Cancer Risk Evaluation in the 21st Century: Implications for Cancer Genetics Nursing

Catherine M. Belt, MSN, RN, AOCN
Cancer Genetics SIG Coordinator – 2014-2016
Senior Administrator, Penn Cancer Network
Abramson Cancer Center, Penn Medicine
Objectives

Participants will be able to:

1. Articulate the complexities and challenges in providing cancer risk evaluation and genetic testing services
2. Define the components of a comprehensive approach to cancer risk evaluation and offering genetic testing services
3. Discuss the impact of new technology such as NextGeneration Sequencing on the approach to cancer risk evaluation
Mid 20th Century - Searching for the Answers
20th Century Breakthroughs Advancing Science

1953 – Watson and Crick – Description of the DNA structure


1966 – Henry Lynch, MD – “Father of Hereditary Cancer” describes Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
20th Century Breakthroughs Advancing Science

1970 Alfred Knudsen – Two Hit Hypothesis
Retinoblastoma as a Hereditary Cancer Syndrome

1971 – President Nixon – “The War on Cancer”
The National Cancer Act
20th Century Breakthroughs Advancing Science

Mary Claire King, MD, PhD
Discovered the BRCA1 gene 1993

Michael Stratton, MD, PhD & Richard Wooster, PhD
Discovered the BRCA2 gene 1994
The Human Genome Project – 1990 - 2003

Funded and coordinated by the US Dept of Energy & NIH

International effort blending academic and commercial research efforts

2000 – Initial draft mapping announced
2003 – Project completed – 99.9% of human genome mapped

Project Objectives

▲ Identify all of the genes in human DNA
▲ Determine the exact sequencing of 3 billion base pairs
▲ Develop databases to store this information
▲ Improve tools for data analysis
▲ Transfer related technologies to the private sector
▲ Address ethical, legal and social issues (ELSI) that may arise

More than 300 genes have been implicated in the diabolical transformation of normal cells into cancer cells, and that has led to major insights into cause, prevention, diagnosis, treatment and cure.

Francis Collins, MD, PhD, Director NIH
Accomplishments of the Human Genome Project

- 1800 Disease causing genes discovered
- Ability to identify genes causing an inherited disease in days instead of decades
- Over 2000 genetic tests for variety of human conditions have been developed
- Spurred the rapid evolution of technology to examine and identify genes, variations and mutations
- Addressed the Ethical, Legal and Social implications of Genetic Testing –
  - Informed consent for genetic testing
  - Communication of genetic information
  - Protection against discrimination
100 Years of Cancer Discoveries

1890
• Gene mutations described in cancer

1909
• Immune system suppression leads to tumor development

1914
• Chromosomal abnormalities lead to cancer; tumor suppressor genes and oncogene functions theorized

1950
• Watson and Crick describe the Double Helix DNA structure

1960
• Philadelphia Chromosome in CML describe – translocation of Ch 22:Ch9

1966
• Henry Lynch, MD describes the first hereditary cancer family syndrome - HNPCC

1971
• Alfred Knudson, MD proves the Two-Hit Hypothesis explaining difference between Inherited and Sporadic Cancer

1973
• David Compings describes the theory of germline inheritance of mutated tumor suppressor genes

1979
• First discovery of tumor suppressor genes – RB and TP53

1983
• Cancer Epigenetics discoveries
• C-ABL1 created by Phila Ch causes Leukemia
• C-Myc causes Lymphoma

1990
• HUMAN GENOME PROJECT INITIATED
• Bcr-abl fusion gene identified

1993
• Mary Clair King discovers the BRCA1 gene
• Henry Lynch discovers the MSH2 & MLH1 genes

1999
• Cancer Profiling – distinguishing between cancer types

2001
• Targeted Cancer Therapy – drug developed for specific targets

Penn Cancer Network
Genetic Information Non-Discrimination Act

2008 – President George W. Bush signs GINA into law

Protects the rights of individuals against discrimination in the workplace or in group health insurance based on genetic testing information.

Ensures privacy and confidentiality of genetic testing information

32 Individual states have also enacted state laws to further strengthen protection against genetic discrimination in varying levels
NCI and NHGRI funding began in 2006

- Tissue Sample Repository
- Goal – chart the genomic changes in over 20 types of cancer
- Objective – identify targets for cancer therapies, early detection and prevention of cancer
- Open and shared data portal for all researchers
By mid-1990’s, some roadmaps constructed
Inherited Cancer Susceptibility Genes Discoveries

- Well described syndromes, defined cancer risk profile
- Evidence based risk management interventions

<table>
<thead>
<tr>
<th>Hereditary Cancer Syndrome</th>
<th>High Risk Gene</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>TP53</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>BRCA1</td>
<td>1993, 1994</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>1998</td>
</tr>
<tr>
<td>Hereditary Colorectal Cancer</td>
<td>APC gene</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>MLH1, MSH2, MSH6, PMS2 genes</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>STK 11 genes</td>
<td>1996</td>
</tr>
<tr>
<td>Hereditary Endocrine Cancers</td>
<td>MEN 2</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>VHL</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>MEN 1</td>
<td>1997</td>
</tr>
<tr>
<td>Hereditary Childhood Cancers</td>
<td>Retinoblastoma – RB gene</td>
<td>1979</td>
</tr>
<tr>
<td></td>
<td>Li Fraumeni – TP53 gene</td>
<td>1979</td>
</tr>
</tbody>
</table>
Cancer as a Genetic Disease

- ALL Cancer is caused by Genetic mutations
- NOT all cancers are inherited in nature

**Sporadic Cancer**

1. **SOMATIC** mutations - NOT inherited
2. Mutations found ONLY in the tumor
3. Accumulation of genetic damage over the course of a lifetime of exposures
4. Usually older age of onset – age >65
5. Social and lifestyle risk factors, environmental risk factors
6. Unlikely to see a pattern of specific cancers in family

**Inherited Cancer**

1. **GERMLINE** mutation in egg or sperm
2. Inherited from mother or father
3. Mutation found in all cells of the body
4. Cancers often occur at early age <50
5. Patterns of cancer found on multiple branches of family
Knudson’s Two Hit Hypothesis

Cancer results from the accumulation of damage to the DNA from multiple exposures over the course of a lifetime.
What Factors Contribute to Cancer?

NOT Everyone with an inherited gene mutation develops cancer

- Modifier Genes
- Response to DNA damage
- Hormonal and reproductive risk factors
- Social habits
- Environmental exposure
- Lifestyle – exercise, weight
How Much Cancer is Inherited?

The majority of all cancers are sporadic in nature.

