Genetic Testing in Colorectal Cancer

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Objectives

• Define at-risk patient population
• Discuss clinical case and management
• Discuss timing of genetic testing
• Discuss specific syndromes
• Discuss potential pitfalls of genetic testing
Clinical Case

- 57 year-old Caucasian male with recently diagnosed invasive adenocarcinoma of sigmoid colon (7/16)
- Colonoscopy #1 (7/15): 17 polyps
  - 13 tubular, 1 tubulovillous
- Colonoscopy #2 (11/15): 7 polyps
  - 6 tubular (1 HGD), 1 tubulovillous
- Colonoscopy #3 (2/16): 4 polyps
  - 4 tubular
- Colonoscopy #4 (3/16): 3 polyps
  - 2 tubular, 1 tubulovillous
- Colonoscopy #5 (7/16): 4 polyps
  - 3 tubular, 1 mod diff invasive adenocarcinoma
Colonoscopy 8/16

1.

2.

3.

4.

Endoscopic Ultrasound 8/16

• T2 vs T3 N0 MX
NCCN Criteria for Further Risk Evaluation

- Revised Bethesda guidelines
- Amsterdam criteria
- >10 adenomas
- Multiple GI hamartomatous polyps
- Family with a known high-risk syndrome +/- known mutation
- Desmoid tumor, cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma

High Risk Syndromes

- Lynch Syndrome
- Classical Familial adenomatous polyposis (FAP)
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Peutz-Jeghers Syndrome (PJS)
- Juvenile Polyposis Syndrome (JPS)
- Serrated Polyposis Syndrome (SPS)
Lynch Syndrome

- MC genetically inherited cause of colon cancer
- 2-4% of all CRC [1]
- MMR germline gene mutation
  - MLH1
  - MSH2
  - MSH6
  - PMS2
- Germline EPCAM mutation
- Lifetime risk of CRC ~80% in carriers [2]
- Mutation in 50-65% of those meeting Lynch criteria [3,4]

Lynch Syndrome Evaluation

- Test for Lynch syndrome if [5]:
  - Fulfillment of revised Bethesda or Amsterdam criteria
  - Endometrial cancer before age 50
  - Family history of Lynch syndrome
  - Risk ≥5% based on PREMM 1,2,6 risk prediction model
- IHC on all newly diagnosed colorectal and endometrial cancers [6]
- All patients with CRC diagnosed prior to age 70 and patients at older ages who meet Bethesda criteria [7]
- Genetic counseling recommended prior to germline mutation testing
- Family or personal history: colorectal, endometrial, gastric, ovarian, pancreatic, ureteral, renal, biliary tract, cerebral, sebaceous gland adenomas, keratoacanthomas, small bowel
Amsterdam Criteria

- At least 3 relatives diagnosed with colorectal cancer; one must be a first-degree relative of the other 2
- Colorectal cancer involving at least 2 generations
- One or more colorectal cancer cases diagnosed before at 50

Amsterdam II criteria
- At least 3 relatives diagnosed with HNPCC-associated cancers (colorectal endometrial, small bowel, ureter, or renal pelvis); one must be a first-degree relative of the other 2
- Colorectal cancer involving at least 2 generations
- One or more colorectal cancer cases diagnosed before at 50

Revised Bethesda Guidelines

- Tumors from individuals should be tested for MSI in the following situations:
  1. Colorectal diagnosed in a patient who is less than 50 years of age.
  2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age.
  3. Colorectal cancer with the MSI-H* histology diagnosed in a patient who is less than 60 years of age.
  4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
  5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

*HNPCC-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.
*MISH = microsatellite instability-high in tumors refers to changes in 2 or more of the five National Cancer Institute-recommended panels of microsatellite markers [?].
*Presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants noted to keep less than 60 years of age in the guidelines.

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**PREMM 1, 2, 6 Prediction Model**

**Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)**

**PREMM:26 Model: Prediction Model for MLH1, MSH2, and MSH6 gene mutations**

The PREMM (Prediction Model for Lynch Syndrome) algorithm can be used to evaluate the risk of developing colorectal cancer in individuals with a family history of Lynch Syndrome. It is recommended that individuals with a family history of Lynch Syndrome be tested for germline mutations in MLH1, MSH2, and MSH6 genes.

**Presumed Information**

- *Percentage* refers to the individual being evaluated; clearly, the individual should have surgical diagnosis.

