Aplastic anemia & inherited bone marrow failure syndromes

AAMAC Education Conference 2026

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Disclosures

- **Relevant relationships with commercial entities:**
  - Novartis - consultancy
- **Potential for conflicts within this presentation:**
  - Nothing to disclose

Objectives

1. Discuss the causes of aplastic anemia with particular focus on immune-mediated and inherited etiologies

2. Discuss the diagnosis and treatment of immune-mediated aplastic anemia

3. Introduce inherited bone marrow failure syndromes as an under-recognized cause of aplastic anemia in adults

APLASTIC ANEMIA

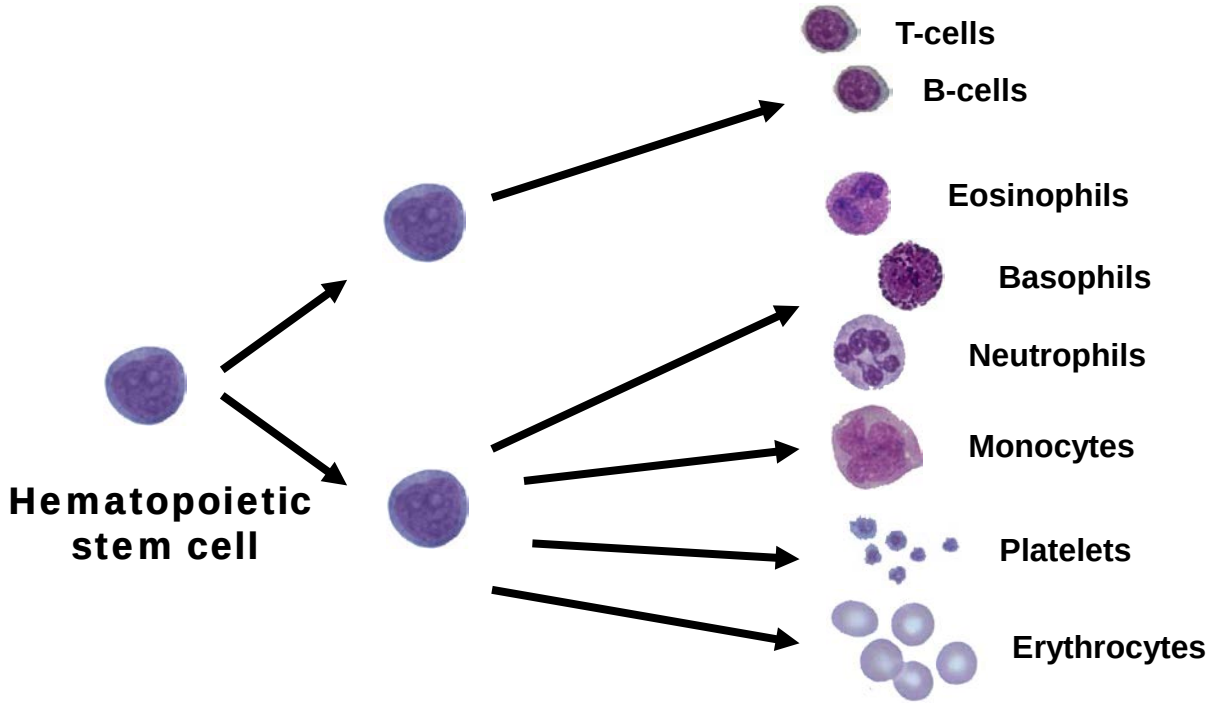
“Aplastic” definition:

failure of a tissue to develop or function normally

APLASTIC ANEMIA

failure of **the bone marrow** to develop or function normally

bone marrow is the site of normal blood cell production



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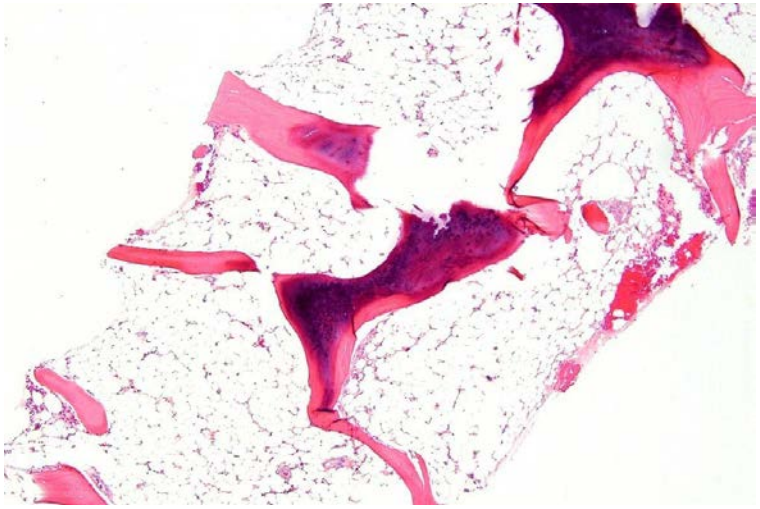