- Sporadic Cancers: 80% of all cancers
- Inherited: 5-10%
- Familial: 5-10%

Sporadic Cancers: 80% of all cancers

Inherited: 5-10%  Familial: 5-10%
When to Suspect a Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis (typically < age 50)
- Multiple primary tumors in one individual
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Certain tumor markers or types of histopathology
- Number and types of colon or gastric polyps
- Physical features characteristic of certain syndromes, i.e., large head circumference, freckling, skin lesions
- Evidence of autosomal dominant transmission – evaluation of a 3 generation family pedigree with evidence of cancers
- Certain ethnic ancestry – Ashkenazi Jewish
Identification of Hereditary Cancer Families

- **Linkage Studies**
  - Recruitment of families with predominance of certain cancers
  - Evaluation of affected family members for common features and genetic mutations
Identification of Hereditary Cancer Families

- Identification of Cancer Associated Mutations

- Discovery of rare genetic mutations associated with specific cancer profiles
- Calculate the penetrance of cancer in mutation carriers families
- Genotype – Phenotype correlations defined
- Determine the prevalence of specific genetic mutations in populations
- Examples:
  - BRCA1 – young onset breast cancer, ovarian cancer
  - Lynch Syndrome – colorectal, uterine, ovarian, Small bowel
Model for Providing Cancer Risk Assessment

♦ Multidisciplinary Team
  • Physician with additional training in cancer genetics
  • Advanced Practice Oncology Nurse, Master’s prepared, board certified, with additional training in cancer genetics
  • Genetic Counselor, Master’s prepared, board certified, licensed

♦ “Traditional” Model – 2 visit model
  • First session – 1:1 with APN or CGC
    – Education and counseling provided on cancer genetics
    – Determination of eligibility for germline genetic testing
    – Informed Consent
  • Second session – Multidisciplinary meeting: Physician, APN, CGC
    – Testing Results reporting
    – Risk Management Interventions and ongoing Health Surveillance recommendations
    – Identification of other at risk family members
    – Research eligibility options
Professionals Practice Guidelines

- **American Society of Clinical Oncologists**

- **American Society of Breast Surgeons**

- **National Society of Genetic Counselors**
  - NSGC Position Statement

- **International Society of Nurses in Genetics (ISONG)**
  - Genetic/Genomic Nursing: Scope and Standards of Practice

- **Oncology Nursing Society**
  - The Application of Cancer Genetics and Genomics Throughout the Oncology Care Continuum
Physician Knowledge of Cancer Genetics

“Competent knowledge of cancer genetics is essential for effectively assessing and managing risks, deciding whether to refer for specialty follow-up and communication with patients and families”

1999-2000  Stratified random sample from the AMA Masterfile
Sample  2079 licensed physicians selected, 1251 participated
Method  15 minute survey with 3 questions: 2 HBOC, 1 CRC

Specialties

<table>
<thead>
<tr>
<th>820 Primary Care</th>
<th>431 Subspecialists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Medicine</td>
<td>Oncology (oversampled)</td>
</tr>
<tr>
<td>General Practitioners</td>
<td>General Surgery</td>
</tr>
<tr>
<td>Family Practitioners</td>
<td>Urology</td>
</tr>
<tr>
<td>Obstetrician/Gynecologists</td>
<td>Gastroenterology</td>
</tr>
</tbody>
</table>

Conclusion: 1. Practicing physicians displayed limited knowledge about 3 key cancer genetics concepts
2. Genetics knowledge was not uniform across medical specialties

Table 1: Physician responses to questions about BRCA1 and 2 mutations, by specialty and practice characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Not sure (%)</th>
<th>OR†</th>
<th>95% CI</th>
<th>10–100 (%)</th>
<th>Not sure (%)</th>
<th>OR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>37.5</td>
<td>10.6</td>
<td>49.0</td>
<td></td>
<td></td>
<td>33.8</td>
<td>27.4</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td><strong>Medical specialty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family/general practice</td>
<td>28.1</td>
<td>10.8</td>
<td>58.0</td>
<td>1.0</td>
<td>–</td>
<td>21.8</td>
<td>26.7</td>
<td>49.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>37.3</td>
<td>11.3</td>
<td>47.7</td>
<td>1.3</td>
<td>0.9 to 1.8</td>
<td>29.5</td>
<td>30.8</td>
<td>36.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Obstetricians/gynaecologists</td>
<td>51.9</td>
<td>11.9</td>
<td>34.4</td>
<td>2.0</td>
<td>1.3 to 3.0</td>
<td>53.6</td>
<td>29.3</td>
<td>16.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Oncologists</td>
<td>66.8</td>
<td>7.6</td>
<td>21.8</td>
<td>3.4</td>
<td>2.2 to 5.3</td>
<td>71.0</td>
<td>21.5</td>
<td>4.2</td>
<td>5.7</td>
</tr>
<tr>
<td>General surgeons</td>
<td>45.0</td>
<td>13.7</td>
<td>38.8</td>
<td>1.7</td>
<td>1.1 to 2.7</td>
<td>57.8</td>
<td>20.5</td>
<td>20.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>24.8</td>
<td>6.7</td>
<td>68.5</td>
<td>0.6</td>
<td>0.3 to 1.4</td>
<td>22.4</td>
<td>19.9</td>
<td>57.9</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>37.3</td>
<td>5.8</td>
<td>53.4</td>
<td>1.0</td>
<td>–</td>
<td>28.7</td>
<td>19.7</td>
<td>49.2</td>
<td>1.0</td>
</tr>
<tr>
<td>40–59</td>
<td>36.7</td>
<td>11.6</td>
<td>48.5</td>
<td>0.9</td>
<td>0.6 to 1.3</td>
<td>34.7</td>
<td>27.5</td>
<td>35.6</td>
<td>1.4</td>
</tr>
<tr>
<td>&lt;40</td>
<td>40.2</td>
<td>11.0</td>
<td>46.6</td>
<td>1.1</td>
<td>0.7 to 1.8</td>
<td>34.8</td>
<td>33.7</td>
<td>29.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

