Hereditary Colorectal Cancer & Models of Genetic Counseling and Testing

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THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

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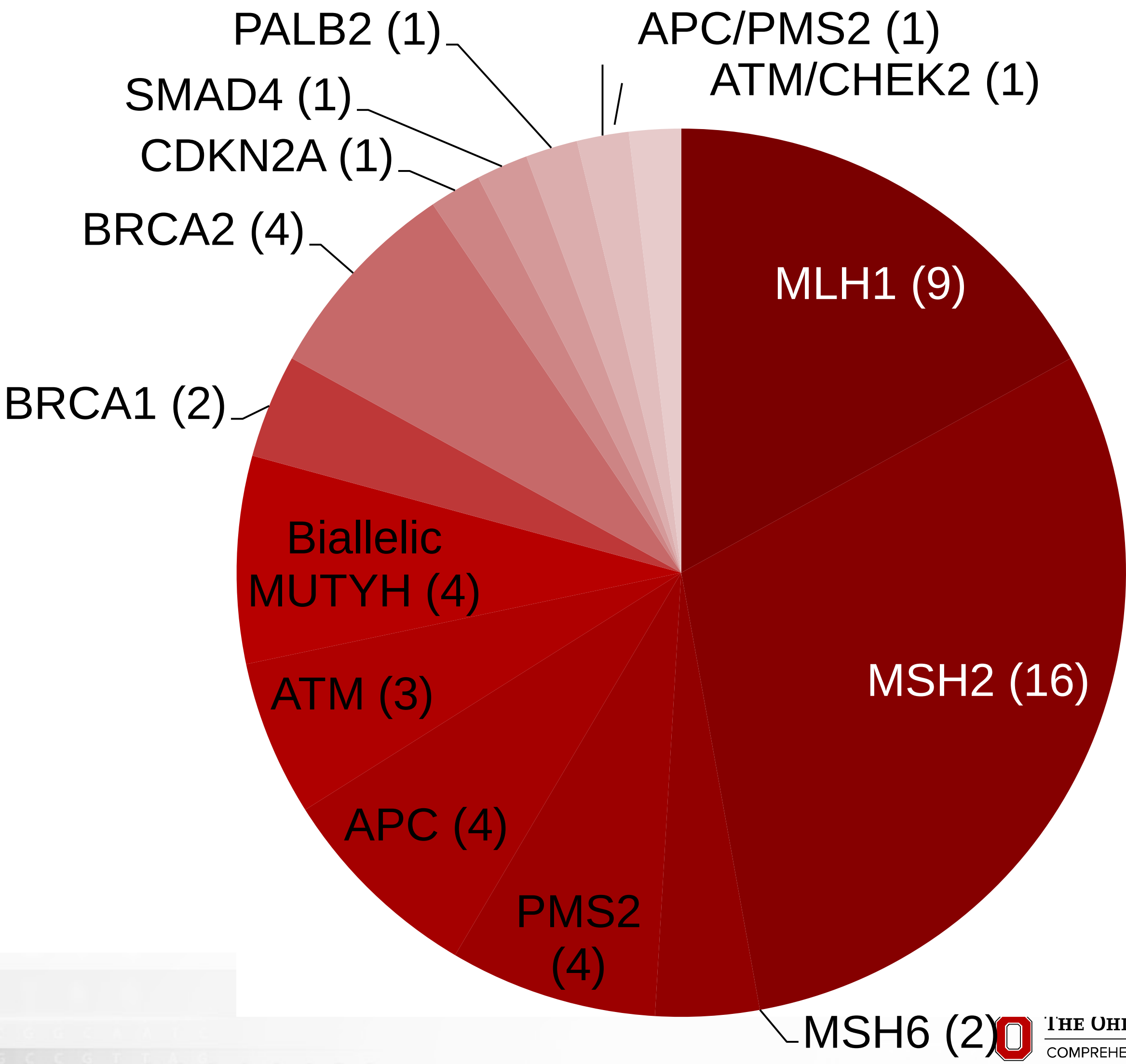
Panel Results: 1,058 Colorectal Cancer Patients

- 9.9% had a pathogenic mutation in one of 25 cancer genes
- 3.1% had Lynch syndrome
- 7% had non-Lynch syndrome gene mutations including:
    - 2.2% had mutations high-penetrance genes (5 *APC*, 3 biallelic *MUTYH*, 11 *BRCA1/2*, 2 *PALB2*, 1 *CDKN2A* and 1 *TP53*)
    - 3.6% had mutations in moderate-penetrance CRC risk genes (19 *MUTYH* heterozygotes, 17 *APC* I1307K, and 2 *CHEK2*)
- Age at dx, family history of CRC, nor personal history of other cancers significantly predicted the presence of mutations in non-Lynch syndrome genes

Yurgelun M, et al. J Clin Oncol. 2017;35:1086-95.

Panel Results: 450 Colorectal Cancer Patients (dx <50)

- 16% had a pathogenic variant in at least one cancer gene
- 8.7% have Lynch syndrome
- 8% have a mutation in another cancer susceptibility gene
- NCCN recommends all CRC patients dx <50 have a cancer genetic evaluation



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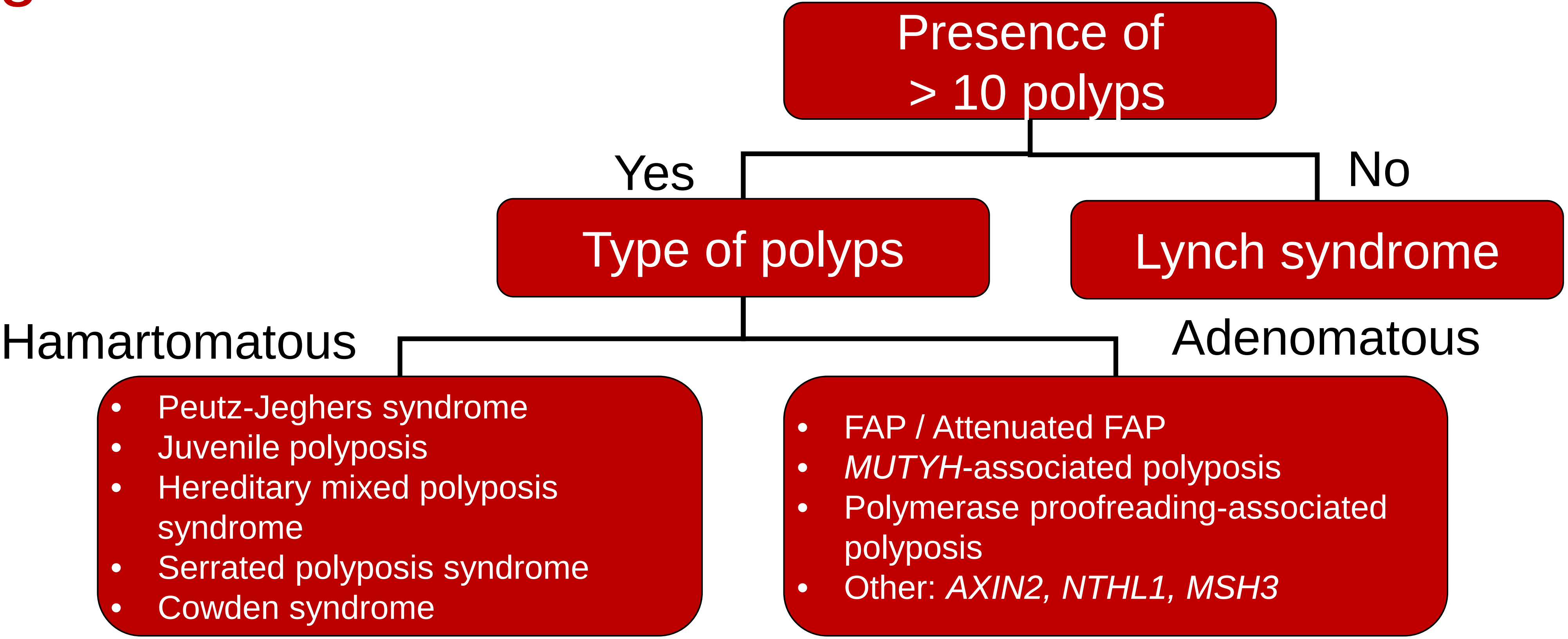
Pearlman R, et al. JAMA Oncology. 2017;3(4):464-71.

