Beyond BRCA

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Hereditary cancer:

Sporadic: not common, distant relation, older ages, etc (acquired/somatic mutations)

Familial: clustered in families, possibly hereditary or environmental, proximity, etc

Hereditary: pattern of cancers in a family suggesting inherited gene mutation eg. FDRs, earlier ages, multiplicity and bilaterality, etc (germline mutation)
Lifetime cancer risks

Chart Title

- high risk
- moderate risk
- familial
- gen population

Series 3  Series 2  Series 1
Variant (mutation) is an alteration: insertion, deletion, inversion, duplication, etc of multiple contiguous nucleotides. Some are pathogenic.
Germline and Somatic
Example of BRCA

Autosomal Dominant Inheritance

Legend
- B: BRCA gene with mutation
- b: normal BRCA gene
- Equally transmitted by men and women

Normal BRCA genes: bb
BRCA mutation: Bb

Susceptible BRCA gene
Population Risk
Inheritance

Great-Great-Great-Grandparents

Great-Great-Grandparents

7–22%

Great-Grandparents

Great-Aunt or Uncle

4–31%

First Cousin twice removed

1–8%

Grandmother or Grandfather

17–34%

Mother or Father

Amount of shared DNA:

49–55%

Aunt or Uncle

20–32%

First Cousin once removed

2–13%

Second Cousin once removed

0–5%

Sibling

33–50%

SELF

(100%)

First Cousin

8–18%

Second Cousin

1–8%

Third Cousin

0–3%

Niece or Nephew

20–32%

Child

49–55%

First Cousin once removed

2–13%

Second Cousin once removed

0–5%

Third Cousin once removed

0–3%

Great-Niece or Nephew

4–31%

Grandchild

17–34%

First Cousin twice removed

1–8%

Second Cousin twice removed

0–4%

Third Cousin twice removed

0–2%
High vs Moderate Risk cancer genes
Definitions and impact on management.

- **High risk**- generally HIGH phenotypic expression of a mutation. If mutation is autosomal dominant, is said to show complete penetrance if clinical symptoms are present in ALL individuals who have the disease-causing mutation. BRCA1 displays high, although incomplete, penetrance, as breast cancer is ‘only’ expressed about 40-80% of carriers of a mutation. There are generally established guidelines for cancer screening and management, and demonstration of pathogenic germline mutation alone is sufficient.

- **Moderate risk**- lower phenotypic expression in a given population of those with (genotypic) mutation. Incomplete co-segregation with cancer phenotype (ie not 1:1 single mutation, more likely polygenic). Much larger populations required to determine if a mutation (variant) is pathogenic. Guidelines may exist, but clinical recommendations are more dependent on family history and other factors, in addition to presence of germline mutation.
Breast Cancer, specifically:
Red flags for hereditary breast cancer:

1. Multiple cancers of same or clustered types (e.g., ovarian and prostate or breast, uterine, thyroid, etc) on one side of family

2. Early age onset, bilaterality and/or multicentricity

3. Rare cancers e.g. Male breast cancer, diffuse gastric cancer, etc

4. Increased risk in defined populations (e.g., Ashkenazi Jewish)

5. Triple negative BC
Positive genetic mutation(s) on testing? Some guidance

High risk gene:
- High risk for specific cancers
- May have increased risks of other cancers
- Recommendations based on identified mutation, established guidelines (e.g., NCCN, ASCO)
- Family members should be counseled and tested, ideally

Moderate risk or new:
- Moderately increased risk for certain cancers
- If newly described, defined level of cancer risk may still be evolving
- Clinical recommendations will more heavily rely on results combined with family history (or polygenic risk scores-new)
- Counseling and consideration for testing
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**MUTYH:** assoc with MAP and increased BC risk in north African jews with G396D variant. **STK11:** P-J hamartomatous polyps, freckles, etc.
**RAD51**: protein interacts with many other proteins, including BRCA1 and BRCA2, to fix damaged DNA.

**BRIP**: The protein encoded by this gene interacts normal double-strand break repair function of breast cancer, type 1 (BRCA1)

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BARD1: BRCA associated Ring Domain. Highly conserved (thus important). The BARD1/BRCA1 interaction is disrupted by tumorigenic amino acid substitutions in BRCA1, implying that the formation of a stable complex between these proteins may be an essential aspect of BRCA1 tumor suppression.
BRCA and Other Genes associated with breast cancer risk

Mutations (pathogenic variants)
- BRCA 1 and 2 (HBOC) RR 7.0
- TP53 (L-FS) RR 5.0 (breast most common)
- PALB2 RR 3.0-5.0
- PTEN (Cowden) RR 3.0-4.5
- CDH1 (hrdtry gastric) RR 3.0-4.0
- ATM RR 2.0-4.0
- CHEK2 RR 1.5-2.0 (L-FS)
- Others (eg STK11/ P-J)

Non-breast cancer risks (variable)
- ovary, panc, pros, mel etc
- sarcomas,adrenocortical,brain, etc
- Pancreas, male breast
- Thyroid, uterine, kidney, colorectal
- Lobular phenotype, diffuse gastric
- Pancreas, prostate
- Colorectal, prostate, other
- Colorectal, panc, stomach, ovary, etc
What about Negative genetic test results?
Proceed with caution

- MAJORITY of patients!
- Cancer risks may still be elevated, but will rely on risk analysis (eg assessment of family history, personal exposures, etc)
- Know what test was used, when it was used, and what was not tested
- Some mutations have yet to be identified
- VUS-special cases, mutation may ultimately prove neg or pos pathogenicity
- Combinations of SNPs? (very early data! Genome-Wide Association Studies (GWASs) have identified numerous single-nucleotide polymorphisms (SNPs) associated that may modify risk based on altering other gene expression)
In summary:

- Recent research indicates that a large proportion of mutations that confer breast cancer risk are NOT BRCA 1 and 2.
- These nonBRCA genes ALSO confer increased risk for additional cancers for which patients and families should be screened/advised.
- Some genes are associated with high risk of cancer, others with moderate risk, and multiple factors must be taken into account when managing; guidelines are rapidly evolving.
- More and more complex gene interactions that modify gene expression and, ultimately, impact risk are being reported on almost daily.
- The majority (80-90%) of those identified as ‘high risk’ due to personal and family cancer history or other red flags, will have ‘negative’ genetic testing.