

# **Inherited or acquired BMF**

## **Strategy for diagnosis**

**Euroblood Net**

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**CeRAMIC**

# COI

- **Fees for boards and expert activities:** Alexion Pharma, Sobi, Novartis, Samsung and Jazz pharma
- **Research grants:** Alexion Pharma, Novartis and Pfizer

# BMF - definition

**Cytopenias** (platelets > erythrocytes > neutrophils)

&

**BM biopsy** : richness < 30 or 50%

- Ery > MNC > MK
- Interstitial oedema
- Lymphocytes (T > B) relative excess
- Mastocytes and plasmacytes
- Iron deposit



# BMF - Cytology

- **Necessary to exclude others diagnosis**
- Empty BM is the rule but the richness could be normal or slightly decrease especially at the beginning
- Moderate dysérythroipoïesis is possible (notably with PNH & FA)
- Relative excess of erythroblasts is possible
- Relative excess of normal lymphocytes/plasma cells/mastocyte

**Dysmegacaryopoiesis and/or dysgranulopoiesis are not usual in acquired aplastic anemia**

**Fibrosis > grade 1 is not usual**

# BMF - Diagnosis

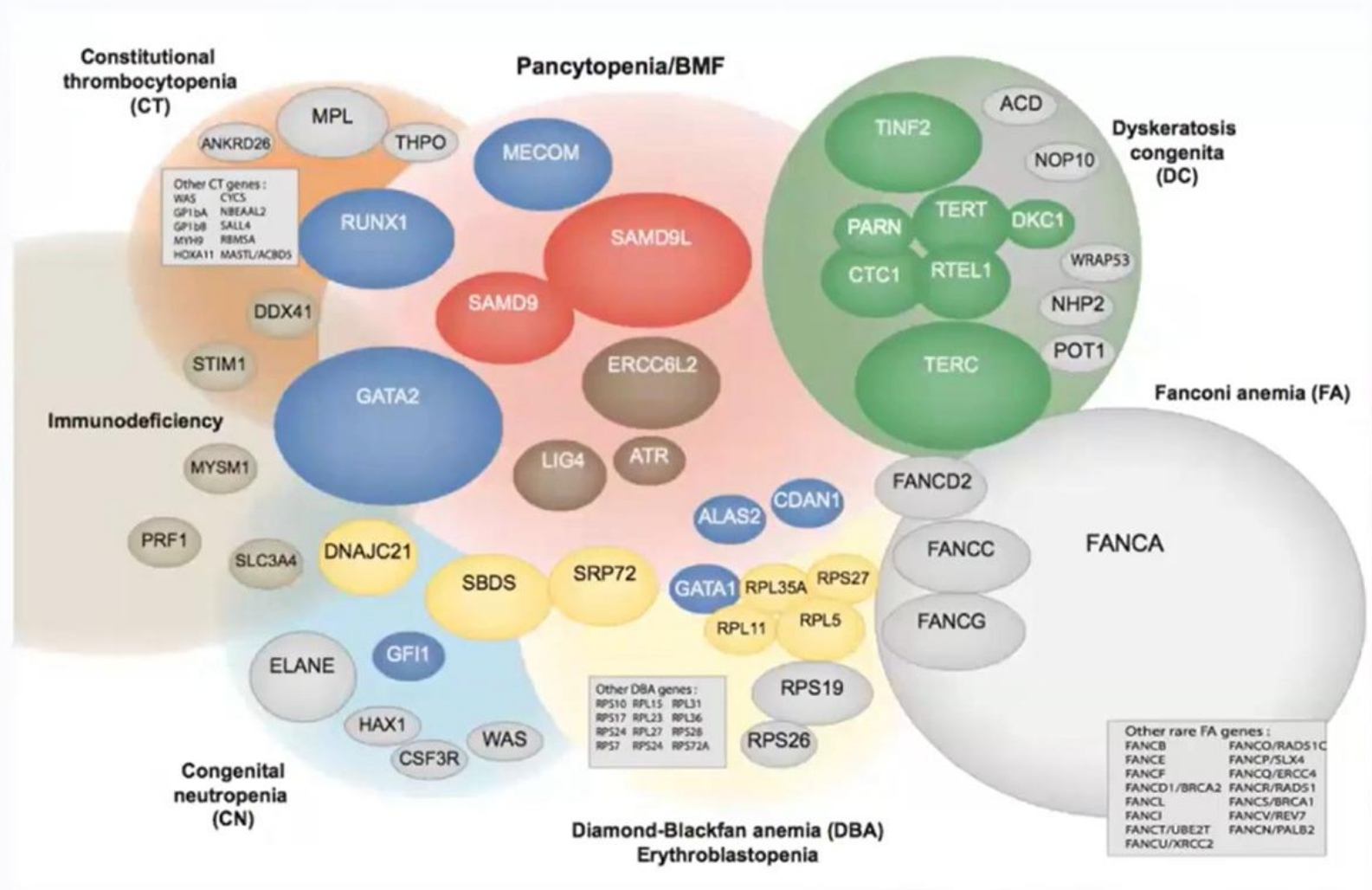
## Acquired BMF

- Idiopathic
- Post hepatitis AA
- AA/HPN
- Pregnancy associated AA
  
- Toxic (Radio or chemo ...)
- Drug induced BMF

## Inherited BMF

- Fanconi anemia
- Short telomeres Sd
- Amegacaryocytosis (MPL, THPO)
- SAMD9/SAMD9L
- MECOM
- ERCC6L2
- ...