Flowchart for Hereditary Colon Cancer Differential Diagnosis



Presence of > 10 polyps

Yes

Type of polyps

Hamartomatous

- Peutz-Jeghers syndrome
- Juvenile polyposis
- Hereditary mixed polyposis syndrome
- Serrated polyposis syndrome
- Cowden syndrome

Adenomatous

- FAP / Attenuated FAP
- *MUTYH*-associated polyposis
- Polymerase proofreading-associated polyposis
- Other: *AXIN2, NTHL1, MSH3*

No

Lynch syndrome

- FAP = Familial Adenomatous Polyposis.

Lynch Syndrome

- Over 1.2 million individuals in the United States have Lynch syndrome
- Inherited condition that causes high risks for colorectal cancer, endometrial cancer, and other cancers
- Preventable cancers with early and more frequent screening
- 95% of affected individuals do not know they have Lynch syndrome

Lynch Syndrome Cancer Risks (to 70)

Cancer Type	MLH1 and MSH2	MSH6	PMS2	General Public
Colon cancer (men)	40%-80%	10%-22%	15%-20%	5.5%
Endometrial cancer	25%-60%	16%-26%	15%	2.7%
Stomach	1%-13%	≤ 3%	< 6%	< 1%
Ovarian	4%-24%	1%-11%	< 6%	1.6 %

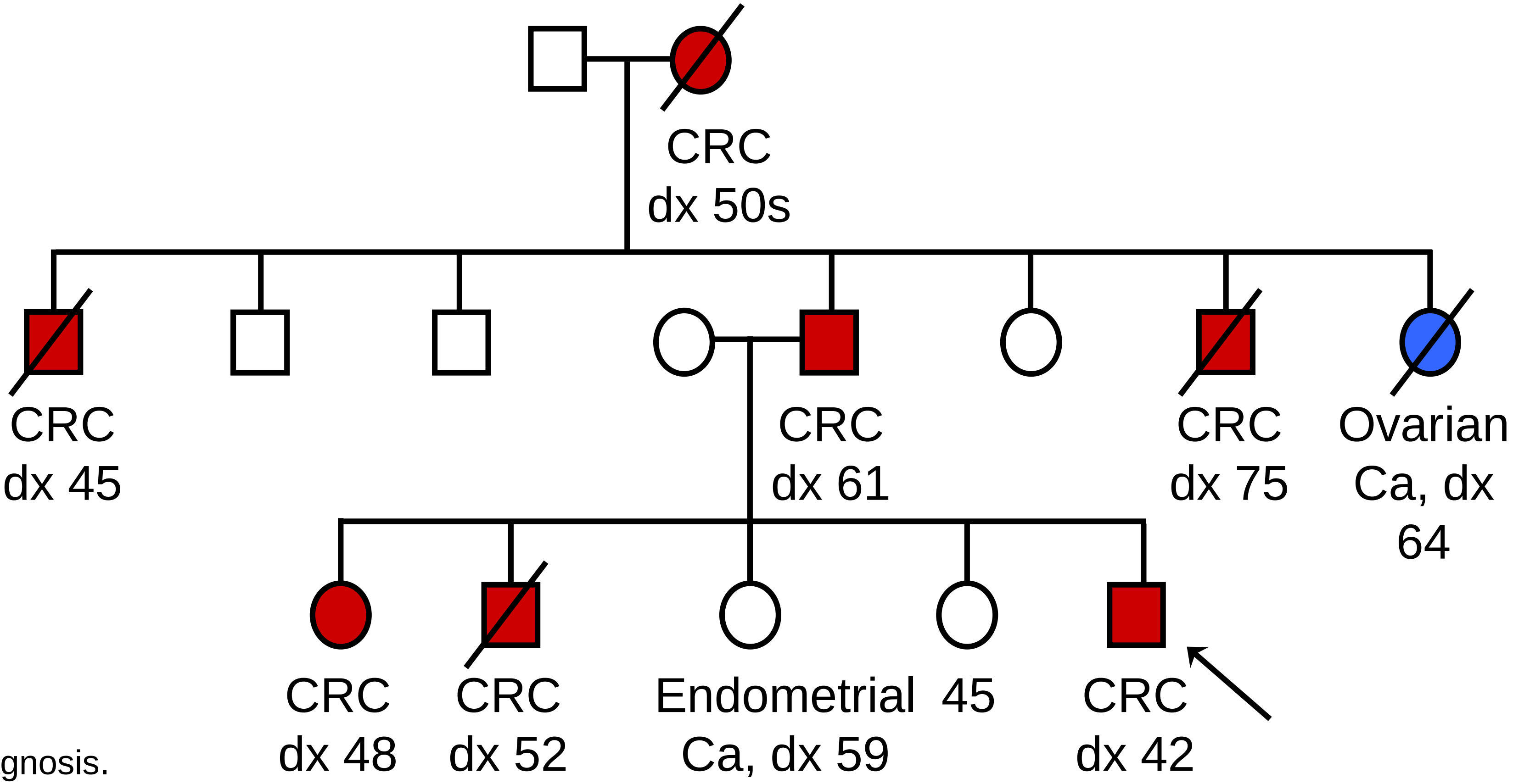
National Comprehensive Cancer Network Guidelines for Colorectal Cancer Screening and Prevention v2.2017; Bonadona V, et al. *JAMA* 2011;305:2304-10; Senter L, et al. *Gastroenterology* 2008;135:419-48.

Lynch Syndrome Surveillance Options

Intervention	Recommendation
Colonoscopy	Every 1-2 y beginning at age 20-25
Endometrial sampling	Every 1-2 y beginning at age 30-35
TAH-BSO	After childbearing
*EGD with visualization of the duodenum	Every 3-5 y beginning at age 40
*Urinalysis with cytology	Every 1 y beginning at age 30-35
Physical/neurologic examination	Every 1 y beginning at age 25-30

NCCN Guidelines for Colorectal Cancer Screening and Prevention v1.2019

Family History Is Key to Diagnosing Lynch Syndrome…or Is It?



- Ca = cancer; dx = diagnosis.

Family History Criteria

Amsterdam Criteria

- Three or more relatives with verified HNPCC-associated cancer in family
- Two or more generations
- One case a first-degree relative of the other two
- One CRC diagnosis < 50
- FAP excluded
- Does not include ovarian, gastric, brain, biliary tract, or pancreatic cancer

Revised Bethesda Criteria

- CRC diagnosis < 50
- Synchronous or metachronous CRC, or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology diagnosis < 60
- CRC with ≥ 1 FDR with an HNPCC-associated tumor, with one cancer diagnosis < 50
- CRC with ≥ 2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age

PREMM$_5$

- Probability of Lynch syndrome gene mutation
- Proband
  - Number of CRCs and youngest age at diagnosis
  - Y/N adenomas and youngest age at diagnosis
  - Y/N EC and youngest age at diagnosis
- FDRs and SDRs
  - Number with CRC and youngest age at diagnosis
  - Number with EC and youngest age at diagnosis
  - Y/N any with another HNPCC cancer
- Balmana et al. says refer anyone with > 2.5% mutation likelihood; NCCN still says > 5%

Warning: Family Histories Can Be Deceiving

- Family size is getting smaller
- Wider use of colonoscopy likely to prevent many colon cancers
- *MSH6* and *PMS2* have lower cancer risks

Tumor Tests to Screen for Lynch Syndrome

- MSI testing
  - Performed on DNA extracted from tumor and normal tissue; requires laboratory
  - Test is positive in 15% of CRC cases
  - Test is positive in 77%-89% of LS cases
- IHC staining
  - Performed on thin slide of tumor; can be done in pathology department
  - 1-2 proteins are absent in 15%-20% of CRC cases
  - 1-2 proteins are absent in 83% of LS cases
- Methylation testing/*BRAF* V600E testing
  - Tumors MSI positive and/or absent *MLH1* and *PMS2* on IHC will be studied for methylation
  - 80% will have acquired methylation (sporadic colon cancer)
  - 20% will have Lynch syndrome
  - 69% of methylated CRCs have the *BRAF* V600E mutation; this is an easier test, so many hospitals do *BRAF* testing when *MLH1* and *PMS2* are absent on IHC

