Cancer Genetic Risk Assessment

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Breast/ Ovarian Cancer Syndrome

- Breast cancer diagnosed in 1/8-1/0 women in US
- 90% are sporadic
- Family history and cancer details can help sort hereditary vs sporadic cases

- Ovarian cancer affects 1/70 women
- Probably 65-75% are sporadic
- We do not depend on family history to sort
Incidence of Hereditary Breast and Ovarian Cancer

Breast Cancer
- Sporadic: 7%–10%
- Family clusters: 20-25%

Ovarian Cancer
- Sporadic
- Hereditary
Differential Diagnosis

- BRCA1/2 and breast cancer syndromes
- GI cancer syndromes (Lynch, polyposis, CDH1)
- Li Fraumeni/ multiple cancer syndrome
- Pancreatic/ melanoma syndrome (CDKN2A)
- Other undefined cancer syndrome
BRCA1-Associated Cancers
Lifetime Risks

Breast cancer ~65% by age 70  (51- 75%)

Second primary breast cancer ~50-60%

Ovarian cancer: ~39% (22 – 51%)

Small increased risk of other cancers (i.e. prostate, pancreatic, melanoma)
BRCA2-Associated Cancers
Lifetime Risks

Breast cancer:
45%
40% 2nd –primary

Male breast cancer: 6%
Prostate cancer: 25%

Ovarian cancer
10-20%

Increased risk of prostate, laryngeal, bile duct, stomach, melanoma and pancreatic cancers
(~1.5 – 3 fold risk)
BRCA Age-Specific Cancer Risks

BRCA1 Mutation Carriers:

- Breast
- Ovary

BRCA2 Mutation Carriers:

- Breast
- Ovary

**Figure 3**  Cumulative risk of breast (♦) and ovarian (■) cancer in BRCA1-mutation carriers.

**Figure 4**  Cumulative risk of breast (♦) and ovarian (■) cancer in BRCA2-mutation carriers.

Antoniou Am J Hum Genet 2003
Frequency of hereditary BRCA mutations

- 1/400 in the general population
- 1/40 in the Ashkenazi (Eastern European) Jewish population
BRCA1/2 Testing Indications

- National Comprehensive Cancer Network (NCCN)
  - Expert consensus revised yearly; http://www.nccn.org

- Family member with known BRCA1/2 mutation

- Personal history of breast cancer, with:
  - Onset age $\leq 45$ (7% prevalence)
  - Onset $< 50$ and one relative affected $< 50$
  - Two primary breast cancers
  - Onset any age, if $\geq 2$ close relatives with breast / ovarian cancer
  - Triple negative (ER/ PR/ Her2 neu negative) $< 60$
  - High-risk ethnicity, such as Ashkenazi (20-25% prevalence)

- Personal history of ovarian cancer (10-15% prevalence)

- Personal history of male breast cancer (12-16% prevalence)

- Close family member meeting above criteria
Genetic Counseling Is Integral to the Process
Goals of Genetic Counseling

- Accurate family history assembly and risk assessment
- Understand the information
- Participate in decision making about their medical care
- Anticipatory guidance about potential outcomes
- Manage associated problems in ways best for them & their families
Taking a Cancer Family History

- Obtain at least a three-generation pedigree
- Ask about all individuals in the family and record:
  - age at cancer diagnosis, age at and cause of death
  - primary vs metastatic cancer
  - precursor lesions, bilateral cancer
- Record ethnicity and race
Verify Family History

Verbally reported pedigree

- Stomach Ca
- Bone Ca d. 59
- Prostate Ca

Revised pedigree based on pathology reports

- Ovarian Ca dx 43, d. 49
- Breast Ca dx 45 d. 59
- BPH dx 54

BPH = Benign prostatic hyperplasia
Ideally, Begin Testing With an Affected Person

If a mutation is found in an affected person, testing will be more informative for other family members.
High Breast Cancer Risk Syndromes

