Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Inherited and Acquired Marrow Failure

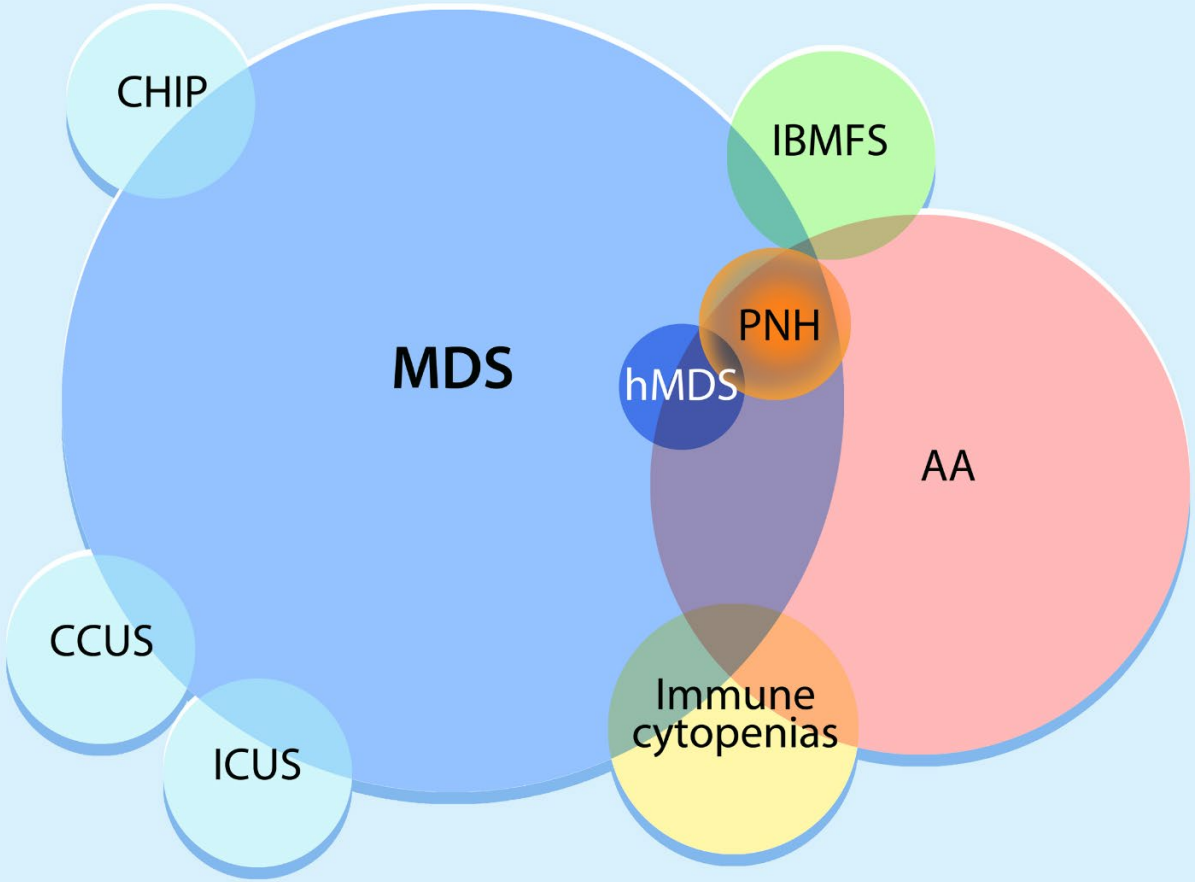
Comprehensive Hematology & Oncology Review Course

Sioḃán Keel, MD
Associate Professor of Medicine

2021

Marrow failure –

Inability of hematopoiesis to meet physiologic demands for the production of healthy blood cells.



Acquired causes

- Acquired aplastic anemia
- PNH

Heritable causes

- Classical Inherited Bone Marrow Failure Syndromes
- Inherited MDS and leukemia predisposition syndromes

Diagnostic work-up of hypocellular marrow + cytopenias

- Severity of the cytopenias should inform how to prioritize work-up

Pancytopenia
Exclude known causes, e.g, B12/ folate deficiency, medication

↓

BM aspirate/biopsy
(morphology, karyotype/array, flow cytometry, iron stain)

↓

Hypocellullar

↓

- History and physical exam
- Peripheral blood
  - HSCT candidate consider HLA typing
  - **Chromosomal breakage study**
    (+ skin fibroblast testing if suspicion is high)
  - Reticulocyte count
  - Flow cytometry for GPI-anchored proteins
  - Telomere length testing by flow-FISH
- Consider genetic testing

Consider heritable cause

Consider heritable causes

- Younger age
- Non-severe disease
- Family history and/or personal history of congenital anomalies (absence of this does not exclude a heritable cause)
- Member of family with known inherited cause
- Antecedent macrocytosis or cytopenias
- **Chromosomal 7 abnormalities & trisomy 8 MDS in peds/young adults**
  - **GATA2 deficiency**
  - **SAMD9/9L (MDS with chromosome 7 abnormalities) –** may account for ~ 20% of pediatric MDS[1]

Schwartz JR, Ma J, Lamprecht T, et al. *Nat Commun*. 2017;8(1):1557

Idiopathic acquired aplastic anemia

- Biphasic age distribution
- Presumed 2^{ndary} to immunologic destruction of hematopoietic stem cells
- Severity – Modified Camitta's criteria[1,2]

Marrow Cellularity
<25% OR 25-50% with <30% residual hematopoietic cells
AND Cytopenias (at least 2 of 3)
ANC < 500 X 10^9/L Plts < 20 X 10^9/L Absolute retic count <60 X 10^9/L

