Genetic Testing in Cancer
Judith A. Westman, MD
Doreen M. Agnese, MD

Who is at High Risk for Hereditary Cancer?
- Hereditary cancer accounts for only a small portion of all cancer
  ✔ 5-10%

Inherited Cancer Susceptibility and Gene Testing
Judith A Westman MD

Start with Cancer Family History
- Pedigree
  ✔ Determine risks to proband and family members
  ✔ Clarify lineages
  ✔ Clarify degree of relatedness

References:
Information to Obtain About Affected Relatives

- Current age
- Age at diagnosis and date of diagnosis/death
- Type, location, stage, and laterality of primary cancer(s)
- Second cancer: metastasis or new primary?
- Environmental exposures (e.g., smoking, sun)
- Ethnicity/race

When to Suspect Hereditary Cancer Syndrome

- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Evidence of autosomal dominant transmission, i.e.
  - Multiple affected generations
  - Presence of congenital anomalies or syndrome-associated benign lesions

When to Suspect Hereditary Cancer Syndrome

- Cancer in two or more close relatives (on the same side of family)
- Early age at diagnosis
- Multiple primary tumors in the same individual
- Bilateral or multiple rare cancers

When Should Genetic Testing Be Considered?

- Patient has a reasonable likelihood of carrying an altered cancer susceptibility gene
- Genetic testing is available that can be adequately interpreted
- Results will influence medical management or aid in the diagnosis of a hereditary cancer syndrome
### Hereditary Breast and Ovarian Cancer Syndrome

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>62%</td>
<td>BRCA1</td>
</tr>
<tr>
<td>32%</td>
<td>BRCA2</td>
</tr>
<tr>
<td>7-10%</td>
<td>Other genes</td>
</tr>
</tbody>
</table>

#### Features That Indicate Increased Likelihood of Having BRCA Mutations
- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

### BRCA1-Associated Cancers: Lifetime Risk
- Breast cancer 50%, 85% (often early age at onset)
- Second primary breast cancer 40%, 60%
- Ovarian cancer 15%, 45%
- Possible increased risk of other cancers (e.g., prostate, colon)
**BRCA2-Associated Cancers: Lifetime Risk**

- **Breast cancer**: (50%–85%)
- **Ovarian cancer**: (10%–20%)
- Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

**Pathology**

- **BRCA1** breast tumors
  - 80% basal subtype (triple negative ER/PR/HER2)
- **BRCA2** breast tumors
  - Typical distribution of molecular subtypes
- **Ovary**
  - Predominantly papillary serous adenocarcinoma
  - May originate from fimbria and fallopian tubes
  - Prognosis may be better than for sporadic ovarian cancer

**BRCA1-Linked Hereditary Breast and Ovarian Cancer**

- **Breast, dx 45, d. 89**: Female carrier
- **Breast, dx 45, d. 89**: Male carrier
- **Breast, dx 36**: Affected with cancer
- **Ovary, dx 59, d. 62**: Affected with cancer
- **Noncarrier**: BRCA1
- **BRCA1-mutation carrier**: ATM

**Other Genetic Conditions Associated with Increased Breast Cancer Risk**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td></td>
<td>(heterozygous carriers)</td>
</tr>
</tbody>
</table>
NCCN Testing Guidelines for BRCA1/2

- Individual from family with known BRCA1/2 mutation
- Personal history of breast Ca plus one or more...
  - Dx <45yr
  - Dx <50yr with >1 “close” relative with breast Ca <50yr or >1 close relative with ovarian/fallopian/primary peritoneal Ca
  - >2 breast primaries with one <50
  - >2 close relatives with breast and/or ovarian
  - Close male relative with breast
  - Personal history of ovarian
  - Founder population with higher mutation frequency
- Personal hx of ovarian/fallopian/primary peritoneal
- Personal hx of male breast cancer

https://familyhealthlink.osumc.edu

Cancer Risk Assessment (a.k.a. genetic counseling)

- Educatess patient in understanding:
  - Risk of having an inherited type of cancer
  - Mode of inheritance
  - Finding the appropriate person to initiate testing
  - Financial and psychological costs of testing if risk sufficient
  - Cancer risks to other family members

Cancer Risk Assessment (a.k.a. genetic counseling)

- Informed consent for DNA testing
  - Likelihood of positive result
  - Likelihood of negative result
  - Likelihood of variant of uncertain significance
Which family member would you want to test first?

