Colon Cancer Syndromes

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Learning Objective

• Describe the appropriate management of colon cancer syndromes as recommended in recent guidelines
All Patients in GI Outpatient Practice...

- Family history of cancer
- Premalignant GI conditions

Determination of the risk of a familial predisposition to cancer
- Clinic AND
- Endoscopy Suite
Initial Assessment

• Essential Elements
  – Type of cancers in 1st and 2nd degree relatives
  – Type of polyps in 1st degree relatives
  – Age at diagnosis and lineage (e.g., maternal)
• Genetic testing for germline mutations should be done on the most informative candidate(s)
• Pre- and post-test genetic counseling to ensure the patient’s informed decision making

Standards for informed consent in GI

1. Specific genetic mutation(s) or genomic variant(s) tested
2. Implications of positive and negative results
3. Possibility that the test will not be informative
4. Options for risk estimation without genomic testing
5. Risk of passing a genetic variant to children
6. Technical accuracy of the test
7. Fees involved in testing and counseling
8. Psychological implications of test results (benefits and risks)
9. Risks and protections against genetic discrimination
10. Confidentiality issues
11. Possible use of DNA testing samples in future research
12. Options and limitations of medical surveillance
13. Importance of sharing results with at-risk relatives
14. Plans for follow-up after testing
Candidates for Surveillance Measures

- Patients who meet clinical criteria for a syndrome
- Those with identified pathogenic germline mutations

Lynch HT and Shaw TG. Practical genetics of colorectal cancer. 2013; 2(2).
http://cco.amegroups.com/article/view/1747/3043
Colon Cancer Syndromes

- Lynch syndrome
- Familial adenomatous polyposis (FAP)
- Attenuated familial adenomatous polyposis (AFAP)
- MUTYH-associated polyposis (MAP)
- Peutz–Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- PTEN syndrome (Cowden)
- Serrated (hyperplastic) polyposis

Who gets Genetic Testing for Lynch?

- Personal history of a tumor showing evidence of mismatch repair deficiency
  - and no demonstrated BRAF mutation or hypermethylation of MLH1
- A known family mutation associated with LS
- Risk of ≥5% chance of LS based on risk prediction models
Lynch Syndrome – Universal Testing

- What is universal testing?
  - All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency
    - Immuno-histochemical testing for the following proteins:
      - MLH1/MSH2/MSH6/PMS2 and/or
    - Microsatellite instability (MSI)
IHC for MMR Proteins in Colon Cancer

Universal Testing

MLH1  MSH2  MSH6  PMS2

Absent

Intact


Lynch Testing Strategies

Ohio State University
- All proteins present (20%)
- Overt under SS, or polyposis, or strong family history
- BRCA1/2 mutation analysis
- MSH6 and/or PMS2 absent, MSH2 only absent (5%)
- Sequence and gene rearrangements for absent proteins

Huntsman Cancer Institute
- All related colon cancers
- IHC analysis
- BRCA1/2 mutation testing
- BRAF/WRC5E testing
- Genetic counseling
- Letter to patient; genetic counseling and possibly additional testing warranted
- Normal results letter
- Negative
- Positive
- MUH panel
- Additional testing warranted

Lyn<ref class="footnote">h Syndrome – Genetic Testing

• Genetic testing of patients with suspected LS should include germline testing for either:

  – MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes

  – Altered gene(s) indicated by IHC testing

Lyn<ref class="footnote">h Mutations

Lynch Syndrome - Surveillance

• Screening for CRC by colonoscopy should be performed \textit{at least} every 2 years, beginning between ages 20 and 25 years

• \textbf{Annual colonoscopy} should be considered in confirmed mutation carriers
  – Strong recommendation
  – Moderate quality of evidence for screening, and
  – Very low quality of evidence for annual surveillance and age of initiation

Lynch Syndrome Colon Cancer and Colectomy

• Colectomy with ileo-rectal anastomosis (IRA)
  – Preferred treatment of patients affected with LS with colon cancer or colonic neoplasia \textit{not} controllable by endoscopy

• Segmental colectomy is an option in patients unsuitable for total colectomy if regular postoperative surveillance is conducted
What Kind of Colectomy in LS Colon Cancer?

