Hereditary Colon Cancer

Devanshi Patel, MS, LCGC
Center for Cancer Risk Assessment
March 27, 2019
An Overview of Our Discussion Today

- What is the function of the colon and rectum?
- What is colorectal cancer?
- What is the difference between sporadic versus hereditary (colorectal) cancer
- Describe hereditary colorectal cancer syndromes
- Identify patients who are candidates for genetic counseling and testing
- Discuss the benefits and limitations of genetics testing
The colon is part of the large intestine, the final part of the digestive system. Its function is to reabsorb fluids and process waste products from the body and prepare for its elimination. The colon consists of four parts: ascending colon, transverse colon, descending colon, and sigmoid colon. The rectum is a chamber that begins at the end of the large intestine, immediately following the sigmoid colon, and ends at the anus. The key role of the rectal is to act as a temporary storehouse for stool.
What is colorectal cancer?

- An abnormal growth of cells lining the colon/rectum that have the ability to invade or spread to other parts of the body.

- Colorectal cancer is the third most common cancer diagnosed in both men and women in the U.S. (American Cancer Society).

- Lifetime risk to develop CRC is about 1 in 20 (approximately 5%).

Image: www.serovera.com/images/colorectal-cancer-sm.jpg
How does colorectal cancer develop?

- Usually begins as a polyp
  - growth on the inner surface of the colon.
  - Often non-cancerous growths, but some can develop into cancer.
  - The two most common types:
    - Hyperplastic and inflammatory polyps. Usually these polyps do not carry a risk of developing into cancer.
    - Adenomas or adenomatous polyps. These if left alone could turn into colon cancer. These are considered pre-cancerous.
- May also develop from areas of abnormal cells in the lining of the colon or rectum, called dysplasia
  - More common in inflammatory diseases of the bowel such as Crohn's disease or ulcerative colitis

Adapted from cancer.org
Risk Factors for Colon Cancer

- Age
- Racial and ethnic background (AA, AJ)
- Certain types of diets (red/processed meats)
- Obesity
- Smoking
- Heavy alcohol use
- Physical inactivity
- Type 2 diabetes
- Personal history of inflammatory bowel disease
- Personal/family history of colorectal polyps cancer
- Hereditary factors

Adapted from cancer.org
Genetic vs. Hereditary

• All cancer **IS** genetic!
  – Cancer is caused by mistakes that accumulate in genes (DNA) in **one to several cells** of the body that leads to uncontrolled cell division & growth (i.e. a tumor)

• All cancer **IS NOT** hereditary!
  – Hereditary cancer means an individual was born with a gene mutation in **every cell** of their body that increases their chances of developing cancer in their lifetime
  – In general, having a hereditary mutation does NOT guarantee cancer development! Other genetic, environmental & lifestyle factors all contribute to a person’s cancer risk!

Courtesy of Sheryl Walker, MS, CGC, 2018
Cancer Etiology:
All cancer is genetic but only a portion is hereditary

http://yorkshirecancerresearch.org.uk/research/cancer-yorkshire
Andrew is a 45 year old man that was recently diagnosed with colon cancer. He has a family history of colon cancer, thyroid cancer, and uterine cancer. He has 2 young children and is concerned about their risk for developing cancer. Given his personal and family history of cancer and his concern regarding this children, he was referred by his oncology team for genetic counseling.
Sporadic Cancer

- Not a strong family history of cancer
- Relatives diagnosed at older ages
- Cancer due to other risk factors
  - BCC and SCC; sun exposure
  - Lung cancer in smokers

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
Familial Cancer

- Clustering of cancer cases seen in the family
- Ages of onset not strikingly young
- Multiple low-penetrant genes may play a role and interact with shared environmental triggers

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
Hereditary Cancer

- Multiple affected individuals across multiple generations
- Younger ages of onset (often <50)
- Individuals with multiple primaries
- Family history consists of unique tumor combinations and/or rare cancer types:
  - sarcoma, breast, brain
  - male breast cancer, ovarian/breast
  - breast, thyroid, uterine cancer
  - lobular breast, diffuse gastric cancer
  - colon, uterine cancer, ovarian, stomach

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
Purpose: Classification > Intervention

Assessment

Risk Classification

Intervention

Family Hx

Sporadic: Low

Standard screening/prevention recommendations

Familial: Moderate

Personalized screening/prevention recommendations

Hereditary: High

Referral for genetic evaluation with personalized screening/prevention recommendations

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
Helpful tool in the diagnosis of hereditary cancer is the compilation of a thorough family history of cancer

- Identify all individuals in three generations of both sides of a family
- Identify individuals with cancer diagnosis
  - Cancer site and pathology
  - Age of onset
- Other non-cancer phenotypes
  - Ex: types of number of polyps

