Beyond BRCA

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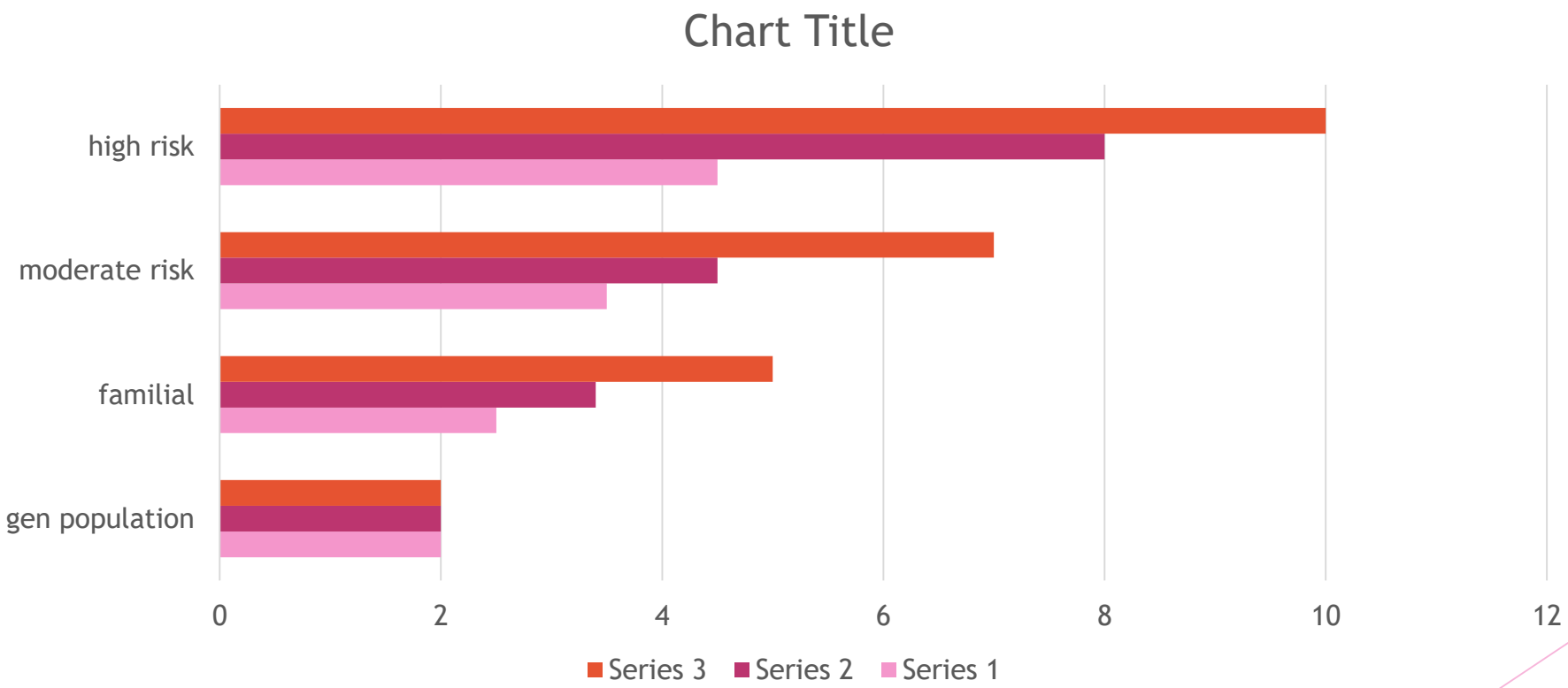
Hereditary cancer:

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

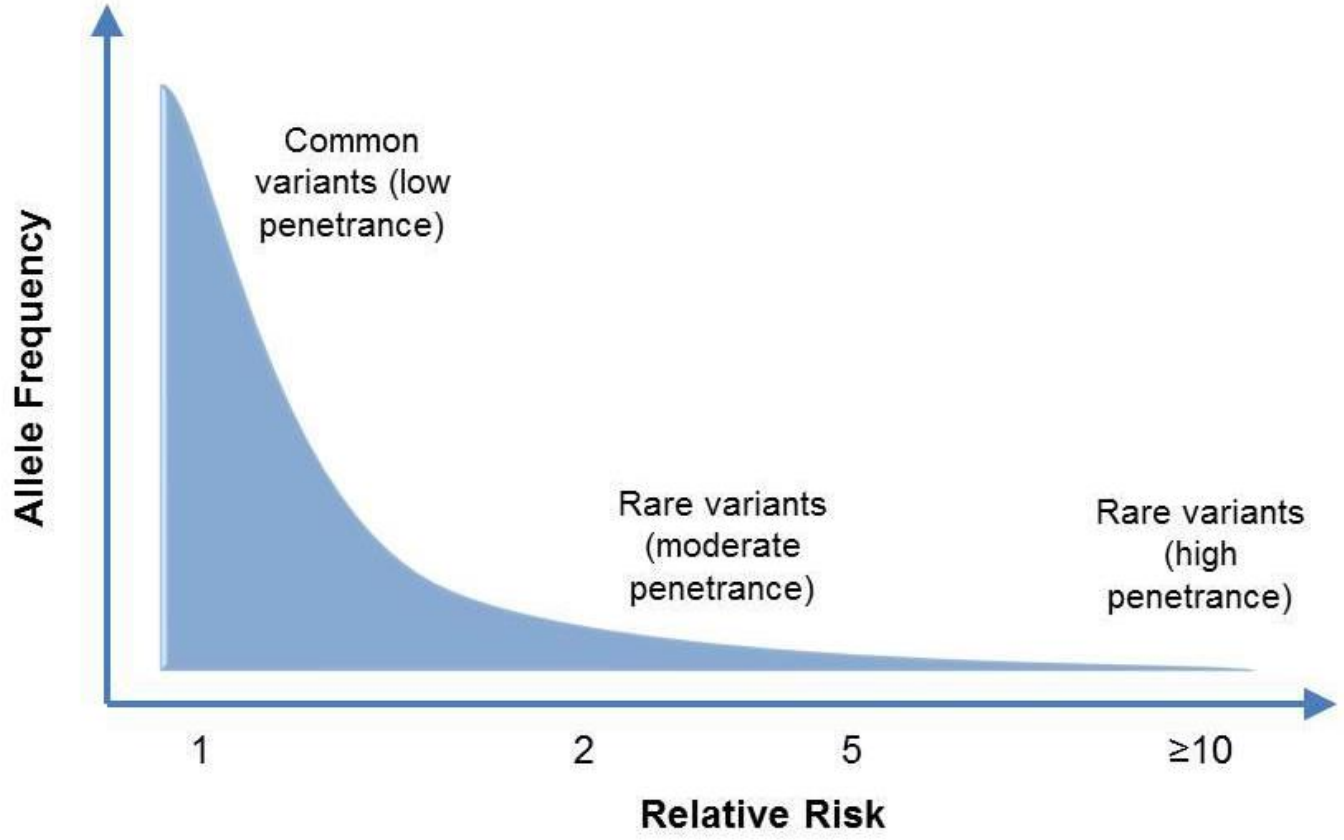
Familial: clustered in families, possibly hereditary or environmental, proximity, etc