In your opinion, what percentage of female breast cancer patients have a BRCA1 or BRCA2 gene mutation?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;50 (%)</th>
<th>≥50 (%)</th>
<th>Not sure (%)</th>
<th>OR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>33.6</td>
<td>13.1</td>
<td>50.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical specialty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family/general practice</td>
<td>30.0</td>
<td>9.3</td>
<td>58.1</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>32.4</td>
<td>17.5</td>
<td>46.7</td>
<td>1.9</td>
<td>1.1–3.0</td>
</tr>
<tr>
<td>Obstetricians/gynaecologists</td>
<td>35.9</td>
<td>5.2</td>
<td>57.6</td>
<td>0.5</td>
<td>0.2–1.1</td>
</tr>
<tr>
<td>Oncologists</td>
<td>44.1</td>
<td>25.1</td>
<td>27.1</td>
<td>2.7</td>
<td>1.5–4.8</td>
</tr>
<tr>
<td>General surgeons</td>
<td>38.0</td>
<td>11.2</td>
<td>50.1</td>
<td>1.2</td>
<td>0.6–2.4</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>49.4</td>
<td>38.9</td>
<td>11.7</td>
<td>6.1</td>
<td>2.8–13.4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>34.2</td>
<td>5.9</td>
<td>57.6</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>40–59</td>
<td>33.8</td>
<td>13.1</td>
<td>50.5</td>
<td>1.9</td>
<td>1.0–3.8</td>
</tr>
<tr>
<td>&lt;40</td>
<td>32.2</td>
<td>19.0</td>
<td>46.6</td>
<td>2.7</td>
<td>1.3–5.9</td>
</tr>
</tbody>
</table>
Family Practice Physician Referral for Genetic Testing

“Family physicians who provide the majority of primary care in the US will be fielding the majority of women self referring for BRCA1/2 testing based on Biotechnology Direct to Consumer marketing. Will physicians make recommendations within published guidelines from the USPSTF on which patients are appropriate for referral for genetic counseling and testing?”

2005-2006: random stratified sample drawn from a longitudinal survey of members of the AAFP

Sample: 10,000 members with half having completed residency less than 15 years ago; 1,035 participated

Method: Web based survey, vignette of low risk patient by USPSTF definition, questions aimed at would they refer for genetic counseling and testing

Results: 8% of physicians would not refer for counseling or testing

92% of physicians referred patient for counseling or testing

Conclusions: Family Practice physicians need to gain greater familiarity and understanding of what risk factors deem a woman to be at high risk.

1996 – in response to advances in cancer genetics, ASCO developed specific recommendations addressing:
- Clinical practice
- Research needs
- Educational opportunities
- Requirements for informed consent
- Indications for genetic testing

ASCO acknowledged the need for specialized knowledge to provide quality cancer genetics services and committed to:
- Publication of a resource document for curriculum development in cancer genetics education
- Created the ASCO Curriculum: Cancer Genetics and Cancer Predisposition Testing course including a set of educational slides
- Conducted “Train the Trainer” education workshops to expand the pool of oncologists equipped to teach fundamental of cancer genetics
- Created a set of clinical cancer genetics self study materials known as ONCOSEP:Genetics
- Conducted a series of 1 and 2 day cancer genetics review courses to provide basic and more advanced level of genetic information to providers
Reiterated previous policy statements related to genetic testing

- Individual being tested has a personal or family history suggestive of a genetic cancer susceptibility
- The genetic test can be adequately interpreted
- Test results have accepted clinical utility

Competently trained providers are responsible for providing

- Pre and Post test counseling
- Coordination of post-test follow-up care and appropriate referral
- Informed consent expanded to include 12 basic elements

Addressed the implications of Next Generation Sequencing panels and Direct to Consumer genetic testing

- Possible identification of low to moderate risk gene mutations
- Acknowledgment that these genes that have no consensus or evidence based risk management guidelines
- Possibility of increased incidence of Variant of Uncertain Significance results which also have limited clinical utility

Oncology Nurse’s Knowledge of Cancer Genetics

- Study to assess oncology nurses’ knowledge of cancer genetics and identify educational needs with regard to cancer genetics

**Sample:**
1200 randomly selected ONS members – 605 participated

51 members of the ONS-Cancer Genetics SIG

**Method:**
54 question paper survey mailed to homes

4 Categories of knowledge evaluated – basic genetics, cancer biology, cancer genetics and cell biology.

**Results:**
Respondents were most knowledgeable about cancer biology but lacked knowledge of cell biology, basic genetics and cancer genetics.

Cancer Genetics knowledge deficit greatest among staff nurses, those with a bachelor’s degree or less and those who have not had continuing education in cancer genetics.

**Conclusion:**
1. results support the need for targeted training programs to prepare oncology nurses to incorporate genetics in practice
2. need to include cancer genetics in nursing curricula

ONS and ISONG Genetics Education Initiatives

♦ ISONG and ANA

- Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics (2005)
- Essential Genetic and Genomic Competencies for Oncology Nurses (2012)
- Professional Credentialing for Advanced Practice Nurse in Genetics – portfolio application relaunched December 2014

♦ ONS

- Genetic Short Course – Train the Trainer educational program (2000)
- “Cancer Biology” and “Cancer Genetics” – online courses
- Cancer Genetic feature article in each edition of Oncology Nursing Forum and Clinical Journal of Oncology Nursing
- **Cancer Genetics Special Interest Group** – content experts for defining scope of practice and standards of care for cancer genetics nursing
Multi-disciplinary Genetics Education

- City of Hope Intensive Cancer Genetics Course, Duarte, CA

![Graph showing knowledge survey scores over pre- and post-sessions for different professions: Physician, Nurse, and Genetic Counsellor.](image)

What External Factors Influence CRA?

- Center for Medicare and Medicaid
- CIGNA Healthcare
- Aetna
- Horizon Blue Cross/Blue Shield of NJ
What External Factors Influence CRA?

- United States Prevention and Screening Task Force

- American College of Surgeons Commission on Cancer

- National Accreditation of Program for Breast Centers

- National Comprehensive Cancer Network
Standard 2.3 Risk Assessment and Genetic Counseling

- Defines the educational and experiential requirements of providers of risk assessment and genetic counseling.
- Defines what board certificated professionals are eligible to provide services – Nursing – GCN, APNG, AOCNS, AOCNP.
- Stipulates pre and post test counseling is required.
- Outlines the specific content provided during counseling.
- Cancer Committee defines the appropriate individuals who will provide risk assessment and counseling.
- Services can be provided by referral to other resources.

