Fred Hutch
Cancer Center

Inherited and Acquired Marrow Failure

Comprehensive Hematology & Oncology Review Course 2025

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Initial laboratory evaluation of hypocellular marrow failure*

Studies I recommend regardless of clinical suspicion*

*Aligns with the Modified Delphi Panel
Cconsensus Rrecommendations for Management of Severe AA

Babushok DV. et al. Blood Advances 2024.

Acquired	Inherited
Acquired AA	**Inherited BMF syndromes or inherited hematologic malignancy predisposition syndromes**
Hypocellular MDS	-Fanconi anemia
	-Short telomere syndromes
	-Shwachman-Diamond Syndrome
	-GATA2 deficiency
Medications/Toxins	-Others

PERIPHERAL BLOOD	DIAGNOSIS
Flow cytometry for PNH	Acquired aplastic anemia (aAA)
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/HHPS
FISH	MDS, IBMF/HHPS
Chromosome genomic array	6p CN-LOH in aAA, IBMF/HMPS, 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 BMF/Hereditary hematologic malignancy predisposition syndromes

Keel S and Geddis A. Hematology 2021: 1.

Acquired PNH clones distinguish acquired AA from inherited BMF/hereditary hematologic malignancy predisposition syndromes (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

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**

DeZernA 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.

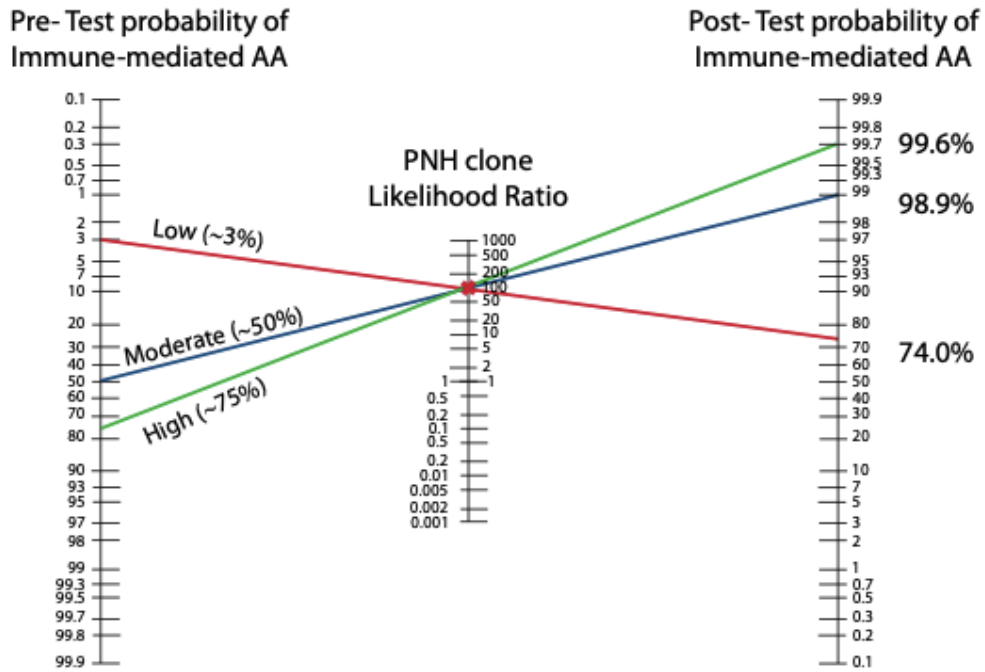
Acquired 6p CN-LOH^{MHC} clones distinguish acquired AA from IBMF/HHMPS

- Detected by chromosomal microarray on a marrow sample
- Present in ~10-15 % of acquired AA
- Occurs in <1% of patients with MDS or in normal aging
- 6p CN-LOH distinguishes acquired AA from IBMF/HHMPS (100% PPV)
  - Loss of HLA class I alleles disrupts antigen presentation and allows immune escape

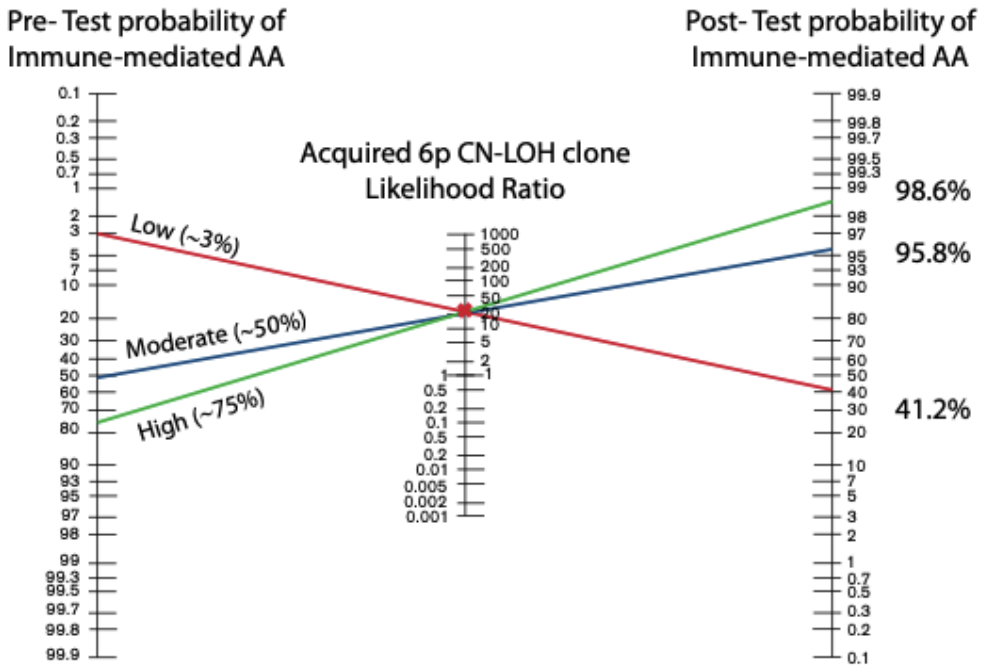
Katagiri T et al. Blood 2011:118.
Afable MG et al. Blood 2011:117.
Babushok DV et al. BJH 2014:164.
Mohamedali AM et al. Leukemia 2015:29.
Score J et al. Leukemia 2015:29.
Betensky M et al. Cancer Genet 2016:209.
Shah YB et al. Blood Adv 2021:5.

Pre-test and post-test probabilities of aAA with positive PNH or 6p CN-LOH^{MHC} results

PNH clone



Acquired 6p CN-LOH clone



Shah YB et al. Blood Adv 2021:5.

Idiopathic acquired aplastic anemia (aAA)

- Biphasic age pattern
- Immune-mediated destruction of HSCs
- Severity
  - Classical – modified Camitta criteria[1,2]
  - Practical – severe neutropenia or transfusion dependence

Modified Camitta 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

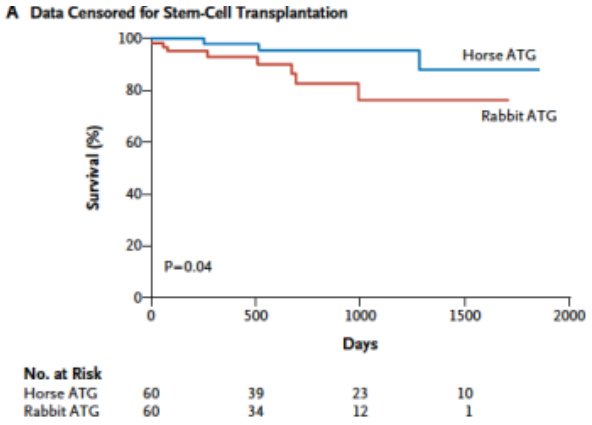
Plts < 20 X 10^9/L

Absolute retic count <60 X 10^9/L

Babushok DV et al. Blood Advances 2024:8.
Camitta BM Blood 1976:48.
Killlick S BJH 2016:172.

Key historical insights on IST (cyclosporine +ATG) in severe aAA

- Horse is better than rabbit ATG[1]
- Response to IST is age-dependent[2]
  - Additional of eltrombopag does not completely overcome age-dependent response[3]
- Adding GM-CSF, G-CSF, or IL-3 does nc
  improve response or survial[4]



Scheinberg P et al. NEJM 2011:365.

Table 2. Hematologic Response, According to Treatment Group.

