Evaluation and care of patients and families with inherited predisposition to develop MDS

MDS Foundation's Educational Patient-Caregiver Forum
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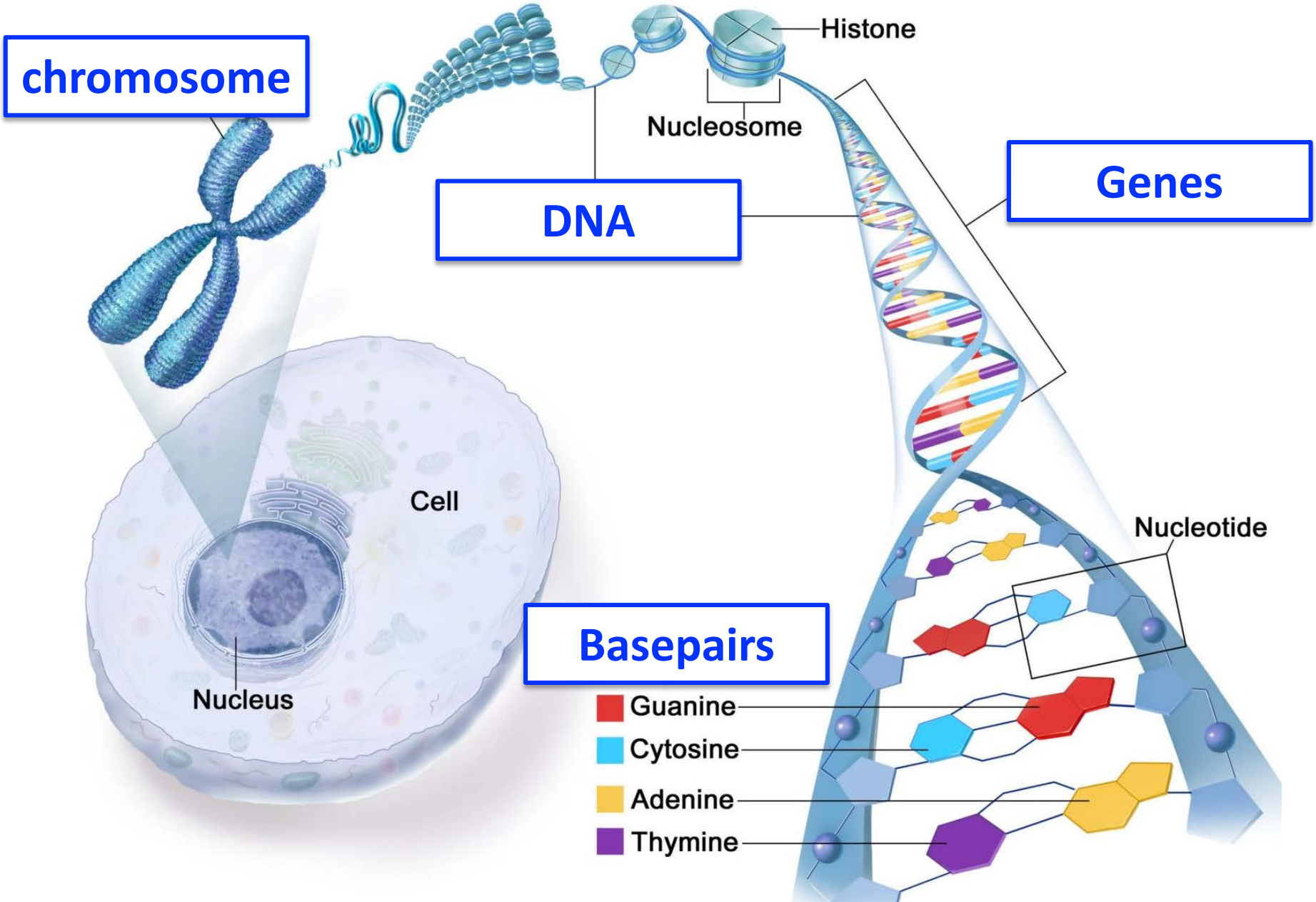
Bone marrow failure definition-

