



**Penn Medicine**  
Abramson Cancer Center

# Hereditary Marrow Failure Syndromes

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# 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

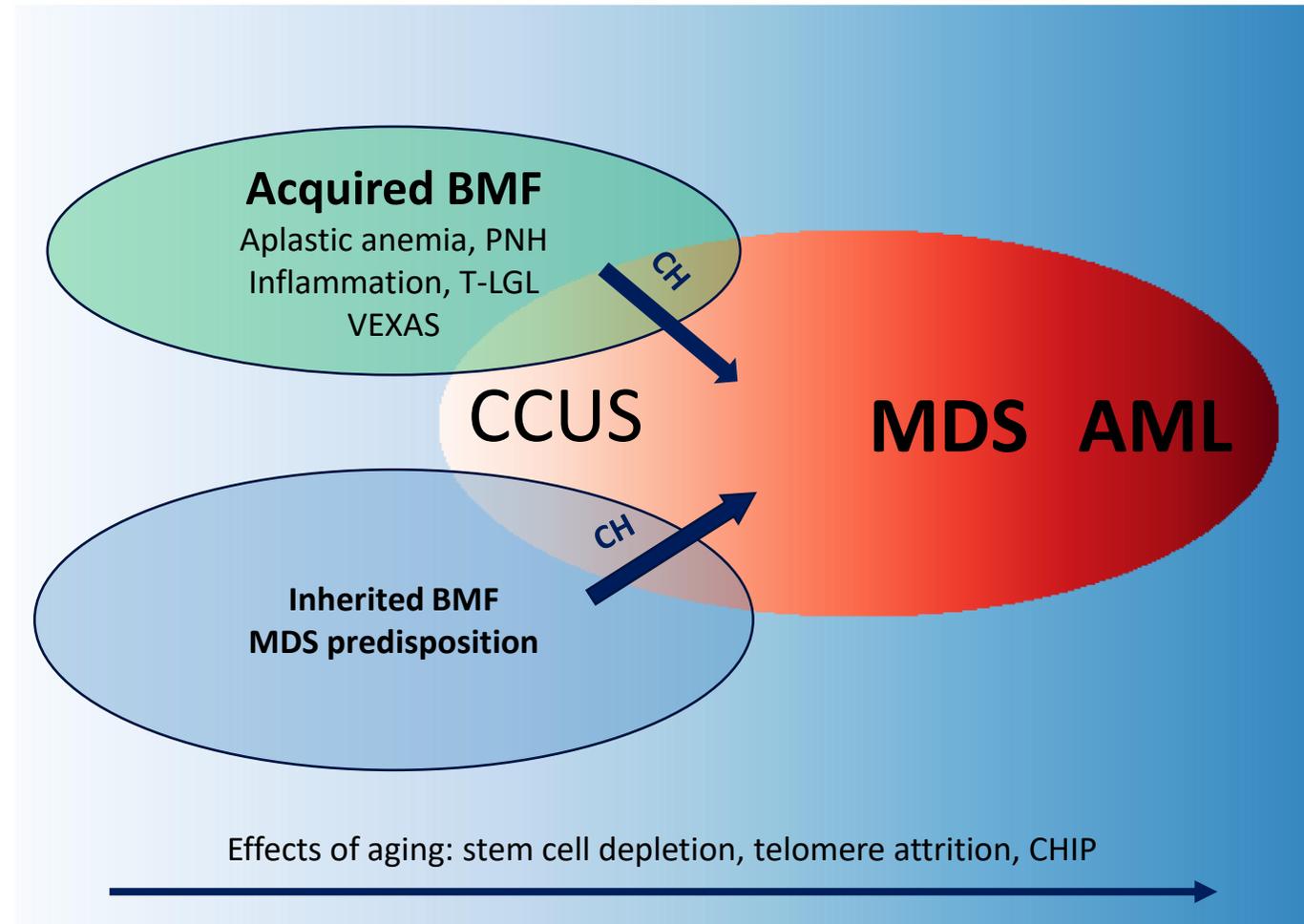
## ▶ **Past medical history**

- 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

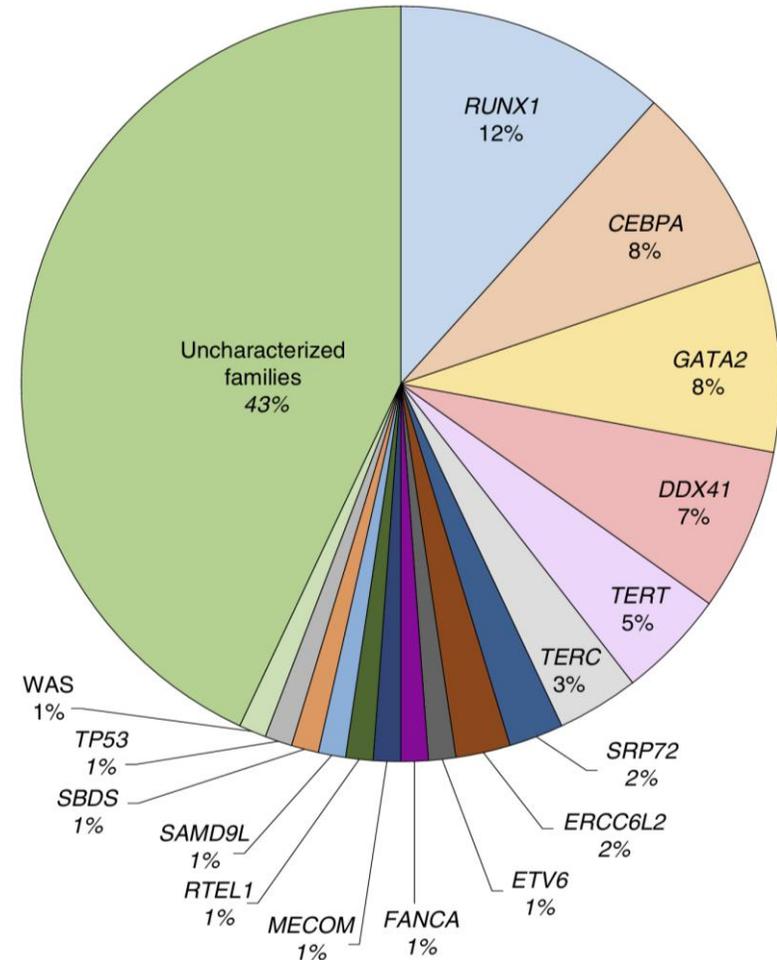
All-comer MDS patients:

- Estimated ~15% with hereditary syndromes

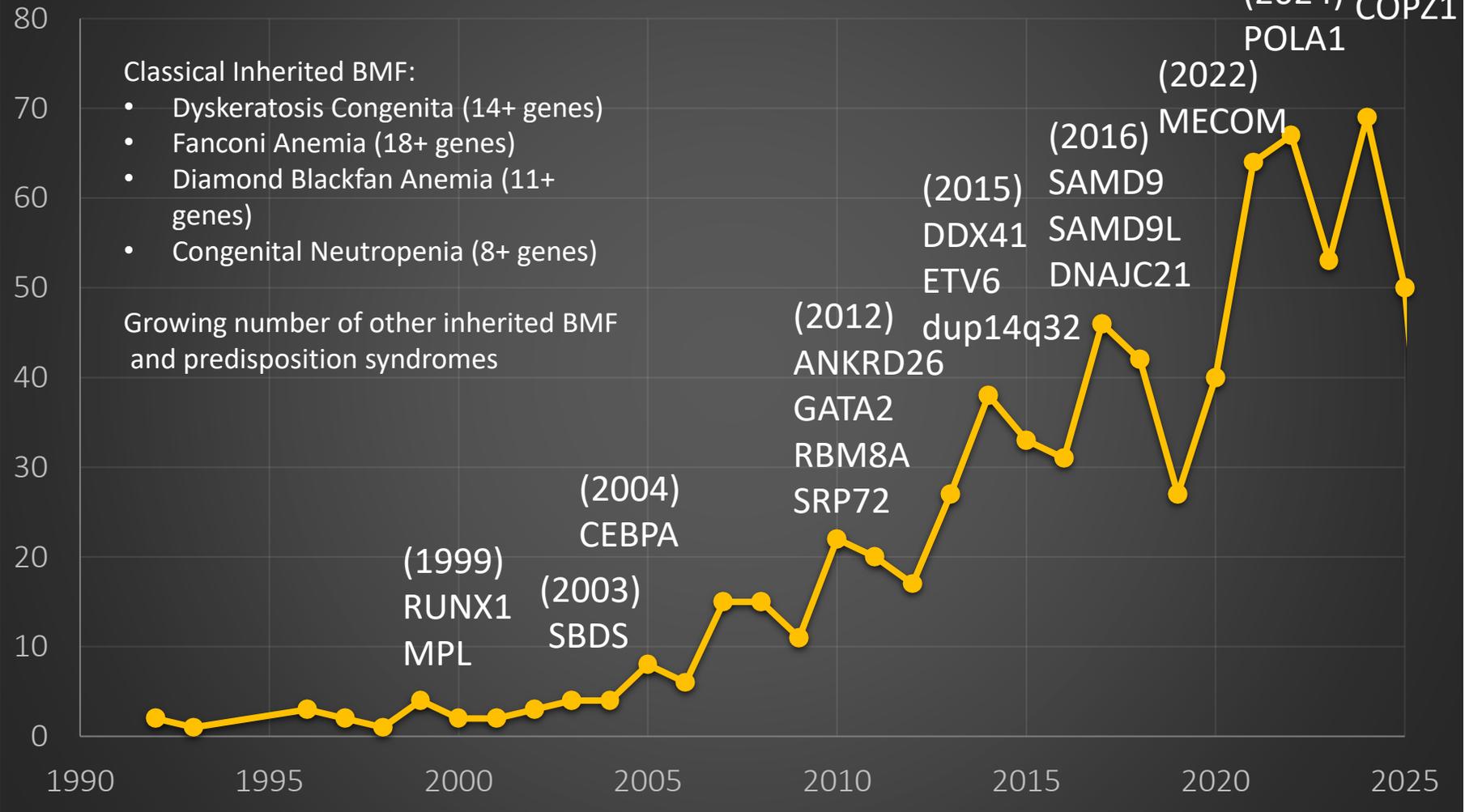
Patients with known familial MDS:

~60% with defined diagnosis

40% without defined diagnosis



## Publications on "inherited bone marrow failure"



# 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 syndromes:
  - 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

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

Autosomal-dominant

- Lymphedema
- Predisposition to MDS/AML
- Warts



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

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

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

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

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

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

## Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56<sup>bright</sup> subset

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

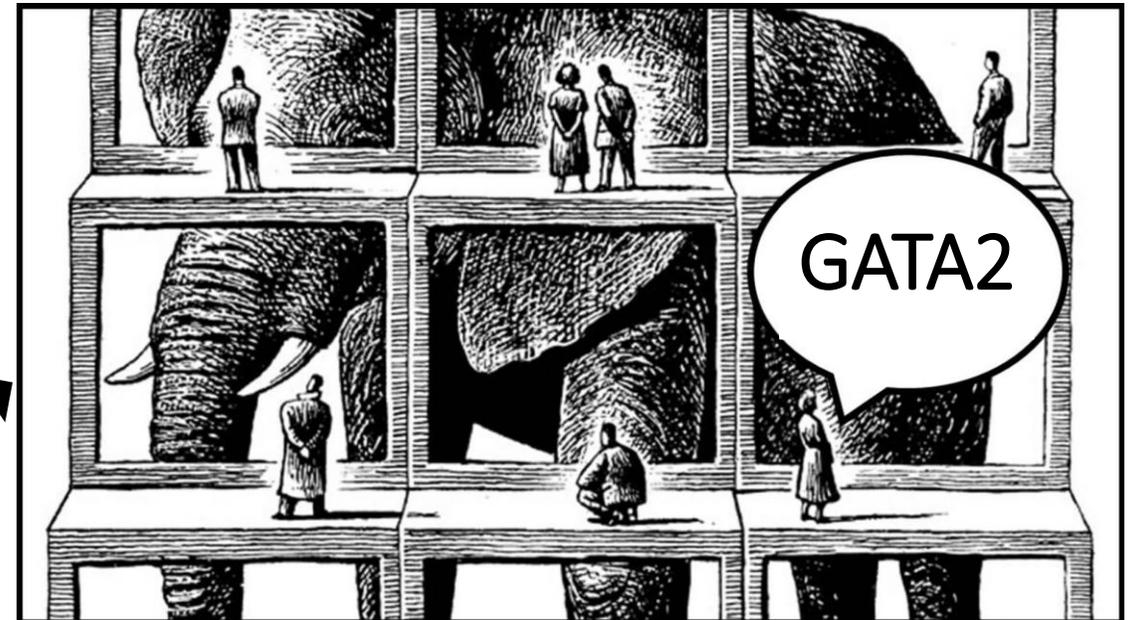
## Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)

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

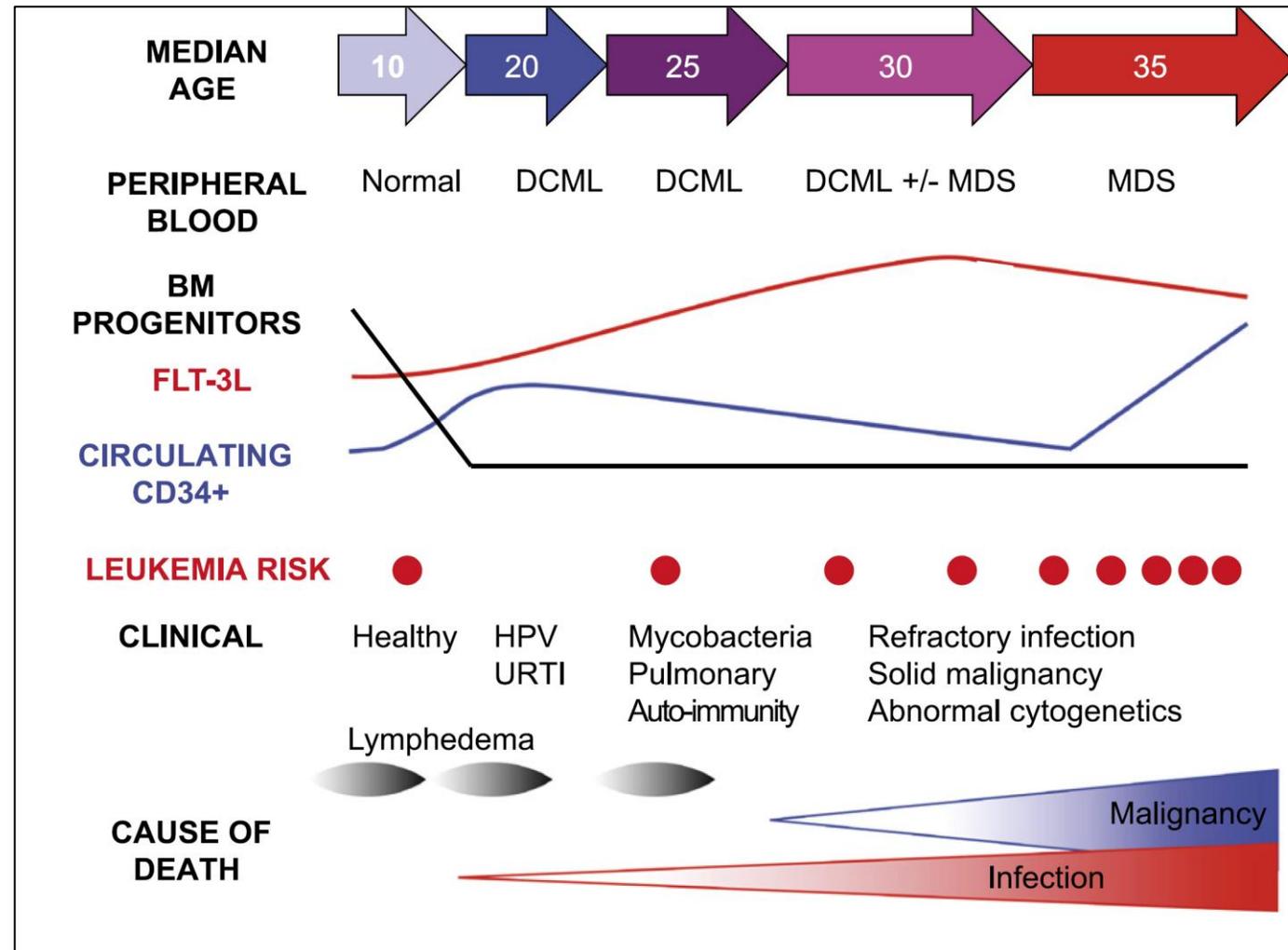
2010-2011

Convergence on *GATA2*

- MonoMAC
- Emberger

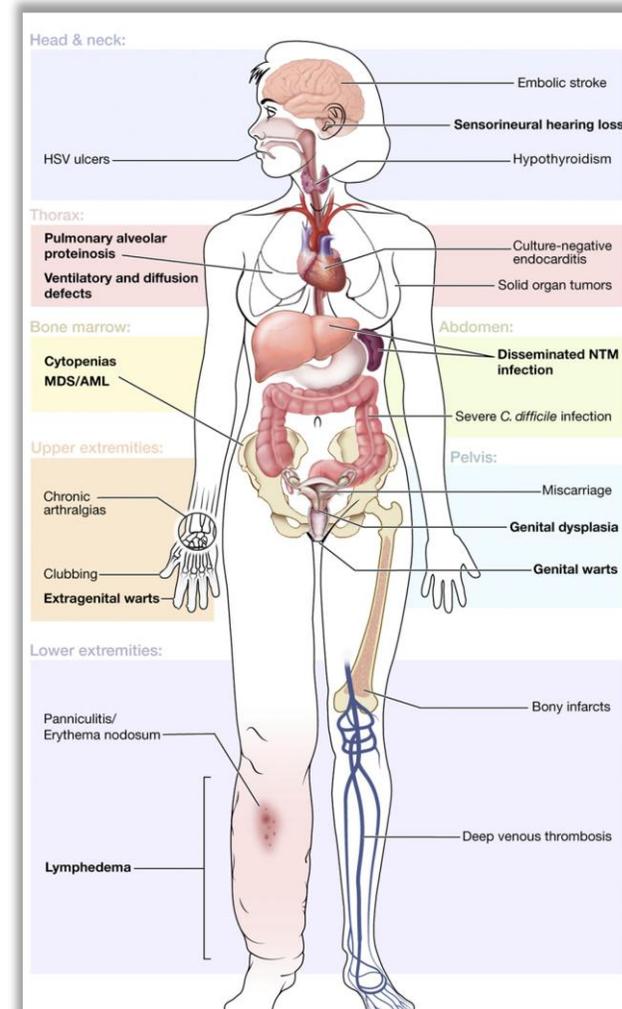


# Recognizing GATA2: evolving clinical symptoms over the lifespan



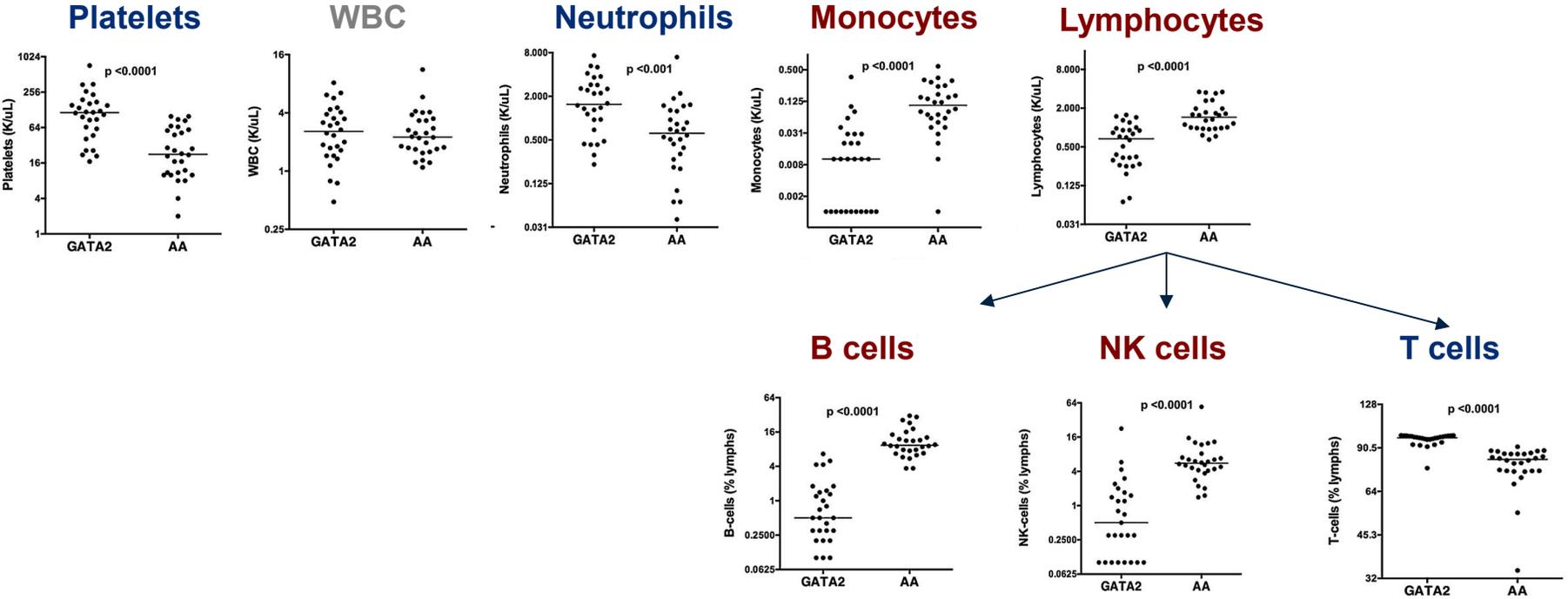
# Recognizing GATA2: clinical, pathologic and lab findings

