Hereditary Cancer Risk Assessment

April 1, 2015
Denise Jeffery APRN
New Hampshire Cancer Collaboration
Disclosures

- Myriad Speakers Bureau
Objectives

- Illustrate why the identification of people at risk for heritable cancer syndromes is important
- Explore the potential impact of genetic testing on the individual and family
- Discuss the possible benefits and limitations of multi-gene panel testing
- Discuss the evolution of genetic testing from syndrome specific to multi-gene panels
Myths

- Paternal family history does not increase risk of breast cancer or inheriting a mutation.
- If you have a mutation there isn’t anything you can do!
- My mother had breast cancer so that means I will.
- No one in my family has had cancer so I won’t get it.
Why is it important to identify those at risk?

- Implications for treatment of a cancer diagnosis
  - BRCA + women with ovarian cancer, triple negative breast cancer
- Eliminate second primary cancers
  - Risk reducing surgeries
- Identify at risk family members
  - First degree relatives have a 50% risk of carrying that same mutation
- Early diagnosis or cancer prevention
  - Increased surveillance or risk reducing surgery
The Evolution of Hereditary Cancer Testing

1990s
Genetic Counselor referral

2000s
Oncologists & surgeons testing affected patients in practice

Current
GIs, radiologists & surgeons testing unaffected patients in practice

Hereditary Breast & Ovarian Syndrome

Hereditary Colorectal Cancer Syndrome
BRCA Mutations Increase Risk of a Second Cancer

- Breast cancer after 5 years: Up to 3.5%
- Breast cancer by age 70: Up to 27%
- Ovarian cancer risk 10 years after breast cancer: ~1%

General Population vs. BRCA Mutation

References:
- JNCI 1999;15:1310-6
- JCO 1998;16:2417-25
- Gynecol Oncol 2005 Jan;96(1):222-6
- JCO 2010;28(14):2404-10
Contrasting Workups
Adjuvant Breast Cancer Work-up Example
Hereditary Colorectal Cancer Associated Risk

Hereditary Colorectal Cancer Increases Secondary Cancer Risk

- General Population
- Lynch Syndrome

Progression Rate and Polyp Burden Require Aggressive Management

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Women with Lynch syndrome may present with a gynecologic cancer first.

- General Population
- Lynch syndrome - Endometrial: Up to 71%
- Lynch syndrome - Ovarian: Up to 12%

* Range of risk for endometrial cancer differs by gene.
Actual Patient Case Study

**Patient Presentation**
- 62 years old
- Stage 2
- Her2/neu-
- ER/PR+

**Outcome**
- 5 years: No evidence of disease
- 7 years: Present with abdominal pain and bloating
- Imaging showed mass on left ovary
- Elevated CA-125
- Diagnosed with stage 3 ovarian cancer
- Hereditary cancer status: BRCA+

**Patient died from Ovarian Cancer**

**Timeline Post Initial Diagnosis**

**Treatment Plan**
- Lumpectomy
- Radiation
- ± Chemotherapy
- Endocrine therapy
- Post treatment follow-up
Optimized Treatment Reduces Risk in BRCA Positive Patients

NCCN recommended Medical Management Reduces Cancer Risks

- Oral Contraceptive: As much as 60%
- Tamoxifen: As much as 53%
- Mastectomy: At least 90%
- Oophorectomy: As much as 96%
Optimized Treatment Reduces Risk in Lynch Positive Patients

NCCN recommended Medical Management Reduces Cancer Risks

- Colonoscopy: As much as 56%
- Colorectal Surgery: As much as 94%
- Hysterectomy/BSO: As much as 99%
Societal Standards and Guidelines

- ACCC – Association of Community Cancer Centers
- ACOG – American Congress of Obstetricians and Gynecologists
- AGA – American Gastroenterological Association
- ASBS – American Society of Breast Surgeons
- ASCO – American Society of Clinical Oncologists
- ASCRS – American Society of Colon and Rectal Surgeons
- NCCN – National Comprehensive Cancer Network
- NSGC – National Society of Genetic Counselors
- ONS – Oncology Nursing Society
- SGO – Society of Gynecologic Oncologists
- SSO – Society of Surgical Oncology
- USPSTF – U.S. Preventive Services Task Force
Red Flags

- Cancer that occurs at a younger age than expected
  - 10-20 years before typical age of onset
- Cancer that occurs in more than one close relative - parents, siblings, aunts, uncles, grandparents
- Cancer that does not usually affect a certain gender
- Bilaterality, multiple cancers in an individual
- Cancers that occur together in a family
  - Breast and ovarian
  - Colon and endometrial
- Ashkenazi Ancestry
Hereditary Cancer Red Flags