Bone marrow is unable to keep up with the body's need for healthy blood cells

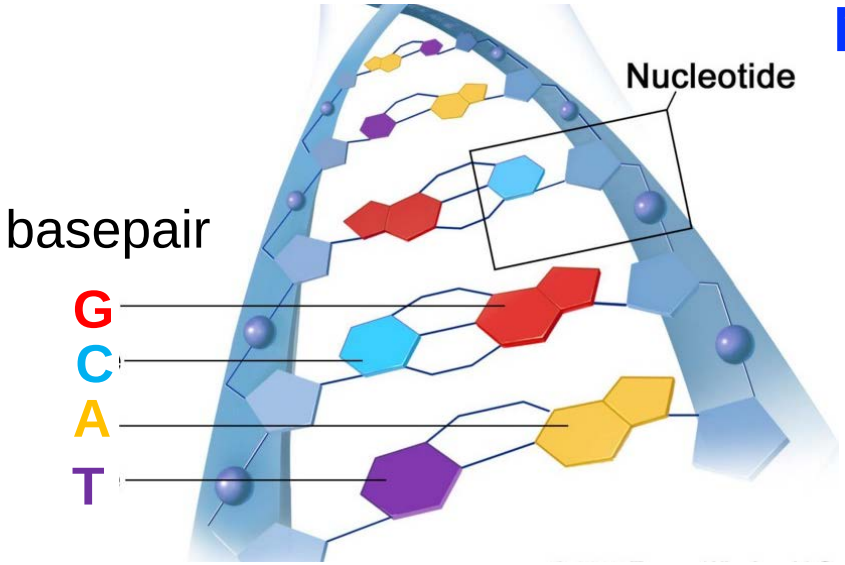
1. Acquired
   - Myelodysplastic syndromes (MDS)
   - Aplastic anemia
   - PNH
   - Toxins (e.g., drugs, irradiation, infections)
2. Inherited*

