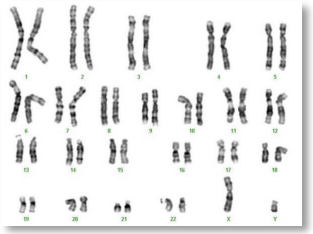
	Median Overall Survival *yr*	MDS Risk
Very low risk	8.8	Lower risk (IPSS-R score ≤3.5; median overall survival, 5.9 yr)
Low risk	5.3	
Intermediate	3.0	Higher risk (IPSS-R score >3.5; median overall survival, 1.5 yr)
High risk	1.6	
Very high risk	0.8	

Stahl M et al. Blood Rev 2023

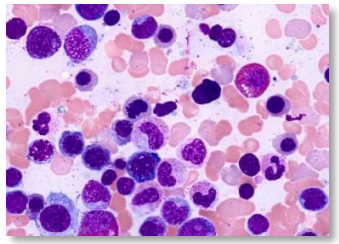
Prognosi: IPSS-R

	Prognostic score value						
	0	0.5	1	1.5	2	3	4
Prognostic category							
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blasts, %	≤ 2		> 2 to < 5		5–10	> 10	
Hgb, g/dL	≥ 10		8 to < 10	< 8			
Platelets, x 10^9/L	≥ 100	50 to < 100	< 50				
ANC, x 10^9/L	≥ 0.8	< 0.8					

Cytogenetic group	**Characteristics**
Very good	−Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), del(5q) + 1 additional abnormality
Intermediate	del(7q), +8, +19, i(17q), other abnormalities not in other groups
Poor	−7, inv(3)/t(3q), −7/del(7q) + 1 additional abnormality, complex (3 abnormalities)
Very poor	Complex (> 3 abnormalities)



