Identifying and Treating Patients with Or at High Risk of Hereditary Cancer Using a Comprehensive Toolkit

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Disclosure

1. This presentation is for educational purposes only.
2. This toolkit will not be sold to anyone.
3. This presentation does not intend to promote any particular services but instead to be used as a tool.
4. The presenter does not have any relevant nonfinancial relationships to disclose.
Objectives

After attending the session, participants will be able to

1. Verbalize how to identify patients at risk for hereditary cancers.
2. Identify a role of a primary care provider in genetics.
3. Identify at least one screening tool that can be used in an outpatient office visit.
4. Verbalize at least three ethical, social, and legal considerations related to genetic testing.
5. Discuss two ways to change practice when providing care to patients in need of genetic services.
Agenda

- Genetics and Cancer
- Gap, need, solution, and role for outpatient community providers.
- Ethical Considerations for genetic testing
- Family History Taking and Barriers
- Billing and Cost
- Most common gene mutations
- Family History Assessment Tools
- Risk Calculation for Breast Cancer and Recommendations
- Genetic Counseling
- Hereditary Breast and Ovarian Cancer and Lynch syndrome: Red flags, when to test, management/surveillance/ recommendations
- Case Studies
- Tools and Resources
- Questions
Genetic Terminology

- Genetics vs Genomics
- Autosomal: inheritance pattern with the gene located on a non sex chromosome.
- Autosomal dominant: a mutated gene passed on through inheritance. Only one gene is needed for an individual to be affected by this type of disorder.
- Autosomal recessive: a mutated gene passed on through inheritance. Two copies are needed to be affected by this type of disorder.
- De novo mutation: gene alteration identified for the first time in one family member resulting from a mutation in a germ cell (the egg or sperm) of one of the parents or in the fertilized egg during early embryogenesis.
- Genome - a whole set of DNA
- Exome: portion of the genome that encodes proteins and functional RNAs (approx 1-2% of genome) which is thought to be functionally relevant.
- Genotype vs Phenotype
Cancer

- Sporadic cancers - Approximately 60% of cancers are sporadic.
- Familial cancers - these are cancers caused by variants in multiple genes and the environment all working together.
- Hereditary cancers - accounts for 5-10% of all cancers. These are cancers that are associated with a change in a single cancer susceptibility gene (like BRCA1 or BRCA2).
• Approximately 10% of the 32 million Americans have a family history of cancer.

• A survey of 860 providers was conducted to understand their cancer risk assessing practices.
• Results of that survey showed only 28.8% PCPs felt qualified to provide genetic counseling to their patients. Only 27% had referred a patient for genetic cancer risk assessment or testing in last the 12 months.

• Bellcross et al (2015) study

• Literature suggests that many patients aren’t receiving these services either in the office or elsewhere in their communities.

Frieder & Seldig, 2016; Vig et al, 2009
Need

- Genetic testing offers an opportunity to help individuals determine their risk and make informed decisions to potentially prevent cancer from developing.

- There is a need for education in the role of genetics in primary care.

- 4 themes of educational needs:
  1. Genetic knowledge
  2. Family history
  3. Ethical considerations and psychosocial effects in relation to genetics
  4. Understanding of the role of clinical genetics services

Houwink et al, 2011
Solution

Educate and gain knowledge

• Toolkit for providers interested in improving their skills in genetic literacy and learning about hereditary cancers, treatment plans, evidence based interventions, guidelines, case scenarios, genetic consultation, and available resources.

• Translating knowledge into practice
Important Role

• Primary care providers (PCP) – Gatekeepers in helping patients gain access to genetic testing and counseling.
  - Screen by educating families, explain outcomes and what to expect, coordinating care with subspecialists, and providing counseling as needed.
• Unique position to consider a patient’s family health
• Shortage of clinical geneticists: PCPs need to answer patient’s questions regarding testing, diagnoses and help patients obtain adequate care.
• Genetic-based medicine is growing, PCPs will start to encounter patients with genetic conditions more often.
Ethical Considerations

- Privacy
  - Right to preserve information should be honored by providers and protected under the Health Insurance Portability and Accountability Act (HIPPA) privacy regulations
- Whole family is affected
- Long lasting effects.
- Discrimination
  - The Genetic Information Nondiscrimination Act (GINA) protects individuals from employment and insurance discrimination in regards to genetic testing results.
- Gaps in GINA
  - There are state specific statutes for regulating genetic information.

Lea, Williams & Donahue, 2005
Importance of Genomics

- It plays a role in 9 out of 10 top causes of death:
  1. Heart disease
  2. Cancer
  3. Stroke
  4. Diabetes
  5. Alzheimer’s disease

- Importance of genetic tests:
  1. Prevention
  2. Risk prediction
  3. Diagnosis
  4. Prognosis
  5. Treatment, including choice of medication and dosage
Need to have a system of identifying patients with elevated risk for hereditary cancer.

Need to have a referral system for patients with identified “red flags” in their personal/family history.