* Are at risk for developing MDS or leukemia

From the Cell to DNA



Mutations – changes in the DNA



Normal DNA

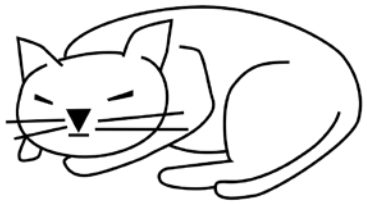
A — T
T — A
G — C
C — G
T — A

DNA with a mutation

A — T
T — G
G — C
C — G
T — A

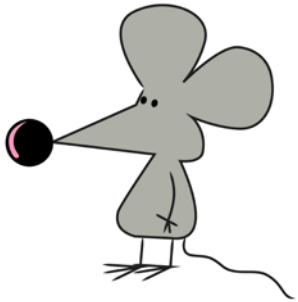
Normal DNA

I have a cat



DNA with a mutation

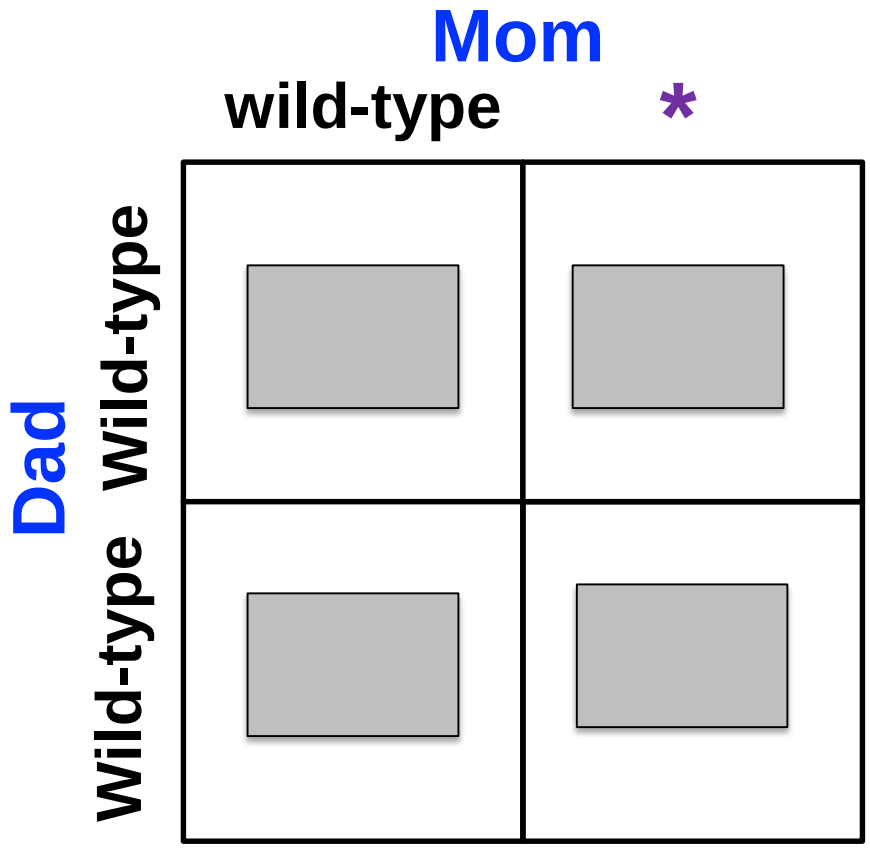
I have a rat

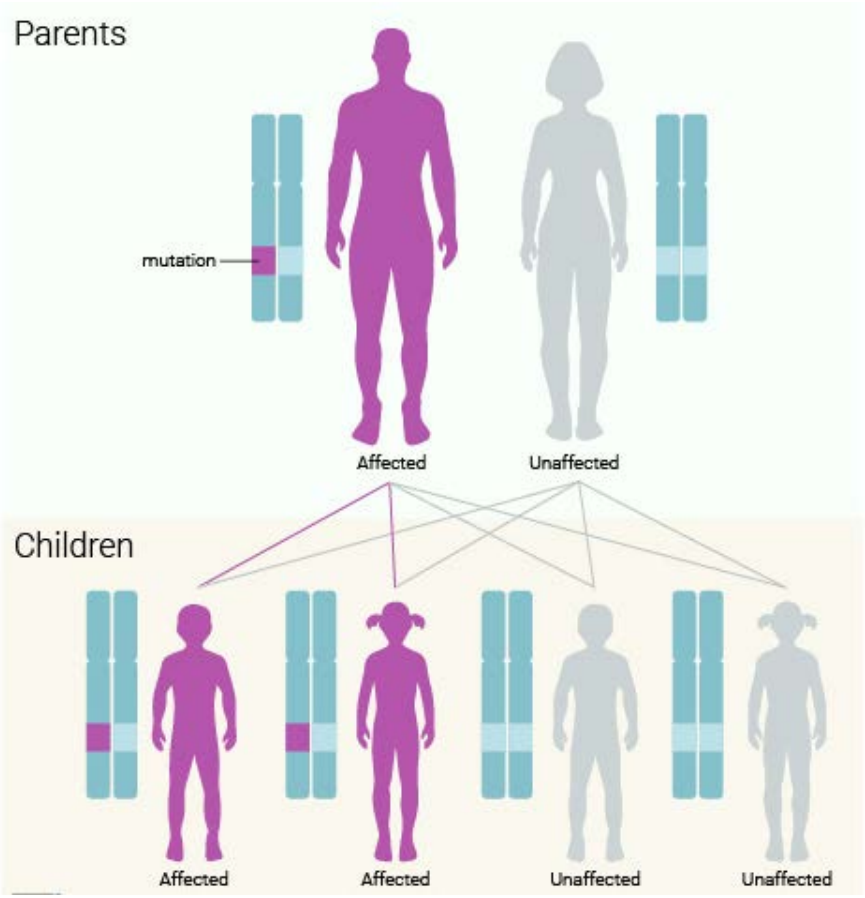


- Mutations can be ***inherited*** **or** ***acquired*** during a person's life