Cohort and Response	Response at 3 Mo				Response at 6 Mo	
	Group A: Horse ATG–Cyclosporine (N=101)	Group B: Horse ATG–Cyclosporine–Eltrombopag (N=96)	Odds Ratio (95% CI)*	P Value	Group A: Horse ATG–Cyclosporine (N=101)	Group B: Horse ATG–Cyclosporine–Eltrombopag (N=95)†
All patients — no. (%)						
Complete response‡	10 (10)	21 (22)	3.2 (1.3–7.8)	0.01	20 (20)	30 (32)
Partial response	21 (21)	36 (38)			21 (21)	35 (37)
No response	70 (69)	39 (41)			60 (59)	30 (32)
Overall response§	31 (31)	57 (59)			41 (41)	65 (68)
Patients with severe aplastic anemia — no./total no. (%)						
Complete response	10/67 (15)	17/62 (27)			15/67 (22)	20/62 (32)
Partial response	17/67 (25)	27/62 (44)			16/67 (24)	26/62 (42)
No response	40/67 (60)	18/62 (29)			36/67 (54)	16/62 (26)
Patients with very severe aplastic anemia — no./total no. (%)						
Complete response	0/34	4/34 (12)			5/34 (15)	10/33 (30)
Partial response	4/34 (12)	9/34 (26)			5/34 (15)	9/33 (27)
No response	30/34 (88)	21/34 (62)			24/34 (71)	14/33 (42)
Patients ≥15 to <40 yr — no./total no. (%)						
Complete response	6/36 (17)	6/29 (21)			11/36 (31)	15/29 (52)
Partial response	6/36 (17)	14/29 (48)			7/36 (19)	8/29 (28)
No response	24/36 (67)	9/29 (31)			18/36 (50)	6/29 (21)
Patients ≥40 yr — no./total no. (%)						
Complete response	4/65 (6)	15/67 (22)			9/65 (14)	15/66 (23)
Partial response	15/65 (23)	22/67 (33)			14/65 (22)	27/66 (41)
No response	46/65 (71)	30/67 (45)			42/65 (65)	24/66 (36)

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

1. Scheinberg P et al. NEJM 2011:365.
2. Bacigalupo A. Blood 2017:129.
3. Peffault de Latour R. et al. NEJM 2022:386.
4. Gurion R et al. Haematologica 2009:9.

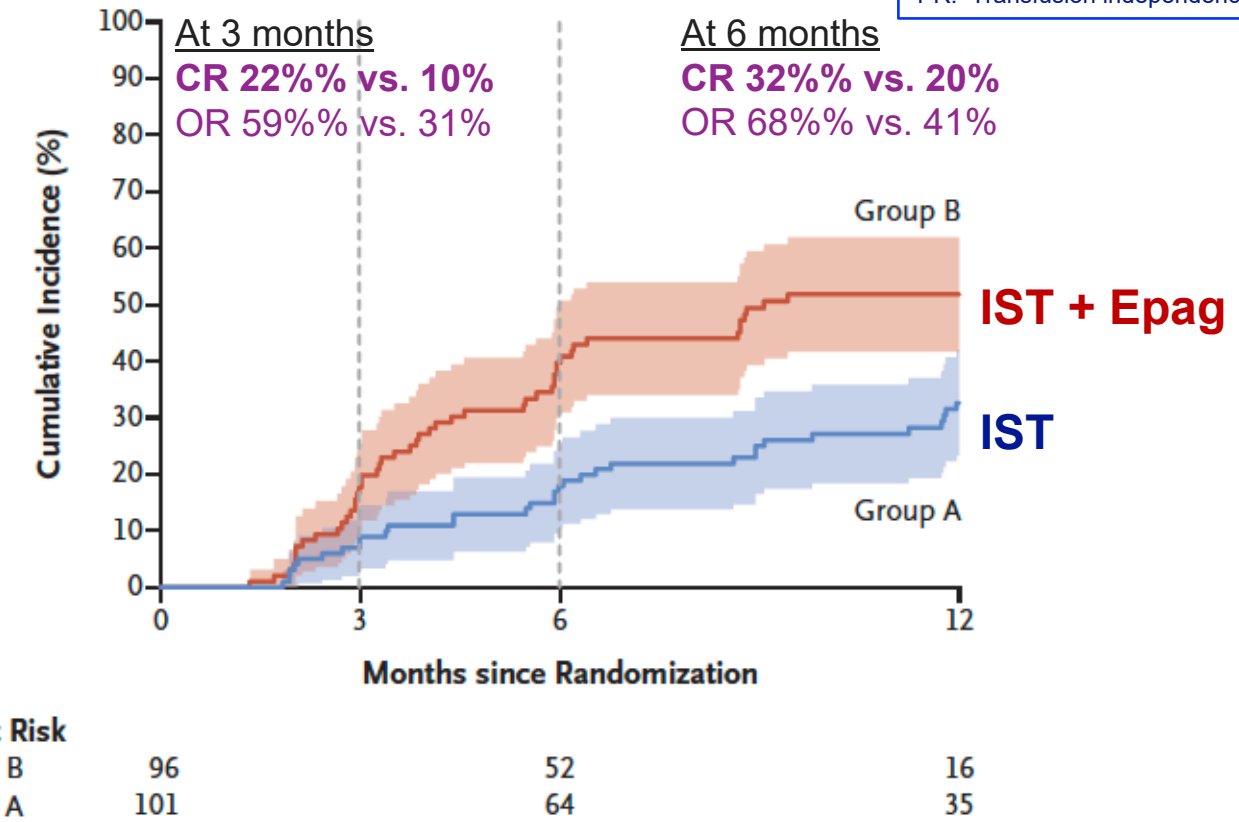
RACE Trial (Phase III): Standard IST ± Epag in severe aAA

Relapsed/refractory – Ph 2 + ext study (43 patients)[1]
- -Epag 150 mg po daily
- -Hematologic response 40% (17/43) @ 12 wks

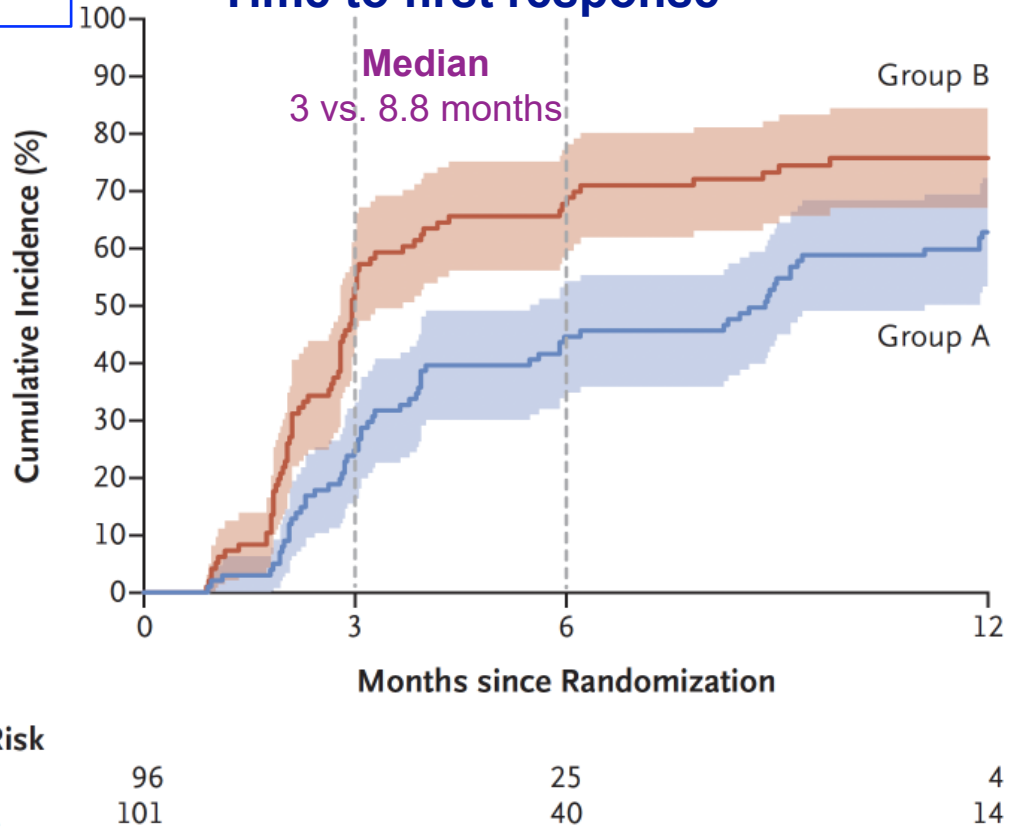
Upfront therapy
- -Phase 1-2 study (92 patients; median f/up 2 yrs)[2]
  - ➢CR 58% and OR 94% @ 6 months

CR: HGB > 10 g/dL, ANC >1000 PLT >100K
PR: Transfusion independence

Complete response



Time to first response



- **EFS at 2 years for IST +EPAG = 46% (95% CI 36 to 57)**

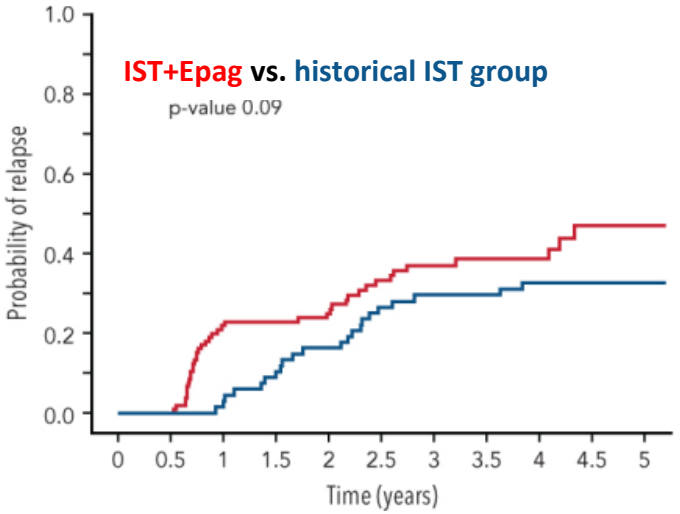
- Epag showed no improvement in ORR or CR at 6 months in pediatric patients (<18 yo)[4]

1. Alvarado LJ et al. Blood 2019:139(19).
2. Desmond R et al. Blood 2014:123(12).
3. Peffault de Letour R. et al. NEJM 2022:386.
4. Groarke EM e al. BJH 2021:192.

