National Cancer Institute

# Cancer Epidemiology

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Fanconi Anemia Adults, February 2011

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

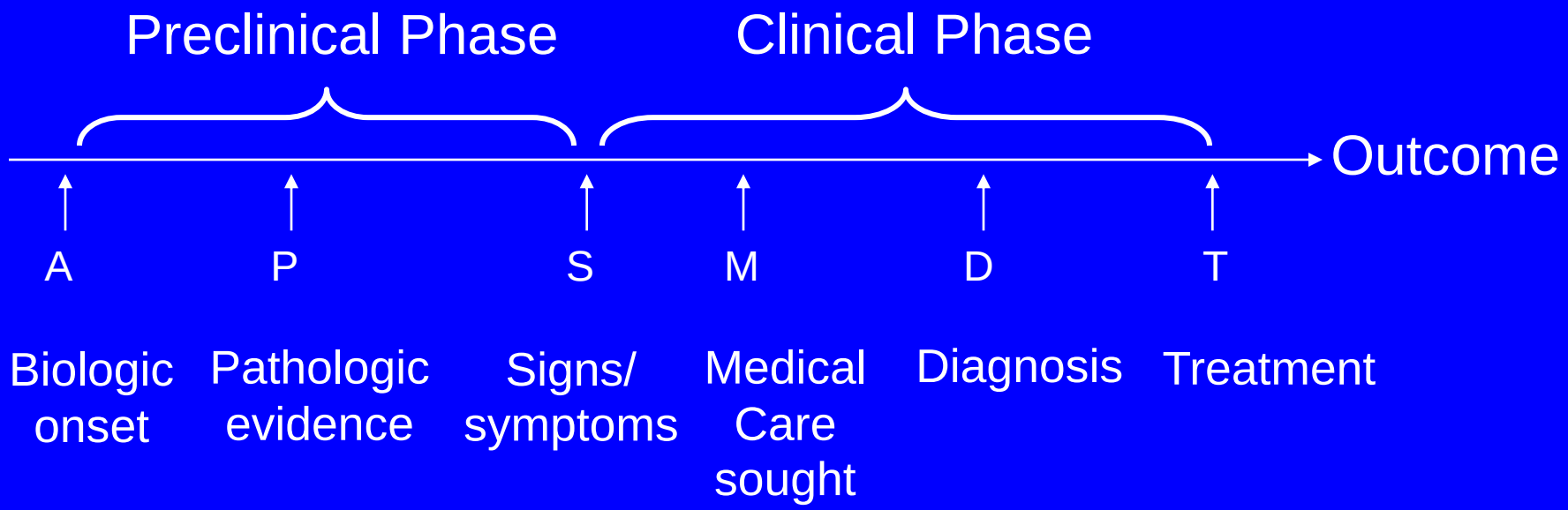
# Outline

- Epidemiology
- FA Literature
- Cancer types
- Mosaicism
- Cancer risks
- Myelodysplastic syndrome (MDS)
- Cancer in FA carriers
- Recommendations

# Epidemiology

- The Science of Public Health
- Study of disease distribution and its determinants
- Identify high-risk sub-groups
- Direct preventive efforts to them

# Natural History of Disease




From Gordis, Epidemiology, 1996

# Cancer Epidemiology

- General population
  - Increasing rate of cancer with age
  - Not obvious as to who will get cancer
- Cancer-prone rare syndromes
  - Develop cancer at younger ages
  - Recognized because of syndromic phenotype
  - Identify individuals with high risk of cancer *BEFORE* they develop cancer

# Prevention

- Primary – action to prevent disease in person who does not have it – *e.g.* stop smoking
- Secondary – identify people with early stage disease, leading to more effective intervention
- Tertiary – prevention of recurrence of disease

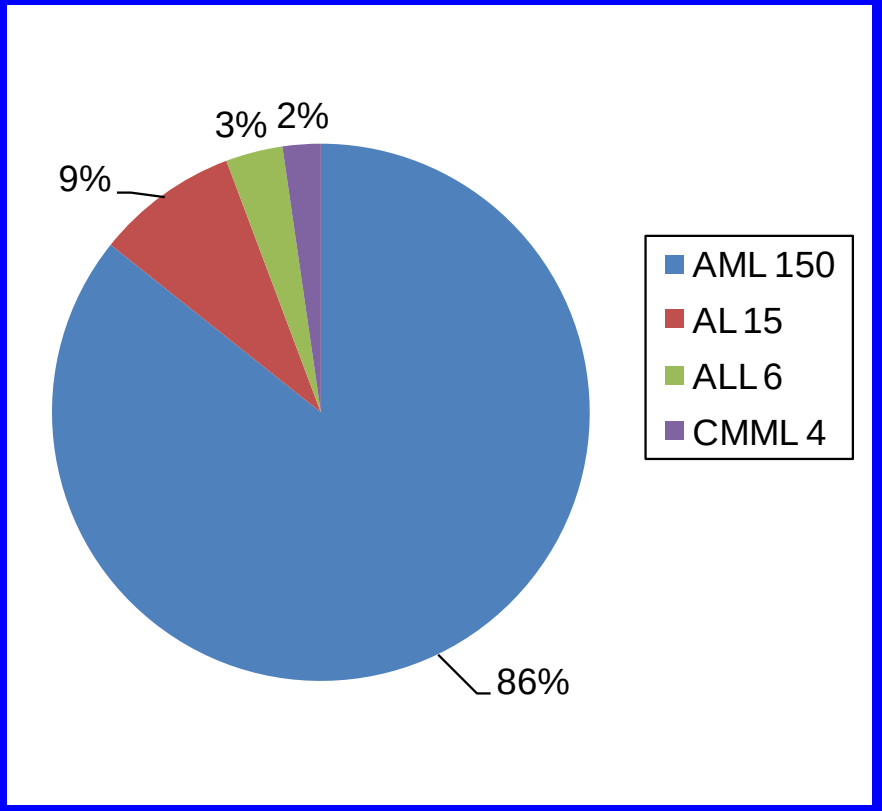
# Possible Causal Factors for Cancer in FA

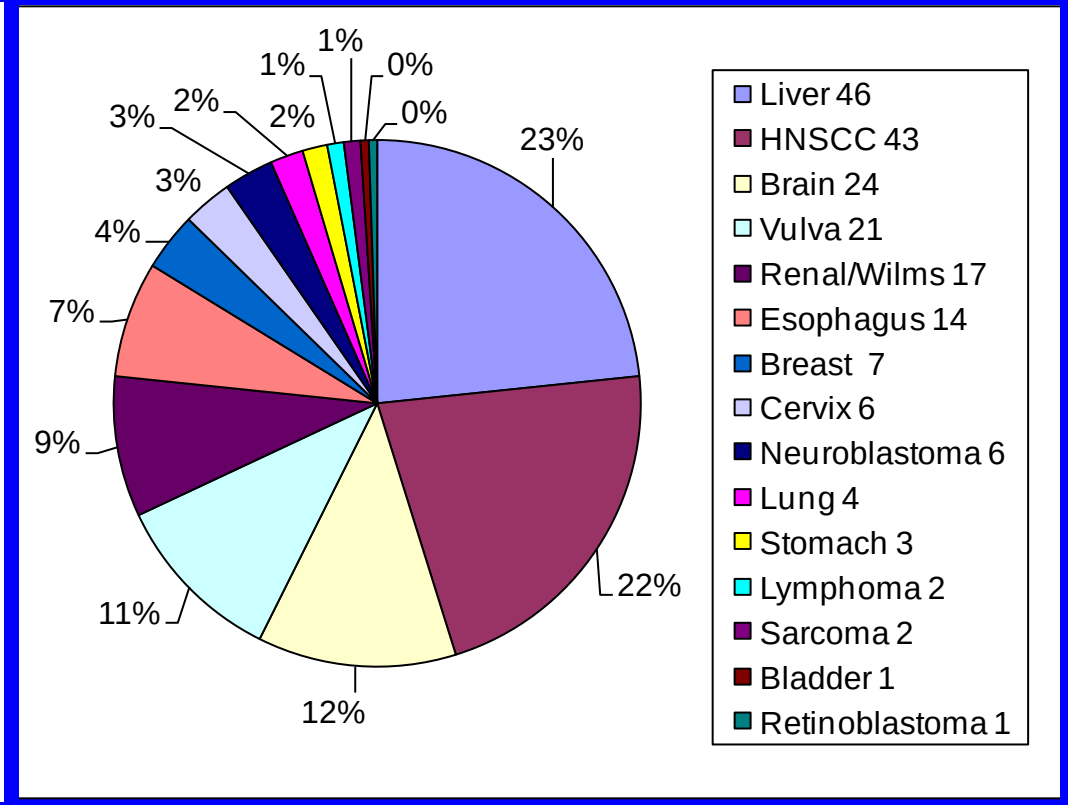
- Genetics
- Stem cell transplant - GVHD, XRT
- HPV
- Immunodeficiency
- Tobacco
- Alcohol
- Dental XRays
- Oral trauma (braces)