Mendelian Inheritance

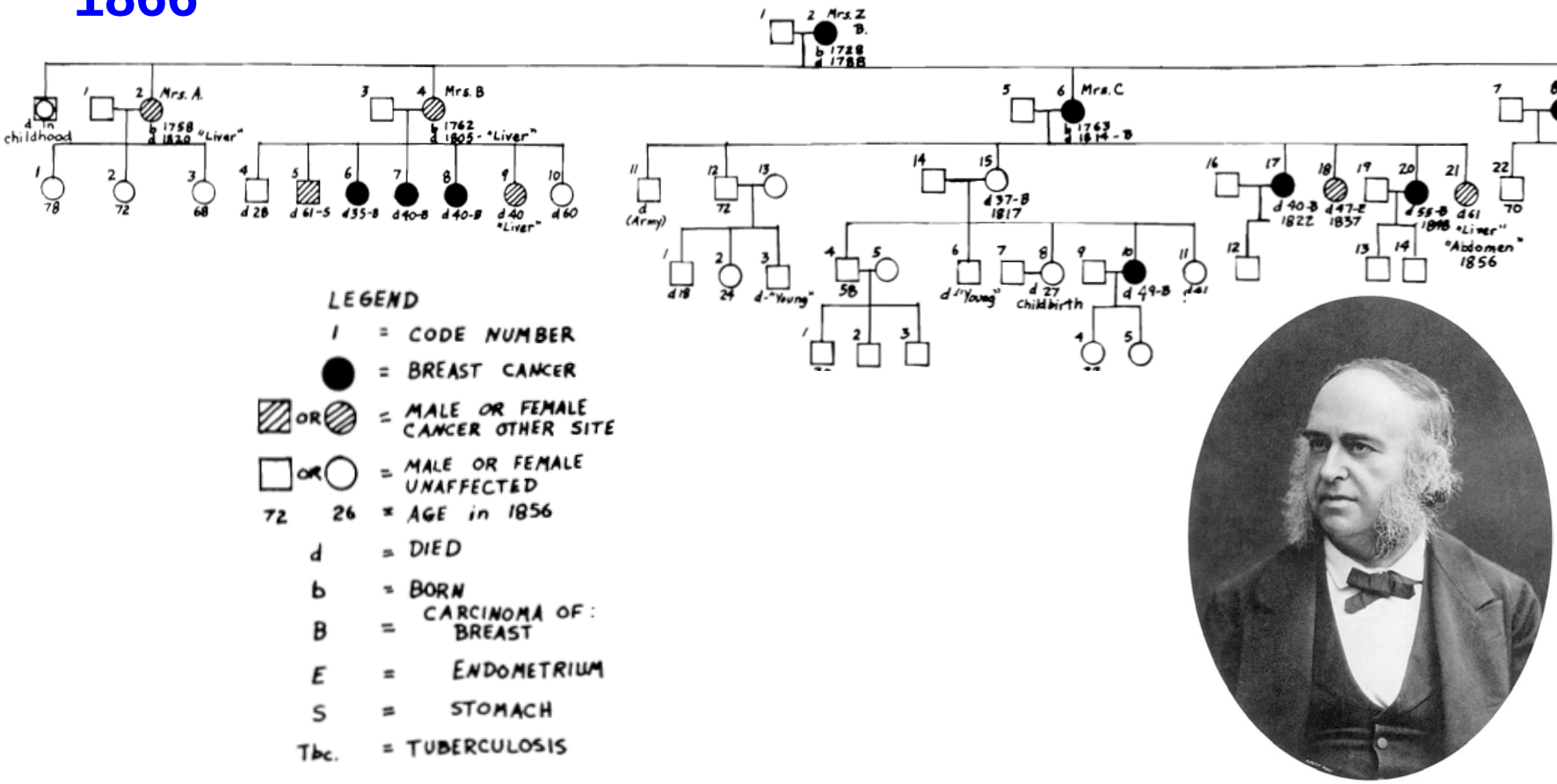
Example - Autosomal dominant





Genetic predisposition to cancer

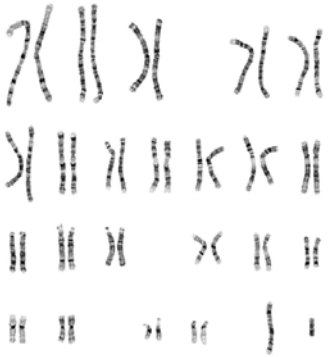
1866[1]

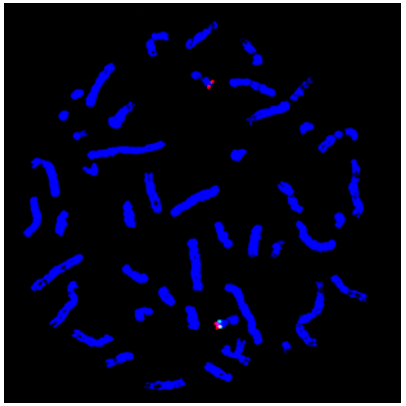


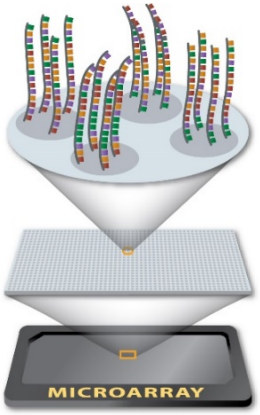
- **1999** 1st reported inherited acute leukemia and MDS predisposition syndrome - Familial platelet disorder with associated myeloid malignancy due to mutations in *RUNX1*.[2]

