

# Pediatric perspectives on childhood marrow failures

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October 24, 2009



# Objectives

- Understand the natural history of bone marrow failure disorders – complex and not well understood
- Understand some of the complications that may arise and how we might look for them
- Recognize that it is essential to develop an individualized plan for children and their treating health care team

# Disclosures

- No commercial conflicts of interest.
- Some of the facts I will discuss are potentially distressing – important to discuss concerns with your treating health care team to find out if they are relevant to you.

# A child's story

- 11 year old boy, previously well, no physical abnormalities
- 3 week history of fatigue, decreased appetite; 1 week history of bruising; severe nose bleed.
- WBC 3 Neutrophils 0.3 Hb 87 platelets 13.
- Bone marrow : marked decreased cells, no leukemia
- Fanconi anemia, PNH, cytogenetics, B12, folate testing all normal
  
- Brother not a match for bone marrow transplant
- Treated Cyclosporin, ATG and prednisone
- Life threatening infection with Staph aureus x 2
- 3 months from presentation: Partial improvement in blood counts for neutrophils; still transfusion dependent for red blood cells.

# What do we mean by bone marrow failure?

- In children, bone marrow present in almost all bones – eg. skull, spine, ribs, legs.
- Bone marrow produces red blood cells, white blood cells and platelets.
- Bone marrow failure – inability of the bone marrow to produce one or more elements of the blood.

# Bone marrow failure

- Single cell line not produced –
  - Anemia (red cells)
  - Thrombocytopenia (platelets)
  - Neutropenia (white cells)
- Aplastic anemia – multiple blood cell abnormalities + bone marrow empty
  - Severe anemia
  - Severe thrombocytopenia
  - Severe neutropenia

# Bone marrow failure (BMF)

- Acquired aplastic anemia – bone marrow fails because of some kind of injury – immune, toxin, drug, infection
- Inherited – genetically determined BMF Syndrome – inherited from parent(s) or new problem in the genes of the child