# Major Cancers in FA

- Leukemia (AML, ALL)
- Myelodysplastic syndrome (MDS)
- Liver: adenomas, carcinomas
- Head and neck squamous cell carcinomas (HNSCC)
- Brain Tumors: medulloblastoma
- Gynecologic: vulva, anus, vagina, cervix
- Kidney: Wilms, renal
- Esophagus: SCC
- Breast

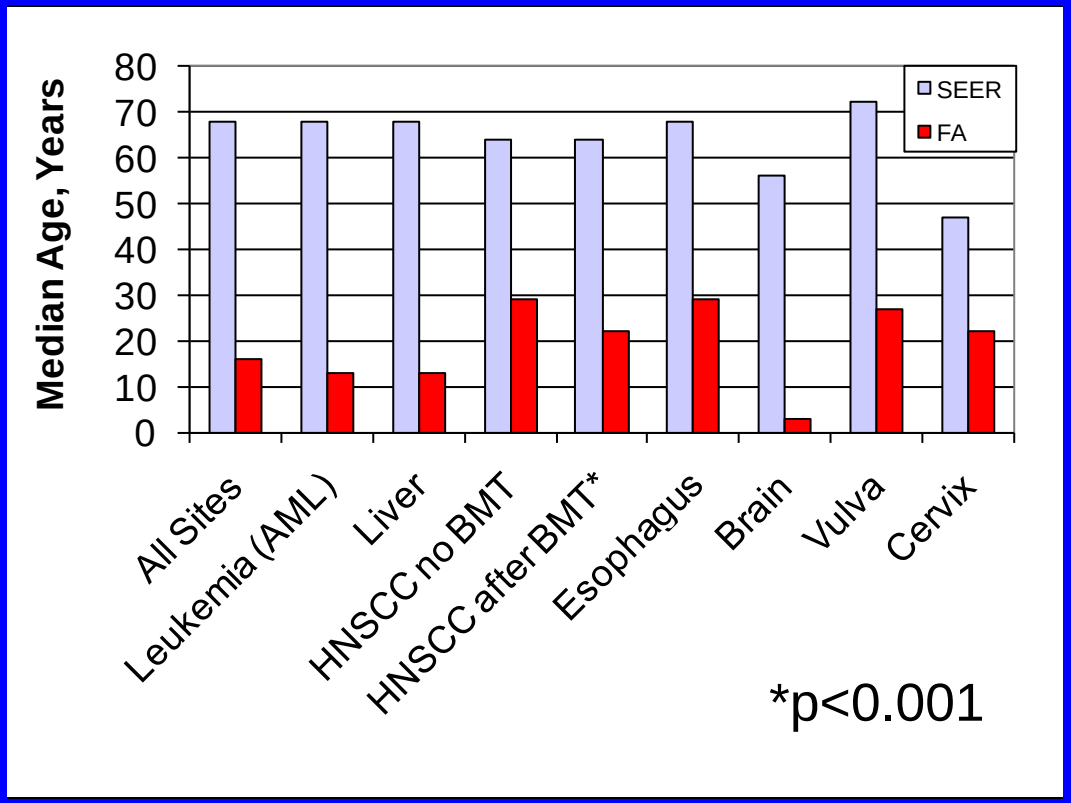
# FA Literature: Cancer Types 1927-2009

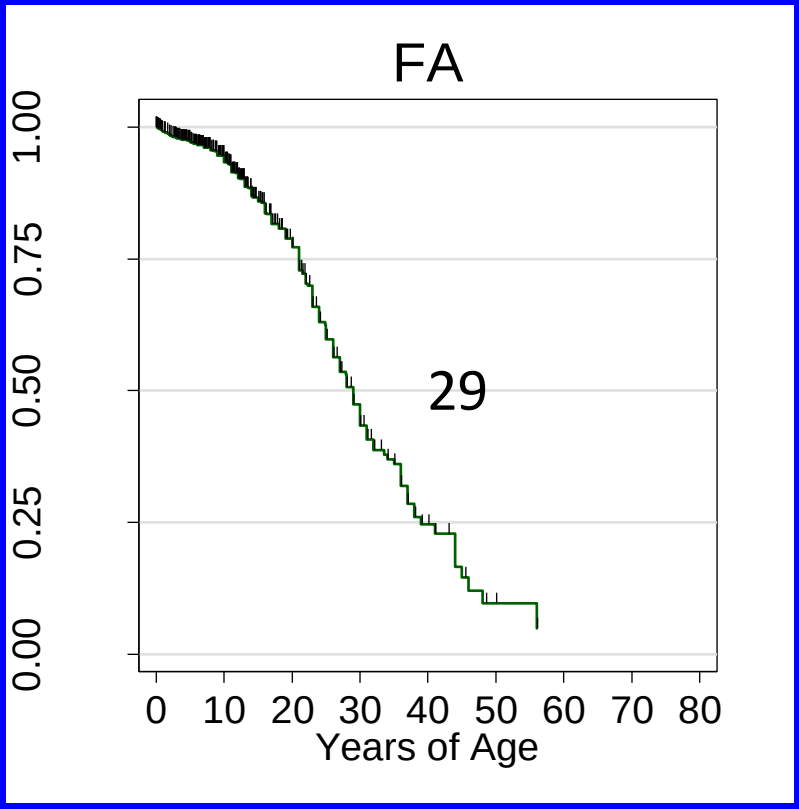



175 leukemias and 197 solid tumors in 320/2000 patients;
26 had 2-4 cancers.