1. Broca P. *Traite des tumeurs.* 1866. 2. Song WJ et al. Nat Genet 1999: 23(2).

Genetic laboratory testing



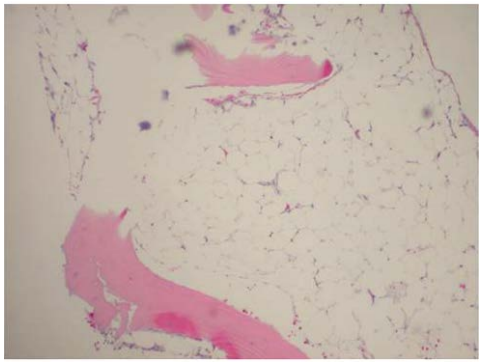


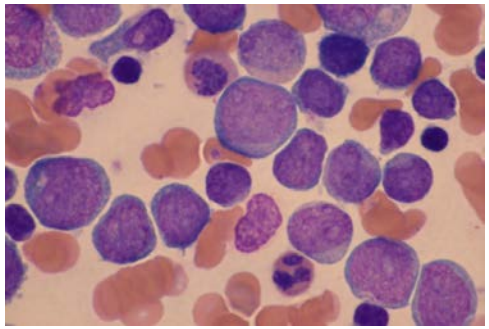


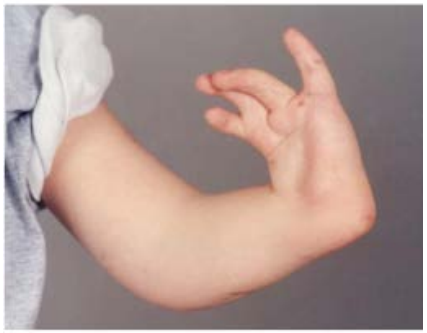
	Karyotype	FISH	Microarray	Next-gen sequencing
Coverage	Genome	Targeted	Genome	Exome/genome
Resolution	Low	High	Higher	Highest
Source	Living cells	Living/fixed cells	DNA	DNA
Detect balanced rearrangements?	Yes	Yes	No	Sometimes

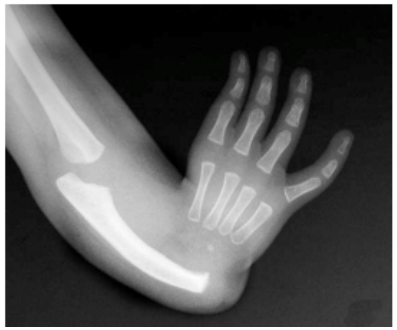
Inherited bone marrow failure & inherited MDS/leukemia predisposition syndromes

- Marrow failure
  - Often hypocellular
- ± Cancer predisposition
- ± Findings on exam









From Kozin, Scott H. Fanconi Anemia Guidelines, 2008. *www.fanconi.org*

Inherited MDS predisposition syndromes

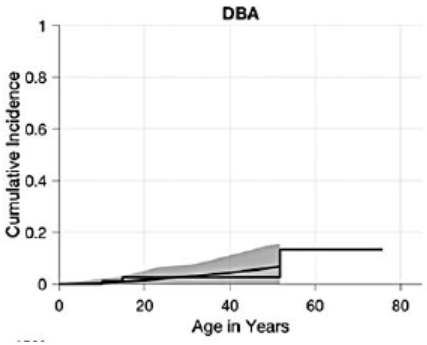
- Classical inherited bone marrow failure syndromes
- Germline predisposition for hematopoietic malignancy
  - *CEPBA*
  - *DDX41*
  - *14q32.2* genomic duplication *(ATG2B/GSKIP)*
- Germline predisposition for hematopoietic malignancy with pre-existing cytopenia(s) and/or other organ dysfunction prior to hematopoietic malignancy presentation
  - *ANKRD26*
  - *ETV6*
  - GATA2 Deficiency Syndrome
  - *RUNX1* - Familial platelet disorder with associated myeloid malignancy
  - *SAMD9* - MIRAGE syndrome; *SAMD9L* - Ataxia Pancytopenia Syndrome
  - *SRP72*
- Germline predisposition for myeloid neoplasms and solid tumor cancers
  - Constitutional mismatch repair deficiency
  - Hereditary breast and ovarian cancer (e.g., *BRCA1, BRCA2*)
  - Li-Fraumei syndrome
  - RASopathies
  - Other rare DNA repair syndromes (e.g., *BLM)*

Modified from 2019 NCCN MDS Guidelines

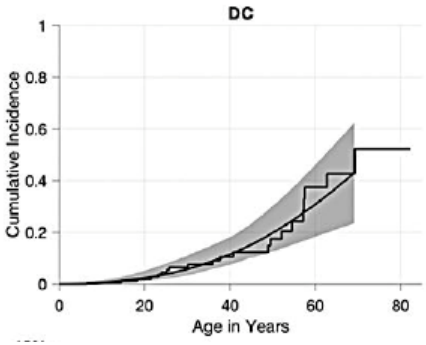
NCCN National Comprehensive Cancer Network®

Cumulative incidence of MDS by age

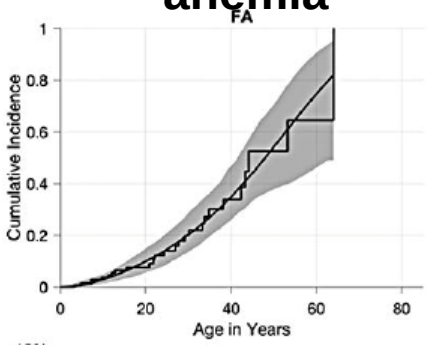
DBA



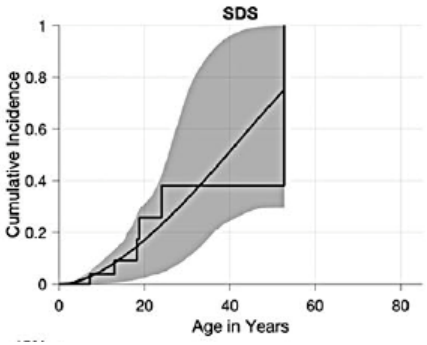
Dyskeratosis congenita



Fanconi anemia



Shwachman-Diamond



- Cumulative incidence of MDS by age 50 were 5% in DBA, 20% in DC, 50% in FA, and 65% in SDS

Alter B. Haematologica 2018: 103(1).