- ▶ 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

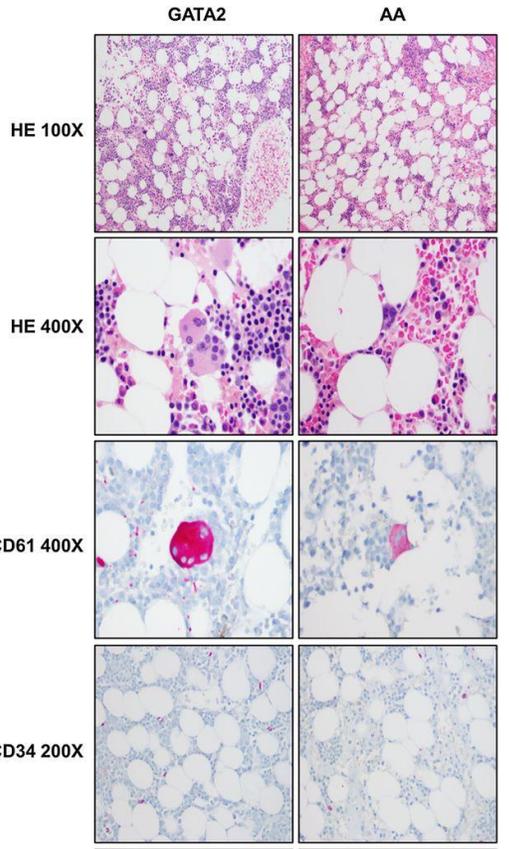


BLOOD, 6 FEBRUARY 2014 • VOLUME 123, NUMBER 6

# Hematologic findings in GATA2 deficiency vs aplastic anemia



## Bone marrow morphology

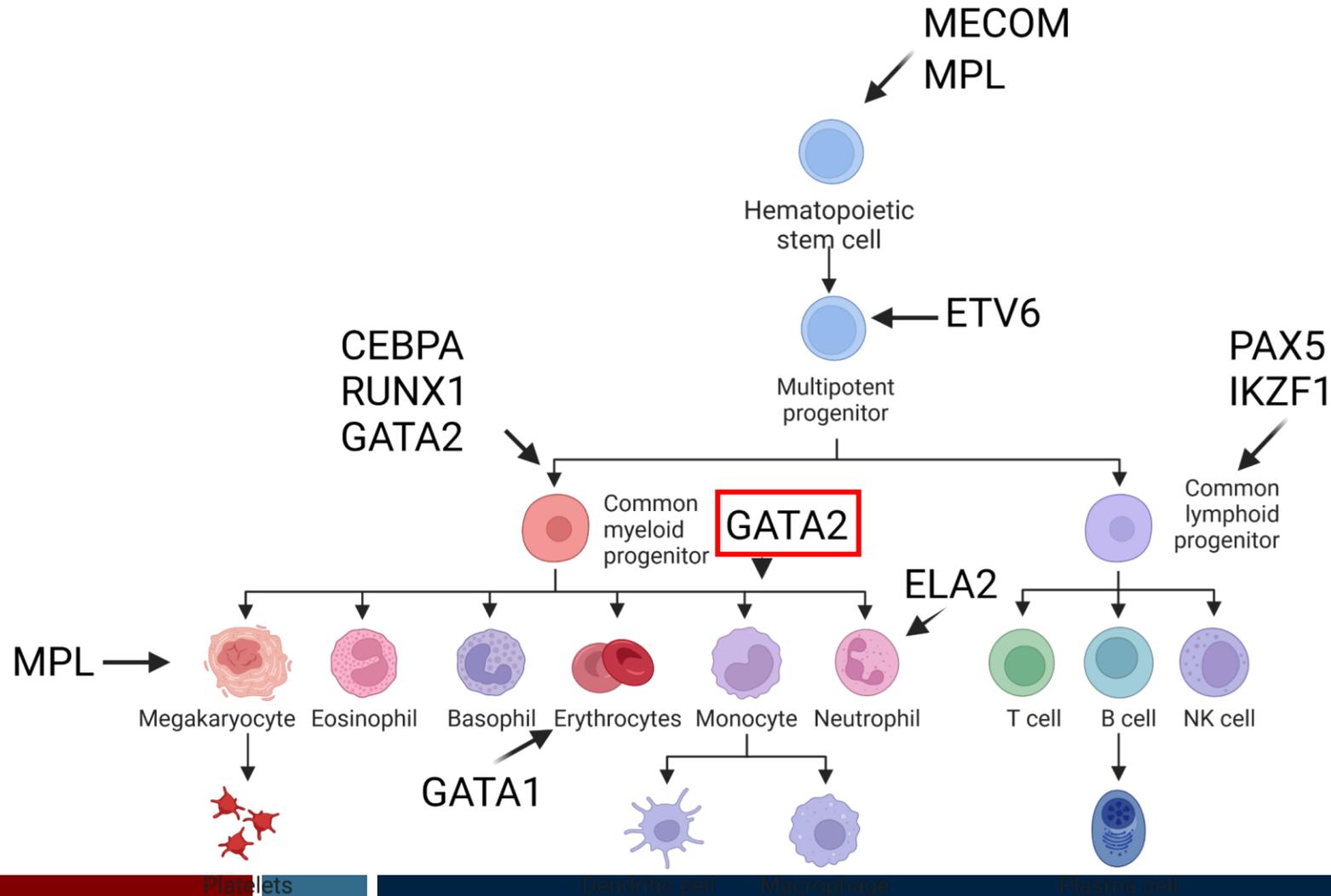


Ganapathi et al. Blood. 2014 Oct 30;125(1):56-70

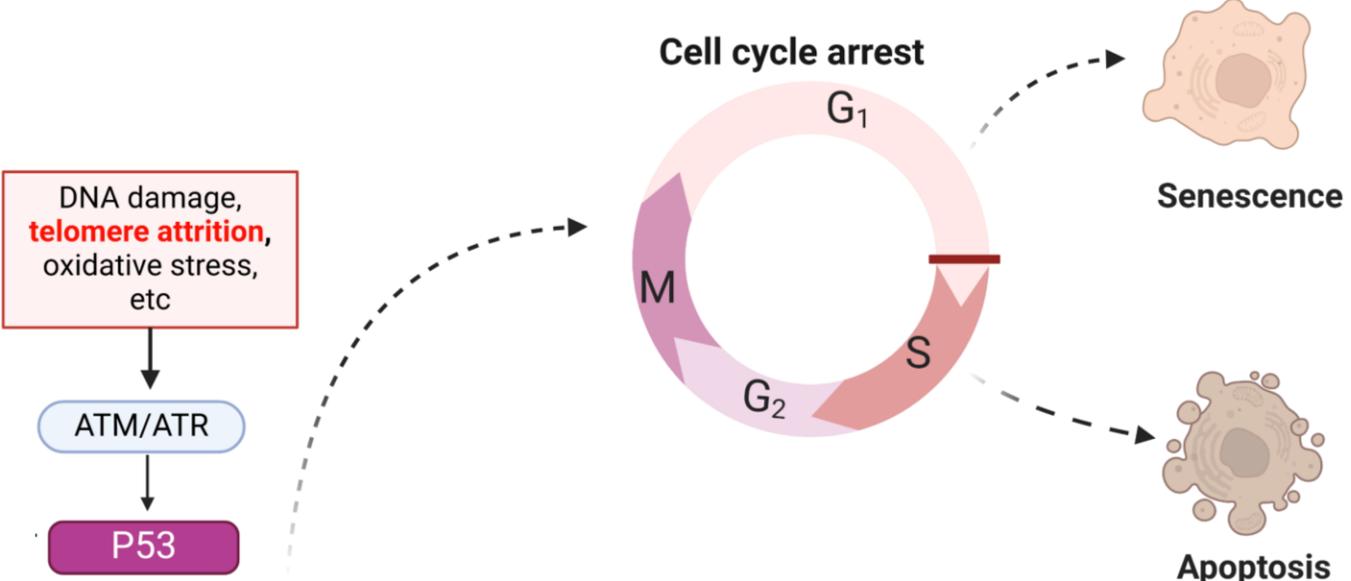
# Clinical management of GATA2 deficiency

- ▶ 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

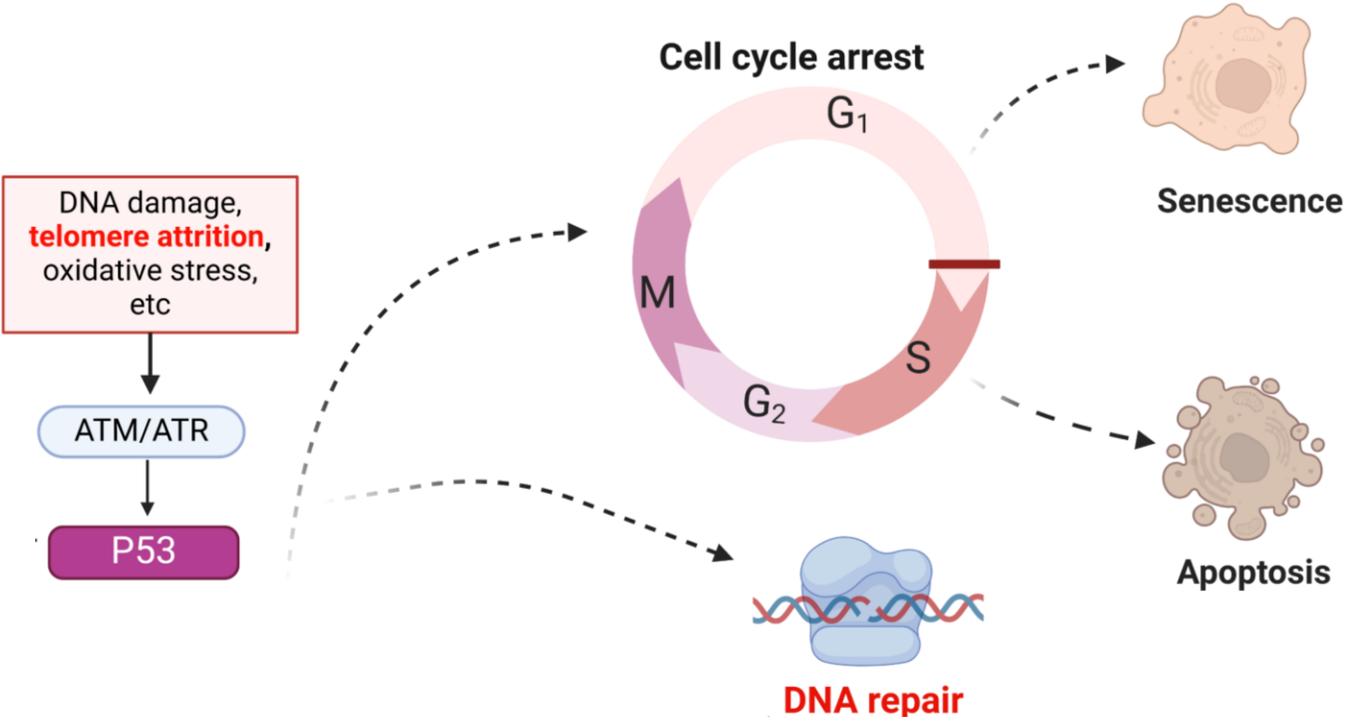
# GATA2 is one of the inherited predisposition syndromes caused by germline defects in hematopoietic regulatory genes



# Classical BMF is caused by germline disruption of core cellular pathways

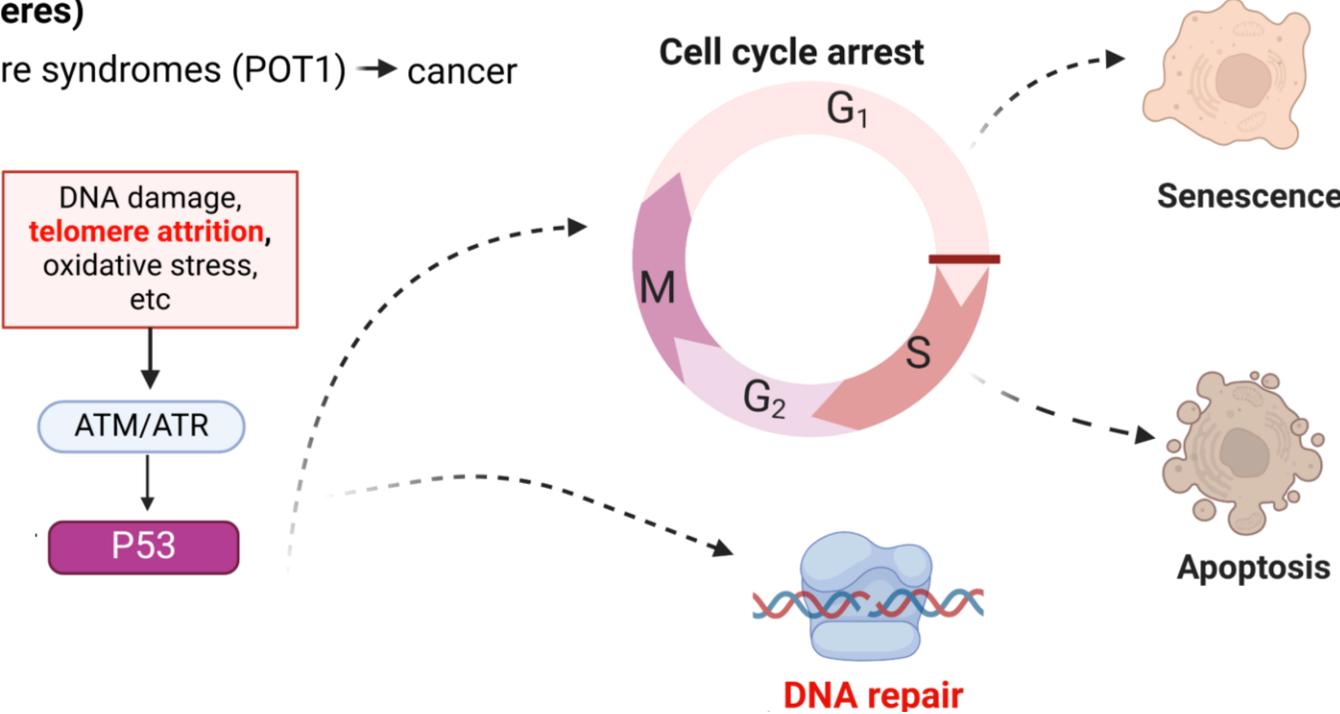


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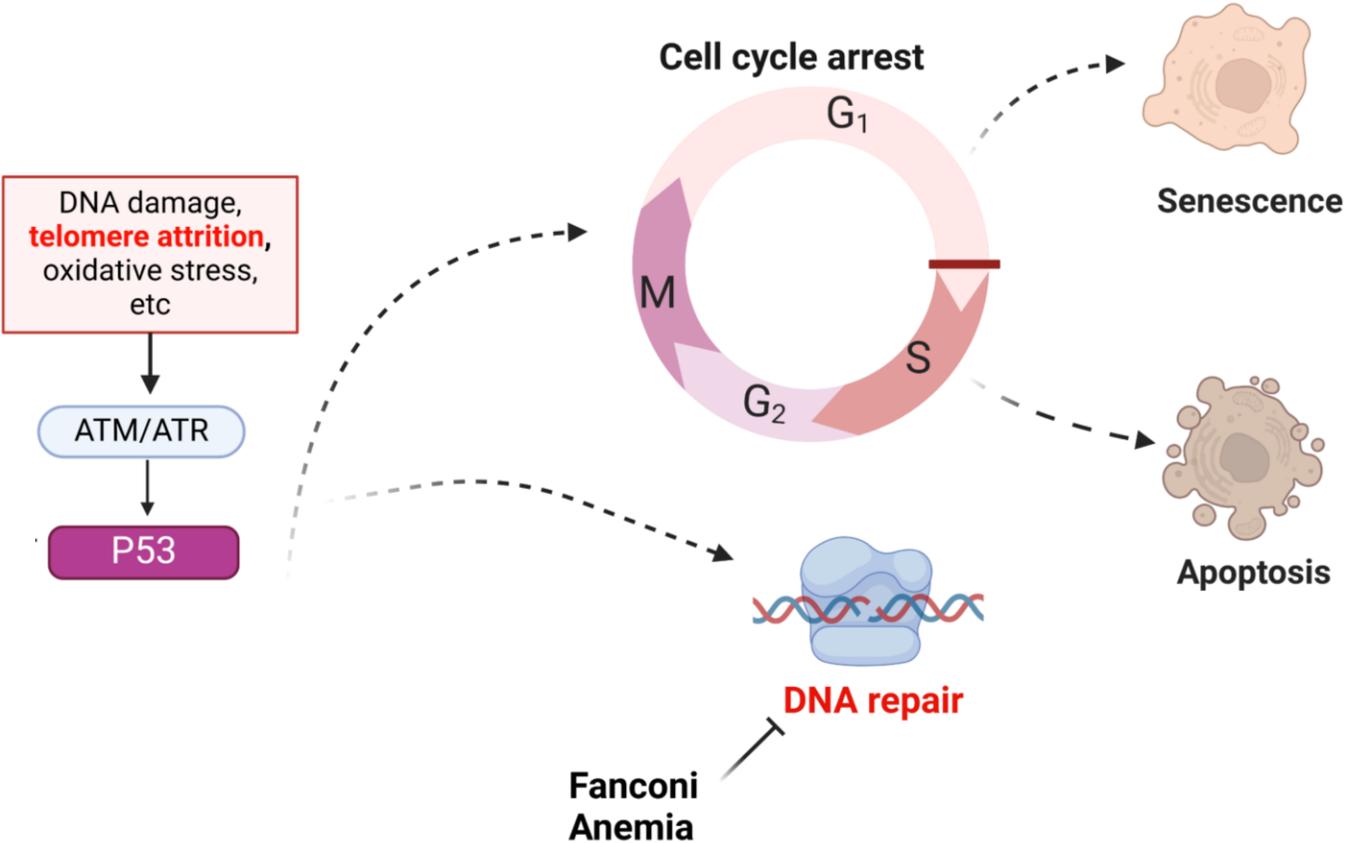


