What You've Always Wanted to Know about Genetics and Genomics in Cancer Prevention and Early Detection

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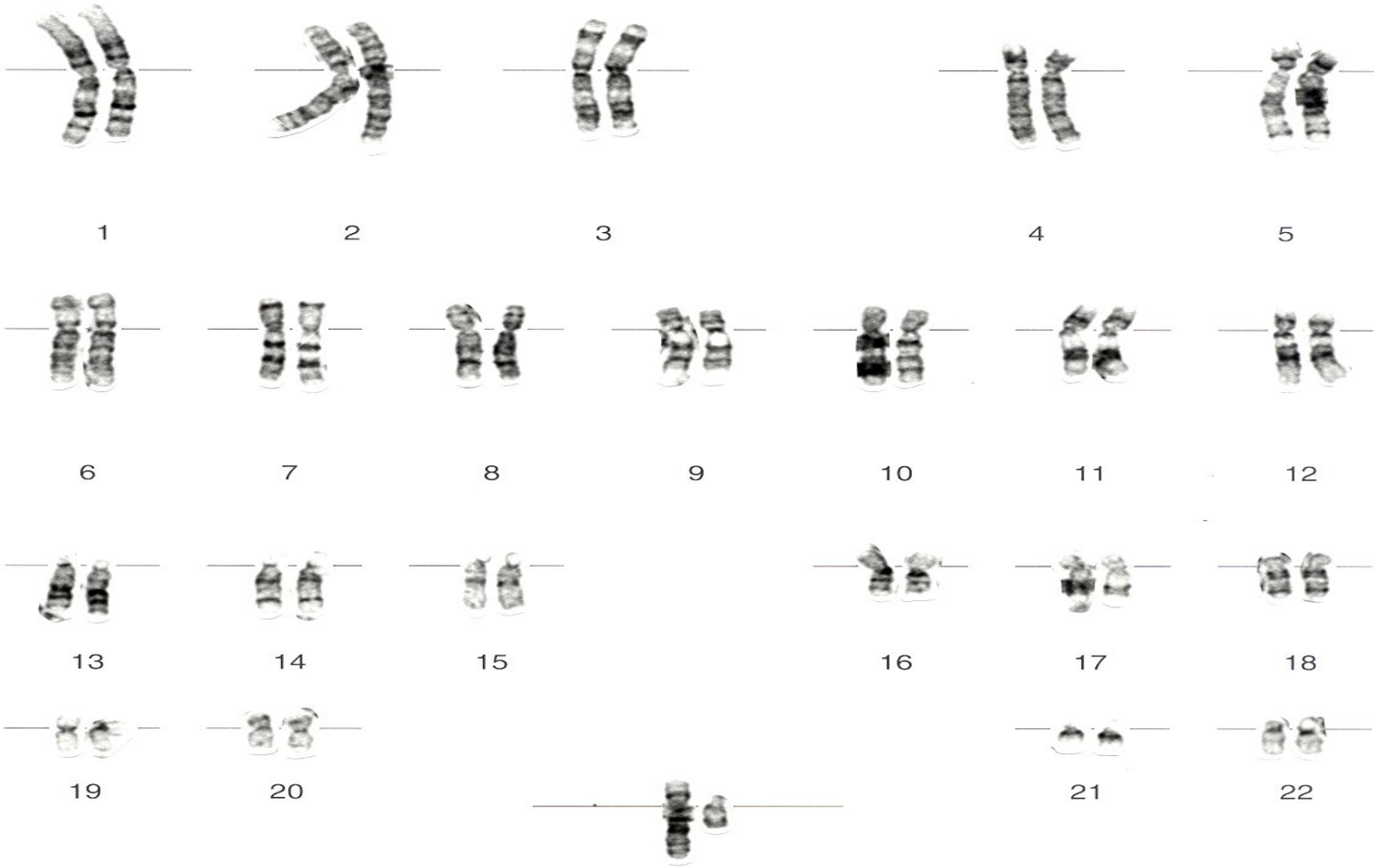
The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