<table>
<thead>
<tr>
<th>Event-free Survival at 5 years</th>
<th>Subsequent CRC</th>
<th>Subsequent Abdominal Surgery</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Surgery or Limited Resection</td>
<td>94%</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>Subtotal Colectomy</td>
<td>74%</td>
<td>63%</td>
<td>88%</td>
</tr>
</tbody>
</table>


City of Hope Cancer Screening & Prevention Program Network

Lifetime Risk for Colorectal Cancer to Age 80

- **Average (sporadic)**
  - 5-6%
- **Moderate (familial)**
  - 80%
  - Moderate Risk Screening Guidelines:
    - Colonoscopy every 5 years
    - Fecal occult blood test annually
- **High Lynch Syndrome**
  - 60%
  - High Risk Screening Guidelines:
    - Colonoscopy every 2-3 years
    - Fecal occult blood test annually

Lifetime Risks for Other Lynch Syndrome Cancers

- **Endometrial (Ovarian) Cancer**
  - 60%
- **Gastric (Stomach) Cancer**
  - 40%
- **Ovarian Cancer**
  - 11-19%
- **Other Cancers**
  - 9-12%
  - 1-7%

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- *Note: Consider annual transvaginal ultrasound and office endometrial sampling.
- Colonoscopy every 2-3 years beginning at 35.
- Consider colonoscopy every 2-3 years beginning at 35.
- Consider annual endoscopy.*
LS - Surveillance Extra-Colonic Cancer

- **Endometrial and ovarian cancers**
  - Endometrial biopsy and trans-vaginal ultrasound annually, starting at age 30 to 35 years if surgery deferred
  - Hysterectomy and bilateral salpingo-oophorectomy
    - Finished child bearing, optimally at age 40–45 years

- **Gastric and duodenal cancers**
  - EGD with gastric biopsy at age 30–35 years
  - Treatment of *Helicobacter pylori* infection when found
  - Ongoing surveillance every 3–5 years may be considered if there is a family history of gastric or duodenal cancer

- **Cancers of the urinary tract, pancreas, prostate, and breast**
  - Alter from average risk routine if family history

LS - Chemoprevention

- Daily aspirin may decrease the risk of CRC and extra-colonic cancer in LS
  - Not sufficiently robust for its standard use

FAP/MAP/Polyposis – Indications for Genetic Testing

- Personal history of >10 cumulative colorectal adenomas
- Family history of adenomatous polyposis (AP) syndrome
- History of adenomas and FAP-type extra-colonic findings
  - Duodenal/ampullary adenomas
  - Desmoid tumors (abdominal>peripheral)
  - Papillary thyroid cancer
  - Congenital hypertrophy of the retinal pigment epithelium
  - Epidermal cysts
  - Osteomas
- Testing should include APC and MUTYH gene mutations

Surveillance in Polyposis

- At risk for or affected with the classic FAP
  - Screening for CRC by annual colonoscopy or flexible sigmoidoscopy
  - Should begin at puberty

- AFAP or MAP
  - Surveillance should be by colonoscopy
When Should AP Patients Have Colectomy?

- **Absolute indications**
  - documented or suspected cancer or
  - significant symptoms

- **Relative indications**
  - the presence of multiple adenomas >6 mm
  - a significant increase in adenoma number
  - an adenoma with high-grade dysplasia
  - inability to adequately survey the colon because of multiple diminutive polyps

Screening for Extra-colonic CA in AP

- **Gastric and proximal small bowel tumors**
  - Upper endoscopy including duodenoscopy
  - Age 25–30 years
  - Surveillance depending on Spigelman stage of duodenal polyposis
    - 0 = 4 years
    - I = 2–3 years
    - II = 1–3 years
    - III = 6–12 months
    - IV=surgical evaluation
  - Examination of the stomach should include random sampling of fundic gland polyps
    - Low-grade dysplasia is common in fundic gland polyps, and surgery should be reserved for high-grade dysplasia or cancer

- **Thyroid tumors**
  - Annual thyroid ultrasound

- **Hepatoblastoma**
  - Biannual screening should be offered to affected infants annually until age 7 years
  - α-fetoprotein and ultrasounds
Duodenal Adenomatisis Staging

Following Total Colectomy

- Postsurgical surveillance should include yearly endoscopy of rectum or ileal pouch
- Examination of an ileostomy every 2 years
FAP Prevention