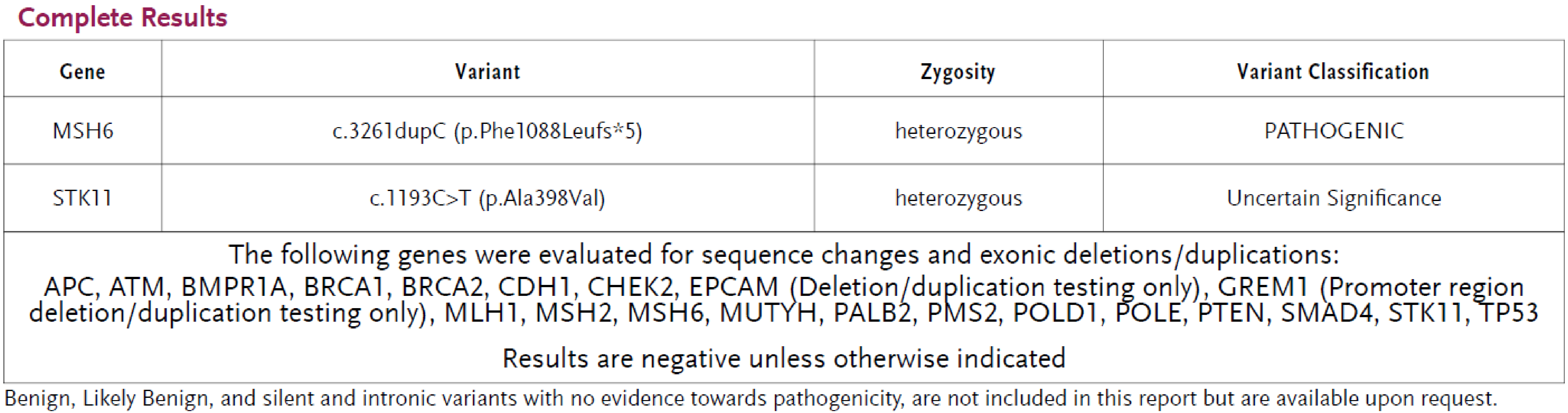
- IHC = immunohistochemistry; LS = Lynch syndrome; MSI = microsatellite instability.

Microsatellite instability in any tumor is predictive of Lynch syndrome

- MSKCC IMPACT study
- 15,045 tumors spanning >50 cancer types
  - 2.2% were MSI-High
    - Small bowel (25%)
    - Endometrial (16%)
    - Colorectal (14%)
- Germline mutations in the MMR genes were found in:
  - 16.3% of MSI-High cancers (53/326);
    - 50% had tumors less commonly or not previously associated with LS
    - 36.4% of the LS patients did not meet testing criteria for LS

Schwark, AL et al. ASCO 2018. https://meetinglibrary.asco.org/record/160759/abstract

Case Example



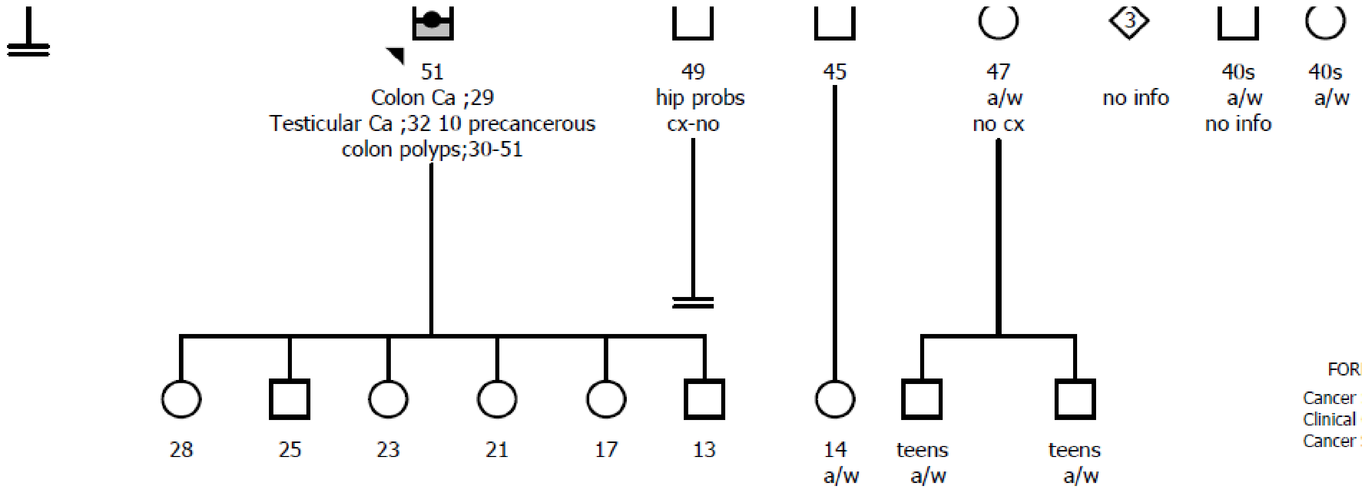
Complete Results

Gene	Variant	Zygosity	Variant Classification
MSH6	c.3261dupC (p.Phe1088Leufs*5)	heterozygous	PATHOGENIC
STK11	c.1193C>T (p.Ala398Val)	heterozygous	Uncertain Significance

The following genes were evaluated for sequence changes and exonic deletions/duplications:
APC, ATM, BMPR1A, BRCA1, BRCA2, CDH1, CHEK2, EPCAM (Deletion/duplication testing only), GREM1 (Promoter region deletion/duplication testing only), MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53

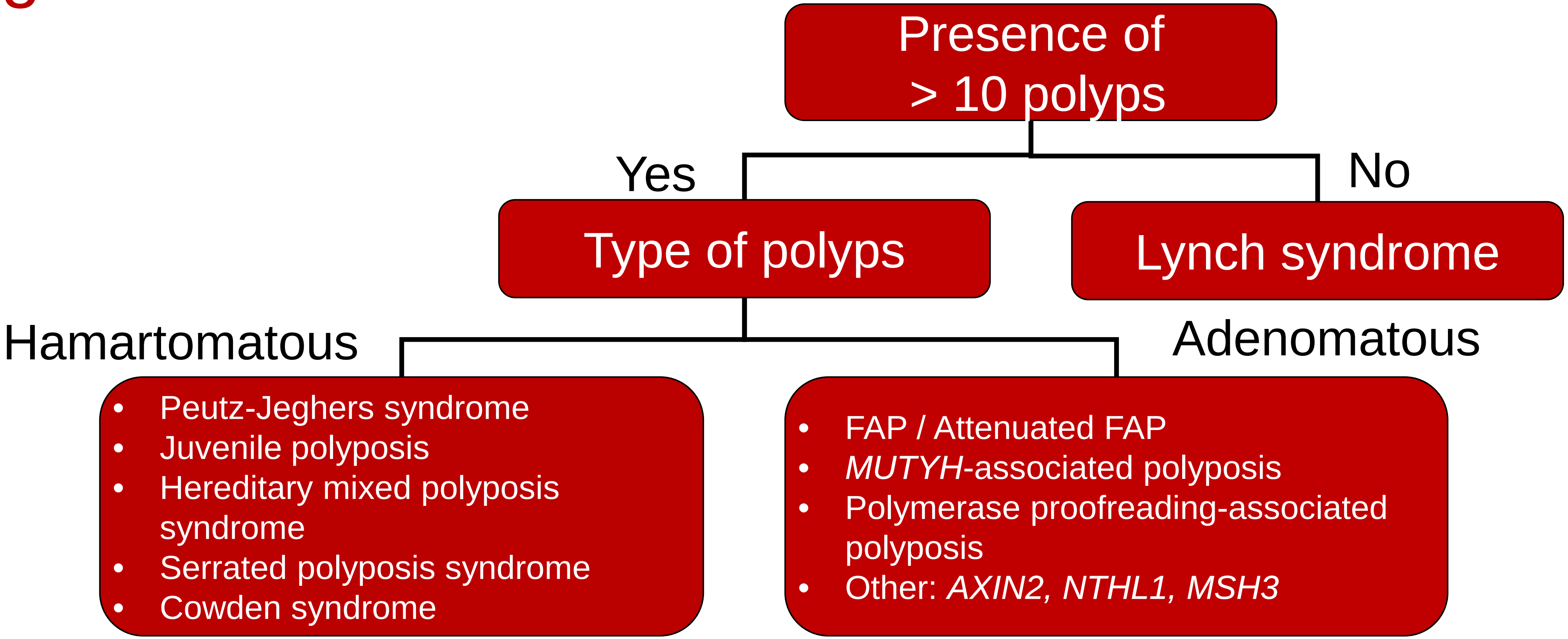
Results are negative unless otherwise indicated

Benign, Likely Benign, and silent and intronic variants with no evidence towards pathogenicity, are not included in this report but are available upon request.



FORMATS
Cancer Subtext 10/2
Clinical Cancer
Cancer SS 10/2016

Flowchart for Hereditary Colon Cancer Differential Diagnosis



Presence of > 10 polyps

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No

Type of polyps

Lynch syndrome

Hamartomatous

Adenomatous

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- FAP = Familial Adenomatous Polyposis.

