Thursdays Webinars

EuroBloodNet

Bone marrow failures genetic diagnostic

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French reference center for aplastic anemia & PNH
French network for rare immunological & hematological disorders (MaRIH)
Hôpital Saint-Louis, Paris, France
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APLASIE MEDULLAIRE centre de référence

MaRIH

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Disclosures

- **Alexion, Novartis, Pfizer**
  - Consultancy
  - Honoraria
  - Research funding
- **Amgen**
  - Research funding

Idiopathic *versus* inherited aplastic anemia

Agenda

- **Initial diagnosis**
- **Etiology**
  - Idiopathic aplastic anemia
  - Fanconi anemia, Dyskeratosis congenita
- **Management**

> Who should be screened for germline mutation at diagnosis?

Idiopathic *versus* inherited aplastic anemia

Diagnosis

- Pancytopenia

- Macrocytosis is common
- Lymphocytes count is usually preserved (!)
- Isolated cytopenia at early stage (thrombocytopenia)

(!) differences between idiopathic and acquired

Idiopathic *versus* inherited aplastic anemia

Diagnosis

- **Pancytopenia**
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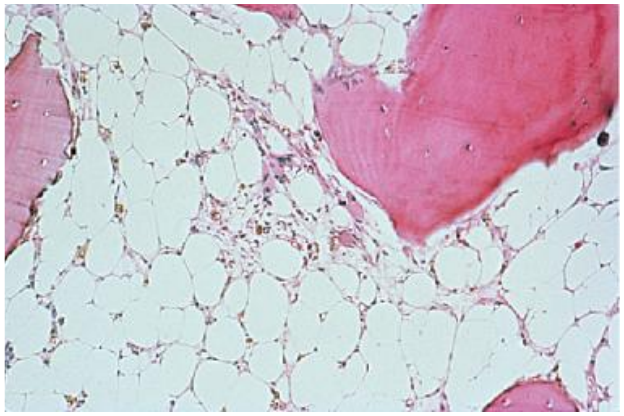
- **Bone marrow aspiration**
  - No abnormal cells

(!) differences between idiopathic and acquired

Idiopathic *versus* inherited aplastic anemia

Diagnosis

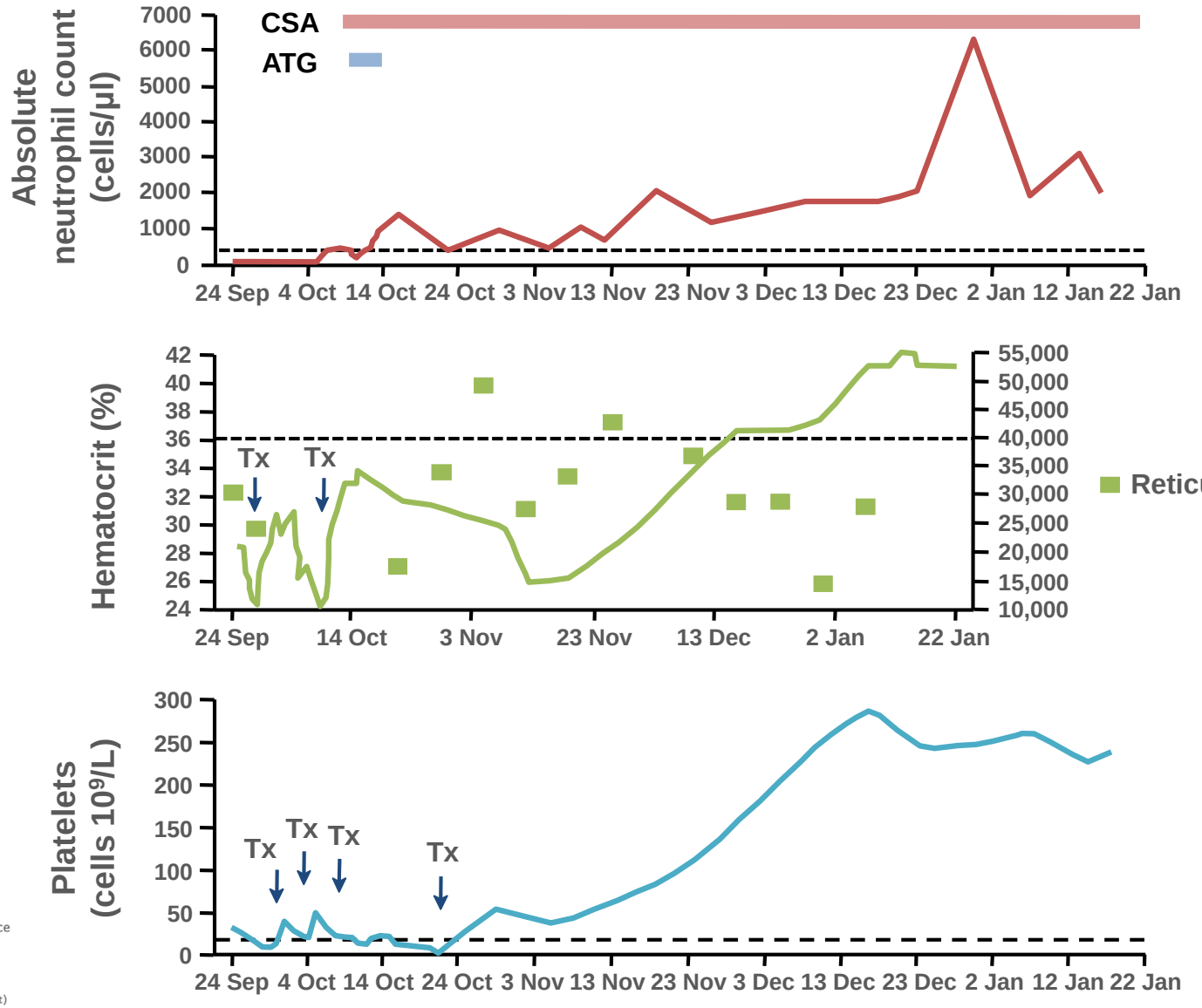
- **Pancytopenia**
  - Macrocytosis is common
  - Lymphocytes count is usually preserved
  - Isolated cytopenia at early stage (thrombocytopenia)
- **Bone marrow aspiration**
  - No abnormal cells
- **Bone marrow biopsy (diagnosis)**
  - Cellularity <30%
  - Dyserythropoiesis (usual)
  - Mast cells, lymphoid hyperplasia, plasma cells, macrophages (!)



(!) differences between idiopathic and acquired

Idiopathic *versus* inherited aplastic anemia

Idiopathic (80%) – immune mediated



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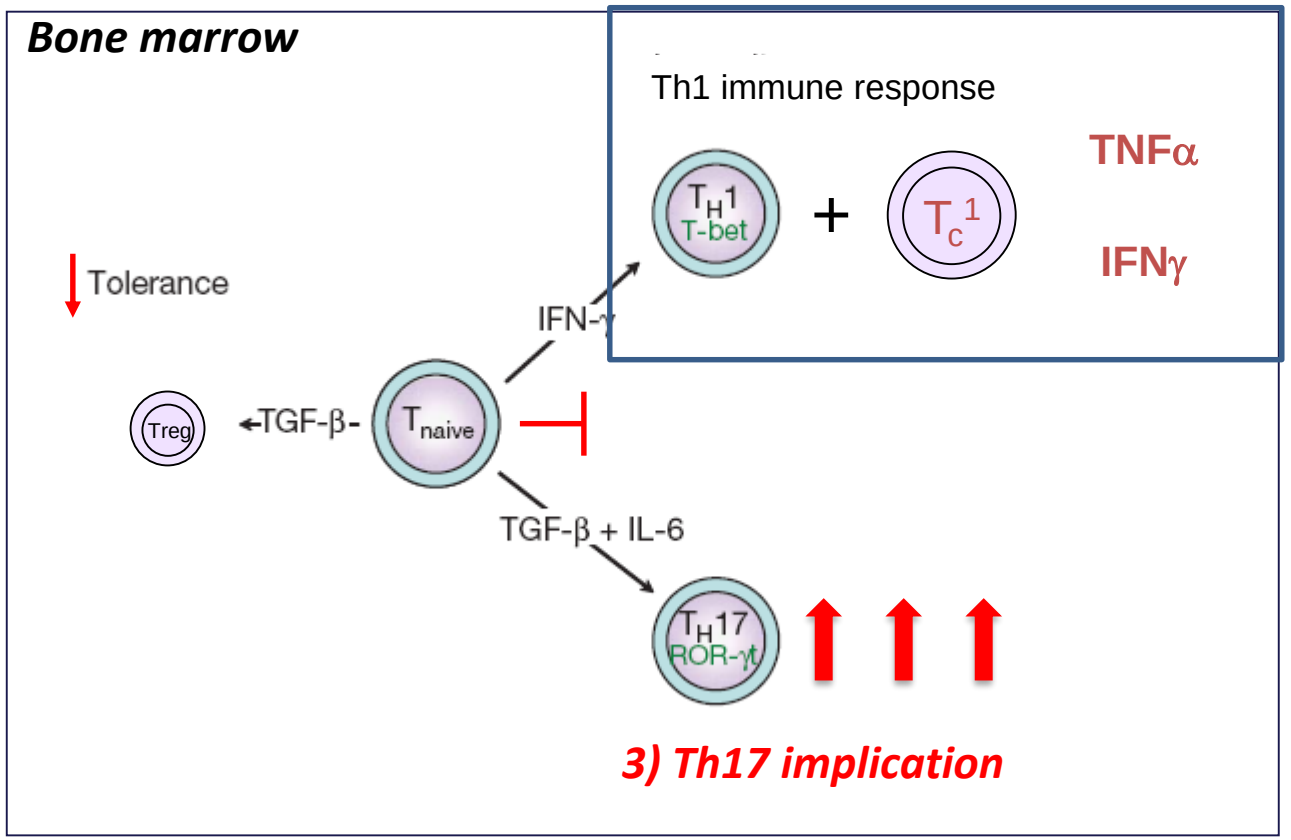
Idiopathic *versus* inherited aplastic anemia

Idiopathic (80%) – immune actors

> Acute phenomena – previous normal CBCs

1) Th1 immune mediated response



2) Tregs quantitative deficit

3) Th17 implication

Solomou *et al*, Blood 2006; Bettelli *et al*, Nature 2008;