Cariotipo normale



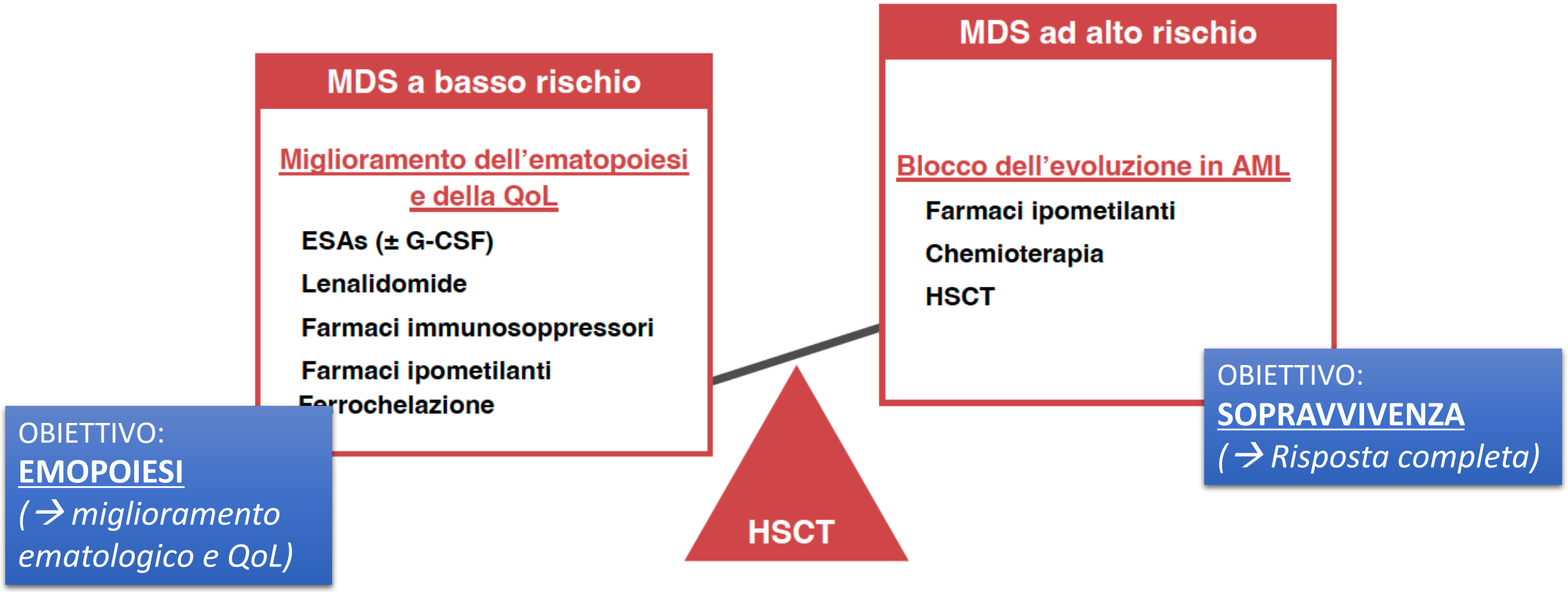
8% blasti

Pancytopenia

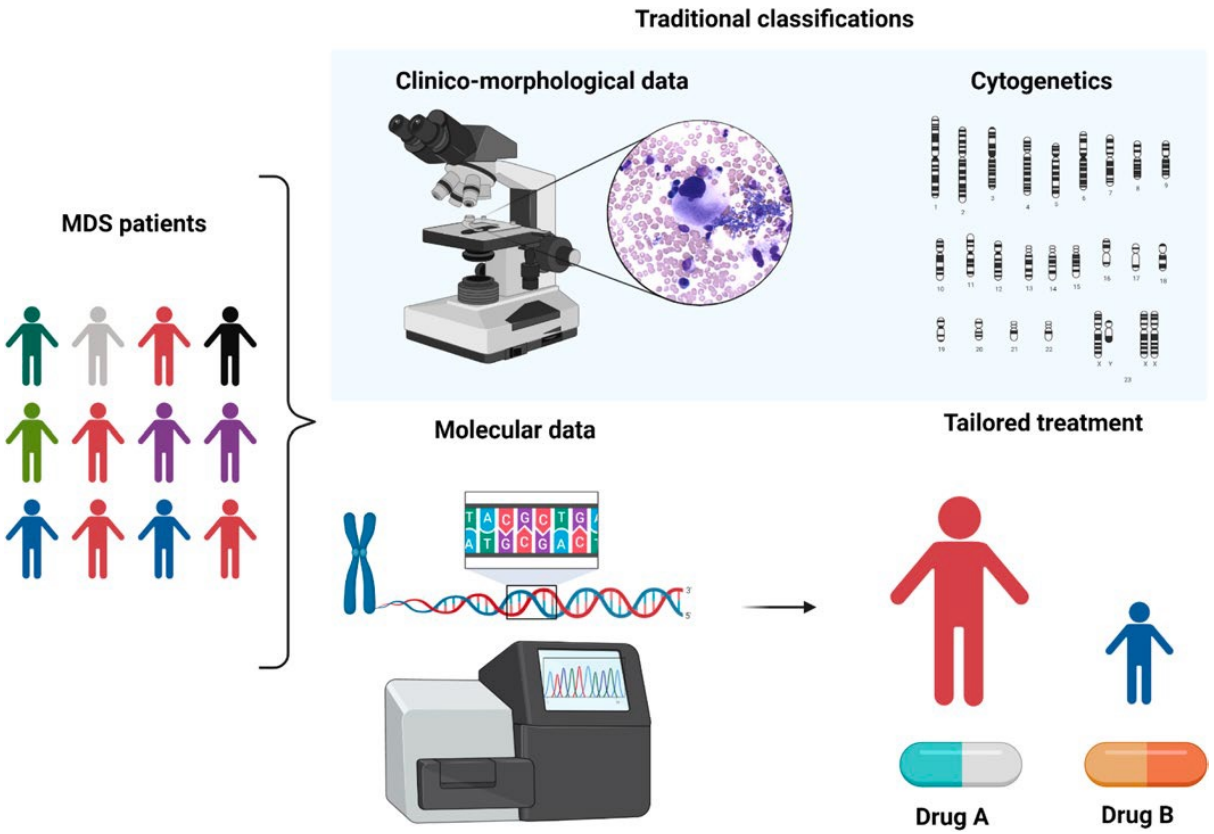
- Hb: 8.5 g/dL
- PLT: 26 x10^9/L
- GB: 2.7 x10^9/L

