Hereditary Gastrointestinal Cancers: Best Practices for Screening, Diagnosis, Risk Assessment and Management

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Disclosure
I have nothing to disclose.

Off Label/Investigational Discussion
In accordance with Annenberg Center policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
A 25-year old woman with a strong family history of endometrial and colon cancer is found to be a germline mutation carrier of a pathogenic *MLH1* gene mutation previously identified in her family. Choose the correct statement

1. She should be advised to undergo prophylactic hysterectomy and oophorectomy by age 35
2. Annual breast MRI should be performed due to the high risk of breast cancer
3. Colonoscopy should be recommended every 3 years due to the family history of colon cancer
4. Total colectomy with ileorectal anastomosis should be recommended if she develops colon cancer
5. She should be advised to take 325 mg aspirin daily
Which of the following statements is correct?

1. A BRCA2 mutation carrier whose affected mother died of pancreatic cancer has a 40% lifetime risk of developing pancreatic cancer
2. Annual EUS/MRI decreases pancreatic cancer incidence and mortality in hereditary pancreatic cancer families
3. A 50-year old individual with three family members with pancreatic cancer should be advised to undergo prophylactic pancreatectomy
4. NCCN guidelines recommend that all Ashkenazi Jews with pancreatic cancer undergo genetic testing
5. Hereditary diffuse gastric cancer families have an elevated risk of breast ductal carcinomas
Management of hereditary cancers is different than sporadic cancers

- Surgical management of cancer
- Screening and surveillance after treatment of initial cancer
- Surveillance for associated cancers
- Screening, surveillance, and risk assessment of family members
- Reproductive counseling
- Options for chemoprevention
- Differences in chemotherapy
Outline

- Hereditary colorectal cancer
  - Lynch syndrome (hereditary nonpolyposis colorectal cancer; HNPCC)
  - Adenomatous polyposis

- Hereditary pancreatic cancer

- Hereditary gastric cancer

- Multigene panel testing for hereditary GI cancers

- The clinician’s responsibility – obtaining and interpreting a cancer family history
Hereditary Colorectal Cancer Syndromes – Traditional Thinking

Figure 1. The fractions of colon cancer cases that arise in various family risk settings.

- Sporadic Cases
- Hamartomatous Polyposis Syndromes <0.1%
- Cases with Familial Risk, 10% to 30%
- FAP<1%
- HNPCC 2% to 3%

(and MAP)

(Lynch syndrome)
Lynch Syndrome Basics

- Formerly known as hereditary nonpolyposis colorectal cancer (HNPCC)

- Autosomal dominant; most common hereditary GI cancer syndrome
  - 3% of all CRCs; 2% of all endometrial cancers
  - Estimated 1 in 279 prevalence in general population

- High lifetime risks of gastrointestinal, gynecologic, and other neoplasms
  - High penetrance (>70% lifetime risk of any Lynch-associated cancer)
  - Often multiple cancers (metachronous or synchronous)
  - Early-onset cancers

- Defined by germline mutation in one of the DNA mismatch repair (MMR) genes
  - 70-75% have mutations in *MLH1* or *MSH2* genes
  - Rest have mutations in *MSH6*, *PMS2*, or *EPCAM*

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Lynch syndrome-associated colorectal cancer

- Predilection for the proximal colon, but can be seen in any part of the colon/rectum

- Often display poorly-differentiated/mucinous/signet ring histology

- "Crohn’s like" reaction with tumor-infiltrating lymphocytes

- Arise from “traditional” adenomas (display accelerated carcinogenesis)

- Essentially never have \( BRAF \) V600E mutations (seen commonly in sporadic MSI-H colorectal cancer)

- Almost universally (>90%) display abnormal MMR protein expression by immunohistochemistry (IHC) and high-level microsatellite instability (MSI-H)
Tumor testing for Lynch syndrome

- MSI analysis
  - PCR to assess for instability at certain microsatellite “hotspots”
    - High-level microsatellite instability (MSI-H) or low-level microsatellite instability (MSI-L)
    - Microsatellite stable (MSS)

- Immunohistochemistry (IHC) for expression of DNA MMR proteins (MLH1, PMS2, MSH2, and MSH6) is a surrogate for MSI status
  - Expression (or absence of expression) is usually paired:
    - MLH1/PMS2
    - MSH2/MSH6

- Previously performed only in CRC patients age <50 and/or with a personal/family cancer history that fulfilled Bethesda guidelines or Amsterdam criteria
  - Will fail to identify up to 40% of Lynch syndrome probands

Lynch Syndrome – Summary Statements

- **ALL** colorectal cancers and endometrial cancers should undergo tumor testing for mismatch repair deficiency as a screen for Lynch syndrome

  - MMR protein IHC and/or MSI tumor testing
    - Tumors with loss of MLH1 staining should undergo BRAF mutation analysis and/or MLH1 promoter hypermethylation testing to rule out sporadic (non-Lynch) MMR-deficiency

- Who should undergo germline testing for Lynch syndrome?