Adenomatous Polyposis Syndromes – Autosomal Dominant

- Familial Adenomatous Polyposis
  - > 100 adenomatous polyps throughout colon
  - Increased risks for colorectal, duodenal, thyroid cancers, medulloblastoma, and hepatoblastoma
  - Gene: *APC* (30% of mutations are de novo)

- Attenuated Familial Adenomatous Polyposis
  - 20-100 adenomas
  - Gene: *APC* (mutations in specific locations lead to milder phenotype)

- Polymerase proofreading-associated polyposis
  - Increased risk of adenomatous colon polyps, colon cancer, uterine cancer, and possibly other cancers
  - Newer syndrome, still being defined
  - Genes: *POLD1, POLE*

- *AXIN2*
  - 20-100 adenomas
  - Oligodontia - > 6 missing adult teeth
  - Sparse hair, thin fingernails
  - Gene: *AXIN2*

- AFAP = attenuated FAP; MAP = MUTYH-associated polyposis.

Adenomatous Polyposis Syndromes – Autosomal Recessive

- MUTYH-Associated Polyposis (MAP)
  - 20-100s of adenomatous polyps
  - Overlap with FAP and Lynch syndrome
  - Gene: *MUTYH* (recessive with 1/50 carrier frequency)
- *MSH3*
  - 20-100 of adenomatous polyps
  - Weak mismatch repair gene
  - Gene: *MSH3* (recessive)
- *NTHL1*
  - 20-100 adenomas
  - Multi-tumor cancer syndrome
  - Increased risk of breast, brain, hematologic, endometrial, urothelial, HAN SCCs, cervical and basal cell carcinomas
  - Specific tumor signature (30) due to C>T transitions
  - Gene: *NTHL1* (recessive)

Hamartomatous Polyposis Syndromes

- Peutz-Jeghers syndrome
  - Peutz-Jeghers polyps primarily in the small intestine but can be throughout GI tract
  - Increased risk for GI cancers and multiple other cancers (breast, SCTAT of the ovaries and testicles, pancreatic)
  - Gene: *STK11*
- Juvenile polyposis syndrome
  - Juvenile polyps throughout GI tract, increased risk for GI cancers
  - > 5 JP is diagnostic criteria
  - Genes: *BMPR1A, SMAD4*
- Serrated polyposis syndrome
  - > 20 serrated/hyperplastic polyps throughout the colon
  - Increased risk for colon cancer
  - Gene: *RNF43* rarely, ?*MUTYH*

- GI = gastrointestinal; JP = juvenile polyposis; SCTAT = sex cord tumor with annular tubules.

Mixed Polyposis Syndromes

- Hereditary mixed polyposis syndrome
  - Syndrome mostly seen in individuals of Ashkenazi Jewish ancestry
  - Adenomatous, hyperplastic, other type of polyps through GI tract
  - Gene: *SCG5/GREM1*

- Cowden syndrome
  - Multiple different types of polyps – ganglioneuromas especially suspicious
  - Increased risk for breast, thyroid, endometrial, and colon cancers
  - Gene: *PTEN*

Who to Test for Lynch Syndrome (the Right Person)?

- Clinical testing criteria
  - Patients who meet Revised Bethesda criteria or Amsterdam II criteria
  - Patients with endometrial cancer diagnosis < 50
  - Individuals with MMR mutation likelihood > 2.5%-5% on PREMM_5 model
  - Individuals with known diagnosis of LS in family
- Routine tumor testing criteria
  - All CRC patients, **OR**
  - CRC patients diagnosed < 70 and CRC patients diagnosed $\geq$ 70 who meet Revised Bethesda guidelines
  - All EC patients, **OR**
  - EC patients diagnosed < 60; **OR** EC patients who meet Modified Bethesda guidelines

- MMR = mismatched repair.

Who to Test for Polyposis (the Right Person)?

- Adenomatous polyposis syndromes
  - Personal history of > 10 adenomas
  - Personal history of a desmoid tumor, CHRPE, hepatoblastoma
  - Known *APC/MUTYH/POLE/POLD1* mutation in family
- Hamartomatous polyposis syndromes
  - Two Peutz-Jeghers polyps
  - Five juvenile polyps
  - Ashkenazi Jewish or macrocephaly plus multiple mixed polyps
- Start testing with affected relative if possible
- If affected relative is deceased, can test at-risk relative but negative result is uninformative
- Can test minors for polyposis syndromes because cancer screening starts in childhood

- CHRPE = congenital hypertrophy of the retinal pigment epithelium.

What Test Should Be Ordered (the Right Test)?

- Tumor screening tests cost ~$500 each
  - Check pathology reports because this may have already been performed
- Next-generation testing panels now available
  - Include many genes
    - Colon specific gene panels (14-25 genes)
    - Common hereditary gene panels (27-42+ genes)
  - Lower cost due to new technology ($250)
- Due to overlap in polyposis syndromes and Lynch syndrome and the need to test more than one gene, this is the best approach to colorectal cancer genetic testing

Traditional Model for Cancer Genetics Services

- Referring to in house Cancer Genetics
- Partnership/Referral to local Cancer Genetics programs
  - Most large academic centers will provide services in person or via telemedicine to affiliates/other community cancer centers
  - Generally still need an onsite person to coordinate the referrals and the visits
  - Billing can be a challenge – will likely bill the hospital and then the hospital can try to recover some of the costs by billing the patient if they have an NP/billable provider as the program coordinator

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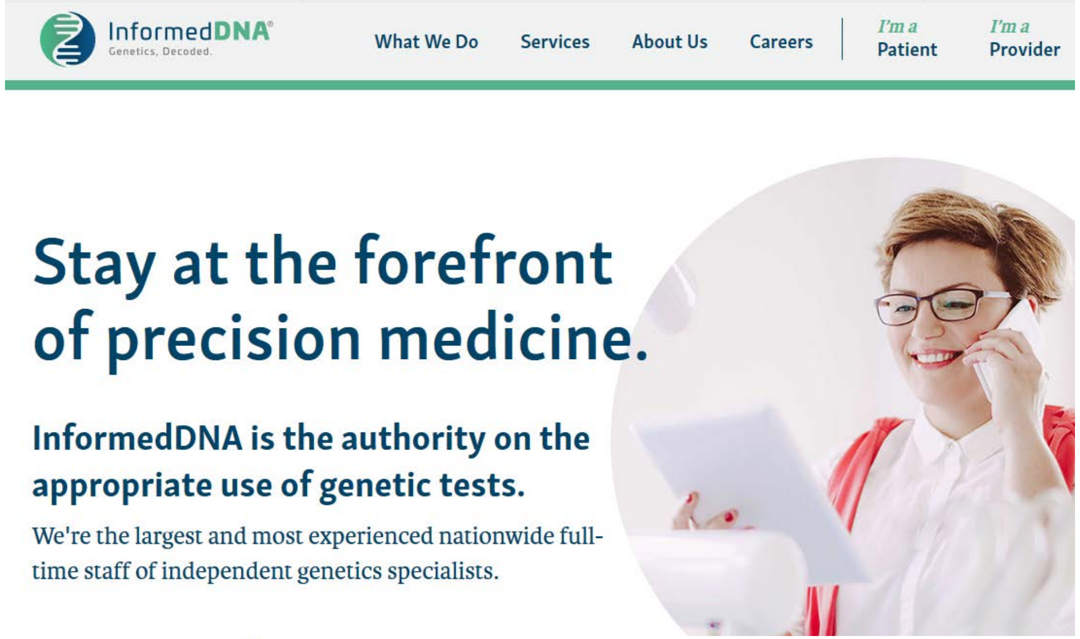
Traditional Model for Cancer Genetics Services

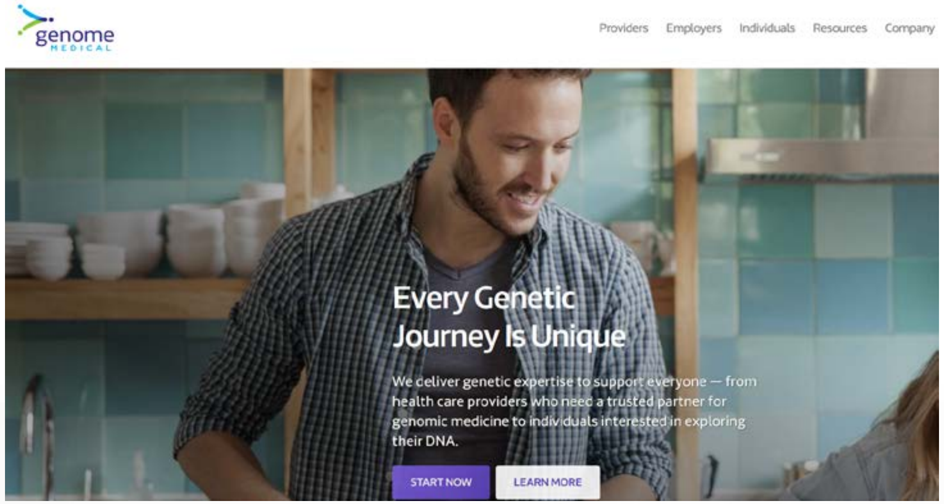
- Partnership/Referral to tele-genetic counseling companies
  - Informed DNA: www.informeddna.com
  - Genome Medical: www.genomemedical.com
  - Advanced Tele-Genetic Counseling: www.at-gc.com
  - Many others
  - Companies will either bill patients directly or the hospital



Stay at the forefront of precision medicine.