# BMF spectrum is very large



# Inherited or acquired diagnosis is essential

## Inherited BMF

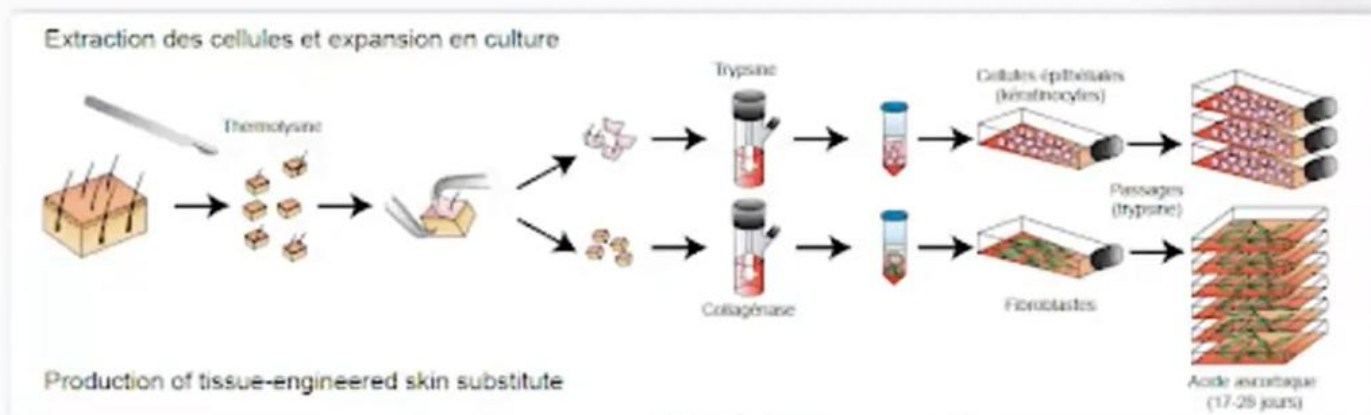
- ◆ No IST
- ◆ Exam for extra hematologic features and FU
- ◆ In case of an indication of allo HSCT :
  - ◆ Conditioning regimen ?
  - ◆ If MRD or haplo donor : genetic exam?
- ◆ Alternatives therapies (androgenes, ARTPO, aspirin, watch and wait...)
- ◆ Genetic counselling for related and in case of pregnancy plan

## Acquired BMF

- ◆ In severe and very severe AA : treatment is an emergency
- ◆ Time from diagnosis to IST and HSCT is prognostic

# Which tests and for whom ?

- Genetic tests in fibroblasts is the better for IBMF
  - Non hematopoïétic cells, no risk of contamination by leukocytes
  - Fonctional testing is possible
  - Allow to confirm that a variant is germinal and not acquired
  - Avoid missing mosaïcisme/somatic genetic rescue
  - But fibroblastes require time to grow (6 weeks)



# Identification of the patients suspect of IBMF

## Clinical history

- ◆ Age at first symptoms (25% < 10 years)
- ◆ Family history (BMF/AML/MDS; liver and pulmonary disease ; solid cancers ; ID ...)
- ◆ Consanguinity
- ◆ Weight and size at birth and at diagnosis
- ◆ Malformations, morphotype, cafés au lait spot and hypopigmentation, phanères, lymphoedema, warts...
- ◆ Previous normal CBC
- ◆ Speed of onset