- **P53 (Li-Fraumeni Syndrome)**
  - Mutation prevalence 1/5,000-20,000; 7-20% de novo
  - Sarcoma, brain, leukemia, colon, childhood cancers
  - ~30% breast cancer, age [31]: prevalence 7% in breast cancers <35

- **PTEN (Cowden’s Syndrome)**
  - Mutation prevalence 1/200,000; >75% de novo
  - Uterine cancers, thyroid dysfunction, mucosal lesions, OFC>98%
  - 40-50% lifetime breast cancer risk; 10% thyroid, increased uterine & colon

- **STK11 (Peutz Jeghers Syndrome)**
  - Mutation prevalence 1/60,000 - 300,000; 50% de novo
  - High risk for breast (50%), colon (40%), ovarian (20%) and other cancers
  - Lip freckles in childhood

- **CDH1 (Hereditary Diffuse Gastric Cancer Syndrome)**
  - Mutation prevalence 1/100,000-300,000? De novo?
  - 60-80% develop gastric cancer
  - 30-40% lifetime risk of lobular breast cancer

Moderate Breast Cancer Risk Syndromes

- **ATM**
  - Mutation prevalence 1/100
  - OR = 2-4 for breast cancer risk; OR = 2 for colon cancer
  - Possible pancreatic risk

- **CHEK2**
  - Mutation prevalence up to 1/66 (Dutch); < 1/100 others
  - Breast (OR = 2.6-4.8), colon (OR = 2) cancer risks
  - Possible prostate and thyroid cancer risk

- **PALB2**
  - Mutation prevalence ~1/1000
  - OR = 3-5 for breast cancer risk
  - Suggestion of increased ovarian and pancreatic cancer risks

**Lower Risk Breast Cancer Genes**

- **BRIP1, BARD1, RAD51C, RAD51D**
  - Prevalence uncertain
  - OR = 2-3 for breast cancer
  - OR 3-6 for ovarian cancer with BRIP1, RAD51D

- **RAD 50, MRE11A, NBN**
  - Prevalence uncertain
  - 1.5-2.5 OR breast cancer risk
  - Possibly ovarian cancer risk

- **NF1, Lynch, MUTYH**
  - Traditionally not breast cancer genes; other defining symptoms
  - Prevalence much more common; 1/3000, 1/300, 1/50
  - Breast cancer risk varies (OR = 2-5 fold)

Test Results

Family Tree

- ENGLISH
  - 70's
  - 80's
  - 61
    - d.BrCA@59
    - HepatoCa@52
      - ProstateCa@56
  - 60
    - P53 positive
  - 26
    - BrCa@ 22
      - Glio@ 26
    - P53 negative

- DANISH
  - 80's
  - 52
    - d.MI
  - 68
    - BrCa@48
    - P53 positive

- 20
  - P53 positive

- 2
  - 2
  - P53 negative
Tumor Sites in Families with TP53 Germline Mutations

- Breast: 24%
- Bone: 12.6%
- Brain: 12%
- Soft tissue: 11.6%
- GI: 7%
- Gynecol: 5.3%
- Hematol: 4.2%
- Adrenal: 3.6%
- Other: 14.1%

### TP53 Cancer Penetrance Data

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Pop.</th>
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<tbody>
<tr>
<td>20</td>
<td>10%</td>
<td>18%</td>
<td>12%</td>
<td>0.7%</td>
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<tr>
<td>30</td>
<td>21</td>
<td>49</td>
<td>35</td>
<td>1.0</td>
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<tr>
<td>40</td>
<td>33</td>
<td>77</td>
<td>52</td>
<td>2.2</td>
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<tr>
<td>50</td>
<td>68</td>
<td>93</td>
<td>80</td>
<td>5.1</td>
</tr>
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</table>


U.S. Supreme Court Strikes Down Human Gene Patents
13 June 2013

Angelina Jolie: I had double mastectomy
May 15, 2013, 1:24 am
AFP

They're our breast cancer genes—we identified them.
It's kind of you to let us have the disease for free.
Breast Cancer Susceptibility Loci

Foulkes NEJM

Relative Risk

Minor Allele Frequency (%)
DNA Repair Pathways; Cancer Risk Genes

Figure 2: Type of DNA damage, repair pathways, and repair enzymes involved in each pathway.

