Penn Medicine
Abramson Cancer Center

Hereditary Marrow Failure Syndromes

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January 22, 2026

Disclosures

- Retro: consulting
- Novartis: participation in PNH Delphi panel

Learning Objectives

- To develop a practical approach to the recognition and diagnosis of bone marrow failure syndromes
- To review the presenting features, prognosis, and treatment of selected hereditary marrow failure and predisposition syndromes:
  - GATA2 deficiency
  - Fanconi Anemia
  - Telomere Biology Disorders
  - Diamond Blackfan Anemia
  - Shwachman Diamond Syndrome
- Distinguishing acquired aplastic anemia from inherited bone marrow failure (PASS Score)

Clinical case #1: 45 yo F referred for MDS

- **Hematologic history:**
  - No prior documented normal CBC
  - Late teens: cytopenias and infections, BM biopsy hypocellular w/mild mega dysplasia and normal karyotype
  - 20s: recurrent bacterial infections; another BM biopsy; moderate neutropenia, diagnosed with T-LGL
  - 30s: worsening pancytopenia, 1.4>9<72. Diagnosed with acquired AA, treated with horse ATG+CSA. Persistent cytopenias.
  - Age 45: progressive cytopenias and transfusion dependence.

    0.6>6.5<25, ANC 0.48, AMC 0.02, ALC 0.04.

Clinical case #1: 45 yo F referred for MDS

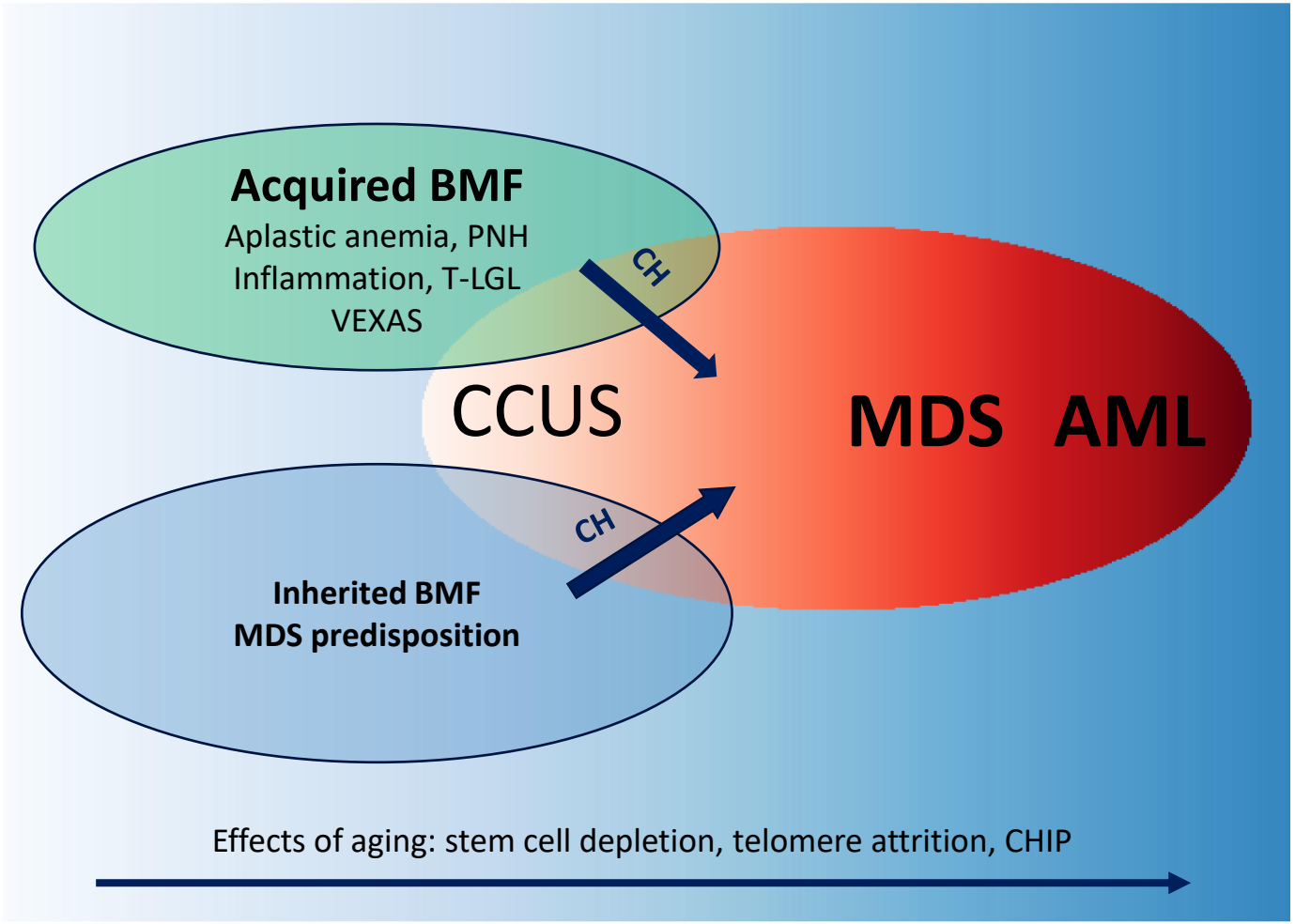
- **Past medical history**
  - Recurrent genital warts, with vaginal, cervical, anal dysplasia, and vulvar cancer.
  - Multiple miscarriages
  - Chronic non-pitting bilateral leg swelling=lymphedema (runs in maternal side of the family).

- **Bone marrow biopsy:** Normocellular (50%). Mega atypia (focally clustered, hypo- and abnormally lobated) (20% of lineage). No increased blasts.
- **Cytogenetics:** monosomy 7
- **Somatic molecular NGS panel:** disease-associated variants in RUNX1 (VAF 7%), GATA2 (VAF 51%). VUS in ETV6 (VAF 8%).

The universe of bone marrow failure and clonal disorders

Diagnosis requires exclusion of secondary causes of cytopenias:

- Nutritional
- Infectious
- Rheumatologic
- Medications/toxins
- Endocrine
- Organ dysfunction (cirrhosis, CKD)
- Peripheral destruction
- Sequestration



Estimated prevalence of predisposition syndromes in MDS patients

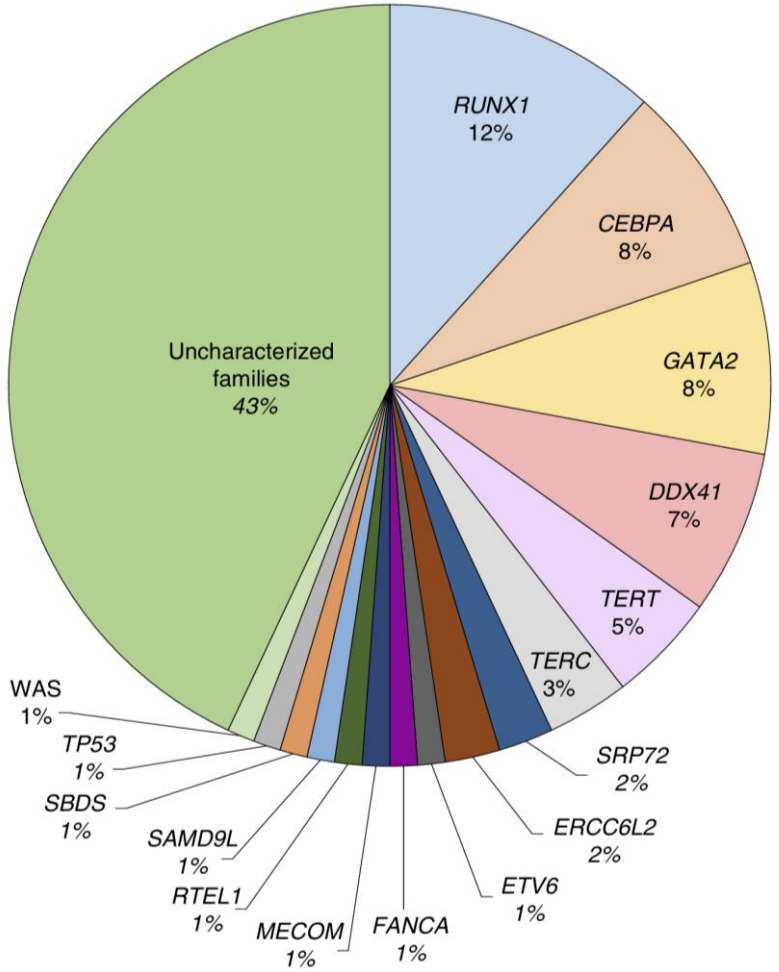
All-comer MDS patients:

- Estimated ~15% with hereditary syndromes

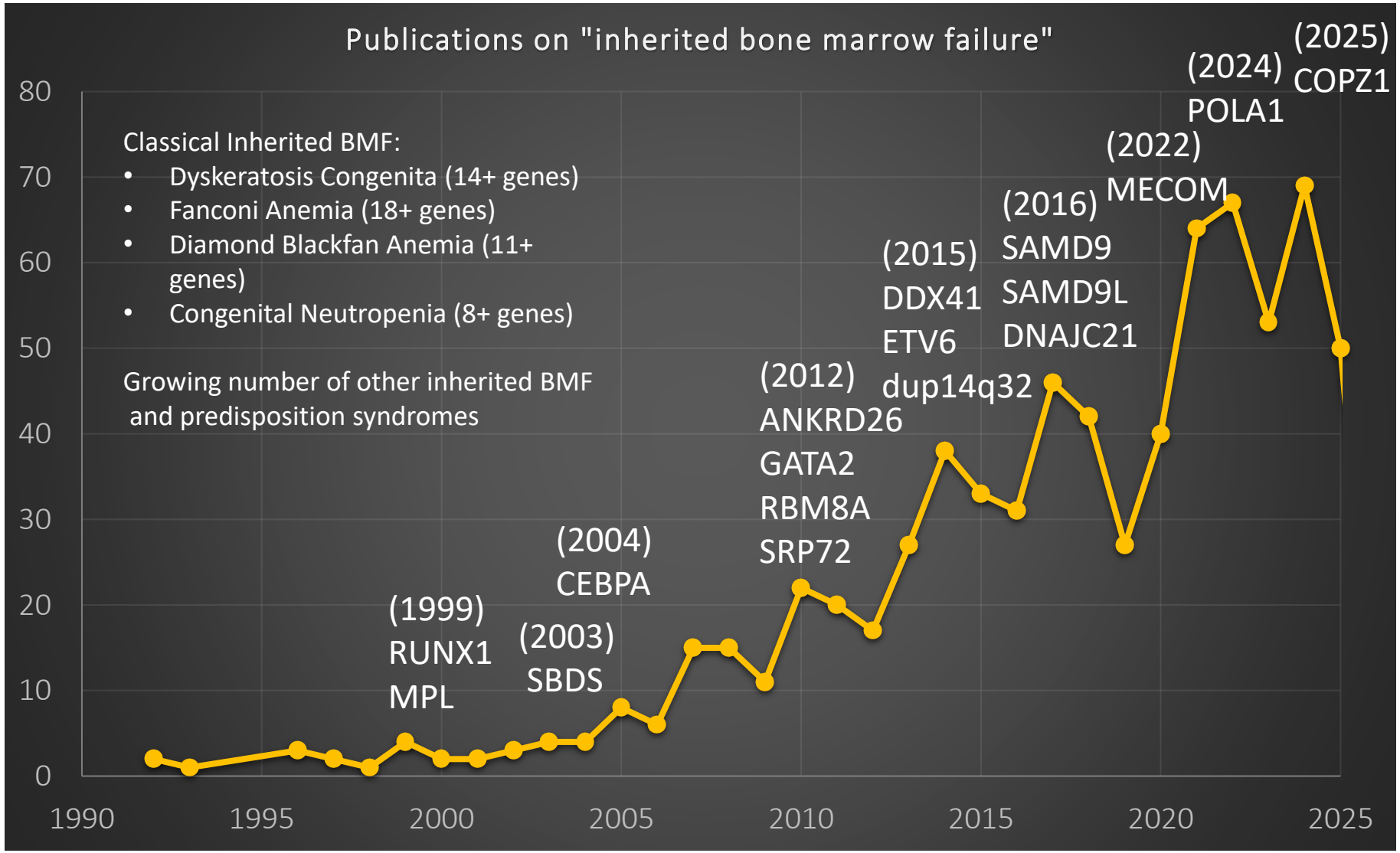
Patients with known familial MDS:

~60% with defined diagnosis

40% without defined diagnosis



NATURECOMMUNICATIONS | (2020) 11:1044


Publications on "inherited bone marrow failure"
Classical Inherited BMF:
• Dyskeratosis Congenita (14+ genes)
• Fanconi Anemia (18+ genes)
• Diamond Blackfan Anemia (11+ genes)
• Congenital Neutropenia (8+ genes)
Growing number of other inherited BMF and predisposition syndromes
(1999) RUNX1 MPL
(2003) SBDS
(2004) CEBPA
(2012) ANKRD26 GATA2 RBM8A SRP72
(2015) DDX41 ETV6 dup14q32
(2016) SAMD9 SAMD9L DNAJC21
(2022) MECOM
(2024) POLA1
(2025) COPZ1
0
10
20
30
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50
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70
80
1990
1995
2000
2005
2010
2015
2020
2025

Whom to evaluate for inherited BMF diseases

- No documented normal blood counts, lifelong cytopenias, aplastic anemia
- MDS in the young(er) age [*e.g., <50 years*]
- Family history of MDS/AML, cytopenias, and associated conditions (*see below*)
- "Red flag" conditions associated with BMF syndomes:
  - monosomy 7 or chromosome 1q gain in young patient w/ MDS
  - congenital malformations and dysmorphology incl. abnormal thumbs
  - solid tumors at a young age
  - failure to recover counts after chemotherapy/radiation
  - immune deficiency, lymphedema
  - cirrhosis, pulmonary fibrosis, early graying, mucocutaneous findings

Key elements of history and physical exam

- Documentation of baseline normal blood counts
- Age of cytopenia onset, type and severity of cytopenias
- Dysmorphology, abnormally short stature, premature graying, skin, nail, thumb findings or lymphedema on physical exam
- Red flags on past medical history
- Red flags on family history
- Awareness of potential germline mutations identified by “somatic” molecular testing

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Cytogenetics: monosomy 7
Somatic molecular NGS panel: disease-associated variants in RUNX1 (VAF 7%), GATA2 (VAF 51%). VUS in ETV6 (VAF 8%).

Diagnosis → confirmed by genetic testing in skin biopsy

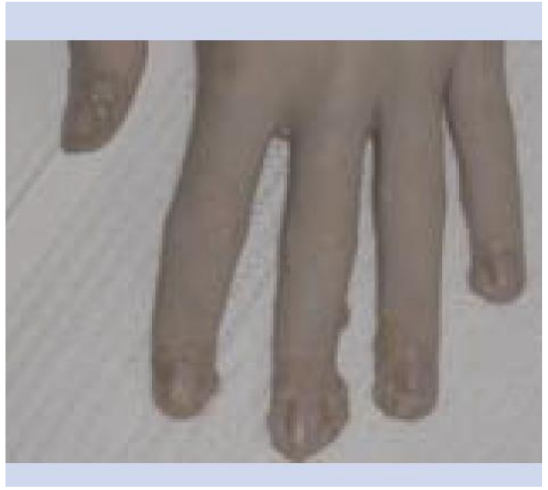
GATA2 deficiency, evolved to MDS

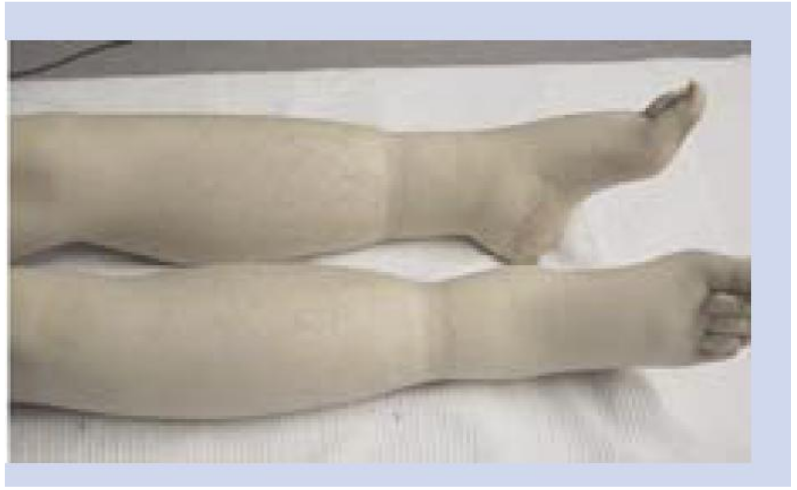
First reported clinically as Emberger Syndrome in 2010

Autosomal-dominant

- Lymphedema
- Predisposition to MDS/AML
- Warts

Emberger Syndrome—Primary Lymphedema With Myelodysplasia: Report of Seven New Cases





Mansour et al. Am J Med Genet A . 2010 Sep;152A(9):2287-96

Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency

Rachel Emma Dickinson,[1] Helen Griffin,[2] Venetia Bigley,[1,3] Louise N. Reynard,[1] Rafiqul Hussain,[2] Muzlifah Haniffa,[1,3] Jeremy H. Lakey,[4] Thahira Rahman,[2] Xiao-Nong Wang,[1] Naomi McGovern,[1] Sarah Pagan,[1] Sharon Cookson,[1] David McDonald,[1] Ignatius Chua,[5] Jonathan Wallis,[3] Andrew Cant,[1,3] Michael Wright,[2,3] Bernard Keavney,[2] Patrick F. Chinnery,[2] John Loughlin,[1] Sophie Hambleton,[1,3] Mauro Santibanez-Koref,[2] and Matthew Collin[1,3]

Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome

Amy P. Hsu,[1] Elizabeth P. Sampaio,[1] Javed Khan,[2] Katherine R. Calvo,[3] Jacob E. Lemieux,[4] Smita Y. Patel,[5] David M. Frucht,[6] Donald C. Vinh,[1] Roger D. Auth,[6] Alexandra F. Freeman,[1] Kenneth N. Olivier,[1] Gulbu Uzel,[1] Christa S. Zerbe,[1] Christine Spalding,[1] Stefania Pittaluga,[7] Mark Raffeld,[7] Douglas B. Kuhns,[8] Li Ding,[1] Michelle L. Paulson,[1,8] Beatriz E. Marciano,[1] Juan C. Gea-Banacloche,[9] Jordan S. Orange,[10] Jennifer Cuellar-Rodriguez,[1] Dennis D. Hickstein,[9] and Steven M. Holland[1]

Loss-of-function germline *GATA2* mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature

*Jan Kazenwadel,[1] *Genevieve A. Secker,[1] *Yajuan J. Liu,[2] Jill A. Rosenfeld,[3] Robert S. Wildin,[4] Jennifer Cuellar-Rodriguez,[5] Amy P. Hsu,[5] Sarah Dyack,[6] Conrad V. Fernandez,[7] Chan-Eng Chong,[8,9] Milena Babic,[8] Peter G. Bardy,[1] Akiko Shimamura,[10,11] Michael Y. Zhang,[10,12] Tom Walsh,[12] Steven M. Holland,[5] Dennis D. Hickstein,[13] Marshall S. Horwitz,[2] *Christopher N. Hahn,[8,9] Hamish S. Scott,[8,9,14] and Natasha L. Harvey[1,9]

Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia

Christopher N Hahn[1,2], Chan-Eng Chong[1,2,14], Catherine L Carmichael[3,14], Ella J Wilkins[3,13], Peter J Brautigan[1], Xiao-Chun Li[1], Milena Babic[1], Ming Lin[1], Amandine Carmagnac[3], Young K Lee[1], Chung H Kok[4,5], Lucia Gagliardi[1], Kathryn L Friend[6], Paul G Ekert[7], Carolyn M Butcher[4,5], Anna L Brown[5], Ian D Lewis[2,5], L Bik To[2,5], Andrew E Timms[8], Jan Storek[9], Sarah Moore[1], Meryl Altree[10], Robert Escher[3,13], Peter G Bardy[5], Graeme K Suthers[10,11], Richard J D'Andrea[2,4,5,15], Marshall S Horwitz[8] & Hamish S Scott[1–3,12,15]

Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56^{bright} subset

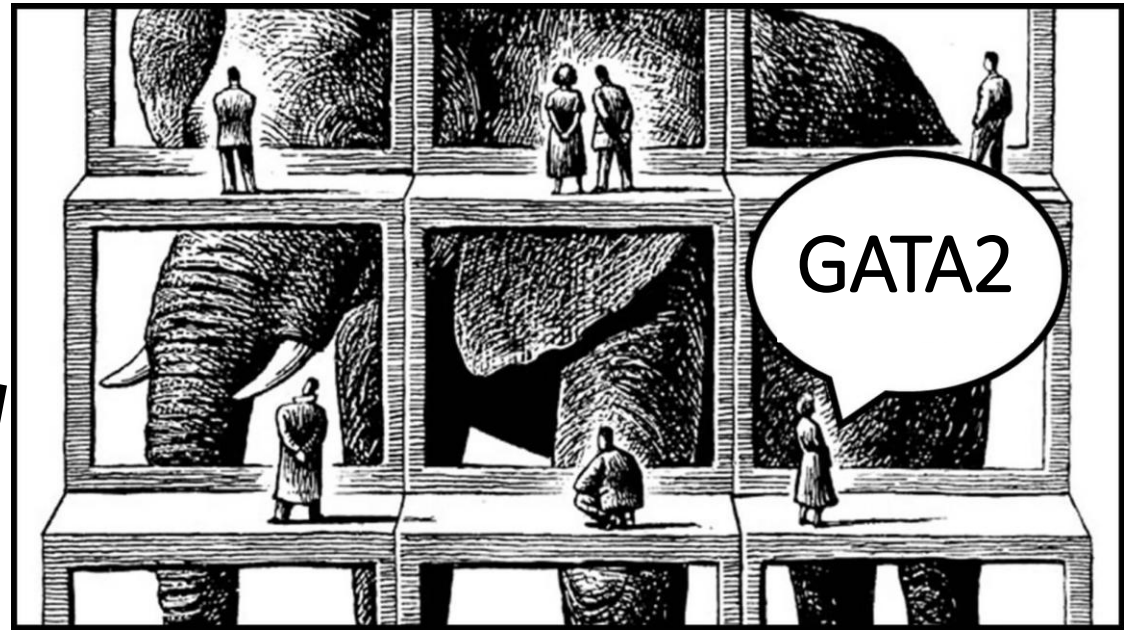
Emily M. Mace,[1,2] Amy P. Hsu,[3] Linda Monaco-Shawver,[4] George Makedonas,[1,2] Joshua B. Rosen,[4] Lesia Dropulic,[5] Jeffrey I. Cohen,[5] Eugene P. Frenkel,[6] John C. Bagwell,[6] John L. Sullivan,[7] Christine A. Biron,[8] Christine Spalding,[3] Christa S. Zerbe,[3] Gulbu Uzel,[3] Steven M. Holland,[3] and Jordan S. Orange[1,2]

Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)