InformedDNA is the authority on the appropriate use of genetic tests.

We're the largest and most experienced nationwide full-time staff of independent genetics specialists.



Every Genetic Journey Is Unique

We deliver genetic expertise to support everyone — from health care providers who need a trusted partner for genomic medicine to individuals interested in exploring their DNA.

Newer Models for Cancer Genetics Services

- Mainstreaming
  - Great for cancers where all patients need genetic testing
    - Pancreatic cancers
    - Metastatic Prostate cancers
    - Ovarian cancers
  - Oncology obtains informed consent
    - Use of pre-test counseling video common
  - Oncology orders genetic test
    - Results copied to Genetics
  - Genetics provides full post-test counseling to mutation positive patients only

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A CANCER-FREE WORLD BEGINS HERE

Hereditary Hematologic Malignancies

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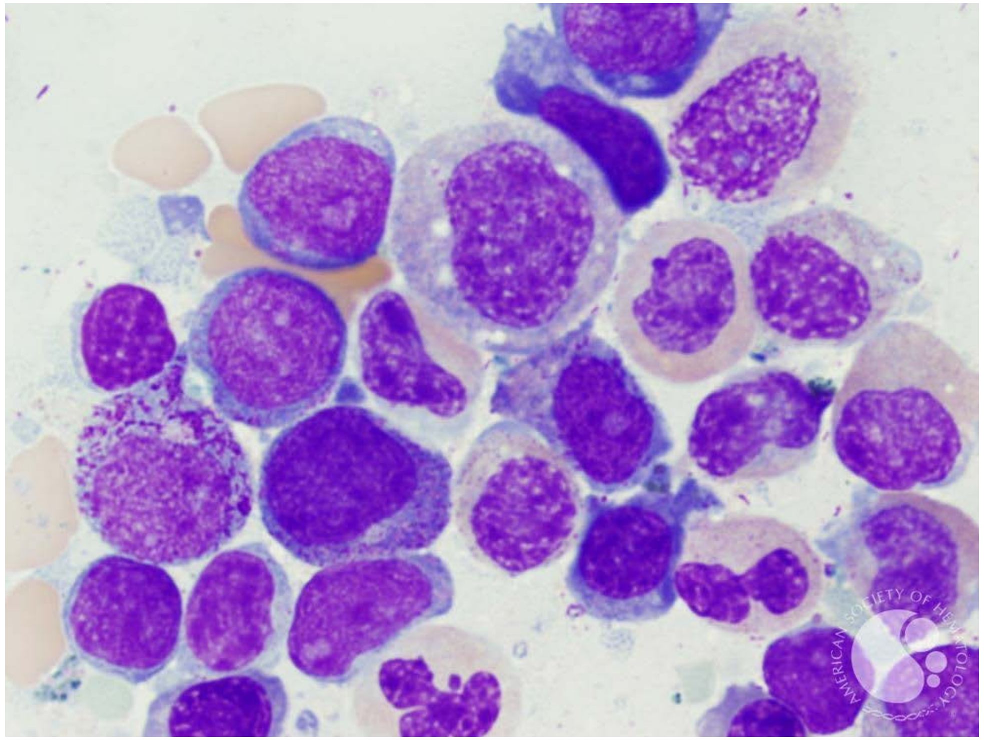
Joanne Jeter, MD, MS

November 13, 2019

Case – Initial Presentation

- 34 year-old man presented with multiple infections, influenza
- CBC:
  - Hgb 5.8, plt 6K
  - 2% circulating blasts
- Bone marrow biopsy:
  - Trilinage dysplasia
  - 90% cellularity
  - 13% blasts
- Diagnosed with very high-risk MDS-EB1
- Workup initiated for stem cell transplant



ASH Image Bank

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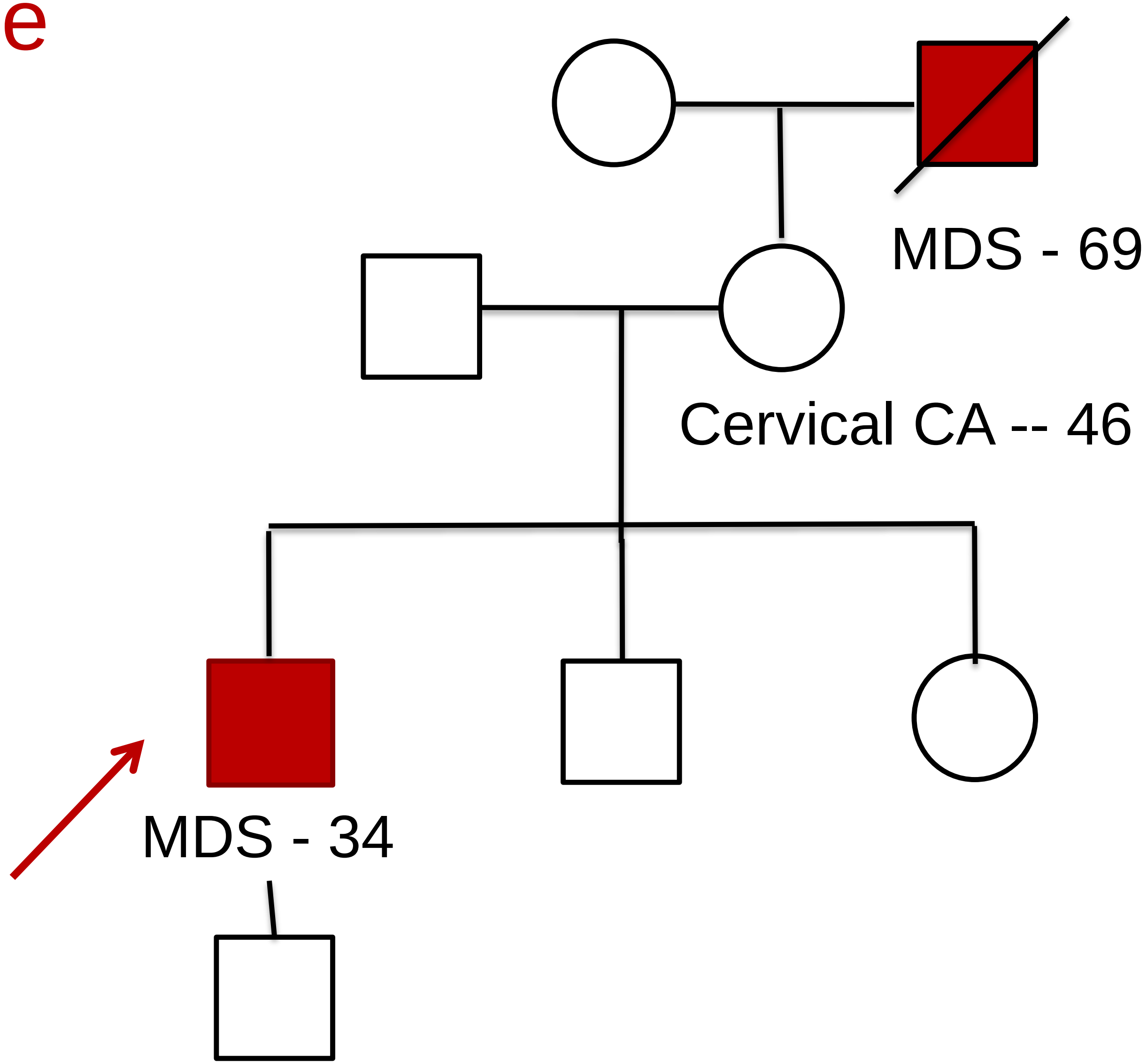
Case -- Additional History