- Change in total duodenal and colorectal polyp burden at 6 months
  - Erlotinib 75 mg daily
  - Sulindac 150 mg twice daily
  - NOT part of guidelines!

https://clinicaltrials.gov/ct2/show/NCT01187901

Peutz-Jeghers Syndrome (PJS)

- Individuals with the following features should be evaluated for PJS:
  - Perioral or buccal pigmentation and/or
  - Two or more histologically characteristic GI hamartomatous polyp(s) or
  - A family history of PJS
Peutz-Jeghers Syndrome

- Prevalence: 1 in 25-280,000
- Hamartomatous and adenomatous polyposis especially of the small intestine
- Inheritance: AD
- Gene: STK11
- Lifetime Cancer risk 37-93%
  - GI Cancers 38-66%
    - CRC 2-39%
    - Gastric 29%
    - Pancreatic 11-36%
  - Breast Cancer 30-54%
  - Uterine Cancer 9-21%

http://www2.hshsl.umaryland.edu/morningreport/med/index.php/2009/08/
http://fer13013.blogspot.com/2014/09/colon-hamartomatous-polyp-including.html

PJS - Surveillance

<table>
<thead>
<tr>
<th>Site</th>
<th>Age Begin Surveillance (years)</th>
<th>Surveillance Interval (years)</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>8, 18</td>
<td>3</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Stomach</td>
<td>8, 18</td>
<td>3</td>
<td>EGD</td>
</tr>
<tr>
<td>Small bowel</td>
<td>8, 18</td>
<td>3</td>
<td>Capsule</td>
</tr>
<tr>
<td>Pancreas</td>
<td>30</td>
<td>1-2</td>
<td>MRCP or EUS</td>
</tr>
<tr>
<td>Breast</td>
<td>25</td>
<td>1</td>
<td>Exam + image</td>
</tr>
<tr>
<td>Ovarian</td>
<td>25</td>
<td>1</td>
<td>Pelvic ex + US</td>
</tr>
<tr>
<td>Endometrial</td>
<td>25</td>
<td>1</td>
<td>Pelvic ex + US</td>
</tr>
<tr>
<td>Cervix</td>
<td>25</td>
<td>1</td>
<td>Pap smear</td>
</tr>
<tr>
<td>SCTAT</td>
<td>25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Testicular</td>
<td>Birth to teen</td>
<td>1</td>
<td>Exam + US</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>-</td>
<td>Smoking cess</td>
</tr>
</tbody>
</table>
**Juvenile Polyposis Syndrome (JPS)**

- **Diagnostic criteria:**
  - Individuals with five or more juvenile polyps in the colo-rectum or
  - Any juvenile polyps in other parts of the GI tract should undergo evaluation for JPS
  - Any number of juvenile polyps and one or more affected family members

- Genetic evaluation should include testing for *SMAD4* and *BMPR1A* mutations

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### JPS - Surveillance

<table>
<thead>
<tr>
<th>Site</th>
<th>Age Begin Surveillance (years)</th>
<th>Surveillance Interval (years)</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>12-15</td>
<td>1-3</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Stomach</td>
<td>12-15</td>
<td>1-3</td>
<td>EGD</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>?</td>
<td>“Periodic”</td>
<td>Enteroscopy, Capsule, CTE</td>
</tr>
<tr>
<td>HHT</td>
<td>1st 6 mos</td>
<td>N/A</td>
<td>Vascular lesions</td>
</tr>
</tbody>
</table>

- Colectomy and IRA or procto-colectomy and IPAA is indicated for polyp-related symptoms, or cannot be managed endoscopically
- CV examination and eval for HHT in *SMAD4* carriers
Cowden Syndrome (PTEN Hamartoma Tumor Syndrome)

- Individuals with multiple GI hamartomas or ganglio-neuromas should be evaluated for Cowden Syndrome (CS) and related conditions

- Genetic evaluation of a patient with possible CS should include testing for PTEN mutations

PTEN (Cowden)