# Classical BMF: defects in telomere maintenance

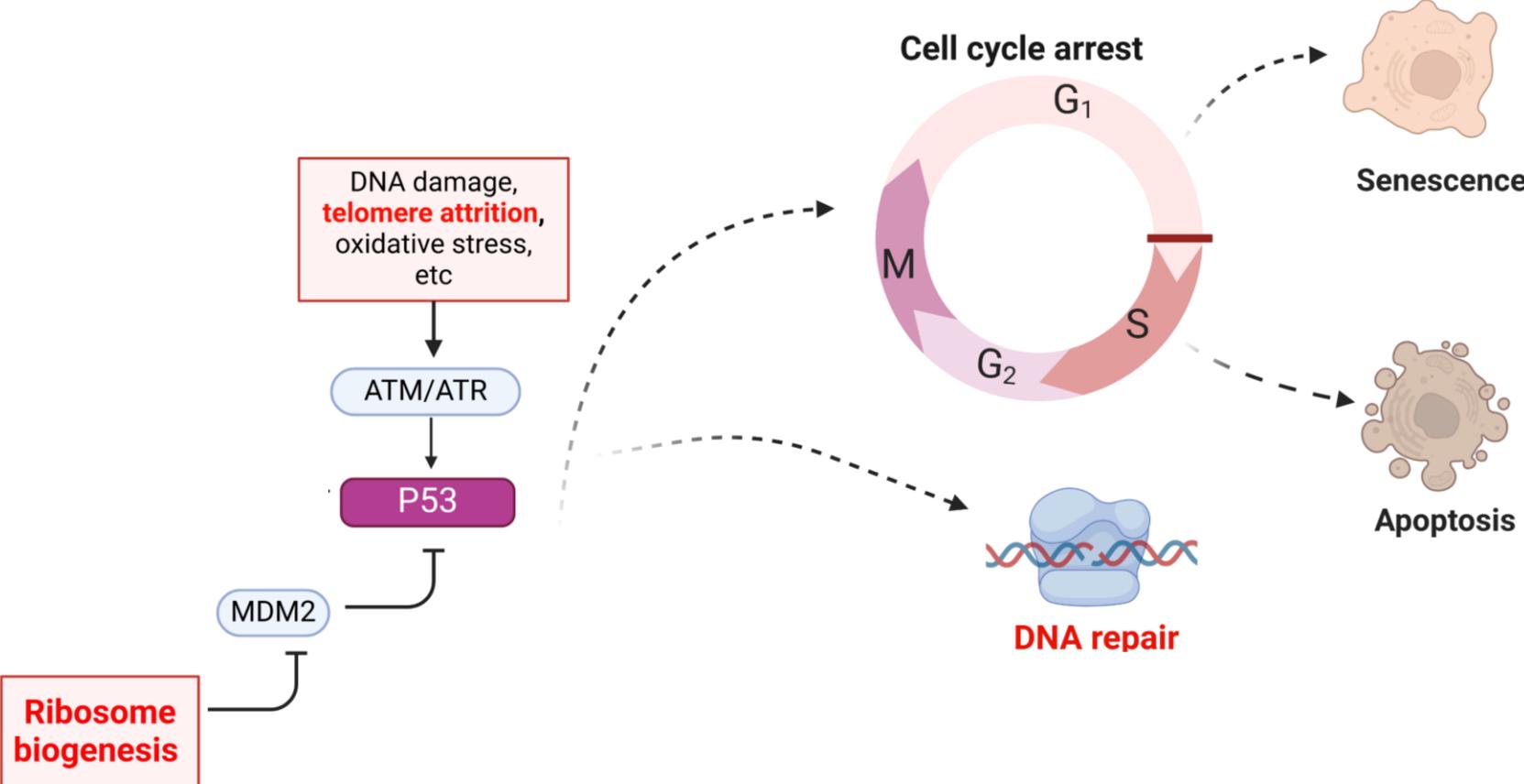
Telomere biology disorders → BMF (short telomeres)  
Long telomere syndromes (POT1) → cancer



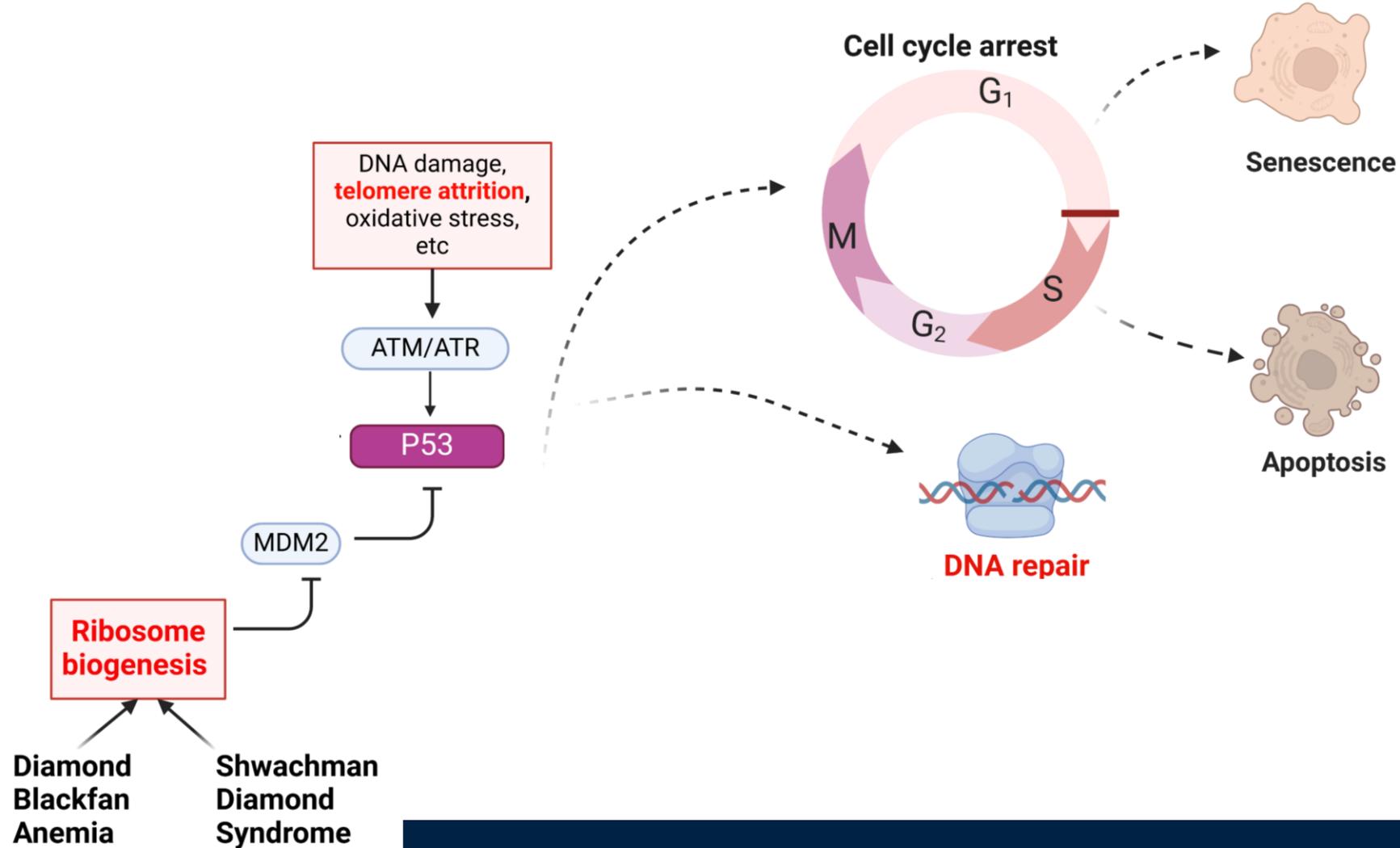
# Classical BMF: defects in DNA repair



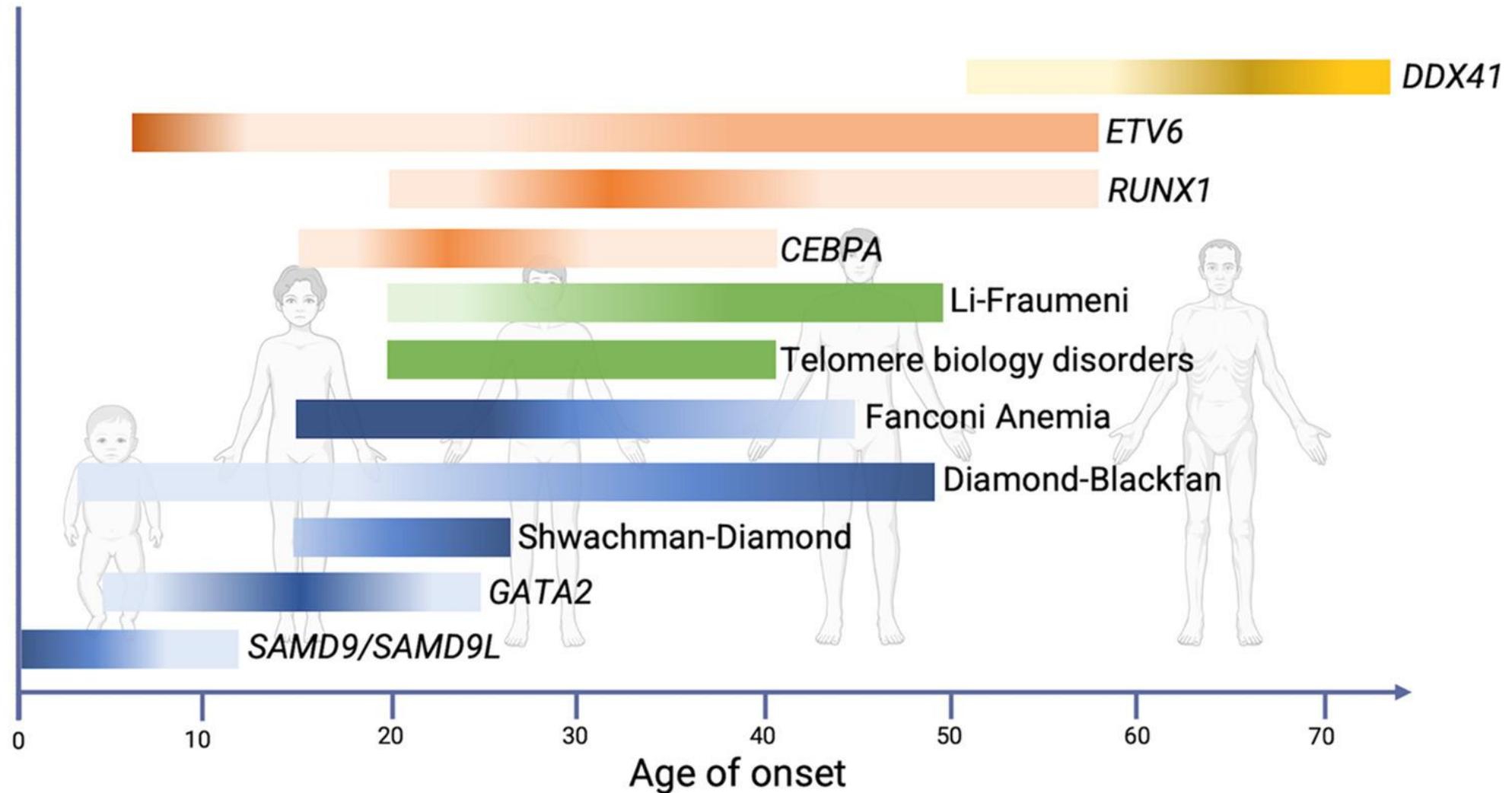
# Classical BMF: defects in ribosome biogenesis



# Classical BMF arises from germline mutations in core cellular pathways



# Inherited BMF can be diagnosed over the lifespan



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

# Hereditary BMF Syndromes

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

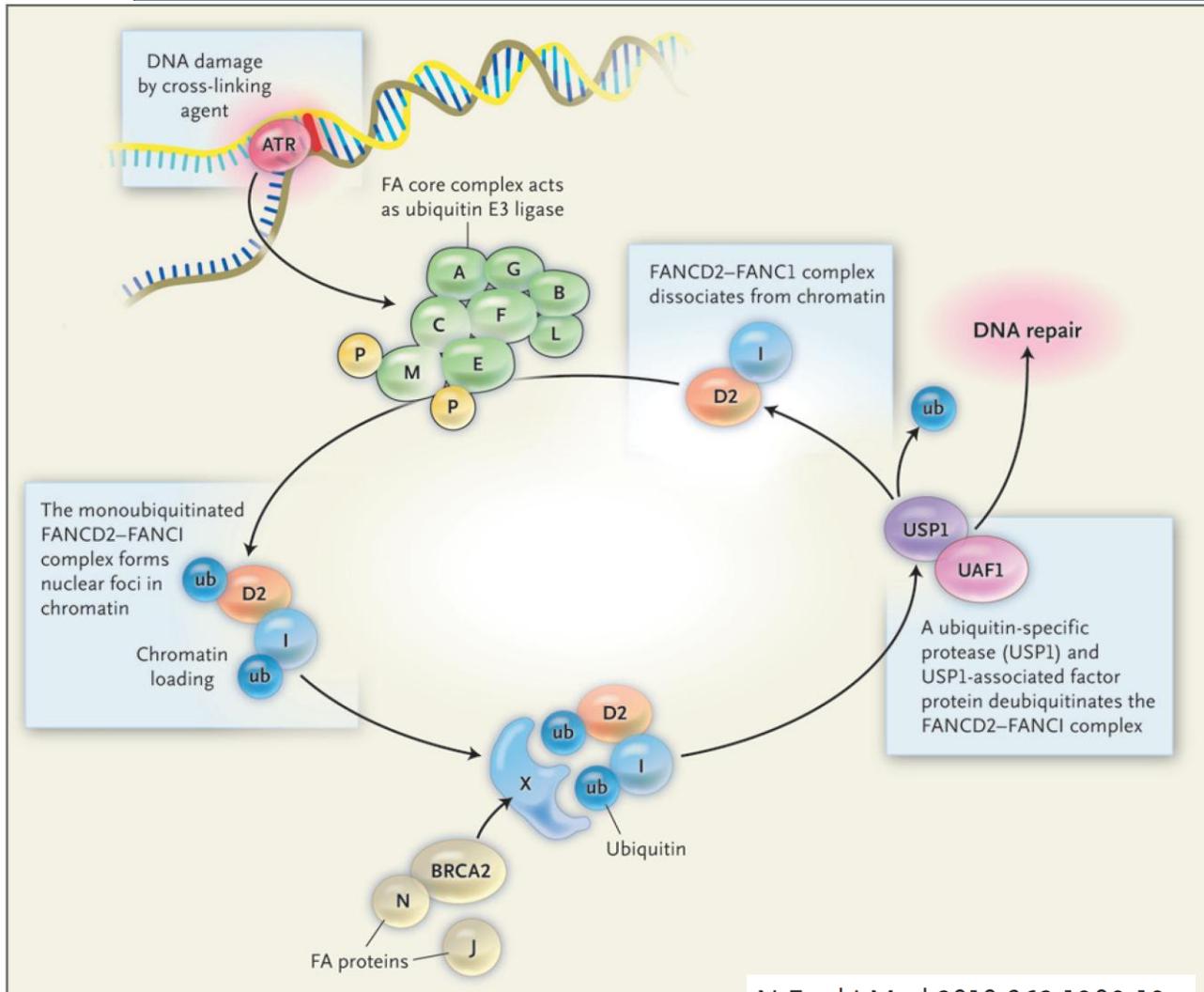
Imaging: incidental finding of congenital absence of one kidney.

## 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



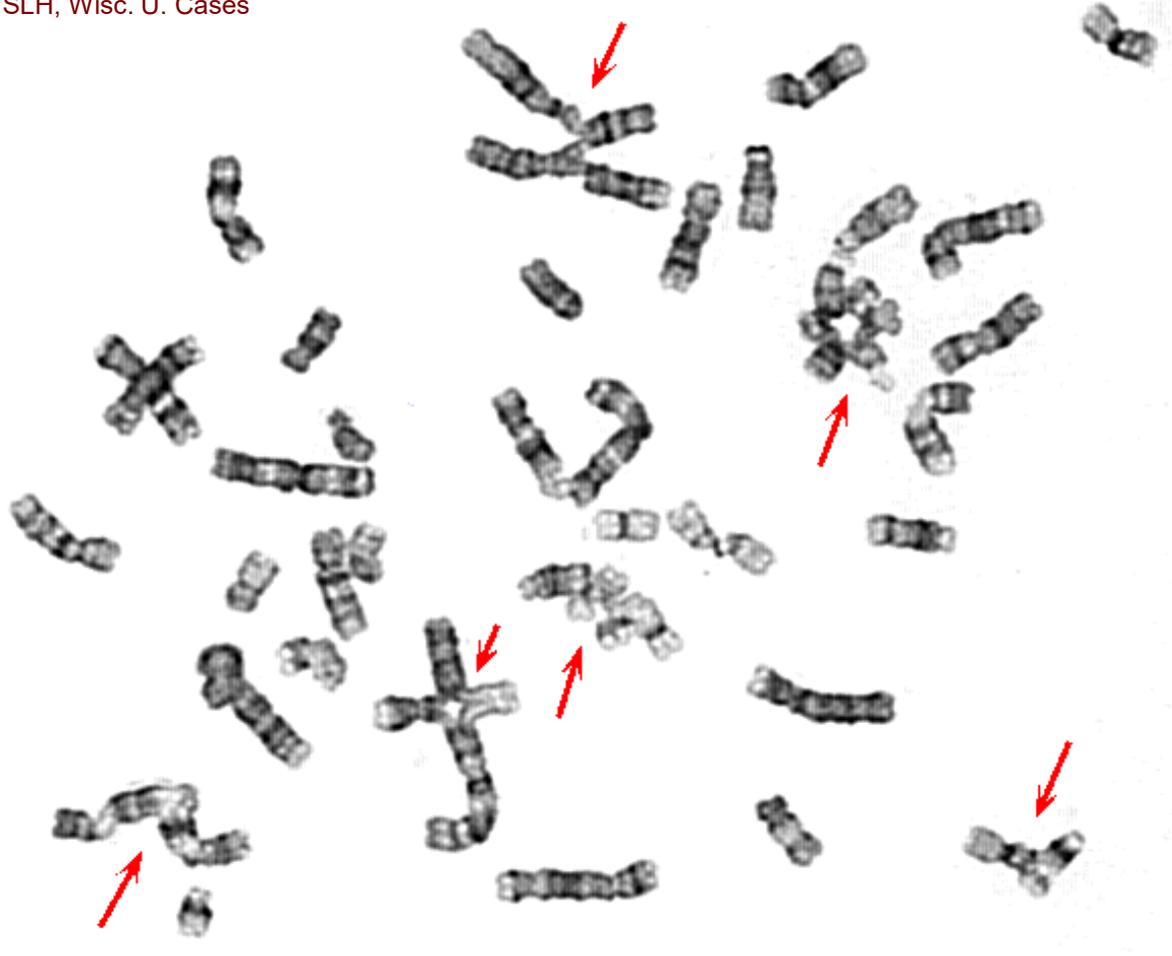
N Engl J Med 2010;362:1909-19.

