Bone marrow failure syndrome: never ending story..

Speaker Dr Camilla Frieri
AORN Moscati Avellino and University of Naples Federico II
ERN-EuroBloodNet Topic on Focus BMF Syndromes
05 April 2022

Co-funded by
the Health Programme
of the European Union

EBMT

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

Conflicts of interest

Nothing to disclose

Practical issues before starting

- ✓ **30-35min presentation (30 slides max) + 15 min Q&A session**
- ✓ **Microphones will be muted by host to avoid back noise**
- ✓ **Please, stop your video to improve internet conexion**
- ✓ **Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.**

Learning objectives of the webinar

- ✓ How to make a diagnosis of constitutional BMF syndrome ?
- ✓ Which is the best therapeutic approach ?
- ✓ How to perform a correct follow-up? How to improve patient follow up?

Clinical case

October 2007: a 27-year-old female was admitted to our Unit…

The patient was pale, asthenic..

Laboratory tests:
WBC count 2,30 x10*9/L , PMN 1,5 x10*9/L
Hemoglobin 10 g/dL, MCV 112
Reticulocyte count 60x10*9/L
Platelet count 95x10*9/L

At physical examination:
Vital signs were normal
Heart, lungs and abdomen were normal

Weight 45 kg
Height 135 cm

Café au lait spots
Hypoplasia of the thumb
Right hearing loss
Congenital hip dislocation

Family history :
1 sister and 2 brothers
mother with colon cancer

No infections or bleeding
No potential exposures

Clinical case

Diagnostic path:

✓ Blood count	→ Macrocytic anemia, neutropenia, thrombocytopenia
✓ Peripheral blood smear	→ Anisocytosis, no pathological cells
✓ Research PNH clone	→ Negative
✓ HbF and alfa-fetus protein dosage	→ Slightly increased
✓ Autoimmune evaluation	→ Normal
✓ Hepatic and renal function	→ Normal
✓ Parvovirus serology	→ Negative
✓ Dosage vitamins	→ Normal

Clinical case

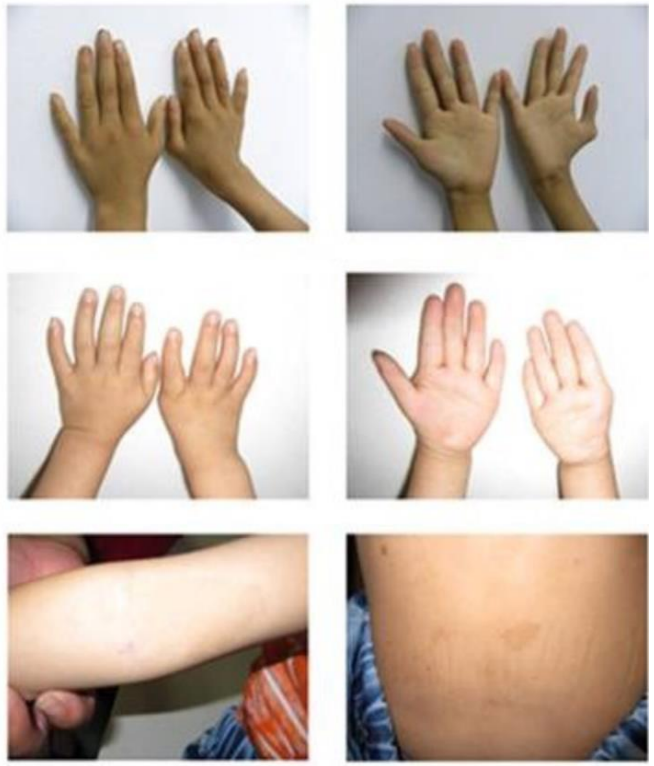
- ✓ **Bone marrow evaluation** → ✓ **Hypo cellularity, no evidence of dysplasia, without pathological cells and fibrosis**
  - ✓ **Karyotype 43 XX[3], 46 XX[8], with multiple chromosomal losses**
- ✓ **Chromosomal breakage analysis test on peripheral blood lymphocytes to DEB** → **Positive**
- ✓ **Molecular test** → **Mut. FANCA**

Clinical case

The patient was diagnosed with Fanconi Anemia

Fanconi anemia

Fanconi anemia (FA) is a rare, phenotypically heterogeneous, inherited disorder clinically characterized by