## Acquired

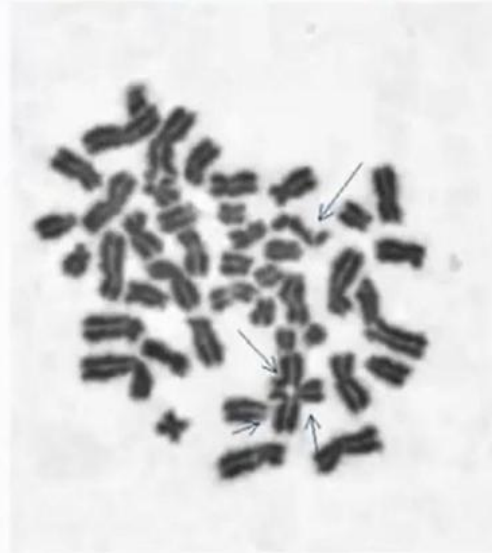
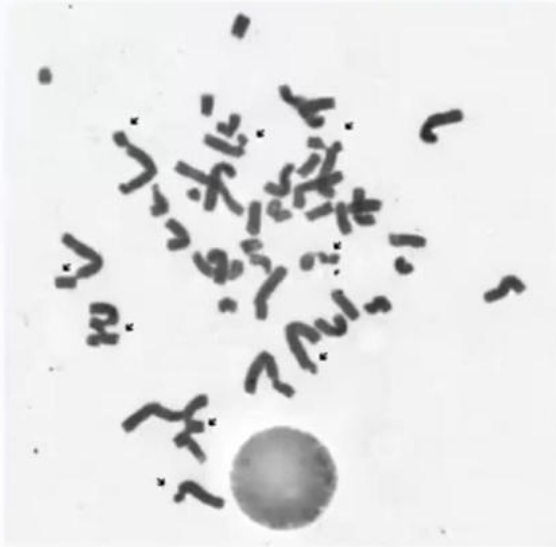
- Age > 10 years
- Normal CBC < 2 years
- Quick onset
- Post hepatitis AA
- PNH clone > 1%
- Telomeres length > 10<sup>e</sup> p

## Inherited

- Age < 10 years
- Abnormal CBC > 2 years
- Family history
- Consanguinity
- Malformations, ...
- Moderate BMF
- HbF > 10%
- $\alpha$ FP elevated
- Télomères < 1<sup>er</sup> p
- Monosmy 7, Tri 1q

## PNH clone by flow cytometry (Blood)

- PNH is tightly associated with immunological AA
- PNH is present in 40% of the pts with aAA (FLAER)
- 20% des patients avec HPN classique → AA
- However in very rare patients PNH could be associated with IBMF (DDX41)
- Not possible in some patients with very severe AA



Cassures  
chromosomiques 72  
heures cultures +PHA +  
**Mitomycine C**

cassures/cellules ~4

Recherche de cassures en PHA - ratio 0.203 [sur 113 métaphases en PHA]

Recherche de cassures en MMC - ratio **3.4** [sur 87 mitose en métaphases]

Présence de cassures chromosomiques spontanées et de **très nombreuses cassures chromosomiques et nombreuses images radiales après exposition à la Mitomycine C.**

