Bone Marrow Failure

Peter E. Newburger, MD
Professor of Pediatrics and
Molecular, Cell, & Cancer Biology
UMass Chan Medical School

Classification of Bone Marrow Failure

Acquired Aplastic Anemia

- Direct causes: radiation, drug, virus
- Associated with:
  - Viruses: Post-viral (probably autoimmune)
  - Immune Disorders: Hypogammaglobulinemia, XLP, thymoma
  - Myelodysplasic syndromes
  - Paroxysmal nocturnal hemoglobinuria (PNH)
- IDIOPATHIC (but some turning out to be late-onset inherited)

Inherited Bone Marrow Failure Syndromes

- Fanconi anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.

Acquired Aplastic Anemia

- First described in 1888 by Ehrlich
- Incidence: 2 cases per 10^6/year
- Biphasic peak age:
  - 15 – 25 and > 60 years of age
- Male:Female 1:1

Direct causes of acquired aplastic anemia

- Radiation
- Drugs/Chemicals
  - Direct Effects
    - Cytotoxic Agents, benzene
  - Idiosyncratic
    - Chloramphenicol; anti-inflammatory, anti-epileptic and other drugs
- Viruses
  - Hepatitis, EBV, HIV, parvovirus B19

Severe Aplastic Anemia Definition

Two of three cytopenias as defined:

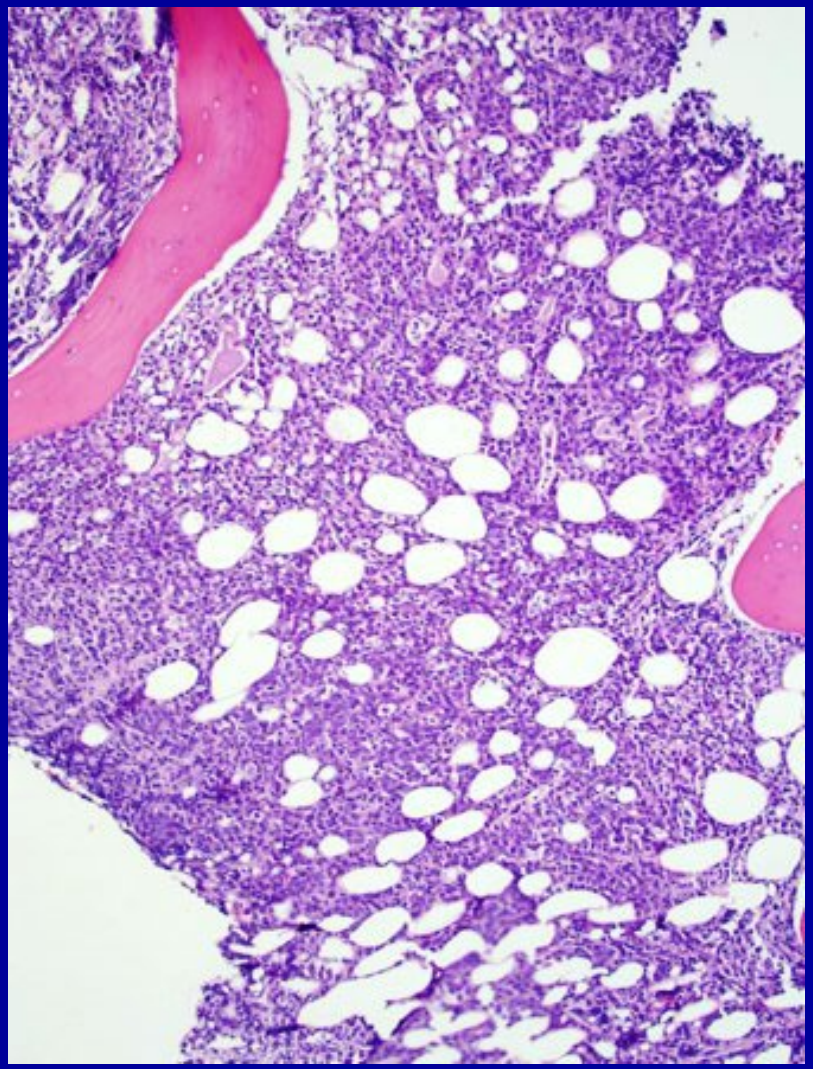
- **Absolute neutrophil count $\leq$ 500/µl**
- **Platelet count < 20K /µl**
- **Reticulocyte count < 40 x 10^9/L**

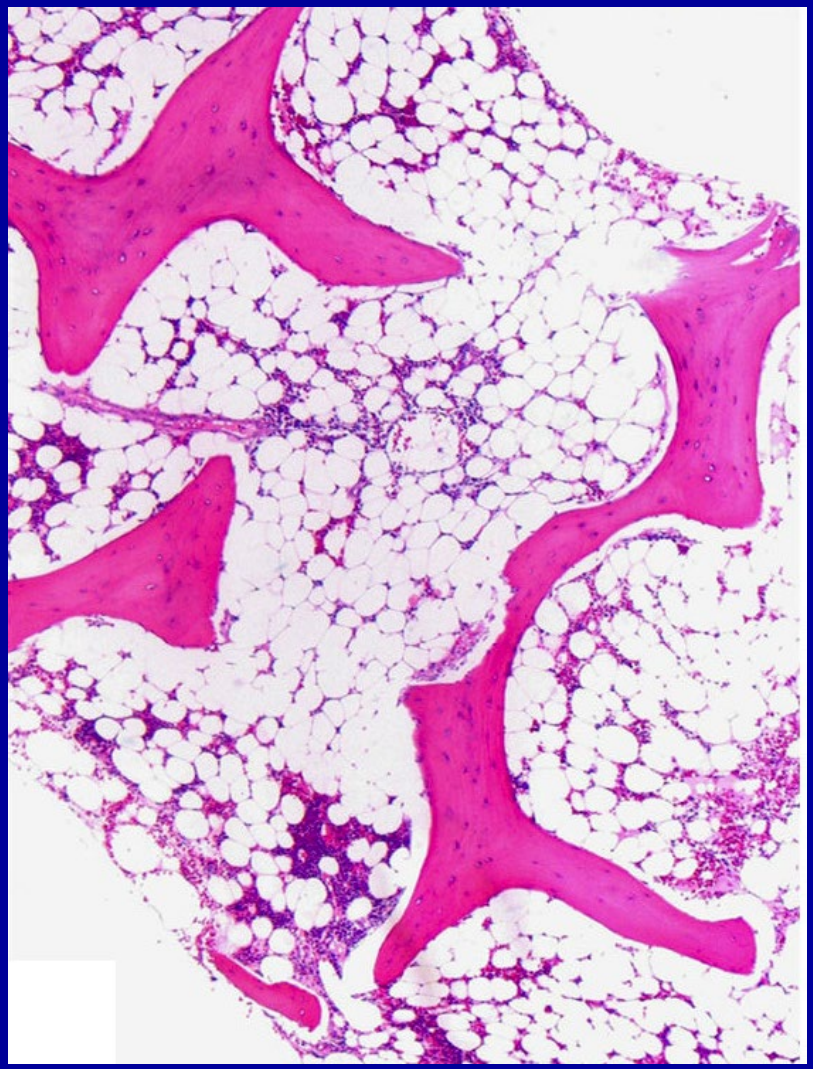
And

- **Bone marrow cellularity <25%**

Mild/moderate aplastic anemia is less precisely defined but refers to less severe cytopenias and marrow hypoplasia

Severe aplastic anemia: hypocellular bone marrow





Severe Aplastic Anemia Therapy

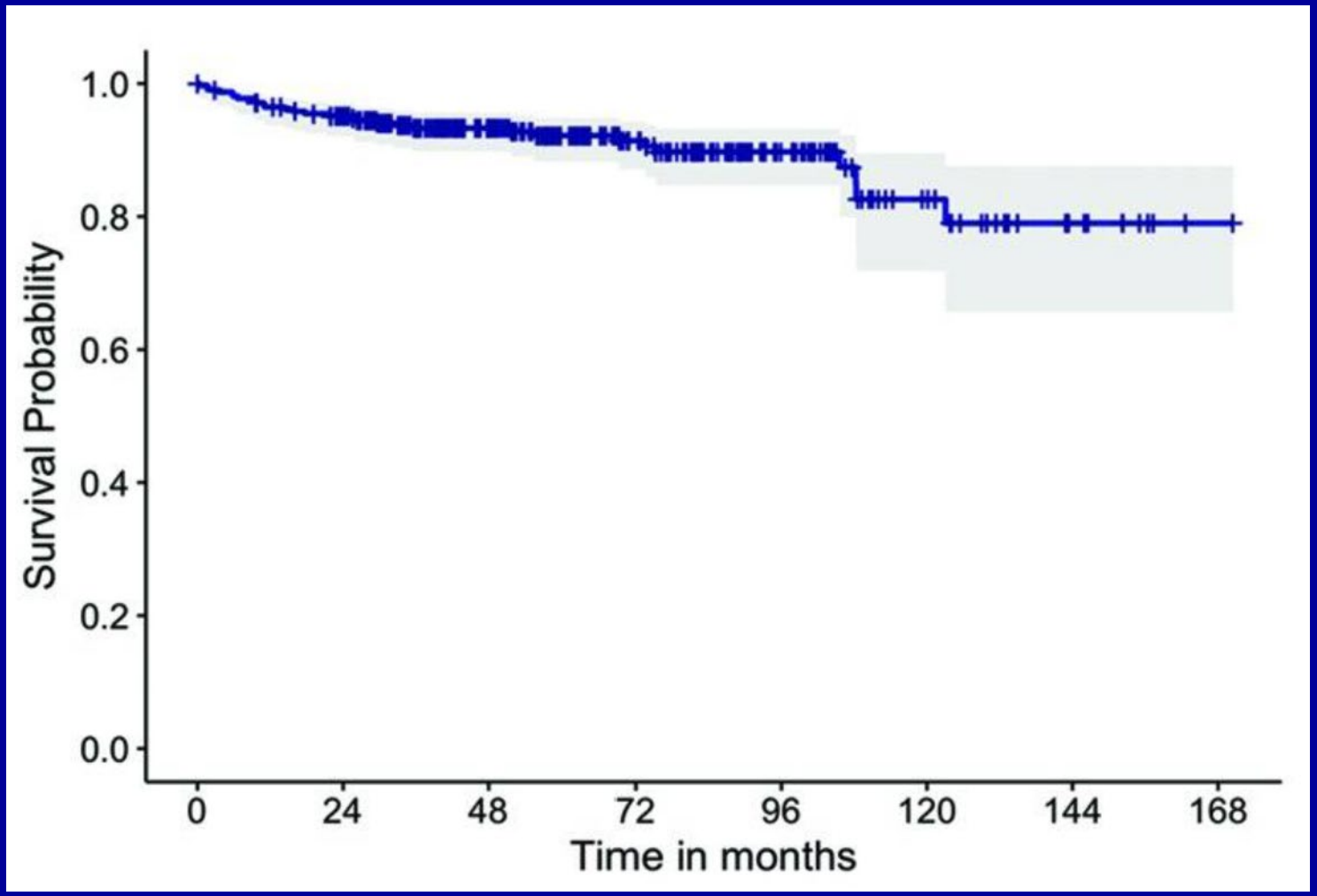
Immunosuppressive therapy (IST):
Anti-thymocyte globulin + cyclosporine A

vs.

Hematopoietic stem cell transplantation

Current randomized trial of MUD transplant vs IST
(TransIT: ClinicalTrials.gov: NCT05600426)

Treatment with IST



Haematologica. 2019; 104: 1974–1983

Treatment with IST

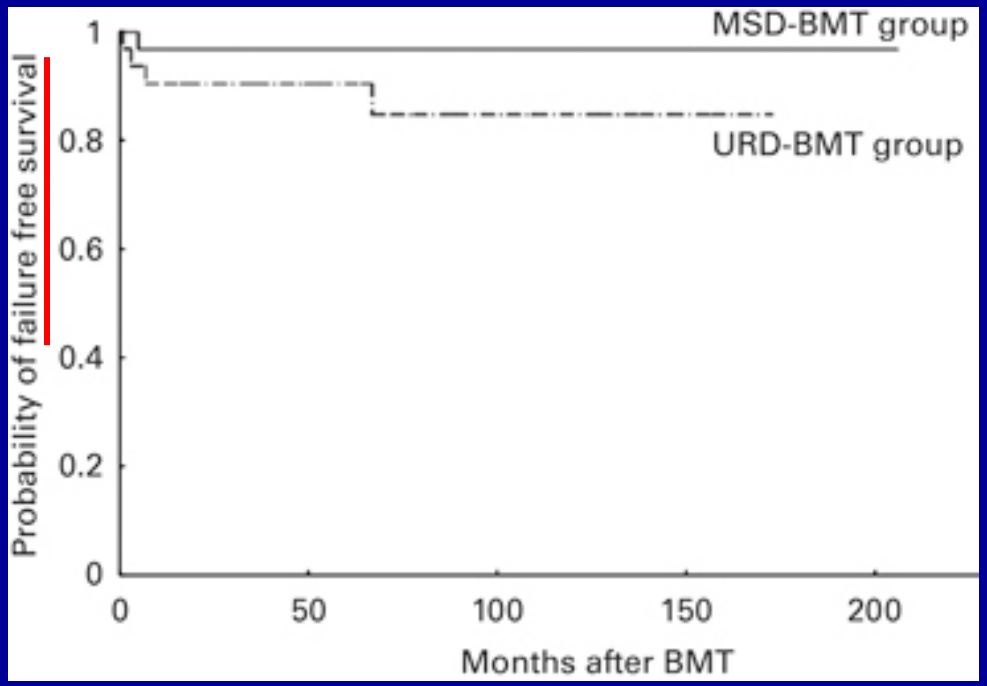
Short-term survival with good to excellent response to IST in approximately 85%, but…

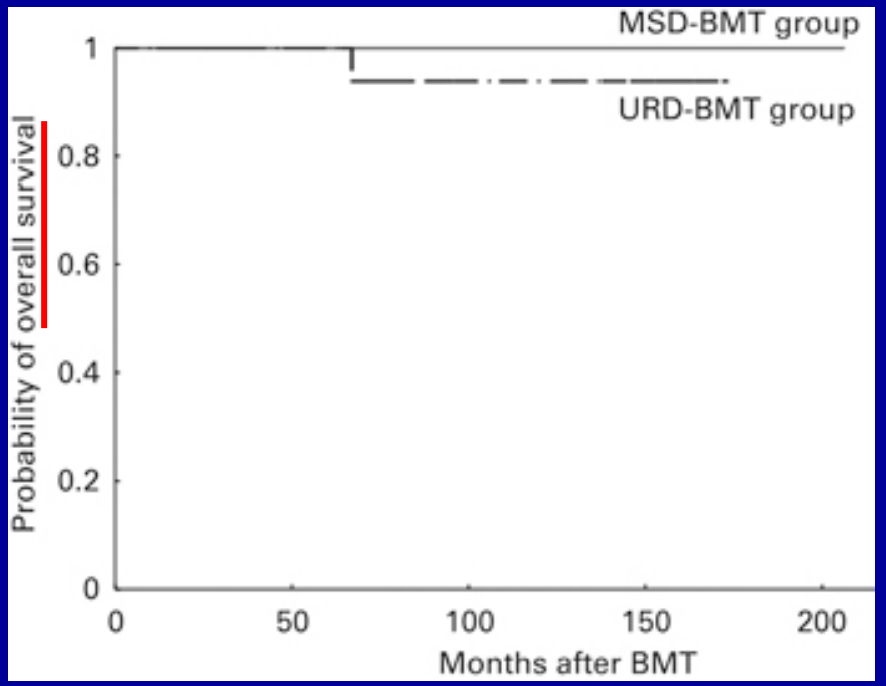
- **15 – 30% require ongoing cyclosporine**

- **25% relapse rate at 5-15 years**

- **Risk of Clonal Disease (MDS, AML or PNH):**
  18 – 30 % @10 years
  vs
  3.1% for transplant

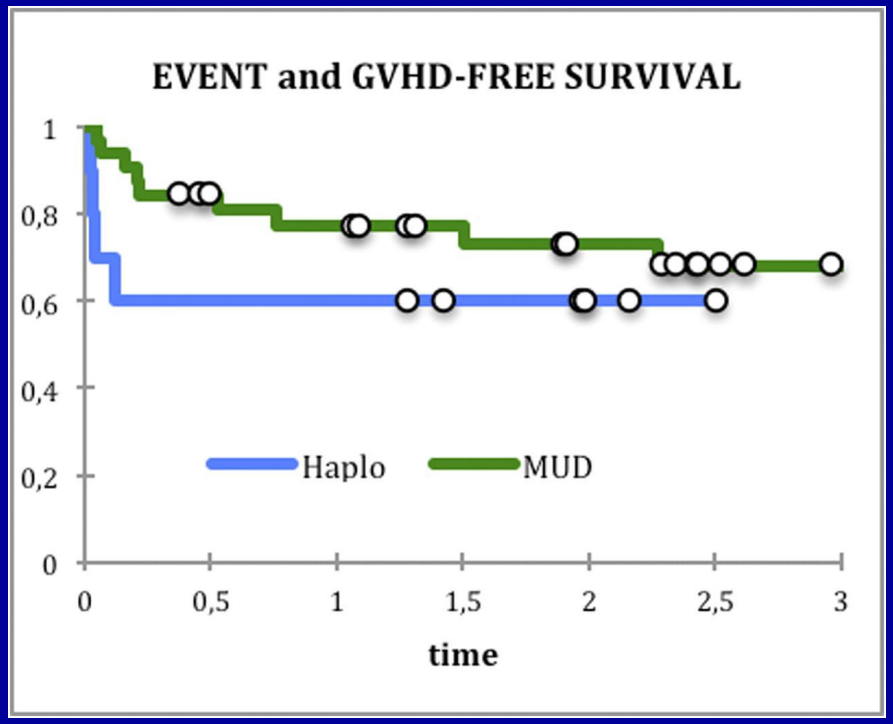
HSCT for severe aplastic anemia: Matched sibling vs unrelated donor