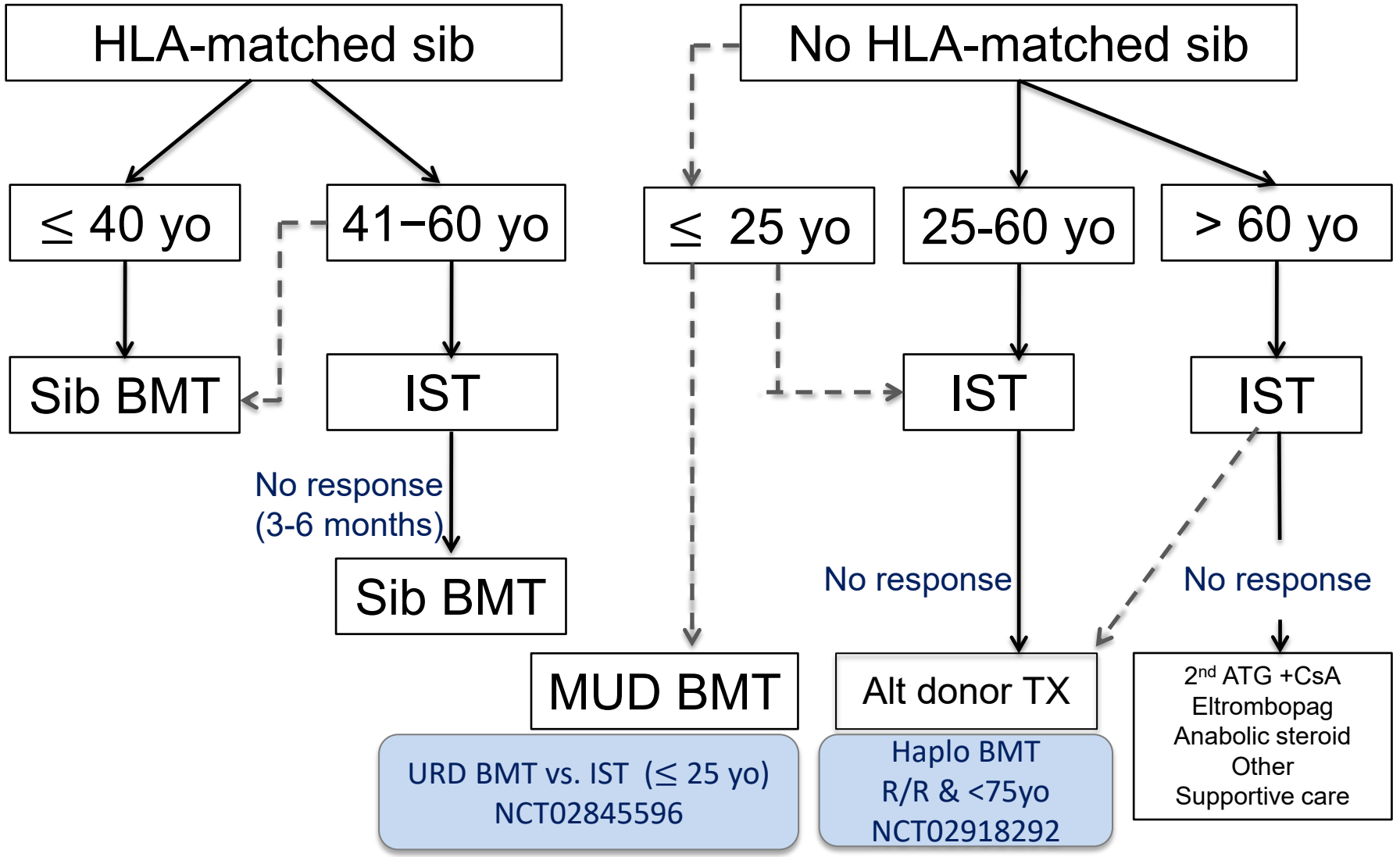
1. Camitta BM. Blood 1976: 48(1). 2. Killlick S. BJH 2016: 172.

Findings which support a diagnosis of acquired aplastic anemia diagnosis (immune-mediated)

- ~ 50% of patients with aAA develop a PNH clone
  - Clone size is generally small in marrow failure patients[1,2]
  - Presence of a PNH clone supports immune-mediated AA and the exclusion of inherited bone marrow failure[2]
- 6p CN-LOH is relatively specific for aAA (not seen in inherited BMF and very rarely in MDS or aging)[3-9]
  - Present in ~ 10-13% of pediatric and adult patients with aAA[6,9]
  - Testing for 6p CN-LOH requires chromosomal microarray analysis

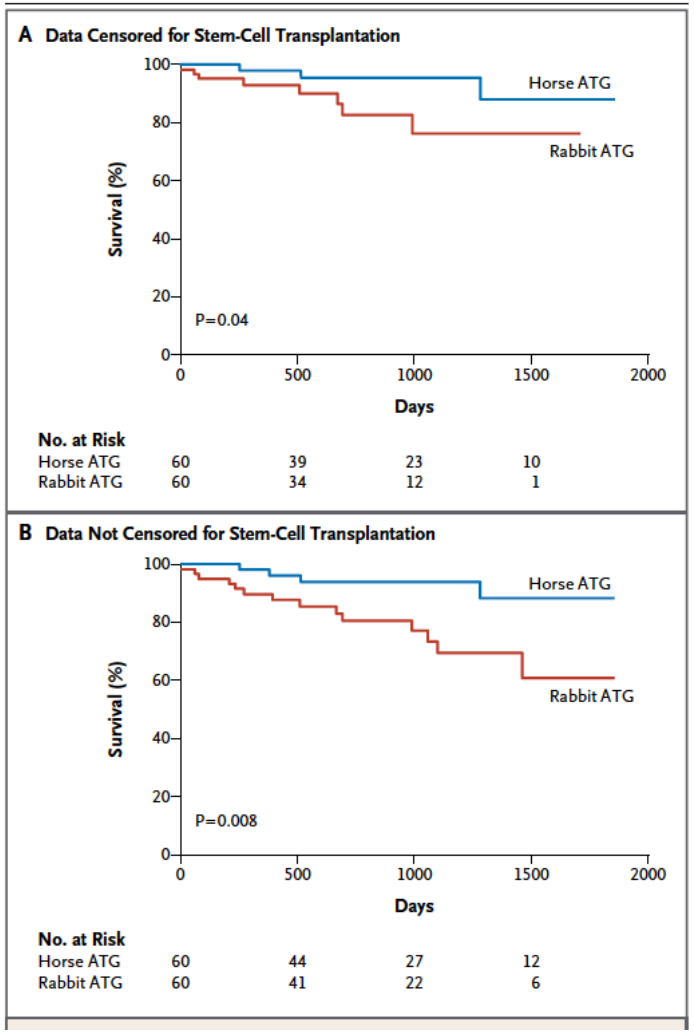
1. Fattizzo B. et al. Leukemia 2021 online ahead of print. 2. DeZern AE. et al. Eur J Haematol 2014: 92(6).
3. Afable MG. et al. Blood 2011: 117(25). 4. Babushok DV. Et al. NEJM 2015: 373(17). 5. Babushok DV. et al BJH 2014: 164(1). 6. Katagiri T. et al Blood 2011: 118(25).
7. Mohamedali AM. et al. Leukemia 2015: 29(9). 8. Score J. et al. Leukemia 2015: 29(7). 9. Betensky M. et al. Cancer Genet. 2016: 209.

Severe idiopathic acquired aplastic anemia



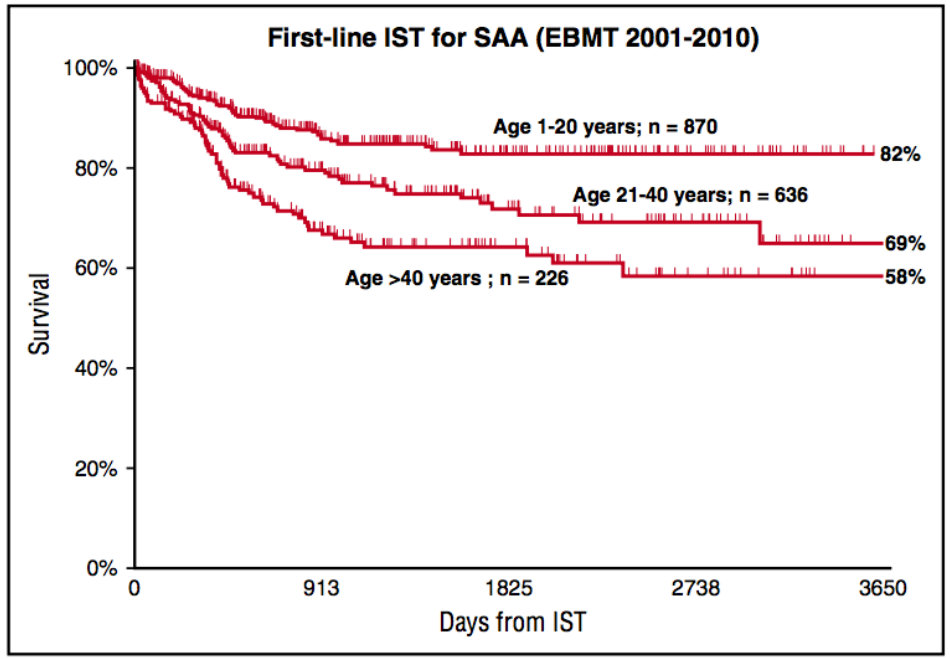
Immune suppressive therapy (IST)

Horse is better than rabbit ATG[1]



Response to IST is age-dependent[2]

- Adding GM-CSF, G-CSF, and IL-3 doesn't improve response or survial[3]



1.Scheinberg P et al. NEJM 2011: 365(35). 2. Bacigalupo A. Blood 2017: 129 (11).
3. Gurion R. et al. Haematologica 2009: 94(5). 4. Young N. et al. Blood 2006: 108(8).

