Access GI Expertise, Educational Resources and Support for You and Your Patients

A Free ACG Member Benefit Designed to Help You and Your Patients!
Learn More and Join Today at GIONDEMAND.COM

2023 ACB HEPATOLOGY SCHOOL & EASTERN REGIONAL POSTGRADUATE COURSE
JUNE 2-4, 2023 | RENAISSANCE HOTEL WASHINGTON, DC

Register online: meetings.gi.org
Moderators

Julie Yang, MD

Elana Levinson, MS, CGC
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2023 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2024 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

NSGC CEU Credit

The National Society of Genetic Counselors (NSGC) has authorized CGA-IGC to offer up to 0.6 CEUs or 6 Category 1 contact hours for the activity CGA-IGC 2023 Webinar Series about Inherited GI Cancers.

The American Board of Genetic Counseling (ABGC) will accept CEUs earned at this program for the purposes of genetic counselor certification and recertification.
HOW TO CLAIM NSGC CEUs

• If you are attending the live event:
  – Sign into the webinar with your first and last name
  – Check your email after the webinar for a link to complete an evaluation form
  – If you do not receive the email, please contact info@cgaigc.com

• If you are watching a previously recorded event:
  – Complete an evaluation form
  – Take a quiz
    • You must score 80%
  – The link to the evaluation form and the quiz are available on the CGA website, below the link you used to access the webinar

FUTURE CGA-IGC WEBINARS

STAY TUNED FOR OUR 2023 WEBINAR SERIES

May 3: Joint webinar with NASPGHAN: Constitutional mismatch repair deficiency syndrome
  Speakers: Carol Durno, MD; Melyssa Aronson, MS, CGC

Summer - date TBD: Living with FAP: Life after prophylactic surgery and other quality of life considerations
  Speakers: Paul Wise, MD; Karen Hurley, PhD

Sep 28: Joint webinar with ACG: Surveillance for hereditary pancreatic cancer
  Speakers: Bryson Katona, MD, PhD; Beth Dudley Yurkovich, MS, MPH, CGC

Nov - date TBD: Emerging topics in the field of hereditary gastrointestinal cancer
ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 13 – Thursday, March 30, 2023
Colon Polypectomy Techniques: Big Polyps, Small Polyps, and Everything in Between
Faculty: Charles J. Kahi, MD, MSc, FACG
Moderator: Jennifer K. Maratt, MD
At Noon and 8pm Eastern

Please NOTE: there will be no ACG Virtual Grand Rounds on April 6 and 13 due to low attendance from Spring Breaks.

Week 16 – Thursday, April 20, 2023
Quality Indicators for Capsule Endoscopy and Deep Enteroscopy: an ACG and ASGE’s Joint Publication
Faculty: Jonathan A. Leighton, MD, FACG
Moderator: Carol E. Semrad, MD, FACG
At Noon and 8pm Eastern

Visit gi.org/ACGVGR to Register
Disclosures

Heather Hampel, MS, CGC
Genome Medical (Advisory Board and Stock)
Natera (Advisory Board)
Promega (Advisory Board)
23andMe (Consultant)
GI OnDemand (Consultant and Stock)
AIM Specialty Health (Consultant)

Peter Stanich, MD
Pfizer (Research Support)
PTEN Research Foundation (Research Support)
Janseen (Research Support)
Entora (Research Support)
Freenome (Research Support)

Julie Yang, MD
Cook (Consultant)
Olympus (Consultant)
Steris (Consultant)
Interscope (Consultant)

Elana Levinson, MS, CGC
Ms. Levinson has no relationships with ineligible companies.