# Acquired Aplastic Anemia in children

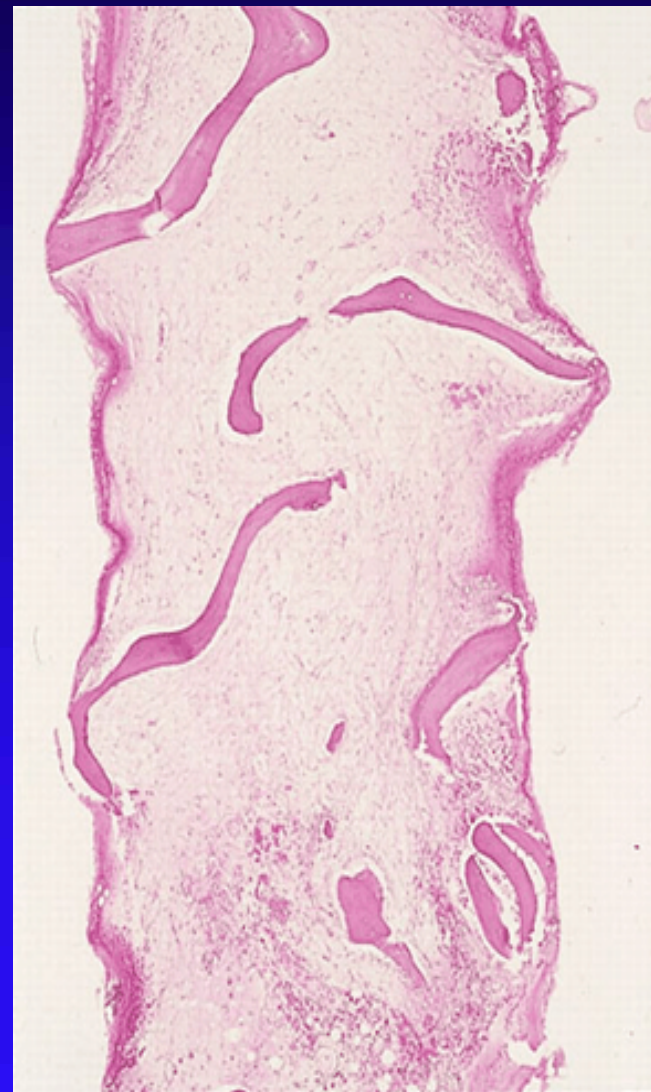
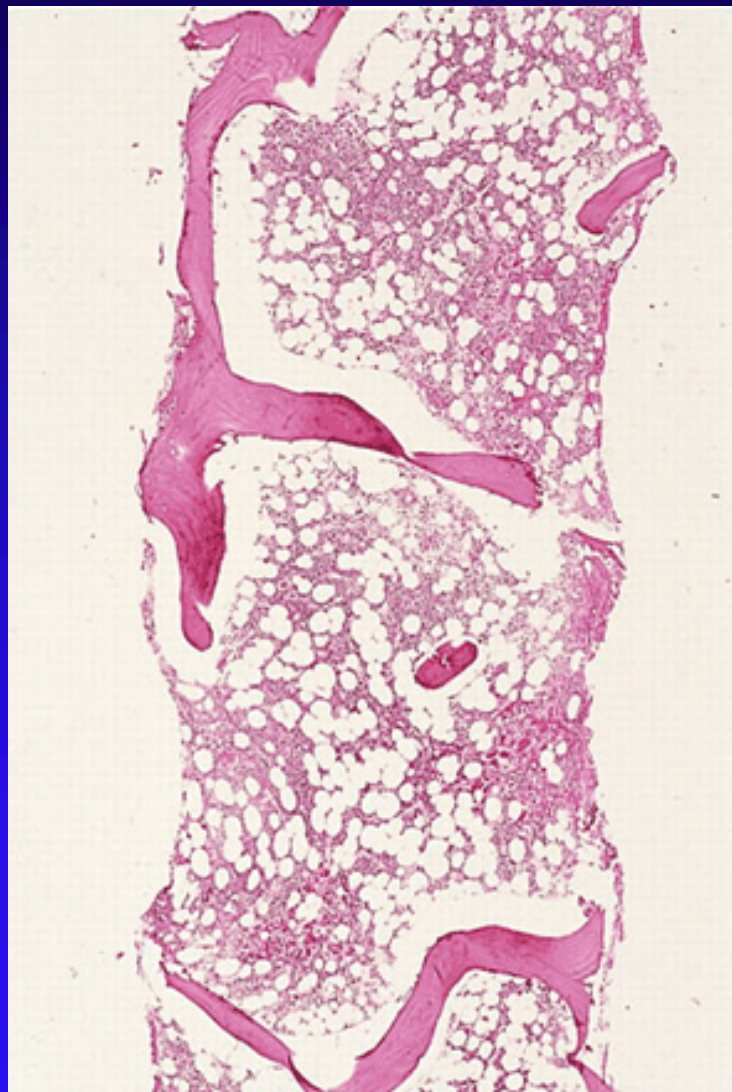
- Rare condition – 1 or 2 children in Maritimes per year
- Peak between 10 -25 years (and > 60)
- Boys equally affected as girls
- Anemia, Easy Bleeding, Infection
- Causes: 80% unknown, infections – hepatitis, medications, toxins (pesticides)