# FA Literature: Cancer Sites, Median Ages

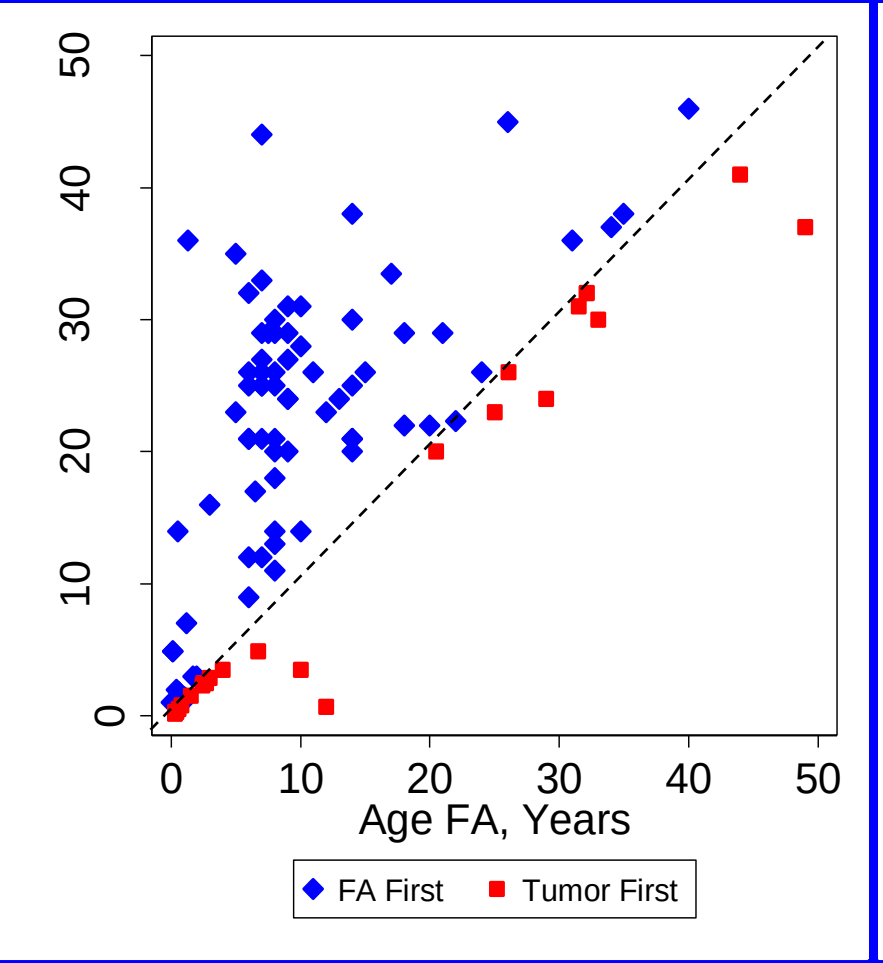


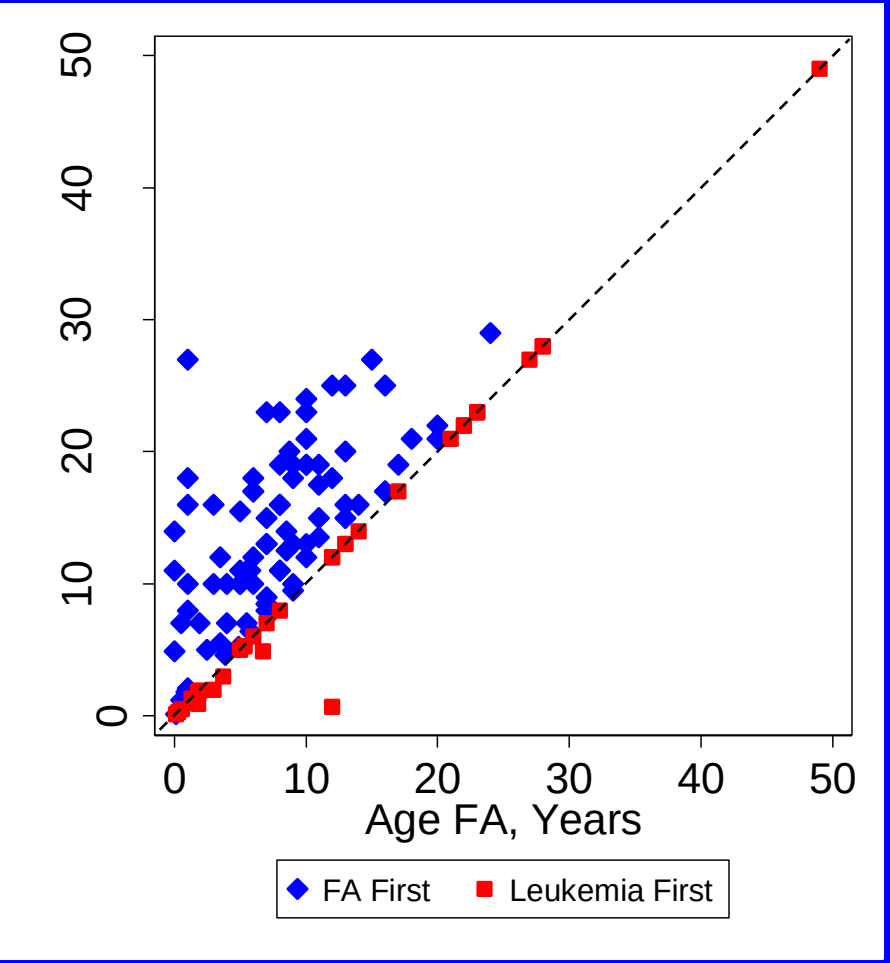




Cancers in FA are at very young ages

Median survival free of cancer = 29 years

# Cancer Diagnosis before FA




Solid tumor or leukemia preceded the diagnosis of FA in 35%.

# Diagnosis of FA *before* Cancer

- Aplastic anemia
- Physical findings
- Family history

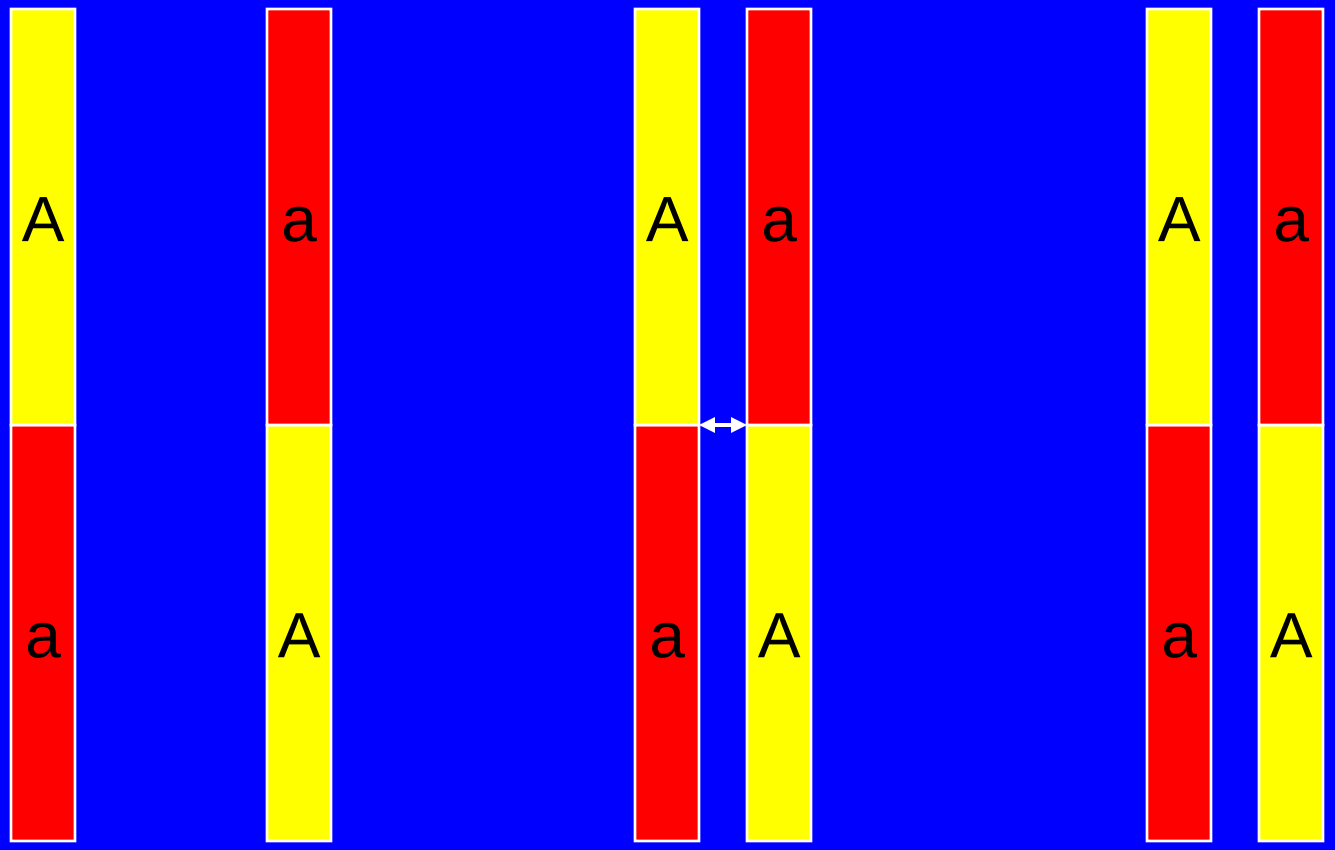
# Diagnosis of FA *after* Cancer

- Clinical suspicion based on phenotype
- Family history
- FA-type cancers, atypically young, no risk factors
- Unrecognized marrow failure
- Absence of marrow involvement (e.g. somatic mosaicism)