Aspect compatible avec une **maladie de FANCONI.**

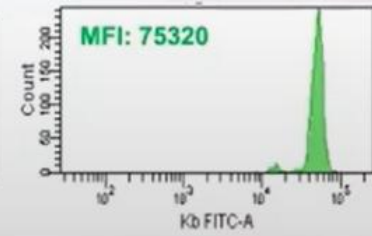
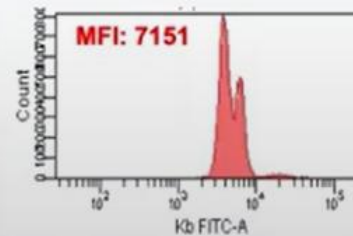
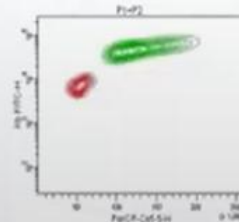
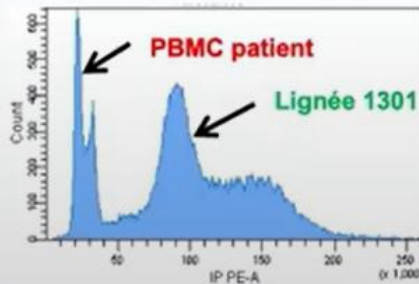
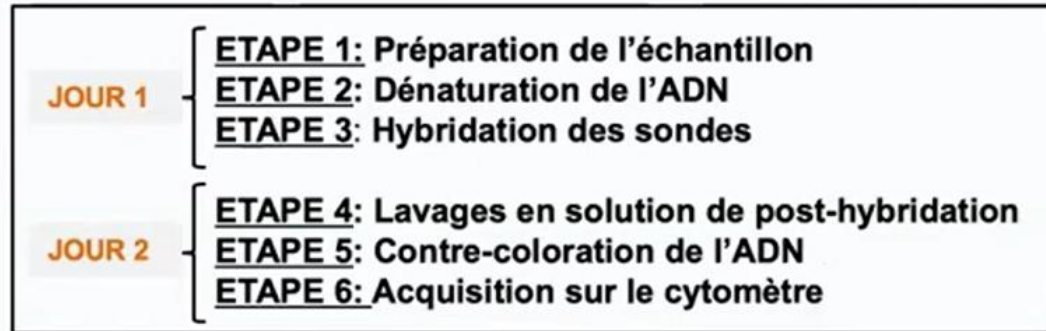
Profil FACore lymphocytes et fibroblastes : **Profil de type FA Core.Maladie de Fanconi**

## Indications of CBT

- BMF
  - All patients < 18 years
  - Other with clinical or biological abnormalities
- MDS
  - Short stature, clinical abnormalities, younger than 50y
- At birth if clinical abnormalities (VACTERL)
- HNSCC without risk factors and in young patients
- IOP and azoospermia

# Leukocytes telomeres length by FLOW-FISH

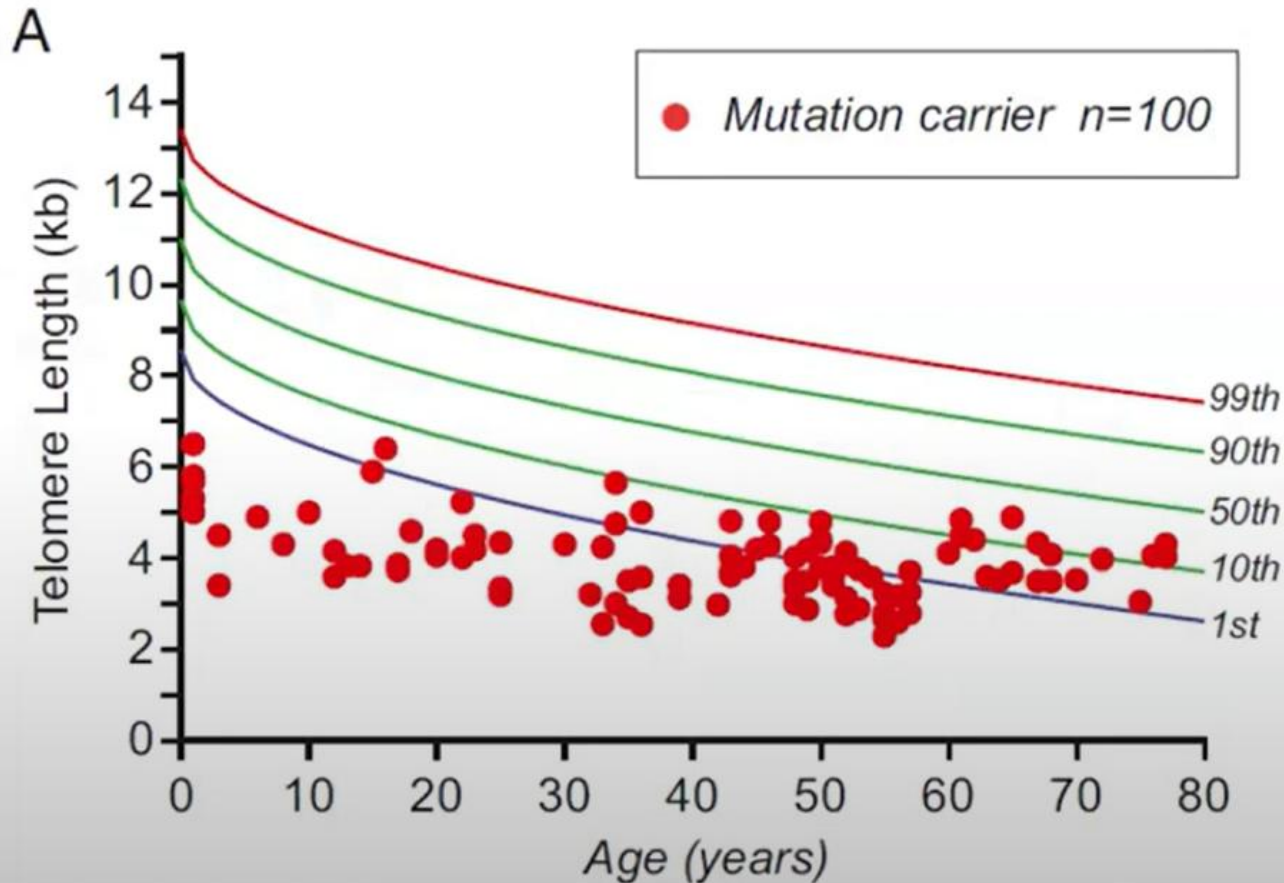
- Hybridation des répétitions télomériques **TTAGGG / CCCTAA** avec des sondes PNA couplées à une molécule fluorescente → **FITC-(C<sub>3</sub>TA<sub>2</sub>)<sub>3</sub> PNA sur des cellules en suspension = FISH**
- Mesure de la fluorescence = quantification/cellule par **CMF= FLOW**