## Comprehensive Cancer Panel
- **Genes:** 32
- **Price:** $3500-$4000
- **Out of Pocket (OOP):** $1500

## Breast/Ovarian Cancer Panel
- **Genes:** 21
- **Price:** $1500
- **Out of Pocket (OOP):** $475

## Colorectal Cancer Panel
- **Genes:** 19
- **Price:** $1500

## Pancreatic Cancer Panel
- **Genes:** 16
- **Price:** $1500

### Create your own panel:

<table>
<thead>
<tr>
<th>Panel</th>
<th>Genes</th>
<th>Price</th>
<th>Out of Pocket (OOP)</th>
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<tbody>
<tr>
<td>Breast</td>
<td>17</td>
<td>$1500</td>
<td>$475</td>
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<tr>
<td>Breast/Ovarian</td>
<td>35</td>
<td>$1500</td>
<td>$475</td>
</tr>
<tr>
<td>Colon</td>
<td>23</td>
<td>$1500</td>
<td>$475</td>
</tr>
<tr>
<td>Pancreas</td>
<td>25</td>
<td>$1500</td>
<td>$475</td>
</tr>
<tr>
<td>Cancer</td>
<td>34, 42</td>
<td>$1500</td>
<td>$475</td>
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</table>

### MyRisk
- **25 cancer gene**
- **Price:** $4000

### UW Medicine

<table>
<thead>
<tr>
<th>Panel</th>
<th>Genes</th>
<th>Price</th>
<th>Out of Pocket (OOP)</th>
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<tr>
<td>BROCA Panel</td>
<td>60 genes</td>
<td>$3350</td>
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<tr>
<td>COLOSEQ</td>
<td>22 genes</td>
<td>$2300</td>
<td></td>
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<tr>
<td>Comprehensive Cancer Panel</td>
<td>32 genes</td>
<td>$3500-$4000</td>
<td></td>
</tr>
<tr>
<td>Breast/Ovarian Cancer Panel</td>
<td>21 genes</td>
<td>$1500</td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer Panel</td>
<td>19 genes</td>
<td>$3500-$4000</td>
<td></td>
</tr>
<tr>
<td>Pancreatic Cancer Panel</td>
<td>16 genes</td>
<td>$1500</td>
<td></td>
</tr>
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</table>
Multigene panels: Advantages

- New cost effective genetic testing
- Broadest available gene panels
- Double the chance of identifying risk mutation
- ~3% have double mutations
- Mutation allows targeted screening and prevention
- Mutation allows relatives site specific testing
Multigene panels: Disadvantages

- Variants of Uncertain Significance Common (25-50%)
- Genes with low risk may not have guidelines
- Low risk mutations may be a partial answer
- Full tumor risk and spectrum not well defined
- “Out of context” mutations; what are the risks?
Multiple genes on these panels have recessive correlates with implications for reproduction:

- Fanconi’s anemia
- Ataxia Telangiectasia
- Nijmegan Breakage
- MUTYH polyposis
- Constitutional MMR
Panel Identified Hereditary Mutations

OVARIAN CANCER MUTATIONS

- BRCA1: 40%
- BRCA2: 23%
- Other genes: 18%

BRCA1/2: 6-10%

BREAST CANCER MUTATIONS

- BRCA1: 30.4%
- BRCA2: 28.6%
- Other genes: 40.4%

Walsh et al, PNAS 2011

Ovarian: 18% BRCA1/2, 6-10% other genes

Figure 1 Relative distribution of variants detected with NGS in 708 HBOC patients. Percentages were based on the number of time the gene was sequenced depending on the version of the capture design.
OTHER cancer predisposition genes have yet to be identified:

A NEGATIVE test result does NOT eliminate genetic risk

Still better to test relatives with the highest carrier risk FIRST if at all possible.