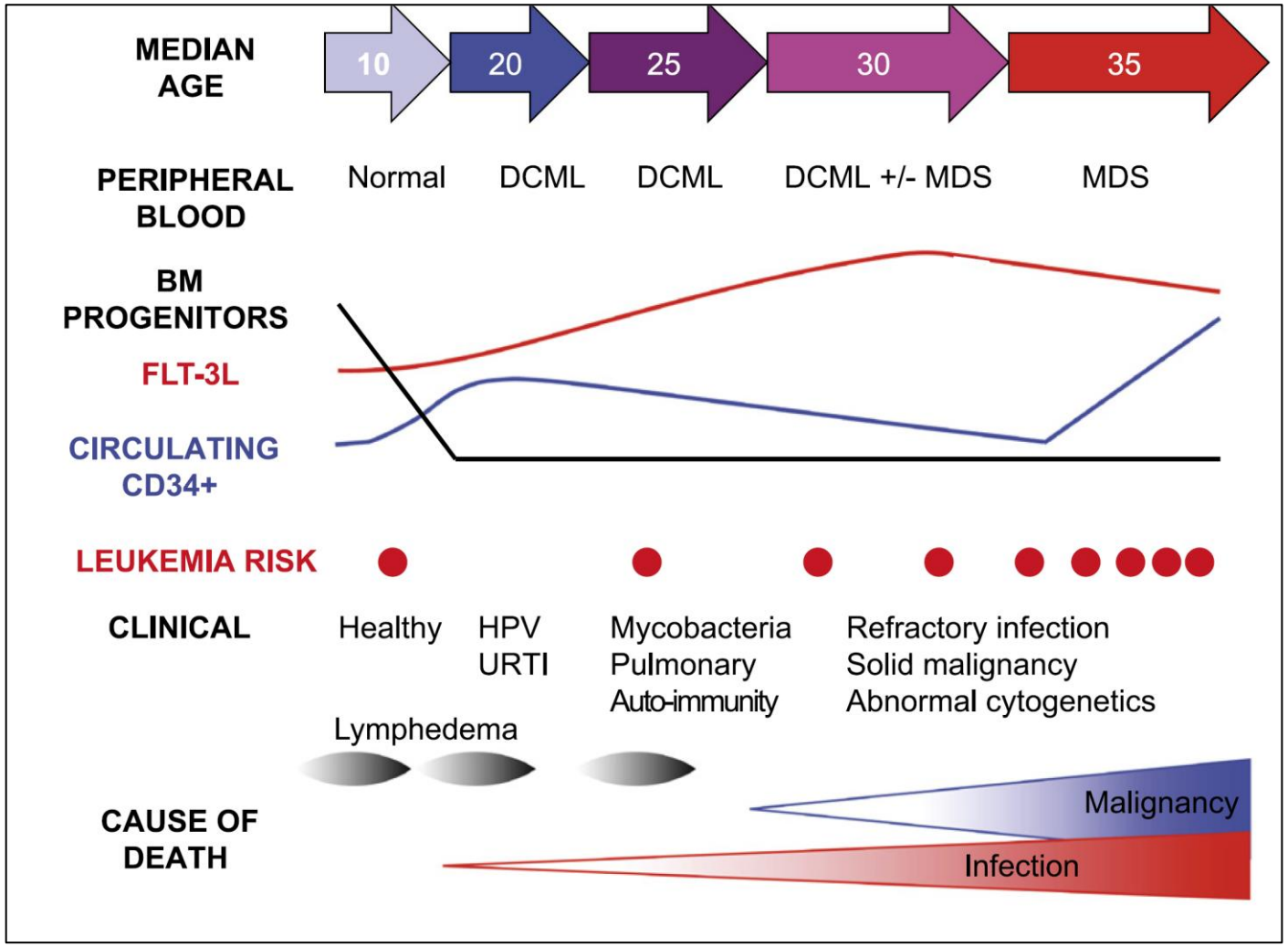
Pia Ostergaard[1,13], Michael A Simpson[2,13], Fiona C Connell[3], Colin G Steward[4], Glen Brice[5], Wesley J Woollard[2], Dimitra Dafou[2], Tatjana Kilo[6], Sarah Smithson[7], Peter Lunt[7], Victoria A Murday[8], Shirley Hodgson[5], Russell Keenan[9], Daniela T Pilz[10], Ines Martinez-Corral[11], Taija Makinen[11], Peter S Mortimer[12], Steve Jeffery[1], Richard C Trembath[2] & Sahar Mansour[5]

2010-2011
Convergence on GATA2

- MonoMAC
- Emberger



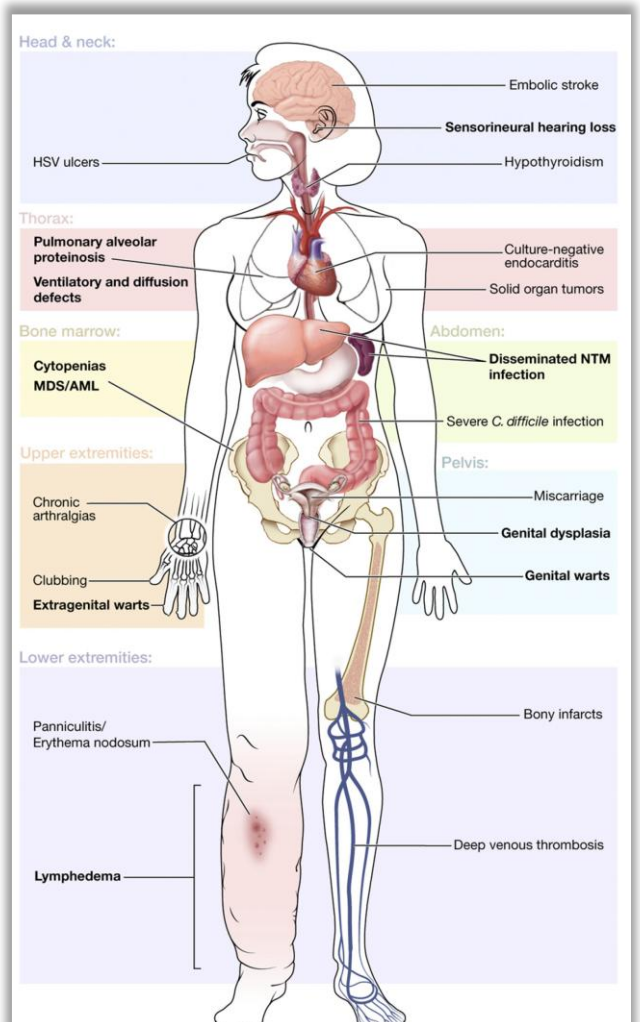
Recognizing GATA2: evolving clinical symptoms over the lifespan



BLOOD, 6 FEBRUARY 2014 • VOLUME 123, NUMBER 6

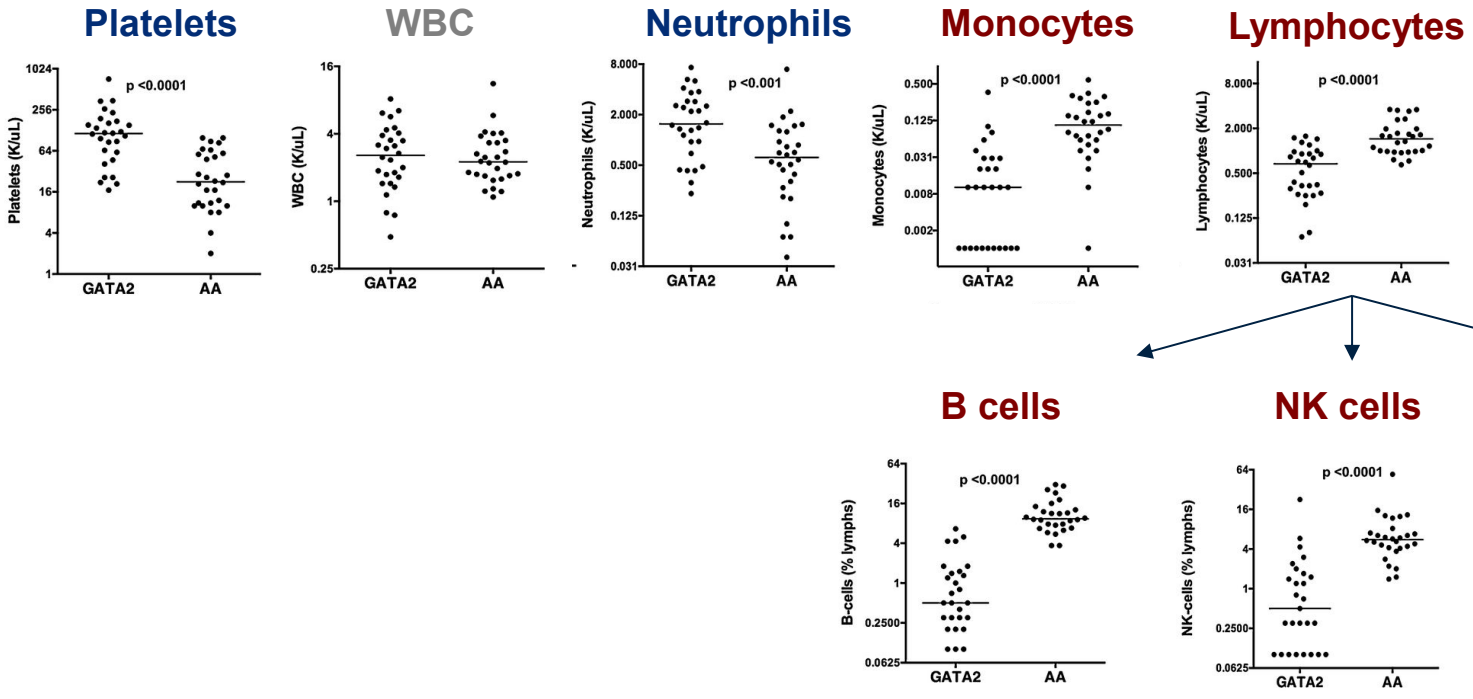
Recognizing GATA2: clinical, pathologic and lab findings

- Monocytopenia
- Deficiency of B, NK cells
- Unusual infections:
  - Non-TB mycobacteria
  - Recurrent HPV warts
- Lung disease
- Lymphedema
- MDS at early age
  - Monosomy 7, Somatic *STAG2* mutations

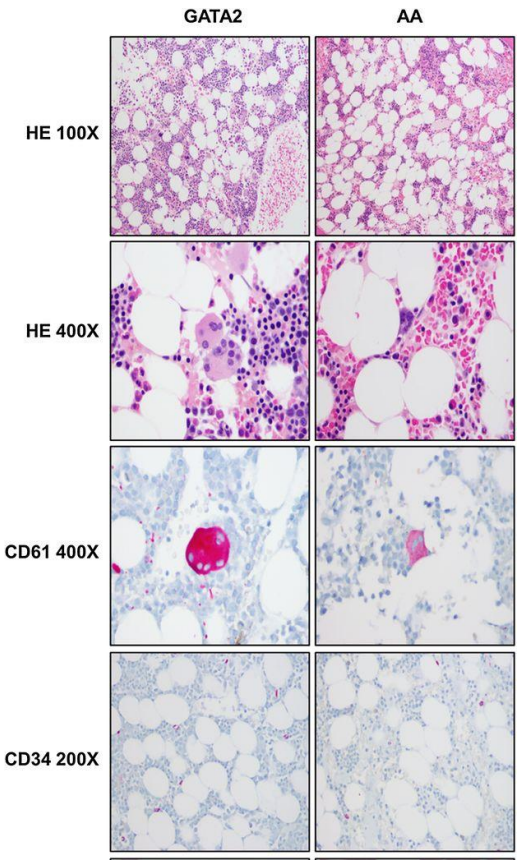


BLOOD, 6 FEBRUARY 2014 • VOLUME 123, NUMBER 6

Hematologic findings in GATA2 deficiency vs aplastic anemia



Bone marrow morphology

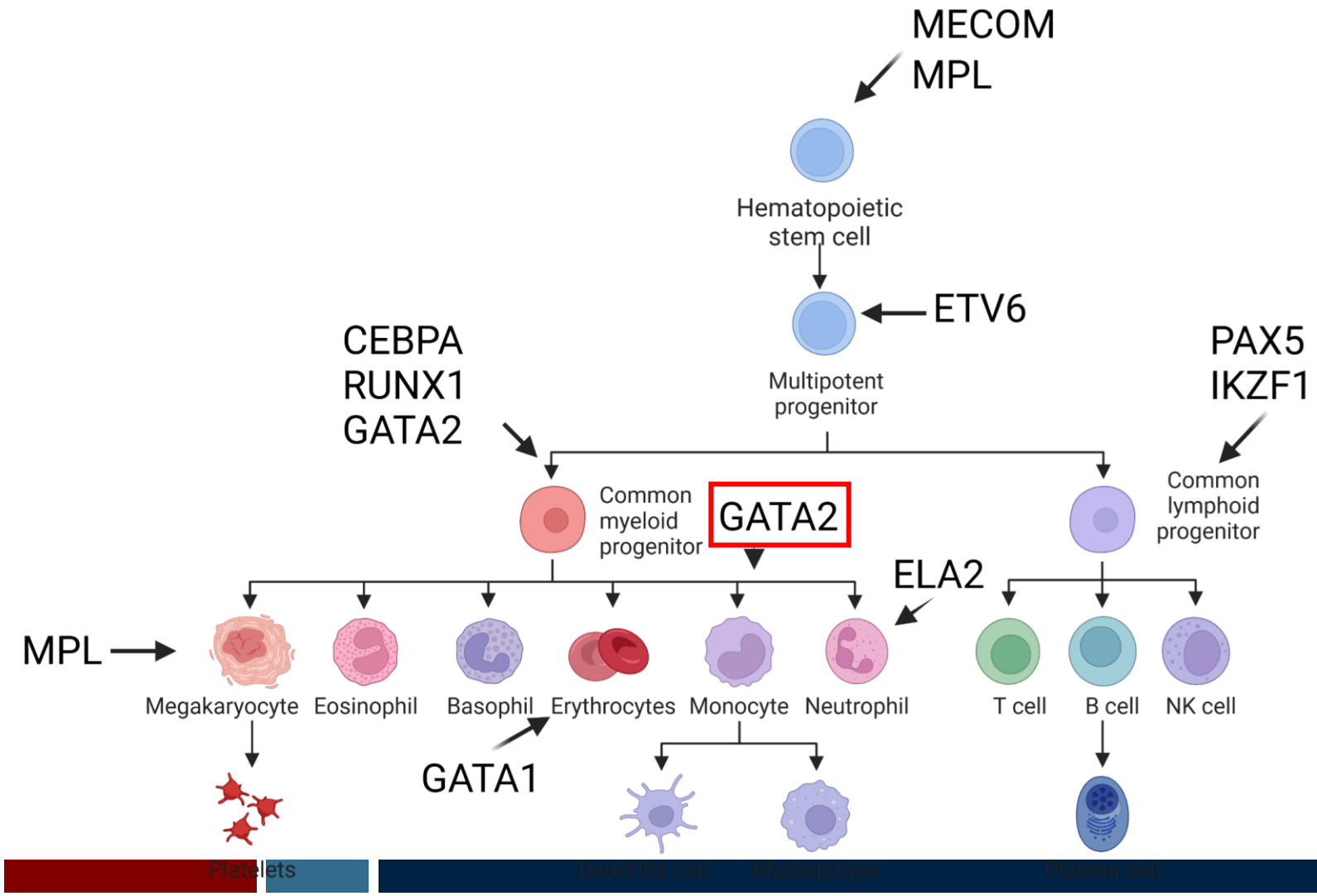


Ganapathi et al. Blood. 2014 Oct 30;125(1):56–70

Clinical management of GATA2 deficiency

- Cytopenias/BMF
  - Supportive management of cytopenias
  - Bone marrow surveillance for MDS/AML evolution
- HSCT is indicated for:
  - Transfusion-dependent BMF
  - Adverse clonal evolution and MDS/AML progression
  - Severe immune deficiency with recurrent opportunistic infections
  - Refractory HPV disease
- Immunodeficiency:
  - Vaccinations, including HPV
  - Prophylactic antimicrobials for severe immunodeficiency
- Multidisciplinary care including:
  - Infectious disease (for opportunistic infections, e.g. mycobacterial, HSV)
  - Gyn (e.g. for genital warts, malignancy screening)
  - Dermatology (e.g. for erythema nodosum)
- Genetic counseling

GATA2 is one of the inherited predisposition syndromes caused by germline defects in hematopoietic regulatory genes



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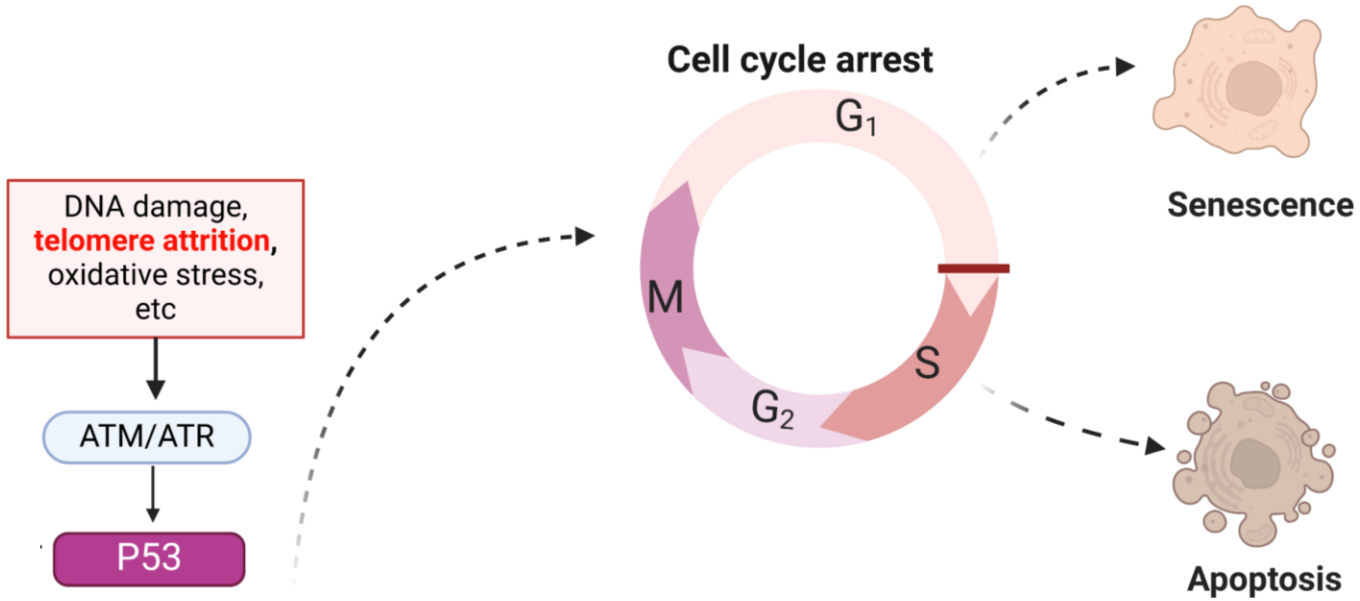
Classical BMF is caused by germline disruption of core cellular pathways



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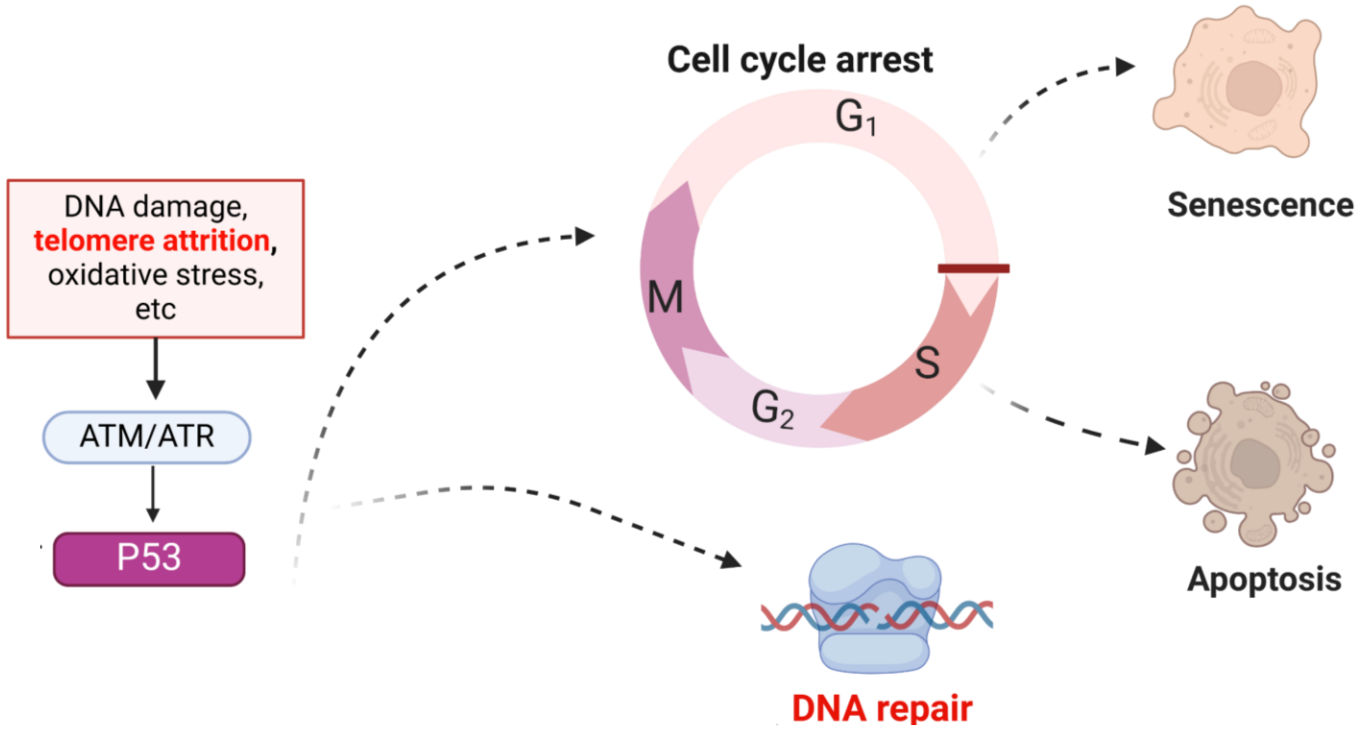

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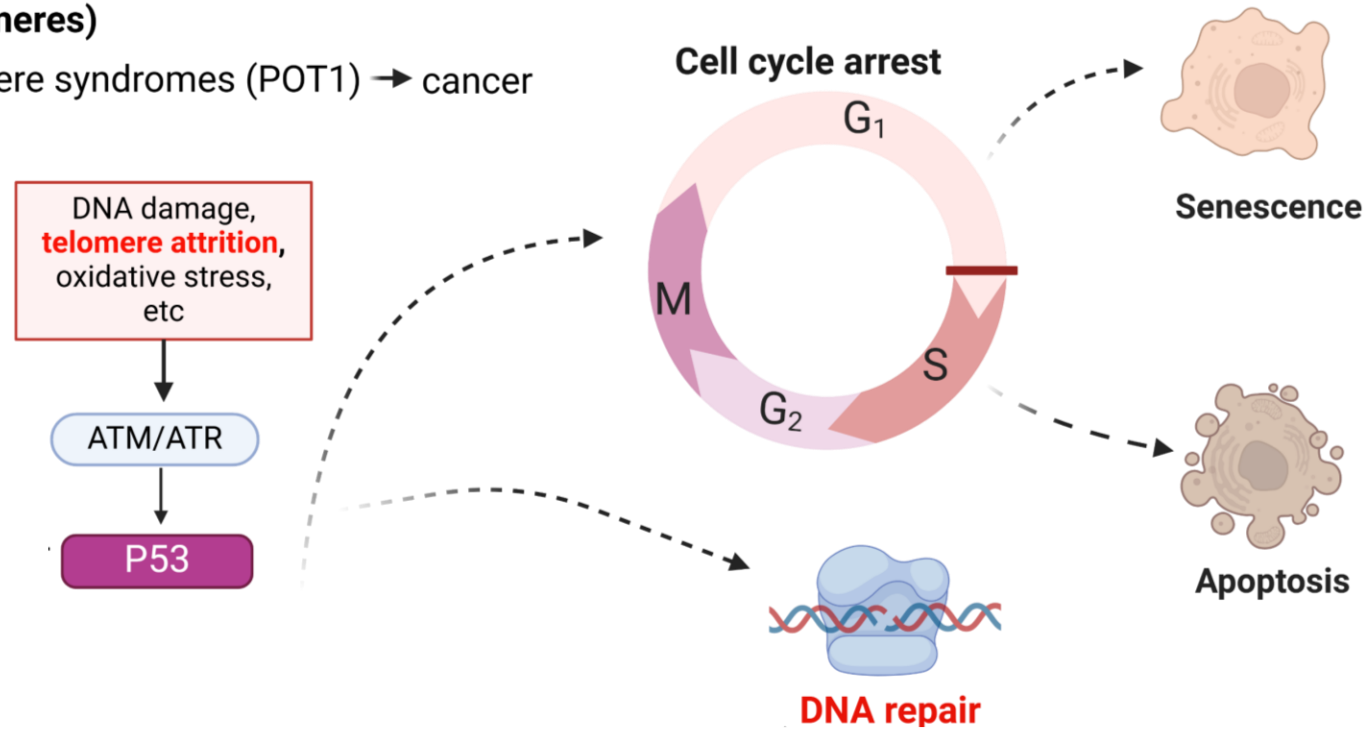
Classical BMF: defects in telomere maintenance