  - Colorectal/endometrial cancer with MMR-deficiency/MSI-high (except those with BRAF mutations or MLH1 promoter hypermethylation)
  
  - Known Lynch syndrome mutation in family
  
  - Predicted risk of ≥5% by PREMM or other risk prediction models

Prediction Models for Identification of Lynch Syndrome

- MMRpredict
- MMRpro
- PREMM$_{1,2}$
- PREMM$_{1,2,6}$
- PREMM$_5$ → Only model to predict for all 5 Lynch genes
PREMM – PREEdiction Model for gene Mutations

- Free, online tool
- Takes ~1 minute to complete

- Proband history
  - Age, sex
  - Presence of colorectal, endometrial, other cancers
    - Age(s) at diagnosis

- Family history
  - Presence of colorectal, endometrial, other cancers
    - Youngest age at diagnosis

Predicted probability of mutation in DNA mismatch repair genes
Genetic evaluation recommended for anyone with ≥2.5% likelihood of having Lynch syndrome by PREMM

http://premm.dfci.harvard.edu

Or

Google “premm”
Management of individuals with Lynch Syndrome

• Cancer screening
  • Colorectal cancers
  • Other cancers

• Surgical management
  • Colectomy?
  • Hysterectomy/Salpingo-Oophorectomy

• Medical management
  • Chemoprevention
Lynch Syndrome – CRC screening recommendations

- In individuals with (or suspected to have) Lynch syndrome, CRC screening by colonoscopy should be performed \textit{at least every 2 years}, beginning ages 20-25.

- Consider annual colonoscopy in confirmed mutation carriers.

- No data regarding the use of other CRC screening modalities in Lynch syndrome (e.g. CT colography, fecal immunochemical testing [FIT], etc).
Colonoscopies Reduce Mortality in Lynch Syndrome

Figure 3. Cumulative overall survival. $^aP = 0.003$ between the screening and control groups including all subjects. $^bP = 0.05$ between mutation-positive subjects of the screening and control groups.

Lynch Syndrome – Surgical Recommendations

- Colectomy with ileorectal anastomosis (IRA) is the preferred surgical treatment of patients with Lynch Syndrome who develop colon cancer
  - Risk of metachronous CRC reduced by 31% for every 10 cm of colon resected

- Consider segmental colectomy when unsuitable for total colectomy if regular post-op surveillance is conducted

*Prophylactic colectomy not routinely recommended*, given the efficacy of colonoscopic screening

Hysterectomy and bilateral salpingo-oophorectomy should be offered to women who are known LS mutation carriers and who have finished child bearing, optimally at age 40-45.

Screening for endometrial cancer and ovarian cancer should be offered to women with LS before undergoing surgery or if surgery is deferred:

- Annual endometrial biopsy and transvaginal ultrasounds
- Begin age 30-35
- No data to support efficacy (prophylactic surgery more effective)
Other Cancer Risks for Individuals with Lynch Syndrome

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>SIR*</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colorectal cancer</td>
<td>16</td>
<td>0.78</td>
<td>20.48</td>
<td>11.71 to 33.27</td>
<td>&lt; 0.001</td>
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<tr>
<td>Endometrial cancer</td>
<td>6</td>
<td>0.20</td>
<td>30.62</td>
<td>11.24 to 66.64</td>
<td>&lt; 0.001</td>
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<td>Ovary cancer</td>
<td>3</td>
<td>0.16</td>
<td>18.81</td>
<td>3.88 to 54.95</td>
<td>&lt; 0.001</td>
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<tr>
<td>Renal cancer</td>
<td>3</td>
<td>0.27</td>
<td>11.22</td>
<td>2.31 to 32.79</td>
<td>&lt; 0.001</td>
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<tr>
<td>Pancreas cancer</td>
<td>2</td>
<td>0.19</td>
<td>10.68</td>
<td>2.68 to 47.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2</td>
<td>0.20</td>
<td>9.78</td>
<td>1.18 to 35.30</td>
<td>0.009</td>
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<tr>
<td>Urinary bladder cancer</td>
<td>2</td>
<td>0.21</td>
<td>9.51</td>
<td>1.15 to 34.37</td>
<td>0.009</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7</td>
<td>1.77</td>
<td>3.95</td>
<td>1.59 to 8.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>3</td>
<td>1.21</td>
<td>2.49</td>
<td>0.51 to 7.27</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Noncarriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colorectal cancer</td>
<td>5</td>
<td>4.88</td>
<td>1.02</td>
<td>0.33 to 2.39</td>
<td>0.97</td>
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<tr>
<td>Lung cancer</td>
<td>3</td>
<td>4.68</td>
<td>0.64</td>
<td>0.13 to 1.87</td>
<td>0.51</td>
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<tr>
<td>Breast cancer</td>
<td>5</td>
<td>6.95</td>
<td>0.72</td>
<td>0.23 to 1.68</td>
<td>0.52</td>
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<tr>
<td>Prostate cancer</td>
<td>9</td>
<td>5.53</td>
<td>1.63</td>
<td>0.74 to 3.09</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Age-, Sex-, and Country-Specific SIRs for Carriers and Noncarriers Compared With the General Population