- Inheritance: Autosomal dominant
- Gene: PTEN
- 25-85% lifetime risk of breast cancer
  - <1% overall of all breast cancer
  - Average age of diagnosis 38-46y
- 5-28% lifetime risk of endometrial cancer
- 3-35% lifetime risk of non-medullary thyroid (follicular) cancer
- 40-93% lifetime risk of polyps (hamartomatous)
  - 9% lifetime risk of CRC
  - Ganglioneuroma
  - 13% of PTEN mutation-associated Cowden syndrome patients developed CRC <50y
- Strongly a/w Lhermitte-Duclos (dysplastic gangliocytoma)
- Trichilemmoma

Surveillance - Cowden

<table>
<thead>
<tr>
<th>Site</th>
<th>Age Begin Surveillance (years)</th>
<th>Surveillance Interval (years)</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>15</td>
<td>2</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>UGI/Small bowel</td>
<td>15</td>
<td>2-3</td>
<td>EGD</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Adolescence</td>
<td>1</td>
<td>Exam + US</td>
</tr>
<tr>
<td>Breast</td>
<td>25</td>
<td>Monthly</td>
<td>Self-exam</td>
</tr>
<tr>
<td></td>
<td>30-35</td>
<td>1</td>
<td>MMG + MRI</td>
</tr>
<tr>
<td>Uterine</td>
<td>30-35</td>
<td>1</td>
<td>Endometrial sampling or US</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>18</td>
<td>1</td>
<td>UA with cytology + US</td>
</tr>
<tr>
<td>Melanoma</td>
<td>By 18</td>
<td>1</td>
<td>Skin exam</td>
</tr>
</tbody>
</table>

Serrated Polyposis Syndrome

- Diagnostic criteria for SPS:
  (i) at least 5 serrated polyps proximal to the sigmoid colon with ≥2 of these being >10 mm
  (ii) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; or
  (iii) >20 serrated polyps of any size, distributed throughout the large intestine
Surveillance - SPS

- A clear genetic etiology has not yet been defined for SPS
  - Not routinely recommended for SPS patients
- Testing for \textit{MUTYH} mutations may be considered for SPS patients with concurrent adenomas and/or a family history of adenomas
- Colonoscopies Q 1–3 years with removal of all polyps >5 mm
- Indications for surgery for SPS include
  - an inability to control the growth of serrated polyps, or
  - the development of cancer.
- Colectomy and IRA is a reasonable option given the risks of metachronous neoplasia
- There is no evidence to support extra-colonic cancer surveillance for SPS
- Screening recommendations for family members are currently unclear pending further data and should be individualized

Cumulative Risks of CRC

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Risk</th>
<th>Average age of diagnosis (years)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic cancer</td>
<td></td>
<td>4.8%</td>
<td>69</td>
<td>SEER(303)</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1/MSH2</td>
<td></td>
<td>27–74% (M: 22–61%)</td>
<td>(30–35, 38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27-60</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td></td>
<td></td>
<td>22–69% (M: 10–30%, F: 12%)</td>
<td>(31, 36, 40, 64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-63</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td></td>
<td></td>
<td>20% (M: 12%)</td>
<td>(37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47-66</td>
<td></td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>(\text{APC})</td>
<td>100%</td>
<td>38-41</td>
<td>(81, 123, 126, 316)</td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td>(\text{APC})</td>
<td>69%</td>
<td>54-58</td>
<td>(88, 90, 126, 317-319)</td>
</tr>
<tr>
<td>\textit{MUTYH}-associated polyposis</td>
<td>\text{MUTYH}</td>
<td>43-100%</td>
<td>48-50</td>
<td>(100, 126, 134, 135, 319)</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>\text{SMAD4}</td>
<td>38-68%</td>
<td>34-44</td>
<td>(126, 220, 320-323)</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>\text{STK11}</td>
<td>39%</td>
<td>42-46</td>
<td>(126, 196, 197)</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>\text{PTEN}</td>
<td>9-16%</td>
<td>44-48</td>
<td>(224, 235, 236, 324)</td>
</tr>
<tr>
<td>Serrated polyposis syndrome</td>
<td>Not known</td>
<td>15-50%</td>
<td>48</td>
<td>(243, 254)</td>
</tr>
</tbody>
</table>
Take Home Points

- Assessment for cancer susceptibility should be a standard part of GI practice
- ~10–15% of patients may need more detailed risk assessment
- Genetic testing is widely available and should be part of standard of care
- Mutation carriers and at-risk individuals require intensive surveillance, with individualized care