*All of the relevant financial relationships listed for these individuals have been mitigated*
Historical and current approaches to identifying individuals with Lynch syndrome

Peter Stanich, M.D.
2023 CGA-IGC President
Gastroenterologist & Associate Professor
Ohio State University Wexner Medical Center, OH

Heather Hampel, M.S., CGC
Clinical Professor & Associate Director
City of Hope, CA

Outline

Lynch Syndrome
- Common & Treatable
- Cancer Risks Management

Family History-Based Identification Methods

Tumor-Based Identification Methods
- Columbus-area HNPCC Study
- Ohio Colorectal Cancer Prevention Initiative

Putting it all into Practice
- Universal MGPT for all Colorectal Cancer Patients
- What is the role of the GI practitioner in this process?
Lynch Syndrome

- Over 1.2 million individuals in the U.S. have Lynch Syndrome
- Inherited condition that causes high risks for colorectal, endometrial, ovarian, gastric, and other cancers
- Preventable cancers with early and more frequent screening
- 95% of affected individuals do not know they have Lynch Syndrome

### Lynch Syndrome Cancer Risks (to 70)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
<th>General Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>46-61%</td>
<td>33-52%</td>
<td>10-44%</td>
<td>8.7-20%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>34-54%</td>
<td>21-57%</td>
<td>16-49%</td>
<td>13-26%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4-20%</td>
<td>8-38%</td>
<td>≤1-13%</td>
<td>1.3-3%</td>
<td>1.3 %</td>
</tr>
<tr>
<td>Renal pelvis or Ureter</td>
<td>0.2-5%</td>
<td>2.2-28%</td>
<td>0.7-5.5%</td>
<td>≤1-3.7%</td>
<td>Not in SEER</td>
</tr>
<tr>
<td>Prostate</td>
<td>4.4-13.8%</td>
<td>3.9-23.8%</td>
<td>2.5-11.6%</td>
<td>4.6-11.6%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Stomach</td>
<td>5-7%</td>
<td>0.2-9%</td>
<td>≤1-7.9%</td>
<td>Not known</td>
<td>0.9%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6.2%</td>
<td>0.5-1.6%</td>
<td>1.4-1.6%</td>
<td>≤1-1.6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

NCCN Guidelines for Colorectal Cancer Screening and Prevention v1.2022
### GI cancer risks in Lynch syndrome

*NCCN Clinical Practice Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2.2022.*

<table>
<thead>
<tr>
<th></th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>46 - 60%</td>
<td>33 - 52%</td>
<td>10 - 44%</td>
<td>8 - 20%</td>
</tr>
<tr>
<td>Gastric</td>
<td>5 - 7%</td>
<td>0.2 - 9%</td>
<td>0 - 8%</td>
<td>NI?</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0.5 - 11%</td>
<td>1 - 10%</td>
<td>0 - 4%</td>
<td>NI</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.2%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Biliary</td>
<td>2 - 4%</td>
<td>0 - 2%</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

### GI cancer screening in Lynch syndrome

*NCCN Clinical Practice Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2.2022.*

- **MLH1** and **MSH2**
  - Colonoscopy every 1-2 years starting at **age 20-25**
  - EGD every 2-4 years at age 30-40
    - Consider enteroscopy
    - Stomach biopsies at initial procedure
  - Consider pancreatic screening at age 50 years if ≥1 close relatives from the side of pathogenic variant with MRI/MRCP and/or EUS
GI cancer screening in Lynch syndrome


- **MSH6 and PMS2**
  - Colonoscopy every 1-2 years starting at age 30-35
  - EGD every 2-4 years at age 30-40
    - Consider enteroscopy
    - Stomach biopsies at initial procedure
  - Consider pancreatic screening at age 50 years if ≥1 close relatives from the side of pathogenic variant with MRI/MRCP and/or EUS
  *Clinical judgement in PMS2

# Lynch syndrome and colonoscopy interval

There is rapid progression from adenoma to CRC in comparison to accepted 10-20 year interval for sporadic polyps

<table>
<thead>
<tr>
<th>Table 5. Dwell Time of Advanced Adenoma and Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Advanced adenoma (mo)</td>
</tr>
<tr>
<td>Mean ± standard deviation (range)</td>
</tr>
<tr>
<td>33.0 ± 16.2 (12-56)</td>
</tr>
<tr>
<td>Colorectal cancer (mo)</td>
</tr>
<tr>
<td>35.2 ± 22.3 (7-96)</td>
</tr>
</tbody>
</table>

Benefit of Frequent Colonoscopy in Lynch

Colonoscopy every 3 years amazingly effective

Optimal interval still remains to be determined

Table 1. Stage Distribution of CRC Cases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Study group (n = 133)</th>
<th>Control group (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

The stages in the study group were significantly more favorable than in the control group (p = 0.03).