IPSS-R: 5 (=ALTO)

Terapia


MDS a basso rischio
Miglioramento dell'ematopoiesi e della QoL
ESAs (± G-CSF)
Lenalidomide
Farmaci immunosoppressori
Farmaci ipometilanti
Ferrochelazione
MDS ad alto rischio
Blocco dell'evoluzione in AML
Farmaci ipometilanti
Chemioterapia
HSCT
HSCT
OBIETTIVO:
EMOPOIESI
(→ miglioramento ematologico e QoL)
OBIETTIVO:
SOPRAVVIVENZA
(→ Risposta completa)

Terapia target



	Mutations	Frequency	Typical features	Treatment options
Favorable	*SF3B1*	30%	Ring sideroblasts	Luspatercept
Unfavorable	*TP53*	7-10%	Chromosomal aberrancies	APR-246, magrolimab
	ASXL1	20-23%	Epigenetic changes	Hypomethylating agents
	EZH2	7-10%		HSCT
Null	*IDH1*	2-3%	Differentiation block	Ivosidenib
	IDH2	4-5%		Enasidenib
Familiar predisposition	DDX41	1-3%	Monocytopenia, Lymphedema, Platelet disorders	Genetic counseling, HSCT, Preferential use of unrelated donors
	GATA2	<1%		
	ETV6	<1%		