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

SLH, Wisc. U. Cases



- 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

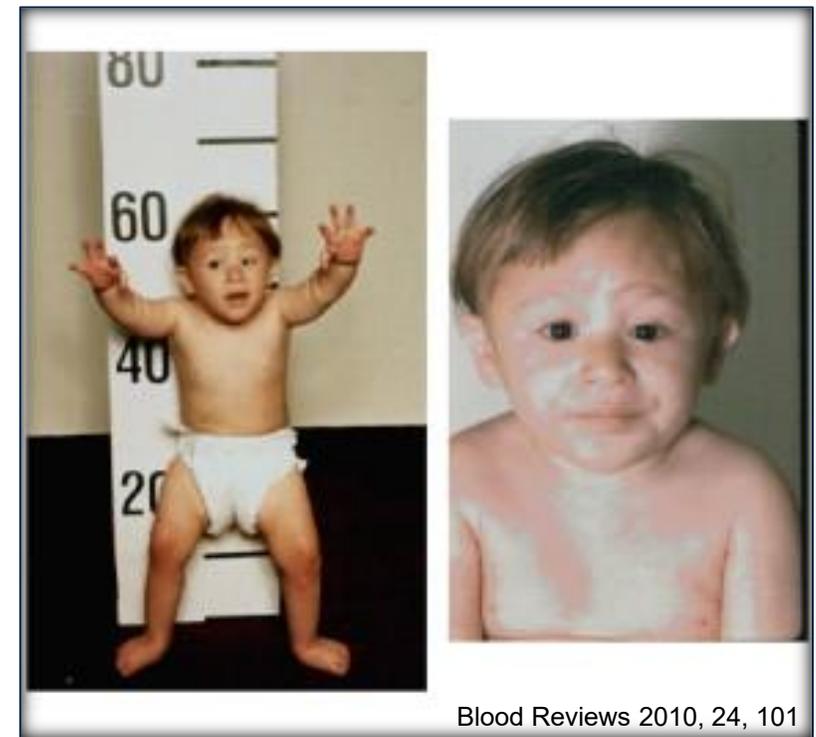
Congenital hip dislocation

Hyper- and hypopigmentation

Imperforate anus

GU anomalies

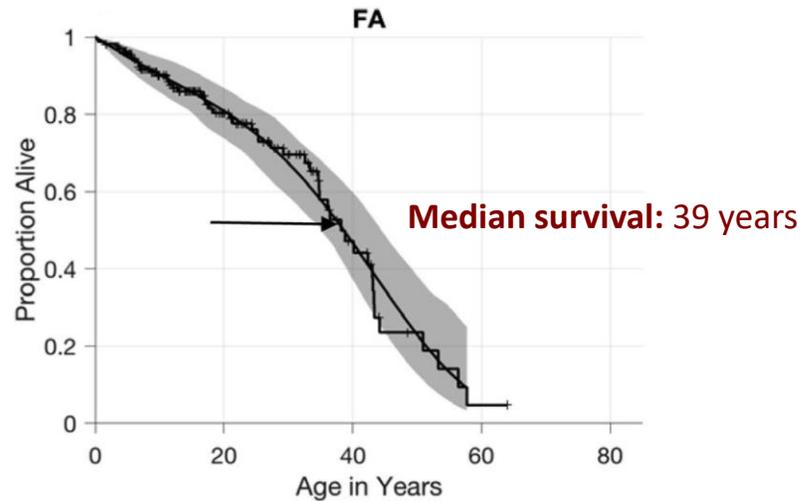
*30% have no apparent extrahematopoietic findings*



FA Handbook, Version 4, 2014

# Overall survival, BMF, MDS, AML and solid tumors

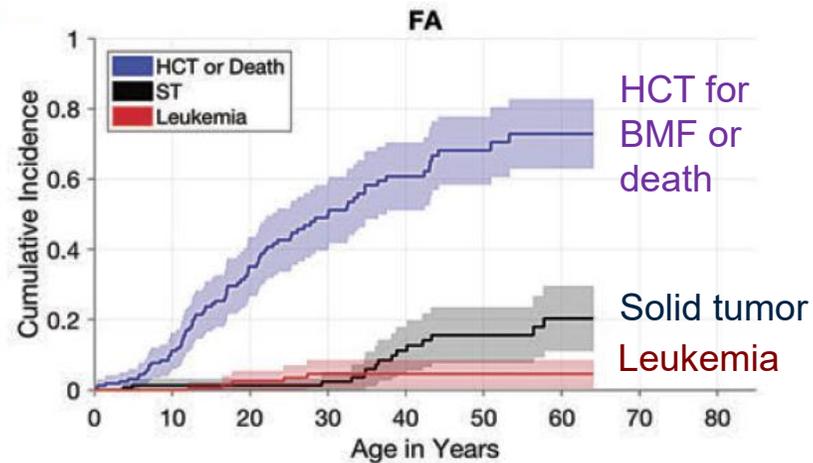
## Overall Survival



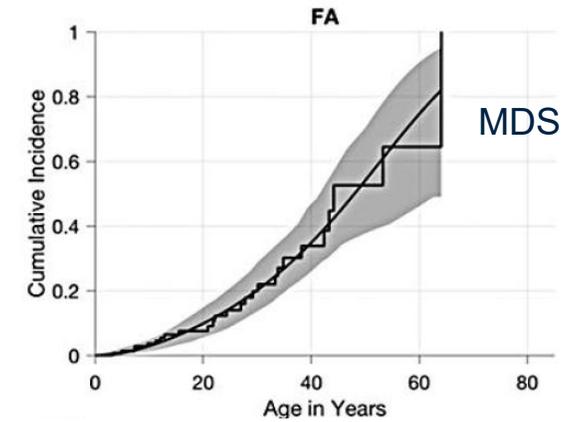
### Cumulative incidence:

- 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

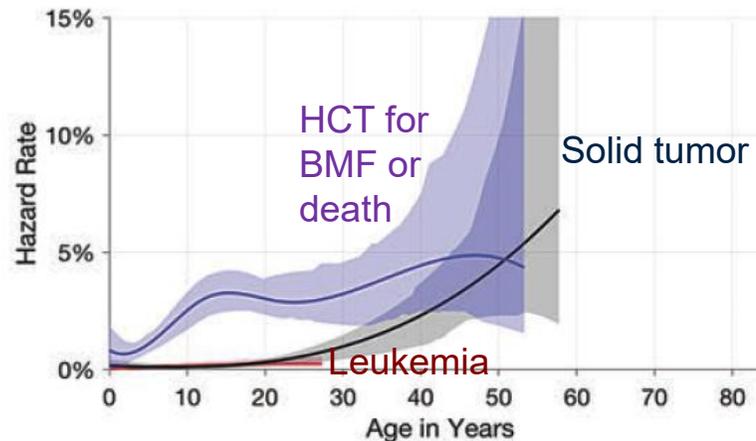
## CI of death/HCT/ST/leukemia



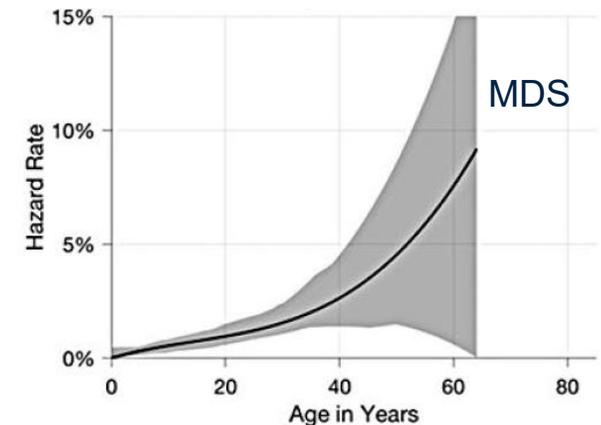
## Cumulative incidence (CI) of MDS



## Annual hazard rate

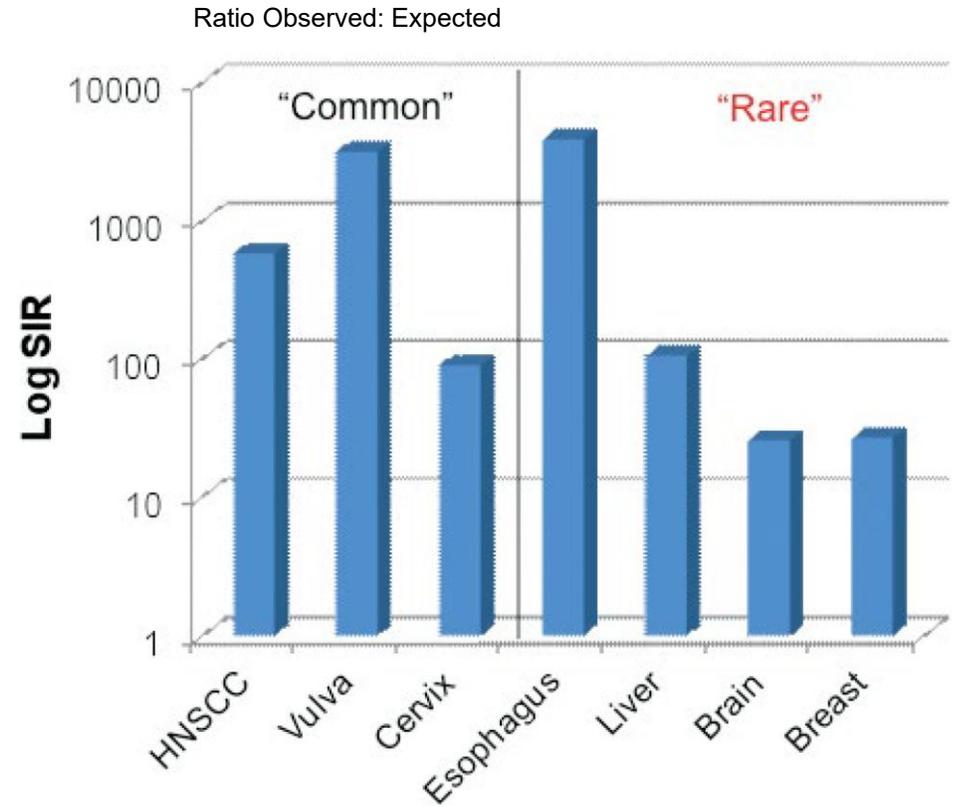
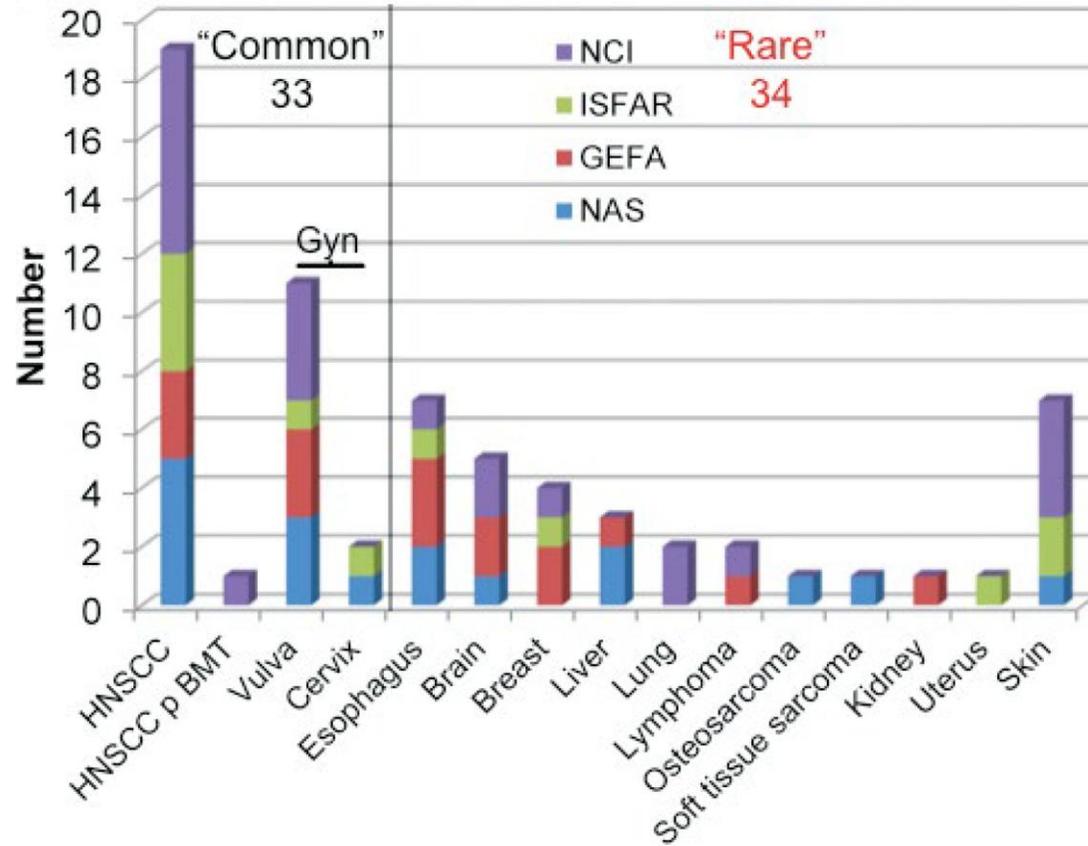


## Annual hazard rate



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

# HNSCC and Gyn cancers are most common



FA Handbook, Version 4, 2014

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](#)



Early detection of oral changes in FA

Learn basics about FA / The Lexicon

Mouth Self-Examination for smart people with increased ris... Watch later Share

POWER 2U

## mouth self examination

FOR SMART PEOPLE WITH INCREASED RISK OF ORAL CANCER

like for example individuals with Fanconi anemia

Watch on YouTube

**HOW TO EXAM?**

- Examine systematically e.g. always from right to left and top to bottom
- Illuminate the areas as much as possible e.g. use a headlamp, cell phone, flashlight or use an illuminated magnifying mirror
- Documentation: Use the mouth map & take pictures (explanations on the next pages)

**WHAT SHOULD YOU LOOK FOR?**

Note down all visible spots that look different or just don't 'look right'. Find examples of lesions at: [www.fanconi.de/icare\\_en](http://www.fanconi.de/icare_en)

**WHAT TO NOTE DOWN**

Are these new spots? How long have you noticed them? What changes do you see? What colors are the spots? What size and texture? Do they hurt or bleed? Can you imagine a reason for them?

**EXAMPLE OF DOCUMENTATION USING A MOUTH MAP**

Mark, number, describe and take a picture!

Date: 02/04/2022

**Number 1:** Has been there since 2021, no changes

**Number 2:** About there a week, slightly sore and a bit painful, white-reddish, about 0,2 inch

Download the mouth map (self-examination documentation sheet) at: [www.fanconi.de/icare\\_en](http://www.fanconi.de/icare_en)

# 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.

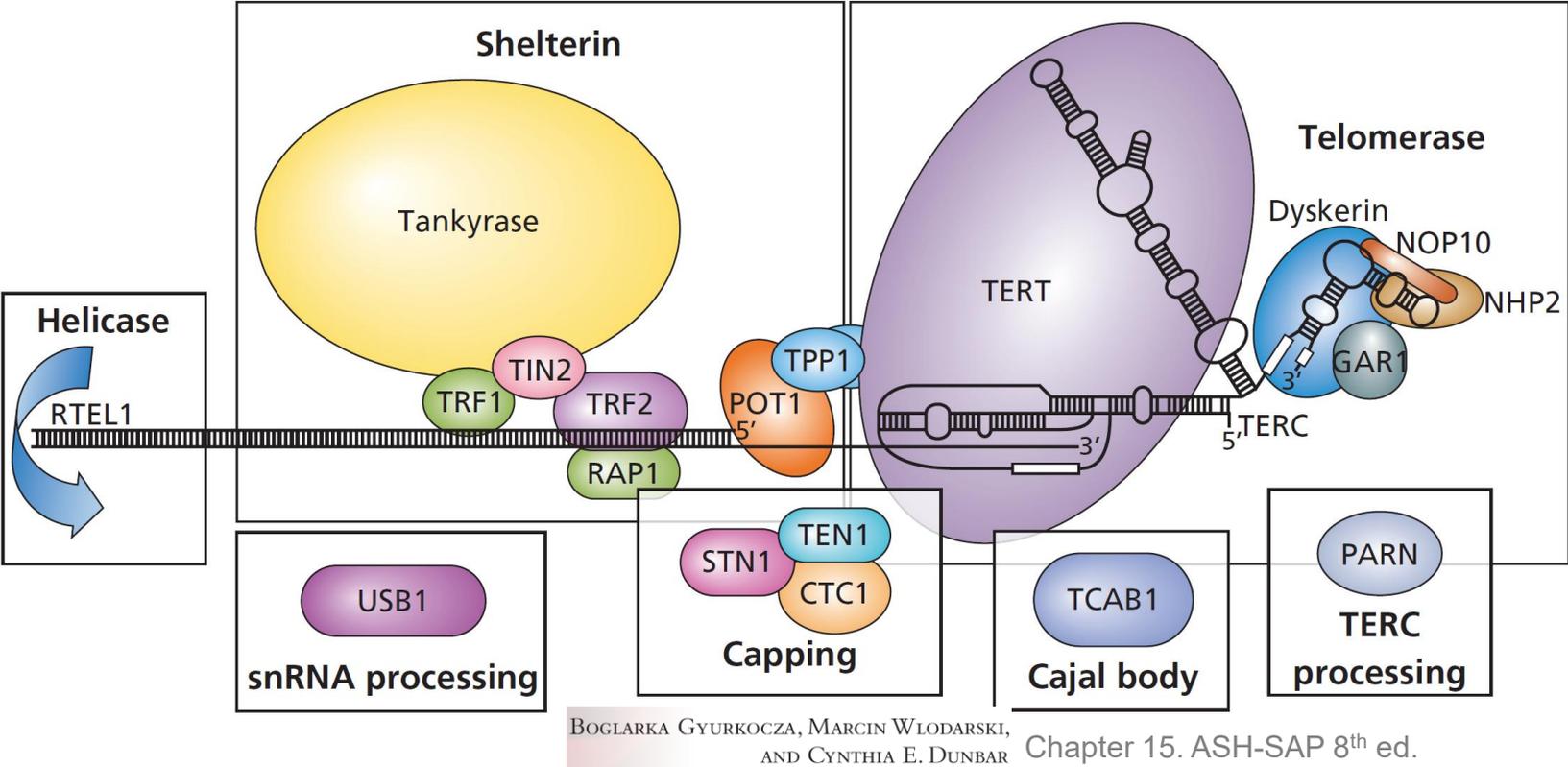
Family history: brother with thrombocytopenia.

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).

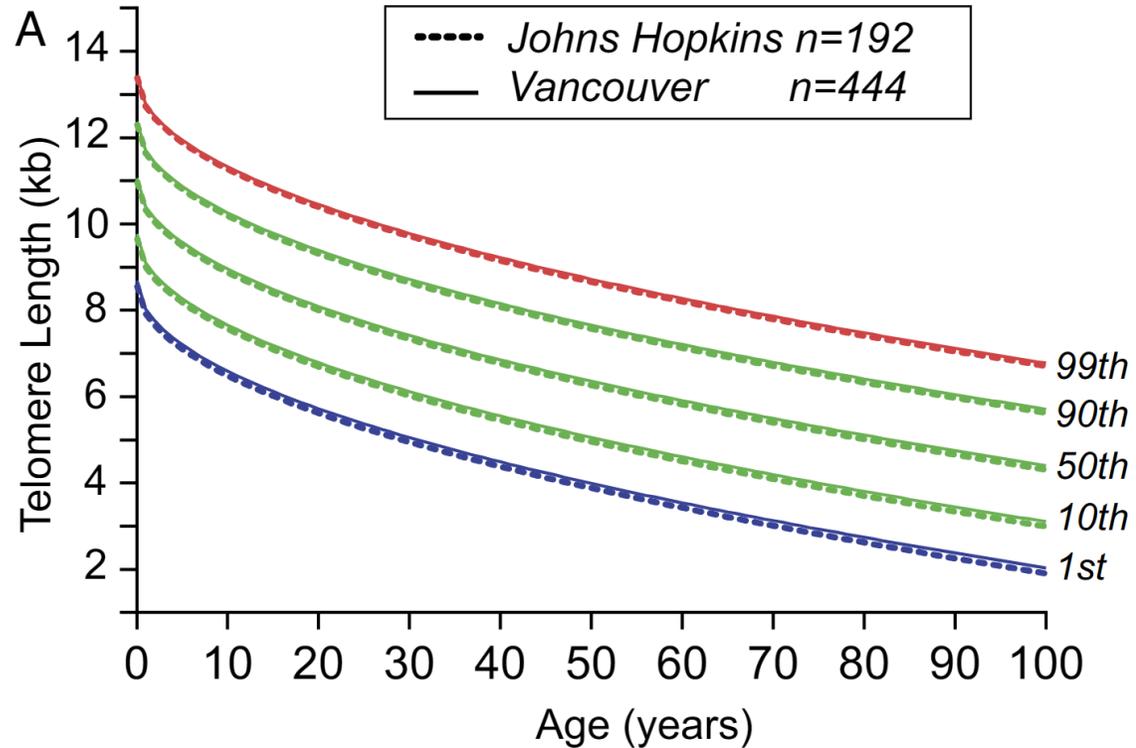
# Telomere Biology Disorders



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

BOGLARKA GYURKOCZA, MARCIN WŁODARSKI, AND CYNTHIA E. DUNBAR Chapter 15. ASH-SAP 8<sup>th</sup> ed.