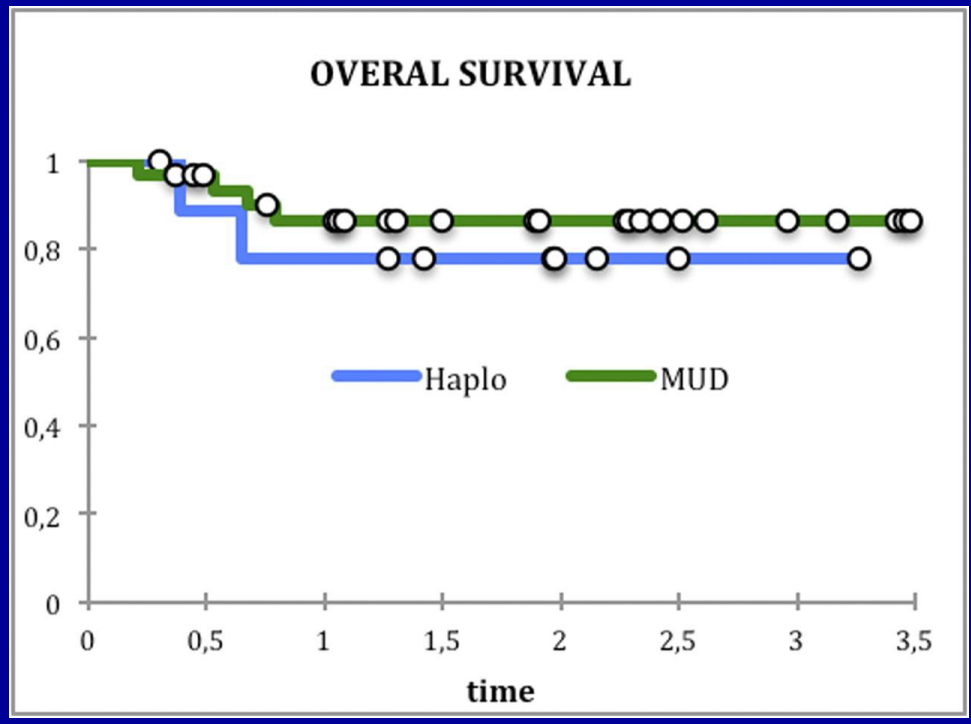




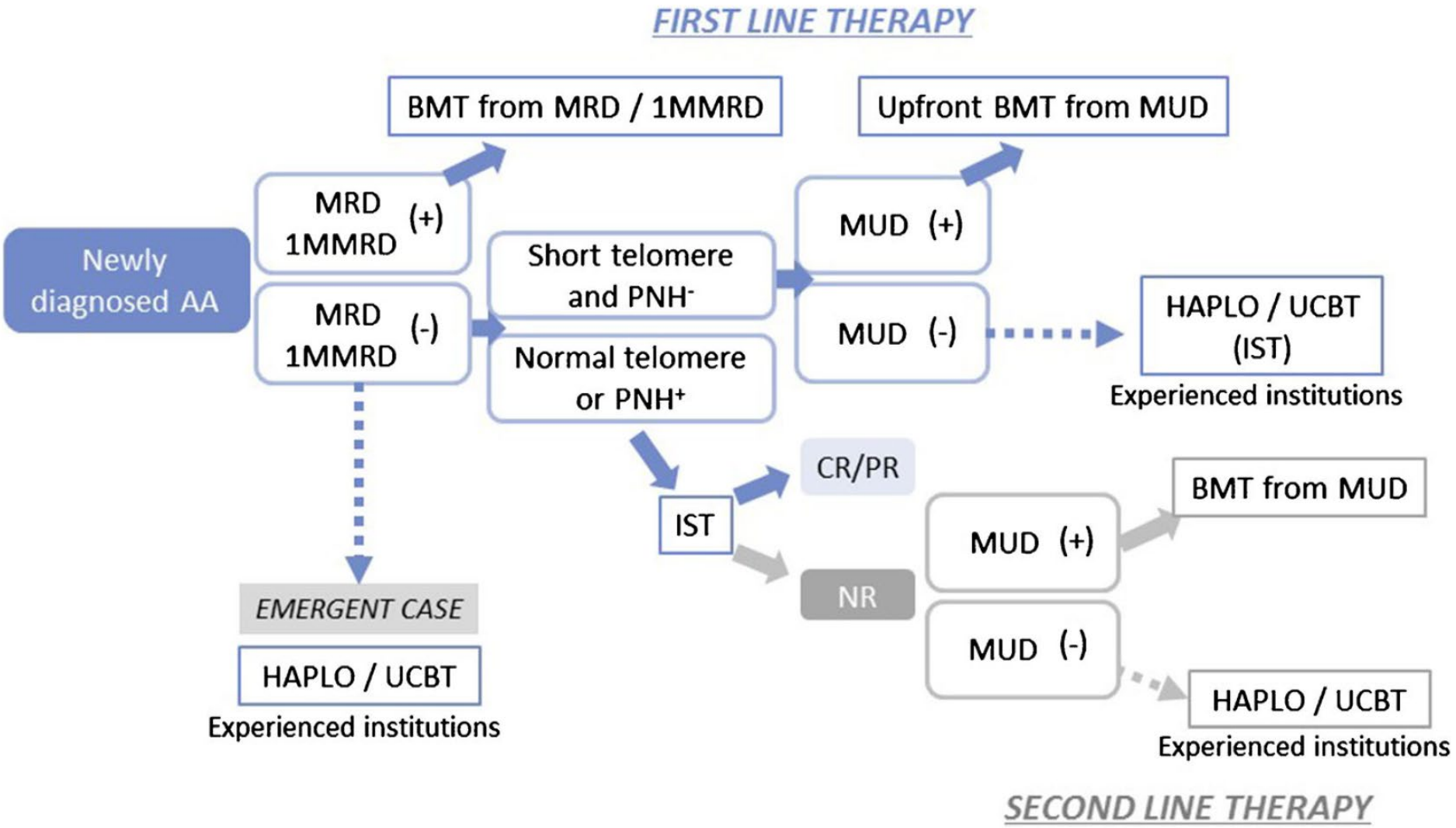
Bone Marrow Transplantation 2010;45:1508

HSCT for severe aplastic anemia: Haplo-identical family vs unrelated donor





Blood 2016;128:2294



Curr Oncol Rep 20, 67 (2018).
https://doi.org/10.1007/s11912-018-0716-8

TransIT trial

STUDY TITLE: A Phase III Randomized Trial Comparing Unrelated Donor Bone Marrow Transplantation With Immune Suppressive Therapy for Newly Diagnosed Pediatric and Young Adult Patients With Severe Aplastic Anemia (TransIT, BMT CTN 2202)

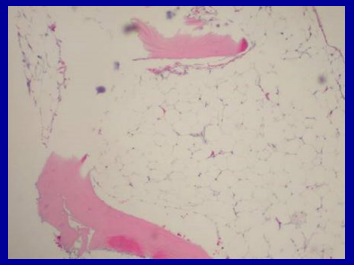
CLINICALTRIALS.GOV IDENTIFIER: NCT05600426

STUDY DESIGN: In this multicenter randomized phase III clinical trial, patients age 25 years and younger with newly diagnosed severe aplastic anemia (SAA) who lack a known human leukocyte antigen (HLA)-matched sibling donor will be randomized 1:1 to receive either immunosuppressive therapy (IST) with cyclosporin and horse antithymocyte globulin (ATG) or an unrelated donor bone marrow transplantation (BMT) with non-myeloablative conditioning (ATG/fludarabine/cyclophosphamide/TBI 2 Gy) and cyclosporine/methotrexate (MTX) as graft-versus-host disease prophylaxis. The primary endpoint is the time from randomization to treatment failure (defined as a recommendation to begin second-line definitive therapy) or death from any cause. A multitude of secondary clinical objectives including assessments of immune reconstitution and gonadal function, along with interesting correlative exploratory objectives focused on germline mutations and clonal hematopoiesis, are included.

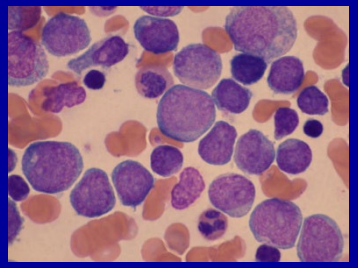
Inherited Bone Marrow Failure Syndromes

Key shared characteristics

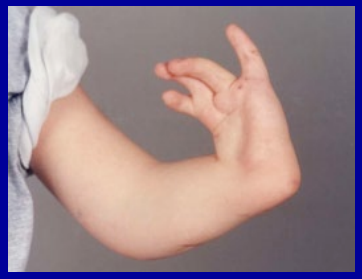
Bone marrow failure



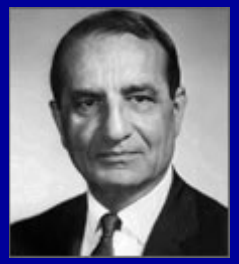
Cancer predisposition



Congenital anomalies



Lots of eponyms: Fanconi, Kostmann, Diamond-Blackfan, Shwachman-Diamond



(same Diamond)

Inherited Bone Marrow Failure Syndromes
Genetics: many genes/phenotype

PANCYTOPENIC:

Fanconi Anemia

mostly AR, very rare XLR

13 DNA repair genes

Dyskeratosis congenita

XLR, AD, AR

at least 16 telomere maintenance genes

Inherited Bone Marrow Failure Syndromes
Genetics

SINGLE LINEAGE:

Diamond Blackfan anemia (erythroid) - AD (21 genes, mostly ribosomal)

Severe congenital neutropenia – mostly AD (*ELANE*), many rare AR, very rare XLR

Shwachman Diamond syndrome (mostly myeloid) - AR (*SBDS*, others?)

Amegakaryocytic thrombocytopenia - AR (*MPL, THPO*)

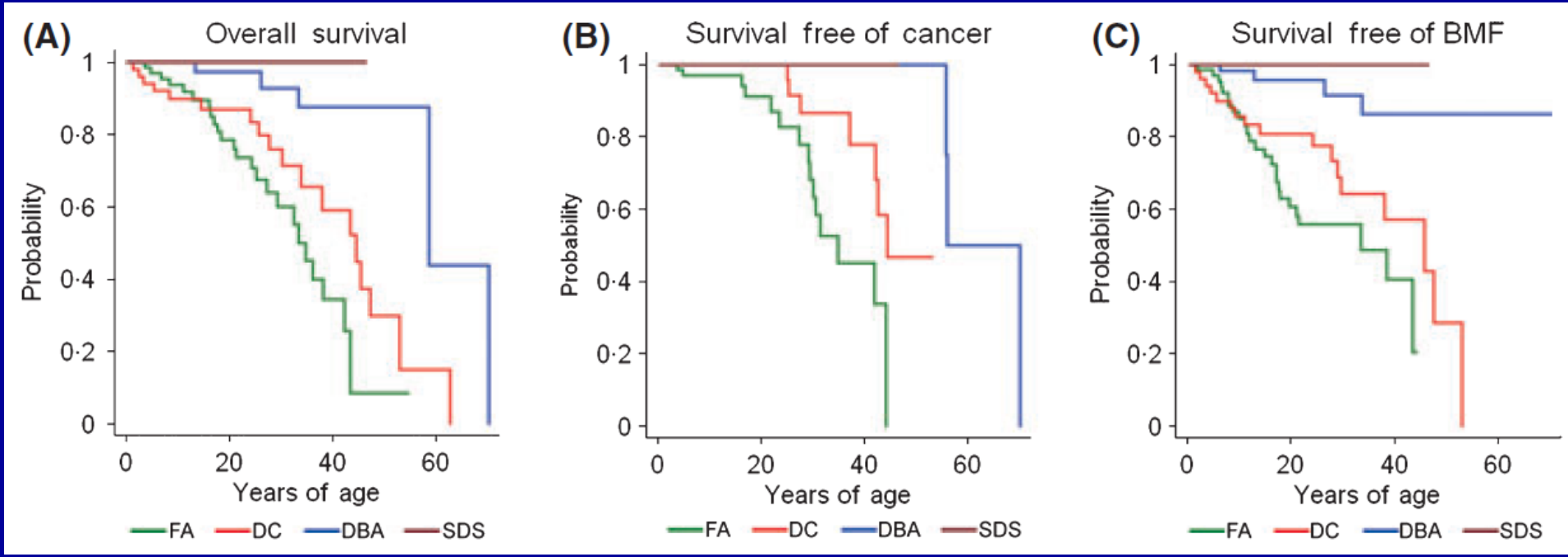
Thrombocytopenia absent radius (TAR) syndrome - AR (*RBM8A*)

Relative Risk for Cancer in Inherited Bone Marrow Failure Syndromes

Type	FA	DBA	SDS	DC
Leukemia	900	90	550	40
Solid tumors	9	1.7	?	13

FA: Fanconi anemia
DBA: Diamond-Blackfan anemia
SDS: Shwachman-Diamond syndrome
DC: Dyskeratosis congenita

Malignancies and survival patterns in the National Cancer Institute IBMFS cohort study



Alter et al., Br J Haematol 2010;150:179-188)

Case #1

- Infant boy presented to genetics for evaluation.
- History significant for:
  - IUGR, FTT
  - Esophageal stricture
  - Small ASD
  - Vertebral hypoplasia
  - Pelvic kidney
  - Hypoplastic thumbs

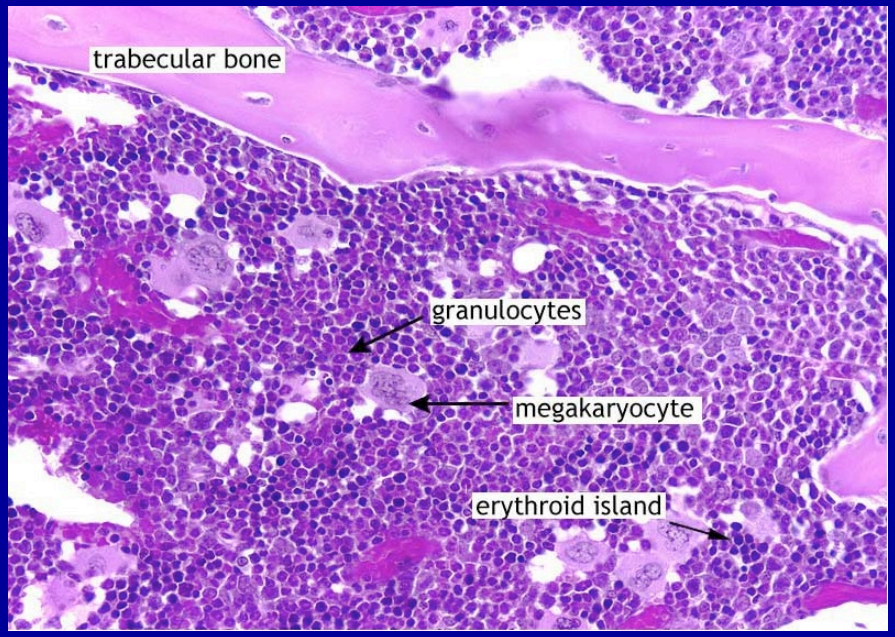
Case #1 (cont)

- Diagnosed with VACTERL syndrome. No further followup.