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<td>Gastric</td>
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<tr>
<td>Other*</td>
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**EARLY**
- Any 1 of the following cancers ≤50 y:
  - Breast, Colon cancer, Endometrial cancer

**MULTIPLE**
- A combination of 2-3 of the following cancers on the same side of the family:
  - Breast, prostate, and pancreatic cancer
  - Colorectal, endometrial, ovarian, gastric, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, and sebaceous adenomas

**RARE**
- Any 1 of these rare cancers at any age:
  - Ovarian cancer
  - Breast cancer: Two primary breast cancers, Male breast cancer, Triple negative breast cancer
  - Colorectal cancer: Abnormal MSI/HIC, MSI associated histology
  - Endometrial cancer: Abnormal MSI/HIC

*Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. *Assessment criteria based on medical society guidelines. For these individual society guidelines go to www.MyriadPro.com/guidelines.

For full list of references visit MyriadPro.com/references.
## Family History

- 1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} degree relatives
- Cancer diagnosis
- Gender
- Age at time of diagnosis
- Age and cause of death
- Ethnicity
## Patients at Risk

### Patients in Your Care Appropriate for Hereditary Cancer Testing

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<tr>
<th>Cancer Type</th>
<th>Risk Percentage</th>
<th>Source</th>
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<tr>
<td>Breast Cancer</td>
<td>37%</td>
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<tr>
<td>Ovarian Cancer</td>
<td>100%</td>
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<tr>
<td>Colorectal Cancer</td>
<td>24%</td>
<td>Kerber</td>
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### Screening Mammography

- Risk: 6%

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Every year, more patients are missed than tested.
Advances in Genetic Testing

+ Multi-gene panel testing
Warren

Breast 42

Breast 54

83

Colon 70

Colon 58

57

Colon 49

55

63

54

36

30
Warren

Meets Amsterdam II Criteria
Warren

- Breast 54
- 83
- Uterus 58
- 72
- Breast 42
- Colon 70
- Colon 49
- 57
- 55
- 36
- 30
Results of the Myriad myRisk™ 25-gene panel testing:

- No mutation in any of the 5 Lynch genes
Warren
Warren

Breast 54

Breast 42

83

Uterus 58

Colon 70

Colon 49

BRCA1

NEG 63

57

36

30

55

72
Objectives

- Discuss the rationale for multi-gene panel testing
- Discuss the potential benefits and drawbacks of the multi-gene panel tests
Rationale for panel testing

- Syndrome specific testing may not provide the answers
- Patient/family presentations can be complex
- The phenotype may not match the genotype
Complexity of Patient Presentation

Study by Jennifer Saam, MS, CGC, PhD presented at The NCCN Annual Conference, March 2014:

Approximately 850,000 patients Tested for HBOC

- Family History of Colorectal Cancer <50 (30.9%)
- Family History of Endometrial Cancer <50 (22.7%)
- Family History of 2 Lynch cancers in the Same Person (16.4%)
- Other (30.0%)

Evaluating The Personal And Family History Overlap Between Hereditary Cancer Syndromes, Jennifer Saam, MS, CGC, PhD, Myriad Genetic Laboratories Inc., Presented at NCCN Annual Conference - March 14, 2014
Complexity of Patient Presentation

Approximately 60,000 Patients Tested for LS

70% Met 2012 NCCN criteria for HBOC

30% Family History of Ovarian Cancer (32.8%)

Personal History of Breast Cancer and 1 Relative with Breast cancer <50 (22.4%)

Personal History of Ovarian Cancer (12.6%)

Other (32.2%)

Evaluating The Personal And Family History Overlap Between Hereditary Cancer Syndromes, Jennifer Saam, MS, CGC, PhD, Myriad Genetic Laboratories Inc., Presented at NCCN Annual Conference - March 14, 2014
Many Genes Contribute to Hereditary Cancer

Multiple Genes Can Increase the Risk of a Single Cancer

- BRCA1/2
- PTEN
- ATM
- PALB2
- CHEK2
- RAD51C
- NBN
- BRIPI
Many Genes Contribute to Hereditary Cancer

Multiple Genes Can Increase the Risk of a Single Cancer

- BRCA1/2
- PTEN
- STK11
- CDH1
- PALB2
- RAD51C
- NBN
- BRIPI

Multiple Cancers Can Be Associated with a Single Gene

- TP53
- BREAST
- ENDOMETRIAL
- PROSTATE
- MELANOMA
- PANCREATIC
- OVARIAN
- GASTRIC
- COLORECTAL
Approximately One-Third of Mutations Would be Missed with Traditional Testing Approaches

