INHERITED CANCER RISK -
BRCA Testing and Beyond

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• No Disclosures
The Supreme Court has effectively invalidated the patents held by Myriad Genetics for the BRCA1 and BRCA2 genes. However, is the ruling all bad news for Myriad?

- The Court unanimously ruled that although naturally isolated DNA is not patentable, synthetically created exon-only strands of nucleotides — complementary (c)DNA — is patentable.

**THE FIGHT TO TAKE BACK OUR GENES**

**VICTORY! IN THE SUPREME COURT**

CHALLENGING PATENTS ON BRCA1 & 2 GENES

**Getting Personal: Multigene Testing for Individual Cancer Evaluation**

*Genetic Engineering & Biotechnology News – Dec 23, 2010 -Patricia F Dimond, PhD*
On Dec. 6, 2013, the FDA demanded that 23andMe suspend its health-related genetic testing until the agency could complete its regulatory

The FDA said 23andMe failed to obtain the necessary authorization to promote its kit, which can produce dangerous false positives and negatives.

My Medical Choice

By ANGELINA JOLIE

Published: May 14, 2013

BRCA1+

Her mother died of ovary cancer at 56. Now her maternal aunt, after having double mastectomy dies of metastatic breast cancer

Breast Cancer

- Familial cancer: 15-20%
  - More cases of a specific type(s) of cancer within a family than expected, but no specific pattern of inheritance
  - Age of onset variable
  - May result from chance clustering of sporadic cases
  - May result from common genetic background (low penetrance gene), similar environment and/or lifestyle factors

- Sporadic cancer: 75-85%
  - Typical age of onset (older age)
  - Even if there is more than one case in the family, there is no particular pattern of inheritance
Breast Cancer

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* Sporadic cancer ~ 75-80%
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**Hereditary syndromes associated with breast cancer**

(most common)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Associated cancers/disease characteristics</th>
<th>Inheritance mode</th>
<th>Lifetime breast cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary non-polyposis colon cancer (HNPCC)</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Ovarian, prostate, endometrial, colorectal</td>
<td>AD</td>
<td>Up to 80%</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>TP53</td>
<td>Breast, sarcoma, brain tumors, leukemia, astrocytoma</td>
<td>AD</td>
<td>60%</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
<td>Breast, thyroid, endometrial, mucocutaneous, hamartomatous</td>
<td>AD</td>
<td>25-50%</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer</td>
<td>CDH1</td>
<td>Diffuse gastric cancer, lobular breast cancer</td>
<td>AD</td>
<td>99% (lobular breast cancer)</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11</td>
<td>Breast, pancreas, GI polyps, sex cord tumors</td>
<td>AD</td>
<td>29% (by age 65)</td>
</tr>
</tbody>
</table>

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**Hereditary Breast Cancer Syndrome**

(less common)

- Lynch Syndrome/HNPCC: Increased risk of colon, ovary, endometrial, small bowel, pancreas, urinary tract, kidney, bile duct and rare breast cancer. However the breast cancer risk associated is unknown. **Autosomal Dominant**

- Ataxia-telangiectasia (A-T): Progressive cerebellar ataxia (ages 1-4), ocular telangiectasias, infections, immune defects, risk of maligancy (including breast), skin, parotid gland, gastric, liver and biliary) as well as leukemia and lymphomas. **Autosomal Recessive**

- Bloom Syndrome: Pre and postnatal growth deficiency, spontaneous fat tissue in infancy and early childhood, short stature, erythematous and sun-sensitive facial skin lesion. A variety of cancers including breast, skin, gastrointestinal and genitourinary. **Autosomal Recessive**

- Werner Syndrome: Features associated with normal aging in 20s and by predisposition to cancer including breast cancer, cancers, melanomas, thyroid cancer, and hematology. **Autosomal Recessive**

- Xeroderma Pigmentosum: Characterized by sun sensitivity, ocular involvement, and increased risk of cutaneous neoplasms. A small percent have neurologic manifestations. Both benign and malignant skin conditions are present. Gliomas of the brain and spinal cord, leukemia, tumors of the lung, breast, ovary, stomach, kidney and testicles have been reported. **Autosomal Recessive**
WHO CAN BENEFIT FROM GENETIC COUNSELING?

- Early age onset of breast cancer (BC) ≤ 50
- Triple-negative breast cancer (BRCA1/BRCA2)
- Two or more breast cancer primaries in the individual (synchronous or metachronous)
- BC + one or more of the following cancers: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestation, leukemia/lymphoma, aggressive prostate, and/or macrocephaly, hamartomatous polyps
- BC + 2 or more 1st, 2nd, or 3rd degree relative with BC ≤ 50
- 2 or more 1st, 2nd, or 3rd degree relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
- Male BC
- Ovarian/fallopian tube/primary peritoneal cancer regardless of age