This provides the MAXIMUM information for the entire family.
2013 PAT: Italy MAT: Italy
27-10-2014

- CRC@ 68
- BrCa@ 69
- Gall Bladder @ 72
- d.?

- CRC@ 80
- BrCa@ 80s
- CvDz

- CRC@ 83
- 40s

- CRC@ 80
- Gastric Ca@ 72
- Tumor Lynch IHC-

- BrCa@ 42
- BrCa@ 52
- d.CRC@ 60

- Pan Ca@ 43
- BRCA2+
- BrCa@ 56

- BrCa@ 56
- Melanoma@ 38

- 60s
- d.Bladder Ca

- 56

- 56

- 35
- 33
- 28
- 24
- 22
- 19
HBOC Pedigree, No Mutation

- Assume inheritance of a mutation we cannot yet identify
  - Collection of blood for ongoing research studies; DNA banking

- Computer models for estimating breast cancer risk:
  - Gail: Underestimates risk (omits second-degree relatives)
  - Claus: Includes first and second-degree relatives, ages of onset
  - IBIS (Tyrer-Cuzick): incorporates personal and family risk factors

- Ovarian cancer risk?
  - Families with breast cancer only: no increase in ovarian risk
  - Families with ovarian cancer, no mutation
    • Risk to first-degree relative: estimated 2-3 fold increase

Woman’s age is 35 years.
Age at menarche was 12 years.
Person is nulliparous.
Person is premenopausal.
Height is 1.6 m.
Weight is 70 kg.
Woman has never used HRT.

Risk after 10 years is 2.463%.
10 year population risk is 0.368%.
Lifetime risk is 24.4%.
Lifetime population risk is 10.06%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.
High Risk Breast Management

- Prophylactic salpingo-oophorectomies ≥40
- Prophylactic bilateral mastectomies
  OR
- Intensive screening (MRI, mammo, CBE)
- Chemoprevention (Tamoxifen, others)
- Annual dermatology screening
- Pancreatic high risk screening if fm hx PanCa
NCCN LFS Screening Guidelines

- **Childhood**: Head MRI, CBC, total body MRI

- **Breast Risk**
  - Annual breast MRI starting at 20-25 (or tailor to fm); consider mammogram at 30
  - Discuss prophylactic bilateral mastectomies

- **Colon Risk**
  - Colonoscopy starting at 25; repeat 2-5 yrs
NCCN LFS Screening Guidelines

- Other Cancer Risks
  - Discuss limits of screening options
  - Annual physical exam with skin and neuro exam
  - Use XRT for treatment with caution
  - Investigate options for novel technologies
    - Whole body MRI, ultrasounds, brain MRI
  - Target screenings based on family history
  - Educate patient on early symptoms
High-Risk Breast Screening

- Addition of breast magnetic resonance imaging:

Dense breast tissue on mammogram

MRI revealed high-grade cancer

Hartman Cancer 2004
Prophylactic Mastectomy (PM)

- 89-95% relative risk reduction in prospective studies; not randomized
- Controversy about nipple-sparing mastectomy; how much risk left?
- NCCN guidelines: “Discuss option of prophylactic mastectomy”


Fig 1. Time to breast cancer diagnosis in female BRCA1 mutation carriers with and without bilateral prophylactic mastectomy (BPM).
Bilateral Salpingo-Oophorectomy (BSO)

- 80-90% relative risk reduction for ovarian, 40-60% for breast if pre-menopausal

- Stringent protocol for removing ovaries and fallopian tubes, checking peritoneum

- Controversy re: hysterectomy; rare uterine papillary serous cancer association?

- NCCN: “Recommend between age 35-40”, given no effective screening

Cancer Chemoprevention

- Tamoxifen: prevents ER/PR-positive cancers in general population
  - Breast Cancer Prevention Trial (N=19 with BRCA1/2 mutation):
  - Case-control studies: some benefit for BRCA1 and BRCA2?
  - Raloxifene: no data in BRCA1/2 mutation carriers

- ER/PR-negative breast cancer prevention?

