WHAT IS NEW IN HEREDITARY CANCER SYNDROMES?

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Objectives

• Identify families who would benefit from genetic risk assessment and testing
• Describe the benefits, limitations, and challenges of genetic testing in managing families with hereditary risk
• Describe emerging trends in genetic care

No relevant financial relationships to disclose
Why should individuals be aware of their risk factors?

- All individuals should take steps to prevent or detect cancer whenever possible.
- Some individuals with many risk factors or hereditary risk for developing cancer may have different recommendations for the detection of cancer.

*Risk factor assessment is important for all nurses regardless of practice setting*
What do families share?
Chromosomes, DNA, and genes
Cancer is a result of uncontrolled cell division

✓ Occurs when there is an alteration in the genes. This is called a mutation.
✓ Gene mutations may be a result of exposure to environmental carcinogens.
✓ Gene mutations could also be inherited from a parent.
How does genetic/genomic information affect clinical oncology practice?

- Somatic mutations in tumors that guide personalized treatment decisions
- Germline mutations in families that guide prevention and early detection decisions
- Pharmocogenomics to guide medication choices
Patients need accurate information

“More and more patients are going to the Internet for medical advice. To keep my practice going, I changed my name to Dr. Google.”
Refer to a genetics professional

- MD with a fellowship in genetics
- Board certified Masters prepared genetics counselor [www.nsgc.org](http://www.nsgc.org)
- Credentialed advance practice nurse through American Nurses Credentialing Center - Advanced Genetic Nursing credential (AGN-BC)
Who is at high risk for hereditary cancer?

Hereditary cancers account for only a small proportion of all cancer.
An accurate family history is the key to:

- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
Cancer arises from gene mutations

Germline mutations
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Parent
Mutation in egg or sperm
Child
All cells affected in offspring

Somatic mutations
- Occur in nongermline tissues
- Are nonheritable

Somatic mutation (eg, breast)
"Your 2 p.m. arrived late, your 2:30 arrived early, and your 2:15 is right on time."
Three generation pedigree

**German/Polish**

- d. 70
- Breast Ca, dx 49
  - d. 52
- Breast Ca, dx 41
  - 62

**English/Irish**

- d. 80
  - 55
  - Diabetes, dx 45
    - 59
    - 52
- d. 85
  - 67
  - 65
  - 35
  - 30
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
Family cancer histories are dynamic

**Initial History**

- Colon Ca, 50

**2 years later**

- Colon Ca, 50
- Endometrial Ca, 44
- Colon polyps, 48
Founder effect

A high frequency of a specific gene mutation in a population founded by a small ancestral group

Original population

Marked population decrease, migration, or isolation

Generations later
When to suspect hereditary cancer syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Evidence of autosomal dominant transmission
- Rare tumors
Factors affecting penetrance

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

Not everyone with an altered gene develops cancer
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
“How do you want it—the crystal mumbo-jumbo or statistical probability?”
Risk of Developing Breast Cancer

- Claus table
- Modified Gail
- BRCAPro
- Hughes
- Tyrer Cruzick

- Different models consider different factors
- Variability in risk figures
- Clinician needs to use clinical judgment in interpretation
Gail Model

Incorporates

• Age
• Reproductive history
• Benign breast disease history
• Breast cancer in mother or sisters

Does *not* incorporate

• Other cancers
• Second-degree relatives
• Paternal history
• Age at diagnosis in relatives
Risk Analysis Using Gail Model

Age: 39

- Age at menarche: 15
- Previous breast biopsies: 0
- Atypical hyperplasia: none
- Age at birth of 1st child: none
- Mother/sisters with breast cancer: 0

Breast Cancer Risk (%)

- Age 15: 3%
- Age 49: 7%
- Age 69: 11%
The Gail Model can underestimate hereditary risk of breast cancer

This woman’s breast cancer risk would be greatly underestimated
Claus Tables

- Statistical model to calculate cumulative breast cancer risk based on family history
- Risk estimates derived from the family history of 5,000 breast cancer cases (age 20-54) and age-matched controls in US
- Family history of breast cancer is the only risk factor considered
### Mutation Probabilities

