How to Identify Patients/Families at Risk for Hereditary Cancer:
Working With a Cancer Genetic Counselor

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Learning Objectives
1. Describe features of families at risk for a familial/hereditary cancer syndrome.
2. Describe features of Hereditary Breast and Ovarian Cancer (HBOC) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch syndrome) and surveillance measures.
3. Describe the process of genetic counseling & testing including genetic discrimination and insurance issues.

How Much Cancer is Hereditary?
- 5 – 10% of the cases are hereditary- due to high penetrance gene.
- 20-30% of the cases are familial (hereditary factors are involved or low penetrance genes).
- Majority of the cases are sporadic.

Goal: Classification
Who needs what?
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Risk Classification</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Hx</td>
<td>Average</td>
<td>Standard prevention recommendations</td>
</tr>
<tr>
<td></td>
<td>Moderate (&quot;Familial&quot;)</td>
<td>Personalized prevention recommendations</td>
</tr>
<tr>
<td></td>
<td>High/Genetic</td>
<td>Referral for genetic evaluation with personalized prevention recommendations</td>
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Cancer Genetic Counseling

- The primary goal of cancer genetic counseling is to identify individuals and families at increased risk of cancer for the purpose of promoting awareness, early detection and cancer prevention.

- Communicating back to primary care/referring physicians so that the information from the risk assessment can be used to appropriately manage cancer risk.

Genetic Counseling for Cancer Risk Assessment

- Collecting a detailed cancer-focused personal and family medical history and assessing a person’s risk of developing cancer based on this information.

- Determining whether the history is suggestive of an inherited cancer syndrome.

- Providing patient education and answering questions about cancer risks, the option of genetic testing, and the pros and cons of genetic testing.

- Reviewing medical management options with or without genetic testing.

- Providing psychosocial support to and facilitating communication between patients and families.

ASCO Guidelines for Genetic Testing

ASCO recommends that genetic testing be offered when:

1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition.

2) the test can be adequately interpreted.

3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

Genetic Information Non-discrimination Act - GINA

- Once enacted in 2009, GINA will offer new Federal-wide protections against discrimination based on genetic information.

- Genetic information is defined as predictive genetic tests, family members’ genetic tests, and family history information.

- GINA’s protections apply to group and individual health insurance as well as to employment practices. It does not cover life, disability, long-term care, and other forms of insurance.
Genetic Discrimination Protection in California

- Legislation prohibits state-regulated health insurers and HMOs from denying coverage for health insurance or charging a higher premium based on genetic information.
- Written informed consent is required for the disclosure of test results to a third party.
- Prohibits employers from discriminating against employees or candidates based on asymptomatic genetic traits.

DNA Transcription and Translation

DNA Replication

- Complementary base pairing
  - A binds with T
  - C binds with G
- Duplicated strand is identical to original

Disease-Associated Mutations

A mutation is a change in the normal base pair sequence

Commonly used to define DNA sequence changes that alter protein function
The Development of Hereditary Cancer

In hereditary cancer, one damaged gene is inherited.

Genes Associated with Cancer Predisposition

Tumor suppressor genes
- DNA damage-response genes
- The cell’s brakes for tumor growth
- Cancer arises when both brakes fail

Oncogenes
- Accelerates cell division
- Cancer arises when stuck in “on” mode

Kristin Kalla, M.S., C.G.C
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What Clinical Features Suggest a BRCA1/2 Mutation May Be Present

- Multiple cases of early-onset breast cancer (<50).
- Ovarian cancer (with breast and/or other ovarian cancer).
- Breast and/or ovarian primary tumors in the same woman.
- Male breast cancer.
- Pattern of associated cancers noted over multiple generations and/or inheritance consistent with autosomal dominant pattern.
- Ancestry with known founder mutation(s) (e.g. Ashkenazi Jewish, Dutch, Icelandic).

BRCA1 Pedigree

Br Ca = Breast cancer
Ov Ca = Ovarian cancer

Factors Affecting Penetrance

- Modifier genes
- Response to DNA damage
- Hormonal/reproductive factors
- Carcinogens

Not everyone with an altered gene develops cancer.
**BRCA1/2 Cancer Risks**

- **BRCA1**
  - Breast cancer to age 80: 55-85%
  - Ovarian cancer to age 80: 28-44%
  - Male breast cancer: Slight incr. ~6%
  - Prostate cancer: Slight incr. ~20%
  - Pancreatic cancer: No incr. 1.5-5%
  - Melanoma: No incr.