Normal bone marrow

Aplastic (empty) bone marrow

Images courtesy of ASH Image Bank

APLASTIC ANEMIA

"Anemia" is a misnomer

All blood cell types are affected: **pancytopenia**

Presentation

- Anemia (low RBC): fatigue, shortness of breath, palpitations

- Leukopenia (low WBC): infections, fever

- Thrombocytopenia (low PLT): bleeding, bruising

Causes of aplastic anemia

Low numbers of hematopoietic stem cells

Immune Mediated	Secondary	Inherited causes
Immune destruction of blood stem cells	*Bone marrow is damaged by:* - chemotherapy - radiation - chemicals - drugs - infection	*Born with a genetic change that interferes with blood development*

To distinguish between these:

- Detailed personal and family medical history
- Careful review of medications / exposures
- Examine the chronicity of blood count changes

Causes of aplastic anemia

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- Detailed personal and family medical history
- Careful review of medications / exposure
- Examine the chronicity of blood count changes

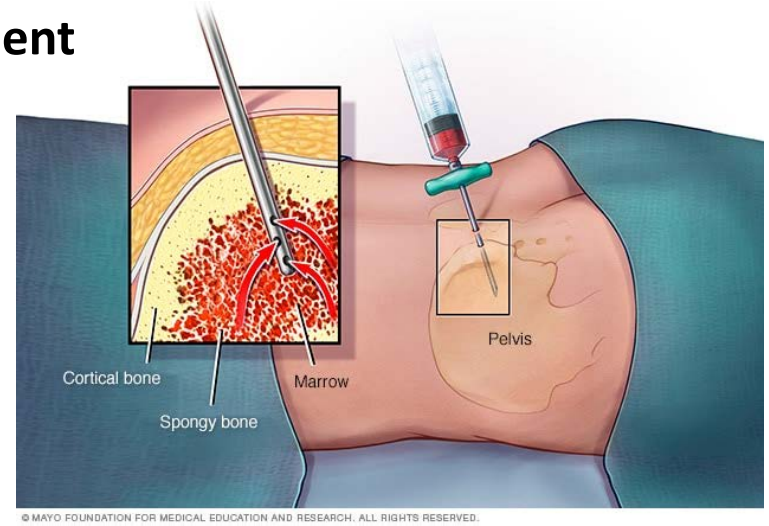
Immune-mediated aplastic anemia

- Incidence: 2 per million per year
- Half of cases arise in people < 30 years old
- Majority of cases of immune-mediated AA are idiopathic (ie: no trigger)
- In minority of cases an immune trigger can be identified:
  - Viral infection (classically 2-3 months after seronegative hepatitis)
  - Thymoma
  - Pregnancy
- carries risk of clonal evolution to MDS/AML: 10-15% at 10 years

Idiopathic aplastic anemia - diagnosis

Diagnosis is established by bone marrow assessment

- Hypocellular bone marrow in the absence of
  - Dysplasia
  - Infiltrate in the bone marrow
  - Fibrosis
  - Clear secondary causes of aplasia



Key to establish the severity of disease

- **Severe aplastic anemia -** BM cellularity < 25% with 2 out of 3 of:
  - PMN < 0.5 x 10^9/L; PLT < 20 x 10^9/L; Reticulocytes < 60 x 10^9/L
- **Very severe aplastic anemia -** Same as SAA, but PMN < 0.2 x 10^9/L
- **Moderate aplastic anemia**

Aplastic anemia - treatment

Severe or very severe aplastic anemia

Without treatment, almost all patients will succumb to infectious or bleeding complications

These patients require prompt institution of therapy

Moderate aplastic anemia

Start by monitoring to determine the tempo and trajectory of blood count changes

Investigate the possibility of an inherited bone marrow failure syndrome

Consider treatment when counts drop to the point of requiring transfusion support

Severe aplastic anemia - treatment

General supportive care:

1) Red cell and platelet transfusion support

2) Infections
- treat active infections
- consider antibiotic and/or anti-fungal prophylaxis (centre-dependent)

3) Adjuncts to minimize bleeding (tranexamic acid; menstrual suppression)

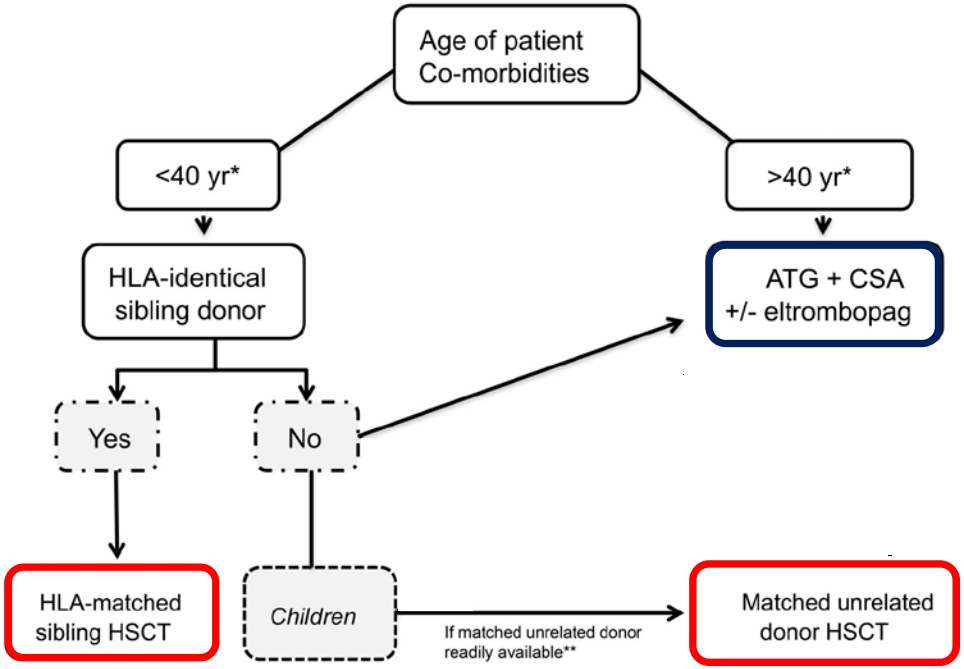
Definitive aplastic anemia therapy:

1) Allogeneic stem cell transplant
- Curative therapy, eliminates risk of clonal progression to MDS/AML

2) Immunosuppressive therapy
- antithymocyte globulin + cyclosporine +/- eltrombopag

How to decide between definitive treatment strategies?

Traditional approach



Transplant: age < 40, healthy & HLA identical sibling donor
healthy children & matched unrelated donor

Immunosuppressive therapy: age 20-40 & no HLA identical sibling donor available
age >40 regardless of donor availabiliy

Kulasekararaj *et al* BJH 2024

How to decide between definitive treatment strategies?

2026 update – expanding indications for transplant

- Starting to relax the strict 40 y.o. age threshold (depending on experience of transplant centre, comorbidities & performance status)

- Starting to consider alternative donor sources (matched unrelated; haploidentical)

    - improvements in HLA typing & conditioning regimens have greatly improved transplant outcomes and lessened GVHD

Bottom line:

- Transplant is curative for aplastic anemia – eliminates the chance of progression to MDS/AML
- Risks include graft failure, GVHD, transplant-related mortality and infertility
- Early donor search is crucial
- Healthy SAA patients should be referred to transplant centre for discussion of available donors

Immunosuppressive therapy (IST) for severe aplastic anemia

Rationale: Suppress the immune attack → restore hematopoiesis

Backbone agents: antithymocyte globulin (ATG) + cyclosporine

ATG: antithymocyte globulin

- Generated by immunizing horse (or rabbit) with human T-cells
- Isolate polyclonal serum with antibodies vs. human T-cells
- Admitted to hospital – receive over 4 days
- Reactions during infusion are very common

Cyclosporine A

- Interferes with the production of cytokines required for T-cell proliferation
- Continue for at least 6 - 12 months until counts plateau, then slowly taper

2/3 patients respond - can take up to 6 months

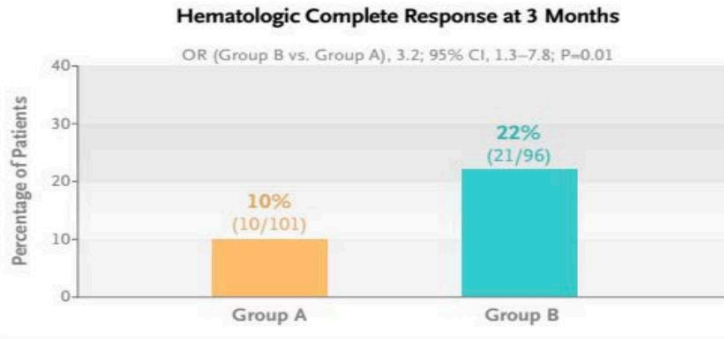
Can we improve on ATG + cyclosporine?

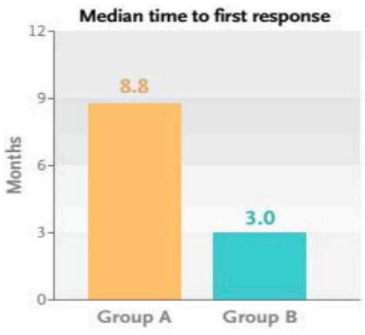
Many approaches have been tried over the years and proven unsuccessful

- Growth factors that stimulate white blood cell / neutrophil production
- Drugs that further suppress the immune system

Finally progress in the 2020s !

- **Eltrombopag:** thrombopoietin agonist – expands hematopoietic stem cells
- When added to ATG/CsA: higher rates of response & faster responses





Note: Eltrombopag not approved / funded in Ontario for this indication at this time

De Latour et al NEJM 2022

How to treat aplastic anemia in the elderly

Treatment of aplastic anemia in older, comorbid patients is a challenge

- both transplant and immunosuppressive therapy are intensive therapies and require excellent heart, lung and kidney function

Treatment approach should be informed by each patient's values and care philosophy

Supportive care (transfusions / antibiotics) -plus-

1) Single agent cyclosporine

2) Single agent eltrombopag

3) Anabolic steroids (danazol)

Causes of aplastic anemia

Low numbers of hematopoietic stem cells

Immune Mediated	Secondary	Inherited causes
Immune destruction of blood stem cells	*Bone marrow is damaged by:* - chemotherapy - radiation - chemicals - drugs - infection	*Born with a genetic change that interferes with blood development*

Inherited bone marrow failure syndromes

- Heterogeneous group of genetic disorders characterized by ineffective hematopoiesis
  - cytopenias, marrow hypocellularity, increased risk of AML/MDS
- Often accompanied by non- hematologic manifestations:
  - congenital malformations, organ impairment, solid tumor predisposition
- Historically thought to be diagnosed in pediatric population, now increasingly identified in adults with more subtle clinical presentations
- Individually rare conditions, but the collectively are quite common