Telomere biology disorders → BMF (short telomeres)

Long telomere syndromes (POT1) → cancer



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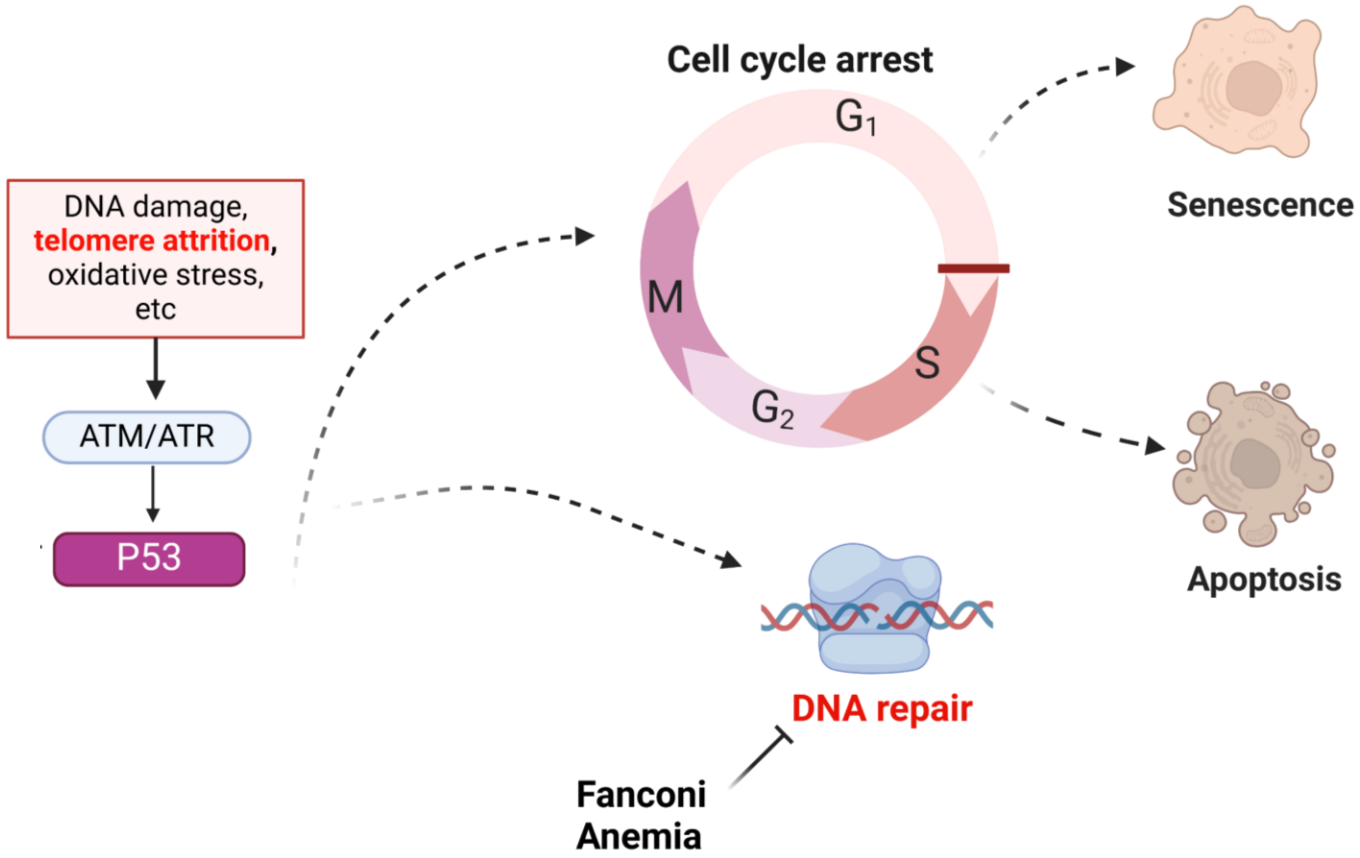
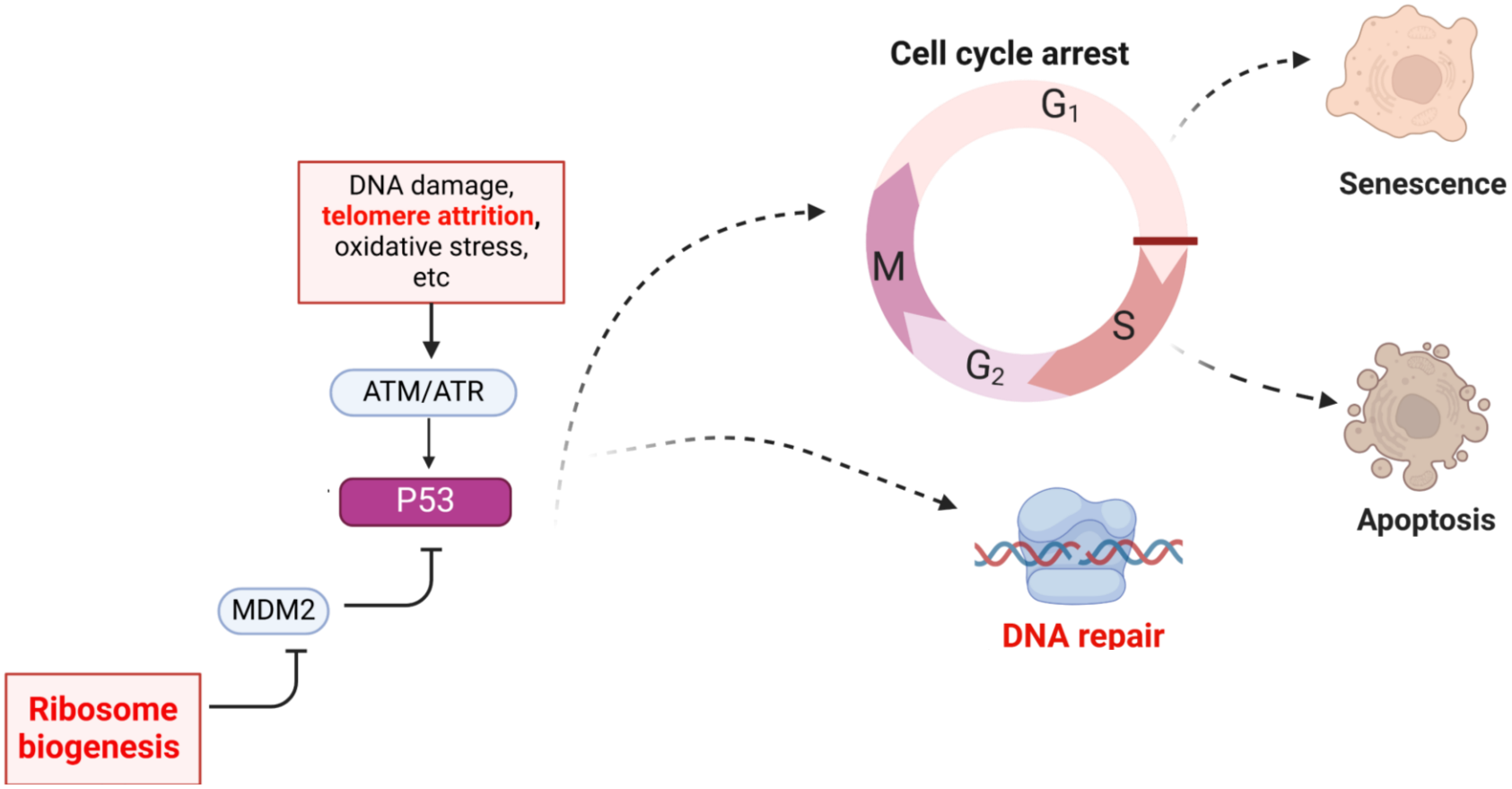
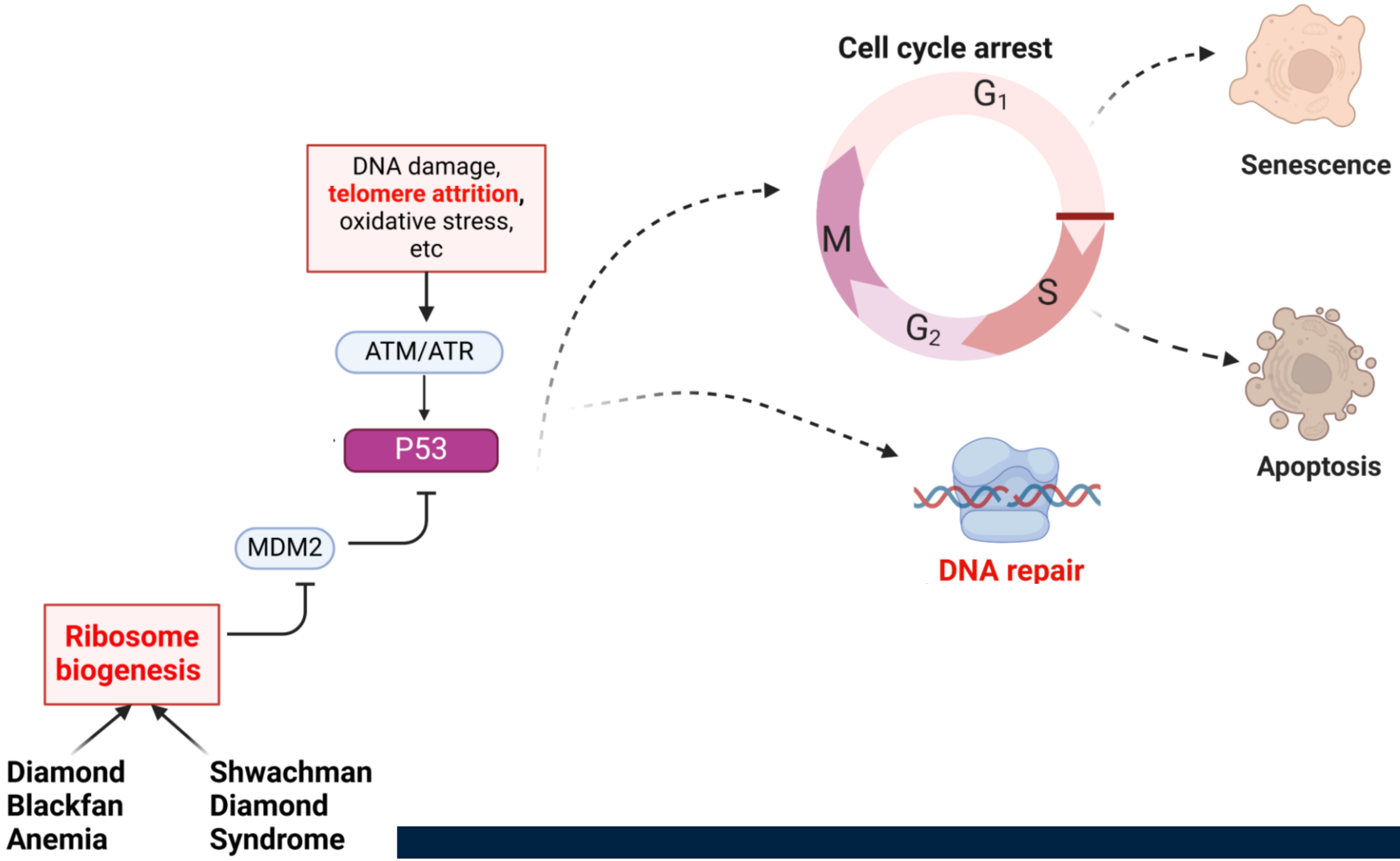
Classical BMF: defects in DNA repair



Classical BMF: defects in ribosome biogenesis



Classical BMF arises from germline mutations in core cellular pathways



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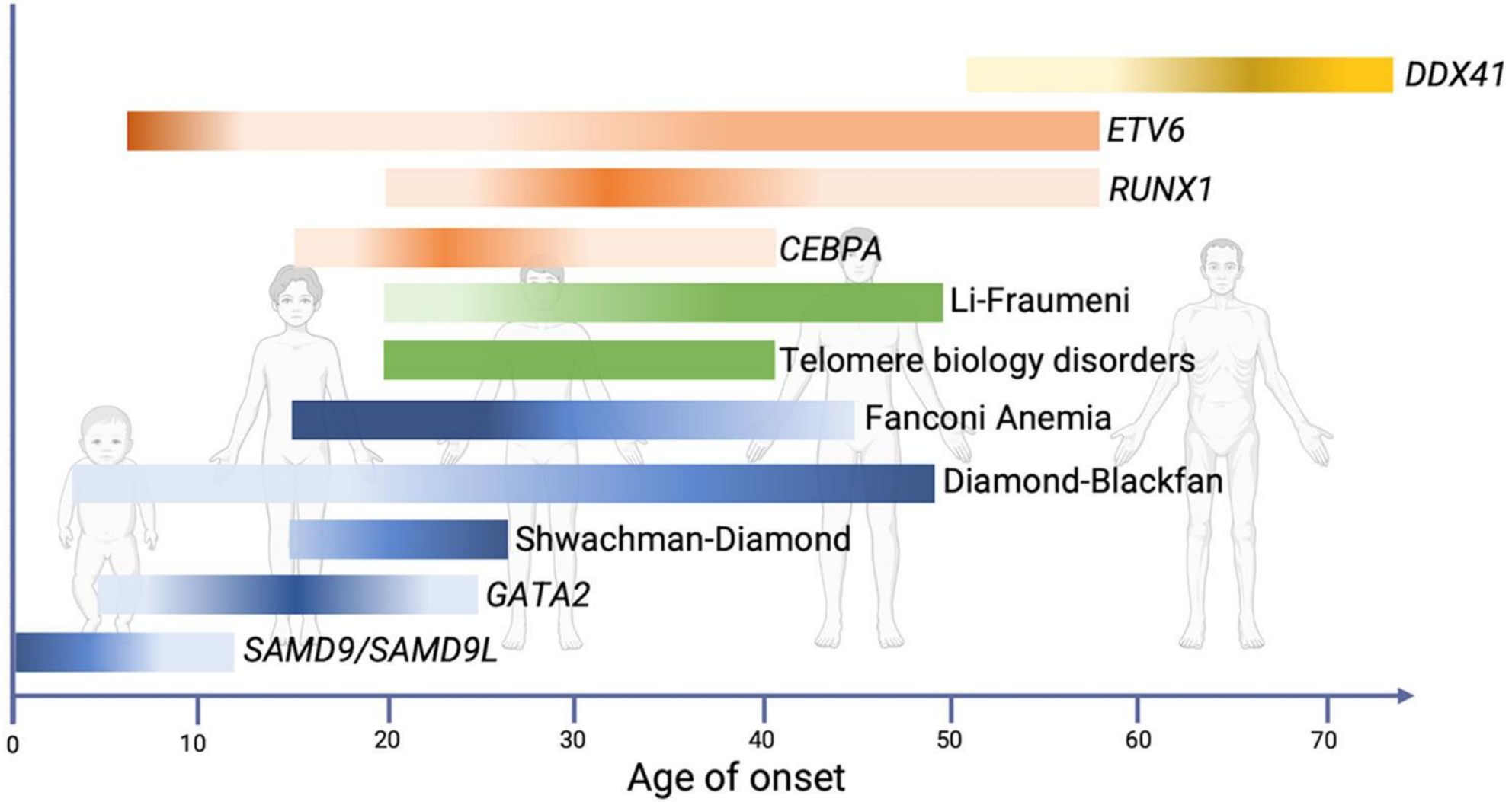
Inherited BMF can be diagnosed over the lifespan



Atluri et al. Semin Hematol. 2025 Jun;62(3):131-140

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Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	Adolescence and adulthood	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

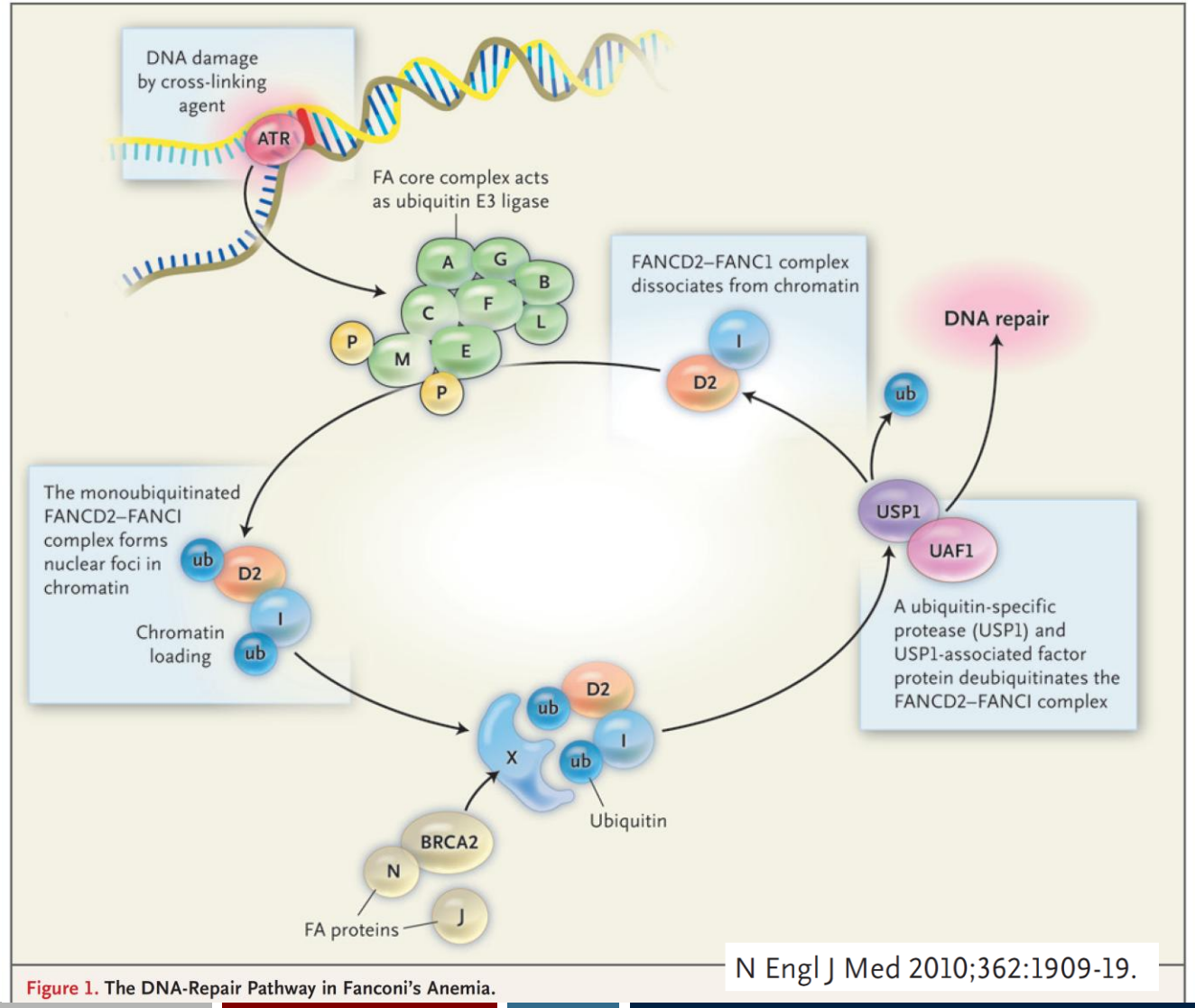
Patient Case #2: 30 yo F with pancytopenia after cisplatin/radiation

HPI: 30 yo F diagnosed with vulvar carcinoma
Physical exam: 5'1'' female, no lymphadenopathy, no organomegaly. Small thumb with a surgical scar overlying thumb.
Labs: mild pancytopenia.
Imaging: incidental finding of congenital absence of one kidney.

Clinical course:
- Following diagnosis of vulvar cancer, patient received cisplatin and radiation from her gyn oncologist.
- Following the first cycle of therapy, she developed profound pancytopenia with marrow aplasia.
- Hematology is consulted.

What is the likely diagnosis?

Fanconi Anemia (FA): Pathogenesis



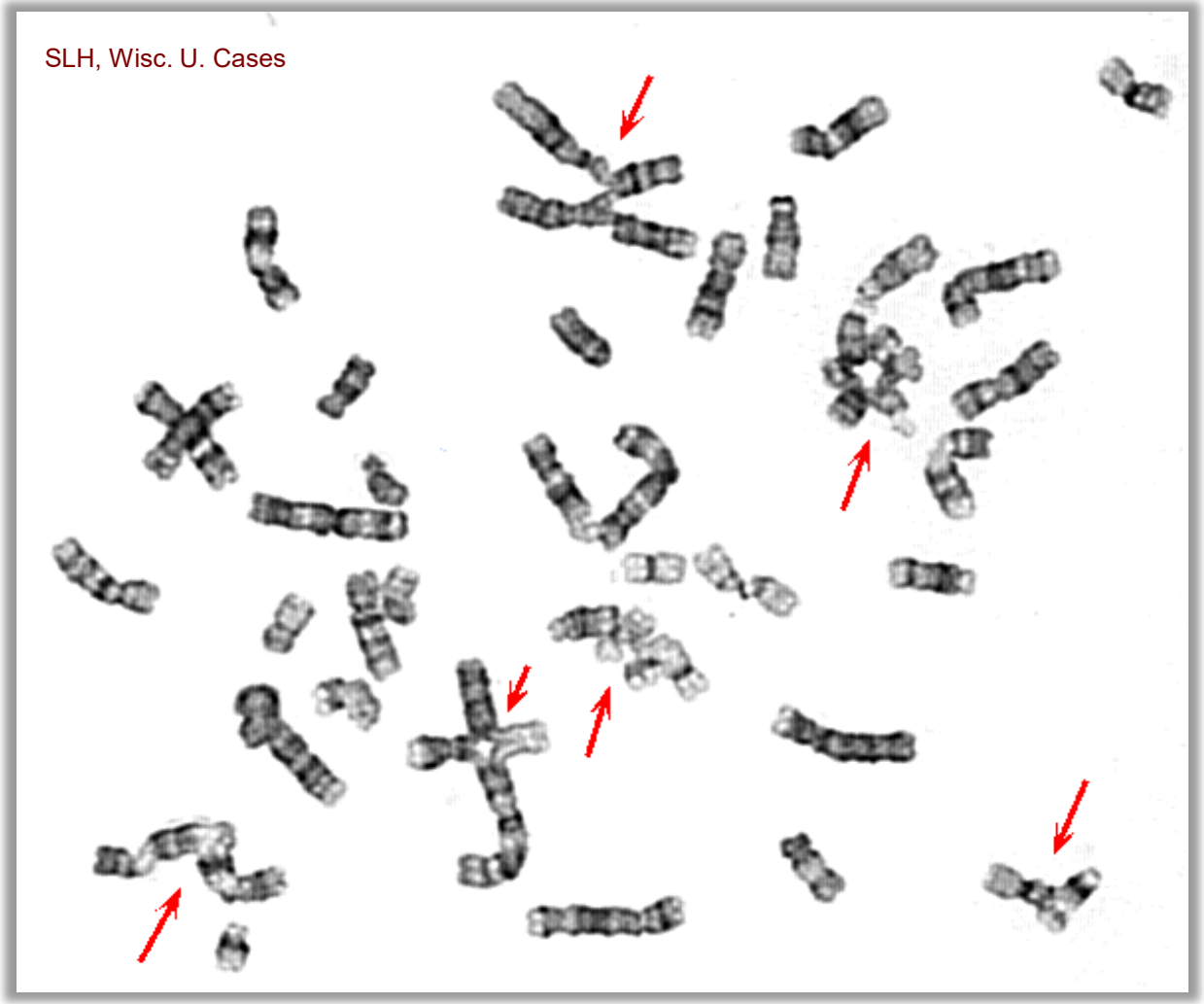
N Engl J Med 2010;362:1909-19.

