Genetics for Cancer Risk
Presenters:

Ayesha Munir MD
Assistant Professor of Interdisciplinary Clinical Oncology
Mitchell Cancer Institute
University of South Alabama-USA Health

Cassie Gurganus MS, CGC
Licensed, Certified Genetic Counsellor
Mitchell Cancer Institute
University of South Alabama-USA Health
Objectives

- Overview of Cancer Genetics
- Somatic vs Germline mutations
- Cancer risk assessment stages
- NCCN guidelines for Genetic risk assessment for common malignancies like Breast, Ovarian, Colorectal/Pancreatic and Prostate.
- Approaching a patient for Genetic counselling
- Defining a positive result on genetic test and its implications for the patient.
Overview of Cancer Genetics

- Cancers arise due to pathogenic variants in certain genes, such as those involved in the regulation of cell growth and/or DNA repair.
- Not all of these pathogenic variants are inherited from a parent.
- However, family studies have documented an increased risk for several forms of cancer among first-degree relatives and second-degree relatives of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more pathogenic variants present in parental germline cells. Cancers developing in these individuals may be classified as hereditary or familial cancers.
Variants associated with Hereditary cancers increase the risk for certain cancers and transmission to offspring through either parent. They often have an early age of onset and exhibit an autosomal dominant inheritance pattern.

Familial cancers vs Hereditary cancers: The former share some but not all features of hereditary cancers. Familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.

An individual suspected of being at risk for hereditary cancer should be offered genetic counseling. This is consistent with recommendations from the USPSTF and NCCN.

Assessment of an individual’s risk for familial or hereditary cancer is based on a thorough evaluation of the personal and family history.

Advances in molecular genetics have identified a number of genes associated with inherited susceptibility to multiple cancers and have provided a means of characterizing the specific pathogenic variant present in certain individuals and families exhibiting an increased risk for cancer.

Cancer genetics has implications in prevention, screening, and treatment of individuals with hereditary or familial cancer.
Cancer risk assessment Stages

Pre-test counseling done prior to ordering testing

Consideration of the most appropriate tests to order

Post-test counseling done when results are disclosed.
General testing criteria

- Who to test?
- Individuals with any blood relative with a known pathogenic gene implicated in cancer pathogenesis.
- Individuals who tested negative with previous limited testing (e.g., single gene analysis) and are interested in pursuing multi-gene testing and have a pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline (e.g. BRCA).
- To aid in systemic therapy and surgical decision-making (e.g., testing implication for type of breast surgery).
- Individual who meets Li-Fraumeni syndrome testing criteria, Cowden syndrome/PTEN hamartoma tumor syndrome or Lynch syndrome.
- Testing may be considered in the following scenario (with appropriate pre-test education and access to post-test management): • An individual of Ashkenazi Jewish ancestry without additional risk factors • Personal history of serous endometrial cancer.
Breast and ovarian cancer susceptibility genes

HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (e.g. BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53).

- Testing is clinically indicated in the following scenarios:
  - Personal history of breast cancer: ≤50 y
  - Any age: Treatment indications - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
  - Triple-negative breast cancer
  - Multiple primary breast cancers (synchronous or metachronous)
  - Lobular breast cancer with personal or family history of diffuse gastric cancer
  - Male breast cancer
  - Ashkenazi Jewish ancestry
  - Any age: Family history - ≥1 close blood relative with ANY: • breast cancer at age ≤50 • male breast cancer • ovarian cancer • pancreatic cancer • prostate cancer with metastatic, or high- or very-high-risk group, ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
  - Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a BRCA1/2 variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).
HIGH-PENETRANCE OVARIAN CANCER SUSCEPTIBILITY GENES (ATM, BRCA1, BRCA2, BRIP1, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, RAD51C, and RAD51D)

Testing is clinically indicated in the following scenarios:

- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- Family history of cancer only An individual unaffected with ovarian cancer (with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 variant based on prior probability models (eg, TyrerCuzick, BRCAPro, CanRisk).
BRCA1/2 management as per NCCN guidelines