Late complications of IST treated patients – relapse is common

- Relapse with IST *without* Epag[1]
  - 29% (24/84) achieved normal blood counts & remained off IST long-term (median follow-up: 11.3 yrs)[1]
- Relapse with IST *with* Epag[2]

Relapse among responders at 6m



- Median follow-up: Epag+IST 4 yrs; historic IST group 7 yrs

Take-Home Points

- IST + Epag relapses: occur "early" (6 months) and "late" (after 2 yrs) when Epag/CSA dosing changes
- Epag promotes early hematologic response: 6-mo ORR 81% vs 67
- Response not sustained after stopping Epag: **12-mo ORR 56 vs. 57%**

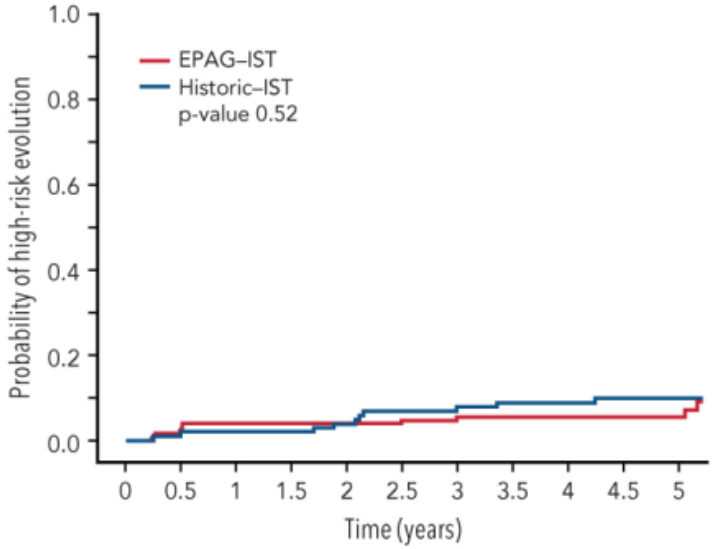
Study evaluating sirolimus (NCT02979873) to prevent relapse after stopping CSA.

1. Frickenhofen N et al. Blood 2003: 101(4).
2. Patel BA et al. Blood 2022: 139 (1).

Late complications of IST ± Epag treated patients – other complications

- **MDS/AML evolution in 10-15% of cases[1,2,3]**
- Renal disease
- Impacts on quality of life

High-risk clonal evolution



Patal BA et al. Blood 2022.

- High-risk clonal evolution– myeloid malignancy or chromosome 7 abnormality
- Incidence similar between groups → occurred earlier in Epag+IST

Median follow-up: Epag + IST 4 yrs; historic IST group 7 yrs

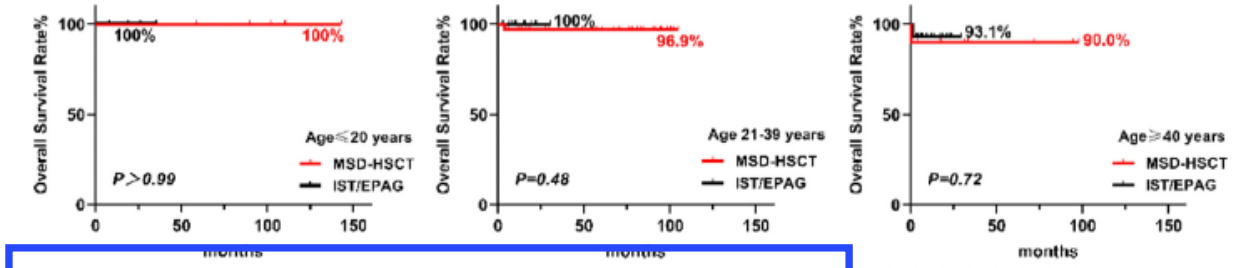
1. Young N et al. Blood 2006:108(8).
2. Frickenhofen N et al. Blood 2003:101(4).
3. Patel BA et al. Blood 2022:139(1).

HLA-Matched Related Donor Transplant vs. IST in Adults

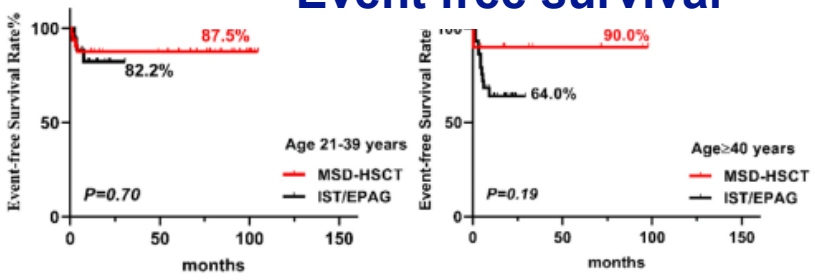
	MSD-HSCT (n = 48)	IST/EPAG (n = 51)	P
Age, year, median (range)	29.5 (23-39)	46 (29-61)	.001
20 years	6 (12.5%)	4 (7.8%)	
21-39 years	32 (66.7%)	18 (35.3%)	
40 years	10 (20.8%)	29 (56.9%)	
Gender			.60
Male	27 (56.3%)	26 (51.0%)	
Female	21 (43.8%)	25 (49.0%)	
Disease severity			.007
SAA	22 (45.8%)	37 (72.5%)	
VSAA	26(54.2%)	14 (27.5%)	

- Conditioning regimen flu, CY, r-ATG or p-ALG

Overall survival



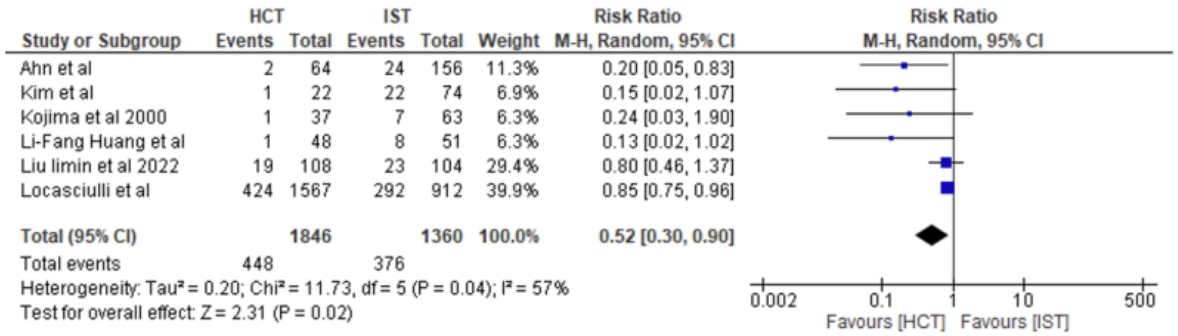
Event free survival



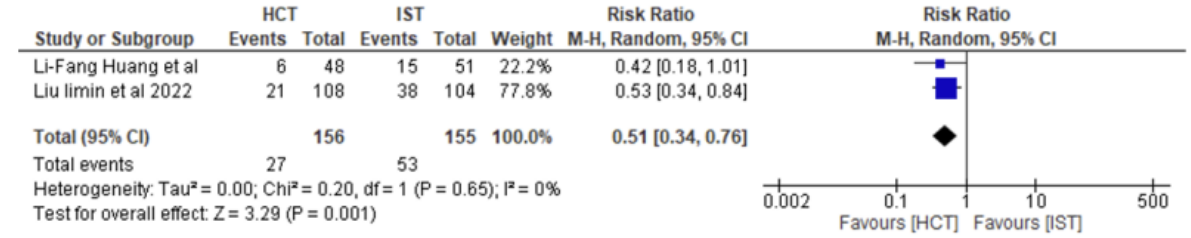
Huang LF. Et al. Trans Cell Ther 2022: 586.

Systematic Review and Meta-Analysis: MRD-HCT vs. IST in adults (Post-2000)

Overall survival



Event-free survival

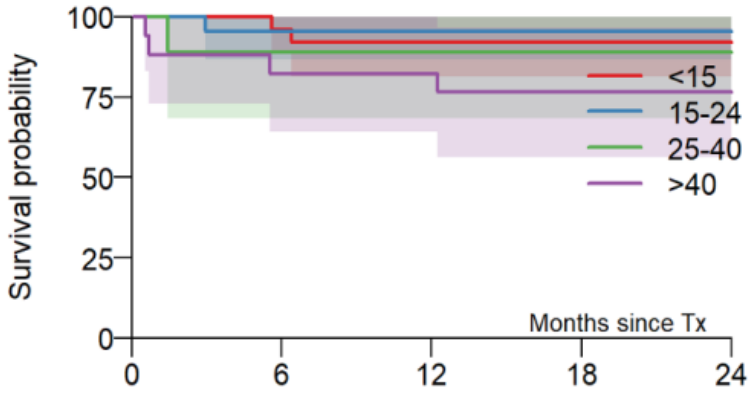


Iftikhar R. et al. Trans and Cell Ther 2024: 30.

