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Precision Medicine and Genetic Counseling : Is Yes always the correct answer?

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Angelina Jolie: A Case Study

- 2013: actress, filmmaker, and human rights activist **Angelina Jolie** made headlines - she had undergone a preventative double mastectomy.
- Why? A family history of breast cancer (her mother had died of it) due to what she called a “faulty gene - BRCA1”

https://thetruthaboutcancer.com/angelina-jolie-brca-gene/

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Family History?

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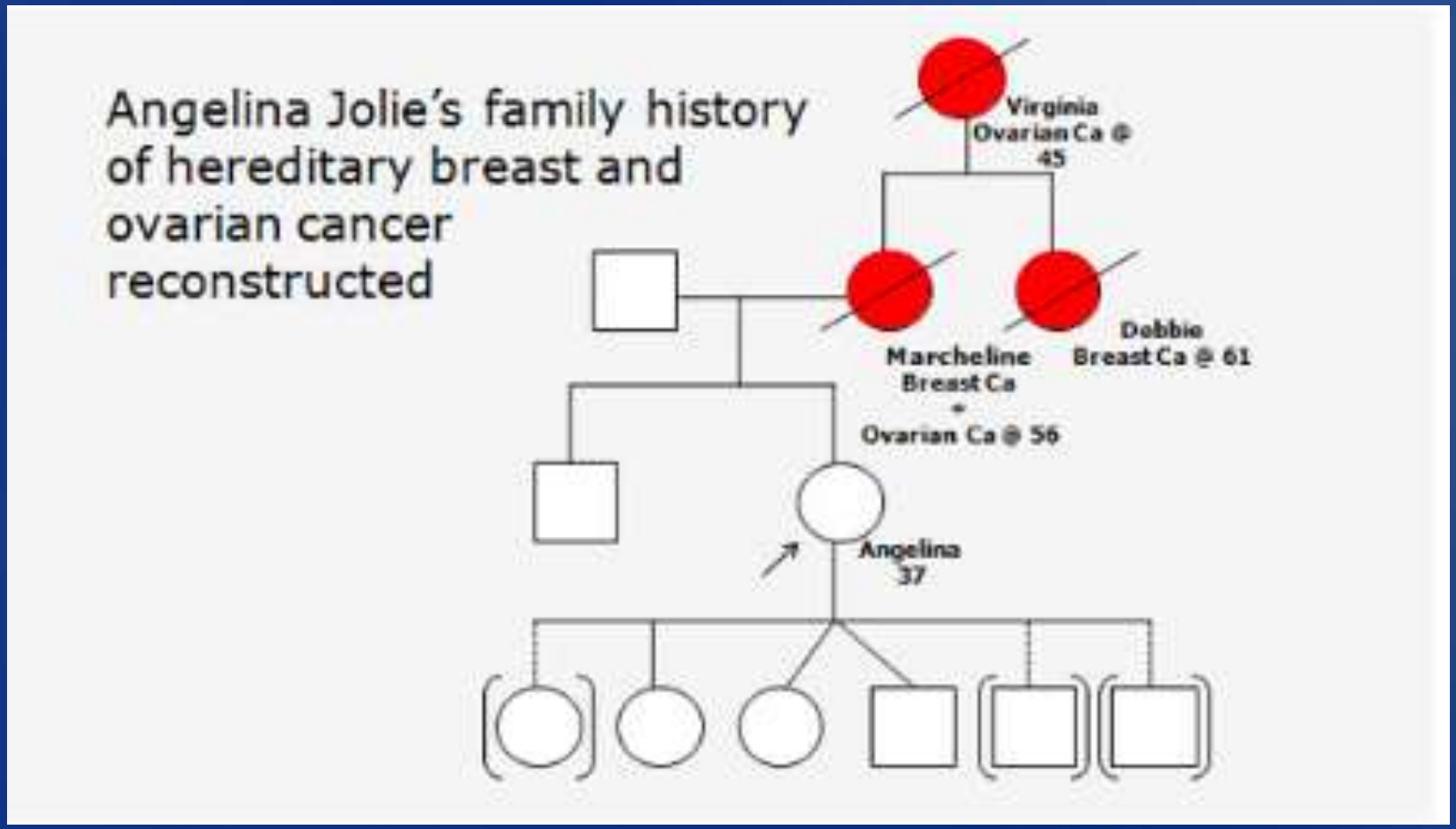
Family History….