Need to be able to coordinate care for patients with elevated risk of cancer. The care includes a plan to reduce risk of cancer through prophylactic interventions as well as early and regular risk screening.

A focused family history can help identify high risk patients.
Components of a Family History:
1. Golden Standard: 3 Generation Pedigree
2. Specific diseases
3. Age of onset
4. Age of death (if applicable)
5. Relationship to patient
A pedigree can be exhaustive but only in unusual circumstances.

Attempt to obtain a three-generation pedigree

First Degree: Parents, siblings, children

Second degree: grandparents, grandchildren, aunts, uncles, nephews, nieces, and half siblings

Third degree: great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousins.

Update family history annually
Family History

- Red Flag patterns include:
  1. Multiple family members with related or same cancer type
  2. Bilateral tumors or paired organ tumors
  3. Age of onset under 50
  4. Ethnic background with a known risk of being a gene carrier such as Ashkenazi Jews.
Barriers to Completing Family History

- Lack of time
- Incomplete records
- Inaccessible family members
- Incorrect or vague diagnosis
- Poor follow-through on questions related to family history
- Fear of discrimination and stigmatization
- Lack of reimbursement
- Difficulty finding family history in EHR or medical chart
Summary of Recommendations

U.S. Preventive Services Task Force

USPSTF recommends using Family History as a tool to screen women for increased risk for mutations in the BRCA1 & BRCA2 genes.

Positive History=genetic counseling, then testing if necessary.

By following USPSTF recommendations:

1. Genetic counseling is covered without cost sharing under ACA
2. Also Department of Health and Human Services urges insurance companies to cover genetic testing without $$.

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade (What's This?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women who have Family Members with Breast, Ovarian, Tubal, or Peritoneal Cancer</td>
<td>The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.</td>
<td>B</td>
</tr>
<tr>
<td>Women Whose Family History is not Associated with an Increased Risk</td>
<td>The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes.</td>
<td>D</td>
</tr>
</tbody>
</table>
• A or B rating by USPSTF = Preventative measures
  ◦ Covered without cost sharing with the patient.
• Insurance is likely to cover patients who are determined to be at elevated or high risk.
• ICD-10 codes:
• Cancer risk consultation can be reimbursable with appropriate ICD-10 codes:

  • Z13.79 – Screening for other disorders and diseases genetic (nonprocreative) chromosomal abnormalities
  • Z14: Genetic carrier associated with a specific disease, can be passed on to offspring
  • Z15: Genetic susceptibility to disease, a person is at risk for developing the disease associated with the gene.
  • Z15.01: Should be listed after and in conjunction with Z31.5
  • Z31.5: Encounter for genetic counseling
  • Z80.3: Family history of malignant neoplasm of breast
  • Z80.41: Family history of malignant neoplasm of ovary
  • 96040: Genetic counseling and medical genetics services, 30 minutes face to face with patient and/or family.

CMS, 2016; Himes et al, 2016
Cost

- Coverage is becoming better: Private insurance and Medicaid
- Genetic testing laboratories can assist with obtaining pre-authorization.
- Genetic tests at full price range from $300-5,000.
- Many patients have little to no out of pocket cost for testing
Family History Assessment Tools

USPSTF recommends 5 family history tools for detection of patients at risk.

1. Ontario Family History Risk Assessment Tool
2. Manchester scoring system
3. Referral Screening Tool
4. Pedigree Assessment Tool
5. Family History Screen 7 (FHS-7)
### Family History Assessment Tools

**FHS-7:**
- It helps identify the need for further management and need for genetic services such as genetic counselor referral
- Only need 1 yes to initiate referral to genetic counselor

| Family History Screening-7 (FSH-7) | Include parents, grandparents, siblings, aunts/uncles, cousins
|------------------------------------|---------------------------------------------------------------|
| Did any of your first-degree relatives have breast or ovarian cancer? | Include age of diagnosis and current age
| Did any of your relatives have bilateral breast cancer? |
| Did any man in your family have breast cancer? |
| Did any woman in your family have breast and ovarian cancer? |
| Did any woman in your family have breast cancer before age 50 y? |
| Do you have 2 or more relatives with breast and/or ovarian cancer? |
| Do you have 2 or more relatives with breast and/or bowel cancer (colon or rectal)? |

USPTF, 2013
Ontario Family History Assessment Tool:

- Used as a clinical scoring tool in primary care.
- Referral threshold &ge;10 = 2x increase for breast or ovarian cancer.
- Other risk factors included are bilateral breast cancer, breast and ovarian cancer found in same person, age at diagnosis, colon and prostate cancer, and cancer in men.
- This tool was studied 3 times with high sensitivity 94%/specificity 51%

Breast Cancer Risk Calculation

Tyrer-Cuzick Model - elevated risk of at least 20%-25% in lifetime triggers a referral and need for breast MRI and Mammograms.

Applies to unaffected individuals in screening for personal breast cancer risk in an individual.