Upfront MUD/mMUD outcomes approximate MRD allo-HCT outcomes

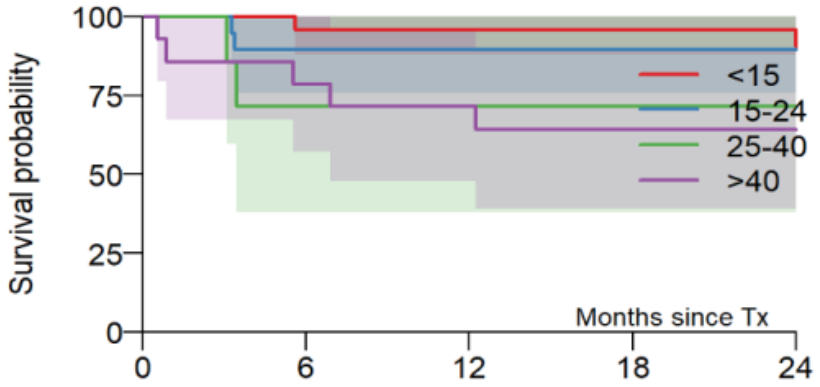
EBMT 2010-2018 Data

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-yr GVHD relapse free survival



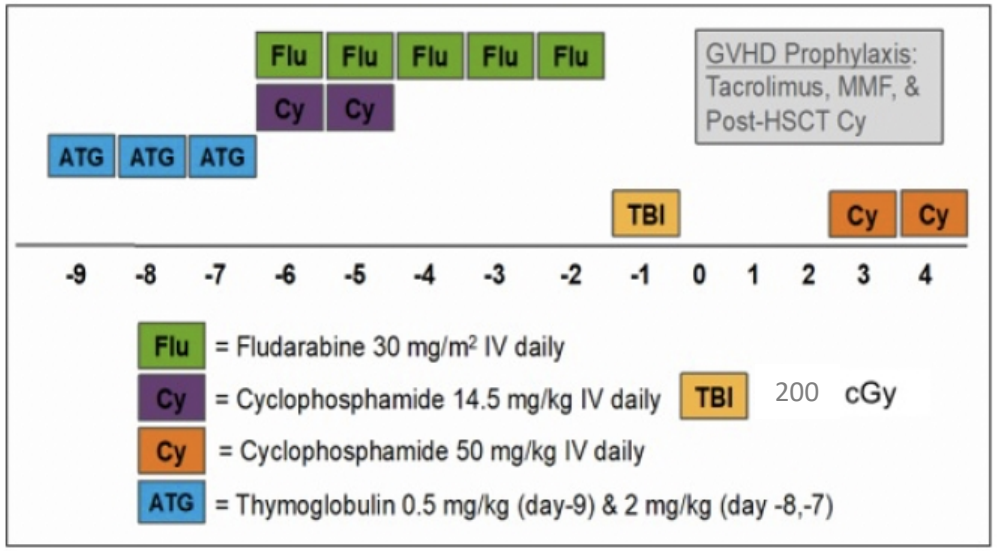
	Groups	Total n	n	24 months
Age	<15	25	18	91% (78-100%)
	15-24	19	12	89% (76-100%)
	25-40	7	3	71% (38-100%)
	>40	14	8	64% (39-89%)

*More recently PTCY has been used to further improve OS and GVHD outcomes with MUD allo HCT for sAA.

Petit AF et al. AJH 2021.

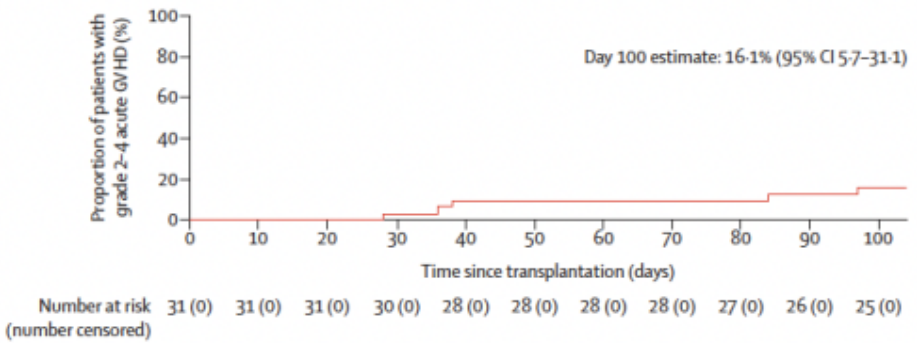
Haplo-HCT with PT-CY for R/R SAA – CTN 1502 "Baltimore protocol"

- Single arm, Ph2 study
- Inclusion
  - R/R SAA
  - No HLA-matched sib or unrelated donor
  - ≤ 70 yo and ECOG 0 or 1
- Study population
  - 32 patients, 31 underwent tx
  - Median ago 24.9 yo, 6/31 >60 yo

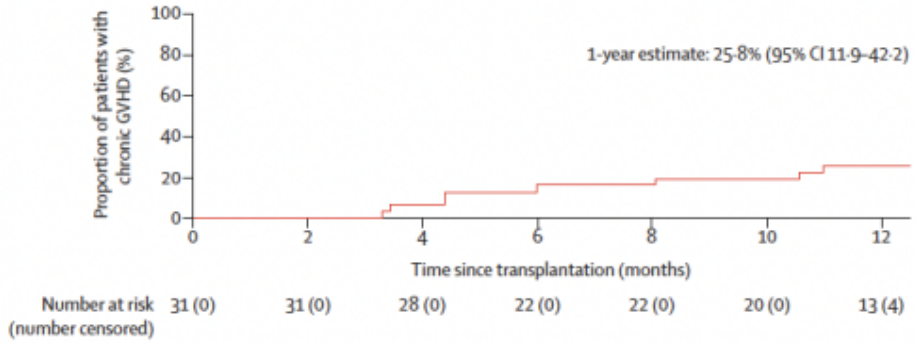


Outcomes
- 1 yr OS 81% (95% CI 62-91)
- 6 deaths (19%)
- 5 primary graft failures (16%) – cell dose mattered
- 16% (95% CI, 6-31) D100 grade acute 2-4 GVHD
- 26% (8) chronic GVHD

Incidence of acute GVHD



Incidence of chronic GVHD

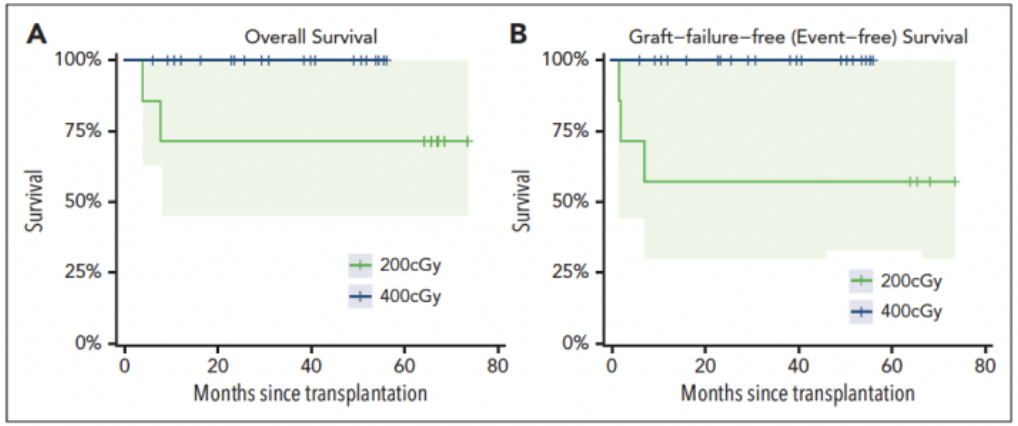


DeZern A. et al. Lancet Haematol 2022:9

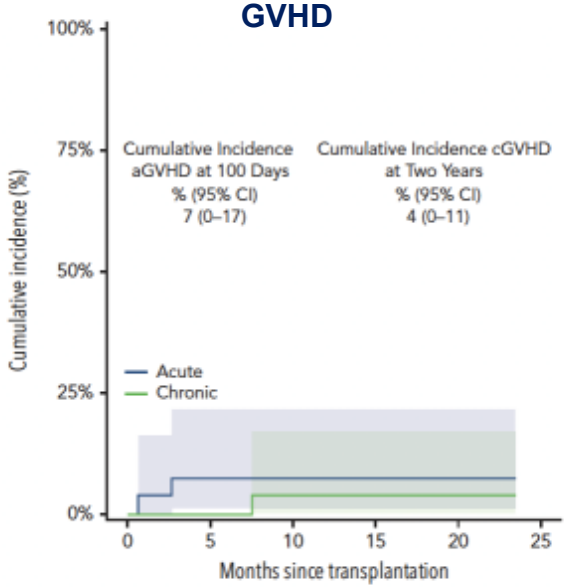
Upfront Haplo-HCT with PT-CY

- Single center, Ph2 study
- Study population
  - 27 patients
  - Median 25 (range 3-63)
- Treatment
  - Flu/Cy/ATG/TBI 200-400 cGy
  - GVHD prophylaxis- PT-CY/Tac/MMF
  - 4 × 10^8 nucleated marrow cells/kg
  - First 7 patients received 200 cGy TBI

Outcomes
- 5-year OS - 100 % in pts tx 400 cGY
- CI Gr 2-4 Acute GVHD at D100 7%
- CI Ch GVHD at 2 years 4%



Incidence of acute and chronic GVHD



DeZern A. et al. Blood 2023: 141.