“*Please note, specialized training in cancer genetics should be ongoing; educational seminars offered by commercial laboratories about how to perform genetic testing is not considered adequate training for cancer risk assessment and genetic counseling.”
National Accreditation Program for Breast Centers

♦ Standard 2.16 Genetic Evaluation and Management

- Referrals for genetics should be based on national guidelines
- Genetic Counseling provided by professional with extensive education in genetics and cancer genetics, counseling and hereditary cancer syndromes
- Defines the credentials required of professional involved in genetic counseling – Nursing – GCN, APNG, AOCNS, AOCNP
- Pre and Post testing counseling
- May refer to tele-genetics companies to provide service

“Please note, specialized training in cancer genetics should be ongoing and documented with CME in the fields of cancer genetics. Educational seminars should include the spectrum of services for breast cancer genetics including genetic risk assessment, genetic counseling, indications and decision-making regarding genetic testing and appropriate post-test counseling.”
Cancer Risk Evaluation

Key Components of Cancer Risk Evaluation

- Assessment of Patient Needs, and Concerns
- Detailed Family History including first, second and third degree relatives, noting cancer history and date of cancer diagnosis
- Detailed Personal Health History including hormonal and reproductive history, lifestyle and social habits, carcinogen exposure, cancer history
- Focused physical examination for features associated with phenotype of specific inherited cancer syndrome
- Pathology confirmation of personal and family cancers, when possible

Development of a Differential Diagnosis

- Utilization of published cancer risk models and mutation probability models
- Pedigree analysis - Evaluation of phenotype-genotype correlations to consider most likely single site genetic testing
- Incorporating physical findings suggestive of syndrome

Breast and/or Ovarian Cancer Genetic Assessment

CRITERIA FOR FURTHER GENETIC RISK EVALUATION
An affected individual with one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- Early-age-onset breast cancer
- Triple negative (ER-, PR-, HER2-) breast cancer
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
  - ≥1 close blood relative with breast cancer ≤50 y, or
  - ≥1 close blood relative with epithelial ovarian cancer at any age, or
  - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age
- From a population at increased risk
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer
- Ovarian cancer
- Male breast cancer

An unaffected individual with a family history of one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- ≥2 breast primaries in single individual
- ≥2 individuals with breast primaries on the same side of family
- ≥1 ovarian cancer primary from the same side of family
- First- or second-degree relative with breast cancer ≤45 y
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer
- Male breast cancer

For populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).
For dermatologic manifestations, see COWD-1.
For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered. See NCCN Guidelines for Genetic Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome. Melanoma has been reported in some HBOC families.
For lobular breast cancer with a family history of diffuse gastric cancer, CDH1 gene testing should be considered.
Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise in cancer genetic counseling should provide counseling.

Referral to cancer genetics professional recommended → See Assessment (BR/OV-2)
ASSESSMENT

Patient needs and concerns:
- Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
- Goals for cancer family risk assessment

Detailed family history:
- Expanded pedigree to include first-, second-, and third-degree relatives (parents, siblings, children, grandparents, aunts, uncles, nieces, nephews, grandchildren, half-siblings, great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins) (See BR/OV-3)
- Types of cancer, bilaterality, age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly pathology reports of primary cancers

Detailed medical and surgical history:
- Any personal cancer history (e.g., age, type, laterality)
- Carcinogen exposure (e.g., history of radiation therapy)
- Reproductive history
- Hormone use
- Previous breast biopsies
- History of salpingo-oophorectomy

Focused physical exam (conducted by qualified clinician):
- Breast/ovarian
- Cowden syndrome/PHTS specific:
  - Dermatologic, including oral mucosa
  - Head circumference
  - Thyroid (enlarged or nodular on palpation)

GENE TESTING

See Targeted Testing Criteria for
- Hereditary Breast/Ovarian Syndrome (HBOC-1)
- Li-Fraumeni Syndrome (LIFR-1)
- Cowden Syndrome/PHTS (COWD-1)

See Multi-Gene Testing (GENE-1)
# NCCN Guidelines Version 2.2014
## Hereditary Breast and/or Ovarian Cancer Syndrome

<table>
<thead>
<tr>
<th>HBOC FOLLOW-UP</th>
<th>FAMILY STATUS</th>
<th>GENETIC TESTING</th>
<th>TEST OUTCOME</th>
<th>SCREENING RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment and counseling, Psychosocial assessment and support, Risk counseling, Education, Discussion of genetic testing, Informed consent</td>
<td>Deleterious familial BRCA1/BRCA2 mutation known</td>
<td>Recommend BRCA1/BRCA2 testing for specific familial mutation</td>
<td>Positive for familial BRCA1/BRCA2 mutation, BRCA1/BRCA2 testing not performed</td>
<td>See HBOC Syndrome Management (HBOC-A)</td>
</tr>
<tr>
<td>HBOC testing criteria met</td>
<td>No known familial BRCA1/BRCA2 mutation</td>
<td>Consider comprehensive BRCA1/BRCA2 testing of patient or if unaffected, test family member with highest likelihood of a mutation, or Variant of unknown significance found (uninformative)</td>
<td>Mutation found, Not tested or no mutation found</td>
<td>See HBOC Syndrome Management (HBOC-A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider multi-gene testing, if appropriate</td>
<td></td>
<td>Offer research and individualized recommendations (e.g., testing next family member with highest likelihood) according to personal and family history</td>
</tr>
</tbody>
</table>

---

**Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed.** A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

**Comprehensive genetic testing includes full sequencing of BRCA1/BRCA2 and testing for large genomic rearrangements.**

**Genetic testing for familial BRCA1/2 in children <18 y is generally not recommended.**

**If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.**

**Testing of unaffected family members when no affected member is available should be considered.** Significant limitations of interpreting test results should be discussed.

**If more than one family member affected, first consider: young age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, and most closely related to the proband/patient. If no living family member with breast or ovarian cancer, consider testing first-degree, second-degree family members affected with cancer thought to be inherited.**

**For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations and ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, comprehensive genetic testing is the approach, if done.**

**If no mutation found, consider other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LIFR-1) and Cowden syndrome (COWD-1) or multi-gene testing (GENE-1).** For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see ADDIT-1.