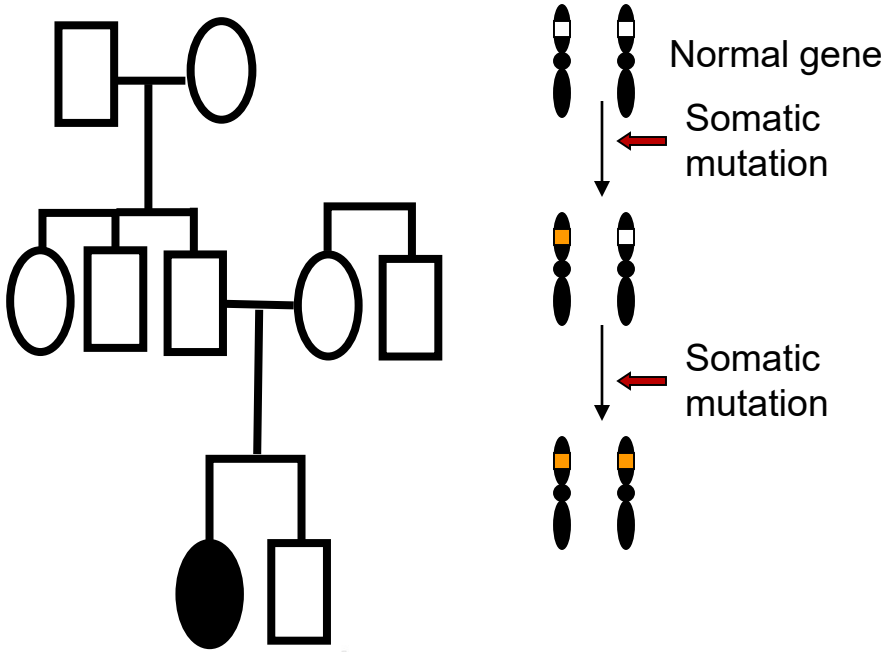
Disclosures

- Scientific advisory boards:
  - InVitae Genetics
  - Genome Medical
  - Promega
- Stock/Stock Options
  - Genome Medical
  - GI OnDemand