Feng X *et al*, Haematologica 2010; Peffault de Latour *et al*, Blood 2010

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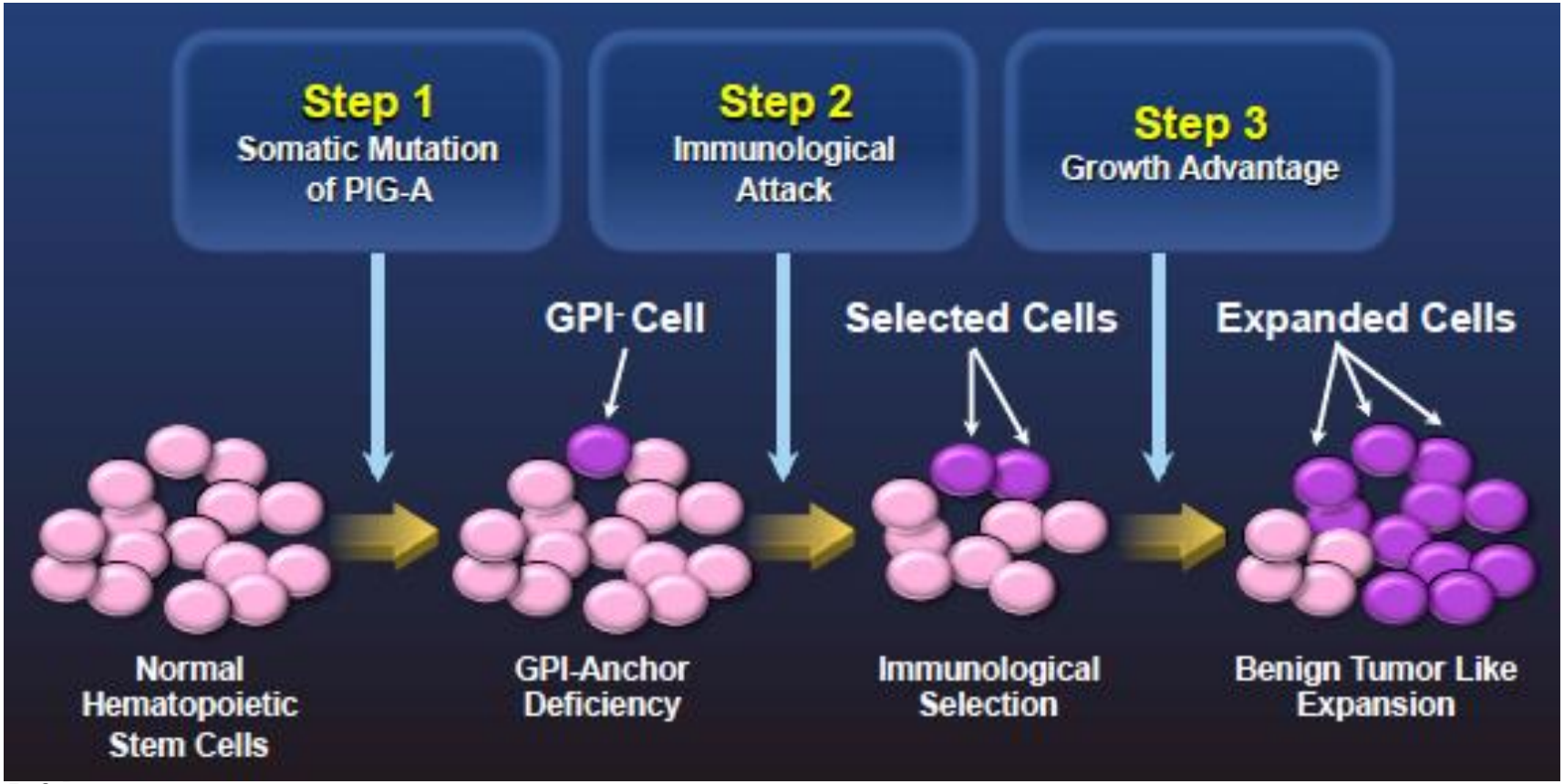
Thursdays Webinars

Idiopathic *versus* inherited aplastic anemia

Idiopathic (80%) – PNH clone

> PNH clone expansion in the context of immune-mediated BMF



Idiopathic *versus* inherited aplastic anemia

Inherited (20%) – Germline mutations

- **Mutations implicated in heterogeneous biological pathways**

  - DNA repair, Fanconi anemia

  - Related Telomere biology disorders, Dyskeratosis congenita

  - Ribosome biogenesis, DBA, Schwachman-Diamond

  - Hematopoietic transcription factors, GATA-2 deficiency

- Physical exam is very useful

Idiopathic *versus* inherited aplastic anemia

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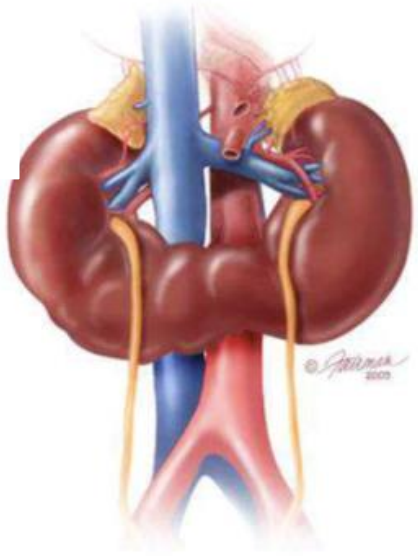
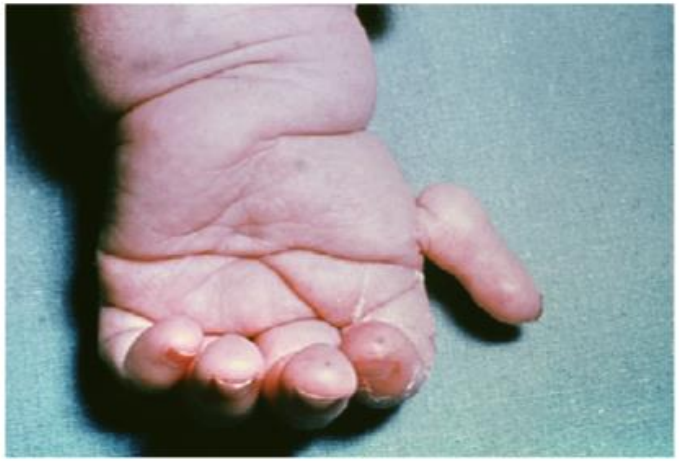
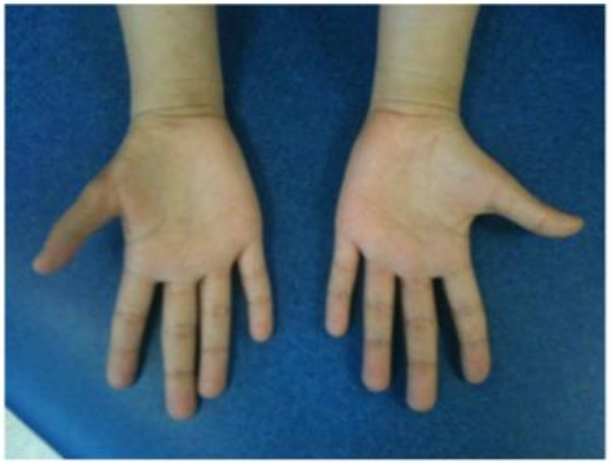
Idiopathic *versus* inherited aplastic anemia

Inherited (20%) – Fanconi anemia

Typical clinical features

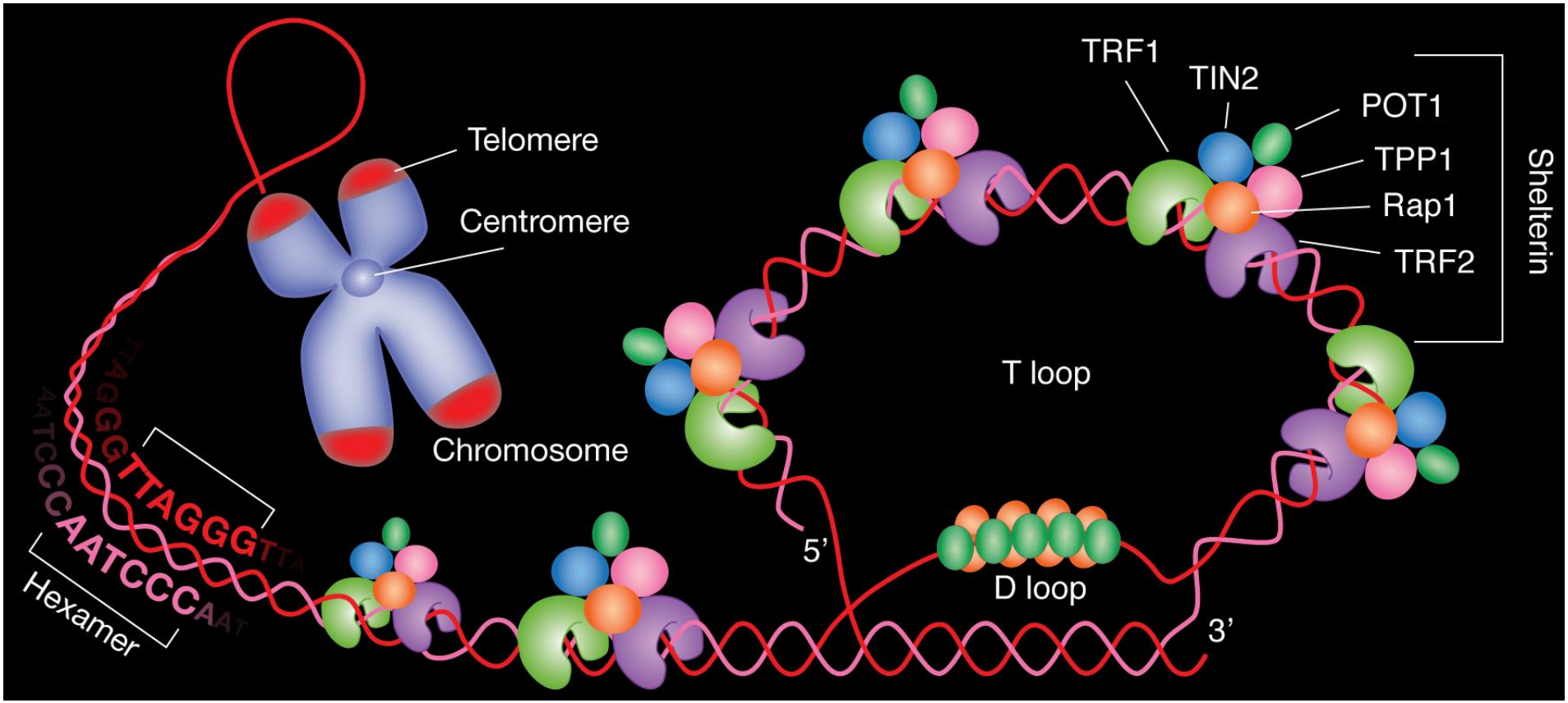






Idiopathic *versus* inherited aplastic anemia

Inherited (20%) – Telomeropathy



Idiopathic *versus* inherited aplastic anemia

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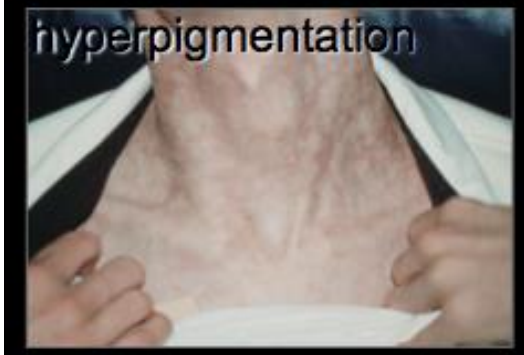


X-linked DKC

DKC1 (encoding dyskerin, protein component of telomerase complex)

Autosomal Dominant DKC

TERC, RNA component of telomerase
TINF2 (shelterin protein)
RTEL1 (DNA helicase)

Autosomal Recessive DKC

TERT, NOP10, NHP2, WRAP3

Courtesy by R. Calado

Idiopathic *versus* inherited aplastic anemia

Inherited (20%) – Others (…)

RED CELLS, IRON, AND ERYTHROPOIESIS

CME Article

A landscape of germ line mutations in a cohort of inherited bone marrow failure patients

Olivier Bluteau,[1-3,*] Marie Sebert,[2,3,*] Thierry Leblanc,[4] Régis Peffault de Latour,[2,5-7] Samuel Quentin,[1] Elodie Lainey,[8] Lucie Hernandez,[2,3] Jean-Hugues Dalle,[2,4] Flore Sicre de Fontbrune,[6] Etienne Lengline,[9] Raphael Itzykson,[2,3,5,9] Emmanuelle Clappier,[1-3] Nicolas Boissel,[2,5,9] Nadia Vasquez,[1] Mélanie Da Costa,[1] Julien Masliah-Planchon,[3] Wendy Cuccuini,[1] Anna Raimbault,[1-3] Louis De Jaegere,[3] Lionel Adès,[2,9] Pierre Fenaux,[2,9] Sébastien Maury,[10] Claudine Schmitt,[11,12] Marc Muller,[11,12] Carine Domenech,[13] Nicolas Blin,[14] Bénédicte Bruno,[15] Isabelle Pellier,[16,17] Mathilde Hunault,[16,17] Stéphane Blanche,[18,19] Arnaud Petit,[20] Guy Leverger,[20] Gérard Michel,[21,22] Yves Bertrand,[13] André Baruchel,[2,4,5] Gérard Socié,[2,6,7] and Jean Soulier[1-3]