Why do we need to recognize these inherited syndromes ?

1. Some syndromes are associated with a risk of developing MDS or leukemia

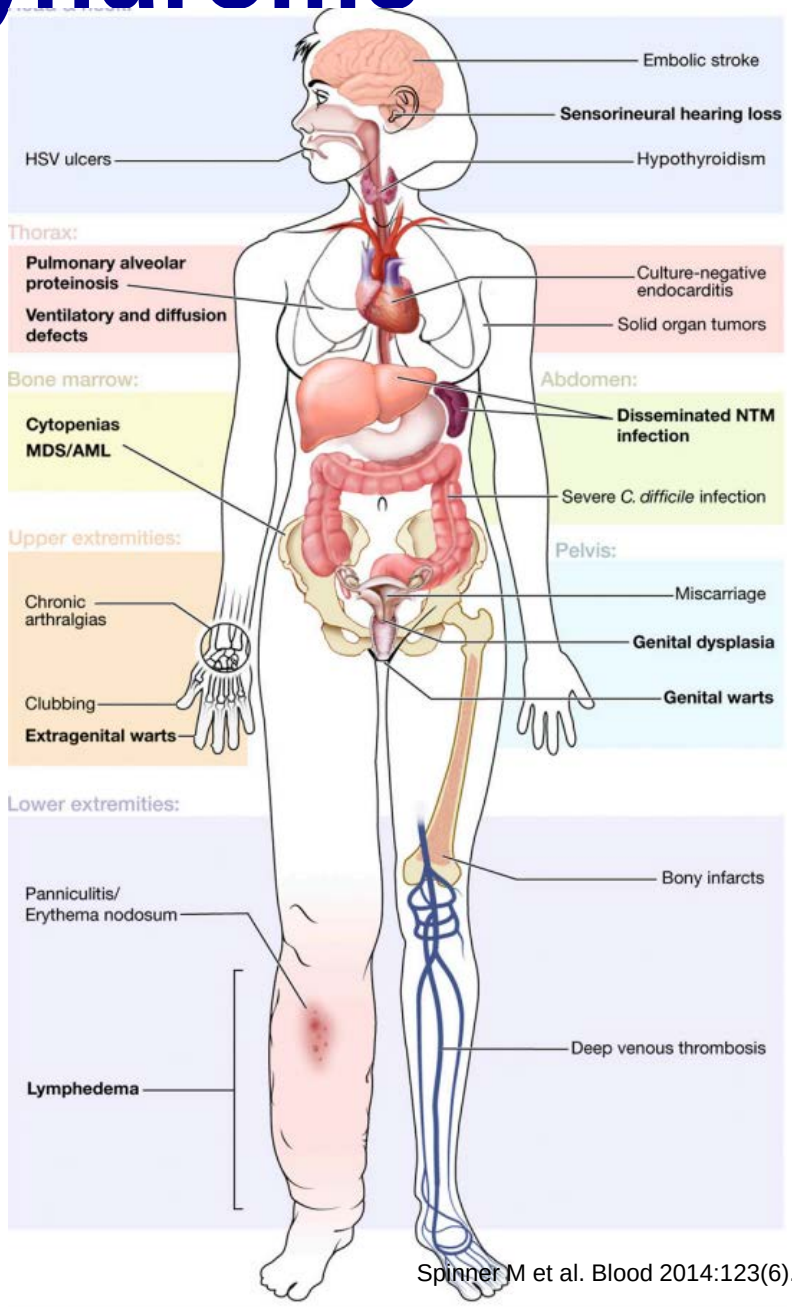
- Allows surveillance *prior* to development of MDS/leukemia.
- Informs hematopoietic stem cell transplant donor selection, timing, and preparatory regimen for patients who develop MDS/leukemia.

2. Follow-up and care for non-blood related complications

GATA2 deficiency syndrome

Surveillance and treatment considerations (before development of MDS)

- CBC and blood count monitoring
- HPV vaccination
- Prophylactic antibiotics for certain infections (NTM)
- Family counseling and follow-up



Spinner M et al. Blood 2014:123(6).