# Severe aplastic anemia

American

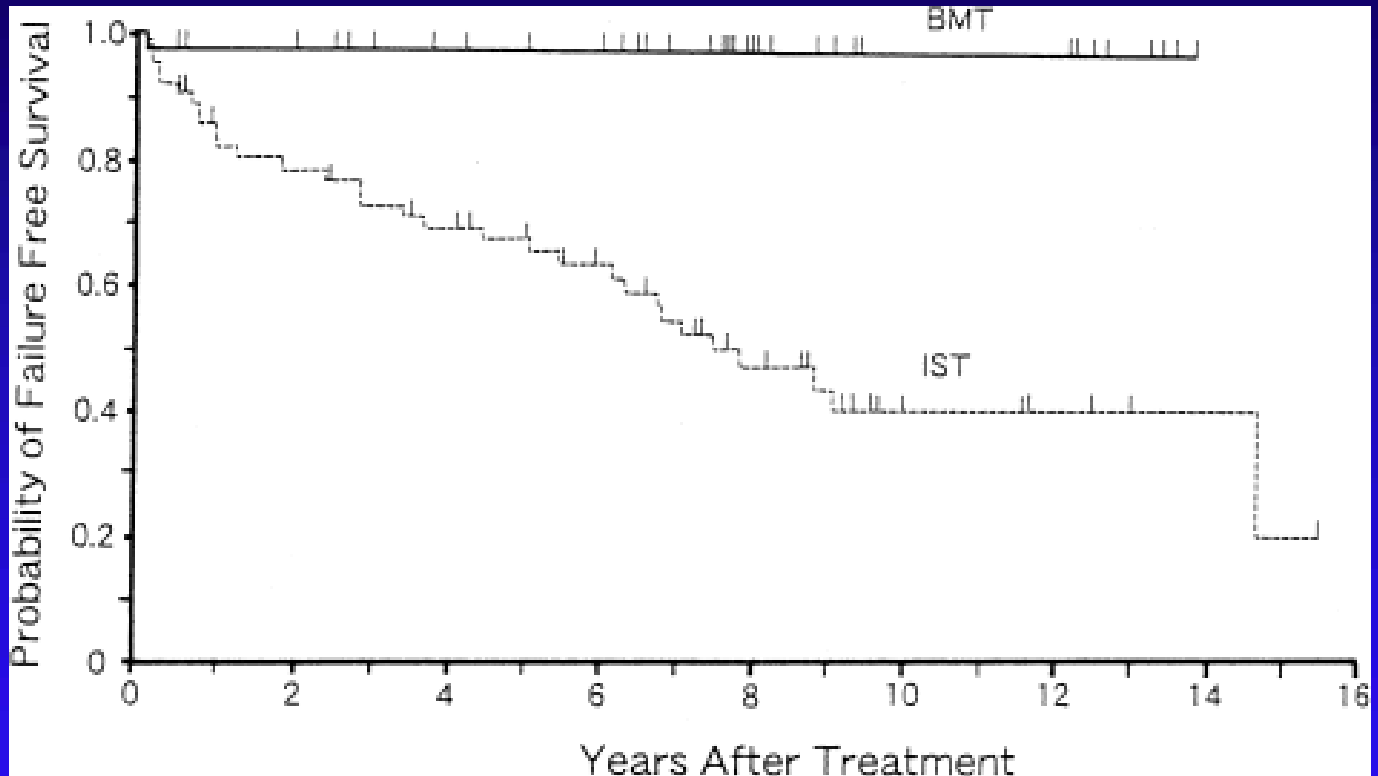
Society of Hematology Image Bank



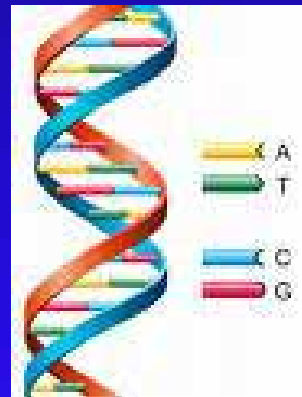
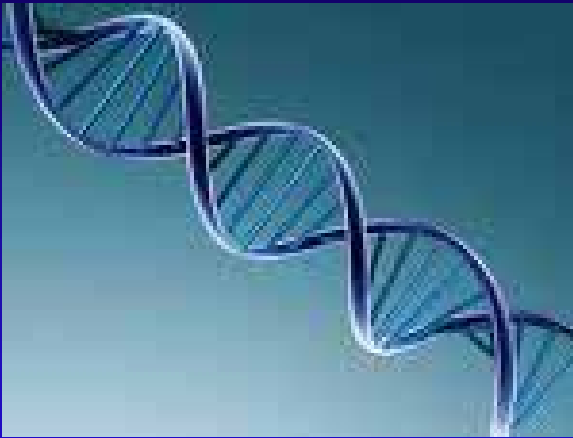
# Severe aplastic anemia in children

- Diagnosis – rule out known acquired causes, rule out mimics (leukemia), rule out inherited marrow failure syndromes
- 25% of children and 10% young adults have an underlying inherited marrow failure syndrome
- Supportive care – transfusions, prevention infections, antibiotics, dental
- Treat bone marrow – bone marrow transplant from sib, or immune suppressive therapy (cyclosporin/ATG)

# Outcomes in children – bone marrow from sibling is better than IST



# Inherited bone marrow failure syndromes



“One must always consider an underlying genetic cause for serious, childhood-onset diseases.”