OBJECTIVES: in a cohort of patients with an unresolved, likely-Inherited BMF:

To identify new IBMF/MDS causes; to draw a broad molecular portrait of this heterogeneous group of patients

N=179 patients from 173 unrelated families

(median age: 8.3 years)

Idiopathic *versus* inherited aplastic anemia

Inherited (20%) – Others (…)

gDNA from skin fibroblast cells (n=179 pts)

⬇

WES

- Sequenced on NextSeq500 or Hiseq1000 systems (illumina)
- Analysis: home made bioinformatics pipeline
- Flagging procedure for known IBMF genes
- Additional manual investigation for potential novel IBMF-causing genes

⬇

Pathogenic effect of the variants using ACMG classification

⬇

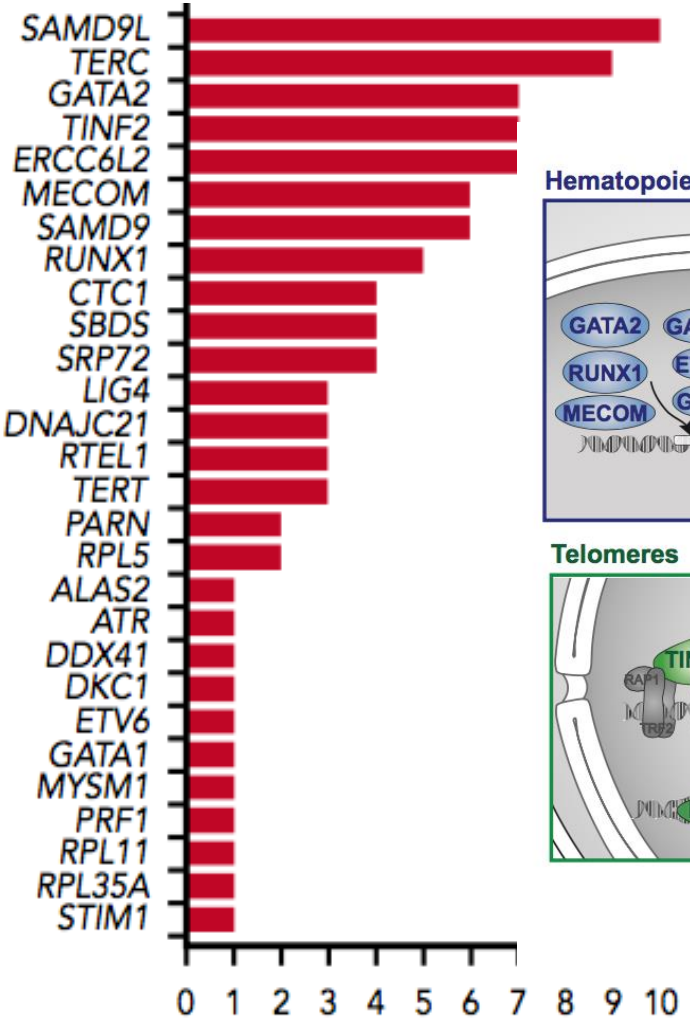
Integrated review for each patient in multidisciplinary roundtable sessions
biological and clinical expertise

⬇

28 genes were assigned to be
causal or very likely causal gene variant (Sanger re-sequenced)

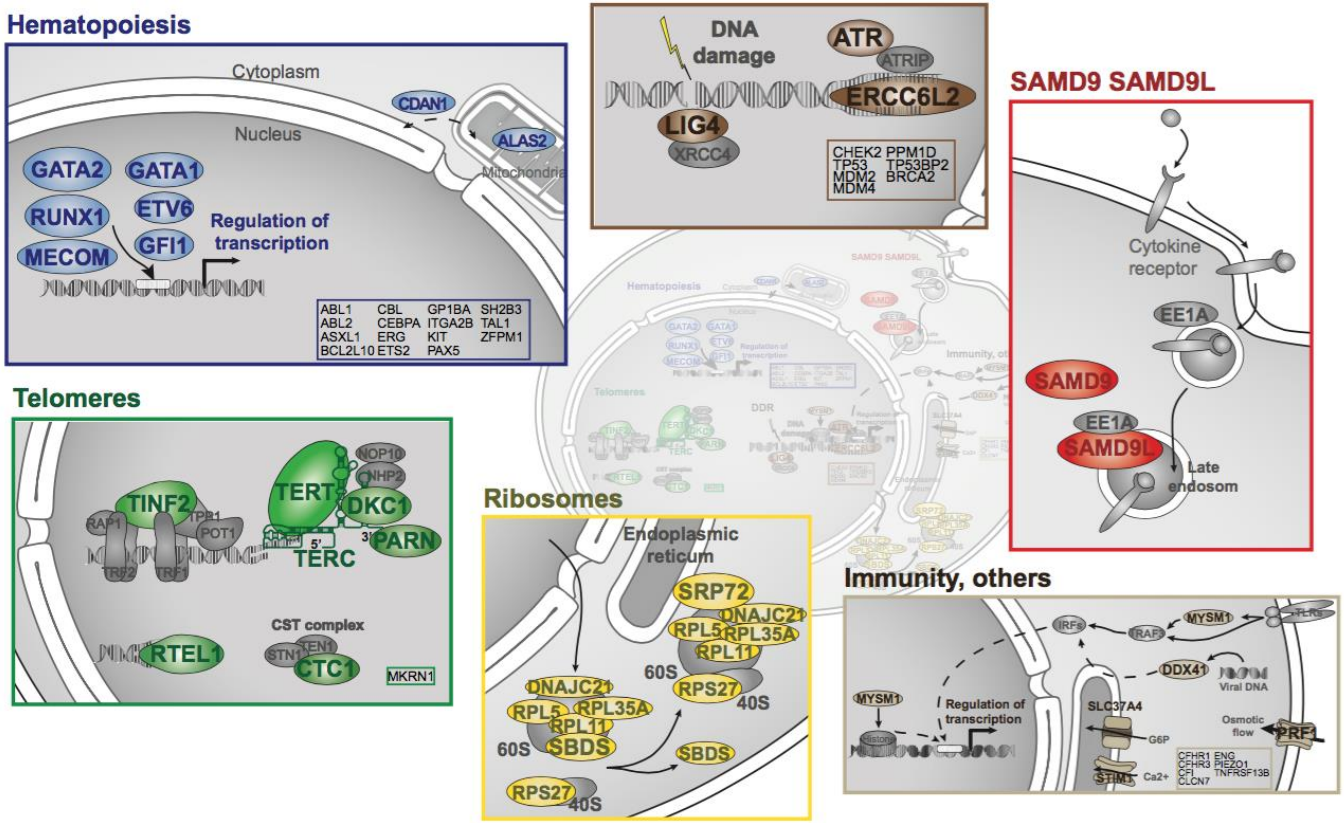
Idiopathic *versus* inherited aplastic anemia

Molecular diagnosis: N=86 patients (almost 50%)



Number of patients with variants

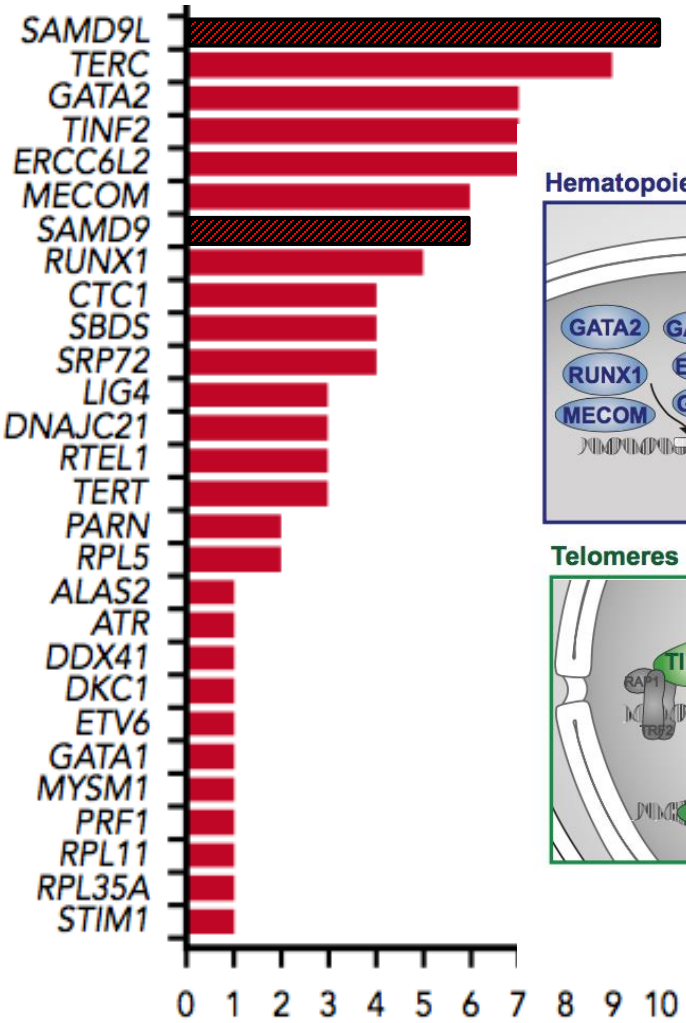
Biological pathways



Bluteau et al, Blood Nov. 2017

Idiopathic *versus* inherited aplastic anemia

***SAMD9L/SAMD9*: N=16 patients (19%)**



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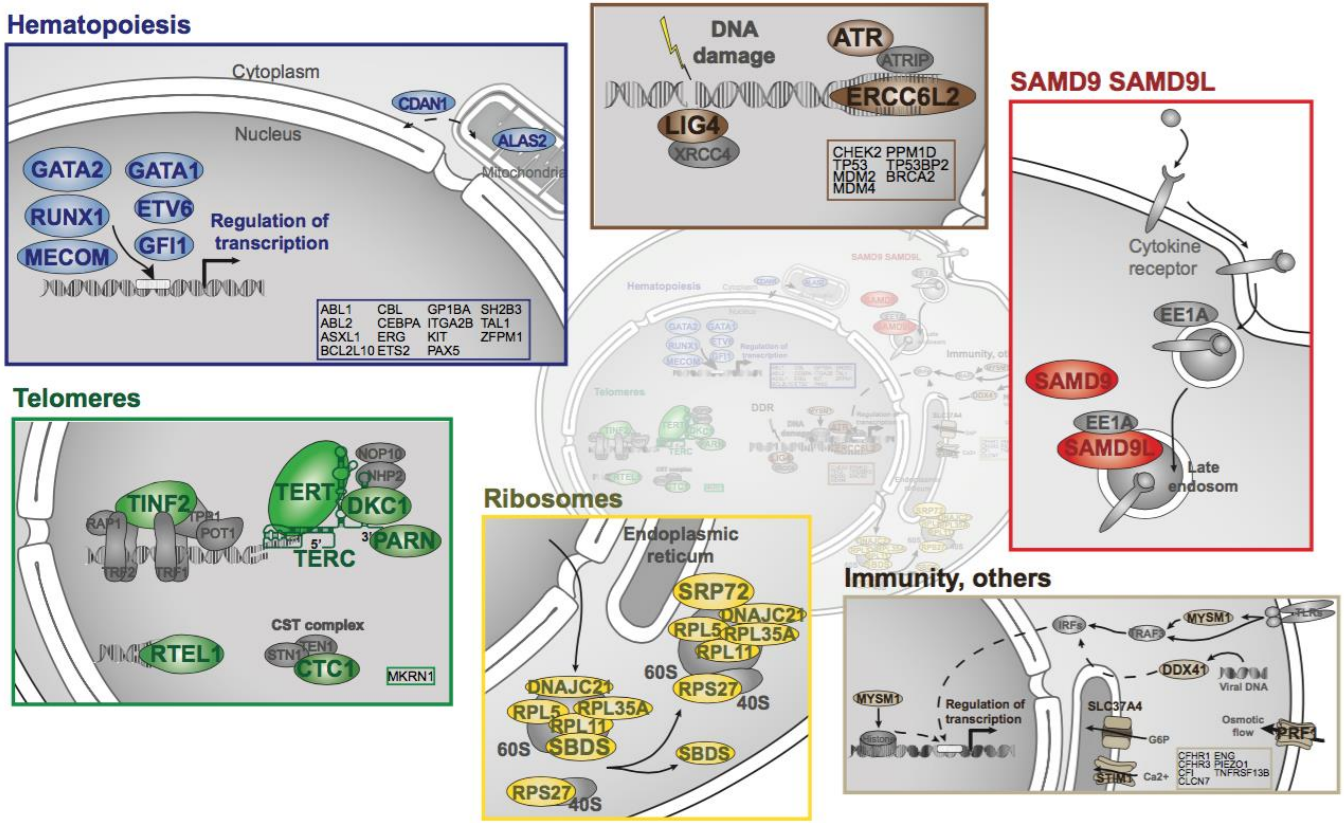