Download: http://www.ems-trials.org/riskevaluator/

The Gail model: helps assess risk of breast cancer. Should not be used when hereditary syndrome is suspected. It does not appropriately help determine the need for MRI of breast since it does not account for enough family history (NCCN, 2016).
Breast Cancer Elevated Risk

- Elevated lifetime risk recommendations with ≥ 20% lifetime risk:
  - Provider can calculate lifetime risk for breast cancer and order annual screening according to these guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>National Comprehensive Cancer Network (NCCN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual Breast MRI from age 30. Annual mammogram from age 40 Annual mammogram from age 40 Clinical breast exam every 1-3 years from age 25-40, then annually. Breast self awareness</td>
</tr>
<tr>
<td>American Congress of Obstetricians &amp; Gynecologists (ACOG)</td>
<td>Annual MRI from age 30 Annual mammogram from age 40 Clinical breast exam every 3 years from age 20-39 and then annually at age 40 Breast self awareness</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>Annual MRI from age 30. Annual mammogram from age 45 or from age 40 per patient choice, then every other year from age 55 or annually. Breast self awareness</td>
</tr>
</tbody>
</table>

Himes et al,2016; NCCN,2016
Genetic Counseling

Counseling before and after

- Family history evaluation
- Discuss pros and cons
- Informed Consent
- Discuss test conclusiveness
- What to do with the info
- Help think through the process
- Education
- Management Recommendations
- Interpretation of Results
Hereditary Breast and Ovarian Syndrome (HBOC)

- Due to mutations in BRCA1 or BRCA2 genes (most common).
- Autosomal dominant inheritance pattern
- Accounts for 5-10% of all breast cancers
- Accounts for 10-15% of all ovarian cancers
- HBOC increases risk of developing cancers such as:

<table>
<thead>
<tr>
<th>Cancer risk up to age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td>Female: 46-71%</td>
</tr>
<tr>
<td>Male: 2.8</td>
</tr>
<tr>
<td><strong>Ovarian</strong></td>
</tr>
<tr>
<td>17-46%</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
</tr>
<tr>
<td>0.1-2.4%</td>
</tr>
<tr>
<td><strong>Pancreatic</strong></td>
</tr>
<tr>
<td>1-7%</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
</tr>
<tr>
<td>7.5%</td>
</tr>
</tbody>
</table>

CDC, 2015
# Hereditary Cancer Syndrome Family History Questionnaire

*Providers at this practice are committed to your health and cancer prevention*

**This section is for female patients only**

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Date of Birth</th>
<th>Height</th>
<th>Weight</th>
<th>Age of 1st Period</th>
<th>Age of 1st Child</th>
<th>Are you Menopausal? (If yes, what age)</th>
<th>Ever taken Hormone Replacement?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Tyrer-Cuzick Score (if applicable)**

**Please indicate if you or your family have a history of any of the following conditions**

<table>
<thead>
<tr>
<th>Personal History (age of diagnosis)</th>
<th>Mother's Side (age of diagnosis/death)</th>
<th>Father's Side (age of diagnosis/death)</th>
<th>Siblings/Children (age of diagnosis/death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast and Ovarian Cancer (BRCA)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colon and Uterine Cancer (Lynch)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional Questions**

- Are you Ashkenazi Jewish descent?
- Do you or your family have any known cancer gene mutations?
- Are you more polyps in a lifetime?

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**Lynch (FACC, SGO)**

**Family and Personal History:**
- One or more relatives with endometrial cancer at any age
- One individual with CRC, Ovarian, or Endometrial plus another LS related cancer at any age
- One person with endometrial cancer and CRC
- One person with endometrial cancer and any other LS related cancer
- One person with endometrial cancer and hereditary non-polyposis colorectal cancer

**HBOC (NCCN Guidelines/USPSTI)**

**Criteria indicating need for genetic assessment**

- One relative with breast cancer (2nd degree relative): breast <50, ovarian (any age), male breast cancer (any age), triple negative breast cancer (1st degree relative)
- One individual with BRCA1 or BRCA2 mutation
- One individual with breast cancer (1st degree relative)
- One individual with prostate cancer (1st degree relative)
- One individual with colorectal cancer (1st degree relative)
- One individual with endometrial cancer (1st degree relative)
- One individual with any other cancer (1st degree relative)
## When to Test for Genetic Mutation (HBOC)

### Personal history

- Ovarian CA any age
- Male breast CA any age
- Triple negative breast CA ≤60 y
- Bilateral breast cancer (1st diagnosed ≤50)
- Breast CA at any age AND 1 up to 3rd degree relative with invasive ovarian CA any age
- Breast CA ≤ 49
- A known mutation
  - ≥2 people (out to 2nd degree relative): at least 1 with breast CA diagnosed ≤ 50 yrs OR pancreatic or prostate diagnosed at any age with breast cancer diagnosed ≤ 50 yrs
  - ≥3 people (out to 3rd degree relative): combo of aggressive prostate, pancreatic, or breast CA at any age
- Person of Ashkenazi Jewish descent AND with ovarian, breast, or pancreatic cancer (at any age)
- Any 3 of the following (personal or family history):
  - Hamartomatous polyps of the GI tract
  - Diffuse gastric cancer
  - Dermatologic manifestations
  - Macrocephaly
  - Breast cancer
  - Pancreatic cancer
  - Melanoma
  - Sarcoma
  - Prostate cancer (Gleason score ≥ 7)
  - Brain tumors
  - Leukemia
  - Adrenocortical carcinoma
  - Colon cancer
  - Kidney cancer
  - Endometrial cancer
  - Thyroid cancer

