

# Other Inherited Leukemias

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# Many Names for this Group of Disorders

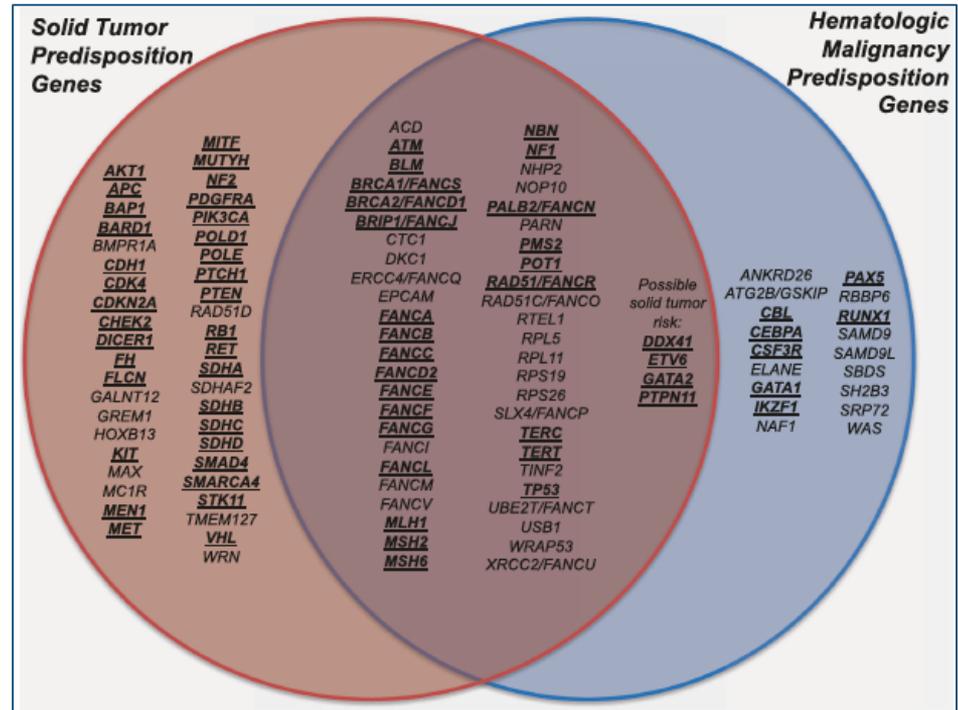
- Inherited leukemia
- Familial leukemia
- Leukemia susceptibility
- Hereditary hematopoietic malignancies
- Hematological malignancy predisposition
  
- GATA2 Deficiency and Familial Platelet Disorder (*RUNX1*) being key examples of this group

# Connection to Inherited Bone Marrow Failure Syndromes (IBMFS)

- IBMFS are rare disorders with inherited germline cause of bone marrow failure in childhood/young adulthood with predisposition for cancer, particularly AML often associated with congenital abnormalities
- Previously hematological malignancy predisposition was thought to be isolated to the IBMFS
- Last ~15 years have made it clear that this is not so
- Significant overlap with primary immunodeficiencies
- Significant overlap with solid tumor predispositions
- Can be isolated hematological malignancy predisposition

