Fred Hutch
Cancer Center

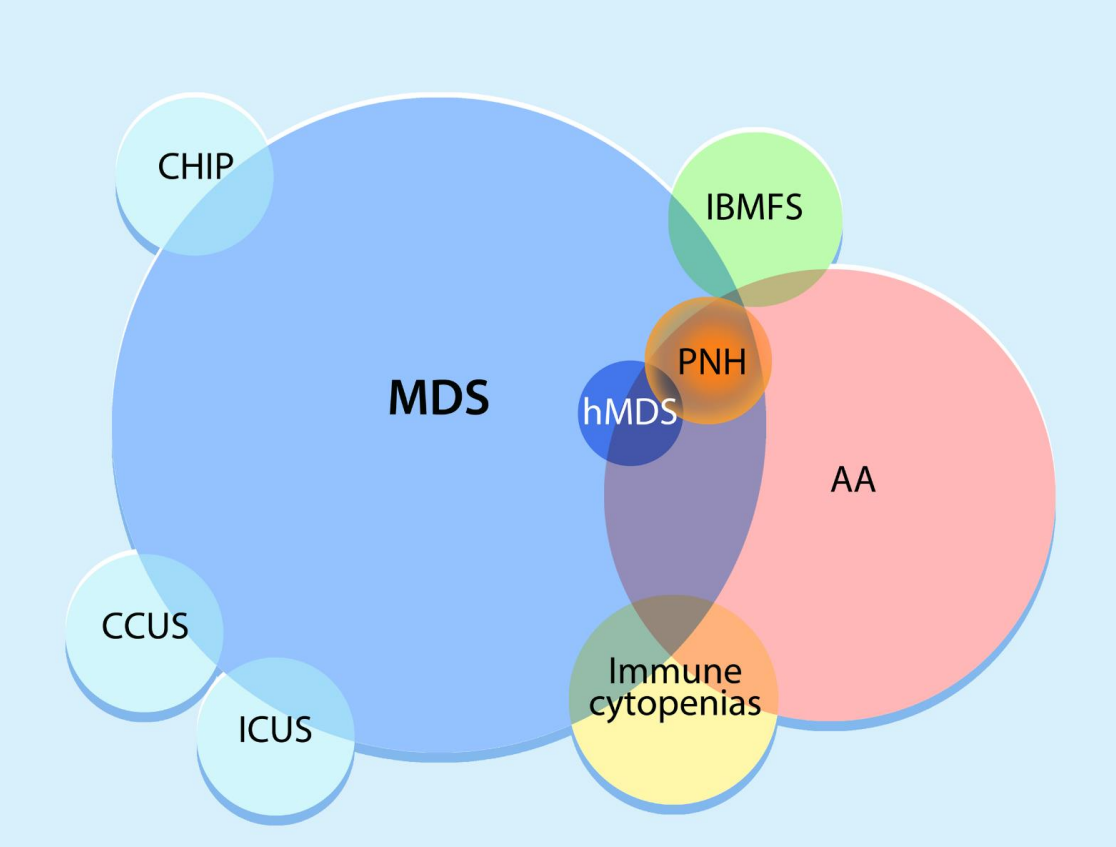
Inherited and Acquired Marrow Failure

Comprehensive Hematology & Oncology Review Course 2024

Bart Scott, MD
Professor of Medicine
University of Washington
Fred Hutchinson Cancer Center

Marrow failure

- Hematopoiesis is unable to meet the physiologic demands for healthy blood cells production.



This talk is about:

- Inherited
  - Classical Inherited Bone Marrow Failure Syndromes (IBMF)
  - Hereditary hematologic malignancy predisposition syndromes (HHMPS)
- Acquired
  - Acquired aplastic anemia
  - PNH

Hypocellular marrow initial laboratory evaluation

Studies I recommend regardless of clinical suspicion

PERIPHERAL BLOOD	DIAGNOSIS
Flow cytometry for PNH	Acquired aplastic anemia
Chromosomal breakage testing	Fanconi anemia
Telomere lengths by flow-FISH	Short telomere syndrome
Immunoglobulins, lymphocyte subsets	Inborn error of immunity, GATA2 deficiency
Pancreatic isoamylase	Shwachman-Diamond Syndrome
HLA typing on patient and potential familial donors	
BONE MARROW	
Morphologic review (including iron staining)	MDS, GATA2 deficiency
Routine karyotype	MDS, IBMF/MMPS
FISH	MDS, IBMF/MMPS
Chromosome genomic array	6p CN-LOH in aAA, IBMF/MMPS, risk stratification nl karyotype MDS, 7q LOH in SAMD9/9L disorders
Multi-gene genetic testing for somatic mutations in myeloid malignancy genes	
CULTURED SKIN FIBROBLASTS	
Germline multi-gene genetic testing	Inherited bone marrow failure and hematologic cancer predisposition syndrome

Acquired PNH clones may distinguish acquired AA from IBMF/HHMPS

- Detectable by flow cytometry in ~ 50% of acquired AA
- PNH clones appear to distinguish aAA from IBMF/HHMPS (~ 100% PPV)
  - Mutant HSPCs escape autoimmune attack

Authors	Year	Flow cytometry sensitivity	PNH + IBMF/MMPS	PNH + aAA	PPV and NPV for aAA
DeZern A. et al.	2014	> 0.01-0.1%	**0/20** (0%)	61/132 (46%)	PPV 100% NPV 54%
Shah YB. et. al	2021	> 0.05-0.1%	**0/9** (0%)	58/126 (46%)	PPV 100% NPV 48.5%
Narita A. et al	2022	> 0.02% grans > 0.037% erythroids	**9/21** (42%)	32/91 (35%)	PPV 78% NPV 17%

DeZern A et al. Eur J Haematol 2014:92.
Shah YB et al. Blood Adv 2021:5.
Narita A et al. Blood Adv 2022: 6.
Borowitz MJ et al. Cyto B Clin Cytom 2010:78.

PNH clones may distinguish acquired aplastic anemia (aAA) from the inherited syndromes

- Detectable by flow cytometry in ~ 50% of acquired aplastic anemia
- PNH clones (> 1% in granulocytes) appear to distinguish aAA from these inherited syndromes (~ 100% PPV)

Authors	Year	Flow cytometry sensitivity	PNH + IBMF/MMPS	PNH + aAA	PPV and NPV for aAA
DeZern A. et al.	2014	> 0.01-0.1%	**0/20** (0%)	61/132 (46%)	PPV 100% NPV 54%
Shah YB. et. al	2021	> 0.05-0.1%	**0/9** (0%)	58/126 (46%)	PPV 100% NPV 48.5%
Narita A. et al	2022	> 0.02% grans > 0.037% erythroids	**9/21** (42%)	32/91 (35%)	PPV 78% NPV 17%
		> 0.1%	**1/21** (5%)		PPV 91%

- **Testing by multi-parameter flow cytometry on PB is more sensitive than on BM sample**

DeZern A et al. Eur J Haematol 2014:92.
Shah YB et al. Blood Adv 2021:5.
Narita A et al. Blood Adv 2022: 6.
Borowitz MJ et al. Cyto B Clin Cytom 2010:78.

Acquired 6p CN-LOH^{MHC} distinguishes acquired AA from IBMF/HHMPS

- Present in ~10-15 % of acquired AA
- Occurs in <1% of patients with MDS or in normal aging
- 6p CN-LOH appears to distinguish acquired AA from IBMF/HHMPS (100% PPV)
    - Loss of HLA class I alleles disrupts antigen presentation and allows immune escape

Katagiri T et al. Blood 2011:118.
Betensky M et al. Cancer Genet 2016:209.
Afable MG et al. Blood 2011:117.
Mohamedali AM et al. Leukemia 2015:29.
Score J et al. Leukemia 2015:29.
Babushok DV et al. BJH 2014:164.
Shah YB et al. Blood Adv 2021:5.

Idiopathic acquired aplastic anemia

- Biphasic age distribution
- Presumed 2^{ndary} to immunologic destruction of HSCs
- Severity – **"classical" definition**
  - Modified Camitta's criteria[1,2]
- Severity – **'practical" definition**
  - Severe neutropenia/transfusions

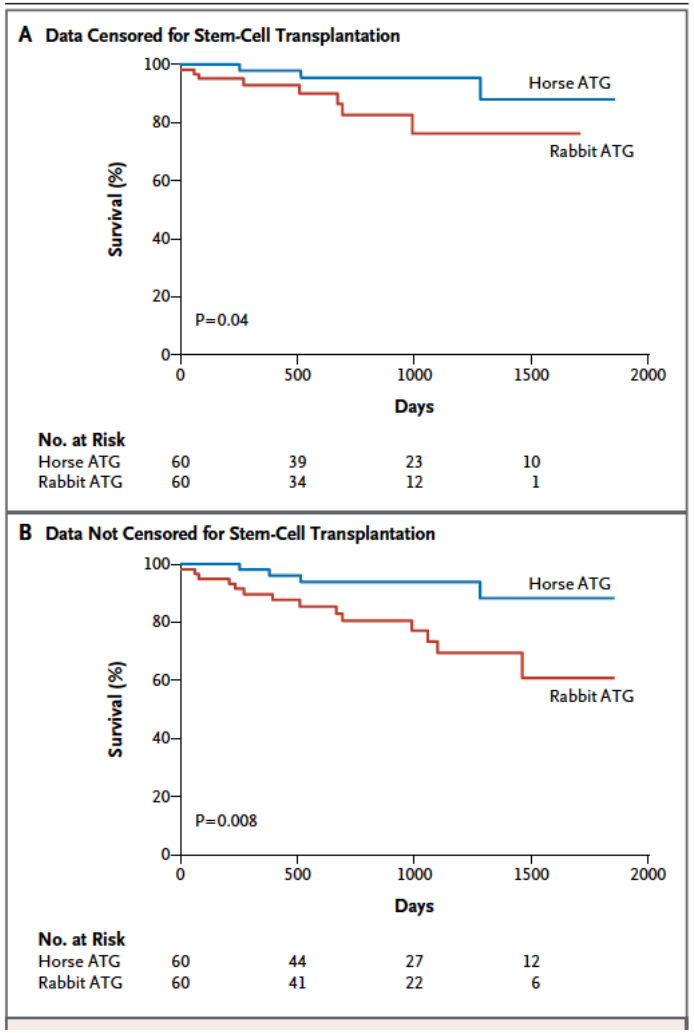
Camitta's Criteria

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

Camitta BM Blood 1976:48.
Killlick S BJH 2016:172.

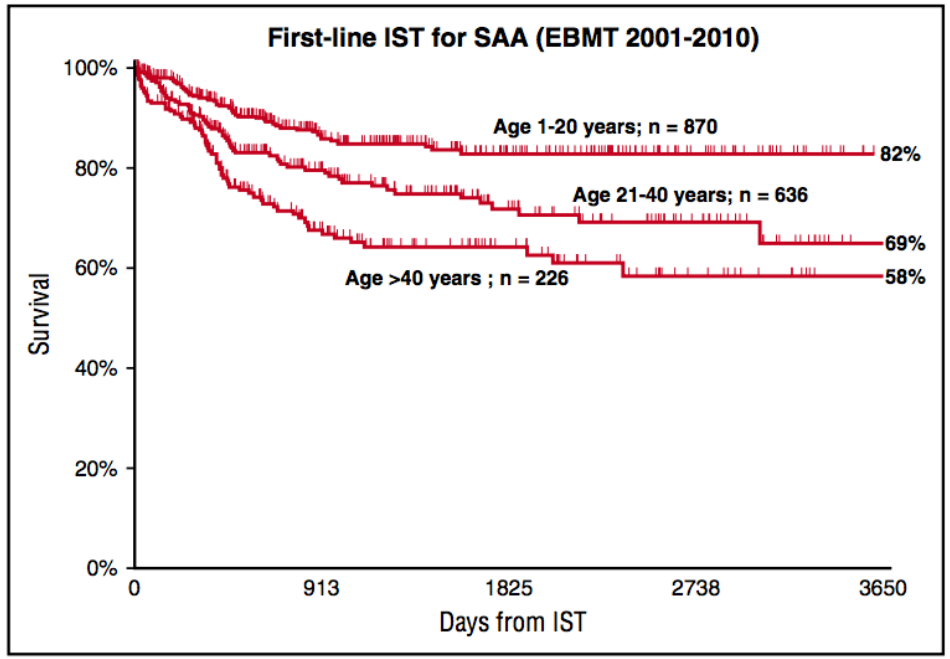
Immune suppressive therapy (IST)

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).