# Proof of Mosaicism in FA

- Peripheral blood lymphocyte chromosome breakage test normal
- Skin fibroblast chromosome breakage test abnormal
- One mechanism is recombination during mitosis

# Mosaicism from Recombination



# Observed/Expected Ratio (O/E)

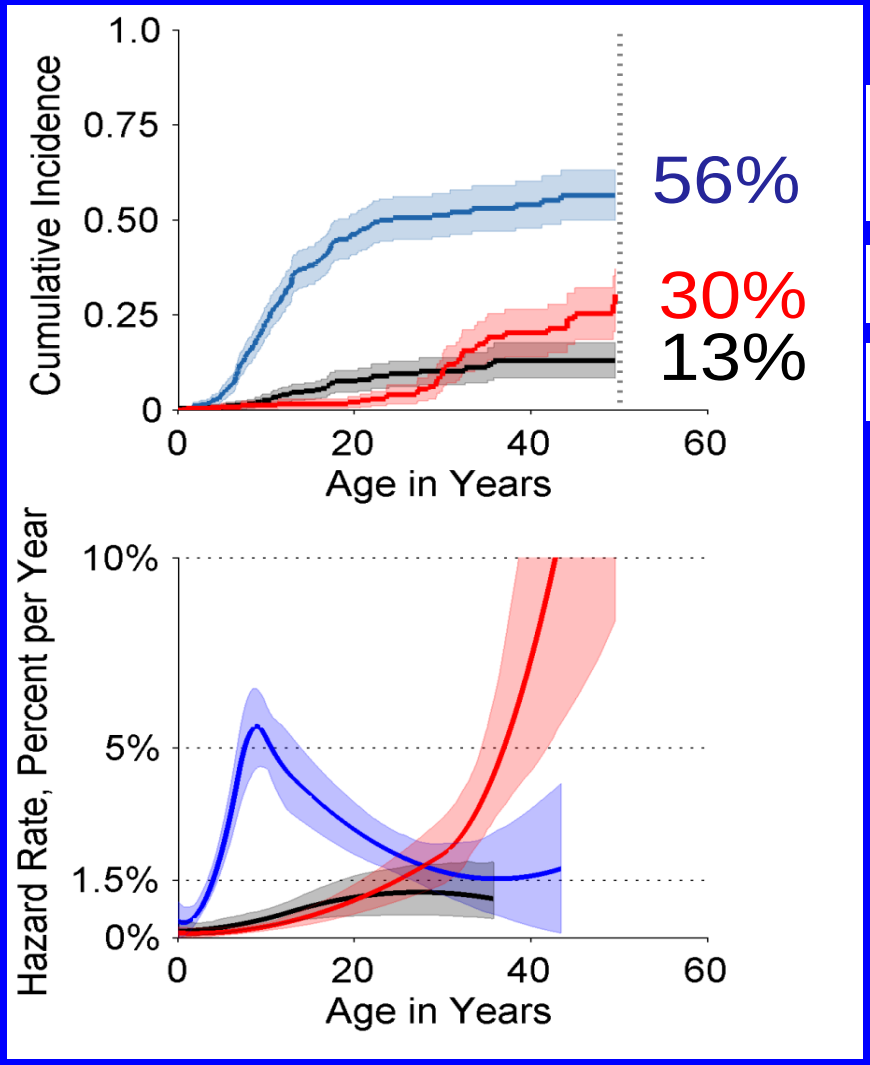
- O = number of cases observed
- E = number of cases expected in the general population, adjusted for age, sex, and birth cohort
- An estimate of the relative risk of cancer in untransplanted patients with FA

# Relative Risk of Cancer*

| Parameter | Result |
|---|---|
| Number of patients | 459 |
| Person Years | 6839 |
| | |
| All types of cancer | 50x |
| All solid tumors | 40x |
| Oral cavity and pharynx | 700x |
| Vulva | 3000x |
| AML | 500x |
| MDS | 7000x |

*Data from the North American, German, Israeli, and NCI FA Cohorts

# Four FA Cohorts



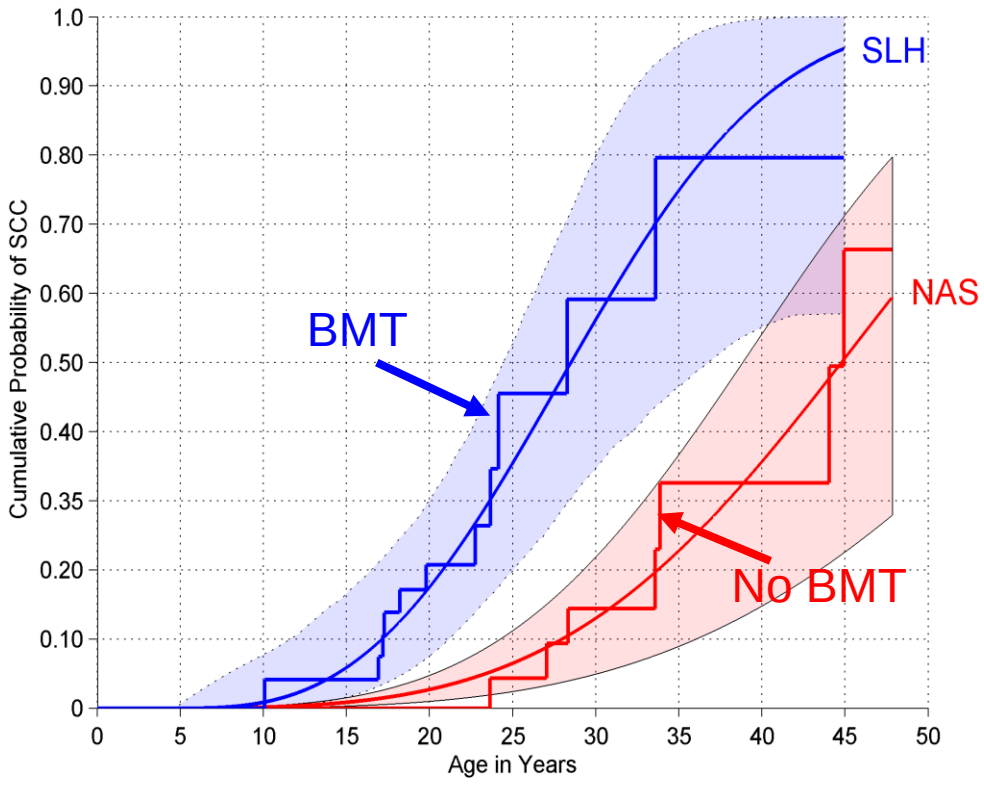

Severe bone marrow failure (death or BMT)