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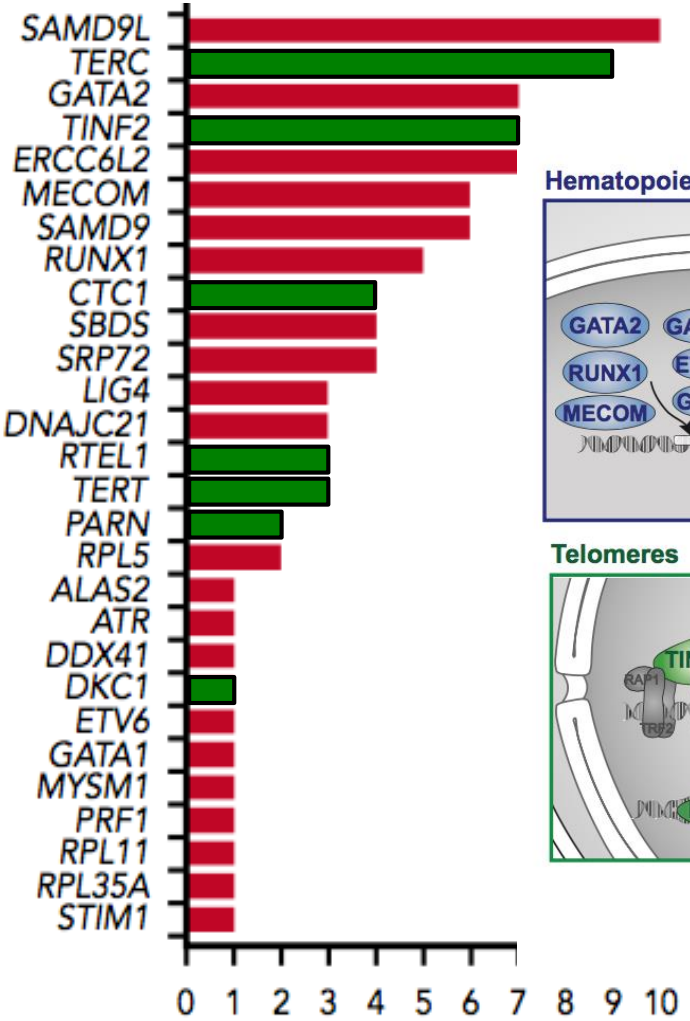
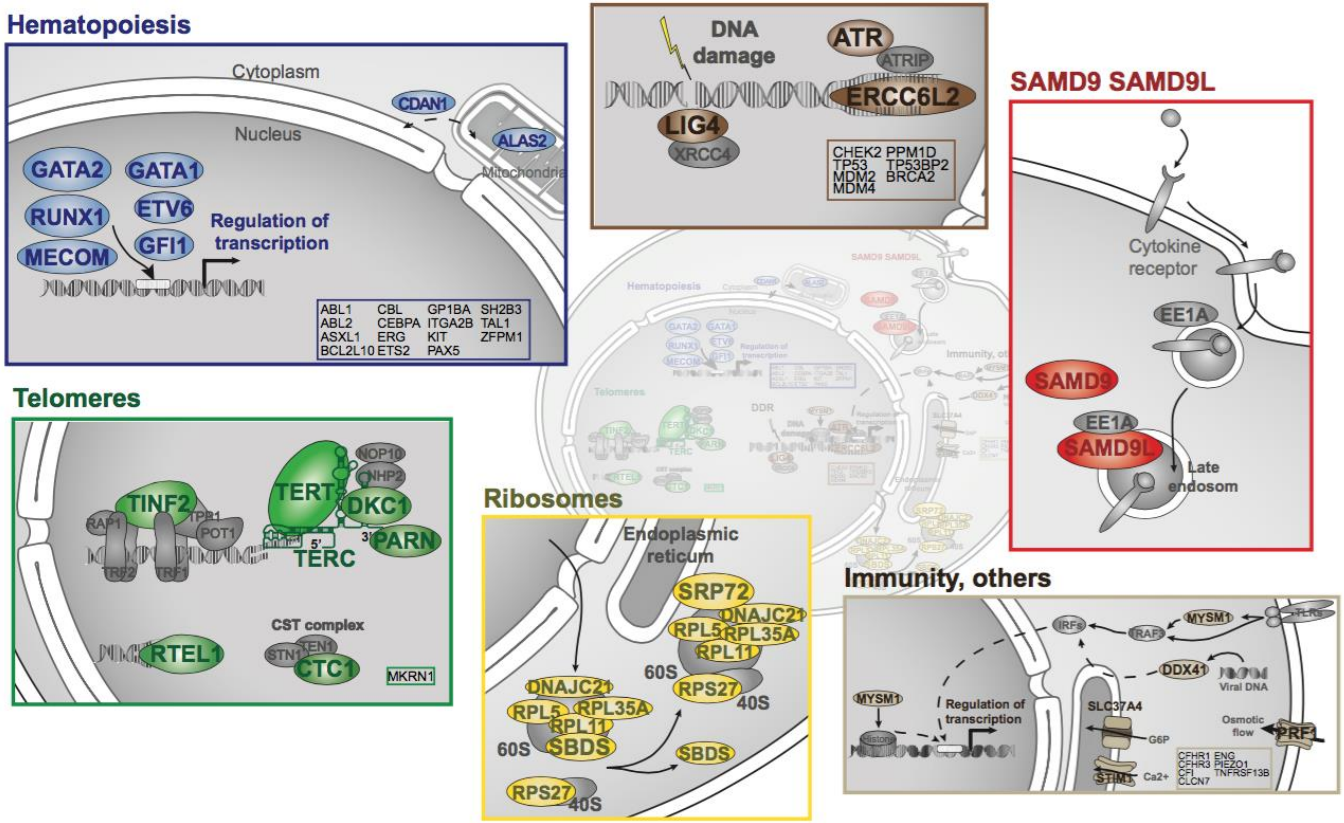
Idiopathic *versus* inherited aplastic anemia

Telomeres genes: N=29 patients (34%)



Number of patients with variants

Biological pathways



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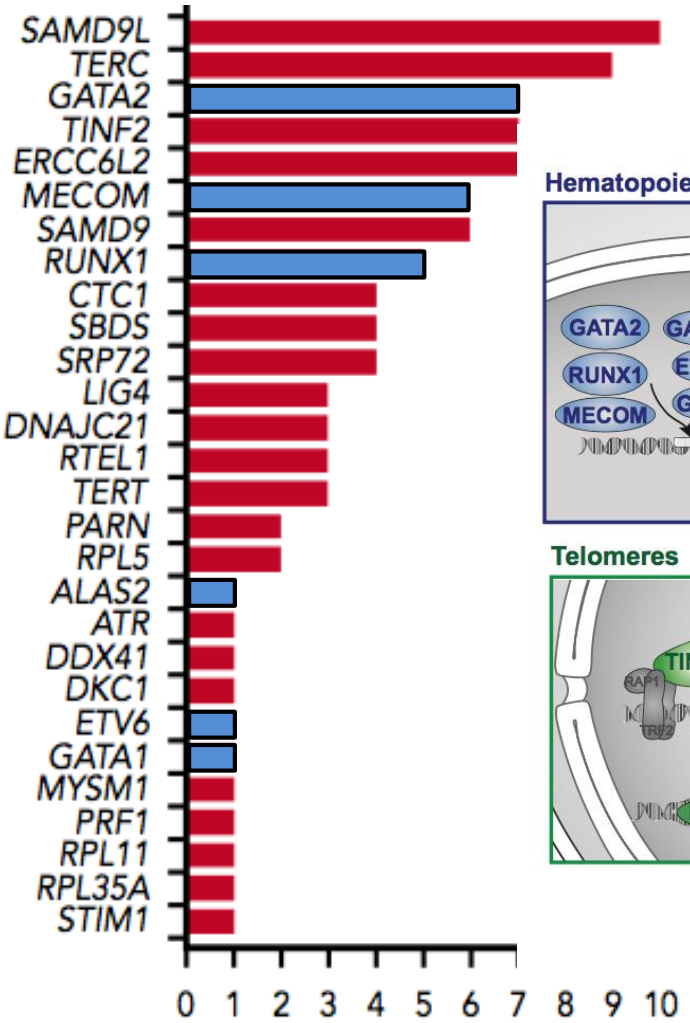
Idiopathic *versus* inherited aplastic anemia

Hematopoietic genes: N=21 patients (24%)