Current clinical trials aimed at assessing role of alternative donor HCT in upfront setting

BMT CTN 2207: Upfront MURD/mmURD vs. haplo in severe aAA

CUREAA – Clinical Trial of Upfront Haploidentical or Unrelated Donor BMT to REstore Normal Hematopoiesis in Aplastic Anemia

Inclusion

- Newly diagnosed sAA and no suitable HLA matched related donor
- > 25 yo (up to 75 yo)

Baltimore protocol (4-Gy TBI)

Primary endpoint

- GVHD-failure-free survival at 1-yr post BMT

Enrolling at FHCC

BMT CTN 2202: MURD/mmURD vs. IST in severe aAA

TransIT – Trial Comparing Unrelated Donor BMT with IST for Pediatric and Young Adult Patients with Severe Aplastic Anemia

Inclusion

- Newly diagnosed sAA and no suitable HLA matched related donor
- ≤ 25 yo

2-Gy TBI, Cy, fludarabine, and ATG-based conditioning with CsA- and MTX-based GVHD prophylaxis.

Primary endpoint

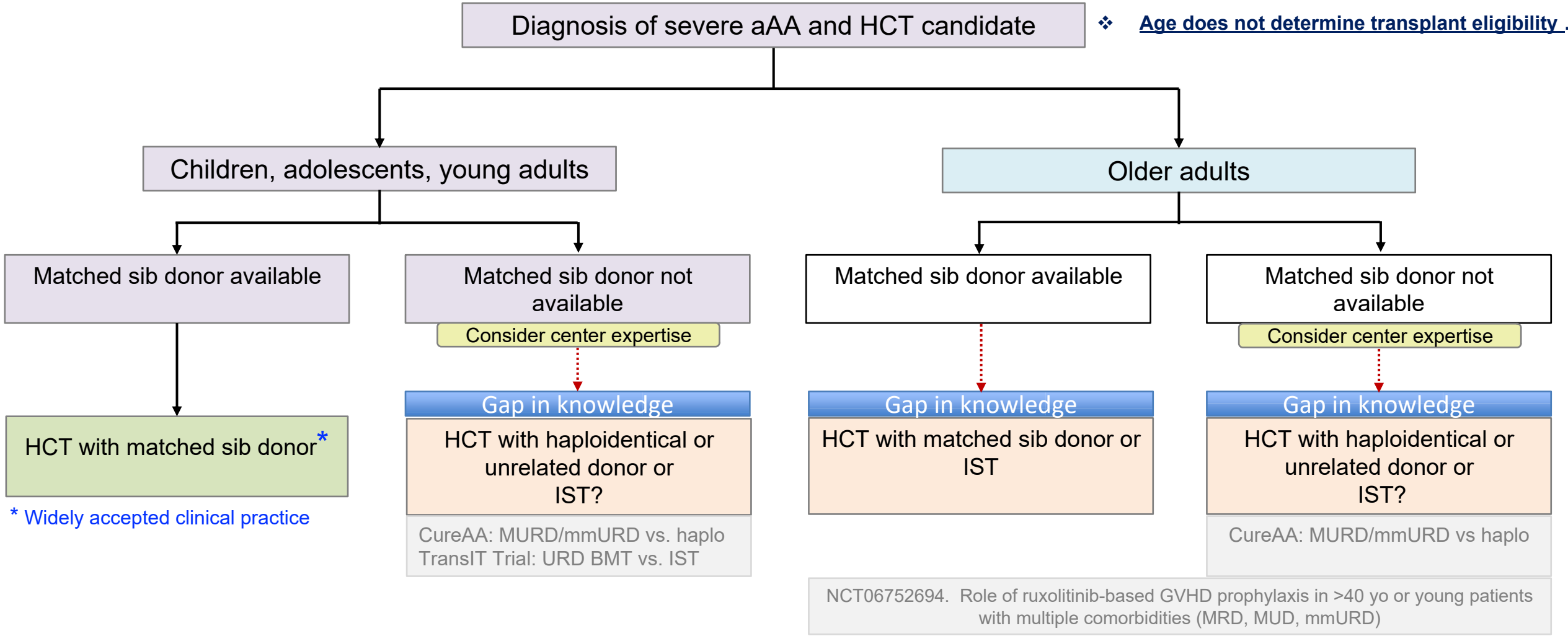
- Time from randomization to treatment failure or death from any cause.

Enrolling at FHCC

**TransIT Feasibility Study - 60% of patients assigned to BMT received BMT by 8 wks of diagnosis. Goal of TransIT is to get to transplant within 8 wks of diagnosis.*

* Pulsipher MA. et al. Pediatr Blood Cancer 2020.

Treatment of Newly Diagnosed Severe Aplastic Anemia (aAA) in Transplant-Eligible Patients



* Widely accepted clinical practice

Available published aplastic anemia guidelines vary in recommendations

American Society for Transplantation and Cellular Therapy (Transpl Cell Ther. 2024:30)

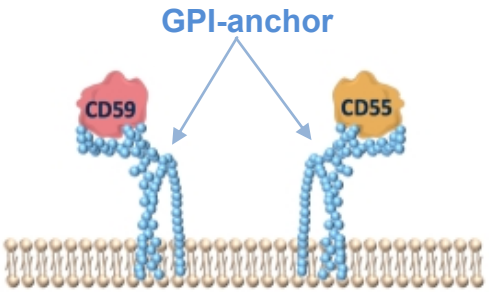
British Society of Haematology guidelines (BJH 2024: 204)

The North American Pediatric Aplastic Anemia Consortium guidelines (Pediatr Blood Cancer 2024: 71)

Modified from Bhatt NS. et al. Blood Advances 2024: 9.

Classical paroxysmal nocturnal hemoglobinuria

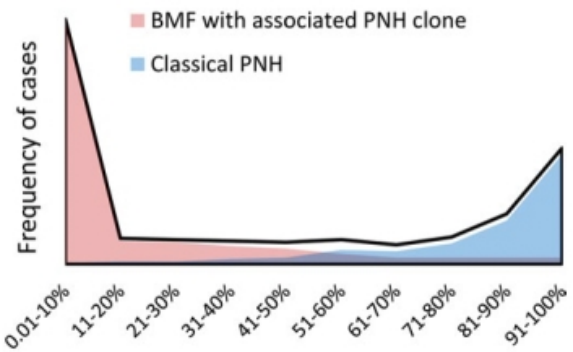
- Clonal expansion of HSCs with somatic mutation in *PIGA*
  - Lack GPI-Linked proteins
- Clinical triad
  - Intravascular hemolysis, thrombosis, bone marrow failure
- Diagnosis - Absent or reduced GPI-linked proteins
  - Mean clone size >70% in classical PNH (vs. 11% in AA with associated PNH clone)