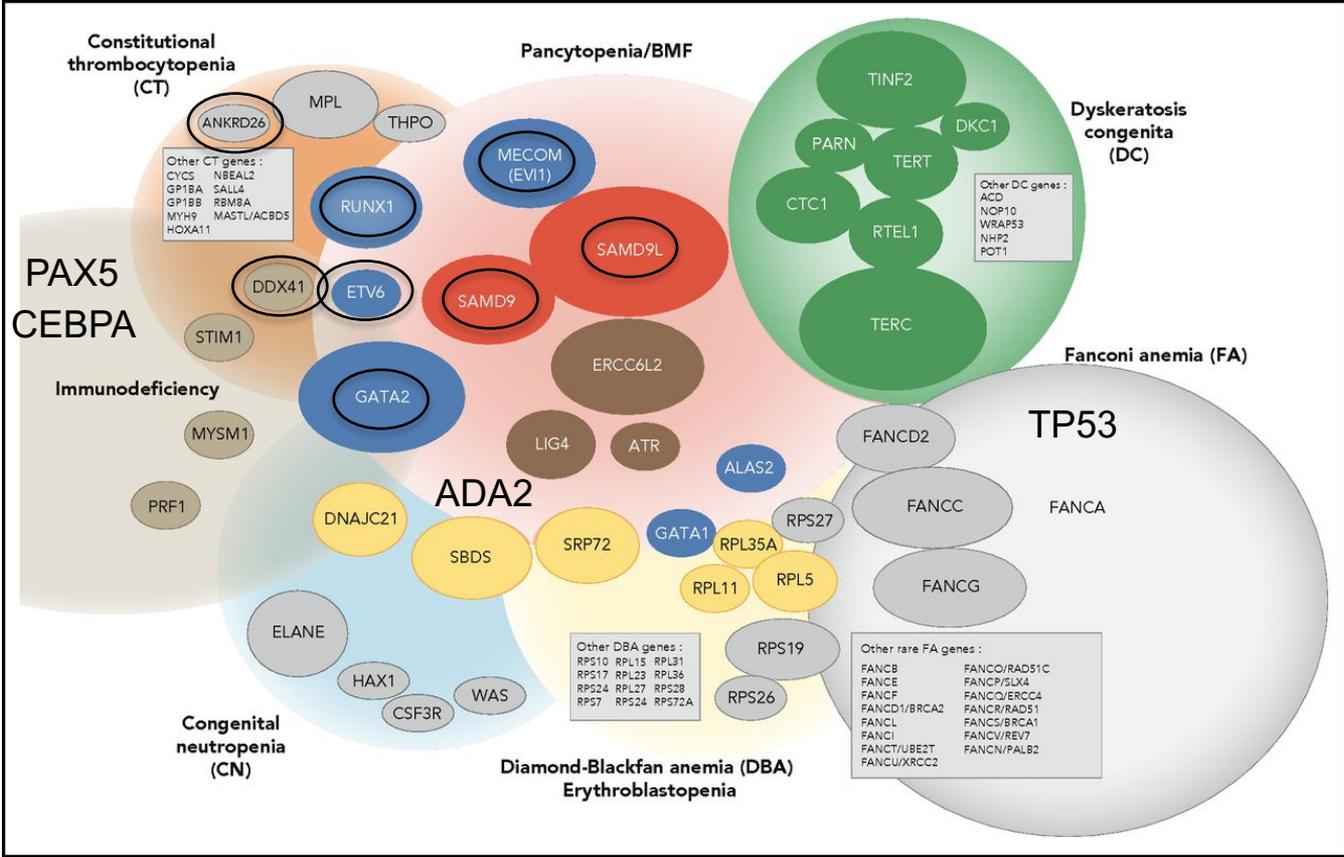
# Large Heterogeneous Group Can be divided by several characteristics

- Underlying biology
- MDS prodrome or not
- Those with or without congenital abnormalities
- Lineage of leukemia
- Those also associated with solid tumor risk



Tawana et al. Leukemia 2018

# IBMFS and Hematological Malignancy Predispositions



Hematopoietic  
Transcription  
Factor Biology

Cell Signaling

Ribosome Biology

Telomere  
Biology

DNA Repair

Bluteau et al. Blood 2018  
with modifications

# The *Other* Inherited Leukemias

IBMFS (MDS->AML)