### Family history

- Up to 2nd degree relative meeting any of the choices to the left

Daly et al, 2010
NCCN Guideline
Last update (2016)
## Management

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA +</td>
<td>Clinical Breast Exam</td>
<td>Every 6-12 months from age 25. Men: Every 12 months from age 35</td>
</tr>
<tr>
<td></td>
<td>Breast self awareness</td>
<td>To be done by patient esp. at the end of menses cycle.</td>
</tr>
<tr>
<td></td>
<td>Annual MRI</td>
<td>From 25-29y</td>
</tr>
<tr>
<td></td>
<td>Annual mammogram AND MRI</td>
<td>From age 30-75y</td>
</tr>
<tr>
<td></td>
<td>Mastectomy</td>
<td>Discuss risk reducing mastectomy: reconstruction options, risks, and protection</td>
</tr>
<tr>
<td></td>
<td>Risk Reducing Salpingo-oophorectomy (RRSO)</td>
<td>Recommend at age 35-40 with BRCA1 and consider at 40-45y with BRCA2 in those who have had risk reducing mastectomy prior to this. After childbearing.</td>
</tr>
<tr>
<td></td>
<td>Transvagal U/S &amp; Serum CA-125</td>
<td>Not a positive recommendation but individualized and to be decided by provider: start at age 30-35 Discuss pros and cons of screening and quality of life Not enough date to say it can detect ovarian ca early enough to change the outcome.</td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>S/s of breast cancer , and ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>Counseling</td>
<td>Genetic counseling should be offered to all patients. Possibility of other family members who have the same mutation. At risk relatives should be offered genetic consultation. Fertility. Risks. Option for preimplantation genetic diagnosis.</td>
</tr>
</tbody>
</table>
# Other Inherited Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer Site Risk</th>
<th>Cancer Site Risk / management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM/CHEK2/NBN/PALB2</td>
<td>Increased risk for breast cancer. CHEK2- colon cancer risk</td>
<td>Screen with annual mammogram from age 40. Consider breast MRI with contrast at age 40. No sufficient evidence for Risk Reducing Mastectomy.</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Increased risk of ovarian cancer</td>
<td>Consider risk reducing salpingo-oophorectomy at age 45-50 years.</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni syndrome- very rare condition, likely to cause breast cancer before 45 years of age. Increased risk multiple set of cancers and primary tumors. Risk is increased for breast cancer, adrenocortical carcinoma, sarcomas, brain tumors, lymphoma, and leukemia.</td>
<td>No sufficient evidence for recommendation. In the past, novel screening modalities linked to research studies have been used.</td>
</tr>
</tbody>
</table>

NCI, 2015; Coit, 2013
Lynch Syndrome

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

- Autosomal dominant disorder
- Accounts for approx. 3-5% of all colorectal cancers and is most common of hereditary colon cancer syndromes.
- 1st described by Henry Lynch, MD
- It occurs if an inherited mutation in one of mismatch repair (MMR)* gene is found.
- Results from an inherited mutation during DNA replication where the MMR gene is inactivated. An accumulation of mutations can increase chances of cancer development.
- 5 genes can disrupt MMR and cause Lynch Syndrome:
  1. MLH1
  2. MSH2
  3. MSH6
  4. PMS2
  5. EPCAM

- Healthy People 2020 and the National Comprehensive Cancer Network (NCCN) have endorsed universal testing for Lynch Syndrome.

*MMR gene= functions to correct base pairing mismatches that take place during DNA replication

Giardiello et al, 2014
Lynch Syndrome

Individuals with Lynch syndrome have an increased risk for developing cancers such as:

- Colorectal (CRC)
- Ovarian
- Endometrial
- Gastric
- Small intestine
- Urinary tract/kidney
- Bile ducts
- Brain (glioblastoma multiforme)
- Sebaceous gland tumors
- Pancreatic

NCCN (2016)
Risk factors to consider

Decrease the risk of CRC:
- Increased diet in vegetables
- Exercise: regular and vigorous
- ASA
  - USPTF: Grade B recommends ASA for adults aged 50 to 59 years with a ≥10% 10-year CVD risk to be used for prevention of colorectal cancer and CVD.
  - NCCN: Not recommended as standard chemoprevention, data not sufficiently robust
- Maintaining healthy weight
- Hormone replacement with both estrogen and progesterone for women
- CRC screening