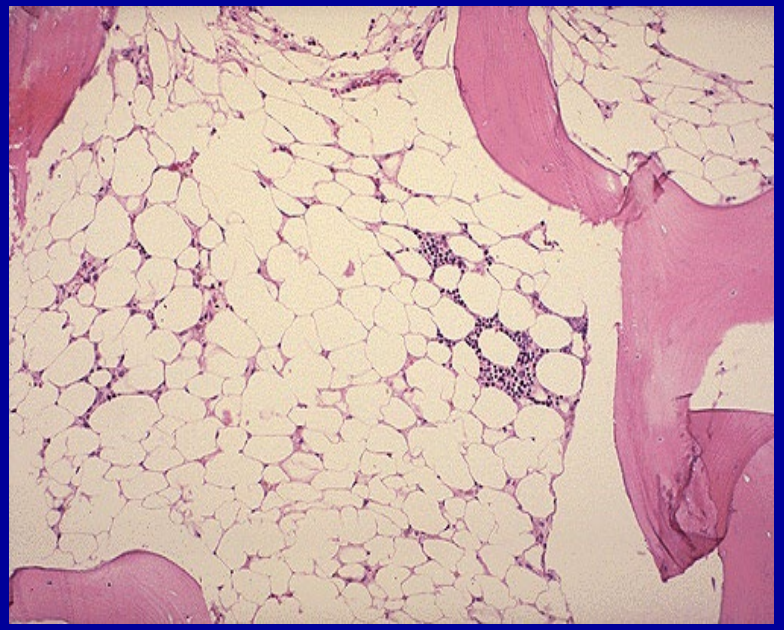
- Presented again at age 12 with petechiae and fatigue
  - WBC: 2.1
    - ANC: 200
  - Hb 6, Hct 18
  - Platelets 12K
  - MCV 104

Case #1 (cont)

- Referred to hematology/oncology



Healthy marrow



Case #1

Diagnosis: Aplastic anemia

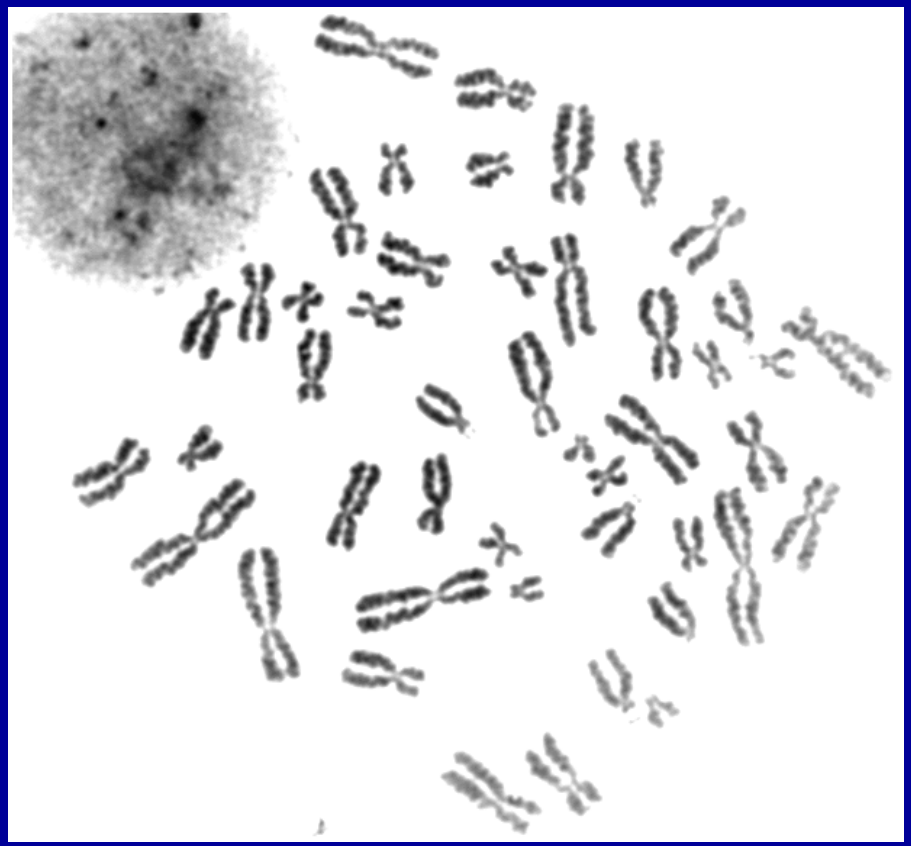
Case #1

- On review of prior labs:
  - Pre-op labs before corrective surgery age 4:
    - WBC 5.8, Normal differential
    - Hb 13, Hct 38
    - **Platelets 105K**
    - **MCV: 103**

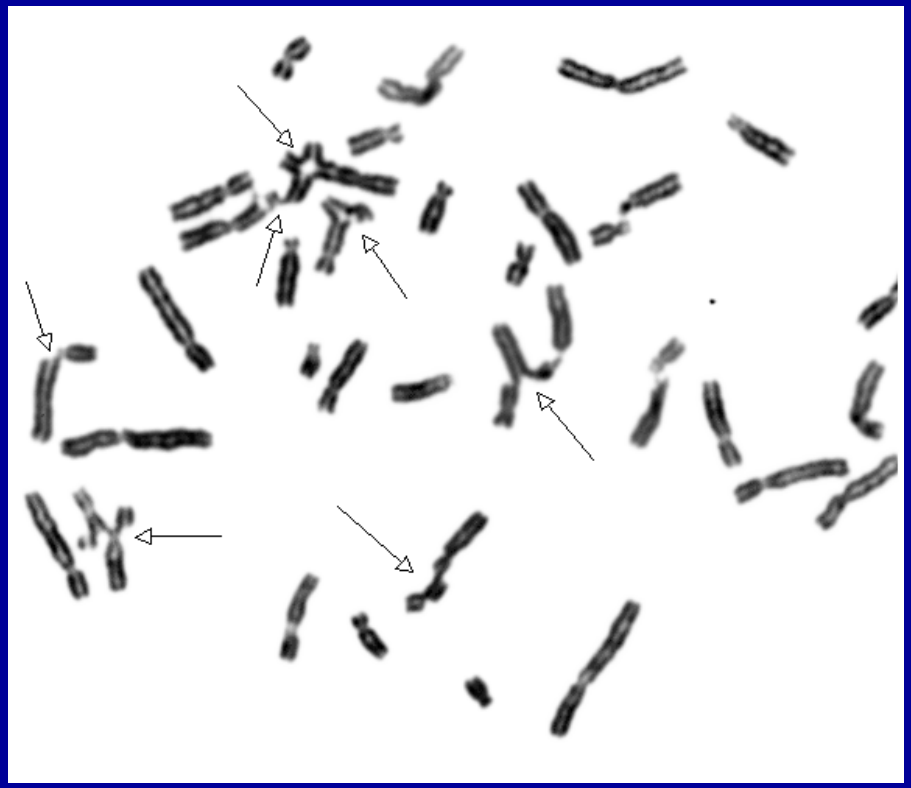
- A diagnostic test was sent…

Chromosome Breakage Analysis

Control



+ DEB or MMC



Courtesy of Lisa Moreau, Dana Farber Cancer Institute

Fanconi Anemia

Described in 1927

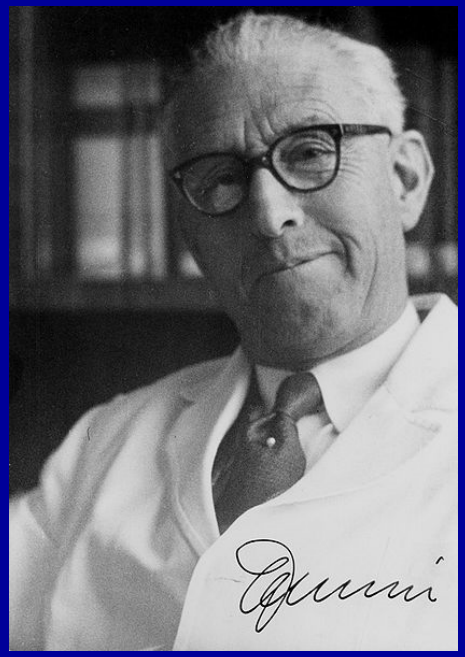
Autosomal Recessive Genetic Disorder (>99%):

- **Heterozygote frequency 1 in 300**
- **1 in 100 in Ashkenazi Jews and Afrikaans**
- **1 in 60 Romani**

X-linked (<1%)

Characterized by:

- **Bone marrow failure**
- **Congenital anomalies**
- **Predisposition to cancer**

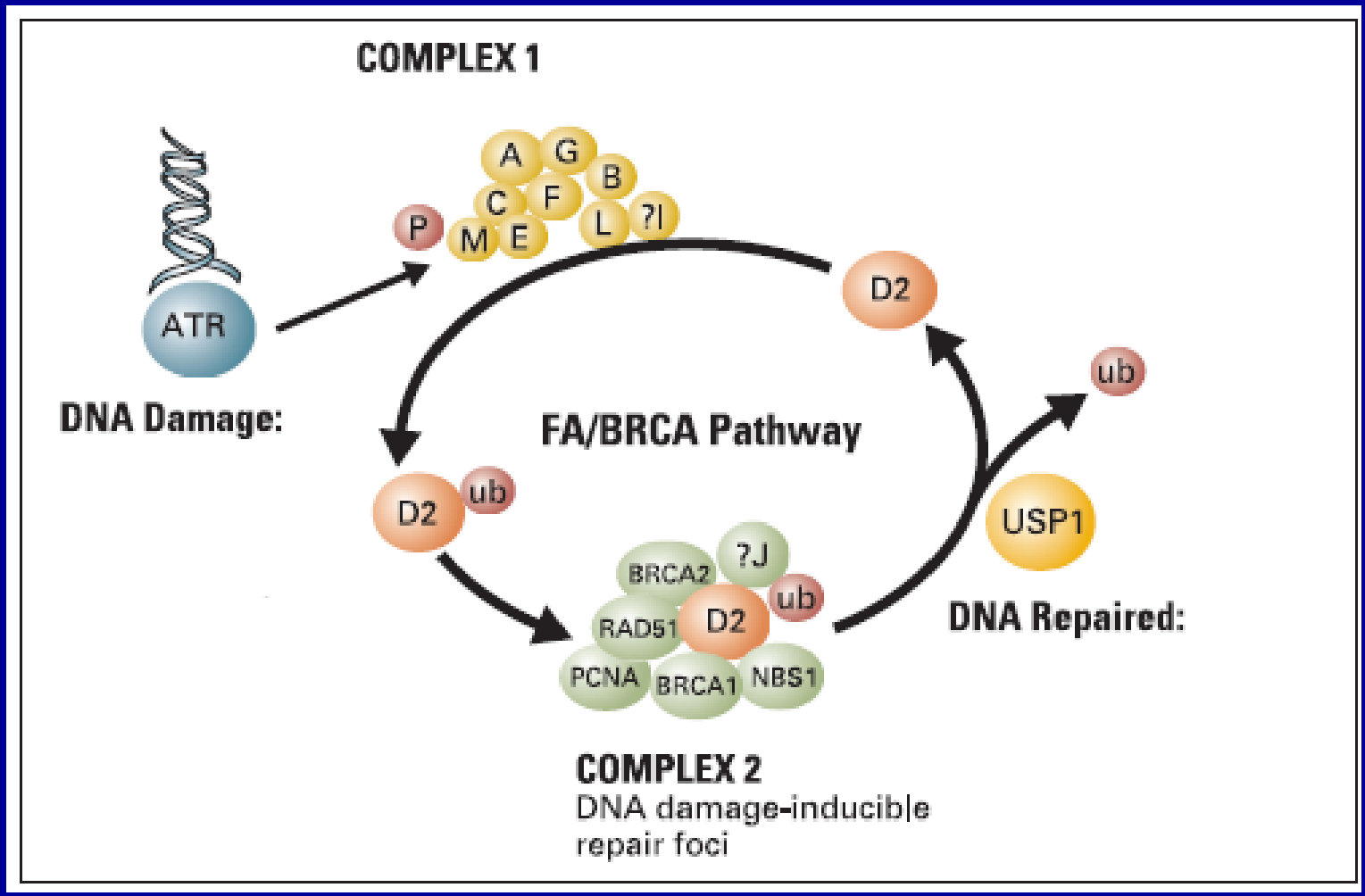


Guido Fanconi (1892-1979)

Fanconi Anemia Genetics

Complementation Group	Locus	% Pts	Protein Product
FANCA	16q24.3	66%	FANCA
FANCB	Xp22.31	<1%	FANCB
FANCC	9q23.3	9.5%	FANCC
FANCD1	13q12.3	3.3%	**BRCA2**
FANCD2	3p25.3	3.3%	FANCD2
FANCE	6p21.3	2.5%	FANCE
FANCF	11p15	2.1%	FANCF
FANCG	9p13	8.7%	FANCG
FANCI	15q26.1	1.6%	FANCI
FANCJ	17q23	1.6%	**BACH1** (*BRCA1*-associated C-terminal helicase)
FANCL	2p16.1	<1%	PHF9
FANCM	14q21.3	<1%	FANCM
FANCN	16p12	<1%	**PALB2** (partner and localizer of BRCA2)

Fanconi Anemia DNA Repair Pathway



J Clin Oncol 2006;24:3799

Fanconi Anemia
Congenital Anomalies

Anomaly	Frequency
Skin	60%
Short Stature	57%
Upper limb	48%
Male hypogonadism	37%
Female hypogonadism	3%
Head	27%
Eyes	26%
Renal	23%

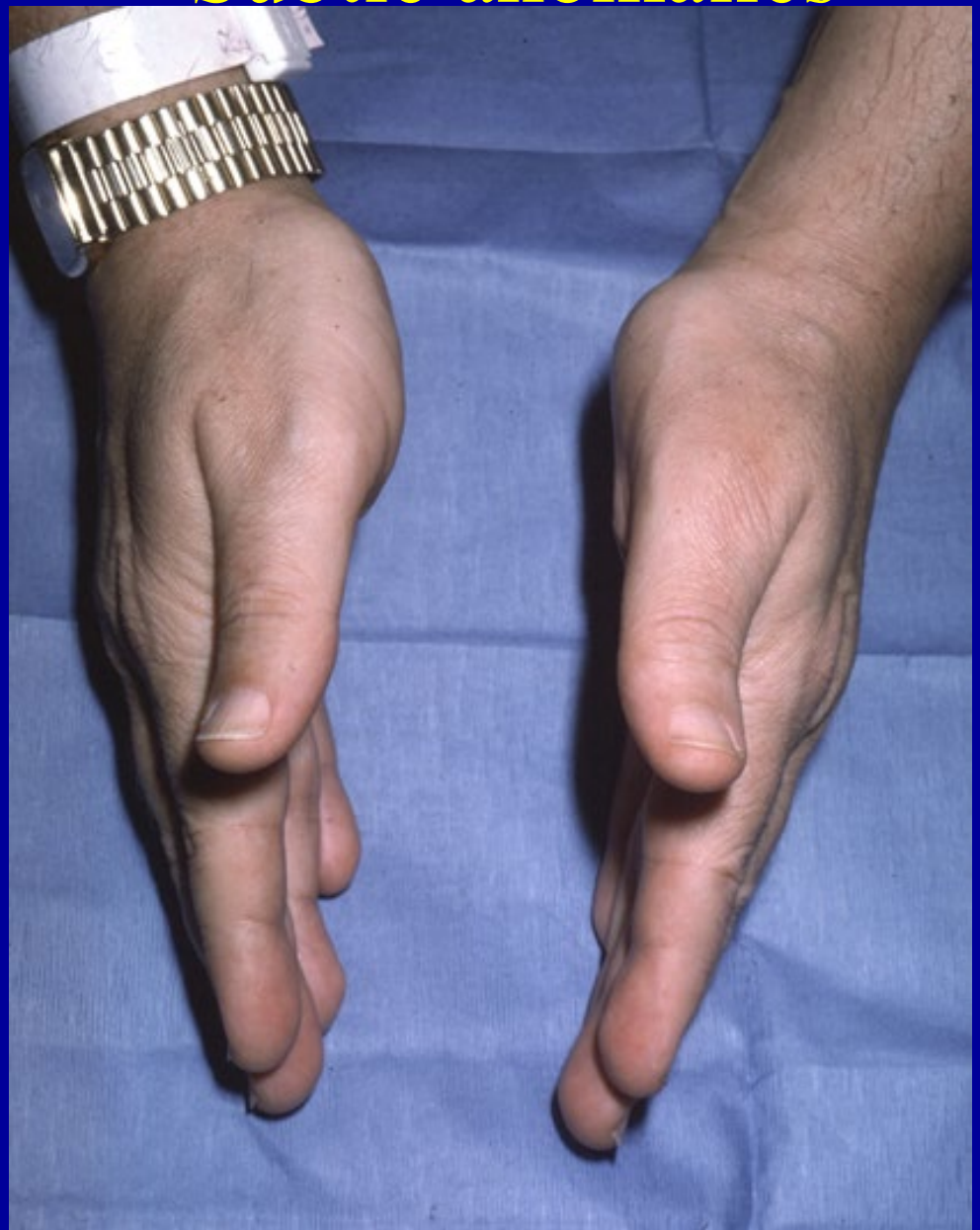
Fanconi Anemia
Congenital Anomalies

Anomaly	Frequency
Low birth weight	12%
Developmental delay	13%
Lower limbs	8%
Ears	10%
Other skeletal	6%
Cardiopulmonary	6%
Gastrointestinal	4%
Other	5%

Congenital Anomalies
Classic phenotype

- Microcephaly
- Hypertelorism
- Webbed neck
- Abnormal thumbs
- Dislocated hips

Fanconi Anemia
Subtle anomalies



Fanconi Anemia
Diagnostic Suspicion

High Suspicion

- **Aplastic anemia/myelodysplasia with characteristic birth defects**
- **Macrocytosis in a patient with characteristic birth defects**
- **Karyotype with spontaneous breaks**
- **Myelodysplasia in childhood**
- **Severe sensitive to chemotherapy**

Fanconi Anemia
Diagnostic Suspicion

Intermediate Suspicion

- **Unexplained macrocytosis**
- **Androgen responsive aplastic anemia**
- **Characteristic birth defects even without hematologic findings**
- **Non-immune thrombocytopenia in a child**
- **Cancer at an atypically early age**
  - **Head/neck/esophagus <40 years of age**
  - **Vulva/anus <30 years of age**