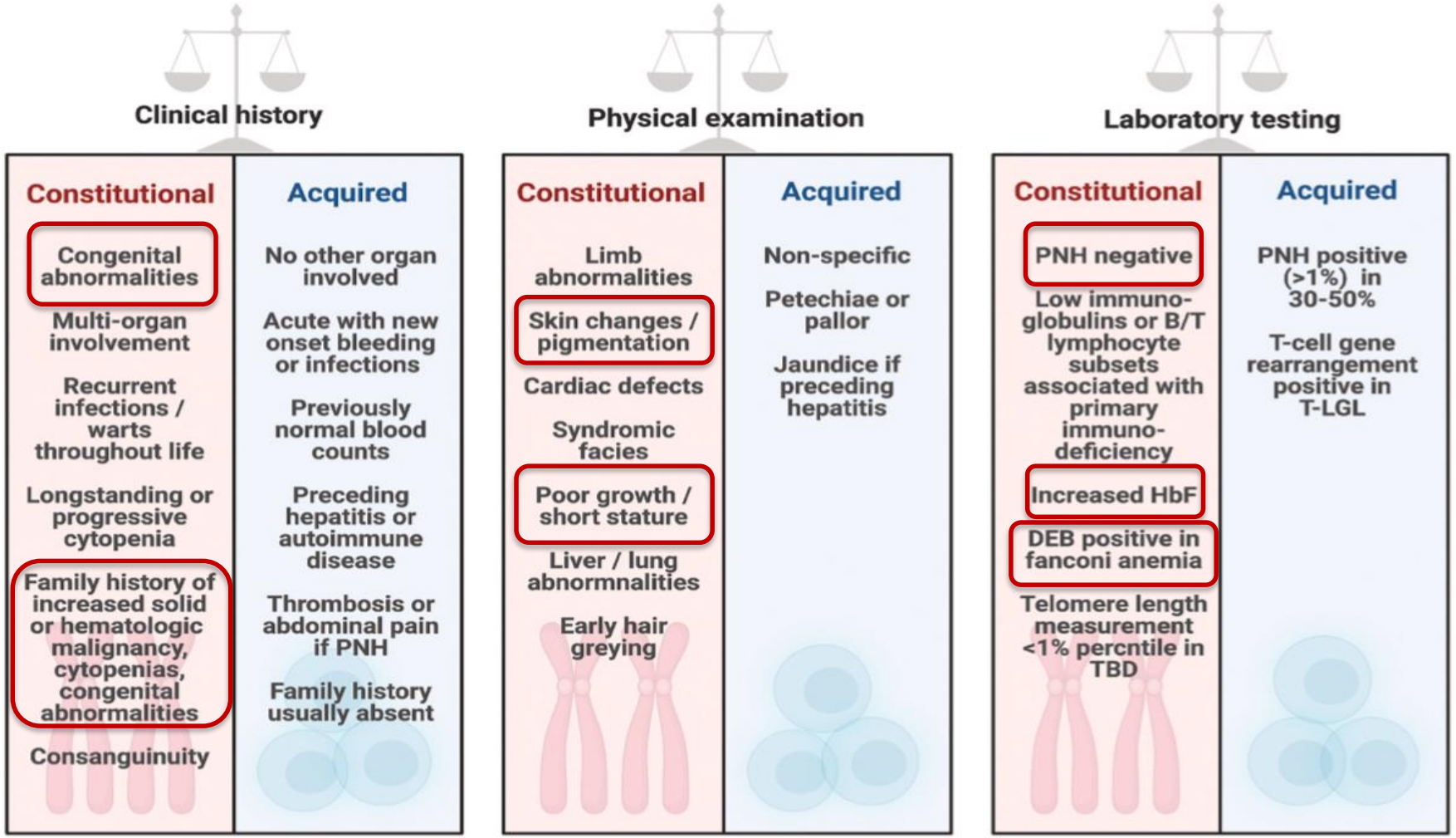
- ✓ **congenital abnormalities,**
- ✓ **progressive bone marrow failure (BMF),**
- ✓ **predisposition to develop malignancies, especially AML and squamous cell carcinoma.**

Fanconi anemia

- ✓ About 20 genes are reported to cause FA
- ✓ FA genes are transmitted as autosomal recessive (except FANCB X-linked and FANCR is AD)
- ✓ FANCA gene is mutated in about 65% of FA cases
- ✓ The proteins encoded by FA genes participate in a complicated network important in DNA repair

Fanconi anemia

E.M. Groarke et al. , 2021



BUT…PAY ATTENTION!!!

