Genetic Predisposition Syndromes in Myeloid Malignancies

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Acknowledgments

Godley Lab
Shawn Albert
John Cao
Jane Churpek
Michael Drazer
Simone Feurstein
Meghana Gadriraju
Kornelia Gladysz
Anastasia Hains
Michaela Siver
Kiran Tawana
Sakshi Uppal
Caroline Weipert
Allison West
Arthur Wolin

Soma Das
Zejuan Li

Jeremy Segal
James Vardiman

Funding: Cancer Research Foundation, The Taub Foundation, The Leukemia and Lymphoma Society

Realizing the goal of precision medicine in oncology

DEFINE:

Baseline genetics

Baseline epigenetics

Acquired genetics in the tumor

Acquired epigenetics in the tumor

to devise an effective treatment strategy for a particular patient

A Hematologic Malignancy-focused Cancer Risk Clinic

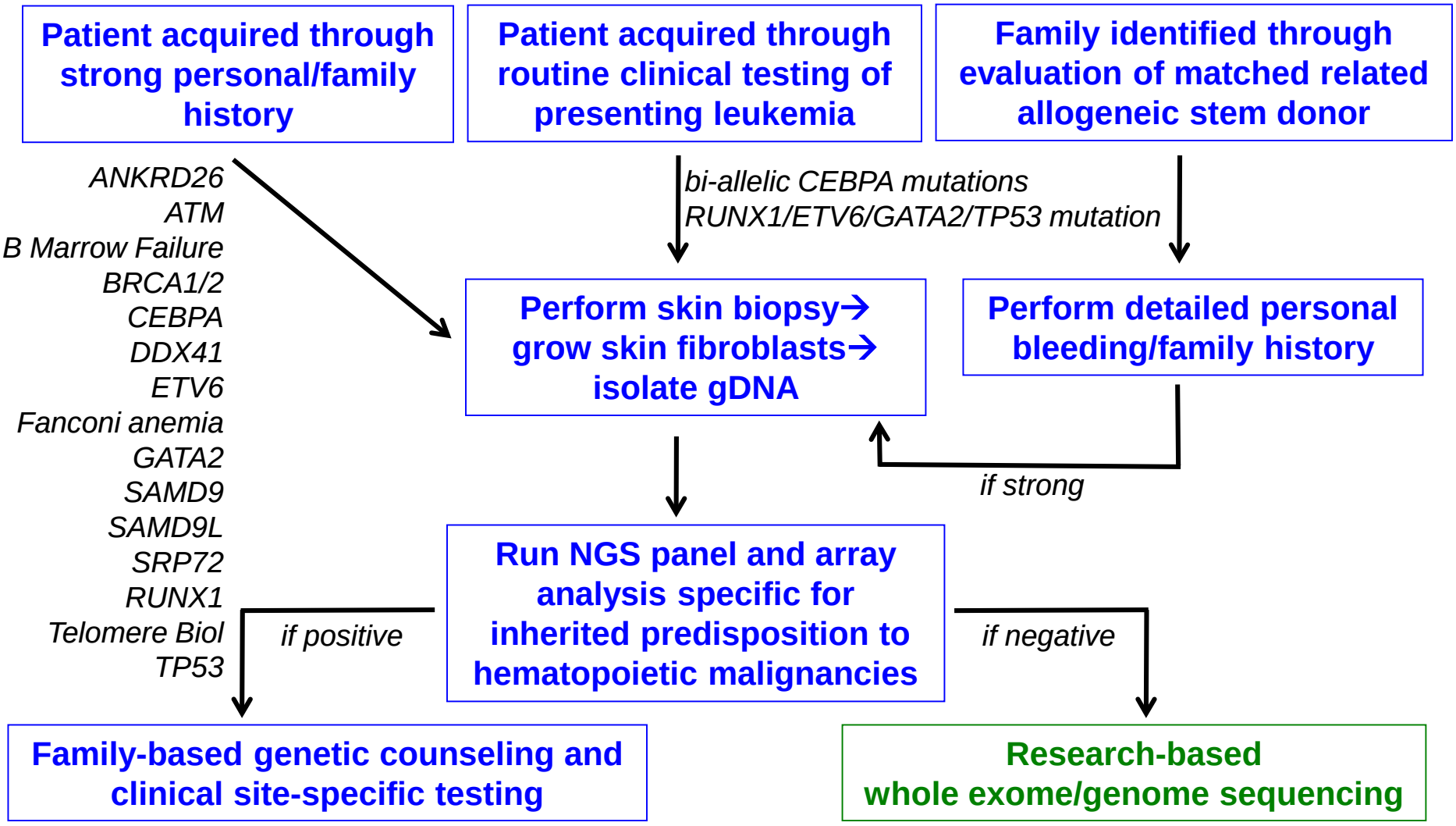
- Genetic counseling for family members
- Early identification allows proper anticipatory medical care for mutation carriers, but the few surveillance guidelines that exist are based on expert experience rather than prospective data
- Careful hematopoietic stem cell transplant donor evaluation, including interdisciplinary discussions regarding donor selection for patients under consideration for a matched related allogeneic stem cell transplant
- Incorporation of genetic predisposition within the new WHO classification scheme and clinical guidelines, including NCCN MDS and European LeukemiaNet

Key aspects of pedigree review

- A high index of clinical suspicion
- Familiarity with the known predisposition syndromes
- Key features within the personal and family history:
  - Multiple cancers within a single individual (e.g., t-MN)
  - Other hematopoietic malignancies within 2 generations
  - Other hematopoietic abnormalities within the family (e.g., macrocytosis, bleeding propensity, severe anemia or anemia in men)
  - NOTE: NOT according to age of onset
- Consider results of molecular analyses performed on leukemic cells

Class	Patient Population	Specific Syndromes
MDS/AL Predisposition Syndromes	MDS AML ALL	FPD/AML *ANKRD26* *CEBPA* *DDX41* *ETV6* *GATA2* *RTEL1* *RUNX1* *SAMD9/SAMD9L* 14q32.2 genomic duplication (*ATG2B/GSKIP*) ALL *only:* *IKZF1 (emerging)* *PAX5* *SH2B3*
Bone Marrow Failure Syndromes	AA MDS AML	Dyskeratosis congenita *SBDS/EFL1/DNAJC21* Fanconi anemia *NAF1* *SAMD9/SAMD9L*
Genetic Syndromes	ALL	Ataxia Telangiectasia (*ATM*) Bloom syndrome (*BLM*) Down syndrome (Trisomy 21) Leopard/Noonan syndrome (*PTPN11*) Neurofibromatosis I (*NF1*) Nijmegen Breakage syndrome (*NBS1*) Wiskott Aldrich syndrome (*WAS*)
Familial MPNs	PV, ET, PMF, CML	14q32.2 genomic duplication (*ATG2B/GSKIP*) *RBBP6*
Familial Lymphomas	CLL HL/NHL	*ASXL1* *CASP10* *CD27/CD40LG* *CTLA4* *DOCK8* *ITK* *MAGT1* *MKL1* *MLL* *PIK3CD*
Cancer Predisposition Syndromes	All	Li-Fraumeni syndrome (*TP53*) Hereditary breast & ovarian cancer (*BRCA1/2*) Lynch syndrome Cowden syndrome (*PTEN*)
Familial MM/LPL	MM, MGUS, LPL	Familial MM/LPL