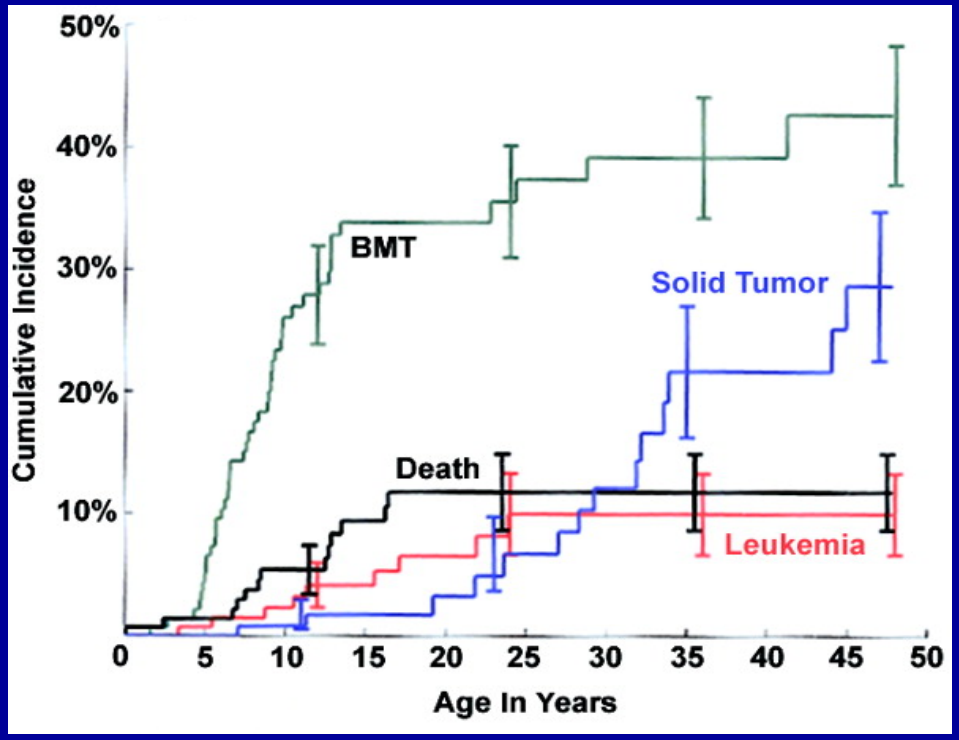
Management and Treatment of Fanconi Anemia

- Careful evaluation of congenital anomalies
- Careful monitoring for cancer
  - Gynecologic, Hematologic, GI
- Supportive care for marrow failure
  - Androgen therapy
  - Hematopoietic growth factors
  - Transfusion support
- Hematopoietic stem cell transplantation
  - Matched related donors
  - (Alternative donors)
- (Gene therapy)

FA: Gene therapy trials

Study Title	NCT Number	Status	Conditions	Interventions
FANCA **Gene Transfer** for **Fanconi Anemia** Using a High-safety, High-efficiency, Self-inactivating Lentiviral Vector	NCT03351868	Unknown status	• **Fanconi Anemia**	• Genetic: **Gene**-modified a cells
Gene Therapy for **Fanconi Anemia**	NCT01331018	Active, not recruiting	• **Fanconi Anemia**	• Procedure: Bone Marrow • Biological: Filgrastim • Biological: Genetically Eng poietic Stem Progenitor C • 5 more
Bone Marrow Cell **Gene Transfer** in Individuals With **Fanconi Anemia**	NCT00272857	Completed	• **Fanconi Anemia**	• Genetic: Retrovirus Constr
Lentiviral-mediated **Gene Therapy** of **Fanconi Anemia** Patients Subtype A	NCT03157804	Completed	• **Fanconi Anemia**	• Procedure: IV administrati Engineered Hematopoieti ors Cells (HSPCs) • Biological: Genetically Eng poietic Stem/Progenitor C • Other: Laboratory Biomar • 3 more
Gene Therapy for **Fanconi Anemia, Complementation Group A**	NCT04248439	Active, not recruiting	• **Fanconi Anemia Complementation Group A**	• Biological: RP-L102

Fanconi Anemia: Competing Risk Analysis for Adverse Events



By age 48 years 93% had either died, received a transplant, or developed a solid tumor or leukemia.

Blood 2003 ;101:822

Case #1 (cont)

- Patients sister was an HLA match
- Sister's exam:
  - Normal height, no congenital anomalies
  - Negative past medical history

- Sister's cbc: WBC 6.0, Hb 12.5, Hct 36, Plt 145, MCV 101. B12 and Folate normal.

- Chromosomal breakage study sent:

+Fanconi anemia

⁂ TEST ALL SIBLINGS OF AFFECTED PATIENT

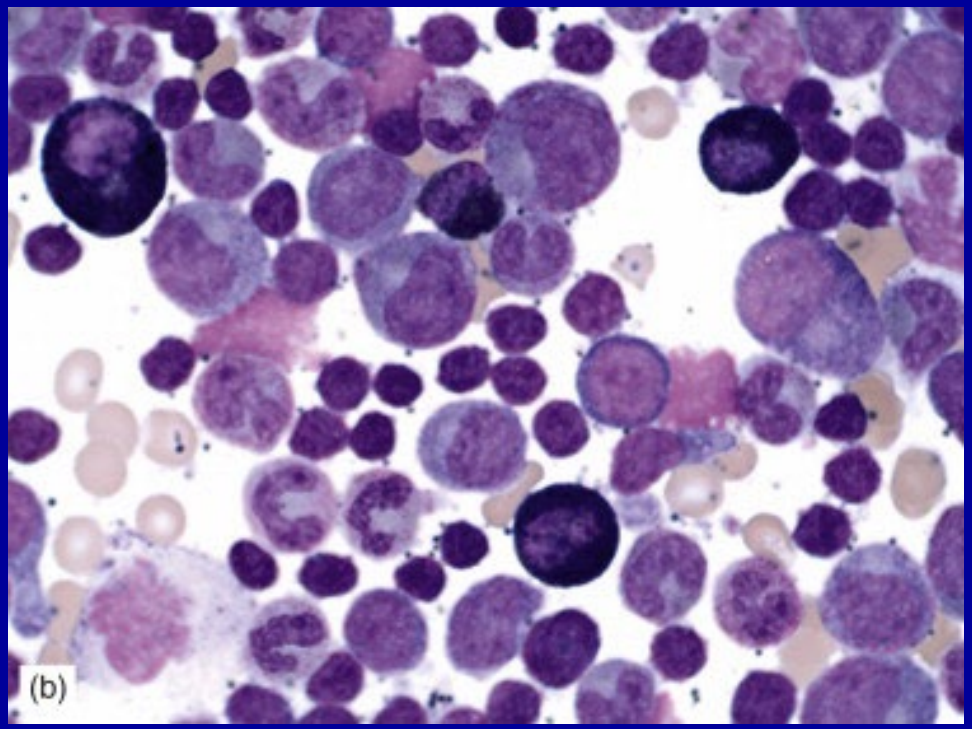
Case #2

2-month-old female with history of pallor since birth

- History significant for:
  - Older sibling transfusion-dependent, died age 2
  - Transfusions at ages 48 hr and 1 month
- Hgb 2.6, retic 0.2%, MCV 95
- WBC and plt normal

Case #2

- Bone marrow: M:E 58:1 (normal 3-4:1), greatly reduced RBC precursors



- Genetics: frameshift mutation in *RPS19*

Genetics of DBA

Multiple ribosomal protein genes

Gene	Frequency of mutation	Chromosome Locus	Protein
GATA1		Xp11.23	Erythroid transcription factor
RPL5	7%	1p22.1	60S ribosomal protein L5
RPL11	5%	1p36.11	60S ribosomal protein L11
RPL15		3p24.2	60S ribosomal protein L15
RPL26		17p13.1	60S ribosomal protein L26
RPL27		17q21.1-q21.2	60S ribosomal protein L27
RPL31		2q11.2	60S ribosomal protein L31
RPL35A	3%	3q29	60S ribosomal protein L35a
RPS7	1%	2p25.3	40S ribosomal protein S7
RPS10	6%	6p21.31	40S ribosomal protein S10
RPS17	1%	15q25.2	40S ribosomal protein S17
RPS19	25%	19q13.2	40S ribosomal protein S19
RPS24	2%	10q22.3	40S ribosomal protein S24
RPS26	3%	12q13.2	40S ribosomal protein S26
RPS27		1q21.3	40S ribosomal protein S27
RPS28		19p13.2	40S ribosomal protein S28
RPS29		14q21.3	40S ribosomal protein S29
TSR2		Xp11.22	Pre-rRNA-processing protein TSR2 homolog

Diamond Blackfan Anemia
Classic Diagnostic Criteria

- Moderate to severe macrocytic anemia
- Reticulocytopenia
- Normal bone marrow cellularity with a paucity of erythroid precursors
- Age less than 1 year

Current Diagnostic Criteria for DBA

Definitive but not essential

Gene mutation described in DBA

Major

Positive family history (or laboratory testing, e.g. elevated eADA)

Anemia, reticulocytopenia, reduced erythroid progenitors in bone marrow

Minor

Elevated erythrocyte adenosine deaminase (eADA) activity

Congenital anomalies (including short stature) described in classical DBA

Elevated fetal hemoglobin

Macrocytosis

Age less than 1 year

No evidence of another IBMFS

No evidence of parvovirus infection

Differential Diagnosis of Childhood Pure Red Cell Aplasia

- Congenital
  - Diamond Blackfan anemia
  - Pearson Syndrome
- Acquired
  - Immune
    - Transient erythroblastopenia of childhood (TEC)
    - Tγ lymphoproliferative disease
  - Parvovirus
    - Acute (chronic hemolytic anemia)
    - Chronic (immune deficiency)
  - Systemic disease: Renal failure, malignancy, autoimmune
  - Pregnancy
  - Nutritional
  - Thymoma
  - Drugs or Toxins

Diamond Blackfan Anemia
vs
Transient Erythroblastopenia of Childhood

	Diamond Blackfan anaemia	Transient erythroblastopenia of childhood
Pure red cell aplasia	Present	Present
Age	Younger than 1 year ✸	Older than 1 year
Inheritance	Sporadic and dominant inheritance	Not inherited
Congenital anomalies	Present	Absent
Mean corpuscular volume (MCV)	Elevated	Normal
HbF	Elevated	Normal
i RBC antigen	Present	Absent
Erythrocyte ADA (eADA) activity	Elevated	Normal

May not be evident if Reticulocyte count is very low

May be elevated in recovery

✸ With genetic testing and increased recognition of DBA, older patients, even adults (e.g. parents) are being diagnosed

Br J Haematol 2008;142:859

Congenital Anomalies in DBA

Craniofacial
Hypertelorism
Microcephaly
High-arched palate
Ear malformations
Eyes
Blue sclera
Congenital cataracts
Glaucoma
Microophthalmos
Strabismus
Neck
Fusion of the vertebrae with flaring of the trapezius muscle (Turner-like appearance)
Elevation of the scapula (Sprengel deformity)
Thumb
Bifid thumb
Duplication
Subluxation
Hypoplasia
Absence
Flat hypoplastic thenar eminence
Weak/absent radial pulses
Triphalangeal thumb*

Urogenital
Dysplastic or horseshoe kidney
Duplication of the ureters
Renal tubular acidosis
Cardiac
Atrial and ventricular septal defects
Hypogonadism
Intellectual disability
Other skeletal abnormalities
Other anomalies

Low birth weight is common
Anomalies present in 30%

1. *Alter BP, Young NS. The Bone Marrow Failure Syndromes. In: Nathan and Oski's Hematology of Infancy and Childhood, Nathan DG, Orkin SH (Eds), W.B. Saunders Company, 1998, p.237.*
2. *Halperin DS, Freedman MH, Am J Pediatr Hematol Oncol 1989; 11:380.*

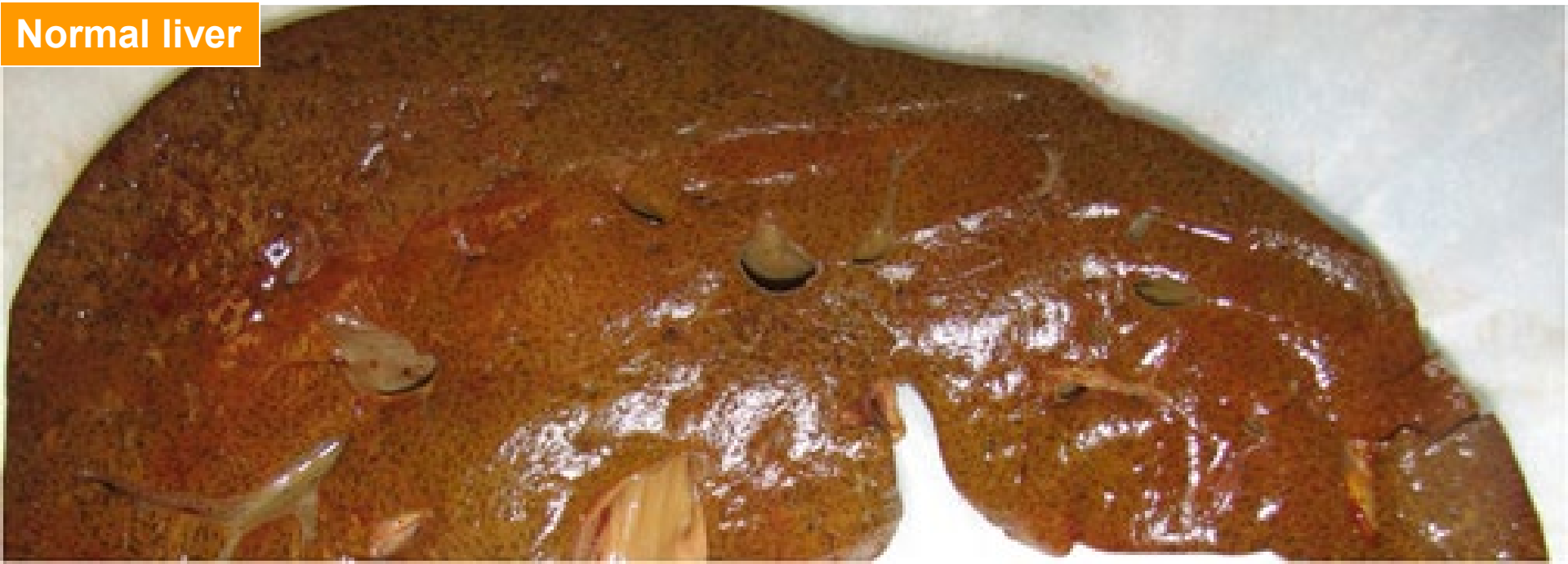
DBA Treatment

- Initial treatment response
  - 79% steroid responsive
  - 17% steroid non-responsive
  - 4% never treated with steroids

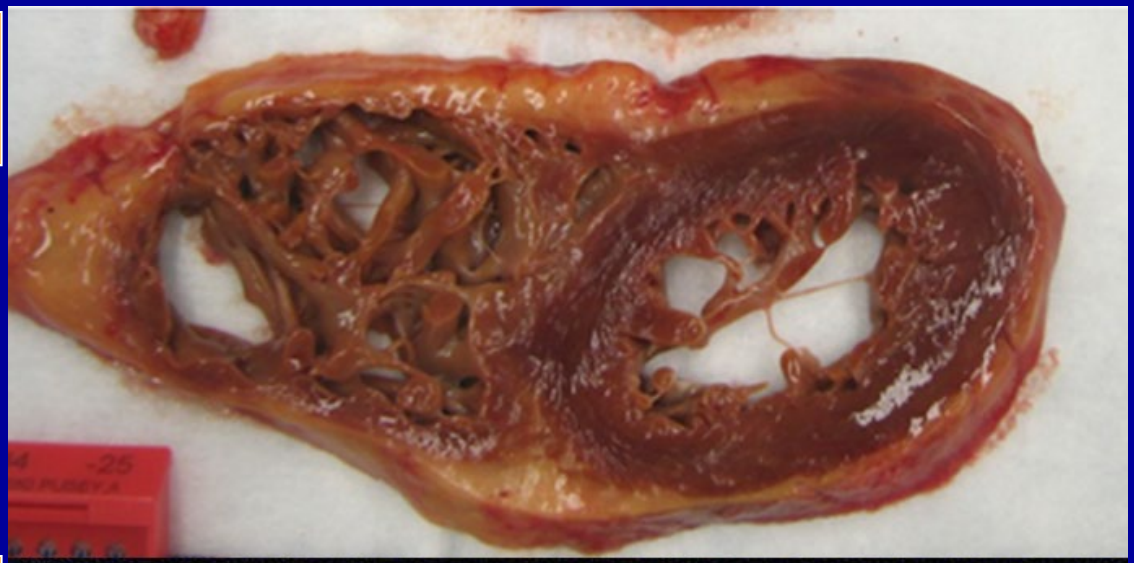
DBA
Transfusion therapy

- Used in first two years of life to avoid steroid-induced growth failure
- Universal iron overload after 2-3 years of chronic transfusion
- Follow ferritin (not very good) and MR measurement of liver/cardiac iron
- Chelation for iron overload