Normal Male Karyotype

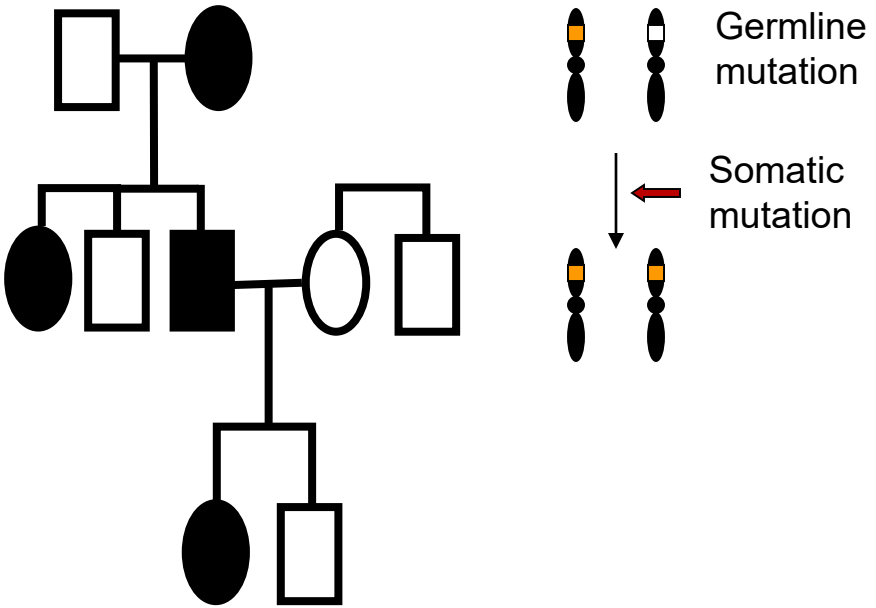


Sporadic



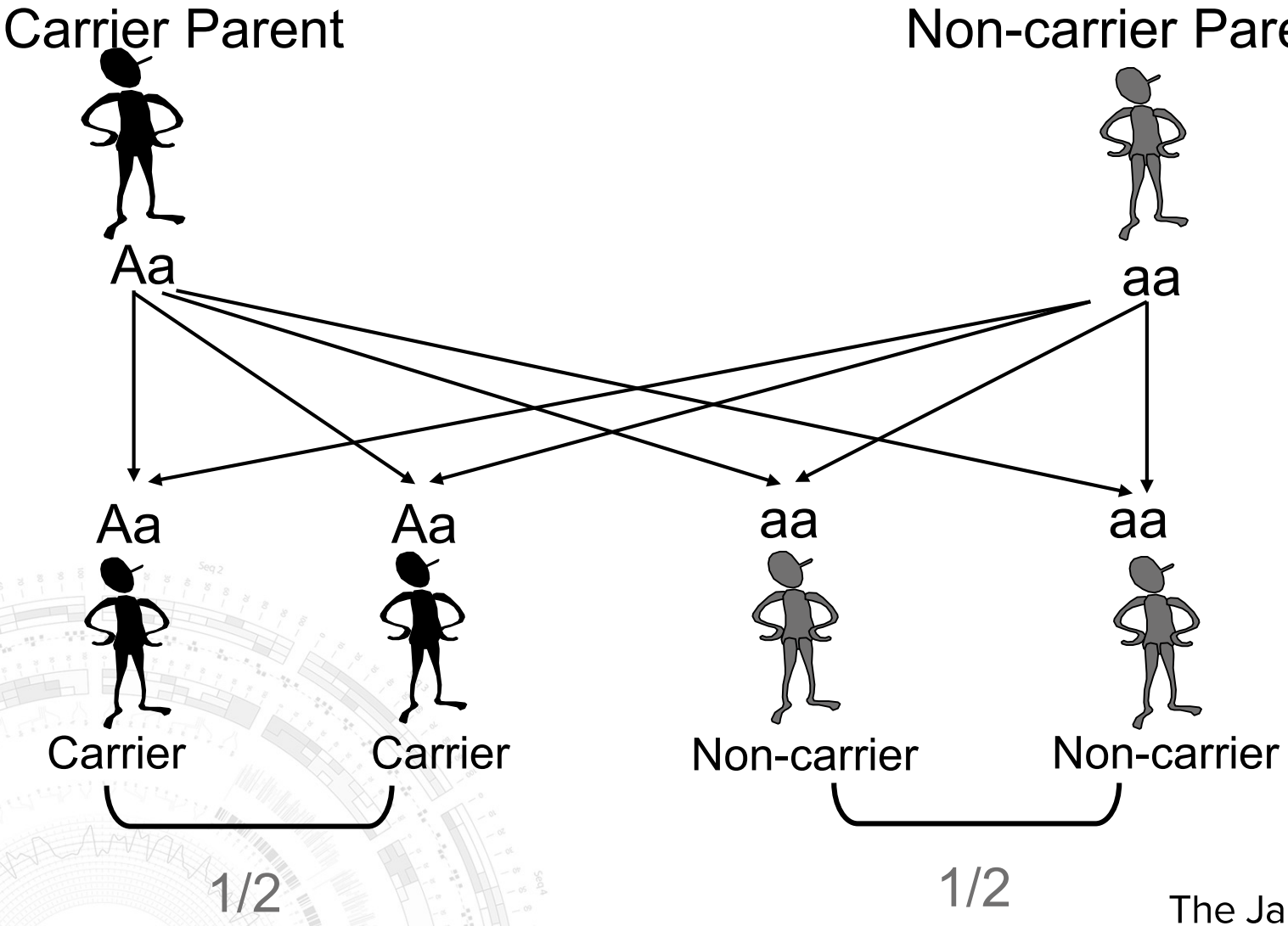
- Later age at onset (>60)
- Little or no family history of cancer
- Single or unilateral tumors

Inherited



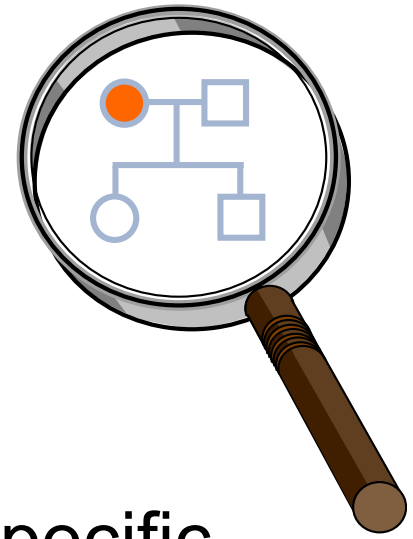
- Early age at onset (<50)
- Multiple generations with cancer
- Bilateral multiple primary cancers
- Clustering of certain cancers (i.e. breast/ovarian)

