Impatto clinico delle nuove classificazioni delle condizioni mielodisplastiche e mieloproliferative

Antonello Cardoni

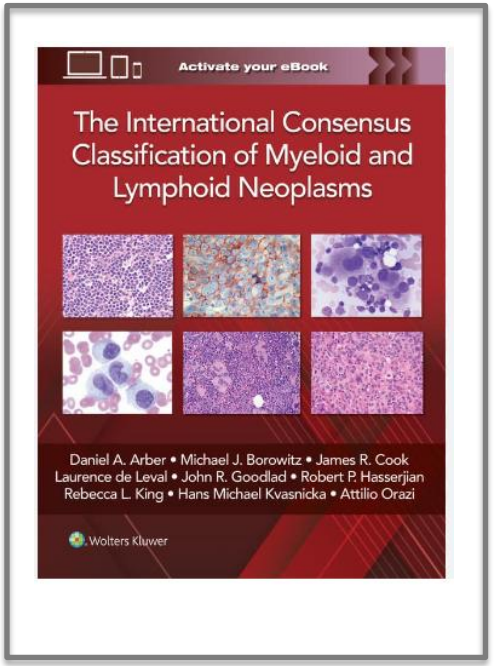
Anatomia Patologica, Ospedale Pediatrico Bambino Gesù, Roma

CONGRESSO NAZIONALE AIEOP
ROMA, 22-24 Settembre 2025
CENTRO CONGRESSI
UNIVERSITÀ CATTOLICA
DEL SACRO CUORE

Disclosures of Antonello Cardoni

I have no disclosures.

Current classifications of haematolymphoid tumours: WHO and ICC (2022 online v.)



Myelodysplastic condition: definition of RCC pattern

Table 20.1 Diagnostic criteria for refractory cytopenia of childhood (RCC)

1. **Persistent cytopenia**
   - **a.** Cytopenia is defined according to age-adjusted values for hemoglobin, absolute neutrophil count, and platelets.
   - **b.** Number of cytopenias[1-3]
2. **Presence of dysplastic changes in at least two lineages or in ≥10% in one lineage**

Specimen	Cellularity	Erythropoiesis	Granulopoiesis	Megakaryopoiesis *
Bone marrow aspirate		-nuclear budding -multinuclearity -megaloblastoid changes	-Pseudo-Pelger-Huët cells -hypo- or agranularity	- separated nuclear lobes -round monolobated nucleus -micromegakaryocytes
Bone marrow Biopsy	-patchy pattern in otherwise hypocellular marrow or - rarely diffuse pattern in normo- or hypercellular marrow**	-patchy (few multi- or unifocal cluster) -left-shift -increased mitosis	-marked decrease	-marked decrease or aplasia -round monolobated nucleus - separated nuclear lobes -micromegakaryocytes

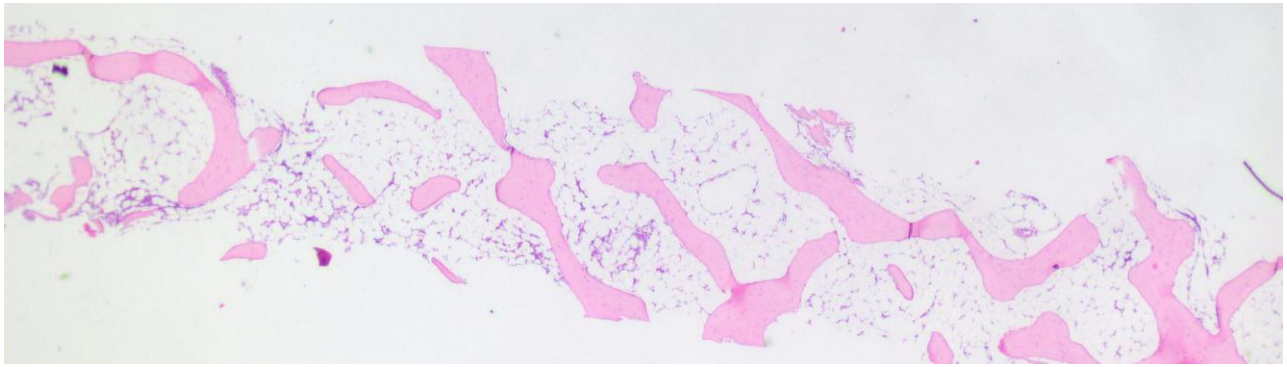
*immunohistochemistry for megakaryocyte markers is required on the biopsy

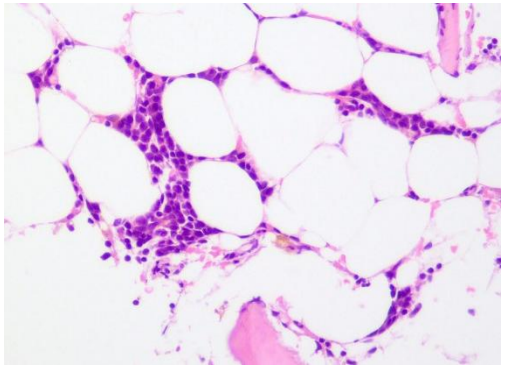
** normo- or hypocellular RCC requires significant dysplasia in megakaryocytes (≥10%)

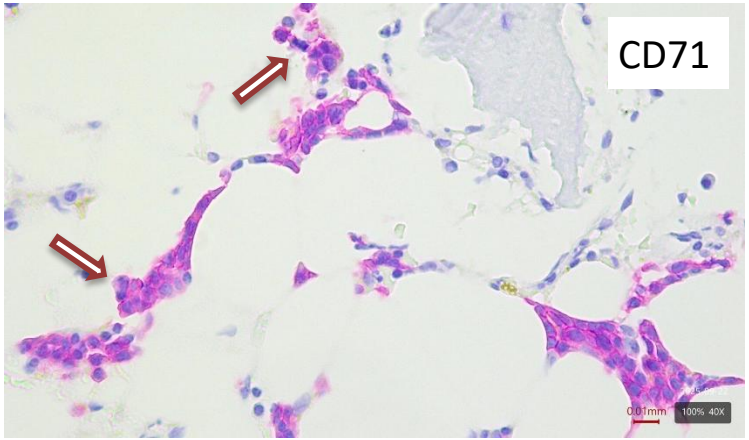
3. **Other criteria**
   - **a.** Blast percentage in peripheral blood <2% and bone marrow <5%
   - **b.** No prior cytotoxic chemotherapy or radiation therapy
   - **c.** No fibrosis