Figure 1. The DNA-Repair Pathway in Fanconi's Anemia.

- One of the most common causes of inherited BMF
- FA incidence 1 in 130,000 live births in the US

- Genetic defect in one of 22 known FA complex genes
- Defect in homologous DNA repair
- Hypersensitivity to DNA crosslinking agents
  - DEB, mitomycin C
  - Others (cisplatin, radiation)

Diagnostic test: Chromosome Breakage Analysis



- PHA-stimulated peripheral blood lymphocytes cultured with crosslinking agents, mitomycin C and diepoxybutane (DEB).

- Increased chromosomal breaks and radials in FA.

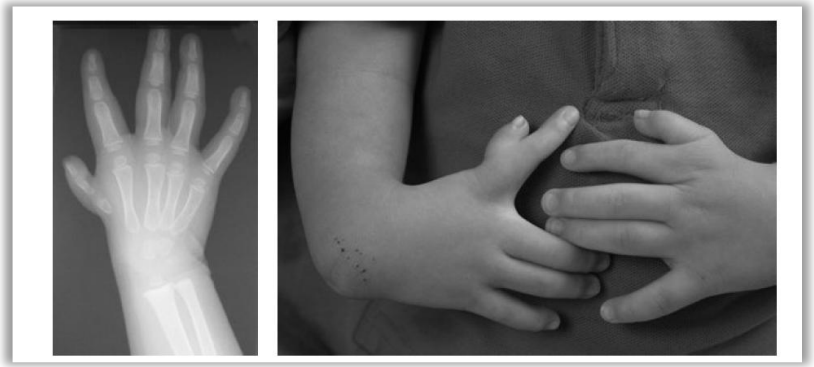
- Note: *In cases with a high suspicion of FA, but an apparent negative test in blood, testing should be repeated in skin fibroblasts, due to ~10-15% rate of reversion mosaicism and false-negative results in blood.*

Multisystem disease diagnosed in children and adults

Short stature
Café a lait spots
Thumb abnormalities
Microcephaly
Triangular face
Congenital hip dislocation
Hyper- and hypopigmentation
Imperforate anus
GU anomalies

30% have no apparent extrahematopoietic findings

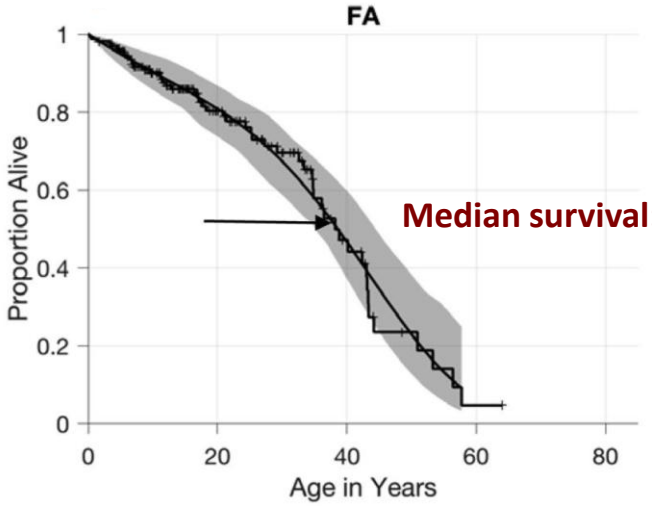
Blood Reviews 2010, 24, 101



FA Handbook, Version 4, 2014

Overall survival, BMF, MDS, AML and solid tumors

Overall Survival

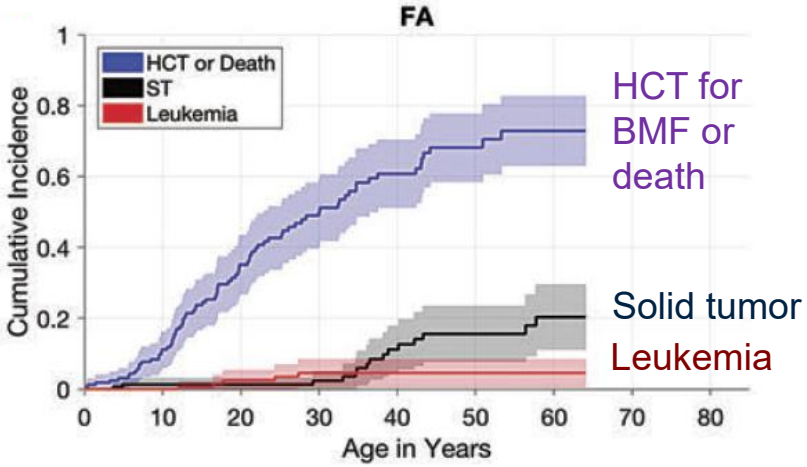


Median survival: 39 years

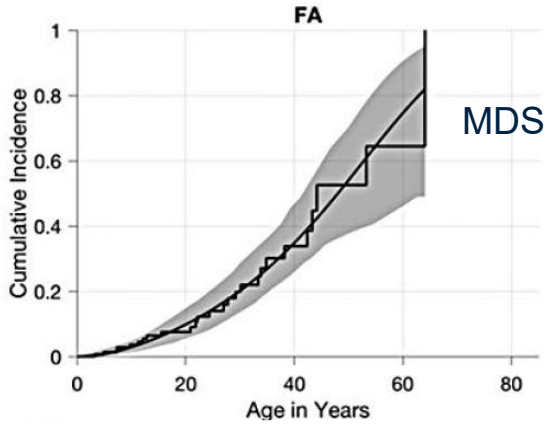
Cumulative incidence:

- severe BMF 70% by age 50
- solid tumors: ~20% by age 65 years
- MDS: 50% by age 50 years
- AML: <5% by age 30 years

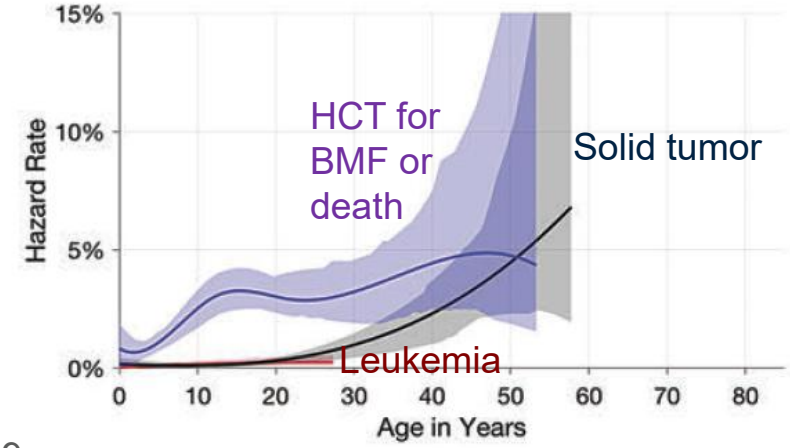
CI of death/HCT/ST/leukemia



Cumulative incidence (CI) of MDS



Annual hazard rate



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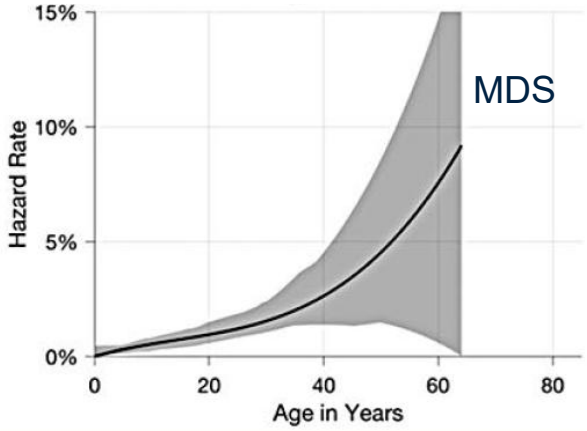
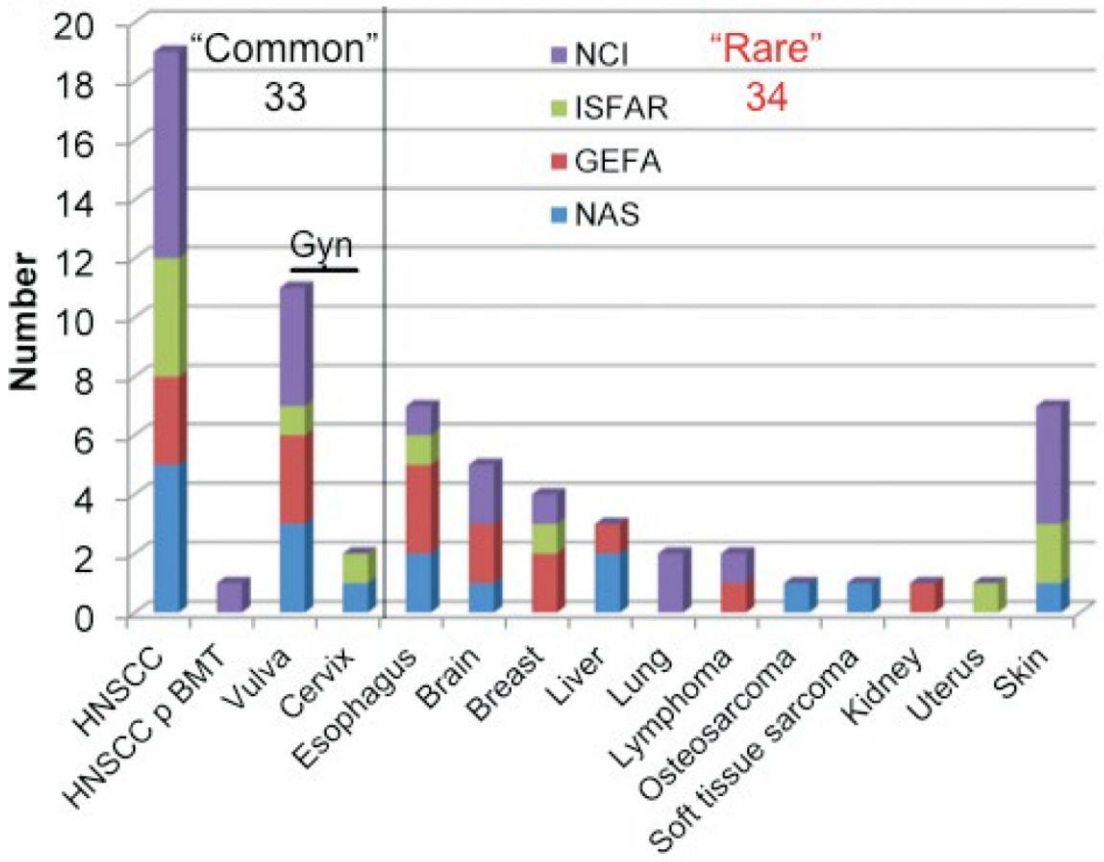
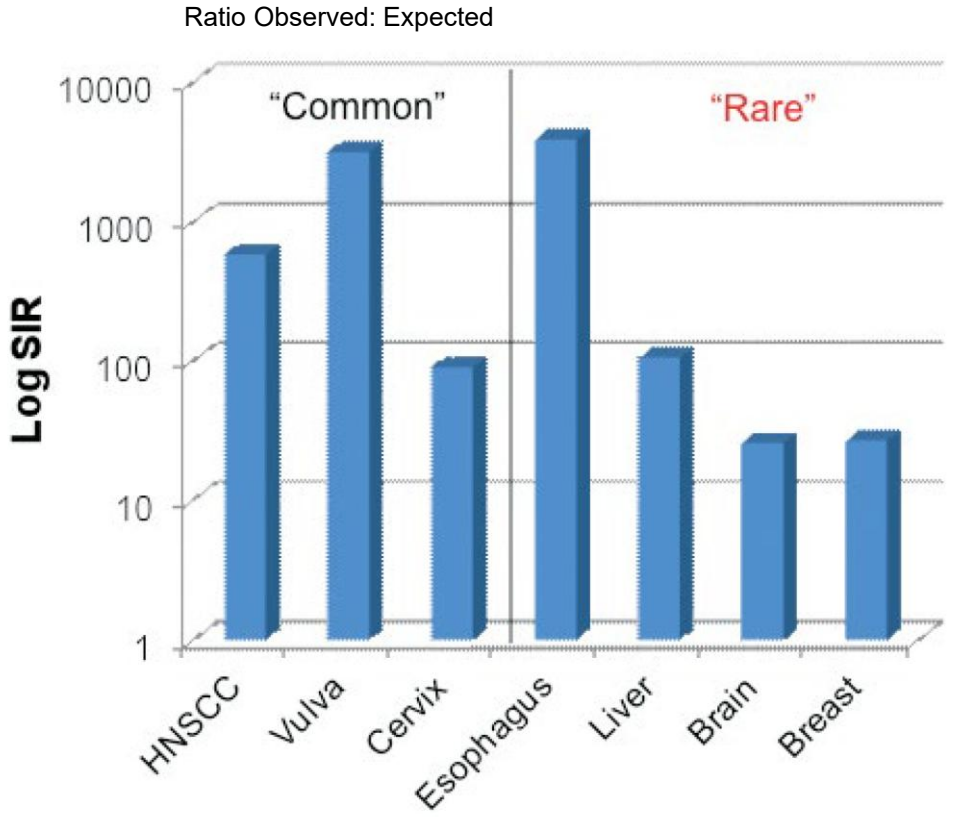


Alter et al. Haematologica 2018 Volume 103(1):30-39

HNSCC and Gyn cancers are most common





FA Handbook, Version 4, 2014

Multidisciplinary management, focused on prevention, BMF and cancer surveillance

- **Bone marrow failure (BMF):**
  - Bone marrow transplant (BMT):
    - The only curative therapy for BMF (but not for other manifestations of FA)
    - Requires lower intensity conditioning
  - Medical management:
    - Anabolic steroids (e.g., Oxymetholone or danazol)
    - Supportive care, transfusions

- **Prevention:** avoidance of radiation and DNA-damaging agents

- **Cancer surveillance:**
  - Oral cancer screening
  - Gyn, GI, and bone marrow surveillance.

- **Experimental/emerging:** gene therapy, antioxidants.

- **Multidisciplinary care:** Endocrinology, ENT, GU, orthopedics/plastics, genetics.

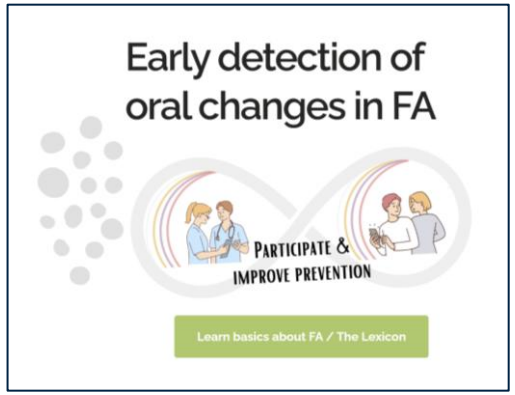
More cases for discussion:

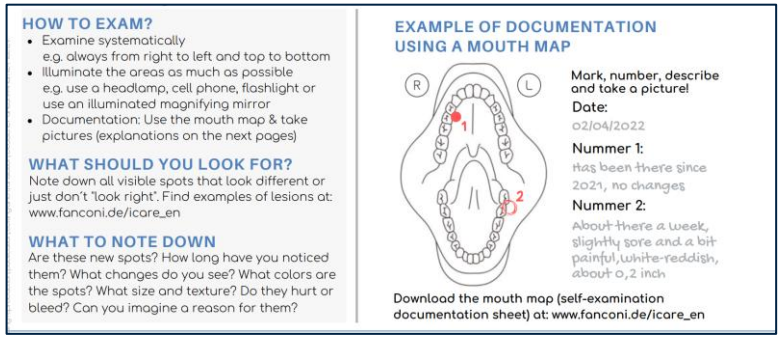
- A 67-year-old previously healthy patient with a recent diagnosis of AML was found to have **one pathogenic *FANCA* gene variant at 50% VAF** on a somatic NGS panel on a bone marrow biopsy.
  - How do you approach this case?
  - What if two FANCA VUS variants were identified?

- A 40-year-old M with chronic **thrombocytopenia, history of oropharyngeal dysplasia, and family history** of a brother who died at a young age of "FA" has a **negative chromosome breakage test**.
  - What is your next step?

Resources for Fanconi Anemia

- Fanconi Anemia Clinical Care Guidelines_5th Edition 2020_web





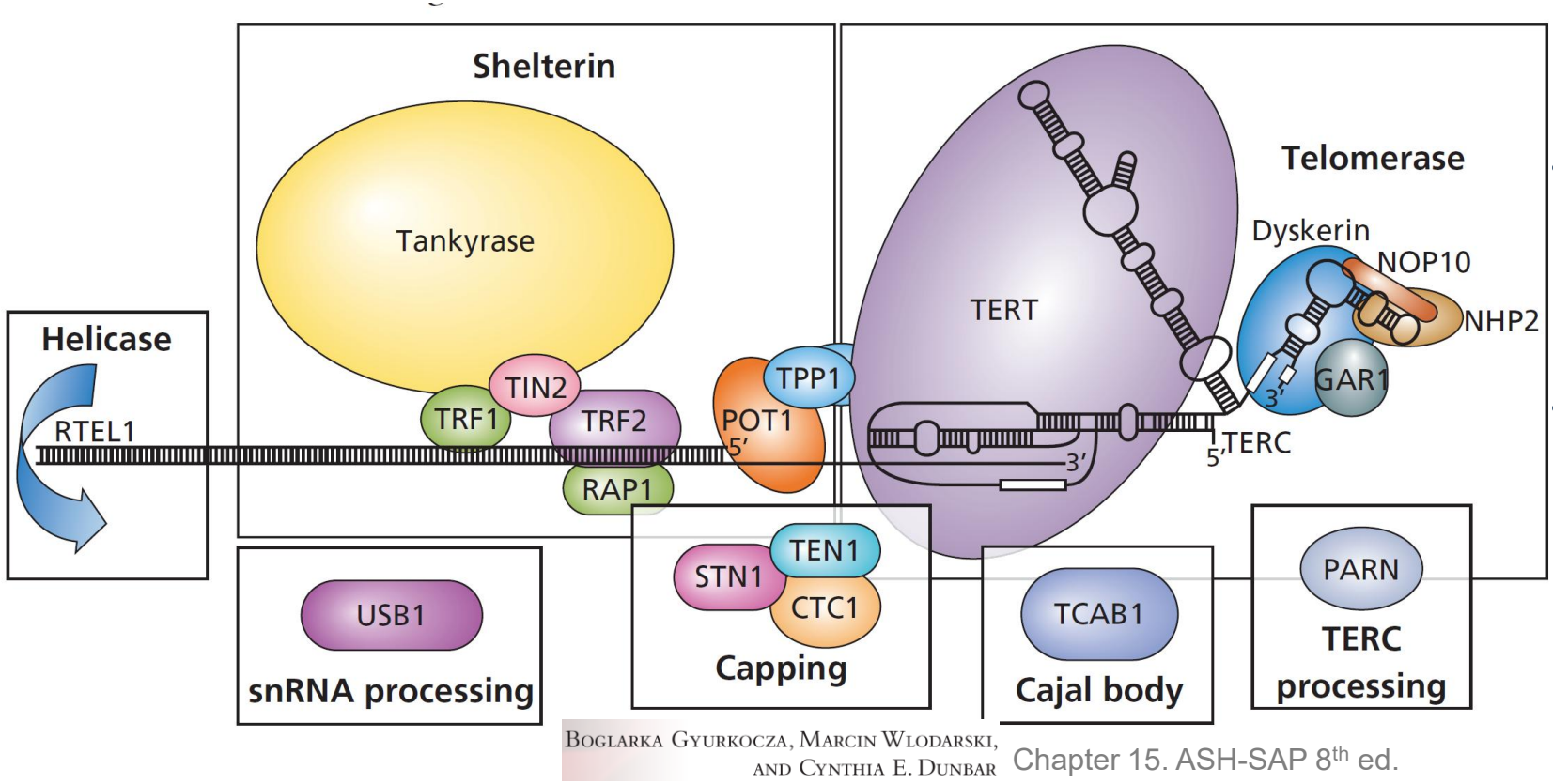
Patient Case 3

HPI: 55 yo M with decades-long thrombocytopenia, referred for evaluation of BMF.
Physical exam: Fit middle-aged male with unremarkable physical exam.
Labs: WBC 2.9, Hgb 10.6, Platelets 29; with 58.9% granulocytes, 6.2% monocytes, and 34.9% lymphocytes. MCV 121.
Family history: brother with thrombocytopenia.
Pathology: Bone marrow hypocellular without dysplastic changes, normal karyotype, and no acquired mutations.

BMF evaluation:

- Chromosome breakage studies were normal.
- Telomere length flow FISH testing showed very low lymphocyte telomere lengths for age
- Panel-based NGS genetic testing for genes mutated in BMF identified a pathogenic variant in *TERC*, confirming the diagnosis of telomere biology disorder (TBD).

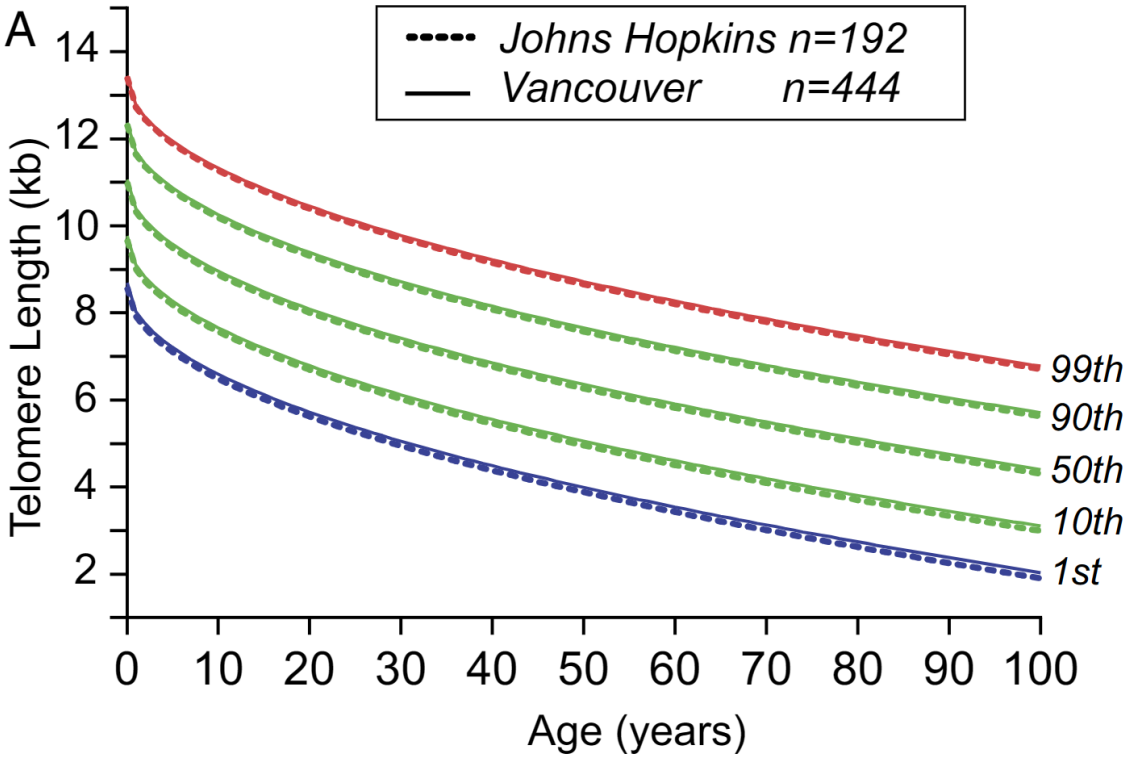
Telomere Biology Disorders



Boglarka Gyurkocza, Marcin Wlodarski, and Cynthia E. Dunbar Chapter 15. ASH-SAP 8th ed.