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

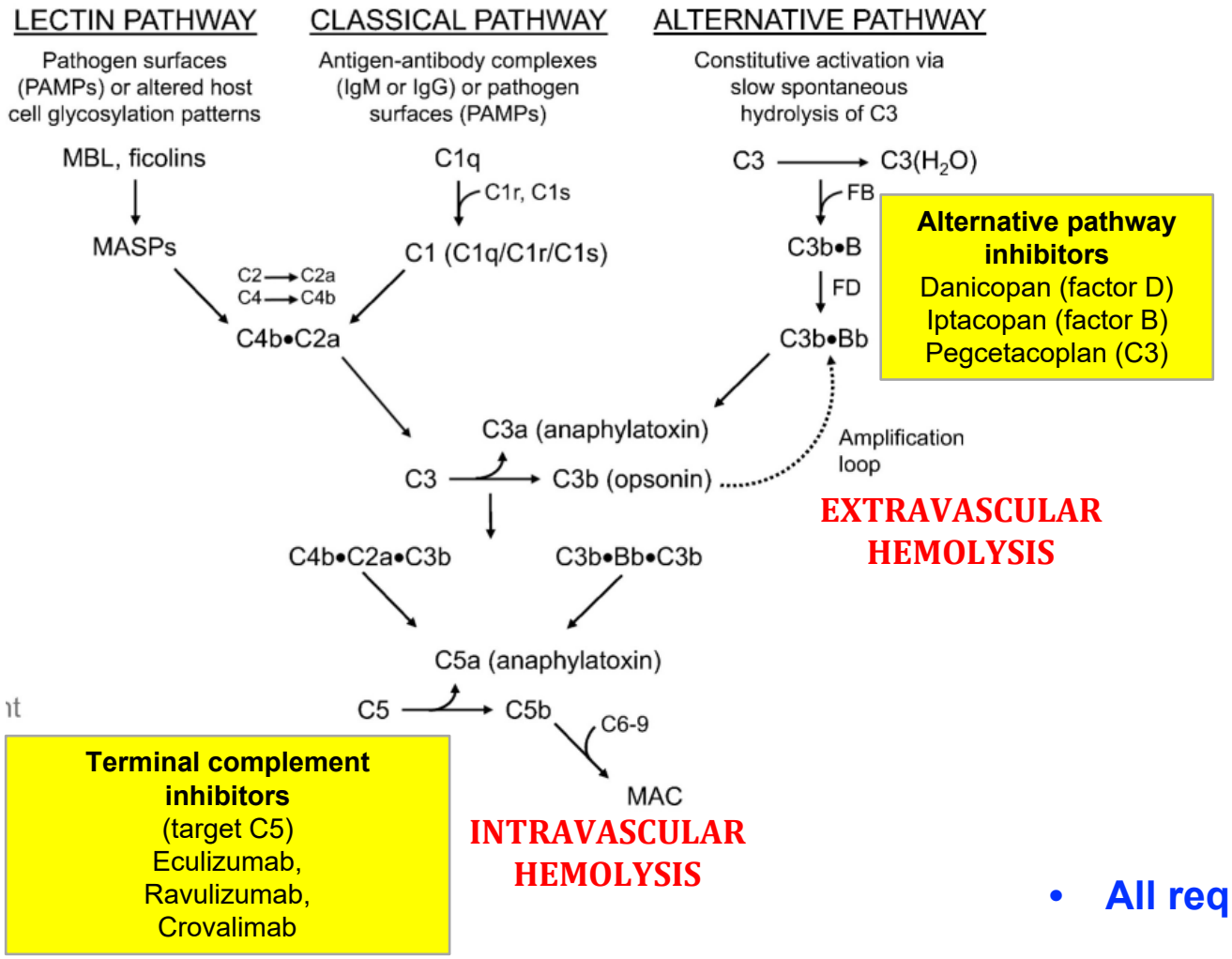
PNH granulocyte clone size



Modified from Babushok D. Hematology 2021.

Babushok D. Hematology 2021.
Luzzatto L and Nakao S. Blood 2025:145.

FDA approved therapies for PNH in 2025



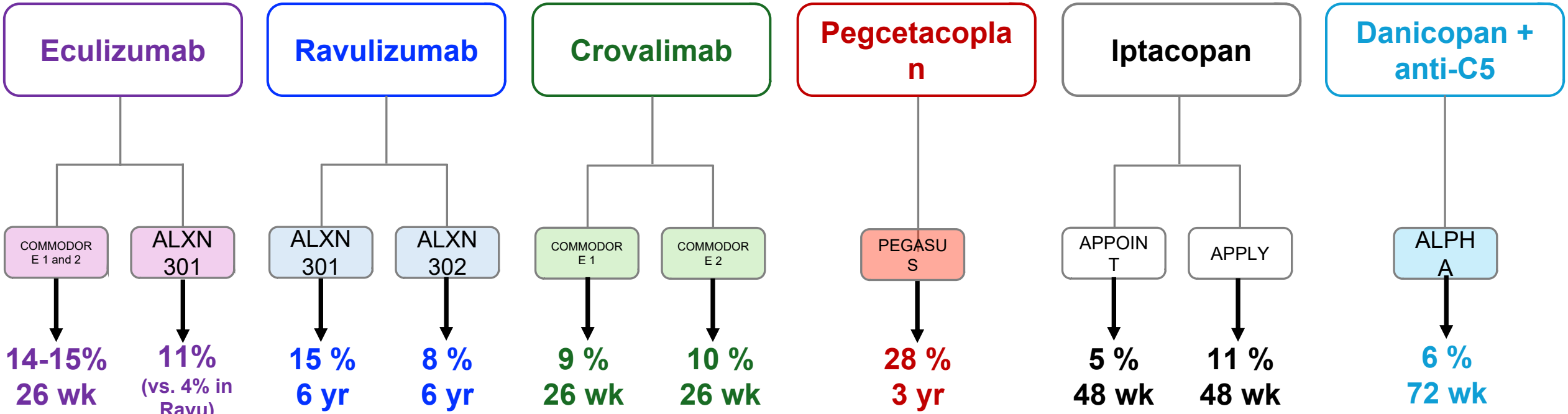
Drug	Target	Dosing	T ½
Eculizumab	C5	• IV infusion • Loading dose wkly X4, then q 2 wks	11.3 d
Ravulizumab	C5	• IV infusion • Loading dose q 2 wks X 2 , then q 8 wks	49.7 d
Crovalimab	C5	• SC injection • 1 IV loading dose followed by 4 wkly SC doses, then q 4 wks SC	53.1 d
Danicopan	Factor D	• Oral • TID	7.9 hr
Iptacopan	Factor B	• Oral • BID without regard to food	25 hr
Pegcetacoplan	C3	• SC infusion • Twice wkly	8.6 d

- **All require Meningococcal, Pneumococcal, H. Flu vaccinations.**

Modified from Gerber GF and Brodsky RA Blood 2025: 145 (8).

Frequency of BT-IVH with PNH with various complement inhibitors

Predictors of severe BT-IVH
- Size of RBC PNH clone
- Suboptimal response to complement inhibition
- Comorbidities/higher infectious risk



- Lee JW. Et al. Blood 2019: 133.
- Kulasekararaj A. et al. Ann Hematol 2025: 104.
- Röth A. et al Am J Hematol 2024: 99 .
- Scheinberg P. et al. Am J Hematol 2024: 99.
- Peffault D. et al. EHA library. 2024:P819 (abst).
- Peffault D. et al. NEJM 2024:390.
- Peffault D. et al. Blood 2023; 142(suppl 1).
- Kulasekararaj A. et al. Blood 2025: 145.

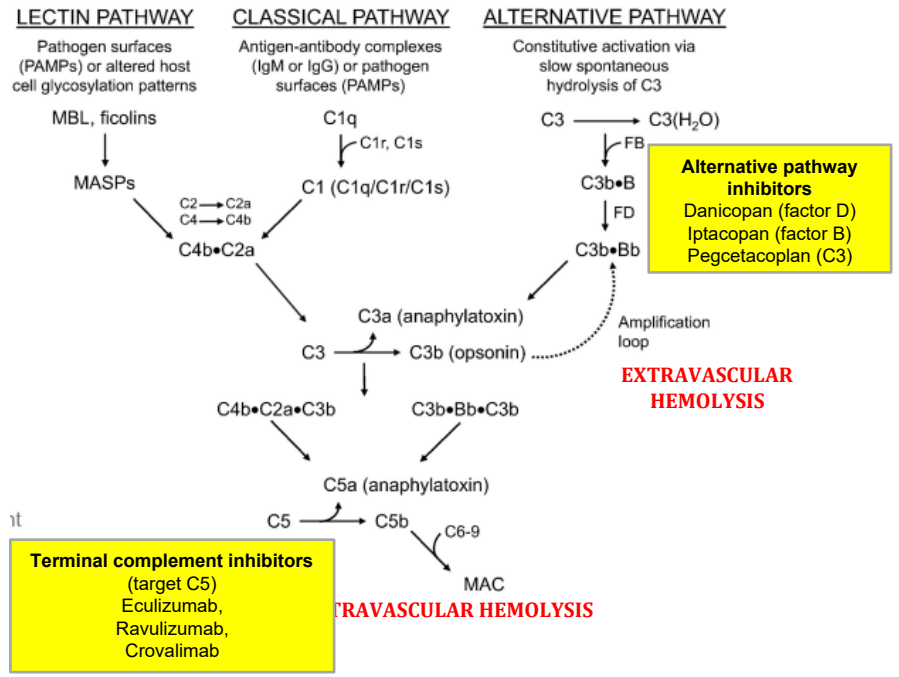
Modified from Fattizzo B. et al Blood 2025: 1456.

