National Cancer Institute

Fanconi Anemia 101

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FA Camp, June 24, 2011

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

When You Hear …., Think …., Or ….

Koalas

Open Minds

"I've never seen this before."

should be

"I've never ***recognized*** this before."

Question

- How many think that the diagnosis of FA was missed by one or more physicians prior to being made?

History: Guido Fanconi

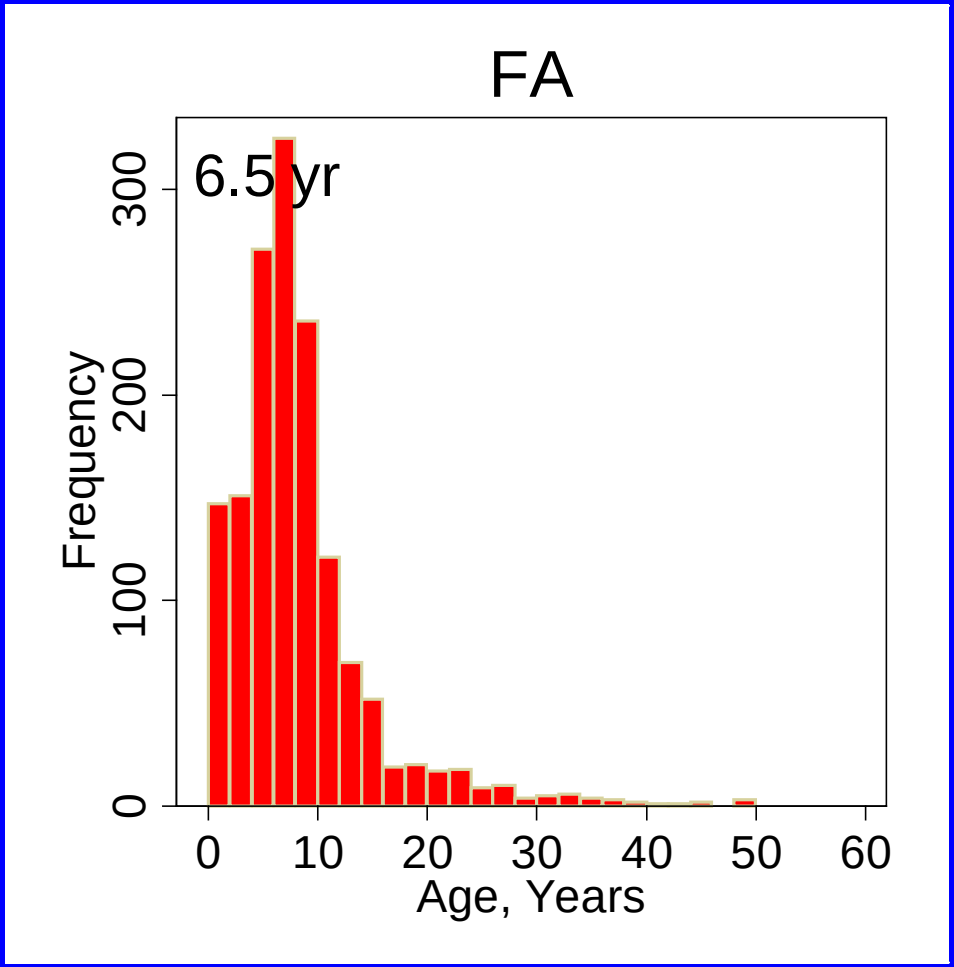
- Fanconi Anemia (Fanconi pancytopenia syndrome): 1927, 3 brothers with pancytopenia and physical abnormalities, “perniziosiforme”
- Fanconi Syndrome (renal Fanconi syndrome): 1936, proteinuria, glucosuria, phosphaturia, aminoaciduria, citraturia, and proximal renal tubular acidosis

Fanconi Anemia: Children

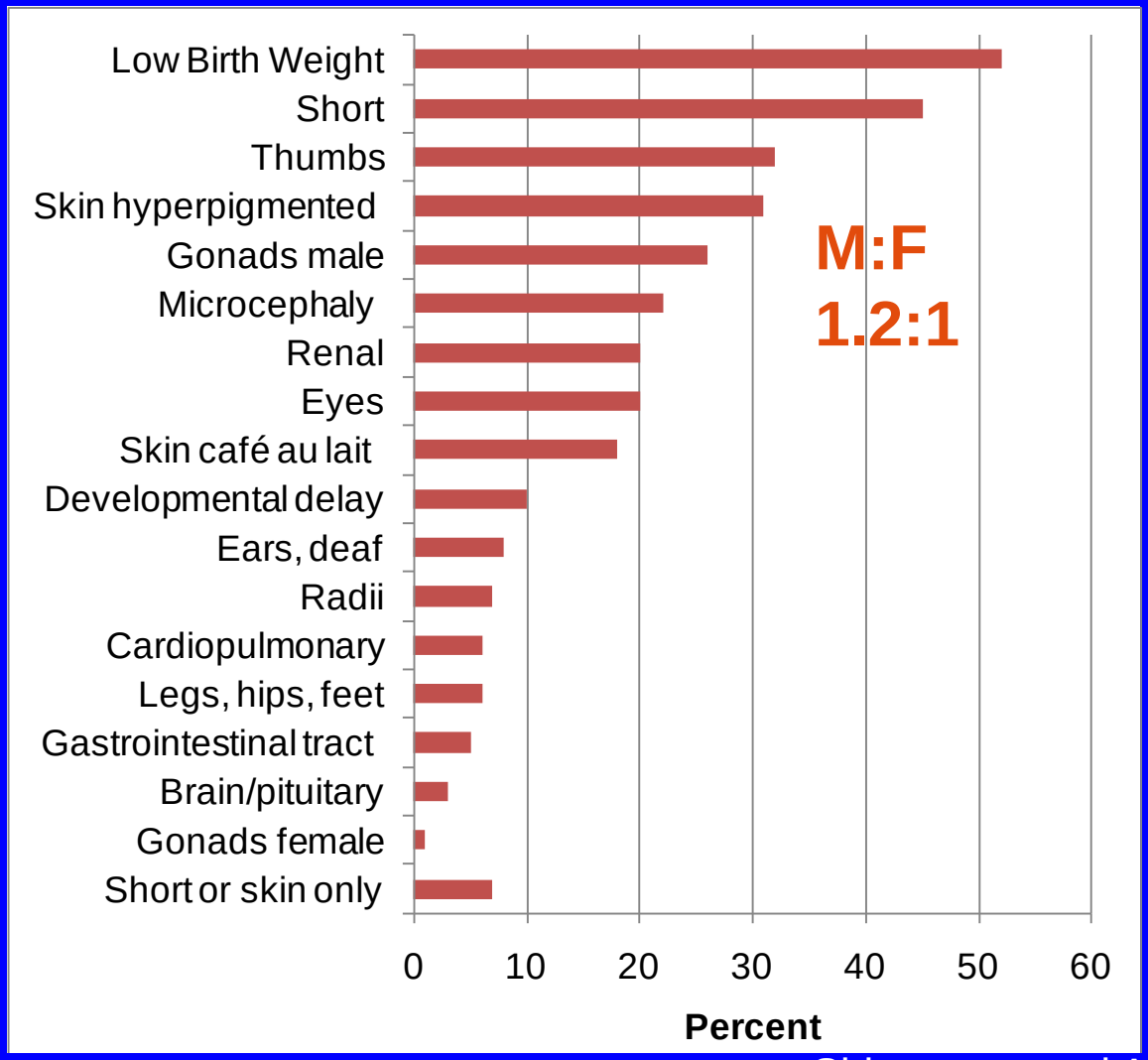
Photos with permission

Fanconi Anemia: Adults

FA: Age at Diagnosis in Literature



FA Literature: Physical Findings, 60%



Shimamura and Alter, Blood Reviews, 2010

Characteristics of Persons with FA

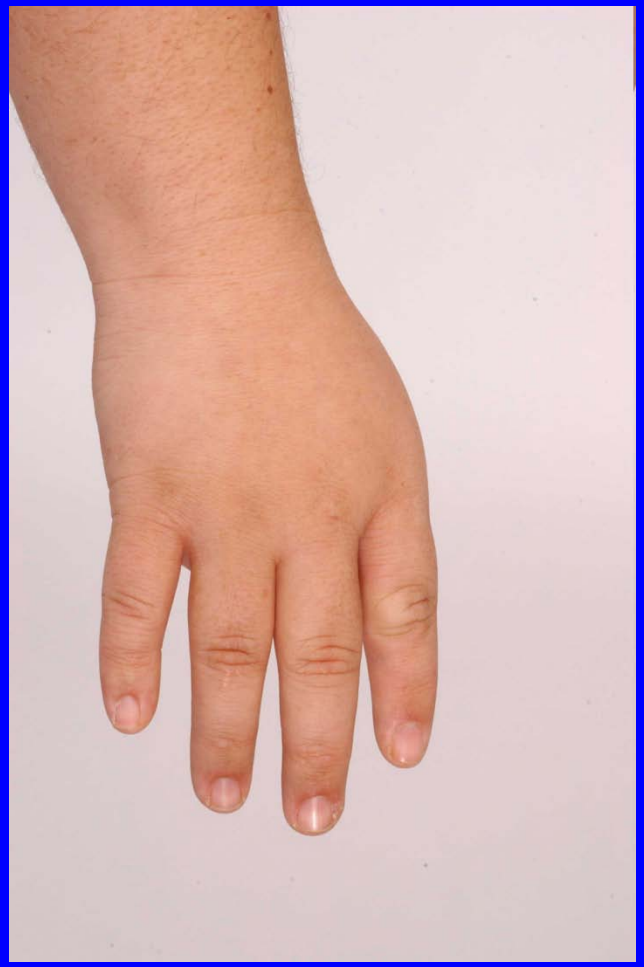
- Physical findings described in the literature may not be found in all persons with FA
  - 11% had short stature and skin findings only
  - At least 25% of those reported had no physical findings
- Some persons without physical findings may be diagnosed at a later age