Table 2. Causes of Death Within the 15-Year Study Period

<table>
<thead>
<tr>
<th>Cause</th>
<th>Study group (n = 133)</th>
<th>Control group (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC*</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

### How was Lynch Syndrome Diagnosed in the Past?

- Had to rely on family history
- **Amsterdam II criteria**
  - 3 cases of LS-associated cancers
  - 2 generations affected at least
  - 1 affected individual is a first-degree relative of the other 2
  - 1 diagnosed <50

- **Bethesda criteria**
  - CRC dx <50
  - 3 cases of LS-associated cancers at any age
  - CRC + 1 relative with a LS-associated cancer dx <50

- None of these models worked very well even if someone was taking a good family history and trying to apply them.

### NCCN Referral Criteria for Lynch Syndrome

**NCCN Guidelines Version 1.2022**

**Lynch Syndrome**

**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 colorectal or endometrial cancer and any of the following:
  - Diagnosed <60 y
  - A synchronous or metachronous LS-related cancer regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer diagnosed <60 y
  - 22 first-degree or second-degree relatives with an LS-related cancer regardless of age
- Family history of any of the following:
  - 21 first-degree relative with a colorectal or endometrial cancer diagnosed <60 y
  - 21 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
  - 3 first-degree or second-degree relatives with LS-related cancers including 1 diagnosed <50 y
  - 3 first-degree or second-degree relatives with LS-related cancers regardless of age
- Increased model-predicted risk for LS
  - An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM, MMRPred, MMRpredict)
  - Individuals with a personal history of CRC and/or endometrial cancer with a PREMM score of ≥2.5% should be considered for MSIPT.
  - For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥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

---

**American College of Gastroenterology**
Tools to Use in Clinic:
PREMM5 - http://premm.dfci.harvard.edu

- Probability of MLH1, MSH2, MSH6, PMS2 or EPCAM mutation
- Proband
  - # of CRCs & youngest age at dx
  - Y/N adenomas & youngest age at dx
  - Y/N EC & youngest age at dx
- FDRs & SDRs
  - # with CRC & youngest age at dx
  - # with EC & youngest age at dx
  - Y/N any with another HNPCC cancer
- Refer patients with ≥ 2.5% chance of having LS
- Distinguishes LS patients with an AUC of 0.83
- Not as good for PMS2 (AUC, 0.64)

Kastrinos, F. JCO. 2017. PMID: 28489507

Tools to Use in Clinic:
Colorectal Cancer Risk Assessment Tool

1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?
   - Colon or rectal cancer
   - Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain

- 17.7% of patients meet high-risk criteria
- Identifies 77% of high-risk individuals
- Identifies 95% of LS families

CITY OF HOPE
Lynch Syndrome Awareness: Historical and Current Approaches to Identifying Individuals With Lynch Syndrome

Genetic Features of Lynch Syndrome

- Genes belong to DNA mismatch repair (MMR) family
- Mutations in MMR genes lead to microsatellite instability (MSI)
  - Test is positive in 15% of colorectal and 24% of endometrial tumors
  - Sensitivity is 77-89% for Lynch Syndrome
- MMR proteins missing in tumor tissue making Immunohistochemical (IHC) staining useful
  - 1-2 proteins absent in 20% of colorectal and 25% of endometrial tumors
  - Sensitivity is 83% for Lynch Syndrome
- Immune therapy very effective in treating patients whose tumors have defective MMR


CITY OF HOPE
Lynch Syndrome Awareness: Historical and Current Approaches to Identifying Individuals With Lynch Syndrome

Feasibility of Screening for Lynch Syndrome Among Patients with Colorectal and Endometrial Cancer