Criteria for referral for genetic risk evaluation -

**Unaffected individual**

- ≥ 2 BC primaries from the same side of the family
- ≥ 1 OC (ovarian cancer) primary from the same side of the family
- BC + one or more of the following cancers: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestation, leukemia/lymphoma, aggressive prostate, and/or macrocephaly, hamartomatous polyps
- Known familial mutation in a breast cancer susceptibility gene
- High-risk population (e.g., Ashkenazi Jewish)
- Male breast cancer
- First or second degree relative with breast cancer at ≤ 45 y
- 2 or more primary breast cancers in one individual

Hereditary syndromes associated with breast cancer (most common)

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<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>Breast (M, F), ovarian, prostate, pancreas, melanoma</td>
<td>AD</td>
<td>Up to 84%</td>
</tr>
<tr>
<td>LI Fraumeni</td>
<td>TP53</td>
<td>Breast, sarcoma, brain tumors, leukemia, adrenocortical tumors</td>
<td>AD</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>PTEN</td>
<td>Breast, thyroid, endometrial, macroadenoma, lipomas, hamartomas</td>
<td>AD</td>
<td>25-60%</td>
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<td>Hereditary diffuse gastric cancer</td>
<td>CDH1</td>
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<td>Breast, pancreas, GI polyps, sex cord tumors</td>
<td>AD</td>
<td>29% (by age 60)</td>
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Multiple laboratories offer BRCA testing

- Comprehensive BRAC Analysis Testing:
  - Full examination of the most common changes of BRCA1 and BRCA2 genes.
  - For people who do not have any known gene mutations in the family.
- Single Site BRAC Analysis:
  - For people who already know a BRCA1 or BRCA2 gene mutation is in the family.
- Multisite BRAC Analysis:
  - Assesses for the three most common BRCA1 and BRCA2 gene mutations in individuals of Ashkenazi Jewish ancestry.
- BRAC Analysis Large Rearrangement Test (BART):
  - There are some much less common gene mutations that can only be found with this test.

Possible test results

- Positive Result
  - Increased Cancer Risk
  - Medical management based on recommendations for people who have the BRCA1 or BRCA2 gene mutations

- Negative Result
  - No Increased Cancer Risk
  - Medical management based on general population cancer screening recommendations

- Uncertain Variant
  - Cancer Risk Not Fully Defined
  - Medical management based on personal and family history of cancer

[Diagram of family tree with BRCA1 and BRCA2 gene statuses]
Li-Fraumeni Syndrome

- Initially described by Frederick Li and Joseph Fraumeni as syndrome associated with sarcomas and other diverse tumors.
- Associated cancer include:
  - soft-tissue sarcoma,
  - osteosarcoma,
  - early-onset breast cancer,
  - brain tumors,
  - adrenocortical carcinoma,
  - and leukemias, primarily acute leukemia.
- Inherited in an autosomal dominant manner.
- Gene mutations: TP53 (tumor suppressor gene)
Cowden syndrome

- An autosomal dominantly inherited hamartoma syndrome with an incidence of at least 1/200,000 (probably an underestimate)
- Pathognomonic cutaneous feature is the trichilemmoma, a benign tumor derived from outer-root sheath epithelium of a hair follicle
- Variable expression
- Associated with inherited alterations in the gene, PTEN gene (Tumor suppressor)

Cancer Risks Associated with Cowden Syndrome:

- Female Breast Cancer: 25%-50% lifetime risk (vs ~11% in general pop.)
- Average age of diagnosis may be around age 38-46
- Thyroid Carcinoma: 3%-10% lifetime risk (vs 1% in general population)
  - Non-medullary
- Endometrial Cancer: 5-10%

Cowden syndrome - Mucocutaneous features

(A) Acral keratotic lesions of the foot (case 1).
(B) Acral keratotic lesions of the dorsal aspect of hands (case 1).
(C) Papillomas on hypertrophic genital mucosa (case 3).
(D) Pekkala papules of the nose (case 4).

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Hereditary Diffuse Gastric Cancer (HDGC)

*CDH1* gene – only gene known to be associated w/ HDGC; however accounts for only 1/3 of hereditary diffuse gastric cancers a poorly differentiated adenocarcinoma that infiltrates into the stomach wall causing thickening of the wall (limits plastica) without forming a distinct mass.

Diffuse gastric cancer is also referred to as signet ring carcinoma or isolated cell-type carcinoma.

*CDH1* mutations confer:

- Increased risk for diffuse gastric cancer
  - 67% lifetime risk for men
  - 83% lifetime risk for women
- Increased risk for lobular breast cancer (39% lifetime risk)
- Majority of cancers diagnosed before age 40

Peutz-Jeghers Syndrome

**Clinical Features**

- Benign growths (polyps) in small intestine (stomach/bowel)
- Abdominal pain and internal bleeding
- Breast, testicular, pancreatic cancers
- Dark-brown or dark-blue spots on lips, gums, inside mouth, around mouth, eyes, nostrils (mucocutaneous macules)
• Beyond BRCA and the “actionable” (less common) hereditary breast cancer syndromes . . .

. . . What’s next??

BRCA/BART neg – now what?