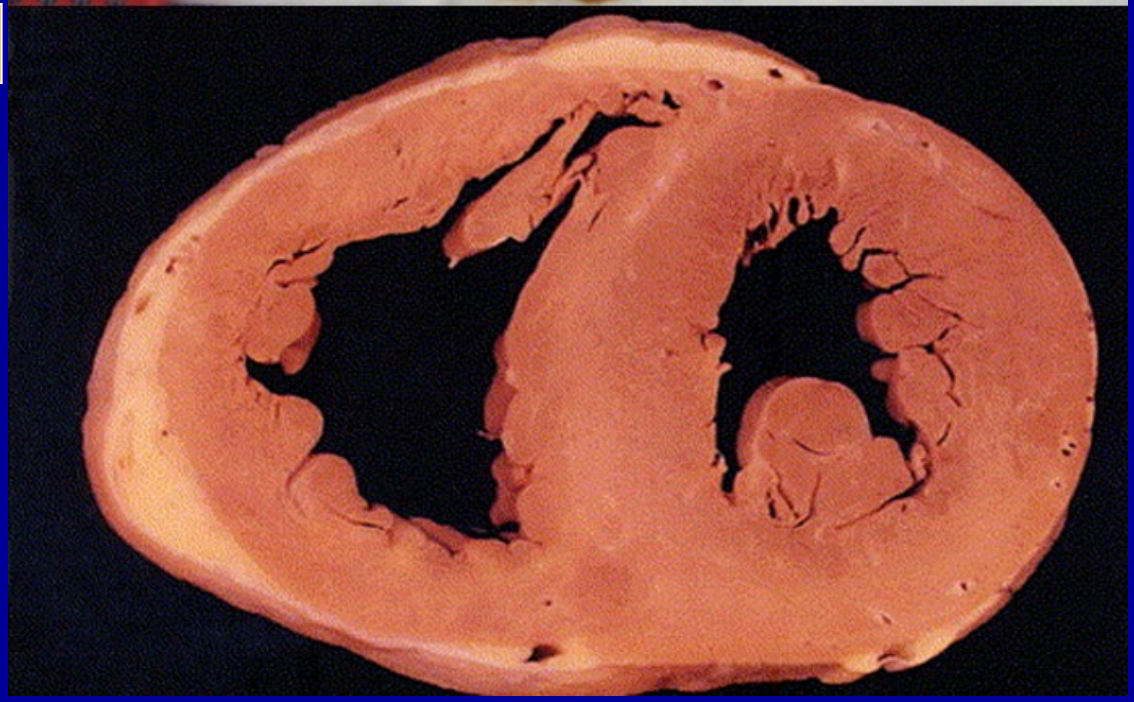

Liver with iron overload


Normal liver

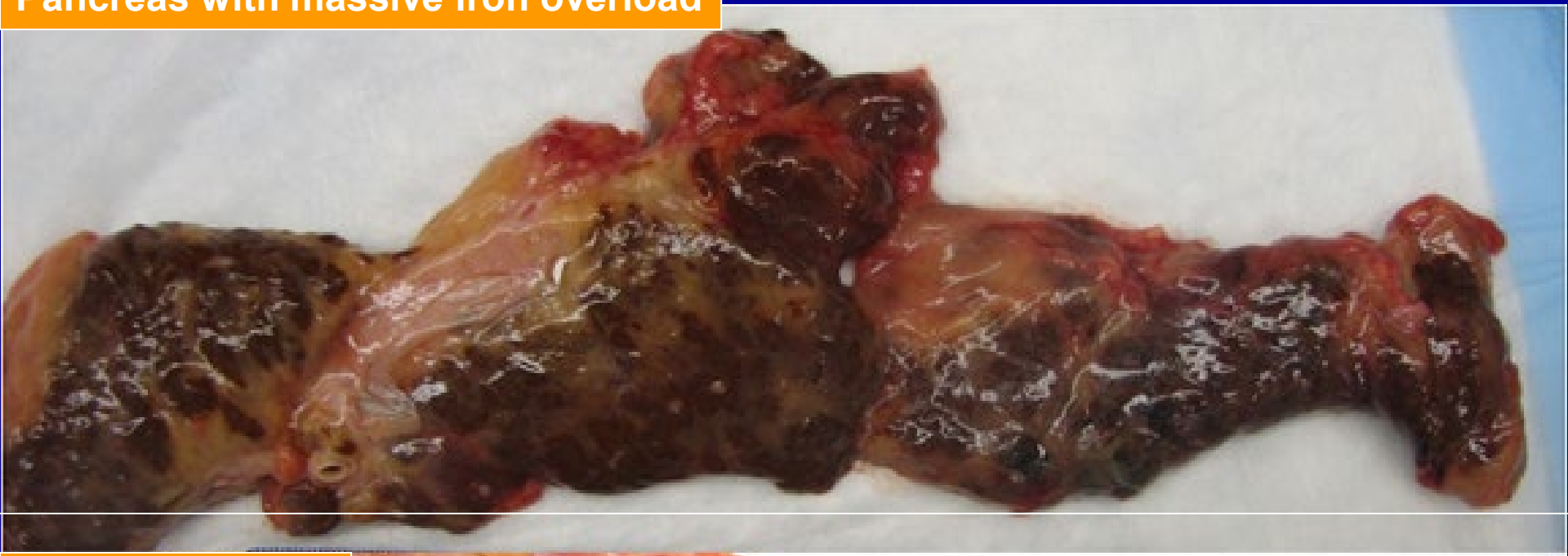
Dilated cardiomyopathy with iron overload



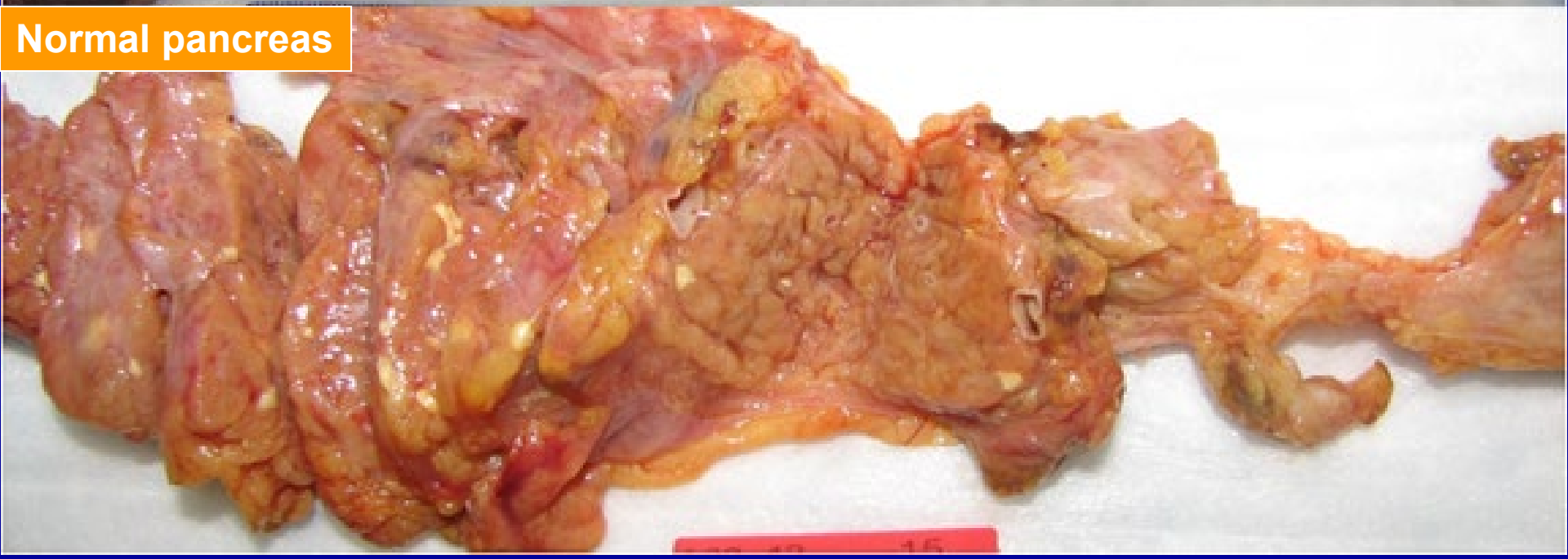
Normal heart



Pancreas with massive iron overload



Normal pancreas



HSCT for DBA

- DBA patients with HLA-identical matched siblings should be considered for early HSCT
- There has been a dramatic improvement in outcome for alternative donor HSCT since 2000.
- Cautions:
  - Possible spontaneous, durable remission at any age
  - Possibility of sibling donor with DBA, but a silent phenotype, resulting in graft failure
  - Possible future gene therapy

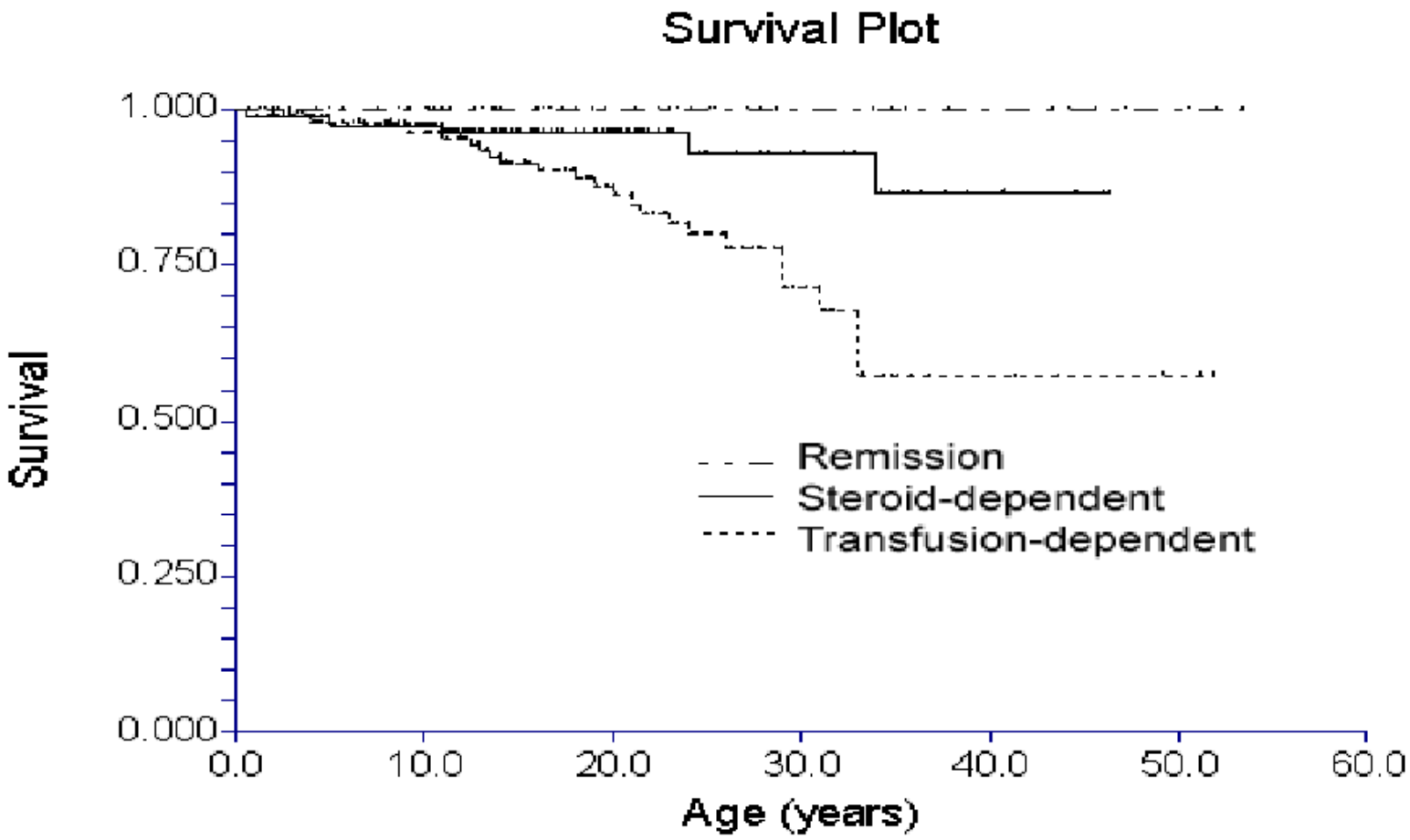
Spontaneous remission in DBA

Likelihood of remission

- 20% by age 25, with
- 72% of those during the first decade of life
  - 44 patients prior to age 10 years
  - 15 patients after age 10 years – a second peak in adolescence seems to be emerging

Risk of relapse:

- Pregnancy, OCP
- D/C steroids


Survival Plot
1.000
0.750
0.500
0.250
0.000
Survival
0.0
10.0
20.0
30.0
40.0
50.0
60.0
Age (years)
Remission
Steroid-dependent
Transfusion-dependent

Cancer in DBA
Epidemiology

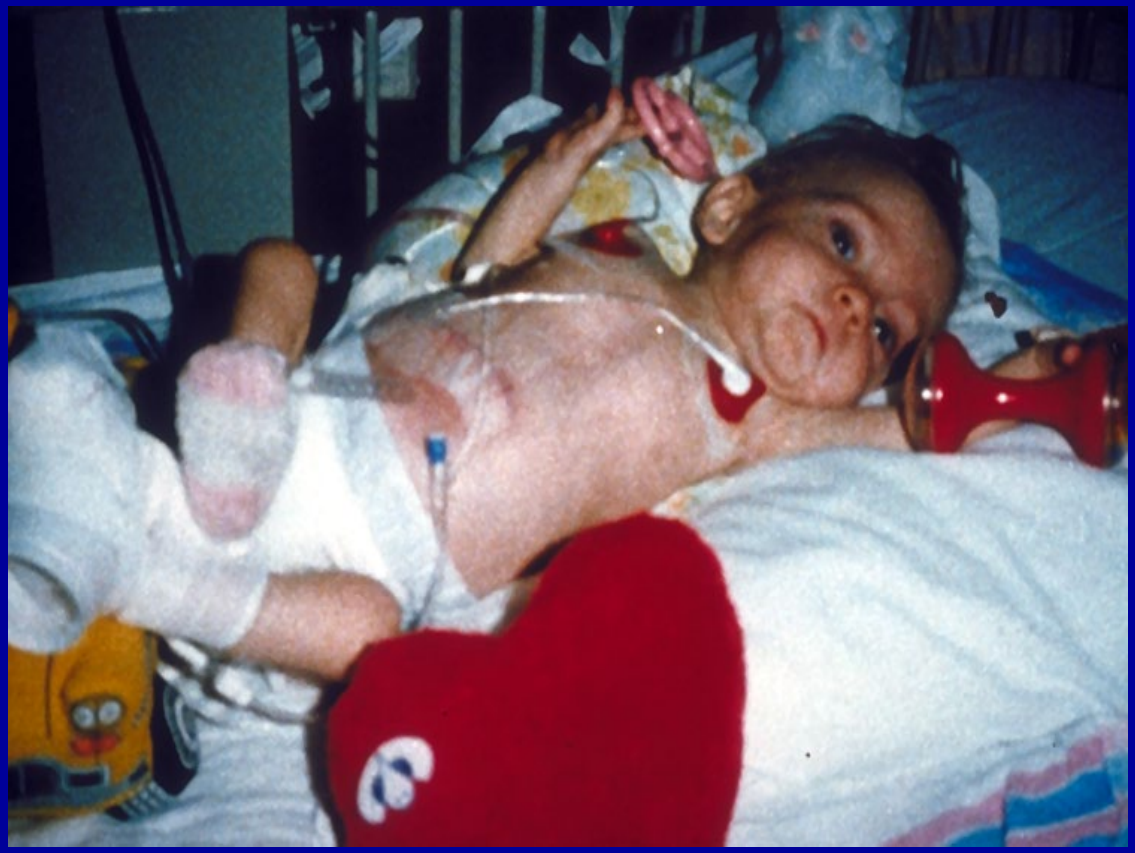
- **30 Cases Reported in the Literature**
  - **ANLL/MDS** **10**
  - **Osteogenic sarcoma** **7**
  - **Hodgkin disease/NHL** **3/1**
  - **Breast carcinoma** **2**
  - **Hepatocellular carcinoma** **2**
  - **Colon** **1**
  - **ALL** **1**
  - **Gastric carcinoma** **1**
  - **Vaginal melanoma** **1**
  - **Malignant fibrous histiocytoma** **1**
- **3 cases of myelodysplastic syndrome**