<table>
<thead>
<tr>
<th>Presumed Test</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Sporadic Colorectal Cancers</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Abnormal IHC/MSI</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Has the Patient had a Personal Cancer?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Overall Predicted Probability of MLH1, MSH2, or MSH6 Mutation:**
- Predicted Probability of MLH1 Mutation: 3.9%
- Predicted Probability of MSH2 Mutation: 1.3%
- Predicted Probability of MSH6 Mutation: 1.1%

**Lynch: Tumor Testing**

- **IHC or MSI testing**
  - 77-89% sensitivity, ~90% specificity [8]
  - 97.5% concordance [7]
- **MSI Classification**
  - MSI-H: 2+
  - MSI-L: 1
  - MSS: 0
- Abnormal IHC/MSI → GENETIC COUNSELING → germline testing of MLH1, MSH2, MSH6, PMS2, EPCAM [5]
- Caution: 10-15% of sporadic CRC exhibit abnormal MLH1 IHC and are MSI-H → test BRAF or for hypermethylation of MLH1 promoter [9]
### Lynch Recommendations

<table>
<thead>
<tr>
<th>Lynch Syndrome</th>
<th>20-25% (MUTYH mutation)</th>
<th>25-30% (MSH6/ PMS2 mutation)</th>
<th>程-程</th>
<th><strong>Gastroscopy</strong></th>
<th>(24, 29, 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial and ovarian</td>
<td>30-35</td>
<td>1</td>
<td>No evidence of survival benefit of surveillance proven (see Table B). Annual pelvic exam; offer annual endometrial biopsy and transvaginal ultrasound to at-risk women. Consider total abdominal hysterectomy/bilateral salpingo-oophorectomy in women who have completed childbearing.</td>
<td>(24, 26, 60, 359)</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3-5</td>
<td>1</td>
<td>Consider magnetic resonance imaging (MRI) and/or endoscopic ultrasound in mismatch repair gene mutation carriers with pancreatic cancer in a first-degree relative.</td>
<td>(73)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>25-30</td>
<td>1</td>
<td>Limited data exist to advocate urinary screening. INCCN recommends considering an annual ultrasound.</td>
<td>(24)</td>
<td></td>
</tr>
<tr>
<td>Small bowel and gastric</td>
<td>30-35</td>
<td>3-5</td>
<td>Consider esophagogastroduodenoscopy with extended duodenoscopy in select individuals.</td>
<td>(24)</td>
<td></td>
</tr>
</tbody>
</table>

Source: American College of Gastroenterology

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### Familial Adenomatous Polyposis

- AD germline mutation in APC gene
  - 70-90% sensitivity in affected families [10]
- <1% of all CRC
- ≥100 synchronous adenomas
- Risk for CRC ~100% by age 50
- Left sided predominance
- AFAP variant
  - Later onset of disease and fewer adenomatous polyps (10-<100) [11]
  - Right sided predilection [12]
  - Risk for CRC ~70% by age 80 [5]
FAP/AFAP Evaluation

• Obtain genetic testing if [5]:
  – Personal history of ≥20 adenomas
  – Known family history of APC mutation
• Consider genetic testing if:
  – History of desmoid tumor, hepatoblastoma, cribriform morular variant of papillary thyroid cancer, extracolonic adenomas, osteomas, epidermal cysts, congenital hypertrophy of the retinal pigment epithelium
  – between 10-20 cumulative adenomas

FAP/AFAP Recommendations

<table>
<thead>
<tr>
<th>Familial adenomatous polyposis (FAP)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon 10-15 1-2* Flexible sigmoidoscopy or colonoscopy*</td>
<td>(24,127)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract 25-30 1-5* Esophagogastroduodenoscopy with a side-viewing instrument</td>
<td>(127)</td>
</tr>
<tr>
<td>Thyroid Left teenage years 1 Annual thyroid examination; annual thyroid ultrasound</td>
<td>(24,171)</td>
</tr>
<tr>
<td>Intraabdominal desmoids 1 Annual abdominal palpation. (AGA Guidelines: Consider abdominal MRI or computed tomography [CT] 1-3 years after colectomy then at 5-10-year intervals with family history of symptomatic desmoids or if suggestive abdominal symptoms occur.)</td>
<td>(24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attenuated FAP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon 18-20 1-2* Colonoscopy</td>
<td>(24,127)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract 25-30 1-5* Esophagogastroduodenoscopy with a side-viewing instrument</td>
<td>(127)</td>
</tr>
<tr>
<td>Thyroid 1 Annual thyroid examination</td>
<td>(24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MUTYH-associated polyposis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon 25-30 1-2* Colonoscopy</td>
<td>(127)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract 30-31 Baseline Esophagogastroduodenoscopy with a side-viewing instrument</td>
<td>(24)</td>
</tr>
</tbody>
</table>