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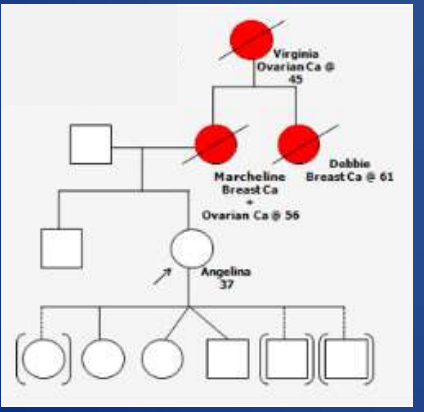
Family History - Deconstructed

- Why is she at risk?
- What is she at risk for?
- What is the value of knowing her risk?
- Who else is at risk?
- How can these risks be managed?



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Optimizing Clinical Utility

- Right Person
- Right Test
- Right Time

- Right Interpretation

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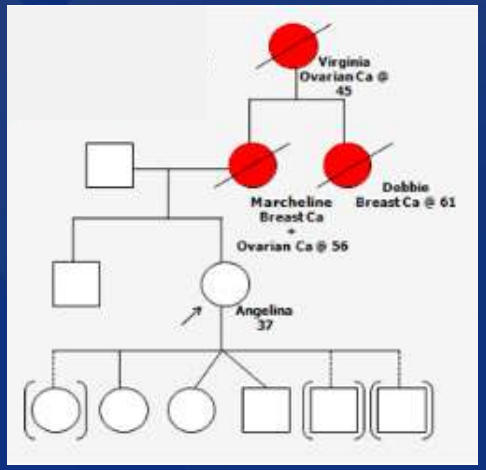
Why was Angelina at Risk?

Is It All in Our Genes?



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What is BRCA1?

- In 1990, Dr. King was the first to demonstrate that a single gene on chromosome 17q21 (which she named BRCA1) was responsible for breast and ovarian cancer in many families.
- Inheritance? Autosomal dominant
  - Each 1st degree relative at 50% risk