Autosomal Dominant Inheritance



When to Suspect Hereditary Cancer Syndrome

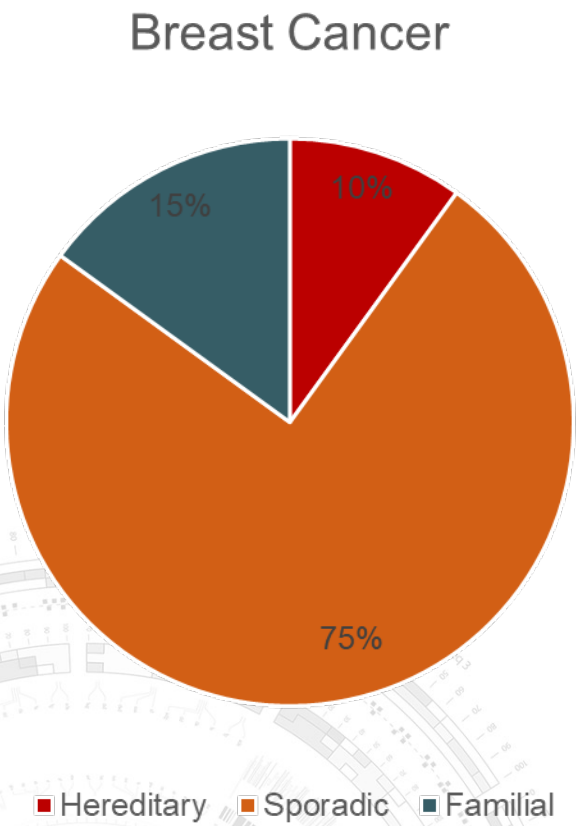
- Cancer in 2 or more close relatives
  (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (eg, breast and ovary)
- Evidence of autosomal dominant transmission