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

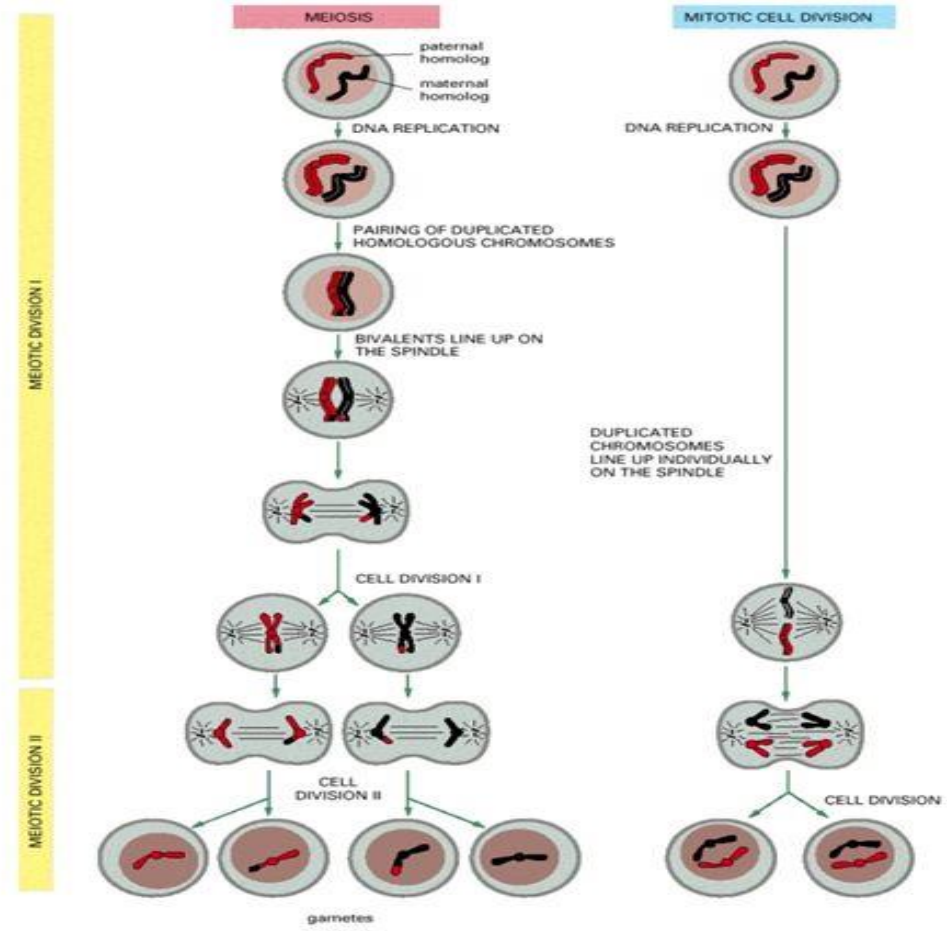
Lifetime cancer risks



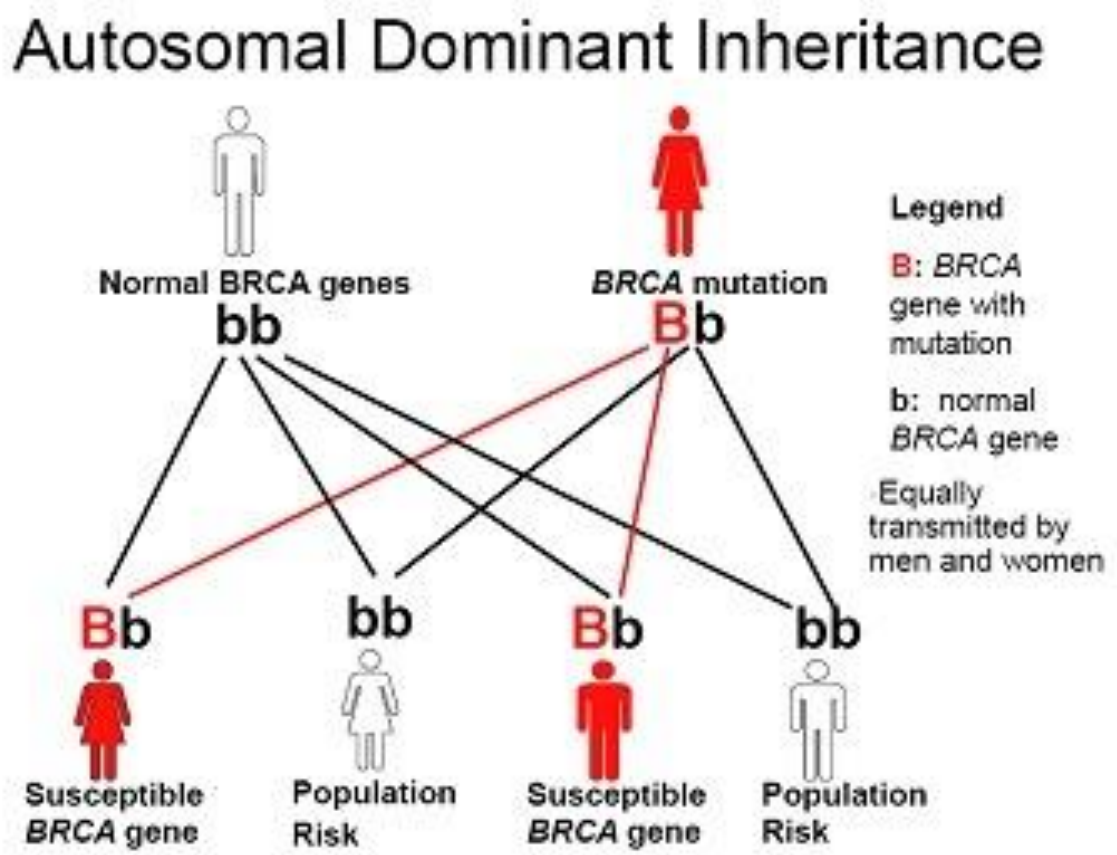
Variant (mutation) is an alteration: insertion, deletion, inversion, duplication, etc of multiple contiguous nucleotides. Some are pathogenic.