Fanconi anemia

30% of FA patients have no somatic abnormalities..

1. **Macrocytic anemia in absence of vitamins deficiency (in particular of B12 and folates)**

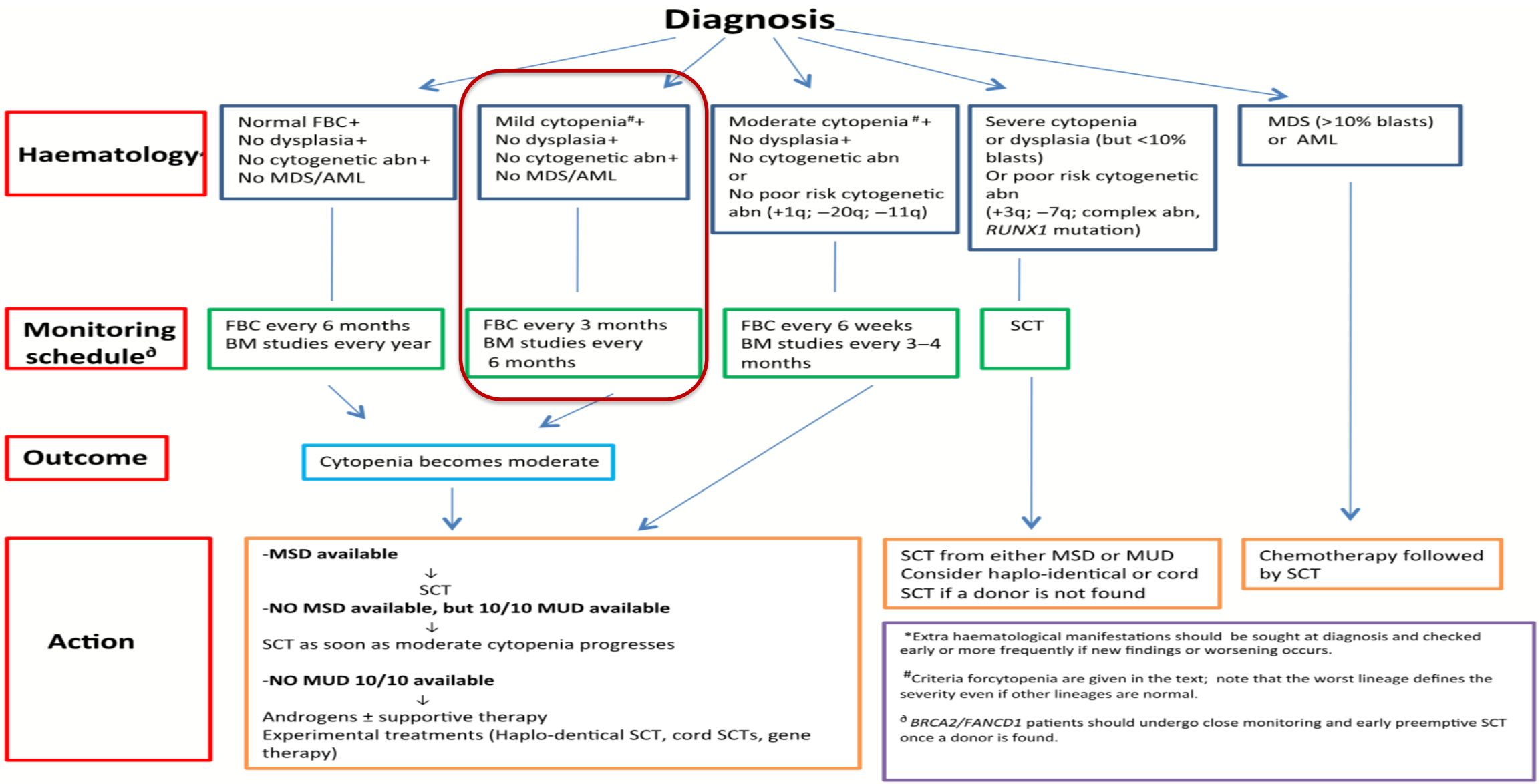
2. A negative PNH clone in a young patient with signs of BMF is strongly suggestive of a constitutional form.