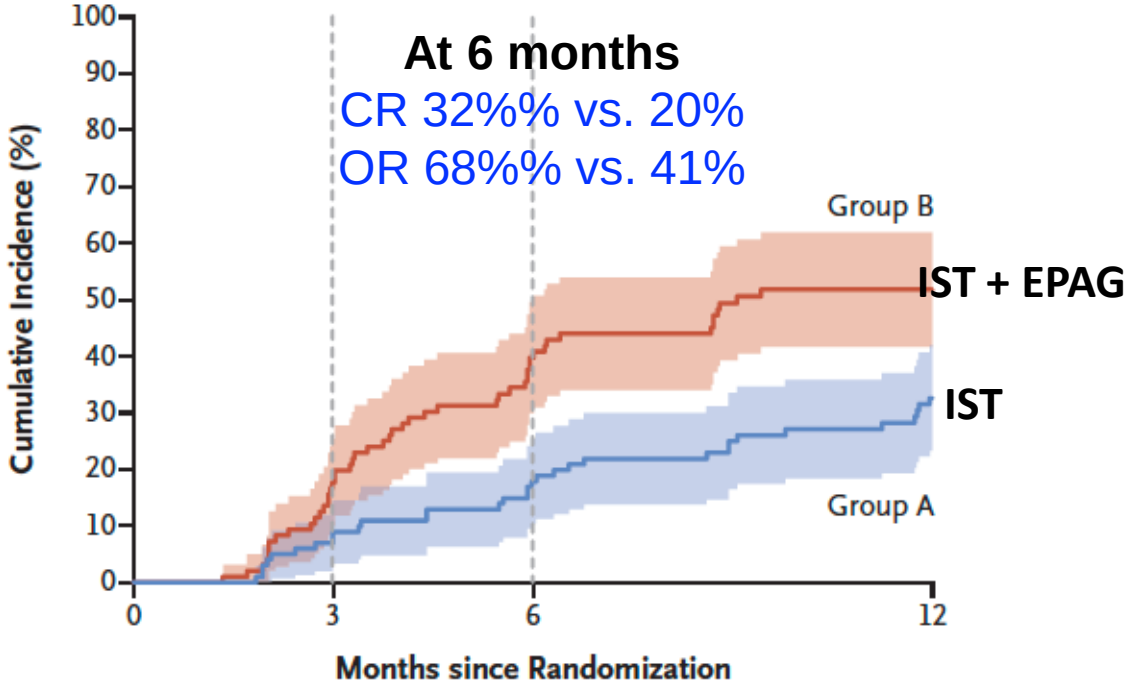
Eltrombopag (Epag) for acquired aplastic anemia

- 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]
    - CR 58% and OR 94% @ 6 months
  - RCT hATG/CsA/Epag (n=96) vs. hATG/CsA (n=101)[4]
    - CR 68%% vs. 41% and OR 68%% vs. 41% 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. NEJM 2022: 386.
5. Groarke EM et al. BJH 2021: 192(3).

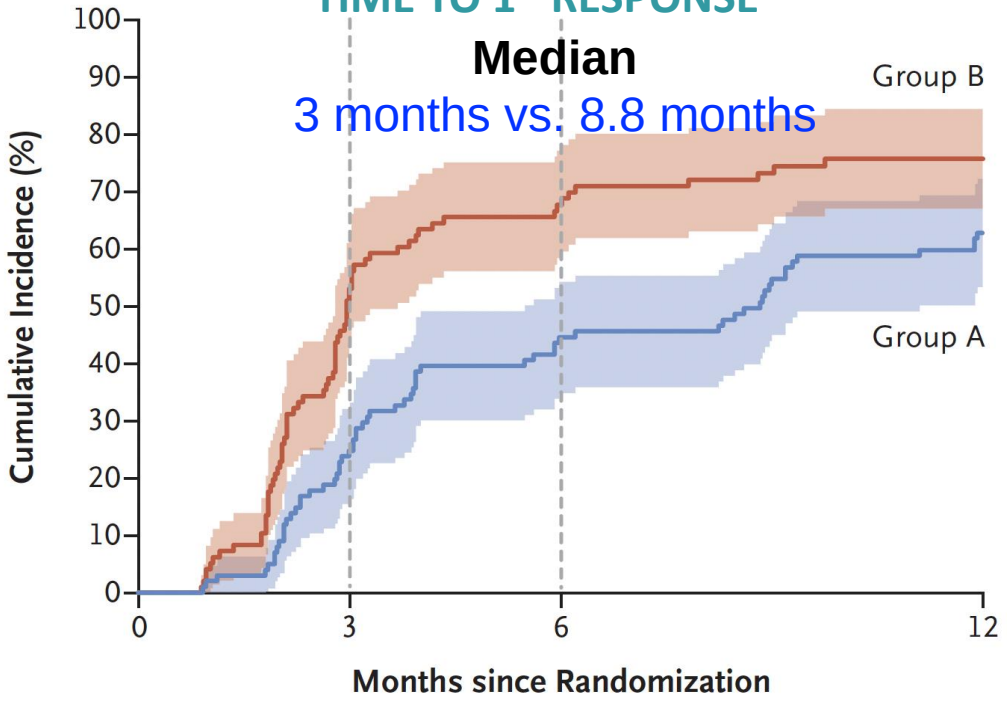
Immune suppressive therapy (IST) ± eltrombopag (EPAG)

COMPLETE RESPONSE



No. at Risk			
Group B	96	52	16
Group A	101	64	35

TIME TO 1st RESPONSE



No. at Risk			
Group B	96	25	4
Group A	101	40	14

Peffault de Letour R. et al. NEJM 2022: 386.

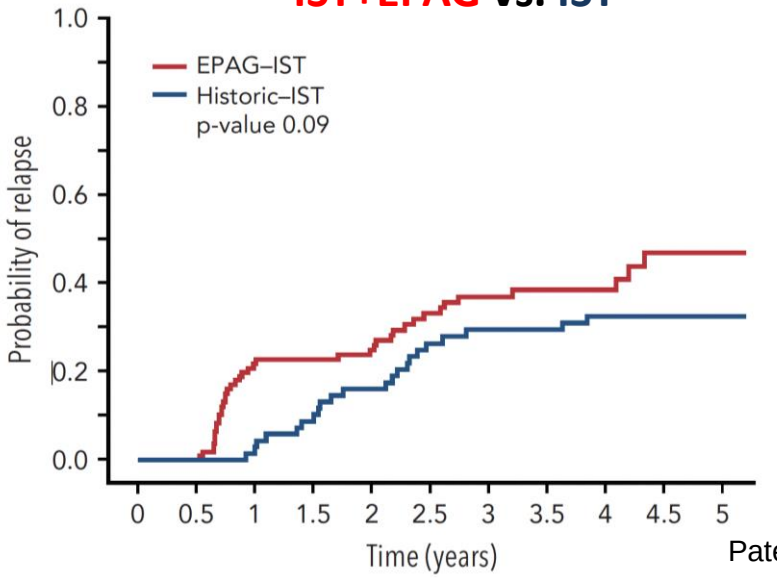
- Phase 1-2 study (92 patients; median f/up 2 yrs) CR 58% and OR 94% @ 6 months
- Addition of EPAG showed no improvement in ORR or CR at 6 months in pediatric patients (<18 yo)

Desmond R et al. Blood 2014: 123(12).
Townsley M et al. NEJM 2017: 376(16).
Groarke EM et al. BJH 2021:192

Late complications of IST treated patients

- Relapse in ~ 1/3 of responders[1]
- IST without EPAG
  - 29% (24/84) with normal blood counts & off IST long-term, median follow-up 11.3 yrs[2]
- IST with EPAG[3]
  IST + EPAG vs. IST
  - EPAG promotes early hematologic response.
    - @ 6 months ORR 81% vs 67%
  - Response is not maintained after EPAG is stopped
    - @ 12 months ORR 56 vs. 57%
  - Incidence of high risk clonal evolution was similar between groups → occurred earlier in EPAG+IST
- MDS/AML evolution in 10-15% of cases[1,2,3]

Relapse among responders at 6 months
IST+EPAG vs. IST



Patel BA et al.

- IST + EPAG relapses occur “early” (6 months) and ”late” (after 2 yrs) when EPAG and CSA dosing changes.

- Study evaluating sirolimus (NCT02979873) to prevent relapse after stopping CSA.

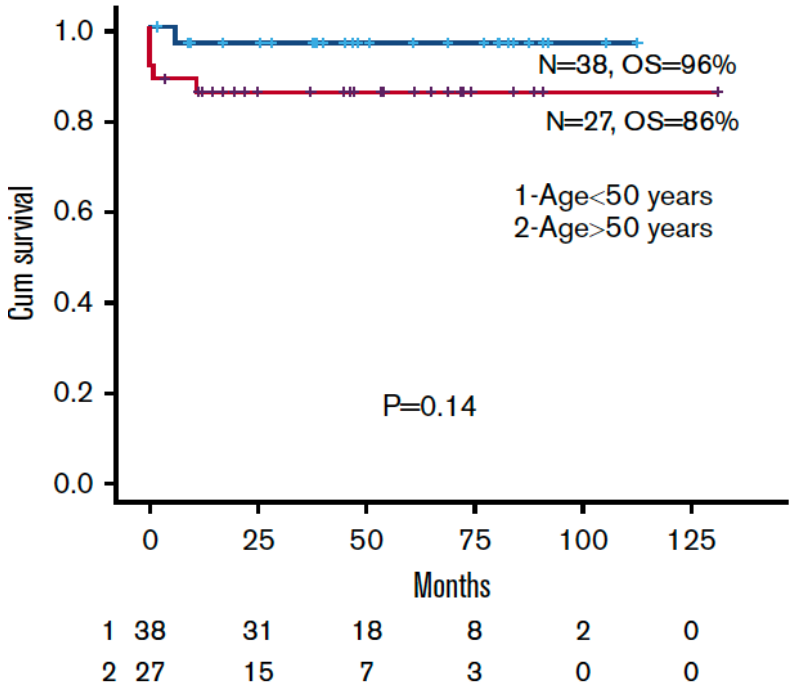
1. Young N et al. Blood 2006: 108(8).
2. Frickenhofen N et al. Blood 2003: 101(4).
3. Patel BA et al. Blood 2022: 139 (1).

HSCT in the elderly (1)

< 50 yo

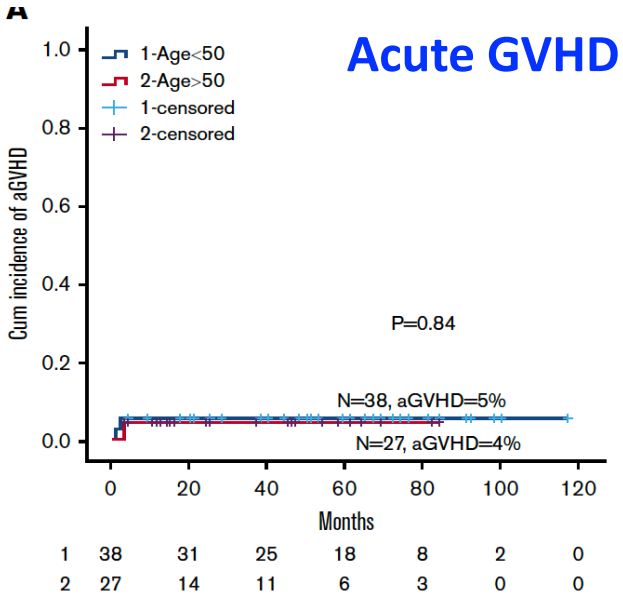
≥ 50 yo

Overall survival

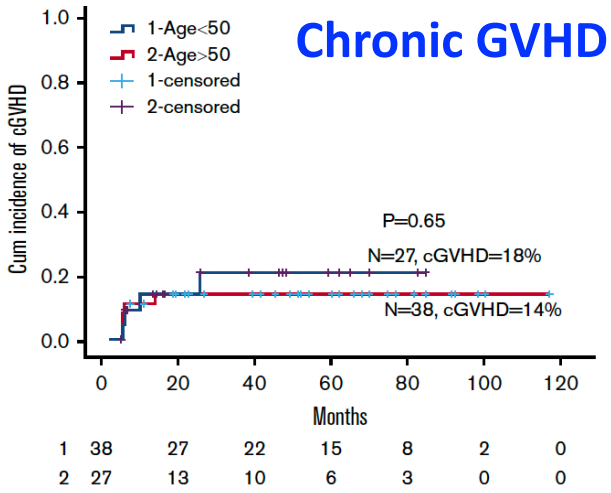


- 51-60 yo vs, 61 to 71 yo
  OS 89% vs. 82%, p=0.82

Acute GVHD

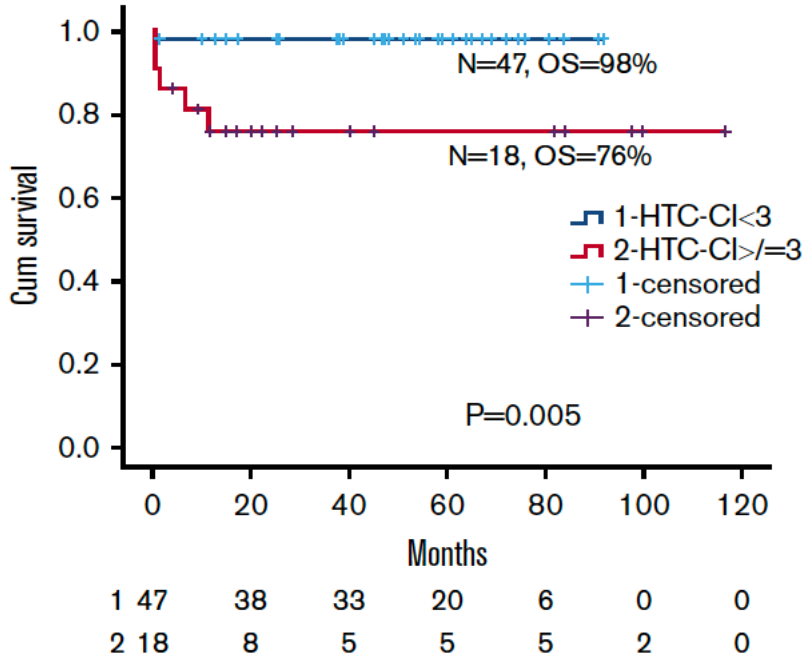


Chronic GVHD



Flu 30mg/m2 D -7 to -4
CY 300 mg/m2 D-7 to -4
Alemtuzumab 0.2 mg/kg D-7 to -3
GVHD Ppx CSA

Overall survival



Sheth VS. et al. Blood Advances 2019: 20(3).