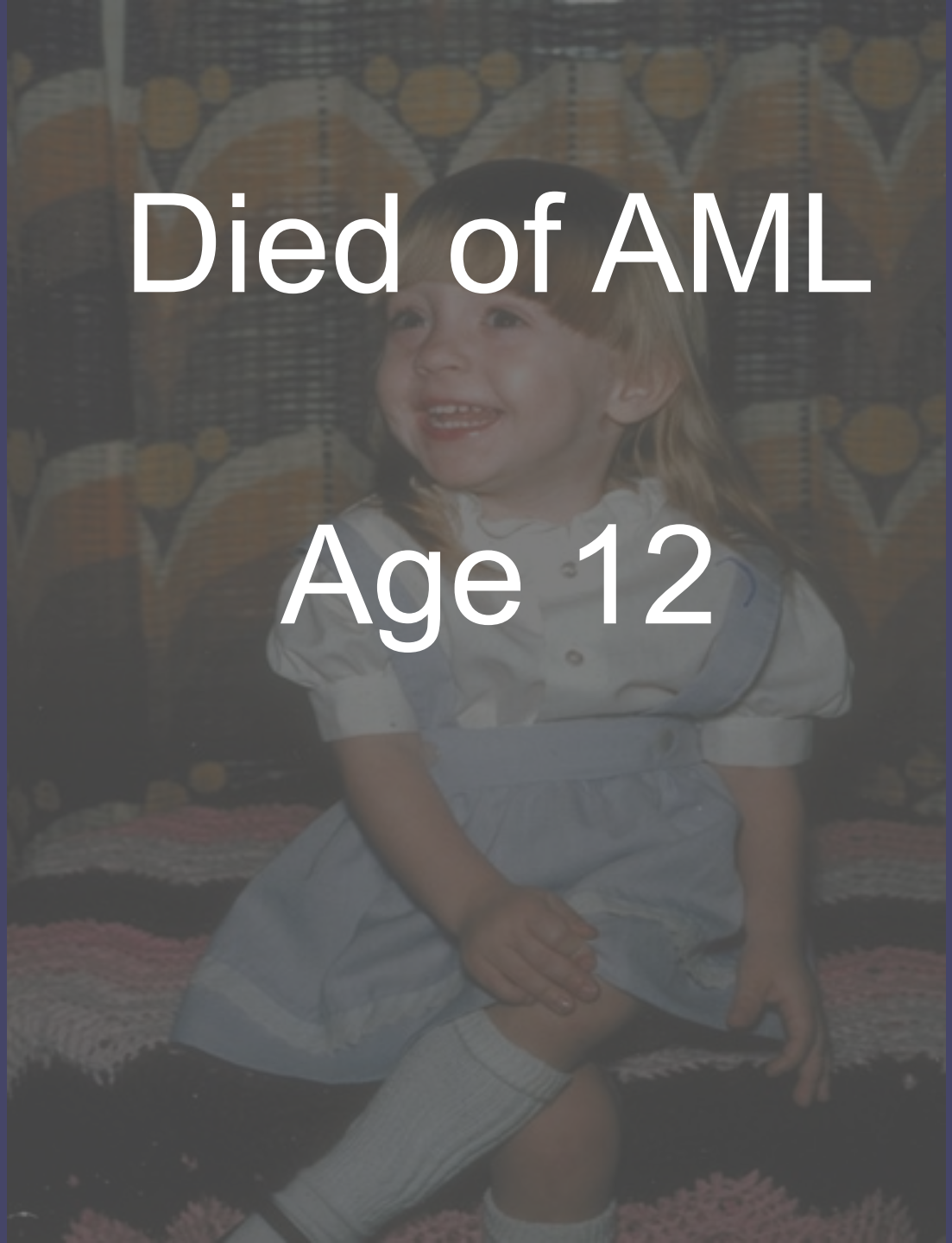
Characteristics of Cancer in DBA

- Young age for cancer diagnosis
  - Colon carcinoma – ages 30, 34, 49 yrs
  - Breast cancer – ages 26, 27, 43 yrs
  - Osteosarcoma - ages 4, 5, 10, 13, 22 yrs
  - MDS/Myelofibrosis – age 17, 45, 52 yrs

Case 3

- Presented age 18 months with stunting, *Staph*. liver abscess, ANC 0, other blood counts normal





Died of AML

Age 12

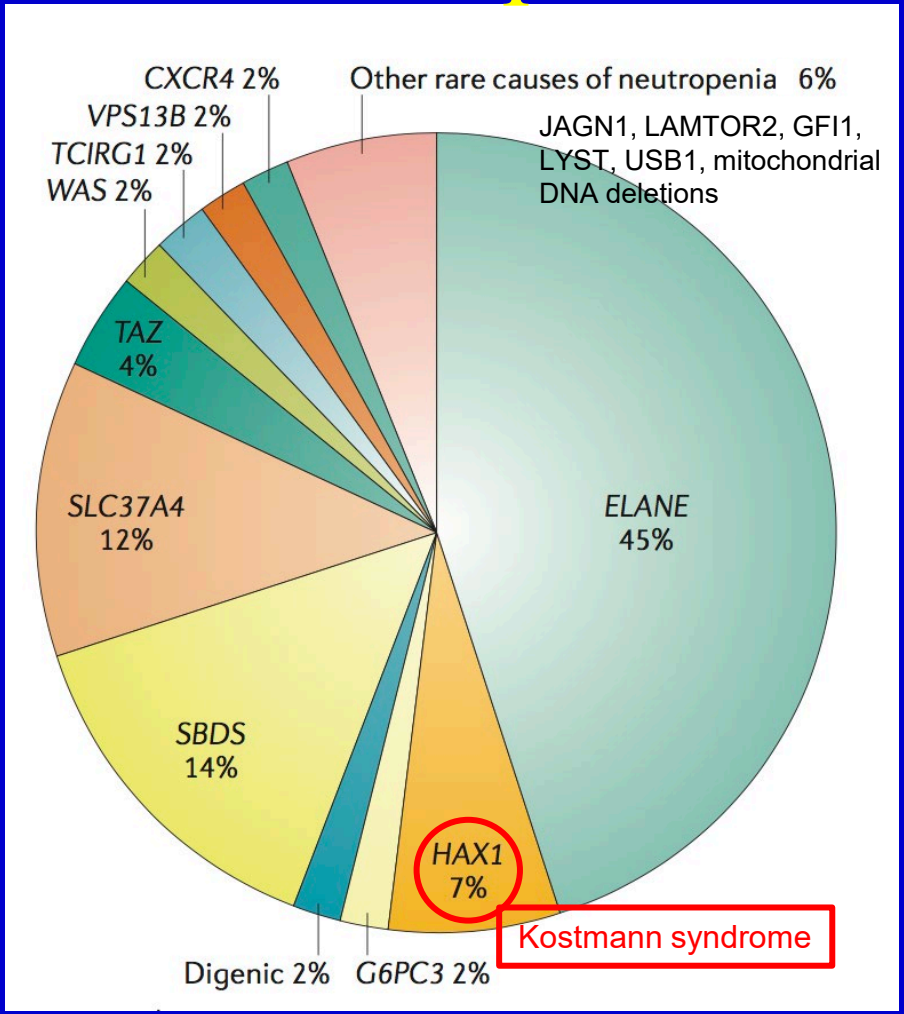
On G-CSF,
age 4 years

Cyclic Neutropenia and Severe Congenital Neutropenia

Genetics

- CN & SCN: Autosomal dominant mutations in the neutrophil elastase (*ELANE*) gene
- SCN only: Rare AD and AR mutations of other genes (e.g. *G6PC3*, *HAX1, GFI1, WAS, JAGN1, VPS45, CSF3R*)
- Only AR (*HAX1)* = "Kostmann syndrome"
- Most SCN-associated mutations in the G-CSF receptor gene (*CSF3R*) are acquired and may be preleukemic

Genetic causes of severe congenital neutropenia



Skokowa et al. *Nat Rev Primer Dis*. 2017; 3:1

Cyclic Neutropenia and SCN

Pathophysiology:

- Increased apoptosis of bone marrow precursors

Cyclic Neutropenia and SCN

Diagnosis:

Cyclic neutropenia:

- CBC 2-3x per week for 6 weeks
  - Reciprocal cycling of neutrophils and monocytes

OR

- *ELANE* gene sequencing

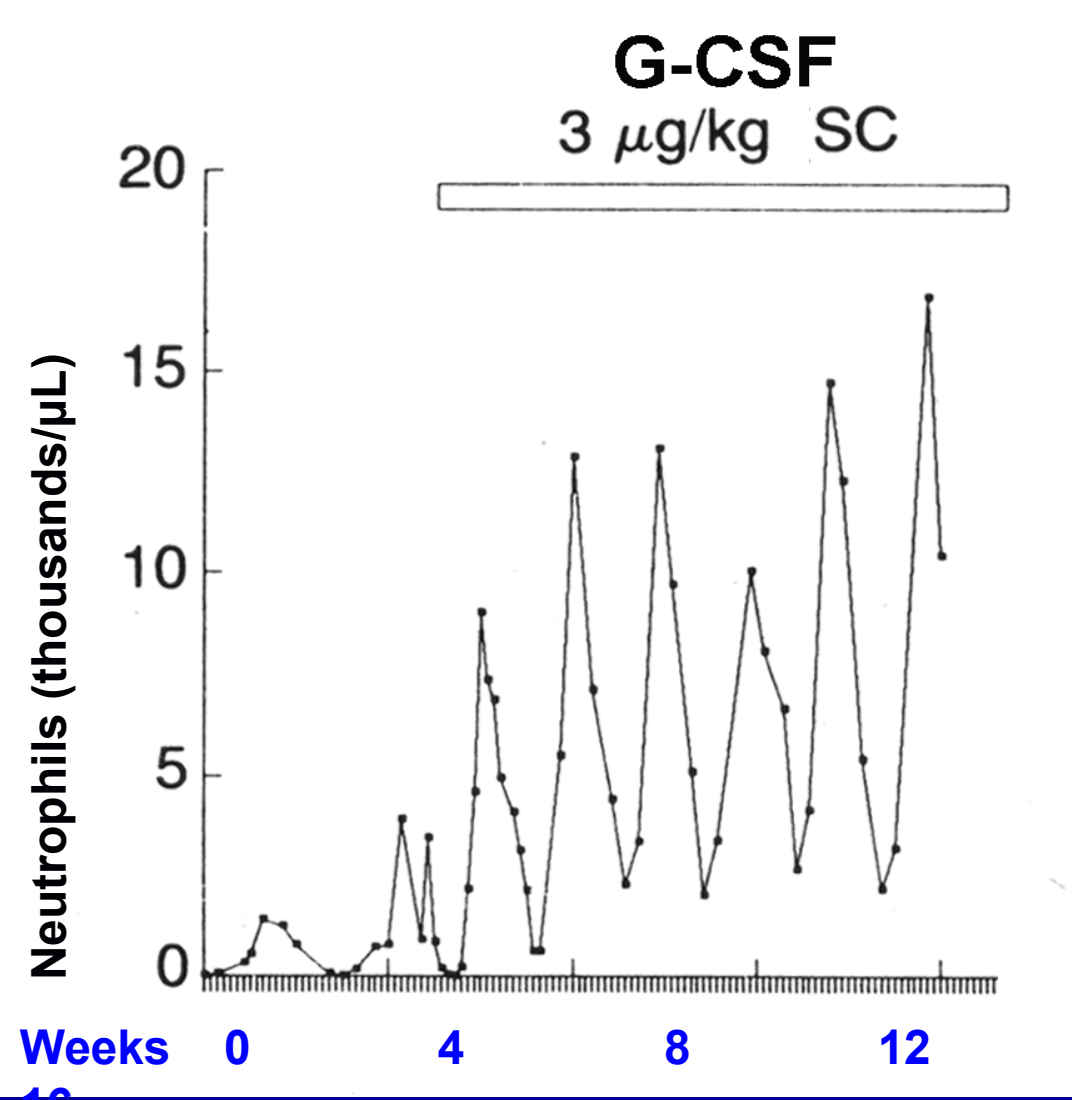
Severe congenital neutropania:

- Three ANCs <500 over ≥1 month
- BM: maturation "arrest" at promyelocyte stage
- Gene sequencing

Management of Cyclic Neutropenia and SCN

- G-CSF (filgrastim, Neupogen, biosimilars)
  - Always: SCN
  - Sometimes: CN (prolonged low nadirs)
  - Safe and probably beneficial in pregnancy
- PEG-filgrastim: Very rarely indicated –
  - Marked leukocytosis, bone pain and, rarely, tissue infiltration by neutrophils
- Hematopoietic stem cell transplantation

Response to G-CSF in Cyclic Neutropenia



NEJM 1989; 320:1306

G-CSF Benefits

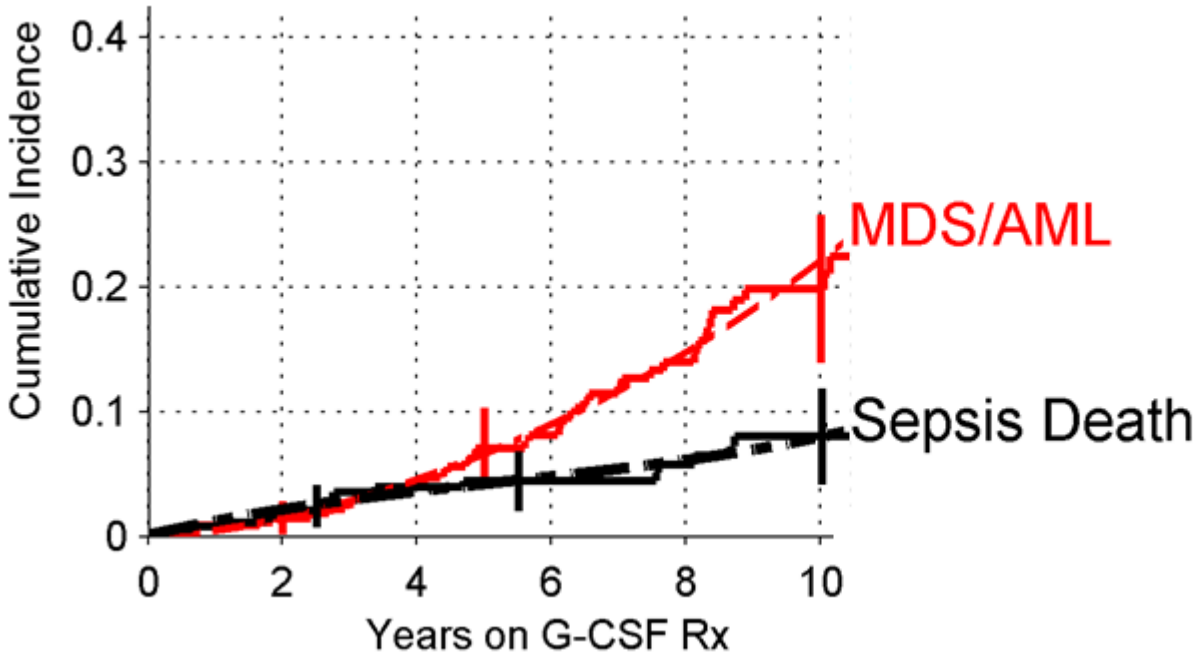
- Survival:
  - in the pre-GCSF era, 50% mortality in the first year of life
- Quality of life:
  - ↓ infections, infectious complications, time in hospital, tooth loss
  - ↑ growth, nutrition

G-CSF risks

- Injection discomfort and inconvenience
- Bone pain
  - avoid large, infrequent dose schedules!
- ? Osteopenia/osteoporosis
- MDS/AML

Severe Congenital Neutropenia

Risk of sepsis and MDS/AML



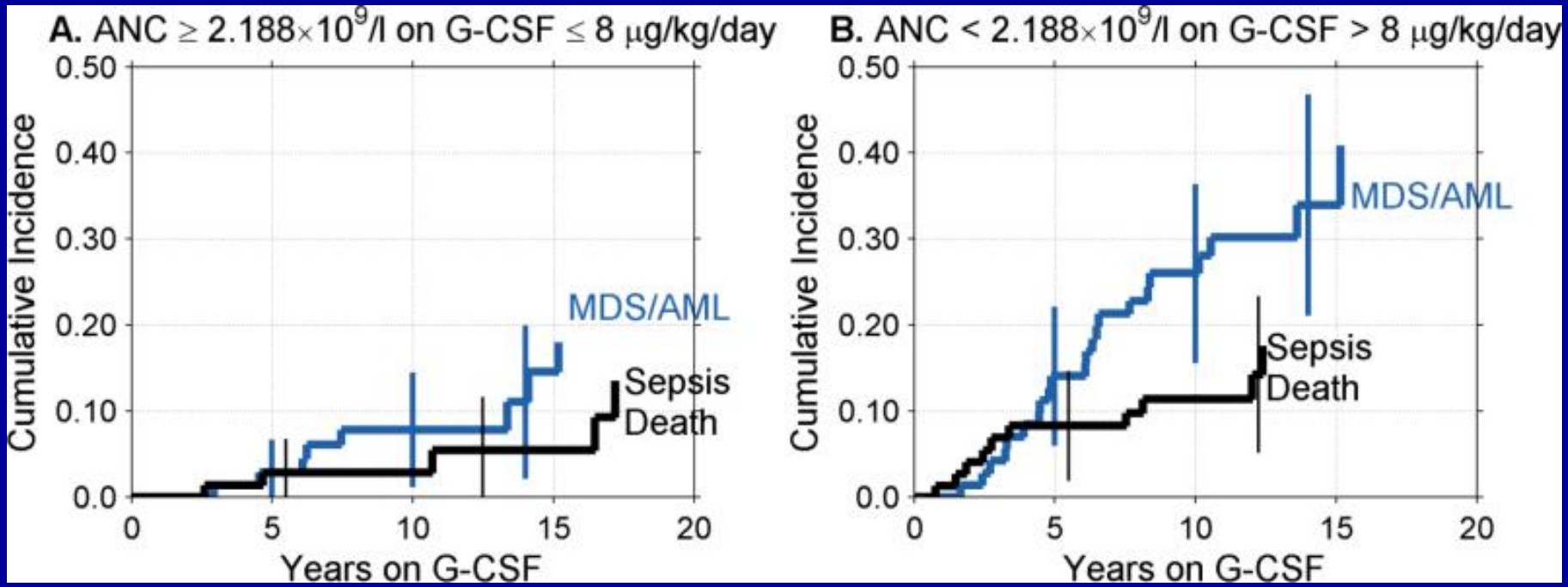
After 10 years on G-CSF, 21% developed myelodysplasia and/or AML

After 10 years on G-CSF, 8% had died of sepsis.

Rosenberg et al. *Br J Haematol* 2010; 140:210

Severe Congenital Neutropenia

Risk of sepsis and MDS/AML



Rosenberg et al. *Br J Haematol* 2010; 140:210

Risk of MDS/AML

Several cases of MDS/AML in SCN prior to G-CSF therapy, and in current refractory patients.

Does G-CSF cause MDS/AML or only permit survival long enough for it to develop as the natural history of the disease?