3. **Appropriate family counseling and follow-up**

Patients Pursuing a Genetic Consultation

Medical Evaluation

Psychosocial Counseling





Hematologic Malignancy Genetics Clinic

Services offered to individuals and families

- Hematologic malignancies cancer risk assessment and genetic testing
- HSCT planning
- Surveillance Program
- Family counseling
- Research opportunities to improve patient care

How do you distinguish between acquired & inherited marrow failure?

- Clinical History
- Physical Exam
- Laboratory Evaluation
- Family History
  - Other members with similar disease
  - Malignancy

Lack of a concerning family history or physical exam findings DOES NOT exclude the possibility of an underlying inherited cause.

Pediatric & young adult patients transplanted for "acquired disorders" had underlying inherited disorders

Study Design

- Fred Hutchinson Cancer Research Center Cell Bank Repository of pre-hematopoietic stem cell transplant DNA
- MDS patients ≤ 40 years-old and transplanted 2001-2011 or MDS or AML with monosomy 7 patients <20 years-old and transplanted 1991-2001

Findings

- **12.7%** (14/110) MDS/AML carried pathologic mutations
- Absence of a family history or congenital anomalies does not exclude a genetic cause

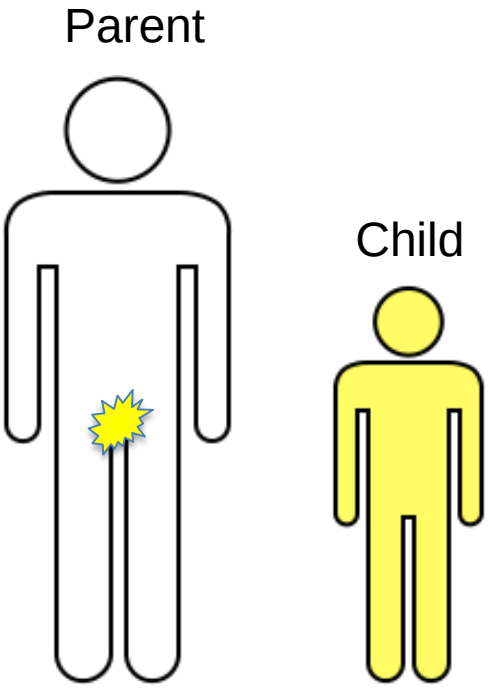
Keel S et al. Haematologica 2016:101(11).

Which patients are we currently testing ?

- Patient with a suggestive personal and/or family history
- Younger patients presenting with marrow failure, MDS, or leukemia
- Family member in a known inherited predisposition family (mutation-directed sequencing)
- Potential sibling allogeneic stem cell donor in a known inherited predisposition family
- Patient with potential inherited mutation found on testing cancer cells

Complexities of genetic testing: inherited vs. acquired mutations

Inherited mutations

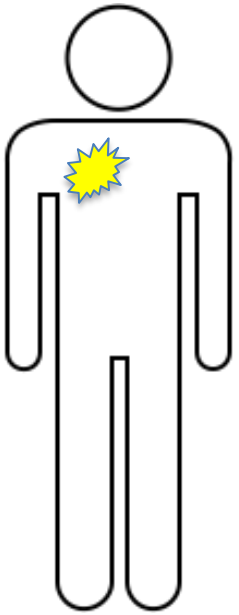


Mutation in egg or sperm

Mutation in all cells in affected child

- Heritable - can pass mutation on to children

Acquired mutations



Mutation in a cancer (e.g., lung cancer)

- Not heritable
- Present only in the cancer

In MDS, <u>cancer is in the blood</u> – so testing blood can be confusing.

Other complexities of genetic testing

- Limitations of different sequencing methods
- Interpretation of sequencing results is complicated
- Evolving field (new genes, new mutations)

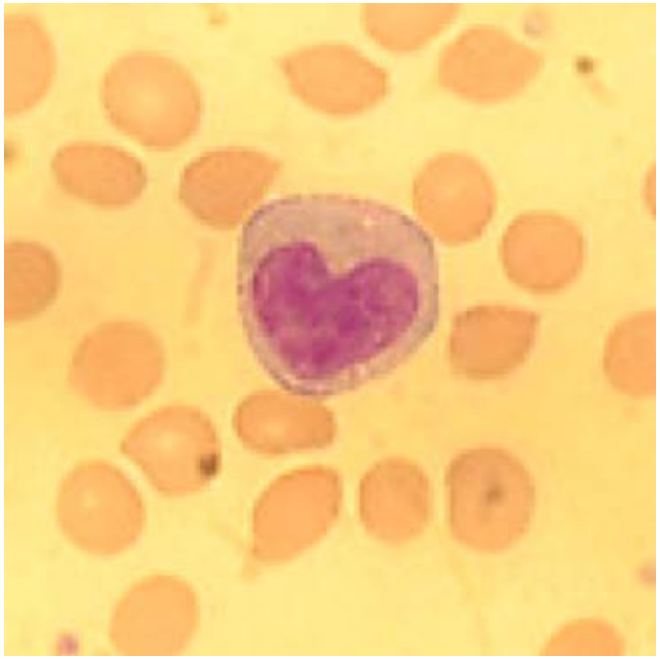
Treatment options

- Depends on specific underlying syndrome
- Cancer surveillance
- Supportive care
- Other therapies depending on disease
  - Androgens (Fanconi anemia)
  - Steroids (DBA)
- Bone marrow transplantation