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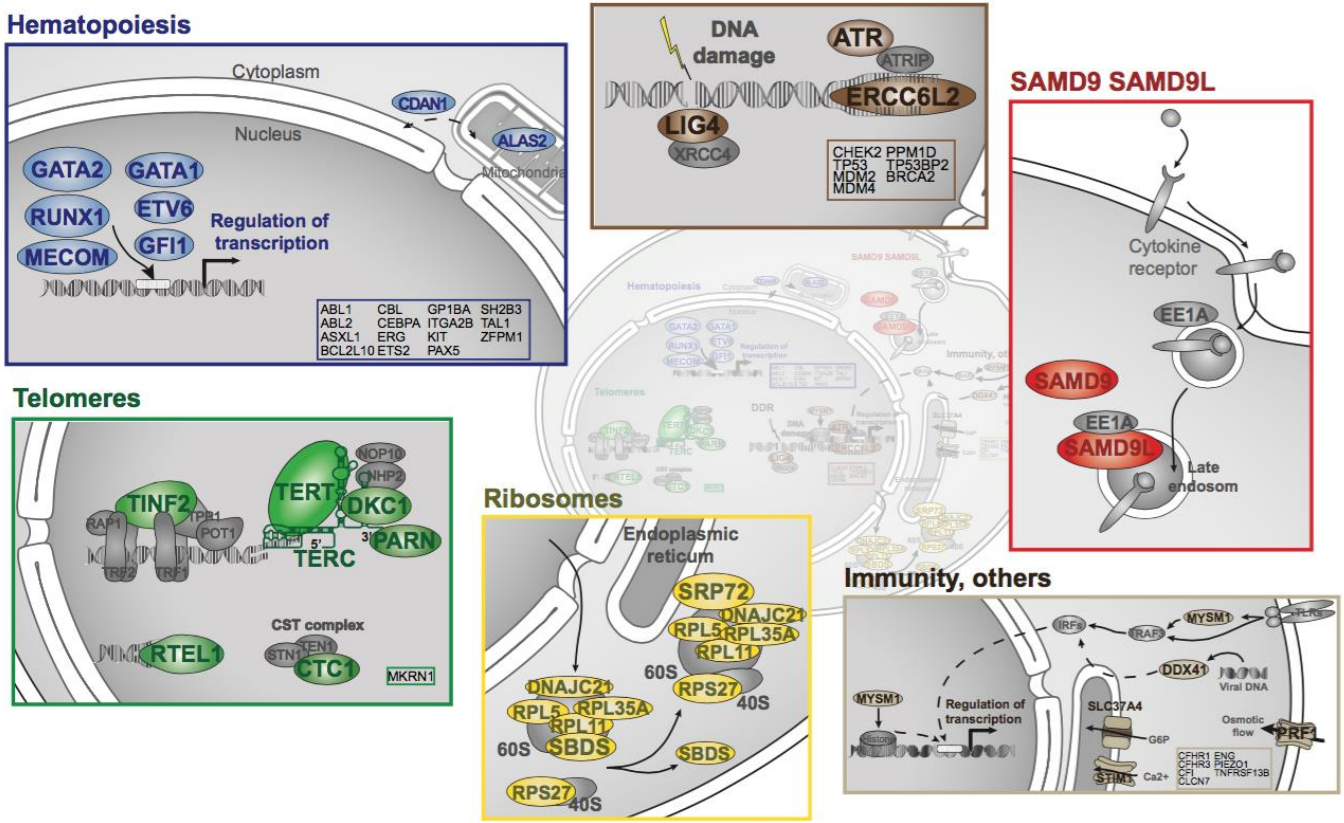
Biological pathways



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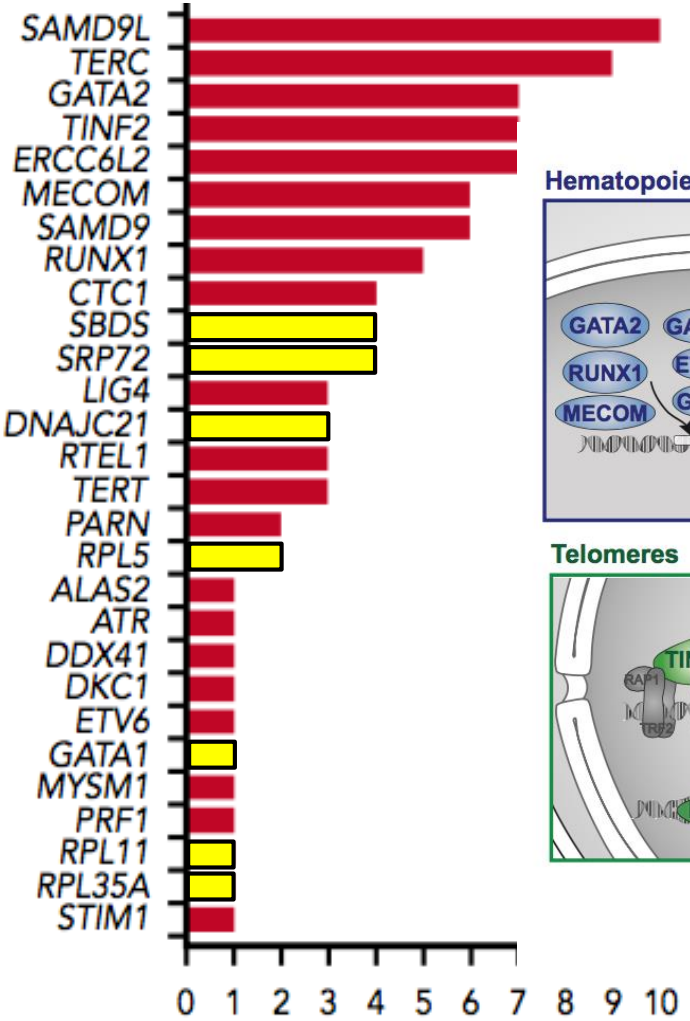
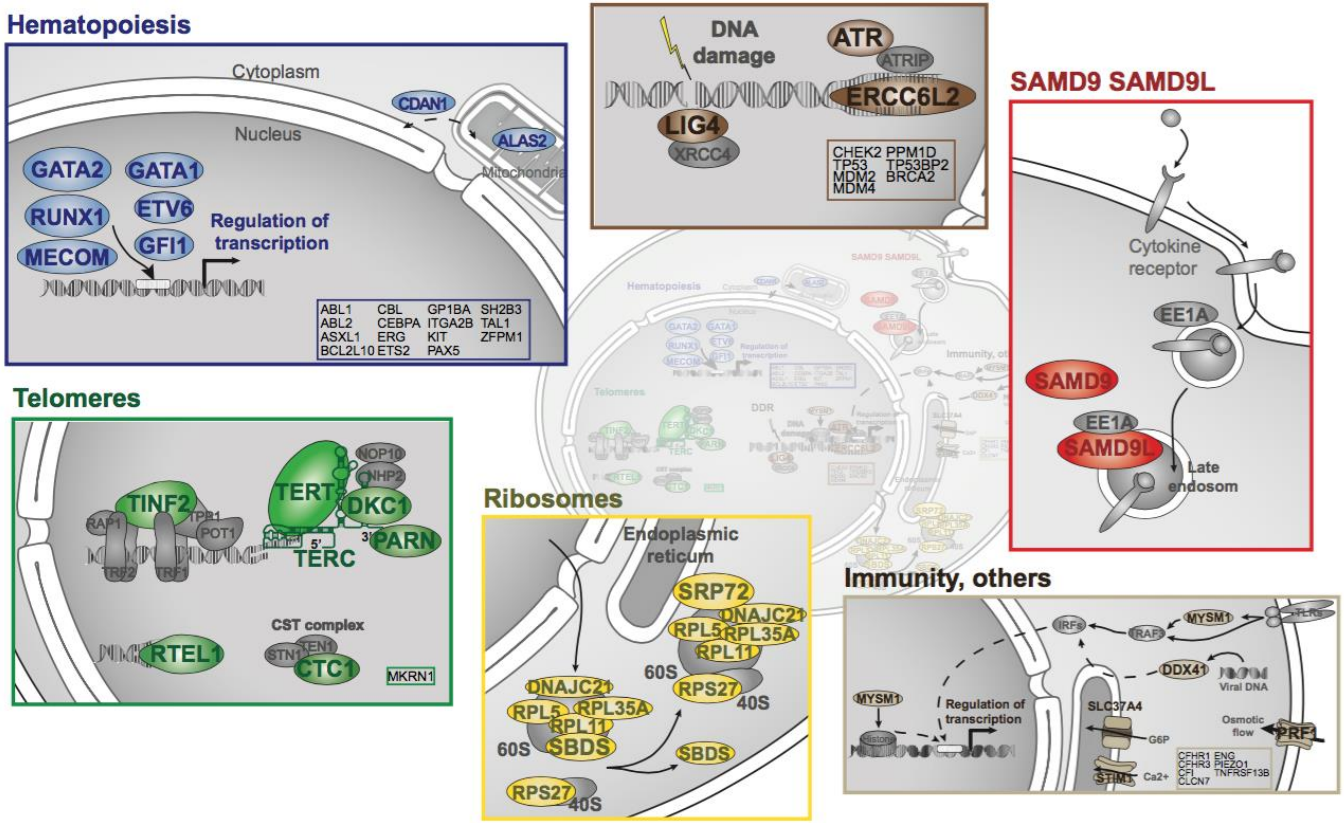
Idiopathic *versus* inherited aplastic anemia

Ribosome biogenesis: N=12 patients (14%)