Late complications of IST treated patients

- Relapse in ~ 1/3 of responders[1]
- Only 29% (24/84) with normal blood counts and off all IST after long-term follow-up (median follow-up 11.3 yrs)[2]
- MDS/AML evolution in 10-15% of cases[1,2]

1. Young N. et al. Blood 2006: 108(8). 2. Frickenhofen N. et al. Blood 2003: 101(4).

Eltrombopag (Epag) for acquired aplastic anemia

- Small molecule TPO mimetic that bypasses IFN-γ-mediated inhibition of endogenous EPO to stimulate c-MPL[1]
- Relapsed/refractory – Phase 2 + extension study (43 patients)[2]
  - Epag 150 mg po daily
  - Hematologic response 40% (17/43) @ 12 wks
- Upfront therapy
  - Phase 1-2 study (92 patients; median f/up 2 yrs)[3]
    - Epag 150 mg po daily D1-6 months + hATG/CsA
    - CR 58% and OR 94% @ 6 months
  - RCT hATG/CsA/Epag (n=96) vs. hATG/CsA (n=101) abstract presented at 2020 EBMT Annual Meeting (RACE study)[4]
    - CR 21.9% vs. 9.9% and OR 59.4% vs. 31.7% at 3 months
    - OR 76.3% vs. 50% at 6 months
- No improvement in ORR or CR at 6 months in pediatric patients (<18 yo)[5]

1. Alvarado LJ. et al. Blood 2019: 139(19).
2. Desmond R et al. Blood 2014: 123(12).
3. Townsley M et al. NEJM 2017: 376(16).
4. Peffault de Latour R et al. Abstract 0018 EBMT 2020.
5. Groarke EM et al. BJH 2021: 192(3).

Practical considerations for IST + Epag

- Optimal delivery appears to be simultaneously on D1.
- Continue full dose CsA and Epag up to six months (if CR at 3 months could consider stopping Epag – await details from RACE trial).
- Stop Epag at 6 months if able and continue CsA at lower doses up to 24 months.
- Study evaluating sirolimus (NCT02979873) to prevent relapse after stopping CsA.

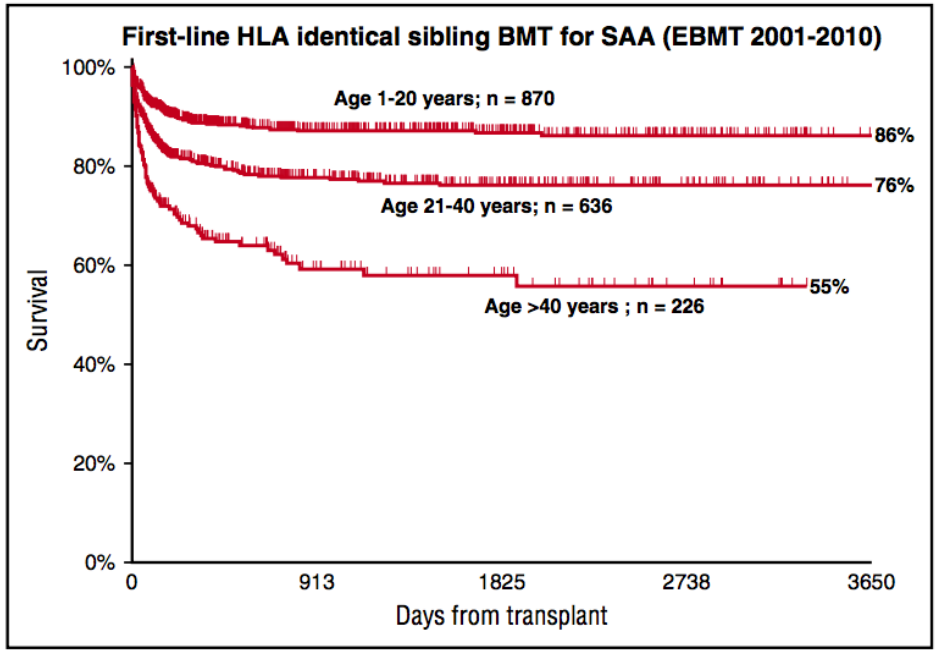
Epag and clonal evolution in aAA

- Impact on malignant evolution uncertain
  - 19% (16/83) of rSAA treated with single-agent Epag early cytogenetic clonal evoluation[1]
- Longer follow-up needed

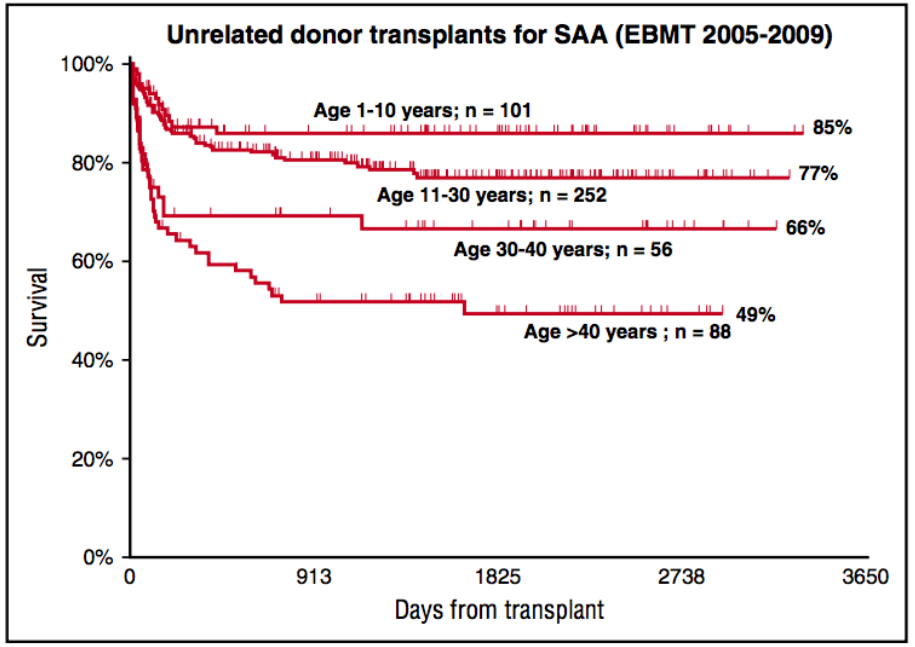
1. Winkler T. et al. Blood 2019; 133(24).