Increase the risk of CRC:
- Family history positive for CRC
- Colorectal polyps
- Obesity
- Sedentary lifestyle
- Smoking

NCI, 2014; NCCN, 2013; USPTF, 2016
Lynch Syndrome Red Flags

- Personal history of CRC (diagnosed < 50y) or Endometrial CA
  - Or
  - One or more
    - Hx of CRC AND > 10 adenomas
    - Multiple GI hamartomatous polyps/ OR serrated polyposis syndrome
    - Diagnosed < 50 y, Lynch Syndrome (LS) related CAs*
    - Out to 1st degree: Any LS cancer < 50y
    - ≥2 people (out to 2nd degree relative): any LS cancers any age

- Family history only
  - One or more
    - 2nd degree relative with endometrial any age or CRC (diagnosed < 50y), OR with another LS related CA*
    - ≥2 people (out to 2nd degree relative): with LS related CA with at least 1 dx <50y
    - ≥2 people (out to 2nd degree relative): any LS cancers any age
    - Known mutation in the family

*Colorectal (CRC), Ovarian, Endometrial, Gastric, Small intestine, Urinary tract/kidney, Bile ducts, Brain (glioblastoma multiforme), Sebaceous gland tumors, Pancreatic

NCCN Guideline, 2016
Criteria: NCCN, Amsterdam II (requires 3 generations of cancer), Revised Bethesda Guidelines
Models: MMR predict, MMR Pro, and PREMM 1,2,6
Tumor Testing: microsatellite instability (MSI), immunohistochemistry (IHC)

Giardiello et al, 2014
## Screening Tools

### Colorectal Risk Assessment Tool

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a 1&lt;sup&gt;st&lt;/sup&gt; degree relative* with any of the following conditions diagnosed before age of 50?</td>
<td></td>
</tr>
<tr>
<td>- Colon or rectal cancer</td>
<td></td>
</tr>
<tr>
<td>- Cancer of the bile ducts, brain, ovary, pancreas, small intestine, stomach, urinary tract such as kidney, bladder, ureter.</td>
<td></td>
</tr>
<tr>
<td>2. Have you been diagnosed with any of the following conditions before age 50?</td>
<td></td>
</tr>
<tr>
<td>- Colon or rectal cancer</td>
<td></td>
</tr>
<tr>
<td>- Colon or rectal polyps</td>
<td></td>
</tr>
<tr>
<td>3. Do you have 3 or more relatives** with a history of colon or rectal cancer?</td>
<td></td>
</tr>
</tbody>
</table>

*1<sup>st</sup> degree relative: mother, father, sister, brother, child  
**Relatives: parents, siblings, children, grandparents, uncles, aunts, cousins

Adapted by permission from Macmillan Publishers Ltd: Development and Validation of a Colon Cancer Risk Assessment Tool for Patients Undergoing Colonoscopy by Kastrinos et al, 2009
Screening Tools
PREMM 1,2,6

- A web-based prediction model
- Designed to be used by healthcare professionals.
- Risk estimate calculator for an individual to be an MLH1, MSH2, and MSH6 mutation carrier.
- Calculates risk by using variables such as family history or personal history of CRC, endometrial or other LS cancer, sex, and proband information.
- Consider for genetic evaluation referral if the overall predicted probability is \( \geq 5\% \).

**Website:** [premm.dfci.harvard.edu](http://premm.dfci.harvard.edu) (Last updated 2013)

- Statistical probability of people

Levels of evidence for NCI rating cancer genetics studies:

- Involves at least 1 well designed AND
- Well controlled from RCT (Level I),
- From non-RTC (Level II),
- From case control or cohort study (Level III).
- From descriptive studies (Level IV) with either cancer end point or intermediate end point.
- Level V involves conclusions from experts based on clinical experience, committees of experts, and/or descriptive studies.
- Rating of evidence using GRADE criteria: Further research is very unlikely (high quality), likely (moderate quality), or very likely (low quality) to have an important impact on the effect and change it.
- Uncertain about any estimate of effect (very low quality).

GRADE Working Group, 2004
## Guidelines for individuals at risk or affected with Lynch Syndrome