- Genetic defect in one of 14 genes associated with telomere maintenance
- Leads to abnormal shortening of telomeres

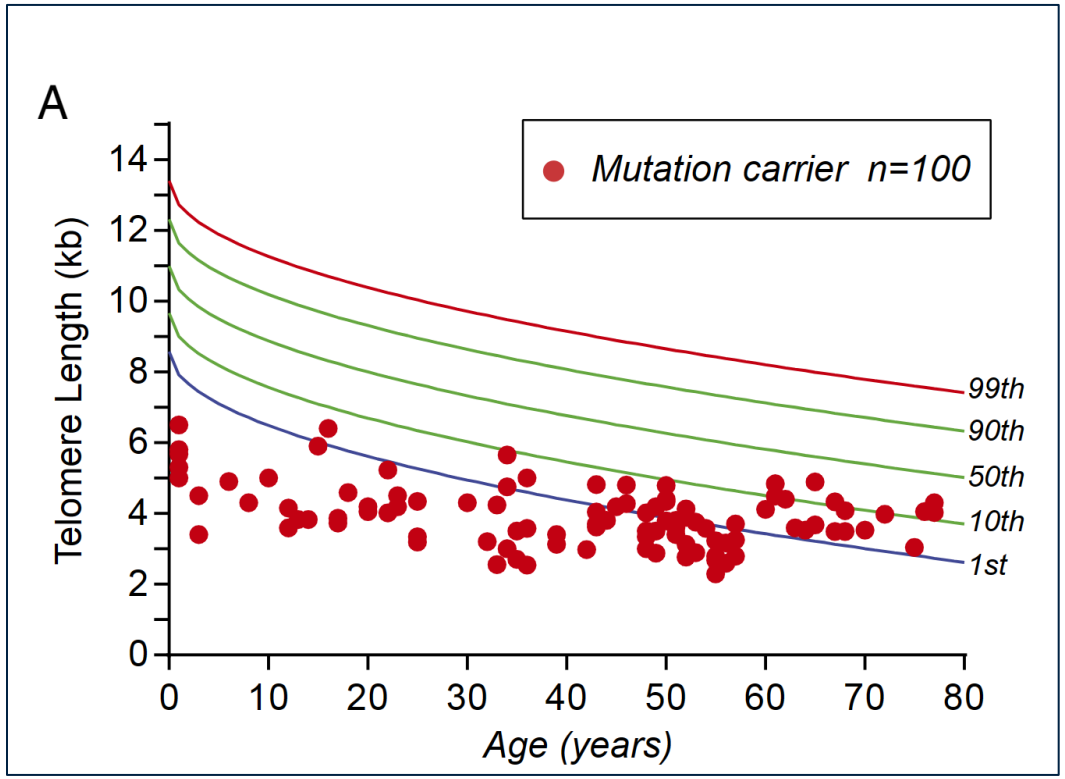
Diagnostic test: Telomere Length Measurement (flow-FISH)

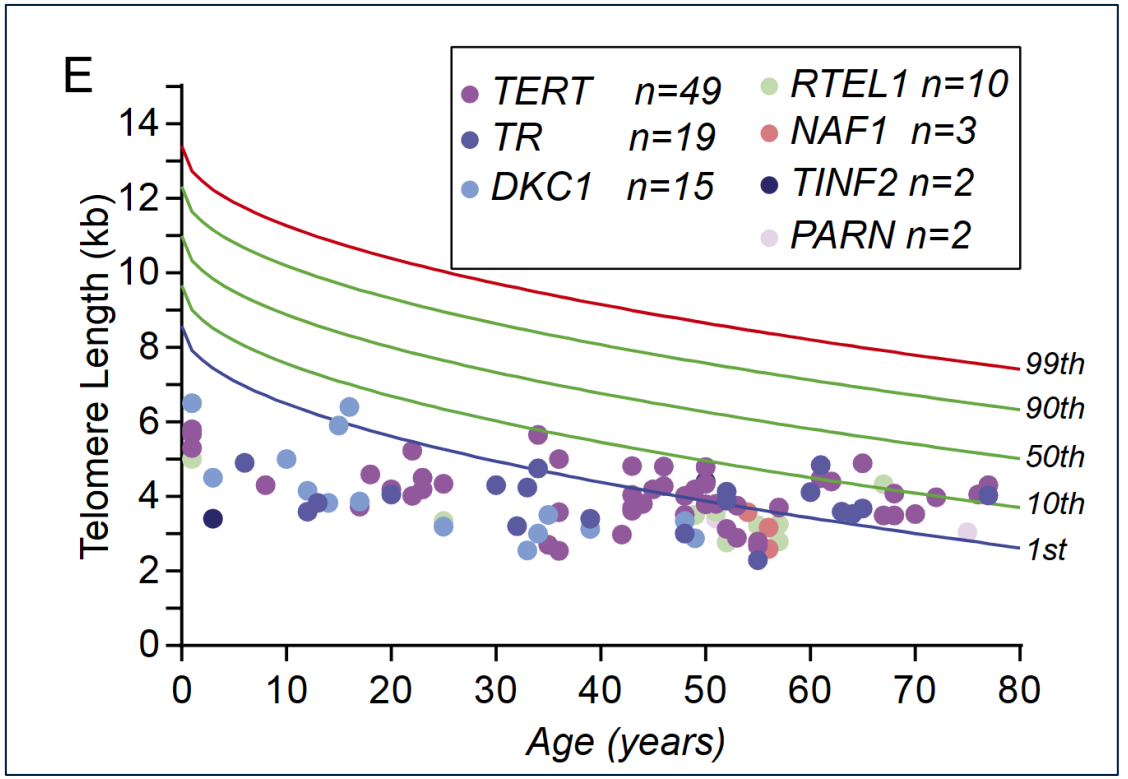


Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

- TL by flow FISH is highly reproducible
- Standardized, age-dependent diagnostic thresholds.
- Low TL test should be followed by genetic testing to establish genetic diagnosis

Lymphocyte TL in genetically confirmed TBD patients

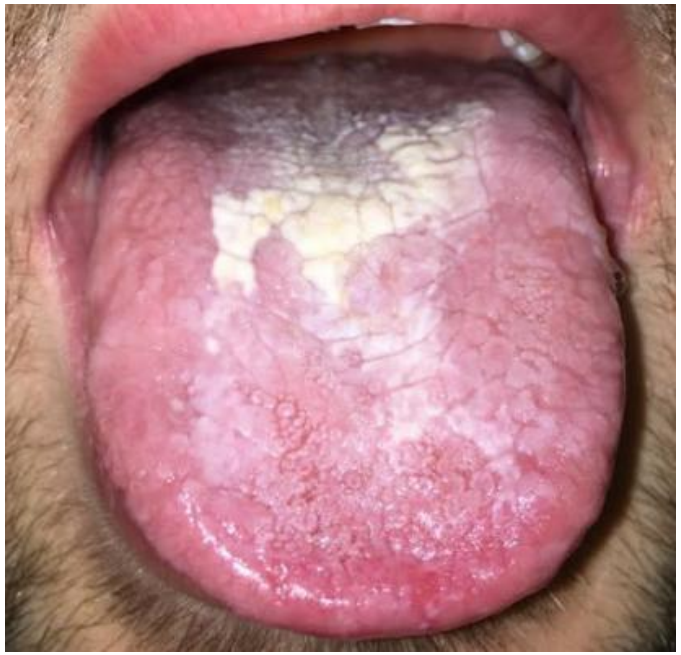




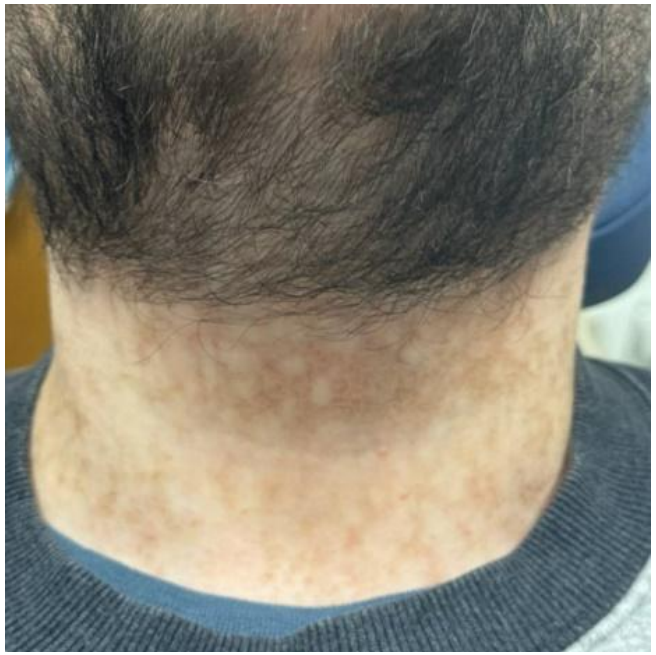
Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

Mucocutaneous Triad in Dyskeratosis Congenita

Oral leukoplakia

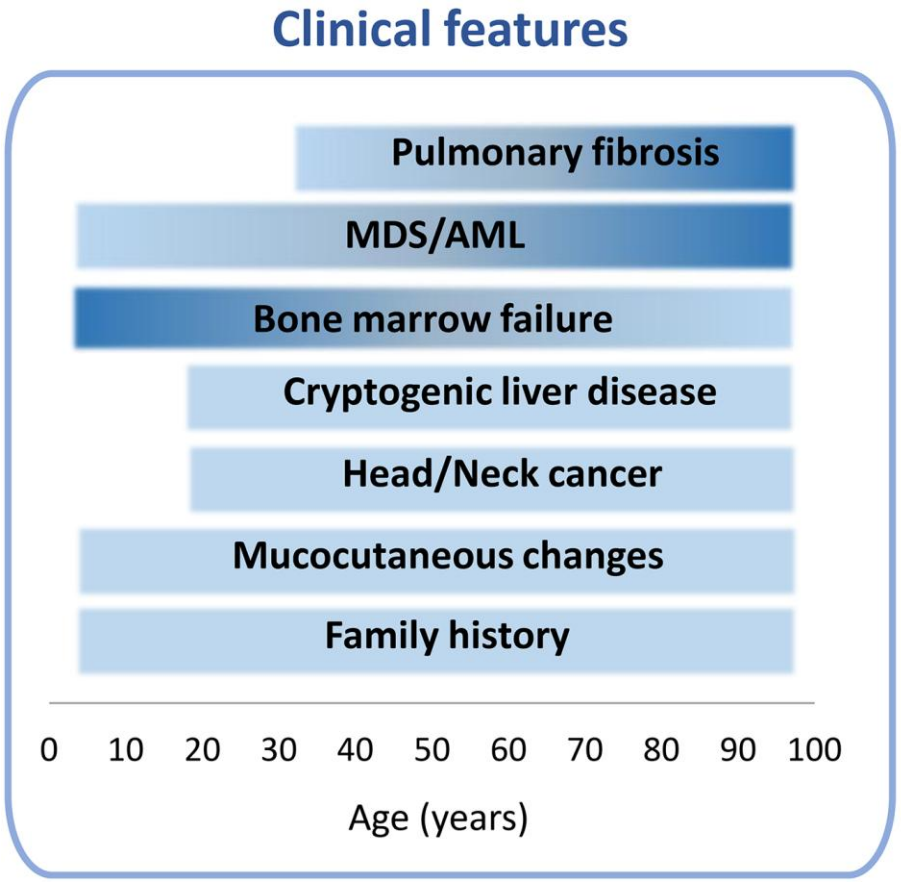


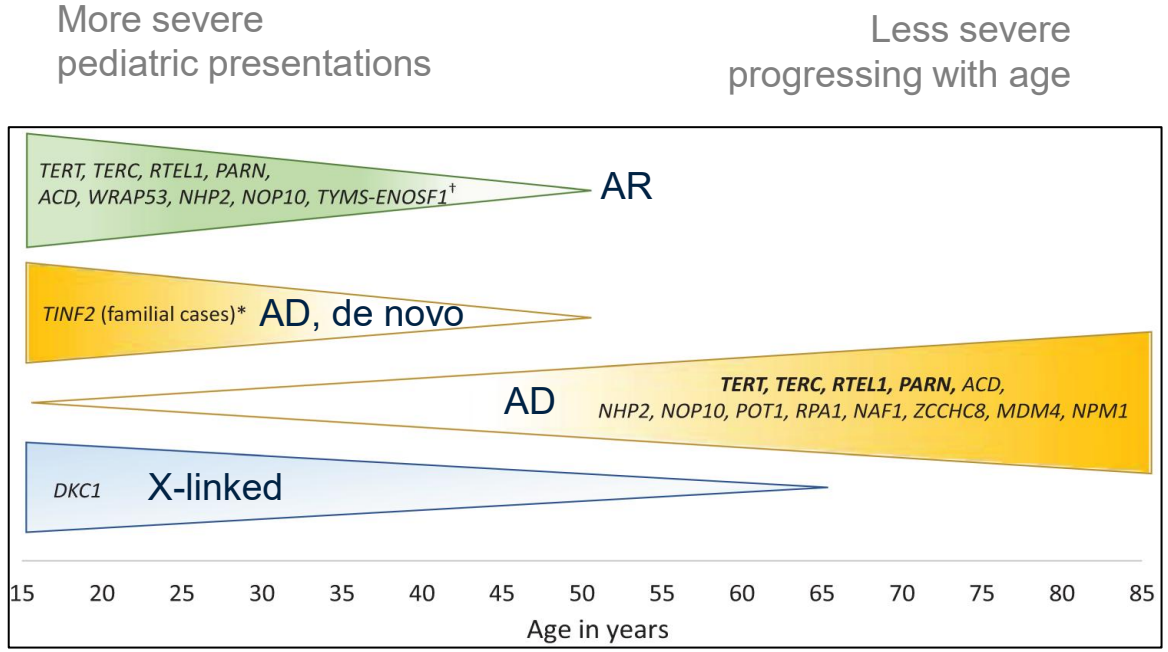
Hypo/hyperpigmentation



Nail dystrophy

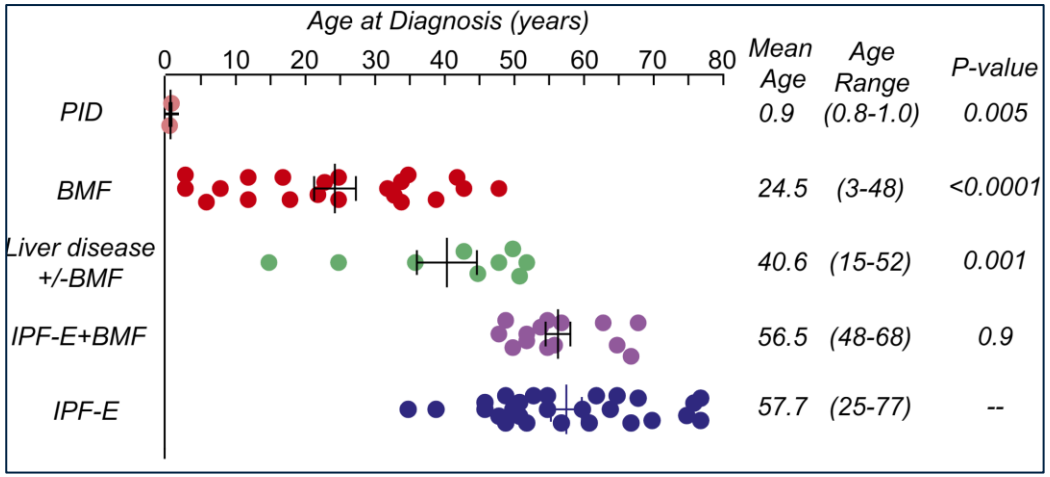
Genetically Heterogeneous Multisystem Progressive Disease

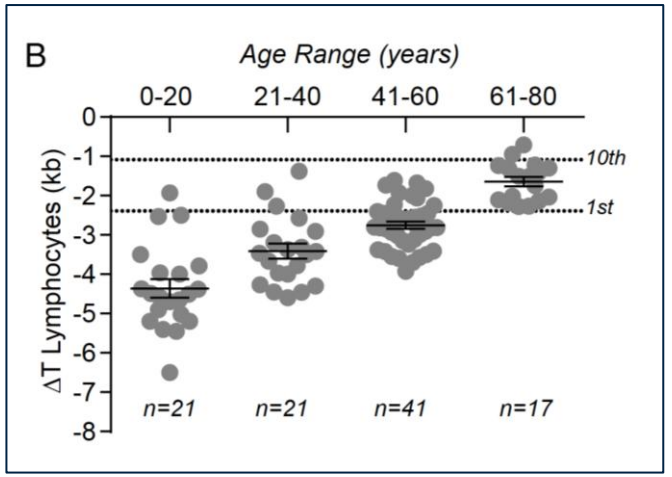


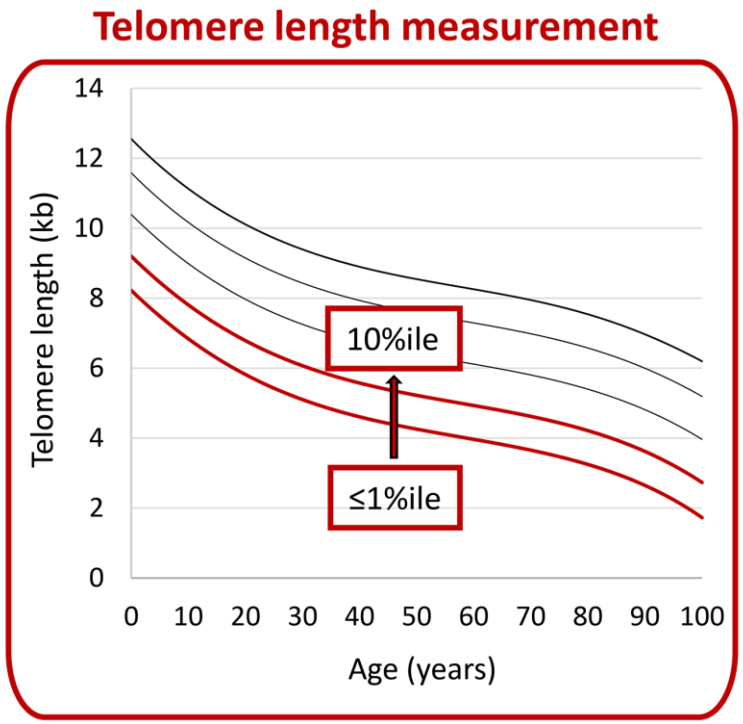


Niewisch, et al. Hematology, 2023

Age and clinical symptom-dependent TL thresholds





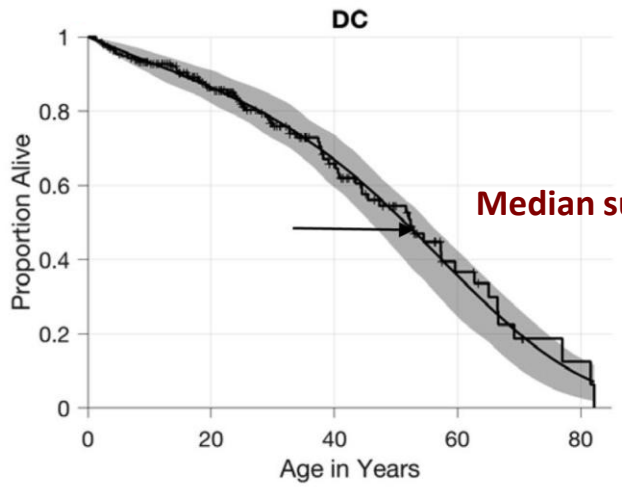


Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

Niewisch, et al. Hematology, 2023

Overall survival, BMF, MDS, AML and solid tumors

Overall Survival

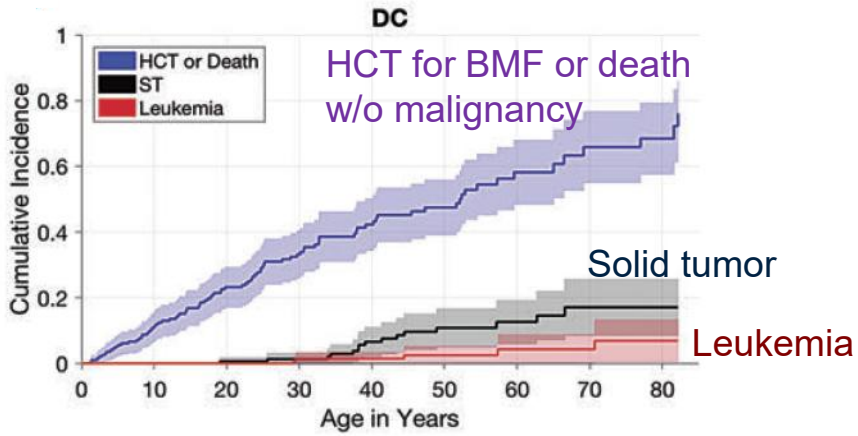


Median survival: 51 years

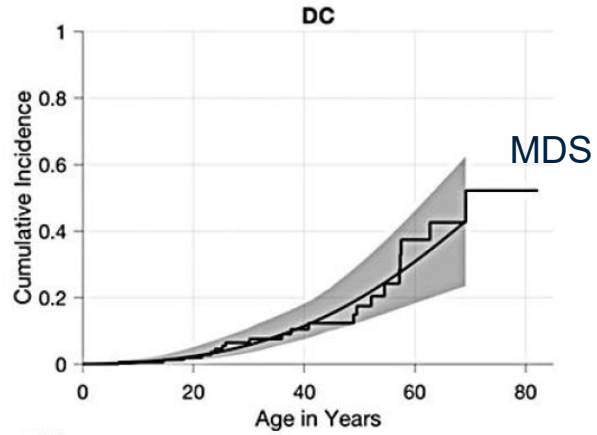
Cumulative incidence:

- HCT for severe BMF or death 70% by age 70
- solid tumors: ~20% by age 65 years
- MDS: 20% by age 50 years
- AML: <10% by age 70 years

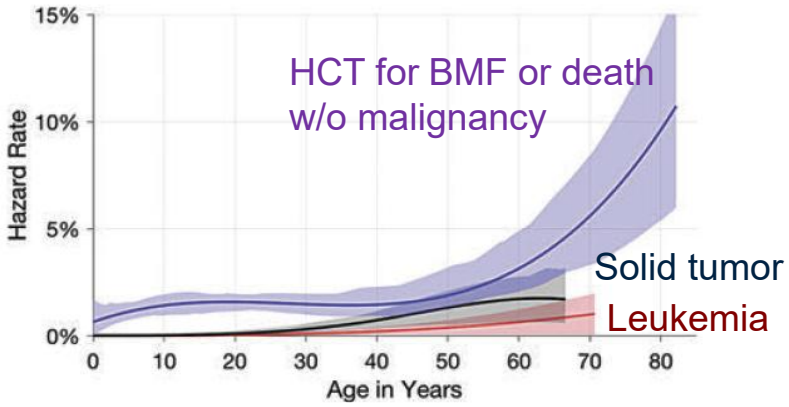
CI of death/HCT/ST/leukemia



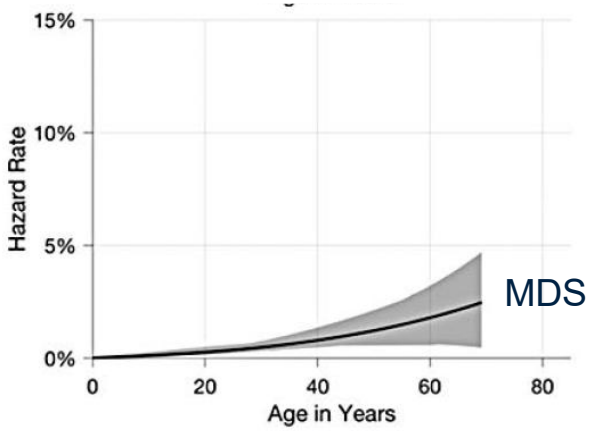
CI of MDS



Annual hazard rate



Annual hazard rate



Alter et al. Haematologica 2018 Volume 103(1):30-39

Solid Tumors in TBD Patients

Table 2. Types and ages of solid tumors in DC literature cases

Type of cancer	No. of cancers	Male	Female	Median age, y (range)	Median age in general population, y
All solid tumors	60 in 51 pts	41	10	28 (1.5-68)	67
HNSCC	24 in 22 pts	14	8	32 (17-49)	62
Skin SCC	8	7	1	21 (4-43)	68
Anorectal	6	6	0	28 (17-52)	61
Stomach	4	4	0	23 (16-44)	71
Lung	4	4	0	56 (52-68)	71
Esophagus	3	3	0	25, 38, 41	69
Hodgkin disease	3	3	0	23, 25, 28	38
Colon	2	2	0	20, 25	71
Pancreas	2	2	0	29, 29	72
Liver	1	1	0	32	65
Retinoblastoma	1	1	0	1.5	2
Cervix	1	0	1	31	48
Lymphoma*	1	1	0	43	67

Alter et al. Blood (2009) 113 (26): 6549–6557.