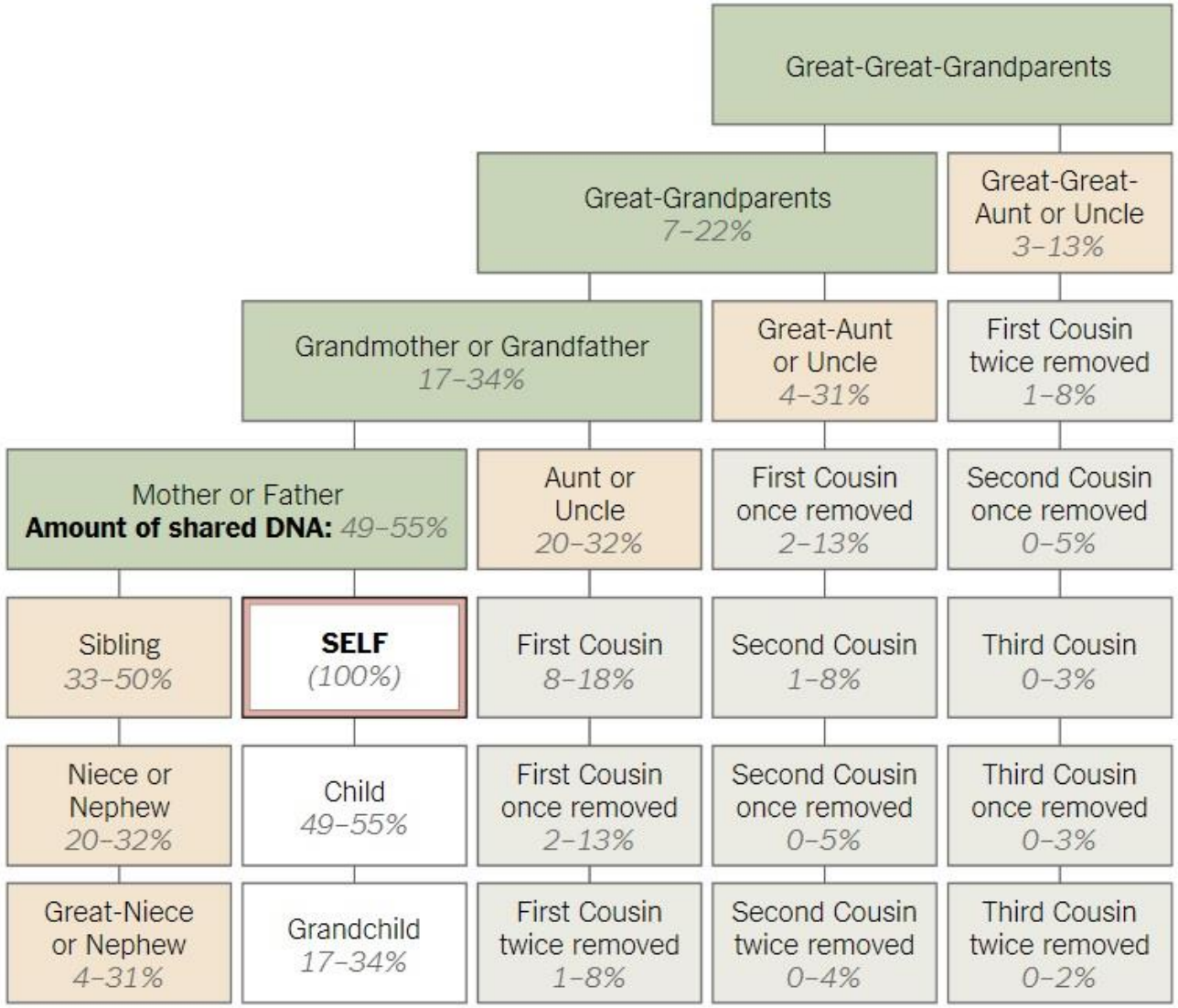
Germline and Somatic



Example of BRCA