3. Chromosome instability is a hallmark of FA cells

Fanconi anemia

Other screenings..

- ✓ Endocrinology evaluation
- ✓ Hearing and visual evaluation
- ✓ Skeletal evaluation
- ✓ Cardiac and abdominal ultrasound
- ✓ Chest X-ray



C. Dufour; British Journal of Haematology, 2017

Clinical case

The patient was lost to follow-up….

Clinical case

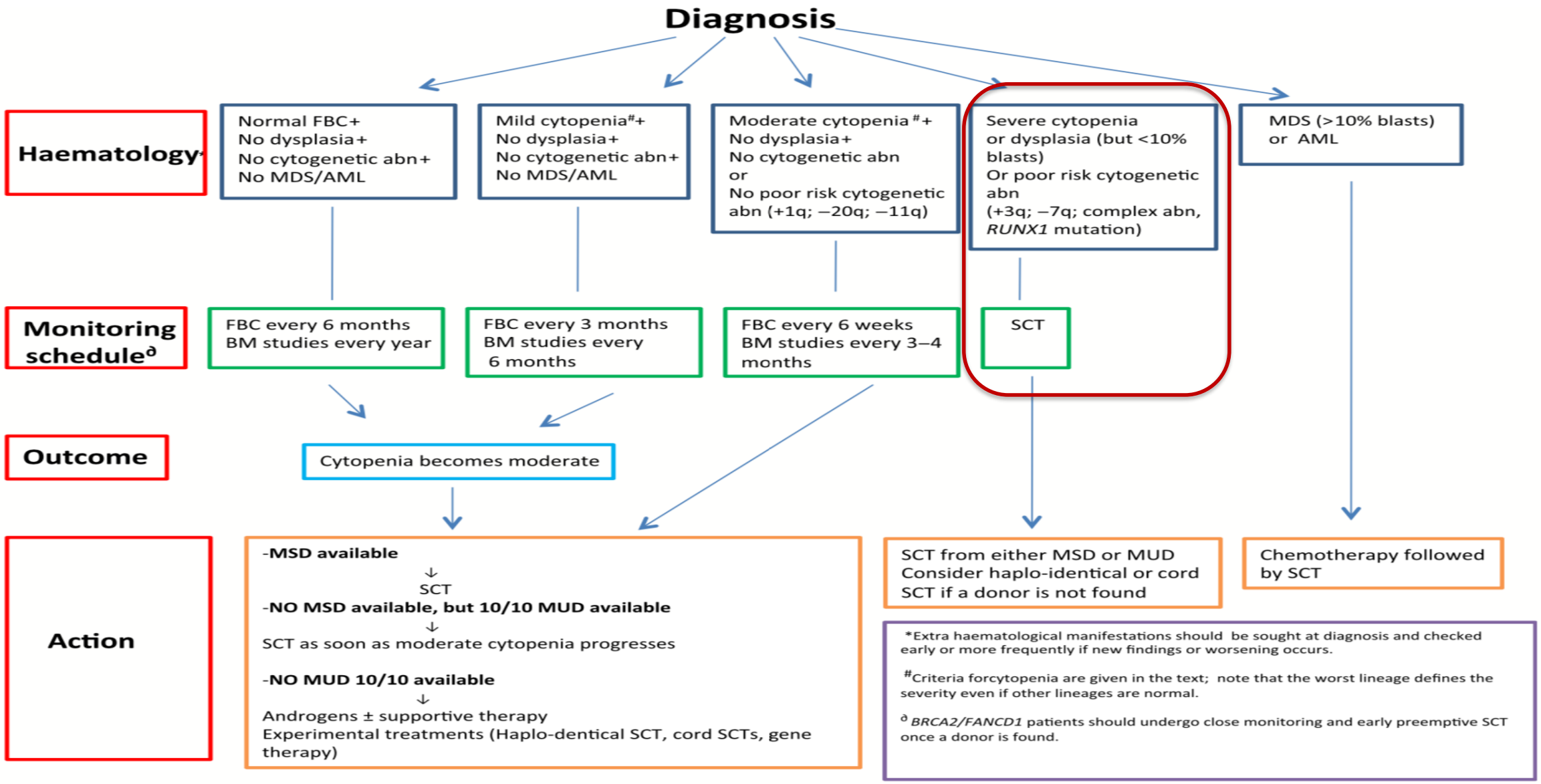
October 2011:

WBC count 2,0 x10*9/L , PMN 0,9 x10*9/L
Hemoglobin 8 g/dL, MCV 112 >>>> RBCs transfusions
Platelet count 45x10*9/L
Reticulocyte count 25x10*9/L

Bone marrow evaluation >> severe hypocellularity, signs of dysplasia, with no pathological cells.