Feurstein *et al* Leukemia 2021: ~19% of patients with MDS diagnosed age <40 years

DeZern *et al* Blood 2021: ~10% of patients with AA diagnosed age < 40 years

Clues to an inherited BMF syndrome

- cytopenia onset at young age with progression over time
- hypocellular bone marrow (often moderate AA)
- congenital malformations
- non-hematopoietic organ involvement (cirrhosis, pulmonary fibrosis, pancreatic insufficiency)
- family history of aplastic anemia / MDS / AML
- personal / family history of other cancers

IBMFS that can present as aplastic anemia

- Fanconi anemia
- Dyskeratosis congenita / Telomere biology disorders

- Schwachman-Diamond syndrome
- GATA2 deficiency
- SAMD9 / SAMD9L disorders
- SRP72 - associated bone marrow failure (BMFS1)
- ERCC6L2 - associated bone marrow failure (BMFS2)
- and others ….

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Fanconi anemia

- Caused by mutations affecting DNA repair

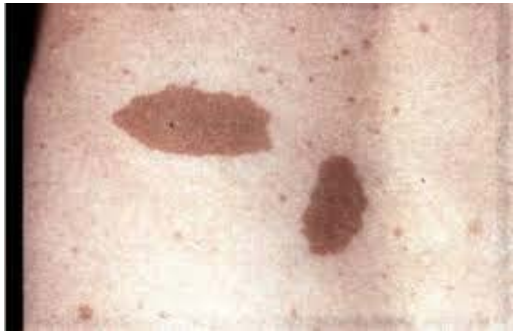
- 22 different genes have been implicated
  - *FANCA* → *FANCW*
  - *FANCD1 = BRCA2*
  - *FANCS = BRCA1*

- Most common mutations are in *FANCA* (60%) - autosomal recessive

Fanconi anemia – clinical manifestations

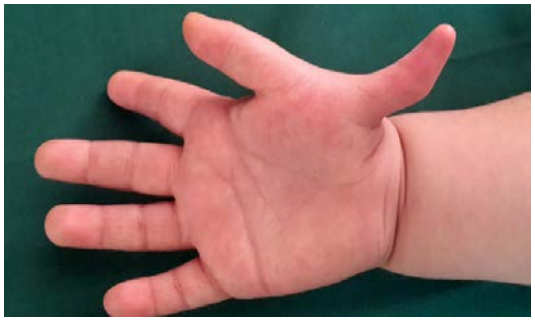
Hematologic:

- pancytopenia / progressive aplastic anemia
- 30% risk of MDS / AML by 50 y.o



Congenital anomalies (~2/3 patients):

- short stature, low birth weight, developmental delay
- skin (café au lait spots; hypo/hyperpigmentation)
- thumb / radial ray abnormalities
- kidney, cardiac, GI tract anomalies



Solid tumors:

- 10% risk by age 50
- most commonly H/N, anogenital squamous cell cancers
- *FANCD1* (*BRCA2*) / *FANCS* (*BRCA1*): increased risk of breast / ovarian cancer

Diagnosis of Fanconi anemia

Step 1: Assess for 'chromosomal fragility'

PB lymphocytes
-or- skin fibroblasts

Exposure to DNA crosslinking agents

- MMC (mitomycin C)
- DEB (diepoxybutane)

Karyotype analysis

With Fanconi anemia
See high numbers of chromosomal breaks

Diagnosis of Fanconi anemia

Step 2: Genetic testing

- Use specialized genetic panels (send out of country, require specialized funding)
- Source of DNA:

Blood & bone marrow DNA (NO!)
- a mix of malignant and germline DNA – cannot confirm that a mutation is germline

Skin fibroblast DNA is the gold standard
- a source of germline DNA free from contamination from any (malignant) hematopoietic cells
- confirms 'germline' transmission

Emerging alternative sources of germline DNA
- Hair follicles / bulbs
- Nail clippings

Management of Fanconi anemia

Multidisciplinary approach: hematology/BMT, genetic counselling, plastic surgery dermatology, dentistry, ENT

From hematology standpoint: main issue is pancytopenia that can progress to MDS/AML require at least yearly bone marrows to monitor

Treatment:

a) allogeneic stem cell transplant

* for severe cytopenias (Hb<80, PLT <30, PMN <0.5)
* if develop MDS/AML
* ideal donor is unaffected sibling (BM source)
* not an easy endeavor - conditioning / immunosuppression increase risk of other cancers

b) androgens (danazol / oxymetholone)

* can temporize counts & delay the need for transplant
* response in majority of patients – but takes 3-6 months

Management of Fanconi anemia

Multidisciplinary approach: hematology/BMT, genetic counselling, plastic surgery dermatology, dentistry, ENT

For non-hematologic manifestations: cornerstone of care is screening/surveillance

- **ENT/Dentist:** twice yearly exams
- **Dermatology:** annual exam
- **Gynecology:** Pap smears
- **Vaccinations:** HPV and others as per guidelines
- **Additional screening:** breast / ovary if FAND1 or FANCS

Guidelines are available from the Fanconi Anemia Foundation:
https://fanconi.org/clinical-care-guidelines/clinical-care/