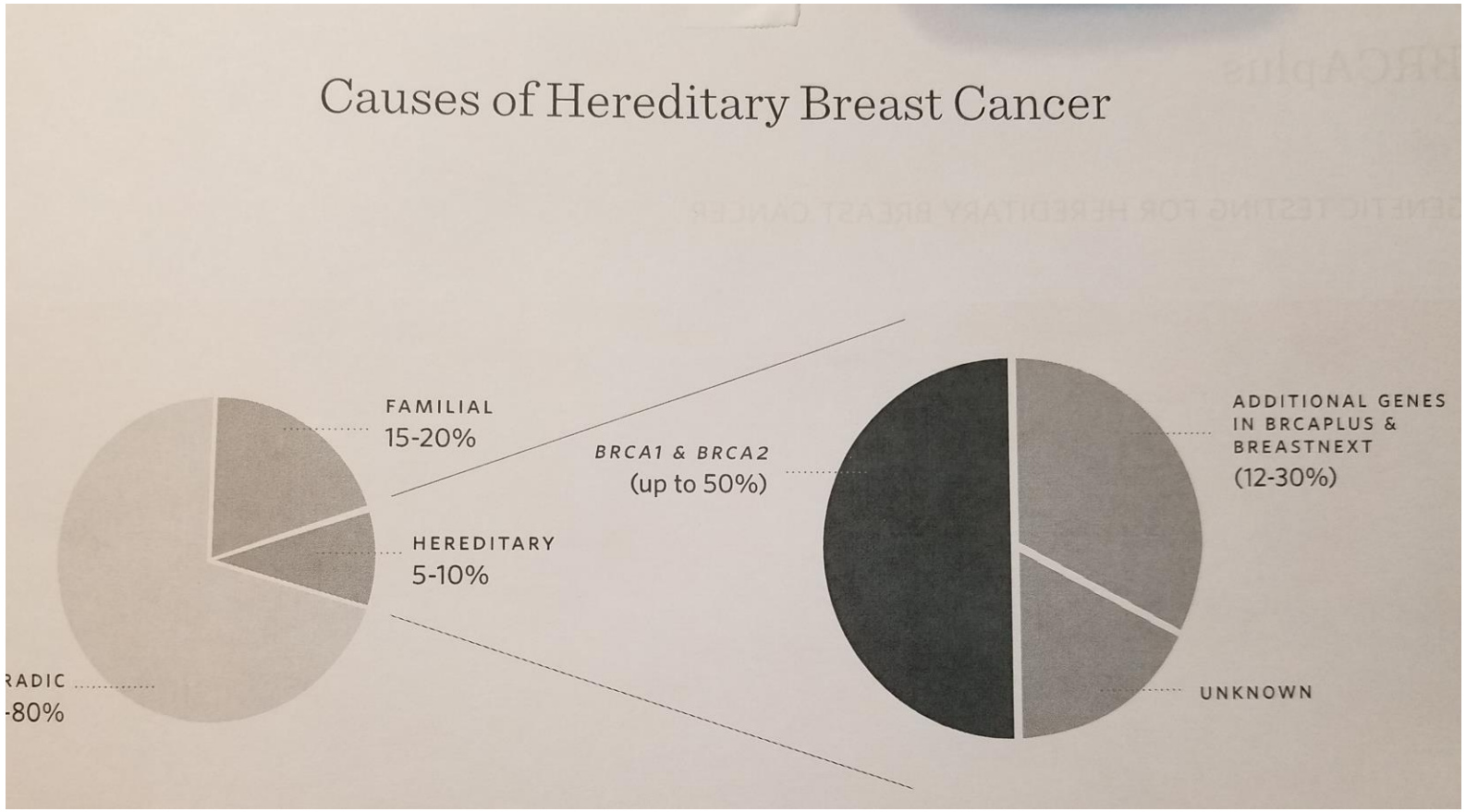
Inheritance (nyt.com ©)