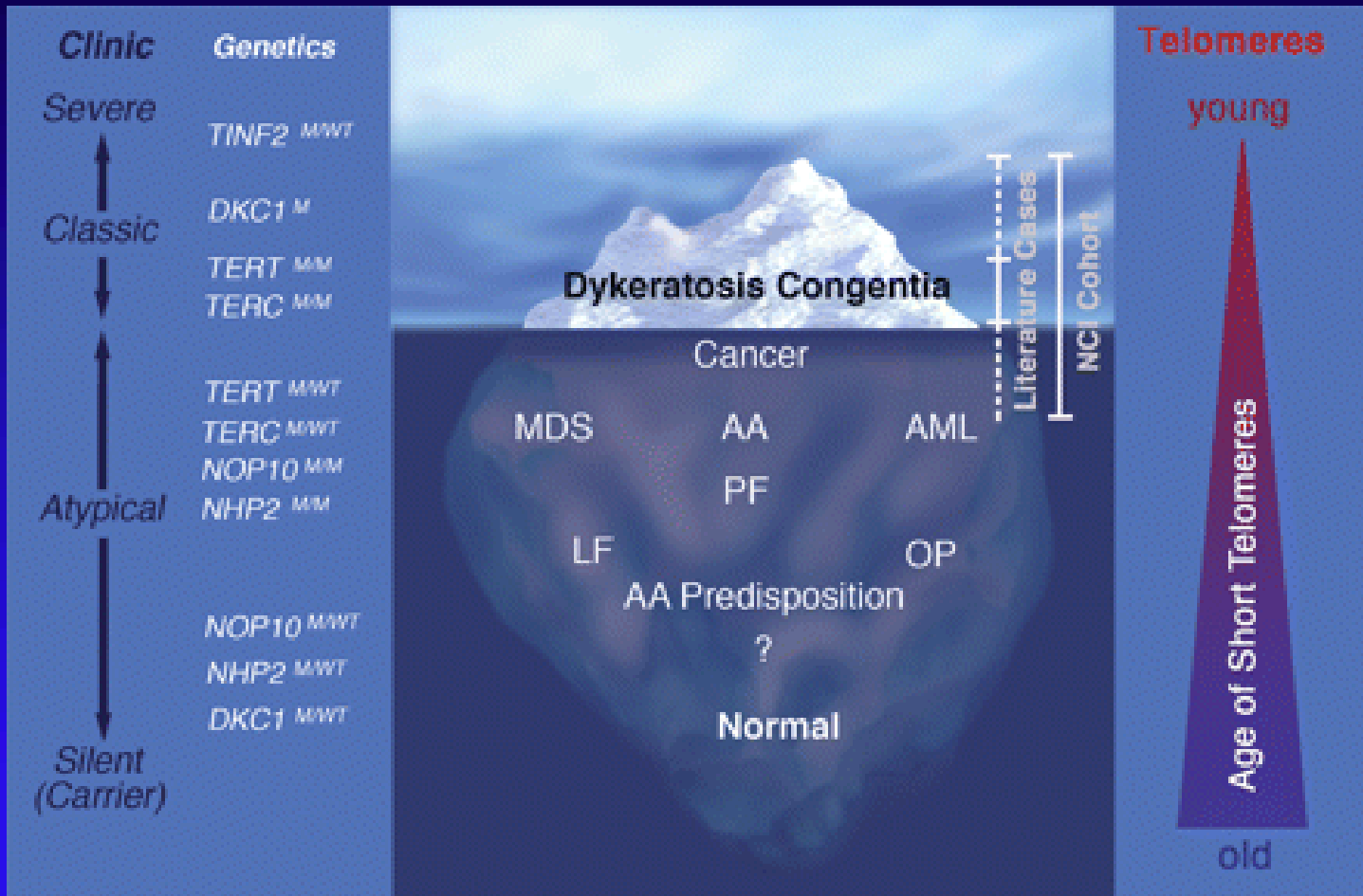
# Natural history = What to expect (and when)

1. We have imperfect knowledge for each type of bone marrow failure syndrome
2. We therefore have imperfect knowledge of what to predict for each individual patient

# Why do we have imperfect knowledge for bone marrow failure syndromes (BMFS)?

- Rare conditions – 1/150,000 to 1 in 1,000,000
- Most information comes from voluntary registries, case series, or retrospective reports
- These tend to be biased to patients who have the most severe features of the BMFS
- Broad spectrum of clinical problems that may occur within a particular BMFS
- Up to 20-25% of BMFS do not have a defined diagnosis – many new genes being discovered

# So called classic triad of DC – skin, nail and leukoplakia likely “the tip of the ice berg”



# Major features of BMFS – lots of variability

	<b>Number reported</b>	<b>Age at diagnosis</b>	<b>Associated physical findings</b>	<b>Aplastic Anemia</b>	<b>Risk for cancer by age 40-50 yr</b>
Fanconi anemia	1850	6.6 yr (0-49)	>75%	Yes	85%
Dyskeratosis congenita	425	15 yr (0-75)	>90%	Yes	35%
Diamond-Blackfan	825	0.25 y (0-64)	30%	Rare	52%
Schwachman-Diamond	500	1 yr (0-41)	?	Yes	71%
Kostmann's	375	3 yr (0-70)	0 %	No	55%
Amegakaryocytic	100	0.1 yr (0-11)	0 %	Yes	53%
TAR	280	0-0.6 yr	100%	No	Very low



