Germline Mutations and Cancer Susceptibility (BRCA1/2 and Lynch Syndrome)

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Overview

- Basics of genetic testing and germline mutations
- Genetic mutations associated with breast cancer
- BRCA1 and BRCA2 mutations: overview and guidelines
- Lynch syndrome: overview and guidelines
- Takeaways
- Two quiz questions

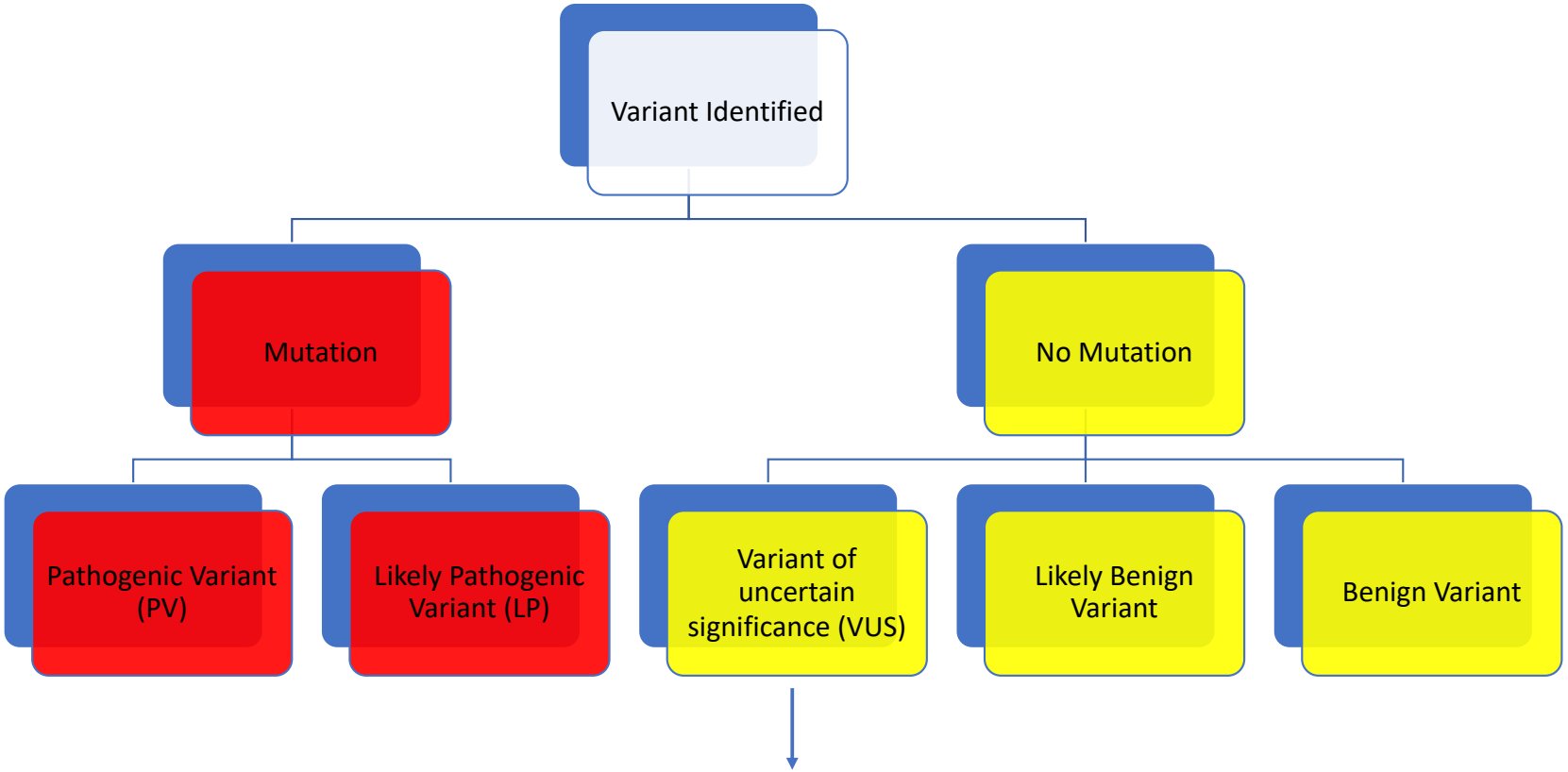
Germline mutations and cancer

- Germline mutations, also called hereditary mutations, are passed on from parents to offspring, and are present in the DNA of all the cells in the body.
- Germline mutations are different than somatic mutations, which are acquired and found in tumor-specific cells/DNA
- Several germline mutations play a role in cancer risk and susceptibility
- Knowledge of these mutations can lead to preventive measures that reduce the likelihood of developing cancer and increase the likelihood that a cancer will be caught at an early stage rather than advanced
- These mutations can also influence treatment selection in patients with cancer

How do we test?