Moderate Penetration Breast Cancer Genes

“Mutations in CHEK2, ATM, NBS1, RAD50, BRIP1, and PALB2 are associated with doubling of breast cancer risks”

Walsh et al. Cancer Cell 2007
Next-Gen Cancer Panels

**Next Generation sequencing:**
a high-throughput sequencing method that parallelize the sequencing process, producing thousands or millions of sequences at once.

Multiple Breast Cancer Susceptibility Genes

<table>
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<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Associated Cancer Risk Other Assosiated Cancer</th>
</tr>
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<tbody>
<tr>
<td>BARD1</td>
<td>HBOC Increased Ovarian</td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>HBOC Increased Ovarian</td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>HBOC Increased Ovarian</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>HBOC 25-35% Ovarian</td>
<td></td>
</tr>
<tr>
<td>RAD50</td>
<td>HBOC 25-48% Ovarian</td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>HBOC Increased Ovarian</td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia Telectangasia ~25-60% Increased</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>Hereditary Breast and Pancreatic ~25-40% Breast, Pancreas</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jegher 30% Colon, Pancreas</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>Hereditary Breast and Colon ~25% Ovarian</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden 25-50% Thyroid, endometrial, renal</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni 50% Sarcoma, brain, adrenocortical, leukemia</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary Diffuse Gastric Cancer 39-52% Gastric, Colon</td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>MUTYH-Associated Polyposis 20-25% Colon</td>
<td></td>
</tr>
</tbody>
</table>

**BREAST CANCER PANEL TEST**

- **AKT1, APC, ATM, ATM, BAP1, BARD1, BMPR1A, BRCAL, BRC2, BRIP1, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, CTNNB1 (Aracn), GAIN2, GEN1, GEM, HOXB13, MEN1, MLH1, MRE11A, MSH2 (+EPCAM), MSH6, MTHYH, NBN, PALB2, PIK3CA, PPM1D, PMS2, POLD1, POLE, PRSS1, PTEN, RAD50, RAD51, RAD51C, RAD51D, RET, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TP53BP1, VHL, and XRCC2**
BRCAplus: BRCA, BRCA2, CDH1, PTEN, TP53, STK11

A NGS panel of 6 clinically actionable genes implicated in hereditary breast cancer. Established NCCN guideline for cancer management exist for all 6 BRCAplus genes.

BRCA1/2 analysis with reflex to BRCAplus
What do we know about BARD1?

- **BARD1** (BRCA-associated RING domain) interacts with the N-terminal region of BRCA1 and is involved in DNA replication checkpoint response.

- Mutations in this gene confer an *increase in breast cancer risk*, and mutations have been reported in *at least 1 person with a history of ovarian cancer* to date.

- BARD1 mutation carriers may be sensitive to specific chemotherapy agents and thus benefit from therapies suggested for BRCA1 and BRCA2 such as poly polymerase inhibitors (PARP inhibitors).
BRCA/BART neg – now what?

PROBAND • Concerned about her breast cancer risk and risk for children/family members • BRCA/BART neg • OvaNext RAD51D Testing pursued

GENETIC WORK-UP

✓ OvaNext Multi-Gene Panel test ordered through Ambry labs: ATM, BARD1, BRCA1/2, MLH1, MSH2, MSH6, PMS2, Epcam, MUTYH, CDH1, PTEN, BRIP1, RAD51C, RAD50, TP53, CHEK2, PALB2, STK11 and MRE11A.

✓ Rad51D testing ordered as an adjunct to panel.

✓ Proband positive for the deleterious Rad51D mutation p.R232X.
What do we know about RAD51D?

- **RAD51D** gene has an active role in DNA repair through a mechanism referred to as homologous recombination along with other genes (**BRCA1, BRCA2, ATM, BRIP1, CHEK2, PALB2, RAD50 and RAD51C**).

- **RAD51D** germline mutations in particular confer an increased susceptibility for breast and ovarian cancer. Relative cancer risk is estimated at 1.32 and 6.3 respectively. This translates to nearly a 10% lifetime risk for ovarian cancer.

- **RAD51D** mutation carriers may be sensitive to specific chemotherapy agents and thus benefit from therapies suggested for **BRCA1** and **BRCA2** carriers as well. These include poly polymerase inhibitors, or PARP, inhibitors.
What do we know about NBN?

- The NBN protein is a member of the MRE11A/RAD50 double-strand break repair complex which consists of 5 proteins. This gene product is thought to be involved in DNA double-strand break repair and DNA damage-induced checkpoint activation, as part of the MRE11A/RAD50/NBN (MRN) complex.
- Because these functions are critical for preventing the formation of cancerous tumors, NBN is described as a tumor suppressor gene.
- Mutations in this gene are associated with Nijmegen breakage syndrome, breast cancer, and other cancers, including prostate, ovarian, and skin cancer.

PROBAND
- Concerned about her breast cancer risk and risk for children/family members
- BRCA/BART neg
  - RAD51D pos - p.R232X
  - OvaNext test result: NBN pos – p.Q492