An Algorithm for Patient Work-Up



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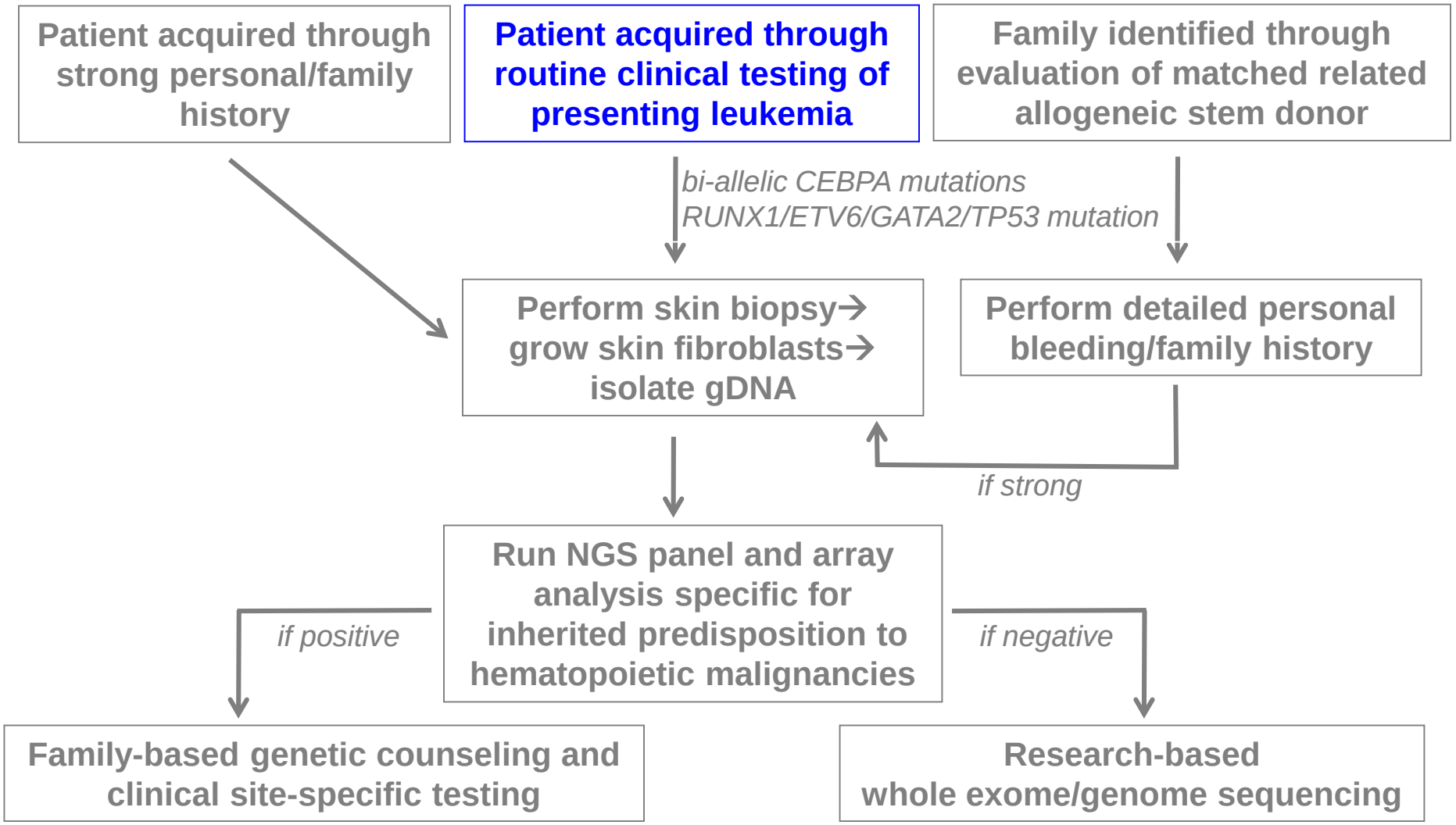
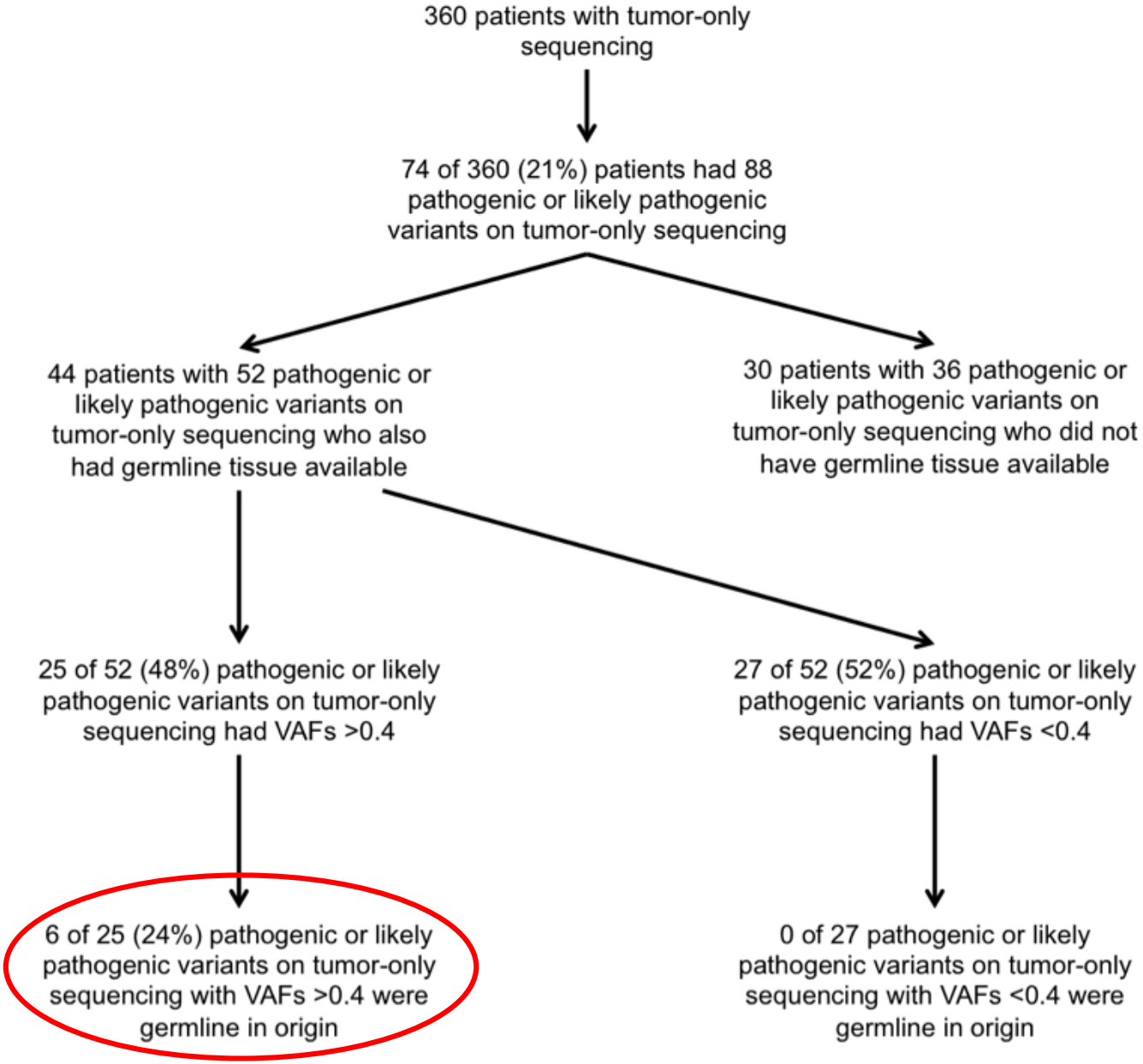