- Sample: Blood, saliva; occasionally skin
- Next generation sequencing of DNA
  - Single gene testing
  - Cancer-specific gene panel
  - Multi-cancer gene panel
- Next generation sequencing of RNA is becoming more utilized

ACMG Variant Classification



A VUS is identified in ~ 40% of pts who undergo germline testing

Who qualifies for testing?

Two populations to consider:

- **Unaffected patients** = those without a cancer diagnosis
- **Affected patients** = those with a cancer diagnosis

Tips on taking a family history

- **Explain that family history includes extended relatives (first through third degree)**
  - Distinguishing maternal vs paternal side is very helpful
  - Labeling which relative had the specific cancer is also very helpful

- **Ask about specific cancers, not just cancer in general (breast, ovarian, pancreatic, prostate ; colorectal and uterine)**
  - Bone cancer usually = metastatic disease to the bone
  - Inquire about family history of genetic mutations

- **Age at diagnosis matters**

- **A male patient with a family history of breast/ovarian cancer could still be at risk!**

Red Flags in a family history

- Clusters of cancer on a specific side of the family
- Premenopausal (age < 50) breast or ovarian cancer
- Few men on a side of the family (can underrepresent a gene's penetrance)
  - e.g. if a patient's dad only has brothers and the paternal grandmother had ovarian cancer, it's very possible that there is a BRCA mutation on the paternal side
- Ashkenazi Jewish ancestry
- If affected family members have negative genetic testing, patients with strong FHx may still benefit from seeking genetic counseling

When in doubt, reach out to a genetic counselor

If I have cancer (affected patient), do I automatically qualify for genetic testing?

Yes: pancreatic and ovarian cancer

Sometimes:

- **Breast**: complicated, more on this soon
- **Prostate**:
  - Metastatic or high risk (tumor extension, PSA level, and/or Gleason score)
  - Intraductal carcinoma (pathology)
  - Ashkenazi Jewish ancestry
- **Colorectal**: complicated, more on this later (Lynch syndrome)
- **Endometrial**:
  - High grade serous carcinoma (? BRCA1)
  - Somatic testing confirms MMRd (mismatch repair deficiency) / qualifies for lynch testing

Breast cancer related genes

- Result in an increased lifetime risk of breast cancer, and often early-onset breast cancer as well as contralateral breast cancer.

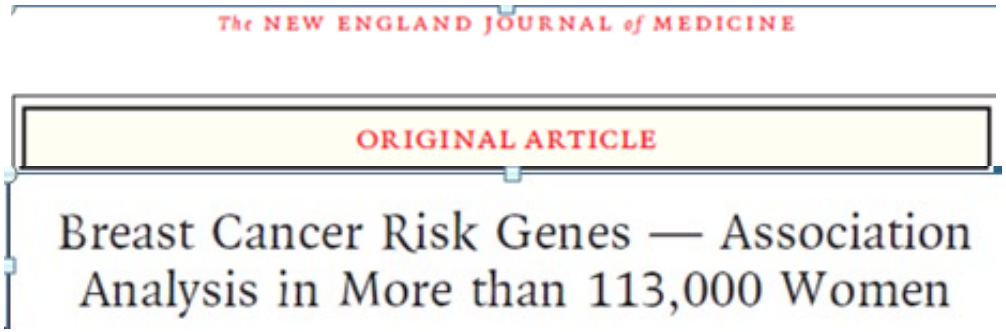
- **Hereditary breast cancer** genes are commonly associated with an increased risk of other cancers, including **ovarian, pancreatic, and prostate cancer**.
  - Reflected in the guidelines

- The guidelines were created to identify high-risk genes and thus do not always capture those with moderate-risk genes

BReastCAncer (BRCA) Genes

- BRCA 1 and BRCA 2 account for the majority (15%) of hereditary breast and ovarian cancers with an identified mutation in a cancer susceptibility gene
- Autosomal dominant inheritance
- Highest prevalence in those with Ashkenazi Jewish ancestry
- How does a BRCA mutation cause cancer?
  - The BRCA proteins are involved in repairing dsDNA breaks during cell division
  - Double hit hypothesis – if/when a second mutation occurs in the one normal copy of the BRCA1/2 gene, the DNA repair system in cells becomes flawed, increasing the likelihood for genetic errors and uncontrolled cellular division