BMT for severe AA

HLA-matched sib



MURD



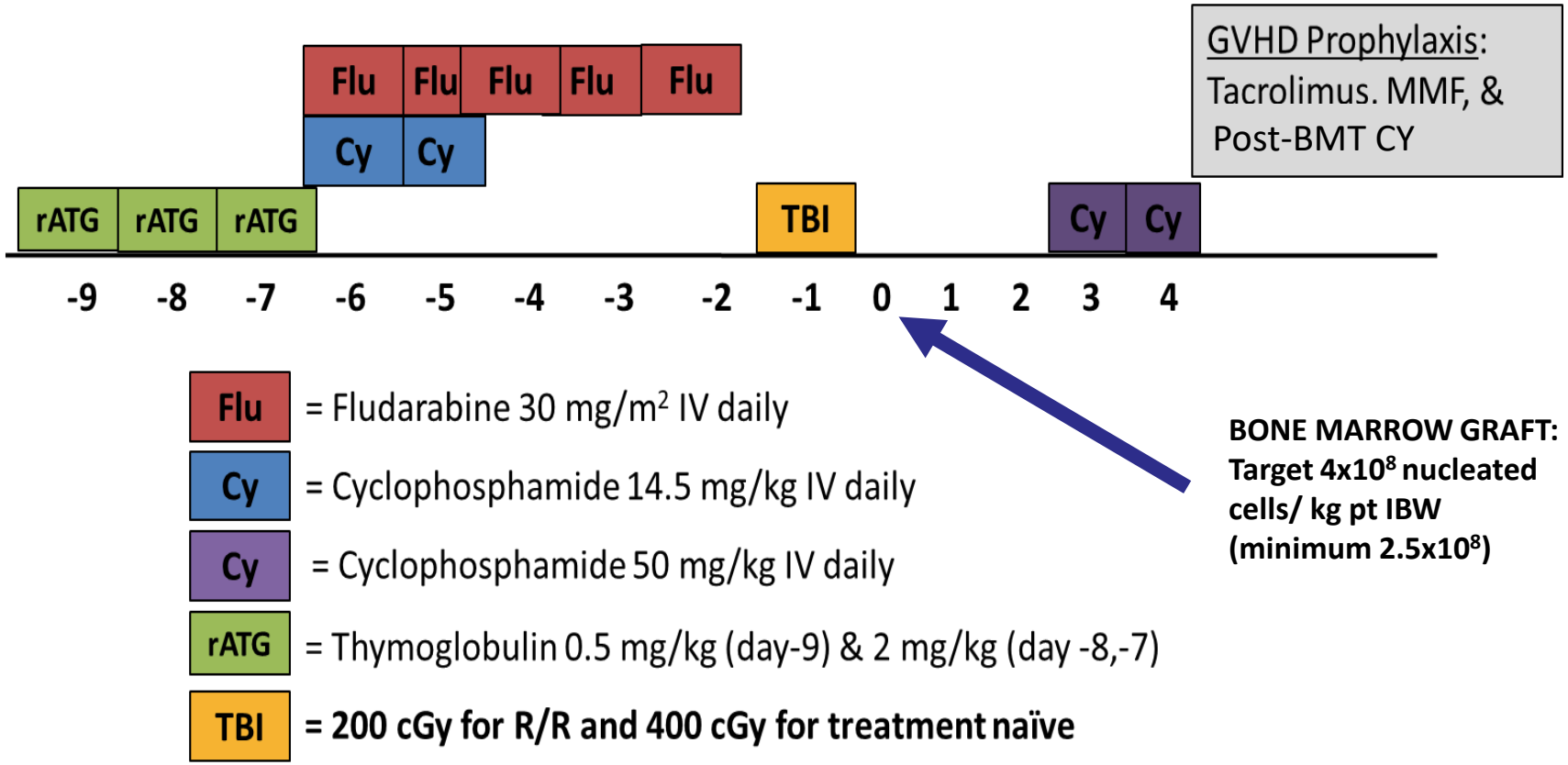
Data from EBMT Registry reviewed in Bacigalupo A. Blood 2017: 129 (11).

Hopkins Phase II trial of Haplo BMT for SAA

- **Relapsed/refractory trial (20 patients)**
  - SAA and ≥3 months after IST & no sib donor
  - Median age 29 yo (5-69)
- **Treatment naïve trial (17 patients)**
  - SAA and untreated & no sib donor
  - Median age 22 yo (3-63)

DeZern A. et al. Blood Adv 2020: 8(4).