- Oral contraceptives:
  - 5 years’ use associated with 30-50% reduction in ovarian cancer
  - Not routinely recommended due to concern about breast cancer

The Rationale for PARP-inhibitors
<table>
<thead>
<tr>
<th>Intervention Warranted based on gene and/or risk level</th>
<th>Recommend MRI&lt;sup&gt;c&lt;/sup&gt; (&gt;20% risk of breast cancer&lt;sup&gt;d&lt;/sup&gt;)</th>
<th>Recommend RRSO</th>
<th>Discuss Option of RRM</th>
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</thead>
<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;sup&gt;e&lt;/sup&gt;</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53</td>
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<tr>
<td>Insufficient evidence for intervention&lt;sup&gt;b&lt;/sup&gt;</td>
<td>BARD1, BRIP1</td>
<td>BARD1, BRIP1, PALB2, RAD51C, RAD51D</td>
<td>ATM, BARD1, CHEK2, PALB2, STK11</td>
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</tbody>
</table>
Psychological Interventions

- Specialized mental health professionals
- On-line support groups
- Genetic counselor network/ assistance with family communication and referrals
- Peer referrals
- Local support resources
Summary:

- Always try to test the most informative relative first: youngest, most affected, living
- Clinical overlap may suggest more than one syndrome
- NGS Panels are cost effective and double detection rate
- None of these genetic tests are comprehensive
- Empiric risk counseling is the default if no mutation
- Genetic counseling is time consuming but critical to assess appropriate tests, understanding the limits of tests, contextualizing the outcomes and options
- Balancing the individual and family needs is an art
Program Members

James Ford, MD  Director, Upper Gl and other Syn.
Allison Kurian, MD, MSc  Associate Director, Breast / ovarian Syn.
Uri Ladabaum, MD  Lower Gl Syn.
Nicki Chun, MS  Genetic Counselor
Kerry Kingham MS  Genetic Counselor
Alexandra Lebensohn, MS  Genetic Counselor
Courtney Rowe-Teeter, MS  Genetic Counselor
Rachel Koff, MS  Genetic Counselor
Meredith Mills  Program Manager
My future's so bright...

I gotta wear shades...
Gene Testing Considerations

- Testing Affected person
- Discrimination fears
- Family Dynamics/Guilt
- Costs
- Inconclusive or Negative Results
- Testing of Minors
- Other Ethical Issues
How much does testing cost?