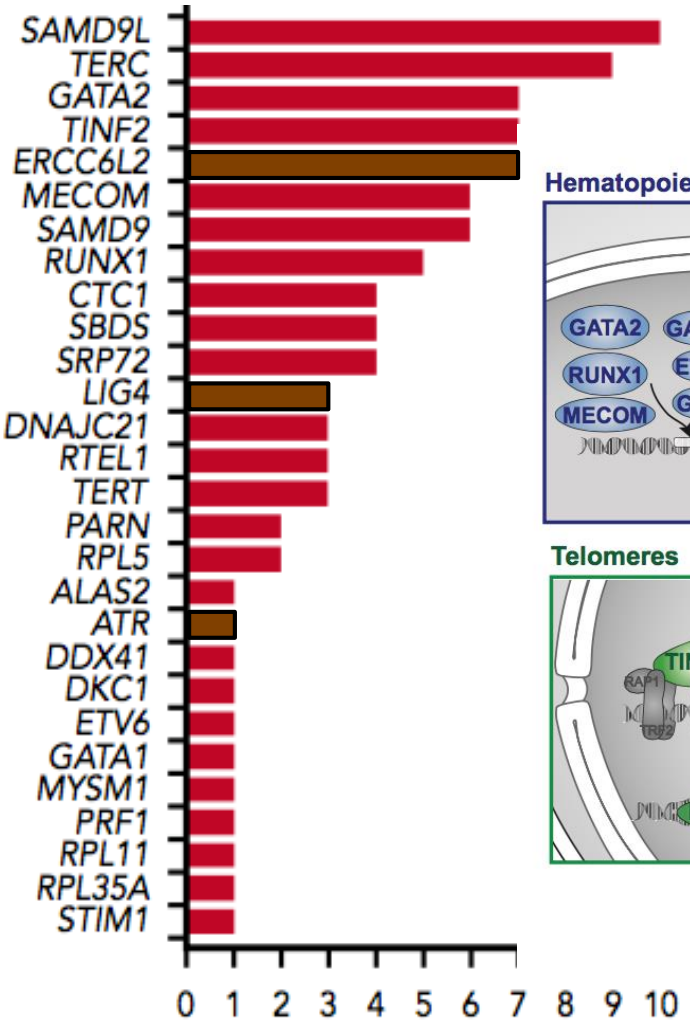
Biological pathways



Bluteau et al, Blood Nov. 2017

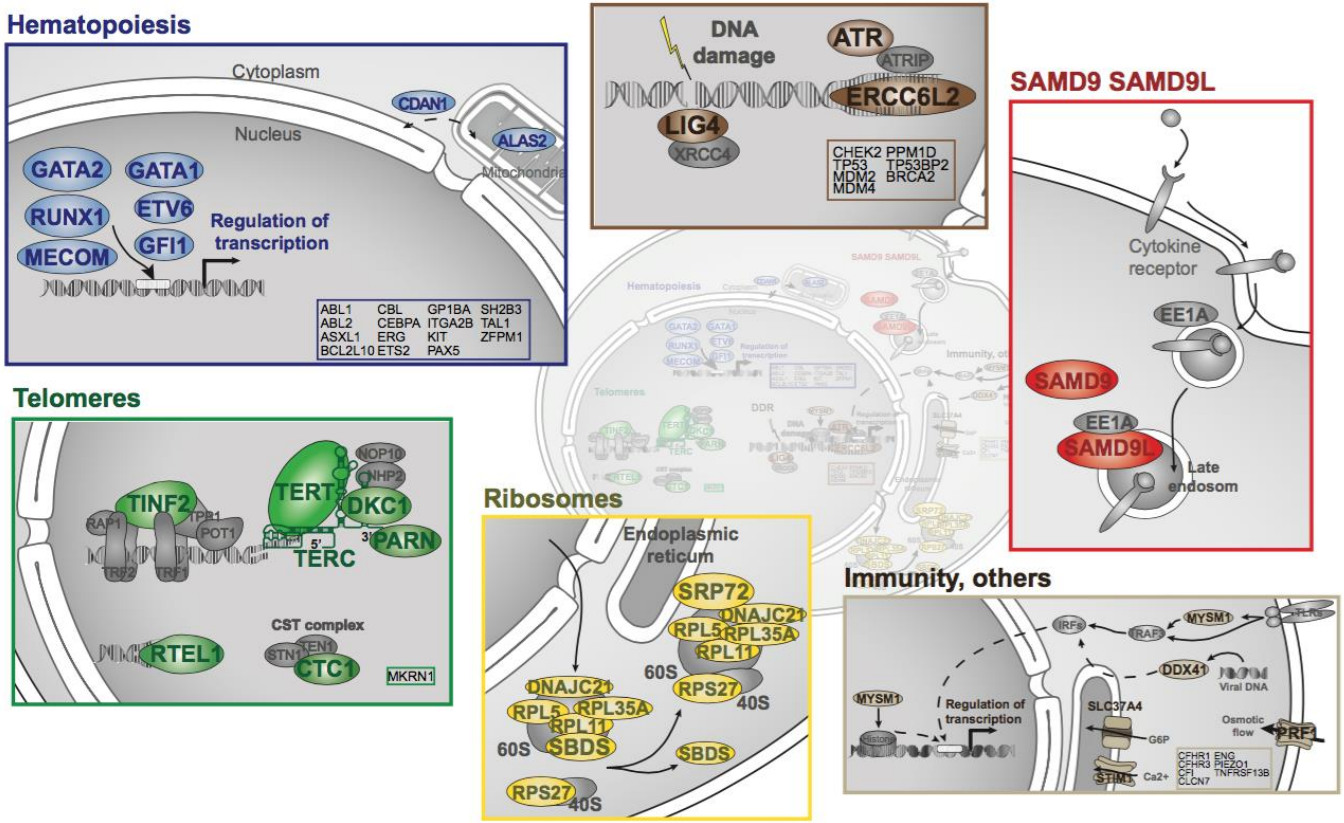
Idiopathic *versus* inherited aplastic anemia

DNA damage: N=11 patients (13%)



Number of patients with variants

Biological pathways



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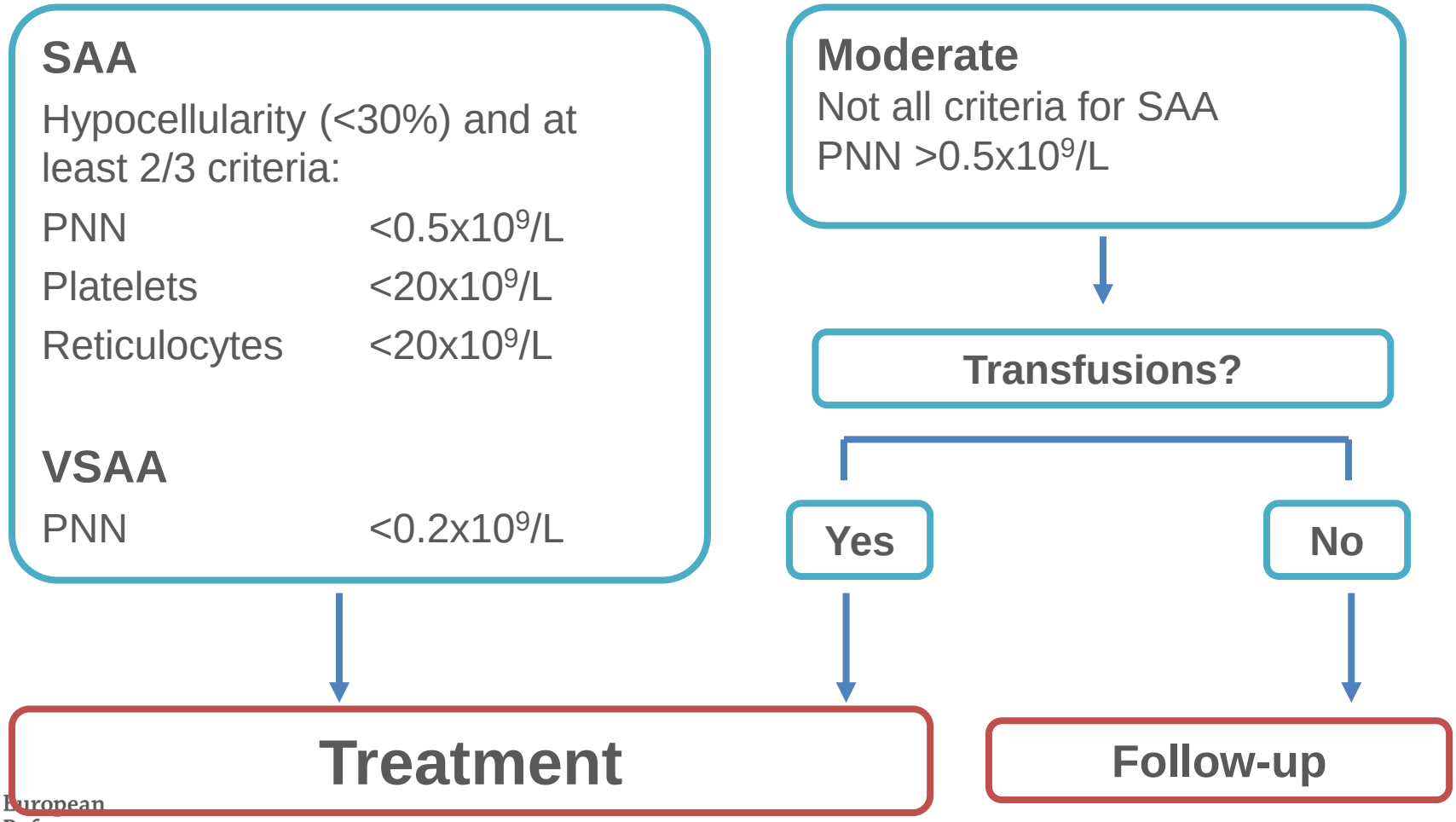
Idiopathic *versus* inherited aplastic anemia

Management



Camitta BM *et al. Blood* 1976;48:63–70
SAA, severe AA; VSAA, very severe AA

Idiopathic *versus* inherited aplastic anemia

Management

- **Treatment**

  - Idiopathic aplastic anemia: immunosuppressive treatment or transplantation

  - Inherited aplastic anemia: androgens or transplantation

Idiopathic *versus* inherited aplastic anemia

Management

- **Treatment**

  - Idiopathic aplastic anemia: immunosuppressive treatment or transplantation

  - Inherited aplastic anemia: androgens or transplantation

- **Long-term follow-up**
  - Clonal evolution for both causes (MDS, AML)
  - Solid cancer for inherited disorders

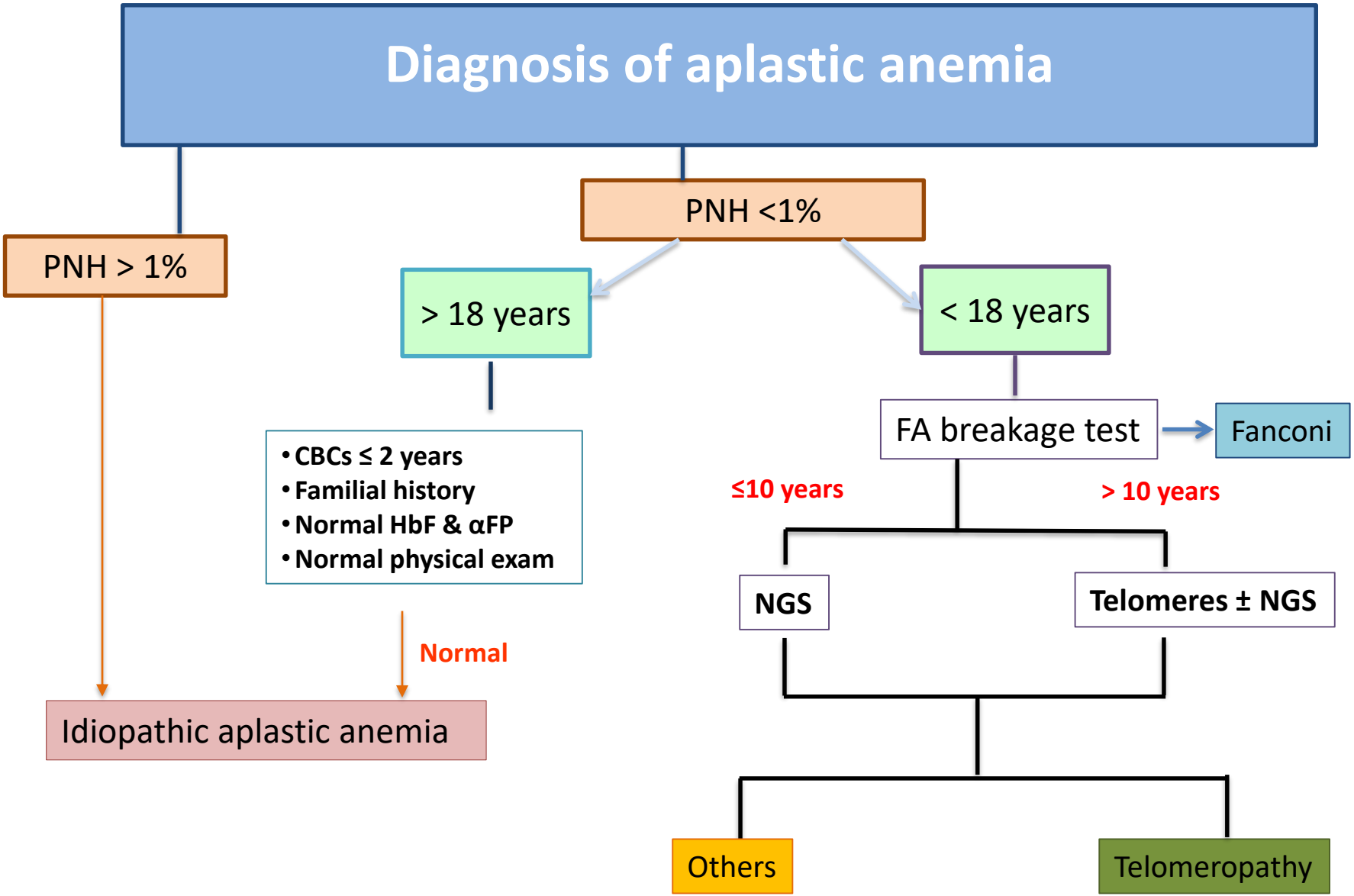
Idiopathic *versus* inherited aplastic anemia

Any difference?

- **Disease installation**
  - Progressive versus acute (CBCs history)
- **Personal history**
  - Early development
  - Physical exam
- **Familial history**
  - Hematological disorders
  - Extra hematological disorder (Lung and cirrhosis)
- **Biology**
  - PNH clone
  - Immune deficiency
  - Hemoglobin F & αFP

Idiopathic *versus* inherited aplastic anemia

Who should be screened upfront for germline mutations?