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>MLH1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couch</td>
<td>MMRpro 0.000</td>
</tr>
<tr>
<td>Shattuck-Eidens</td>
<td>MSH2 0.000</td>
</tr>
<tr>
<td>BRCA2</td>
<td>MSH6 0.000</td>
</tr>
<tr>
<td>BRCA2</td>
<td>MMRpro 0.000</td>
</tr>
<tr>
<td>Any BRCA</td>
<td>MMRpro (+MSH6) 0.000</td>
</tr>
<tr>
<td>Myriad</td>
<td>Weijnen 0.000</td>
</tr>
<tr>
<td>NCI CART</td>
<td>Myriad</td>
</tr>
<tr>
<td>BRCA2</td>
<td>No Calc</td>
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<tr>
<td>p16</td>
<td>Pancreas Gene: 0.004</td>
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<table>
<thead>
<tr>
<th>Cancer Risks</th>
<th>5-Year</th>
<th>Lifetime</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gail</td>
<td>0.033</td>
<td>0.289</td>
</tr>
<tr>
<td>Claus</td>
<td>0.016</td>
<td>0.143</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.001</td>
<td>0.029</td>
</tr>
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<td>Ovarian</td>
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MODIFIED GAIL
Race/Ethnicity:
The tool may underestimate risk for African American women with one or more biopsies.

5 Year Risk
This woman (age 41) 2.2%
Average woman (age 41): 0.7%

Lifetime Risk
This woman (to age 90): 27%
Average woman (to age 90): 9.9%
Case

Tyrer Cruzik Model

Woman’s age is 41 years.
Age at menarche was 11 years.
Person is nulliparous.
Person is premenopausal.
Height is 5 ft 6 ins.
Weight is 0 st 186 lb.
Woman has never used HRT.
Woman has had atypical hyperplasia.

Risk after 10 years is 25.9%.
10 year population risk is 1.74%.
Lifetime risk is 80.96%.
Lifetime population risk is 9.633%.
Probability of a BRCA1 gene is 0.684%.
Probability of a BRCA2 gene is 3.928%.
Risk of Developing Breast Cancer

- Claus table 29%
- Modified Gail 27%
- BRCAPro 14%
- Tyrer Cruzick 81%
Why Assess the Risk?

- NCCN and ACS recommend more aggressive screening when risk of breast cancer is greater than 20%
  - Mammography at a younger age
  - Biannual professional examination
  - Discuss breast awareness
  - Consider breast MRI
Risk of a Mutation

- Some syndromes have clinical criteria for offering testing
- Some syndromes can calculate risk of mutation
Risk of a Mutation

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Clinical criteria for testing

Hereditary Breast Cancer

• Diagnosed age ≤45 years
• Two breast primaries when first breast cancer diagnosis occurred prior to age 50
• Diagnosed age <60 y with a triple negative breast cancer (ER-, PR-, HER2-)
• Diagnosed at any age, with ≥2 close blood relatives with breast and/or ovarian cancer
• Male breast cancer
• Ovarian cancer
• Ethnicity associated with higher mutation frequency
• A close relative with a known BRCA1 or BRCA2 gene mutation

Colon Polyposis

• A beneficiary with ≥20 cumulative colorectal adenomas over a lifetime.
• Testing for APC gene mutations should precede testing for the less common MYH mutation.
Mission not so impossible
A multi-step process:
Pretest genetic counseling

**Assess**
- Personal and family medical history
- Risk perception and motivation for testing

**Educate**
- Basic genetics and inheritance
- Cancer genetics and risk

**Discuss**
- Risks, benefits, and limitations of testing
- Test procedure - blood work
- Alternatives to testing
- Management options – depending on test results
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.

Breast, 42
Breast, 38
d.45
Breast
45

Test first, if possible

Person seeking counseling (proband)
Why get counseling?