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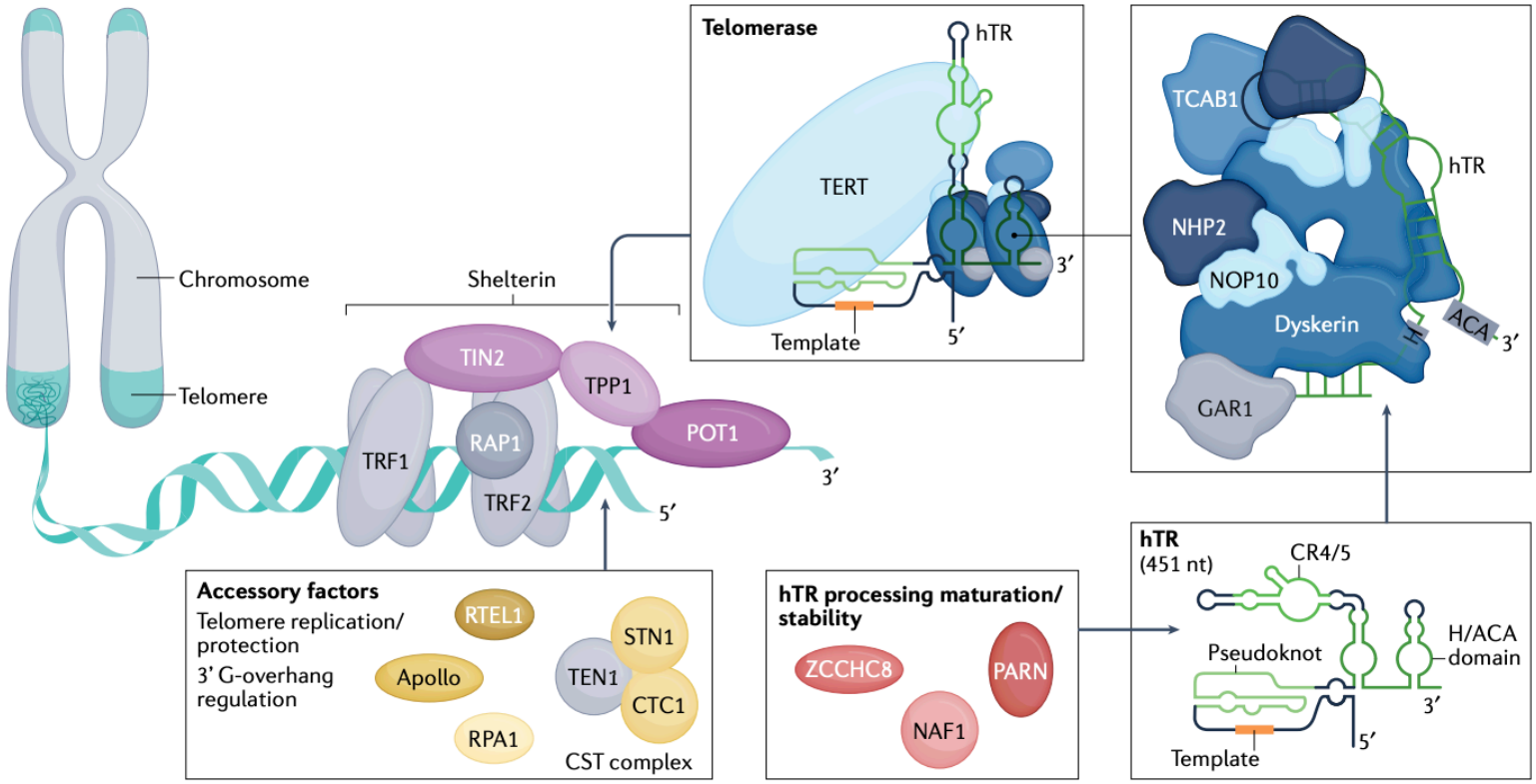
Telomeres and the telomerase complex

- **Telomeres** are protective caps on the ends of chromosomes that shorten with age
- **Telomerase complex** is responsible for maintaining telomeres



Revy *et al* Nat Reviews 24(2) 2023

Dyskeratosis congenita / telomere biology disorders

- a **telomeropathy** – mutation in genes associated with telomerase complex leads to pathologic premature shortening of telomeres

Gene [1, 2]	MOI	Proportion of DC/TBD Attributed to Pathogenic Variants in Gene[3]
ACD	AD or AR	<1%
CTC1	AR	1%-3%
DKC1	XL	20%-25%
NAF1	AD	<1%
NHP2	AR	<1%
NOP10	AR	<1%
PARN	AR or AD	<1%
POT1	AR [14]	<1%
RPA1	AD	<1%
RTEL1	AD or AR	2%-8%
STN1	AR	<1%
TERC	AD	5%-10%
TERT	AD or AR	1%-7%
TINF2	AD	12%-20%
WRAP53	AR	<1%
ZCCHC8	AD	<1%

Savage and Niewisch GeneReviews 2023
Niewish *et al* Am Soc Hematol Educ Program 2023