FA: Laboratory Findings

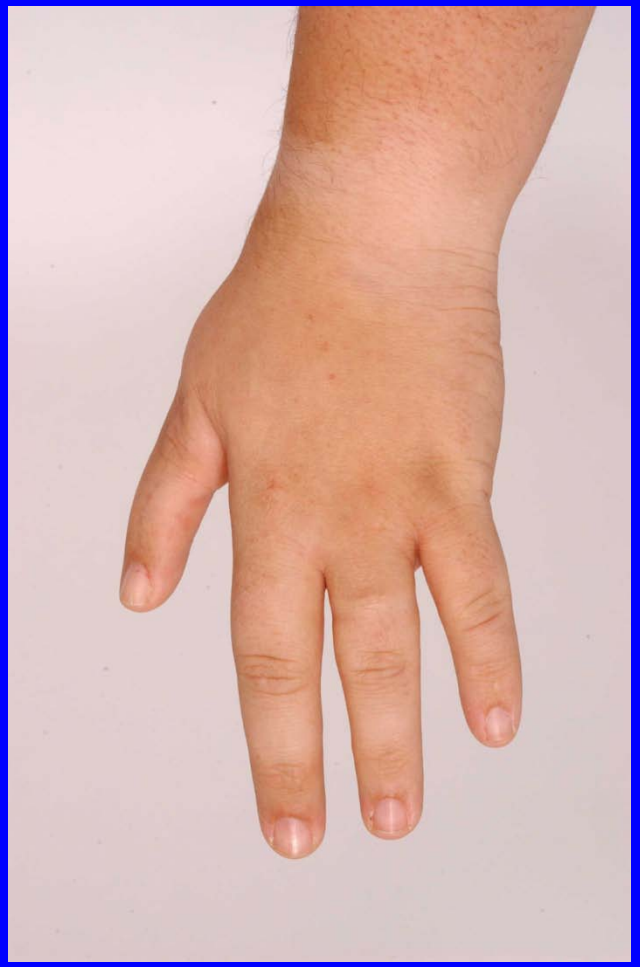
- Low blood counts (pancytopenia)
- Large red cells (macrocytosis)
- Increased fetal hemoglobin (Hb F)
- Chromosome breakage in lymphocytes or fibroblasts cultured with a DNA crosslinker, e.g. diepoxybutane (DEB) or mitomycin C (MMC)

FA: Hands

Right



Left

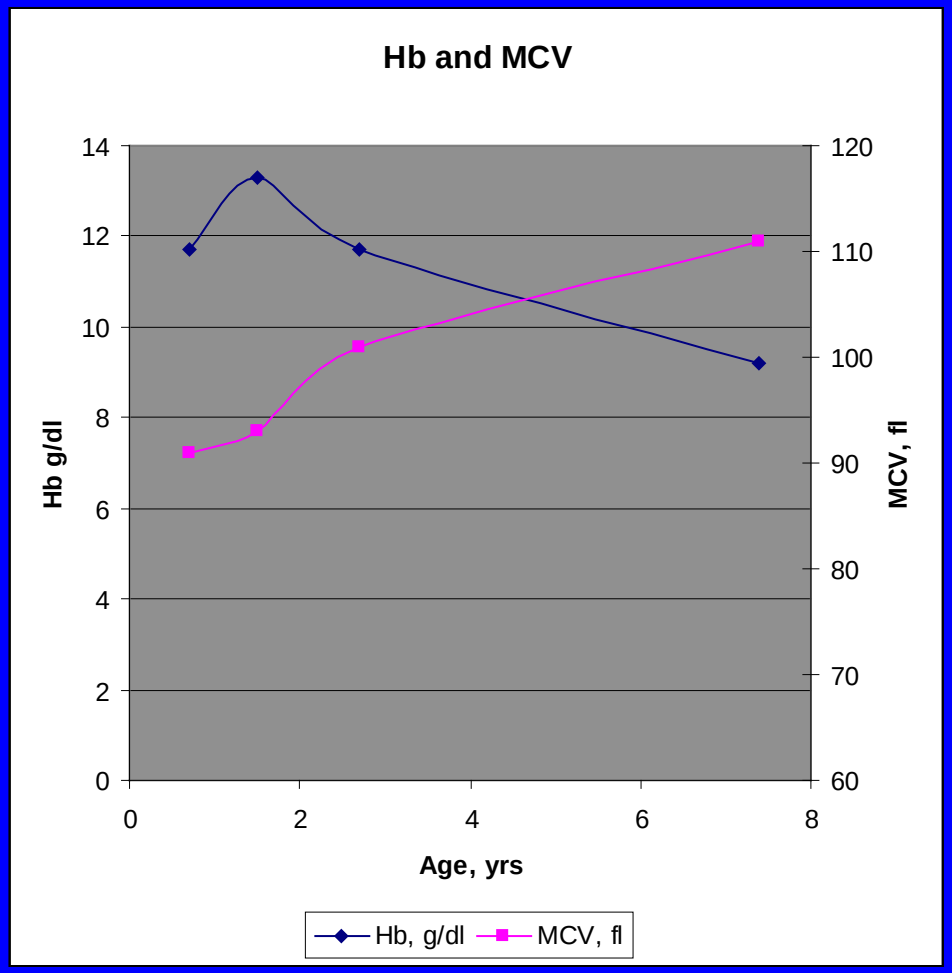


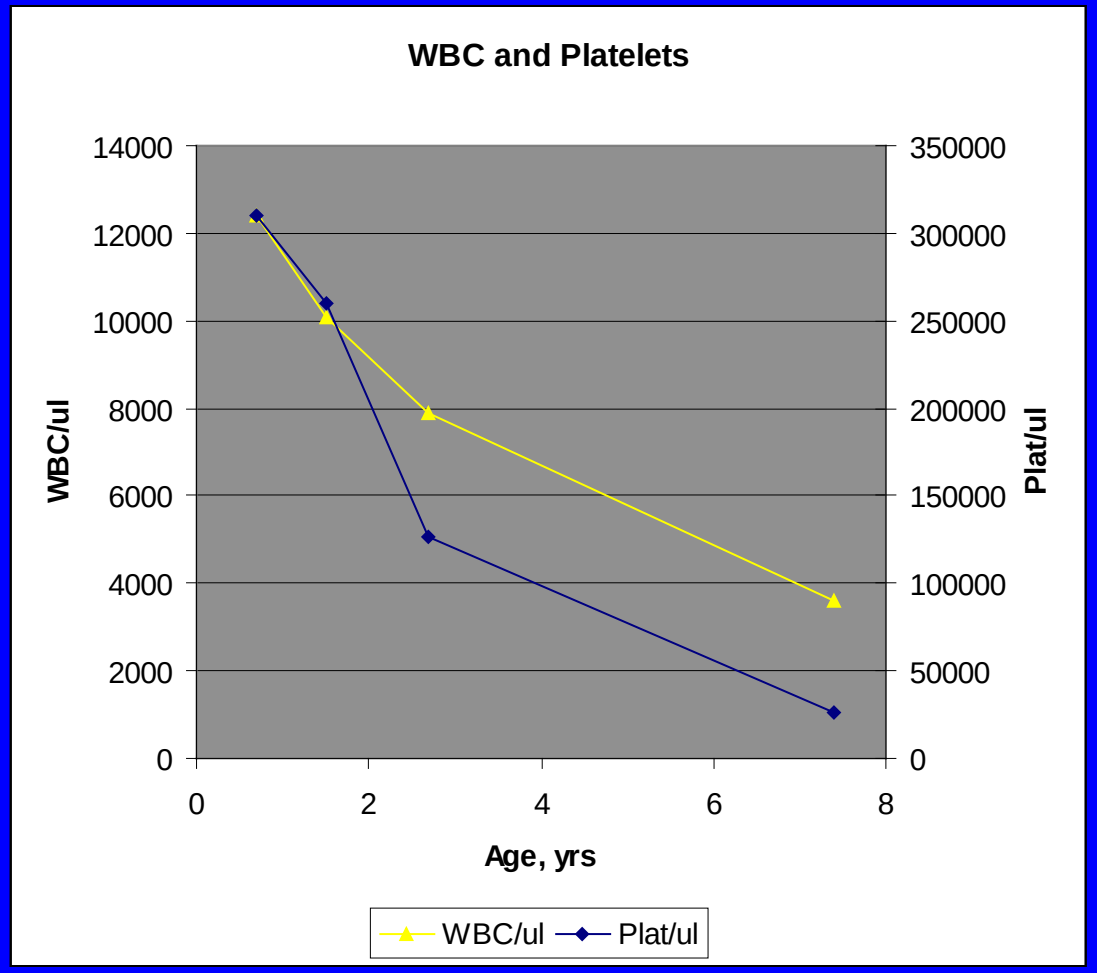
FA: Carrier Frequency

- 1:300 in New York State in 1971 (Swift, 1971)
- ~1:100 in Ashkenazi Jews, Afrikaners, Spanish Gypsies, black sub-Saharan Africans

- 1:181 in US in 2010
- 1:93 in Israel in 2008 (Rosenberg et al, 2010)

FA: CBCs - Hand Surgery





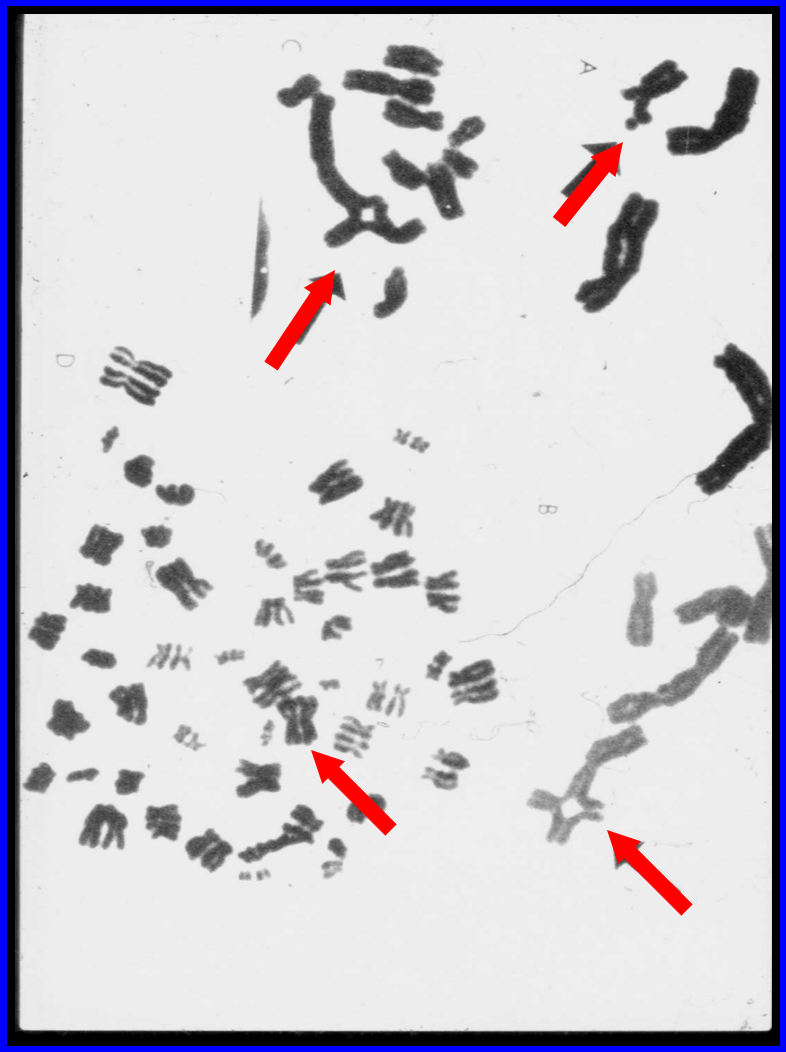
Alter, J Hand Surg, 1992

FA: Surgery

- Recommendations to surgeons and anesthesiologists:
  - Hb, platelets
  - MCV - increased early in marrow failure
  - *Trends* may precede abnormal values