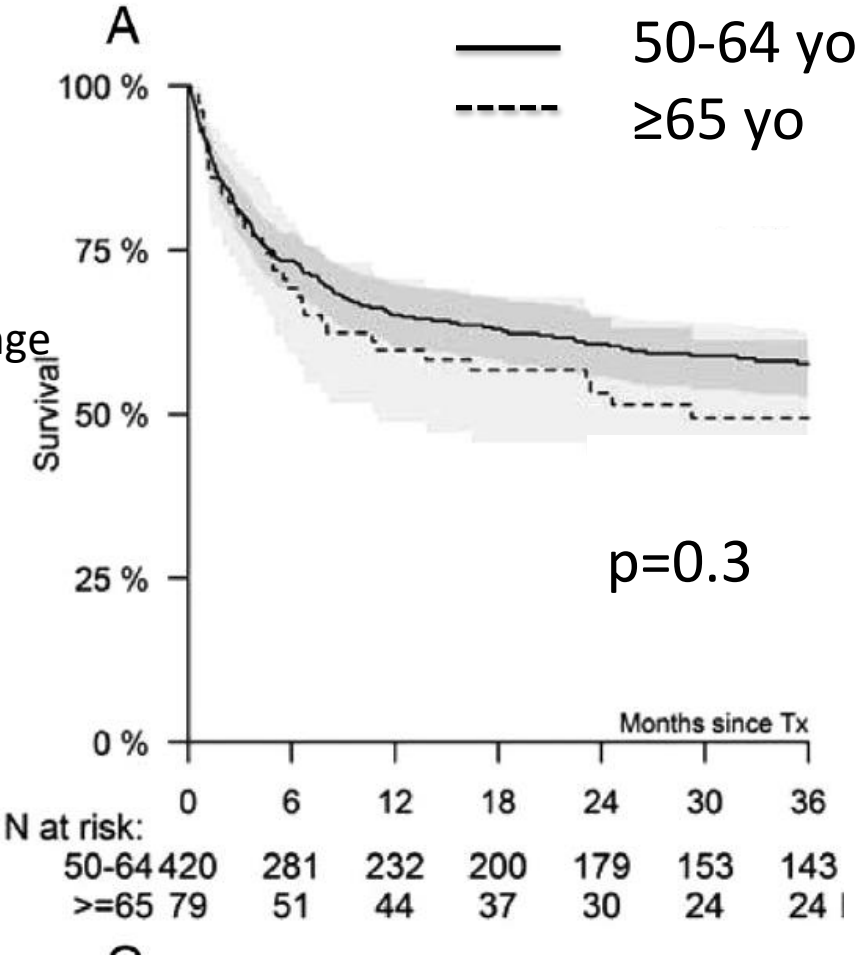
HSCT in the elderly (2)

- 3 yr OS 56% for entire cohort
  - 59% MRD and 52% MURD

Retrospective study of 499 SAA

- n=79, > 60 yo
- 89.6% received prior IST

		#	% or range
	Missing	36	7.0
Interval from diagnosis to treatment	≤12 yr	307	61.5
	>12 yr	192	38.5
Donor	Matched unrelated	187	37.5
	HLA-identical sibling	275	55.1
	Missing	37	7.4
Graft source	Bone marrow	266	53.3
	Peripheral blood	233	46.7
Regimen	Cy + ATG	91	18.2
	Cy + Flud ± ATG	92	18.4
	TBI 200 + Cy + Flud + ATG	57	11.4
	TBI 200 + Cy ± ATG	28	5.6
	Alkylating agent + Flud ± ATG	65	13
	Alemtuzumab	60	12
	Flud + Cy + alemtuzumab	40	
	Alemtuzumab + other	20	
	Other non-TBI regimen	73	14.6
	Other TBI regimens	18	3.6
	Missing	15	3
GVHD prophylaxis	CNI + MMF	117	23.4
	CNI + MTX	246	49.3
	CNI ± other drug	67	13.4
	Other	43	8.6
	Missing	26	5.2
HSCT year	2005-2009	191	38.3
	2010-2014	308	61.7
Age, yr	Median (range)	499	57.8 (50-77.7)

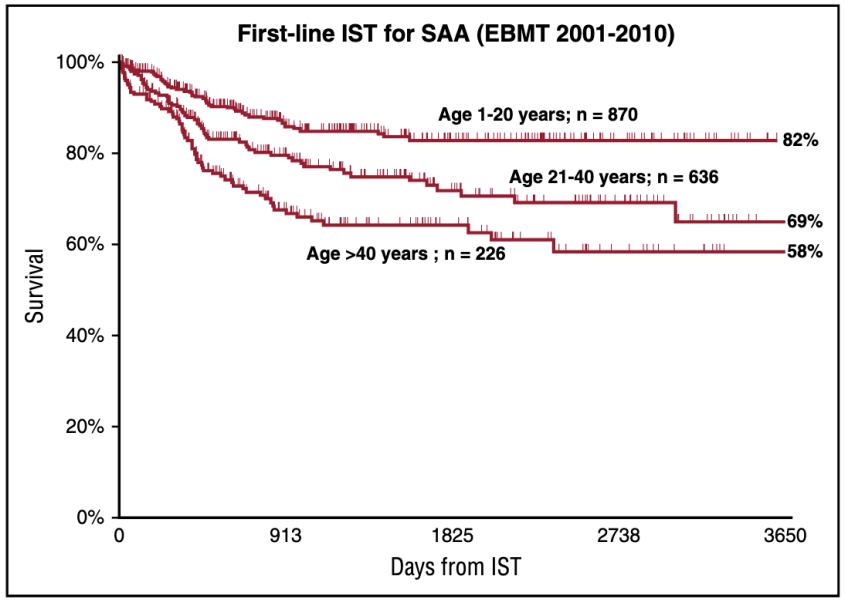


Rice C. et al. Biol Blood Marrow Transplant 2019: 25.

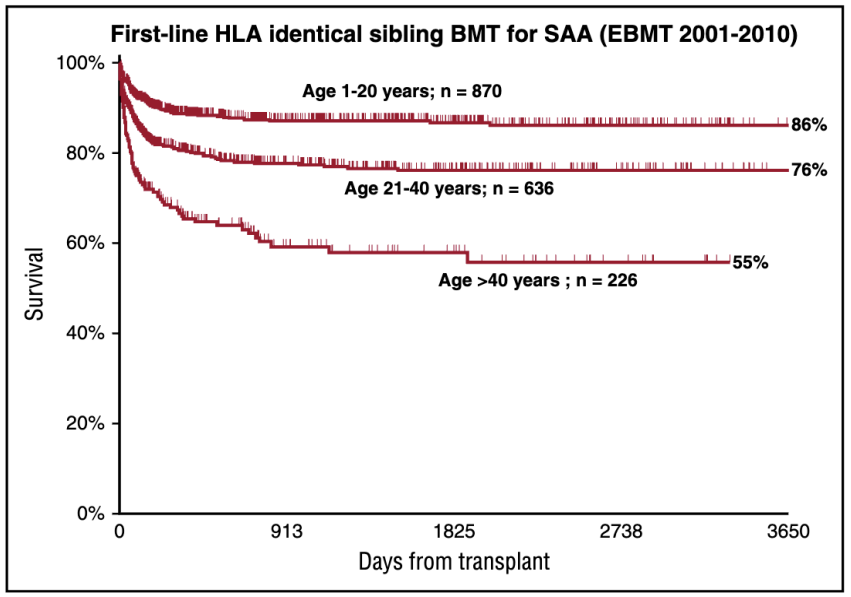
EBMT registry data

European Society for Blood and Marrow Transplantation

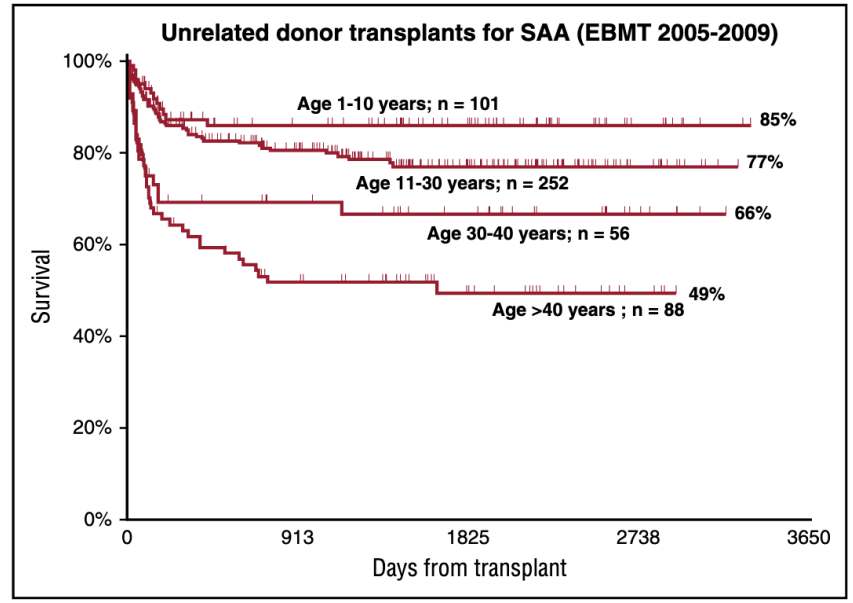
IST



HLA matched sibling BMT



Matched URD BMT (MURD)

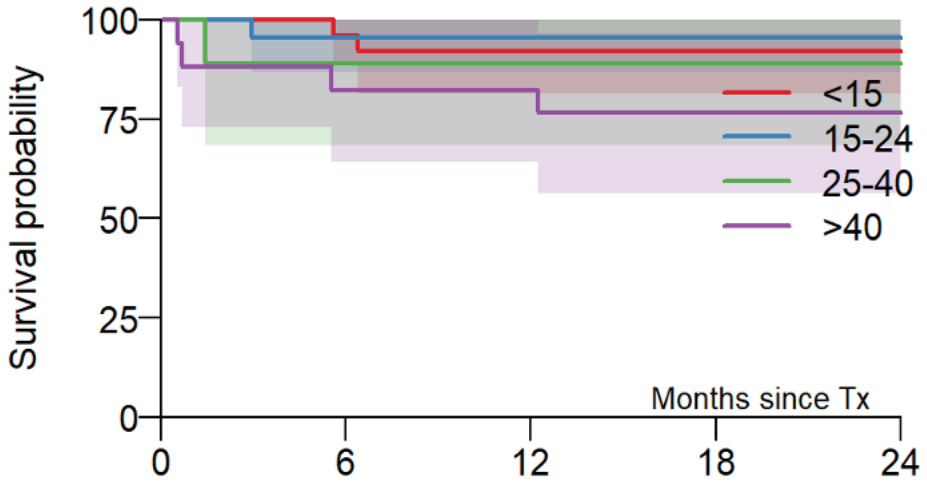


Baciagalupo, A et al. Blood 2017

Upfront MUD/mMUD allogeneic hematopoietic stem cell transplantation

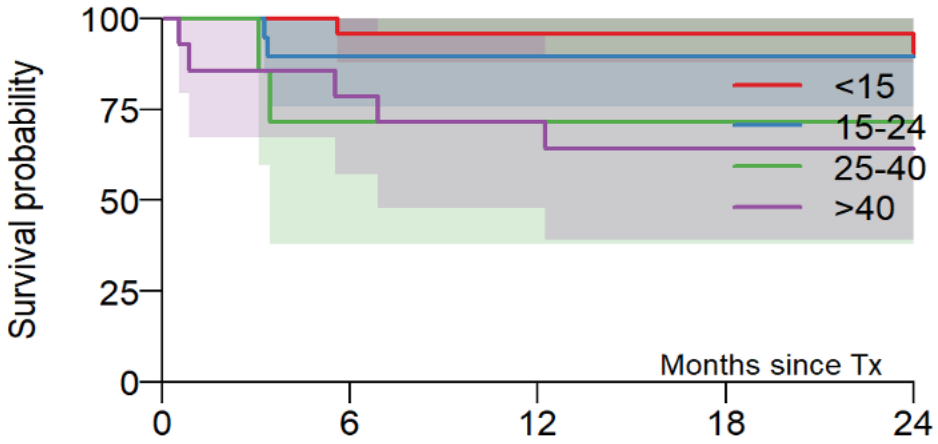
EBMT 2010-2018

2-year OS



	Groups	Total n	n	24 months
Age	<15	26	18	92% (81-100%)
	15-24	22	15	95% (87-100%)
	25-40	9	6	89% (68-100%)
	>40	17	12	76% (56-97%)