# How do we make sense of these complex conditions?

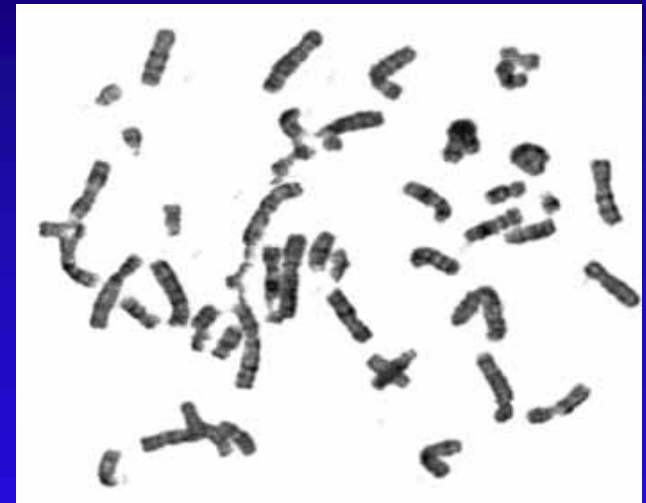
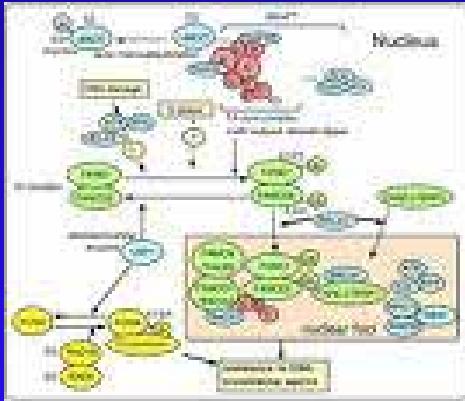
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**“At your age, Tommy, a boy’s body goes through changes that are not always easy to understand.”**

# Example of Fanconi anemia

- Many lessons to teach us

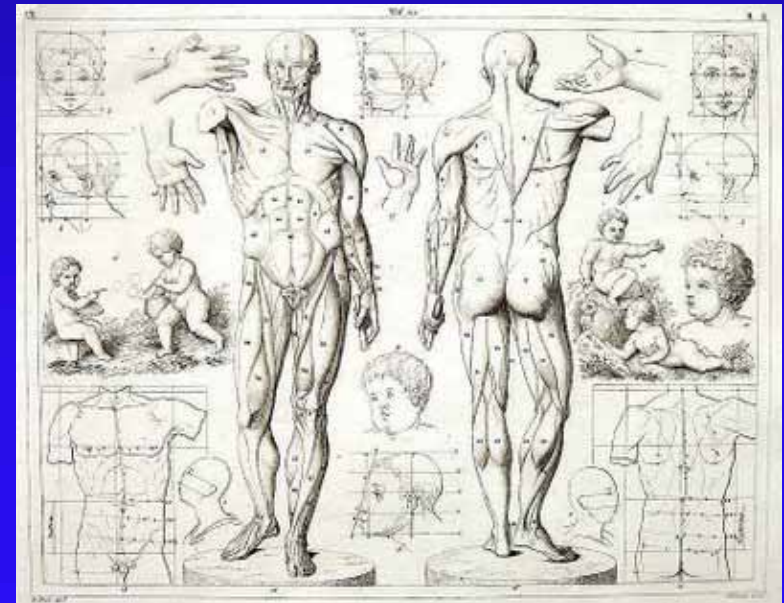


# Fanconi anemia

- Most common inherited bone marrow failure syndrome
- Wide variation in physical findings
- More than 13 gene defects may be causative
- Leads to abnormal chromosome repair
- Many organs may be affected
- Earlier death (average age 23 yr) from aplasia, leukemia, cancer

# Physical/organ findings in Fanconi anemia

- Skin – pigment changes – 65%
- Short stature – 60%
- Abnormal thumbs, radii – 50%
- Skeleton abnormalities – 30%
- Genital changes – 40%
- Small head, eyes – 25%
- Kidneys – 25%
- Development – 25%
- Bowel or anus – 10%
- No problems – 25%



# Fanconi anemia – what to expect?

- Aplastic anemia up to 50% by age 7 yr
- Myeloid leukemia up to 40% by age 35 yr
- Solid tumor up to 50-75% by age 50 yr
  - Esophagus, vulva, head and neck, breast, brain
  - Squamous cell carcinoma associated with the HPV virus, esp. in patients with FA