- **BRCA2**
  - Breast cancer to age 80: 55-85% up to 27%
  - Ovarian cancer to age 80: Slight incr.
  - Male breast cancer: Slight incr. ~6%
  - Prostate cancer: No incr. ~20%
  - Pancreatic cancer: No incr. 1.5-5%
  - Melanoma: Slight incr.
Surveillance for Female Mutation carriers

NCCN Guidelines

- Breast self-exam (BSE) training and education and monthly BSE starting at 18y.
- Clinical breast exam, semiannually, starting at 25y.
- Annual mammogram and breast MRI screening starting at age 25y, or individualized based on earliest age of onset in family.
- Discuss option of risk-reducing mastectomy on case-by-case basis.

Surveillance for Female Mutation carriers

Continued

- For those patients who have not elected risk-reducing oophorectomy—concurrent transvaginal ultrasound and CA-125 every 6 mo starting at 35y or 5 – 10 years earlier than the earliest age of ovarian cancer diagnosis in the family.
- Recommend risk-reducing salpingo-oophorectomy ideally between 35 and 40 y, or upon completion of child bearing, or individualized based on earliest onset of ovarian cancer in the family.
- Consider chemoprevention options for breast and ovarian cancer.
- Consider investigational imaging and screening studies, when available.

Surveillance for Male Mutation carriers

Continued

- Breast self-exam training and education and regular monthly BSE
- Consider baseline mammogram; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study.
- Adhere to screening guidelines for prostate cancer.
Other Recommendations for HBOC

- Education regarding signs and symptoms of cancer.
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.
- Discuss reproductive options.

Average risk for Breast Cancer

- No family history of breast cancer and no other known risk factors
- Others who may be at average risk (?):
  - One 1st degree relative diagnosed >60 yrs
  - One or two 2nd degree relatives diagnosed >60 yrs
- Current screening recommendations:
  - Monthly SBE
  - Annual CBE
  - Annual mammography starting 40-50 yrs

“Moderate/Familial Risk”

- Clustering of cancer cases seen in the family.
- Ages of onset not strikingly young.
- Risks for first degree relatives increased.
  - Risk depends on number of family members affected, how closely related, ages of onset
- Multiple low-penetration genes may play a role and interact with environmental triggers.
- Low to moderate penetrance genes yet to be discovered.

Risk Based Management

Moderate/Familial:

Moderate Risk of Breast Cancer: Lifetime risk of 15-40% with low risk of BRCA1 or 2 mutations and no indication of other cancer syndromes.

- Screening recommendations ACS:
  - BSE monthly; CBE once or twice a year.
  - Annual MRI for women with ≥ 20 % lifetime risk.
  - Mammogram once a year starting at 35 or 5-10 yrs prior to earliest case of breast cancer.
  - Immediate biopsy of any suspicious findings
  - Option: Chemoprevention.
  - Lifestyle modifications.
ACS Guidelines for MRI Screening for Familial Breast Cancer

- Women at high risk (> 20% lifetime risk) should get an MRI and a mammogram every year.
- Models used to estimate lifetime risk for familial cancer – Gail, Claus, BRCAPRO and Tyrer-Cusick.
- Models used to estimate risk to carry a BRCA1/2 gene mutation and also provide lifetime risk for breast cancer – BRCAPRO, Boadicea.

CA Cancer J Clin 2007;57:75-89

Familial Risk for CRC

- Approximately lifetime CRC risk (%)

<table>
<thead>
<tr>
<th>Affected family members</th>
<th>0%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3%</td>
<td>6%</td>
<td>8%</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>One 1st and two 2nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>One 1st and two 2nd</td>
<td></td>
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Modified with permission from the American Cancer Society, Atlas of Baseline Screening.

Hereditary Non-Polyposis Colorectal Cancer - HNPCC

- Caused by mutations in any of 5 mismatch repair genes
  - MLH1, MSH2, MSH6, PMS1, or PMS2. (~80% mutations are in either MLH1 or MSH2)
- These genes correct mispairing of bases in single stranded DNA during the cell cycle.
- Accumulation of mismatches in tumor suppressor genes and oncogenes result in cancer.