Also helps determine what genetic test to offer and who first to test in the family

- If possible, offer testing to affected relatives first
Pedigree: Sporadic

[Pedigree diagram with numbers and symbols]
Pedigree: Hereditary
GENES ASSOCIATED WITH COLORECTAL CANCER
and their associated risk ranges

General population risk to age 80: 3.4%

Biallelic MUTYH
- 43-100%

APC
- 70-99%

MLH1
- 52-82%

MSH2
- 52-82%

EPCAM
- 52-82%

MSH6
- 10-69%

BMPR1A
- 40-50%

SMAD4
- 40-50%

STK11
- 39%

PMS2
- UP TO 20%

PTEN
- 9-16%

Monoallelic MUTYH
- 3.4-10%

ELEVATED RISK OF COLORECTAL CANCER, BUT NO DEFINED NUMBER AVAILABLE

TP53  POLE
CDH1  POLD1
CHEK2  GREM1

Courtesy of Andrea Forman, MS, LCGC; Myriad Genetics Laboratories Counseling Aids
Epidemiology of Colon Cancer

Sporadic (~60%)

Familial (~30%)

Lynch syndrome (HNPCC) (3-5%)

FAP (~1%)

MAP (~1%)

Rare Syndromes (~4%)

Distribution of Hereditary Colorectal Cancer

Cancer 1996;78:1149-67
Gastroenterology 2000;119:837-53
Am J Path 2003;162:1545-8
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<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Common Cancers</th>
<th>Non-cancer</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Lynch syndrome (aka Hereditary Non-polyposis Colorectal Cancer (HNPCC))</td>
<td><em>MLH1, MSH2, MSH6, PMS2, EPCAM</em></td>
<td>colorectal, uterine, gastric, ovarian, hepatobiliary tract, urinary tract, small bowel, brain*, sebaceous* neoplasms, pancreatic cancer* (in some families*)</td>
<td>Colon adenomas</td>
<td>MSI-high tumors, few polyps</td>
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<td>Familial Adenomatous Polyposis (FAP)</td>
<td><em>APC</em></td>
<td>colorectal, small intestinal, thyroid, gastric (rare)</td>
<td>colon adenomas, upper GI polyps, desmoid tumors</td>
<td>&gt;100 polyps</td>
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<td>Attenuated FAP (AFAP)</td>
<td><em>APC</em></td>
<td>colorectal, small intestinal, thyroid, gastric (rare)</td>
<td>colon adenomas, upper GI polyps</td>
<td>20-100 polyps</td>
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<td>MYH-Associated Polyposis (MAP)</td>
<td><em>MYH</em></td>
<td>colorectal cancer</td>
<td>colon adenomas, upper GI polyps</td>
<td>&gt; 10 polyps, overlapping phenotype with Lynch, A/FAP; Autosomal Repeats</td>
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</table>
### Other Hereditary Cancer Syndromes with Colorectal Cancer as Non-predominant Tumor

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<th>Syndrome</th>
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<th>Common Cancers</th>
<th>Non-cancer</th>
<th>Notes</th>
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<td>Cowden (PTEN Hamartoma Tumor)</td>
<td>PTEN</td>
<td>breast, thyroid, uterine, colon</td>
<td>macrocephaly, skin findings, hamartomatous GI polyps</td>
<td>trichilemmomas, papillomatous papules, acral keratoses</td>
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<td>Li-Fraumeni</td>
<td>TP53</td>
<td>sarcoma, breast, brain, adrenocortical, leukemia, colon</td>
<td>GI polyposis, mucocutaneous pigmentation (may fade in adulthood)</td>
<td>50% of cancer occur before age 50, many childhood tumors</td>
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<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>esophagus, stomach, small intestine, colon, pancreas, lung, breast, ovary (sex cord), endometrial</td>
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<td>pigmentation may fade in adulthood</td>
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<td>Hereditary Diffuse Gastric Cancer</td>
<td>CDH1</td>
<td>diffuse gastric cancer, (lobular) breast cancer, ?colon cancer</td>
<td></td>
<td>gastric cancer must be diffuse</td>
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</table>
**Other Colon Cancer Genes: BMPR1A, SMAD4**

- **Juvenile polyposis syndrome (JPS)**
  - Predisposition to hamartomatous polyps in the gastrointestinal (GI) tract, specifically in the stomach, small intestine, colon, rectum.
  - Cancer risks: colon, stomach, upper GI, pancreas
  - *SMAD4* mutations can also cause JPS/HHT (Hereditary Hemorrhagic Telangiectasia): life threatening arteriovenous malformations of lungs, brain and liver, nosebleeds.
Other Colon Cancer Genes