Detecting germline mutations through tumor mutational profiling



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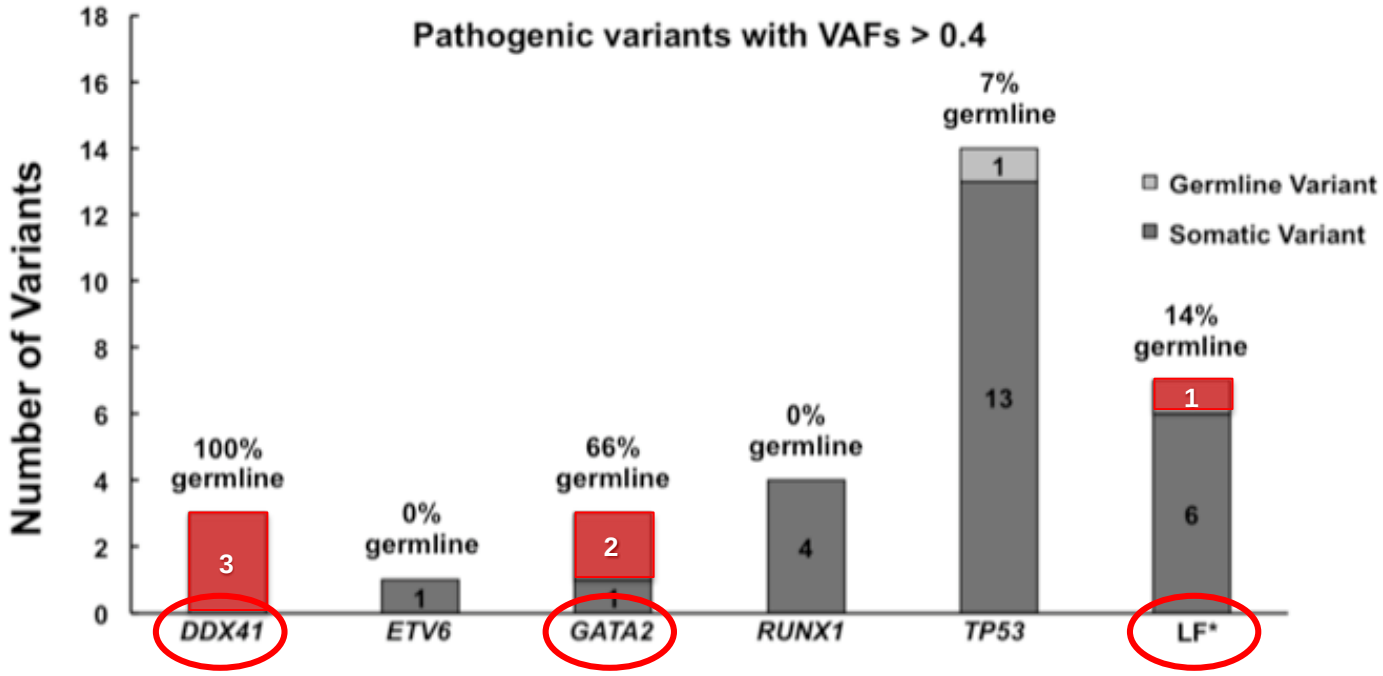
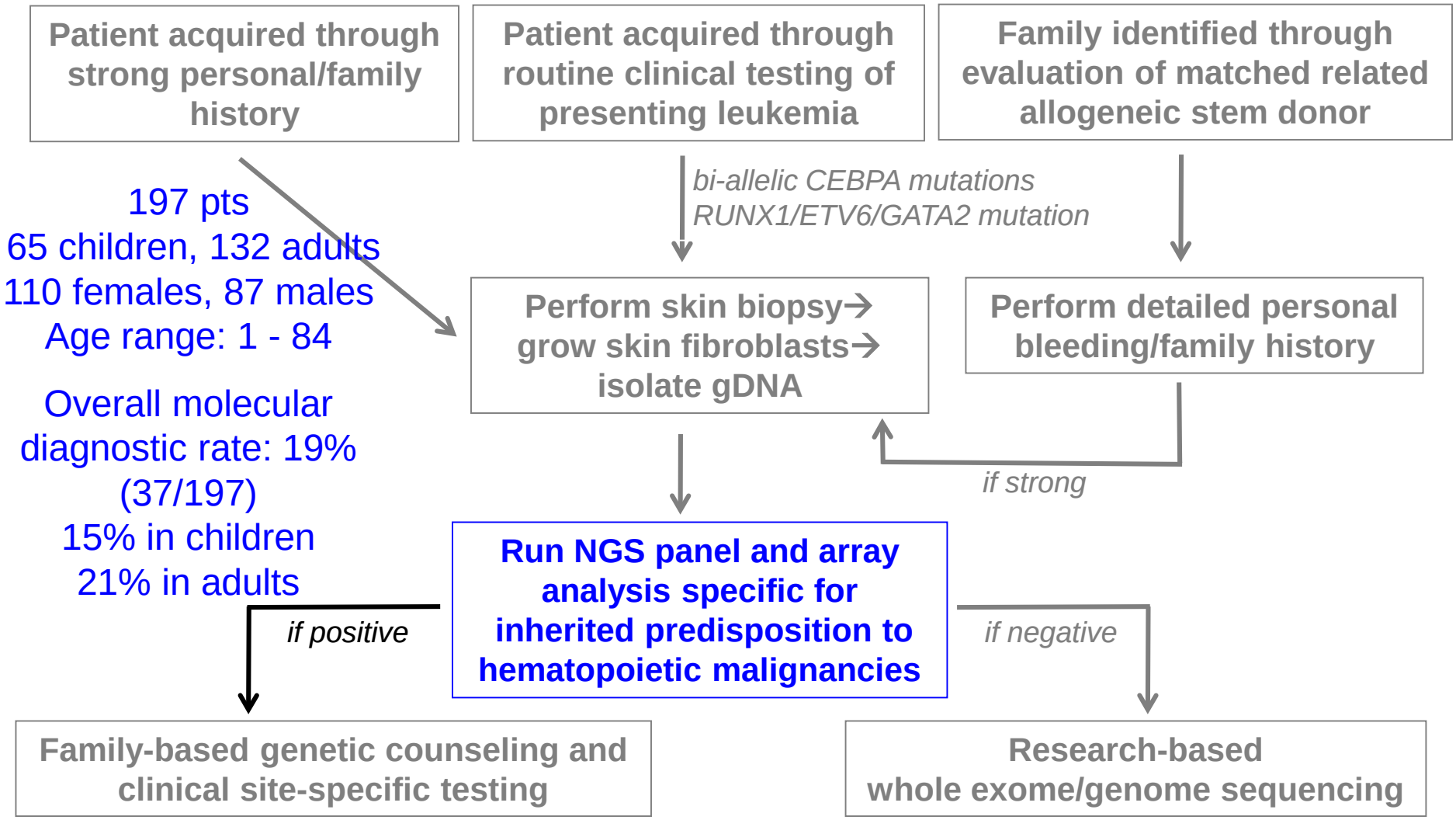


LF = *TP53* mutation associated with Li-Fraumeni Syndrome

An Algorithm for Patient Work-Up



Guidugli L. *et al. Leukemia* 31: 1226-1229 (2017)

What will familial MDS/AL predisposition genes teach us?

