Inherited predisposition to developing MDS

Saturday June 18th, 2022

Sioban Keel, MD

Associate Professor of Medicine

Cancer is **GENETIC**

BUT

Not ALL Cancers are inherited (hereditary)

Inherited hematologic malignancy predisposition syndromes

- Classical inherited bone marrow failure syndromes (e.g. Fanconi anemia)
- Germline predisposition for blood cancers (e.g. *DDX41*)
- Germline predisposition for blood cancers with pre-existing low blood counts/other organ dysfunction (e.g. GATA2 Deficiency syndrome, SAMD9/SAMD9L disorders)
- Germline predisposition for myeloid neoplasms & solid tumor cancers (e.g. hereditary breast and ovarian cancer, Li-Fraumeni syndrome)

Modified from 2021 NCCN MDS Guidelines
(mutations associated with hereditary myeloid malignancy)

NCCN National Comprehensive Cancer Network®

Why care about these syndromes?

- May require surveillance for cancer and non-blood related complications
- In the setting of bone marrow transplantation → specialized evaluation of a related donor and potential use of a modified conditioning regimen
- Appropriate cancer and counseling of family members

These are now included in practice guidelines and disease classifications[1-3]

1. NCCN 2021 MDS Clinical Practice Guidelines.
2. Arber D. et al. Blood 2016: 127.
3. Dohner H. et al Blood 2017: 29.

Why care about these syndromes?

TO THE EDITOR:

Donor-derived MDS/AML in families with germline *GATA2* mutation

Galera P. et al. Blood 2018: 132 (18).

CORRESPONDENCE

Donor cell leukemia arising from preleukemic clones with a novel germline DDX41 mutation after allogenic hematopoietic stem cell transplantation

Kobayashi S. et al. Leukemia 2017: 31.

Inherited mutations in cancer susceptibility genes are common among breast cancer survivors who develop therapy-related leukemia

Churpek J. et al. Cancer 2016 : 122.

Identifying Inherited and Acquired Genetic Factors Involved in Poor Stem Cell Mobilization and Donor-Derived Malignancy

Rojek K. et al. Bio Blood Marrow Trans 2016: 22.

Inherited cancer predisposition is common among pediatric & young adults with MDS

- Germline *GATA2* mutations among 7% of pediatric/adolescent MDS patients[1]
  - 37%of patients whose MDS was characterized by monosomy 7
- Germline mutations in *SAMD9/9L* among ~ 20% of pediatric MDS patients[2]
  - All were characterized by chromosome 7 abnormalities

1. Wlodarski MW et al. Blood 2016:127(11).
2. Schwartz JR. et al. Nature Comm 2017:8(1).

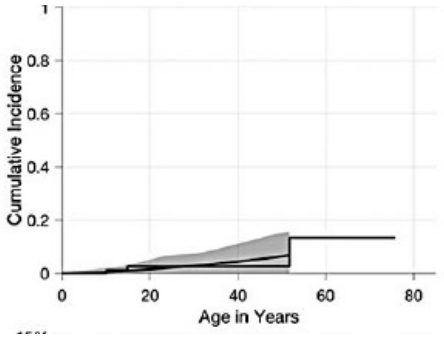
DDX41 mutations are the most common germline mutations predisposing to AML/MDS in adults

- Reported in **~2–6% of adult patients with myeloid cancers**
- AML/MDS diagnosed at same age as “typical” AML/MDS (long-latency)
- May or may not have a history of prior low blood counts
- Appears to predispose to other hematologic cancers & solid tumors
- Often lacks a family history of blood cancers
- Currently no DDX41-specific diagnosis/management guidelines

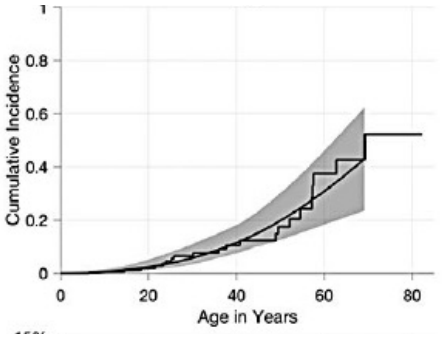
1. Sebert M. et al. Blood 2019: 134.
2. Polprasert C. et al. Cell 2015: 27.
3. Lewinsohn M. et al. Blood 2016: 127.