- Absolute Breast cancer risk: >60% lifetime risk
- Contralateral Breast cancer risk: 20-year cumulative risk is 30%-40%
- Male breast cancer: Absolute risk is 0.2%-1.2% by age 70
- Ovarian Cancer Absolute risk: 39%-58%
- Pancreatic cancer: Absolute risk: ≤5%
- Prostate cancer: Absolute risk: 7%-26%
- BRCA2 Primary Breast Cancer: Absolute risk: >60%
- Contralateral Breast Cancer 20-year cumulative risk: 25%
- Male breast cancer: Absolute risk: 1.8%-7.1% by age 70
- Ovarian Cancer Absolute risk: 13%-29%
- Pancreatic cancer: Absolute risk: 5%-10%
- Prostate cancer: Absolute risk: 19%-61%
Breast Cancer screening/preventative strategies in BRCA1/2 positive Individuals:

- Breast awareness starting at age 18 years.
- Clinical breast exam, every 6-12 months, starting at age 25 years.
- Breast screening, Age 25-29 years: annual breast MRI screening with and without contrast (or mammogram, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
- Age 30-75 years: annual mammogram and breast MRI screening with and without contrast.
- Age >75 years: management should be considered on an individual basis.
- For individuals with a BRCA pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue.

Discuss option of Risk reducing prophylactic mastectomy.

Consider risk reduction agents as options for breast cancer, including discussion of risks and benefits.
Ovarian/ Fallopian Tube/ Peritoneal/ Uterine Cancers screening/preventative strategies in BRCA1/2 positive Individuals:

- Non-surgical risk reduction: Consultation with gynecologic oncologist or gynecologist with expertise/experience in genetic susceptibility to gynecologic cancer recommended. Consideration of combination estrogen/progestin contraception (such as oral contraceptive pills) for ovulation suppression.

- Surgical risk reduction with bilateral salpingoophorectomy

- BRCA1: Recommend RRSO between 35 and 40 years. BRCA2: can delay RRSO until age 40-45 years in patients with BRCA2 variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery.

- CA-125 and pelvic ultrasound are recommended for preoperative planning.

- Hormone replacement therapy is generally not contraindicated and thus should be discussed with premenopausal patients who do not have a personal history of breast cancer.

- RRSO likely reduces incidence of Breast Cancer but data is not strong and Breast Cancer management should be dependent on pathogenic Gene identified.
The Genetic Counseling Process

Referral
- Receive referral from provider/patient
- Review indication and request records

Initial Consult
- Collect Patient Information (Personal/family history of cancer, medical history, hormone history)
- Discuss genetic testing for cancer - methods, risks/benefits, cost, insurance implications, results, recommendations, etc.
- Obtain consent

Testing
- Coordinate sample collection (blood or saliva) and mailing
- Write clinic note and scan pedigree into EMR
- Place orders

Results
- Write result letters to patient and provider
- Call out results to patient
- Send results and recommendations to referring provider and care team
- Coordinate referrals to other specialties as needed
During the appointment
**Pedigree**

**Classic BRCA2 Pedigree**

**Lynch Syndrome Pedigree**

*Pedigree credits to the National Cancer Institute*
Red Flags for Hereditary Cancer

- Cancer at early ages (<50)
- Multiple cancers in one person; bilateral cancers
- Multiple cases of the same or related cancers on one side of a family
- Multiple generations with cancer diagnoses
- Rare cancers
- Combination of cancers and benign findings that can be related
  - Ex. ≥ 10 colon polyps in one person
Tumor Suppressor Gene

PROTECTION AGAINST TUMOR DEVELOPMENT

Tumor Suppressor Gene w/ pathogenic variant (mutation)

DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT
Autosomal Dominant

Parents

Children

U.S. National Library of Medicine
Genetic Information Non-Discrimination Act (GINA)

- Prevents discrimination based on genetic test results by employers and health insurance companies
  - Exceptions include individuals who work for (or obtain health insurance from) the federal government, military, or a small business of less than 15 employees, or individuals

- GINA does not cover life, long-term care, or disability insurance companies
  - Recommend that unaffected individuals have life, long-term care, or disability policies in place before pursuing genetic testing
Testing and Results
Cancer Genetic Testing

- **Somatic vs. Germline**
  - **Somatic** = tumor DNA - Used to target treatments to the patient’s tumor
  - **Germline** = patient’s DNA (what they were born with) - Used to identify patient’s risk for other cancers and the risk to relatives

- Germline testing is typically done on a blood or saliva sample and is usually covered by insurance
  - Most labs offer a maximum “self-pay” price of $250

- **Panel test** - Many genes tested at one time

- ~4 week turnaround time
Variant Interpretation

- Pathogenic variant
- Likely pathogenic variant
- Variant of uncertain significance (VUS)
- Likely benign variant
- Benign variant
Positive Result

The result report gives information about the cancer risks for that specific variant.