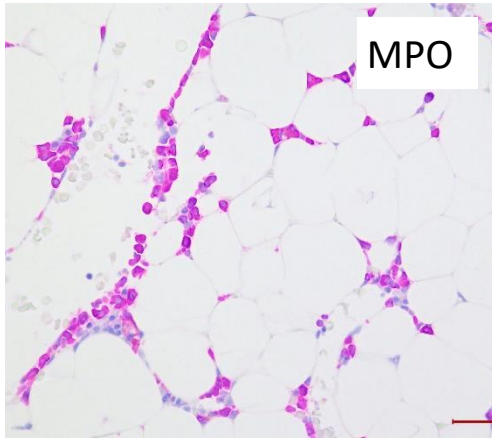
Rudelius M. et al., Virchows Archiv 2023

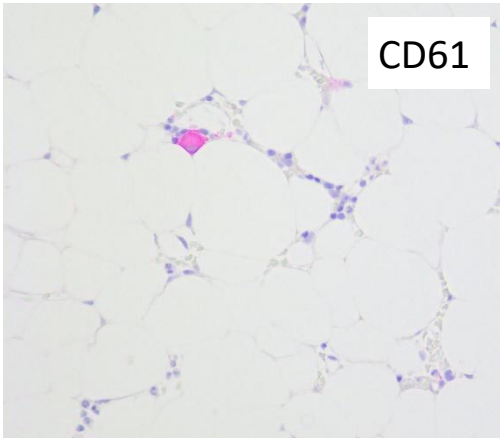
RCC pattern in bone marrow biopsy



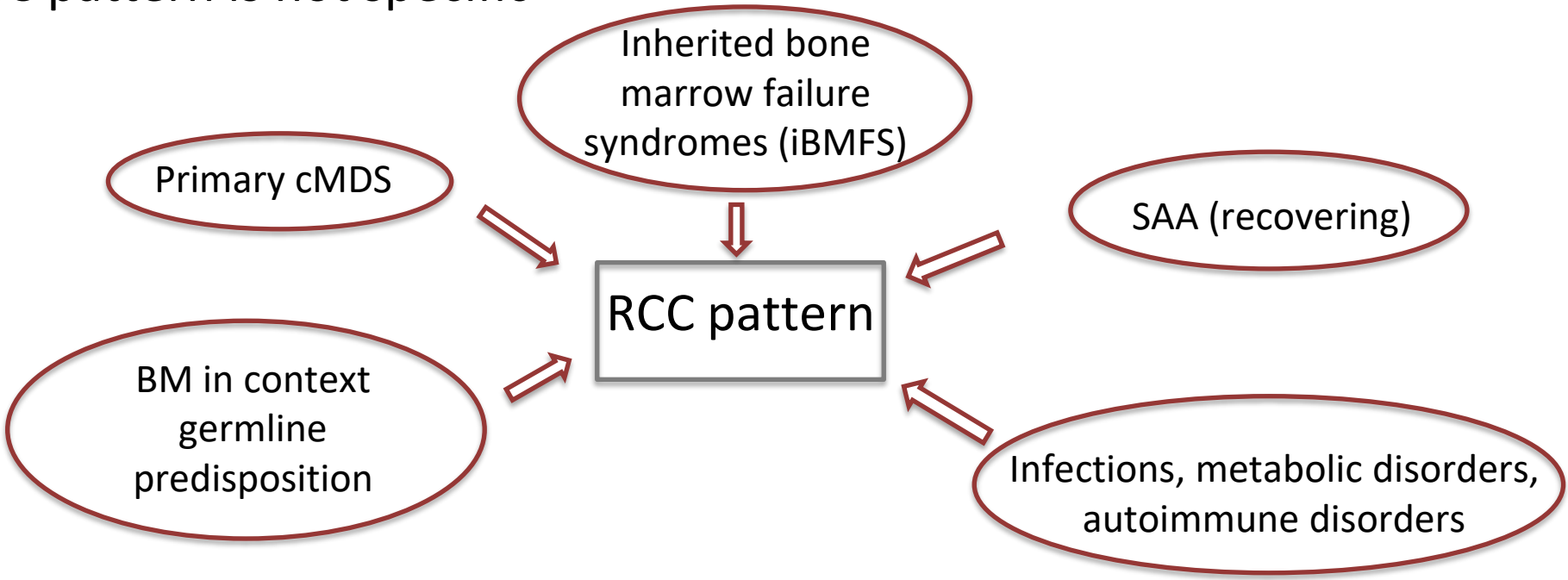








RCC pattern is not specific



Final diagnosis need an integrated approach
(clinical, histological, molecular)

Dinstinction between primary and secondary neoplasms

WHO (Adult) Classification	WHO (Pediatric) Classification	ICC Classification
		SECTION 6 Pediatric and/or Germline Disorders 159
Myelodysplastic neoplasms	**Myeloid neoplasms**	
Myelodysplastic neoplasms of childhood Childhood myelodysplastic neoplasm with low blasts Childhood myelodysplastic neoplasm with increased blasts	*Myelodysplastic syndromes* Refractory cytopenia of childhood (childhood myelodysplastic neoplasm with low blasts) Myelodysplastic syndrome with excess blasts (childhood myelodysplastic neoplasm with increased blasts)	20 Refractory Cytopenia of Childhood and Pediatric Myelodysplastic Syndromes 166
Secondary myeloid neoplasms *Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions* Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions: Introduction Myeloid neoplasm post cytotoxic therapy Myeloid neoplasms associated with germline predisposition Myeloid proliferations associated with Down syndrome	*Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions* Myeloid neoplasms associated with germline predisposition Myeloid proliferations associated with Down syndrome	21 Hematologic Malignancies With Germline Predisposition 171

Hematologic neoplasms with germline predisposition

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems
- Myeloid neoplasms with germline *CEBPA* mutation
- Myeloid or lymphoid neoplasms with germline *DDX41* mutation
- Myeloid or lymphoid neoplasms with germline *TP53* mutation