**Testing family members for a variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional.**
Pedigree Analysis
Risk Management Strategies

- **Results Reporting and Medical Management**
  - Results reporting with explanation of significance of outcomes
    - Positive for genetic mutation
    - Uninformative Negative genetic testing
    - True Negative genetic testing
    - Variant of Uncertain Significance (VUS)
  - Individualized Risk Reduction Management plan based on:
    - Age
    - Reproductive life stage – premenopausal, postmenopausal
    - Affected versus Unaffected with cancer diagnosis
    - Evidence based risk management guidelines for interventions
  - Identification of “At risk” family members who should have counseling

- **High Risk Annual Follow-up**
  - Annual follow-up for high risk individuals – monitor risk management

High Risk Annual Follow-up
Considerations for Genetic Testing

- **Pre-test Genetic Counseling**
  - Discussion about the clinical and genetic aspects of suspected cancer syndrome, including mode of inheritance
  - Risk, benefits and limitation of genetic testing for gene mutations
  - Informed consent prior to testing considering patients preferences and values
  - Possible testing outcomes and significance to personal and family healthcare needs and spectrum of risks for cancer
  - Consideration of impact of testing outcomes on family dynamics, psychological and relationship implications, privacy and confidentiality
  - **Communication plan for results reporting to family members and identification of other family members at risk**

Importance of Family Communication
21st Century Cancer Genetics – New Paradigms
Events Changing the Genetics Landscape

Next Generation Sequencing Technology

SCOTUS Legal Ruling

Angelina Jolie’s Personal Journey

Technology Advances

Legal System

Social Media
Angelina Jolie’s Personal Story

May 14, 2013
Angelina Jolie
Op Ed in NY Times

- Announced that she was a BRCA1 mutation carrier
- Made decision to undergo prophylactic bilateral mastectomies with breast reconstruction

March 24, 2015

- Announced that she had risk reducing bilateral salpingo-oophorectomy
Media Coverage of a Personal Story

Because of you, we'll have donated $50 million to charity over the past seven years.

What's the gene that led to Jolie's double mastectomy?

By Holly Yan, CNN
Updated 10:05 AM ET, Thu May 16, 2013

BRCA test leads Angelina Jolie to get double mastectomy: Who should get it?

By RYAN MASLOW / CBS NEWS / May 14, 2013, 3:15 PM

Medscape MULTISPECIALTY

News & Perspective | Drugs & Diseases | CME & Education

NOW APPROVED

Introducing the Neulasta® with the On-body Infusion System for Neulasta® (pegfilgrastim)

Palbociclib for Breast Cancer Inches Toward FDA Approval

Four Years After NLST, Lung Screening Uptake 'Way Too Slow'

Medscape Medical News from the 2014 Breast Cancer Symposium (BCS)

Angelina Jolie Effect: BRCA Testing Doubles

Zosia Chustecka
September 03, 2014
The impact of Angelina Jolie's (AJ) story on genetic referral and testing at an academic cancer centre.

Subcategory: High Risk

Category: Risk Assessment, Prevention, Early Detection, and Screening

Meeting: 2014 Breast Cancer Symposium

Session Type and Session Title: General Poster Session B: Risk Assessment, Prevention, Early Detection, Screening, and Systemic Therapy

Abstract Number: 44

Citation: J Clin Oncol 32, 2014 (suppl 26; abstr 44)
Angelina Jolie, breast cancer testing, Myriad Genetics and the Supreme Court

David Sell
POSTED: WEDNESDAY, MAY 15, 2013, 8:45 AM

Movie star Angelina Jolie's revelation Tuesday of having had a double mastectomy to help avoid breast cancer had business and legal angles.

Myriad Genetics, the Utah-based company at the center of a legal debate about the acceptability of gene patenting, has a monopoly on the testing Jolie had before opting for surgery. With the news of Jolie breaking in the morning, the company's stock rose to a three-year high of $34.70 during...
May 7, 2013

Myriad Genetics Reports Third Quarter Fiscal Year 2013 Results

Third Quarter Revenue Up 21%; EPS Up 34% -- Company Raises FY13 Guidance

SALT LAKE CITY, May 7, 2013 (GLOBE NEWSWIRE) -- Myriad Genetics, Inc. (Nasdaq:MYGN) today announced results for its third fiscal quarter and nine months ended March 31, 2013. Revenue for the third fiscal quarter increased 21 percent over the same period in the prior year to $156.5 million. Third fiscal quarter earnings per diluted share were $0.46, an increase of 34 percent over the same period of the prior year.

"I am pleased with not only the solid revenue growth across all of our business segments during the third quarter but also the Company's ability to drive financial leverage as we continue to invest in our extensive product pipeline," said Peter D. Meldrum, President and Chief Executive Officer of Myriad Genetics, Inc. "We are very optimistic regarding the future outlook as we seek to expand our core markets, diversify our business through new product introductions, and expand internationally."

Third Fiscal Quarter 2013 Results

- Molecular diagnostic testing revenue in the third fiscal quarter equaled $148.4 million, an increase of 20 percent compared to the prior year period. Revenue from the Oncology segment equaled $95.8 million, an increase of 13 percent over the third fiscal quarter of 2012. Women's Health revenue totaled $52.6 million, an increase of 35 percent over the same period in the prior year.

  - Revenue from the BRACAnalysis® test, which represented 74 percent of total revenue in the third quarter, was $115.4 million, a 9 percent increase over the same period of the prior year.
## The BRCA Gene Patent Controversy

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>MC King identified BRCA1 through linkage mapping in Chr 17q21</td>
</tr>
<tr>
<td>1991</td>
<td>Myriad Genetics Laboratory founded</td>
</tr>
<tr>
<td>1994</td>
<td>BRCA1 sequencing published</td>
</tr>
<tr>
<td>1995</td>
<td>BRCA 2 sequencing published</td>
</tr>
<tr>
<td>1996</td>
<td>BRCA Analysis test launched, cost $1600</td>
</tr>
<tr>
<td>1998</td>
<td>BRCA 1 and BRCA2 genes patented in USA</td>
</tr>
<tr>
<td>1999</td>
<td>Myriad begins enforcement of patent protection</td>
</tr>
<tr>
<td>2002</td>
<td>Myriad begins Direct to Consumer marketing of products</td>
</tr>
<tr>
<td>2004</td>
<td>European Patent Office reject Myriad patents</td>
</tr>
<tr>
<td>2006</td>
<td>Myriad stops sharing VUS data with scientific community</td>
</tr>
<tr>
<td>2007</td>
<td>BART testing – deletion, duplication, rearrangement testing introduced at additional $750 cost</td>
</tr>
</tbody>
</table>

The Impact of the BRCA gene patents

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest repository of BRCA1 and BRCA2 genetic mutations</td>
<td>Essential monopoly on testing availability – no other company in US could provide testing</td>
</tr>
<tr>
<td>Variant classification process and inventory of VUSs</td>
<td>Cost of procedure doubled over years while technology advances reduced cost of testing</td>
</tr>
<tr>
<td>Turn around time for results reporting</td>
<td>Cost limited access to patients with limited insurance coverage</td>
</tr>
<tr>
<td>Streamlined insurance preapproval process</td>
<td>University research testing could not be disclosed to patient unless commercial testing verified by Myriad</td>
</tr>
<tr>
<td>Advances in testing technology by other companies restricted – NGS could not include BRCA1 and BRCA2</td>
<td></td>
</tr>
</tbody>
</table>
Challenges to Myriad Genetics BRCA patents