- **CHEK2**
  - Well-established
  - Increased risk, ~2-fold
  - NCCN Recommends:
    - Colonoscopy screening every 5y, beginning at age 40 (or 10 years prior to earliest colon cancer)

- **Up and comers?**
  - *RPS20, RNF43, GALNT12, ATM, BLM, RECQL*
Newer Polyposis Genes

- **GREM1/SCG5**
  - Hereditary Mixed Polyposis syndrome
    - Serrated polyps, PJS polyps, juvenile polyps, conventional adenomas, mixed histology polyps.
    - CRC risk undefined; no extra-colonic features identified

- **POLE, POLD1** Polymerase Proofreading Associated Polyposis (PPAP)
  - Adenomatous polyposis (small and large bowel), CRC
    - **POLE**: small bowel adenomas and gastric fundic gland polyps
    - **POLD1**: possible association with endometrial cancer

- **AXIN2**
  - Polyposis and oligodontia

- **NTHL1, MSH3**
  - Recessive
    - *MSH3* possible association with endometrial cancer
Tumor Suppressor Genes and Hereditary Cancer
Sporadic vs. Hereditary Cancer

**Sporadic Cancer**
- 2 normal genes
- 1 mutated gene
- 2 mutated genes
- Tumor develops

**Hereditary Cancer**
- 1 mutated gene
- 2 normal genes
- 1 normal gene
- Tumor develops

Adapted from Myriad Genetics Teaching Aid
General Implications for Medical Management

**Increased screening**
- Earlier starting age
  - 25yo for breast screening
  - 20-25 yo for colon screening
- Greater frequency
  - Annual colonoscopy
  - Alternating mammogram and MRI every 6 months
- More aggressive
  - Breast MRI in addition to mammogram

**Prevention**
- Chemoprevention
  - Tamoxifen (breast cancer risk)
  - Oral contraceptives (ovarian cancer risk)
  - NSAIDs (colon cancer/polyp risk)
- Surgical
  - Risk reducing mastectomy
  - Salpingo-oophorectomy
  - Prophylactic colectomy
We’ve Come a Long Way In Cancer Genetics

1996-2006
- Single gene testing
- Single syndrome testing

2006-2013
- Improvements in gene coverage sensitivity

2013-2018
- Multi-gene panels
- Other testing labs

Present

Courtesy of Stephanie Hicks, MS, LCGC
## Multi-Gene Cancer Panels

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<th>GENES</th>
<th>BREAST &amp; GYN</th>
<th>ENDOCRINE</th>
<th>GASTROINTESTINAL</th>
<th>GENITOURINARY</th>
<th>HEMATOLOGIC</th>
<th>NERVOUS SYSTEM/Brain</th>
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Invitae Genetics
Multi-gene panel options at a leading commercial laboratory

Gene Dx Laboratory
Pre-test Genetic Counseling

• Impact on personal cancer risk and medical management
  – surveillance, surgery, medication

• Psychological implications
  – peace of mind, anxiety, vulnerability, depression, difficult decisions

• Family dynamics
  – Affect relationship with family members/can be upsetting to relatives and strain relationship (burden of disseminating information, guilt, survivor guilt, non-p/maternity)

• Insurance coverage

• Confidentiality/Insurance Issues (ie. Discrimination)
  – Health insurance/Large Employer (Protected by law)
  – Life insurance/Disability/Long Term Care (No protection)
Genetic Discrimination

• 2008 – a federal law was put into place called:
  – The Genetic Information Non-Discrimination Act (GINA)
    • Health insurance
    • Employment

• But this doesn’t cover everything
  – Life insurance
  – Disability policies
  – Long-term care policies
A federal law was put into place called the Genetic Information Non-Discrimination Act (GINA) in 2010. This act covers health insurance and employment but does not cover life insurance, disability policies, or long-term care policies.

**Types of Results a Patient May Receive After Genetic Testing**

- **Negative**: Negative for the genes tested. Important to consider if there is a known mutation in your family.
- **VUS (Variant of Uncertain Significance)**: Unknown at this time if change identified is harmful.
- **Positive**: Positive for a gene that increases the risk of cancer.

Courtesy of Andrea Forman, MS, LCGC; Myriad Genetics Laboratories Counseling Aids
WHAT DO THESE TEST RESULTS MEAN?

GENETIC TESTING RESULTS

- Negative
- Variant of uncertain significance
- Deleterious or Suspected deleterious

IMPLICATIONS

- Medical management based on personal and family history of cancer
- Medical management based on cancer risks specific to gene mutation

Courtesy of Andrea Forman, MS, LCGC; Myriad Genetics Laboratories Counseling Aids
Case Results

- Andrew’s Results
- Family Results
  - True Negative: Average Risk
  - Phenocopy
Thank you!

Questions?