- BRCA1 and BRCA2 gene testing now available through multiple labs: $2000-$3000
- $200-500 if mutation already found in family
- $400-575 Ashkenazi panel
- Included in most cancer gene panels
## Screening Breast MRI Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>PPV</th>
<th>MRI Sensitivity</th>
<th>MRI Specificity</th>
<th>Mam Sensitivity</th>
<th>Mam Specificity</th>
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<tbody>
<tr>
<td>Kuhl Radiology 2000</td>
<td>192</td>
<td>64%</td>
<td>MRI: 95%</td>
<td>MRI: 93%</td>
<td>Mam: 34%</td>
<td>Mam: 95%</td>
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<tr>
<td>Tilanus Br Ca Res Treat 2000</td>
<td>109</td>
<td>33%</td>
<td>MRI: 100%</td>
<td>MRI: 95%</td>
<td>Mam: 0%</td>
<td>Mam: 95%</td>
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<tr>
<td>Stoutjesdijk J Natl Cancer Inst 2001</td>
<td>179</td>
<td>43%</td>
<td>MRI: 100%</td>
<td>MRI: 93%</td>
<td>Mam: 42%</td>
<td>Mam: 99%</td>
</tr>
<tr>
<td>Podo J Exp Clin Ca Res 2002</td>
<td>105</td>
<td>89%</td>
<td>MRI: 100%</td>
<td>MRI: 93%</td>
<td>Mam: 13%</td>
<td>Not reported</td>
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<tr>
<td>Morris Am J Radiol 2003</td>
<td>367</td>
<td>24%</td>
<td>Not reported</td>
<td>MRI: 88.6%</td>
<td>Mam: 25%</td>
<td>MRI: 95%</td>
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<tr>
<td>Warner JAMA 2004</td>
<td>236</td>
<td>26%</td>
<td>MRI: 77%</td>
<td>MRI: 95%</td>
<td>Mam: 36%</td>
<td>Mam: 99.8%</td>
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<tr>
<td>Kriege N Engl J Med 2004</td>
<td>1909</td>
<td>57%</td>
<td>MRI: 71%</td>
<td>MRI: 90%</td>
<td>Mam: 40%</td>
<td>Mam: 95%</td>
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<tr>
<td>Leach Lancet 2005</td>
<td>649</td>
<td>7%</td>
<td>MRI: 77%</td>
<td>MRI: 81%</td>
<td>Mam: 40%</td>
<td>Mam: 93%</td>
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<tr>
<td>Lehman Cancer 2005</td>
<td>367</td>
<td>13%</td>
<td>MRI: 100%</td>
<td>MRI: 92%</td>
<td>Mam: 25%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Riedl Clin Cancer Res 2007</td>
<td>327</td>
<td>20%</td>
<td>MRI: 86%</td>
<td>MRI: 92%</td>
<td>Mam: 50%</td>
<td>Mam: 98%</td>
</tr>
</tbody>
</table>

- No randomized trials; effect on breast cancer mortality unknown
Moderate Penetrance: Fanconi Pathway

- Homologous recombination
- Biallelic BRCA2 mutations: FA
- Breast cancer risk, 2-3 fold:
  - ATM
  - BARD1
  - BRIP1
  - CHEK2
  - MRE11
  - NBN (NBS1)
  - PALB2
  - RAD50
  - RAD51C
- Ovarian cancer risk:
  - RAD51C
  - RAD51D (6-fold)
  - Other FA genes
Partners in DNA Double Stranded Break Repair

**Figure 3:** Proteins involved in the homologous recombination (HR) system.

**Figure 4:** Proteins involved in the nonhomologous end joining (NHEJ).

Li Fraumeni Testing Criteria

- Individual from a family with known P53 mutation

- Classic Li-Fraumene Syndrome (LFS):
  - Proband with sarcoma <45 AND
  - First-degree relative with cancer <45 AND
  - 1st or 2nd relatives with cancer <45 or sarcoma at any age; same side of family

- Chompret criteria (25-35%):
  - Proband with LFS tumor <46 (sarcoma, brain, breast, ACC, leukemia, lung) AND 1st or 2nd degree relative with LFS tumor <56
  - OR multiple primary tumor at any age
  - OR proband with multiple tumors; 1st <46 AND 2 in LFS spectrum
  - OR Adrenal Cortical Carcinoma or Choroid Plexus Carcinoma at any age

- Eeles criteria (8%): LFS tumors in two 1-2 degree relatives at any age (sarcoma, brain, breast, leukemia, ACC, melanoma, prostate and pancreatic)

- Proband with breast cancer <35 AND BRCA ½ negative
### Clinical Studies of Multiple-Gene Panels