**Rendu en RLT (Relative Length Telomere) = en % de la lignée 1301**  
→ Le 100% = Lignée 1301 (LAL-T tétraploïde avec télomères longs et stables)  
**Taille Télomère Patient = %1301 = RLT2 x 100/ (RLT1/2)**

# Leukocytes telomeres length by FLOW-FISH

Flow fish = reference



← = 1% de la population

Dr E La

Alder et al., PNAS



**Severe AA**  
Clinical evaluation  
PNH, aFP, HbF  
+/- CBT (age)

**Treatment without  
additional exams**

Post hepatitis AA  
PNH clone > 1%  
Quick onset  
Age > 20 y without abnormalities

**IST without waiting  
the results & additional exams**

No clinical abnormalities  
Telomeres < 1<sup>st</sup> percentile  
HbF 5-10%  
Age 5 - 10 years

**No treatment  
& additional exams**

Clinical element for IBMF  
Télomères < 1<sup>er</sup> percentile  
HbF > 10%  
Age < 5 ans

**Clinical  
decision  
meeting**

# Fanconi Anemia

## **FANC pathway deficiency, interstrand crosslinking repair deficiency**

- ◆ 1/350 000 birth, median age at diagnosis 6 years
- ◆ AR (sauf FancB, lié X 2%)
- ◆ Fanc A (66%), Fanc C (10%), FancG (10%)
- ◆ IUGR, small size, cafés au lait spots, morphotype, malformations (radial axis, kidney, heart,...)
- ◆ BMF during infancy, MDS/AML AYA and adults
- ◆ Solid cancers > 15 y : HNSCC and genital cancers
- ◆ Infertility : fertility preservation before 15 y
- ◆ Chemo and radiosensibility +++
- ◆ AlloHSCT if transfusion requirement or HR clonal evolution (MRD, MUD and haplo)
- ◆ Multidisciplinary follow up with cancers screening +++
- ◆ SGR ++ (carefull screening for family donors )

# Short telomeres syndrome

## Large number of genes coding for telomere maintenance

- ◆ Underdiagnosed: more than 100 index cases by years in France
- ◆ Multisystemic disease : hematological/pneumological/hepatologic / rheumatologic/ ID
- ◆ Anticipation
- ◆ Premature greying, hyper and hypopigmentation, ungual dysplasia, leucoplasia
- ◆ Thrombopenia, BMF, MDS/AML
- ◆ Pulmonary fibrosis, FFPE, emphysema
- ◆ Porto-sinusoidale vascular disease, stéatose, cirrhose, HCC
- ◆ Ostéoporosis, avascular osteonecrosis
- ◆ Increased risk of B cell NHL
- ◆ Androgènes if severe BMF without MDS/AML
- ◆ AlloHSCT MRD/MUD with alemtuzumab and fludarabine