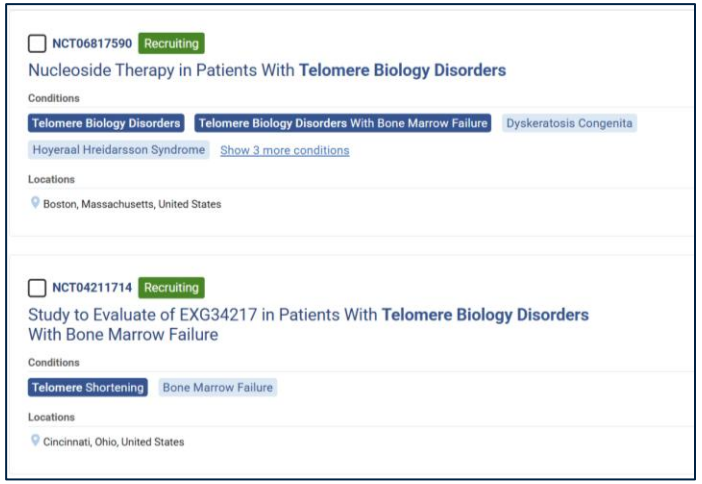
Comprehensive management focused on affected organs and cancer surveillance

- Referral to a center with experience in multidisciplinary management of telomere biology disorders

- BMF/immune deficiency/MDS/AML:
  - Medical management:
    - Anabolic steroids (e.g., danazol)
    - Transfusion support
    - Avoidance of myelosuppressive agents
  - BMT:
    - Low intensity bone marrow transplant can cure BMF or primary immune deficiency
    - Higher intensity is required for treatment of MDS/AML, but has high rates of TRM.

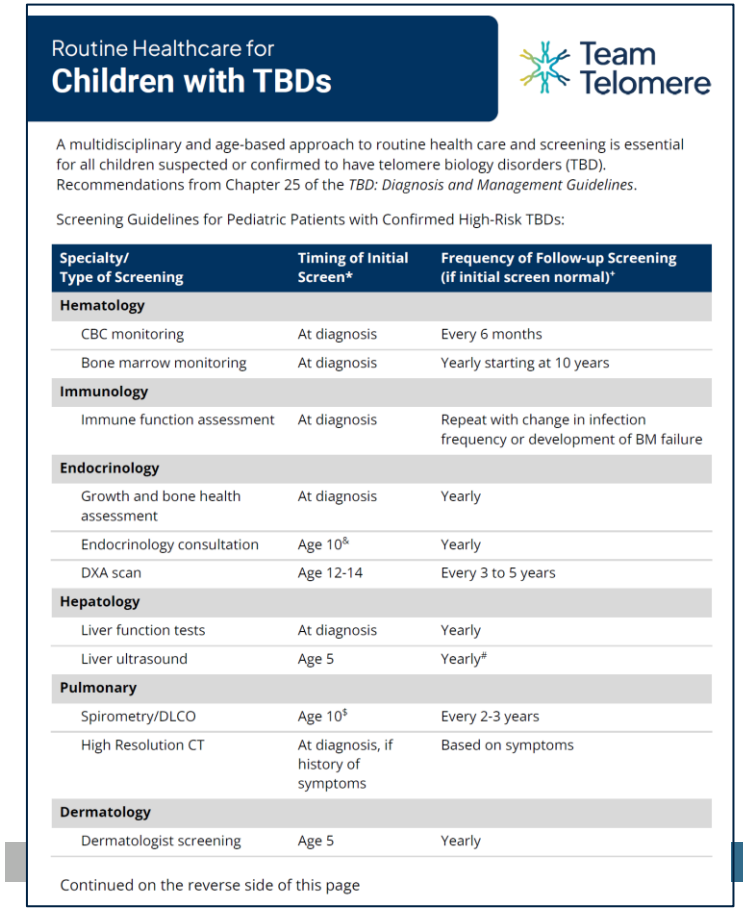
- ILD: Antifibrotics, lung transplant
- Immune deficiency: vaccination
- Cirrhosis: medical management, liver transplant
- AVN: joint replacement
- GI/GU strictures: dilation.
- Mucocutaneous: dermatology/oral medicine
- Cancer surveillance: ENT, GI, bone marrow surveillance.
- Genetics: genetic testing/counseling of patient and family.

Clinical trials



A helpful resource: Team Telomere Management Handbook

Team Telomere | A Community for Telomere Biology Disorders



Routine Healthcare for
Children with TBDs

Team Telomere

A multidisciplinary and age-based approach to routine health care and screening is essential for all children suspected or confirmed to have telomere biology disorders (TBD). Recommendations from Chapter 25 of the *TBD: Diagnosis and Management Guidelines*.

Screening Guidelines for Pediatric Patients with Confirmed High-Risk TBDs:

Specialty/ Type of Screening	Timing of Initial Screen*	Frequency of Follow-up Screening (if initial screen normal)*
Hematology		
CBC monitoring	At diagnosis	Every 6 months
Bone marrow monitoring	At diagnosis	Yearly starting at 10 years
Immunology		
Immune function assessment	At diagnosis	Repeat with change in infection frequency or development of BM failure
Endocrinology		
Growth and bone health assessment	At diagnosis	Yearly
Endocrinology consultation	Age 10[&]	Yearly
DXA scan	Age 12-14	Every 3 to 5 years
Hepatology		
Liver function tests	At diagnosis	Yearly
Liver ultrasound	Age 5	Yearly[#]
Pulmonary		
Spirometry/DLCO	Age 10[$]	Every 2-3 years
High Resolution CT	At diagnosis, if history of symptoms	Based on symptoms
Dermatology		
Dermatologist screening	Age 5	Yearly

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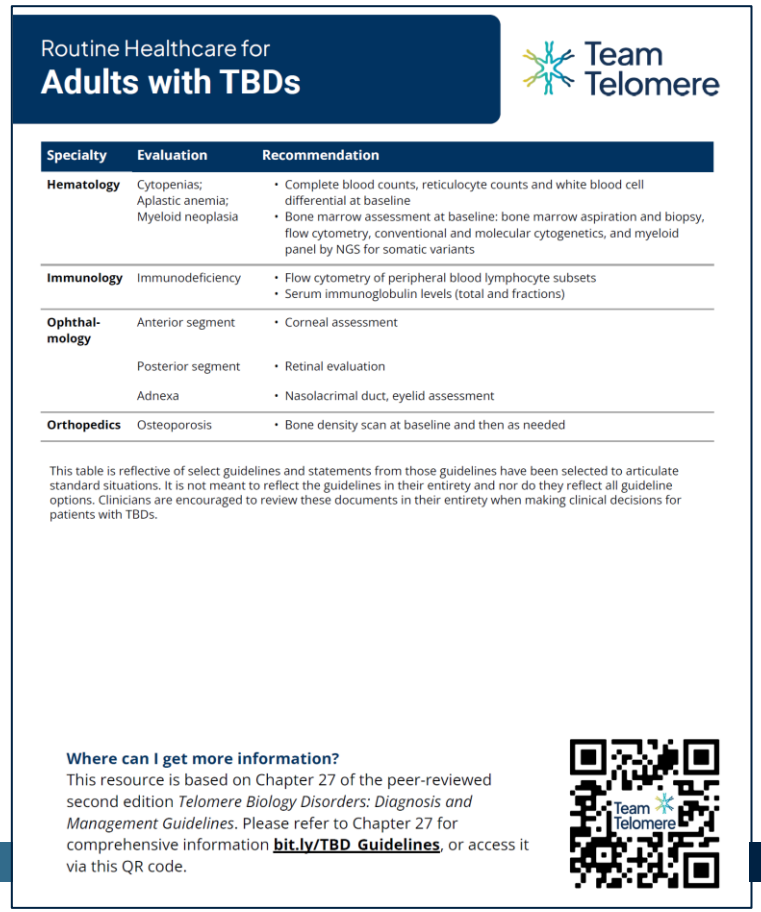


Routine Healthcare for
Adults with TBDs

Team Telomere

Specialty	Evaluation	Recommendation
Hematology	Cytopenias; Aplastic anemia; Myeloid neoplasia	• Complete blood counts, reticulocyte counts and white blood cell differential at baseline • Bone marrow assessment at baseline: bone marrow aspiration and biopsy, flow cytometry, conventional and molecular cytogenetics, and myeloid panel by NGS for somatic variants
Immunology	Immunodeficiency	• Flow cytometry of peripheral blood lymphocyte subsets • Serum immunoglobulin levels (total and fractions)
Ophthal-mology	Anterior segment	• Corneal assessment
	Posterior segment	• Retinal evaluation
	Adnexa	• Nasolacrimal duct, eyelid assessment
Orthopedics	Osteoporosis	• Bone density scan at baseline and then as needed

This table is reflective of select guidelines and statements from those guidelines have been selected to articulate standard situations. It is not meant to reflect the guidelines in their entirety and nor do they reflect all guideline options. Clinicians are encouraged to review these documents in their entirety when making clinical decisions for patients with TBDs.

Where can I get more information?
This resource is based on Chapter 27 of the peer-reviewed second edition *Telomere Biology Disorders: Diagnosis and Management Guidelines*. Please refer to Chapter 27 for comprehensive information **bit.ly/TBD_Guidelines**, or access it via this QR code.

Team Telomere

Patient Case 4

HPI: 2 month old previously healthy boy brought to pediatrician with pallor.

Family History: 2 brothers, healthy. No blood conditions in the family.

Labs: Anemia (Hgb 4 g/dl), reticulocytes 0.1%, MCV 103 (macrocytic).

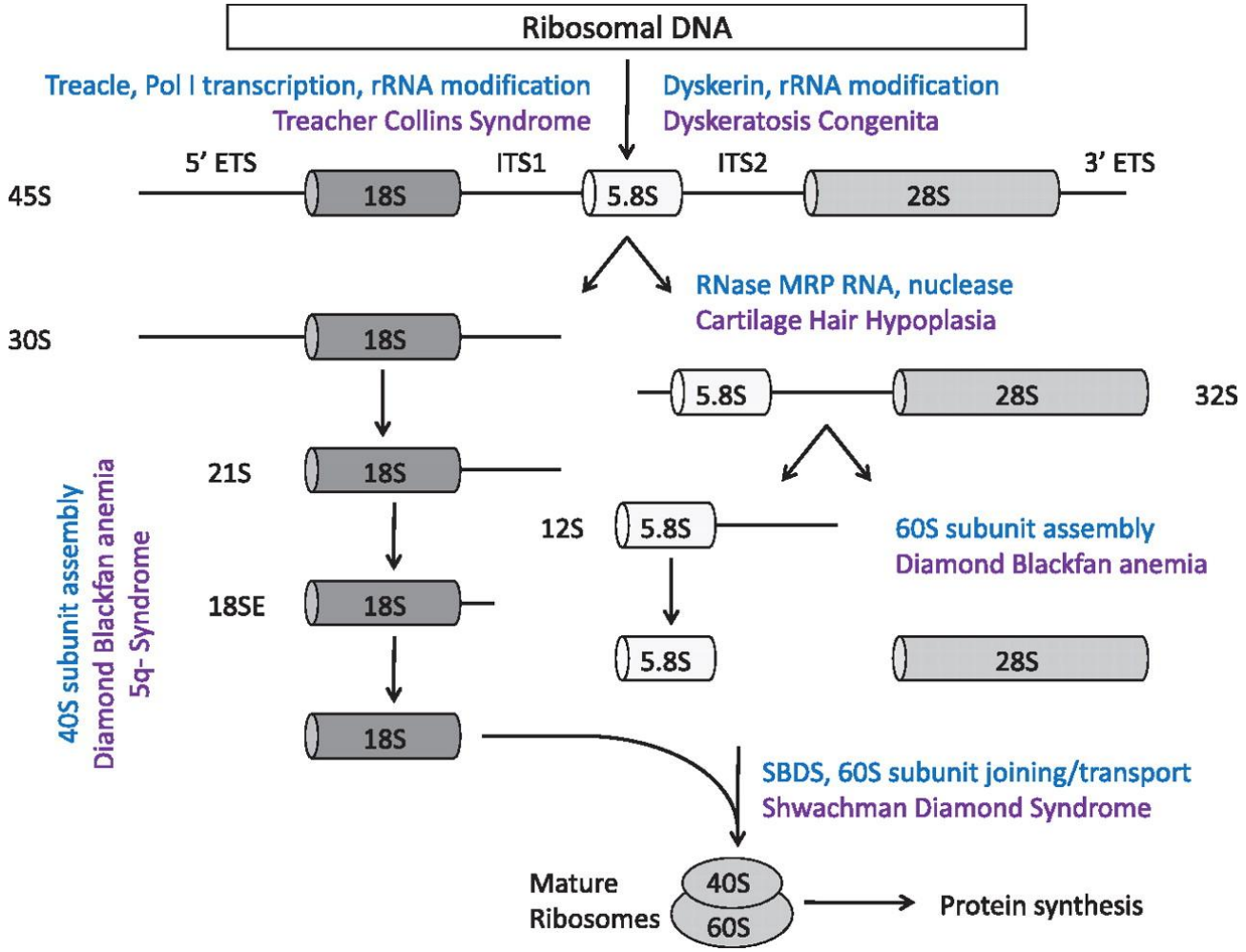
Physical exam: Small for age. Pallor, otherwise no apparent abnormality.
Holosystolic murmur.

Bone marrow aspiration and biopsy: absence of erythroid precursors.

Cytogenetics and somatic molecular testing are normal.

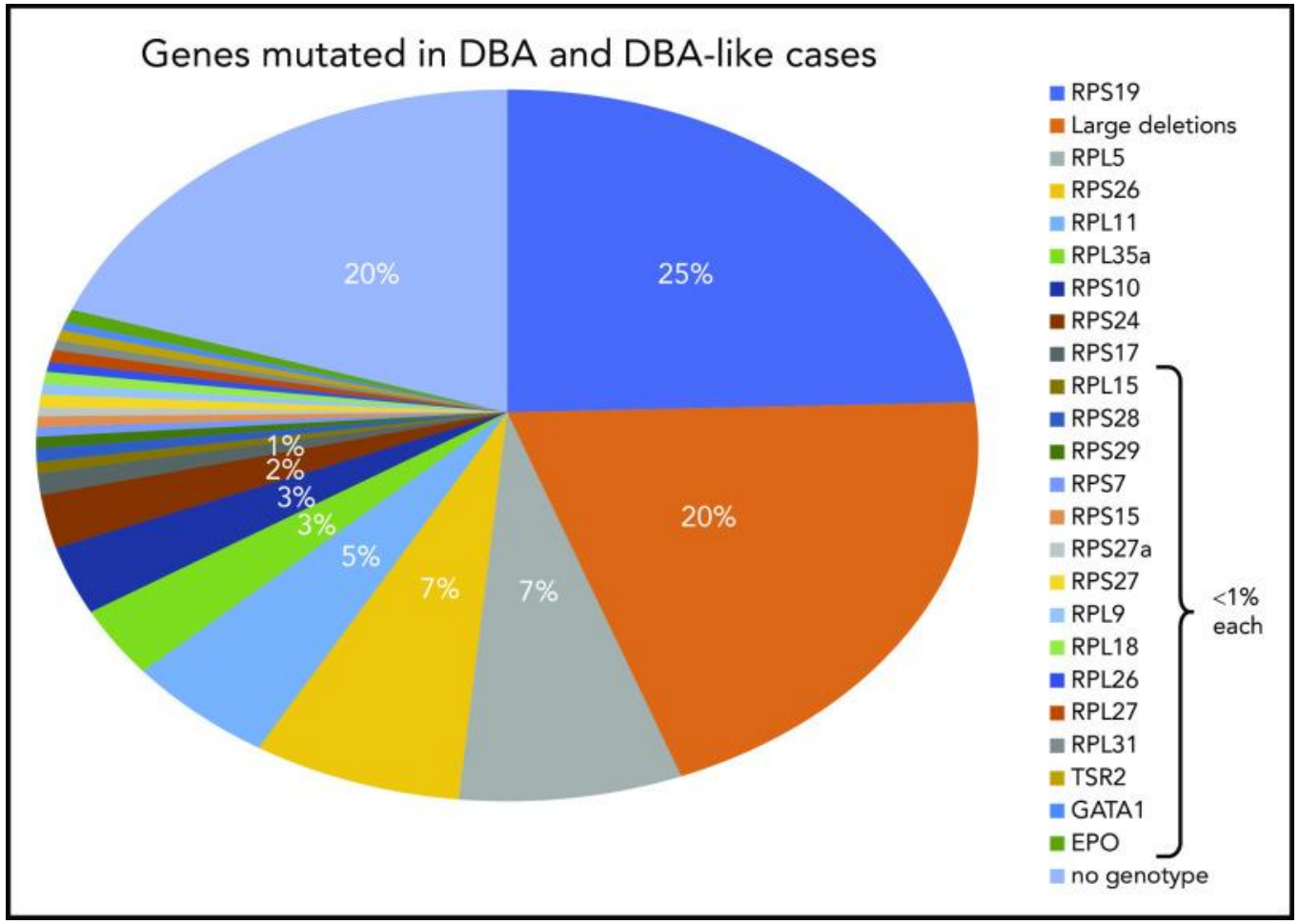
What is the likely diagnosis?
What testing should be ordered?

Diamond Blackfan Anemia (DBA): Caused by Ribosome Biogenesis Defects



Narla A , and Ebert B L Blood 2010;115:3196-3205/Liu and Ellis Blood 2006

Genetic causes of DBA



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

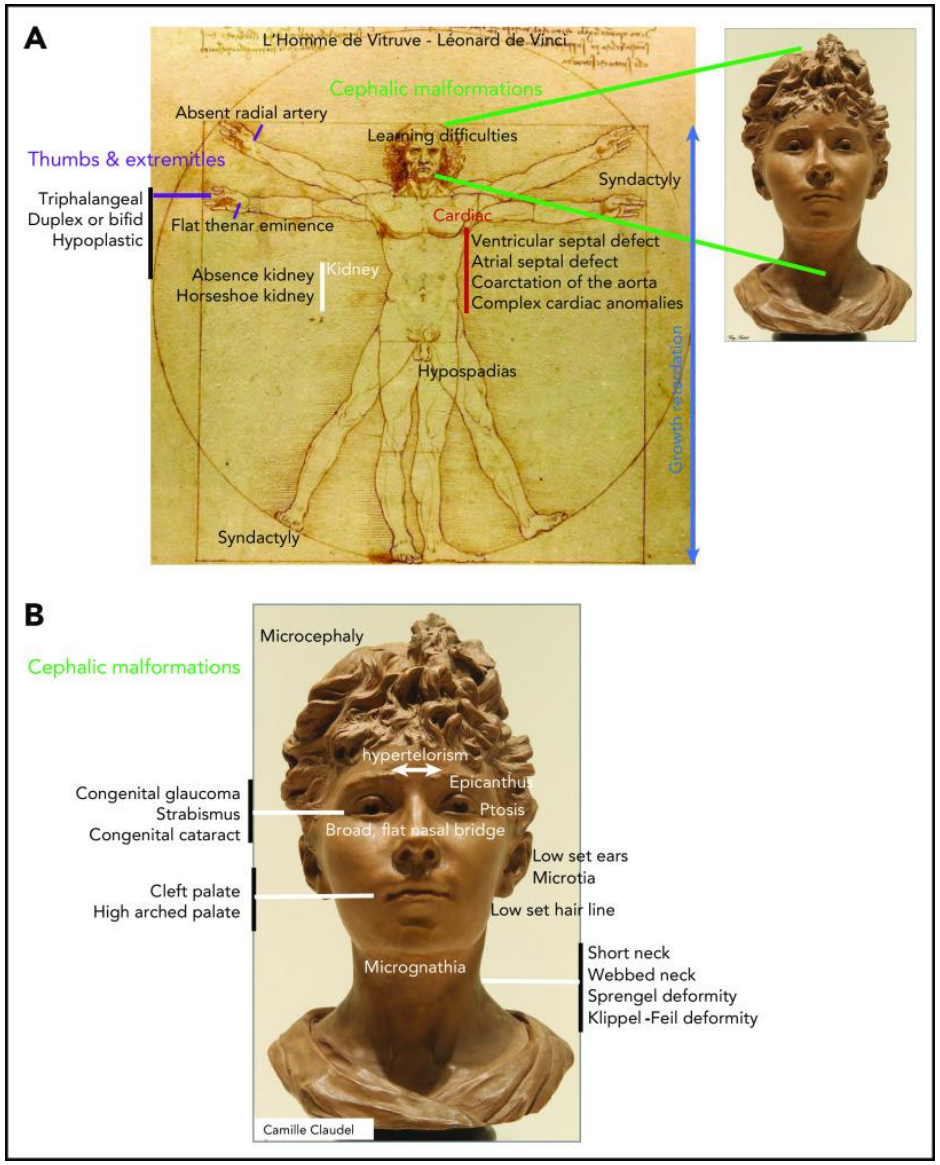
- AD, haploinsufficiency in RP
  - Most common: RPS19, RPL5, RPL11
- X-linked: GATA1, TSR2
- AR: EPO

- Mutations and large deletions

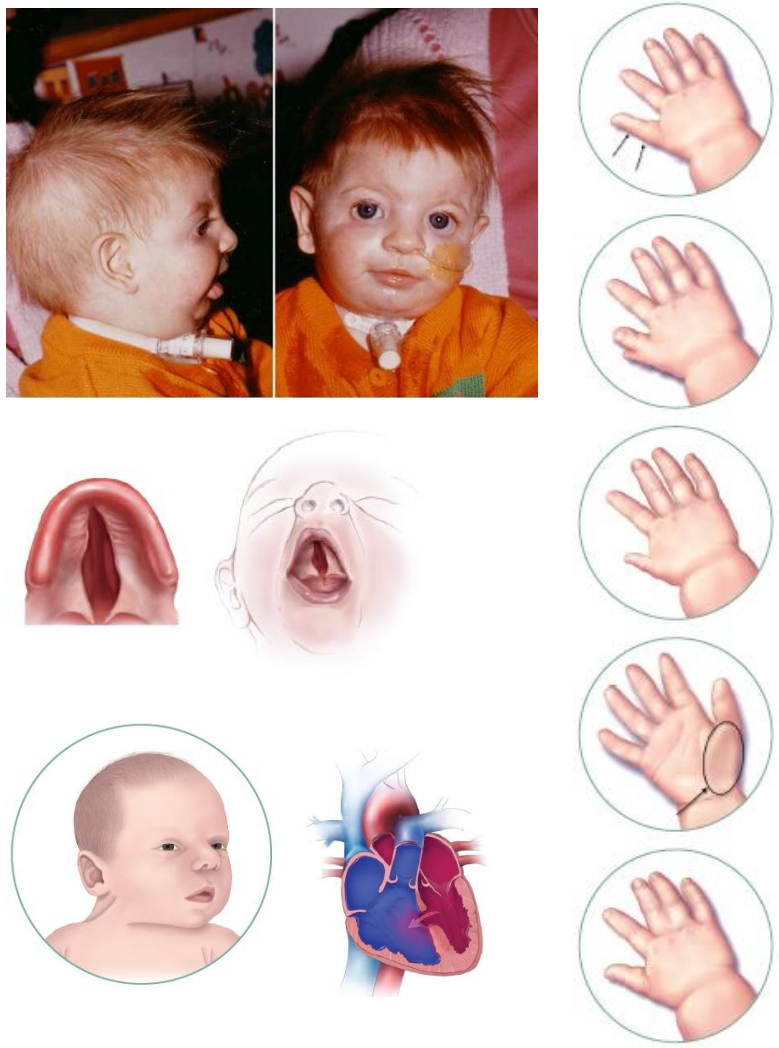
- Diagnosis is established by:
  - Genetic testing