CARRIERS study (USA):
28 genes; n= 64,000

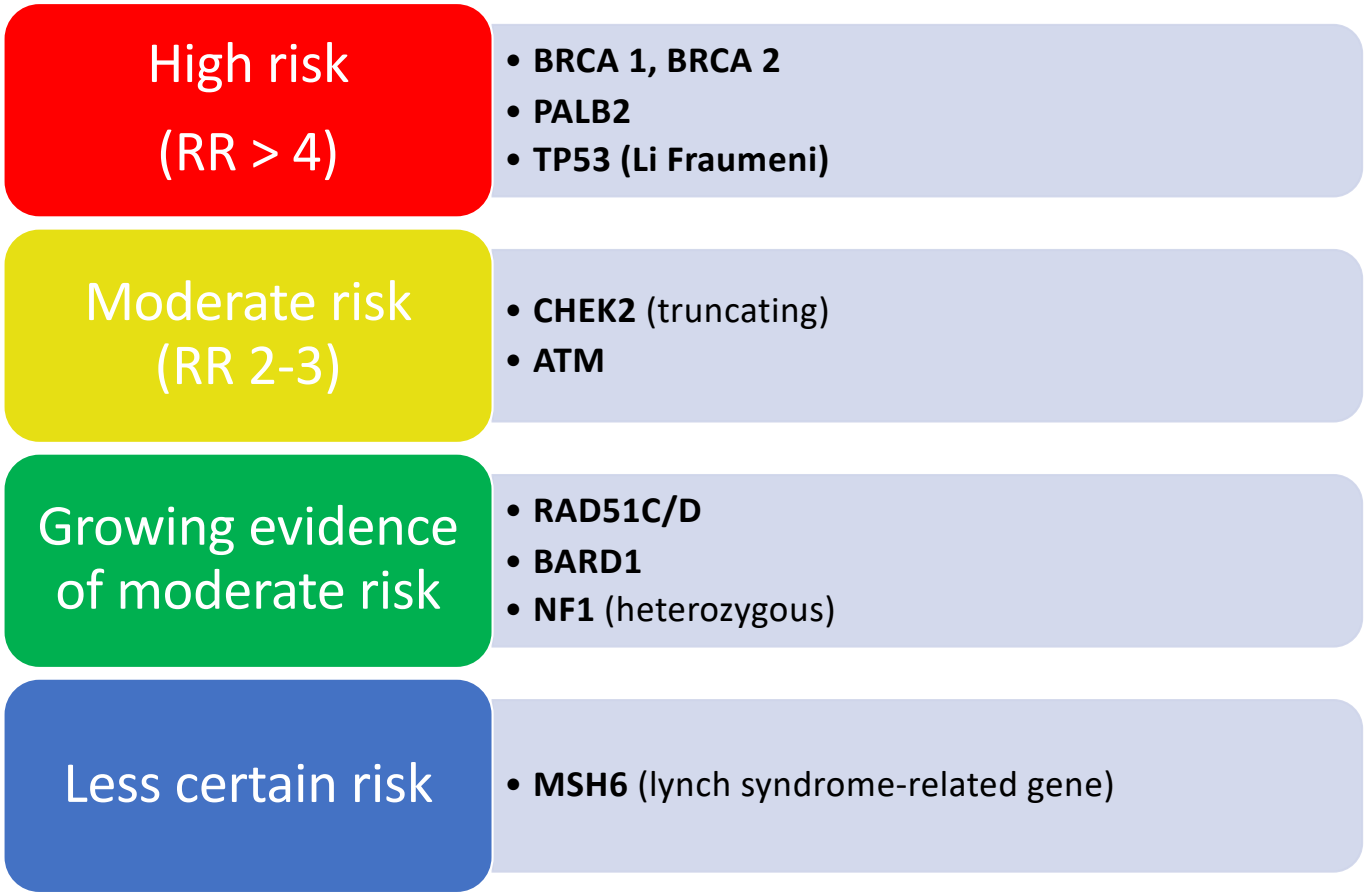


BCAC study (International)
34 genes; n= 113,000

- **CONFIRMED: *BRCA1/2*, *PALB2, ATM*, *CHEK2***
- RARE (syndrome-related): ***TP53***, *CDH1*, *PTEN*, *STK11*
- GROWING EVIDENCE: ***RAD51C/D*, BARD1**, NF1 (het)
- LESS CLEAR EVIDENCE : *MSH6 (lynch syndrome-related gene)*
- NO EVIDENCE: *NBN, RAD50, BRIP1 (ovarian Ca)*