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
- Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
- Myeloid neoplasms with germline *ANKRD26* mutation
- Myeloid or lymphoid neoplasms with germline *ETV6* mutation

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
- Myeloid neoplasms with germline *GATA2* mutation
- Myeloid neoplasms with germline *SAMD9* mutation
- Myeloid neoplasms with germline *SAMD9L* mutation
- Myeloid neoplasms associated with bone marrow failure syndromes
  - Fanconi anemia
  - Shwachman-Diamond syndrome
  - Telomere biology disorders including dyskeratosis congenita
  - Severe congenital neutropenia
  - Diamond-Blackfan anemia
- Myeloid or lymphoid neoplasms associated with Down syndrome

⇒

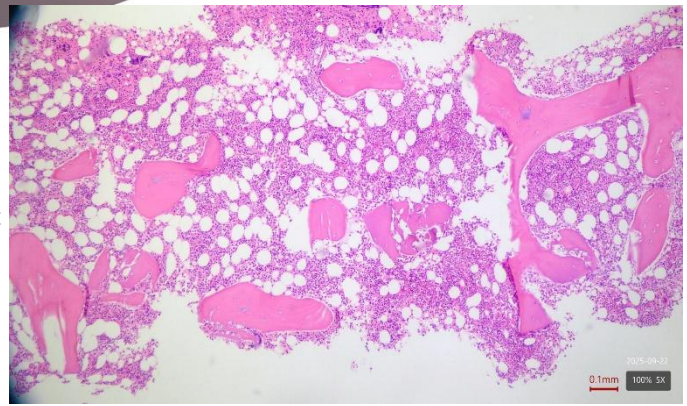
- **Baseline dyshematopoiesis** (must be differentiated from overt MDS)
- May have variable clinical / morphological expressivity and risk of progression

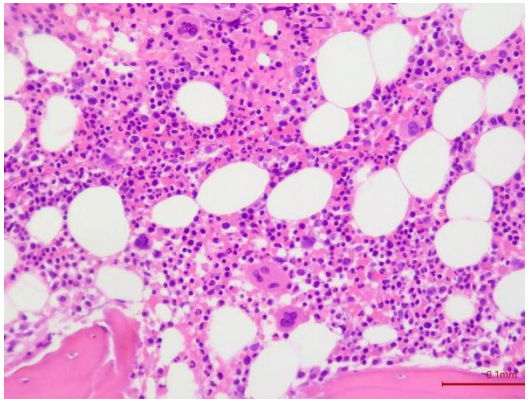
⇩

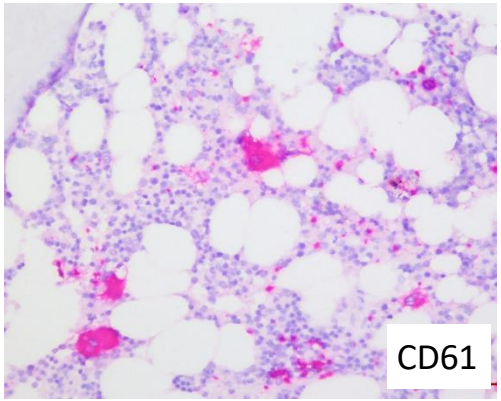
Clinico-pathological-molecular follow-up

Rudelius M. et al., Virchows Archiv 2023

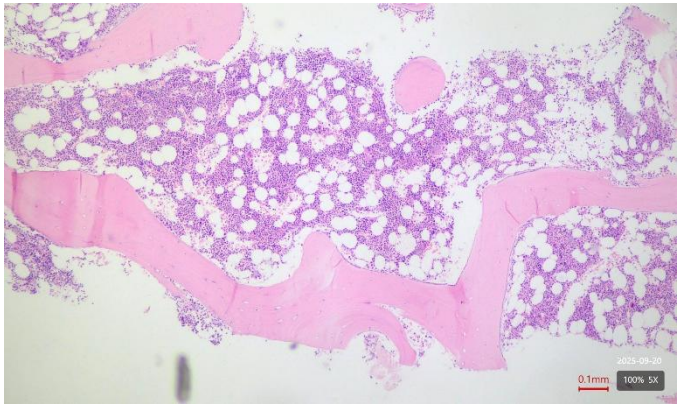
2022
GATA2 mut
Normal CBC
Normal karyiotype