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Race</th>
<th>Panel</th>
<th>Mutation (non-BRCA1/2)</th>
<th>VUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh et al, Proc Natl Acad Sci 2011</td>
<td>360</td>
<td>Ovarian cancers, unselected</td>
<td>Not reported</td>
<td>BROCA (Univ. of WA, 21 genes)</td>
<td>6.1%</td>
<td>No report</td>
</tr>
<tr>
<td>Harrell et al, Am Soc Hum Genet 2013</td>
<td>1412</td>
<td>Ovarian cancers (extension of above)</td>
<td>Not reported</td>
<td>BROCA (Univ. of WA, 41 genes)</td>
<td>5.5%</td>
<td>No report</td>
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<tr>
<td>Walsh et al, Am Soc Hum Genet 2013</td>
<td>800</td>
<td>BRCA1/2-negative, ≥3 br./ov. cancers</td>
<td>Not reported</td>
<td>BROCA (Univ. of WA, 41 genes)</td>
<td>15.8%</td>
<td>No report</td>
</tr>
<tr>
<td>Olopade et al, Am Soc Hum Genet 2013</td>
<td>395</td>
<td>Cancer genetics clinical testing sample</td>
<td>100% African American</td>
<td>BROCA (Univ. of WA, 41 genes)</td>
<td>4.1%</td>
<td>No report</td>
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<tr>
<td>Tung et al, San Antonio Br. Sym. 2013</td>
<td>1955</td>
<td>Clinical br./ov. cancer test (Myriad database)</td>
<td>Mostly White</td>
<td>MyRisk (Myriad, 25 genes)</td>
<td>4.9%</td>
<td>97.3%</td>
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<tr>
<td>Castera et al, Eur J Hum Genet 2014</td>
<td>708</td>
<td>Hereditary breast/ovarian cancer (clinical criteria)</td>
<td>Not reported</td>
<td>Custom designed (16 genes)</td>
<td>5.6%</td>
<td>No report</td>
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<tr>
<td>Kurian et al, J Clin Oncol 2014</td>
<td>198</td>
<td>BRCA1/2 guidelines (141 BRCA1/2-negative)</td>
<td>70% White 20% Asian</td>
<td>Custom designed (Invitae, 42 genes)</td>
<td>11.4%</td>
<td>88%</td>
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<tr>
<td>Ford, Kurian et al, Montreal HBOC Sym. 2014</td>
<td>380</td>
<td>Extension of above (all BRCA1/2-negative)</td>
<td>Similar to above</td>
<td>Cancer Panel (Invitae, 29 genes)</td>
<td>9%</td>
<td>35%</td>
</tr>
<tr>
<td>LaDuca et al, Genet Med 2014</td>
<td>2079</td>
<td>Clinical testing (Ambry database)</td>
<td>72% White 2-3% Af., As., His.</td>
<td>Breast, Ova, Colo, CA.Next (Ambry, 13-24 genes)</td>
<td>7.2-9.6%</td>
<td>15-25%</td>
</tr>
</tbody>
</table>
Function of BRCA1 and BRCA2
PARP-1 is a key enzyme involved in repair of single strand DNA breaks.

- DNA single strand break (SSB) damage
- Inhibition of PARP-1 prevents recruitment of DNA repair enzymes
- Leads to failure of SSB repair
- Accumulation of SSBs
- Degeneration into double strand breaks

During S-phase, replication fork is arrested at site of SSB.
Colorectal Multistep Carcinogenesis

Chromosomal Instability

Normal Colorectal Epithelium
- APC
- K-ras
- DCC
- p53
- ??

Early Adenoma
- APC
- K-ras
- DCC
- p53
- ??

Intermediate Adenoma
- APC
- K-ras
- DCC
- p53
- ??

Advanced Adenoma
- APC
- K-ras
- DCC
- p53
- ??

Advanced Carcinoma
- APC
- K-ras
- DCC
- p53
- ??

Colorectal Carcinoma
- APC
- K-ras
- DCC
- p53
- ??

Invasive Carcinoma
- APC
- K-ras
- DCC
- p53
- ??

Metastatic Carcinoma
- APC
- K-ras
- DCC
- p53
- ??

Microsatellite Instability

hMSH2
- APC
- TGFBRII
- MSH3
- IGFIIR
- MSH6
- BAX
- PTEN
- ??

hMLH1
- APC
- TGFBRII
- MSH3
- IGFIIR
- MSH6
- BAX
- PTEN
- ??