Solid tumors

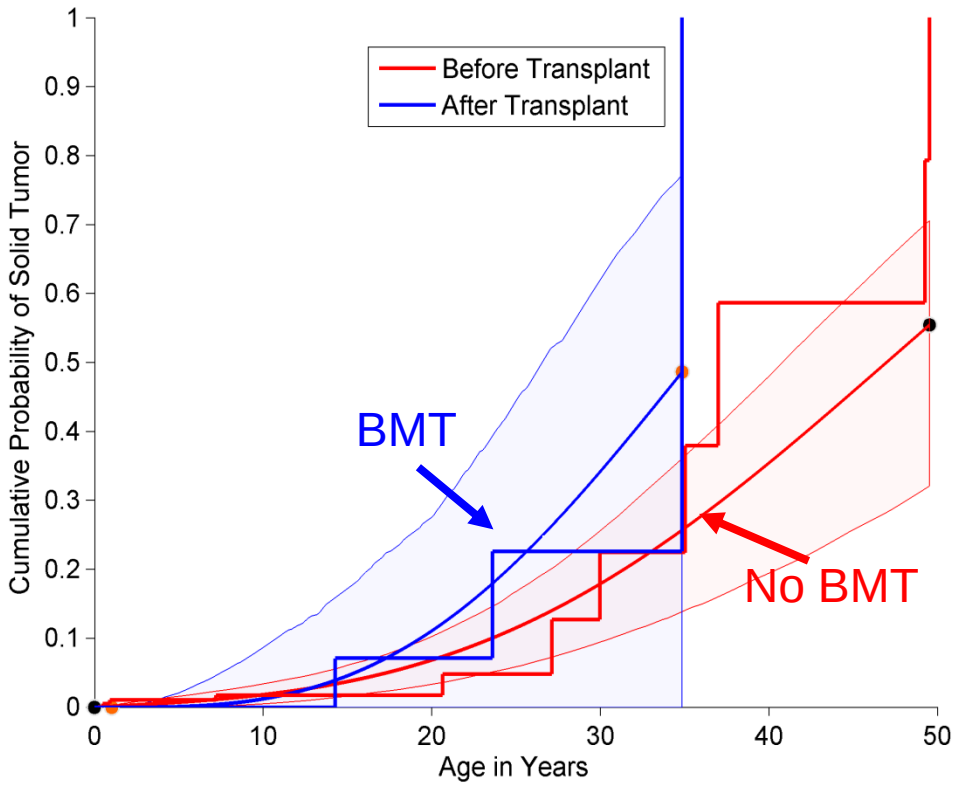
AML

# Transplant and Head and Neck Cancer

**NAS and Paris**



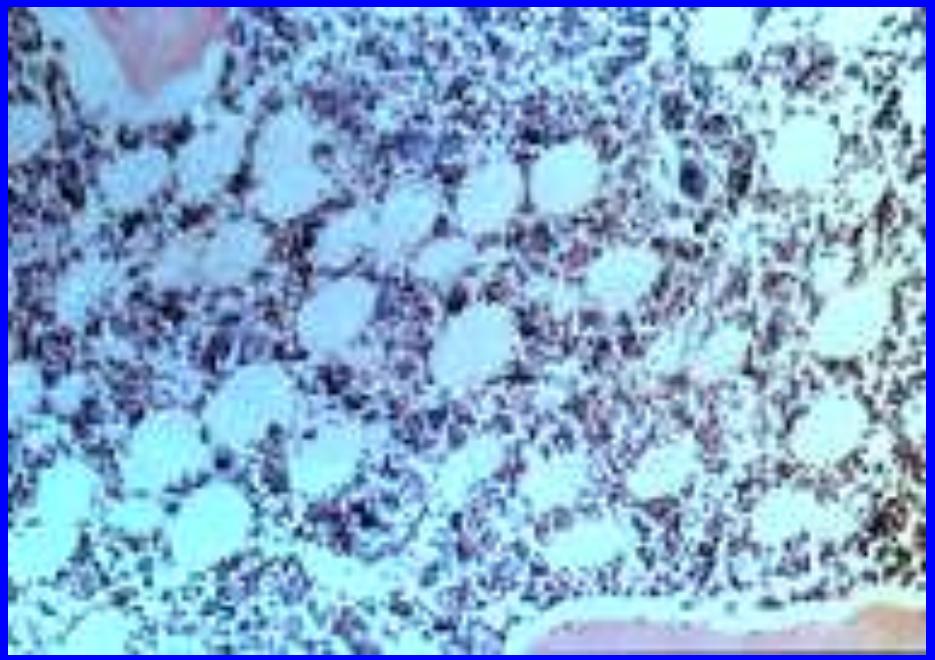

**GEFA**



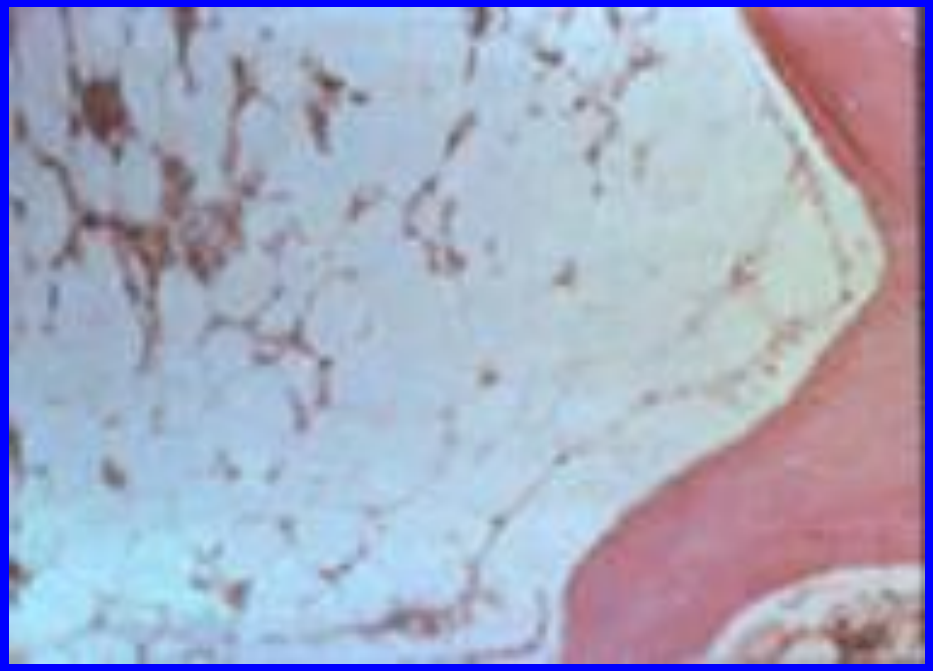

BMT increased risk of HNSCC 4-fold, and 16 years earlier.