- Construction worker
- “Skin cancer” on back of his hand, s/p surgical resection
- Additional skin lesions on back of hand
- History of multiple dental caries

Pedigree


MDS - 69

Cervical CA -- 46

MDS - 34

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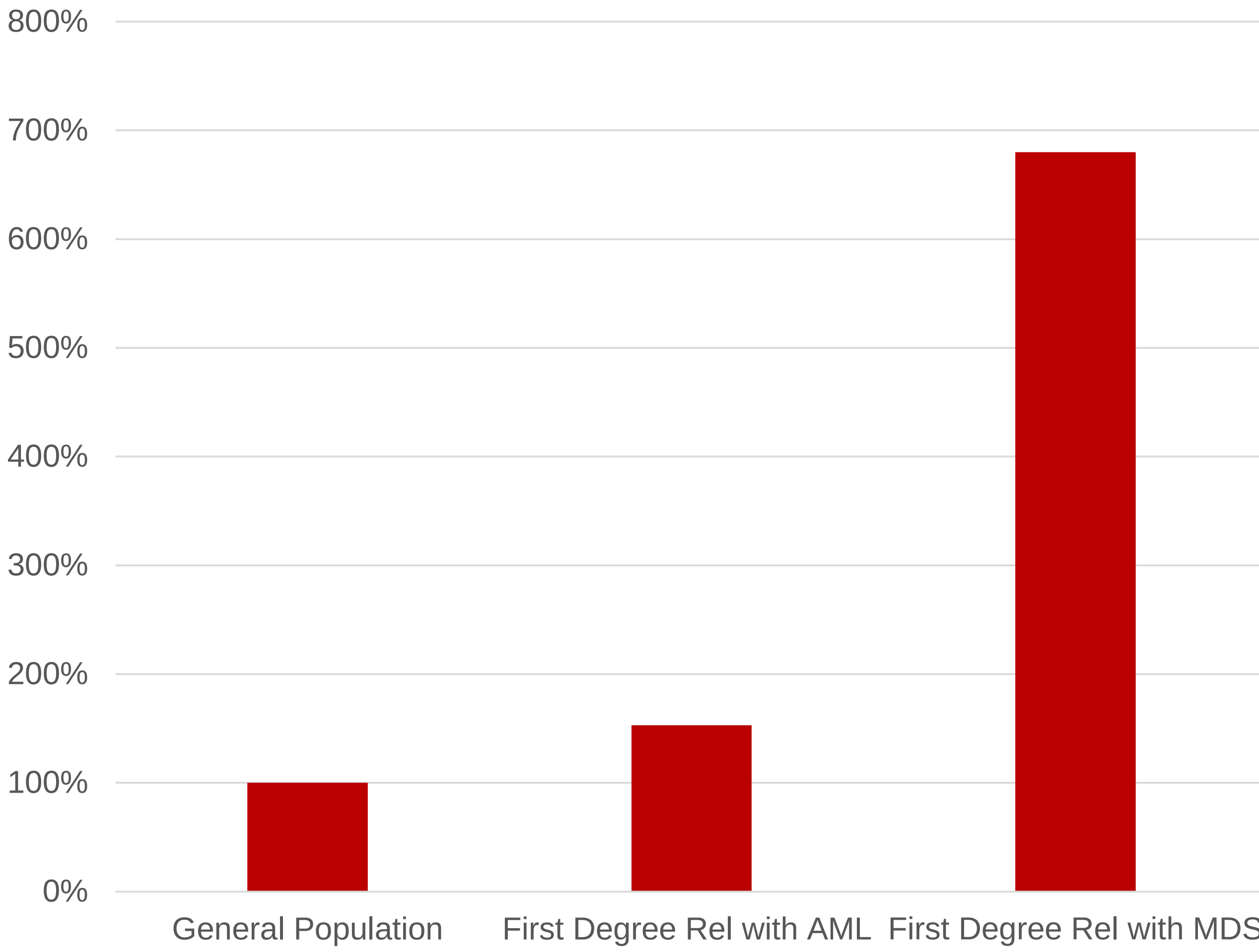
AML/MDS

- General population incidence: 5/100,000
- Associated with
  - Li Fraumeni syndrome (*TP53*)
  - Constitutional mismatch repair syndrome (MMR genes)



Sud et al, Blood 2018

Li Fraumeni Syndrome

- Germline mutation in TP53
- Characterized by childhood cancers, sarcoma, adrenocortical cancers
- Autosomal dominant inheritance
- Affected individuals have extensive monitoring regimen
  - Full body MRI
  - Breast MRI
  - Brain MRI
- Beware of CHIP!

Clonal Hematopoesis of Indeterminate Potential

- Defined as:
  - VAF ≥2% of acquired mutation in leukemia-associated gene, found in myeloid cells
  - Normal peripheral blood counts
  - No clinical or pathological evidence of heme malignancy
- Common genes:
  - DNMT3A, TET2, ASXL1, JAK2, TP53
  - At least 16 additional genes can be involved less frequently
- Increased all-cause mortality (HR 1.4)
- Transition to AML is 0.5%-1%/ year

Constitutional Mismatch Repair Deficiency Syndrome

- Biallelic mutations in mismatch repair genes
- Autosomal recessive inheritance
  - Carriers – Lynch syndrome
- Increased predisposition to colon cancers, brain tumors, leukemia, lymphoma
- Microsatellite instability of tumors
- Responses of glioblastomas to PD-1 inhibition

AML/MDS

- No pre-existing disorder/organ dysfunction
  1) AML with CEBPA
  2) Myeloid neoplasm with DDX41*
- Pre-existing platelet disorder
  1) Myeloid neoplasm with RUNX1*
  2) Myeloid neoplasm with ANKRD26*
  3) Myeloid neoplasm with ETV6*

AML/MDS

- Associated with other organ dysfunction
  1) Myeloid neoplasm with GATA2
  2) Myeloid neoplasm with marrow failure syndrome
  3) Myeloid neoplasm with telomere disorder
  4) Juvenile myelomonocytic leukemia / neurofibromatosis or Noonan syndrome
  5) Myeloid neoplasm with Down syndrome

Bone Marrow Failure Syndromes

- Fanconi Anemia (>18 genes)
- Schwachman-Diamond (*SBDS*)
- Diamond- Blackfan (*GATA1*, 11 others)
- *GATA2* deficiency

Fanconi Anemia

- Most common inherited cause of bone marrow failure.
- Usually AR inheritance
- 11-34% have MDS and 10-37% have AML by age 50.
- Assoc with café au lait spots, short stature, radial ray abnormalities, microcephaly, microophthalmia, renal abnormalities, hypogonadism.
- Hypersensitivity to crosslinking agents
  - Need alternative pretransplant conditioning regimens

Fanconi Anemia Genes

Gene	Incidence	Inheritance
FANCA	70%	AR
FANCB	Rare	XLR
FANCC	10%	AR
FANCD1 (BRCA2)	Rare	AR
FANCD2	Rare	AR
FANCE	10%	AR
FANCF	Rare	AR
FANCG (XRCC9)	10%	AR

Gene	Incidence	Inheritance
FANCJ (BRIP1)	Rare	AR
FANCL	Rare	XAR
FANCM	Rare	AR
FANCN (PALB2)	Rare	AR
FANCO (RAD51C)	Rare	AR
FANCP	Rare	AR
FANCFO	Rare	AR

Schwachman-Diamond Syndrome

- Prevalence 1 in 77,000 – 168,000
- Associated with bone marrow failure, exocrine pancreatic insufficiency, skeletal changes, immunodeficiency, hepatic abnormalities, dental dysplasia, low IQ.
- 90% have biallelic mutations in *SBDS*.
- 20% have severe aplastic anemia at median age 3.
- Particularly associated with AML-M6 (erythroid).