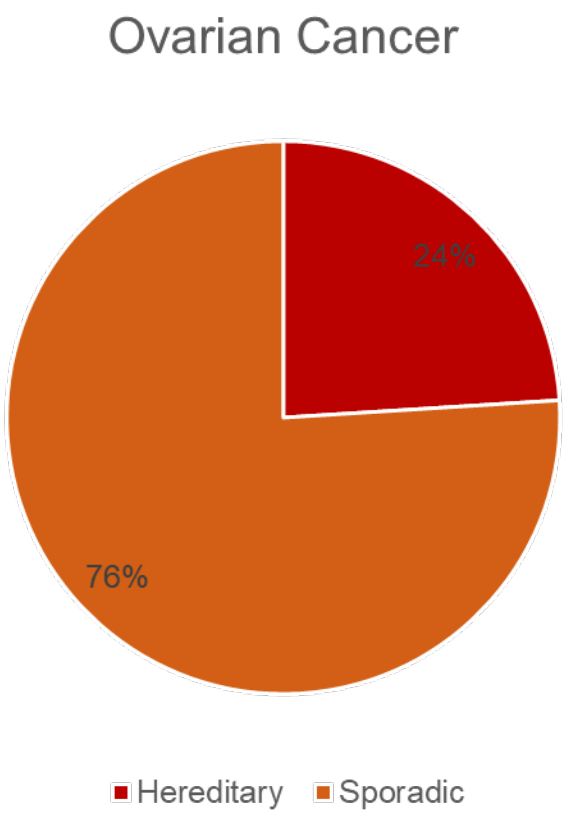


The Most Common Hereditary Cancer Syndromes

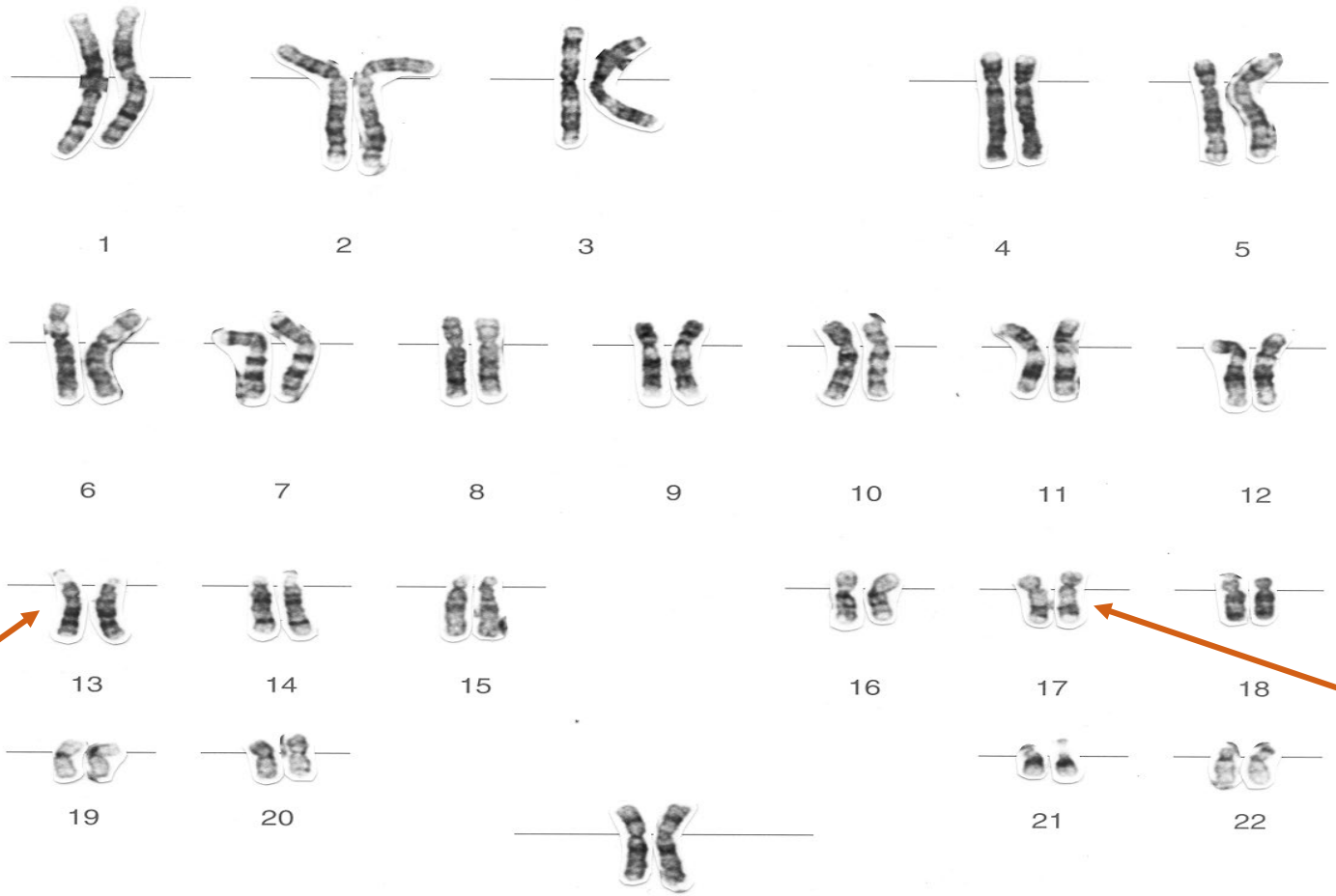
- Hereditary Breast-Ovarian Cancer Syndrome
  - Due to mutations in the BRCA1 and BRCA2 genes
- Lynch Syndrome
  - Due to mutations in MLH1, MSH2, MSH6, PMS2, and EPCAM genes
- Considered Tier One Genetic Diseases by CDC along with Familial Hypercholesterolemia
  - Common
  - Easy to test for
  - Actionable
- Geisinger MyCode assessed for Tier 1 conditions in 50,000 health plan participants
  - 1.32% (1 in 76 individuals) had one of these conditions
  - Compare to the 1 in 800 positive rate in newborn screening programs

How Much Breast and Ovarian Cancer Is Hereditary?





Hereditary Breast-Ovarian Cancer Syndrome (HBOC)



Hereditary Breast Ovarian Cancer Risks (to 80)

Cancer Type	BRCA1	BRCA2	General Public
Breast cancer	72%	69%	12.9%
Ovarian cancer	39-58%	13-29%	1.3%
Prostate cancer	12.5-29%	27-60%	12.5%
Pancreatic cancer	≤5%	5-10%	1.7%

National Comprehensive Cancer Network Guidelines for Genetic/Familial Breast, Ovarian, Pancreatic Cancer Screening and Prevention v1.2021

Relevance of Ashkenazi Jewish Descent

- 1 in 40 (2.5%) Ashkenazi Jews (males and females) carry a *BRCA1* or *BRCA2* founder mutation
- 1 in 400 (0.25%) in non-Jewish populations
- 3 mutations account for 95% of HBOC in Jewish individuals:
  - *BRCA1*: 185delAG, 5382insC
  - *BRCA2*: 6174delT
- Other founder examples: Iceland, Denmark, Finland: *BRCA2:* 999del5

HBOC Breast Cancer Management

NCCN Guidelines v2.2021

- Breast awareness starting at age 18 y.
- Clinical breast exam, every 6–12 months starting at age 25 y.
- Age 25–29 y, annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
- Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast.
- Age >75 y, management should be considered on an individual basis.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks.
  - Prophylactic mastectomy has been shown to reduce the risk for developing breast cancer by about 90%
- Discuss options for risk reduction agents (e.g. chemoprevention with Tamoxifen) including risks and benefits of each medication