Prostate, dx 70
BrCa, dx 82

BrCa, dx 38

BrCa, dx 44
OvCa, dx 54

OvCa, dx 66

Throat, dx 64

31

Results Disclosure

- Time of high anxiety for most at-risk women or women concerned about having passed risk on to next generation
- Disclosure method
  - Face-to-face
  - Support person present who is not biologically related (strongly recommended)
  - Telephone results only if set as appointment with patient in a private seated location (not driving) and with support person
- Results should be given by health care provider prepared to answer questions

Results: Disclosure and Use

Test Results and Interpretation

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 sequencing</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
<tr>
<td>5-site rearrangement panel</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
<tr>
<td>STRC2 sequencing</td>
<td>Y1084X (E002C+G)</td>
<td>Deleterious</td>
</tr>
</tbody>
</table>

Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes and a test for five specific BRCA1 rearrangements.

The results of this analysis are consistent with the germline BRCA2 mutation Y1084X, resulting in a nonsense termination of the BRCA2 protein at amino acid position 1084. Although the risk of breast and ovarian cancer associated with this specific mutation has not been determined, studies of this type of mutation or high-risk families indicate that deleterious mutations in BRCA2 may confer a risk as high as 20% of breast cancer and a 25% risk of ovarian cancer by age 75 in women.

BRCA2 mutations have been reported to occur in 10% of a series of breast cancer patients with two breast cancer cases in first-degree relatives. Knowledge of these results may be useful in counseling at-risk individuals and their family members, and in the development of plans of care.

The results of this analysis are positive for a deleterious mutation.

Family members can be tested for this specific mutation with a single site analysis.
Duty to Warn Family Members

- Patient must be informed that other family members are at risk
  - Availability of medical interventions to reduce the risk of developing a disease or to lessen the ensuing harm
- *Pate v Threlkel (1995)*
  - Familial medullary thyroid cancer
  - Daughter developed MTC, sued, won
  - Physician needed to inform patient of risks to family

Duty to Warn Resolution

- HIPAA ultimately prevails
- AMA: Physicians should “make themselves available to assist patients in communicating with relatives to discuss opportunities for counseling and testing, as appropriate.”
- ASCO: “The cancer care provider’s obligations to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing.”
- Recommend written documentation to patient and maintained in file as part of pre-testing informed consent and at time of results disclosure
### Individuals with a BRCA mutation and breast cancer

Doreen M. Agnese M.D.

#### Surgical Decision Making

If positive for BRCA1 or BRCA2:
- Woman may choose mastectomy rather than lumpectomy/radiation
- May choose simultaneous contralateral prophylactic mastectomy
  - 40-60% risk for a contralateral primary
  - One recovery period
  - Even reconstruction
- Gene test results available in 1-3 weeks

#### Primary prevention of breast cancer if BRCA1/2 mutation

- Prevents cancers from occurring in the first place
- Prophylactic mastectomy
  - 95-98% reduction
- Pre-menopausal oophorectomy (<40 years)
  - 40-60% reduction in breast cancer risk
- Chemoprevention (tamoxifen)
  - 50% reduction in breast cancer risk in both BRCA1 and BRCA2

#### Medical Decision Making

- BRCA1/2 normally involved in signaling and repairing if double strand DNA damage present in cell
- PARP1 – poly[ADP-ribose]polymerase 1
  - Involved in repair of single strand DNA damage
  - If PARP1 not working, BRCA1/2 system corrects errors in DNA
  - If neither system working, cell death occurs
- Preliminary evidence that use of PARP inhibitors in people with BRCA1/2 mutations has impressive reduction of tumor size
Breast Cancer: Chemoprevention

- Matched case-control study
  - 269 women with bilateral breast ca and BRCA1 or BRCA2 mutation
  - 384 women with unilateral breast ca and BRCA1 or BRCA2 mutation
- Tamoxifen protected against contralateral breast cancer
  - BRCA1 odds ratio 0.38 (95% CI 0.19–0.74)
  - BRCA2 odds ratio 0.63 (95% CI 0.20–1.50)