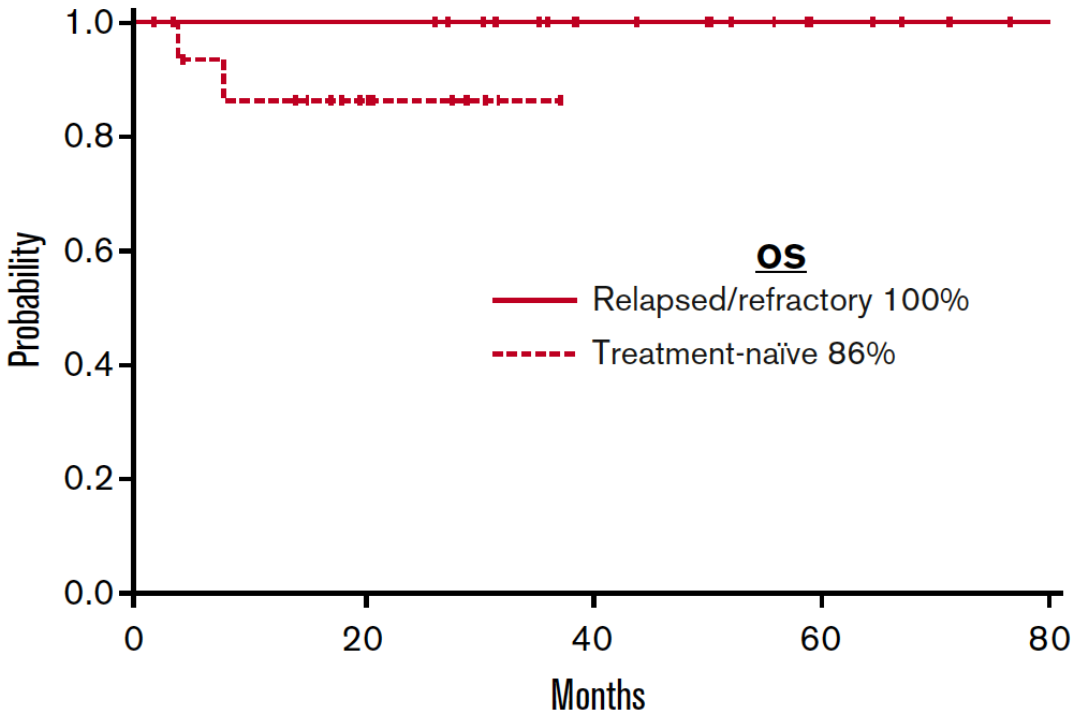
Conditioning and GVHD Prophylaxis



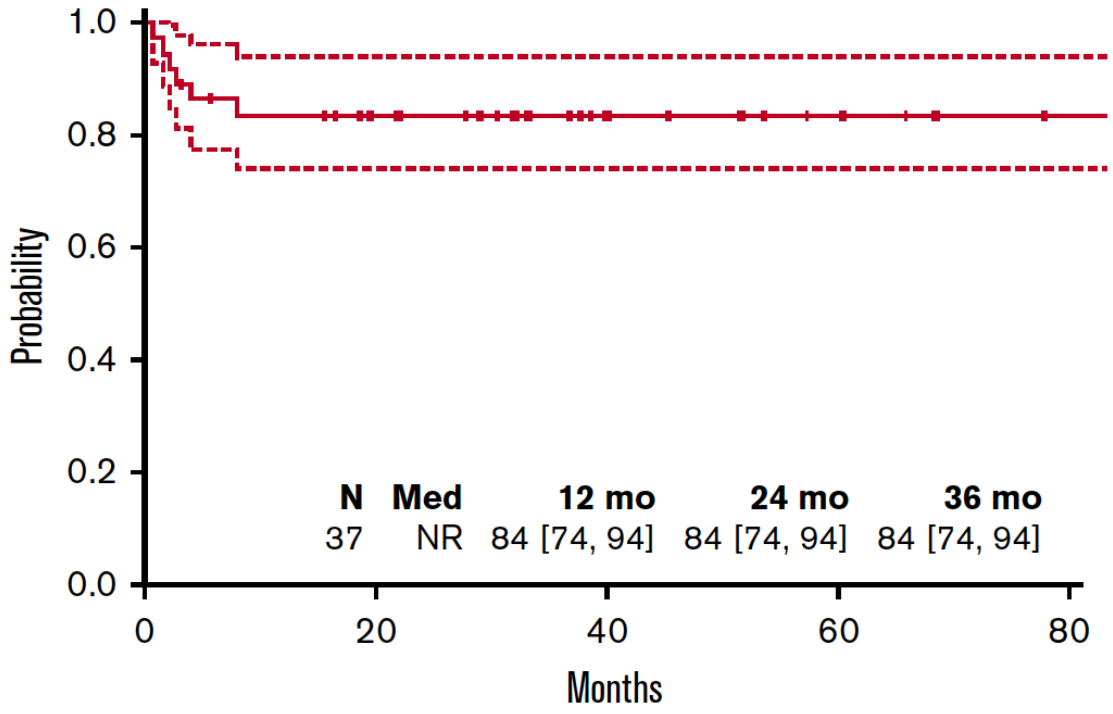
** After initial 7 treatment-naïve patients treated at 200 cGy, increase TBI to 400 cGy

DeZern A. et al. Blood Adv 2020: 8(4).

Overall survival



GVHD-free survival



- CTN 1502 CHAMP study NCT02918292 (relapsed/refractory SAA up to 75 yo)

DeZern A. Blood Adv 2020: 8(4).

Paroxysmal nocturnal hemoglobinuria

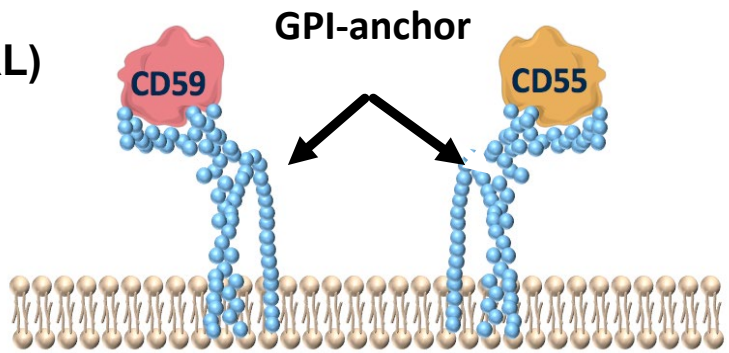
- Nonmalignant clonal expansion of HSCs with a somatic mutation of *PIGA*
- Classical PNH clinical triad - intravascular hemolysis, thrombosis, bone marrow failure
- PNH cells lack surface proteins that require a GPI anchor which normally protect against complement-mediated hemolysis
- Diagnosis - Absent or reduced GPI-linked proteins
  - Clone size in classical PNH is usually large[1]

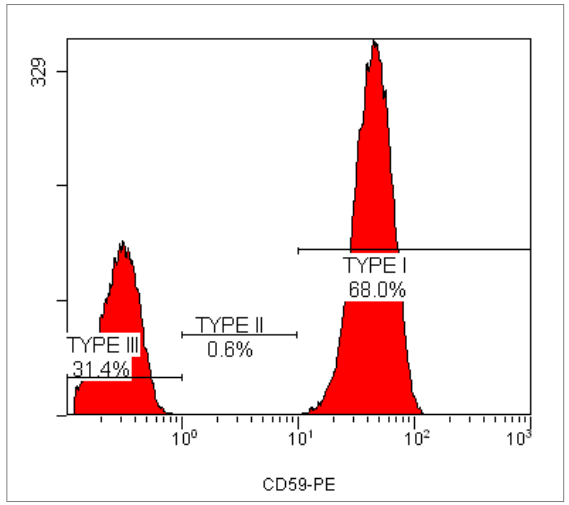
CD59

Membrane inhibitor of reactive lysis (MIRL)
Inhibits assembly of the membrane attack complex

CD55

Decay accelerating factor (DAF)
Inhibits the formation and stability of the C3 convertases





Cannizzo E. et al. Ann Hemat 2019: 98(5).

PNH Treatment

- Folic acid ± iron supplementation, role for prophylactic anticoagulation unclear
- Eculizumab or ravulizumab treatment indicated for significant disease manifestations attributable to hemolysis[1,2].
  - ~5-25% of patients continue to experience anemia EVH (C3b)[3]
    - First-in-class C3 inhibitor pegcetacoplan FDA approved (superior to ecuizumab in improving Hgb and normalizing hemolytic markers)[4]
  - ACIP recommends meningococcal vaccination (MenACWY and MenB vaccines)
  - Vaccination does not eliminate risk

1. Lee JW. Blood 2019: 133(6).
2. Kulasekararaj AG. et al. Blood 2019: 133(6).
3. Brodsky RA. et a.l Haematologica 2021: 106(1).
4. Hillman P. et al. NEJM 2021: 384(11).

Classical inherited bone marrow failure syndromes and leukemia/MDS predisposition syndromes

- **Classical inherited bone marrow failure syndromes**
  - Diamond Blackfan anemia
  - Fanconi anemia
  - Shwachman-Diamond syndrome
  - Telomere biology disorders
- **Germline predisposition for hematopoietic malignancy**
  - *DDX41*
- **Germline predisposition for hematopoietic malignancy with pre-existing cytopenia(s) and/or other organ dysfunction prior to hematopoietic malignancy presentation**
  - GATA2 Deficiency Syndrome
  - *RUNX1* - Familial platelet disorder with associated myeloid malignancy
- **Germline predisposition for myeloid neoplasms and solid tumor cancers**
  - Hereditary breast and ovarian cancer (e.g., *BRCA1, BRCA2*)
  - Li-Fraumeni syndrome

Modified from 2021 NCCN MDS Guidelines
(mutations associated with hereditary myeloid malignancy)

Why care about these cancer predisposition syndromes?

- Affected patients with MDS/acute leukemia
  - Informs hematopoietic stem cell transplant donor selection
  - May inform choice of chemotherapy/radiation
- Cancer and end organ damage surveillance programs
- Care and counseling of family members
- Incorporation of genetic predisposition in 2016 WHO myeloid neoplasm and AL classification[1] and NCCN MDS and European LeukemiaNet guidelines[2]

1. Arber D. et al. Blood 2016: 127. 2. Dohner H. et al. Blood 2017: 129.

Somatic versus constitutional (aka germline)?