Definition
- Rav, crov, and peg studies: 1 new or worsening sign/symptoms of IVH and LDH of ≥ 2X ULN (after prior reduction to < 1.5 ULN).
- Iptacopan studies: HGB ≥ 2 g/dL or PNH symptoms and LDH >1.5X ULN

- Breakthrough thromboses are rare

Alternative pathway inhibitors

- Treat persistent extravascular hemolysis (not controlled by C5 inhibitors
- All their targets have very short half-lives: hours to days
- Strong classical pathway stimulus (infections, trauma, surgery) can lead to massive BT-IVH
- **B-IVH can potentially be more severe**
  - With C5 inhibitors → only 1 MAC per escaped C5
  - With alternative pathway inhibitors
    1. Incomplete C3 inhibition → multiple C5 cleavages → more MACs
    2. Larger RBC PNH clone due to better RBC survival → higher risk for severe breakthrough hemolysis



Classification of IBMF/HHMPS (*modified from 2025 NCCN MDS Guidelines*)

Classical inherited bone marrow failure syndromes

- Diamond Blackfan anemia
- Fanconi anemia
- Shwachman-Diamond syndrome
- Short telomere syndromes
- Congenital neutropenia

Classical IBMF

Germline predisposition for heme malignancy <u>without</u> pre-existing cytopenia(s) or other organ dysfunction

- *CEBPA*
- Others

No pre-exisiting Disorder

Germline predisposition for hematopoietic malignancy <u>with</u> pre-existing cytopenia(s) ± other organ dysfunction

- *DDX41*
- *GATA2*
- *RUNX1*
- Others

Preexisting Disorder

Germline predisposition for heme malignancy & solid tumor cancers

- Constitutional mismatch repair deficiency, hereditary breast and ovarian CA, Li-Fraumeni (TP53), Others

"Solid tumor" Predisposition syndromes

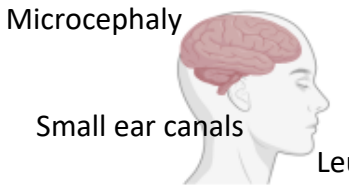
Whom to suspect?

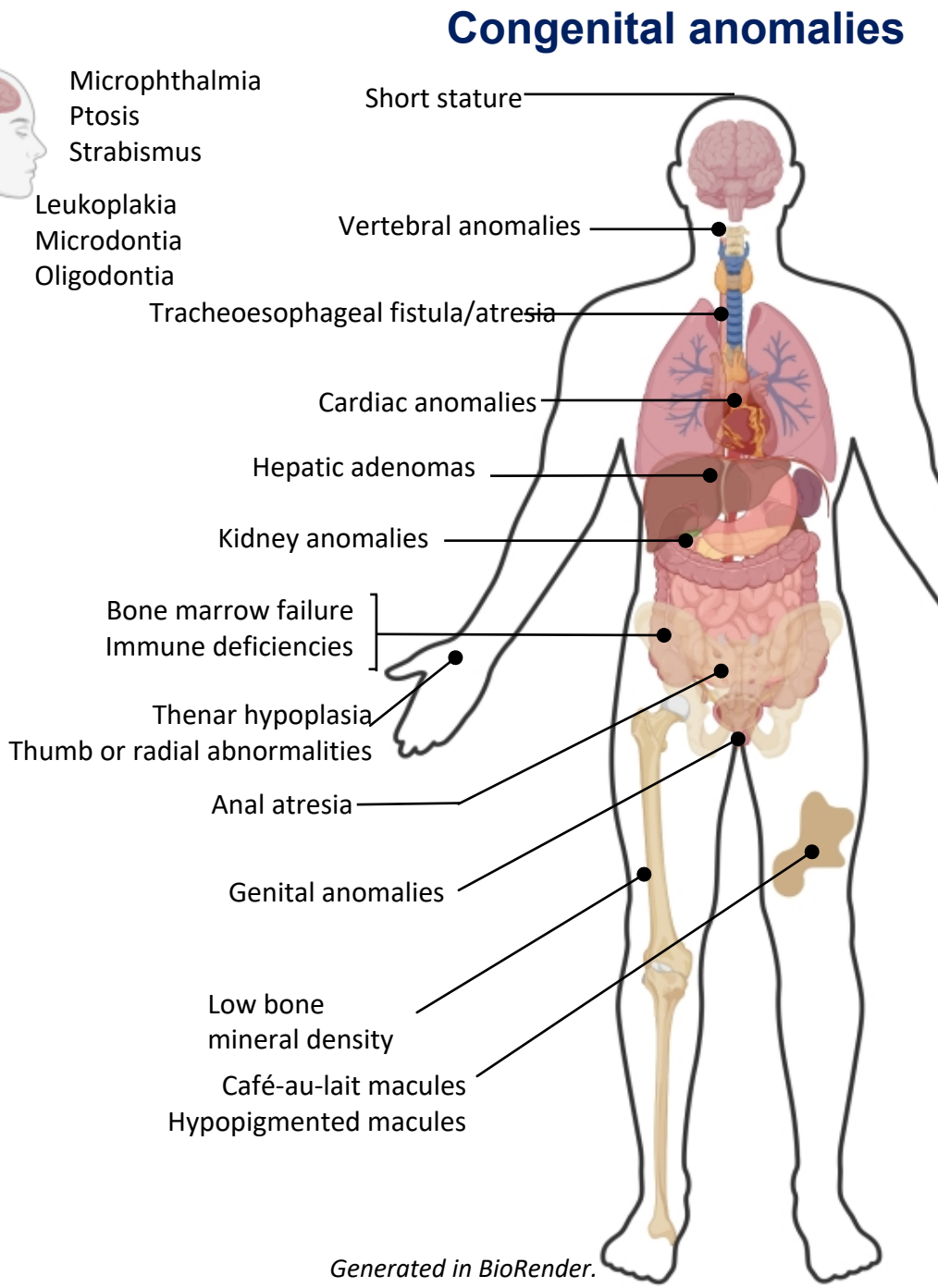
- AML/MDS diagnosed at <50 yrs
  - Especially younger MDS patients with chromosome 7 abnormalities (SAMD9/9L disorder and GATA2 Deficiency Syndrome)
- Hypocellular MDS or aplastic anemia
  - Particularly “non-severe” aplastic anemia
- Personal history of MDS/AML plus ≥ 1 additional cancer(s)
- Antecedent unexplained macrocytosis or cytopenias
- Known or suspected genetic predisposition syndrome at any ag
- Absence of congenital anomalies or family history does not exclude a heritable cause

Wlodarski MW et al Blood 2016:127.
Schwartz JR et al Nat Comm 2017:8.
Singhal D et al. Leukemia 2021:35.
Keel SB et al. Haematologica 2016:101

Fanconi anemia

- Mutations in DNA cross-link repair genes
- Inheritance AR except FANC B: x-linked; FANCD: AD
- Congenital anomalies (~1/3 lack congenital anomalies)
- Hypocellular marrow ± cytopenias
- Predisposition to cancer: AML, oral/esophageal/ vulvar SCC, HCC
- Radiosensitivity (DNA damage)
- Diagnosis: chromosomal breakage test (gold standard) + genetic testing
  - Somatic mosaicism in lymphocytes in ~ 10-25% of cases[1]





1. Nicolleti E et al. Ann Hematol 2020:99.

Diamond Blackfan Anemia

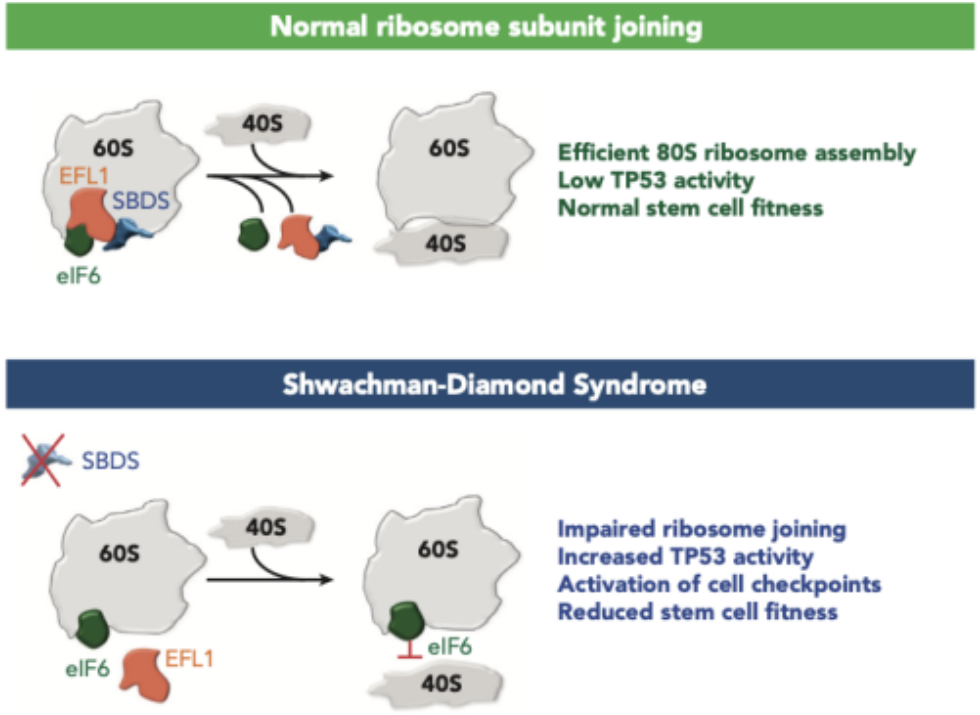
- Congenital pure red cell aplasia
  - BM with absent or reduced erythroid precursors
  - Can see neutropenia/thrombocytopenia
- Cancer risk (colorectal and osterosarcoma)
- eADA elevated in 75-90% of cases
  - 90% PPV and NPV compared to other IBMFS
- ~ 50% have physical abnormalities (excepting short stature)
- Genetic testing – heterozygous pathogenic mutations in ribosomal or related proteins disrupt rRNA maturation & ribosome biogenesis
  - No molecular defect in ~ 20% of cases
- Corticosteroids: 80% initial response; 50–60% long-term response