Fanconi Anemia: Definition

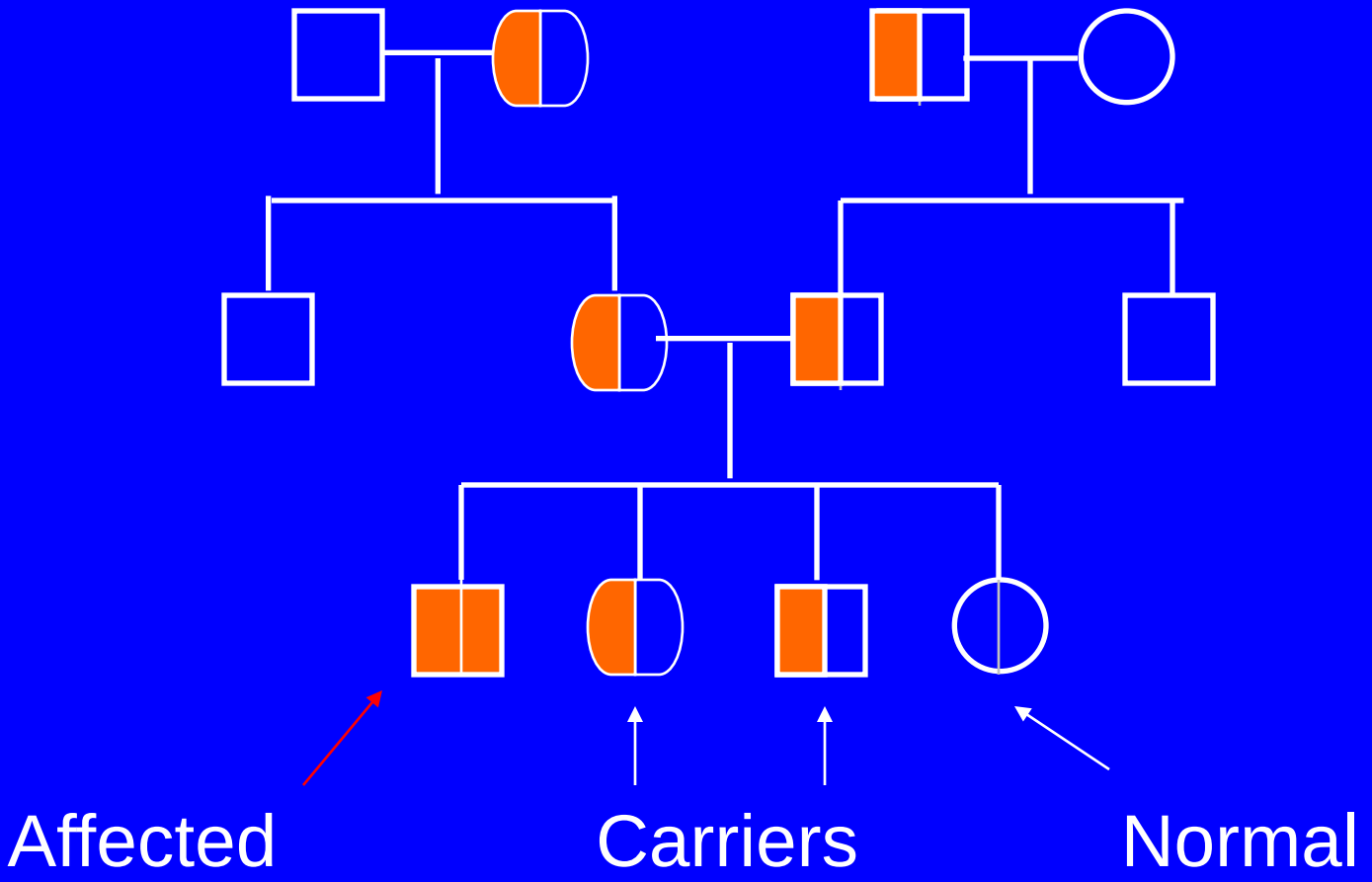
- Autosomal recessive
  - 1 X-linked recessive gene
- Physical findings
- Aplastic anemia
- Leukemia
- Solid tumors
- Chromosome instability
- DNA repair defect
- >15 genes ?



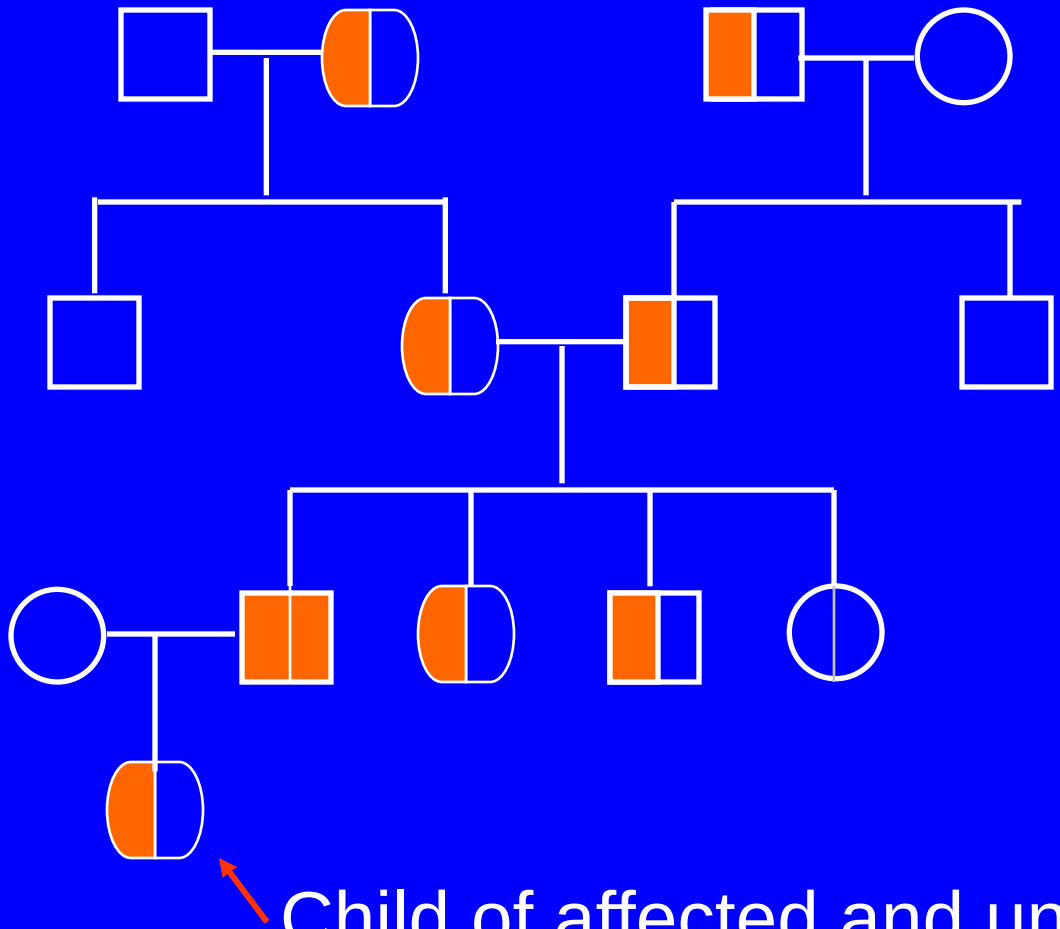
FA Inheritance

- Persons with FA:
  - Unaffected parents carry one FA gene and one normal gene (carriers)
  - Affected offspring get one FA gene from each parent
- Children of persons with FA:
  - Each child will have one FA gene (carriers)