FA, DC, SDS, DBA, TAR, CAMT

Present with MDS and Can Evolve to AML

*RUNX1, GATA2*

*TP53, SCNs*

*SAMD9/L, DDX41, ANKRD26, MECOM*

Present with AML

*CEBPA*

*TP53*

ALL associated

*PAX5, ETV6*

*NBN, ATM, BLM, Turcot*

JMML

*NF1*

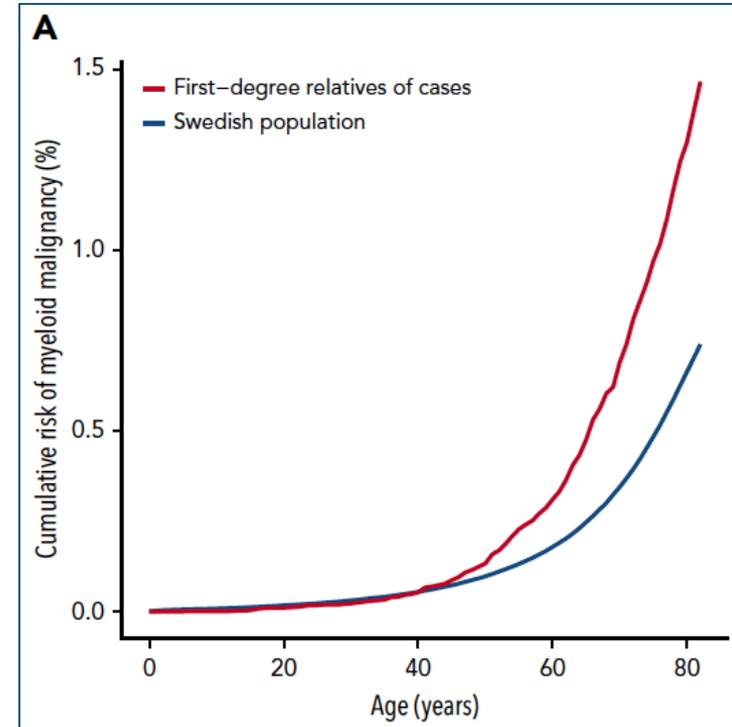
*Noonan*

# Who Should be Evaluated for a Hematological Malignancy Predisposition

- Pediatric or <40yo patient with MDS or aplastic anemia
- Patients <40yo with cytopenias and FMH of cancer or lung disease
- Patients with cytopenias and notable infectious history or dysmorphology
- Patients with new cytopenia or leukemia with a history of *ITP*
- Patients with leukemia and biallelic *CEBPA* or *RUNX1* mutations
- Patients with hypodiploid ALL
- Patients with unusual radiation or chemotherapy sensitivity
- **More common than suspected- Look for it**

# Why is it important to recognize inherited predisposition?

- Genetic counseling and family planning
- HCT donor and regimen choice
- Treatment optimization
- Cancer surveillance and syndrome specific disease monitoring
- More research is needed to fully understand this group of disorders



# Studying MDS and AML in the IBMFS

- The “classic” IBMFS have been extensively studied, and the risk of cancer in these patients is now well documented.
- Much of this work comes from the long standing NCI IBMFS study