# Fanconi anemia – Care options

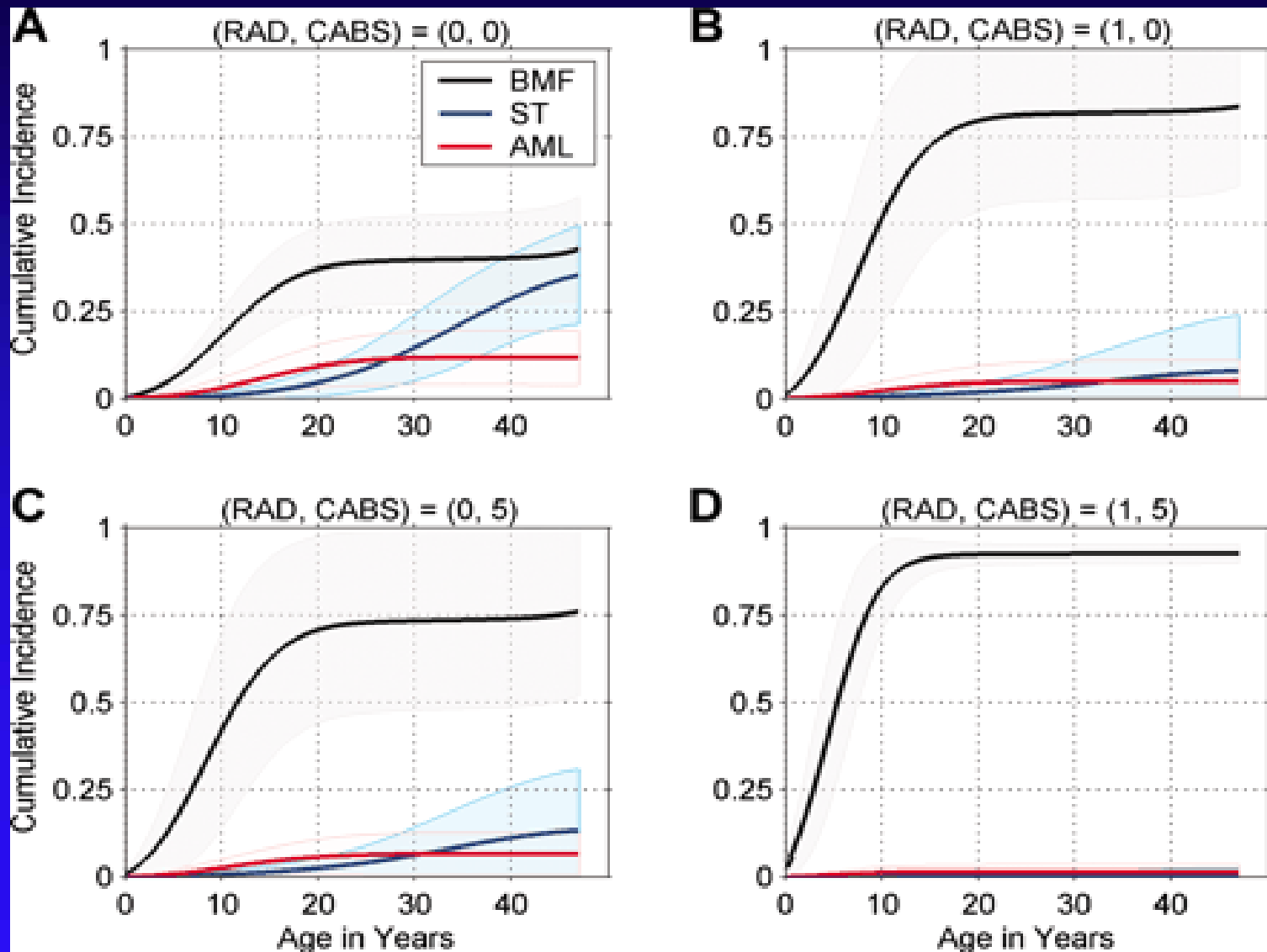
- Supportive care – androgens, red blood cell and platelet transfusions, growth factors: GCSF/EPO, antibiotics
- Cure for marrow dysfunction - bone marrow transplant (does not reduce cancer risk)
- Each of these treatments has potential side effects – short term and long term

# Can we predict who with FA will develop these complications?

- Radial ray abnormalities
  - +
    - Congenital anomalies (CABS)
      - Developmental delay
      - Heart/lung abnormality
      - Kidney abnormality
      - Hearing impaired
      - Head size small for age