Autosomal Recessive Inheritance

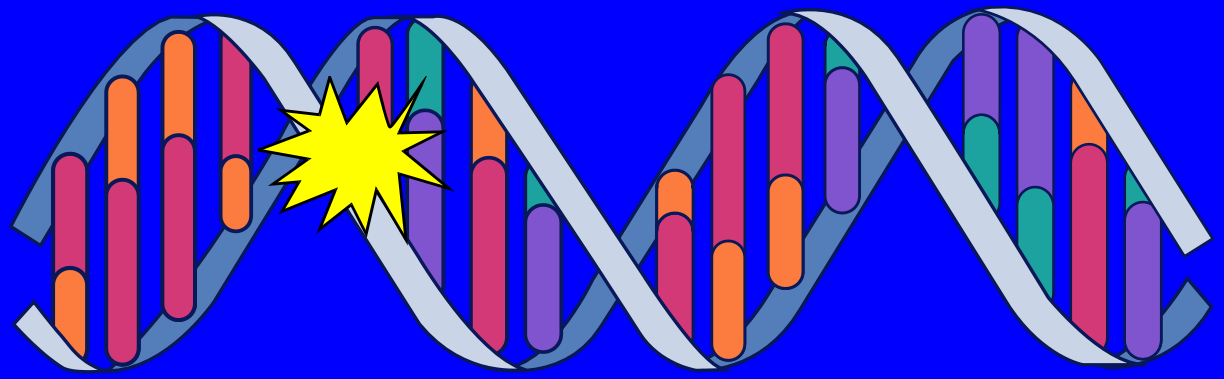


Autosomal Recessive Inheritance



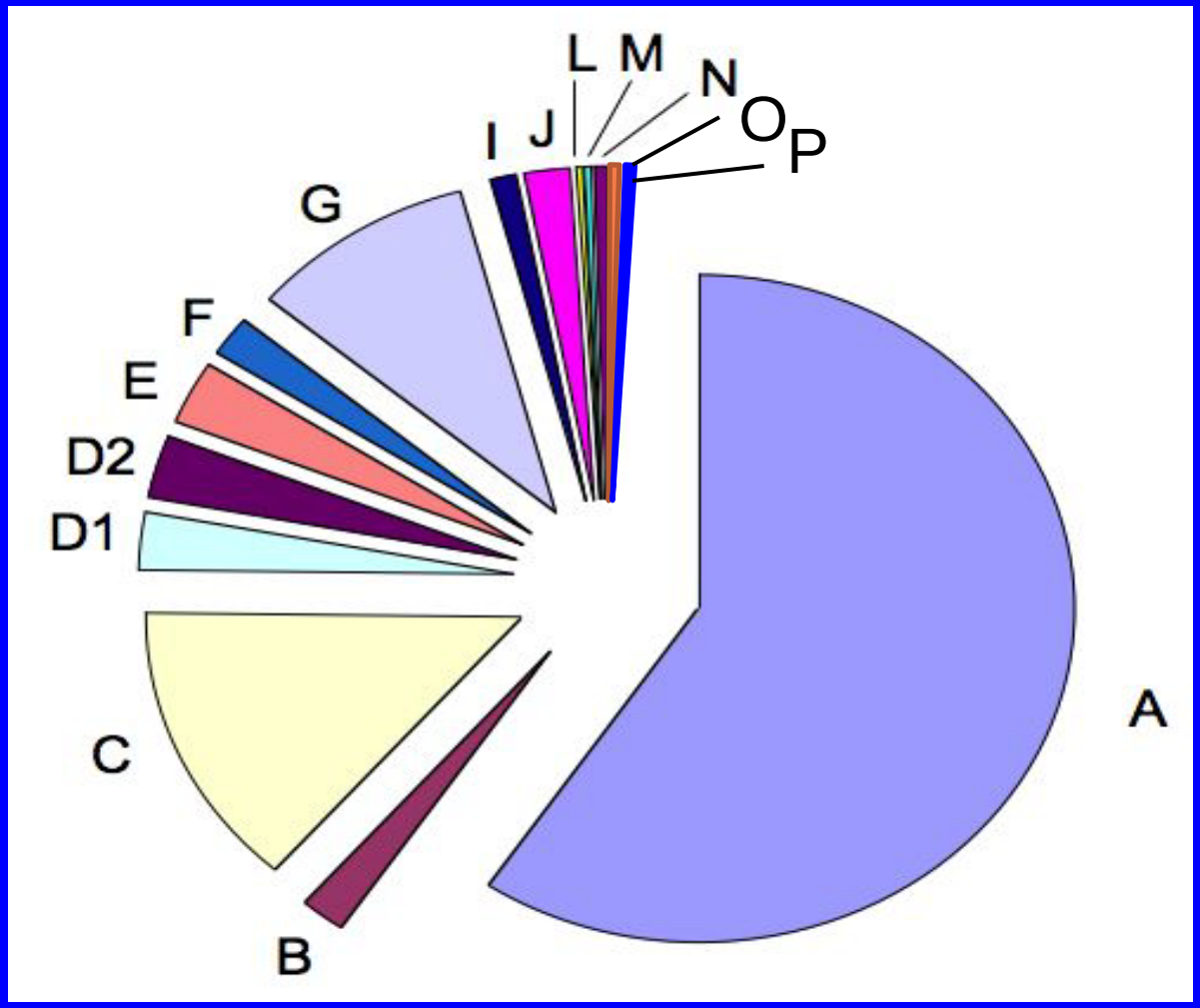
Disease-Associated Mutations

A mutation is a change in the normal base pair sequence



Commonly used to define DNA sequence changes that alter protein function

15 FA Genes (?)



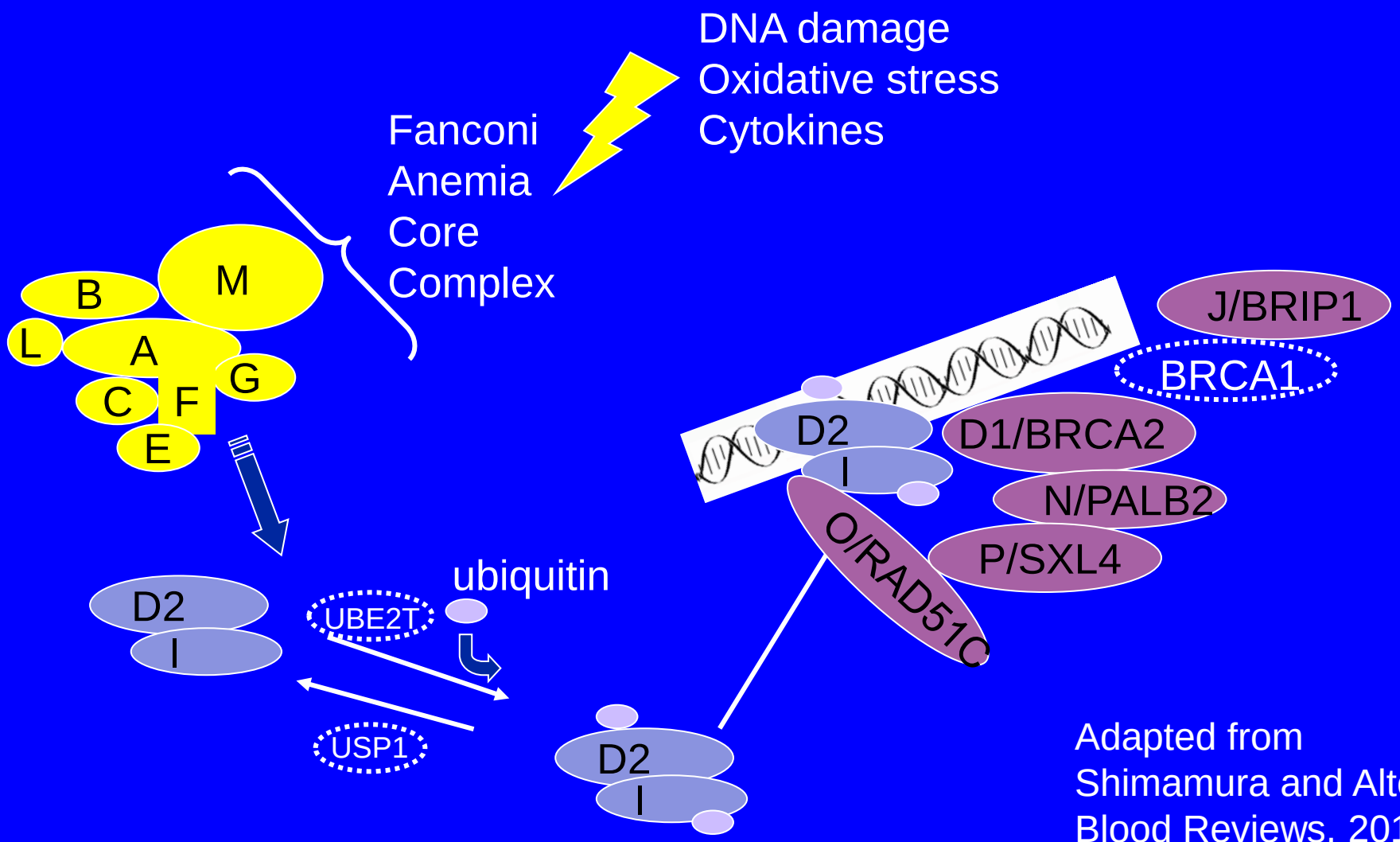
Data from Leiden Open Variation Database, http://chromium.liacs.nl/LOVD2/FANC/home.php

FA: Complementation Groups/Genes

Group	Locus	cDNA	Exons	AA	%
A	16q24.3	5.5	43	1455	~70
B	Xp22.31	2.8	10	859	Rare
C	9q22.3	4.6	14	558	~10
*D1/BRCA2**	13q12.3	11.4	27	3418	Rare
D2	3p25.3	5	44	1451	Rare
E	6p21-22	2.5	10	536	~5
F	11p15	1.3	1	374	Rare
G/XRCC9	9p13	2.5	14	622	~10
I/KIAA1794	15q25-26	4.5	38	1328	Rare
*J/BACH1/BRIP1**	17q22.3	4.6	20	1249	Rare
L/PHF9/POG	2p15-16.1	1.7	14	375	Rare
M/Hef	14q21.3	6.5	22	2014	Rare
*N/PALB2**	16p12.1	3.5	13	1186	Rare
*O/RAD51C**	17q25.1	2.7	9	76	Rare
*P/SLX4**	16p13.3	26.6	15	1834	Rare

*Breast cancer genes

FA/BRCA DNA Repair Pathway



Adapted from
Shimamura and Alter,
Blood Reviews, 2010

Who Should be Tested for FA?

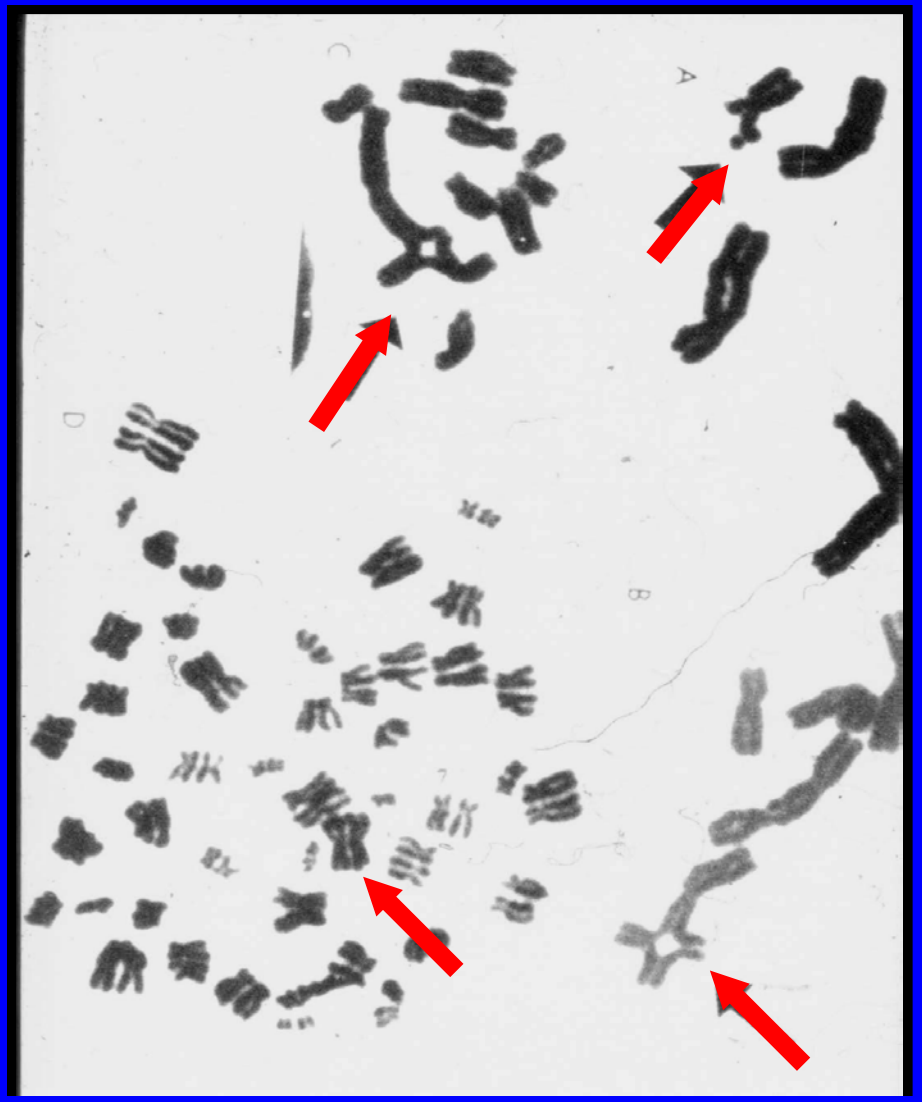
- Characteristic birth defects (eg thumbs, kidneys, poor growth, etc)
- Aplastic Anemia (AA)
- Myelodysplastic Syndrome (MDS)
- Acute Myeloid Leukemia (AML)
- Decreased fertility
- Early characteristic cancer
- Siblings of persons with FA

What are the FA Tests?