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 (eg. ovarian and prostate or breast, uterine, thyroid, etc) on one side of family

2. Early age onset, bilaterality and/or multicentricity

3. Rare cancers eg. Male breast cancer, diffuse gastric cancer, etc

4. Increased risk in defined populations (eg 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 (eg 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

CancerNext: High Risk Genes and Associated Cancers

GENES	BREAST	OVARIAN	COLORECTAL	UTERINE	PANCREATIC	PROSTATE	STOMACH	MELANOMA	OTHERS
APC			✓		✓				✓
BMPR1A			✓				✓		
BRCA1	✓	✓			✓	✓			✓
BRCA2	✓	✓			✓	✓		✓	✓
CDH1	✓						✓		✓
CDKN2A					✓			✓	✓
CDK4								✓	✓
EPCAM		✓	✓	✓	✓	✓	✓		✓
MLH1		✓	✓	✓	✓	✓	✓		✓
MSH2		✓	✓	✓	✓	✓	✓		✓
MSH6		✓	✓	✓	✓	✓	✓		✓
MUTYH biallelic	✓		✓	✓					
PMS2		✓	✓	✓	✓	✓	✓		✓
PTEN	✓		✓	✓				✓	✓
SMAD4			✓				✓		
STK11	✓	✓	✓		✓				✓
TP53	✓	✓	✓	✓	✓	✓	✓	✓	✓

MUTYH: assoc with MAP and increased BC risk in north African jews with G396D variant. STK11: P-J hamartomatous polyps, freckles, etc

CancerNext: Moderate Risk Genes and Associated Cancers

GENES	BREAST	OVARIAN	COLORECTAL	UTERINE	PANCREATIC	PROSTATE	STOMACH	MELANOMA	OTHERS
ATM	✓				✓	✓			
BRIP1	✓	✓							
CHEK2	✓	✓	✓			✓			✓
GREM1			✓						
NF1	✓								✓
PALB2	✓	✓			✓	✓			
POLD1			✓						
POLE			✓						
RAD51C	✓	✓							
RAD51D	✓	✓				✓			
TP53	✓	✓	✓		✓	✓	✓	✓	✓

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)

- *BRIP1*, *RAD51C*, and *TP53* were associated with moderate risk (OR >2.0) of TNBC
  - *RAD51C* was associated with a high risk (OR >5.0) of TNBC among African Americans, but only a moderate risk (OR >2.0) among Caucasians

Gene-Specific Risks of TNBC Among Caucasian Women

TNBC associated genes	Ambry TNBC Cohort		TNBCC TNBC Cohort	
	OR	p-value	OR	p-value
BARD1	5.92	2.20×10^{-9}	4.35	7.60×10^{-4}
BRCA1	16.27	$<2.2 \times 10^{-16}$	26.90	$<2.2 \times 10^{-16}$
BRCA2	5.42	$<2.2 \times 10^{-16}$	6.33	$<2.2 \times 10^{-16}$
BRIP1	2.28	5.55×10^{-3}	2.46	0.02
MSH6	2.38	0.04	2.07	0.39
NF1	2.13	0.05	N/A	N/A
PALB2	14.41	$<2.2 \times 10^{-16}$	7.63	7.05×10^{-9}
*RAD51C**	2.64	3.09×10^{-3}	2.88	0.01
*RAD51D***	6.97	3.10×10^{-4}	11.62	3.23×10^{-5}
TP53	2.75	0.02	1.49	0.65
TP53<=40y	8.49	2.19×10^{-4}	5.92	0.05

* *RAD51C was associated with a higher risk of TNBC among African American women*

** *Novel association identified between RAD51D and TNBC risk*

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.