• Baseline upper endoscopy (EGD) at age 30-35
  • Treatment of *H. pylori* if found
  • Consider ongoing EGD every 3-5 years, especially if family history of gastric/duodenal cancer

• Insufficient data to recommend specialized screening for:
  • Pancreaticobiliary cancers
  • Small intestine cancers
  • Urothelial cancers
  • CNS cancers
  • Prostate cancers
  • Breast cancers

• In practice, we increase surveillance if component tumors are present in the family
Aspirin chemoprevention in Lynch Syndrome

• CAPP2 trial: randomized placebo-controlled trial of aspirin (600 mg/day) versus placebo in patients with Lynch syndrome
  • Initial report (2008): No significant difference in aspirin versus placebo (mean follow-up 29 months)
  • Subsequent report (2011): mean follow-up 55.7 months
    • Among subjects taking ≥2 years of 600 mg/day aspirin (versus placebo):
      • Lower incidence of CRC (HR 0.41)
      • Lower incidence of any Lynch-assoc cancers (HR 0.45)
    • No significant difference in adverse events
    • Protective benefit not seen until several years of follow up

• Ongoing study (CAPP3) comparing different doses of aspirin

• Current guidelines highlight uncertainty in the optimal dose and duration of aspirin when used as chemoprevention in Lynch Syndrome

## Familial adenomatous polyposis (FAP)

### “Classic-type” FAP
- Most have germline *APC* mutations
- 100s-1000s colorectal adenomas
  - Beginning 2nd-3rd decades of life
- Extracolonic manifestations
  - Desmoid tumors
  - Fundic gland polyps
  - Duodenal/ampullary adenomas/cancers
  - Thyroid neoplasia

### Attenuated FAP (AFAP)
- Minority have germline *APC* mutations
- Dozens (20-100) lifetime adenomas
  - Beginning later in life
- Extracolonic manifestations less common
**MUTYH-associated polyposis (MAP)**

- **Autosomal recessive** – requires biallelic inheritance of *MUTYH* gene mutations

- Wide spectrum of polyp burden and CRC risk
  - Usually displays “attenuated” phenotype
  - >50% of MAP patients with CRC have <10 lifetime adenomas at the time of CRC diagnosis

- MAP-associated CRC particularly likely to harbor *KRAS* G12C mutations

References:
Chemoprevention in FAP

• Sulindac has efficacy in reducing size/number of colorectal adenomas in FAP
  • Does not prevent onset of colorectal adenomas
  • Unclear whether it reduces likelihood of cancer
  • Unable to prevent need for colectomy in most FAP patients
  • Modest efficacy in reducing duodenal polyposis burden

• Prior FDA approval of celecoxib for reduction of colorectal/duodenal polyposis in FAP was withdrawn due to lack of follow up studies

Placebo-controlled trial of erlotinib (75 mg QD) and sulindac (150 mg BID) in FAP patients

- Significant reduction in duodenal polyposis burden after 6 months of treatment
  - Benefit seen in patients with both high- and low-level duodenal polyposis at baseline
- 87% participants on treatment arm with Grade 1/2 rash
- Too early to determine whether this translates into clinically meaningful benefit

Hereditary Pancreatic Cancer

- Having a family history of pancreatic cancer increases one’s risk of pancreatic cancer

- Up to 10% of all pancreatic cancers occur in patients with a family history of pancreatic cancer
  - The minority of such families have an identifiable genetic syndrome
    - Most commonly *BRCA1/2*
    - Lynch genes, *PALB2*, *ATM*, and *CDKN2A* also seen

- ~4% prevalence of germline mutations in one study of unselected pancreatic cancer patients