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POT1	AR [14]	<1%
RPA1	AD	<1%
RTEL1	AD or AR	2%-8%
STN1	AR	<1%
TERC	AD	5%-10%
TERT	AD or AR	1%-7%
TINF2	AD	12%-20%
WRAP53	AR	<1%
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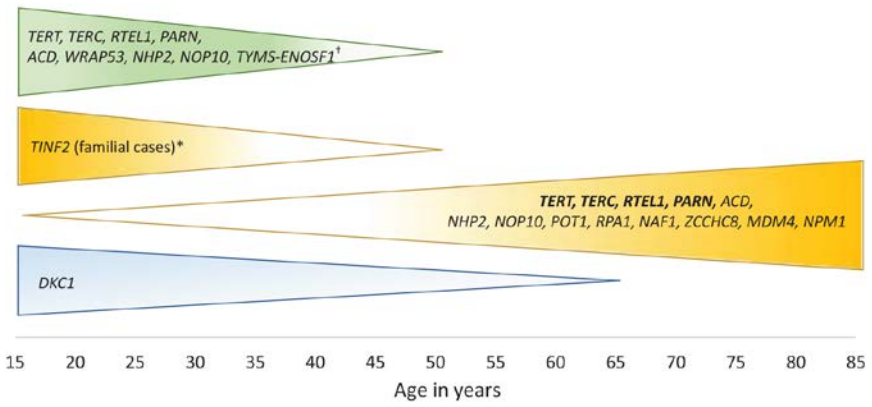
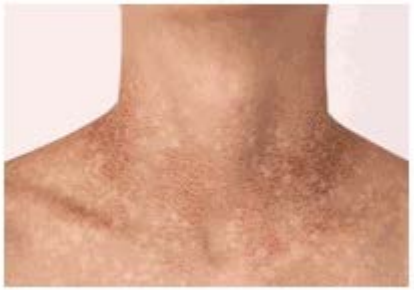


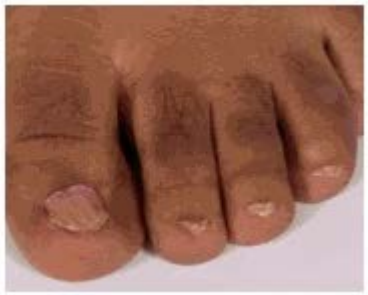
XL - AR - AD

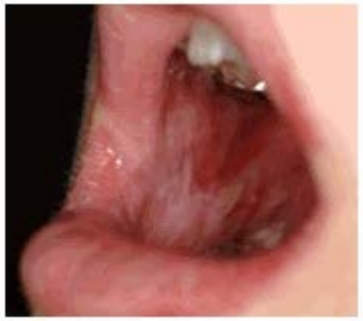
Savage and Niewisch GeneReviews 2023
Niewish *et al* Am Soc Hematol Educ Program 2023

Telomere biology disorders / dyskeratosis congenita

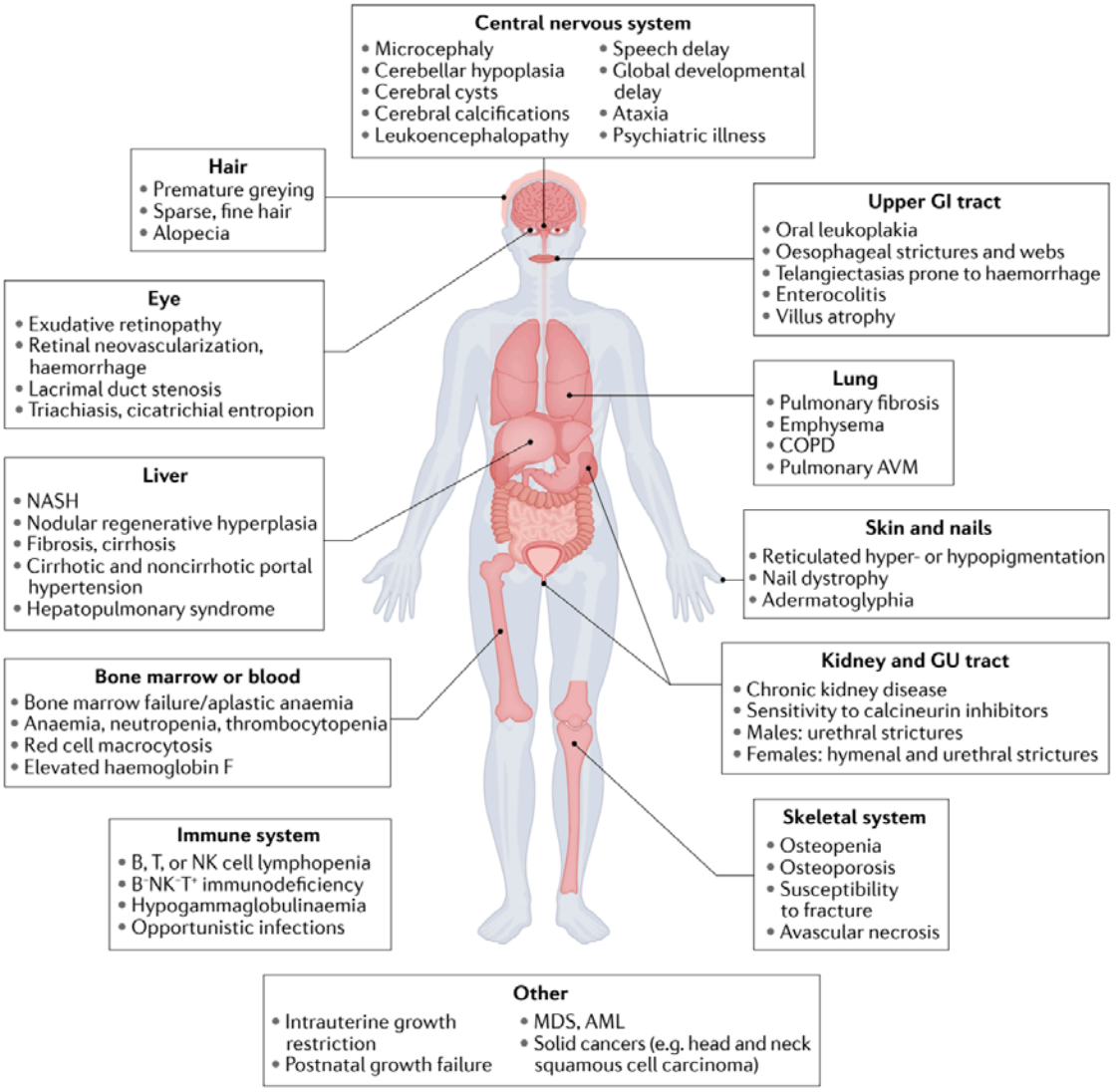
Classic triad of dyskeratosis congenita: skin pigmentation, oral leukoplakia, nail dystrophy