# Can we predict who with FA will develop these complications?





# What do we do with this information?

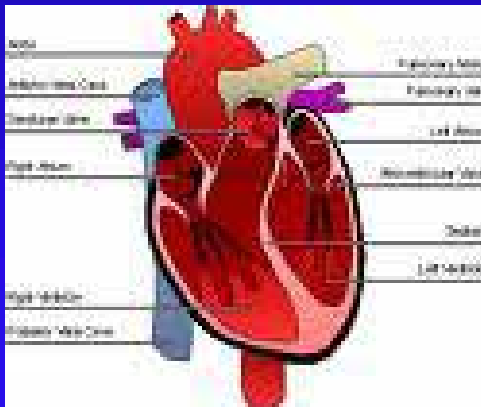
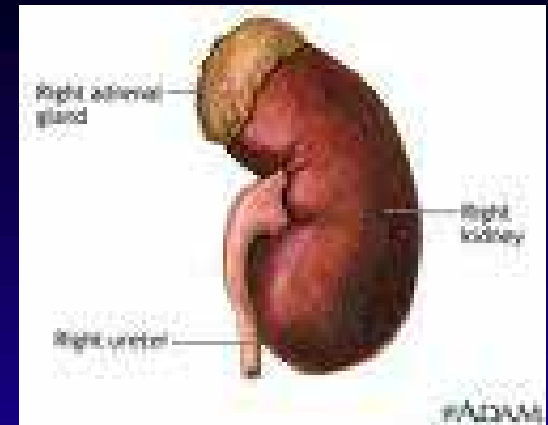
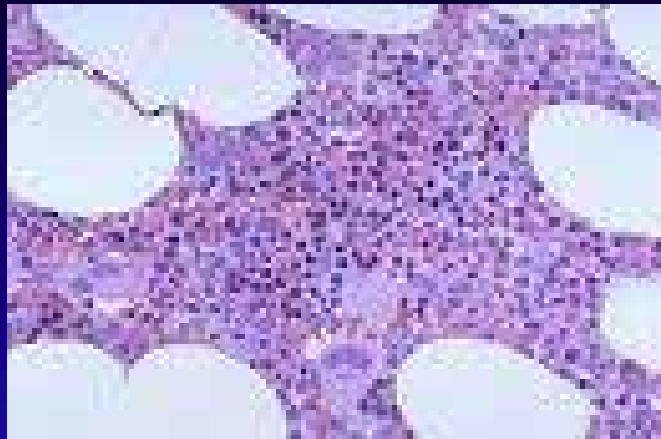
- Is there a suitable transplant donor?
- Are there medical problems (temporary or permanent)?
- Are the risks warranted at this point in time?
- Does this change monitoring?
- What else is happening for the family?

# Fanconi anemia – emerging problems

- Endocrine problems increasingly recognized
  - High rate of osteoporosis
  - High rate of growth hormone deficiency
  - High rate of cholesterol, blood sugar disturbance
  - Fertility difficulties

# Fanconi anemia: principles of follow up

- Monitor for complications of BMFS – leukemia, aplastic anemia, cancer
- Monitor for problems known at diagnosis – hearing, kidney, learning...
- Monitor for side effects of treatment – HSCT, iron overload, infections...
- Monitor for problems that may emerge
  - Medical issues : hormones, bones, life style
  - Psychological supports : child and family



# How do we translate lessons from FA to other BMFS?

- Monitor for complications of BMFS – leukemia, aplastic anemia, cancer
- Monitor for problems known at diagnosis
- Monitor for side effects of treatment
- Monitor for problems that may emerge
- Prevention

# Issues specific to type of BMFS

- SDS – growth and development, malabsorption related to pancreatic dysfunction, recurrent infections, dental health
- DC – risk of pulmonary and liver fibrosis, eye, mouth and dental care, osteoporosis, genital problems
- DBA – rare kidney or hearing disorders, heart defects
- TAR – dislocated hips, abnormal kidney, cryptic testes, hemangiomas

# Those at risk for aplastic anemia and leukemia

- Regular complete blood counts – 1-3months
- Regular bone marrow biopsy/aspirates – 1 yr
- Regular assessment of bone marrow genetics
- Incorporate risk factors – physical findings, genes, other?
- Education of child, family and health care providers regarding what to watch for – *fatigue, poor appetite, bleeding, bruising, pain, fever*

# Those at risk for cancer

- Regular physical exam by experienced doctor(s)
- Target areas that are at risk for cancer: skin, PAP smears and vulvar exams, breast exams, mouth exam by dentist, endoscopy of esophagus
- Incorporate risk factors – physical findings, genes, other ?
- Education of child, family and health care providers regarding what to watch for – *persistent pain, lumps, changing skin, poor appetite, weight loss, difficulty swallowing*



# Who else in the family might be affected?

- Some BMFS are inherited but variable in how and when they show themselves – oldest adult with FA and bone marrow failure = 48 yr old.
- Siblings, parents, and relatives may be affected but not yet symptomatic.
- Discuss with doctor the possible inheritance patterns the disorder.
- Genetic counseling.