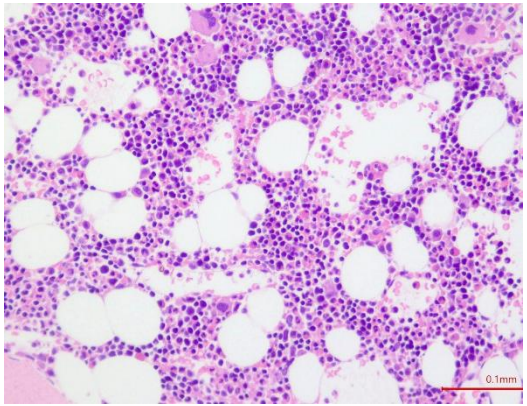


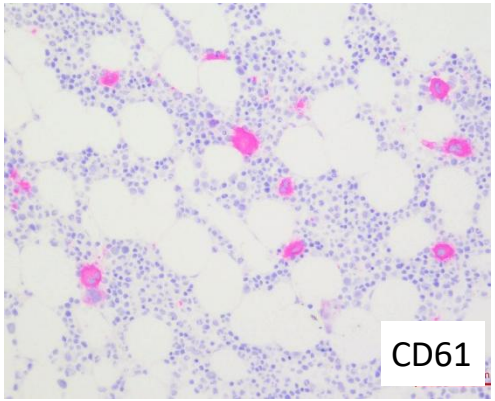




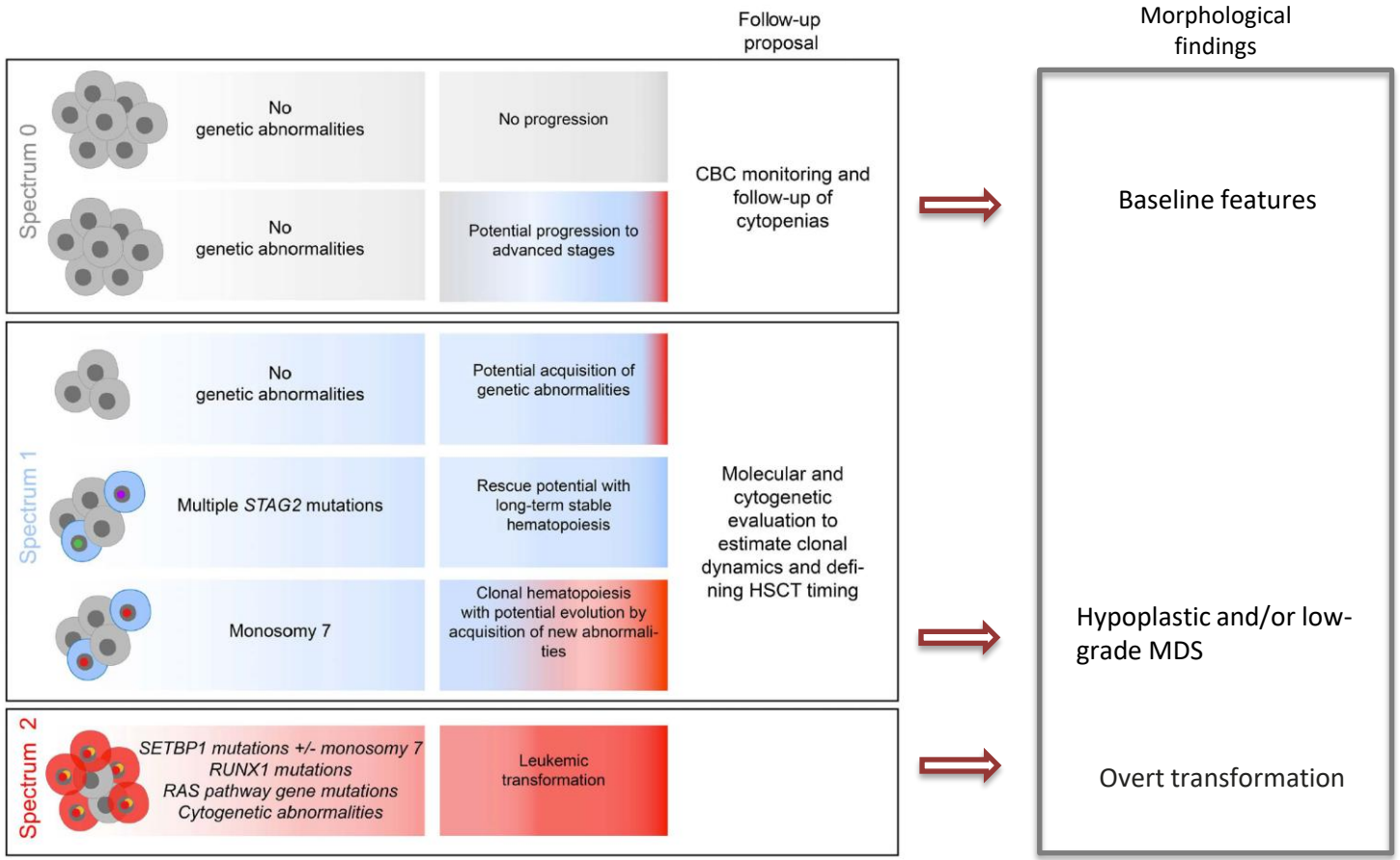
2024
GATA2 mut
Normal CBC
Normal karyiotype



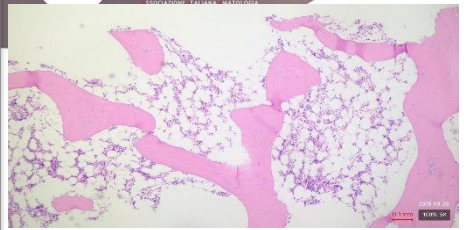




GATA2 deficiency – associated somatic alterations and progression

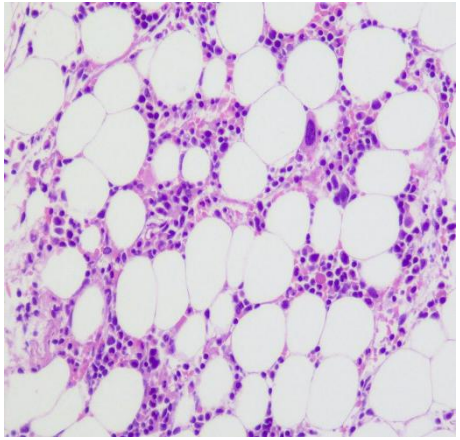


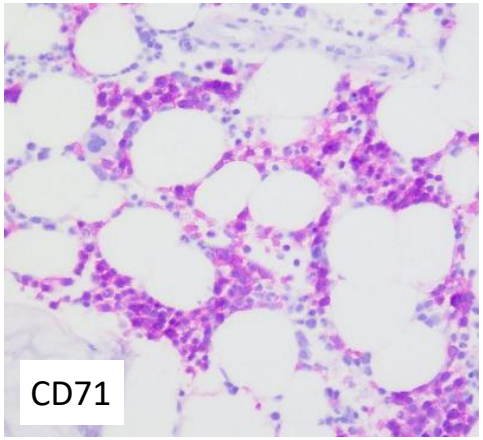
Largeaud L et al., Haematologica. 2023

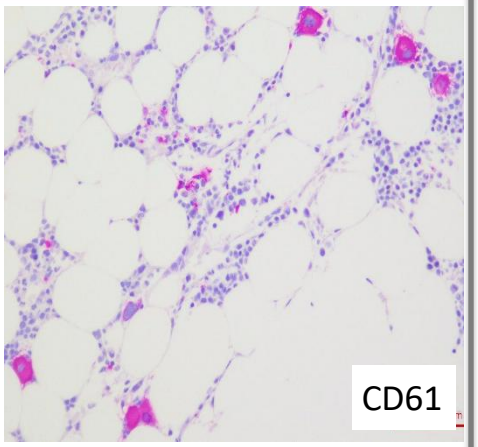


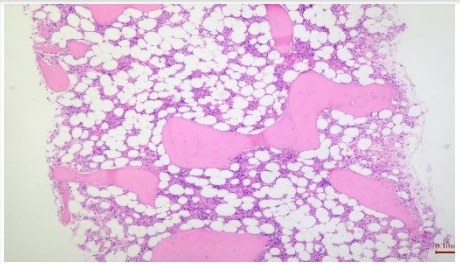
Patient 1)