Transcription Factors

RUNX1
CEBPA
GATA2
ETV6
p53

Telomere Biology

TERT
TERC

DNA Repair

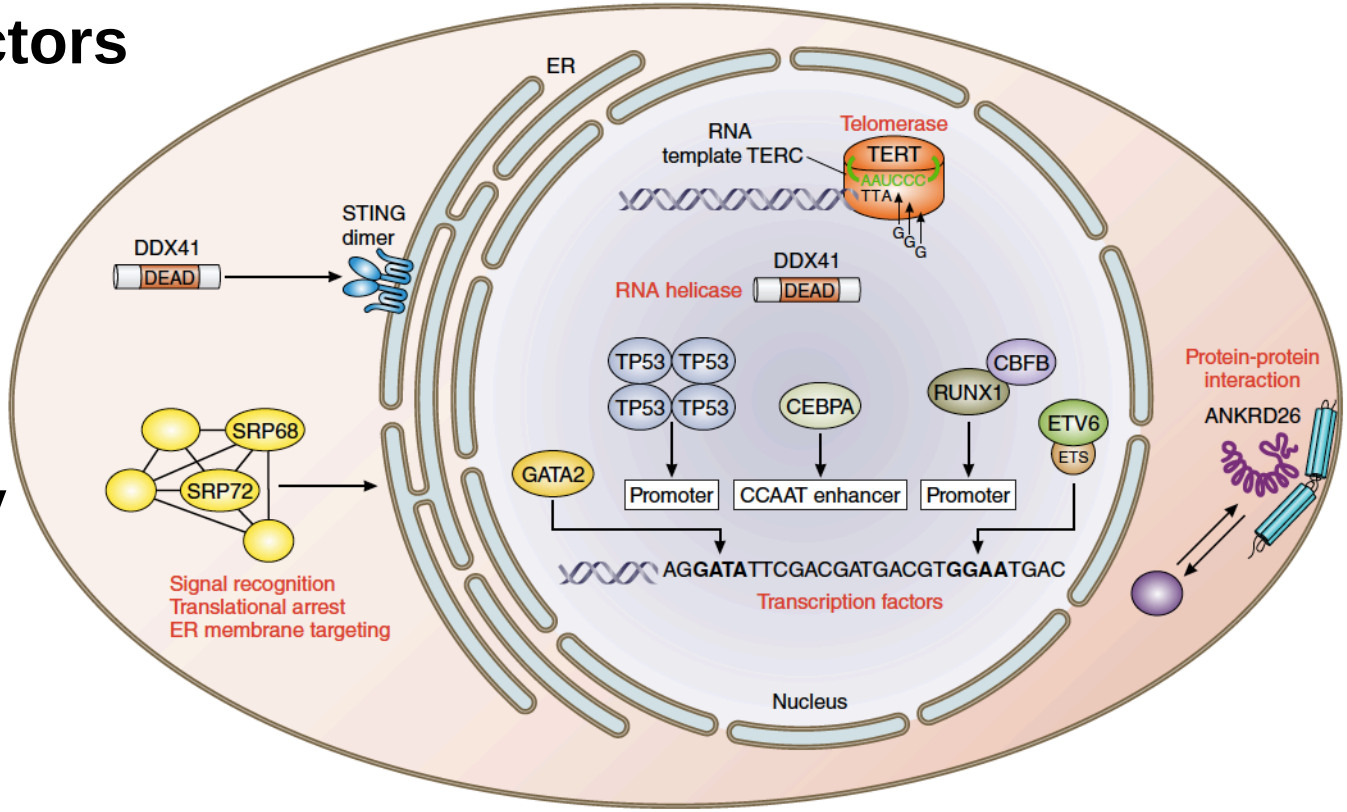
ATM
BRCA1
BRCA2

Ribosomopathy

SBDS
DNAJC21

New Paradigms

ANKRD26, DDX41, SAMD9, SAMD9L



All Other Classes Commonly Mutated as Acquired Events

Chromatin remodeling

Splicing

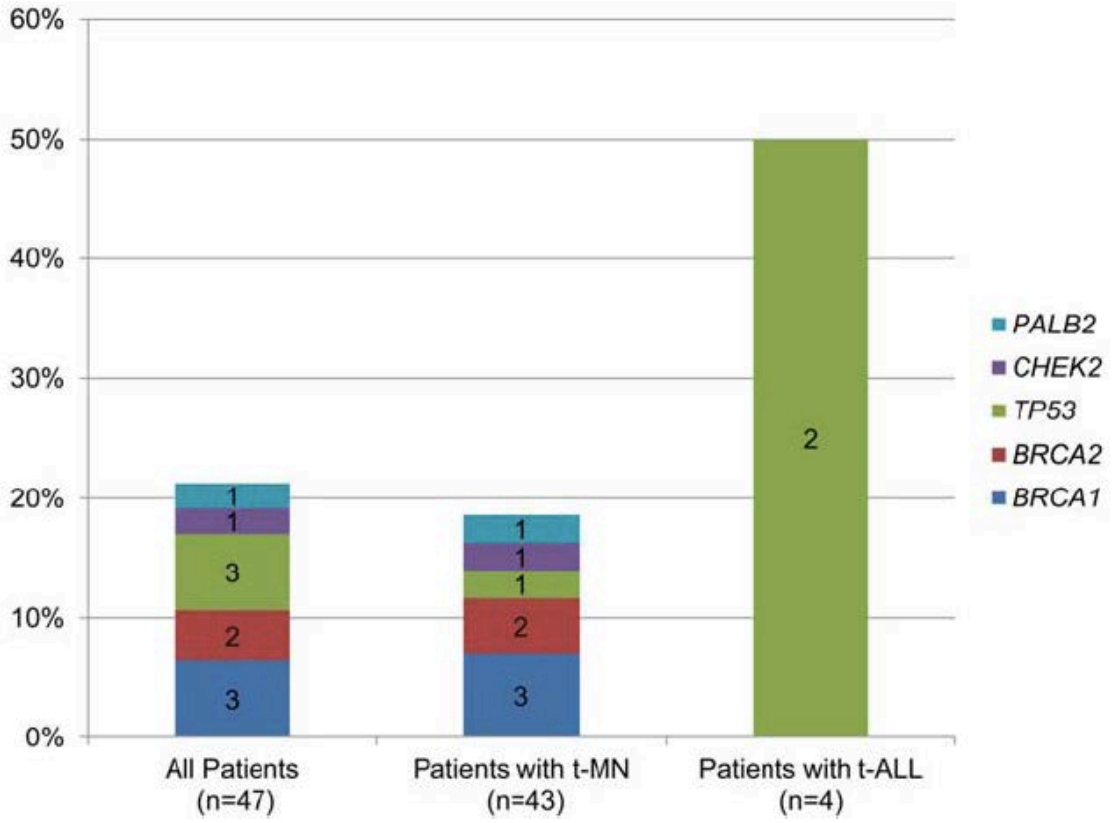
Growth factor receptors

Metabolism

Specific considerations regarding particular cancer predisposition syndromes

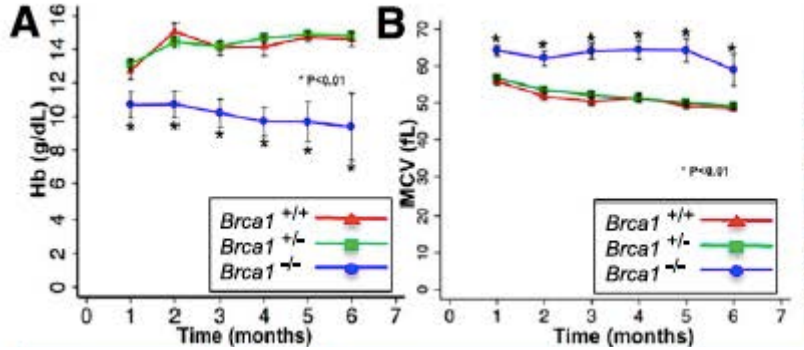
Cancer is a genetic disease–
'Solid tumor' gene syndromes do not exist

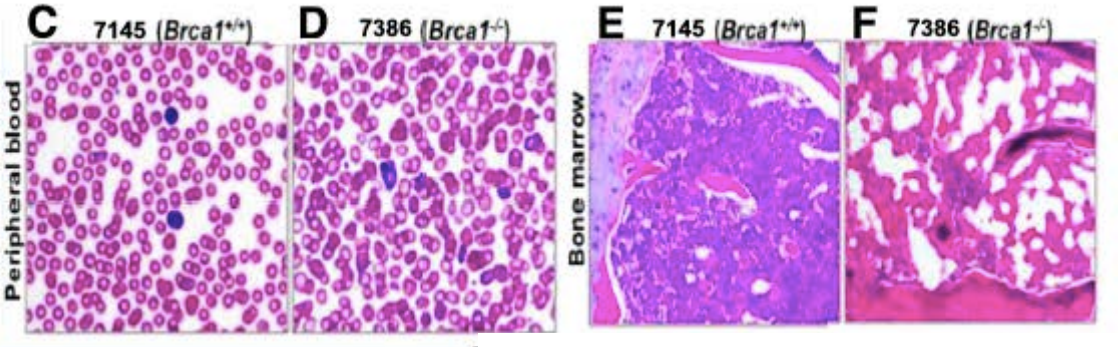
- Lynch: *MSH2/6, MLH1, PMS2*
- Li-Fraumeni: *TP53*
- Hereditary Breast/Ovarian CA: *BRCA1/2 are Fanconi anemia-like genes*



Churpek, JE *et al.* *Cancer* 122: 304-311, 2016

Brca1 is a Fanconi-like gene



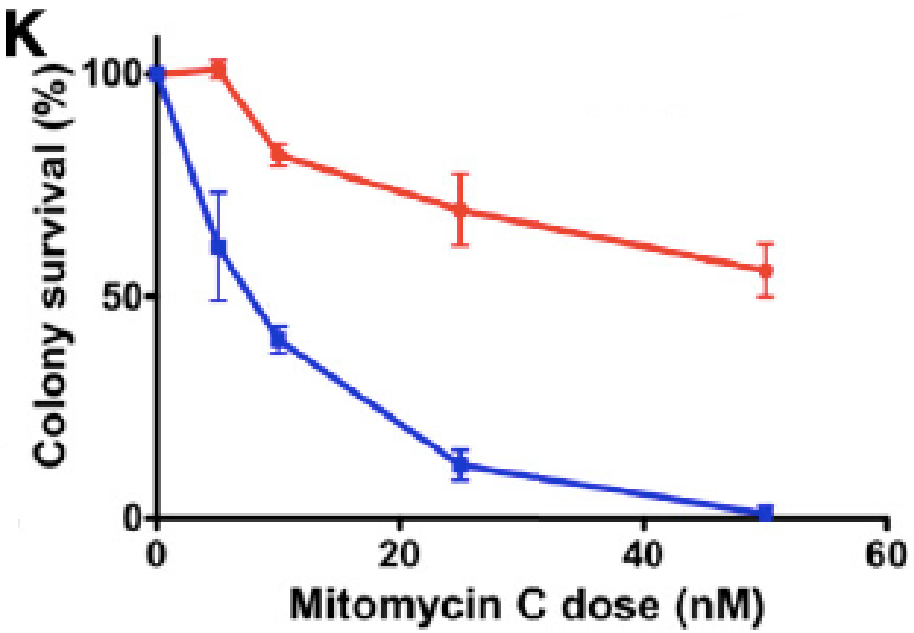


***Brca1* +/+**

***Brca1* +/-**

***Brca1* -/-**

Cytogenetic abnormalities
40,XX[13]
40,XX,chrb(4)(C2)[1]
40,XX,chtb(2)(H1),chtg(6)(B1)[1]
40,XX,chtb(1)(H5),chrg(5)(D)[1]
40,XX,chrg(2)(E2)[1]
39,XX,chtb(2)(B),chrb(3)(F1),chrg(13)(C3),chrg(15)(E),-16,chtb(17)(B)[1]
40,XX,chte(2;5)(F1;C2),chte(9;12)(F1;E),pcd(16)(A)[1]
40,XX,t(1;17)(H4;A2)[1]