Genes associated with DBA		Inheritance	Frequency (%)
RIBOSOMOPATHY GENES			
RPS (40S Subunit)	RPS19	AD	25
	RPS26	AD	6.6
	RPS10	AD	3
	RPS24	AD	2.4
	RPS17	AD	1
	RPS7	AD	<1
	RPS15A	AD	<1
	RPS20	AD	<1
	RPS27	AD	<1
	RPS28	AD	<1
Cleft palate	RPS29	AD	<1
Thumb abnormalities	RPL5	AD	7
RPL (60S Subunit)	RPL11	AD	5
	RPL35A	AD	3
	RPL4	AD	<1
	RPL8	AD	<1
	RPL9	AD	<1
	RPL15	AD	<1
	RPL17	AD	<1
	RPL18	AD	<1
	RPL26	AD	<1
	RPL27	AD	<1
	RPL31	AD	<1
	RPL35	AD	<1
Ribosomal Protein Chaperones	TSR2	X	<1
	HEATR3	AR	<1
OTHER GENES			
	GATA1	X	<1
	TP53 (gain of function)	AD	<1

Da Costa L. et al. Blood 2020:136.
Wlodarski MW et al. Lancet Haematol 2024:11.

Shwachman Diamond Syndrome (SDS)

- Autosomal recessive; biallelic *SBDS* mutations in ~ 90% of cases.
- SBDS involved in joining 60S & 40S subunits to form the 80S ribosome
- Bone marrow failure, exocrine pancreatic dysfunction (improves in >50% with age), neurocognitive disorders, skeletal abnormalities, and cancer predisposition
  - Neutropenia is most common hematopoietic abnormality
- HSCT is the only curative treatment for the hematologic complications of SDS



From Reilly C. et al. 2023: 131.

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

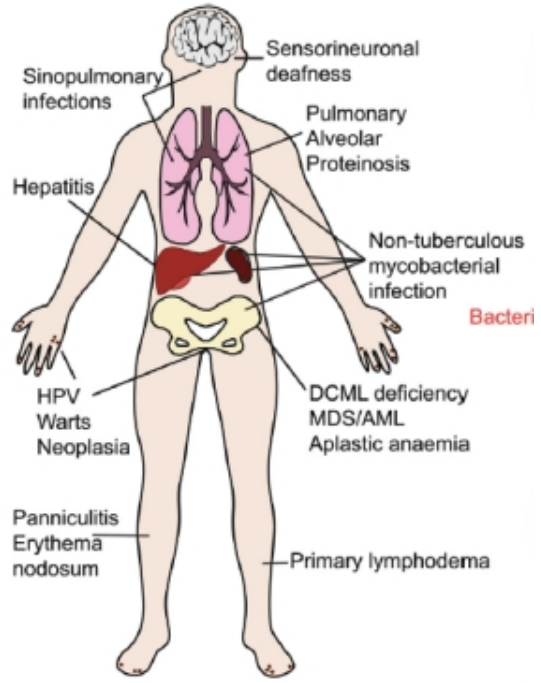
DDX41-associated susceptibility to myeloid neoplasms

- Involved in pre-mRNA splicing, RNA processing, ribosome biogenesis, and small nucleolar RNA processing
- Most common germline predisposition in adult MDS/AML (underlies ~5%)
- MDS/AML typically diagnosed at age of 65-70 yrs with male predominance
- ~ 60-80% of germline *DDX41*-mutated MDS/AML have a second somatic DDX41 mutation (R525H or G530D/C/S)
  - Somatic mutations otherwise rare in MDS/AML
- Rarely associated with other hematologic malignancies (CLL, CML, lymphoma, multiple myeloma)
- Minimal risk of MDS/AML before age 40

Polprasert C. et al. 2015 Cancer Cell: 27.
Lewinsohn M. et al. Blood 2016:127.
Makishima H. et al Blood 2023:142.

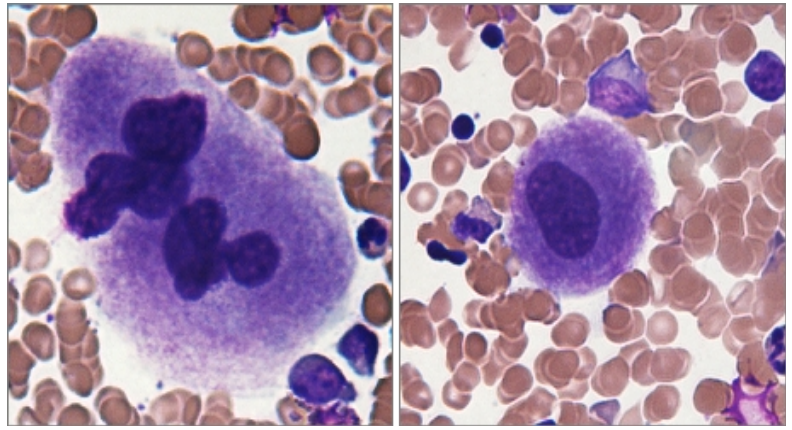
GATA2 deficiency syndrome

- Autosomal dominant ; ~50% de novo mutations
- Multiple presentations: MonoMAC, DCML deficiency, familial MDS/AML, chronic neutropenia, Emberger syndrome (lymphedema, MDS/AML ± congenital sensorineural hearing loss)
- Lifetime MDS/AML risk ~75-90%
- Marrow clue – megs with separated nuclear lobes and mononuclear forms
- Accounts for ~7% of pediatric MDS and 72% of adolescent MDS with monosomy 7
- Immune phenotypes include antibody-negative pulmonary alveolar proteinosis (PAP)

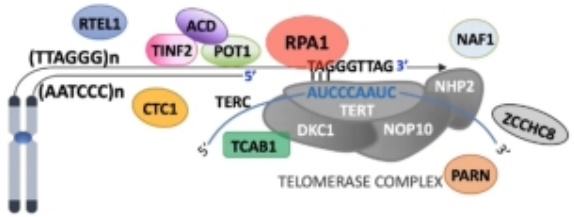


From Bigley V et al. Sem Cell Dev Bio 2019.

Megakaryocytes with widely separated nuclear lobes and mononuclear forms

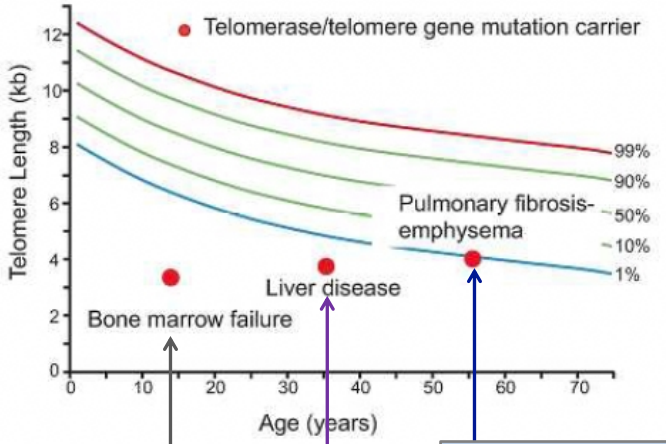


Spinner MA. Et al. Blood 2014:123.
Wlodarski MW et al. Blood 2016:127(11).



Short telomere syndrome syndromes

Age- and telomere length-dependent presentations



-Severe bone marrow failure
-B and T cell immunodeficiency
-Enteropathy
-Esophageal stricture
-Immunodeficiency
Dyskeratosis congenita

-Liver fibrosis
-Hepatopulmonary syndrome

-Pulmonary fibrosis (3-5% of sporadic & ~ 20% of familial)
-Emphysema
-Macrocytosis
-MDS/AML (~ 15% lifetime risk)

- Most common IBMFS
- "Accelerated aging" syndrome caused by germline mutations that lead to short telomeres
- Multisystem involvement: skin, bone marrow, GI tract, lungs
- Phenotype reflects the severity of telomere shortening relative to age
- Demonstrates genetic anticipation
- Classical DC: childhood onset with skin pigmentation changes, nail dystrophy, oral leukoplakia, ± aplastic anemia
- Pulmonary fibrosis is the most common adult presentation
- ~ 15% lifetime risk of AML/MDS
- Sensitive to chemo and radiation therapies

From Mangaonkar A. et al. Mayo Proceedings 2018:93 and Gorgy AI et al. Chest 2015:148.

Schratz K et al. Cancer Cell 2023:41.

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 AL. et al. Blood Adv 2020:4.
Brown AL et al. Blood 2020:136.

Question

22 yo male was referred for HSCT for MDS characterized by monosomy 7 (IPSS-R high risk). The patient's 24 yo 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.

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D. Bone marrow aspirate and biopsy
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The End