YES

Supportive Care

- Regular dental care – no antibiotic prophylaxis for procedures (unless coincident heart disease)
- Normal immunization schedule
- NOT indicated: social isolation, “neutropenic diet,” surface sterilization

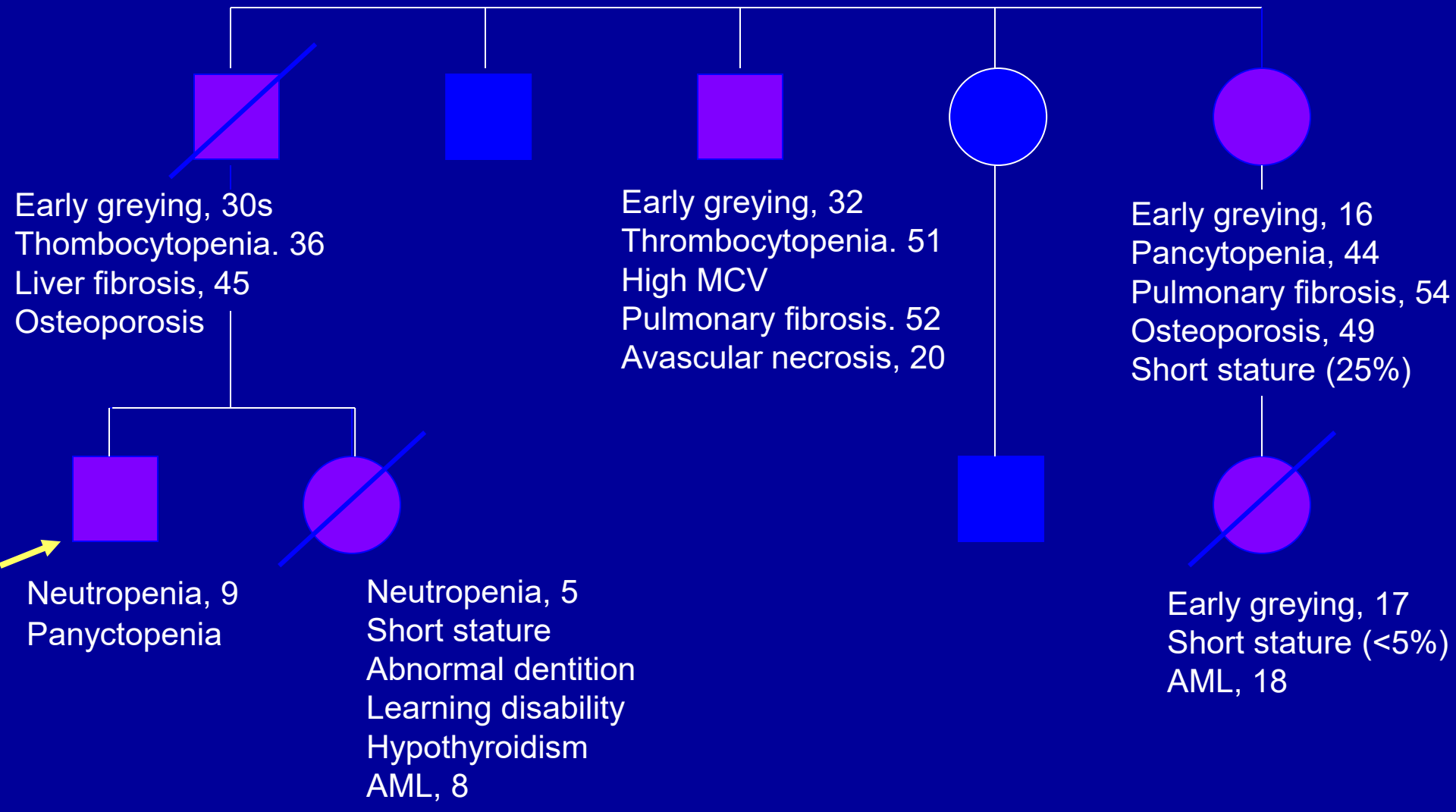
Case #4

- 15 year old boy presents with fatigue and shortness of breath.

- History significant for:
  - Increasing exercise intolerance, shortness of breath
  - Chronic neutropenia (ANC around 700) since early childhood
  - Dropping hct and platelet count over last year (currently Hct 28, Platelets 50K)

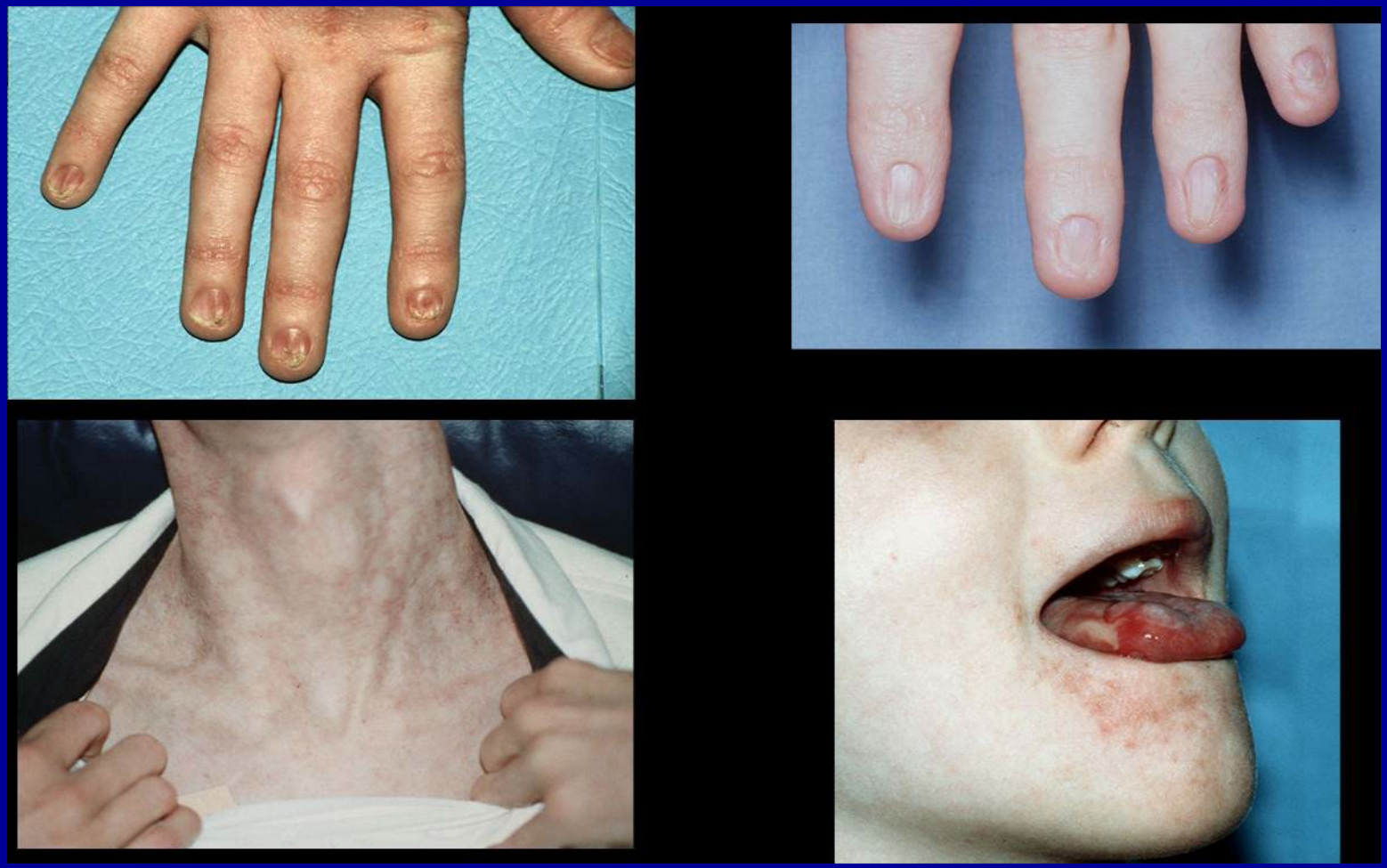
- Exam:
  - No physical anomalies

Family history



Dyskeratosis Congenita

Classic phenotype: dystrophic nails, reticulated hyperpigmentation, oral leukoplakia



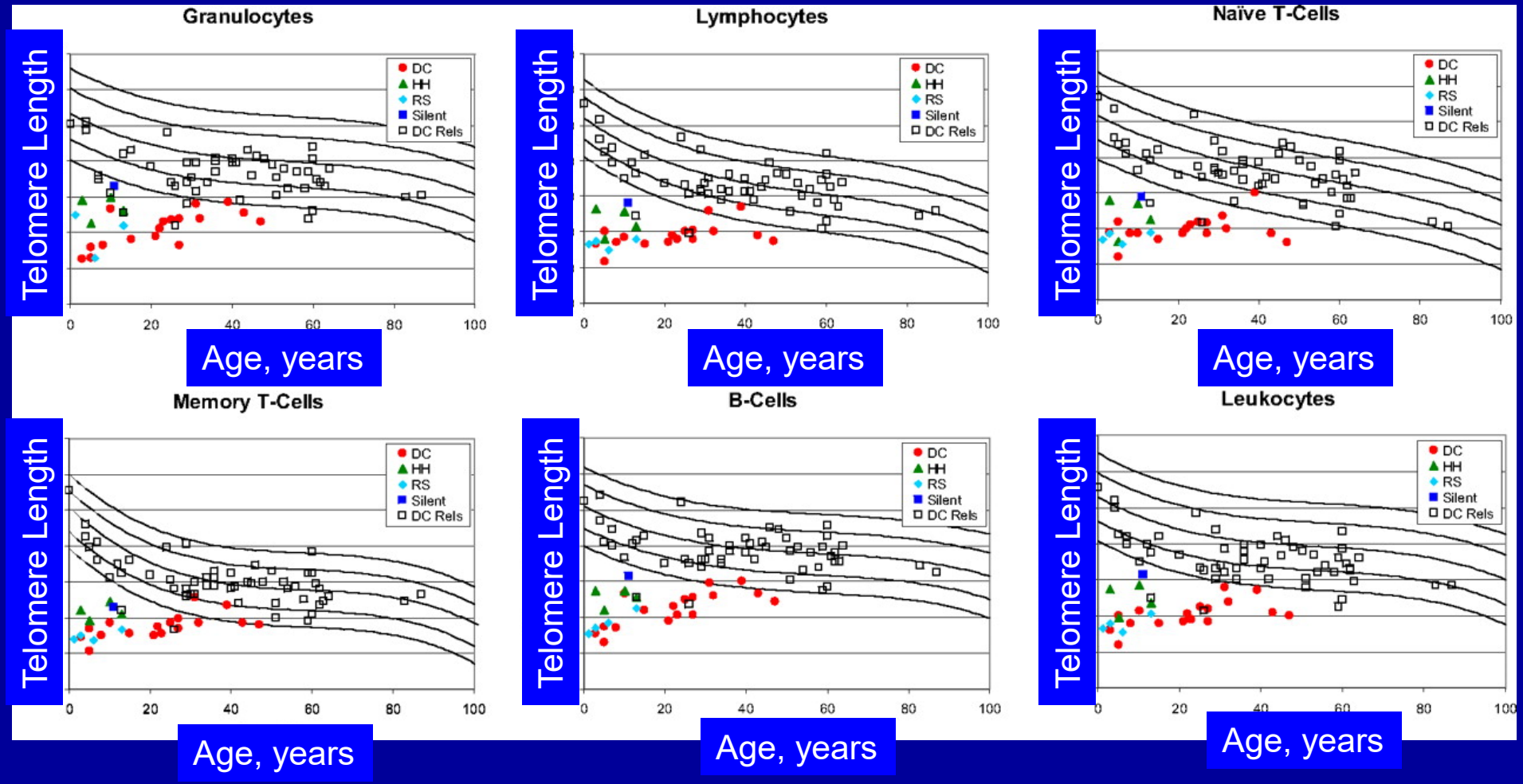
Dyskeratosis congenita: Non-hematologic clinical features

Pulmonary disease
Dental anomalies
Esophageal stricture
Hair loss, early greying
GI disorders
Ataxia
Ocular anomalies
Hyperhidrosis
Hypogondadism
Immunologic abnormalities

Liver cirrhosis/fibrosis
Microcephaly
Urethral stricture/Phimosis
Osteoporosis
Deafness
Cognitive/developmental delay
Exudative/vascular retinopathy
Cerebellar hypoplasia
Cardiac anomalies
Arterial-venous malformations