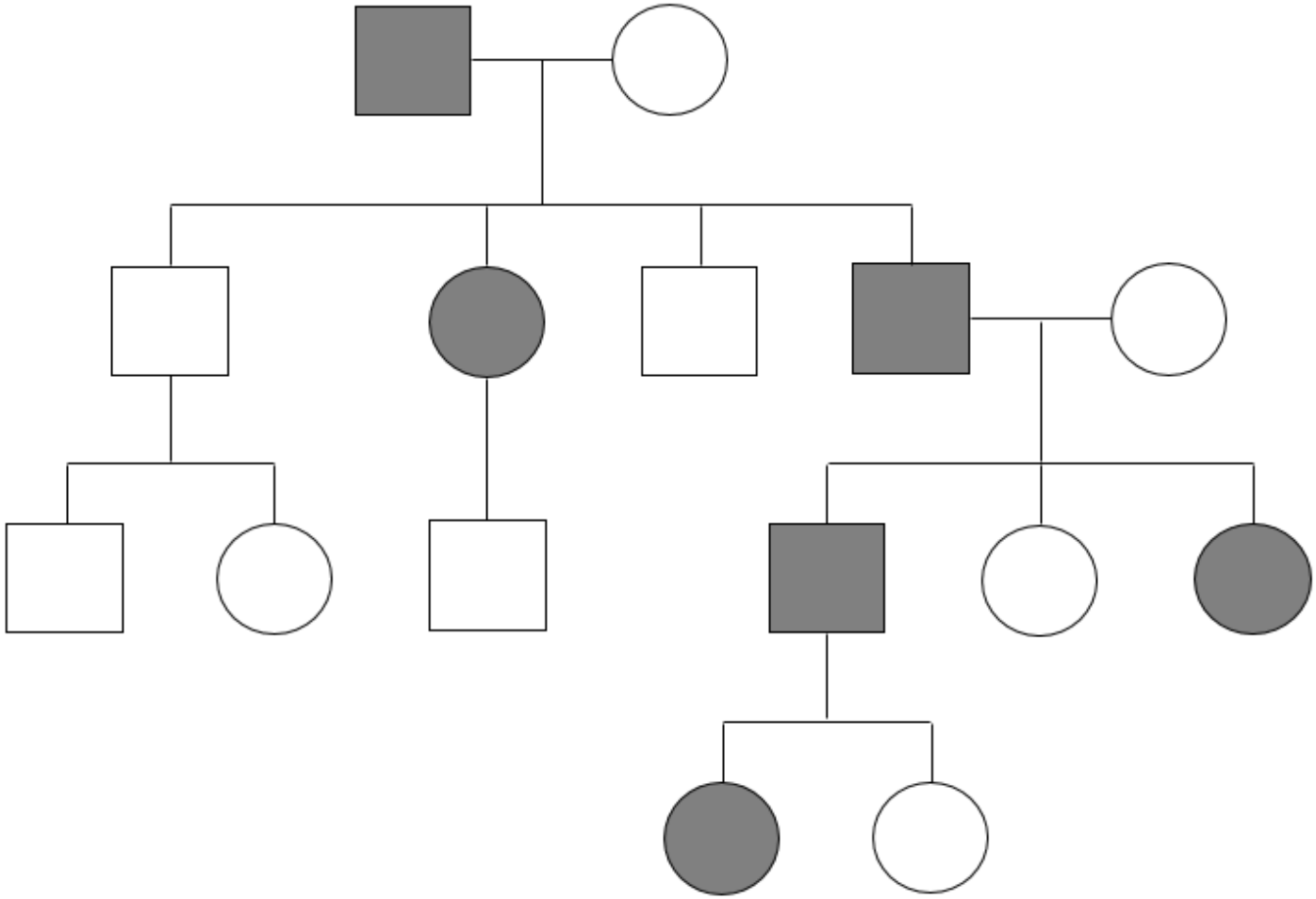
Concluding thoughts

- Recognition of an underlying inherited predisposition to develop MDS guides medical care.
- Goal of diagnosis and follow-up is to keep people healthy.

Questions?



Example pedigree: Autosomal dominant disease



Defined inherited bone marrow failure or MDS/AML predisposition syndromes – 74 patients