Vasanthakumar, A *et al.* *Blood* 127: 310-313 (2016)

Known Familial MDS/AL Syndromes

Myeloid malignancies only

1. Familial AML with mutated *CEBPA* (*CEBPA*)
2. Familial MDS/AML due to *DDX41* mutation (*DDX41*)
3. Familial MPNs--14q32.2 genomic duplication (*ATG2B/GSKIP)*
   -- germline *RBBP6* mutation

Decreased Platelet Number/Function

1. Familial platelet disorder with propensity to myeloid malignancies (*RUNX1*)
2. Thrombocytopenia 2 (*ANKRD26*)
3. Thrombocytopenia 5 (*ETV6*)

Additional Organ Systems Affected

1. GATA2 deficiency syndromes (*GATA2*)
2. Autosomal dominant telomere syndromes (*TERT* and *TERC*)
3. Familial aplastic anemia/MDS due to *SRP72* mutation (*SRP72*)
4. Ataxia-Pancytopenia Syndrome (*SAMD9L* mutation) and
   MIRAGE syndrome (*SAMD9* mutation)
5. Shwachman-Diamond Syndrome (new causative genes: *EFL1* and
   DNAJC21)

Key Management Issues

Myeloid malignancies only

1.Familial AML with mutated *CEBPA* (*CEBPA*)

- Near complete penetrance
- 10% AMLs with bi-allelic *CEBPA* mutations have germline mutation
- Most often, the inherited allele has a mutation in the 5' end of the gene, with acquisition of a mutation in the second allele at the 3' end of the gene

2.Familial MDS/AML due to *DDX41* mutation (*DDX41*)

- Average age of diagnosis: 62yo
- Three pedigrees now with pediatric cases of leukemia
- Some mutations may also predispose to lymphoid malignancies; colon ca/gastric ca

3.Familial MPNs--14q32.2 genomic duplication (*ATG2B/GSKIP)*
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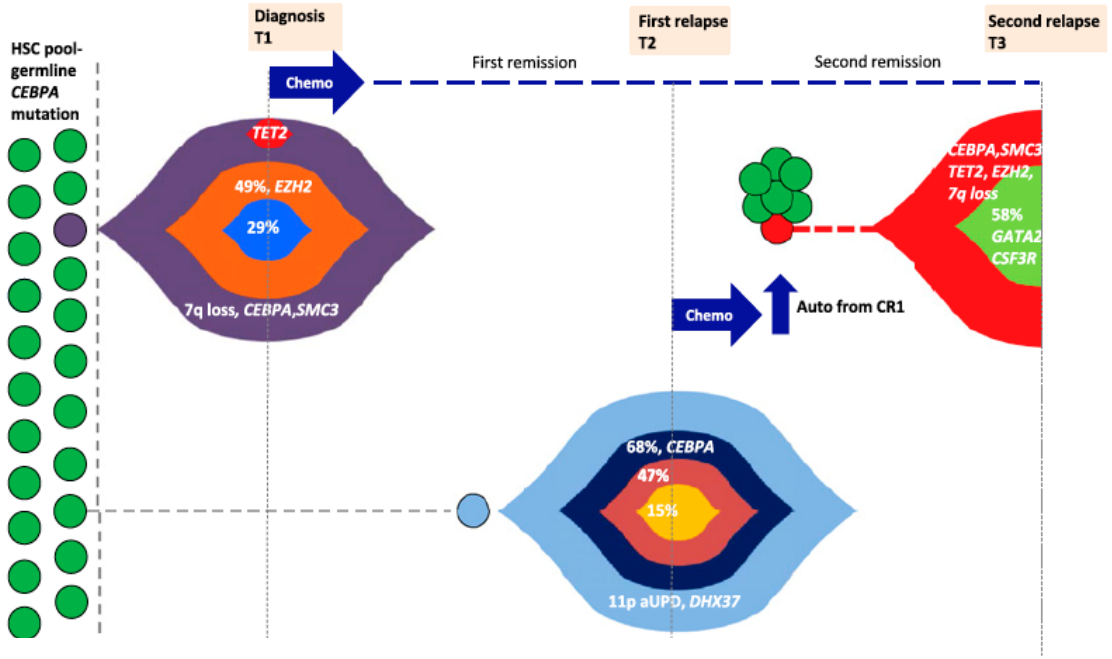
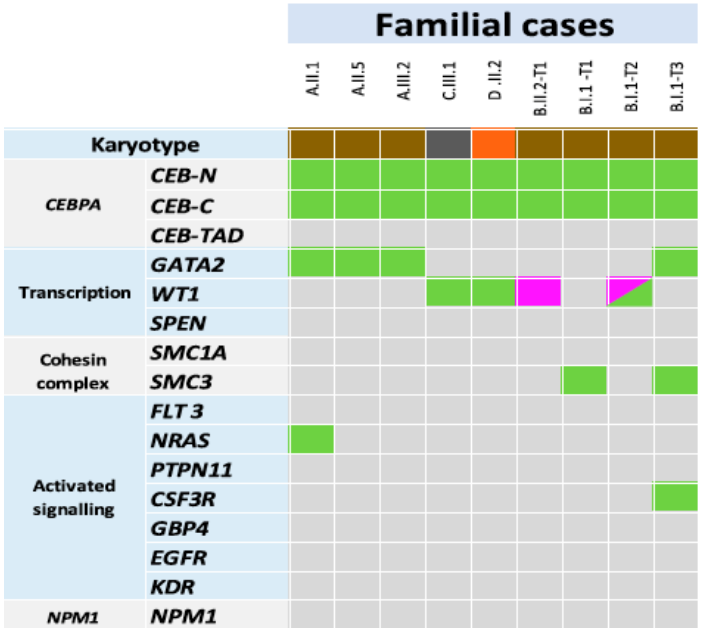
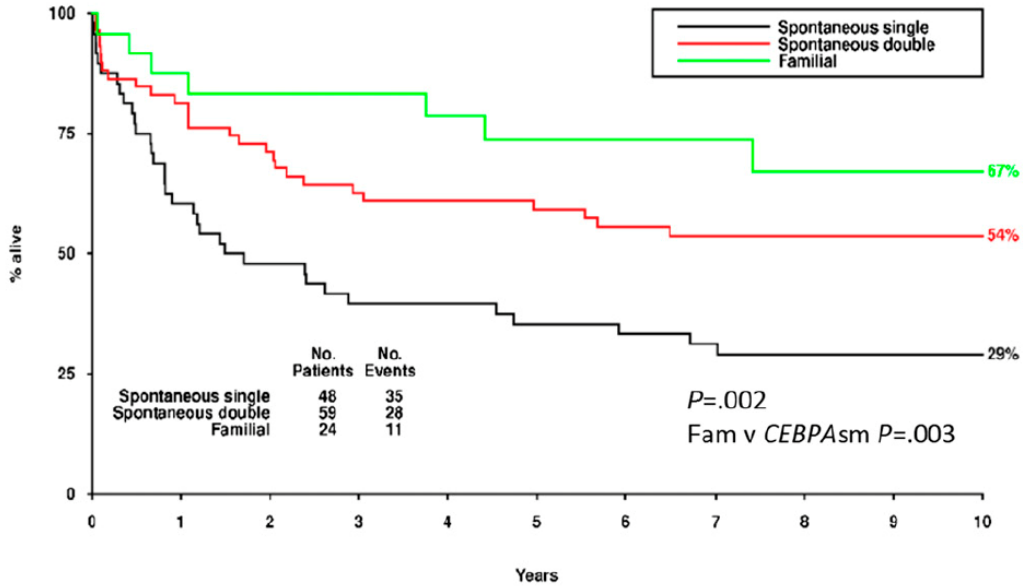
Familial leukemia with *CEBPA* mutation







Clonal Evolution in AMLs:

- "Relapses" appear to be independent leukemias, since acquired *CEBPA* mutation is distinct.
- Acquired mutations in *GATA2* and *WT1* are common and mutually exclusive.
- AMLs are chemosensitive.