Diamond-Blackfan Syndrome

- 1:100,000 -1:200,000 live births
- Autosomal dominant inheritance
- Children under the age of 1
- Macrocytic anemia without other significant cytopenias
- Low reticulocytes
- Craniofacial, upper-limb, heart, and genitourinary malformations in 50%
- Also has an increased risk of sarcoma

Telomere Disorders – Dyskeratosis Congenita

- Classic triad:
  - dystrophic nails
  - skin rashes
  - leukoplakia
- *RTEL1, TERT, TERC, DKC1, TINF2*
- - Androgens used to improve peripheral blood counts

Townsley et al, NEJM, 2016

AML/Down Syndrome

- 5-30% DS patients born with transient leukemia of DS
- Can be fatal in 15-23%
- Survivors at increased risk of AML by age 4
- Also has increased susceptibility to ALL
- Preclinical data on aurora kinase inhibitors (alisertib) as potential therapeutic target

Case – Genetic Testing

- Bone marrow failure panel ordered on peripheral blood
  - Heterozygous for pathogenic variant (truncating mutation) in *RTEL1*
  - *Is this a somatic variant or a germline variant?*
- Telomere studies ordered
  - Very low telomere length
  - Confirms diagnosis of Dyskeratosis Congenita

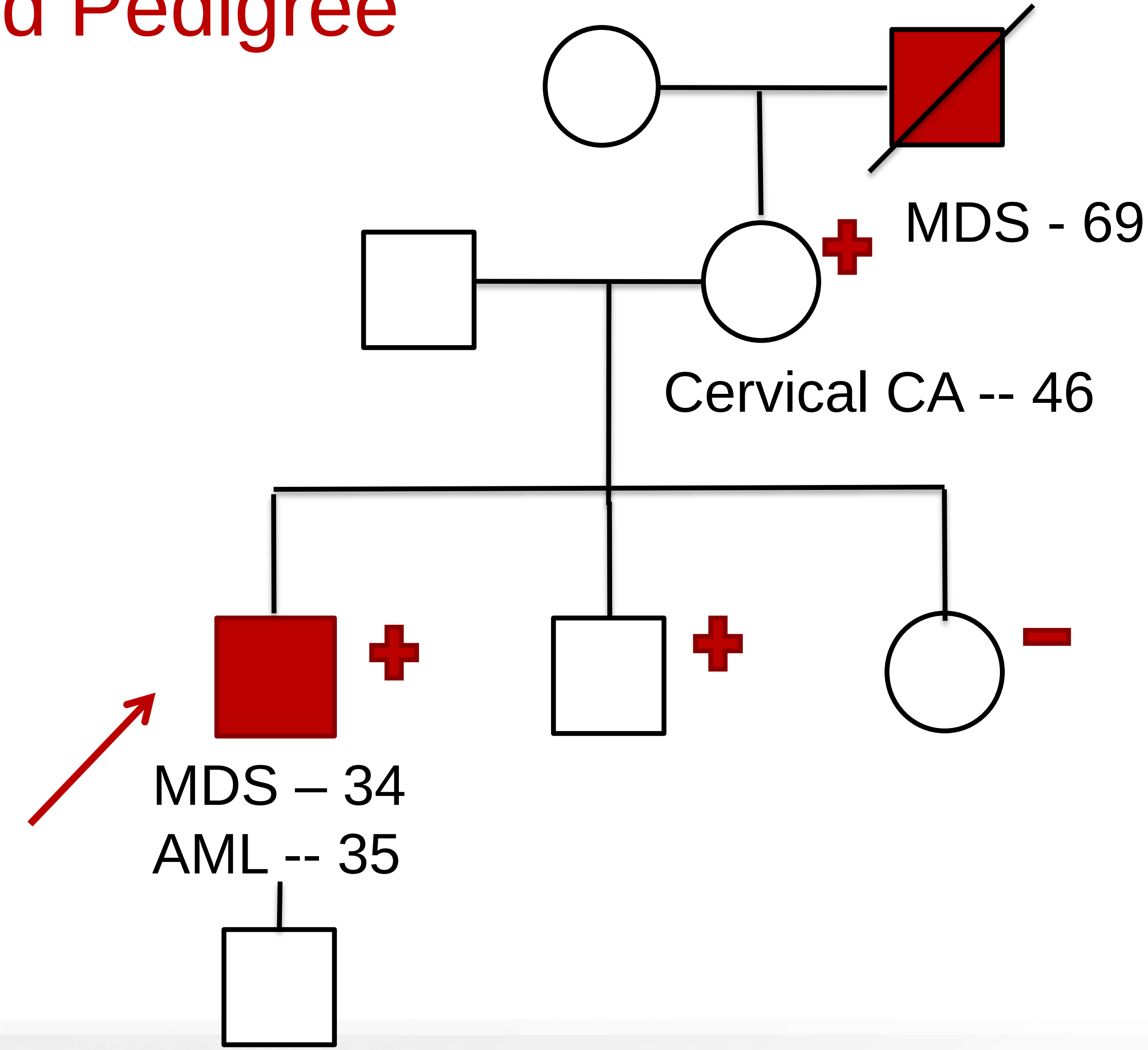
Case – Testing of Family Members

- *RTEL1* mutations can have different inheritance patterns
    - Affected patient heterozygous for mutation – Autosomal dominant
    - Children, siblings have 50% chance of carrying mutation
- STAT testing initiated for siblings for stem cell donor assessment
- Testing also performed on mother
- Recommend testing in childhood; patient deferred for his children at this time

Case – Outcome

- Mother tested and positive for *RTEL1* variant
  - Declined referral for surveillance
- Sister negative for *RTEL1* variant
  - Underwent workup for potential stem cell donation
- Brother positive for *RTEL1* variant
  - Declined referral for surveillance at this time
- Patient’s MDS transformed to AML
  - Plan to treat with chemotherapy and transplant in first remission

Updated Pedigree



Recommended Surveillance for Dyskeratosis Congenita

- Annual dermatology evaluation
- Baseline evaluation by ophthalmology
- Dental evaluation every 6 months
- Annual evaluation by otolaryngology
- Annual pulmonary function testing
- Annual gynecologic evaluation
- Consider annual urologic evaluation for males
- Consider annual CBC
- Encourage smoking cessation

ALL

- General population incidence 3.4/100,000 children
- Rarely familial
- Associated with:
    - Down syndrome
    - Neurofibromatosis type 1 (*NF1*)
    - Bloom syndrome (*BLM*)
    - Ataxia-telangiectasia (*ATM*)
    - *PAX5* mutations
    - *ETV6* mutations
    - Li Fraumeni syndrome (*TP53*)

When to Refer

- Leukemia diagnosed prior to age 18 if
  - Café au lait spots, hypopigmented spots, evidence of NF1,
  - Consanguinous parents,
  - Family history of Lynch syndrome cancers,
  - Second primary cancer, OR
  - Sibling with childhood cancer
- Leukemia plus
  - Another Li Fraumeni cancer in the same person, OR
  - Li Fraumeni cancer in 2 close relatives, one before age 46

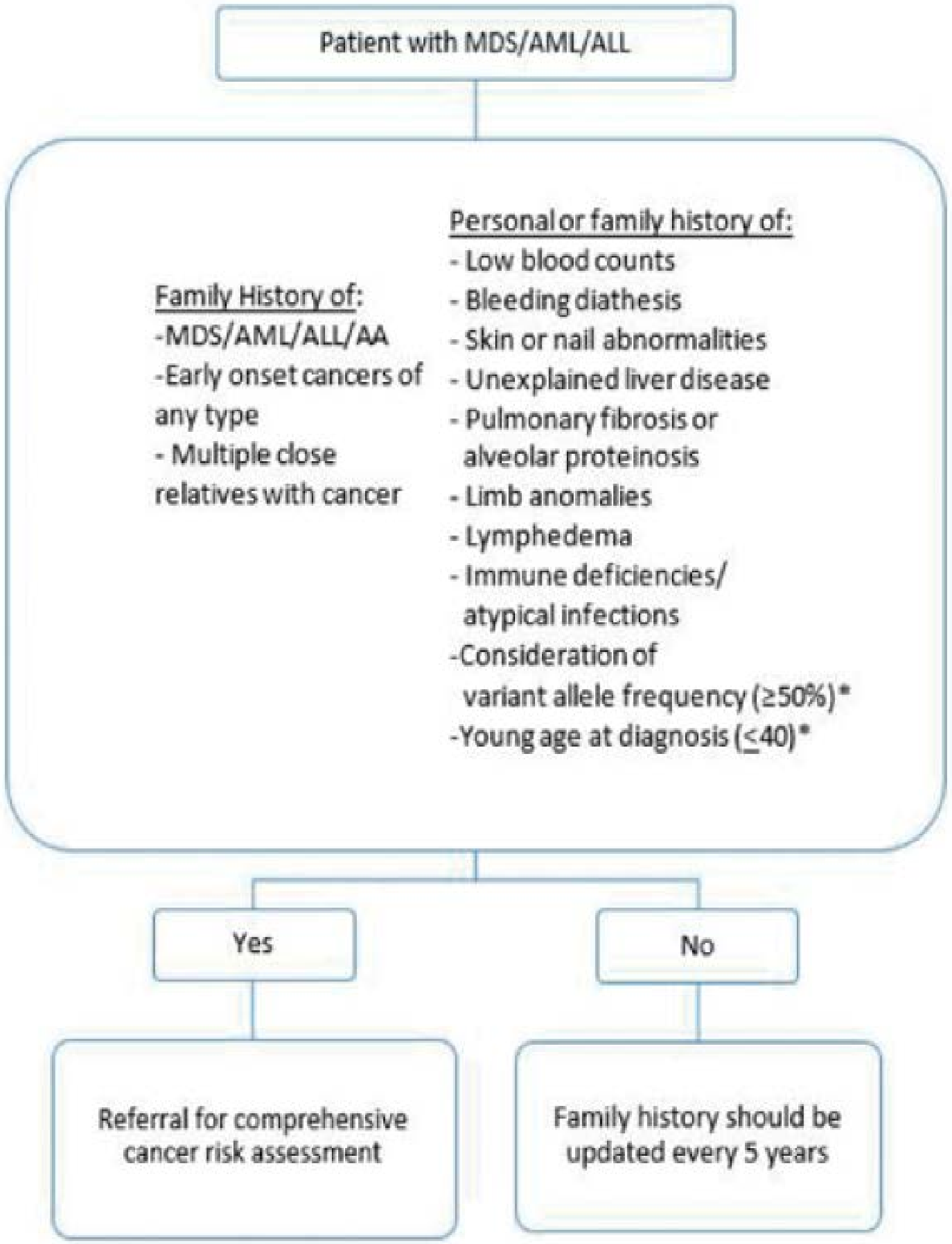
Hampel et al, Genetics in Medicine, 2015