• Accurate assessment of risk
• Motivation for testing
• Anticipatory guidance
• Patient and family education
• Issues in test selection
• Care for the entire family
• Options for research studies
Genetic Testing Has Implications for the Entire Family

- Consider the impact of testing on all family members
- Ultimately, testing is the individual’s choice
Informed consent: Potential risks of genetic testing

- Psychological distress
- Loss of privacy
- Discrimination by employers and insurers
- Change in family dynamics
- False sense of security
Informed consent: Potential benefits of genetic testing

- Improved cancer risk management
- Relief from uncertainty and anxiety about cancer risk
- Information for individual and family members
- Lifestyle decision making
Informed consent: Limitations of genetic testing

- Not all mutations are detectable
- Uncertain significance of some mutations
- Negative result is fully informative only if mutation has been identified in family
- Results indicate probability, not certainty, of developing cancer
Process of clinical DNA testing

• Blood or saliva
• Costs $440 - $4,000
• Results available in 2-16 weeks
Interpreting Test Results

- Positive
- Negative
- Undetermined Significance

Range of VUS results
Follow-up is critical
Primary cancer prevention
Secondary cancer prevention

“Td have been here sooner if it hadn't been for early detection.”
Tertiary cancer prevention

Cancer Treatment & Survivorship
Facts & Figures 2012-2013

Estimated Numbers of Cancer Survivors as of January 1, 2012

Note: State estimates may not sum to US total due to rounding
The IRS Mess / Syria's YouTube War / The End of Alimony

THE ANGELINA EFFECT

Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind

BY JEFFREY KLUGER & ALICE PARK
What are the characteristics of hereditary breast cancer?

- Early age of onset (< age 50)
- Strong family history
  - >2-3 relatives –
    - Multiple generations
- Bilateral cancer
- Ovarian cancer in the patient or family
- Ashkenazi ancestry
- Male breast cancer in the family
BRCA1-2 mutations increase risk of multiple cancers

- Breast cancer by age 50: 33% - 50% (BRCA mutation carriers), 2% (General population)
- Breast cancer by age 70: 56% - 87% (BRCA mutation carriers), 7% (General population)
- Ovarian cancer by age 70: 27% - 44% (BRCA mutation carriers), <2% (General population)
Management of high risk families

- Increased surveillance
  - Mammography at an earlier age
  - More frequent breast exams
  - Consider breast MRI
- Chemoprevention
  - Tamoxifen
- Prophylactic surgery
  - Mastectomy
  - Oophorectomy
- Pancreatic screening
- Melanoma screening
- Prostate cancer screening
- Clinical trials
Benefits of preventive measures

- Tamoxifen: 49% reduction in breast cancer risk
- Mastectomy: 90% reduction in breast cancer risk
- Oophorectomy: Up to 68% reduction in breast cancer risk, 96% reduction in ovarian cancer risk
- Oral contraceptives: Up to 60% reduction in breast cancer risk
Risk of Colorectal Cancer

- General population: 6%
- Personal history of colorectal neoplasia: 15%–20%
- Inflammatory bowel disease: 15%–40%
- HNPCC mutation: 60%–80%
- FAP: >95%
Management of high risk families with FAP

- Annual colonoscopy starting at age 10 to 15 years
- Surgical removal of the colon when the polyp burden becomes too high
- Chemoprevention with aspirin/NSAIDs/Cox2
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
Rationale for Frequent Colonoscopy

Accelerated progression from adenoma to cancer

General Population 5-10 years

Lynch Syndrome 1-3 years
Cancer Risks in Lynch Syndrome up to age 70 compared to general population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>HNPCC Risks</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
<td>46 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
<td>42.5 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2%-7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
</tr>
</tbody>
</table>
Management of high risk families

- Annual colonoscopy with upper endoscopy starting at age 25
- Careful gynecologic exam ages 25 until total hysterectomy
- Total hysterectomy age 35 to 45
- Consider annual urinalysis and pelvic ultrasound
Previvor care

- Prevention decisions
- Support
- Care for other at-risk relatives
- Screening for other cancers

[FORCE logo]
Facing Our Risk of Cancer Empowered
Fighting Hereditary Breast and Ovarian Cancer
Limitations of providing genetics care outside of formal genetics counseling

• Direct to consumer testing
• **Wrong genetic test is ordered**
• Genetic test results are misinterpreted
• Inappropriate or inadequate genetic counseling results in psychosocial distress or other negative outcomes
• **Poorly coordinated care for the rest of the family**
Direct to consumer testing

"YOUR DNA TEST SHOWS YOU'RE PREDISPOSED TO SUE DOCTORS."