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Intervention</th>
<th>Recommendation based on Gene mutation</th>
<th>Quality/GRADE Rating of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colonoscopy</td>
<td>MLH1 &amp; MSH2: Every 1 – 2 y starting at age 20 – 25 y. If before age 25, then 2 – 5 y earlier than earliest diagnosis in the family. MSH6: Start at age 30y PMS2: Start at age 35y every 2-3 y, after 50 every 1-2 y Annual colonoscopy in MMR mutation carriers</td>
<td>Level III/ Moderate quality</td>
</tr>
<tr>
<td></td>
<td>Consider: Daily Aspirin (for risk reduction)</td>
<td>Daily ASA NCCN: Not recommended as standard chemoprevention, data not sufficiently robust USPTF: Grade B recommends ASA for adults aged 50 to 59 years with a ≥10% 10-year CVD risk to be used for prevention of colorectal cancer and CVD.</td>
<td>Level I/Moderate quality</td>
</tr>
<tr>
<td></td>
<td>Colectomy with ileorectal anastomosis</td>
<td>Individuals with colon cancer or colorectal neoplasia that cannot be removed by endoscopy. Consider less extensive surgery if individual &gt; than age 60 – 65 y</td>
<td>Level III/ Moderate</td>
</tr>
<tr>
<td>Endometrial/Ovarian</td>
<td>Hysterectomy and bilateral salpingooophorectomy</td>
<td>MLH1, MSH2, MSH6: After completion of childbirth or at age of 40. EPCAM, PMS2: no specific management guideline</td>
<td>Level IV/Moderate-quality</td>
</tr>
<tr>
<td></td>
<td>Optional: Endometrial sampling, Pelvic examination</td>
<td>MLH1, MSH2, MSH6, EPCAM Annually: begin at age 30 – 35 y</td>
<td>Level V/Low quality</td>
</tr>
<tr>
<td></td>
<td>Transvaginal U/S</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Educate</td>
<td>Teach self awareness of dysfunctional uterine bleeding. Educate about endometrial cancer symptoms. Patient to report symptoms to provider (NCCN 2016)</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>Offer: EGD with biopsy of the gastric antrum</td>
<td>MLH1, MSH2, EPCAM: Start at age 30 – 35 y, then if needed consider every 2 – 3 y depending on patient risk factors (family history or Asian ancestry)</td>
<td>Level V/Low quality</td>
</tr>
<tr>
<td>Ureter/Renal</td>
<td>Urinalysis</td>
<td>Consider Annual: begin at age 30 – 35 y</td>
<td>Level V/Low quality</td>
</tr>
</tbody>
</table>

3 Main Management Options

1. Medical Surveillance
2. Chemoprevention
3. Prophylactic Surgical Intervention

The most widely used option is medical surveillance with Medical Oncology, Gynecological and GI specialist involvement.
# Genetic Testing

## Cancer Predisposition Gene Panel

<table>
<thead>
<tr>
<th>Total Genes</th>
<th>Breast</th>
<th>Ovarian</th>
<th>Colon</th>
<th>Pancreatic</th>
<th>Renal</th>
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<tr>
<td>1. BRCA1</td>
<td>1. BRCA1</td>
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<td></td>
<td>1. CDH1</td>
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<td>2. BRCA2</td>
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<td>2. STK11</td>
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<tr>
<td>4. STK11</td>
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<td></td>
<td>4. TP53</td>
<td>4. STK11</td>
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<tr>
<td>5. PTEN</td>
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<td>5. MUTHYH</td>
<td>5. TP53</td>
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<tr>
<td>6. TP53</td>
<td>6. TP53</td>
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<td></td>
<td>6. CHEK2</td>
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<tr>
<td>7. PALB2</td>
<td>7. PALB2</td>
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<td></td>
<td>7. RET</td>
<td>7. PALB2</td>
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<td>8. BARD1</td>
<td>8. BARD1</td>
<td></td>
<td></td>
<td>8. MLH1</td>
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<td>9. BRIP1</td>
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<td>10. NF1</td>
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<td>34. PCNA</td>
<td>34. VH1</td>
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</tr>
</tbody>
</table>

**High Risk Breast and/or Ovarian Cancer**

Low-Moderate Risk of Breast or Ovarian Cancer

**High Risk for Lynch Syndrome**

Other Familial Cancer Genes
Results: Positive/Negative/Dreaded VUSs

- Positive results in genetic testing
- Negative results in genetic testing
- Variants of Unknown Significance
- What does that mean?
- Are they good or are they bad?
- New incoming research may help reclassify a VUS but until then, patients and providers need to wait.
- What to do in the meanwhile?
Who is the Family Has Cancer Include 1st and 2nd relatives Don’t Limit to a Certain Type of Cancer

Algorithm
Steps to Making a Referral for Cancer Genetic Counseling

Step 1: Collect Family History
- Who is the Family Has Cancer
- Include 1st and 2nd relatives
- Don’t Limit to a Certain Type of Cancer
- Type: Prompt patient to distinguish primary and metastatic cancer
- Age at Diagnosis: Look for ≤ 50 years of age
- Any Benign Tumors or Other Medical Problems?
- Any Known Genetic Mutation in the Family?

Step 2: Identify Risk Factors
- Early Age of Onset: ≤ 50 y
- At Least One Relative with Multiple Primaries/Bilateral Disease
- Rare Cancer in Patient or Family: Ovarian, Male Breast, Medullary Thyroid
- Same Cancer or Related CA in ≥ 2 generations on same side (breast/ovarian, endometrial/colon, colon/ovarian)
- Known Mutation in the Family (1st and 2nd relatives)

Step 3: Discuss Results of Assessment
- Communicate the Significance of Their Family History: - or +
- Negative: “The reason I collect family history is because for some people, the chances of developing certain cancers increase. Your history does not show increased risk, but if anything changes in your family history, please let me know.”
- Positive: “The reason I collect family history is because for some people, the chances of developing certain cancers increase. Your history (recite pertinent history) alerts me about a possibility that you may be at risk for developing these types of cancers. You can benefit from a more in depth screening and a referral to the genetic counselor.