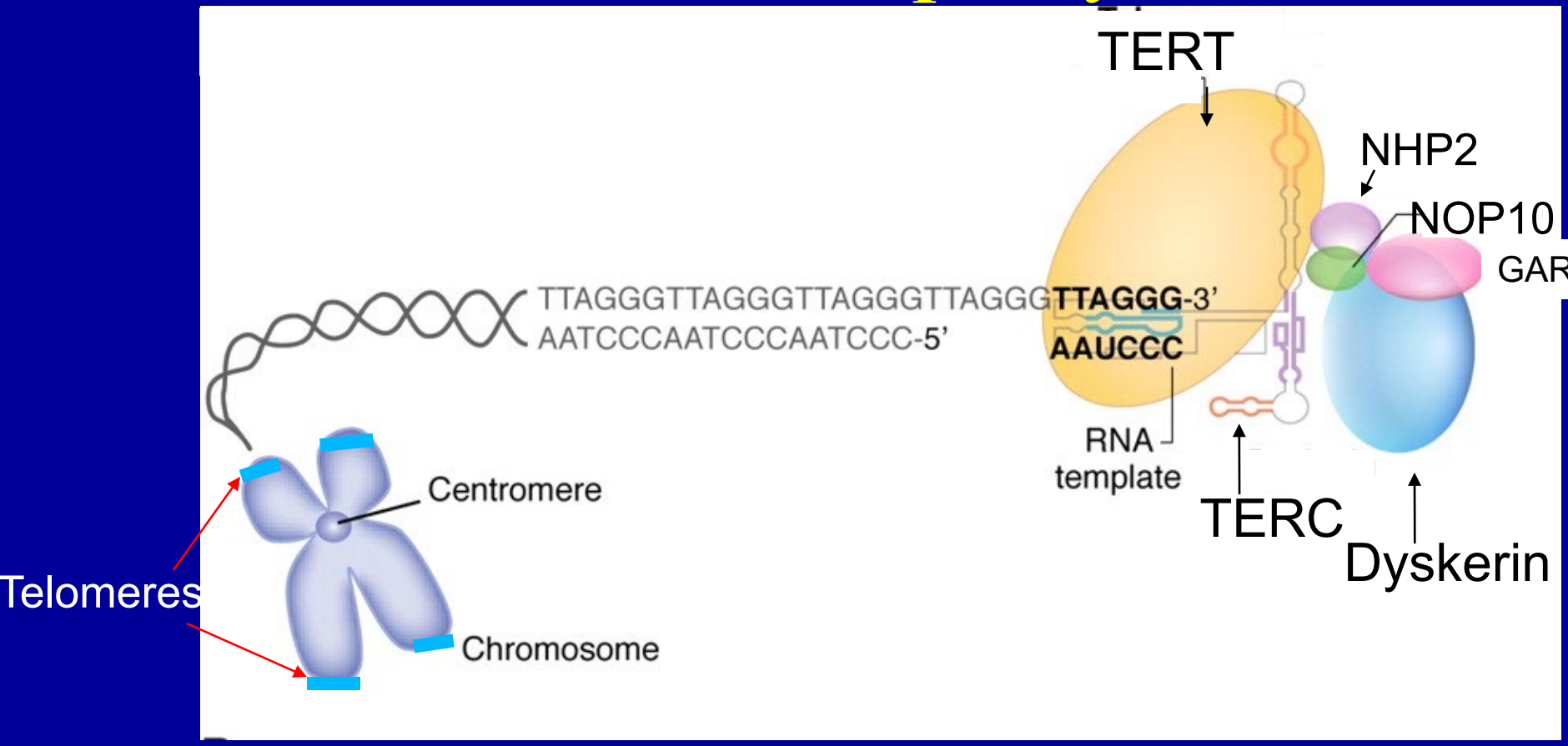
Br J Haematol 2000; 110: 768-779

Telomere length according to age in patients with dyskeratosis congenita



Blood 2007;110:1439-1447

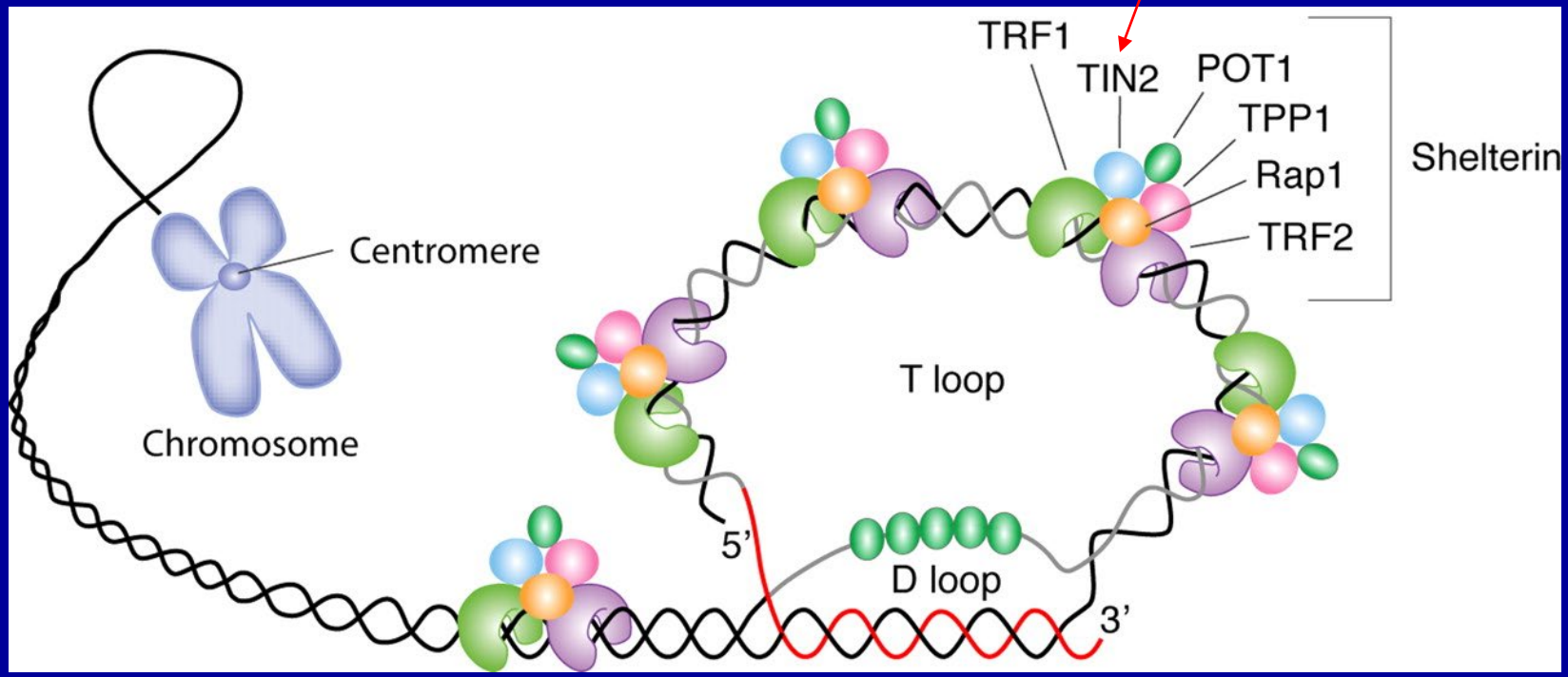
Dyskeratosis congenita: A telomeropathy



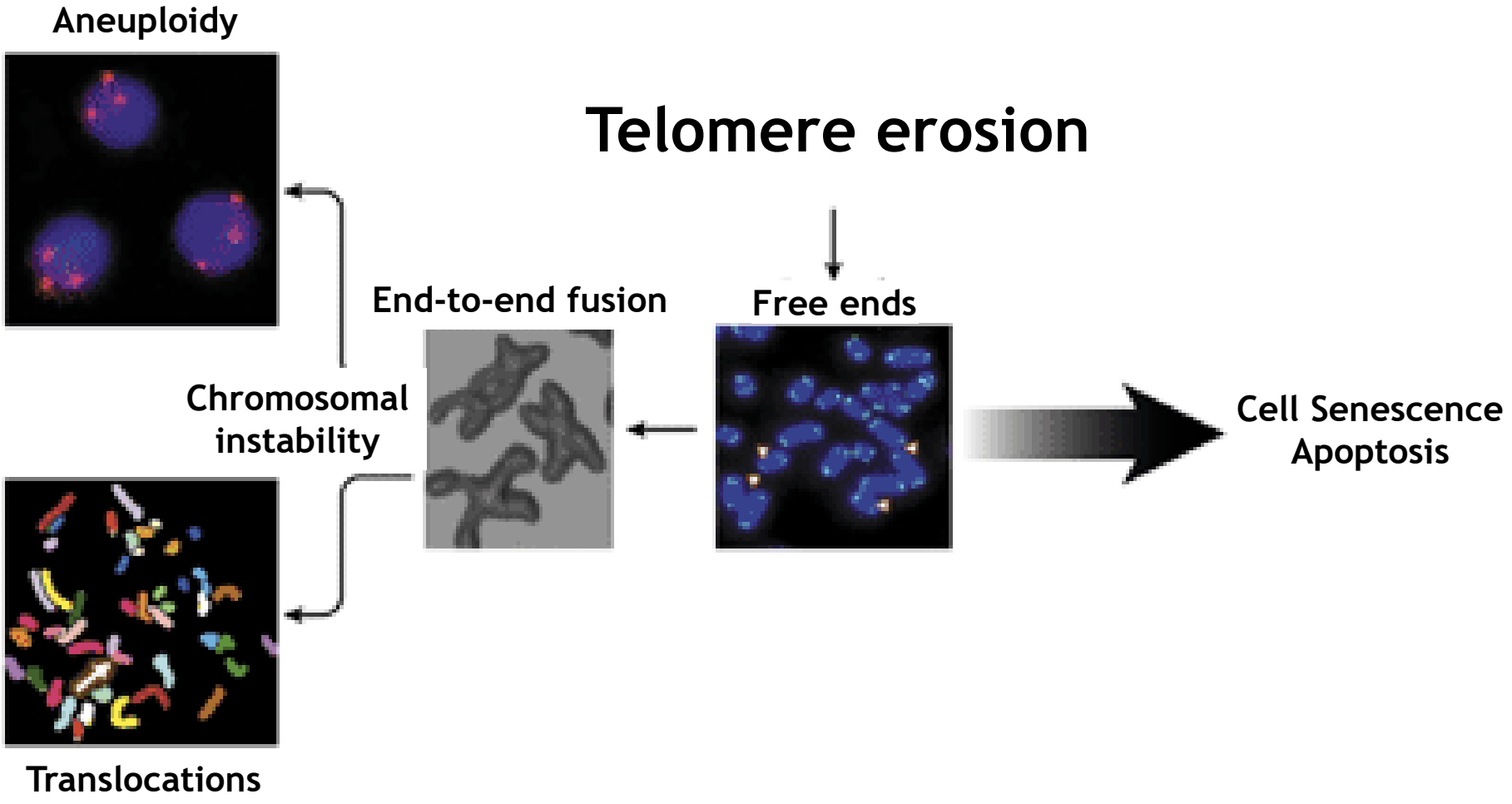
Modified from Calado, R. T. et al. Blood 2008;111:4446-4455

Dyskeratosis congenita: A telomeropathy

TINF2: Autosomal Dominant DC

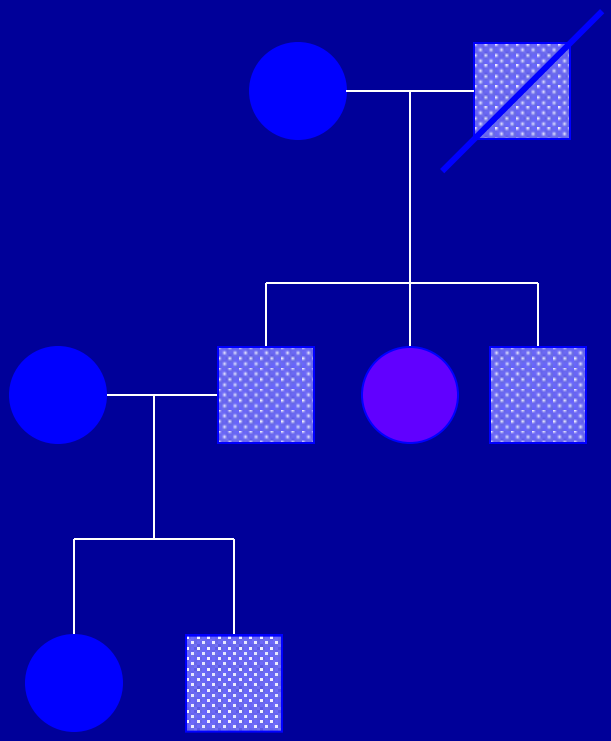


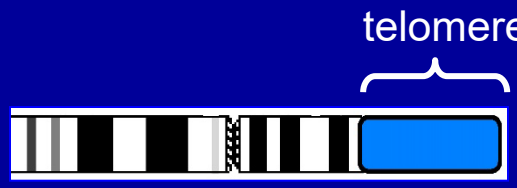
Blood 2008;111:4446-4455



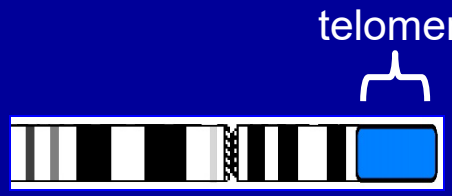
NEJM 2009. 361:2353-2365

Disease anticipation in autosomal dominant DC

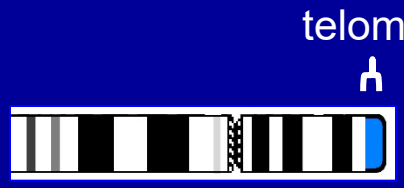




Asymptomatic



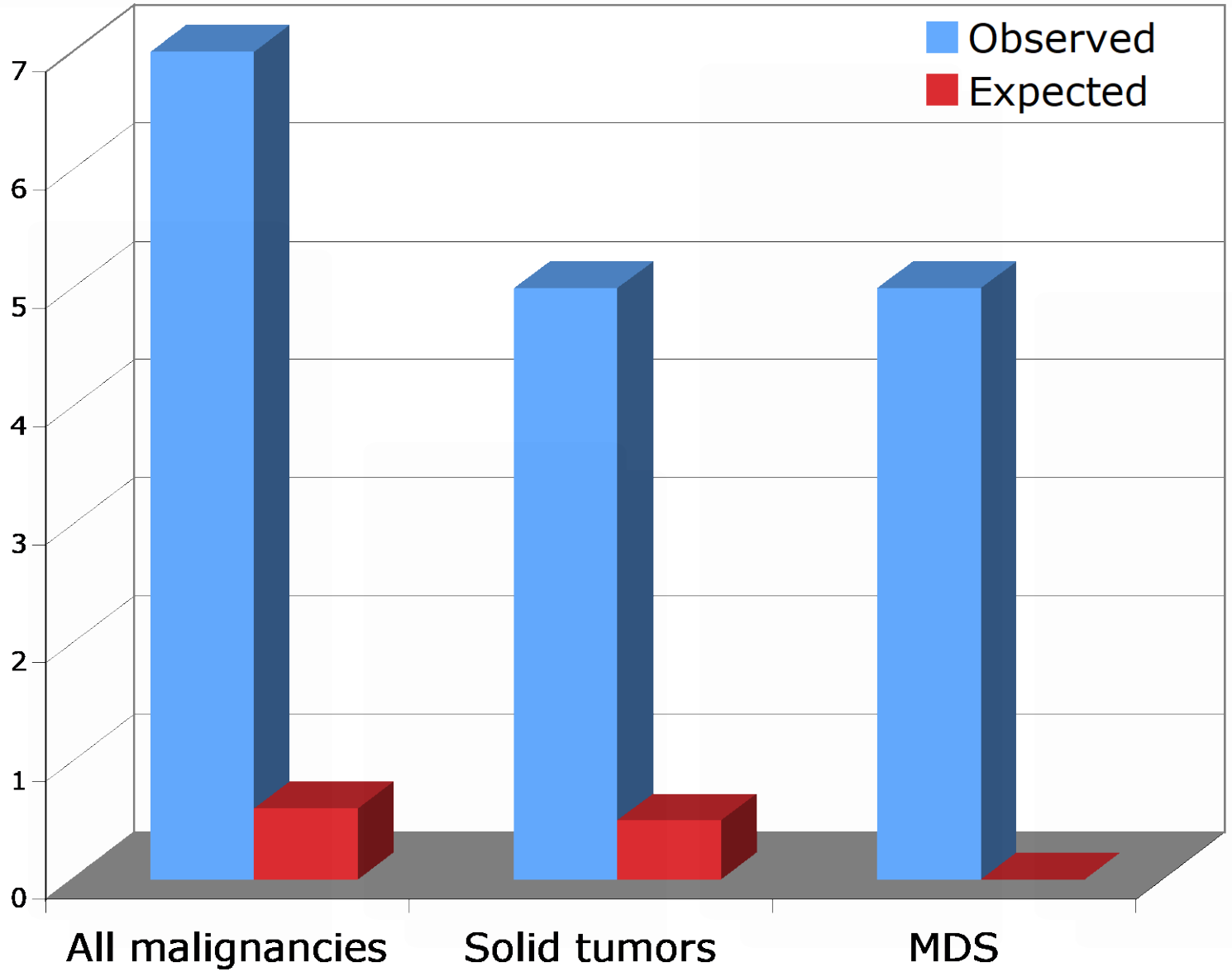
Asymptomatic until age 40+



Asymptomatic until teenage years

Curr Op Genet Dev. 2005; 15: 249-257

Dyskeratosis congenita: Cancer incidence



Blood 2009;113:6549-6557

Diagnosis of Inherited BMF syndromes

- Phenotype may drive functional and genetic testing
- Specific tests:
  - Fanconi: chromosome breakage analysis
  - DBA: erythrocyte adenosine deaminase
  - SCN: bone marrow (myeloid maturation arrest)
  - Dyskeratosis congenita: telomere length
  - Shwachman-Diamond: pancreatic isoamylase (age >3 y)

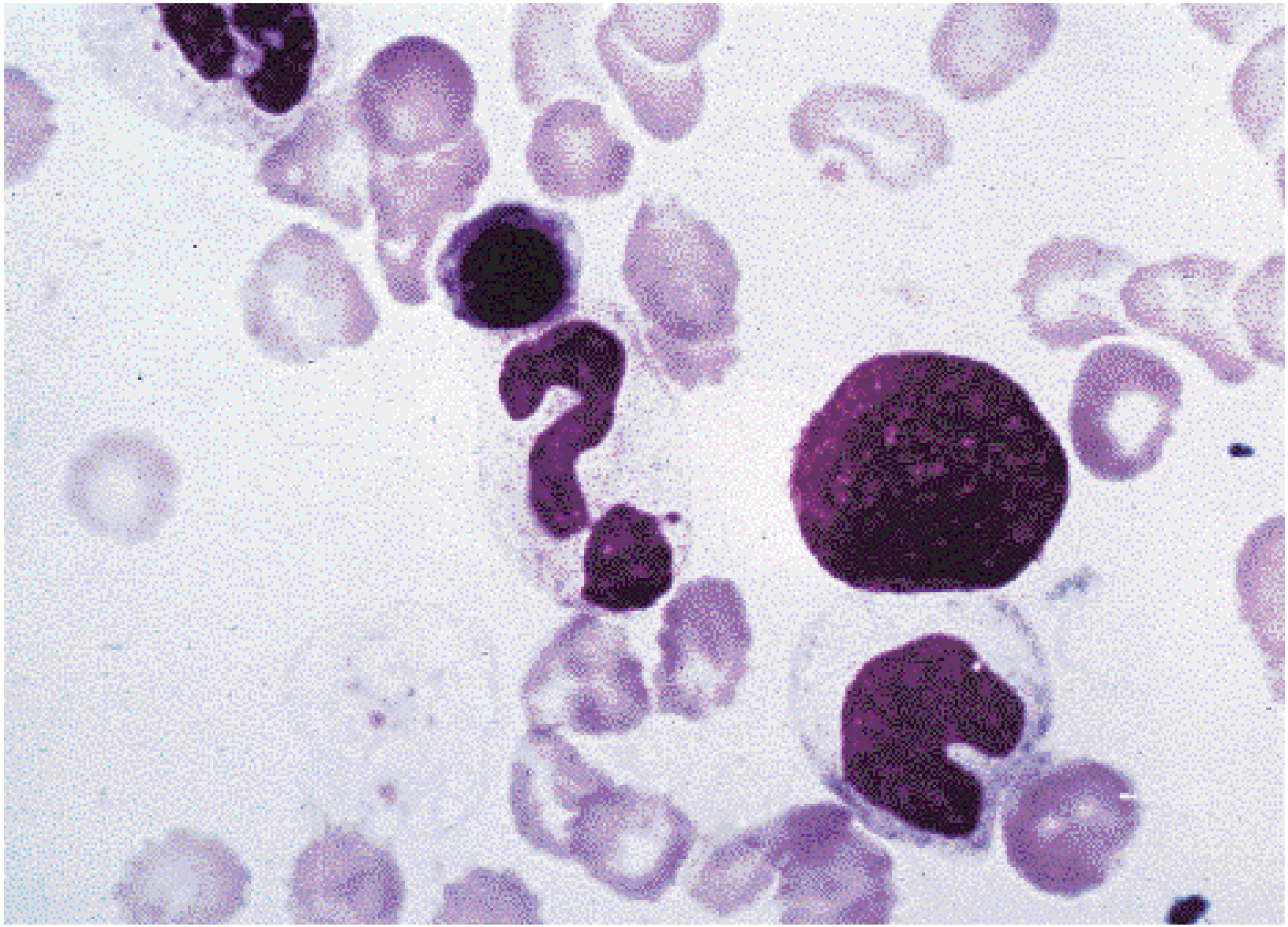
Genetic Diagnosis of Inherited BMF

- Single gene: if known family history/gene
- Sequential single genes: expensive and inefficient
- NGS panel: current standard of care

Genetic Diagnosis of Inherited BMF

- Single gene: if known family history/gene
- Sequential single genes: expensive and inefficient
- NGS panel: current standard of care*
- WES: if high suspicion and negative panel* (probably future standard of care)
- WGS: currently on a research basis*

* Need skilled interpretation of data, VUSs



Ely and Rainer NEJM 1997;336:1364