2-year GVHD free relapse free survival

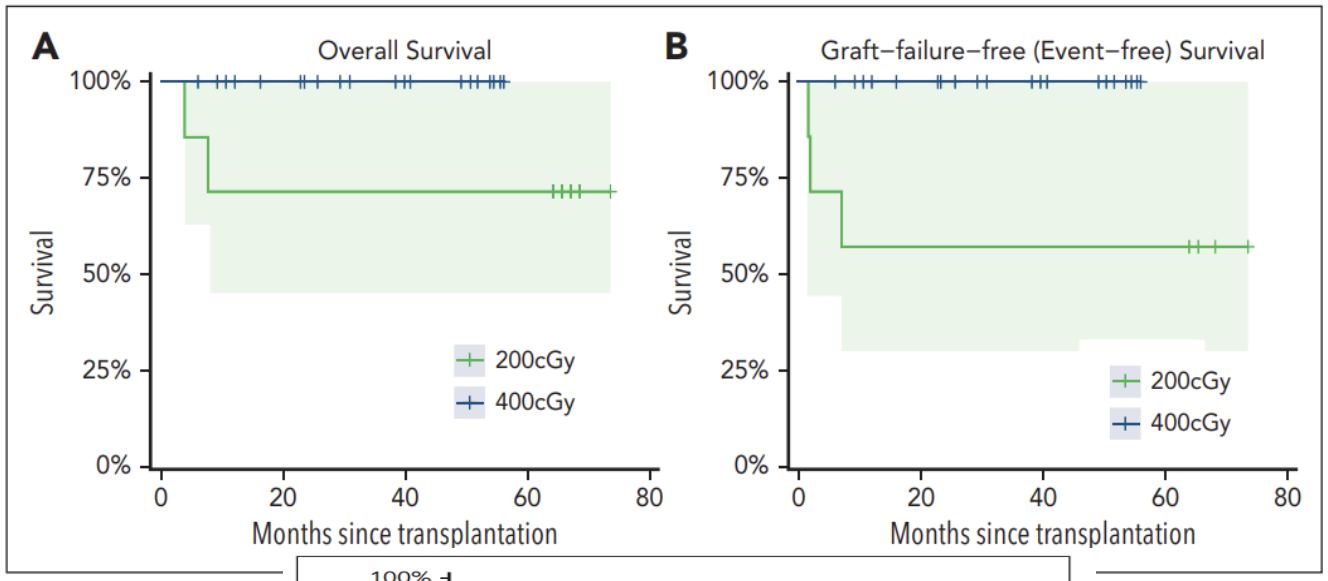


	Groups	Total n	n	24 months
Age	<15	25	18	91% (78-100%)
	15-24	19	12	89% (76-100%)
	25-40	7	3	71% (38-100%)
	>40	14	8	64% (39-89%)

Petit AF et al. AJH 2021.

Upfront Haplo-HCT with PT-CY

- Single center prospective Ph 2 trial
- Patients enrolled – 27
- Median age 25 (range 3-63)
- Flu/Cy/ATG/TBI 200-400 cGy
- GVHD prophylaxis- PTCY/Tac/MMF
- 4×10^8 nucleated marrow cells/kg of the recipient ideal body weight
- First 7 patients received 200 cGy TBI
- 5-year OS - 100 % in pts receiving 400 cGY
- CI Gr 2-4 Ac GVHD at D100 7%
- CI Ch GVHD at 2 years 4%



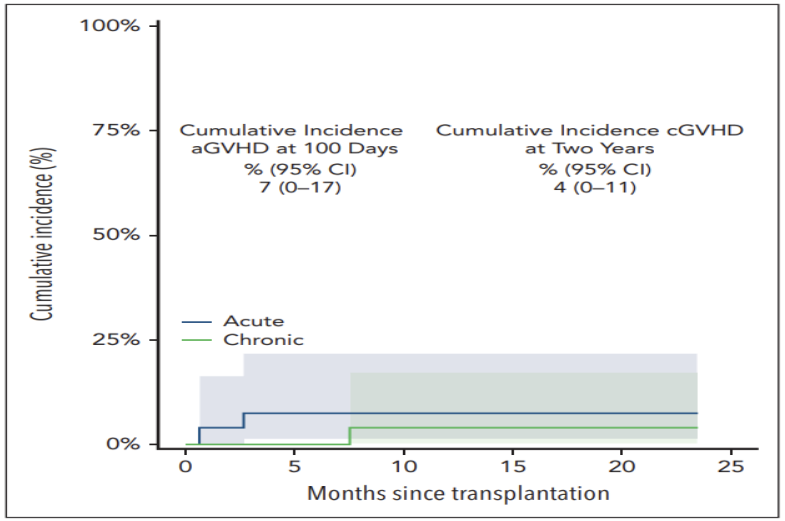
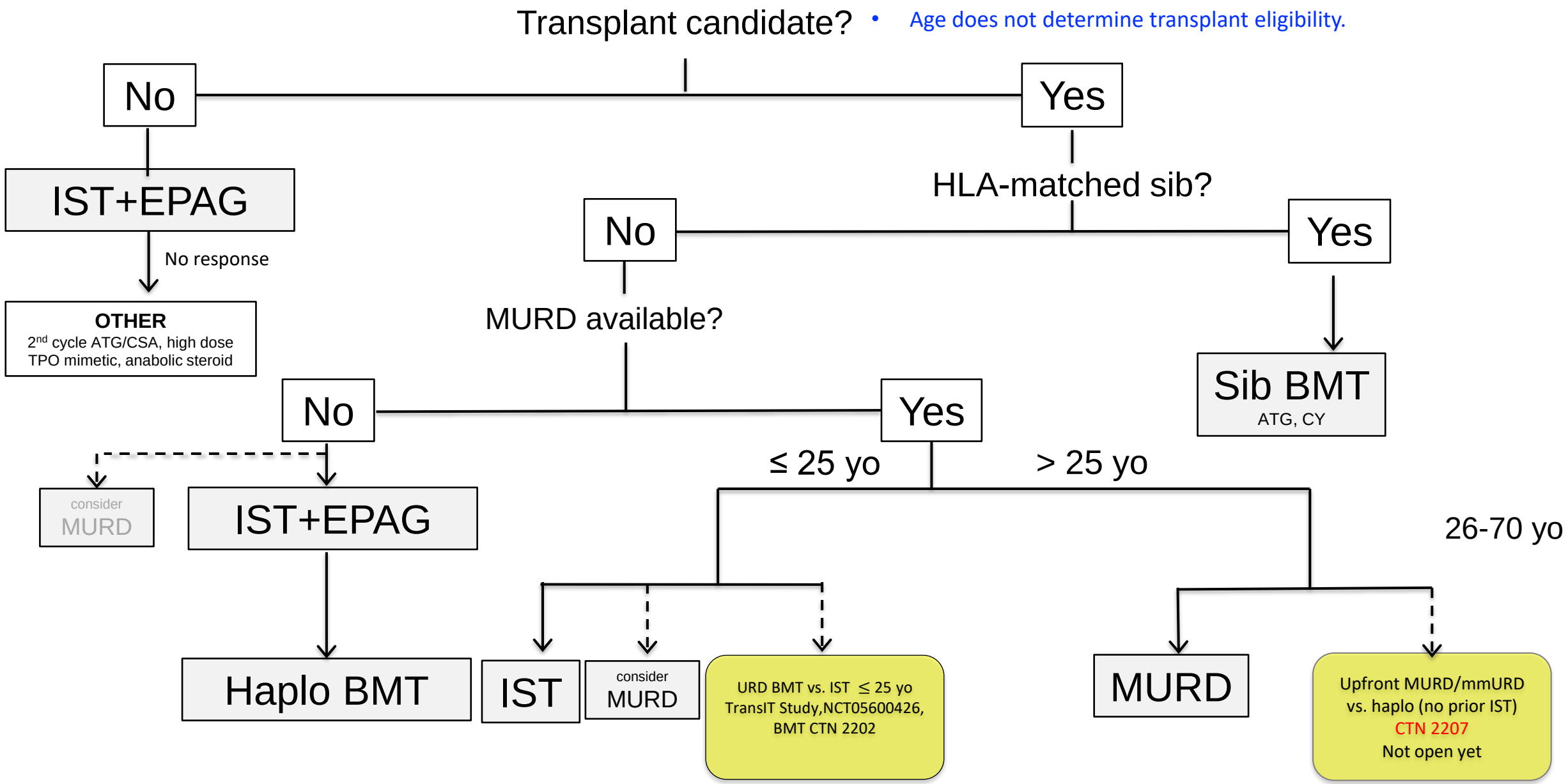


Figure 2. Cumulative incidences of acute and chronic GVHD.

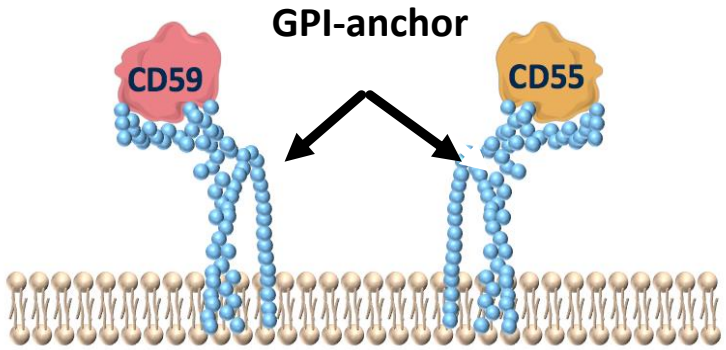
DeZern et al. Blood 2023.

Upfront treatment for severe aAA



Paroxysmal nocturnal hemoglobinuria

- Clonal expansion of HSCs with somatic mutation in *PIGA x chromosome*
  - Lack GPI-Linked proteins
- Clinical triad
  - Intravascular hemolysis, thrombosis, bone marrow failure
- Diagnosis - Absent or reduced GPI-linked proteins
  - Mean clone size >70% in classical PNH (vs. 11% in BMF with associated PNH clone)



CD59

Membrane inhibitor of reactive lysis
Inhibits assembly of the membrane attack complex

CD55

Decay accelerating factor
Inhibits the formation and stability of the C3 convertases

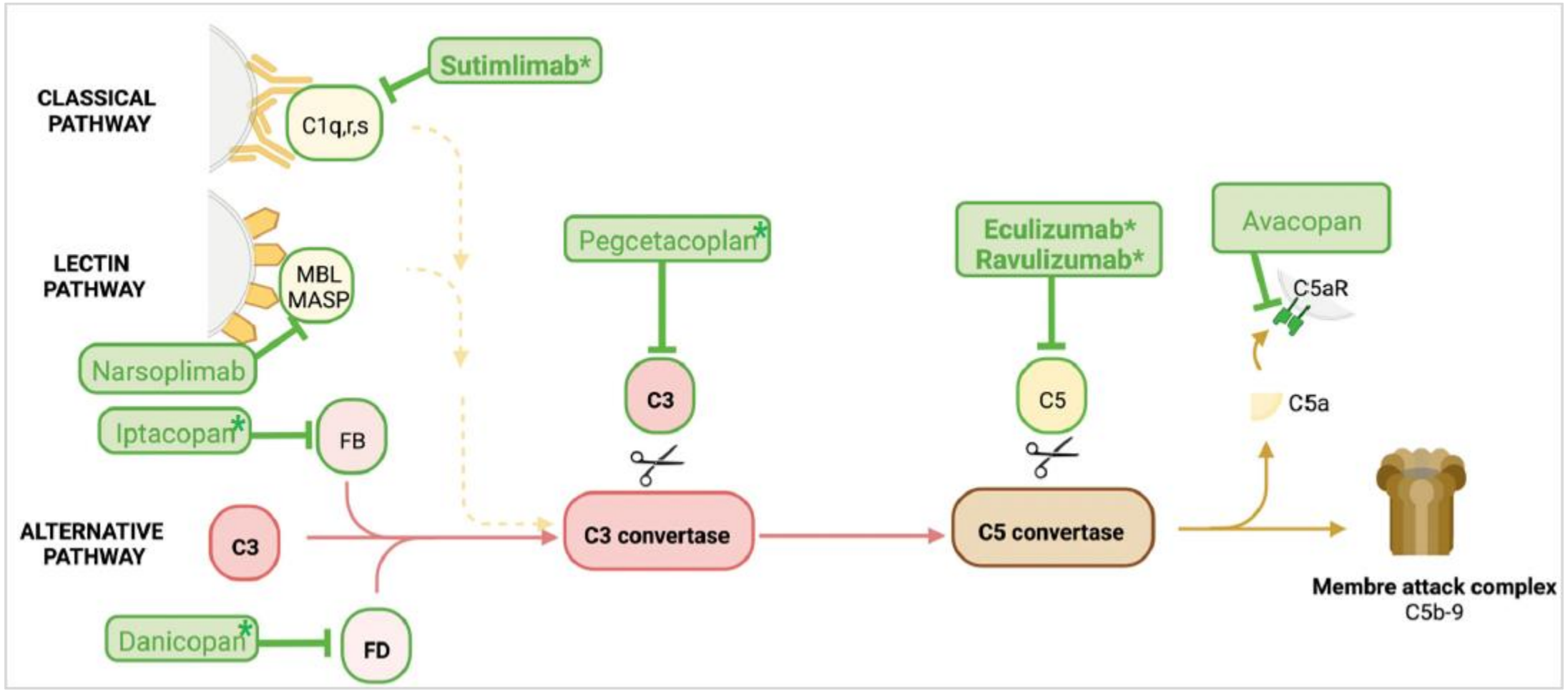
Cannizzo E. et al. Ann Hemat 2019: 98(5).
Richards SJ. et al BJH 2020:189(5).