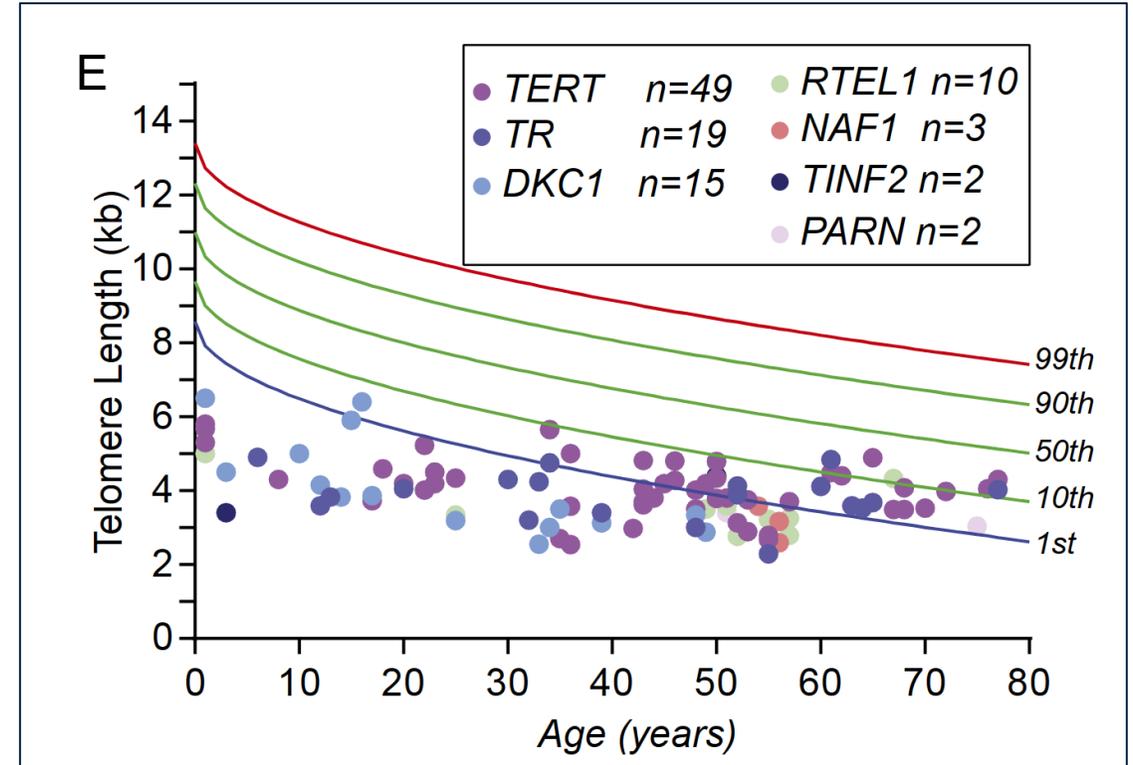
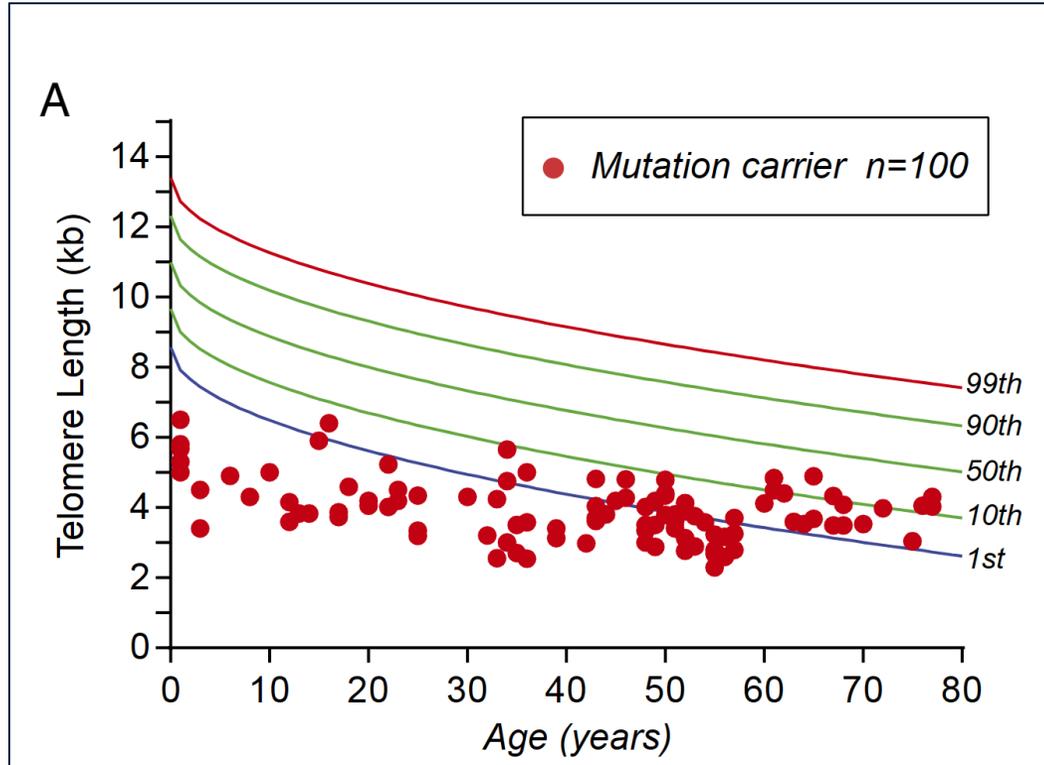
# Diagnostic test: Telomere Length Measurement (flow-FISH)



- ▶ 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

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

# 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

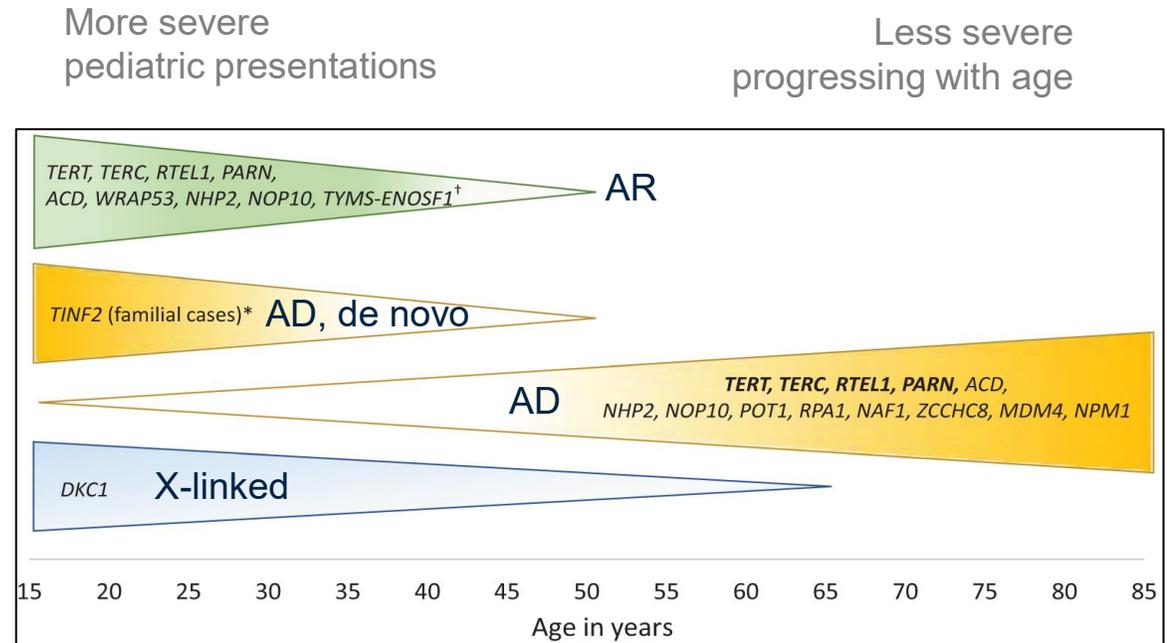
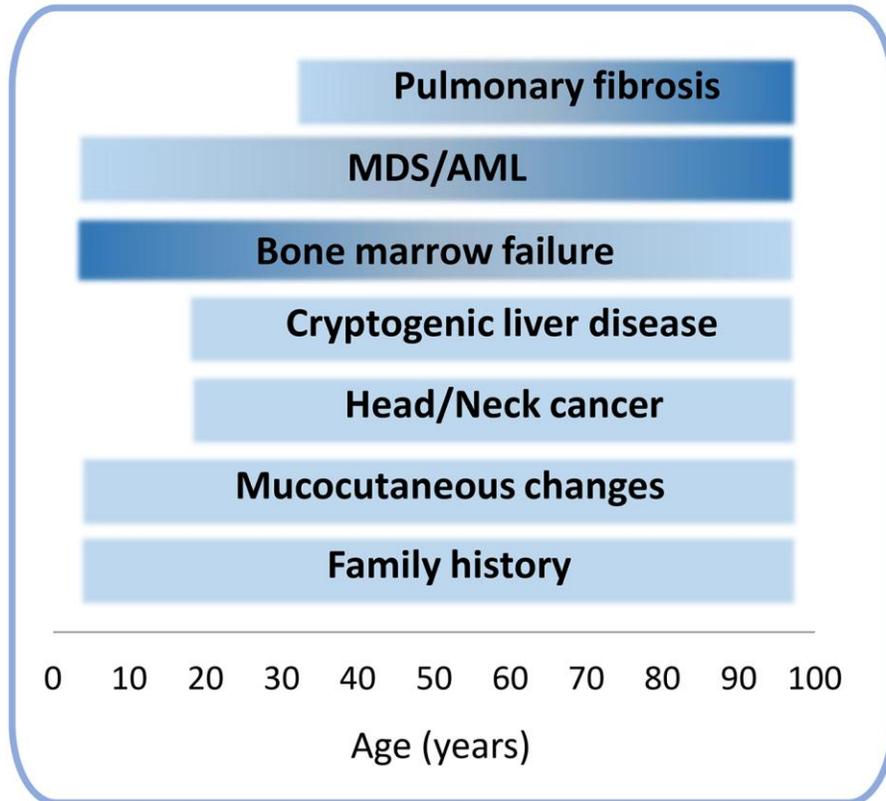


Nail dystrophy



# Genetically Heterogeneous Multisystem Progressive Disease

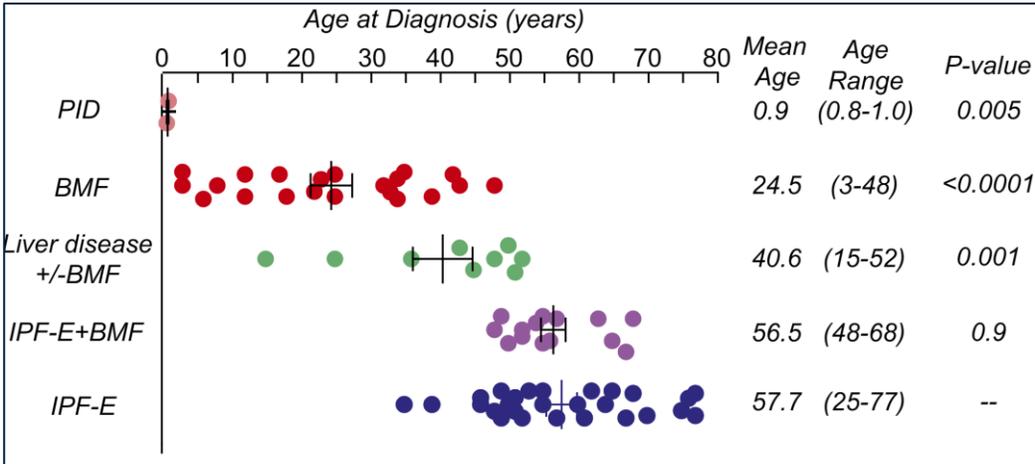
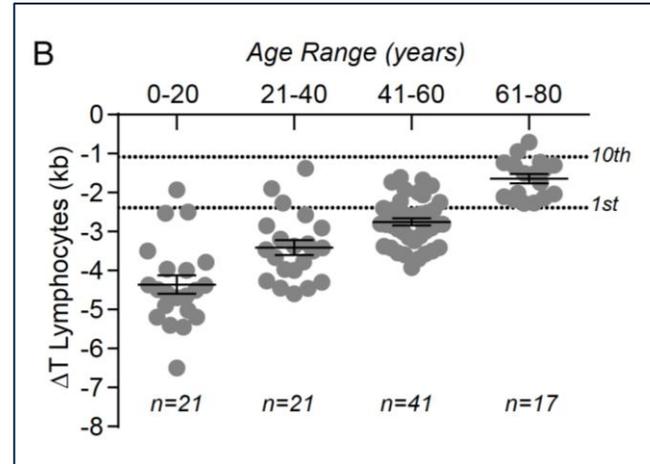
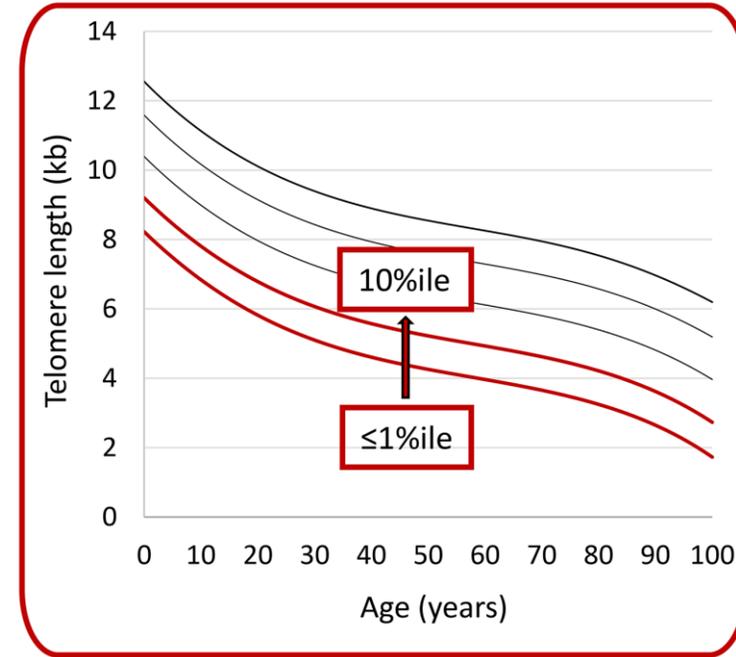
## Clinical features



Niewisch, et al. Hematology, 2023

# Age and clinical symptom-dependent TL thresholds

## Telomere length measurement

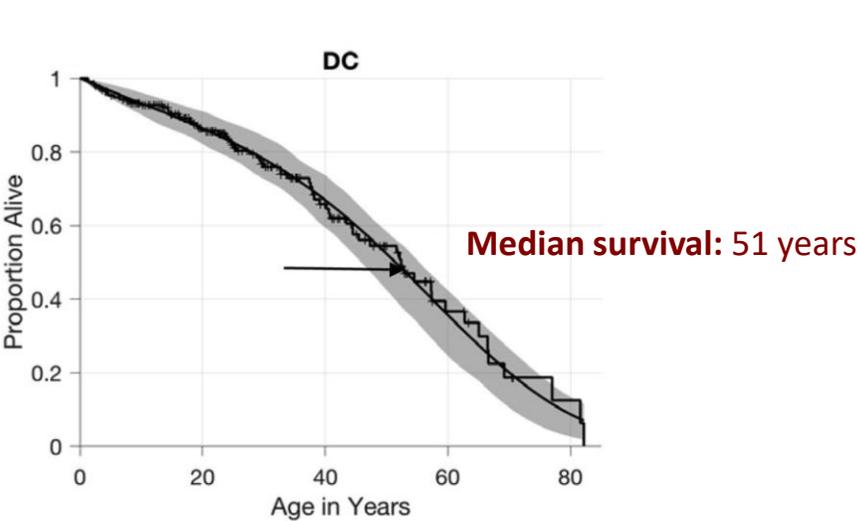


Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

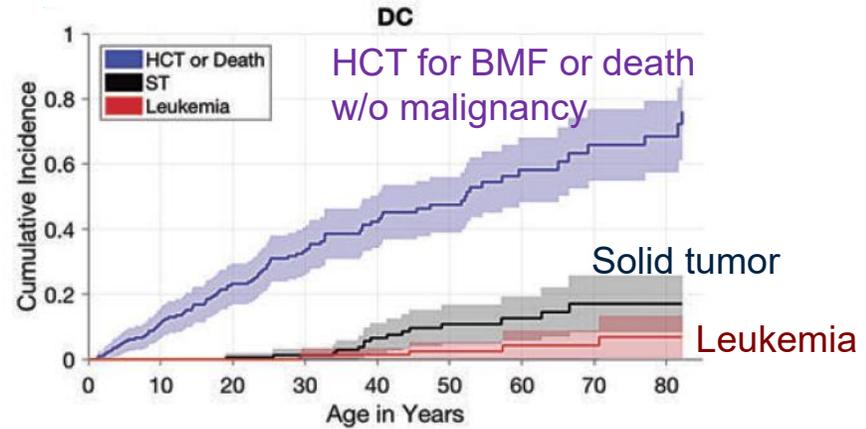
Niewisch, et al. Hematology, 2023

# Overall survival, BMF, MDS, AML and solid tumors

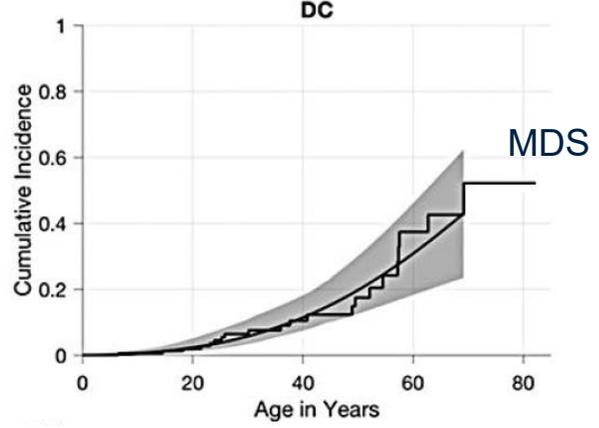
## Overall Survival



## CI of death/HCT/ST/leukemia



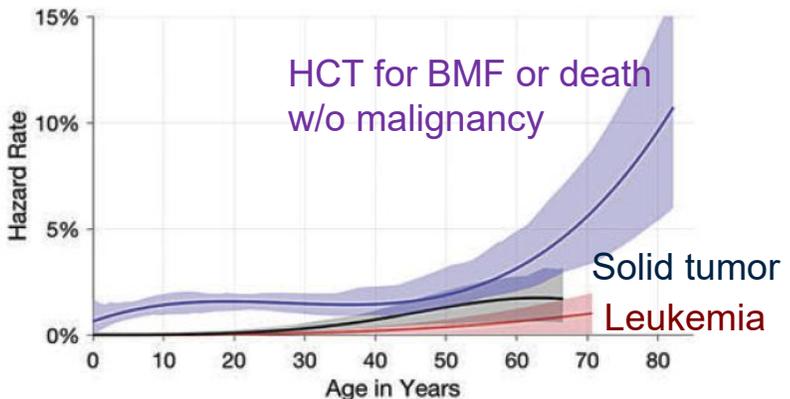
## CI of MDS



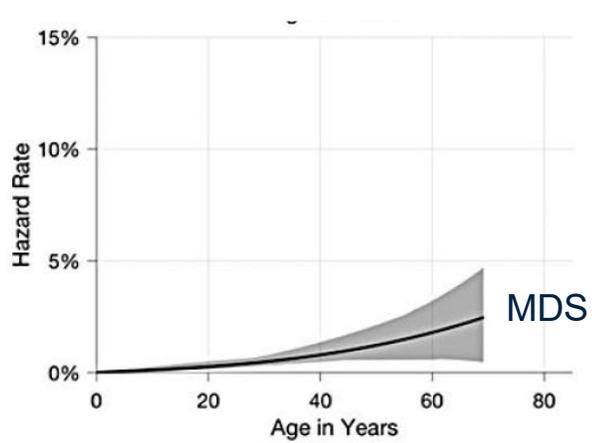
### Cumulative incidence:

- 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

## 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

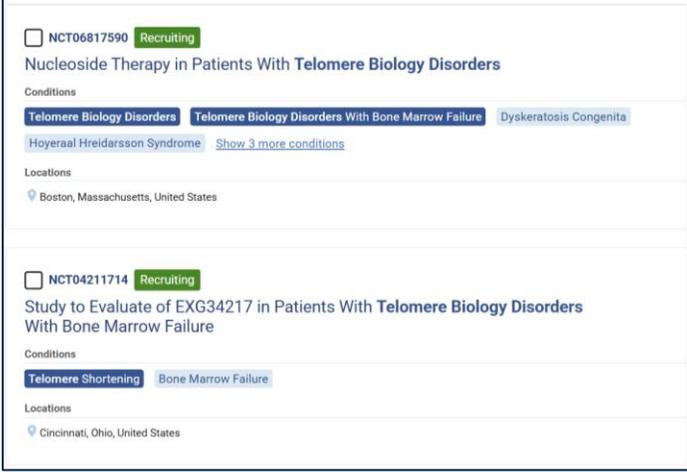
Alter et al. Blood (2009) 113 (26): 6549–6557.