# SAMD9/SAMD9L syndrome

## **BMF, GOF variant, AD, others abnormalities**

Young children

- ◆ Family history of transient cytopenias or BMF
- ◆ Cytopenia, BMF, SMD/LAM +/- ataxie cérébelleuse
- ◆ Monosomy 7 : SGR
- ◆ Others SGR : UPD, somatic variants
- ◆ Inherited variant maybe absent in the blood : fibro ++
- ◆ In case of non very severe BMF or HR clonal evolution : watch and wait (including monosomy 7)
- ◆ Neurological screening with MRI
- ◆ Genetic counselling for related and in case of pregnancy plan

# THPO syndrome

## HMZ LOF TPPO variants

- ◆ Diagnosis usually during infancy or AYA
- ◆ Less severe than MPO
- ◆ No others abnormalities
- ◆ ARTPO (eltrombopag are efficient)
- ◆ HSCT if non efficient.....

# TBXAS1 – Ghosal Syndrome

## HMZ LOF TBXAS1 variants

- ◆ Characterized by BM fibrosis with pancytopenia with predominant anemia and erythromyelemlia
- ◆ Metaphysal dysplasia with bone pain
- ◆ Usually diagnosed during infancy but the disease could present in adults, spontaneous transient improvement is possible
- ◆ Sensitive to steroids but dependance is the rule
- ◆ Aspirin is very efficient and well tolerated as recently publishes by us and other
- ◆ Impact of HSCT is not known

# Post hepatitis AA

## Immunological BMF

- ◆ 5 % of all BMF in Europe
- ◆ Mainly children and adolescent, boy +++
- ◆ BMF 3 weeks to 3 months after non viral hepatitis
- ◆ Severity of hepatitis is heterogeneous : from mild transitory jaundice to fulminant hepatitis
- ◆ Hepatitis are usually sensitive to steroids/ anticalcineurins
- ◆ T cell lymphocytes in the liver and the BM have the same profiles
- ◆ Treatment is the same than others aAA
- ◆ HSCT is feasible in liver transplant recipients if indicated
- ◆ If the history is typical : no other exam is required

# Is there a place of systematical somatic NGS screening at BMF diagnosis ?

## **Somatic variants are frequent in aAA at diagnosis**

- ◆ Frequency increase with age
- ◆ Most have no prognosis value
- ◆ TET2, ASXL1 associated with an increased risk of MM
- ◆ Could be transitory as cytogenetical abnormalities
- ◆ Some inherited genes are included in somatic panels....

**A somatic variant isolated is not an indication to change treatment at diagnosis and during FU in aAA**

## **Women 29 years old.**

Thrombocytopenia treated by immunoglobulins, ARTPO and rituximab from 1 year

Obesity with NASH and cirrhosis

Hb 7.7 g/dL, VGM 96 fl, retic 70 G/L, PNN 0.7 G/L, platelets 7 G/L

Hematological exams :

- BM aspiration : moderate dyserythropoiesis
- Cytogenetic: failure
- BM biopsy: severe hypoplastic BM.
- Gammaglobulines 16 g/L
- No PNH clone
- aFP : 2 ng/ml
- HbF 10%
- Somatic NGS normal

We recommend to perform telomere length and genetical exams for IBMF and to wait before to start IST

Telomere length: 5% (< 1<sup>st</sup> percentile, 7.6%)

**TERC r.58 C>U**

Danazol 400 mg x2/J

Complete response with Hb > 10, platelets > 100  
G/l and PNN > 1 G/L

Hepatic tolerance was good

Treatment was progressively stopped and she keep  
partial good response

Liver (MRI) and pulmonary survey

## National French Reference Center for AA and PNH



Hôpital Saint-Louis



Hôpital Robert Debré



IUH St Louis

R Peffault de Latour, T Leblanc, M Fadh, JH Dalle  
N Vasquez, L Larcher, W Cuccuini, J Soulier (Fanconi)  
C Kannengiesser, E Lainey, L Da Costa (Telomeres)  
Patients

Diagnosis and treatment meeting every 1<sup>st</sup> et 3<sup>rd</sup> wednesday –  
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