Albert de la Chapelle, MD, PhD
Heather Hampel, MS, LGC

**COLORECTAL CANCER**
n=1566

- MSI positive
  - n=188 (12%)
- Immunohistochemistry
- Methylation of MLH1 Promoter
- Complete genetic testing
- Pathogenic Mutation
  - n=44 (2.8%) with Lynch syndrome


**ENDOMETRIAL CANCER**
n=563

- MSI positive
  - n=131 (23%)
- Immunohistochemistry
- Methylation of MLH1 Promoter
- Complete genetic testing
- Pathogenic Mutation
  - n=14 (2.5%) with Lynch syndrome

Hampel H et al. *Cancer Res.* 2007;67:9603
Lynch Syndrome Awareness: Historical and Current Approaches to Identifying Individuals With Lynch Syndrome

44 Colorectal Cancer Patients with Lynch Syndrome

- Age at diagnosis: 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria
- Mutations:
  - 20.5% MLH1
  - 52.3% MSH2

14 Endometrial Cancer Patients with Lynch Syndrome

- Age at diagnosis: 51.4 (range 39-69)
- 65% diagnosed over age 50
- 65% did not meet either Amsterdam or Bethesda criteria
- Mutations:
  - 14.3% MLH1
  - 21.4% MSH2
  - 64.3% MSH6
  - 0% PMS2
Cascade Testing: Follow Mutation through Lynch Syndrome Families

297 Relatives Tested

130 Positive

Average 6 relatives tested per family revealing 3 with Lynch Syndrome

Differentiators of Citywide Initiative
1. Free genetic counseling
2. Free genetic testing
3. Counseling provided locally

Citywide 1999-2008

Universal Tumor Screening for Lynch Syndrome Cost Effective and Recommended

- Incremental Cost Effectiveness Ratio = $31,391 per year of life saved
  - Experts agree that interventions with an Incremental Cost Effectiveness Ratio <$50,000 per year of life saved are cost effective

- Universal tumor screening for Lynch Syndrome is recommended by:
  - Evaluation of Genetic Applications in Practice & Prevention (CDC)
  - National Comprehensive Cancer Network
  - American College of Gastroenterology
  - US Multi-Society Task Force on Colorectal Cancer
  - Society for Gynecologic Oncology & American College of Obstetrics and Gynecology
  - Healthy People 2030 goal: Increase # of newly diagnosed colorectal patients screened for Lynch Syndrome at diagnosis

Slow Adoption of Universal Tumor Screening for LS

Cancer Center Adoption Rates:

| NCI-Comprehensive Cancer Centers | 89% |
| COS-accredited Community Hospital Comprehensive Cancer Programs | 81% |
| Community Hospital Cancer Programs | 75% |

80% of cancer patients are treated in community hospitals with lowest adoption rates

Beamer et al, JCO 2012;30(10):1058-63

Supported by Pelotonia

$ 4.5 Million

Research Project

1. Universal Screening for Lynch Syndrome
2. Adherence to Colorectal Cancer Screening
3. Molecular Epidemiology of Colorectal Cancer

Statewide 2012-2017
Results

- 64.7% of dMMR cases

- 7.1% of all patients had a PGV in a CSG; 16% of those tested.

- 4.0% of methylated cases

Potential Impact

- 151,030 new cases of CRC in the US in 2023
- 4,550 have Lynch syndrome (3%)
- 13,650 of their relatives have LS (~3 per proband)
- 69,950 new cases of EC in the US in 2023
- 2,100 have Lynch syndrome (3%)
- 6,300 of their relatives have LS (~3 per proband)
- Total of 26,600 individuals who could be diagnosed with LS per year with universal screening

Universal Genetic Testing in CRC

![Diagram showing genetic testing process](image)

1. **Individual with personal history of CRC**
   - **Age <50 at CRC diagnosis?**
     - Yes: **Germline multigene panel test (MGPT) evaluation for LS and other hereditary cancer syndromes**
     - No: **Known MMR deficiency in tumor**
   - **No**
     - **Utilize tumor and family history-based criteria for evaluation of LS**
     - **Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer (HRB-5)**
     - **Rationale, Pros, and Cons of Multigene Panel Testing for Lynch Syndrome and Other Cancer Risk Genes (HRS-4)**

The Ohio State University Wexner Medical Center

Results of genetic testing on patients with CRC

- Multigene panel testing performed in 34,244 at commercial lab
  - Pathogenic germline variant (PGV) found in 4,864 (14.2%)
  - 3,111 (9.1%) had a pathogenic variant associated with increased CRC or polyposis risk
  - Across all ages and races/ethnicities, the rate of clinically actionable PGVs on was 7.9% or greater.


