Genetic Cancer Risk Assessment 101

Ellen Totten, MS, LCGC
Advocate Medical Group

September 26th, 2015
Outline

• What does a genetic cancer risk assessment (GCRA) entail?

• Case examples illustrating key concepts
  • Cancer surveillance and medical management options
  • Utility of multi-gene panels
  • Counseling of moderate-risk genes
  • Empiric risk counseling when genetic test is uninformative
GCRA Process

• Pre-test appointment
  • Collect medical history
  • Collect and interpret family history
  • Determine appropriate testing strategy (is testing appropriate, if so, what test, who to test)
  • Provide pre-test counseling
  • Obtain informed consent

• Post-test counseling:
  • Test result interpretation
  • Cancer surveillance protocol/medical management
  • Psychosocial support
  • How this impacts family members
Medical History

• View pathology report
  • Example: Epithelial ovarian cancer versus germ cell ovarian cancer
  • Immunohistochemistry for mismatch repair genes
  • Triple-negative
• Collect other pertinent history
  • Colonoscopy history and polyp pathology
  • Dermatologic findings
• Physical exam
  • Collect head circumference
Family History

- Assess BOTH sides
- First, second and third degree relatives, ages at cancer dx, age at and cause of death; other diagnoses
- Ethnicity

NCCN Guidelines Version 2.2015
Genetic/Familial High-Risk Assessment: Breast and Ovarian
Determining a testing strategy

1. Is testing appropriate?
   • Does the patient/family meet NCCN guidelines or expert opinion to offer testing?

2. What are the test options?
   • Are the features suggestive of a single-gene condition, or is a multi-gene panel the more appropriate and cost-effective test?

3. Who is the optimal individual to test?
   • Ideally, test the individual with the “most suspicious” cancer (earliest age at onset, bilateral disease, or multiple primary cancers).
   • Testing for unaffected individuals, when no affected member is available should be considered; significant limitations of interpreting test results must be discussed.
Benefits and limitations of genetic testing

Benefits:
• May provide a more specific cancer risk
  • Provide an opportunity for personalized cancer screening and risk reduction options
• May provide an “answer”
• May decrease cancer anxiety
• Impact on family
  • Can provide family members more concrete information about cancer risk

Limitations
• Interpretation of a “negative” test result
  • Does not eliminate increased cancer risk
• Uncertain results
• Cost
• Increase in anxiety
• Concerns about genetic discrimination
and others). Genetic counseling is performed by a cancer genetics professional who has extensive experience and educational background in genetics and cancer genetics, counseling and hereditary cancer syndromes, to provide accurate risk assessment and empathetic genetic counseling to cancer patients and their families.

**STANDARD 2.3**

Risk Assessment and Genetic Counseling

Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.
Case examples
Case 1

- 34 year-old Asian woman felt a mass in her right breast on self breast exam; this led to imaging and biopsies, and a diagnosis of ER+/PR+ DCIS in the right breast and ER+/PR+ DCIS in the left breast.

- Family history of a maternal aunt with lymphoma at 30 and pancreatic cancer at 47, maternal grandmother deceased with ovarian cancer at 83, and a paternal first cousin with “uterine and ovarian cancer” diagnosed at 40. No relatives had genetic testing in the past.

- BRCA1/2 analysis showed deletion of exons 22-24 in BRCA2.
BRCA1 and BRCA2 lifetime cancer risks

Breast cancer (+ early age at onset) (50-85%)
Second primary breast cancer (40-60%)
Male breast cancer (5-6%)
Ovarian cancer (20%-40%)
Prostate cancer (30-40%)
Increased risk of pancreatic cancer, melanoma, colon and other cancers
NCCN recommendations for female BRCA2 mutation carriers

• Breast MRI, starting at 25 y, yearly mammogram starting at 30 y, alternating with MRI such that one or the other is done every six months
• Discuss option of risk-reducing mastectomy
• Recommend removal of ovaries and fallopian tubes (in consultation with a gynecologist oncologist), typically between 35 and 40 y, and upon completion of child bearing.
• Consider risk reduction agents as options for breast and ovarian cancer.
Management guidelines continued

- No specific screening guidelines exist for pancreatic cancer and melanoma; screening is individualized based on cancers observed in the family.
- Recommend genetic counseling and consideration of genetic testing for at risk relatives.
- For patients of reproductive age, advise about preconception and prenatal options.
NCCN recommendations for male BRCA2 carriers

- Breast self-exam training and education starting at age 35 y.
- Clinical breast exam every twelve months starting at age 35 y.
- Recommend prostate cancer screening starting at age 40 y.
Advocacy and support groups
Case 2

- A 44-year-old woman of German and Swedish descent diagnosed with endometrial cancer; IHC for mismatch repair genes was normal.