TBDs – much more than the triad



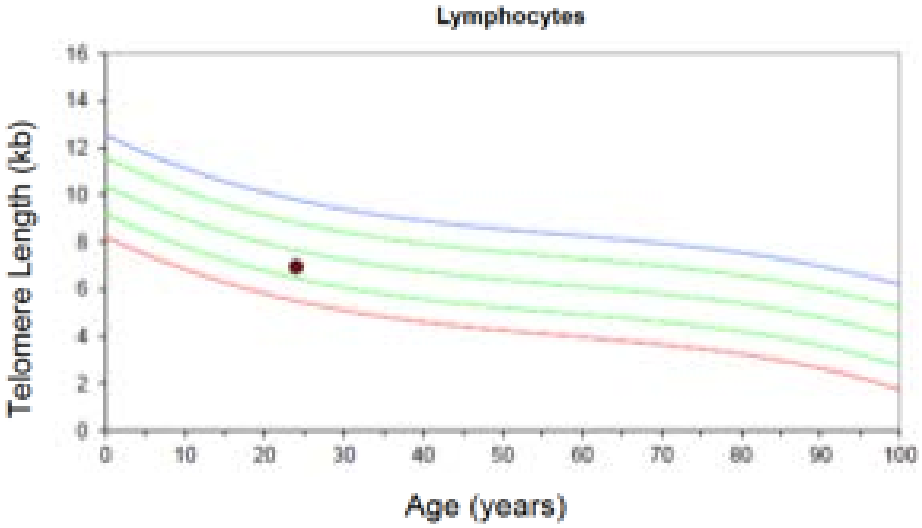
Revy *et al* Nat Reviews 24(2) 2023

Diagnosis of telomere biology disorders

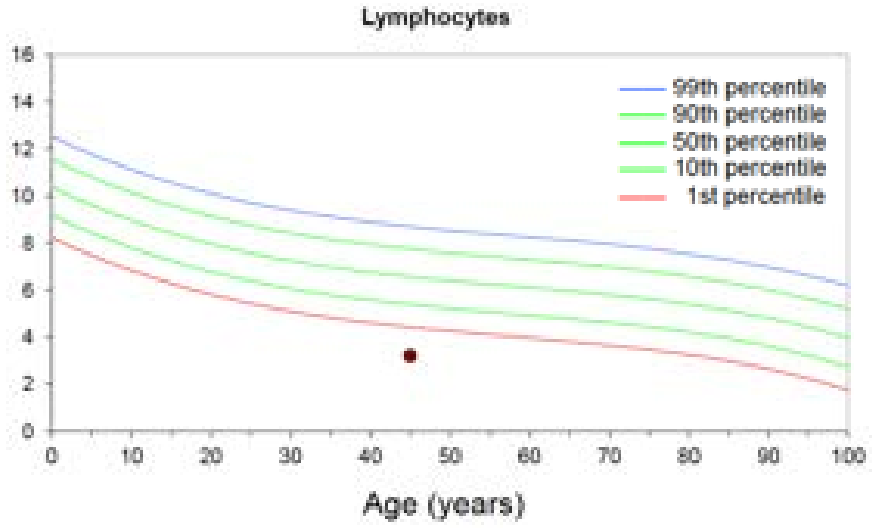
Step 1: Measure telomere lengths – Flow-FISH

- Fluorescent probes bind to telomeres in intact cells

- Use flow cytometer to quantify 'brightness' (ie: telomere length) in various cell types
- As telomeres shorten with age, normal ranges are dependent on age



NORMAL TELOMERES
30th percentile



VERY SHORT TELOMERES
Less than 1st percentile

Diagnosis of telomere biology disorders

Step 2: Genetic testing

- Use specialized genetic panels (send out of country, require specialized funding)
- Source of DNA:

Skin fibroblast DNA is the gold standard

- a source of germline DNA free from contamination from any (malignant) hematopoietic cells
- confirms 'germline' transmission
- somatic reversion can occur in the blood – leading to false negatives

Emerging alternative sources of germline DNA

- Hair follicles / bulbs
- Nail clippings

Management of telomere biology disorders

Multidisciplinary approach: hematology/BMT, genetic counselling, respirology hepatology, dermatology, dentistry, ENT