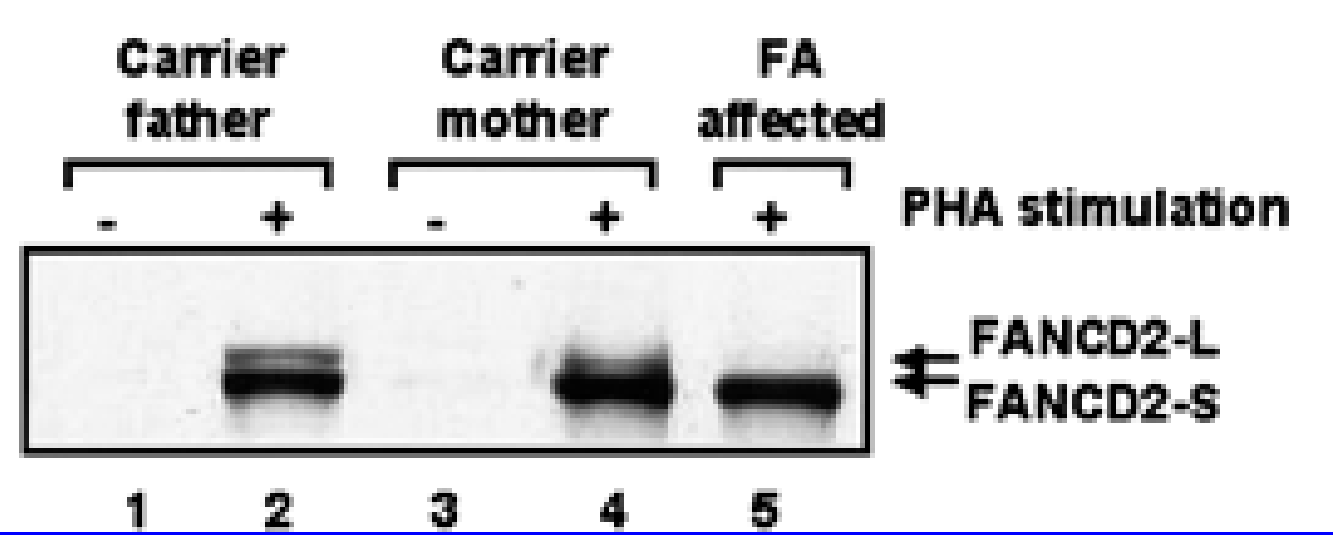
- Chromosome breakage, DEB or MMC
- D2 ubiquitination (Western blot)
- BRCA2 (Western blot)
- Complementation with cell lines
- Complementation with retroviruses
- Sequencing of candidate genes (eg FANCC IVS4+4 A->T)
- Sequencing of all cloned genes