Risk factors for thrombosis in PNH

- PNH granulocytes clone size (≥ 50%)
  - Each 10% rise in the granulocyte clone size associated with ~ 1.6 higher odds of thrombosis
  - LDH ≥ 1.5 X ULN
  - High disease activity (abdominal pain, dyspnea, chest pain, hemoglobinuria, male erectile dysfunction)
  - Prior thromboembolic events

Hill A. et al. Blood 2013: 121.

Complement Inhibitors



FDA approved therapies for PNH in 2024

Medication	Eculizumab	Ravulizumab	Pegcetacoplan	Iptacopan	Danicopan
Mechanism	C5 inhibition Blocks IVH	C5 inhibition Blocks IVH	**C3 inhibition** Blocks IVH and EVH	**Factor B inhibitor** Blocks IVH and EVH	Factor D Inhibitor Blocks IVH and EVH
Approved Label	PNH patients to reduce hemolysis	Adult PNH patients	Adult PNH patients	Adult PNH Patients	Add on therapy to ecu/ravu for adult PNH patients with EVH
Dosing	• IV infusion • Loading weekly x 4 doses • Maintenance q2 wks	• IV infusion • Loading q2 weeks x 2 doses • Maintenance q8 wks	• SQ infusion, patient-administered • Twice weekly	• Oral agent BID	• Oral agent TID
Vaccination needs	Meningococcal	meningococcal	Meningococcus, strep, neiserria, HIB	Meningococcus, strep, neiserria, HIB	Meningococcus, strep, HIB

Classification of IBMF/HMPS (*modified from 2023 NCCN MDS Guidelines*)

Classical inherited bone marrow failure syndromes
• Diamond Blackfan anemia • Fanconi anemia • Shwachman-Diamond syndrome • Short telomere syndromes • Congenital neutropenia
Germline predisposition for heme malignancy <u>without</u> pre-existing cytopenia(s) or other organ dysfunction
• *CEBPA* • Others (14q32.2 genomic duplication, *XPC*^{delTG}, *ERCC6L2*
Germline predisposition for hematopoietic malignancy <u>with</u> pre-existing cytopenia(s) ± other organ dysfunction
• *DDX41* • *GATA2* • *RUNX1* • *SAMD9/SAMD9L* • Others (*ETV6, LIG4, SRP72*)
Germline predisposition for heme malignancy & solid tumor cancers
• Constitutional mismatch repair deficiency, Hereditary breast and ovarian CA, Li-Fraumeni (TP53), RA

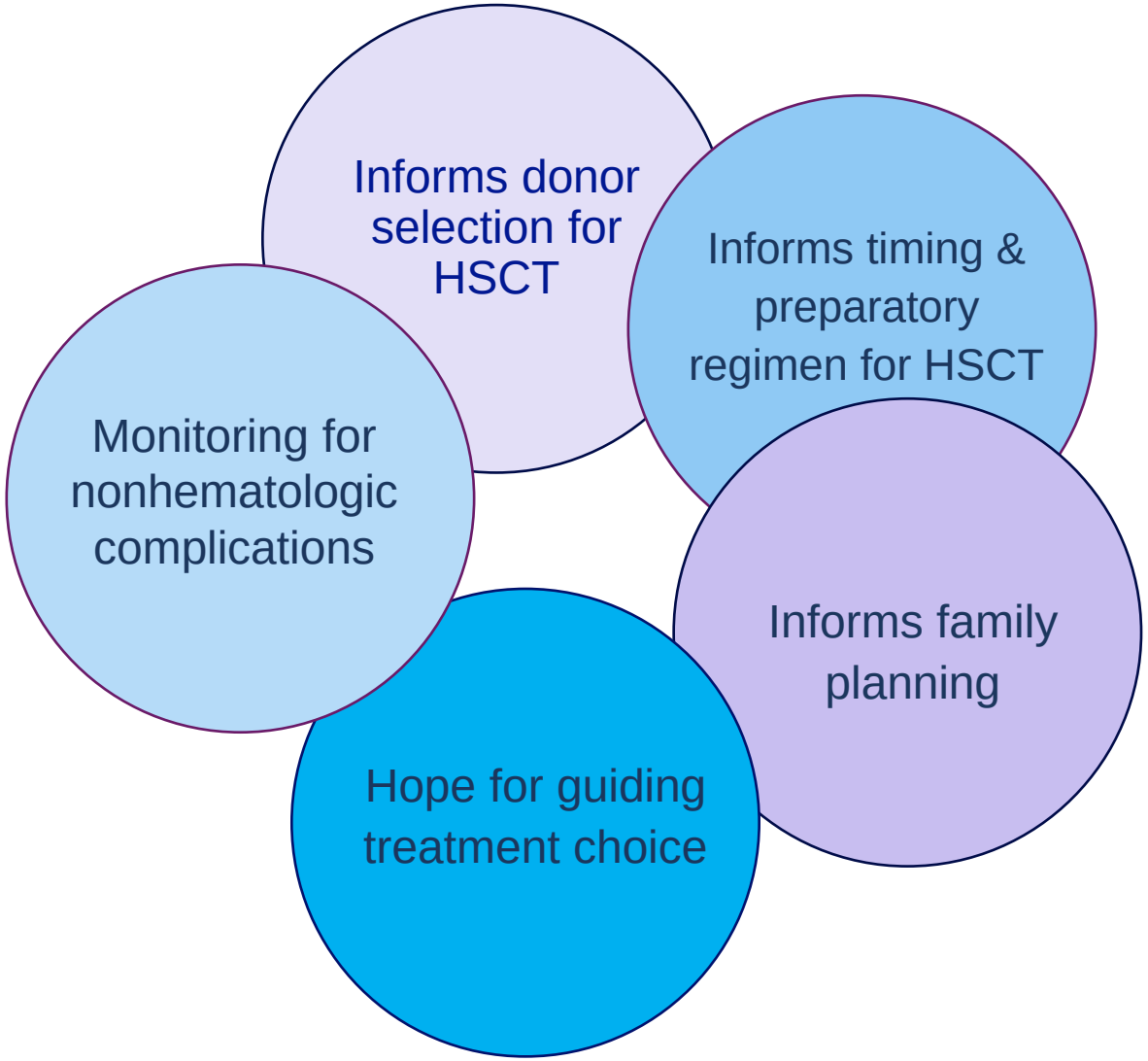
Classical IBMF

No pre-exisiting Disorder

Preexisting Disorder

"Solid tumor" Predisposition syndromes

Why do we need to diagnose IBMF/HHMPS?



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]

Keel SB et al. Haematologica 2016:101.

Somatic versus constitutional (aka germline)?

- Same genes can have somatic OR constitutional mutations
- Variant allele frequency (VAF) does not definitively distinguish somatic vs. germline
- Test non-hematopoietic tissue (skin fibroblasts) or test other family members
- Panel genetic testing designed for somatic vs. germline genetic mutations are not always equivalent

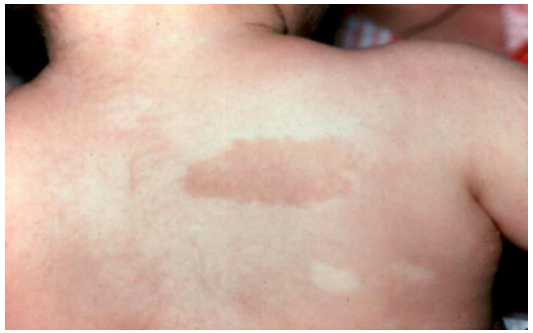
Examples:

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

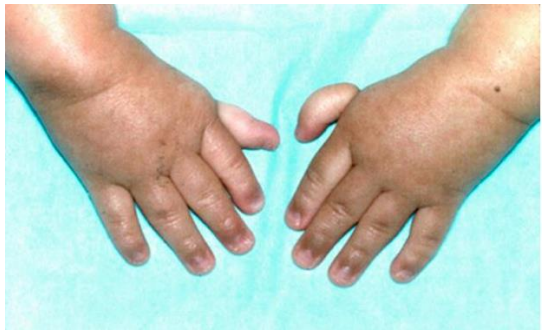
Fanconi anemia

- Hypersensitivity to genetic damage induced by DNA cross-linking agents
- 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)
- Radiosensitivity (DNA damage)

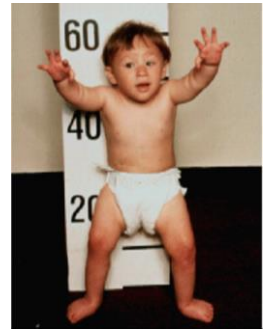
café au lait spot



thumb abnormalities



short stature



- Phenotype-genotype cohort study in Altintas B. et al Haematologic 2023: 108

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

FA Diagnosis

Chromosomal breakage test (aka chromosome fragility)

- Screen for Fanconi anemia
  - Genetic testing does not replace this assay
  - Somatic mosaicism in lymphocytes in ~ 10-25% of FA patients

Genetic testing

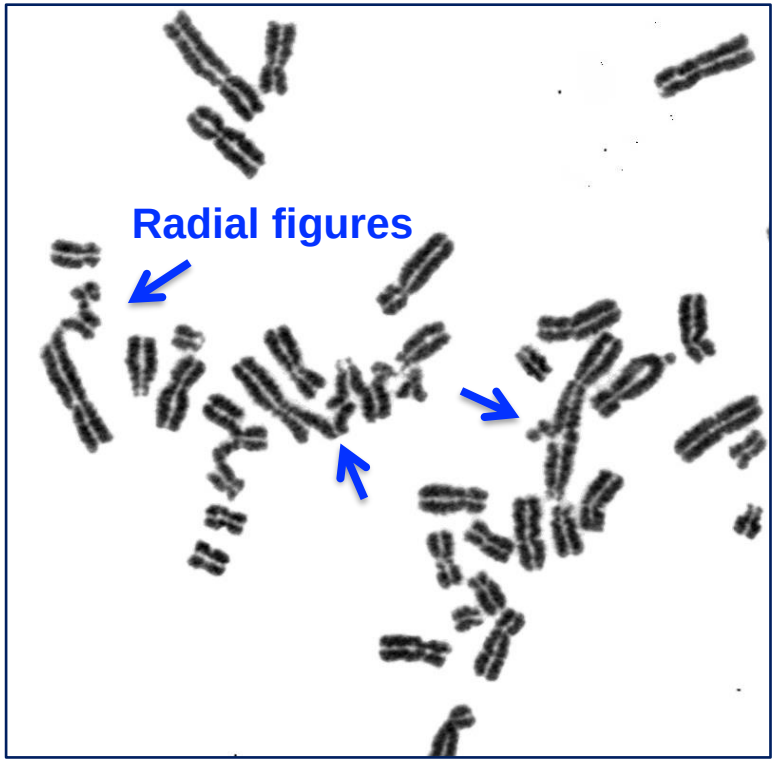


Image courtesy of Lisa Moreau,
Dana-Farber Cancer Institute

Nicolleti E et al. Ann Hematol 2020:99.