Tawana K *et al.* *Blood* 126: 1214-1223, 2015

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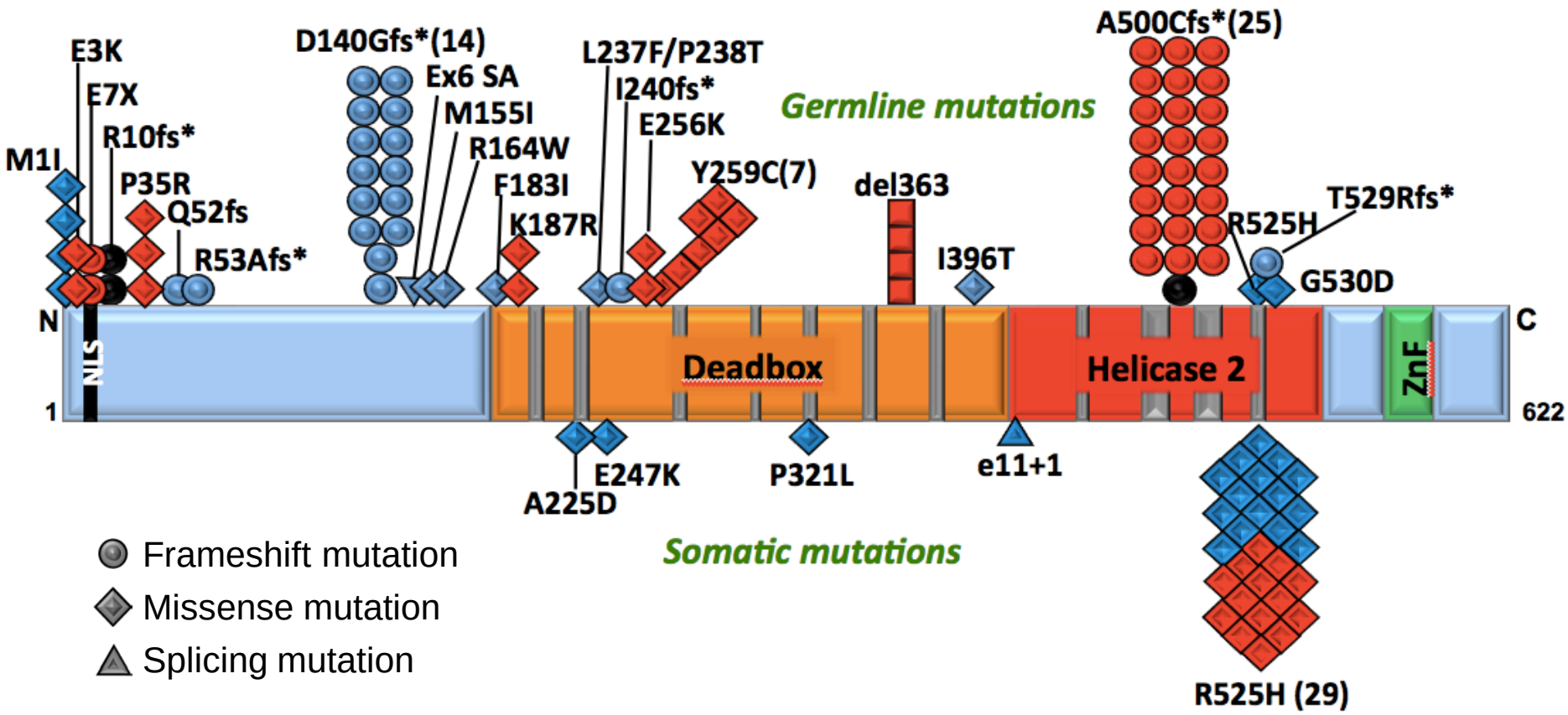
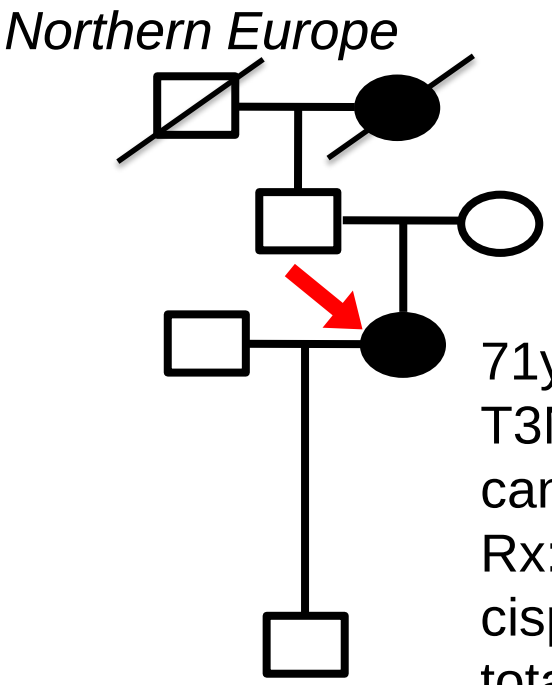
DDX41 on 5q35.3 encodes a DEAD/H-Box helicase



Blue, Caucasian
Red, Asian

Polprasert C, Schulze I *et al.* *Cancer Cell* 27: 1-13, 2015
Lewinsohn, M *et al. Blood* 127: 1017-1023, 2016
Li R *et al. Haematologica* 101: e228-231, 2016

Detecting a germline syndrome from tumor mutational profiling



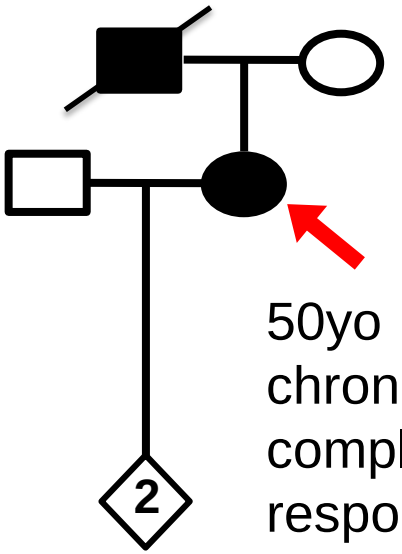
paternal grandmother
non-smoker
no alcohol intake
head and neck cancer in 60's

71yo
T3N0M0 grade 3 gastric cancer
Rx: neoadjuvant chemo: cisplatin/5-FU→
total gastrectomy→
FOLFOX, completed 3/6 planned cycles due to cytopenias

73yo
t-MN
Panel testing:
DDX41 D140fs→ skin biopsy confirmed germline

Detecting a germline syndrome from tumor mutational profiling

Middle East- Jordan



father
AML at 60yo

50yo
chronic phase CML→
complete molecular
response on Gleevec

53yo
'myeloid blast' phase CML→
no detectable *BCR-ABL*→
Panel testing: DDX41
P78fs
R525H
Skin biopsy confirmed P78fs is
a germline mutation.