- Same genes can have somatic OR constitutional (aka germline) mutations.
- Variant allele frequency (VAF) does not definitively distinguish somatic vs. germline
- Test non-hematopoietic tissue (skin fibroblasts) or test other family members

Caveat

- Panels designed for somatic vs. germline genetic mutations are not always equivalent
  - May include different sets of genes
  - May cover different regions of a given gene

Examples:

- *RUNX1*
- *GATA2*
- *ETV6*
- *CEBPA*
- *DDX41*
- *BRCA1/2*
- *BRAF*
- *TP53*
- *MPL*
- *JAK2*
- *CSF3R*
- *SAMD9/SAMD9L*
- *Ras pathway genes*

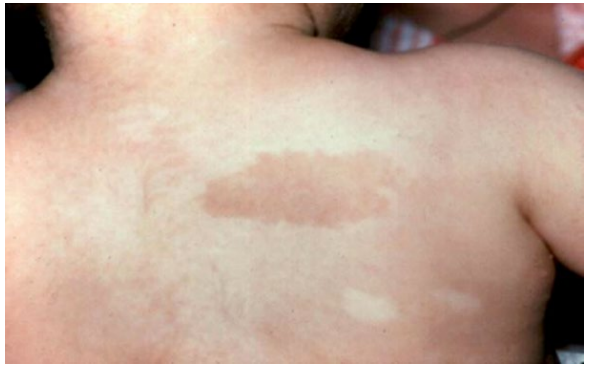
Classical inherited bone marrow failure syndromes

Inherited BMF syndrome	Genetics	Classical findings	Hematology & oncology	Diagnostic tests	Solid tumors
Fanconi anemia	AR and x-linked recessive DNA repair genes (e.g., *FANCA*)	Congenital anomalies (1/3 lacking)	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Increased chromosome fragility	SCC (head/neck/ vulva/vagina) Hepatocellular carcinoma
Short telomere syndromes/ Dyskeratosis congenita	AD, AR, x-linked recessive Telomere maintenance genes (e.g., *DKC1, RTEL1 TERT, TERC*, *TINF2, RTEL1*)	Dystrophic nails, lacey reticular rash, oral leukoplakia Adult presentations – immune deficiency, liver cirrhosis, premature graying, pulmonary AVMs, pulmonary fibrosis	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Very short telomeres for age	SCC (head & neck) ,
Diamond- Blackfan anemia	AR Ribosomal proteins (e.g. *RPS19*)	Short stature, Cathie's facies	Macrocytosis, erythroid hypoplasia, MDS, leukemia, solid tumors	Elevated erythrocyte adenosine deaminase	Sarcomas, colon CA
Shwachman-Diamond syndrome	AR *SBDS, EFL1, DNAJC21*	Exocrine pancreatic insufficiency, short stature, skeletal abnormalities	Macrocytosis, cytopenia (especially neutropenia), hypocellular marrow/AA, MDS, leukemia	Low pancreatic isoamylase(>3 yo) and low fecal elastase (peds & adults), Low fat-soluble vitamin levels	

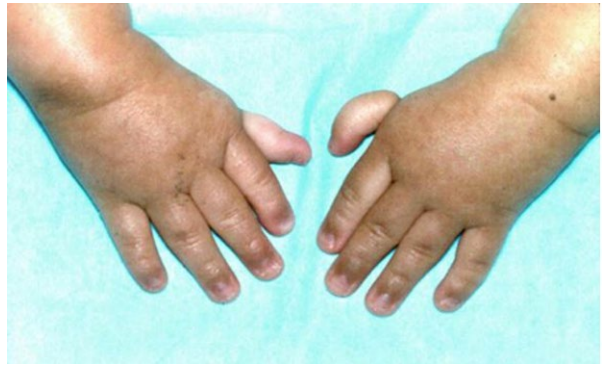
Fanconi anemia

- Mutations in at least 22 gene involved in DNA damage repair pathway
  - All AR except FANC B is x-lined recessive and FANCR is AD
  - US estimates ~ 1/130,000 live births
- Congenital anomalies
  - **~1/3 lack congenital anomalies**
- Hypocellular marrow ± cytopenias
- Predisposition to cancer (AML; oral, esophageal, vulvar SCC, HCC)
- Chemotherapy sensitivity or radiosensitivity (DNA damage)

café au lait spot



thumb abnormalities



Alter BP, Young NS. In Nathan DG, Oski DA, eds. Hematology of Infancy and Childhood 1993.

FA diagnosis - Chromosome fragility testing (aka chromosome breakage testing)

- Based on the hallmark of genomic instability[1,2]
- 20% have mosaic lymphocytes (genetic reversion)[3,4]
  - *If clinical suspicion is high → test skin fibroblasts*
- Genetic testing

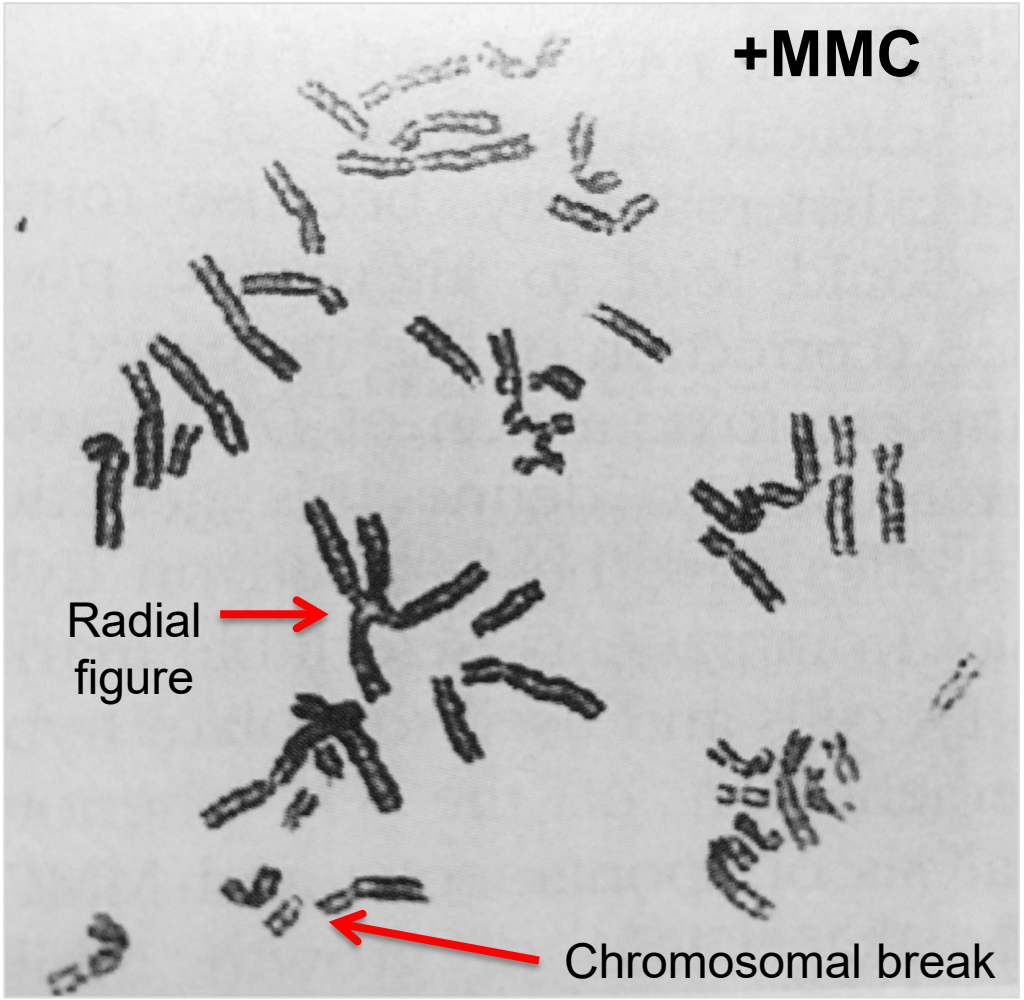


Image from Clinical Hematology editors Young N, Gerson S, High K. 2006.