# Bone Marrow Biopsy

Normal

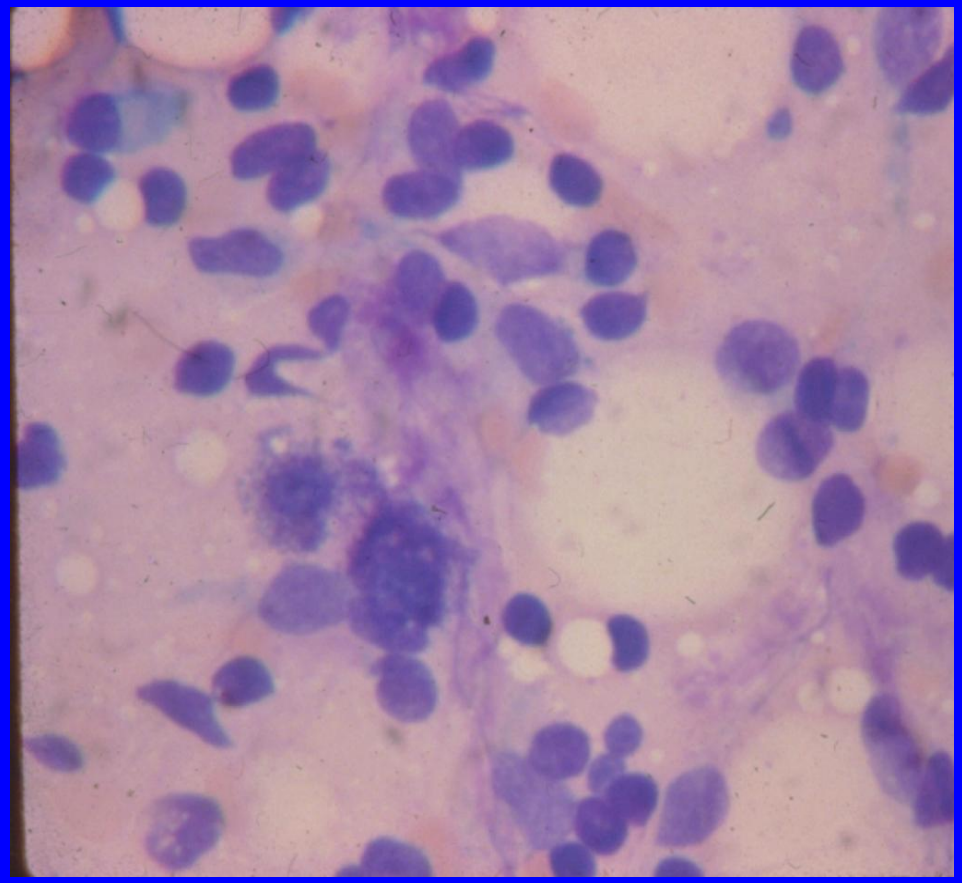


Aplastic

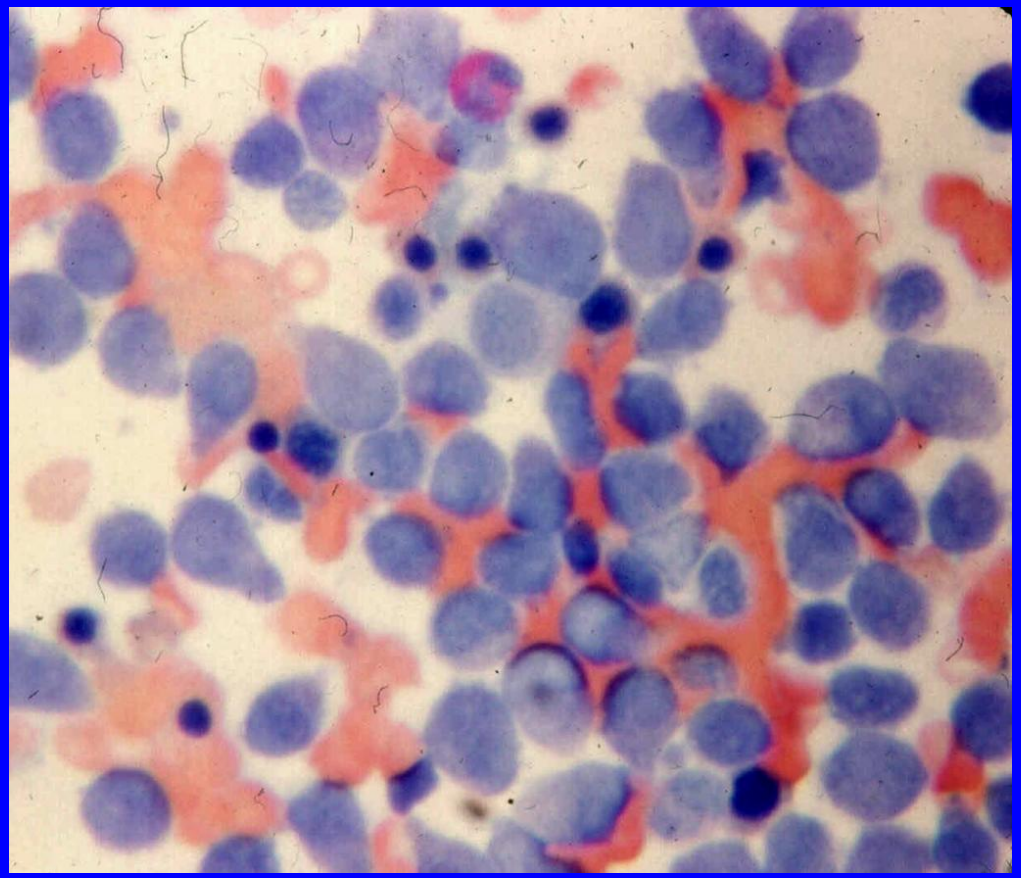


# Abnormal Bone Marrow

Aplastic

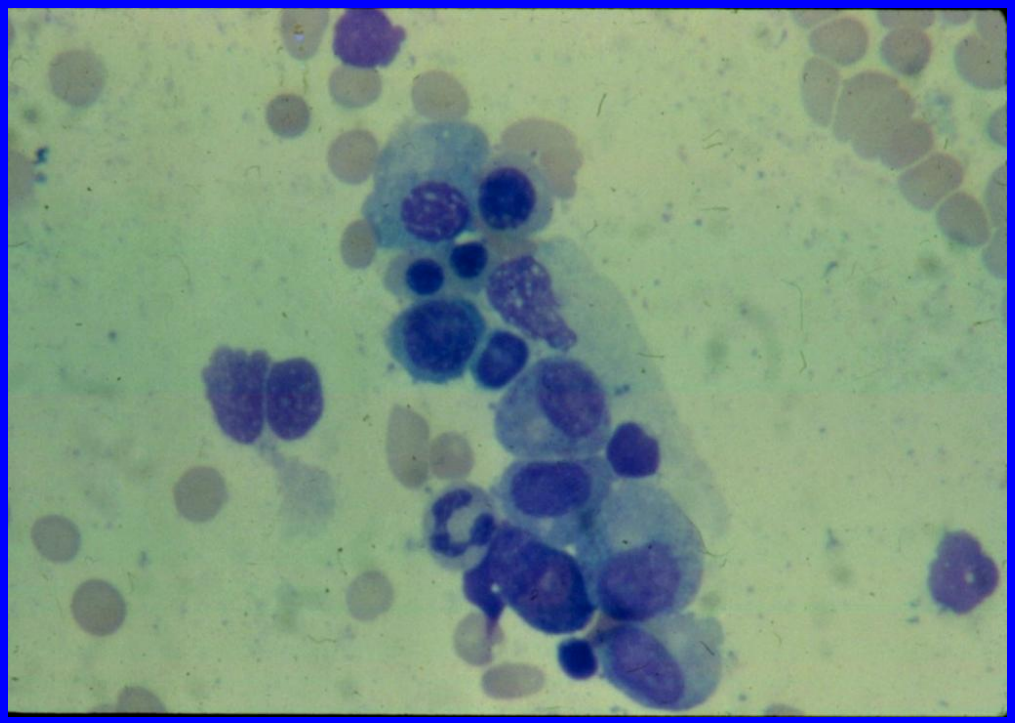


Leukemia

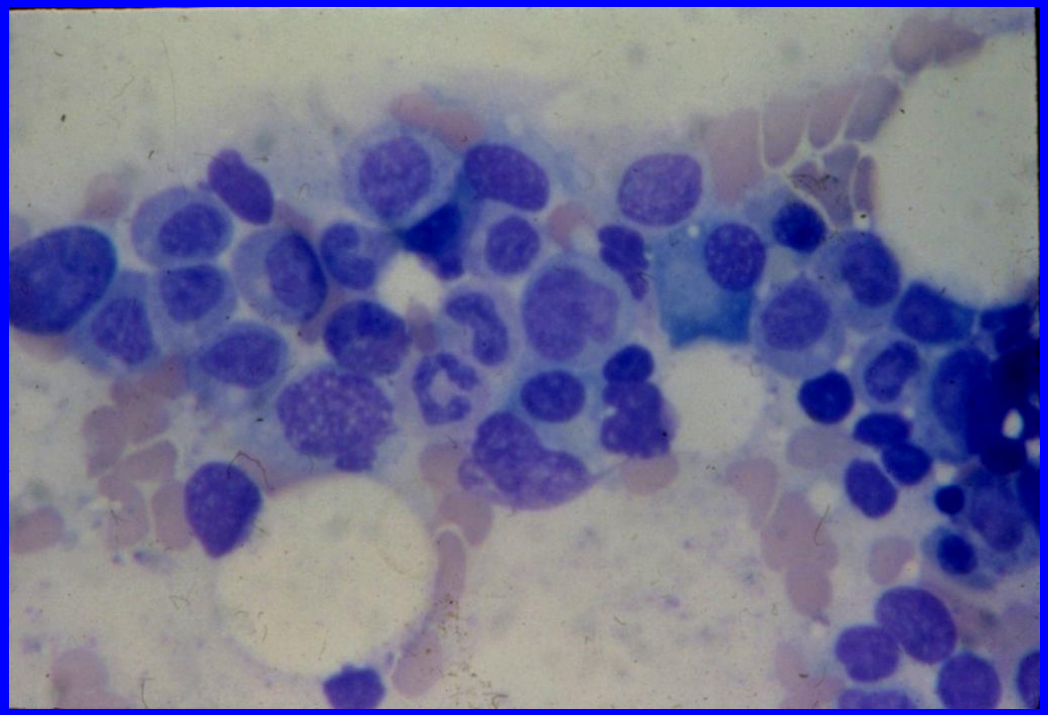


# Normal Bone Marrow

Erythroid (red cells)

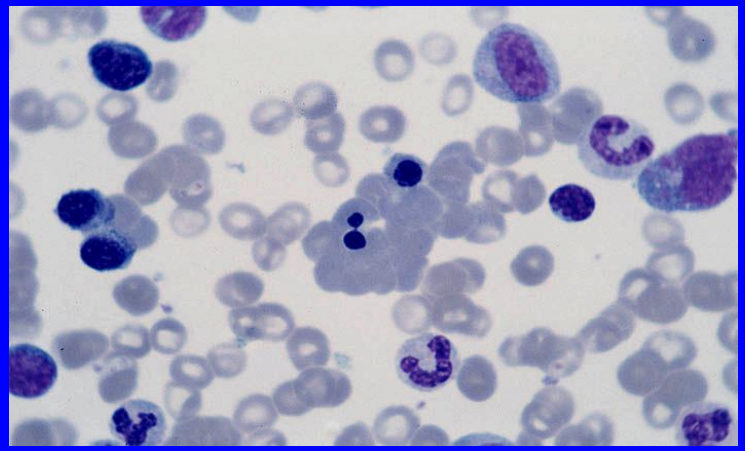