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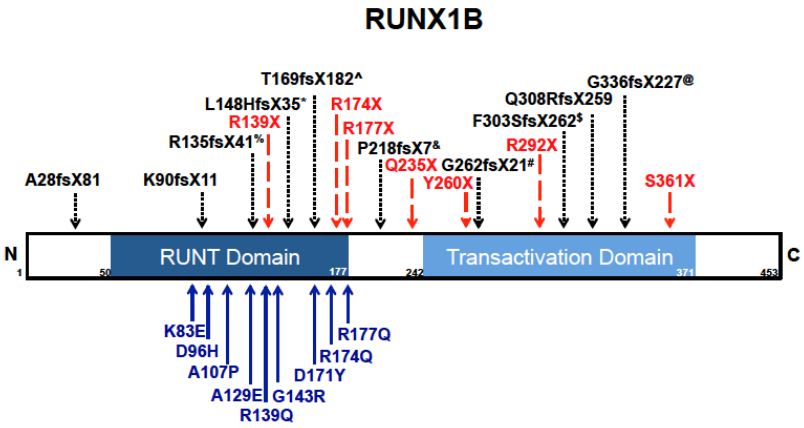
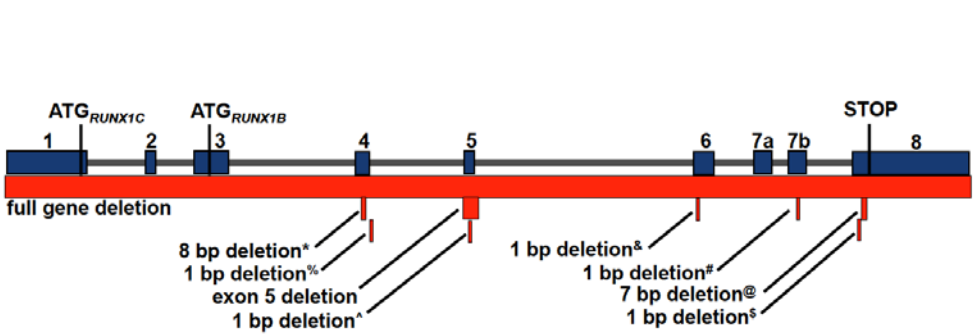
- Both germline *RUNX1* and *ETV6* mutations predispose to both myeloid and lymphoid malignancies; to date, germline *ANKRD26* mutations have only been associated with development of myeloid malignancies

- Patients can bleed out of proportion to their platelet counts, since the platelets have abnormal aggregation. Therefore for surgery/childbirth, we recommend transfusion of normal platelets

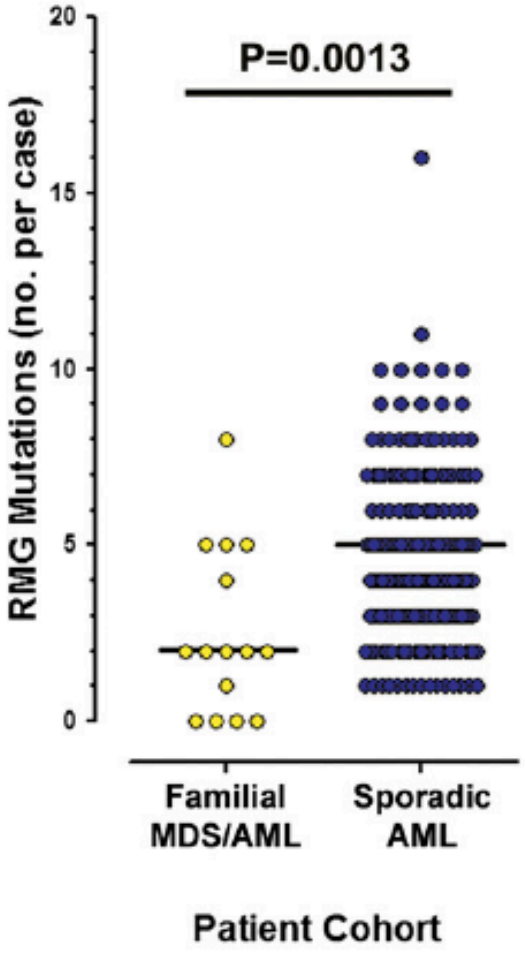
Key Management Issues

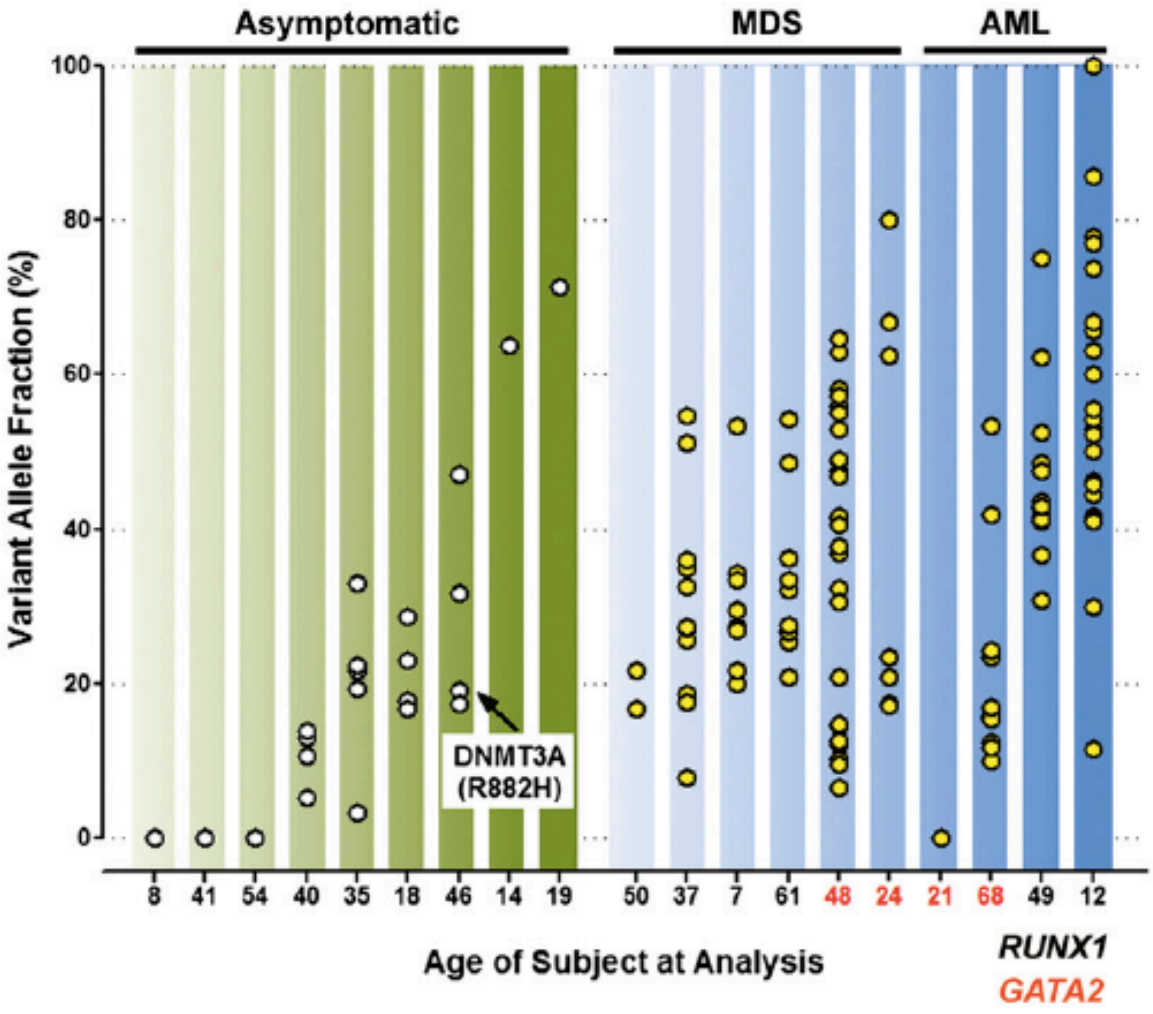
Familial platelet disorder with propensity to myeloid malignancies (*RUNX1*)