- Decision appealed by Myriad Genetics Laboratory

- **June 13, 2013** Association for Molecular Pathology vs Myriad Genetics, Inc – Supreme Court of the United States unanimously ruled to bar the patents on naturally occurring genes, vacating Myriads patents.
Aftermath of SCOTUS Patent Ruling

“OPENING THE FLOOD GATES”
Next Generation Sequencing Panels

February 2012 – Ambry Genetics Laboratories

- Introduced Breast Next NGS panels, excluding BRCA 1 & 2
- Panel included 14 genes with reported breast cancer risk
- OvaNext, ColoNext and CancerNext panels followed

July 2013 – Ambry – after SCOTUS ruling

- BRCA 1 & BRCA 2 included in panel

Summer-Fall 2013 to Present

- Other commercial companies began offering NGS panels with BRCA 1 & 2
  - Gene DX
  - University of Washington
  - Quest Laboratories
  - LabCorp – Integrated Genetics
# Inventory of Genetic Testing Companies

- Open access inventory of current Biotechnology companies offering germline testing for inherited syndromes

**BRCA 1/2 (No Panel)**

<table>
<thead>
<tr>
<th>Company / Lab</th>
<th>Myriad Genetics-UT</th>
<th>Ambry Genetics-CA</th>
<th>GeneDX-MD</th>
<th>UW-VWA</th>
<th>DNA Traits-TX</th>
<th>Quest</th>
<th>LabCorp</th>
<th>Invitae</th>
<th>Baylor</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2 COMPLETE</td>
<td>$4,040</td>
<td>$2,200</td>
<td>$2,200</td>
<td>$2,200</td>
<td>$995</td>
<td>$2,495</td>
<td>$2,095</td>
<td>$1,500</td>
<td>$395 (seq only)</td>
</tr>
<tr>
<td>deldup alone</td>
<td>$700</td>
<td>$500</td>
<td>$1,000</td>
<td>$1,000</td>
<td>?</td>
<td>$500</td>
<td>$700</td>
<td>n/a</td>
<td>$1,499 ($395 self-pay)</td>
</tr>
<tr>
<td>AJ3</td>
<td>$575</td>
<td>$500</td>
<td>$450</td>
<td>$450</td>
<td>$70</td>
<td>$550</td>
<td>$600</td>
<td>n/a</td>
<td>$200</td>
</tr>
</tbody>
</table>

**Single Site**
- Yes, 24-mo interest-free payment plan
- Yes. Also, 10% discount if paid in full.

**Financial Assistance?**
- 15% discount for self-pay in paid in full. No charity care.
- Requires pre-payment, no insurance accepted
- Yes, low income, no insurance accepted
- Yes

**Preverification?**
- Yes. Patients notified if out of pocket cost over $375.
- Yes. Patients notified if out of pocket cost over $100.
- Benefit investigation is performed using in-network lab benefits and patients are notified if COO is over $100.
- Yes. Working on becoming an in-network provider.

**TAT**
- <2 weeks
- 2 weeks
- 2 Weeks
- 3 weeks, will soon be reduced to 2
- 2 weeks pre-auth + 2 weeks
- 2 weeks pre-auth + 12-21 days
- 2-3 weeks
- <2 weeks

**Specimen Type(s)**
- Blood or saliva
- Blood or Saliva
- Blood
- Blood or saliva: Prefer for patients to use their buccal cell kits.
- Blood
- Blood
- Blood

**Variant Program**
- Yes - Family Studies Program (free testing to informative relatives)
- Yes - Family Studies Program (free testing to informative relatives)
- Reports VUS rate of ~5% or less.
- unknown
- unknown
- unknown
- Yes - Free testing to informative relatives

**Analytical Sensitivity**
- >99.98%
- >39%
- >99%
- >99%
- tbd
- unknown
- unknown
- >99%

Open access on NSGC website or via link - [http://bit.ly/1kiqfet](http://bit.ly/1kiqfet)

Printed with permission Andrea Forman, MS, LCGC, Fox Chase Cancer Center, Philadelphia, PA
open access NSGC.org website
Genetic Testing Technology Advances

1990’s – Sanger Sequencing – “Gold Standard”
- Costly and time consuming
- May miss large structural changes such as deletions or rearrangements

MLPA – Multiplex Ligation-Dependent Probe Amplification
- Variation of PCR technology
- Accurate and time efficient
- Technique used to detect genomic deletions, insertions

NGS – Next Generation Sequencing
- Massively parallel sequencing (MPS) platforms enabling whole-exome sequencing and whole-genome sequencing
- Efficient and cost effective, screening panels of genes simultaneously, rather than step-wise gene by gene testing
Sanger Sequencing – Identifying gene mutation

Normal sequence

Mutated sequence

New stop codon
MLPA PCR Analysis – detect for deletions
Next Generation Sequencing
Challenges of NGS Panel tests

- Panels include multiple gene targets
  - High risk, high penetrant genes
    - BRCA 1 & 2, CDH1, PTEN, STK11, APC, TP53
  - Moderate risk genes, unknown penetrance genes
    - ATM, CHEK2, PALB2
  - Newer genes, not well studied, no lifetime risk defined
    - BARD1, BRIP1, CDK4, RAD51C, RAD51D

- Counseling challenges
  - How to choose panel test, what criteria to utilize
  - How to counsel and educate patient on potential outcomes of testing

- Likelihood of obtaining Variant of Uncertain Significance
  - BRCA 1 & BRCA 2 VUSs not shared by Myriad since 2006

- Medical Management – No lifetime risks nor guidelines for risk management or surveillance

Stadler, Schrader, Vijai, Robson & Offit, 2014
## Risks and Benefits of NGS Panel testing

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant cost reduction</td>
<td>Difficult to identify the target population for panel testing</td>
</tr>
<tr>
<td>Increased efficiency of gene sequencing</td>
<td>Difficult to define eligibility criteria for panel testing</td>
</tr>
<tr>
<td>Simultaneous testing of multiple gene targets associated with cancer risk</td>
<td>Interpretation of testing results complicated</td>
</tr>
<tr>
<td>Ability to assess genetic risks in those who do not meet the standard high risk criteria</td>
<td>Limited availability of data on the risk associated with moderate penetrant genes and with VUS results</td>
</tr>
<tr>
<td></td>
<td>Unclear how to determine lifetime risks for carriers</td>
</tr>
<tr>
<td></td>
<td>Is a negative result really a negative?</td>
</tr>
<tr>
<td></td>
<td>More likely to find more than one mutation</td>
</tr>
<tr>
<td></td>
<td>No clear clinical management</td>
</tr>
</tbody>
</table>