SAMD9L mut
No other alterations
CBC stable
Watch and wait



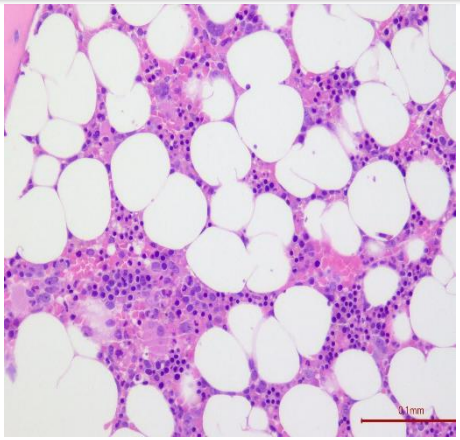


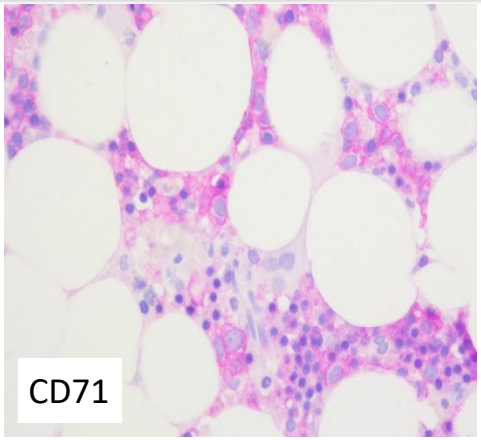


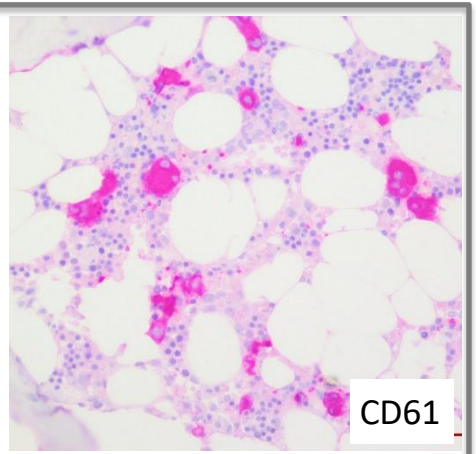


Patient 2)

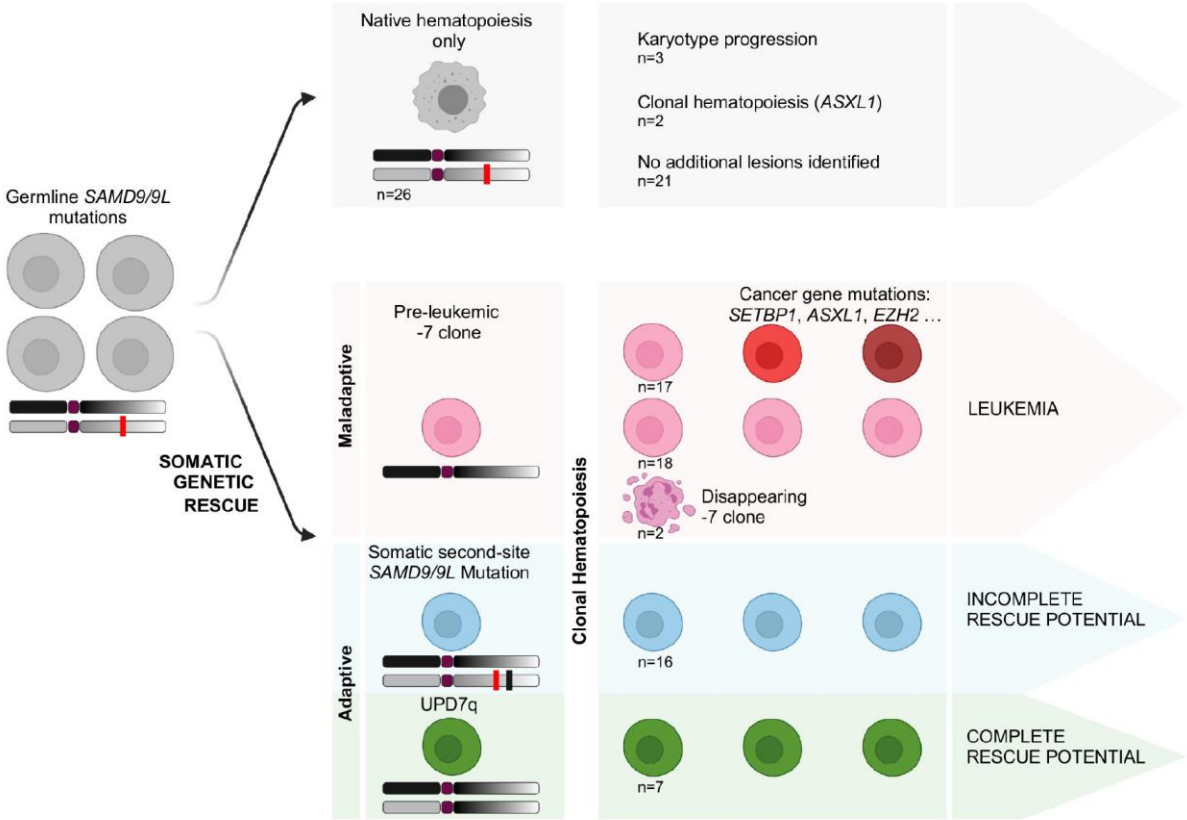
SAMD9L mut
Chr 7 loss
HSCT







SAMD9/SAMD9L syndrome associated somatic alterations and somatic genetic rescue



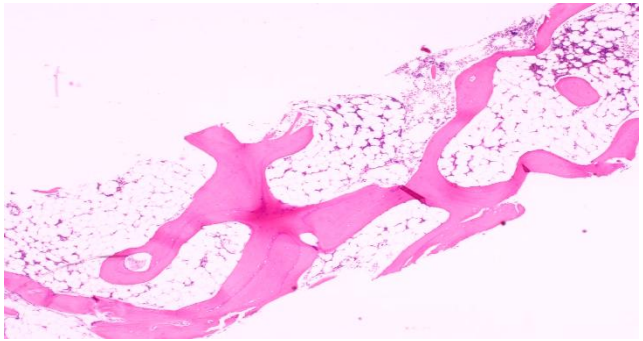
Possible outcomes:

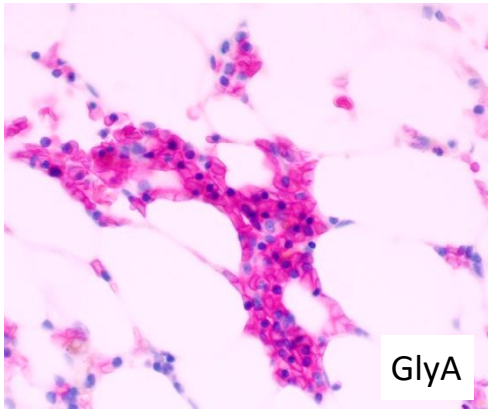
- Stable disease
- Remission
- High risk / progression

⇩

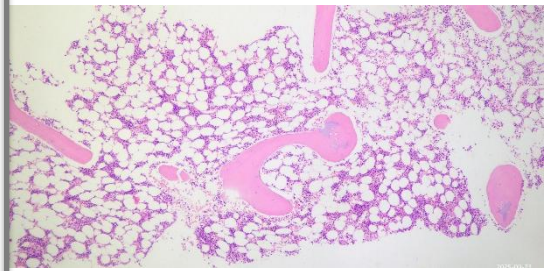
Clinical implications

Sahoo SS et al., Nat Med. 2021

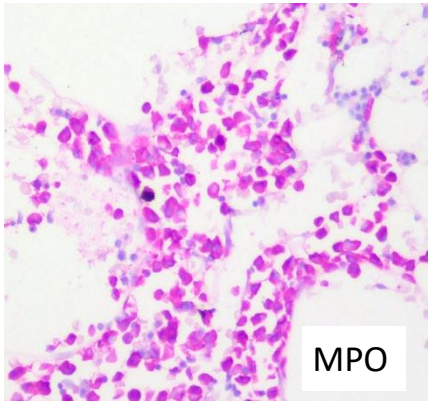


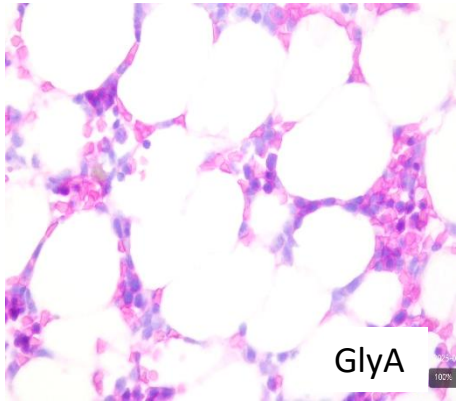


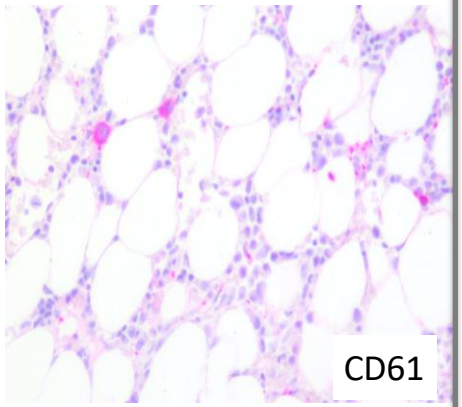
Fanconi Anemia (IBMFS)



Shwachman-Diamond syndrome (IBMFS)







When to consider MDS progression in patients with germline predisposition?

Table 2 Features associated with progression to myelodysplastic syndrome in patients with germline predisposition (these are guidelines and are not intended as absolute criteria; clinical judgement must be applied in each case

Two out of three of the following:

- Acquired pathogenic genetic alteration
- Monosomy 7, monosomy 5, del(7q), del(5q), multi-hit *TP53* mutations (defined as 2 or more distinct *TP53* mutations each with VAF ≥ 10%, or a single *TP53* mutation with (1) 17p deletion on cytogenetics, (2) VAF of ≥ 50%, or (3) copy neutral LOH at the 17p*TP53* locus), *TP53* mutation (VAF ≥ 10%) and complex karyotype (often with loss of 17p), or *SF3B1* mutation (VAF ≥ 10%) are considered MDS-defining**
- Cytopenia in a new lineage(s) or progressive cytopenia***, particularly in the context of increasing marrow cellularity
- Multilineage dysplasia****

Or:

- Increased blasts

oo ≥ 5% in marrow; ≥ 2% in peripheral blood

Rudelius M. et al., Virchows Archiv 2023

Classification of primary MDS

WHO (Adult) Classification

Myelodysplastic neoplasms

Myelodysplastic neoplasms of childhood

- Childhood myelodysplastic neoplasm with low blasts
- Childhood myelodysplastic neoplasm with increased blasts

Secondary myeloid neoplasms

Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions

- Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions: Introduction
- Myeloid neoplasm post cytotoxic therapy
- Myeloid neoplasms associated with germline predisposition
- Myeloid proliferations associated with Down syndrome

WHO (Pediatric) Classification

Myeloid neoplasms

Myelodysplastic syndromes

- Refractory cytopenia of childhood (childhood myelodysplastic neoplasm with low blasts)
- Myelodysplastic syndrome with excess blasts (childhood myelodysplastic neoplasm with increased blasts)

Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions

- Myeloid neoplasms associated with germline predisposition
- Myeloid proliferations associated with Down syndrome