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Cancer Risks in Individuals with HNPCC up to Age 70 Years

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Gen Pop Risks</th>
<th>HNPCC Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>&lt;1%</td>
<td>2%-7%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1%-3%</td>
</tr>
</tbody>
</table>

Clinical Features of Hereditary Nonpolyposis Colorectal Cancer

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors, brain

DNA Mismatch Repair

- Base pair mismatch
- Normal DNA repair
- Mutation introduced by unrepaired DNA

The Family History Is Key to Diagnosing HNPPC

Cancer Risks in Individuals with HNPCC up to Age 70 Years

- Colon
- Endometrium
- Stomach
- Ovary
- Hepatobiliary tract
- Urinary tract
- Small bowel
- Brain/CNS

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HNPCC: Clinical Diagnostic Criteria

- Amsterdam II Criteria (3-2-1 rule)
  - 3 or more relatives with an HNPCC-related cancer, one of whom is a 1st degree relative of the other two
  - 2 or more successive generations affected
  - 1 or more cancers diagnosed before age 50

Criteria for MSI/IHC screening

Revised Bethesda Criteria, 2004

- CRC or endometrial CA <50 yrs
- 2 HNPCC cancers in same person
- CRC with “MSI-H histology” diagnosed <60 yrs
  - Infiltrating lymphocytes, Crohns-like lymphocytic reaction, mucinous/signet ring differentiation, medullary growth pattern
- CRC and one or more 1st degree relative with an HNPCC-related cancer, one diagnosed <50 yrs
- CRC and two or more 1st or 2nd degree relatives with HNPCC-related cancers, any age

MSI/IHC screening

- Microsatellite Instability (MSI) on tumor tissue
  - can be used to screen for HNPCC in select cases
- Immunohistochemistry (IHC) on tumor tissue
  - can be used to detect the presence or absence of the mismatch repair proteins (MSH2, MLH1, etc.)
  - BRAF V600E mutation analysis with reflex to MLH1 methylation study if MLH1 is absent.
- “Screen positive” individuals can be offered cancer genetic counseling/assessment and targeted genetic testing.
  

NCCN Guidelines Surveillance Guidelines for HNPCC

- Colonoscopy starting at age 20-25y or 10 yrs earlier than the earliest of onset in the family. Repeat every 1-2 yr.
- Upper endoscopy at age 25-30y and repeat every 1-3 y.
- Urothelial cancer: Consider annual urinalysis and imaging of the renal collecting system.
- CNS cancer: Annual physical examination; no additional screening recommendations have been made.
NCCN Guidelines Surveillance Guidelines for HNPCC Cont’d

- Endometrial and ovarian screening starting at age 25-35 and including transvaginal ultrasound and office endometrial sampling annually, with concurrent serum CA-125 (efficacy unknown) every 6-12 months in pre-menopausal women.
- Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk reducing option for women who have completed childbearing.
- Pancreatic Screening: No recommendations have been made.

Features of Familial CRC
- Family history of CRC with no clear inheritance pattern
- Age at onset typical of sporadic CRC
- Multiple causes
- Few or no adenomas

CRC Risk Management

**Moderate/Family history Age to begin**
1. Two 1st degree relatives with CRC any age or one 1st degree relative with CRC < 60
   - Colonoscopy every 5 yrs beginning at age 40 years*
2. One 1st degree relative with CRC >60 or two 2nd degree relatives with CRC any age
   - Average risk screening

* Or 5-10 yrs earlier than earliest case in family

Questions To Ask Patients Who Have Had Cancer Or Regarding Relatives With Cancer

- Age at time of diagnosis.
- Number of tumors- important to know if other tumor are new primaries or recurrence.
- Pathology of malignant and benign tumors.
- Treatment regimen (surgery, chemotherapy, radiation.
- Cancer status in 1st and 2nd degree relatives and in both sides of the family and ethnic background.

Gastroenterology. 2003;124:544-560
J Genet Couns. 2004; 3(2):83-114
Consider Cancer Genetic Counseling Referral If:

- Patient and/or family history meet criteria listed in "Indications for Referral" handout.
- Multiple closely related family members with genetically related cancers.
- Two or more primary tumors in the same individual.
- Patient has extreme anxiety about their cancer family history.
- Patient has had genetic testing for a hereditary cancer syndrome and needs additional education and/or help identifying family members at risk.

Cancer Genetic Counseling Process At Scripps Cancer Center

- Complete and sign FAX referral form and FAX to genetic counseling office.
- GC will contact patient and schedule appointment if patient agrees.
- GC will send FAX if genetic testing is drawn and expected date of results.
- GC will FAX results to physicians office and schedule result disclosure appointment with patient.
- Complete GC consult summary is sent to referring physician.

Web Based Resources

- State and federal legislation: http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm
- Genetests - Overview of well known hereditary genetic disorders: http://www.genetests.org