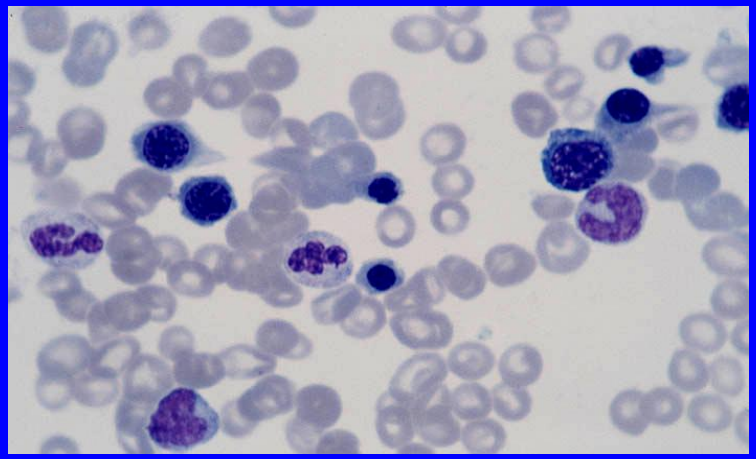
Myeloid (white cells)



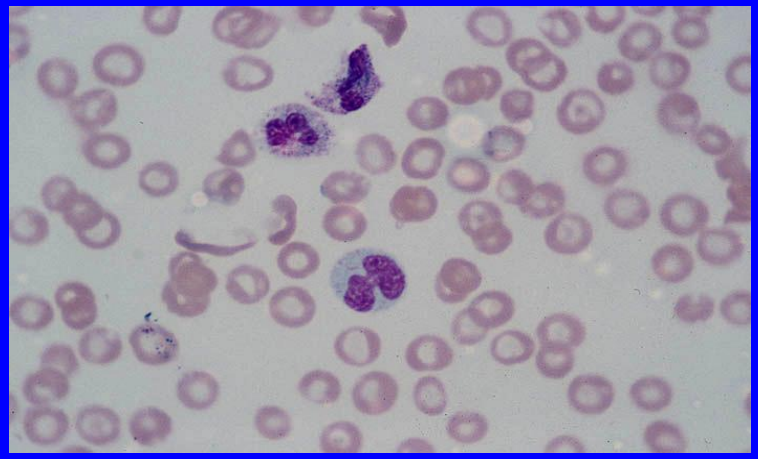
# Bone Marrow in MDS

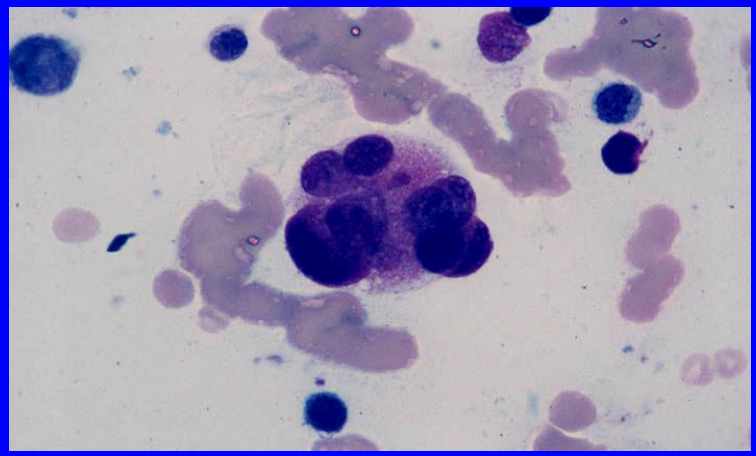
Red cells





White cells





Mega-karyo-cyte

# Myelodysplastic Syndrome (MDS)

- Blood: cytopenias
- Marrow:
  - Hypercellular
  - Hypocellular in FA
  - Dyspoieses (dysplastic, abnormal looking cells)