Narod Lancet 2000, 356: 1876

Prophylactic Mastectomy

- Study of 483 women with disease-associated mutations in BRCA1/2, mean F/U 6.4 years
  - 2/105 (1.9%) women developed breast cancer after bilateral prophylactic mastectomy (subcutaneous)
  - 184/378 (48.7%) matched controls who did not have procedure developed breast cancer
- Significantly reduces breast cancer risk in BRCA1/2 mutation carriers
  - 90% risk reduction in women with intact ovaries
  - 95% risk reduction in women with prophylactic BSO


Prophylactic Mastectomy

- Total mastectomy is recommended
- Prospective study of 139 women with BRCA1 or BRCA2 mutations, mean f/u 3 years
- No breast cancers in 76 women who underwent prophylactic mastectomy
- 8 breast cancers in 63 women undergoing regular surveillance

Meijers-Heijboer NEJM 2001; 345(3): 159

Skin-sparing Mastectomy
Reconstruction:
Tissue expander/implant

Skin-Sparing Mastectomy
With DIEP Reconstruction

Reconstruction:
TRAM Flap

Secondary prevention of breast cancers

- Early detection of tumors when surgery alone would be feasible
- Early clinical surveillance (begin at age 25)
  - Clinical breast exams every 6-12 months
  - Annual mammography
  - Annual MRI (risk >>> 20%)
  - Monthly breast self-exams
### Is Mammogram Safe?

- Meta-analysis suggesting that there may be a net harmful effect for young women with BRCA gene mutations who undergo earlier annual mammography, due to an increased risk of radiation-induced breast cancer
- The authors believe that the harms of annual screening may outweigh the benefits in younger women, though not in older women

### Limitations of MRI

- Expensive
- Difficult for patients to undergo
- Requires special coil
- More biopsies required to identify those additional cancers
- More follow-up ultrasound and interval MRIs
- There can still be false negatives!

### Ovarian Cancer Risk Management

- Screening poor -- detects Stage III-IV
  - Screen from age 25 until childbearing complete
  - Transvaginal U/S with Doppler, simultaneous CA-125
- Oral contraceptives, 3-6 years cumulative
  - Reduces ovarian cancer risk by 40%
- Tubal ligation after childbearing complete
  - Reduces ovarian cancer risk by 30-40%

### Prophylactic Oophorectomy

- Significantly decreases risk of ovarian cancer (primary peritoneal carcinoma may still occur)
- Significantly reduces risk of breast cancer
  - By 76% if done prior to age 40
  - By 50% if done prior to age 50
- Induces surgical menopause—HRT?
- Laparoscopic procedure reduces postsurgical morbidity

---

<table>
<thead>
<tr>
<th>Laparoscopic-Assisted Vaginal TAH BSO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary Colorectal Cancer</strong></td>
</tr>
<tr>
<td>** Syndromes **</td>
</tr>
<tr>
<td>• Adenomas</td>
</tr>
<tr>
<td>✓ Lynch syndrome</td>
</tr>
<tr>
<td>• Hereditary nonpolyposis colorectal cancer</td>
</tr>
<tr>
<td>✓ Familial adenomatous polyposis</td>
</tr>
<tr>
<td>✓ MUTYH (or MYH) associated polyposis</td>
</tr>
<tr>
<td>• Hamartomas</td>
</tr>
<tr>
<td>✓ Cowden syndrome</td>
</tr>
<tr>
<td>✓ Peutz Jeghers syndrome</td>
</tr>
<tr>
<td>✓ Juvenile polyposis</td>
</tr>
<tr>
<td>• Sessile serrated polyps/hyperplastic polyps</td>
</tr>
<tr>
<td><strong>Lynch Syndrome</strong></td>
</tr>
<tr>
<td>• Autosomal dominant inheritance</td>
</tr>
<tr>
<td>• Colorectal cancer &lt;50 yr</td>
</tr>
<tr>
<td>• Endometrial cancer &lt;50 yr</td>
</tr>
<tr>
<td>• 2 or more LS-related cancers in person or multiple close relatives</td>
</tr>
<tr>
<td>✓ Colorectal, endometrial, ovarian, gastric, pancreas, ureter and renal pelvis, biliary tract, glioblastoma, small intestinal, sebaceous gland adenomas and keratoacanthomas</td>
</tr>
<tr>
<td>• Colorectal cancer &lt;60 yr and IHC (MLH1, MSH2, MSH6, PMS2) and/or microsatellite instability</td>
</tr>
<tr>
<td>• 2-3% of all colorectal and endometrial cancers in central Ohio</td>
</tr>
</tbody>
</table>
Typical Lynch Family