# 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



The screenshot displays two clinical trial listings. The first trial, NCT06817590, is titled 'Nucleoside Therapy in Patients With Telomere Biology Disorders' and is currently recruiting. It lists conditions such as Telomere Biology Disorders, Telomere Biology Disorders With Bone Marrow Failure, and Dyskeratosis Congenita. The location is Boston, Massachusetts, United States. The second trial, NCT04211714, is titled 'Study to Evaluate of EXG34217 in Patients With Telomere Biology Disorders With Bone Marrow Failure' and is also recruiting. It lists conditions Telomere Shortening and Bone Marrow Failure. The location is Cincinnati, Ohio, United States.

# A helpful resource: Team Telomere Management Handbook

## Team Telomere | A Community for Telomere Biology Disorders

### Routine Healthcare for Children with TBDs



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)*
<b>Hematology</b>		
CBC monitoring	At diagnosis	Every 6 months
Bone marrow monitoring	At diagnosis	Yearly starting at 10 years
<b>Immunology</b>		
Immune function assessment	At diagnosis	Repeat with change in infection frequency or development of BM failure
<b>Endocrinology</b>		
Growth and bone health assessment	At diagnosis	Yearly
Endocrinology consultation	Age 10 <sup>§</sup>	Yearly
DXA scan	Age 12-14	Every 3 to 5 years
<b>Hepatology</b>		
Liver function tests	At diagnosis	Yearly
Liver ultrasound	Age 5	Yearly*
<b>Pulmonary</b>		
Spirometry/DLCO	Age 10 <sup>§</sup>	Every 2-3 years
High Resolution CT	At diagnosis, if history of symptoms	Based on symptoms
<b>Dermatology</b>		
Dermatologist screening	Age 5	Yearly

Continued on the reverse side of this page

### Routine Healthcare for Adults with TBDs



Specialty	Evaluation	Recommendation
<b>Hematology</b>	Cytopenias; Aplastic anemia; Myeloid neoplasia	<ul style="list-style-type: none"> <li>Complete blood counts, reticulocyte counts and white blood cell differential at baseline</li> <li>Bone marrow assessment at baseline: bone marrow aspiration and biopsy, flow cytometry, conventional and molecular cytogenetics, and myeloid panel by NGS for somatic variants</li> </ul>
<b>Immunology</b>	Immunodeficiency	<ul style="list-style-type: none"> <li>Flow cytometry of peripheral blood lymphocyte subsets</li> <li>Serum immunoglobulin levels (total and fractions)</li> </ul>
<b>Ophthalmology</b>	Anterior segment	<ul style="list-style-type: none"> <li>Corneal assessment</li> </ul>
	Posterior segment	<ul style="list-style-type: none"> <li>Retinal evaluation</li> </ul>
	Adnexa	<ul style="list-style-type: none"> <li>Nasolacrimal duct, eyelid assessment</li> </ul>
<b>Orthopedics</b>	Osteoporosis	<ul style="list-style-type: none"> <li>Bone density scan at baseline and then as needed</li> </ul>

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](https://bit.ly/TBD_Guidelines), or access it via this QR code.



# 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.

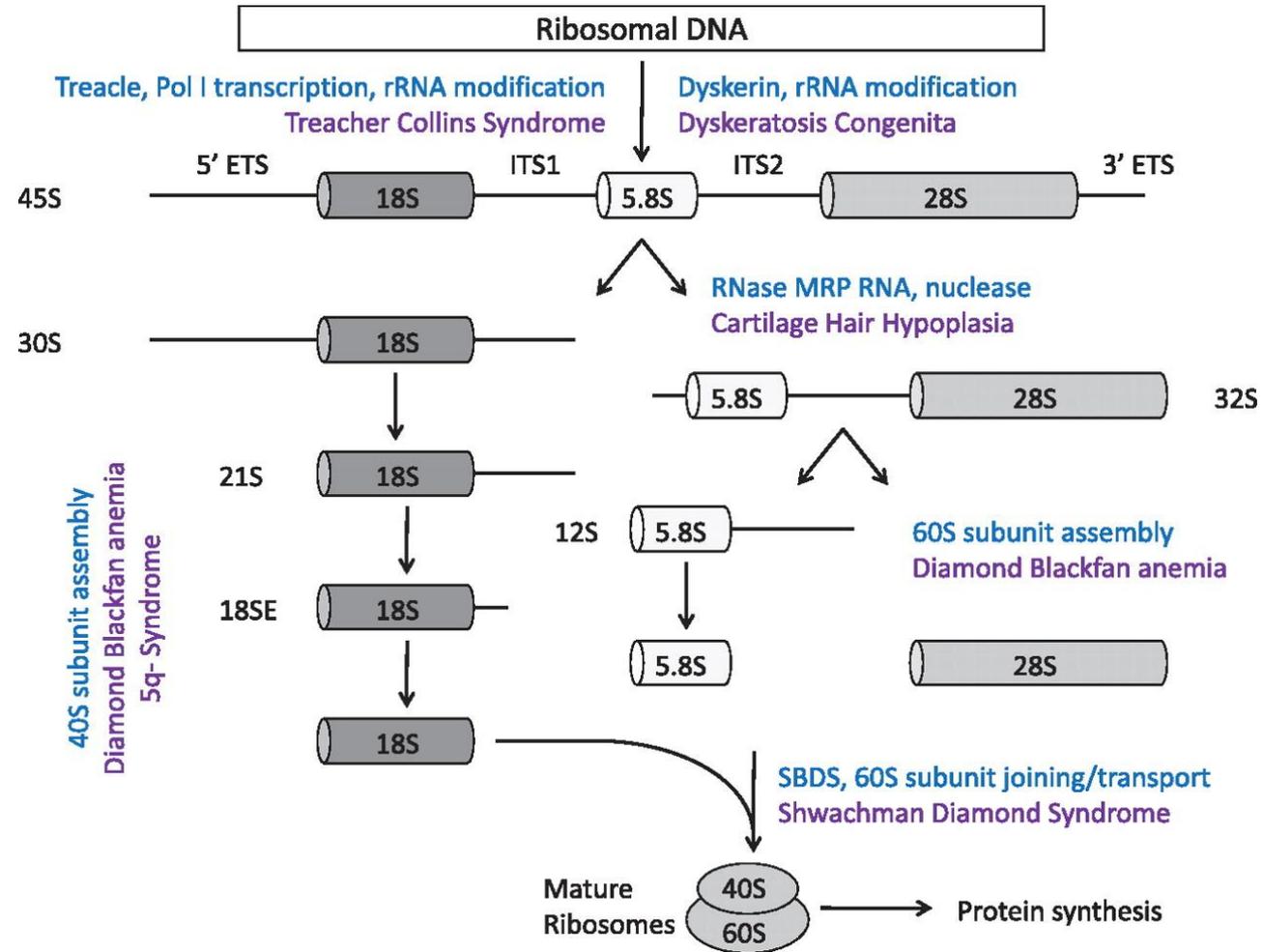
Bone marrow aspiration and biopsy: absence of erythroid precursors.

Cytogenetics and somatic molecular testing are normal.

**What is the likely diagnosis?**

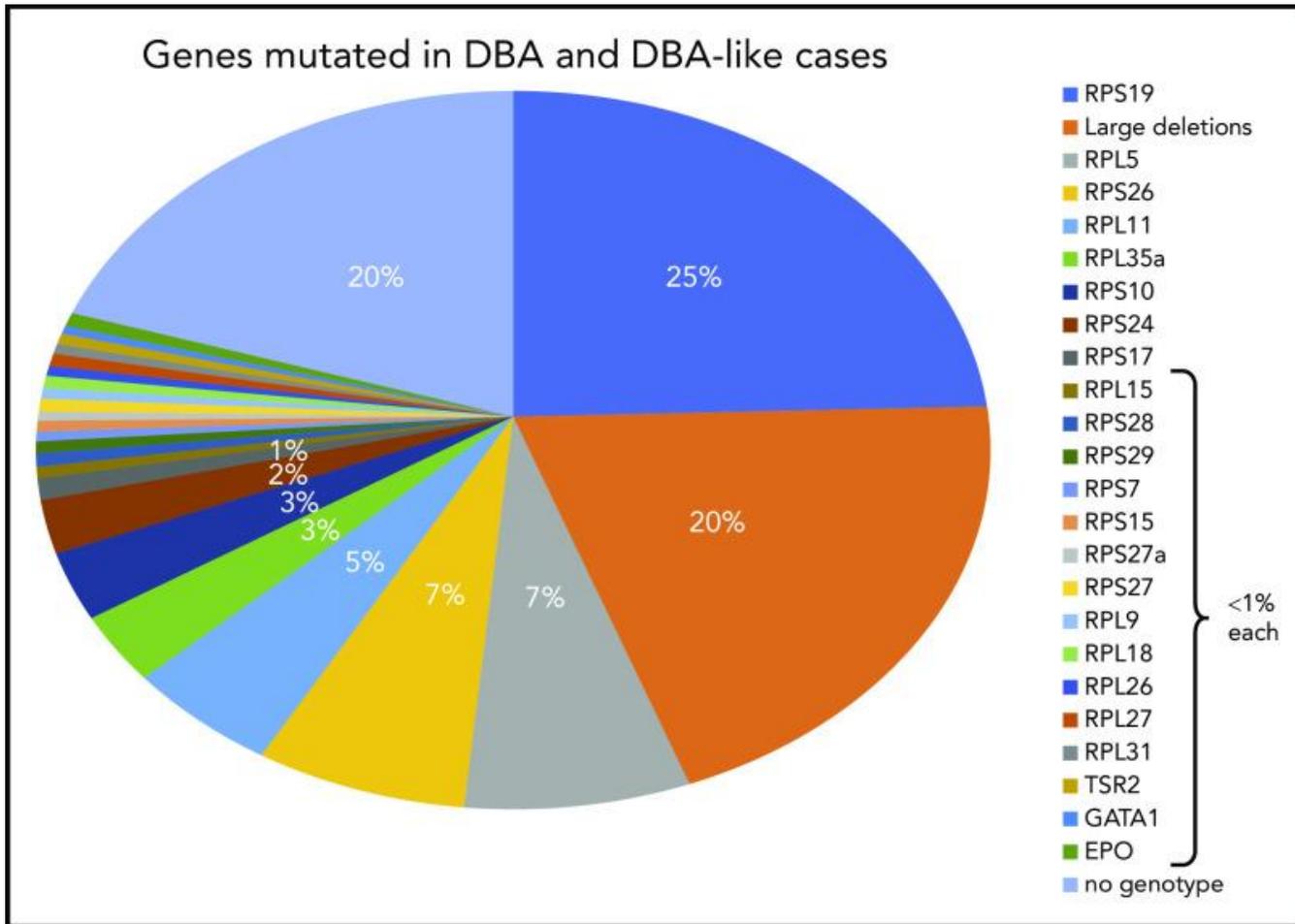
**What testing should be ordered?**

# 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

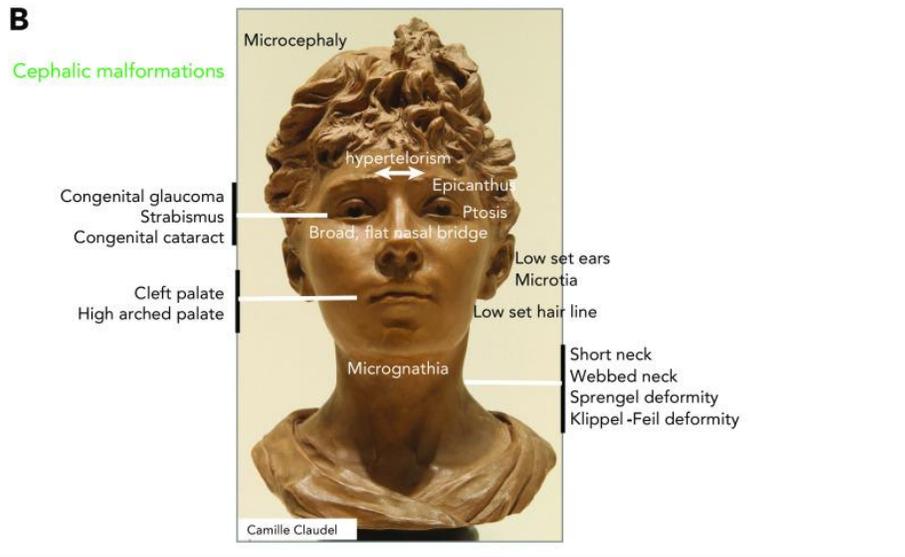
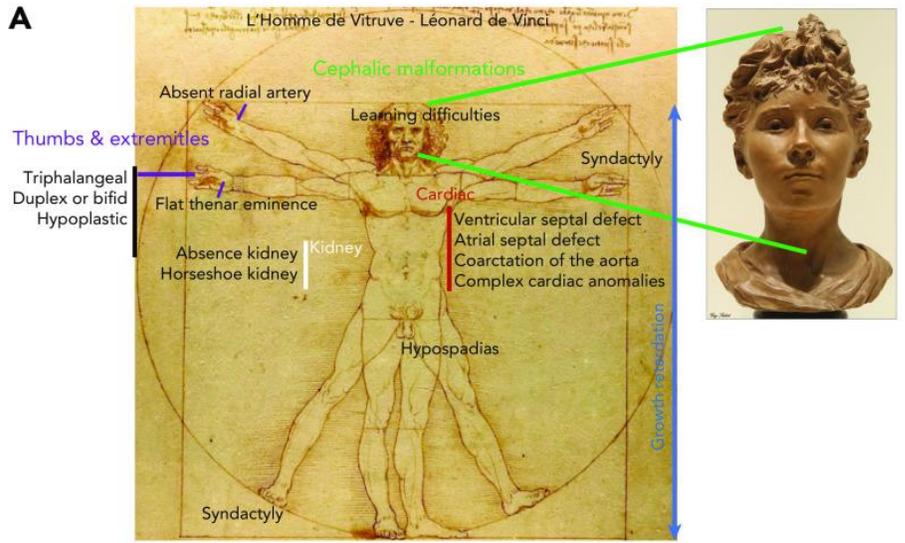


- AD, haploinsufficiency in RP
  - Most common: RPS19, RPL5, RPL11
- X-linked: GATA1, TSR2
- AR: EPO
- Mutations and large deletions
- Diagnosis is established by:
  - Genetic testing

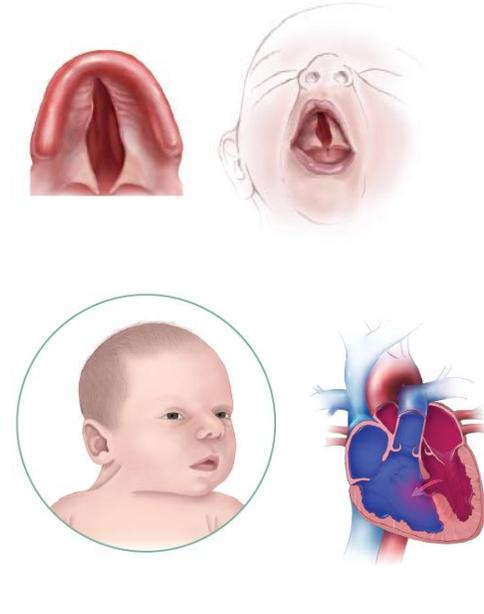
Diagnosed at 3 months of age: 50%  
 ..... at 6 months of age: 75%  
 ..... by 1 year: 92%

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

# Clinical Presentation in DBA



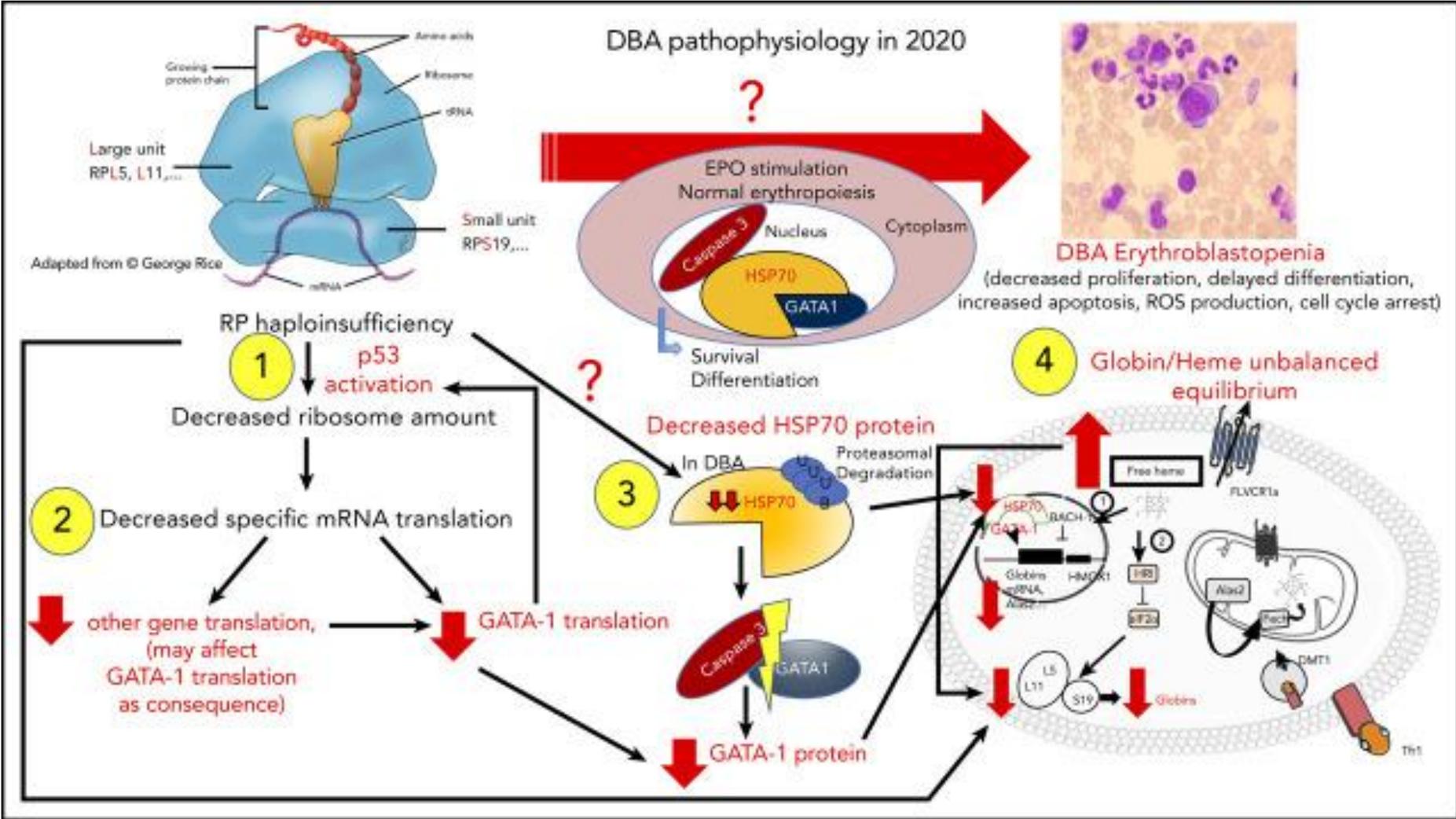
- Macrocytic, hypoproliferative anemia with absence of red cell precursors in bone marrow.
- ~ HALF have congenital anomalies.