From hematology standpoint: main issue is pancytopenia that can progress to MDS/AML monitor with serial bone marrow examinations

Treatment:

a) allogeneic stem cell transplant

***** for severe cytopenias (Hb<80, PLT <30, PMN <0.5)
* if develop MDS/AML

b) androgens (danazol)

* for non-transplant candidates and/or clinically significant cytopenias
* hematologic response in ~80% of patients & can be sustained for years
* do not delay (or promote) progression to AML/MDS
* emerging evidence that danazol may prevent telomere shortening

TBD Guidelines: Teamtelomere.org
Townsley et al NEJM 2016

Telomere biology disorder management

Multidisciplinary approach: hematology/BMT, genetic counselling, respirology hepatology, dermatology, dentistry, ENT

For non-hematologic manifestations: cornerstone of care is screening/surveillance

- **Hepatology:** liver enzymes/function; Fibroscan
- **Respirology:** pulmonary function tests ; CT scan
- **ENT/Dentist:** annual exam for oro/nasopharyngeal malignancies
- **Dermatology:** annual exam
- **Gynecology** / Pap smears
- **Vaccinations:** HPV and others as per guidelines

TBD Guidelines: Teamtelomere.org

Aplastic anemia & IBMFS - summary

1) Aplastic anemia: low blood counts + hypocellular bone marrow

1. immune-mediated (idiopathic) aplastic anemia
2. secondary aplastic anemia (chemo / radiation / drugs)
3. inherited bone marrow failure syndromes

2) Idiopathic aplastic anemia – frontline treatments

- traditionally if <40 with matched donor: **transplant**
- alternative is **immunosuppressive therapy** (ATG / cyclosporine +/- eltrombopag)

- In 2026: improved outcomes with older patients and with ADT have led to a shift towards expanded transplant indications

3) Inherited bone marrow failure syndromes

- suspect if 'moderate' aplastic anemia, family history, non-hematopoietic manifestations
- increasingly recognized by adult hematologists with subtle presentations
- to diagnose: specialized genetic testing
- management is complex & multidisciplinary – require specialized clinics

Establishment of an adult bone marrow failure clinic

Sunnybrook HEALTH SCIENCES CENTRE

Established Dec 2023

Clinical lead: Dr. James Kennedy
Physician Assistant: Graeme Oliver
Genetics: Talia Mancuso ; Dr. Lea Velsher
Pathology: Dr. Hubert Tsui

Key collaborators: Dr. Yigal Dror (Sick Kids)
Dr. Tommy Alfaro Moya (PMCC)
Dr. Stephanie Lee (Unity Health)

Objectives:

1. Develop workflows to facilitate the genetic investigation of patients with suspected IBMFS

2. Develop a transition-of-care framework for patients with IBMFS / AA as they 'graduate' from the Hospital for Sick Children

3. Foster clinical expertise, collaboration and research in the field of iBMFS

1. Workflow to facilitate the diagnosis of patients with IBMFS

Skin biopsy → fibroblast culture → DNA extraction. → specialized out of country genetic testing

---

Referral centre for workup of adults with suspicion of or confirmed IBMFS:

- **85** active patients

  - second opinion from adult hematology
  - referral from clinical genetics
  - transition of care from Hospital for Sick Children

2. Develop transition of care framework

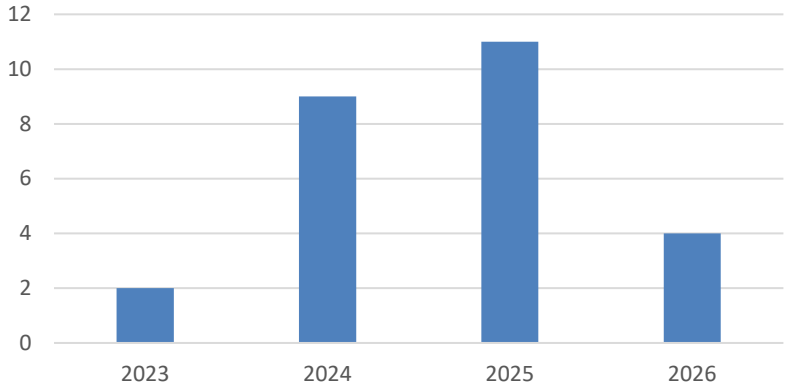
IBMFS diagnosed in childhood are managed in specialized pediatric clinics

Transition to adult care is an stressful time for patients/families and a very high risk period to fall behind on screening and be lost to follow-up

Adult IBMFS clinics are historically an unmet clinical need

Hospital for Sick Children – Sunnybrook collaboration since Dec 2023

26 transfers to date



3. Foster clinical expertise, collaboration & research

City-Wide Bone Marrow Failure Rounds

- pediatric hematology
- adult hematology
- bone marrow transplant
- genetics

Research activities

Familial Cancer (2025) 24:31
https://doi.org/10.1007/s10689-025-00455-x

CORRESPONDENCE

Azacitidine and venetoclax for the treatment of AML arising from an underlying telomere biology disorder

Arjun Pandey[1] · Talia Mancuso[2] · Lea Velsher[1,3] · James A. Kennedy[1,4]

Biobanking initiatives

Canadian Inherited Marrow Failure Registry

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Questions?

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