Step 4: Make referrals for Counseling and Testing
- Have a List of Genetic Services in Your Area: Genetic Clinic Directory
  https://www.genetests.org/clinics/?region=usa&list=CA
- Genetic Counseling is Often Covered by Insurance After Offering the Referral, Encourage Patient to Call and Find Out Their Coverage
- Reach Out to Local Genetic Counselors for Any Questions: Appropriate referrals, the process, coverage, any educational material for your office.

Discuss Genetic Counseling and Testing Briefly
- Genetic Counseling is Often Covered by Insurance
- After Offering the Referral, Encourage Patient to Call and Find Out Their Coverage

What is the gene?
Who in the Family Carries it?
What Lab Was Used?
Case Scenario 1:
Mrs. Williams is a 39 year old African American female who is here for her annual woman examination. She is married with 3 children, but states she is concerned about her family history of breast cancer. She received a family history questionnaire when she called the office and brought a completed one to the appointment. She denies personal history of breast cancer. She had her first child at age 27 and her menses started at age 12.

Family History:
Sister age 38 with history of Breast CA at age 31.
Twin sisters age 46, with one twin who had hx of breast CA at age 33.
Paternal aunt history of breast CA at age 23 and died at age 29.
Paternal grandmother side: Great aunt diagnosed with breast CA at age 35, died at age 40.

Question 1: What are the red flags?
Answer: Multiple family members with history of breast CA before age 50. Patient should be referred to genetic counseling. Her affected members should be tested first because it would give better information regarding a possibility of HBOC in the family.

If the result comes back positive for a gene mutation, the high risk family members should be offered single site testing for that particular mutation.
Case Scenario 2:
42 year old female patient with history of breast CA at age 38.
Family History:
Sister age 52 with Hx of breast CA dx’d at age 40
Paternal aunt in her 80s with hx of breast CA at age 54.

Question 1: Does this patient have a high risk?
Answer: yes. She has personal history of cancer and one family member with history of breast cancer at a young age.

Question: What would be recommended if there is no mutation found in the patient or family?
Answer: Review recommendations since the patient is still at increased risk of breast CA considering her family history. High risk breast cancer screening should be offered to all of patient’s unaffected female family members.

Recommend annual mammogram and breast MRI beginning age 28 (10 years before earliest diagnosis in the family).
Case Studies

**Case scenario 3:**
45 year old female with significant family history.
Family Hx:
Brother with Hx of colon CA at age 44
Mother with Hx of endometrial CA at age 50.
What hereditary cancer syndrome are you thinking about?
**Question:** What are the red flags? Should this patient be tested?
For what condition?

**Case scenario 4:**
75 year old male with personal history:
Colorectal @ age 65
Bladder @ age 61
Melanoma @ age 50
Family History:
Mother died at 85 with history of colorectal @ age 47 and hepatobiliary @ age 49
**Question:** What are the red flags? Should this patient be tested?
For what condition?
## Tools & Resources

<table>
<thead>
<tr>
<th>Genetic Services</th>
<th>Description/Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Clinic Directory</td>
<td>Find providers specializing in genetics Website: <a href="https://www.genetests.org/clinics/?region=usa&amp;list=CA">https://www.genetests.org/clinics/?region=usa&amp;list=CA</a></td>
</tr>
<tr>
<td>Genetic Testing Registry</td>
<td>Genetic test and lab search with extensive information about genetic tests. Ability to filter options. Lab information that provides certain tests can be found here. Website: <a href="http://www.ncbi.nlm.nih.gov/">http://www.ncbi.nlm.nih.gov/</a></td>
</tr>
<tr>
<td>The Clinical Genome (ClinGen) and ClinVar</td>
<td>Find resources linked to conditions, genes, and medications. ClinGen- rates genes by level of evidence vail article. Why it’s important to choose a right lab. You cannot patent a gene, they allowed other people to use ClinVar- search for specific variants. Public database Website: <a href="https://www.clinicalgenome.org/tools/web-resources/clinician/">https://www.clinicalgenome.org/tools/web-resources/clinician/</a></td>
</tr>
<tr>
<td>NCI Cancer Genetics Services Directory</td>
<td>Find genetic specialists by specialty( type of cancer or family cancer syndrome), location, or name Website: <a href="https://www.cancer.gov/about-cancer/causes-prevention/genetics/directory">https://www.cancer.gov/about-cancer/causes-prevention/genetics/directory</a></td>
</tr>
<tr>
<td>Informed DNA</td>
<td>Genetic counseling brought to the patient using telephone and web based technology anywhere in USA. No cost to the practice, accepts most insurance plans, handles all reimbursement arrangements. Patients are sent for genetic counseling and back to provider for follow-up care and treatment. Referral: <a href="http://www.informeddna.com/images/pdfs/RefCancer-2-18-16.pdf">http://www.informeddna.com/images/pdfs/RefCancer-2-18-16.pdf</a></td>
</tr>
<tr>
<td>Low Income/Underinsured/Uninsured</td>
<td></td>
</tr>
<tr>
<td>California Health Collaborative: Every Woman Counts</td>
<td>Assists uninsured/underinsured women in receiving breast and cervical cancer screening and follow-up services in order to identify disease early. Federally Qualified health centers Website: <a href="http://www.healthcollaborative.org/EveryWomanCounts-i-301-19.html">http://www.healthcollaborative.org/EveryWomanCounts-i-301-19.html</a> Offices in many locations in California</td>
</tr>
</tbody>
</table>
# Tools & Resources