MMR
- APC
- TGFBRII
- MSH3
- IGFIIR
- MSH6
- BAX
- PTEN
- ??
Mismatch Repair Genes

New DNA strand

Template DNA
- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+
The Development of Hereditary Cancer

Nonhereditary

2 normal genes
1 damaged gene
1 normal gene
Loss of normal gene

Hereditary

Mother or Father
1 damaged gene
1 normal gene

1 damaged gene
1 normal gene
Loss of normal gene
Most Cancer Susceptibility Genes Are Dominant With Incomplete Penetrance

- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer
Sporadic vs. Familial vs. Hereditary Cancer

**Sporadic Cancers**
- account for the vast majority of tumors
- occur without marked family history or early age

**Familial Cancers**
- 5 - 20% of most common tumors show familial clustering
- may be due to chance, shared environmental factors or genes

**Hereditary Cancers**
- account for 5 - 10% of cancers
- recognizable inheritance pattern (usually autosomal dominant)
- early age of onset, multiple primary cancers
- identified germline genetic alterations
Cardinal Features of Hereditary Cancers

- Early age of cancer onset
- Multiple primary cancers showing specific combinations within the patient’s family
- Excess of multifocal, bilateral or multiple primary cancers
- Physical stigmata
- Distinctive pathological features
- Occasional differences in survival and clinical severity
- Dominant pattern of transmission, with marked variability in phenotypic expressivity and gene penetrance
Colon Cancer

- Second most common cause of cancer death
- Lifetime risk 6%, about 1 in 17
- 93% of cases occur ≥ age 50 years
- 33% of cases from familial or hereditary risks
- Arises from polyps
Categories of colorectal cancer (CRC)

- **Sporadic** (~65%)
- **Familial** (~30%)
  - Familial Adenomatous Polyposis (FAP) (1%)
  - Hereditary Nonpolyposis Colorectal Cancer (Lynch) (5%)
- **Rare CRC syndromes** (<0.1%)
# Genetics of Colorectal Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td><em>MLH1, MSH2, MSH6, PMS2, EPCAM</em></td>
</tr>
<tr>
<td><strong>Adenomatous polyposis</strong></td>
<td></td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis(FAP)</td>
<td><em>APC</em></td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td><em>APC</em></td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td><em>MYH (biallelic)</em></td>
</tr>
<tr>
<td><strong>Hamartomatous polyposis</strong></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td><em>STK11</em></td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td><em>SMAD4/BMPR1A</em></td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td><em>PTEN</em></td>
</tr>
</tbody>
</table>
Clinical Features of Lynch Syndrome

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates (2/3rds)
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, brain, sebaceous skin tumors
- Autosomal pattern of inheritance
Contribution of Gene Mutations to HNPCC Families

Sporadic
Rare CRC syndromes
FAP
HNPCC
Familial Unknown
~30%

MSH2
~30%
MLH1
~30%

MSH6 (rare)
PMS2 (rare)
Amsterdam Criteria for HNPCC

- 3 or more relatives with verified CRC or HNPCC associated cancer in family
- One case a first-degree relative of the other two
- Two or more generations
- One CRC by age 50
- FAP excluded

≥ 2/3rds of families that meet criteria have germline mutations in Mismatch DNA Repair genes
Cancer Risks in HNPCC

- Colorectal 78%
- Endometrial 43%
- Stomach 10%
- Urinary tract 10%
- Biliary tract 15%
- Ovarian 9%
## Surveillance Options for LS Mutation Carriers

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>Colonoscopy</td>
<td>Begin at age 20 – 25, repeat every 1 – 2 years</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>Transvaginal ultrasound</td>
<td>Annually, starting at age 35</td>
</tr>
<tr>
<td></td>
<td>Endometrial aspirate</td>
<td></td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>EGD</td>
<td>Begin at age 30 - 35, repeat every 2 – 3 years</td>
</tr>
<tr>
<td>Renal/Ureteral</td>
<td>Urine cytology</td>
<td>Annually, starting at age 30</td>
</tr>
</tbody>
</table>
Colonoscopy Improves Survival of Genetically-Confirmed HNPCC

Survival rates:
- Surveillance: 92.2%
- No surveillance: 73.9%

Follow-up time (years): 0 to 15