Blood lymphocytes, skin fibroblasts

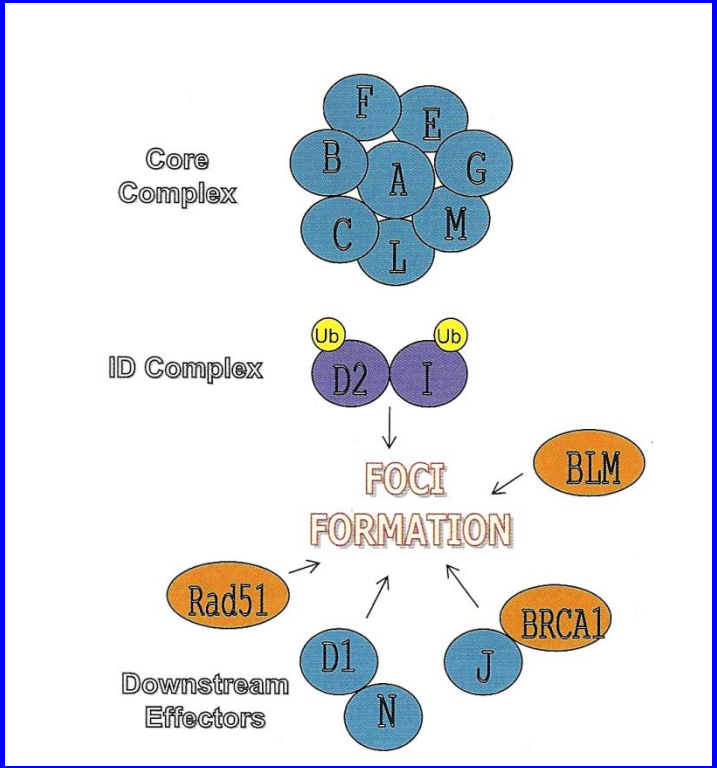
Chromosomes



FA: D2 Ubiquitination



Shimamura et al, Blood, 2002

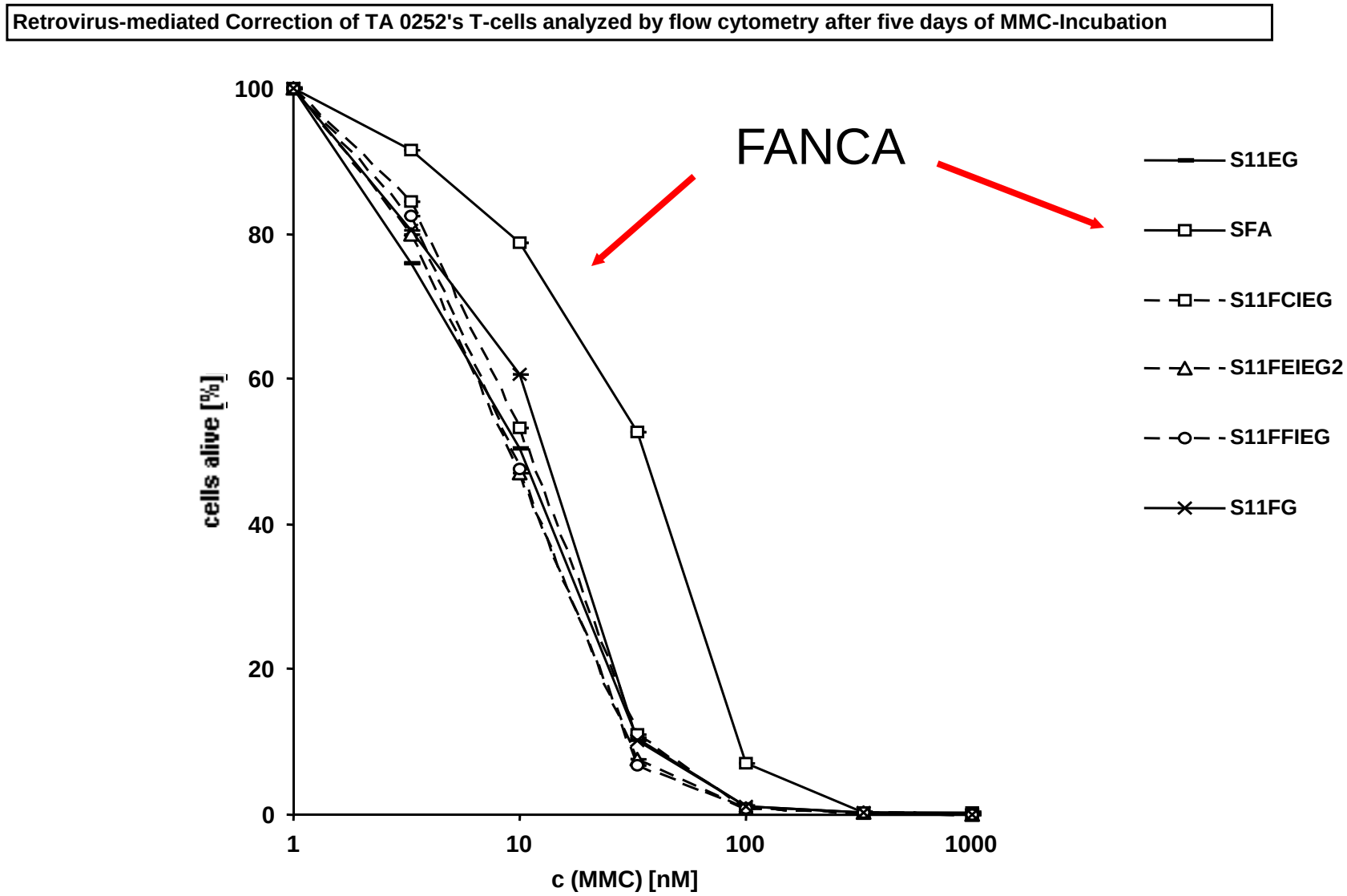


Green and Kupfer,
HemOnc Clin NA, 2009

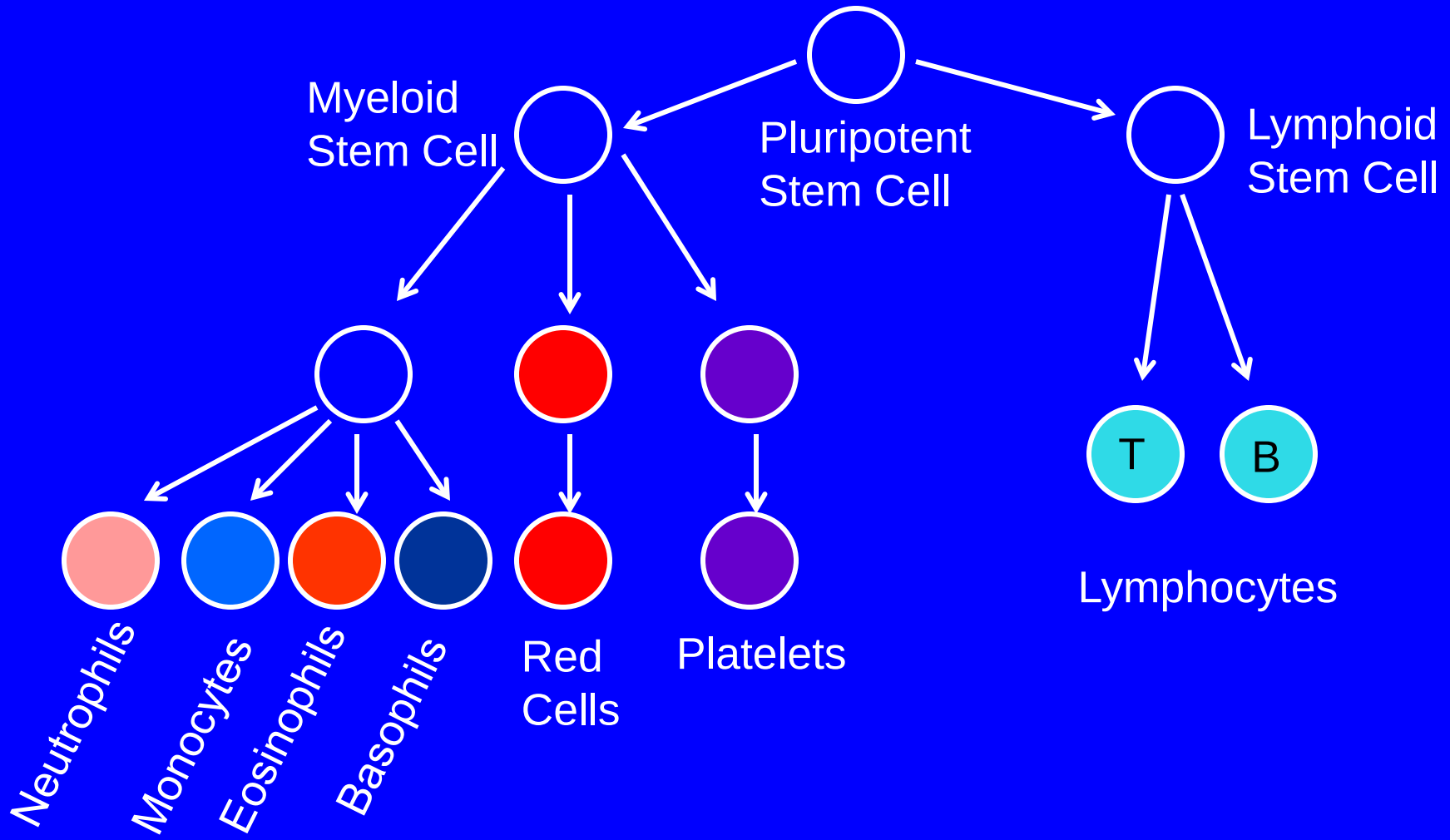
Complementation Analysis, Cloned FANC Genes

- FA cells are sensitive to DEB or MMC
- Introduce specific cloned FA genes
- Cells no longer sensitive
  - Normal gene ‘complemented’ patient cells, defining the complementation group
- Cells still sensitive
  - Normal gene not identified for patient cells

Retrovirus-mediated Correction of FA Cells

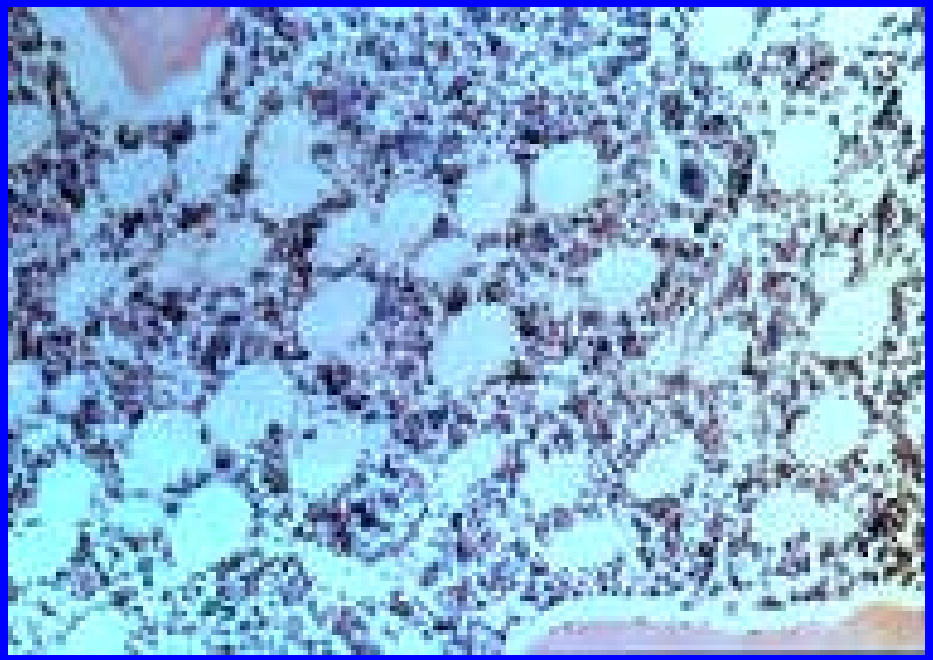


Blood Production (Hematopoiesis)

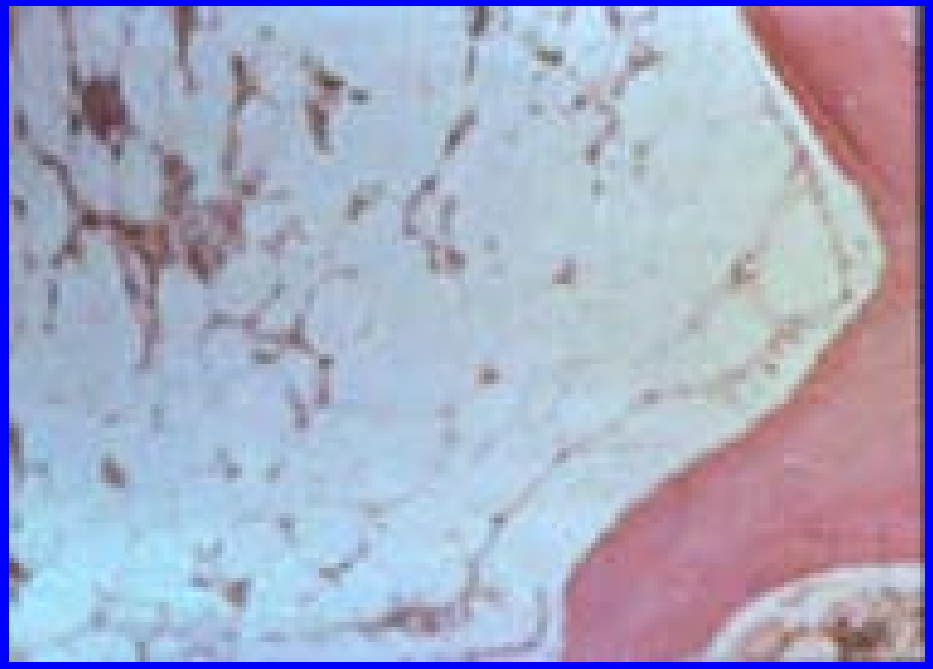


Bone Marrow Biopsy

Normal



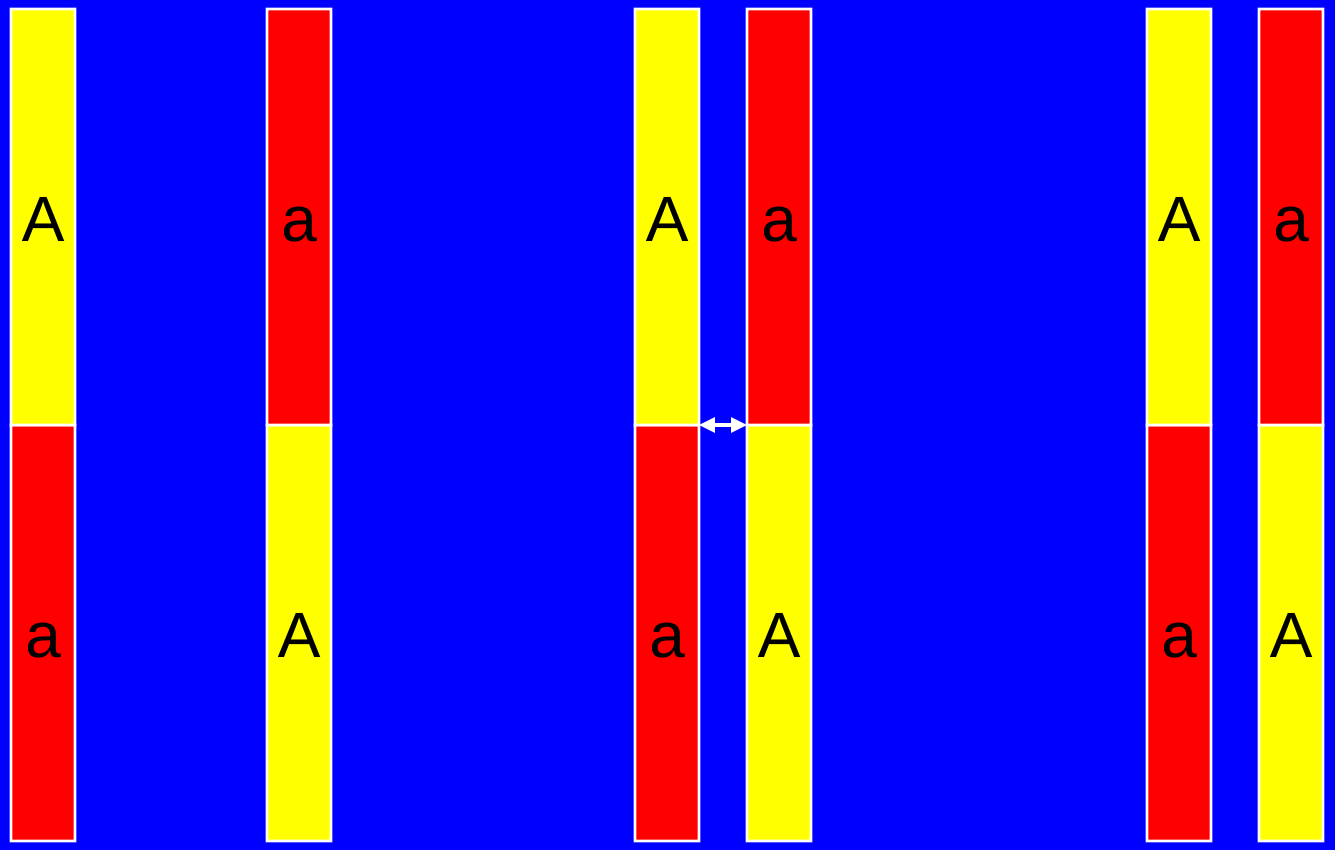
Aplastic



Proof of Mosaicism in FA

- Peripheral blood lymphocyte chromosome breakage test normal
- Skin fibroblast chromosome breakage test abnormal

Mosaicism from Recombination



FA: Gastroenterology

- Anatomical
  - Esophageal atresia, tracheoesophageal fistula, duodenal atresia, imperforate anus
- GI Symptoms
  - Reflux, gastric emptying delay, poor appetite
- Liver disease
  - Androgens: abnormal liver function, peliosis, adenomas, hepatomas,
  - Transfusions: iron overload
- Nutrition
  - Enteral supplements via NG or NJ tubes or gastrostomies