ICC Classification

SECTION 6 Pediatric and/or Germline Disorders 159

20 Refractory Cytopenia of Childhood and Pediatric Myelodysplastic Syndromes 166

21 Hematologic Malignancies With Germline Predisposition 171

WHO (Adult) Classification	ICC Classification
• **Childhood myelodysplastic neoplasm** with low blasts (cMDS-LB) (blasts <5% BM, <2% PB) - cMDS-LB, hypocellular (*Acceptable:* refractory cytopenia of childhood)	• **Refractory cytopenia of childhood** (RCC) (blasts <5% BM, <2% PB)
- cMDS-LB-NOS*	• Myelodysplastic syndrome (NOS)*
• Childhood myelodysplastic neoplasm with increased blasts (cMDS-IB) (≥ 5% and < 20% in BM and/or ≥ 2% and < 20% in PB)	• MDS with excess blasts (MDS-EB) (≥ 5% and < 20% in BM and/or ≥ 2% and < 20% in PB)

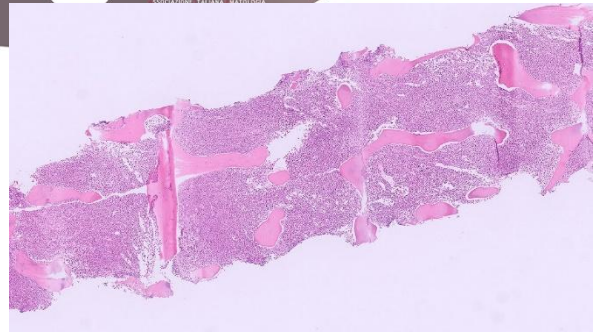
*pediatric MDS without excess blasts that do not present with the histomorphological pattern of RCC; cases with monosomy 7 and del(7q) in the absence of cytopenia and/or dysplasia

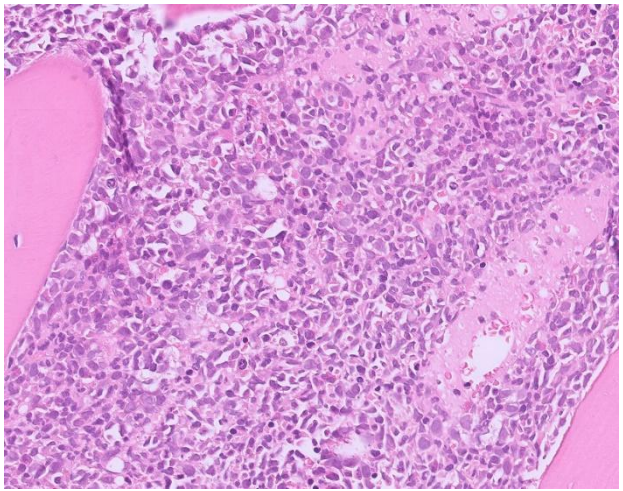
cMDS-LB / RCC - Essential criteria

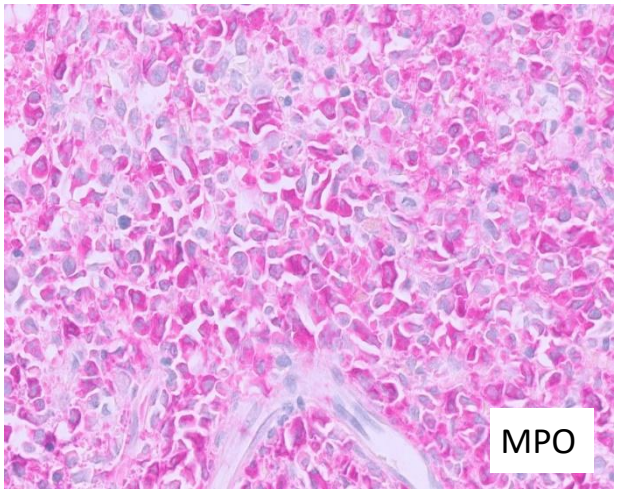
- Persistent cytopenia (≥1 lineage)
- Dysplastic changes in at least two hematopoietic lineages or in ≥ 10% of cells in one lineage (main dd with severe aplastic anemia - SAA) (histological pattern of RCC in about 80% of cases)
- No blast excess
- At least one of the following two criteria:
  (1) detection of clonal cytogenetic and/or molecular abnormality
  (2) **exclusion** of other causes of cytopenia (non-neoplastic - infection, metabolic disorders, autoimmune diseases - and germline mutations)

Childhood myelodysplastic neoplasm with increased blasts (cMDS-IB) – Diagnostic criteria

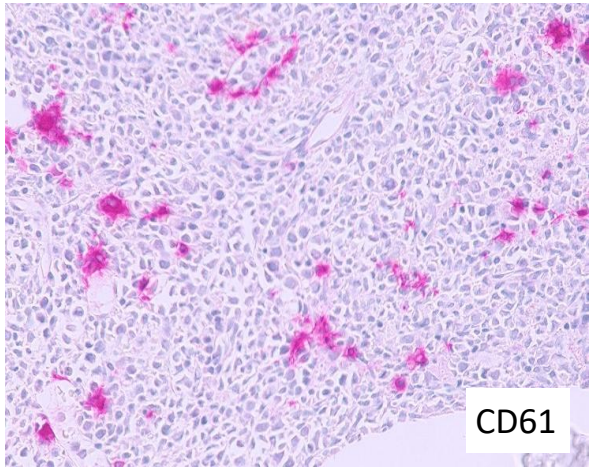
- Cytopenia (≥1 lineage)
- Dysplasia (≥1 lineage)
- ≥ 5% and < 20% blasts in BM and/or ≥ 2% and < 20% blasts in PB
- Exclusion of Down Syndrome and Juvenile myelomonocytic leukaemia
- Exclusion of **acute myeloid leukaemia (AML) with defining genetic abnormalities** (and with current <20% threshold for diagnosis, i.e. $NPM1_{mut}$, KMT2A-r, bi-allelic $CEBPA_{mut}$, multi-hit TP53), crucial for therapy decision
- *Desirable*: clonal cytogenetic and/or molecular abnormality (more frequently than cMDS-LB - commonly in RAS pathway)