1. Schroeder TM. Humangenetik 1966: 2. Sasaki MS. Et al. Cancer Res 1973: 33.
3. Soulier et al. Blood 2005: 105. 4. Lo Ten Foe JR, et al. Eur J Human Genet 1997:

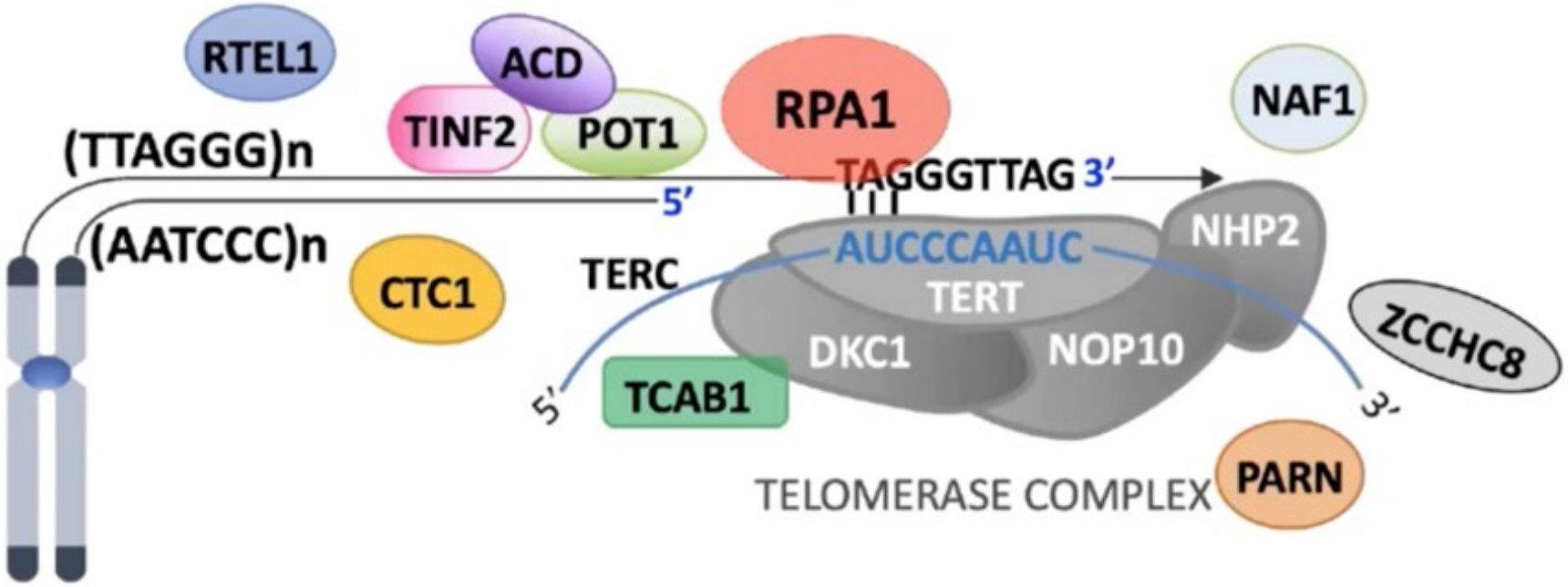
FA surveillance and treatment

- Avoid tobacco and radiation
- Surveillance for solid tumors in all adults – early detection key!
- Monitor bone marrow failure and leukemia/MDS
- Androgens improve hematopoiesis (oxymethalone 0.5-1 or danazol 2-4 mg/kg/day)
  - Stimulates erythroid progenitors and increases telomerase gene expression[1]
  - Erythroid and trilineage responses in ~ 60-80%[2]
  - Monitor LFTs, liver US (hepatic adenomas and peliosis hepatis), virilization
- HSCT
- Chemotherapy – non-DNA damaging chemotherapy

2020 Fanconi anemia guidelines for diagnosis and management
https://www.fanconi.org/explore/clinical-care-guidelines

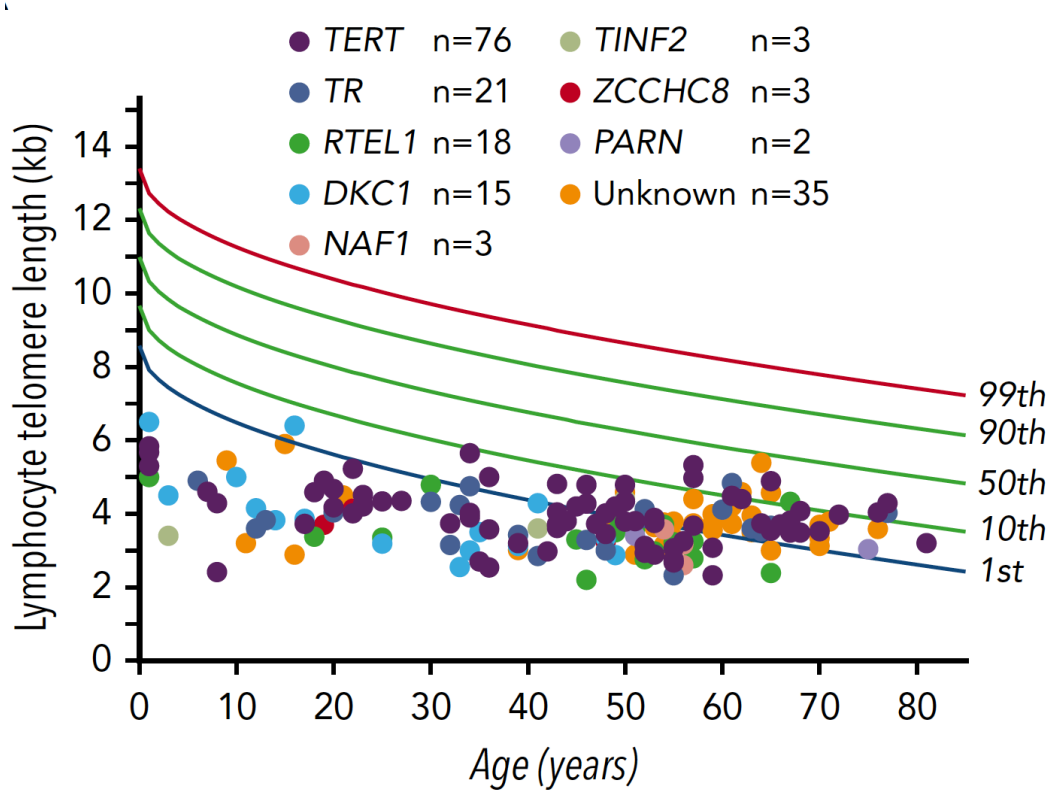
1. Calado RT et al. Blood 2009: 114. 2. Calado RT and Cle D. ASH Education Book 2017. Bone Marrow Failure: Inherited.