- Germline mutations that predispose to pancreatic cancer do *NOT* seem to cause young-onset pancreatic cancer

- 12-17% of pancreatic patients with Ashkenazi Jewish ancestry will have a germline mutation (Ashkenazi founder mutations in *BRCA1/2*, *MSH2*, or *MSH6*)

- NCCN guidelines now recommend genetic evaluation for
  - Any pancreatic cancer patient of Ashkenazi Jewish ancestry
  - Any pancreatic cancer patient with a close relative with breast, ovarian, pancreatic, or prostate cancer
  - Any patient (including cancer-free patients) with a family history of ≥3 *BRCA*-associated cancers (including pancreatic cancer)

## Genetic syndromes associated with increased pancreatic cancer risk

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Culprit gene(s)</th>
<th>Pancreatic cancer risk</th>
<th>Other manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast cancer</td>
<td>BRCA1, BRCA2, PALB2</td>
<td>Up to 6-fold increased risk</td>
<td>Breast cancer (BRCA1/2 and PALB2), ovarian cancer (BRCA1/2), melanoma, biliary</td>
</tr>
<tr>
<td>Lynch syndrome (HNPCC)</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>8-10-fold increased lifetime risk</td>
<td>Colorectal, endometrial, ovarian, gastric, urothelial, biliary, small bowel, sebaceous neoplasms</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>Up to 132-fold increased lifetime risk; probably early-onset pancreatic cancer</td>
<td>Mucocutaneous pigmentation, GI “Peutz-Jeghers” hamartomatous polyps, colorectal cancer, stomach cancer, breast cancer, cervical adenoma malignum, Sertoli cell cancers</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1</td>
<td>Up to 60-fold increased risk</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Familial multiple mole and melanoma (FAMMM) syndrome</td>
<td>CDKN2A/p16</td>
<td>Up to 13-fold increased lifetime risk</td>
<td>Melanoma, multiple large moles and dysplastic nevi</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>??</td>
<td>Breast cancer, sarcomas, adrenocortical cancers, gliomas, leukemias, multiple cancers</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM</td>
<td>??</td>
<td>Cerebellar ataxia, oculomotor apraxia, cutaneous/conjunctival telangiectasias, lymphomas, leukemias</td>
</tr>
</tbody>
</table>
Familial Pancreatic Cancer (FPC)

- Family with ≥2 individuals affected with pancreatic cancer who are first-degree relatives of one another
- Most such families will not have identifiable germline mutations
?? Should we be screening this family for pancreatic cancer ??
Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals

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• 216 patients from FPC families (n=195) or known hereditary syndrome (n=21)

• Screening with CT, MRI, and EUS
  • 42% of patients had focal pancreatic lesions (most commonly cystic lesions)
    • Most patients with cysts had multiple cysts
  
  • Incidence of abnormalities increased with age
    • 14% of pts age <50
    • 34% of pts age 50-59
    • 53% of pts age 60-69

• CT had much lower sensitivity than MRI and EUS

• 2% of patients went on to pancreatectomy
  • All had multifocal PanIN; no adenocarcinomas
411 European patients from FPC families (n=214), germline CDKN2A mutation (n=178) or other known hereditary syndrome (n=19)

Prospectively undergoing screening with annual MRI/MRCP and/or EUS

- 13/178 (7.3%) CDKN2A carriers found to have pancreatic cancer (mean f/u: 53 months)
  - Cumulative pancreatic cancer incidence: 14% by age 70
  - Mean age at diagnosis: 58 years
  - 10/13 had surgically resectable disease at diagnosis (9 had surgery)
  - 5-year overall survival: 24% (one patient died of metastatic melanoma; rest from pancreatic cancer)

First signal of efficacy for pancreatic cancer screening in high-risk patients, though (in this paper) potential benefit most notable in CDKN2A mutation carriers (particularly common in Dutch populations)
Pancreatic Cancer Screening – Recommendations

• Pancreatic cancer surveillance should ideally be performed under research conditions, in experienced centers, and using multidisciplinary approach

• Potential candidates for pancreatic cancer screening:
  • Known carriers of mutations in genes linked to pancreatic cancer who have a family history of pancreatic cancer
  Or
  • Members of FPC families who have a first-degree relative with pancreatic cancer

• Surveillance with EUS and/or MRI annually starting at age 50
  • Or 10 years younger than the earliest pancreatic cancer in the family
  • Individuals with Peutz-Jeghers syndrome should start at age 35
Hereditary Gastric Cancer