Diagnosed at 3 months of age: 50%
…….... at 6 months of age: 75%
…….. by 1 year: 92%

Clinical Presentation in DBA



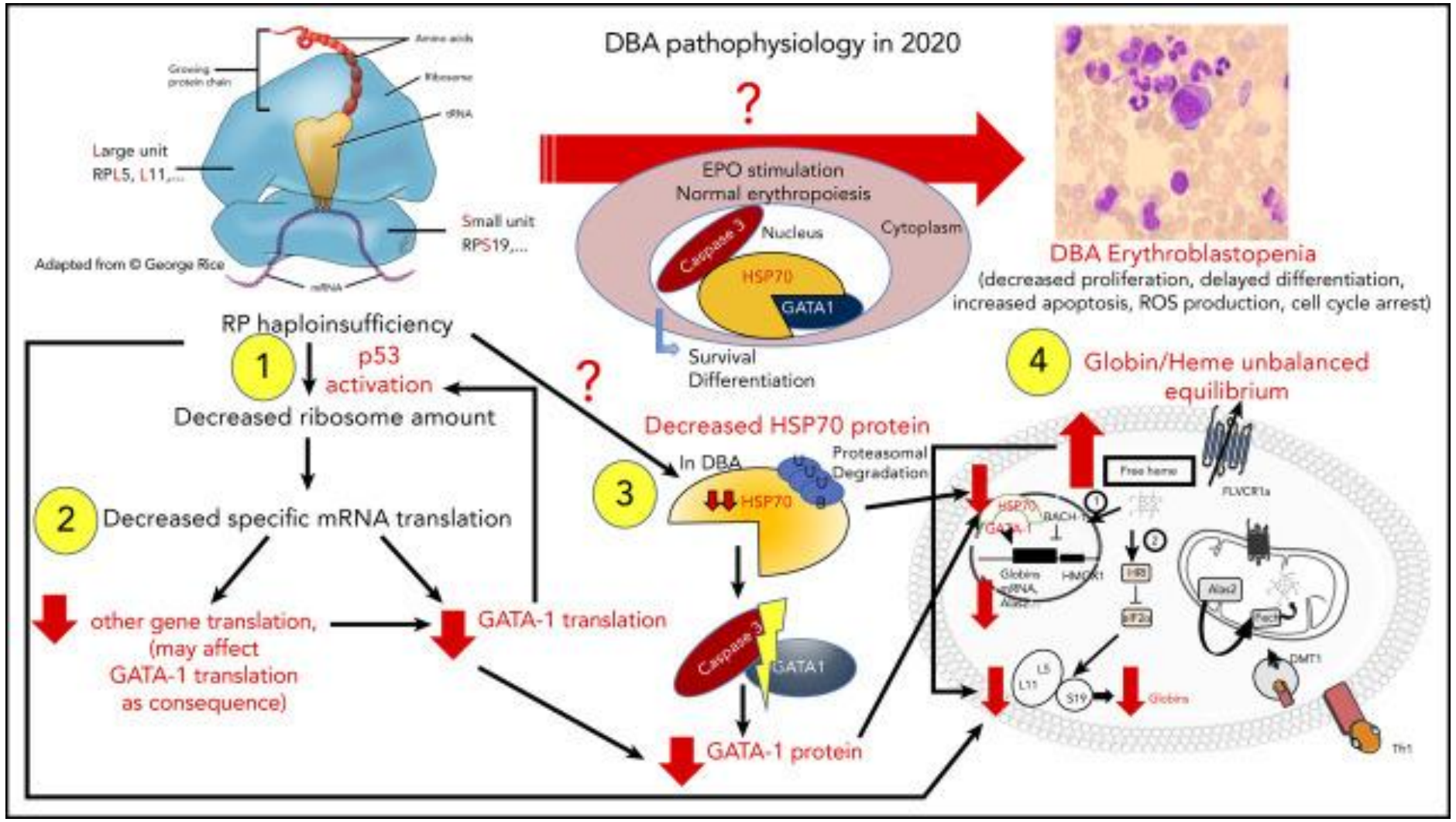
- Macrocytic, hypoproliferative anemia with absence of red cell precursors in bone marrow.
- ~ HALF have congenital anomalies.



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

Hematol Oncol Clin North Am. 2009 April; 23(2): 261–282.

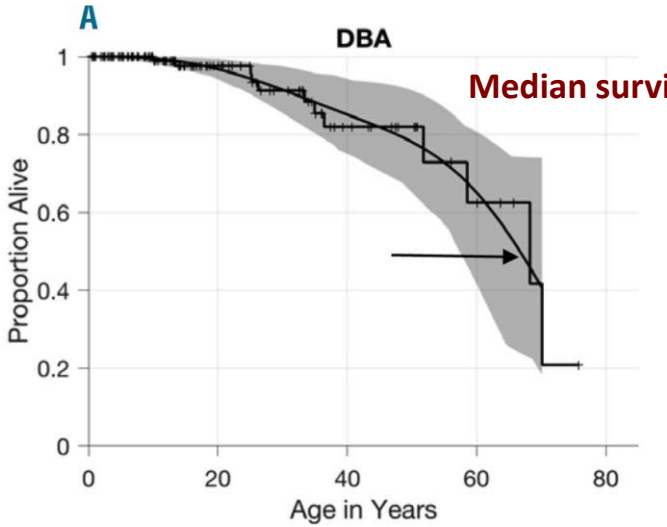
DBA Pathogenesis



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

Overall survival, BMF, MDS, AML and solid tumors

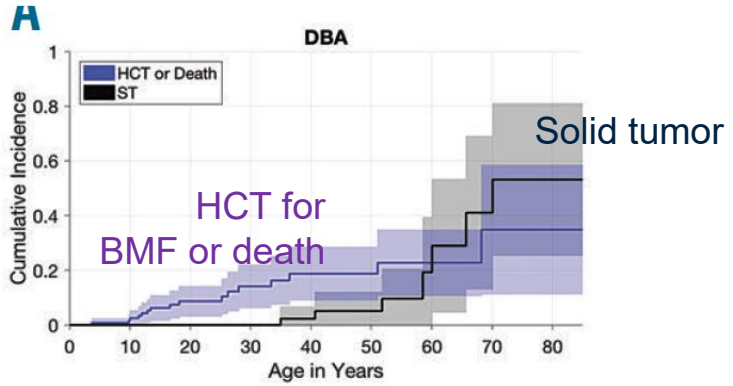
Overall Survival



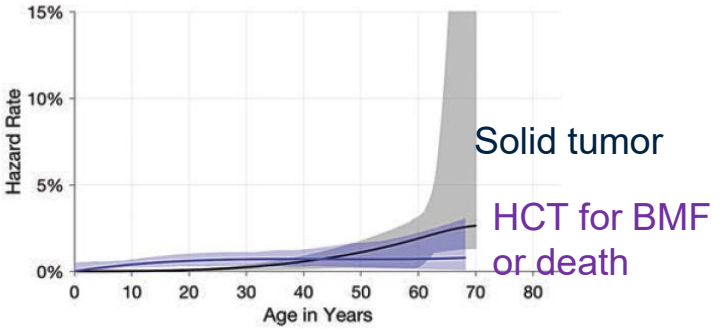
Cumulative incidence:

- Severe BMF >40% by age 70
- solid tumors: >50% by age 70 years
- MDS: 5% by age 50 years
- AML: not increased

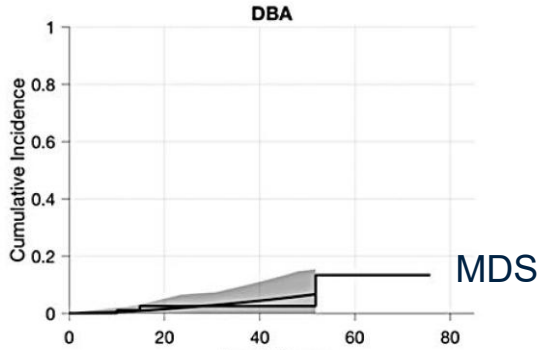
CI of death/HCT/ST/leukemia



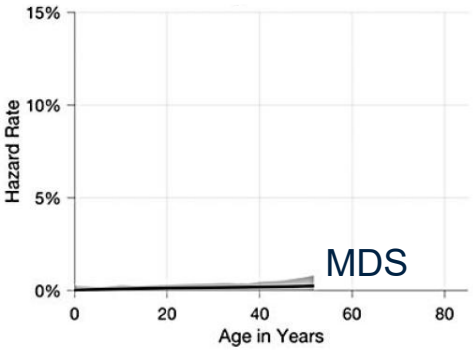
Annual hazard rate



Cumulative incidence of MDS



Annual hazard rate



Alter et al. Haematologica 2018 Volume 103(1):30-39

Increased risk of solid tumors in DBA

Table 3. Cancers in patients in the NCI IBMFS cohort who did not have HCT

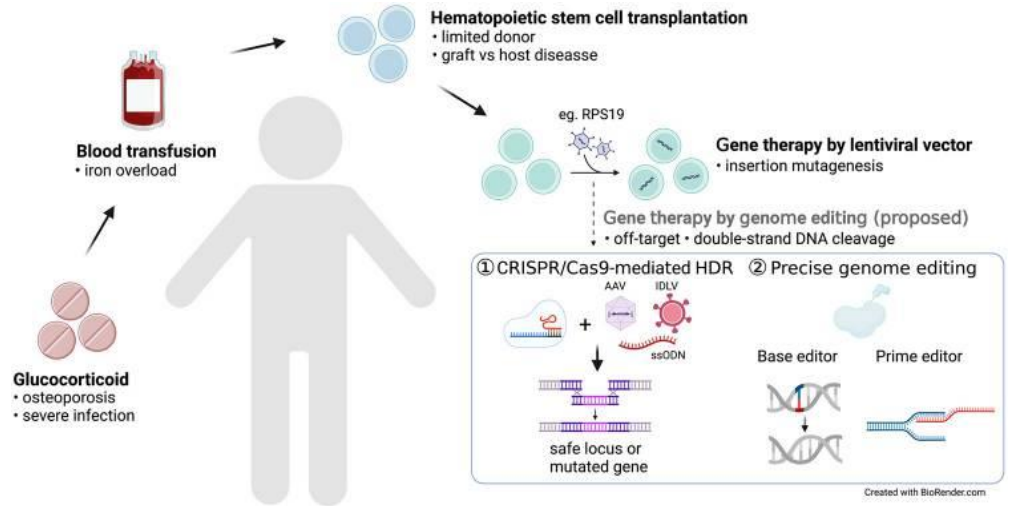
Syndrome	Cancer	Ages (years) Median (range)	Observed N	Expected N	O/E	95% CI
DBA	**All sites***	**49 (17-70)**	**9**	**3.68**	**2.5**	**1.1-4.7**
N=135	**Solid Tumors***	**49 (17-70)**	**9**	**3.12**	**2.9**	**1.3-5.5**
PY=3458	**Lung***	**53 (47-70)**	**4**	**0.34**	**12**	**3.2-30**
	Colon*	**34, 55**	**2**	**0.18**	**11**	**1.4-41**
	Cervix*	**17, 40**	**2**	**0.05**	**37**	**4.6-136**
	Liver	34	1	0.04	27	0.7-151
	MDS*	**13**	**1**	**0.02**	**42**	**1.1-234**
	Skin 8 ca, N = 5	45 (39-63)	8			
	1 NMS, N = 1		1			
	1 SCC, N = 1		1			
	6 BCC, N = 4		6			

Alter et al. Haematologica 2018 Volume 103(1):30-39

Clinical Management

- Anemia:
  - Transfusion support
  - Most patients respond to corticosteroids (high dose, 2mg/kg daily x 4 weeks, then taper slowly to some maintenance dose of corticosteroid)
  - Leucine (low efficacy)
  - BMT
  - Clinical trial
- Mitigation of corticosteroid toxicities:
  - PJP prophylaxis while on high dose steroids
  - Calcium/vitamin D + bone density surveillance

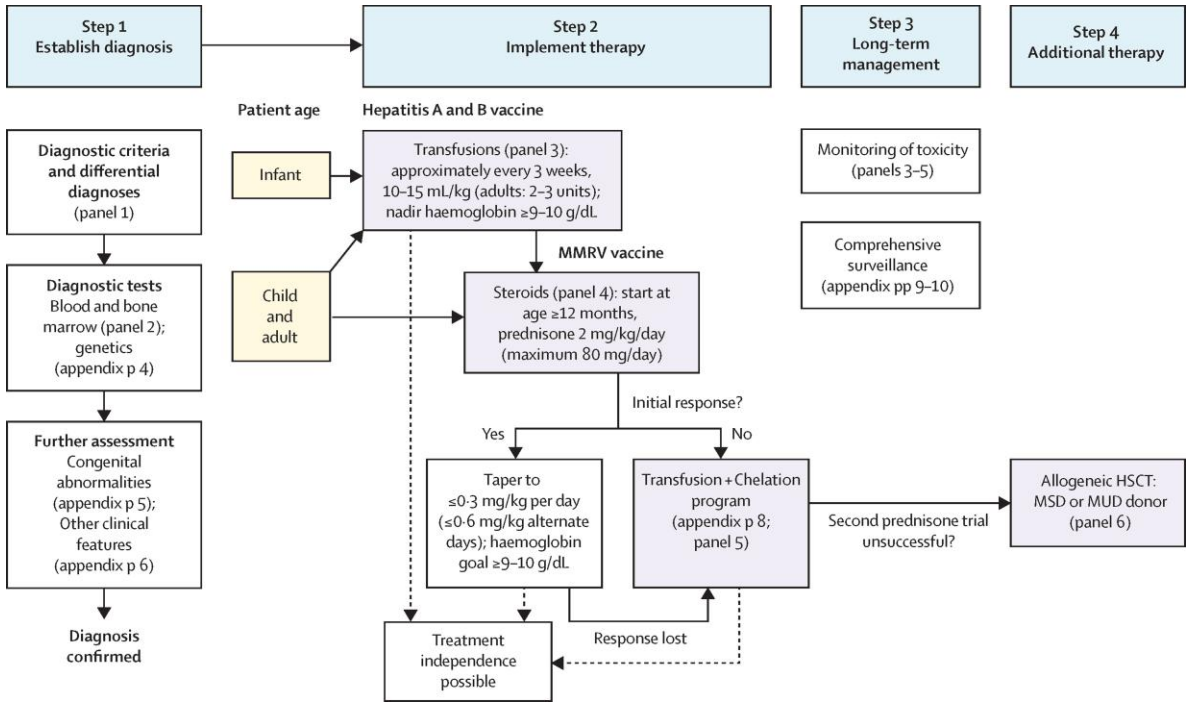
- Management of iron overload:
  - Chelation therapy
- Cancer screening:
  - Colonoscopy
  - Age-appropriate cancer screening
- Multidisciplinary care of affected organ systems (e.g. Cardiology, endocrinology, orthopedics)
- Genetic counseling



Liu et al. Leukemia. 2024; 38(1): 1–9.

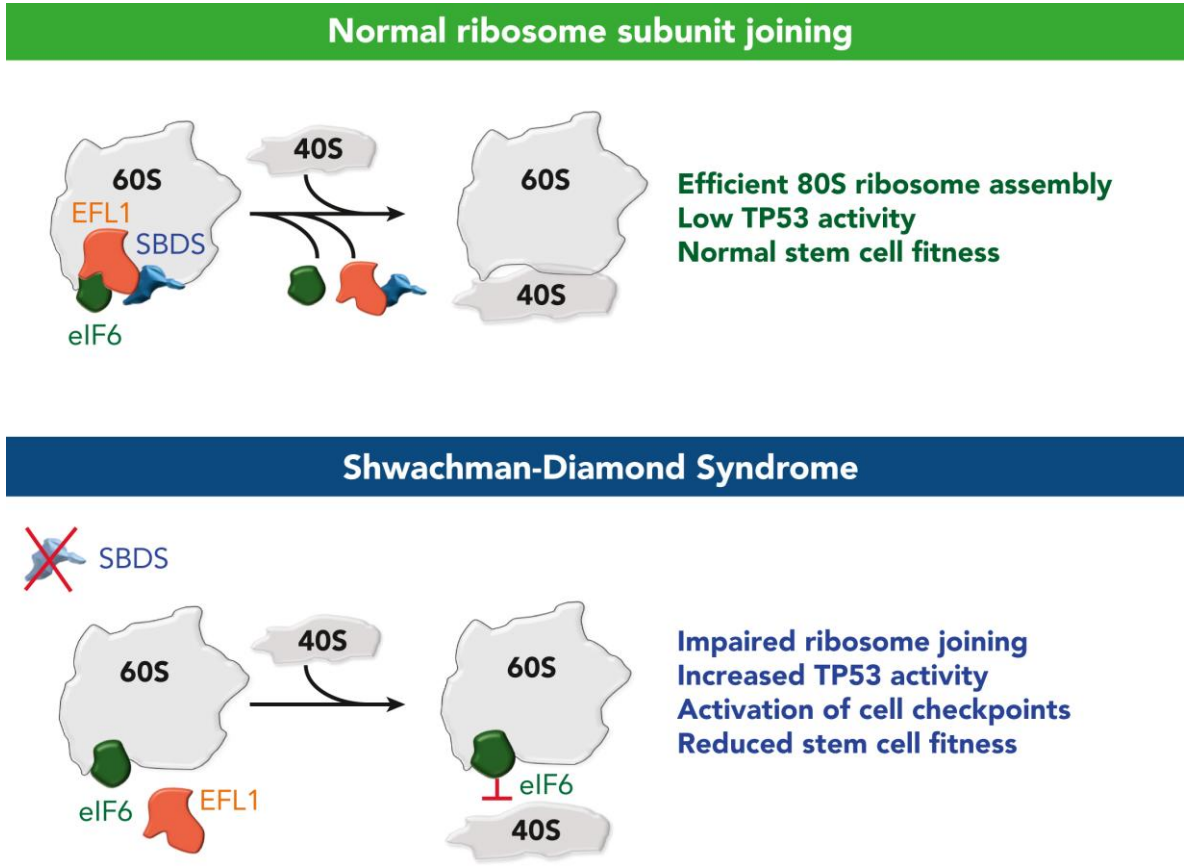
A helpful resource: 2024 DBA International Consensus Statement

- Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement - The Lancet Haematology



Shwachman-Diamond Syndrome (SDS): Caused by a Defect in Ribosome Joining

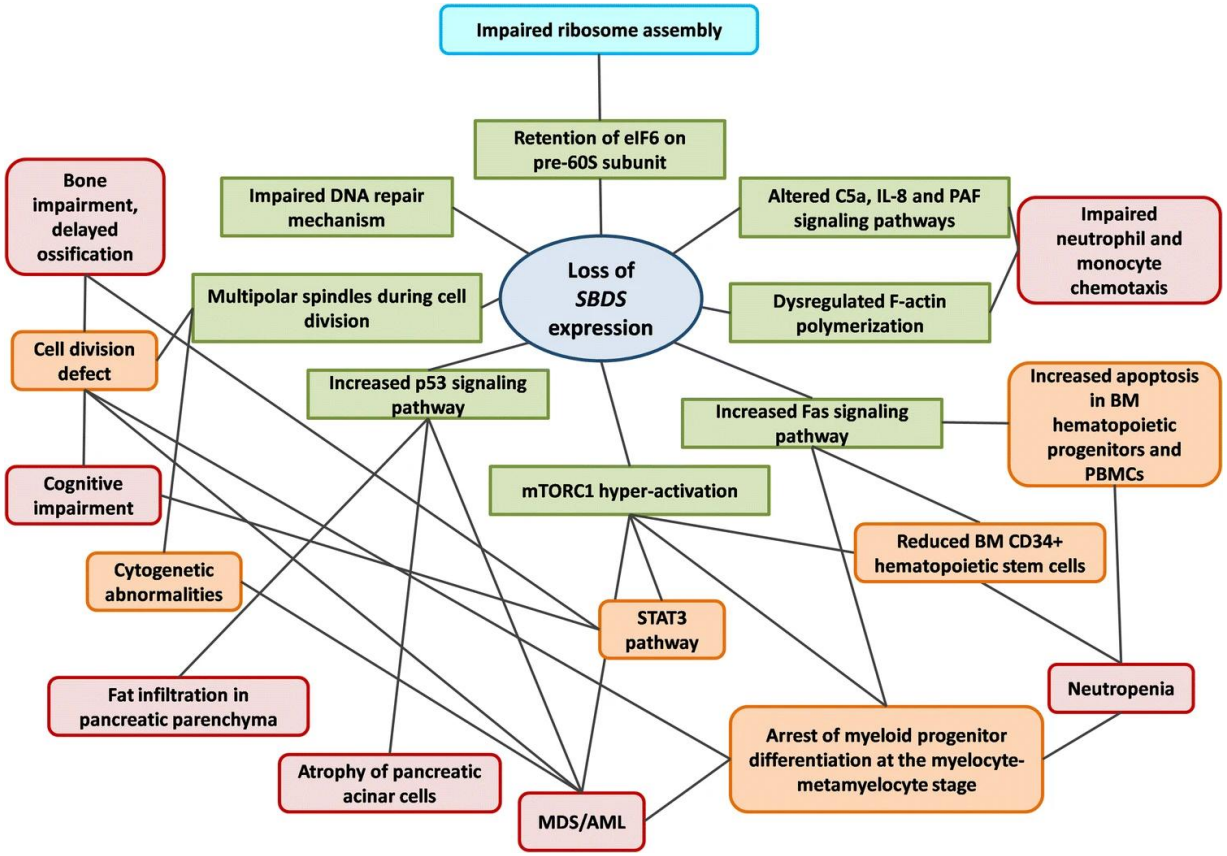
- Diagnosed by a combination of clinical criteria and genetic testing
- Autosomal recessive inheritance
- Biallelic mutations in SBDS (>90%)
- Rare SDS-like syndromes:
  - *SRP54 (AD)*
  - *DNAJC21 (AR)*
  - *EFL1 (AR)*



Reilly and Shimamura. Blood (2023) 141 (13): 1513–1523.

Clinical manifestations of SDS

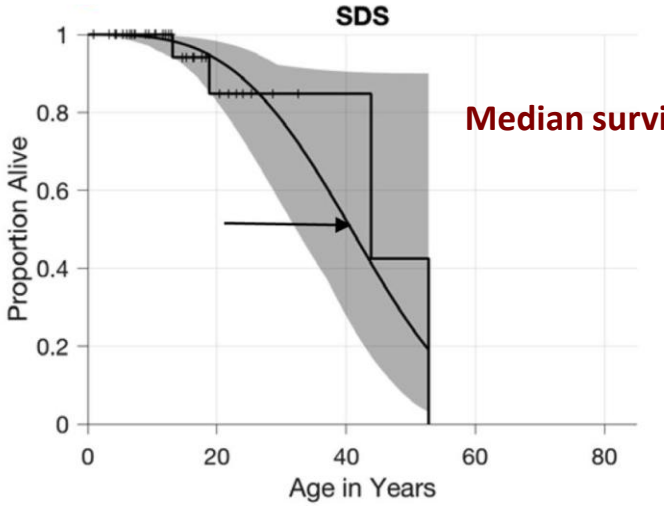
- Skeletal abnormalities
- Pancreatic insufficiency
- Short stature
- Cytopenias (mainly neutropenia)
- ~High risk of MDS/AML



Bezzerri, et al Mol Diagn Ther 23, 281–290 (2019).