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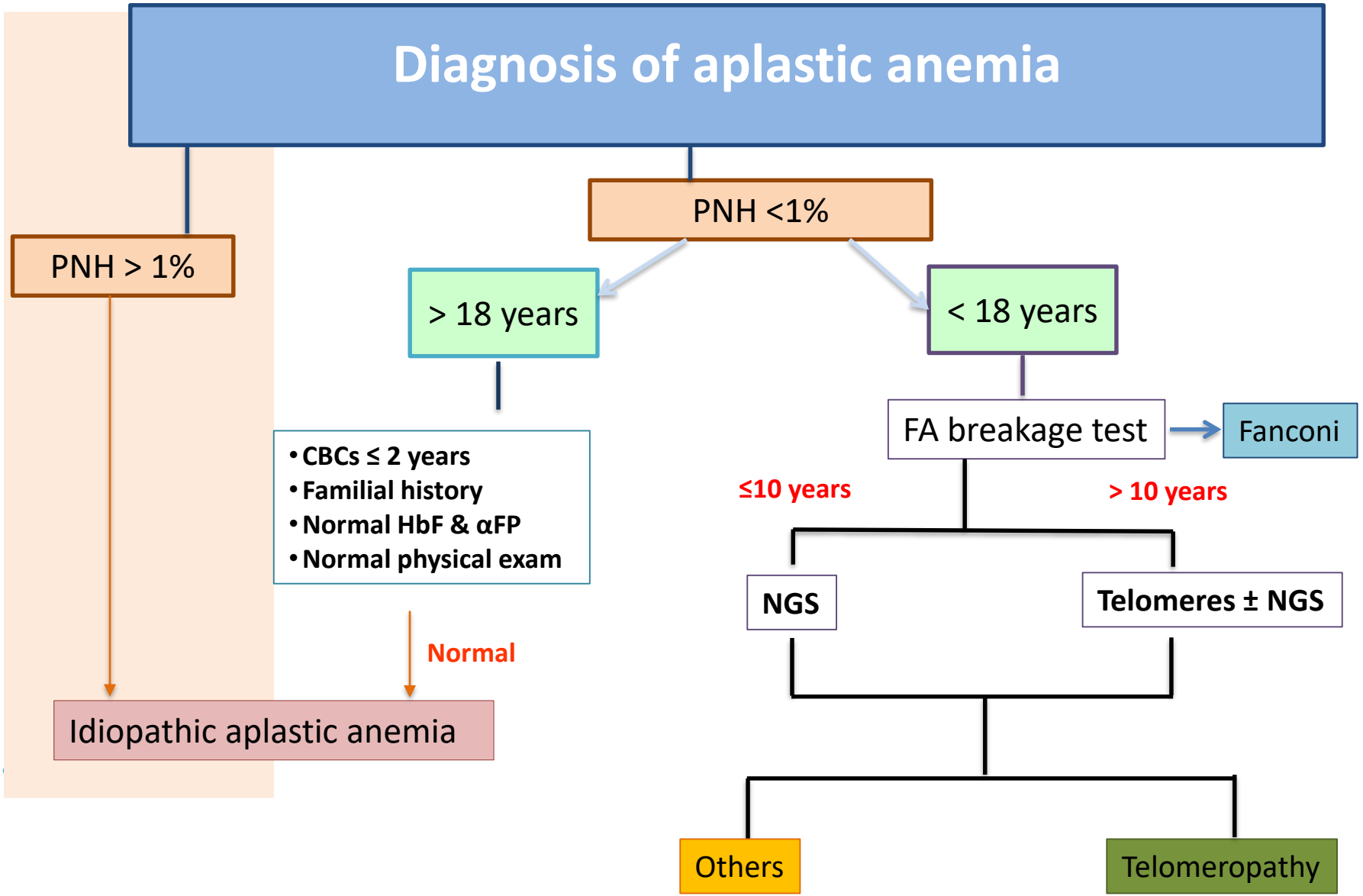

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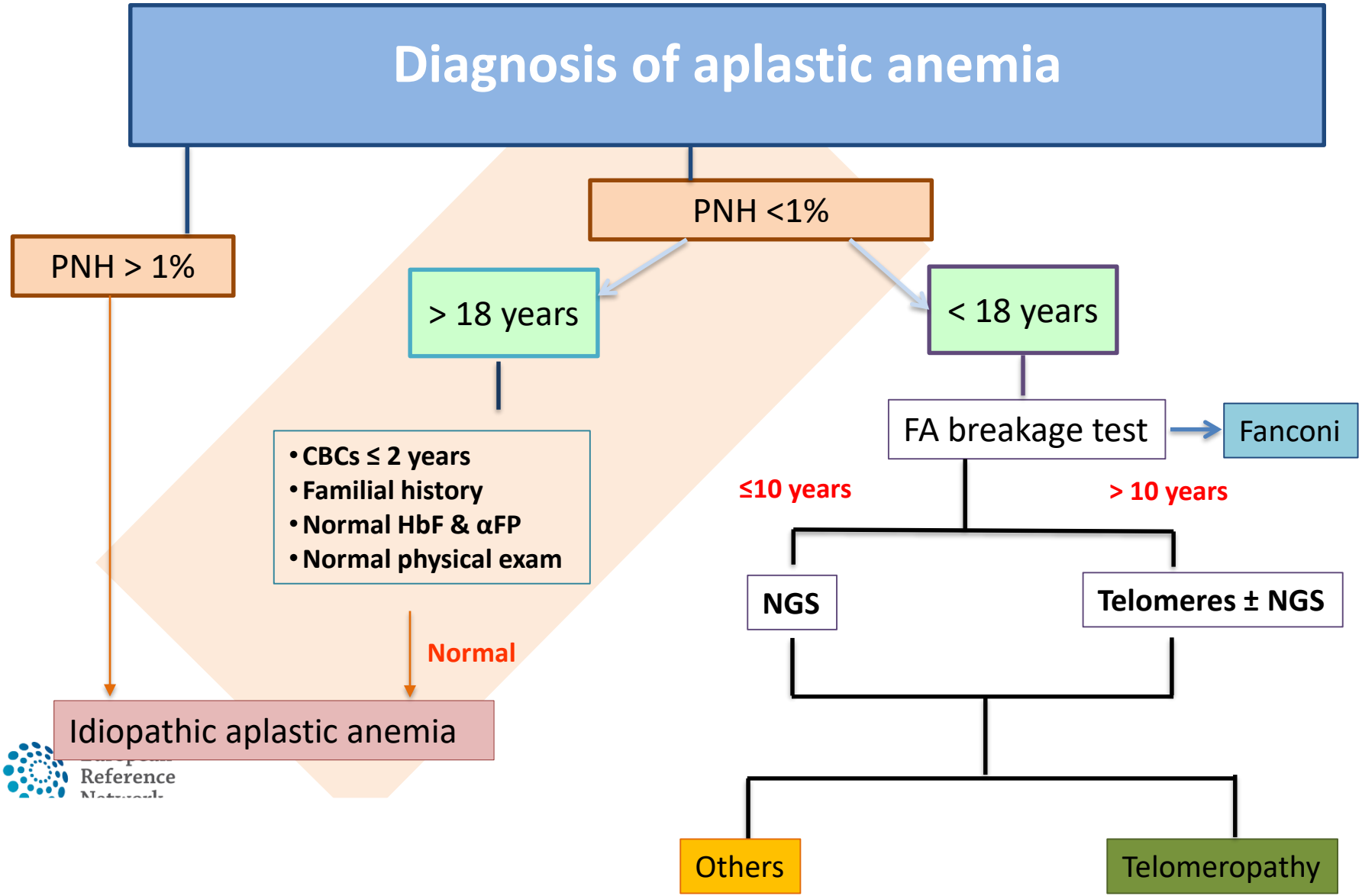

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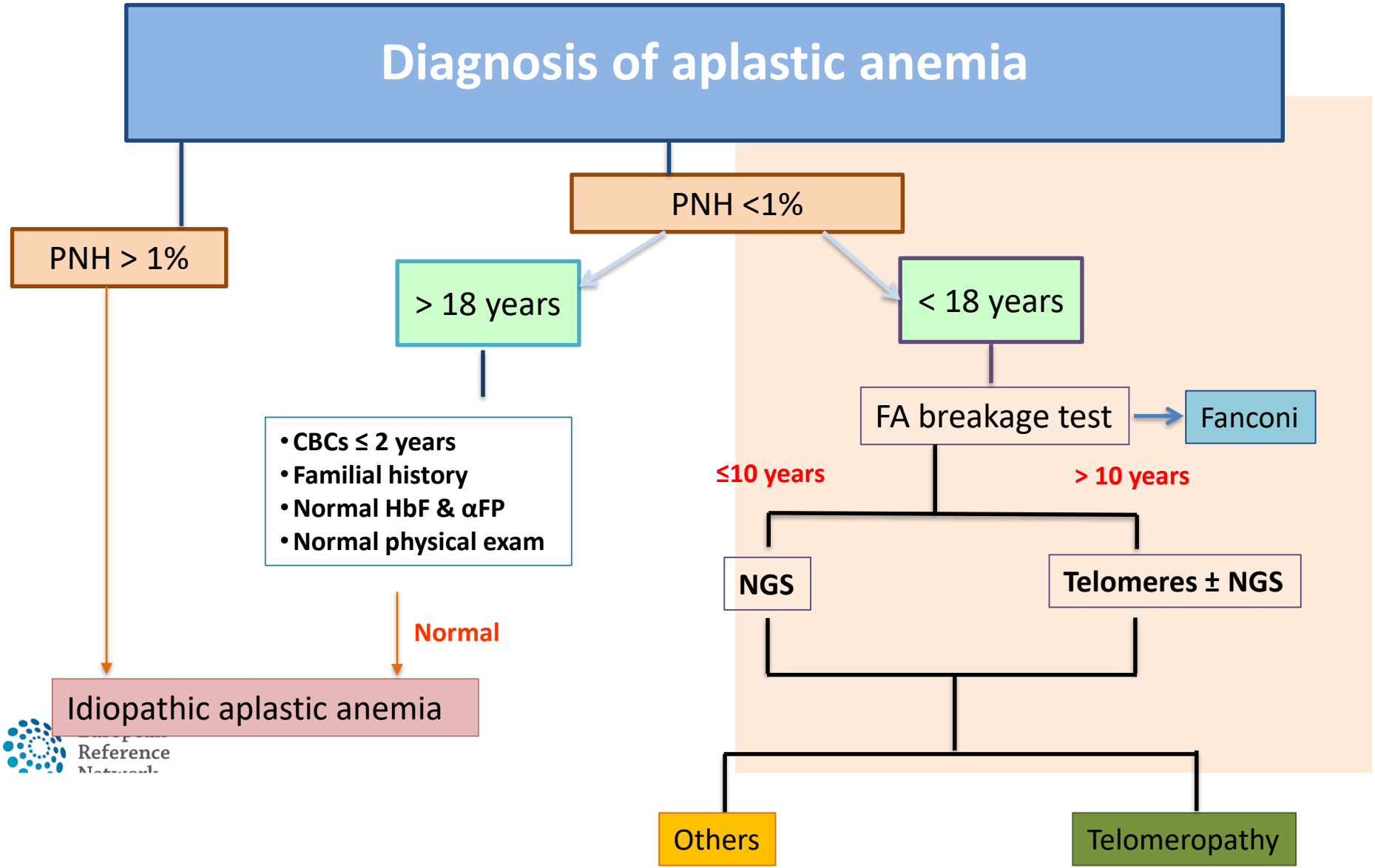