- CRC dx 45
- CRC dx 48
- CRC dx 52
- CRC dx 61
- Endometrial Ca, dx 59
- Ovarian Ca, dx 64
- CRC dx 42
- CRC dx 50s
- CRC dx 55
- CRC dx 61
- CRC dx 75
- Ovarian Ca, dx 64

Cancer Risks in Lynch Syndrome

- Colorectal 80%
- Endometrial 20-60%
- Stomach 19%
- Ovarian 12%
- Urinary tract 4%
- Brain 1-3%

Testing for Lynch Syndrome

- Microsatellite instability on tumor block
  - 80% sensitivity, 90% specificity
- Immunohistochemistry on tumor block
  - MLH1/PMS2 and MSH2/MSH6
  - Absent MLH1/PMS2 → 20% Lynch, 80% sporadic
    - BRAF gene testing
    - Presence of V600E mutation means sporadic cancer
  - Absent PMS2 → ~95% Lynch
  - Absent MSH2/MSH6 → ~95% Lynch
  - Absent MSH6 → ~50% Lynch
- Gene testing based on IHC and BRAF results

Management changes in Lynch syndrome

- Cancers tend to have a better prognosis than non-Lynch colon cancers of the same stage
- Cancers resistant to cisplatin and 5-FU
  - 2-fold increase in mortality for stage III CRC
  - 3-fold increase in mortality for stage II CRC
  - Also holds for MLH1 absent sporadic cancers
Surgery for colon cancer in Lynch Syndrome

• Total abdominal colectomy with ileorectal anastomosis
  ✓ Patients with Lynch-associated colon cancer, due to risk of second cancer, screen rectal stump
  ✓ Patients with adenomas (especially if advanced) or those not willing or able to undergo regular screening.
• Hysterectomy/Salpingo-oophorectomy
  ✓ Consider if
    • Post-menopausal
    • Childbearing complete

FAP: Age and Development of Adenomas and CRC

Adenomatous Polyposes

• Familial adenomatous polyposis
  ✓ Autosomal dominant
  ✓ >100 polyps, colon cancer by age 40
  ✓ Other cancers, polyps in other areas of GI tract
• Attenuated FAP
  ✓ Autosomal dominant
  ✓ <100 polyps, cancer mean age >50
• MUTYH-associated polyposis (MAP)
  ✓ a.k.a. MYH-associated polyposis
  ✓ Autosomal recessive
  ✓ Similar to attenuated FAP

Testing for Polyposes

• FAP and attenuated FAP
  ✓ APC gene for both
  ✓ ~75% detection for FAP
  ✓ ~40% detection for attenuated FAP
• MUTYH associated polyposis
  ✓ APC negative first
  ✓ Test checks for 2 most common mutations
    • 80% sensitivity if northern european and >20 polyps
  ✓ Have to specifically request full sequencing of gene
### Treatment of Manifestations

- For classic FAP, colectomy is recommended once polyps emerge.
- For attenuated FAP and MAP:
  - Colectomy may be required.
  - 1/3 are adequately treated with surveillance with periodic polypectomy.
- Surgical Options:
  - Subtotal colectomy with ileorectal anastomosis when rectum is spared of polyps.
  - Total proctocolectomy with pouch.

### Management changes for polyposes

- Management (i.e. colectomy) based on numbers of polyps and distribution of polyps rather than results of genetic testing.
- Surveillance of colon remaining after surgery very important.
- Upper endoscopy may be added if APC mutation detected.

### Treatment of Manifestations

- Small bowel polyps:
  - Removal of duodenal polyps considered if villous change, severe dysplasia, >1 cm, or cause symptoms.
  - Whipple may be occasionally necessary to treat severe duodenal adenomas.
- Desmoid tumors:
  - May be treated with surgical excision, but high recurrence risk.
  - Other options include NSAIDs, anti-estrogens, chemotherapy, and radiation.

### Chemoprevention

- NSAIIDs have been shown to cause regression of adenomas and decrease number of polyps in remaining rectum in individuals with FAP.
- Celecoxib approved by FDA for individuals with FAP only.
  - Cardiac toxicity reported in individuals with sporadic adenomas.
- Aspirin and sulindac showed decreased adenomas but increased GI toxicity.
- Combination therapy with lower doses are under study.

*Expert Opin Pharmacother 2009 10:211-9*