- Hereditary Diffuse Gastric Cancer (HDGC)
  - Lifetime risk of gastric cancer >60%
  - CDH1 gene mutations (autosomal dominant)
  - EGD screening is ineffective
    - Prophylactic gastrectomy specimens show multifocal submucosal cancers in mutation carriers
- Association with lobular breast cancer
- Some families also will have cleft lip/palate
Hereditary Diffuse Gastric Cancer (HDGC) – Summary Statements

• Individuals with any of the following should be evaluated for HDGC with CDH1 mutation analysis:
  • $\geq 2$ cases of diffuse gastric cancer in the family, with at least one diagnosed $<50$ years
  • $\geq 3$ cases of documented diffuse cancer in first- or second-degree relatives independent of age of onset
  • Diffuse gastric cancer diagnosed $<40$ years
  • Personal or family history of diffuse gastric cancer and lobular breast cancer with one diagnosed at $<50$ years

• For CDH1 mutation carriers:
  • Prophylactic gastrectomy is recommended ($>80\%$ gastric cancer risk by age 80)
    • Optimal age unclear
  • Breast cancer surveillance is recommended in women beginning at age 35
    • Annual mammography and breast MRI
    • Clinical breast exams every 6 months
    • Consider risk-reducing mastectomy
Syndrome-specific versus multi-gene risk assessment

- **Syndrome-specific genetic testing**: Individuals undergo testing for a given syndrome if their personal/family history fulfill criteria for that syndrome
  - Examples:
    - Lynch syndrome testing for MMR-deficient colon cancer
    - *APC* and *MUTYH* testing for individuals with ≥20 lifetime colorectal adenomas

- **Multi-gene panel testing**: Next-generation germline sequencing of dozens of cancer genes in parallel
  - Organ-specific panels versus pan-cancer panels
  - Each commercial laboratory has their own panel(s) of genes; new genes constantly added
  - Scientific data about the use of such panels is only beginning to emerge
  - The more you look, the more you find…
Multi-gene panel testing in young-onset CRC

- 450 individuals with newly diagnosed CRC under age 50 across state of Ohio
- 72 (16%) with a germline mutation
- 13% with mutations in genes linked to CRC
  - 8.4% with Lynch syndrome
  - 1.1% with FAP
  - 0.9% with MUTYH-associated polyposis
  - 2.5% with low-/moderate-penetrance mutations
- 3% with mutations in genes not linked to CRC (*BRCA1/2* in 1.3% of cohort)
- 33% of mutation carriers failed to meet clinical criteria for the gene/syndrome they were ultimately found to carry
- 32.3% of all patients with ≥1 germline variant of uncertain significance (VUS)
  - High potential for misinterpretation and overtreatment of individuals with such uninformative results

Multi-gene panel testing in CRC

- 1058 CRC patients seen at Dana-Farber
  - No pre-selection for age, family history, MMR/MSI

- 105 (9.9%) with pathogenic germline mutation
  - 3.1% with Lynch syndrome (97% MSI-H/MMR-D)

- 7.0% with non-Lynch mutations
  - 1.1% with \textit{BRCA1/2}
  - 65% of high-penetrance non-Lynch mutation carriers lacked clinical features of their syndrome
  - Neither age nor personal/family history were significant predictors of carrying non-Lynch mutations

- 31% with germline VUS

- More answers, but also more uncertainty/questions
Multi-gene panel testing in CRC

Figure 1. The fractions of colon cancer cases that arise in various family risk settings.
A family history of cancer and premalignant gastrointestinal conditions that provides sufficient information to develop a preliminary determination of the risk of a familial predisposition to cancer should be obtained.

Essential elements of a family history include presence and type of cancers in 1st and 2nd degree relatives, and presence and (ideally) type of polyps in 1st degree relatives.

- 1st degree relatives: parents, siblings, children
- 2nd degree relatives: grandparents, grandchildren, aunts, uncles, nieces, nephew, or half-siblings

Age and lineage should be noted for each diagnosis.
Genetic Malpractice

- Failure to make a genetic diagnosis and use proper diagnostic tools
- Failure to recommend adequately aggressive cancer surveillance
- Failure to recommend consideration of appropriate prophylactic surgery for associated cancers
- Family of “duty to warn” family members
Personal and family history are still the best screening tool for inherited diseases

Need to systematize family history assessments in clinical practice

Genetic testing is now part of standard-of-care and is increasingly going to be done using multigene panels
  • More answers but also more uncertainty

Surveillance and management of cancer risk is based on specific syndrome and family history

Important to incorporate (and document) recommendations for patients’ at-risk family members

Spectrum of genetic syndromes is going to continue to expand