MDS Risk in the Classical Inherited Bone Marrow Failure Syndromes

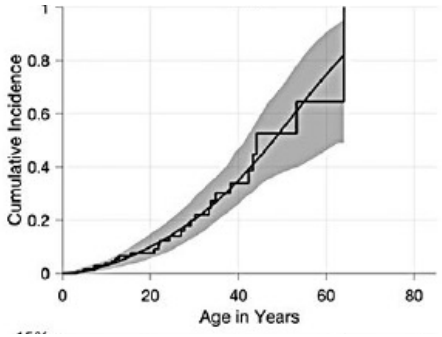
DBA



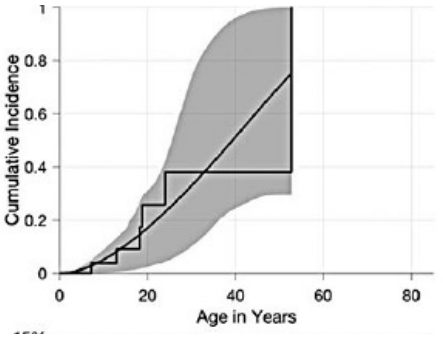
Dyskeratosis congenita



Fanconi anemia



Shwachman-Diamond



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

Alter B. Haematologica 2018: 103(1).

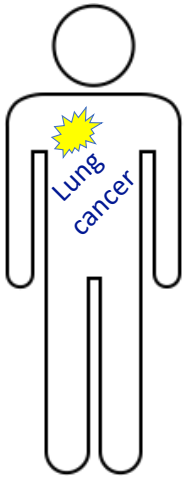
Where is the mutation?

- In MDS, cancer is in the blood – so testing blood can be confusing

Acquired Mutation

(**aka somatic**)

- Occurs in the cancer
- Cannot be inherited



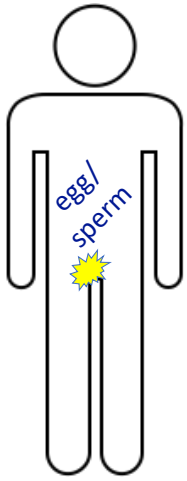
Inherited Mutation

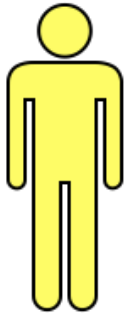
(**aka germline**)

- Present in egg or sperm
- Can be inherited

Parent

Mutation in egg or sperm





Child

Mutation in all cells

Heritable mutations as “incidental” findings from tumor-based genetic testing

360 patients with blood cancers with tumor-based genetic testing

- 52 pathogenic mutations in genes associated with inherited cancer risk
- **12% (6/52) mutations were germline (aka inherited) – *DDX41, GATA2, TP53***

Cultured skin fibroblasts (from a skin biopsy) is usually the preferred DNA source for **germline** genetic testing.

Drazer, MW. et al. Blood 2018: 2.

Can’t rely on a family history of cancer or physical exam findings to identify all inherited cancer risk

- Small families
- Variable presentations in an individual
- Variable “penetrance”
- Cancer risk can have a long latency
- Heritable genetic changes can be newly acquired in an individual (”de-novo”)

Which AML/MDS patients do we consider for germline genetic testing?

- AML or MDS patients diagnosed at <50 years-old
- Suggestive personal and/or family history
- “Hypocellular MDS”
- Patient with potential inherited mutation found on testing cancer cells
- Personal history of MDS or AML and one or more additional cancer(s)
- Potential bone marrow transplant donor in a known inherited predisposition family
- Family member in a known inherited predisposition family (mutation-directed sequencing)

Pediatric and adult hematologic malignancy and marrow failure genetics program

Seattle Children's Hospital

- Katie Bergstrom – *Genetic Counselor*
- Amy Geddis – *Hematologist*
- Megan Nash – *Social Worker*
- Chelsea Olson – *Nurse*
- Roberta Roberta – *ARNP*

Fred Hutchinson Cancer Center

- Marshall Horwitz – *Medical Geneticist*
- Sioban Keel – *Hematologist*
- Cynthia Handford – *Genetic Counselor*
- Mercy Laurino – *Genetic Counselor*
- Amanda Weatherford – *Nurse*