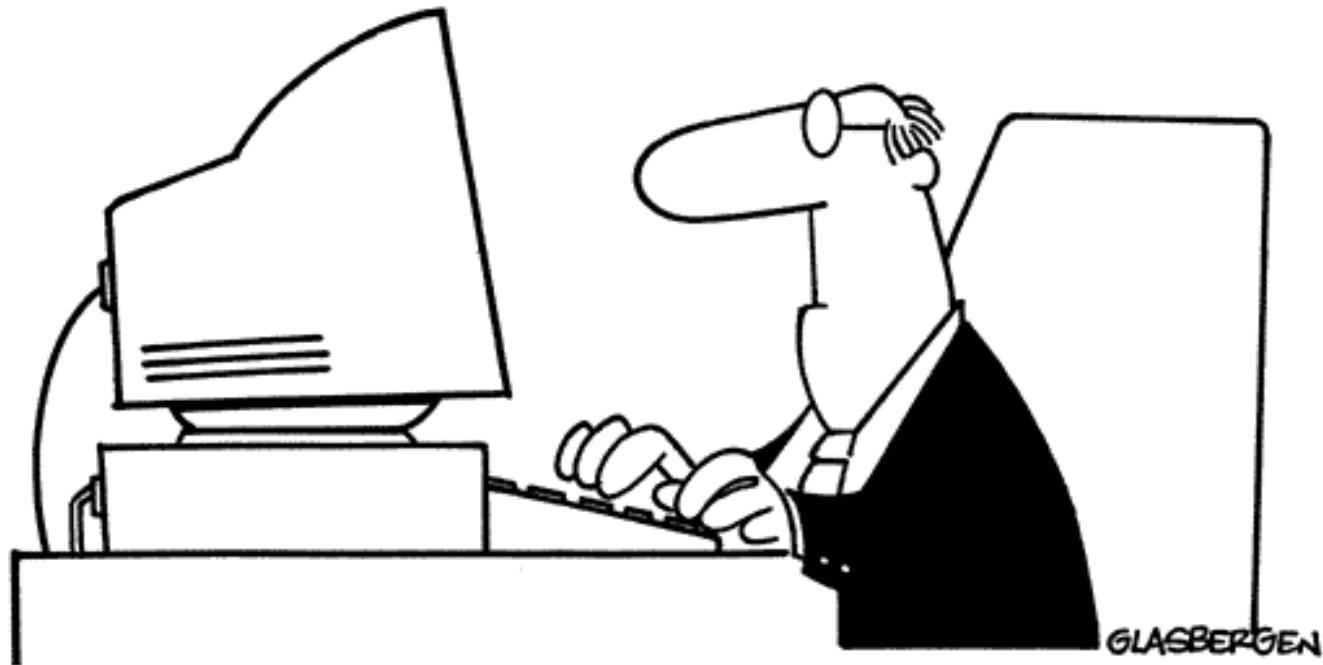
# How do we reduce risk of complications in BMFS?

1. Have a plan for monitoring – catching a condition early is better than late.
2. Multidisciplinary care
3. Life style – exercise, healthy diet, tobacco, sun
4. Vaccinations – Flu, Boosters, HPV vaccine
5. Avoid ionizing radiation
6. Transition plans



# Imperfect knowledge = be cautious

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**“MEMO: It has come to my attention that every time we solve one problem, we create two more. From now on, all problem solving is forbidden.”**

# Conclusions

- Bone marrow failure disorders are complex, and incompletely understood.
- Complications : related to the primary marrow failure, associated physical or organ problems, and/or the treatment of aplastic anemia.
- Some BMFS have a significant risk of leukemia and solid cancers. Prevention and monitoring key.
- It is essential to develop an individualized plan for those who have a BMFS.

# Resources

- Fanconi Anemia: <http://www.fanconi.org/>
- Fanconi Canada: <http://www.fanconicanada.org/>
- Diamond-Blackfan Anemia: <http://www.dbafoundation.org/>
- Shwachman-Diamond Syndrome: <http://www.shwachman-diamond.org/>
- Severe Congenital Neutropenia: <http://depts.washington.edu/registry/>
- Diamond-Blackfan Anemia Registry: <http://www.dbar.org/>
- Dyskeratosis Congenita Outreach Network: <http://www.dcoutreach.com/>
- Aplastic Anemia & MDS International Foundation, Inc: <http://www.aplastic.org/>
- National Cancer Institute: <http://www.marrowsfailure.cancer.gov/>

# Discussion

