GENETIC TESTING FOR BREAST CANCER RISK

TAKE-HOME MESSAGES:
1) TEST MORE INDIVIDUALS
2) USE EXPANDED PANEL
3) VUS (VARIANT OF UNCERTAIN SIGNIFICANCE) - NO CAUSE FOR ALARM.
BRCA+ carriers identified & informed:

- Over 220,000* Unaffected carriers (U.S.): 5-6% identified and informed
- Over 35,000 Breast Cancer patients have deleterious BRCA mutations: 30% identified and informed

A Positive Test for a Known Family Mutation

• Directs Appropriate Resource Utilization
  o “High Risk” Surveillance (MRI, WBUS...)
  o Chemoprevention
  o Preventative surgery
    ✤ BSO (mastectomy in selected cases)
• about Targeting Resources (Not mastectomy)

Negative Test with Known Familial Mutation

- Ordinary Population-level Risk*
  - (Previously controversial)

- Stop wasting resources, reduce distress
  - Ordinary screening vs “high risk” screening
    - Corrects the biopsy threshold
    - Ordinary screening vs fear-based mastectomies

Pathogenic/Deleterious Mutations

- Thousands of BRCA mutations with *unambiguous severe effects* on cancer risk identified.
  - Nearly all *truncate or delete* their host gene.
  - *In addition*: About a dozen amino acid substitutions proven to cause loss of BRCA function.
    - Great majority of AA substitutions: **benign**
IS THERE A BRCA 3?

HIGH RISK FAMILIES WHO TESTED NEGATIVE FOR BRCA 1 & 2

WITH RAPID "NEXT GENERATION" SEQUENCING OF DNA, IT TURNS OUT THERE ARE MANY POTENTIAL MUTATIONS THAT ARE RESPONSIBLE.

SIGNAL TRANSDUCTION PATHWAYS
Most breast cancer-related genes are:

**DNA repair genes**

![Diagram of DNA repair genes]

- RAD51
- BRCA2
- PALB2
- CHEK2
- ATM
- BRCA1
- MRG15

DSB (DNA double-strand break)

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Pathogenic Mutations in Panel testing: Almost 50% “other than” BRCA Genes

![Pie chart showing relative distribution of variants detected with NGS in 708 HBOC](image)

Figure 1 Relative distribution of variants detected with NGS in 708 HBOC

## Genetic Variant Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Probability Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Likely Pathogenic</td>
<td>95-99%</td>
</tr>
<tr>
<td>VUS</td>
<td>5 - &lt;95%</td>
</tr>
<tr>
<td>Likely Not Pathogenic</td>
<td>1- &lt;5%</td>
</tr>
<tr>
<td>Not Pathogenic</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Average healthy person:**

- about 10 million SNPs (single nucleotide polymorphisms)
VUS – VARIANT OF UNCERTAIN SIGNIFICANCE

- HIGHLY UNLIKELY TO INCREASE CANCER RISK
- IT’S LIKE A DIFFERENT SPELLING OF A WORD.
- IN THIS COUNTRY WE SPELL THE WORD “COLOR” DIFFERENTLY FROM BRITAIN, WHERE THEY SPELL IT “COLOUR”
- IT’S STILL THE SAME WORD WITH THE SAME SOUND AND THE SAME MEANING. IN SIMILAR FASHION, A VUS STILL PRODUCES THE SAME PROTEIN WITH THE SAME FUNCTION
Most breast cancer-related genes are: DNA repair genes

BRCA1, RAD51, BRCA2, CHEK2, ATM, PALB2, MRG15

WHO SHOULD BE TESTED?

- NCCN – NATIONAL COMPREHENSIVE CANCER NETWORK – ONLINE GUIDELINES UPDATED REGULARLY – A NETWORK OF CANCER CENTERS
WHO SHOULD BE TESTED?

WOMEN WITH BREAST CANCER & "RED FLAG"

- <=45Y AT DIAGNOSIS

- <=50Y AT DIAGNOSIS PLUS: a) 2\textsuperscript{ND} PRIMARY BREAST CANCER, b) RELATIVE WITH BREAST, PANCREATIC, OR PROSTATE CANCER

- <=60 AT DIAGNOSIS, WITH TRIPLE NEGATIVE BREAST CANCER

- ANY AGE AT DIAGNOSIS PLUS: a) ONE CLOSE RELATIVE WITH BREAST CA <50 OR OVARIAN CANCER OR MALE BREAST CANCER b) TWO CLOSE RELATIVES WITH BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER.
WHO SHOULD BE TESTED?
THOSE WITH OTHER CANCERS

- INDIVIDUAL WITH **OVARIAN** CANCER OR **MALE BREAST** CANCER
- INDIVIDUAL WITH HIGH-RISK **PROSTATE** CANCER AND CLOSE FH OF BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER
- INDIVIDUAL WITH **PANCREATIC** CANCER AND CLOSE FH OF BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER
- INDIVIDUAL WITH **PANCREATIC** CANCER AND ASHKENAZI JEWISH ANCESTRY
WHO SHOULD BE TESTED?
CANCER-FREE BUT WORRISOME FAMILY:

- INDIVIDUAL FROM A FAMILY WITH A KNOWN BRCA MUTATION
- FIRST-DEGREE OR SECOND-DEGREE RELATIVE MEETING ANY OF THE CRITERIA ON PREVIOUS SLIDE
- THIRD-DEGREE RELATIVE WITH BREAST +/- OR OVARIAN CANCER AND 2 CLOSE RELATIVES WITH BREAST OR OVARIAN CANCER
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