- Family history of mother diagnosed with ovarian cancer at 53, deceased at 57, no genetic testing. Maternal grandfather deceased with prostate cancer in his eighties. The patient has no sisters, maternal aunts or great aunts, and a relatively small family. The patient has 2 healthy daughters, ages 17 and 14.
24% of women with ovarian cancer carried germline mutations (18% BRCA1 or BRCA2, and 6% BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, or p53)
Case 2 test results

- A pathogenic mutation in MSH2, c.2004delTinsCA was identified on a multi-gene hereditary cancer panel, consistent with a diagnosis of Lynch syndrome.
Cancer Risks with MSH2

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk$^1$</th>
<th>$MLH1$ or $MSH2^{1,2}$</th>
<th>Risk</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>40%–80%</td>
<td>44–61 years</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%–60%</td>
<td>48–62 years</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1%–13%</td>
<td>56 years</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%–24%$^5$</td>
<td>42.5 years</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%–4%</td>
<td>50–57 years</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%–4%</td>
<td>54–60 years</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%–6%</td>
<td>47–49 years</td>
<td></td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1%–3%</td>
<td>~50 years</td>
<td></td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%–9%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Pancreas$^4$</td>
<td>&lt;1%</td>
<td>1%–6%</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>
NCCN recommendations for female MSH2 mutation carriers

- Colon cancer:
  - Colonoscopy at age 20-25 years, and repeat every 1-2 years
  - Data to suggest that aspirin may decrease risk of colon cancer in Lynch syndrome; however not a recommendation for its standard use at this time.
- Endometrial and ovarian cancer:
  - Prophylactic hysterectomy and BSO is a risk-reducing option that should be considered by women who have completed childbearing.
- Urothelial cancer:
  - Consider annual urinalysis starting at 25-30 y
- Central nervous system cancer:
  - Annual physical exam starting at 25-30 y

Additionally, recommend genetic counseling and consideration of genetic testing for at risk relatives.
Case 3

• 38 year old woman of Polish and Czech ancestry presented to the surgeon’s office with a breast fibroadenoma.

• Family history of paternal grandfather deceased at 57 with pancreatic cancer, paternal grandmother’s sister with breast cancer in her fifties, paternal grandmother’s sister with colon cancer in her fifties, and paternal grandmother’s mother with breast cancer in her fifties. Father is 74 and no personal history of cancer. Father declined testing.

• A pathogenic mutation in CHEK2, p.I157T, was identified on a multi-gene cancer panel.
Phenotypic effect size and frequency of cancer susceptibility genes
CHEK2

- **Cancer Risks**
  - Breast cancer
    - 20% or higher lifetime risk; modified by family history
  - Colon cancer
    - 2-fold the general population risk
  - Other cancers
    - There are other cancers seen in families with CHEK2 mutations, but absolute risks are not yet available

- **Screening recommendations**
  - NCCN recommends breast MRI
  - Insufficient evidence to discuss RRM based on a CHEK2 mutation alone; intervention may still be warranted based on family history and other clinical factors
  - Colonoscopy beginning at age 40 and interval not to exceed 5 years.
Case 4

- A 30-year-old Filipino woman with no personal history of cancer.

- Family history of mother diagnosed with breast cancer at 56, maternal aunt diagnosed with breast cancer at age 40, and maternal grandmother diagnosed with breast cancer at 50. The affected relatives were unable or unwilling to be tested.

- A multi-gene breast cancer predisposition panel did not identify a mutation.

- Therefore, patient was given empiric risk estimates during post-test counseling.
Empiric risk of breast cancer

- Tyrer-Cusick: 36.5%
- Claus: 27%

Average Risk Guidelines: 1%
Median Risk Guidelines: 11%
High Risk Guidelines: 40%
Cancer surveillance for this patient

• NCCN and ACS recommend women who have a lifetime risk of breast cancer >20% as defined by models largely dependent on family history have breast MRI as adjunct to mammogram and clinical breast exam.

• Risk of ovarian cancer is estimated to be the general population risk of 1.6%, because no family history of ovarian cancer.

• The option of chemoprevention was not assessed in detail because patient is <35 years old.
How to refer a patient for genetic cancer risk assessment

- Advocate Medical Group, Genetics Department
- 847-723-7705
Thank you

Any questions?