Source: American College of Gastroenterology
MUTYH Associated Polyposis

- Autosomal recessive inheritance of biallelic germline MUTYH mutations [13]
- Most commonly 20-99 adenomas [14,15]
  - Multiple hyperplastic and/or sessile serrated polyps may occur
  - Patients may meet criteria for SPS
- Risk of CRC by age 60 ~43% [14]

MAP Evaluation

- Obtain genetic testing if [5]:
  - Family history of MAP and known MUTYH mutations
    - \( \geq 20 \) adenomatous polyps
- Consider genetic testing if:
  - \( \geq 10 \) adenomatous polyps
# MAP Recommendations

<table>
<thead>
<tr>
<th>Familial adenomatous polyposis (FAP)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>10-15, 1-2&quot;</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>25-30, 1-6&quot;</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Late teenage</td>
</tr>
<tr>
<td>Intraabdominal desmoids</td>
<td>1</td>
</tr>
</tbody>
</table>

- Flexible sigmoidoscopy or colonoscopy
- Esophagogastrodupodenoscopy with a side-viewing instrument
- Annual thyroid examination, annual thyroid ultrasound

<table>
<thead>
<tr>
<th>Attenuated FAP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>18-20, 1-2&quot;</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>25-30, 1-6&quot;</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
</tr>
</tbody>
</table>

- Annual abdominal palpation. (NCCN Guidelines: Consider abdominal MRI or computed tomography (CT) 1-3 years after colectomy then at 5-10-year intervals with family history of symptomatic desmoids or if suggestive abdominal symptoms occur)
- Annual colonoscopy

<table>
<thead>
<tr>
<th>MUTYH-associated polyposis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>25-30, 1-2&quot;</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>30-35 Baseline</td>
</tr>
</tbody>
</table>

- Esophagogastrodupodenoscopy with a side-viewing instrument

Source: American College of Gastroenterology

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## Peutz-Jeghers Syndrome

- Autosomal dominant inheritance
- Characterized by hamartomatous polyps
- Hyperpigmentation of lips, buccal mucosa, vulva, fingers, toes
- Lifetime risk of CRC ~39%
- Increased risk of cancer of breast, pancreas, ovary, gallbladder
PJS Continued

- Most cases are due to germline mutations of STK11 (LKB1) [19,20]
  - ~50% of patients do not have detectable STK11/LKB1 mutations
- Clinical diagnosis criteria (at least 2 of the following): [5]
  - ≥2 PJS-type polyps of the small bowel
    - Non-dysplastic, normal overlying epithelium, arborizing pattern of growth with MM extending into branching fronds of polyp
  - Hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - Family history of PJS

PJS Recommendations

<table>
<thead>
<tr>
<th>Problem</th>
<th>Age</th>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>10</td>
<td>Colonoscopy</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>18</td>
<td>Esophagogastroduodenoscopy</td>
<td>3</td>
</tr>
<tr>
<td>Small bowel</td>
<td>18</td>
<td>Video capsule endoscopy</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>30</td>
<td>Magnetic resonance cholangiopancreatography or endoscopic ultrasound</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>Annual self-exam starting age 18, annual breast MRI, and/or mammogram starting at age 25</td>
<td>1</td>
</tr>
<tr>
<td>Ovary</td>
<td>25</td>
<td>Pelvic exam and pelvic or transvaginal ultrasound, CA-125 probably not helpful</td>
<td>1</td>
</tr>
<tr>
<td>Endometrium</td>
<td>25</td>
<td>Pelvic exam and pelvic or transvaginal ultrasound</td>
<td>1</td>
</tr>
<tr>
<td>Cervix (adenoma malignum)</td>
<td>25</td>
<td>Pap smear</td>
<td>1</td>
</tr>
<tr>
<td>SCTAT (sex cord tumor with annular tubules)</td>
<td>25</td>
<td>Same as uterine and ovarian, almost all women develop SCTAT, but 20% become malignant</td>
<td>1</td>
</tr>
<tr>
<td>Testicular (Sertoli cell tumor)</td>
<td>Birth to teenage years</td>
<td>Testicular exam, ultrasound if abnormalities palpated or if teratoma occurs, 10 to 20% of benign Sertoli cell tumors become malignant</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Provide education about symptoms and smoking cessation</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: American College of Gastroenterology
Juvenile Polyposis Syndrome

- Autosomal dominant inheritance
- Characterized by multiple hamartomatous polyps of the colon/rectum that manifest during childhood
  - 90% of patients present with bleeding or anemia \[21\]
- Increased risk for colon/rectal, gastric, duodenal, and pancreatic cancers
- CRC risk approaches 68% by age 60 \[22,23\]

JPS Continued

- 50-64% of cases due to germline mutations in BMPR1A and SMAD4 \[24\]
  - ENG
- Clinical diagnostic criteria (at least one of the following) \[24\]:
  - At least 5 juvenile polyps of the colon
  - Juvenile polyps in other parts of the GI tract
  - At least one polyp in an individual with a family history of JPS
Juvenile Polyposis Syndrome

1. 2.