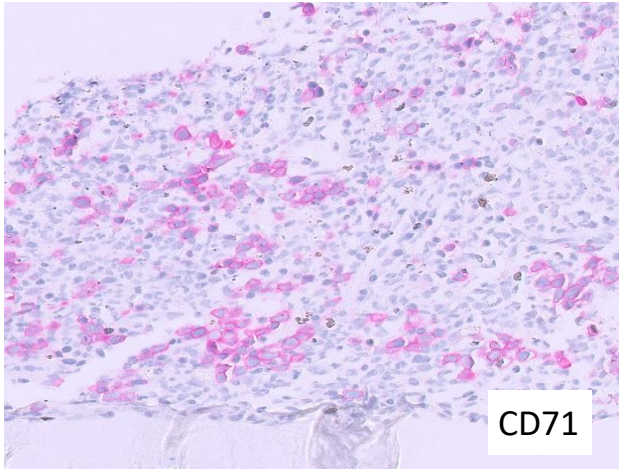


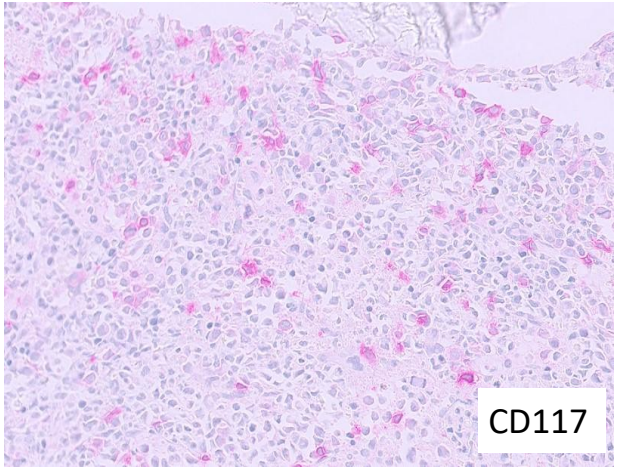




cMDS-IB with *UBTF-TD*







Myeloid neoplasm post cytotoxic therapy – a different group

Secondary myeloid neoplasms

Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions

- Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions: Introduction
- Myeloid neoplasm post cytotoxic therapy
- Myeloid neoplasms associated with germline predisposition
- Myeloid proliferations associated with Down syndrome

Subtype(s)

Myelodysplastic neoplasm post cytotoxic therapy; myelodysplastic/myeloproliferative neoplasm post cytotoxic therapy; acute myeloid leukaemia post cytotoxic therapy

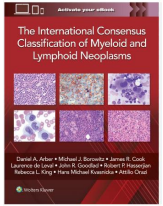
Juvenile myelomonocytic leukemia – a distinct pediatric entity

<u>JMML subtypes</u>:

- *PTPN11*-mutated
- *NRAS*-mutated
- *KRAS*-mutated
- *RRAS, RRAS2, RIT*-mutated
- JMML in neurofibromatosis type 1
- JMML in children with *CBL* syndrome

- Fusion-driven JMML (*ALK*, *PDGFRB*, *ROS1*, *FLT3*, and *PDGFRA)*

- JMML-like disorders in children with Noonan syndrome



- JMML (PTPN11, NRAS, KRAS, RRAS, NF1, CBL)

- JMML-like (ALK, ROS1, FIP1L1::RARA, CCDC88C::FLT31 rearrangements)

- Noonan syndrome–associated myeloproliferative disorder

Juvenile myelomonocytic leukemia – diagnostic criteria

WHO (Adult) Classification

Clinical, haematological, and laboratory criteria (all five criteria are required):

- Peripheral blood monocyte count ≥ 1×10^9/L
- Blast and promonocyte percentage of < 20% in peripheral blood and bone marrow
- Clinical evidence of organ infiltration, most commonly splenomegaly
- No Philadelphia (Ph) chromosome or *BCR::ABL1* fusion
- No *KMT2A* (*MLL1*) gene rearrangement

Genetic criteria (one criterion is required):

- Mutation in a component or a regulator of the canonical RAS pathway:
  - Clonal somatic mutation in *PTPN11*, *KRAS*, or *NRAS*[a], **or**
  - Clonal somatic or germline *NF1* mutation and loss of heterozygosity or compound heterozygosity of *NF1*, **or**
  - Clonal somatic or germline *CBL* mutation and loss of heterozygosity of *CBL*[b]
- Non-canonical clonal RAS pathway pathogenic variant[c] or fusions causing activation of genes upstream of the RAS pathway, such as *ALK*, *PDGFRB*, and *ROS1*

ICC Classification

Table 5 Diagnostic criteria for juvenile myelomonocytic leukemia

I. Clinical and hematologic features (the first two features are present in most cases; the last two are required)
- PB monocyte count ≥ 1×10^9/L[#]
- Splenomegaly[§]
- Blast percentage in PB and BM < 20%
- Absence of *BCR::ABL1*

II. Genetic studies (1 finding required)
- ••Somatic mutation in *PTPN11** or *KRAS** or *NRAS** or *RRAS**
- ••Germline *NF1* mutation and loss of heterozygosity of *NF1* or clinical diagnosis of neurofibromatosis type 1
- ••Germline *CBL* mutation and loss of heterozygosity of *CBL*†

[#]This monocyte threshold is not reached in approximately 7% of cases

[§]Splenomegaly is absent in 3% of cases at presentation

[*]Germline mutations (indicating Noonan syndrome) need to be excluded

[†]Occasional cases with heterozygous splice site mutations

Juvenile myelomonocytic leukemia – diagnostic criteria

WHO (Adult) Classification

Other criteria:

Cases that do not meet any of the genetic criteria listed above (or for which genetic testing is not available) must meet at least two of the following criteria in addition to the aforementioned clinical, haematological, and laboratory criteria:

- Increased haemoglobin F for age
- Myeloid (promyelocytes, myelocytes, metamyelocytes) and erythroid precursors on peripheral blood smear
- Thrombocytopenia with hypercellular marrow often showing a decreased number of megakaryocytes; dysplastic features may or may not be evident
- Hypersensitivity of myeloid progenitors to GM-CSF as tested in clonogenic assays in methylcellulose or by measuring STAT5 phosphorylation in the absence of or with a low dose of exogenous GM-CSF

(Monosomy 7 or any other chromosomal abnormality (WHO 4th ed.) ----> Removed)

ICC Classification

X

Acknowledgements:

Rita Alaggio, Rita De Vito, Sabrina Rossi, Alessandra Stracuzzi, Francesca Diomedi, Paola Francalanci, Silvia Vallese, Emma Rullo, Francesca Arienzo, Isabella Giovannoni, Sabina Barresi, Chantal Tancredi