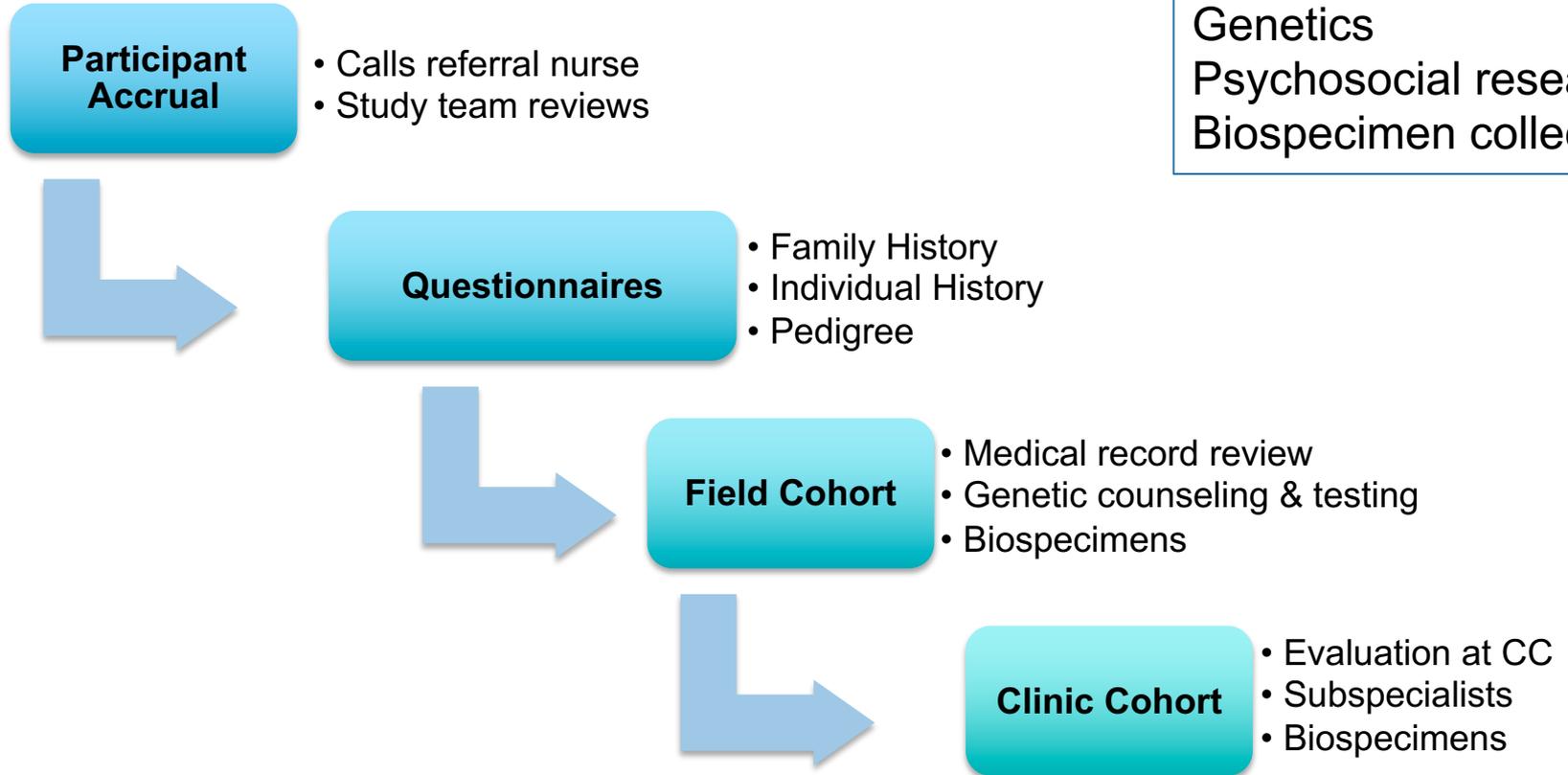
## The NCI IBMFS Study

Opened in January 2002 by Dr. Blanche Alter

- **Family Study**
- > 500 families > 2000 individuals
- <http://marrowfailure.cancer.gov>

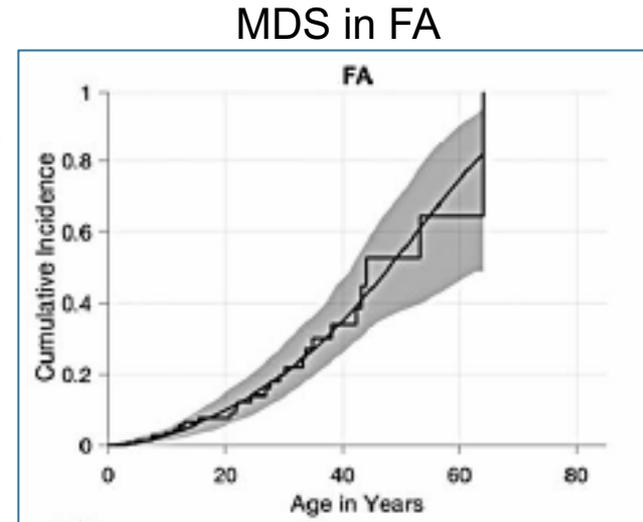
# Family Predisposition Study Process

Phenotyping  
Epidemiology  
Genetics  
Psychosocial research  
Biospecimen collection



# Findings from the NCI IBMFS study

- Cancer types, rate, and survival in IBMFS patients
- MDS: in FA  $\uparrow$ 5000X, in DC  $\uparrow$ 500X
- AML: in FA  $\uparrow$ 20X, in DC  $\uparrow$ 70X
- Seven novel genes identified
- Identification of new phenotypes
- Descriptive epidemiologic studies of gynecologic, pulmonary, vascular, dermatologic, endocrine, ENT, neurologic, and dental complications of IBMFS



Alter et al. Haematologica 2018.

# Planned Protocol to Study Hematological Malignancy Predispositions

- Joint DCEG-CCR Protocol with the NIH Myeloid Malignancy Scientific Interest group
- Natural history protocol for patients on NIH treatment protocols and those treated elsewhere
- Not enrolling *RUNX1*, *GATA2*, LFS patients, refer to disease specific protocols
- Family history questionnaires, genetic counseling, exome sequencing
- Identify families with known genes and novel gene discovery
- Longitudinal follow-up

# Acknowledgements

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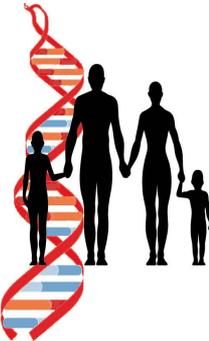
**Myeloid Malignancies Section, NHLBI**

Christopher Hourigan

## Patients & Families

Have a patient with a suspected hematological malignancy predisposition or IBMFS? Please refer them.

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