Human telomere complex



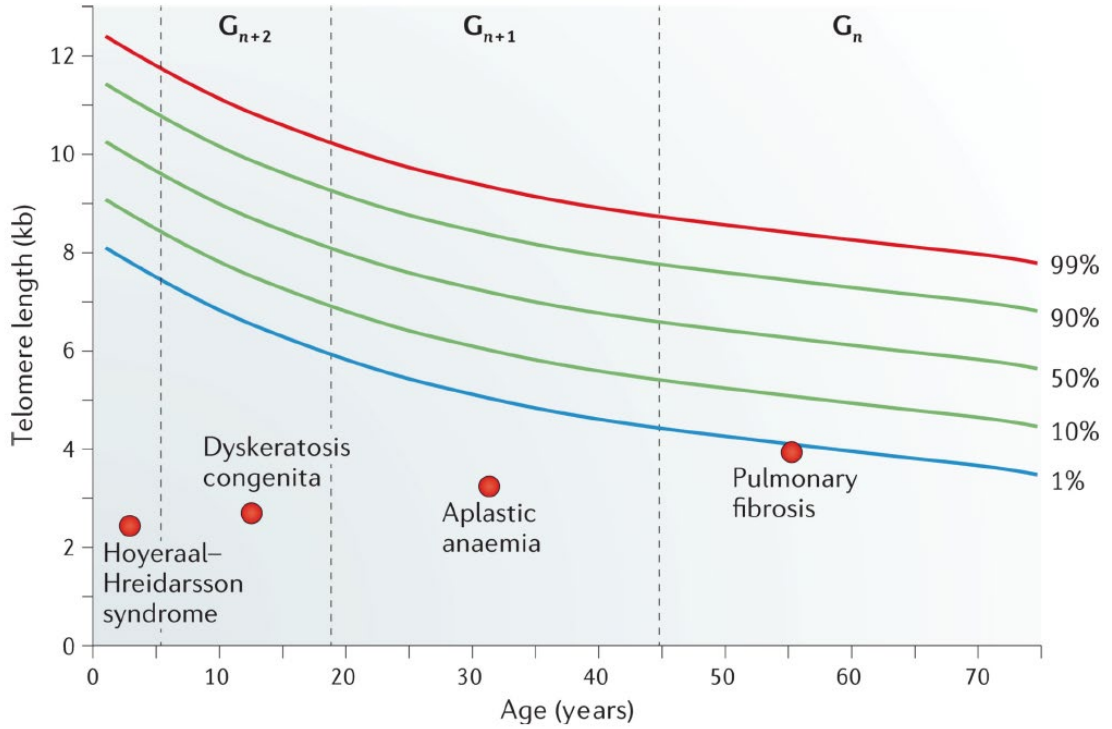
From Mangaonkar A. et al. Mayo Proceedings 2018: 93.

Age-dependent interpretation of telomere lengths



Schratz,K. et al. Blood 2020:135.

Age-dependent presentations of STS



Armanios M. et al. Nat Rev Genetics 2012: 13(10).

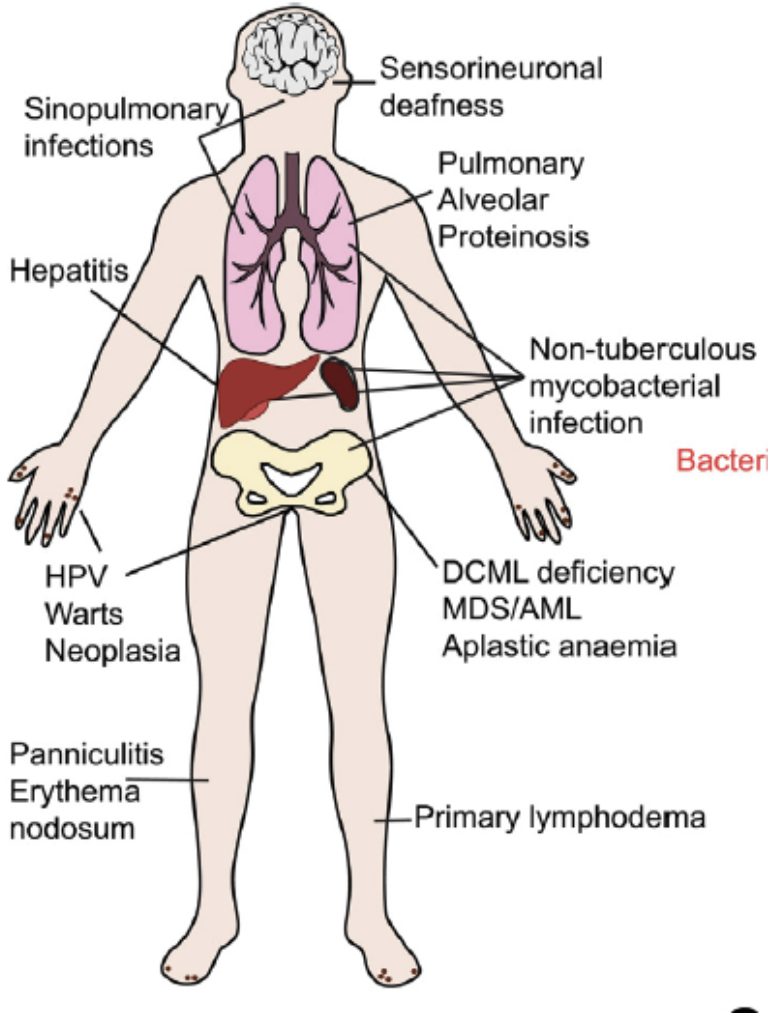
Spectrum of Telomere Biology Disorder phenotypes

Representative disorders	Key clinical features
Dyskeratosis congenita (DC)	Mucocutaneous triad (nail dysplasia, abnormal skin pigmentation, and oral leukoplakia), bone marrow failure, pulmonary fibrosis, pulmonary arteriovenous malformations, liver disease, avascular necrosis of hips or shoulders , urethral stenosis, lacrimal duct stenosis, esophageal stenosis, cancer, and/or developmental delay
Aplastic anemia*	Progressive multi-lineage cytopenias, non-immune mediated
MDS and AML*	
Hepatic disease*	Cryptogenic cirrhosis, noncirrhotic portal hypertension (nodular regenerative hyperplasia), hepatopulmonary syndrome
Idiopathic Pulmonary Fibrosis*	May occur in absence of DC-associated features. ~30% of familial PF and 3-5% of sporadic IPF. Other pulmonary phenotype – pulmonary AVMs

Gorgy A. et al. Chest 2015: 148(4).

GATA2 deficiency Syndrome

- Autosomal dominant
  - Most mutations are de novo (can't rely on family history!)
- High risk of developing AML/MDS
- Cellular immunodeficiency develops with age
  - NTM infections
- Multiple clinical syndromes
  - MonoMac
  - Familial MDS/AML
  - Emberger's syndromes
  - Isolated cytopenias
- Germline GATA2 mutations among 7% of pediatric/adolescent primary MDS patients[1]
  - 37%of patients whose MDS was characterized by monosomy 7



1. Wlodarski MW et al. Blood 2016:127(11).

Familial Platelet Disorder with Associated Myeloid Malignancy: RUNX1 disorder

- Autosomal dominant
- Mild/moderate thrombocytopenia
- Hints - mild bleeding tendency – platelet dense granule deficiency, family history of MDS/AL
- High risk of developing MDS/AML

Germline DEAD-box helicase 41 gene (*DDX41*) mutations are common in adult MDS

- Tumor suppressor gene in myeloid neoplasms (chr 5q35.3)
- Involved in the splicing of pre-mRNAs, rRNAs and innate immunity signaling
- Germline mutations associated with hereditary hematologic malignancy[1]
  - **2.4% incidence adult MDS/AML**[3]
  - Mean age of onset of MDS or AML 62 years-old (long-latency)[1,2]
  - Characterized by normal karyotype and 2nd somatic mutation in *DDX41*[3]

1. Polprasert C. et al. Cell 2015: 27. 2. Lewinsohn M. et al. Blood 2016: 127. 3. Sebert M. et al. Blood 2019: 134.

High yield pearls

- Randomized control study data demonstrates superior response and survival with horse ATG/CsA compared to rabbit ATG/CsA in upfront therapy of sAA
- Recognition of an underlying inherited BMF or inherited leukemia/MDS predisposition syndrome is important.
- Important to distinguish somatic vs. germline mutations.
- Consider GATA2 deficiency in patients presenting with disseminated nontuberculous mycobacterial infections or monosomy 7 MDS in young adults.