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

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

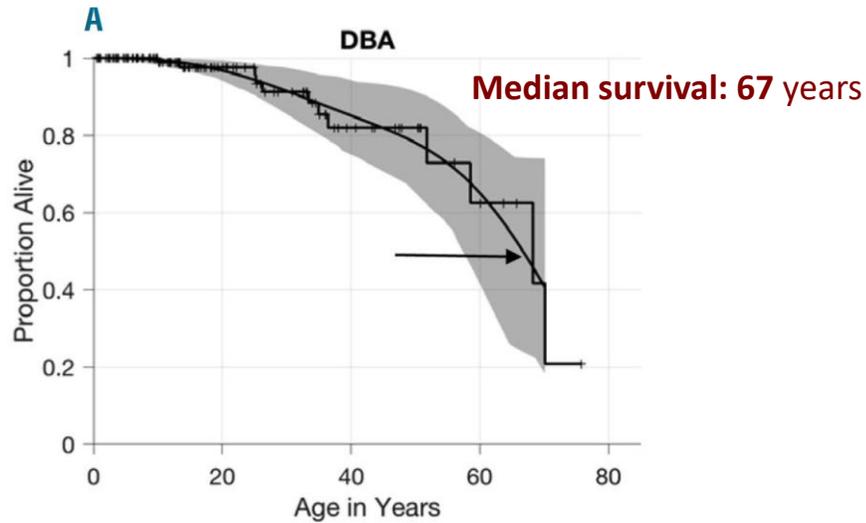
# DBA Pathogenesis



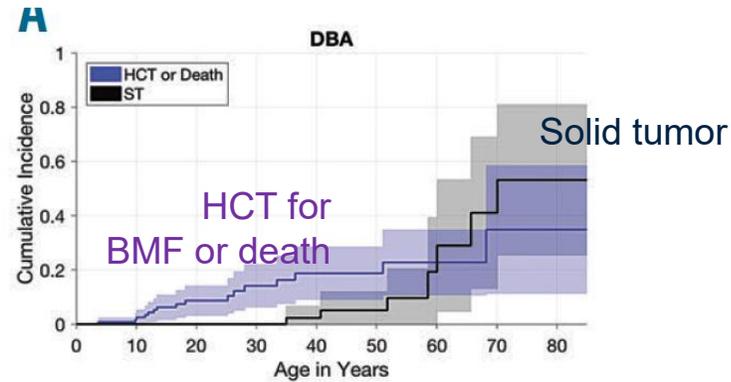
Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

# Overall survival, BMF, MDS, AML and solid tumors

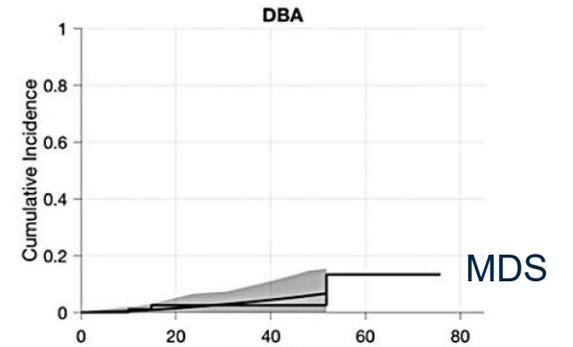
## Overall Survival



## CI of death/HCT/ST/leukemia



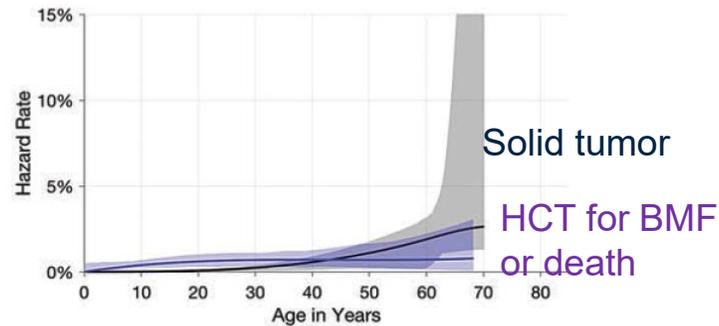
## Cumulative incidence of MDS



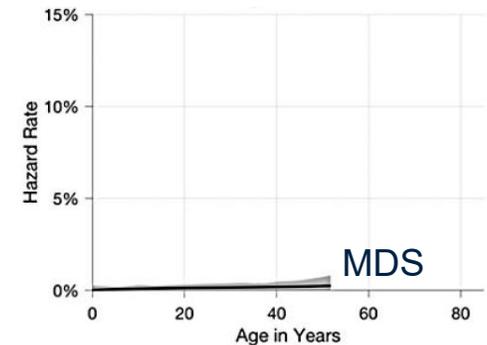
### Cumulative incidence:

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

## Annual hazard rate



## 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	<b>All sites*</b>	<b>49 (17-70)</b>	<b>9</b>	<b>3.68</b>	<b>2.5</b>	<b>1.1-4.7</b>
N=135 PY=3458	<b>Solid Tumors*</b>	<b>49 (17-70)</b>	<b>9</b>	<b>3.12</b>	<b>2.9</b>	<b>1.3-5.5</b>
	<b>Lung*</b>	<b>53 (47-70)</b>	<b>4</b>	<b>0.34</b>	<b>12</b>	<b>3.2-30</b>
	<b>Colon*</b>	<b>34, 55</b>	<b>2</b>	<b>0.18</b>	<b>11</b>	<b>1.4-41</b>
	<b>Cervix*</b>	<b>17, 40</b>	<b>2</b>	<b>0.05</b>	<b>37</b>	<b>4.6-136</b>
	Liver	34	1	0.04	27	0.7-151
	<b>MDS*</b>	<b>13</b>	<b>1</b>	<b>0.02</b>	<b>42</b>	<b>1.1-234</b>
	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

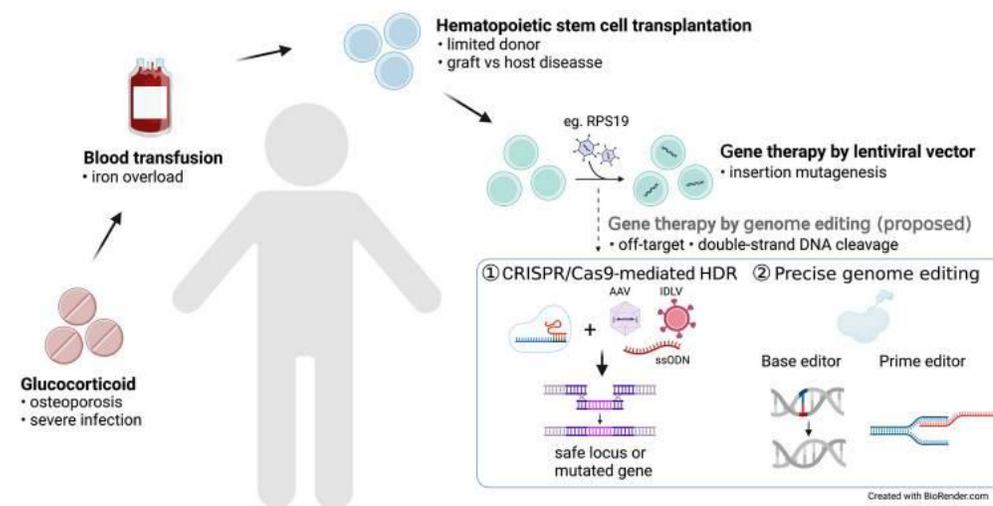
## ▶ Anemia:

- 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

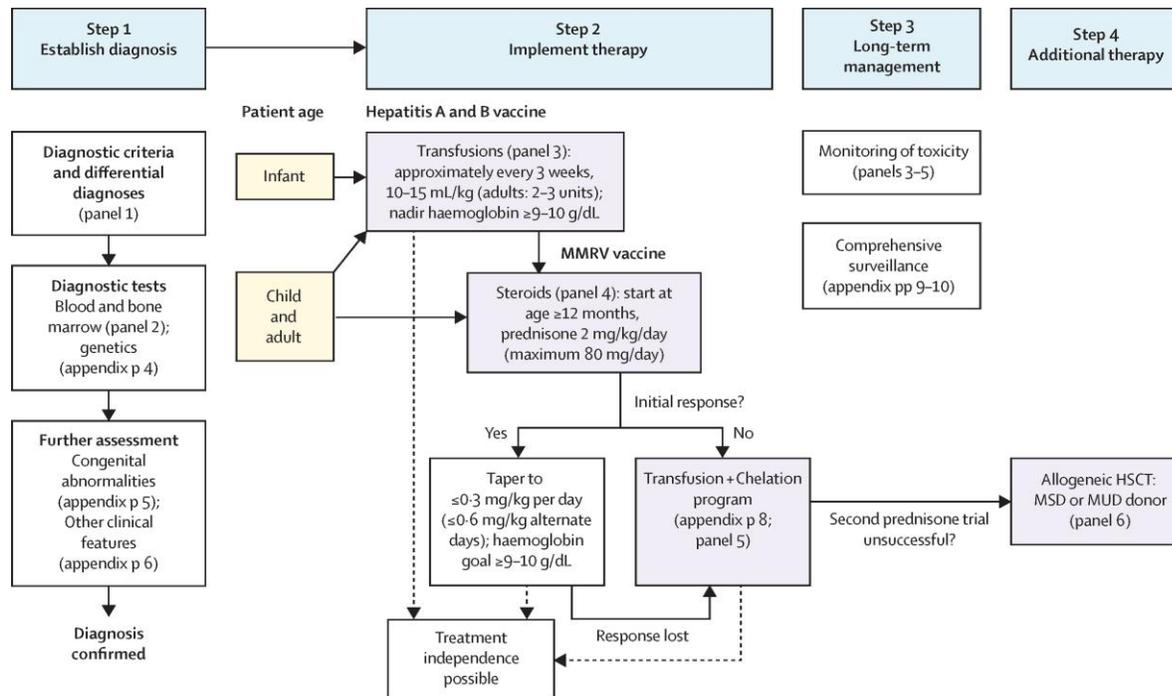
- Management of iron overload:
  - Chelation therapy
- Cancer screening:
  - Colonoscopy
  - Age-appropriate cancer screening
- Multidisciplinary care of affected organ systems (e.g. Cardiology, endocrinology, orthopedics)
- Genetic counseling



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

# A helpful resource: 2024 DBA International Consensus Statement

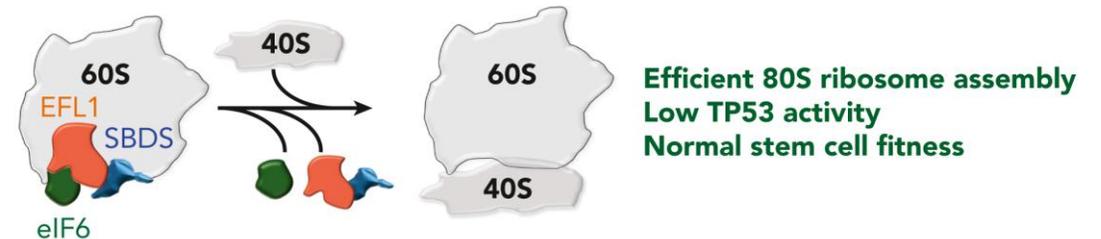
- ▶ Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement - The Lancet Haematology



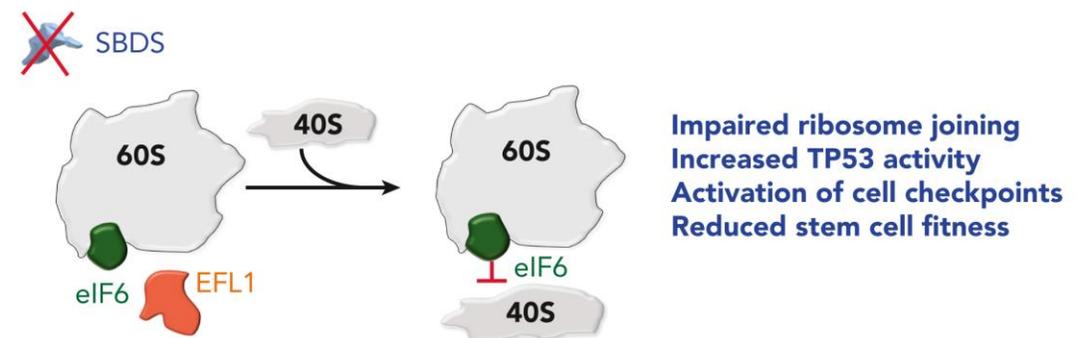
# Shwachman-Diamond Syndrome (SDS): Caused by a Defect in Ribosome Joining

- ▶ 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)

## Normal ribosome subunit joining



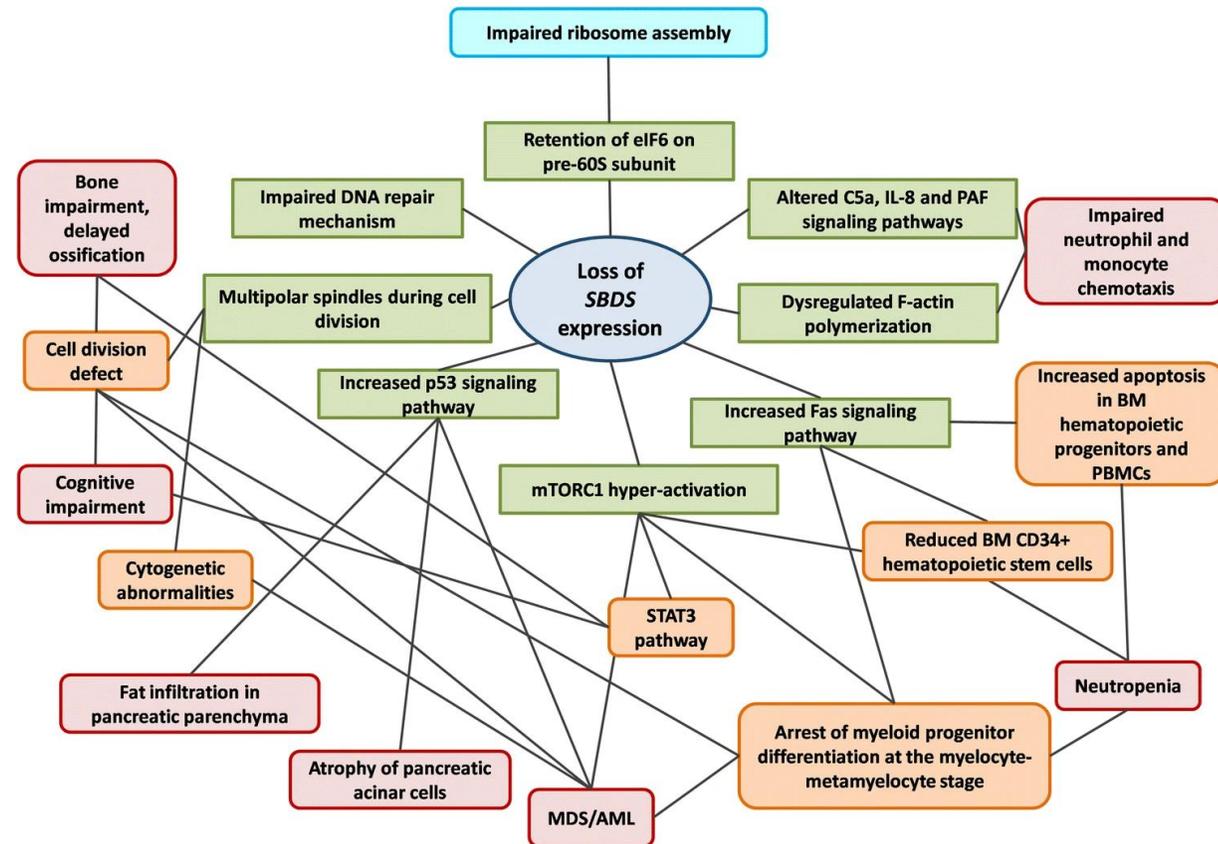
## Shwachman-Diamond Syndrome



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

# Clinical manifestations of SDS

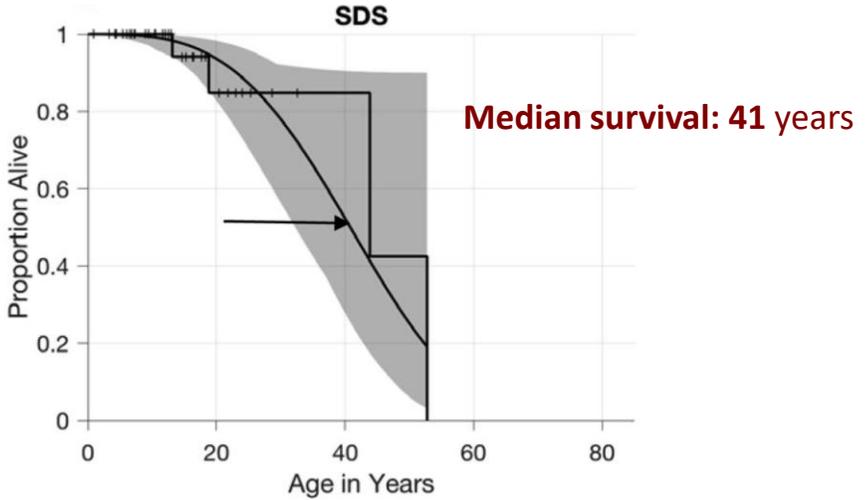
- ▶ Skeletal abnormalities
- ▶ Pancreatic insufficiency
- ▶ Short stature
- ▶ Cytopenias (mainly neutropenia)
- ▶ ~High risk of MDS/AML



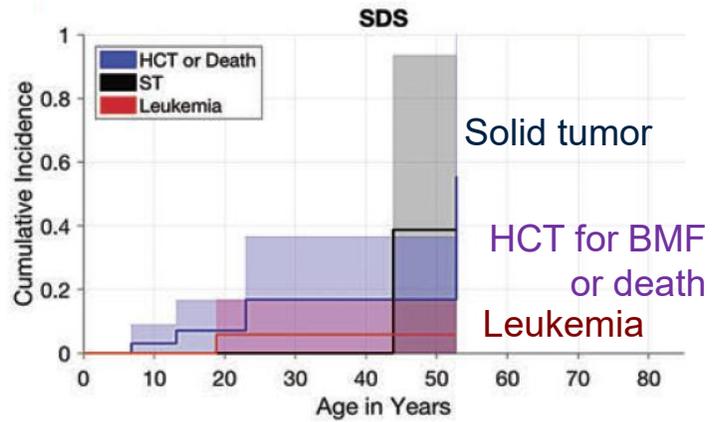
Bezzerri, et al Mol Diagn Ther 23, 281–290 (2019).