3. 4.

JPS Recommendations

<table>
<thead>
<tr>
<th>Juvenile polyposis syndrome</th>
<th>12-15</th>
<th>2-3</th>
<th>Colonoscopy ¥</th>
<th>(24,210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>12-15</td>
<td>2-3</td>
<td>Esophagogastroduodenoscopy ¥</td>
<td>(24,208)</td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
<td>Rare, undefined lifetime risk. Periodic enteroscopy, capsule endoscopy and/or CT enterography</td>
<td>(24,209)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td>Rare, undefined lifetime risk. No screening recommendations given</td>
<td>(24)</td>
</tr>
<tr>
<td>HHT (hereditary hemorrhagic telangiectasia)</td>
<td>Within first 6 months of life</td>
<td>—</td>
<td>Undefined lifetime risk. In individuals with SMAD4 mutations, screen for vascular lesions associated with HHT</td>
<td>(24,361)</td>
</tr>
</tbody>
</table>

Source: American College of Gastroenterology
Serrated Polyposis Syndrome

- Serrated polyps include hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas [25]
- CRC is thought to arise independent of the adenoma→carcinoma sequence
- >50% lifetime risk of CRC [26]
- Clinical diagnosis
  - No currently identified genetic mutation
  - Genetic testing not routinely recommended
  - May consider MUTYH testing for SPS patients with concurrent adenomas and/or family history of adenomas [27]
- Smoking is thought to increase phenotypic expression [28]

Clinical Criteria for SPS

- Clinical diagnosis of SPS if ≥1 of the following:
  - At least 5 serrated polyps proximal to the sigmoid colon with ≥2 being >10 mm
  - Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
  - >20 serrated polyps of any size, distributed throughout the colon
Serrated Polyposis Syndrome

1. Prophylactic or therapeutic colectomy when:
   - Inability to control growth of serrated polyps
   - HGD in serrated polyp that cannot be entirely removed
   - Development of cancer
2. No recommendation regarding screening for extracolonic malignancy
3. Recommendation discordance for screening individuals with family history of SPS
   - ACG: individualize screening based on results from family members
   - NCCN: FDRs should have colonoscopy at earliest of the following:
     - Age 40
     - Same age as youngest SPS diagnosis in family
     - 10 years before CRC in family in patient with SPS

Source: American College of Gastroenterology
Additional High Risk Syndromes

- Li-Fraumeni Syndrome
  - TP53 germline mutation [32]
- Cowden Syndrome (PTEN Hamartoma Tumor Syndrome)
  - PTEN germline mutation
  - 9-16% lifetime risk of CRC [33,34]
  - Colon surveillance with colonoscopy at age 15, repeat every 2 years [31]
  - UGI surveillance with EGD at age 15, repeat every 2-3 years based on number of duodenal polyps

Clinical Case Summary

- 57 year-old male with 31 cumulative polyps in 13 months
- Newly diagnosed invasive adenocarcinoma of the rectosigmoid
- Negative metastatic evaluation with EUS revealing stage IIa disease
EGD 8/16

Genetic Counseling/Testing

- Genes tested:
  - ATM, APC, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53→ MUTYH c.1187G>A (p.Gly396Asp) Homozygous
Management Options

• Segmental resection or left hemicolectomy
  – Ongoing risk of metachronous disease
  – Polyps identified throughout colon
  – Known accelerated dwell time
  – Uncertain surveillance intervals

• Total proctocolectomy
  – Associated morbidity
  – Decreased quality of life
  – Unnecessarily radical procedure

Management Course

• Per NCCN/ACG guidelines based on MUTYH mutation and existing colonic adenocarcinoma
• Total proctocolectomy with ileostomy formation
  – Moderately differentiated adenocarcinoma of rectosigmoid
  – T2: into but not through MP
  – 0/26 mesenteric lymph nodes
  – Diffuse polyposis coli with tubular, tubulovillous and flat adenomatous polyps without additional foci of carcinoma or HGD
• EGD per Spigelman classification
• Annual thyroid US
• Ileoscopy every 2 years
Conclusion

• Importance of genetic counseling
  – Genetic testing interpretation
  – Clinical implications of testing
• High risk patients should undergo proper genetic testing
  – Family members
  – Screening and surveillance
  – General lack of awareness in physician community
• Genetic testing limitations
  – JPS, PJS, SPS, FAP

Questions??
References


References

References


References