When to Refer

- Bone marrow failure / MDS before age 51
- Strong personal/family history of malignancy
- Mutations in *CEBPA, GATA2, RUNX1*, etc on NGS panels for prognostication

DiNardo et al. Clin Lymph Myel Leuk 2016

Algorithm for MDS/Leukemia Referral



Patient with MDS/AML/ALL

Family History of:
-MDS/AML/ALL/AA
-Early onset cancers of any type
- Multiple close relatives with cancer

Personal or family history of:
- Low blood counts
- Bleeding diathesis
- Skin or nail abnormalities
- Unexplained liver disease
- Pulmonary fibrosis or alveolar proteinosis
- Limb anomalies
- Lymphedema
- Immune deficiencies/ atypical infections
-Consideration of variant allele frequency (≥50%)*
-Young age at diagnosis (≤40)*

Yes → Referral for comprehensive cancer risk assessment

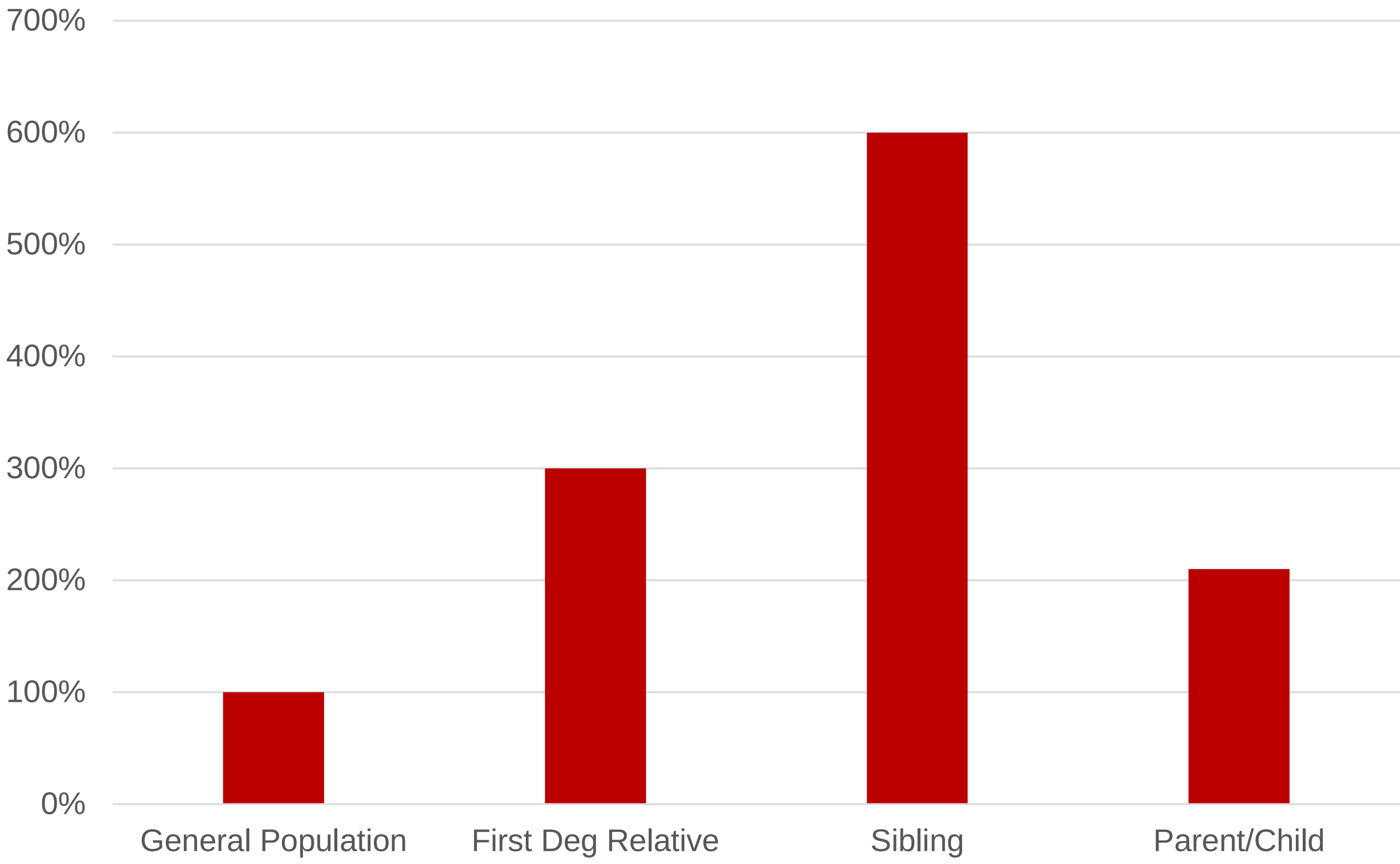
No → Family history should be updated every 5 years

*Criteria added to the algorithm by the authors

- Clifford et al, Leukemia Lymph 2019

Hodgkin Lymphoma

- General population risk: 2-3/100,000 (adults)
- Family history in 4.5%
- No established commercial testing
- Educate on symptoms and monitor



Kharazmi et al, Blood, 2015

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Non-Hodgkin Lymphoma

- General population 2.1% lifetime risk
- Overall risk for 1° relative 3.6%
- CMMRD – mediastinal T cell lymphomas in childhood
- No established commercial testing (except MMR genes with appropriate history)
- Active surveillance of (non-CMMRD) family members not currently recommended

Cerhan et al, Blood 2015

Multiple Myeloma

- General population incidence 4-5/100,000
- Approximately 3/1000 MM cases are familial
- 1° relatives have 3.7-fold increased risk
- *LSD1/KDM1A*
    - 1.23% of all MM
    - 9x increased risk in germline mutation carriers
    - Testing not currently available commercially

Lynch et al. JNCI 2001

Wei et al, Cancer Research 2018

Chronic Leukemias

- Chronic Lymphocytic Leukemia
  - General population incidence 3-7/100,000 per year
  - 6-9% of patients have family member with CLL
  - 1° relatives have 3-8x increased risk
  - Median age of onset ~10 years earlier for familial cases
  - No established commercial testing
  - Educate on symptoms and monitor

- Chronic Myelogenous Leukemia
  - General population incidence 1-2/100,000 per year
  - 1° relative did not convey increased risk

Sud et al, Blood 2018

What's New?

- *SAMD9/SAMD9L*
  - Predisposes to childhood MDS with monosomy 7
- Recent report of increased incidence of NHL in children with *BRCA2* mutations

Testing Considerations

- Skin biopsy for diagnostic testing in those with heme malignancy
- Testing the right person in the family (for disease with high mortality)
- Insurance coverage?

Implications of Testing

- Implications for the patient
    - Chemotherapy choice/dosing
    - Cascade testing for related HSCT donors
    - Risk for other malignancies

- Implications for family members
    - No proven surveillance
    - Screening for disease with rapid onset/transformation?
    - Reproductive decision making

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