Universal Genetic Testing in CRC

12.2% - High or moderate risk genes

The Very Near-Future
Genetic Testing of All Cancer Patients

- 2,984 cancer patients
- 1 in 8 patients (13.3\%) with pathogenic variant
- 48\% outside of guidelines

Samadder JAMA Oncol 2020

Potential benefit of universal germline testing

- More equitable distribution of genetic referrals
- Traditionally underserved patients are also under-represented in those receiving genetic evaluation
- 89\% of underserved patients had their sample collected for genetic testing when offered
  - 86\% rate in overall population

Who should refer to Genetics in CRC?

- Possible options –
  - GI doctor at time of endoscopic diagnosis or pathology
  - Colorectal surgeon at time of resection or pathology
  - Oncologist during treatment
  - Any clinician in the CRC diagnosis/treatment pathway

- Referral can be done at any time
  - Early referral can impact treatment options
  - Potentially easier to complete than during chemo/radiation?

Timing of referral to Genetics for GI physicians

- Easy to arrange at time of pathology result discussion
  - Order CEA, CT chest/abdomen/pelvis
  - Colorectal Surgery referral
  - Genetic counseling referral
Genetic testing points for patients

There are many myths about genetic testing but this is now very common and very easy to obtain!

- **Cost** – this is very commonly covered by insurance. If not, the out of pocket price is usually $250 (if ordered through GC with lab knowledge)
  - Medicare/Medicaid free through many labs
  - Family testing free for several months after a positive result for many labs!
- **GINA** is an act of congress that prohibits genetic discrimination
  - Protects from employment and health insurance discrimination based on genetic testing
  - Life insurance is not protected

Identifying Lynch patients prior to CRC

- Community GI practice incorporated a tablet with PREMM into clinic and endoscopy
  - Genetic testing offered to those who qualified
- 5.6% of patients qualified as high risk and 86% of those eventually had genetic testing
- All providers were satisfied with the incorporation and patients had high rates of understanding information

### When to refer patients to Genetics... in past

#### Table 2. Features that warrant evaluation and possible testing for HCCS

- CRC in patients younger than 50 yr
- Personal history of multiple cancers (e.g., CRC and endometrial cancer, colonic polyposis, and thyroid cancer)
- Personal and family history suspicious for LS\(^a\)
- Tumor testing with deficient mismatch repair\(^b\)
- More than 10–20 cumulative colonic adenomas
- More than 3 colonic hamartomas or 2 small bowel hamartomas\(^c\)
- Family members with known genetic diagnosis of HCCS

---

### When to refer patients to Genetics in 2023

#### Table 2. Features that warrant evaluation and possible testing for HCCS

<table>
<thead>
<tr>
<th>Colorectal cancer at any age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal and family history suspicious for LS(^a)</td>
</tr>
<tr>
<td>More than 10–20 cumulative colonic adenomas</td>
</tr>
<tr>
<td>More than 3 colonic hamartomas or 2 small bowel hamartomas(^c)</td>
</tr>
<tr>
<td>Family members with known genetic diagnosis of HCCS</td>
</tr>
</tbody>
</table>
Thank you!

Questions

Heather Hampel, MS, CGC

Julie Yang, MD

Peter Stanich, MD

Elana Levinson, MS, CGC
CONNECT AND COLLABORATE IN GI

ACG & CCF IBD Circle
ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG Women in GI Circle

ACG GI Circle
Connect and collaborate within GI

ACG’s Online Professional Networking Communities
LOGIN OR SIGN-UP NOW AT: acg-gi-circle.within3.com