FA: Endocrine

Finding	Per cent
Any	73
Short and/or growth hormone deficient	51
Abnormal lipids	55
Hypothyroid	37
Glucose/insulin	39
Obese	27
Metabolic syndrome	21
Midline brain anomalies (50% small pituitary)	17
Pubertal gonadal dysfunction (menses, fertility)	65
Adult osteopenia/osteoporosis	92

FA: Complications

- Aplastic Anemia
- Acute Leukemia
- Myelodysplastic Syndrome
- Solid Tumors
- Liver Tumors

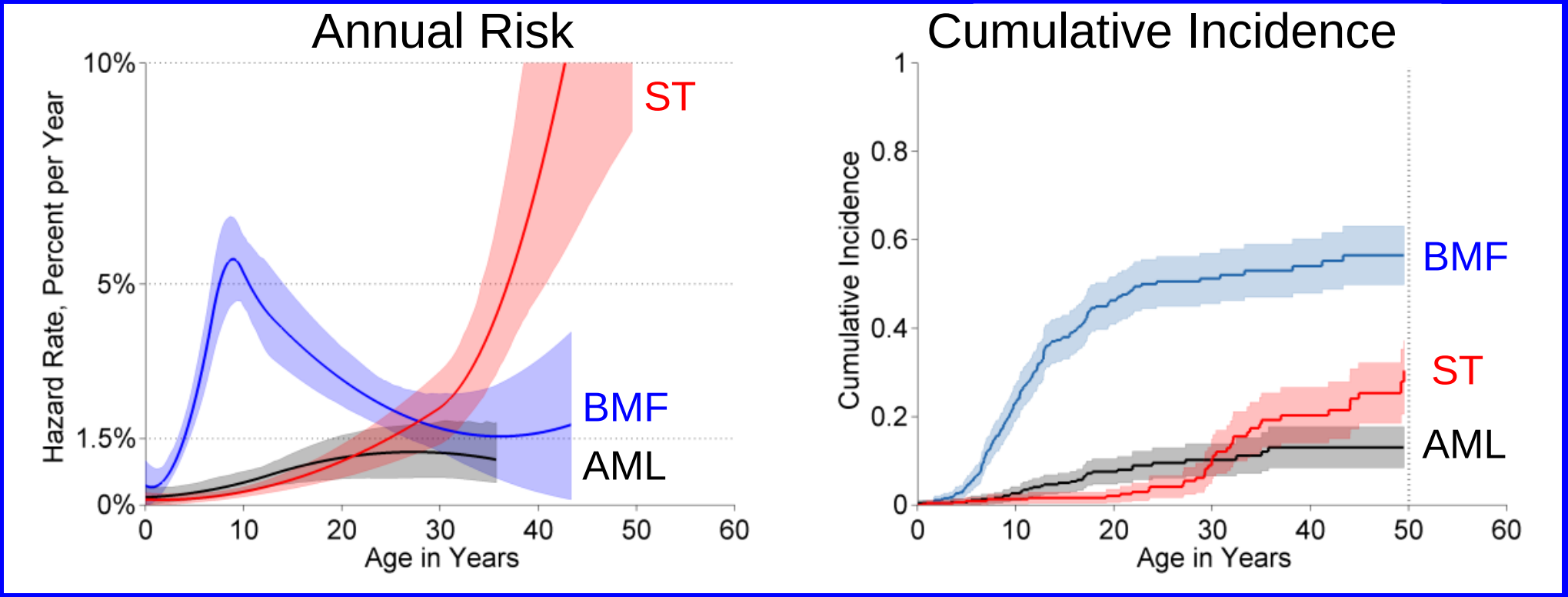
Definitions

- Aplastic Anemia (AA)
  - Pancytopenia
  - Hypocellular bone marrow
- Acute Leukemia (AL)
  - Malignant proliferation of immature cells
- Myelodysplastic Syndrome (MDS)
  - Cytopenias with hypercellular bone marrow

Aplastic Anemia: Signs and Symptoms

- Thrombocytopenia
  - bruises, petechiae
- Anemia
  - fatigue, lassitude, dyspnea
- Neutropenia
  - infections

FA Events


Annual Risk
Hazard Rate, Percent per Year
10%
5%
1.5%
0%
0
10
20
30
40
50
60
Age in Years
ST
BMF
AML
Cumulative Incidence
Cumulative Incidence
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Age in Years
BMF
ST
AML

“MDS” in FA

- Clone alone does *not* have a bad prognosis.
- Morphologic MDS + significant cytopenias require treatment.

Clone alone does not define MDS in FA.

FA: When to Treat Bone Marrow

- Cytopenias
  - Hb <8 g/dL or symptoms
  - Platelets <30,000/mm^3
  - WBC <500/mm^3
- Leukemia
  - Blasts in blood
  - >20% blasts in marrow
- MDS
  - Morphologic + cytopenias
  - Not for clone alone

FA: Treatment for Bone Marrow

- Transplant
- Androgen +/- corticosteroid
- Hematopoietic growth factors
- Gene therapy?

FA: Treatment with Transplant

- Bone marrow, cord blood, or peripheral blood stem cells
- HLA-related donor
  - when meet any treatment criteria
- Alternate donor (mismatched unrelated [MUD], partial match family member)
  - Leukemia or clinical MDS (not clone alone)
  - Refractory aplastic anemia

FA: Medical Treatment

- Oxymetholone
  - 2-5 mg/kg/day oral
- Danazol
  - ~200-400 mg/day oral
- Folic acid
  - 1 mg/day oral

FA: Treatment with G-CSF

- 5 μg/kg/day subcutaneous
- Decrease dose and/or give on alternate days
- Keep absolute neutrophil count >1000/mm^3

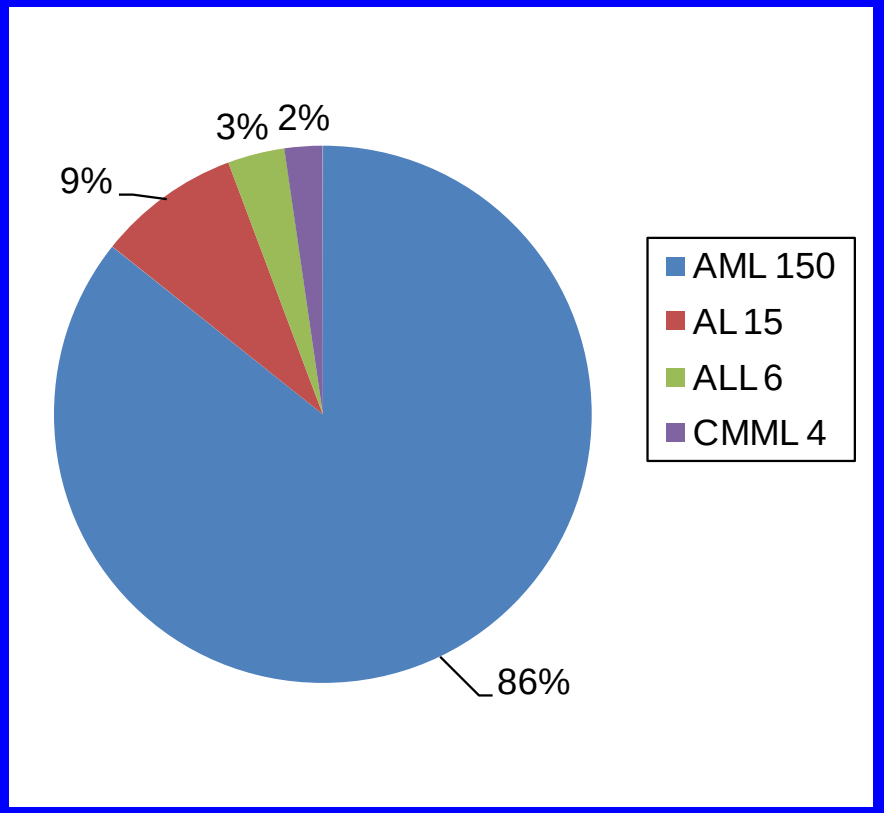
FA: Supportive Care

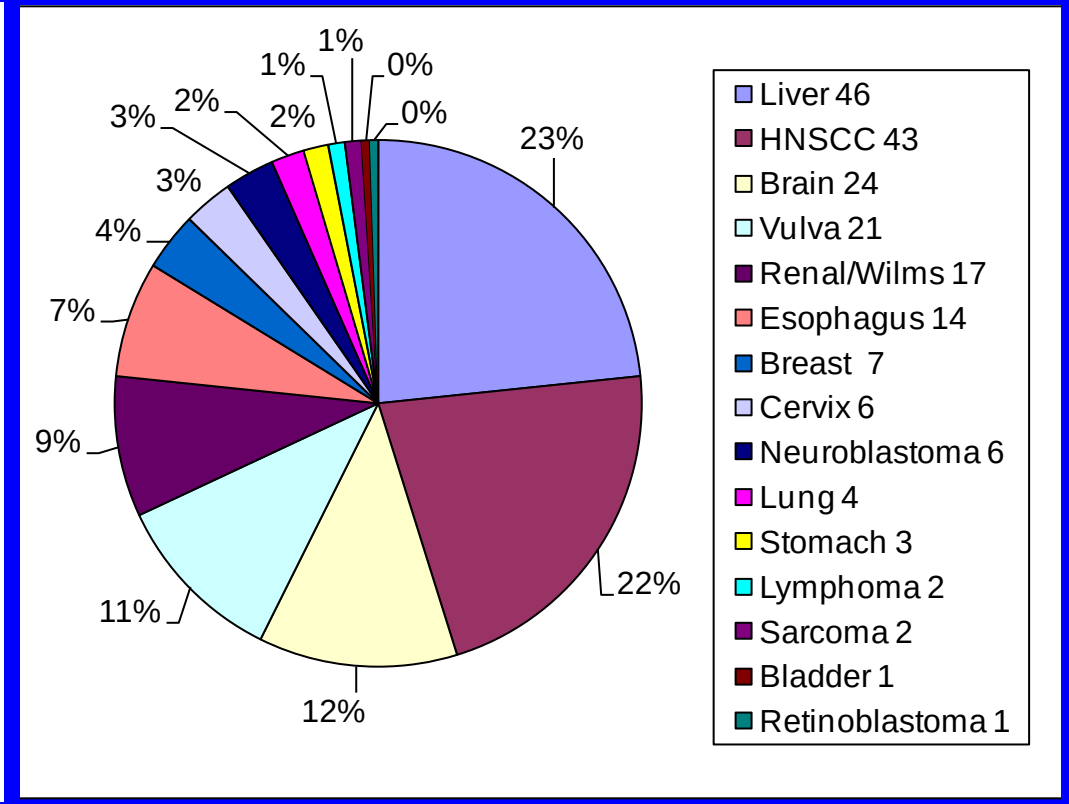
- RBCs - for Hb <8 g/dl or symptoms
- Platelets - for platelets <10,000/mm^3 or symptoms
- Blood products
  - no family member donors
  - Leukopoor, possibly irradiated
- Antibiotics
  - as needed for infections