Voso, Hematology 2021

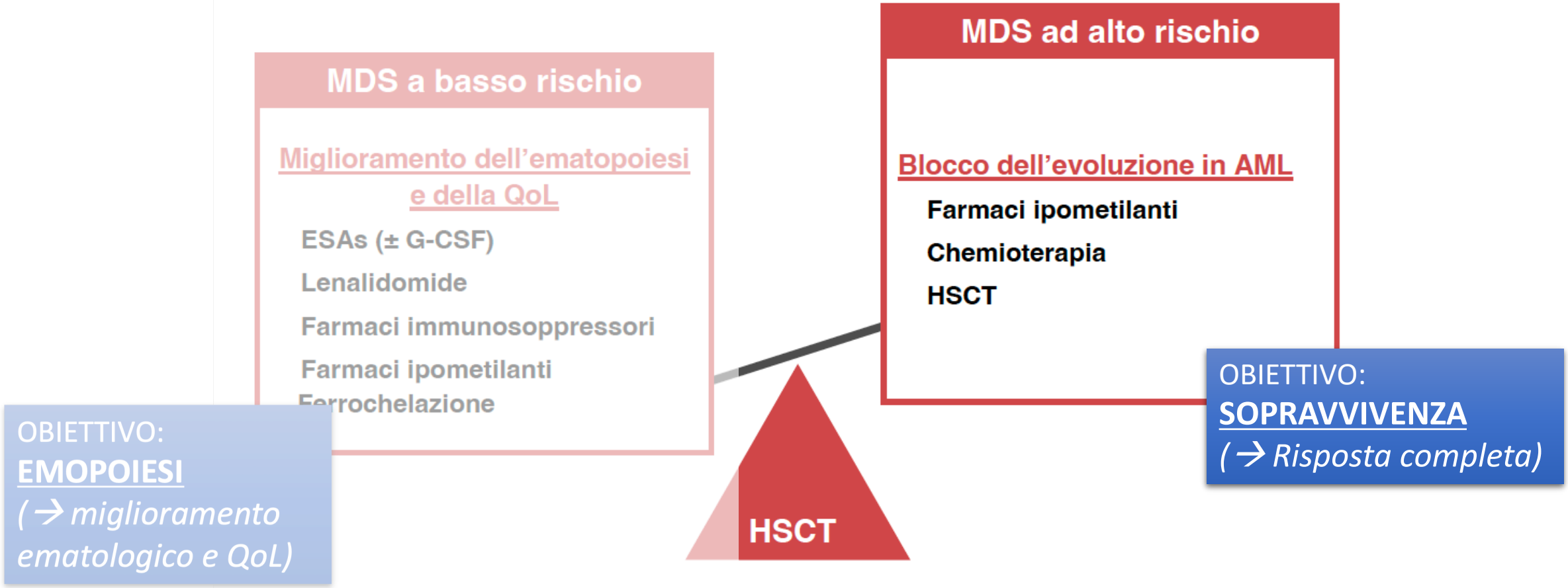
Back to the patient

- **70 anni**
- **2 figli in buona salute, non Fratelli**

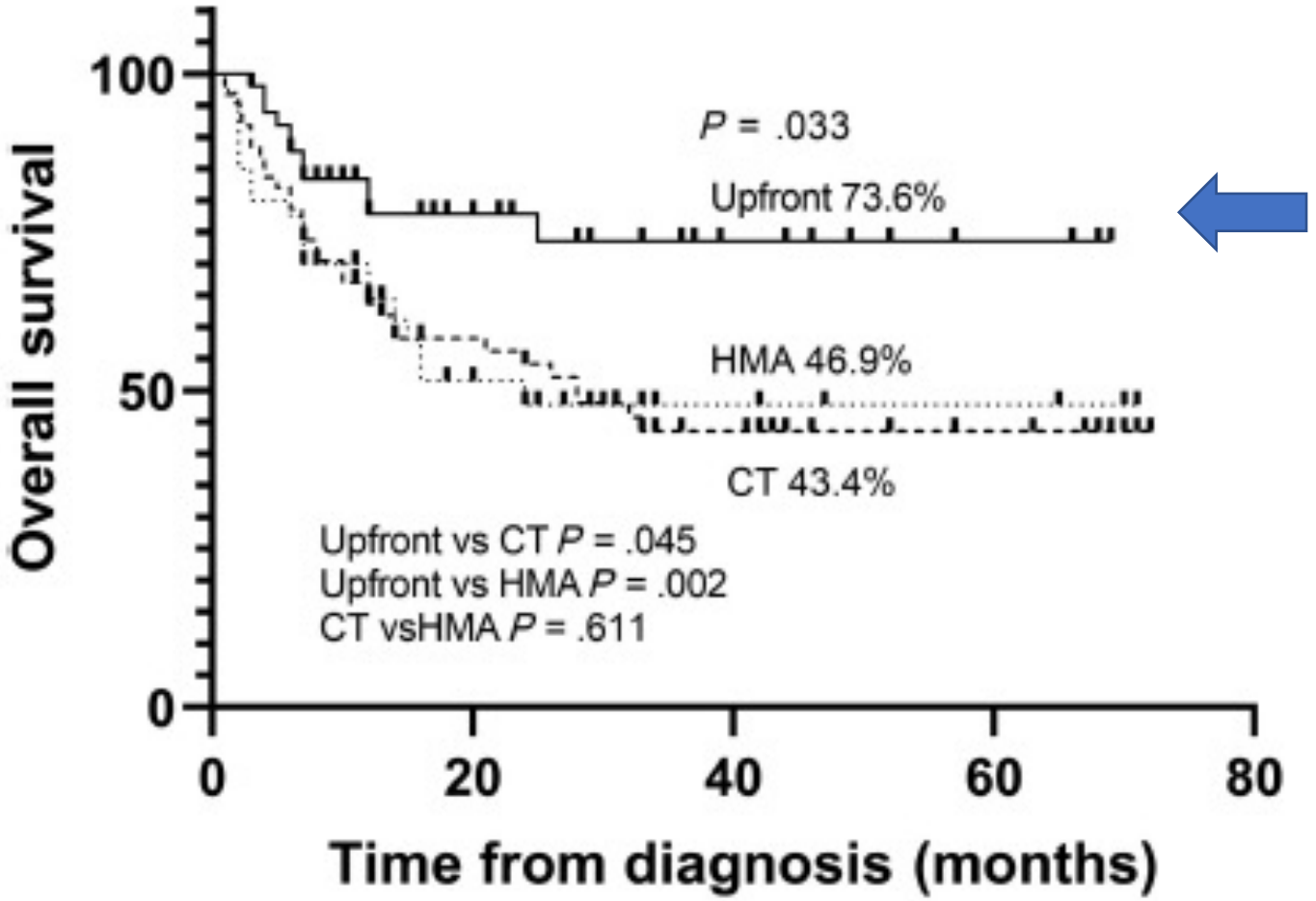
- **MDS with increased blasts (MDS-IB) type I (WHO 2022)**
  MDS with excess blasts (MDS-EB) (ICC 2022)
- **IPSS-R: ALTO**
- **PS: 90%**
- **Comorbidità:**
  - Precedente ischemia miocardica acuta
  - Diabete mellito in trattamento con ipoglicemizzanti orali (*Metformina*)
  - Tumore alla prostata 3 anni fa (chirurgia + chemio)