The karyotype was the same as the diagnosis.

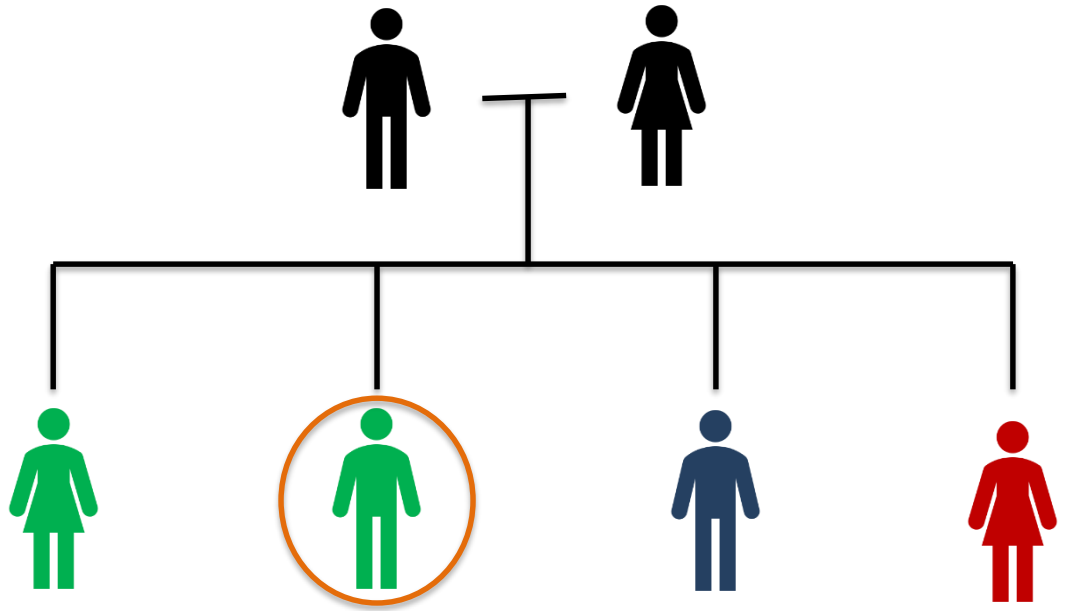
What to do next???



C. Dufour; British Journal of Haematology, 2017

Clinical case

- ✓ **Family evaluation**
  - ✓ **HLA typing**



- ✓ **Patient evaluation**
  - ✓ **PS, blood test , cardiac and renal function, spirometry..**

The patient was eligible for transplantation and she had a donor!

Clinical case

November 2011: **Hematopoietic stem cell transplantation**
Donor: HLA-sibling
Source: BM
ABO D/R : B pos/ B pos
CMV D/R : +/+
EBV D/R : +/+

Conditioning regimen: Fludarabine: 30mg/m2 day -4,-3,-2
Cyclophosphamide 10 mg/kg day -5,-4,-3,-2

GVHD prophylaxis: CsA 1mg/kg, adapted to blood levels
MMF 30 mg/Kg
ATG 3,75 mg/kg day -3,-2

EBV prophylaxis : Rituximab 200 mg day +5

Infections prophylaxis: Acyclovir, Fluconazole, Levofloxacin

Clinical case

24 November 2011 day 0
CNT: 10,887 x10^8/kg
CD34+: 16,3 x10^6/kg
CD3+: 61,8 x10^6/kg

Engraftment
PMN day +15
Platelets day + 18

Mucositis grade I-II

No signs of GVHD or infections during hospitalization

Clinical case

Day + 30

WBC count 3,96 x10*9/L , PMN 2,8 x10*9/L
Hemoglobin 11,6 g/dL,
Platelet count 190x10*9/L
Reticulocyte count 40x10*9/L

Renal and hepatic functions were normal.