HBOC Ovarian Cancer Management
NCCN Guidelines v2.2021

- Risk-reducing bilateral salpingo-oophorectomy between the ages of 35-40, or after child bearing is complete. Because ovarian cancer in women with *BRCA2* mutations occurs later than in *BRCA1*, it is reasonable to delay risk-reducing BSO until age 40-45 unless family history warrants earlier age of prophylactic surgery
- Some evidence of slight increased risk for serous uterine cancer among BRCA1 mutation carriers – discuss consideration of hysterectomy with BSO
- If delaying BSO: transvaginal ultrasound with color Doppler imaging at age 30-35 with concurrent serum CA-125 - not been shown to be sufficiently sensitive to support a positive NCCN recommendation
- Consider oral contraceptives – discussion of risk/benefit

Cancer Screening in Males

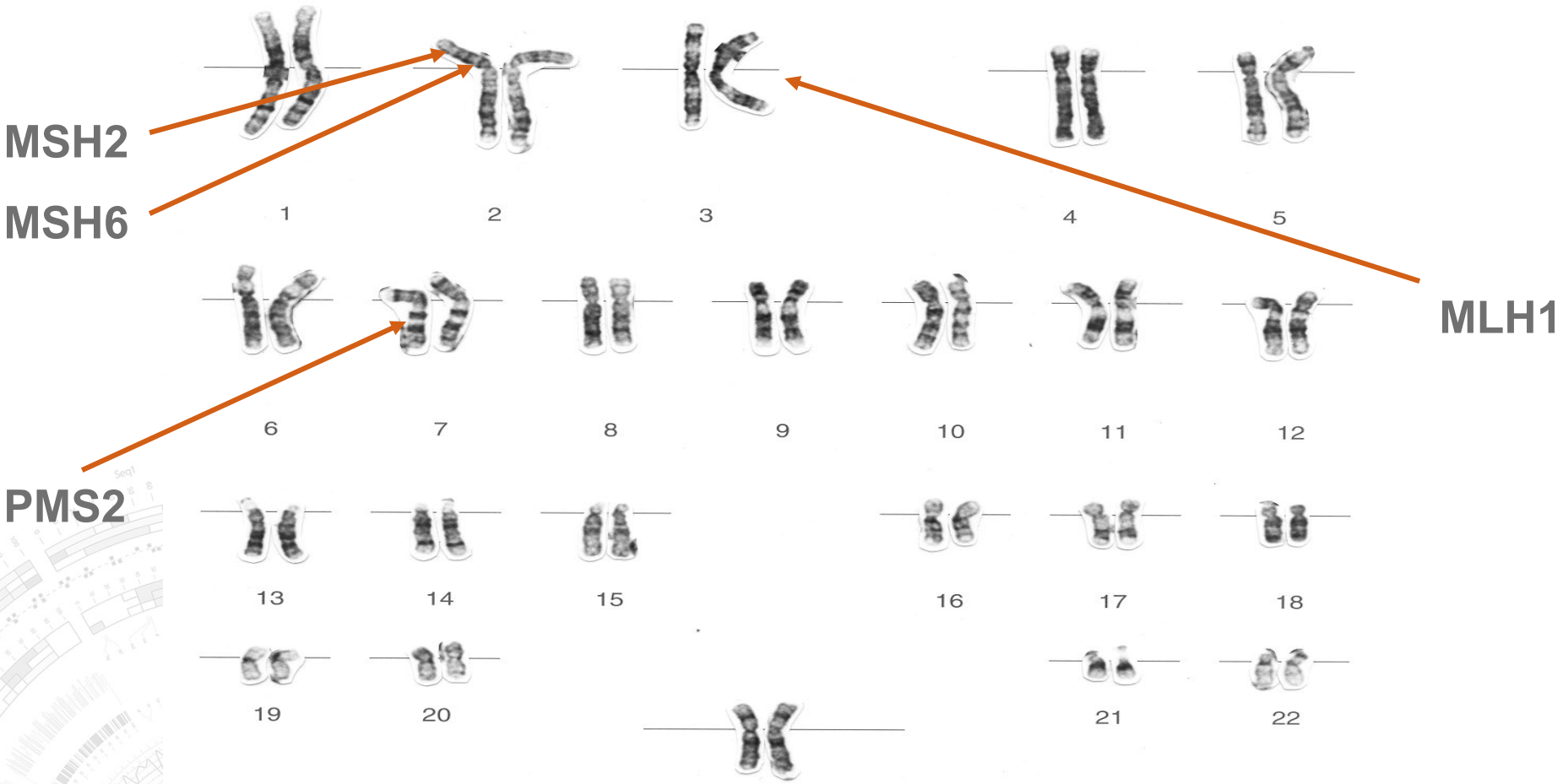
NCCN Guidelines v2.2021

- Breast self-examination training and education beginning at age 35.
- Clinical breast examination every 12 months beginning at age 35.