<table>
<thead>
<tr>
<th>Tools for Providers</th>
<th>Description/Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Gynecology Oncology (SGO)</td>
<td>Guidelines, education for patients and providers Website: <a href="https://www.sgo.org/clinical-practice/guidelines/">https://www.sgo.org/clinical-practice/guidelines/</a></td>
</tr>
<tr>
<td>Genetics in Primary Care Institute</td>
<td>Offers educational webinars for providers about genetic medicine along with important skills to build upon. Information for patients. Website: <a href="https://geneticsinprimarycare.aap.org/YourPractice/Patient-Management-and-Guidelines/Pages/Patient-Management-and-Guidelines.aspx#jump-3">https://geneticsinprimarycare.aap.org/YourPractice/Patient-Management-and-Guidelines/Pages/Patient-Management-and-Guidelines.aspx#jump-3</a></td>
</tr>
<tr>
<td>G2C2 Genetics/Genomics Competency Center</td>
<td>Genomics educational materials, discipline specific genomic competencies. Website: <a href="http://www.g-3-c.org/">http://www.g-3-c.org/</a></td>
</tr>
<tr>
<td>G3C3 Global Genetics and Genomics</td>
<td>Standardized patients and case studies. Ability to go through case studies at your own pace. Website: free login <a href="http://genomicscases.net/en/auth/login">http://genomicscases.net/en/auth/login</a></td>
</tr>
<tr>
<td>American Society of Human Genetics (ASHG)</td>
<td>Genetic testing resources, education resources for practitioners, definitions of genetic terms, presentation resources Website: <a href="http://www.ashg.org/press/healthprofessional.shtml">http://www.ashg.org/press/healthprofessional.shtml</a></td>
</tr>
<tr>
<td>Tools</td>
<td>Description/Website</td>
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<tr>
<td>Genetic Information Nondiscrimination Act (GINA)</td>
<td>Information about GINA and printer friendly information sheets for patients</td>
</tr>
<tr>
<td>Website: <a href="http://www.ginahelp.org/">http://www.ginahelp.org/</a></td>
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<tr>
<td>The American College of Medical Genetics and Genomics (ACMG)</td>
<td>Professional membership organization. Find genetic services, practice guidelines, policies.</td>
</tr>
<tr>
<td>Website: <a href="https://www.acmg.net/ACMG/FindGenetic_Services/ACMG/I">https://www.acmg.net/ACMG/FindGenetic_Services/ACMG/I</a> SGweb/FindaGeneticService.aspx</td>
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</tr>
<tr>
<td>Tool for Patients</td>
<td></td>
</tr>
<tr>
<td>FORCE: Facing Our Risk of Cancer Empowered</td>
<td>Offers patients resources, information, advice, risk management guidelines, screening, prevention, overview of hereditary cancer and gene mutations, and much more.</td>
</tr>
<tr>
<td>Website: <a href="http://www.facingourrisk.org/understanding-brca-and-hboc/information/hereditary-cancer/hereditary-genetics/?subcat_nice_name=hereditary-genetics&amp;tab_type=index">http://www.facingourrisk.org/understanding-brca-and-hboc/information/hereditary-cancer/hereditary-genetics/?subcat_nice_name=hereditary-genetics&amp;tab_type=index</a></td>
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<tr>
<td>Health insurance appeals Templates by FORCE</td>
<td>Templates that can be used if insurance refuses to cover the cost of a particular genetic service. Includes: genetic counseling and BRCA testing, ovarian cancer, breast screening MRI, risk reducing salpingo-oophorectomy, bilateral mastectomy for BRCA mutation carriers, or for people with other risk factors.</td>
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<td>Website: <a href="http://www.facingourrisk.org/understanding-brca-and-hboc/information/finding-health-care/health-insurance-appeals/">http://www.facingourrisk.org/understanding-brca-and-hboc/information/finding-health-care/health-insurance-appeals/</a></td>
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Questions?

Please fill out the post-evaluation

Thank You
References


Centers for Disease Control and Prevention (2014). More detailed information on key tier 1 applications - hereditary breast and ovarian cancer (HBOC).
Retrieved from
https://www.cdc.gov/genomics/implementation/toolkit/hboc_1.htm


References


References