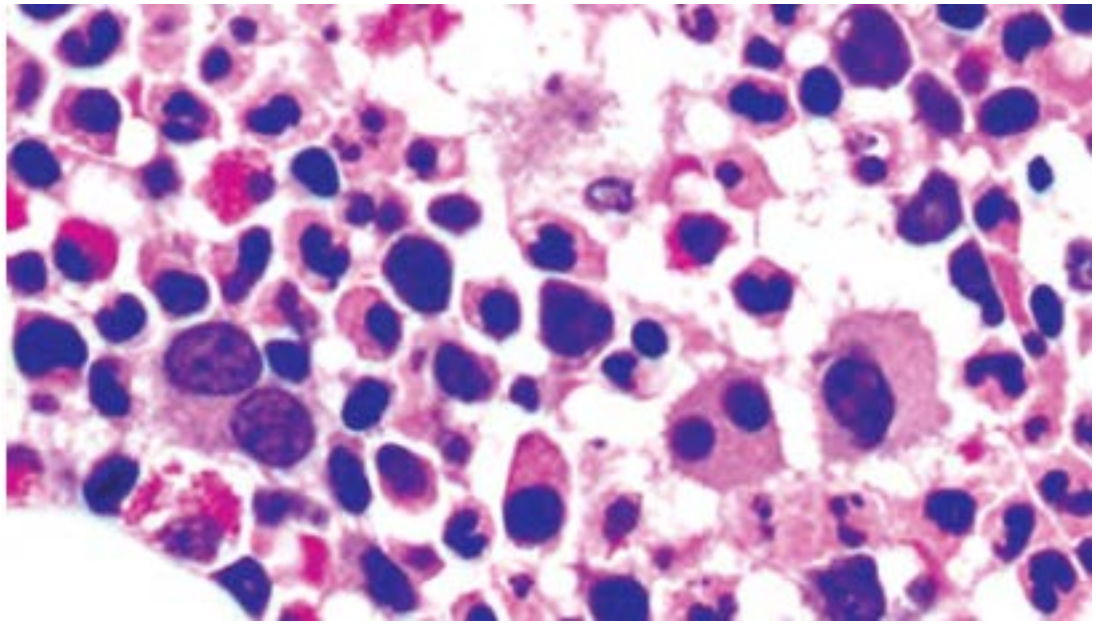
Clonal evolution in FPD/AML





Churpek, JE *et al. Blood* 126: 2484-2490, 2015

ANKRD26 mutations confer a distinctive bone marrow pathology at baseline



hyposegmented and binucleated megakaryocytes

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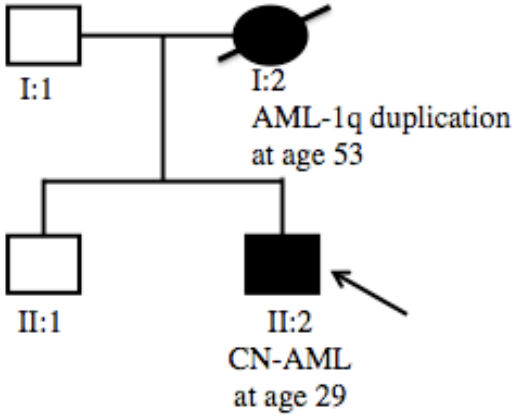
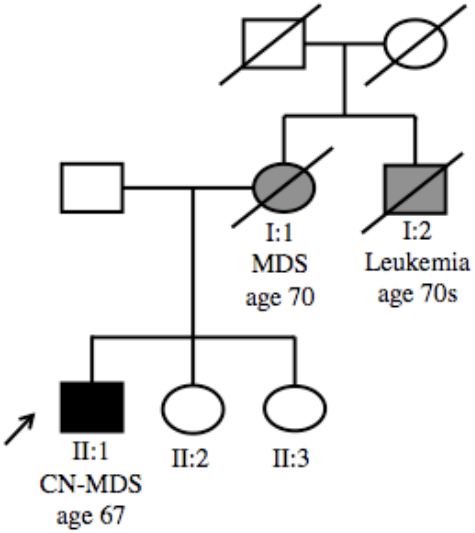
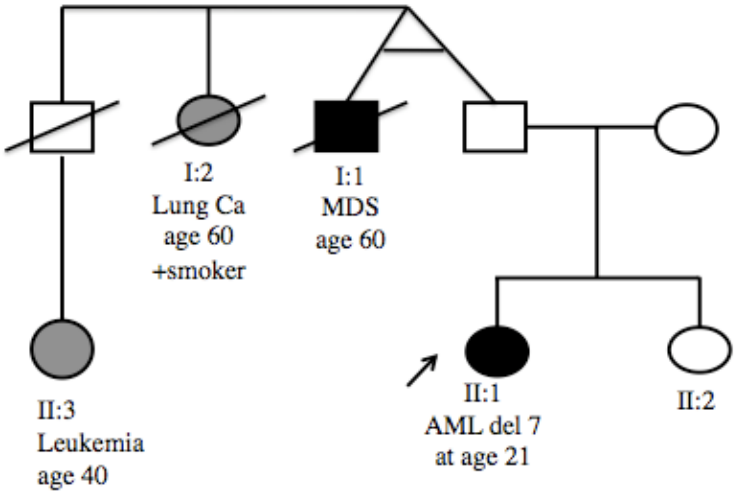
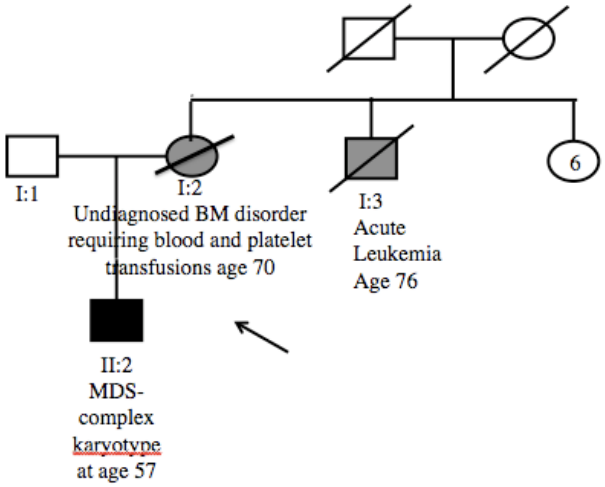
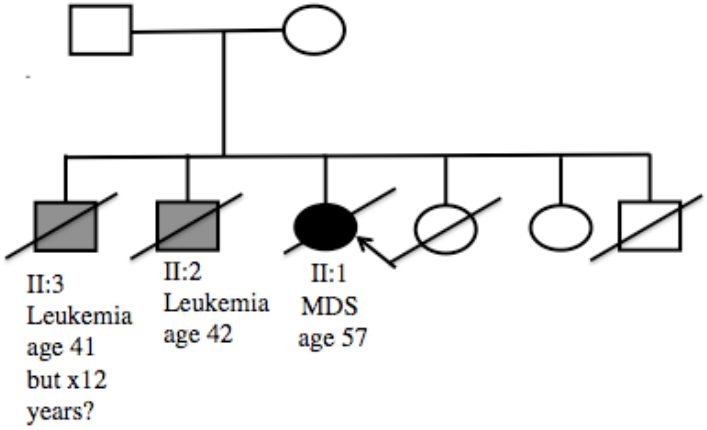
Research Opportunities



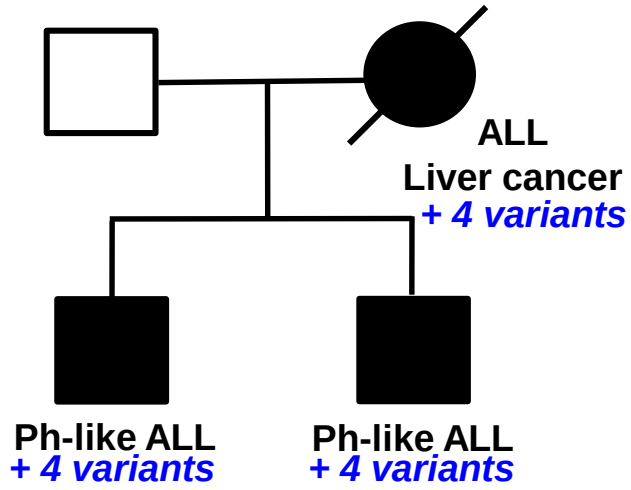








The next frontier: inherited lymphoid malignancies



2 GATA3 intron variants homozygous

Realizing the goal of precision medicine in oncology

DEFINE:
Baseline genetics
Baseline epigenetics
Acquired genetics in the tumor/stem cell product
Acquired epigenetics in the tumor

to devise an effective treatment strategy for a particular patient

- Family history (FHx) is an important tool in hematology.
- Consider familial syndromes for all patients with hematopoietic malignancies→ *How can we test patients systematically?*
  How can we diagnose cases without relying on FHx?
  Special consideration at the time of allogeneic stem cell transplantation!
- Both point mutations and genomic rearrangements can lead to germline predisposition, so testing should be comprehensive for both.
- It is critical to test true germline DNA (e.g., skin fibroblasts).
- Additional syndromes and pathways in leukemogenesis will be identified!