- (BRCA2) Recommend prostate cancer screening including annual digital rectal examination and PSA test beginning at age 40.
- (BRCA1) Consider prostate cancer screening including annual digital rectal examination and PSA test beginning at age 40.

Screening for other cancers

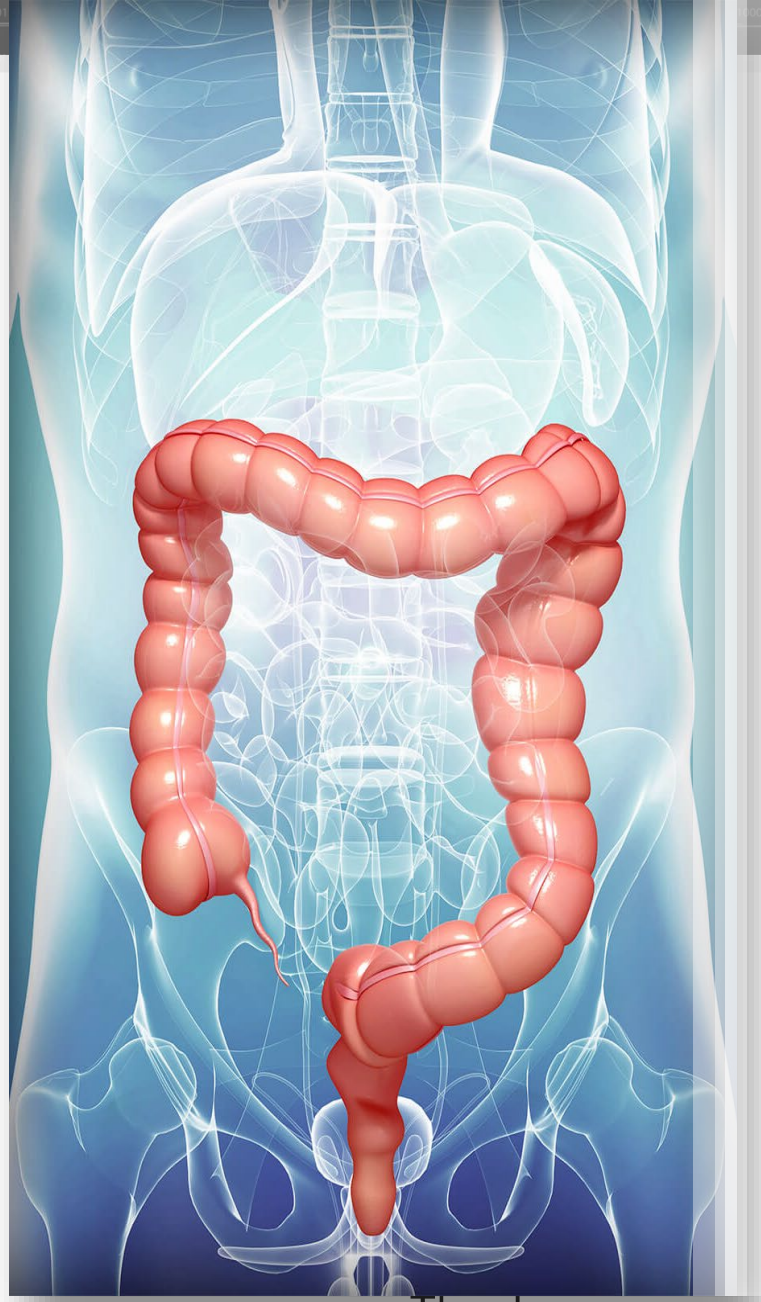
- Melanoma: No specific screening guidelines fbut general melanoma risk management is appropriate, such as annual full-body skin exaination and minimizing UV exposure.
- Pancreatic cancer: Individuals with *BRCA1/2, ATM, PALB2, TP53*, or Lynch genes (except *PMS2*) with a FDR or SDR with pancreatic cancer:
  - Consider pancreatic cancer screening beginning at age 50 or 10 years younger than the earliest dx in family.
  - Annual contrast-enhanced MRI/MRCP and/or EUS with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening.
  - Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any intervention.
- Follow American Cancer Society guidelines for other cancer surveillance