CMV and EBV were negative.

Chimerism day +30 was full donor.

No signs of GVHD.

Fanconi anemia and BMT

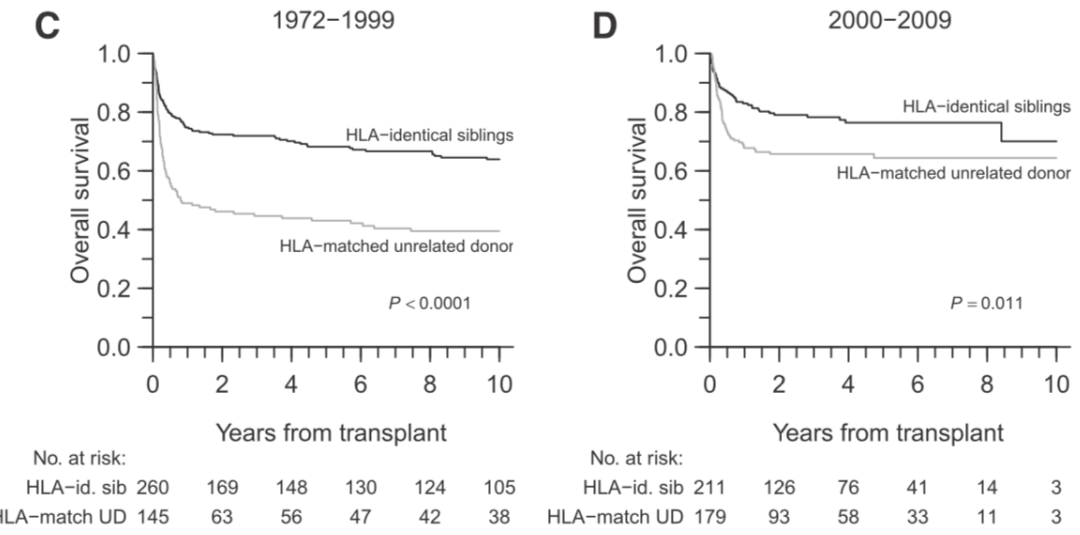
Hematopoietic stem cell transplantation still represents the only curative option for BMF

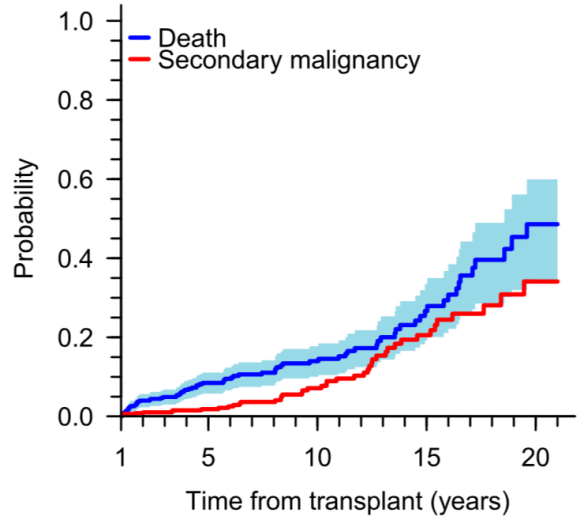
When?

- ✓ **Bone marrow failure (transfusion dependency, severe neutropenia)**
- ✓ **MDS, AML**
- ✓ **Consider the age of patient**

How?

- ✓ **Type of donor**
- ✓ **Use of Fludarabine**





Peffault de Latour et al, Blood 2013

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

News from EBMT 2022

EBMT 48th Annual Meeting
19-23 March 2022 | Prague Hybrid

Outcome of haematopoietic cell transplantation in 813 children with Fanconi anaemia: A study on behalf of the EBMT SAAWP and PDWP

Su Han Lum,et al.