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 (oxymetholone 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

Diamond Blackfan Anemia Diagnosis

- Congenital pure red cell aplasia
  - Misnomer – can see neutropenia and thrombocytopenia
  - BM with absent or reduced erythroid precursors
- eADA elevated in 75-90% of cases
  - 90% PPV and NPV compared to other IBMF syndromes[1]
- ~ 50% have physical abnormalities (excepting short stature)
- Genetic testing

1. Fargo JH. Et al. BJH 2013: 160(4).

Genes mutated in Diamond Blackfan Anemia

RPS19	**25%**
Large deletions	**10-25%**
RPL5 - cleft-lip	7%
RPL26	6.6%
RPL11 – classic triphalangeal thumb	5%
RPL35a	3%
RPS10	3%
RPS24	2.4%
RPS17	1%
RPS7, RPS15, RPS 27, RPS27a, RPS28, RPS29, RPL9, RPL15, RPL18, RPL26, RPL27, RPL31,	rare
TSR2 (x-linked)	rare
GATA2 (x-linked)	rare
EPO	rare

- Mutations present in one of 20 RP (autosomal dominant), or TSR2, GATA1, EPO
- No molecular defect in ~ 20-30% of cases

Modified from Da Costa L. et al F1000Researh August 2017.

DBA treatment and surveillance

- ~80% response to corticosteroids
  - Starting dose 1-2 mg/kg/day[1]
  - ~40% will remain on corticosteroids long-term
- Anemia spontaneously remits in ~ 20% of patients (often at onset of puberty)
- Hematopoietic stem cell transplantation
- Age-appropriate cancer screening
  - Odd ratio for colon cancer- 45;odds ratio for osteogenic sarcoma - 42[2]

1. Vlachos A. et al. Blood 2012: 119(16). 2. Vlachos A. et al. Blood 2018: 132(20).

Shwachman Diamond Syndrome (SDS)

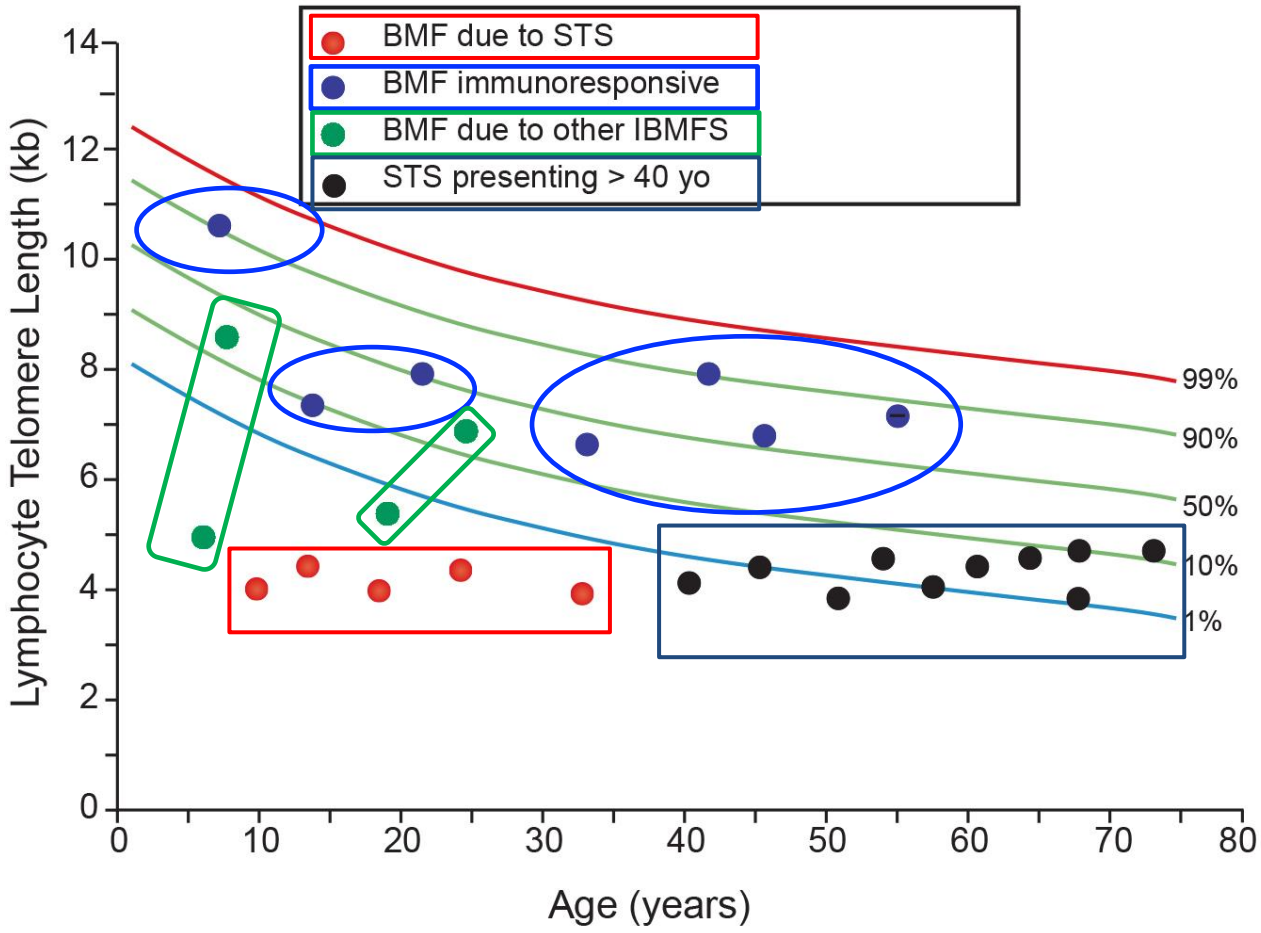
- Majority of cases are autosomal recessive
- Bone marrow failure, bone malformations, pancreatic insufficiency, cognitive disorders, and cancer predisposition
  - Hypocellular marrow
  - Neutropenia is most common hematopoietic abnormality
  - Pancreatic insufficiency improves in >50% of patients with aging
    - Serum pancreatic isoamylase (pediatric and adult patients) and serum trypsinogen (pediatric patients) are often low.
- Biallelic mutations in *SBDS* in ~ 90% of patients
  - Involved in joining 60S & 40S subunits in the assembly of 80S ribosome

Finch AJ. Et al Genes Dev 2011: 25.
Weis F. et al. Nat Struct Mol Biol 2015: 22.

Short telomere syndrome 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

Utility of telomere length testing in the diagnosis of hypocellular marrow failure

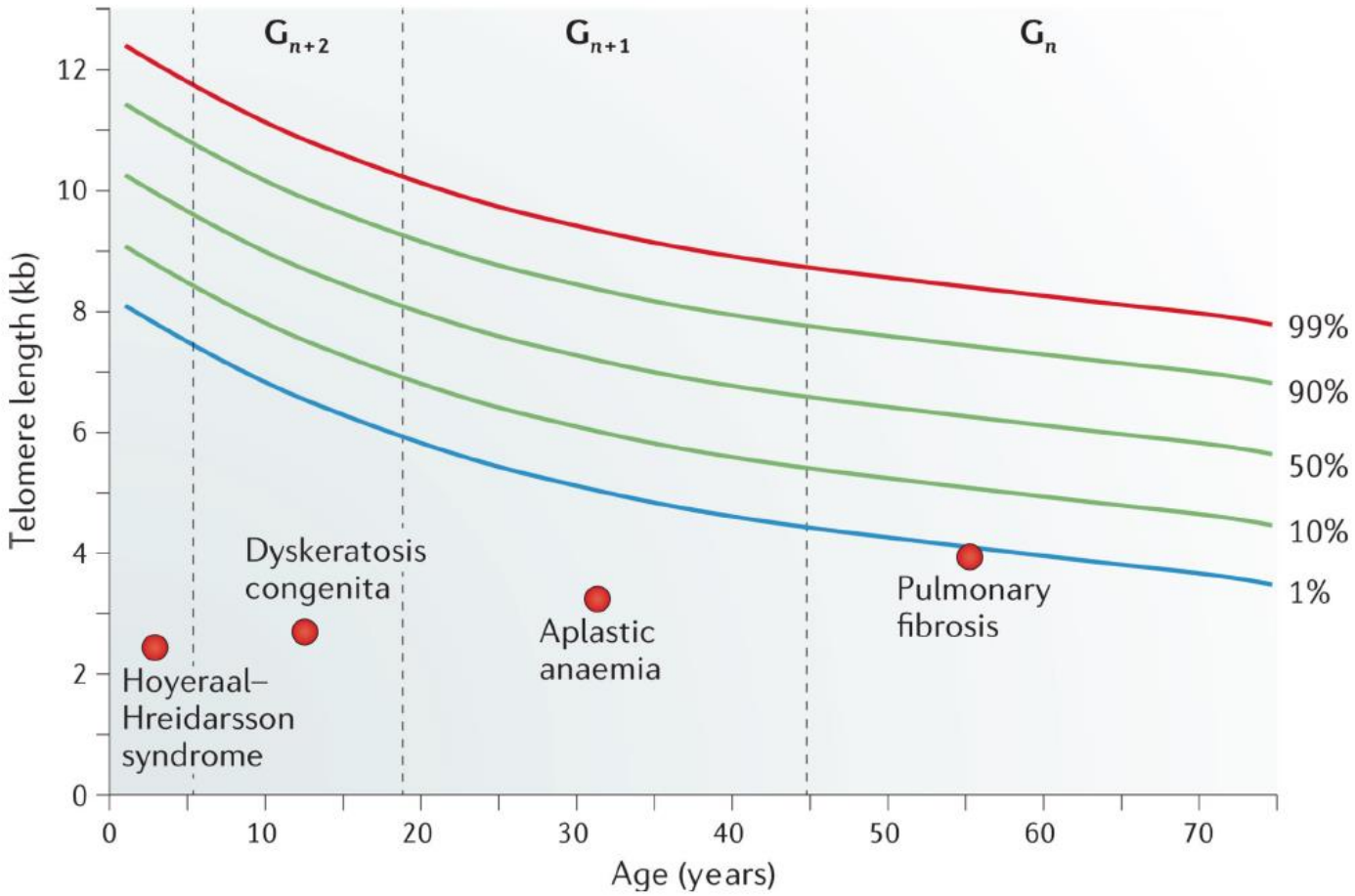


Based on data from Alder JK et al. PNAS 2018:115 and courtesy of Mary Armanios, Johns Hopkins University

Lymphocyte telomere lengths:

1. > age-adjusted 50th percentile excludes a STS
2. < age-adjusted 1st percentile in patients < 40 yo strongly supports a STS (lacks specificity)

Age- and telomere length-dependent presentations of STS

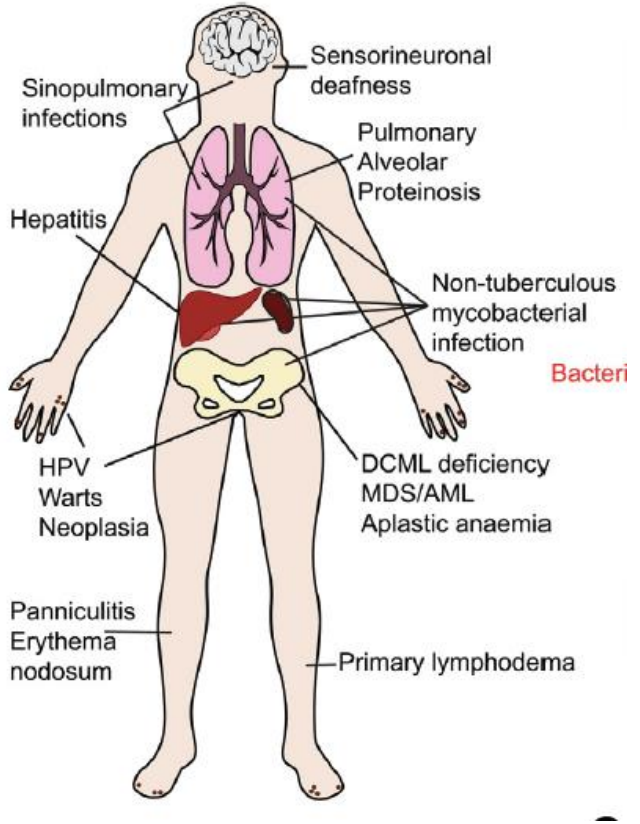


- STS are also associated with genetic anticipation.

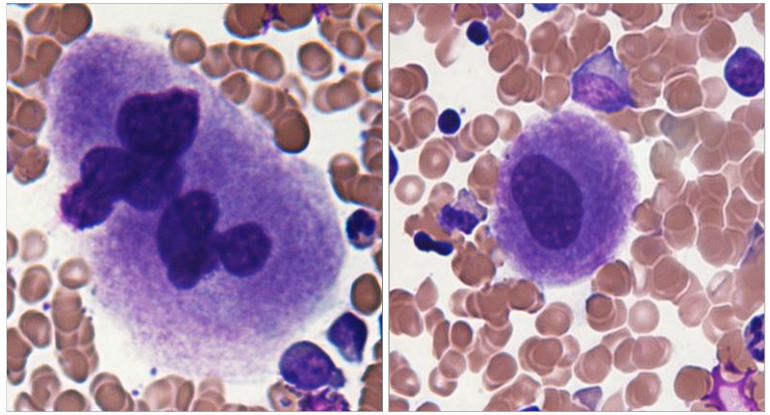
Armanios M. et al. Nat Rev Genetics 2012: 13(10).