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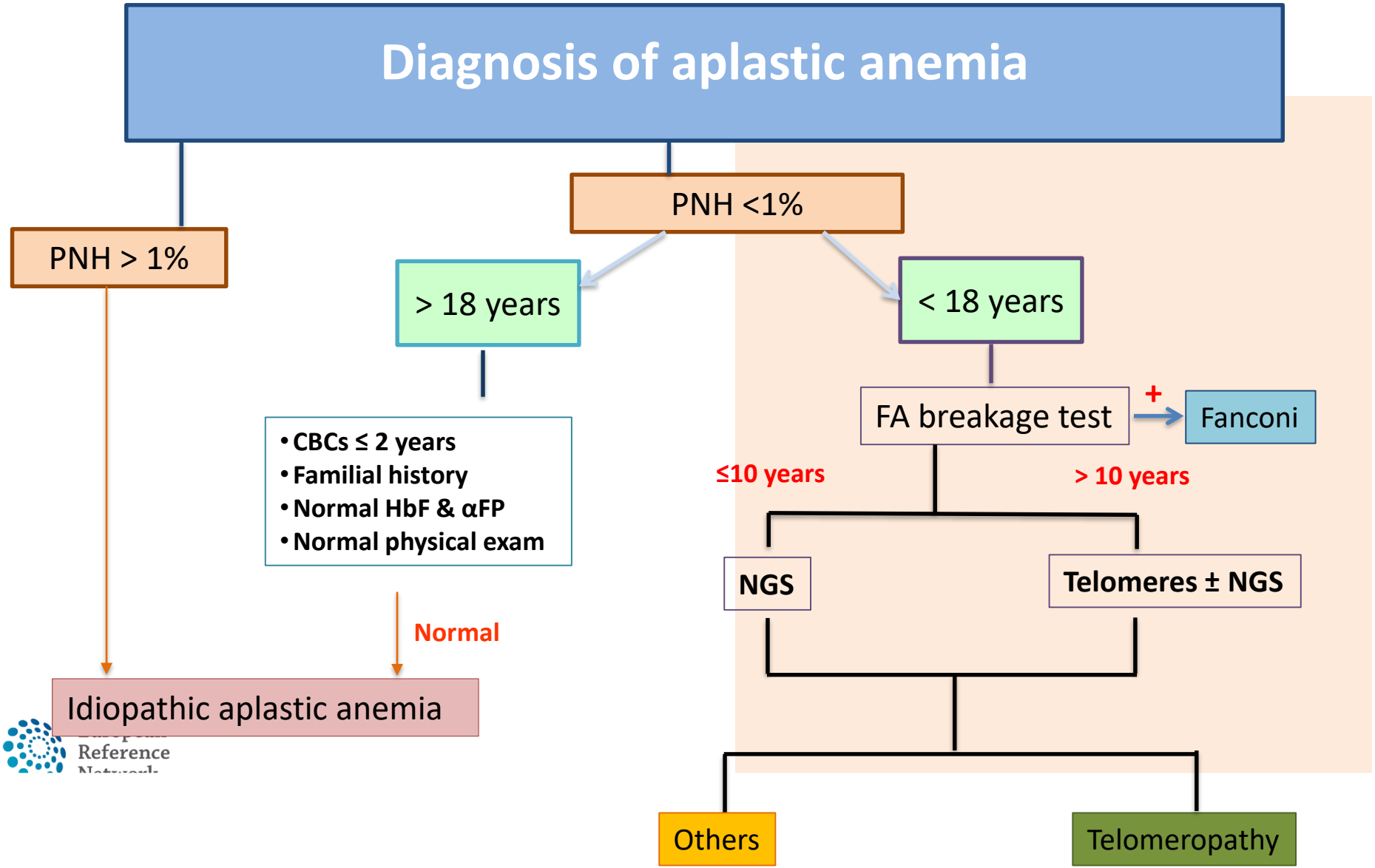

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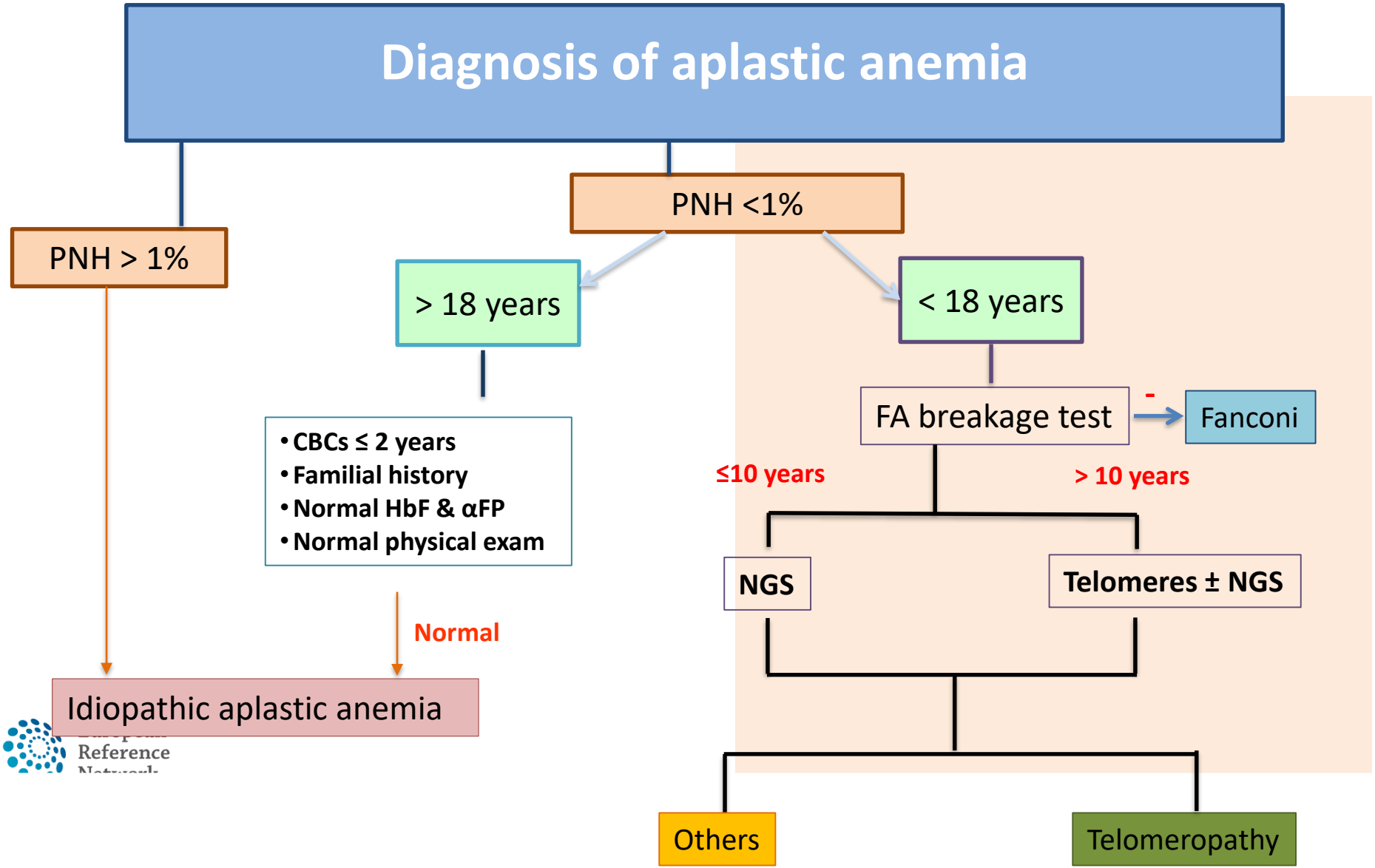

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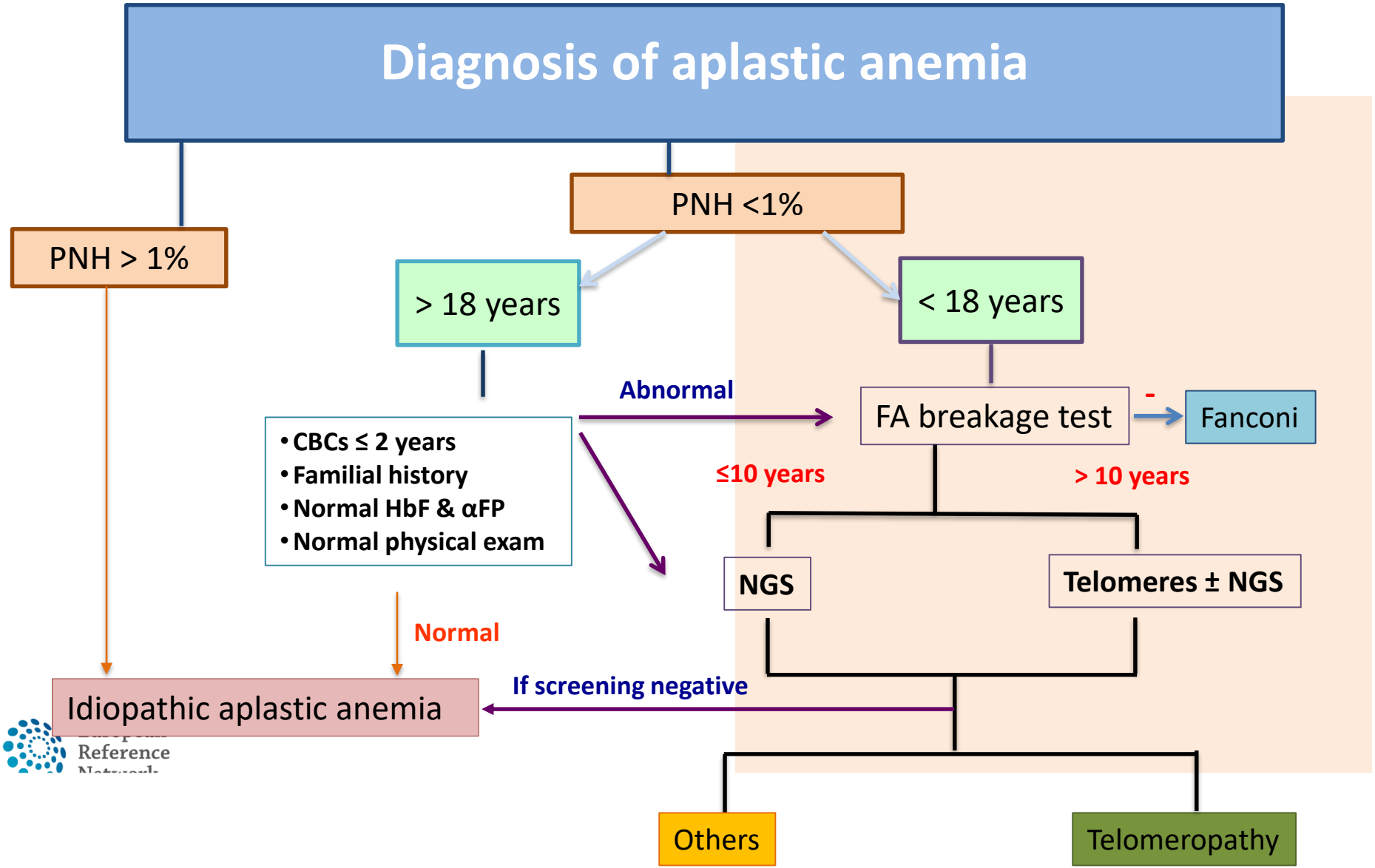

Idiopathic *versus* inherited aplastic anemia

- **Who should be screened at diagnosis of aplastic anemia for germline mutations?**
  - All patients aged 10 or less
  - All patients aged 18 or less without PNH, FA or telomeropathy
  - All adult patients without PNH, FA or telomeropathy **but with suspected features of inherited disorders**

Thank you!

The French Reference Center for aplastic anemia and PNH in Paris

Saint-Louis Hospital

Robert Debré Hospital

Institute of Hematology, IUH St-Louis

F Sicre, T Leblanc, A Baruchel, G Socié (clinic)

N Vasquez, W. Cuccuini, M Sebert, J Soulier (Fanconi Team),

C Kannengiesser, E Lainey, L Da Costa (Telomeres team)

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European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

MaRIH Filière de santé Maladies Rares ImmunoHématologiques

SFGM TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

2016 EBMT European Society for Blood and Marrow Transplantation