Lynch Syndrome



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 80)

Cancer Type	MLH1 and MSH2	MSH6	PMS2	General Public
Colon cancer	33-61%	10-44%	9-20%	4.2%
Endometrial cancer	21-57%	16-49%	13-26%	3.1%
Stomach	0.2-9%	≤1-8%	?	0.9%
Ovarian	4-38%	1-13%	3%	1.3%

National Comprehensive Cancer Network Guidelines for Colorectal Cancer Screening and Prevention v1.2020

Lynch Syndrome Surveillance Options NCCN v1.2020

Intervention	Recommendation
Colon Cancer	MLH1 & MSH2: Colonoscopy every 1-2 y beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if <25 MSH6 & PMS2: Colonoscopy every 1-2 y beginning at age 30-35 (or 2-5 years younger than earliest diagnosis if <25
Endometrial Cancer	Education regarding symptoms Consideration of hysterectomy after childbearing Endometrial biopsy every 1-2 y beginning at age 30-35 can be considered
Ovarian Cancer	Education regarding symptoms TVUS and CA-125 surveillance could be considered by no evidence of efficacy BSO can be considered after childbearing
Gastric & Small Bowel Cancer	Risk factors: male sex, older age, MLH1 or MSH2 pathogenic variants, FDR with gastric cancer, Asian ethnicity, chronic autoimmune gastritis, gastric intestinal metaplasia and gastric adenomas. Consider EGD with random biopsy of the proximal and distal stomach for H.pylori, autoimmune gastritis, and intestinal metasplasia beginning at age 40 and surveillance EGD every 3-5 y in those with the above risk factors.

Lynch Syndrome Surveillance Options
NCCN v1.2020

Intervention	Recommendation
Urothelial cancer	No clear evidence to support. Consider in select individuals with a family history of urothelial cancer and individuals with *MSH2* pathogenic variants (especially males). Annual urinalysis starting at age 30-35
Pancreatic Cancer	Consider pancreatic cancer screening beginning at age 50 or 10 years younger than the earliest dx in family. Annual contrast-enhanced MRI/MRCP and/or EUS with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any intervention.
Prostate Cancer	General population screening
Breast Cancer	General population screening
Brain Cancer	Annual physical/neurologic examination starting at age 25-30y
Reproductive Risks	Advise about prenatal diagnosis and assisted reproduction including preimplantation genetic testing Advise about risk of rare recessive syndrome called CMMR deficiency if both partners are carriers of pathogenic variants in the same MMR gene

Aspirin as chemoprevention for CRC

- Numerous studies have demonstrated benefit of aspirin and COX-2 inhibition in adenoma and CRC prevention
  - USPSTF recommends ASA 81mg for adults age 50-59 for primary CRC prevention (and CV disease prevention)
- CaPP2 study
  - Patients with Lynch syndrome randomized 2x2 factorial to ASA 600 mg/day and resistant starch (or placebo)
  - Early adenoma outcomes = no difference
  - At >4 years follow-up, those who took ASA for at least 2 years experienced reduction in CRC (Incidence rate ratio/IRR 0.37) and non-CRC LS cancers (IRR 0.49)
- Expert groups have awaited follow-up confirmatory studies before endorsing these data (CaPP3)
  - Also concern for toxicities associated with this dose of ASA

CaPP3
Cancer Prevention Programme

- Baron JA. N Engl J Med 348(10):2003; Sandler RS. NEJM 348(10):2003; Cole BF. JNCI 101(4):2009; Arber N. NEJM 355(9):2006; Burn J. Lancet 378(9809): 2011.

GINA

- Prevents **health insurers** from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.
  - Group and self-insured policies
- Insurers may not request that an individual undergo a genetic test.
- **Employers** cannot use genetic information to make hiring, firing, compensation, or promotion decisions.
- Sharply limits a health insurer's or employer's right to request, require, or purchase someone's genetic information.

Take Home Messages

- All cancer is genetic, but NOT all cancer is hereditary (inherited)
- In risk assessment:
  - Age at dx more important than # of cases
  - Ancestry critical
  - More rare tumors (ov ca) make a bigger impact to risk
- Identification of high risk families allows for:
  - proper cancer screening
  - education about testing options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