Management guidelines for the gene come from the National Comprehensive Cancer Network (NCCN).

Mail the patient a letter explaining the cancer risks and management guidelines, along with a copy of their test results, that way they can share with other family members.
Variant of Uncertain Significance (VUS)

A patient can have multiple VUS or may have a positive result and a VUS

VUS results do not impact medical management!

Unless the patient also has a positive result, make screening recommendations based off the family history of cancer

VUS may be re-classified in the future - recommend that the patient check in every few years for updates
Negative Result

A negative points towards the cancer being due to sporadic or environmental causes.

Depending on the patient’s family history, it may be possible that another family member has a pathogenic variant that the patient did not inherit.

A negative may be the result of limited technology* 

Make recommendations for cancer screening based on the family history.

*Limited technology refers to the capabilities and limitations of the testing methods used.
# Prostate Cancer

TESTING CRITERIA FOR PROSTATE CANCER SUSCEPTIBILITY GENES
(Specifically ATM, BRCA1, BRCA2, CHEK2, and HOXB13) (GENE-A)\textsuperscript{a,aa,bb}

### Testing is clinically indicated in the following scenarios:

- See General Tumor Criteria on CRIT-1.

### Personal history of prostate cancer with specific features:

- By tumor characteristics (any age)
  - Metastatic\textsuperscript{p}
  - Histology
    - high- or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
- By family history and ancestry
  - \geq 1 close blood relative\textsuperscript{q} with:
    - breast cancer at age \leq 50 y
    - triple-negative breast cancer at any age
    - male breast cancer at any age
    - ovarian cancer at any age
    - pancreatic cancer at any age
    - metastatic,\textsuperscript{p} high-, or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age
  - \geq 3 close blood relatives\textsuperscript{q} with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer
  - Ashkenazi Jewish ancestry

### Family history of cancer

- An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)\textsuperscript{q}

### Testing may be considered in the following scenario:

- Personal history of prostate cancer with intermediate-risk prostate cancer with intraductal/crribiform histology (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age
# Prostate Cancer Genes and Risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased</td>
<td>Consider screening at age 40</td>
</tr>
<tr>
<td>BRCA1</td>
<td>7-26%</td>
<td>Consider screening at age 40</td>
</tr>
<tr>
<td>BRCA2</td>
<td>19-61%</td>
<td>Recommend screening at age 40</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Increased</td>
<td>Consider screening at age 40</td>
</tr>
<tr>
<td>HOXB13</td>
<td>Increased</td>
<td>Consider screening at age 40</td>
</tr>
<tr>
<td>PALB2</td>
<td>Increased</td>
<td>Consider screening at age 40</td>
</tr>
<tr>
<td>TP53</td>
<td>Increased</td>
<td>Recommend screening at age 40</td>
</tr>
</tbody>
</table>

Prostate Cancer Screening = Yearly PSA and Digital Rectal Exam (DRE)
Pancreatic Cancer Screening

PANCREATIC CANCER SCREENING

• Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:
  1. A known P/LP germline variant in a pancreatic cancer susceptibility gene (ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, and TP53; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline P/LP variant; or
  2. A family history of exocrine pancreatic cancer in ≥1 first-degree and ≥1 second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant (many centers would enroll individuals with one affected first-degree relative and one second-degree relative); or
  3. Some groups have recommended pancreas surveillance for P/LP variant carriers in the absence of a family history.

• For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.