Hu et al. NEJM epub Jan 20, 2021
Dorling et al. NEJM epub Jan 20, 2021

Overall risk of breast cancer



Risk of breast cancer by gene (odds ratio)

	Risk of breast cancer overall Odds Ratio (95% CI)	
Gene	CARRIERS Study	BCAC (truncating PV)
BRCA1	**7.62 (5.33-11.27)**	**10.57 (8.02-13.93)**
BRCA2	**5.23 (4.09- 6.77)**	**5.85 (4.85-7.06)**
PALB2	**3.83 (2.68-5.63)**	**5.02 (3.73-6.76)**
ATM	**1.82 (1.46-2.27)**	**2.1 (1.71-2.57)**
CHEK2 **(truncating)**	**2.47 (2.02-3.05)**	**2.54 (2.21-2.91)**
BARD1	1.37 (0.87-2.16)	**2.09 (1.35-3.23)**
RAD51C	1.2 (0.75-1.93)	**1.93 (1.20-3.11)**
RAD51D	1.72 (0.88-3.51)	**1.80 (1.11-2.93)**
MSH6	1.22 (0.77-1.96)	1.96 (1.15-3.33)

High risk

Mod risk

Mod risk?

Unaffected patient – who qualifies for testing?

Ashkenazi Jewish ancestry
and/or
Known mutation in the family
and/or

<u>Close family history</u>

1 relative with:
- BC ≤ 50 years old
- Male BC
- Ovarian, pancreatic, or high risk prostate CA

2 relatives with breast CA (any age) or prostate CA (any risk)

3 total diagnoses of BC

Affected patient – who qualifies for testing?

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Ashkenazi Jewish ancestry
and/or
Known mutation in the family
and/or

Close family history

1 relative with:
- BC ≤ 50 years old
  - Male BC
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2 relatives with breast CA (any age) or prostate CA (any risk)

3 total diagnoses of BC

Patient characteristics

- Age ≤ 50 years old
  - American College of Surgeons (2024): ≤ 65 years old
- Male
- Prior testing is outdated (expanded testing ~ 2016)

Breast cancer characteristics

- Metastatic
- Multiple primaries
- Triple negative
- High risk HER2 negative (treatment impact)
- Lobular BC + PMH/FH gastric Ca (CDH1)

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BRCA 1 vs BRCA 2 – overview

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	Breast Ca	Ovarian/fallopian/peritoneal Ca
BRCA 1	**- Absolute risk: 60-72%** - Absolute risk for men: 0.2%–1.2% by 70 - **TNBC** is the most common histology - High risk for premenopausal BC: average age is **39-43** **-** High risk for **contralateral** breast cancer (based on age at first diagnosis)	**- Absolute risk: 39-58%** - Most common histology is **serous** adenocarcinoma and high grade
BRCA 2	**- Absolute risk: 55-69%** **- Absolute risk for men: 1.8%–7.1% by 70** - **ER+** is the most common histology - Both pre and post menopausal BC: average age is **51-60** - High risk for **contralateral** breast cancer (based on age at first diagnosis)	**- Absolute risk: 13-29%** - Most common histology is **serous** adenocarcinoma and high grade

Management recommendations for unaffected carriers of BRCA 1 and BRCA 2

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	Breast Ca	Ovarian/fallopian/peritoneal Ca
BRCA 1	- Prevention: **Risk reducing mastectomy** (RRM) **- High risk screening:** ➢ Clinical breast exam starting at age 25 (q6-12 mo) ➢ Annual MRI starts at 25; mammogram at 30 (stagger q6 mo) ➢ Continue until age 75; individual management after 75 **For men:** - Clinical breast exam annually, starting at age 35	**- Prevention: RRSO between 35-40 yo** - Risk reduction: OCPs/IUD - Considerations: ➢ Fertility ➢ HRT
BRCA 2	- Prevention: **Risk reducing mastectomy** (RRM) *- Risk reduction: consider chemoprevention* **- High risk screening:** ➢ Clinical breast exam starting at age 25 (q6-12 mo) ➢ Annual MRI starts at 25; mammogram at 30 (stagger q6 mo) ➢ Continue until age 75; individual management after 75 **For men:** - Clinical breast exam annually, starting at age 35 - Consider annual mammogram if gynecomastia and high risk starting at age 50, or 10 years earlier than FHx male BC	**- Prevention: RRSO between 40-45 yo** - Risk reduction: OCP/IUD - Considerations: ➢ Fertility ➢ HRT