mygene profile
Inborn Talent Genetic Test
Buccal Sampling Test Kit

SPECIMEN BAG
Next Generation Genetic Testing Panels
Hereditary breast cancer
<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated Cancers and Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>Female Breast (57-84%), Ovarian (24-54%), Prostate (16-20%), Male Breast (4%), Pancreatic (3%), Fallopian tube, Primary peritoneal, Endometrial (serous)(^1,10,11,12,13)</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>Female Breast (41-84%), Ovarian (11-27%), Prostate (20-34%), Pancreatic (5-7%), Male Breast (4-7%), Melanoma, Fallopian tube, Primary peritoneal, Endometrial (serous)(^1,10,11,12,13)</td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>Female Breast (39-52%), Diffuse gastric cancer (40-83%), Colon(^14,15,16)</td>
</tr>
<tr>
<td><strong>EPCAM(^*)</strong></td>
<td>Ovarian (1-24%), Colorectal (15-80%), Endometrial (12-61%), Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms(^5,17,18,19,20,21,22,23,24)</td>
</tr>
<tr>
<td><strong>MLH1</strong></td>
<td>Ovarian tumors (21%), Colorectal (39%), Pancreatic (11-36%), Gastric (29%), Lung (15%), Small intestine (13%), Cervical (10%), Endometrial (9%), Testicular tumors (9%)(^5,18,29)</td>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td>Female Breast (25-50%), Thyroid (10%), Endometrial (5-10%), Colon, Renal, Melanoma(^25,26,27)</td>
</tr>
<tr>
<td><strong>MSH6(^*)</strong></td>
<td>Female Breast (32-54%), Ovarian tumors (21%), Colorectal (39%), Pancreatic (11-36%), Gastric (29%), Lung (15%), Small intestine (13%), Cervical (10%), Endometrial (9%), Testicular tumors (9%)(^5,18,29)</td>
</tr>
<tr>
<td><strong>PMS2(^*)</strong></td>
<td>Female Breast, Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies, Adrenocortical carcinoma Overall risk for cancer: nearly 100% in females, 73% in males(^4,32,31,30,33,34)</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Female Breast, Colon, Pancreatic(^25,30,37)</td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Female Breast, Male Breast, Colon, Prostate, Thyroid, Endometrial (serous), Ovarian(^2,7,28,29)</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Female Breast, Male Breast, Pancreatic, Ovarian (^2,40,41,42,43)</td>
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<tr>
<td><strong>ATM</strong></td>
<td>Female Breast, Male Breast, Colon, Prostate, Thyroid, Endometrial (serous), Ovarian(^2,7,28,29)</td>
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<tr>
<td><strong>CHEK2</strong></td>
<td>Female Breast, Male Breast, Colon, Prostate, Thyroid, Endometrial (serous), Ovarian(^2,7,28,29)</td>
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<tr>
<td><strong>PALB2</strong></td>
<td>Female Breast, Male Breast, Pancreatic, Ovarian (^2,40,41,42,43)</td>
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<tr>
<td><strong>BARD1</strong></td>
<td>Female Breast, Ovarian(^2,44)</td>
</tr>
<tr>
<td><strong>BRIP1</strong></td>
<td>Female Breast, Ovarian(^45,46)</td>
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<tr>
<td><strong>FANCC</strong></td>
<td>Female Breast(^47)</td>
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<tr>
<td><strong>NBN</strong></td>
<td>Female Breast, Melanoma, Non-Hodgkin lymphoma(^48,49)</td>
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<tr>
<td><strong>RAD51C</strong></td>
<td>Female Breast, Ovarian(^50)</td>
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<tr>
<td><strong>RAD51D</strong></td>
<td>Female Breast, Ovarian(^51)</td>
</tr>
<tr>
<td><strong>XRCC2</strong></td>
<td>Female Breast, Pancreatic(^52,53)</td>
</tr>
</tbody>
</table>
Exome Sequencing
Uncertainties still exist

- Gene penetrance
- **Variants of unknown significance**
- Marked variability in expression of phenotype
- Cancer risks
  - cancer site
  - age specific
- Medical management
  - prevention
  - surveillance
  - treatment
- Psychological and social issues
The super giant-size soft drink is the best buy...

...but you'll miss most of the movie with so many trips to the restroom!