• Consider screening using annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening. Studies have typically started screening with contrast-enhanced MRCP and/or EUS in individuals at increased risk for pancreatic cancer. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

| Screening | Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
| All individuals with P/LP germline variants in STK11 |
| All individuals with P/LP germline variants in CDKN2A | Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
| Individuals with P/LP germline variants in one of the other pancreatic cancer susceptibility genes (ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53 | **GENE-A**
  ▶ Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified P/LP germline variant.
  ▶ The panel does not currently recommend pancreatic cancer screening for carriers of P/LP variants in genes other than STK11 and CDKN2A in the absence of a close family history of exocrine pancreatic cancer.
CRITERIA FOR THE EVALUATION OF Lynch syndrome based on personal or family history of cancer

- Known LS pathogenic variant in the family

- An individual with a LS-related cancer\(^{b}\) and any of the following:
  - Diagnosed \(< 50\) y
  - A synchronous or metachronous LS-related cancer\(^{b}\) regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer\(^{b}\) diagnosed \(< 50\) y
  - \(\geq 2\) first-degree or second-degree relatives with an LS-related cancer\(^{b}\) regardless of age

- Family history\(^{c}\) of any of the following:
  - \(\geq 1\) first-degree relative with a colorectal or endometrial cancer diagnosed \(< 50\) y
  - \(\geq 1\) first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer\(^{b}\) regardless of age
  - \(\geq 2\) first-degree or second-degree relatives with LS-related cancers\(^{b}\) including \(\geq 1\) diagnosed \(< 50\) y
  - \(\geq 3\) first-degree or second-degree relatives with LS-related cancers\(^{b}\) regardless of age

- Increased model-predicted risk for LS
  - An individual with a \(\geq 5\)% risk of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM\(_{5}\), MMRpro, MMRpredict)
    - Individuals with a personal history of CRC and/or endometrial cancer with a PREMM\(_{5}\) score of \(\geq 2.5\)% should be considered for MGPT.
    - For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM\(_{5}\) score threshold of \(\geq 2.5\)% rather than \(\geq 5\)% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the \(\geq 2.5\)% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age\(^{b,d}\)

\(^{a}\) This assumes criteria for evaluation for a polyposis syndrome on hereditary risk assessment has not been met.

\(^{b}\) LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.
# Lynch Syndrome Cancer Risks

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>General Population Risk</th>
<th>MLH1</th>
<th>MSH2/EPCAM</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>4.5%</td>
<td>46-61%</td>
<td>33-52%</td>
<td>10-44%</td>
<td>8.7-20%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.7%</td>
<td>34-54%</td>
<td>21-57%</td>
<td>16-49%</td>
<td>13-26%</td>
</tr>
<tr>
<td>Breast</td>
<td>13%</td>
<td>10-18%</td>
<td>1-12%</td>
<td>11-12%</td>
<td>8-13%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.3%</td>
<td>4-20%</td>
<td>8-38%</td>
<td>1-13%</td>
<td>1.3-3%</td>
</tr>
<tr>
<td>Gastric</td>
<td>&lt;1%</td>
<td>5-7%</td>
<td>0.2-9%</td>
<td>&lt;1-7.9%</td>
<td>NE</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.5%</td>
<td>6.2%</td>
<td>0.5-1.6%</td>
<td>1.4-1.6%</td>
<td>&lt;1-1.6%</td>
</tr>
<tr>
<td>Bladder</td>
<td>2.5%</td>
<td>2-7%</td>
<td>4.4-12.8%</td>
<td>1-8.2%</td>
<td>&lt;1-2.4%</td>
</tr>
<tr>
<td>Biliary Tract</td>
<td>&lt;1%</td>
<td>1.9-3.7%</td>
<td>0.02-1.7%</td>
<td>&lt;1%</td>
<td>0.2-&lt;1%</td>
</tr>
<tr>
<td>Urothelial</td>
<td>&lt;1%</td>
<td>0.2-5%</td>
<td>2-28%</td>
<td>0.7-5.5%</td>
<td>&lt;1-3.7%</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>&lt;1%</td>
<td>0.4-11%</td>
<td>1-10%</td>
<td>&lt;1-4%</td>
<td>0.1-0.3%</td>
</tr>
<tr>
<td>Prostate</td>
<td>11.6%</td>
<td>4.4-13.8%</td>
<td>4-16%</td>
<td>2.5-12%</td>
<td>5-12%</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>0.7-1.7%</td>
<td>2.5-7.7%</td>
<td>0.8-1.8%</td>
<td>0.6-&lt;1%</td>
</tr>
</tbody>
</table>
## Lynch Syndrome Screening