Continuum of Translational Research in Genomics

Phase I – Transformation of a gene discovery into a practical application – i.e. development of a gene test

Phase II – Assess the genomic application in effort to develop evidence-based guidelines for clinical use
- time intensive and challenging phase
- involves assessment of analytic and clinical validity, clinical utility and ethical, legal and social issues surrounding a genetic test

Phase III – application of evidence-based guidelines into clinical practice
- knowledge dissemination to clinicians
- integration of new practices into existing
- adoption of new technology or clinical practice evidence

Phase IV – assess population level outcomes research

21st Century – Moderate Risk Gene Discoveries

<table>
<thead>
<tr>
<th>Gene</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>2002</td>
</tr>
<tr>
<td>ATM</td>
<td>2006</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2006</td>
</tr>
<tr>
<td>NBS1</td>
<td>2006</td>
</tr>
<tr>
<td>RAD50</td>
<td>2006</td>
</tr>
<tr>
<td>MRE11</td>
<td>2006</td>
</tr>
<tr>
<td>PALB2</td>
<td>2007</td>
</tr>
</tbody>
</table>

Population Frequency and Relative Risk

BRCA 1, BRCA2, TP53, PTEN, CDH1

CHEK2, PALB2, ATM
BRIP1, RAD51

# Cancer Susceptibility Panels

<table>
<thead>
<tr>
<th>Gene</th>
<th>Myriad MyRisk</th>
<th>Ambry Cancer Next</th>
<th>Ambry Breast Next</th>
<th>Ambry Ova Next</th>
<th>Ambry Colo Next</th>
<th>Ambry Panc Next</th>
<th>Ambry Renal Next</th>
<th>Ambry PGL Next</th>
<th>U WASH BROCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>BRCA2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>STK11</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>TP53</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CDH1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PTEN</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>ATM</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PALB2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CHEK2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>BRIP1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>NBN</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>RAD51C</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>RAD51D</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MLH1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MSH2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MSH6</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MUTYH</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PMS2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>APC</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>SMAD4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CDK4</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MRE11A</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>RAD50</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>NF1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ambry Renal Next</th>
<th>Ambry PGL Next</th>
<th>U WASH BROCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHA</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SDHB</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SDHC</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SDHD</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>VHL</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RET</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>FH</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>FLCN</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>MITF</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>TSC1</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>TSC2</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>MAX</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SDHAF2</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>TMEM127</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

1PLUS: AKT1, ATR, BAP1, CHEK1, CTNNA1, FAM175A, GALNT12, GEN1, GREM1, HOXB13, MEN1, PIK3CA, POLD1, POLE, PPM1D, PRSS1, RAD51A, TP53BP1, XRCC2

Courtesy of Kara N. Maxwell, MD, PhD
Penn Medicine
### Multiplex panel testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Ambry Cancer Next</th>
<th>Myriad myRisk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk breast cancer genes</strong></td>
<td>BRCA1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>STK11</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Moderate risk breast cancer genes</strong></td>
<td>ATM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRIP1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CHEK2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NBN</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>RAD50</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Less well understood br/ov cancer genes</strong></td>
<td>BARD1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MRE11A</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAD51C</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>RAD51D</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Colon cancer genes</strong></td>
<td>APC</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BMPR1A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MSH2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MUTYH (AR)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>SMAD4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Genes a/w other cancers</strong></td>
<td>CDK4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- **NCCN guidelines exist for testing and intensive clinical management of breast and other associated cancer risks**
- **Breast cancer risks variably defined (or controversial)**
- **No guidelines for testing or management of carriers**
- **Unclear associated cancer risks**
- **Established risks and guidelines for other cancers**
- **Breast cancer risk unclear**

*Courtesy of Kara N. Maxwell, MD, PhD University of Pennsylvania*
Challenge #1 – Unexpected Testing Discoveries

♦ “Incidental” Findings
  • Discovery of unanticipated deleterious mutations
  • Inherited Cancer Syndrome phenotypes are often incomplete
    – Small families
    – Predominantly male family members
    – Adoptions
    – Lack of family health history information
    – “Atypical” family presentations

♦ Adaptations to Pretest Counseling Approaches
  • Differential Diagnosis – careful review and testing selection
  • Emphasis on obtaining complete family history, attempt to verify cancer diagnoses with pathology reports
  • Pre-test counseling about testing outcomes and preparation for results reporting becomes critical
Unexpected Gene Mutation
Unexpected Discordant Laboratory Results

[Genetic Tree Diagram]

LEGEND
■ Breast cancer
□ Brain cancer
△ Lung cancer
Challenge #2 – Increased risk of VUS results

- Initial outcomes of NGS panel testing indicated double digit VUS rates
  - As more testing is completed and evidence is gathered, the VUS rates will lessen

- International Agency for Research in Cancer (IARC)
  - has developed standard for reclassification of VUS
    - Direct evidence related to:
      - Observation of disease and mutation transmission
      - Co-segregation of the phenotype in families
      - Higher frequency of VUS in cancer cases versus controls
      - Occurrence in families with a strong history of the cancer
      - Lack of co-occurrence with a known pathogenic mutation
    - Indirect evidence related to:
      - Evaluating the structure and function of the gene and protein
      - Evaluating the conservation of the gene across species

Stadler, Schrader, Vijai, Robson & Offit, 2014
## Attempting to estimate prevalence of non-BRCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive Mutation</th>
<th>VUS finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2079 patients tested</td>
<td>Ovarian Panel – 7.2% (16)</td>
<td>VUS – 25.6% (57)</td>
</tr>
<tr>
<td>March 2012-May 2013</td>
<td>Colon Panel – 9.2% (51)</td>
<td>VUS – 15% (84)</td>
</tr>
<tr>
<td>Ambry panels prior to</td>
<td>Cancer Panel – 9.6% (41)</td>
<td>VUS – 23.5% (100)</td>
</tr>
<tr>
<td>BRCA1/2 added</td>
<td>Most common – CHEK2, ATM, PALB2</td>
<td></td>
</tr>
<tr>
<td>Maxwell, et al (2014)</td>
<td>High Risk genes – 2.5% (7)</td>
<td>VUS – 18% (49)</td>
</tr>
<tr>
<td>278 research patients</td>
<td>Moderate Risk Genes - 8.6% (24)</td>
<td></td>
</tr>
<tr>
<td>Previously tested negative for BRCA1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed with BRCA &lt; age 40 at diagnosis</td>
<td>Most common – ATM, CHEK2</td>
<td></td>
</tr>
<tr>
<td>2 cohorts Myriad Labs</td>
<td>NGS nonBRCA – 4.7% (76)</td>
<td>B1/2 VUS – 2.4% (42)</td>
</tr>
<tr>
<td>25 gene Panel test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A – 1781 new tests</td>
<td>Cohort B – NGS nonBRCA – 3.7% (15)</td>
<td>VUS – 39.3% (700)</td>
</tr>
<tr>
<td>25 gene Panel test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B – 377 previously tested neg BRCA1/2</td>
<td>Most common – CHEK2, ATM, PALB2</td>
<td></td>
</tr>
</tbody>
</table>
Reporting of a VUS Result