Overall survival, BMF, MDS, AML and solid tumors

Overall Survival

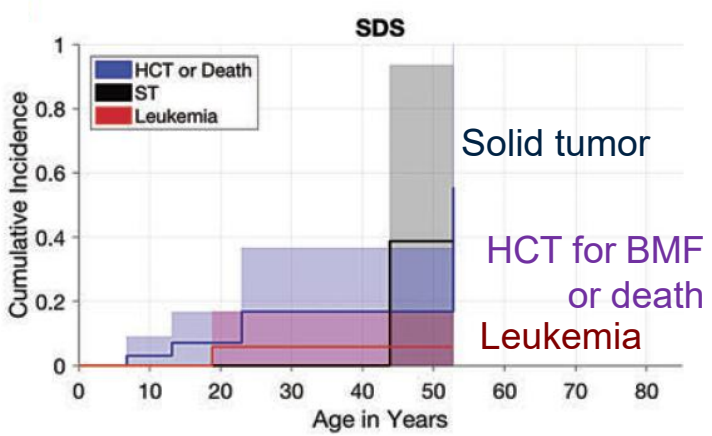


Median survival: 41 years

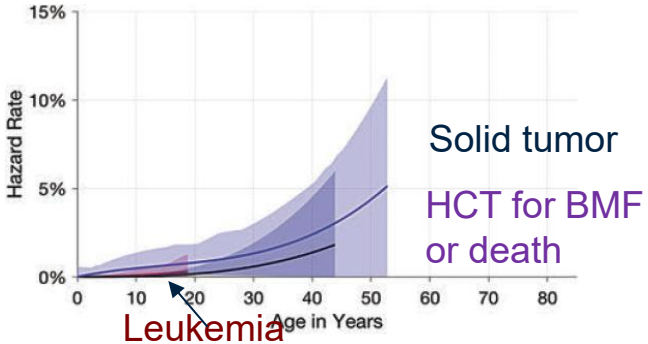
Cumulative incidence:

- Severe BMF maximal rate 20%
- solid tumors: 40% by age 45 (but very few cases analyzed to that age)
- MDS: 65% by age 50 years
- AML: under 5% by age 20

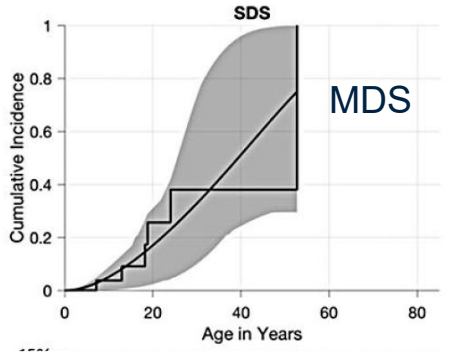
CI of death/HCT/ST/leukemia



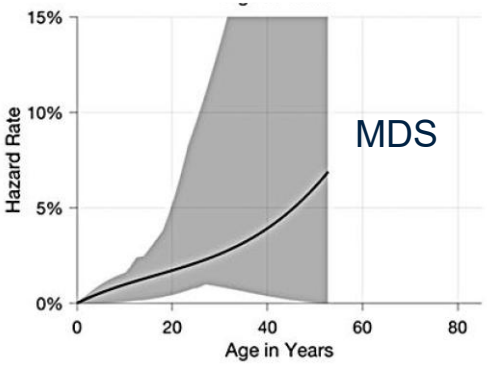
Annual hazard rate



Cumulative incidence of MDS

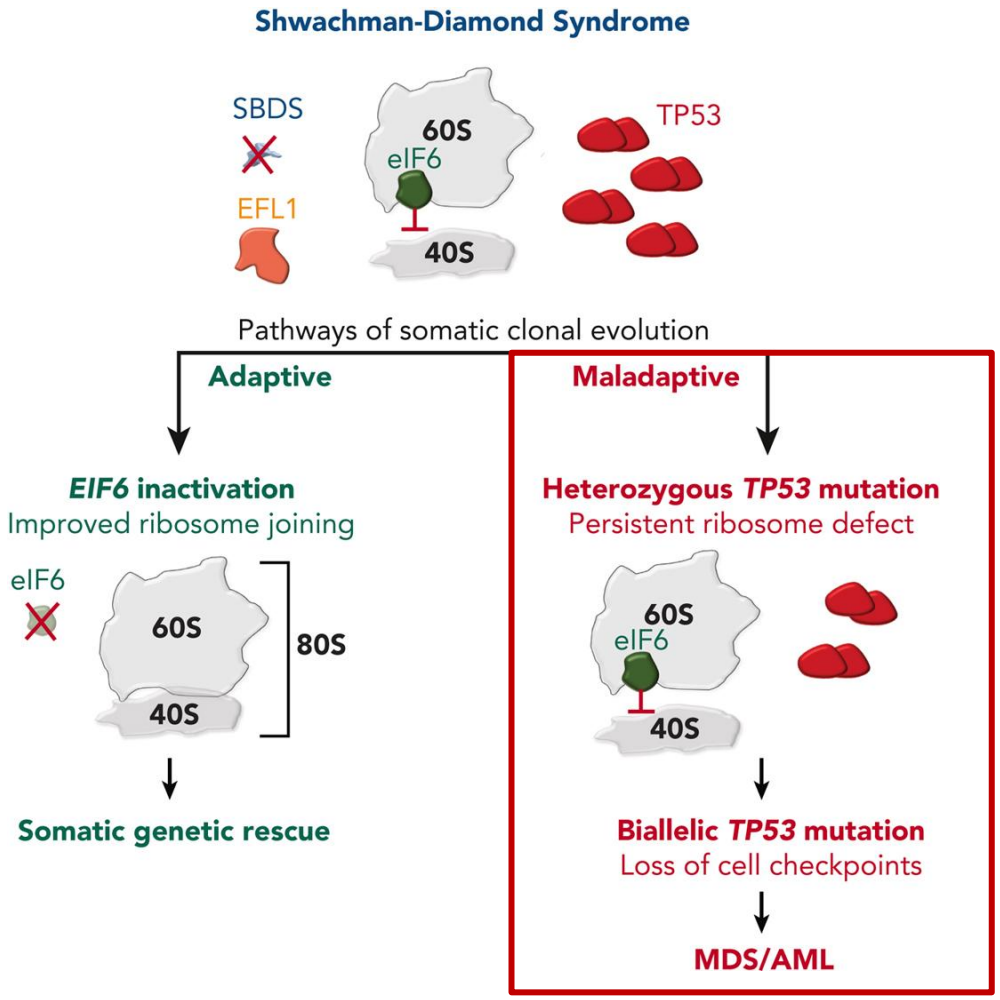


Annual hazard rate



Alter et al. Haematologica 2018 Volume 103(1):30-39

Clinical Management of SDS



- Cytopenias/BMF
  - Neutropenia can be managed supportively, with G-CSF to maintain ANC, particularly with infections
  - Annual bone marrow surveillance
  - HSCT for transfusion-dependent BMF, MDS/AML, ***and, increasingly, for high-risk features***
- Multidisciplinary care:
  - Gastroenterology
    - Pancreatic enzyme supplementation
    - Fat soluble vitamins
  - Endocrinology
  - Orthopedics evaluation
- Genetic counseling

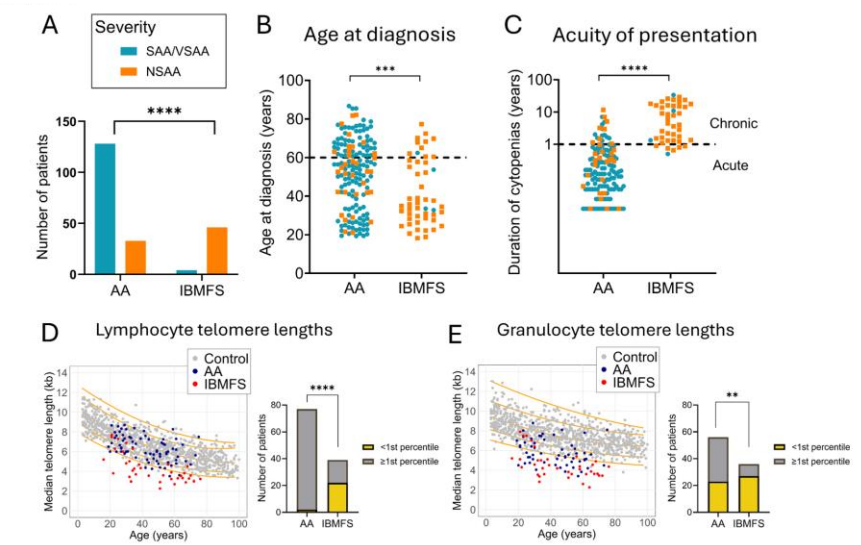
Reilly and Shimamura.
Blood (2023) 141 (13): 1513–1523.

Learning Objectives

- To develop a practical approach to the recognition and diagnosis of bone marrow failure syndromes
- To review the presenting features, prognosis, and treatment of selected hereditary marrow failure and predisposition syndromes:
  - GATA2 deficiency
  - Fanconi Anemia
  - Telomere Biology Disorders
  - Diamond Blackfan Anemia
  - Shwachman Diamond Syndrome
- Distinguishing acquired aplastic anemia from inherited bone marrow failure (PASS Score)

Distinguishing acquired aplastic anemia from inherited BMF Predictive Aplastic Score System (PASS)

- Retrospective study.
- Training cohort: 212 adults (162 AA, 50 IBMFS).
- 4 external cohorts: 716 patients (585 AA, 131 IBMFS).
- Using logistic regression with LASSO, 7 clinical variables were selected for inclusion into prediction model.



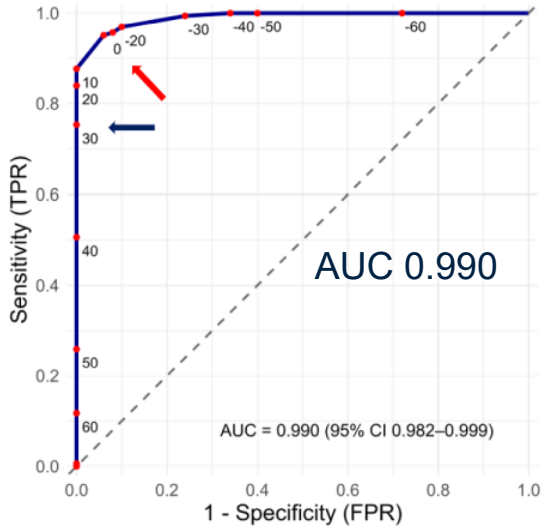
	1 Severity	2 Acuity	3 Age at evaluation	4 IBMFS "red flag"	5 AA-associated conditions	6 (optional) AA-associated somatic findings	7 (optional) Lymphocyte TL <1st percentile
Favors AA	SAA or VSAA +20	Acute +10	≥ 60 yrs +10	No known red flags +10	Present +10	Present +20	No 0
or Favors IBMFS	NSAA 0	Chronic if SAA/VSAA: −10 if NSAA: −20	< 60 yrs if SAA/VSAA: 0 if NSAA: − 10	IBMFS red flag present − 20	No known conditions 0	Absent 0	Lymph TL <1st − 20
Individual criteria:							FINAL PASS SCORE:

Gabriel Aleixo, et al. Development and Validation of the PASS Score: A Simplified Tool to Diagnose Acquired Aplastic Anemia in Adults, 22 January 2026, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-7725283/v1]

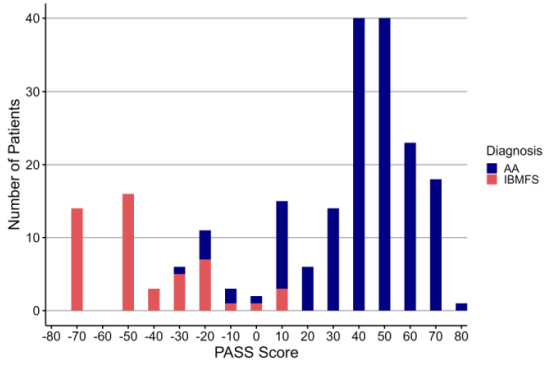
PASS has outstanding discriminatory performance of AA vs IBMFS

Training cohort

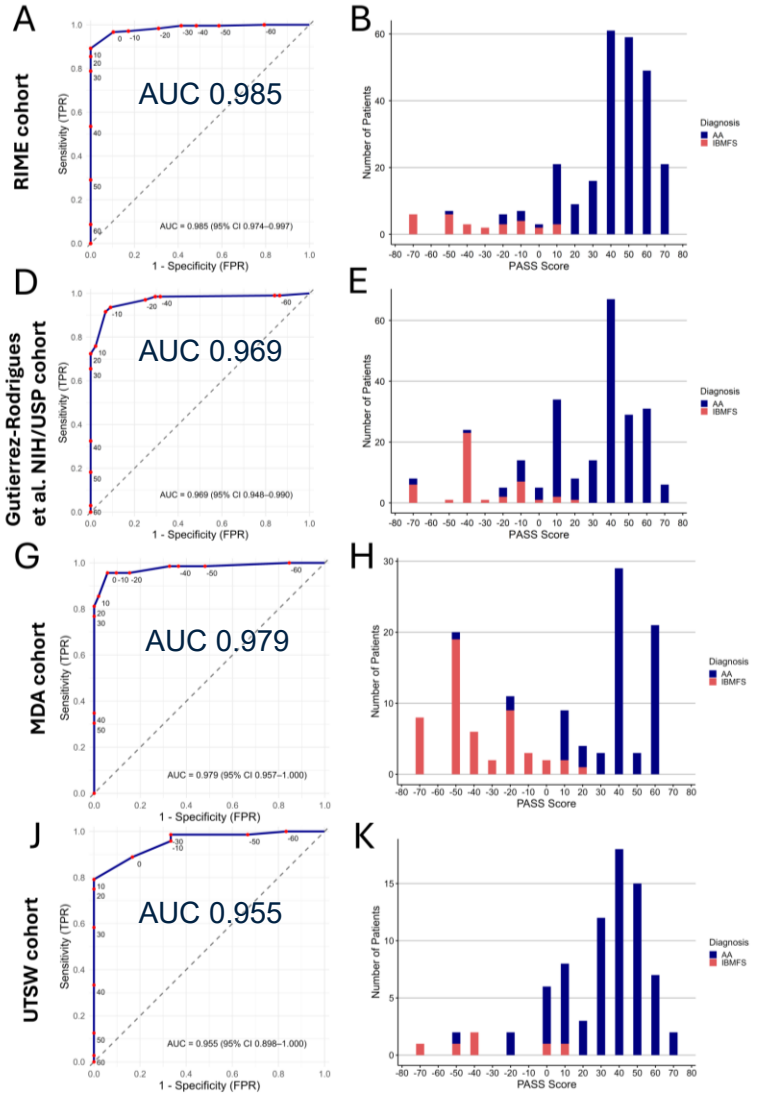
ROC curve



PASS score distribution



Four independent validation cohorts



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Penn Medicine Abramson Cancer Center

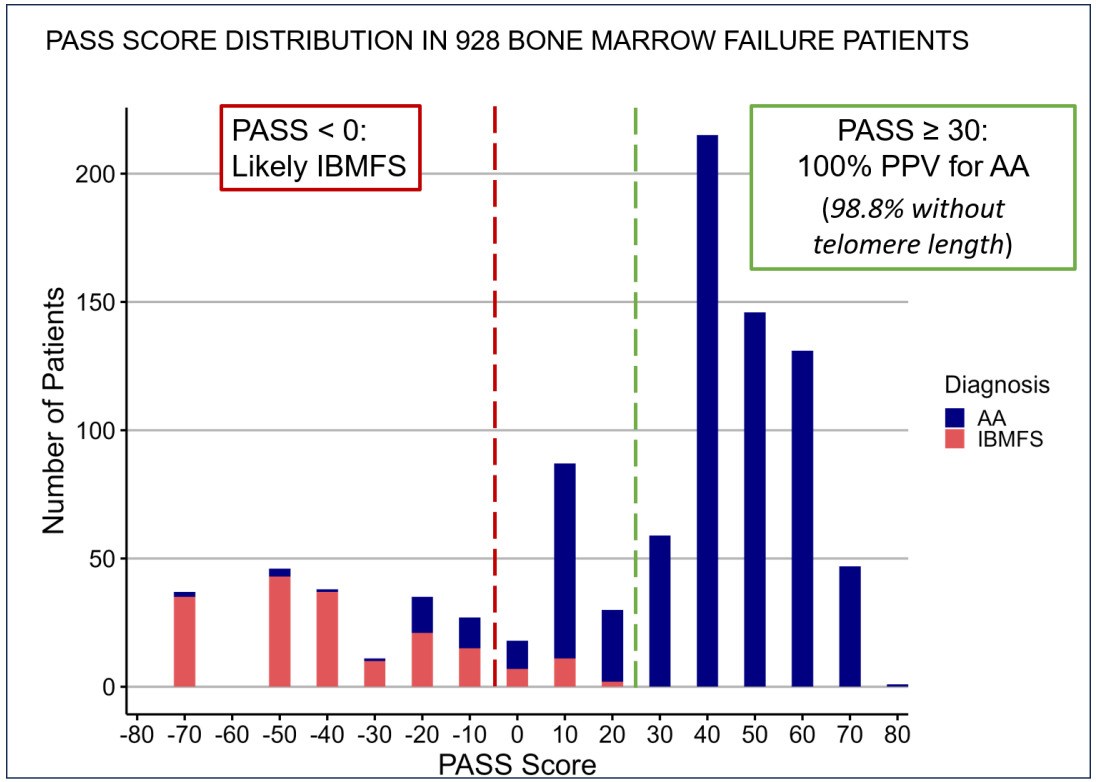
PASS can rapidly triage adult patients presenting with apparent AA

Training and Validation Combined

N = 928 (747 AA, 181 IBMFS)

ROC 0.981 (0.974 – 0.988)

- PPV for AA of PASS ≥ 30 = 100% (599/599)
- PPV for IBMFS of PASS <0 = 83.0% (161/194)
- PPV for AA for PASS 0-20: 85.2% (115/135)



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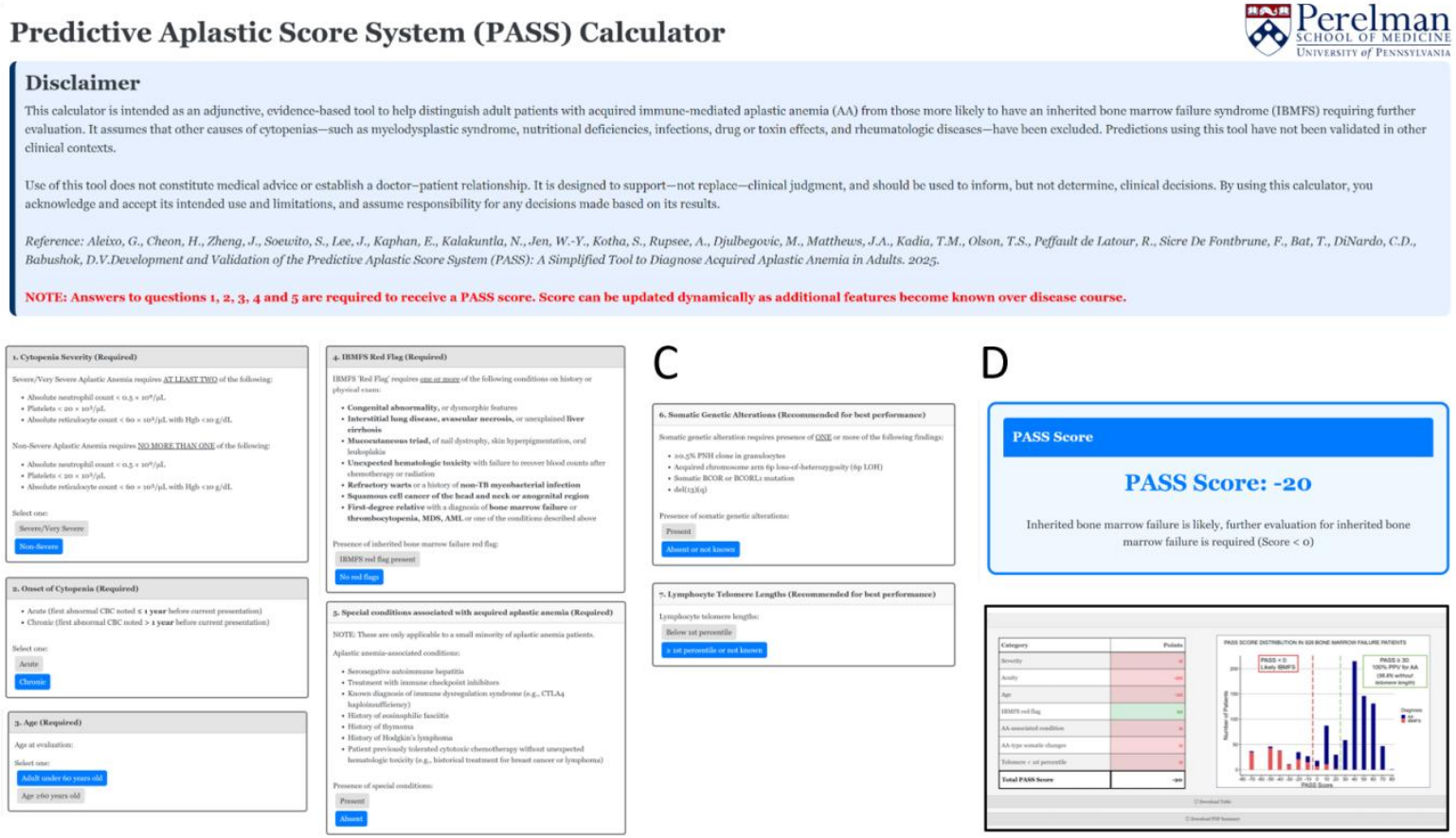
PASS Calculator Online: pennmedicine.shinyapps.io/passcalc/



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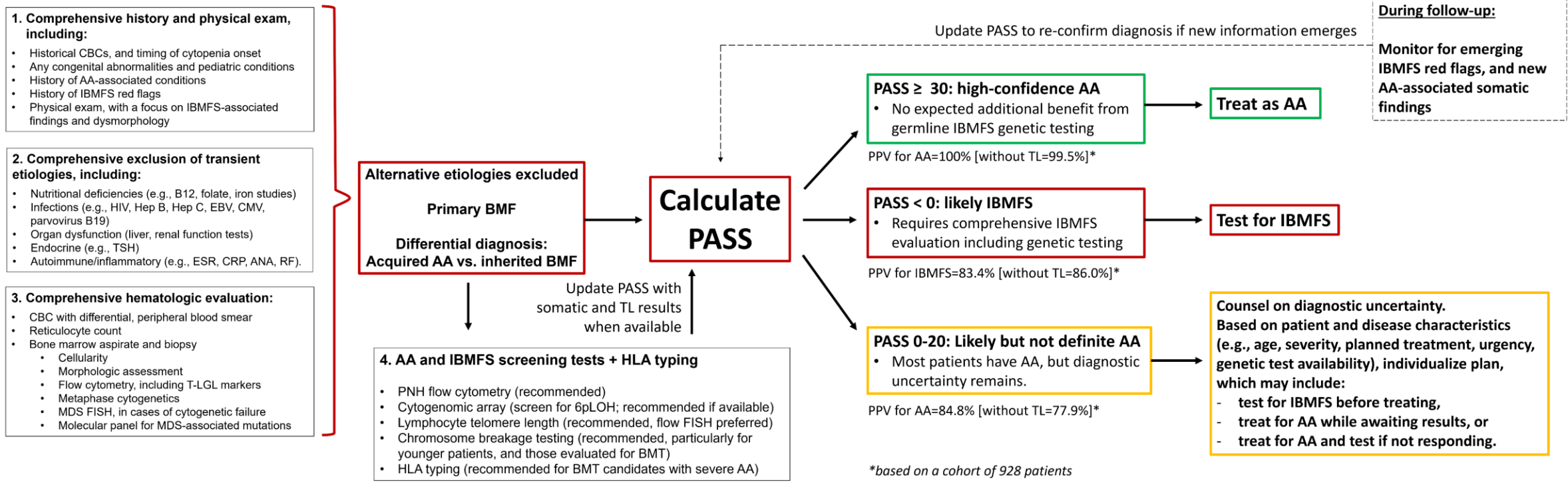
Recommended diagnostic approach for adult patients (≥ 18-years-old) with suspected acquired AA



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Thank you!

Questions?

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