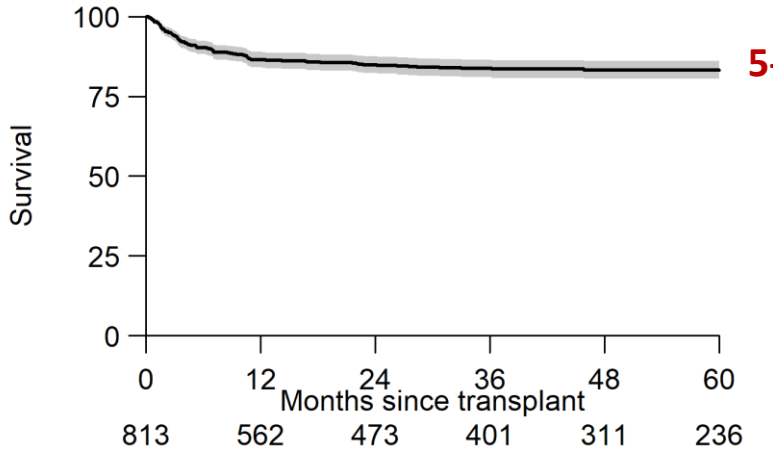
Retrospective cohort analyses

Study period: 2010 to 2018

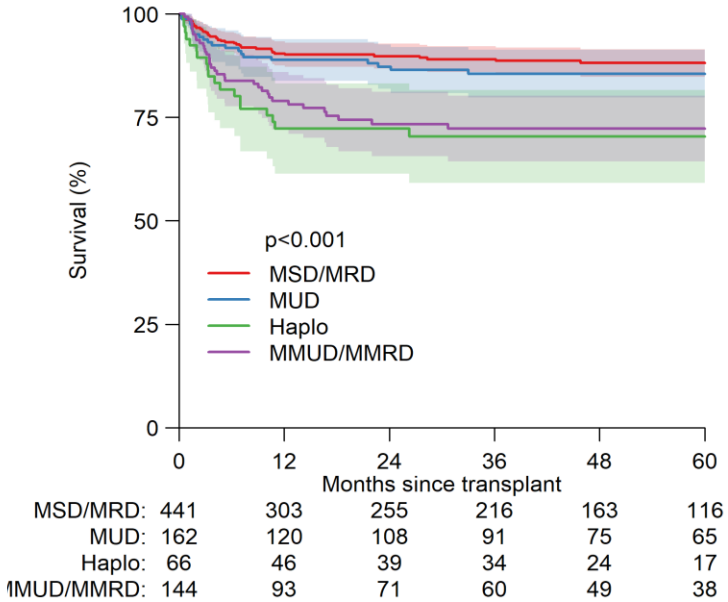
Inclusion criteria:

1.Age ≤18 years at time of HSCT

2.First transplant



5-year OS: 83% (80-86%)



Largest study on allo-HSCT in paediatric Fanconi anaemia

Improved OS (83%) and EFS (78%)

EFS and GRFS is higher in younger patients

OS/EFS/GRFS: MFD = MUD > MMUD/MMFD = Haplo

5-year OS
MFD: 88% (85-91%)
MUD: 86% (80-91%)

MMUD/MMFD: 72% (64-80%)
Haplo: 70% (59-82%)
(N=66; TCD 47 (71%); PTCY 13 (20%); 6 missing data)

***p*<0.001**

EuroBloodNet

Clinical case

May 2018:

Difficulty in swallowing, unexplained weight loss, nausea..

Vital signs were all within normal limits

Laboratory tests were normal

An upper endoscopy is performed and biopsies taken from lesion

Clinical case

The patient was diagnosed with squamous cell carcinoma of the gastro-esophageal junction

PET-CT was negative for metastatic lesions

September 2018 >>> Ivor- Lewis esophagectomy

No CHT or RTX

Clinical case

Today 2022

The patient is fine.

She continues haematological follow-up and not only..

- ✓ every 6 months: evaluation by head and neck tumour specialist, a stomatologist and a gynaecologist
- ✓ every year: skin examination for nevi

It is recommended :
No smoking, no alcohol use and correct oral hygiene for oral cancer prevention

Take home messages

- ✓ **Distinguishing acquired from constitutional BMFS is challenging but important given the clinical implications.**
- ✓ **Medical history, family history and physical examination are crucial.**
- ✓ **BMT is a good option for hematological manifestations but it is not a cure for congenital malformation and it doesn't reduce the risk of solid tumors.**
- ✓ **Identification of constitutional BMFS prior to HSCT is important to allow for modifications to HSCT conditioning as well as exclusion of family donors harboring the same inherited gene defect.**
- ✓ **Patients with constitutional BMFS often have multi-organ involvement, requiring care from multiple sub- specialists, as well as an increased cancer risk necessitating long term surveillance.**


THANK YOU