Lifestyle modifications can also reduce the risk of breast cancer – counsel pts on diet, weight, exercise, and ETOH reduction

Additional considerations:

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Family planning:

- Partner should be tested (bi-allelic BRCA1/2/PALB2 mutations → **Fanconi anemia**)
- **Consider referral to IVF center:**
  - **Preimplantation genetic testing** (ensures that embryo is not a carrier of the germline mutation)
  - **Embryo or egg freezing** prior to RRSO

Hormone replacement therapy (HRT) following RRSO – work closely with gynecologist

- Tailored depending on each patient's personal history of breast cancer and/or breast cancer risk reduction strategies
- **Generally safe in those without a history of breast cancer or other contraindications to HRT**
  - Strongly consider in those s/p RRSO at age 35-40
  - Recommend stopping at age of natural menopause (45-50)
- In patients **without a uterus, estrogen alone for HRT is preferred** since it poses a **smaller risk to breast cancer** compared to combination HRT

BRCA 1 and BRCA 2 – overview of other cancers

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	Prostate Ca	Pancreatic Ca	Melanoma
BRCA 1	- Absolute risk: 7-26%	- Absolute risk: < 5%	- No known association
BRCA 2	**- Absolute risk: 19-61%** - Aggressive phenotype; metastatic disease is common	**- Absolute risk: 5-10%**	- **Possible** association

Less common cancers:
High grade serous endometrial carcinoma (BRCA1)
Gastric (BRCA1 and 2), biliary tract (BRCA1), esophageal (BRCA2)
Uveal melanoma (BRCA2)

Management recommendations for unaffected carriers of BRCA 1 and BRCA 2

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Screening	Prostate Ca	Pancreatic Ca	Melanoma
BRCA 1	- Screen starting at age 40 if +FHx or patient preference	If FHx or personal preference, starting at age 50, or 5-10 years before FHx age at diagnosis	Not indicated but can consider
BRCA 2	- Screen starting at age 40	Start at age 50, or 5-10 years before FHx age at diagnosis	Screen (dermatology)
How to screen:	Age 40-75: DRE/PSA every 1-2 years; if abnormal, prostate MRI (individual assessment after age 75)	Involves use of EUS and MRCP	- Dermatology skin evaluation q6-12 months (practice at BIDMC, not guideline-based) - Sun protective behavior

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Lynch Syndrome - overview

- Germline mutations in genes encoding for **mismatch repair proteins**
  - **Genes: MLH1, MSH2, MSH6, PMS2, EPCAM (deletion)**
  - **Autosomal dominant** inheritance with incomplete penetrance
  - Each gene is associated with a specific cancer risk profile
- Somatic tumor testing:
  - **MMRd or dMMR** = mismatch repair deficiency / deficient mismatch repair
  - **MSI-H** = microsatellite instability (high) → prompts testing for MMRd
- Associated cancers:
  - **Colorectal cancer (CRC)**, **gastric cancer**, small bowel cancer, biliary tract cancer, pancreatic cancer
  - **Endometrial cancer**, **ovarian cancer**, prostate cancer, urinary tract cancer
  - Brain cancer (usually glioblastoma)
  - Skin cancers (sebaceous adenomas/carcinomas, keratoacanthomas)

Affected patients – who qualifies for testing?

- A diagnosis of a tumor of the Lynch syndrome spectrum with one of the following on tumor tissue (somatic) testing:
  - MSI-H (PCR/IHC and/or NGS)
  - MMRd (IHC and/or NGS)
- A diagnosis of colorectal cancer or endometrial cancer with one of the following:
  - Diagnosed before age 50
  - Synchronous or metachronous Lynch syndrome-related cancers
  - At least 1 first degree relative with a Lynch associated cancer before age 50
  - At least 2 first degree relatives with Lynch associated cancer at any age

Adapted from revised Bethesda Guidelines and National Comprehensive Cancer Network Guidelines

Unaffected patients – who qualifies for testing

- A family member with colorectal or endometrial cancer who meets any of the criteria for “affected patients”
- A family member with confirmed diagnosis of Lynch Syndrome
- ≥5% probability of having a pathogenic variant in one of the 5 genes based on risk assessment models (PREMM5, MMRPredict, MMRPro)
  - Predict the likelihood of identifying a germline pathogenic variant in one of the 5 genes
  - Some data suggest utilizing a lower threshold of ≥2.5% for the PREMM5 predictive model.