GATA2 deficiency syndrome

- Autosomal dominant
  - Most mutations are de novo
- Multiple clinical syndromes
  - Familial AML/MDS
  - Isolated cytopenias
  - Lymph edema and MDS (Emberger's syndrome)
  - MonoMac (monocytopenia, opportunistic infections, viral associated cancers, B and NK cell lymphopenia)
- Rheumatologic manifestations[1]
- Lifetime risk of MDS/AML ~75-90%
- Marrow megakaryocyte morphology and absent hematogones (by flow) may be a clues

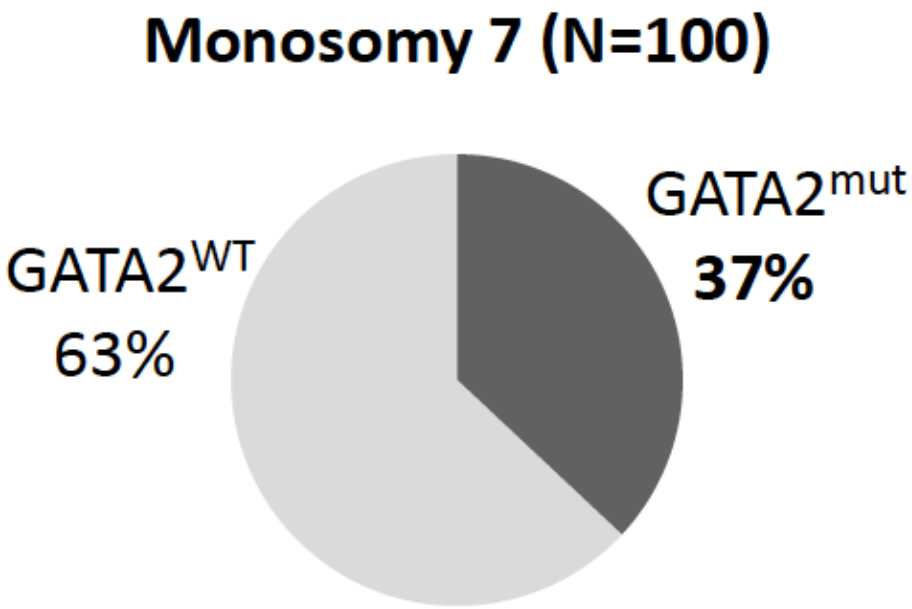


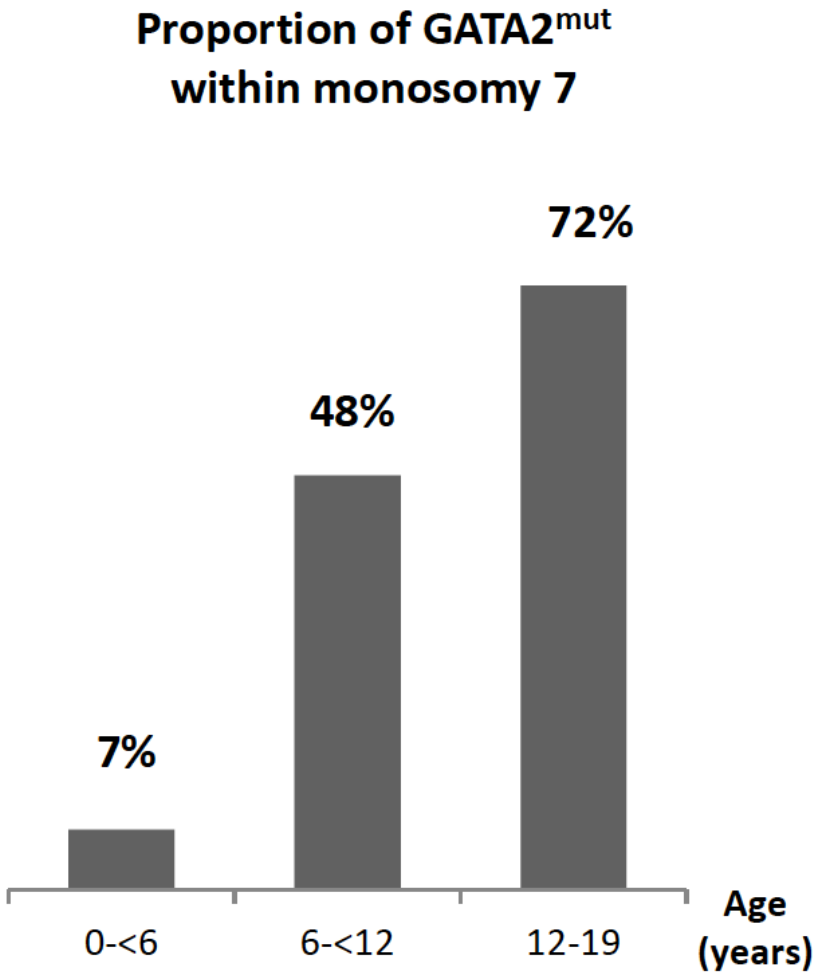
Bigley V et al. Sem Cell Dev Bio 2019.



1. Amarnani AA. et al. Sci Reports 2020:10..

Consider GATA2 deficiency in Monosomy MDS in young adults

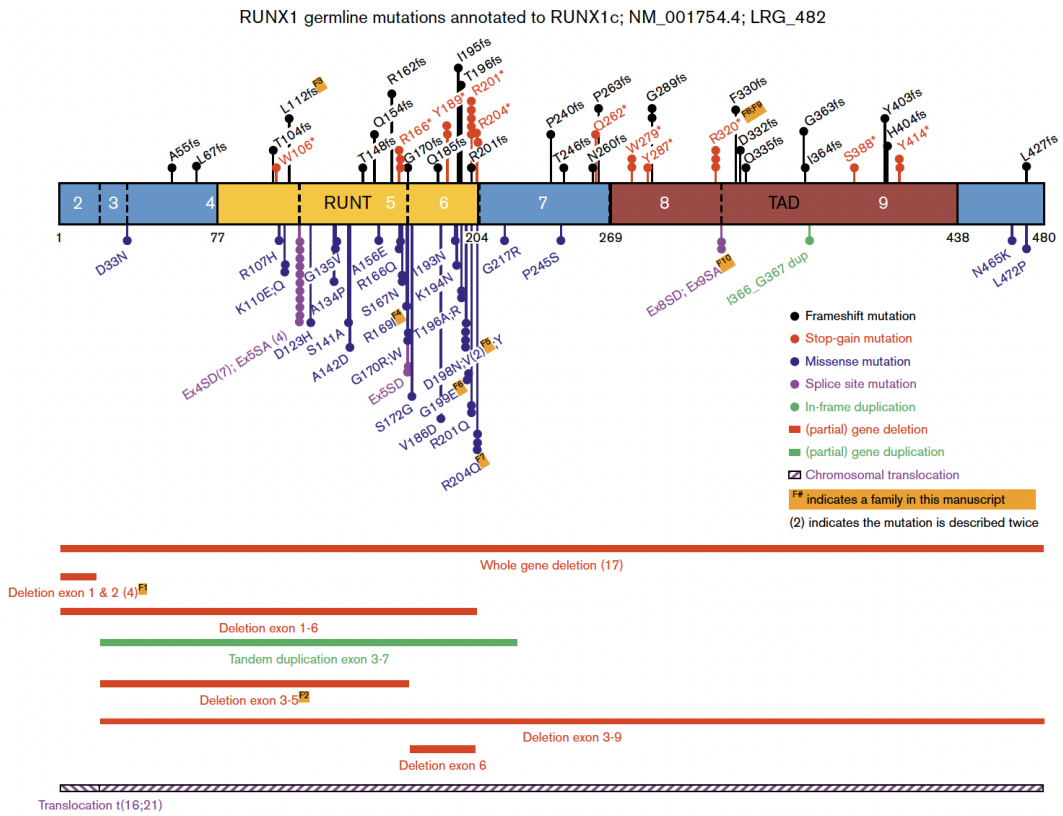




Wlodarski MW et al. Blood 2016:127(11).

Familial platelet disorder with associated myeloid malignancy (FPD-MM)

- Autosomal dominant due to mutations in RUNX1
- Mild/moderate thrombocytopenia
- Mild bleeding tendency – platelet dense granule deficiency
- Family history of MDS/AL
- ~40% lifetime risk for MDS/AML/T-ALL, median age ~30 years



Brown A. et al. Blood Adv 2020: 4(6).

Germline DEAD-box helicase 41 mutations (DDX41)

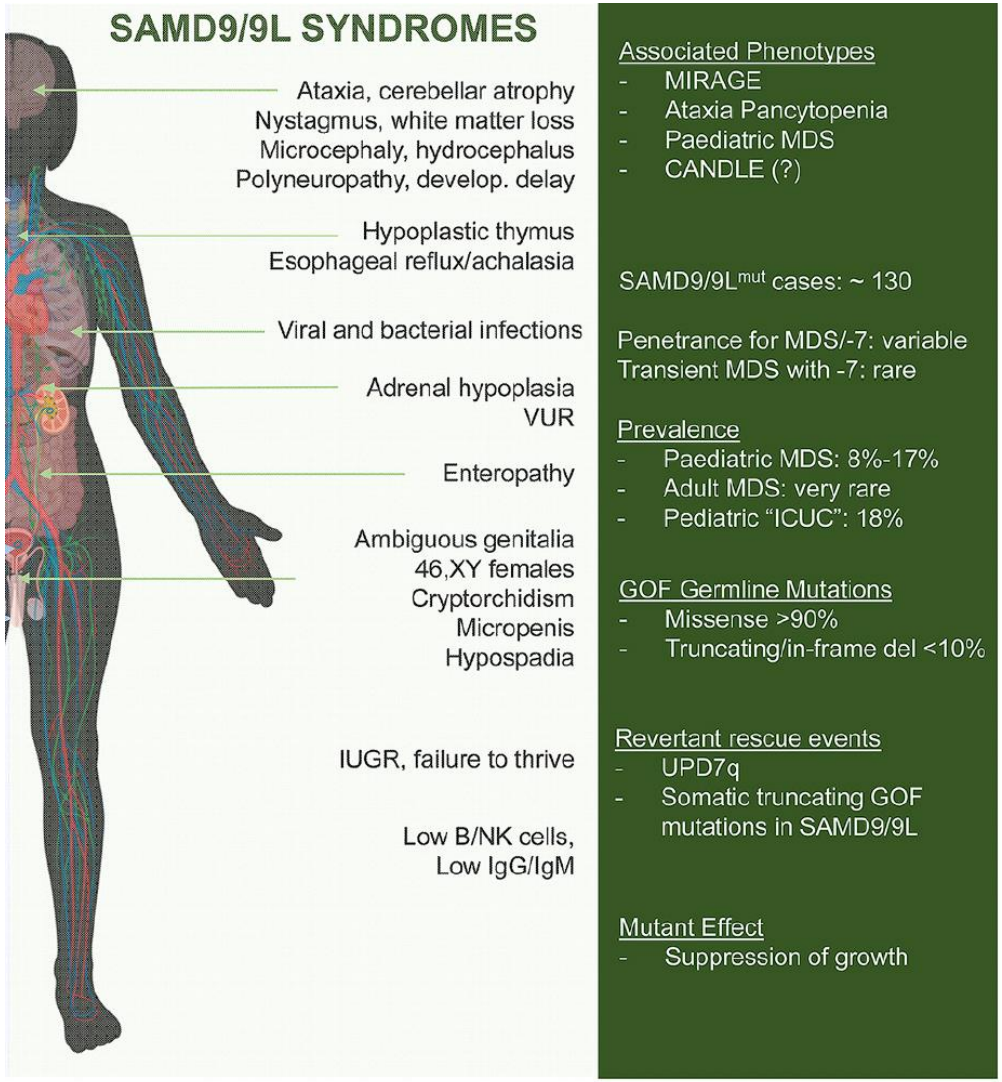
Most common germline myeloid malignancy predisposition syndrome in adults

- Tumor suppressor gene in myeloid neoplasms
- Involved in the splicing of pre-mRNAs, rRNAs and innate immunity signaling
- Germline mutations associated with HHM[1]
  - **~3-5% incidence in adult patients with MDS/AML**[3,4]
  - Somatic mutations are rare
  - Mean age of onset of MDS or AML 62 years-old (long-latency) [1,2,3] with a male predominance (~75%) -
  - Characterized by normal karyotype and 2nd somatic mutation in *DDX41* (often R525H)[3,*4*]

1. Polprasert C. et al. Cell 2015: 27. 2. Lewinsohn M. et al. Blood 2016: 127. 3. Makishima H. et al Blood 2022 *Online.* 4. Sebert M. et al. Blood 2019: 134.