❖ American College of Medical Genetics and Genomics
  • Categorized nomenclature for labeling genetic variants
  • Guidelines for standardizing information provided on test reports

❖ Variant Tracking programs
  • Biotechnology companies will offer free testing for affected family members to attempt to identify other carriers of the VUS
  • DO NOT offer VUS testing to other family members, especially unaffected family members

❖ Variant Reclassification
  • Biotechnology companies will periodically re-evaluate the evidence on VUS and when possible reclassify VUS as either pathogenic mutation or benign polymorphism
  • Critical for ongoing contact and follow-up with VUS carrier
How should VUS carriers be managed?

- **Risk Management Plan**
  - Should NOT be managed with the same level of intervention, i.e., prophylactic surgery as a known deleterious mutation.
  - Family history of cancers should guide surveillance and prevention recommendations.
  - Base risk assessment on patterns and ages of onset of cancers in the family.
  - Encourage enrollment in Variant Tracking program from testing company.
  - Encourage long-term follow-up, ideally in a clinical research program, to maintain contact with patient and family.
  - Communicate with patient regularly, especially when reclassification notices are received from testing company.

MISSION – to provide open access to patients with VUS or positive mutation in low or moderate penetrant genes in order to better understand these genes.

Patient Crossroads
- Patient portal
- Patients self enroll their de-identified information including genetic testing results

Registration Website
Participants can register and begin participation by visiting www.promptstudy.org
Challenge #2 – Reclassification of VUS

Legend:
- Lung cancer
- Breast cancer
- Ovarian cancer
Challenge #2 – Variant Tracking
NGS Panel – Variant of Uncertain Significance
Challenge #3 – Lack of Evidence for Management

- Moderate penetrance genes
  - 2 fold to 3 fold increase in BRCA risk over general population
  - Can’t precisely estimate the age specific cancer risks, nor the scope of cancers associated with specific gene
  - No evidence on risk-benefit ratio of risk interventions or screening interventions – Chemoprevention, Breast MRI
  - Insufficient evidence to support recommendations of irreversible, invasive interventions such as prophylactic surgery
  - Cannot generalize the management recommendations from guidelines written for high penetrance genes – which have 5 fold – 10 fold increased risk depending on gene
  - “Polygenic” effect implicated by many of the moderate genes because they don’t consistently track with cancer in the family.
  - Can’t answer the question – “is a True Negative really at population risk or are they still at increased risk of cancer?”

Retrospective review of all NGS panels ordered from April 2012 to January 2013

- All testing done on Ambry NGS Panels prior to BRCA ruling
- NGS testing was ordered as a second tier test after negative single-gene testing was performed (90%)

Outcomes: 1,233 single-gene tests – 131 positive mutations (10.6%)

- 60 patients ordered NGS testing
  - 10 patients cancelled due to insurance denying coverage
  - 50 patients completed NGS testing – positive 10% (5)
  - VUSs identified – 30% (15)

Recommendations –

- Data support NCCN recommendations that:
  - NGS panels only be ordered in consultation with a cancer genetic professional
  - NGS panels should be used as a second tier genetic test
- Management should be conservative, based on published literature and knowledge of genetic mechanisms
- Estimate risks of family penetrance by careful review of pedigree

NGS Panel – Moderate Risk Gene Discovery

Paternal Ethnicity: Irish/English No AJ

Maternal Ethnicity: English/Dutch No AJ

d. 80 BRCA78

d. 85 BRCA37

78 Lung CA 66

Victoria, 63 Uterine CA, 57 CHEK2 +

Shelby, 37 BRCA 37 CHEK2 +

Courtney, 34 CHEK2 +

Brittany, 29 CHEK2 -

20 mos

d. 84

d. 75

d. 85

d. 88 CRC, 60

d. 70

d. 75

d. 67

d. 58

d. 62

d. 58

68

62

60

58

58

58

20
What’s a Cancer Genetics Nurse to Do??

❖ **Cancer Genetic Professional Expertise**
  • Lifelong Learning is Critical – Read, Read, Read
  • Ensure proper education and training and make it an ongoing priority – ISONG, ONS, City of Hope
  • Team members need to be committed to developing expertise in Cancer Genetics – rapidly evolving science

❖ **Model of Care Delivery**
  • Implement a structured care delivery model that incorporates thorough pre-test and post-test counseling
  • Informed consent is critical – Medicare requires a signed consent form be submitted with each testing kit

❖ **Management of Patients**
  • Adherence to NCCN guidelines – criteria for testing
  • Annual Follow-up critical – for mutation and VUS carriers
  • Medical Management appropriate for testing outcomes
  • Partner with an academic or research center in the area
Educational Opportunities

BASSER RESEARCH CENTER for BRCA

3rd Annual Scientific Symposium

Recent Advances in Breast and Ovarian Cancer Genetics

Keynote Speaker and Basser Global Prize Awardee: Mary-Claire King, PhD

Monday May 11, 2015
Smilow Center for Translational Research Auditorium/Commons
(enter through Perelman Center for Advanced Medicine)

Tuesday May 12, 2015
Biomedical Research Building

For more information, contact Basserinfo@uphs.upenn.edu or call 215.662.4348.
Our technology advances are progressing at a rapid pace, new genes are being discovered at an accelerated rate. The science required to fully characterize these genes, their penetrance in the population, the associated cancer risks, the phenotype of these syndromes and the appropriate management is just beginning.

“Let us never consider ourselves finished nurses . . . we must be learning all of our lives.”

Florence Nightingale
“You don’t look anything like the long haired, skinny kid I married 25 years ago. I need a DNA sample to make sure it’s still you.”
Catherine M. Belt, MSN, RN, AOCN
Abramson Cancer Center, Philadelphia, PA
Cathy.belt@uphs.upenn.edu
References

- Peterson SK, Rieger PT, Marani SK, deMoor C, Gritz ER (2001) Oncology Nurses’ Knowledge, Practice and Educational needs regarding cancer genetics. American Journal of Medical Genetics, 98: 3-12.
References