In 1,781 patients with Breast Cancer

- 68% BRCA1/2
- 32% Other
- 73% LS genes
- 27% Other
- 60% BRCA1/2
- 34% Other

Multi-gene panel testing in patients suspected to have Lynch syndrome, Matthew B. Yurgelun et. al. Presented at ASCO June 2014
Approximately One-Third of Mutations Would be Missed with Traditional Testing Approaches

In 1,260 Patient Suspicious for Lynch Syndrome

- 68% BRCA1/2
- 32% Other
- 73% LS genes
- 27% Other
- 60% BRCA1/2
- 34% Other


Multi-gene panel testing in patients suspected to have Lynch syndrome, Matthew B. Yurgelun et. al. Presented at ASCO June 2014

Approximately One-Third of Mutations Would be Missed with Traditional Testing Approaches

In 648 Patients with Ovarian Cancer

- 68% BRCA1/2
- 32% Other
- 73% LS genes
- 27% Other

- 60% BRCA1/2
- 34% Other
- 6% LS


Multi-gene panel testing in patients suspected to have Lynch syndrome, Matthew B. Yurgelun et al. Presented at ASCO June 2014

## Genes and Associated Cancer Risks

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<th>Genes</th>
<th>Breast</th>
<th>Ovarian</th>
<th>Colorectal</th>
<th>Endometrial</th>
<th>Melanoma</th>
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## Panel Comparison

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*Other panels may include one or more inherited conditions. Not all combinations are available at this time. This includes BARD1, BRIP1, and CDK4.
Genetic Labs

- Myriad-
  - MyRisk Panel - Pan Cancer panel

- Ambry
  - BreastNext, OvaNext, ColoNext, CancerNext

- University of Washington- BROCA panel

- Invitae

- Quest

- Gene Dx
  - Partial listing of labs
**Potential Benefits of Multi-gene panel testing**

More than one mutation may be found

Limited family history or atypical presentation may make it difficult to choose a test

+ More options are available
+ Next generation sequencing
  + Ability to read multiple genes
+ Panels may be more cost effective and efficient
+ Increase likelihood of finding a mutation
+ More than one mutation may be found
+ Limited family history or atypical presentation may make it difficult to choose a test
Potential Limitations of genetic testing

- Clinical labs may differ on their interpretation of results
- Increased likelihood of variants of uncertain significance, counsel patients
- Insurance coverage and costs vary between labs
- Un-informative or unexpected results
- Lack of clear guidelines on risk management for some of the genes

Turn around times may not be efficient for someone making treatment decisions
Limited data on the risks of cancer associated with some of the genes
Finding Risks, Not Answers, in Gene Tests

By DENISE GRADY and ANDREW POLLACK  
SEPT. 22, 2004

Tamika Matthews has had breast and thyroid cancer, and had genetic screening. She is concerned her son may be at risk. Chester Higgins Jr./The New York Times
Identification of Patients at Risk

- Screen all patients for family history
  - Oncologists, surgeons, primary care, OB/GYN
  - Institute a process in the office
  - Are there any red flags for inherited cancer syndrome

- Refer for genetic risk assessment
  - Evaluate patient- comprehensive family history,
  - Make recommendations
  - Pre test counseling
  - Post test counseling
  - Management
Pre-Test Conversation Talking Points with Patients

- Introduction to Cancer Types: Sporadic, Familial, and Hereditary
- Personal and/or Family History Suggestive of Hereditary Cancer
- People with Gene Mutations have a Much High Risk of Getting Certain Cancers
- Risk-Reducing Surgeries and Preventive Medication Strategies Reduce Cancer Risk
- Testing Options
- Possible Test Results: Positive, Negative, Uncertain (VUS)
- Family Impact
- Test Coverage
- Privacy: HIPAA, GINA, and Test Results Disclosures
- Benefits and Limitations of Genetic Testing
- Next Steps and Management Plan
Conclusions

+ The screening of patients for Inherited cancer syndromes is the standard of care.
+ Accurate patient and family history is the key to identifying people who are appropriate for referral.
+ Cancer Risk assessment with pre and post test counseling is critical.
Availability of Services in NH

- Elliot Breast Health
- Dartmouth Familial Cancer Risk Program
- Dana Farber @ Elliot Londonderry and Concord Hospital
- St Joseph’s Hospital
- Southern NH Regional Medical Center
- Wentworth Douglas Hospital
Thank you