Adapted from revised Bethesda Guidelines and National Comprehensive Cancer Network Guidelines

MMR genes: details

- Population prevalence: 1:279 (0.36%)
  - PMS2 > MSH6 > MLH1 > MSH2 >> EPCAM deletion

Gene	Notes
MLH1	Highest risk for **CRC, young age** of cancer onset, high risk for multiple primary tumors; risk of any lynch cancer: **F 80.2%, M 68.5%**
MSH2	Highest risk for **extracolonic cancers;** risk of any lynch cancer: **F 83.4%, M 80.5%**
MSH6	**CRC at later onset** with more distally located tumors; possible association with breast cancer; risk of any lynch cancer: **F 55.2%, M 28.5%**
PMS2	**Lowest risk** for Lynch-associated cancers (22%); CRC age of onset may still be early; risk of any lynch cancer: **F 40.1%, M 57.3%**
EPCAM deletion	**Rare; significantly increased risk of early onset CRC** (75% cumulative risk). Low risk for extra-GI tumors

Lynch-related cancers: details and screening

Cancer	Risk	Average age at dx	Screening:
CRC	**- MLH1, MSH2: 40-50%** - Less for MSH6, PMS2	**40s-60s** - MLH1, MSH2: 44 - MSH6: 42-69 - PMS2: 61-66	- Colonoscopy q 1-2 yrs, starting at age 20-25 - Use of aspirin (at least 81 mg) if high risk
Endometrial	By age 70 **- MSH2: 46%** **- MSH6: 41%** **- MLH1: 35%** **-** PMS2: 12-26%	**40s-50s** - MSH2, MSH6, MLH1: 47-50 - PMS2: 53-55	- Yearly education/evaluation of symptoms - Consider TAH after childbearing - Consider TVUS and endometrial bx every 1-2 yrs, starting at 30-35
Ovarian	By age 70: - **11-17%** - PMS2: lower	**40s** (43-46)	- Yearly education /evaluation of symptoms - Consider RRSO after childbearing

Cancer	Risk	Screening
Gastric/small bowel	Gastric - MLH1 and MSH2: 8-16% - Relatively low for MSH6 and PMS2 - Small bowel: 0.4-12%	- Gastric/duodenal: EGD q2-4 years at age 30-35, esp if +FHx or Asian descent - Distal small bowel: If symptoms, capsule endoscopy and small bowel enterography
Urothelial cancer	Transitional carcinomas are most common	If MSH2/EPCAM, male, +FHx, or tobacco use: UA + cytology starting at age 30-35
Prostate	- Average age 59-63 - MSH2: 16% - other MMR: 5-7%	- High risk prostate ca screening starting at age 40 (DRE/PSA +/- MRI prostate)
Pancreatic	Numerous studies show a/w lynch	If +FHx, alternating EUS and/or MRI/MRCP
Brain	- 14%, primarily MSH2 - Glioblastoma (56%) > astrocytoma (22%) > oligodendroglioma (9%)	
Sebaceous neoplasms	1-9%, mostly MSH2	Q 1yr dermatology evaluation starting at 40-45
Breast	- ? MSH6	- No guidelines at present

Take aways

- Taking a detailed personal and family history of cancer can save lives!
- Germline mutations, also called hereditary mutations, are passed on from parents to offspring, and are present in the DNA of all the cells in the body.
- Mutations in the BRCA 1 and 2 genes are the most common cause of hereditary breast and ovarian cancer
- Lynch syndrome includes a wide spectrum of cancers caused by mutations/deletions in genes encoding mismatch repair proteins
  - The two most common cancers are colorectal and endometrial cancer
- When you think of cancer syndromes, think of relationships between:
  - Breast, ovarian, pancreatic and prostate cancer
  - Colorectal and endometrial cancer (Lynch)
- When in doubt, reach out to a genetic counselor for help

Quiz Questions:

- **If a patient has a family history of breast cancer, what other cancers should you make sure to ask about?**
  - Ovarian, prostate, and pancreatic
- **At what age should female BRCA carriers undergo RRSO?**
  - BRCA1: 35-40 years old
  - BRCA2: 40-45 years old

Thank you!

To all the **PCPs** and providers who refer patients to our cancer genetics team

To **Nadine Tung** for creating this genetics program and teaching me everything that I know

To the **genetic counselors** who are brilliant and wonderful to work with

And of course to the **patients** who allow us to be involved in their care