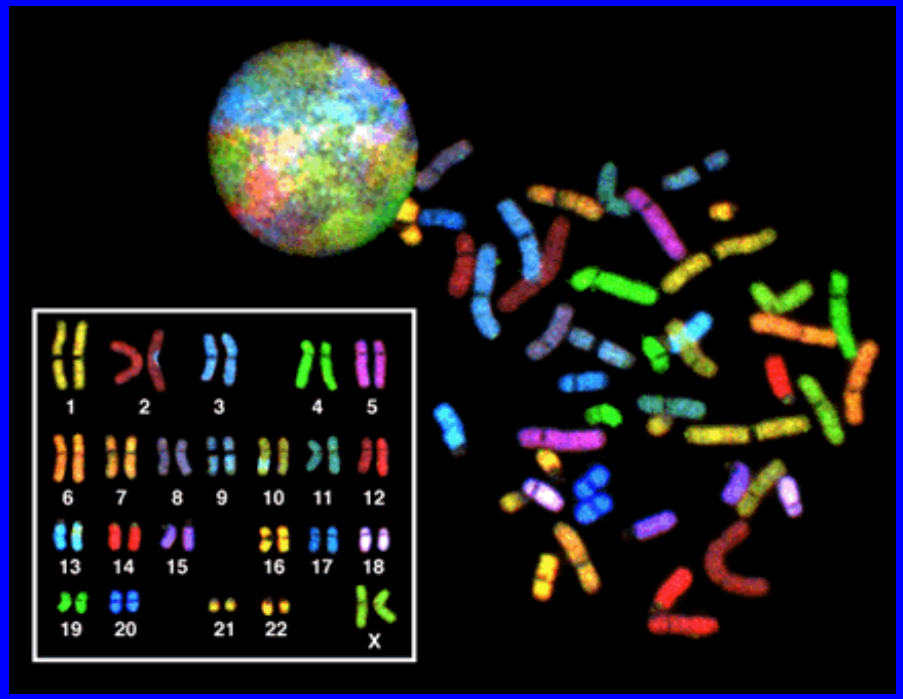
# Cytogenetic Clones

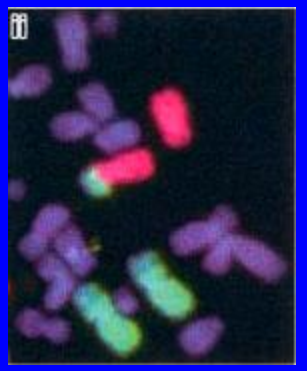
- “Clone”: offspring that are identical to their parent
- In blood disorders, several cells that are abnormal
- Loss of a chromosome in at least 3 cells
- Gain of a chromosome in at least 2 cells
- Other abnormalities in at least 2 cells

# Metaphase

G-banding

SKY: Spectral karyotyping



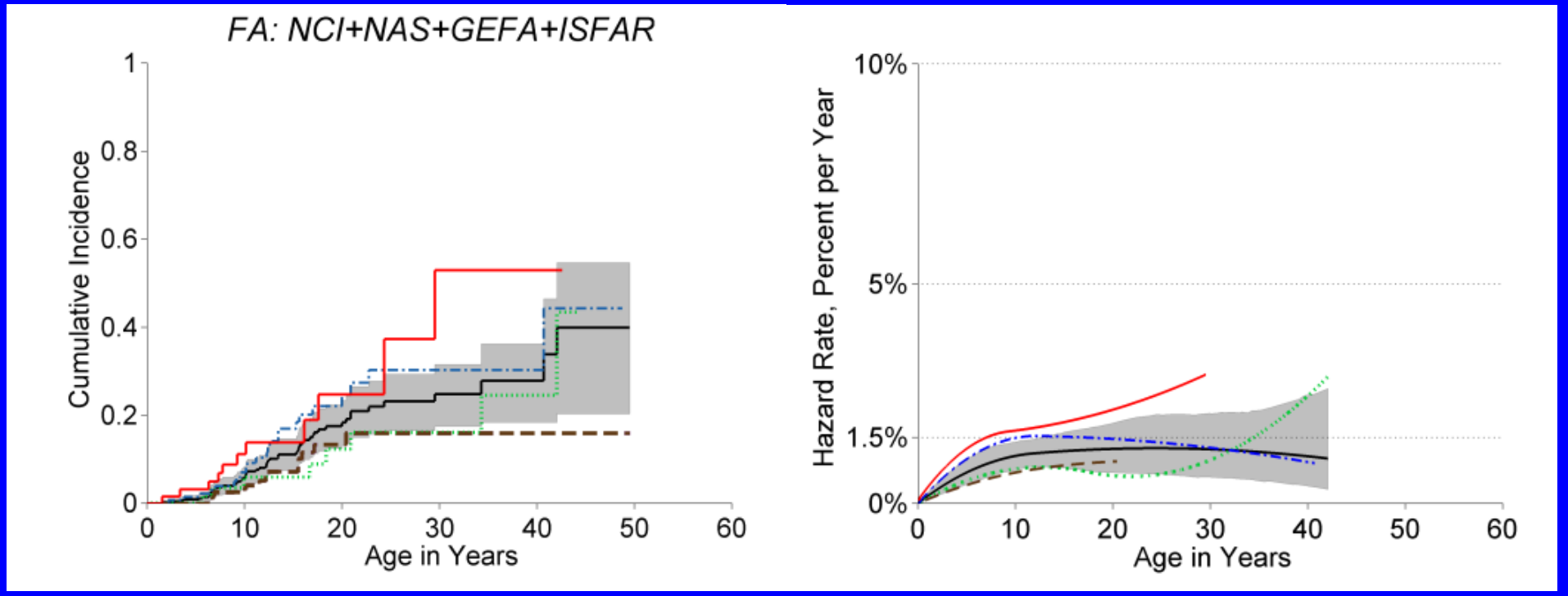
From Tonnies et al, Blood 2003

# MDS in FA

- Clone alone may ***not*** have a bad prognosis.
- Morphologic dysplasia ***plus*** significant cytopenias require treatment.

*Clone alone* does not define MDS in FA.

# MDS


FA: NCI+NAS+GEFA+ISFAR
Cumulative Incidence
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Age in Years
Hazard Rate, Percent per Year
10%
5%
1.5%
0%
0
10
20
30
40
50
60
Age in Years

# Cancer Risk in FA Carriers: IFAR

| | No. | All Ca | Breast | Prostate | p |
|---|---|---|---|---|---|
| Families | 312 | | | | |
| GPs | 784 | 0.9 | | | 0.04 |
| Carriers | 298 | 1.0 | | | 0.45 |
| Non-Carriers | 297 | 0.8 | | | 0.02 |
| GMs | 414 | | 1.3 | | 0.05 |
| **Carriers** | **154** | | **1.7*** | | **0.03** |
| Non-Carriers | 161 | | 1.1 | | 0.38 |
| GFs | 370 | | | 1.3 | 0.08 |
| Carriers | 144 | | | 1.3 | 0.24 |
| Non-Carriers | 136 | | | 0.9 | 0.43 |

***2.4 in *FANCC* carriers**

Berwick et al, Cancer Res 2007

# FA Adult Care Recommendations

- Complete Blood Count every 4-6 mo
- Blood for lipids, liver enzymes, etc. yearly
- Bone Marrow aspirate/biopsy/chromosomes
- Dental
- Head and neck with laryngoscopy
  - ***Self exam or mouth and neck, frequently***
- Gyn exam with Pap and HPV
- Liver enzymes and ultrasound
- Consider esophageal endoscopy

# FA Surveillance: Hematologic Disease

- CBC every 4 months or more often
- BM annually
  - aspirate for morphology
  - biopsy for cellularity
  - Cytogenetics (G-banding, CGH, FISH as needed)
  - special stains
  - flow cytometry

# FA Surveillance:Cancer

- Oral cavity and pharynx exam, nasolaryngoscopy
  - Age >10 years, or BMT >1 year
- Gynecologic exam, Pap and HPV
  - Age >16 years, or Menarche
- Liver, enzymes, ultrasound
  - Androgens or no androgens
- Skin

# Summary/Conclusions

- Patients known to have FA have a high risk of neoplasia
- Patients with atypical presentations of neoplasms may have undiagnosed FA
- The specific risk may depend on the specific gene and mutation
- Be cautious with term “pre-transplant” – some may be “non-transplant”.

# www.marrowfailure.cancer.gov

cancer.gov

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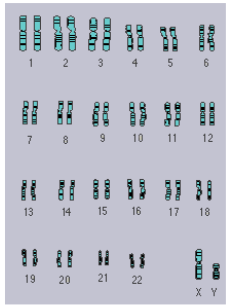
## Inherited Bone Marrow Failure Syndromes

Home
Contact Us

- What is the NCI IBMFS Cohort and Who is Eligible
- What are the IBMFS Disorders
- How can I Participate and What can I Expect
- What are "Gene Mutations"
- Useful Links
- 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.

Home | Cohort | Disorders | Participate | Gene Mutations | Links | Research Team | Glossary | Press Materials | Contact Us

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