SAMD9/9L disorders

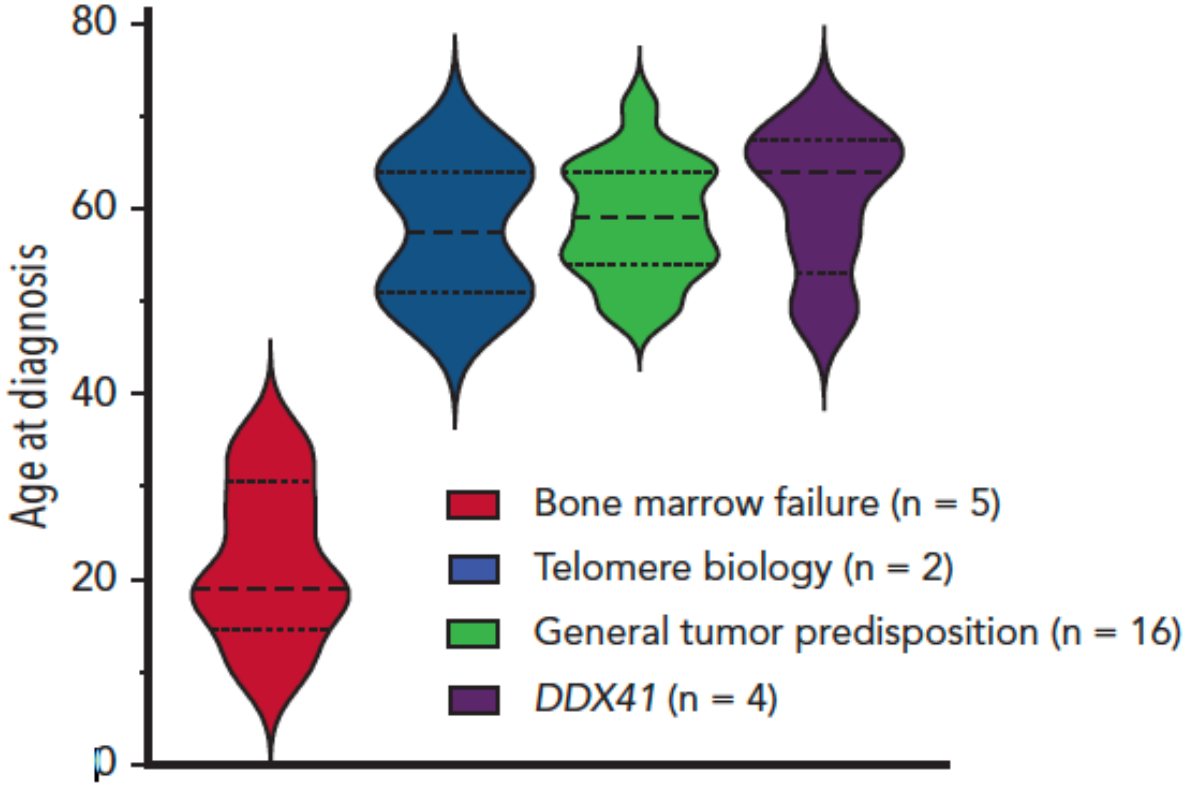
- On chromosome 7; gain of function mutations
- Act as growth suppressors and overexpression leads to cytopenias
- Multi-system disorder, including adrenal hypoplasia, chronic diarrhea, immunodeficiency, genital underdevelopment, neurologic abnormalities
- ~ 10-20% of pediatric MDS
- Highest rate of somatic mosaicism in a human disease to date

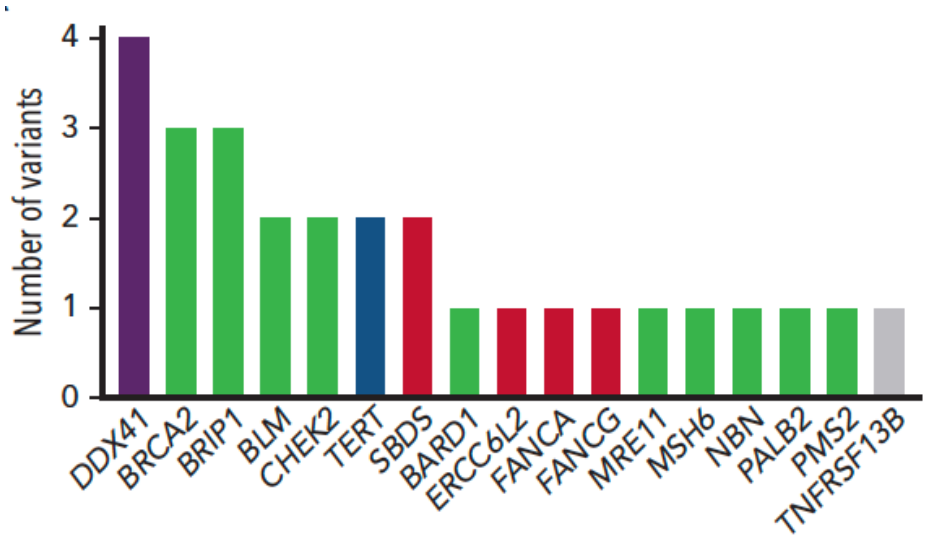


Sahooo S. et al. Clin Haem. 2020:33 and Sahoo S. et al. Nature Medicine 2021: 27.

Germline predisposition occurs in MDS patients of all ages

- ~7% of patients with MDS harbor deleterious germline mutations





- Age at presentation is a surrogate for the biologic pathway involved.

Feurstein S. et al. Blood 2022:140.

Question

22 yo male was referred for hematopoietic stem cell transplantation for MDS characterized by monosomy 7 (IPSS-R high risk). The patient's 24 year-old sister is reportedly healthy apart from recurrent herpes stomatitis. She is a 10/10 HLA allele-match to the patient. He has no other siblings. His mother is 44 years of age and has mild thrombocytopenia. His father is 51 years of age and is healthy.

Which of the following studies is most likely to establish a diagnosis?

A. Genetic testing of peripheral blood
B. Telomere length testing
D. Bone marrow aspirate and biopsy
E. Genetic testing of cultured skin fibroblasts
F. Platelet aggregometry

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Lab		**Reference Range**
HGB	**10.8 g/dL**	12-16 g/dL
MCV	**104 fL**	80-100 fL
WBC	5300/μL	4300-10,000/μL
ANC	4000/μL	1800-7,000/μL
Lymphocytes	1100/μL	1000-4800/μL
Monocytes	**0/μL**	0-800/μL
PLT	**125,000/μL**	150,000-400,000/μL

Marrow - hypocellular for age with normal blast percentage and atypical megakaryocytes.
No immunophenotypic abnormalities.
Routine karyotype 46, XY.

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Question

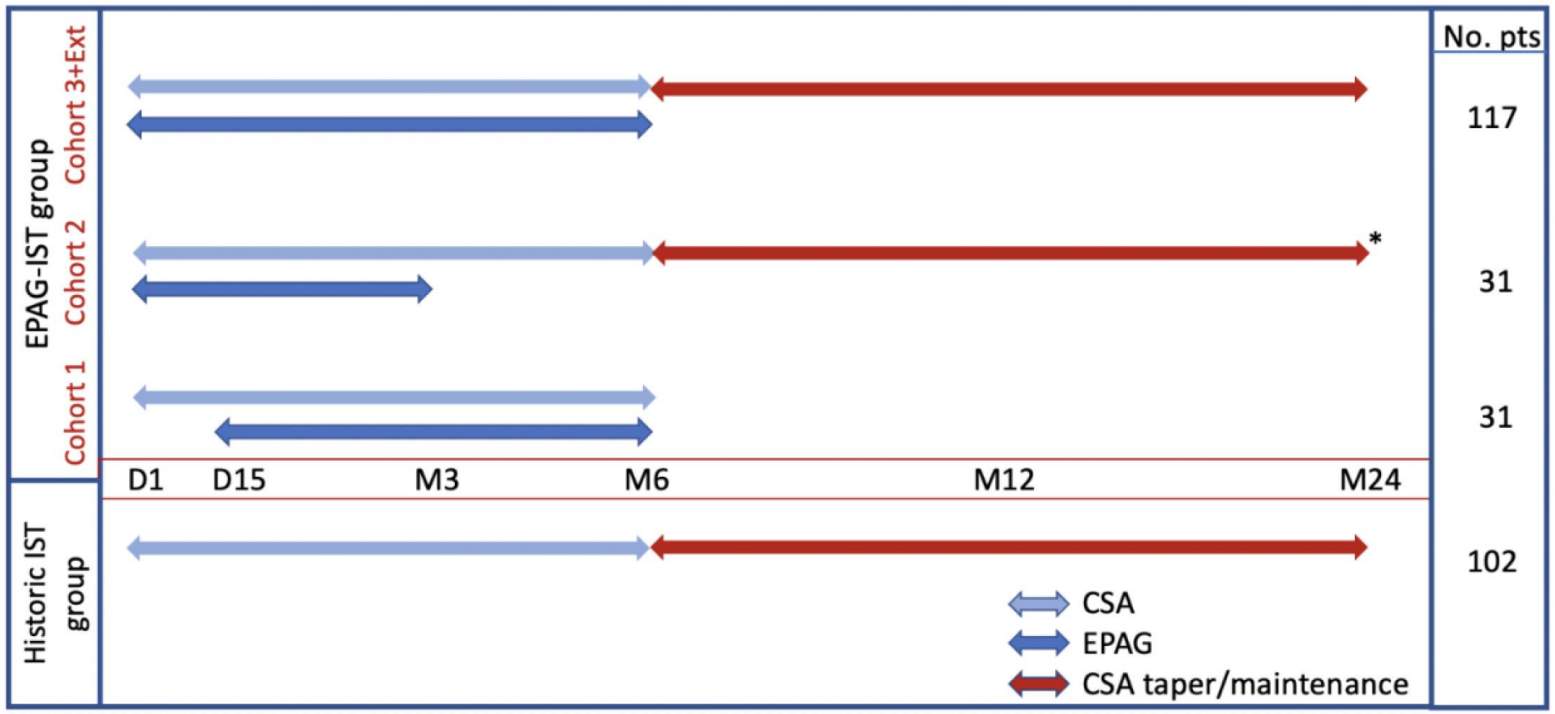
Which of the following is not a feature described in the genetic syndrome affecting this family?

A. Alveolar proteinosis
B. Atypical mycobacterial infections
C. Recurrent genital HPV infections
D. Lymphedema
E. Recurrent bacterial infections

The End

Features of select iBMF/HMPS that may present with hypocellular marrows

Syndrome	Congenital findings	Malignancy risk	Screening test	Genetics	Other hints
Fanconi anemia	Ear abnormalities, heart defects, short stature, skin pigmentation (café-au-lait spots or hypopigmentation), skeletal anomalies (thumbs, arms), TE fistula, triangular facies, urogenital defects	AML, MDS, GYN CA, Head and neck CA, and others	Increased chromosome breakage	FANCA, C, G account for 95% of cases	Sensitivity to chemotherapy
GATA2 deficiency	Lymphedema, immunodeficiency w/ atypical mycobacterial infections	AML, MDS		GATA2	Megakaryocyte atypia, pediatric MDS with monosomy 7, del7q, trisomy 8, der(1;7)
SAMD9/SAMD9L disorders	MIRAGE (SAMD9): MDS, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. Ataxia-pancytopenia syndrome (SAMD9L): cerebellar atrophy & white matter hyperintensities, gait disturbance, nystagmus	AML, MDS		SAMD9, SAMD9L	Pediatric MDS with monosomy 7, del7q, or CN-LOH 7q
Short telomere syndromes	Young adults: infections, nail dystrophy, oral leukoplakia, skin hyperpigmentation Adults: emphysema, early hair graying, immune deficiency, liver fibrosis/ cirrhosis, macrocytosis, pulmonary AVMs & HPS	AML, MDS Rectal adenocarcinoma SCC anus/oral cavity/tongue	Short telomere lengths (correlates w/ phenotype)	DKC1, RTEL1 TERT, TERC TINF2,, RTEL1 account for majority of cases	
Shwachman-Diamond Syndrome	Pancreatic insufficiency (can improve with age), skeletal abnormalities	AML, MDS	Low pancreatic isoamylase(>3 yo) and low fecal elastase (peds & adults)	SBDS, SRP54, ELF1, DNAJC21	Isolated neutropenia. somatic mutations in EIF6 & TP53


EPAG-IST group
Cohort 3+Ext
Cohort 2
Cohort 1
Historic IST group
No. pts
117
31
31
102
*
D1
D15
M3
M6
M12
M24
CSA
EPAG
CSA taper/maintenance

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).