FA: Surveillance

- CBC every 4 months or more often
- BM annually
  - aspirate for morphology
  - biopsy for cellularity
  - cytogenetics
  - special stains
  - flow cytometry
- Liver enzymes, ultrasound annually

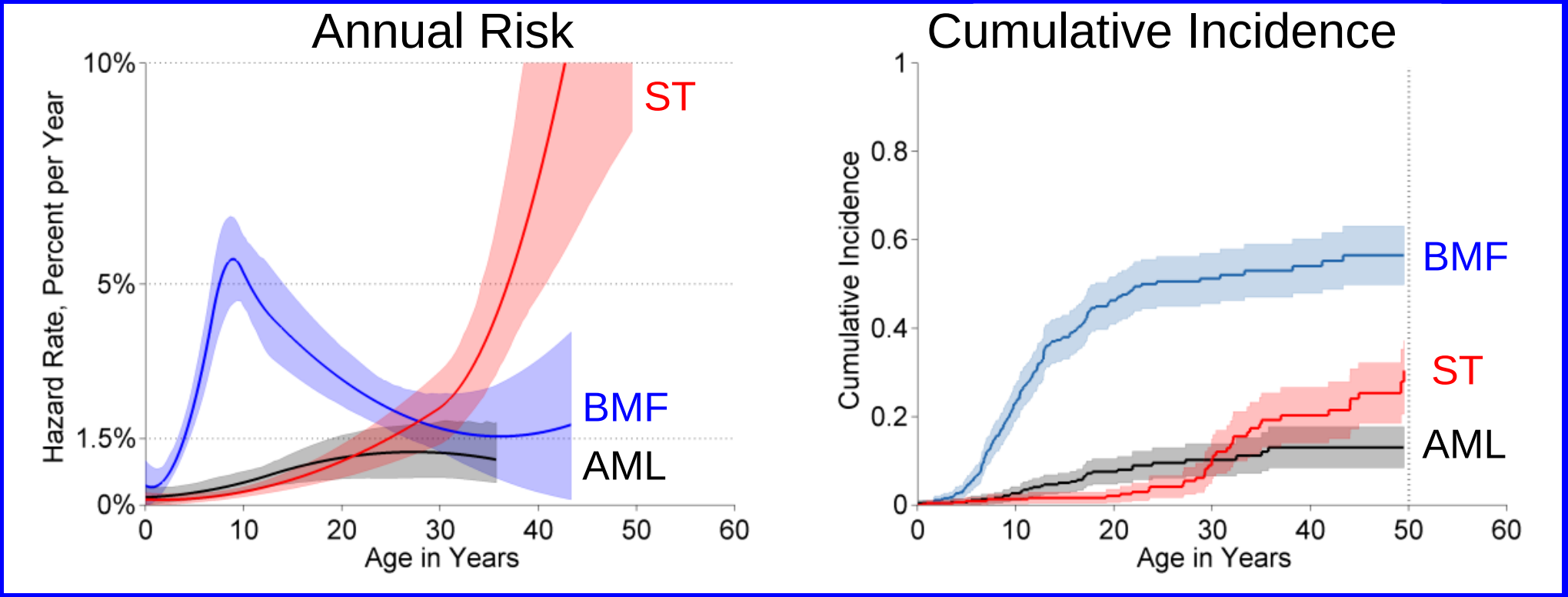
FA Literature: Cancer Types 1927-2009





175 leukemias and 197 solid tumors in 320/2000 patients;
26 had 2-4 cancers.

FA Adverse Events



Relative Risk of Cancer in FA

Parameter	Obs*	Exp*	Overall
Number of Patients	459		**459**
Person-Years	6839		**6839**
All Cancers	85	1.8	**~50x**
All Solid Tumors	46	1.3	**~40x**
Oral Cavity/Pharynx	14	0.02	**~700x**
Vulvar	10	0	**~3000x**
AML	6	0.06	**~500x**
MDS	55	0	**~7000x**

*Observed; Expected

FA: Adult Males

- Short stature
- Infertility
- Endocrine problems: cholesterol, thyroid, growth hormone, metabolic syndrome, small pituitary, osteopenia
- Cancer
  - AML
  - HNSCC
- HPV vaccine?

FA: Adult Females

- Late onset of menses (14-16)
- Heavy periods if platelets low
- Early onset of menopause (30s)
- Decreased fertility
- Increased need for Caesarean sections
- Worsening of bone marrow function during pregnancy
- Osteoporosis
- Cancer
  - AML
  - HNSCC
  - Vulva, vagina, cervix
  - Human papilloma virus
  - HPV Vaccine

FA Surveillance: Cancer

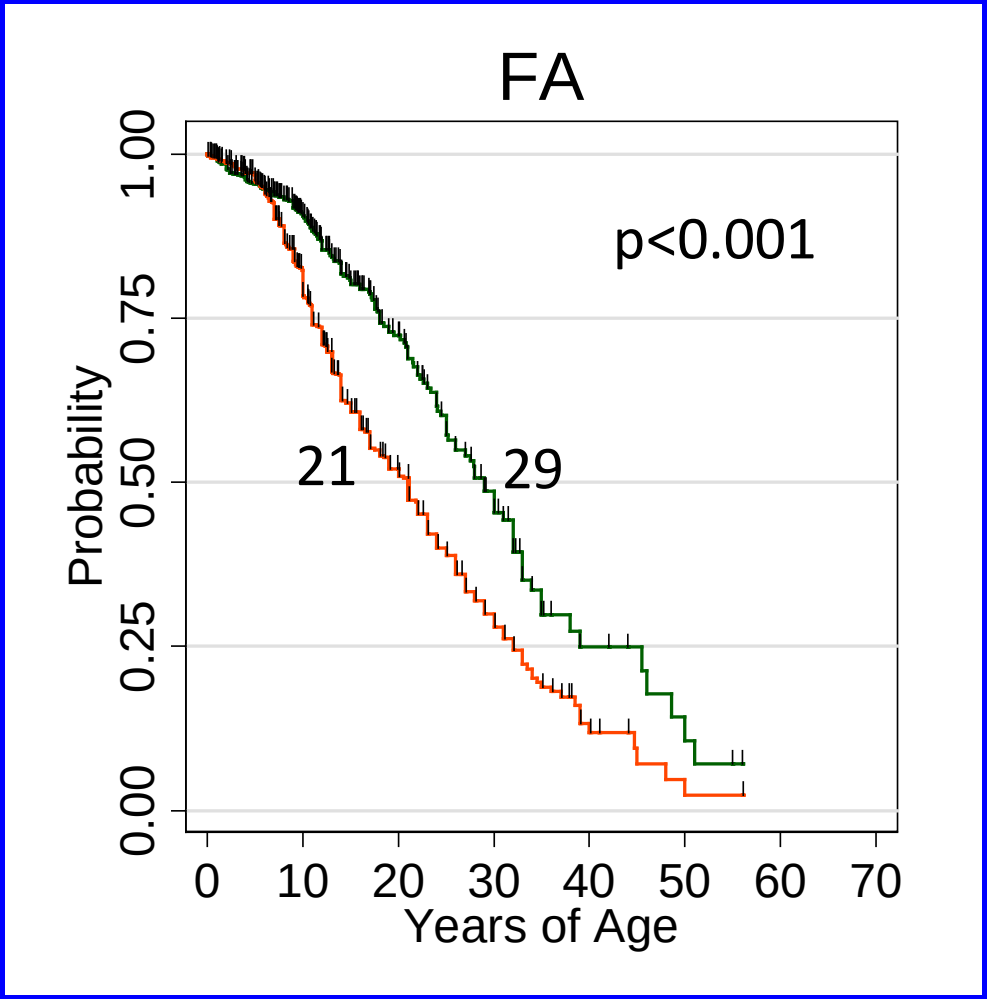
- Oral cavity and pharynx
  - Age >10 years
  - BMT >1 year
- Gynecologic
  - Age >16 years
  - Menarche
- Liver
  - Liver enzymes every 3-4 months
  - Liver ultrasound every 6-12 months
- Skin
  - Annual exam

Field Trip

FA Adult Care: Recommendations

- CBC every 4-6 months
- BM aspirate/biopsy/chromosomes every year
- Dental every year
- Head and neck with laryngoscopy every year
- Gyn exam with Pap and HPV every year
- HPV vaccine
- Consider esophageal endoscopy?

FA Survival 1927 to1999; 2000-2009




HAGAR THE HORRIBLE
CHRIS BROWNE
AFTER EXTENSIVE TESTS, I'VE FINALLY REACHED A CONCLUSION, HAGAR...
WHAT IS IT, DR. ZOOK ?
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WE HAVE TO TAKE MORE TESTS
1-31
CHRIS BROWNE

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Inherited Bone Marrow Failure Syndromes

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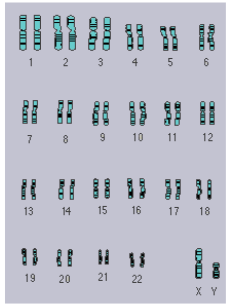
- More Information About the Research Team that is Responsible for the IBMFS Project
- Glossary of Terms
- Press Materials



Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes (IBMFS)

Inherited bone marrow failure syndromes (IBMFS) are rare disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood), associated with a family history of the same disorder. Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. There are several well-described syndromes, which can be recognized by health care experts. There are also patients who are harder to classify, but who appear to belong in this category.

Patients with these syndromes have a very high risk of development of cancer (either leukemia or certain solid tumors). At the moment we cannot predict which specific patient with an IBMFS is going to develop cancer. The NCI IBMFS Cohort Study will enroll North American families in which at least one member has or had an IBMFS. We plan to:

- include individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children);
- collect clinical information from study participants and their physicians;
- perform detailed physical examinations, x-rays and routine laboratory tests on those who are interested in traveling to the NIH to be seen in person by our team;
- attempt (on a research basis) identification of the specific genetic mutation that is associated with each family's disease;
- screen participants for early changes related to the specific cancers that occur in each syndrome;
- perform detailed research laboratory studies on blood and tumors collected from study participants, in an effort to understand the process by which cancers develop;
- monitor study participants in an ongoing fashion to determine the rate at which complications develop related to each disease, and to identify those complications more precisely;
- provide suggestions to study participants and their physicians regarding how to best take care of family members who are affected with a particular IBMFS; and
- offer genetic counseling, and an opportunity to learn the results of mutation testing, for those persons who decide that this information will be of use to them.

The Principal Investigator responsible for this study is Blanche P. Alter, MD, MPH. For further information regarding her credentials and experience, please see: http://dceg.cancer.gov/biographies/Alter.html.

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care which can be offered to persons with these disorders.

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