# Overall survival, BMF, MDS, AML and solid tumors

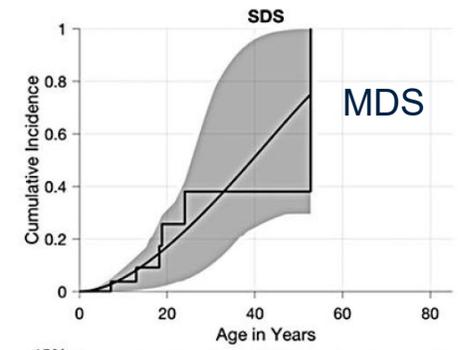
Overall Survival



CI of death/HCT/ST/leukemia



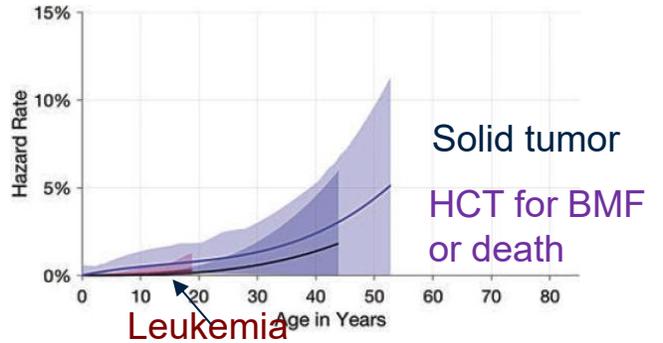
Cumulative incidence of MDS



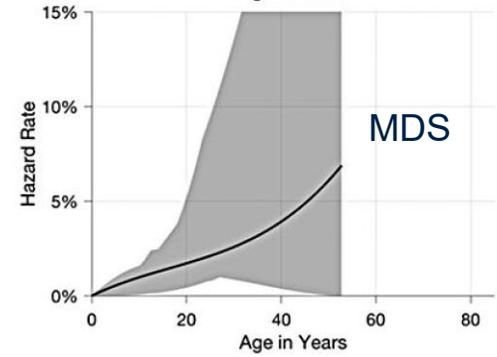
Cumulative incidence:

- 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

Annual hazard rate



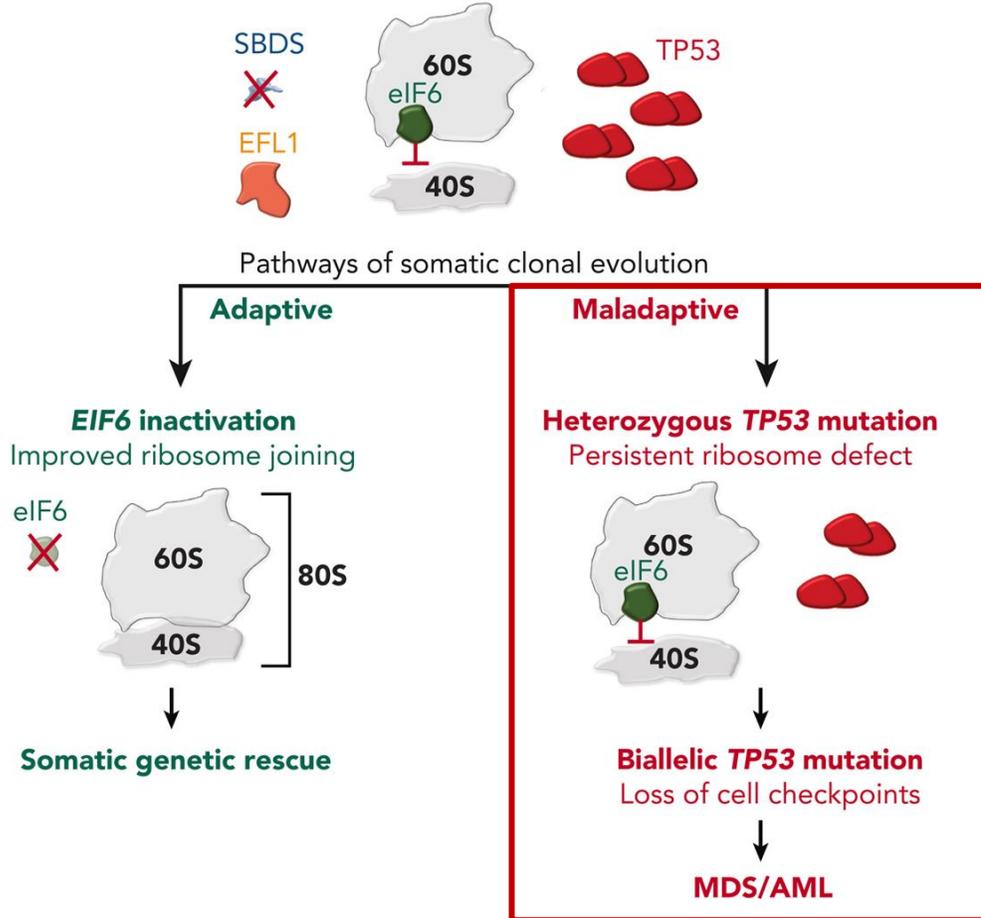
Annual hazard rate



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

# Clinical Management of SDS

## Shwachman-Diamond Syndrome



- ▶ 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.

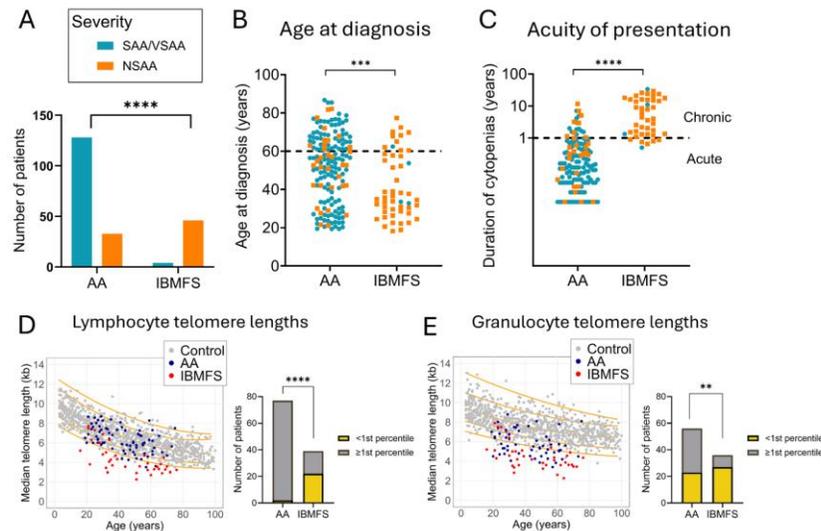
# Learning Objectives

- ▶ 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.



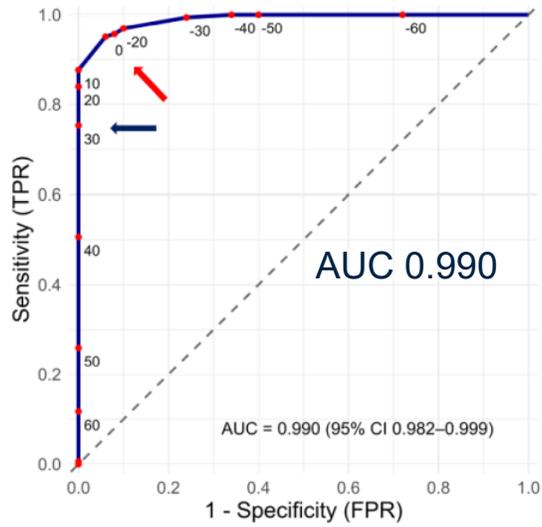
	1	2	3	4	5	6 (optional)	7 (optional)	
	Severity	Acuity	Age at evaluation	IBMFS "red flag"	AA-associated conditions	AA-associated somatic findings	Lymphocyte TL <1 <sup>st</sup> percentile	
<b>Favors AA</b>	SAA or VSAA <b>+20</b>	Acute <b>+10</b>	≥ 60 yrs <b>+10</b>	No known red flags <b>+10</b>	Present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

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>]

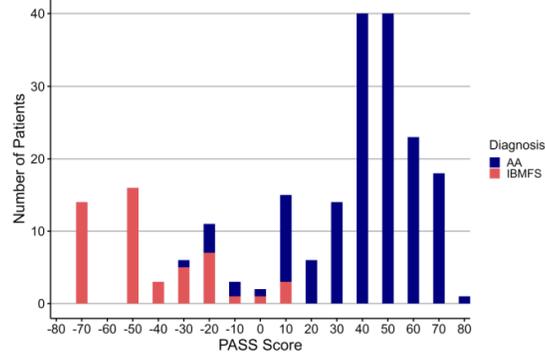
# PASS has outstanding discriminatory performance of AA vs IBMFS

Training cohort

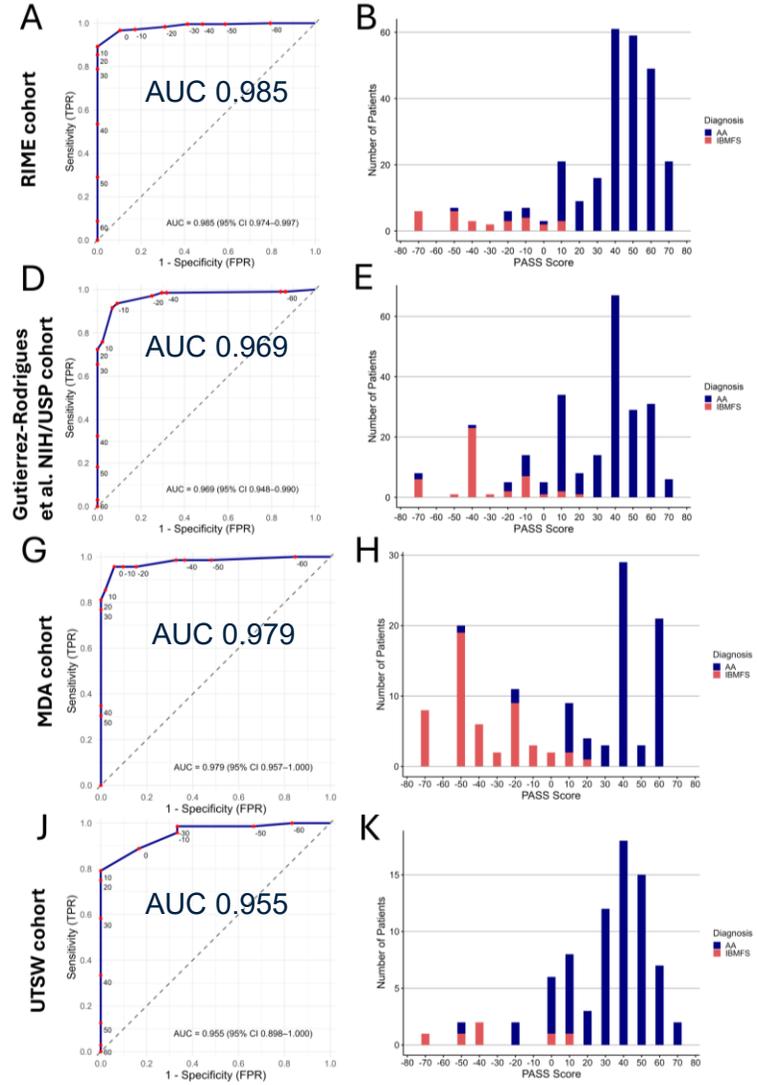
ROC curve



PASS score distribution



Four independent validation cohorts



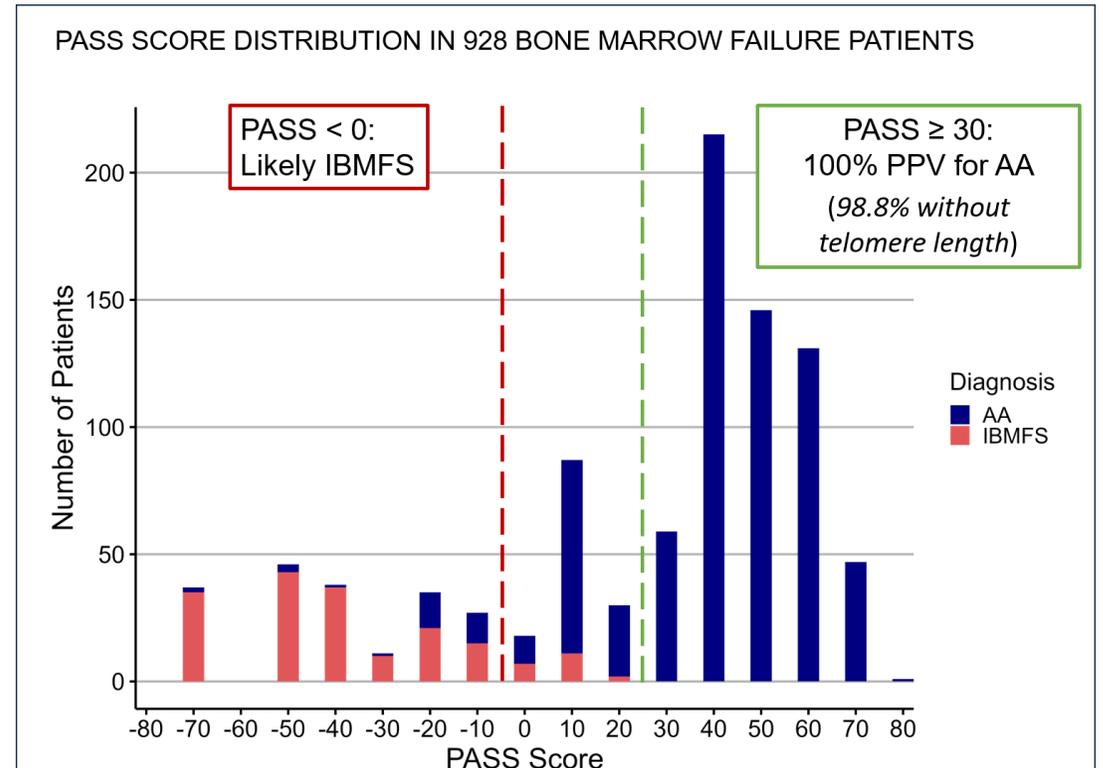
# PASS can rapidly triage adult patients presenting with apparent AA

## Training and Validation Combined

N = 928 (747 AA, 181 IBMFS)

ROC 0.981 (0.974 – 0.988)

- ▶ PPV for AA of PASS  $\geq 30$  = 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/](https://pennmedicine.shinyapps.io/passcalc/)

## Predictive Aplastic Score System (PASS) Calculator



### Disclaimer

This calculator is intended as an adjunctive, evidence-based tool to help distinguish adult patients with acquired immune-mediated aplastic anemia (AA) from those more likely to have an inherited bone marrow failure syndrome (IBMFS) requiring further evaluation. It assumes that other causes of cytopenias—such as myelodysplastic syndrome, nutritional deficiencies, infections, drug or toxin effects, and rheumatologic diseases—have been excluded. Predictions using this tool have not been validated in other clinical contexts.

Use of this tool does not constitute medical advice or establish a doctor–patient relationship. It is designed to support—not replace—clinical judgment, and should be used to inform, but not determine, clinical decisions. By using this calculator, you acknowledge and accept its intended use and limitations, and assume responsibility for any decisions made based on its results.

Reference: Aleixo, G., Cheon, H., Zheng, J., Soewito, S., Lee, J., Kaphan, E., Kalakuntla, N., Jen, W.-Y., Kotha, S., Rupsee, A., Djulbegovic, M., Matthews, J.A., Kadia, T.M., Olson, T.S., Peffault de Latour, R., Sire De Fonbrune, F., Bat, T., DiNardo, C.D., Babushok, D.V. Development and Validation of the Predictive Aplastic Score System (PASS): A Simplified Tool to Diagnose Acquired Aplastic Anemia in Adults. 2025.

**NOTE: Answers to questions 1, 2, 3, 4 and 5 are required to receive a PASS score. Score can be updated dynamically as additional features become known over disease course.**

**1. Cytopenia Severity (Required)**

Severe/Very Severe Aplastic Anemia requires AT LEAST TWO of the following:

- Absolute neutrophil count <  $0.5 \times 10^9/\mu\text{L}$
- Platelets <  $20 \times 10^9/\mu\text{L}$
- Absolute reticulocyte count <  $50 \times 10^9/\mu\text{L}$  with Hgb <  $100 \text{ g/L}$

Non-Severe Aplastic Anemia requires NO MORE THAN ONE of the following:

- Absolute neutrophil count <  $0.5 \times 10^9/\mu\text{L}$
- Platelets <  $20 \times 10^9/\mu\text{L}$
- Absolute reticulocyte count <  $50 \times 10^9/\mu\text{L}$  with Hgb <  $100 \text{ g/L}$

Select one:

Severe/Very Severe

Non-Severe

**4. IBMFS Red Flag (Required)**

IBMFS 'Red Flag' requires ONE of the following conditions on history or physical exam:

- Congenital abnormality, or dysmorphic features
- Interstitial lung disease, osseous necrosis, or unexplained liver cirrhosis
- Mucocutaneous triad, of nail dystrophy, skin hyperpigmentation, oral leukoplakia
- Unexpected hematologic toxicity with failure to recover blood counts after chemotherapy or radiation
- Refractory warts or a history of non-TB mycobacterial infection
- Sequence of cell cancer of the head and neck or orogenital region
- First-degree relative with a diagnosis of bone marrow failure or thrombocytopenia, MDS, AML or one of the conditions described above

Presence of inherited bone marrow failure red flag:

IBMFS red flag present

No red flag

**6. Somatic Genetic Alterations (Recommended for best performance)**

Somatic genetic alteration requires presence of ONE or more of the following findings:

- $\geq 0.2\%$  PNH clone in granulocytes
- Acquired chromosome with 1p loss-of-heterozygosity (by LOH)
- Somatic BCOR or BCORL1 mutation
- del(12)(q)

Presence of somatic genetic alterations:

Present

Absent or not known

**5. Lymphocyte Telomere Lengths (Recommended for best performance)**

Lymphocyte telomere lengths:

Below 1st percentile

$\geq 1\text{st}$  percentile or not known

**3. Age (Required)**

Age at evaluation:

Select one:

Adult (under 60 years old)

Age  $\geq 60$  years old

**2. Onset of Cytopenia (Required)**

- Acute (first abnormal CBC noted  $\leq 1$  year before current presentation)
- Chronic (first abnormal CBC noted  $> 1$  year before current presentation)

Select one:

Acute

Chronic

**5. Special conditions associated with acquired aplastic anemia (Required)**

NOTE: These are only applicable to a small minority of aplastic anemia patients.

Aplastic anemia-associated conditions:

- Sero-negative autoimmune hepatitis
- Treatment with immune checkpoint inhibitors
- Known diagnosis of immune dysregulation syndrome (e.g., CTLA4 haploinsufficiency)
- History of eosinophilic fasciitis
- History of myositis
- History of Hodgkin's lymphoma
- Patient previously tolerated cytotoxic chemotherapy without unexpected hematologic toxicity (e.g., historical treatment for breast cancer or lymphoma)

Presence of special conditions:

Present

Absent

**C**

**6. Somatic Genetic Alterations (Recommended for best performance)**

Somatic genetic alteration requires presence of ONE or more of the following findings:

- $\geq 0.2\%$  PNH clone in granulocytes
- Acquired chromosome with 1p loss-of-heterozygosity (by LOH)
- Somatic BCOR or BCORL1 mutation
- del(12)(q)

Presence of somatic genetic alterations:

Present

Absent or not known

**D**

**PASS Score**

**PASS Score: -20**

Inherited bone marrow failure is likely, further evaluation for inherited bone marrow failure is required (Score < 0)

Category	Points
Severity	-2
Acuity	-10
Age	-10
IBMFS red flag	+10
AA associated conditions	+10
AA type genetic changes	+10
Telomere $\geq 1\text{st}$ percentile	+10
<b>Total PASS Score</b>	<b>-20</b>

PASS SCORE DISTRIBUTION IN 538 BONE MARROW FAILURE PATIENTS



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## Recommended diagnostic approach for adult patients ( $\geq 18$ -years-old) with suspected acquired AA

### 1. Comprehensive history and physical exam, including:

- Historical CBCs, and timing of cytopenia onset
- Any congenital abnormalities and pediatric conditions
- History of AA-associated conditions
- History of IBMFS red flags
- Physical exam, with a focus on IBMFS-associated findings and dysmorphology

### 2. Comprehensive exclusion of transient etiologies, including:

- Nutritional deficiencies (e.g., B12, folate, iron studies)
- Infections (e.g., HIV, Hep B, Hep C, EBV, CMV, parvovirus B19)
- Organ dysfunction (liver, renal function tests)
- Endocrine (e.g., TSH)
- Autoimmune/inflammatory (e.g., ESR, CRP, ANA, RF).

### 3. Comprehensive hematologic evaluation:

- CBC with differential, peripheral blood smear
- Reticulocyte count
- Bone marrow aspirate and biopsy
  - Cellularity
  - Morphologic assessment
  - Flow cytometry, including T-LGL markers
  - Metaphase cytogenetics
  - MDS FISH, in cases of cytogenetic failure
  - Molecular panel for MDS-associated mutations

Alternative etiologies excluded

Primary BMF

Differential diagnosis:  
Acquired AA vs. inherited BMF

Calculate  
PASS

### 4. AA and IBMFS screening tests + HLA typing

- PNH flow cytometry (recommended)
- Cytogenomic array (screen for 6pLOH; recommended if available)
- Lymphocyte telomere length (recommended, flow FISH preferred)
- Chromosome breakage testing (recommended, particularly for younger patients, and those evaluated for BMT)
- HLA typing (recommended for BMT candidates with severe AA)

Update PASS with somatic and TL results when available

Update PASS to re-confirm diagnosis if new information emerges

**PASS  $\geq 30$ : high-confidence AA**

- No expected additional benefit from germline IBMFS genetic testing

PPV for AA=100% [without TL=99.5%]\*

Treat as AA

**PASS  $< 0$ : likely IBMFS**

- Requires comprehensive IBMFS evaluation including genetic testing

PPV for IBMFS=83.4% [without TL=86.0%]\*

Test for IBMFS

**PASS 0-20: Likely but not definite AA**

- Most patients have AA, but diagnostic uncertainty remains.

PPV for AA=84.8% [without TL=77.9%]\*

**Counsel on diagnostic uncertainty.**  
Based on patient and disease characteristics (e.g., age, severity, planned treatment, urgency, genetic test availability), individualize plan, which may include:

- test for IBMFS before treating,
- treat for AA while awaiting results, or
- treat for AA and test if not responding.

During follow-up:

Monitor for emerging IBMFS red flags, and new AA-associated somatic findings

\*based on a cohort of 928 patients

Thank you!

Questions?

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