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td><em>MLH1 &amp; MSH2</em>: colonoscopy every 1-2 years beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if &lt;25)</td>
</tr>
<tr>
<td></td>
<td><em>MSH6 &amp; PMS2</em>: colonoscopy every 1-2 years beginning at age 30-35 (or 2-5 years younger than earliest diagnosis if &lt;25)</td>
</tr>
<tr>
<td>Gastric and Small Bowel Cancer</td>
<td>Upper GI screening with EGD starting at age 30-40 and repeating every 2-4 years, preferably in conjunction with colonoscopy</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>Education regarding symptoms</td>
</tr>
<tr>
<td></td>
<td>Consideration of hysterectomy after childbearing</td>
</tr>
<tr>
<td></td>
<td>Can consider endometrial biopsy every 1-2 years beginning at age 30-35</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>Education regarding symptoms</td>
</tr>
<tr>
<td></td>
<td>Consider BSO after childbearing</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>Consider screening with MRCP/EUS beginning at age 50 in patients with close family history of pancreatic cancer</td>
</tr>
<tr>
<td>Urothelial Cancer</td>
<td>Consider annual urinalysis beginning at age 30-35 in patients with family history of urothelial cancers or <em>MSH2</em> mutations</td>
</tr>
</tbody>
</table>
Hereditary Colon Polyposis

ADENOMATOUS POLYPOSIS TESTING CRITERIA
- Recommend testing if a personal history of ≥1 of the following criteria:
  - Personal history of ≥20 cumulative adenomas
  - Known pathogenic variant in adenomatous polyposis gene in family
  - Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Consider testing if a personal history of ≥1 of the following criteria:
  - between 10–19 cumulative adenomas,
  - desmoid tumor,
  - hepatoblastoma,
  - cribriform-morular variant of papillary thyroid cancer,
  - unilateral CHRPE, or
  - individual meets criteria for SPS (SPS-1) with at least some adenomas
  - Family history of polyposis and family unwilling/unable to have testing

RISK STATUS
- Pathogenic variant(s) known
- No known pathogenic variants in any polyposis gene

TESTING STRATEGY
- Genetic testing for familial pathogenic variant
- Germline multi-gene testing

RESULTS
- Positive for familial APC pathogenic variant
- Positive for biallelic MUTYH pathogenic variant
- Positive for known familial pathogenic variant in another polyposis gene
- Genetic testing not done
- Negative for familial pathogenic variant
- Positive for monoallelic (single copy) MUTYH pathogenic variant

TREATMENT/SURVEILLANCE
- To determine classical FAP vs. AFAP, see FAP/AFAP-1
- MAP-1
- GENE-3
- Manage as if positive for the known familial pathogenic variant
- CPUE-1
- NCCN Guidelines for Colorectal Cancer Screening
- GENE-9
- See appropriate hereditary CRC syndrome
- If individual has >10 adenomas, see CPUE-1
Hereditary Polyposis Genes

- **APC** - Familial Adenomatous Polyposis (FAP), autosomal dominant
- **AXIN2** - autosomal dominant
- **MUTYH** - MUTYH-associated polyposis (MAP), autosomal recessive
- **POLD1 & POLE** - Polymerase Proofreading-Associated Polyposis (PPAP), autosomal dominant
- **BMPR1A & SMAD4** - Juvenile Polyposis Syndrome (JPS), autosomal dominant
- **GREM1** - Hereditary Mixed Polyposis Syndrome, autosomal dominant
- **MLH3 & MSH3** - autosomal recessive
- **NTHL1** - autosomal recessive
- **PTEN** - Cowden syndrome/PTEN Hamartoma Tumor Syndrome, autosomal dominant
- **STK11** - Peutz-Jeghers Syndrome (PJS), autosomal dominant
Questions?

Cassie Gurganus, MS, CGC
✉ cagurganus@health.southalabama.edu
📞 251-410-4903

Ayesha Munir MD
✉ amunir@health.southalabama.edu
References:

1. *NCCN guidelines: Detection, Prevention, and Risk Reduction Version 3.2024* (Slides produced with permission from NCCN)
2. *ASCO Breast Cancer Guidelines*
3. *National Cancer Institute*