Quale trattamento?

Terapia

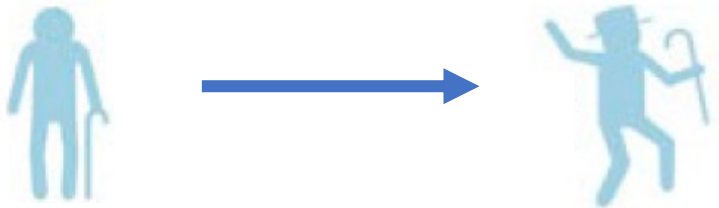

MDS a basso rischio
Miglioramento dell'ematopoiesi e della QoL
ESAs (± G-CSF)
Lenalidomide
Farmaci immunosoppressori
Farmaci ipometilanti
Ferrochelazione
MDS ad alto rischio
Blocco dell'evoluzione in AML
Farmaci ipometilanti
Chemioterapia
HSCT
HSCT
OBIETTIVO:
EMOPOIESI
(→ miglioramento ematologico e QoL)
OBIETTIVO:
SOPRAVVIVENZA
(→ Risposta completa)

MDS-IB1/MDS-EB: alloSCT frontline



Chen et al., Int. J. Cancer. 2021

Eligibility to alloSCT in elderly pts is challenging



Hematological malignancies ≥ 60 yr old

AlloSCT elegible

Patient's characteristics

FRAILTY

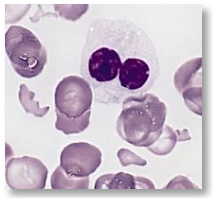
Age related vulnerabilities

Polypharmacy

Comorbidity

alloSCT elegibility

Disease characteristics



Disease risk

Previous treatment

Status Disease

- 70 anni
- 2 figli in buona salute, non Fratellii

- **MDS with increased blasts (MDS-IB) type I (WHO 2022)**
  MDS with excess blasts (MDS-EB) (ICC 2022)

- **PS: 90%**

SCORE	Our patient
SORROR / HCT-CI *Sorror, Blood, 2005*	5
FIL SCORE *Polverelli, BMT, 2020*	FIT
SIMPLIFIED COMORBIDITY INDEX *Shouval, Blood Advances, 2019*	2
CLINICAL FRAILTY SCORE *Rockwood, CMAJ, 2005*	2

Paziente elegibile a trapianto

↓

Trova un donatore da registro full matched

↓

Va a trapianto e ottiene RC