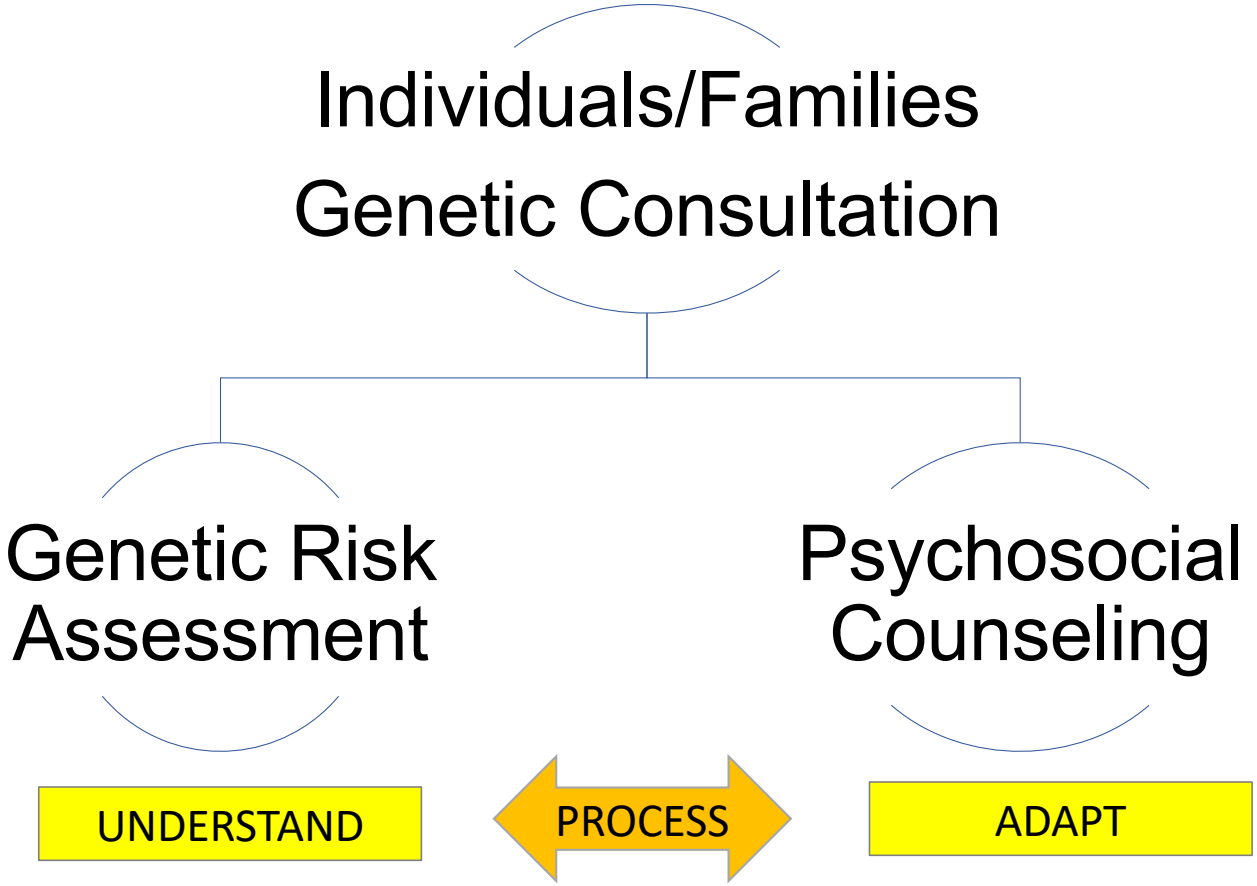
Services offered

- Hematologic malignancy cancer risk assessment & genetic testing
- Hematopoietic stem cell transplantation planning
- Surveillance care
- Family counseling, cascade genetic testing, referral to reproductive medicine services

Genetic counseling

- Genetic counselors specialize in providing education and emotional support to patients about inherited conditions

Goal: provide information that helps patients make the right decisions for themselves and their families & to provide longitudinal support and education.

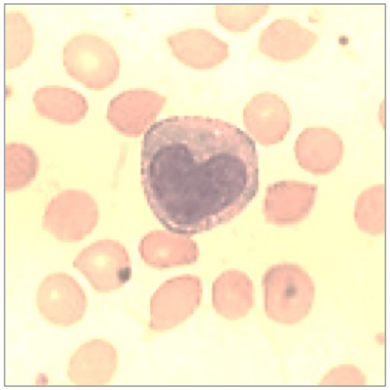

Individuals/Families
Genetic Consultation
Genetic Risk Assessment
Psychosocial Counseling
UNDERSTAND
PROCESS
ADAPT

Challenges – we are still learning

- Interpreting genetic sequencing results – is a mutation disease-causing or not?
- What are the optimal treatment and surveillance strategies for patients/families?

Concluding thoughts

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




Questions?