Mary-Claire King, PhD

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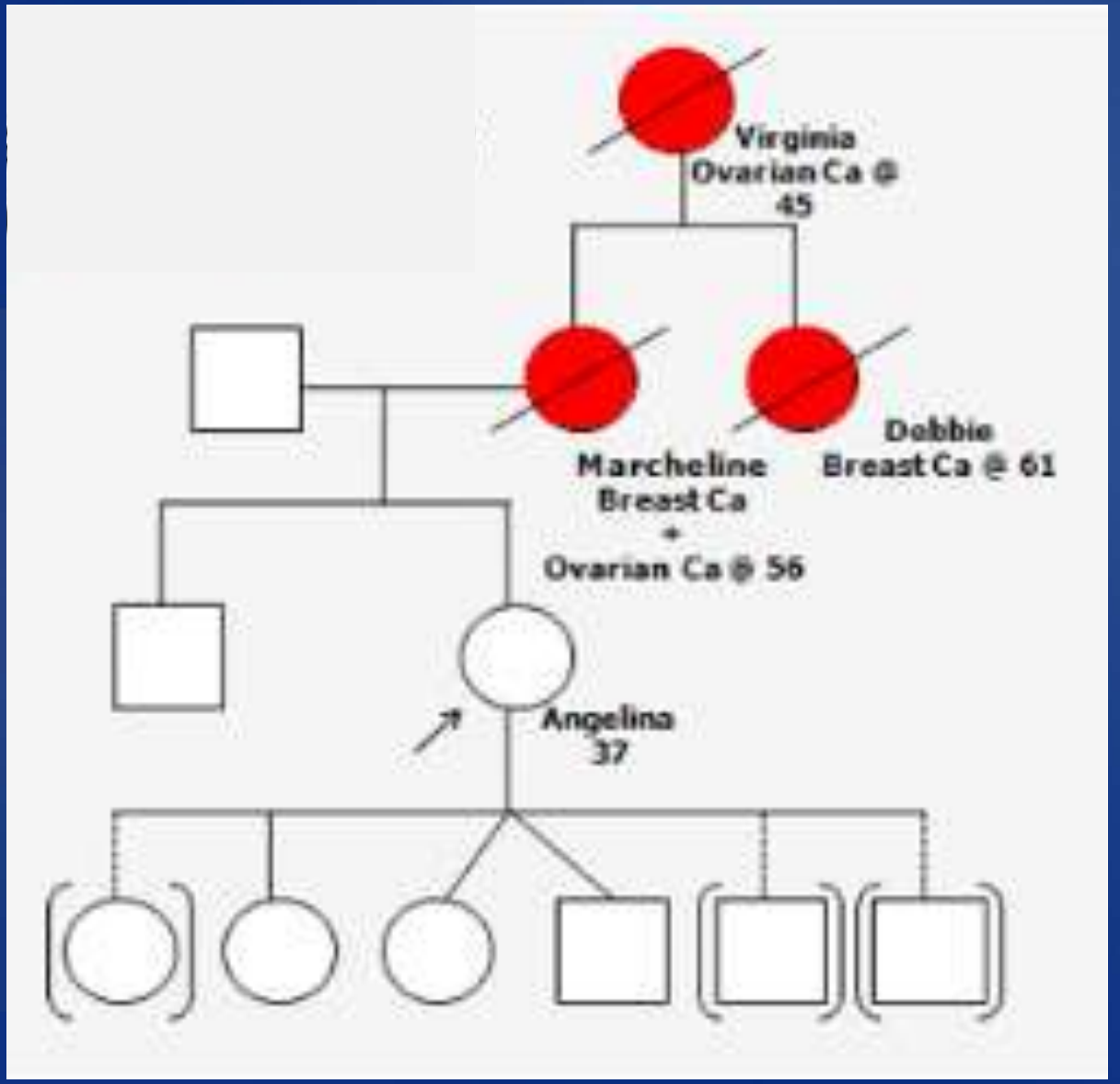

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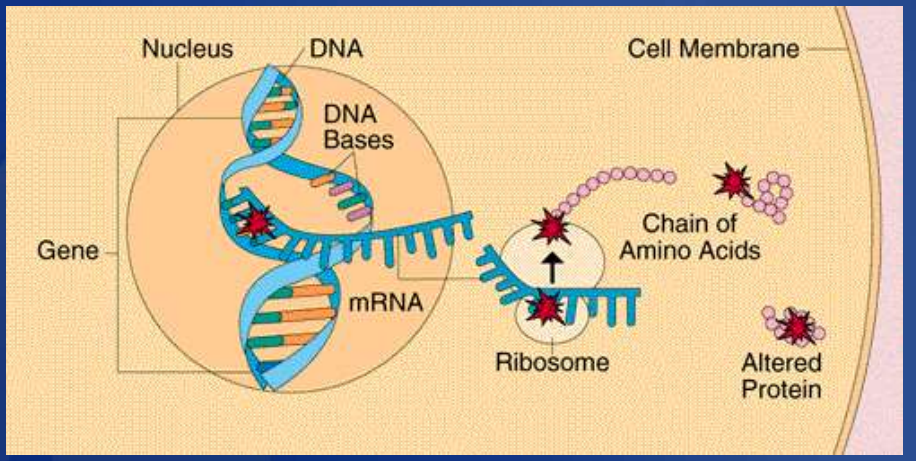
What is a Genetic Test?

Translation of Genetic Information

DNA→ RNA →Protein



Genetic testing is the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration (or alterations) that is likely to be associated with a genetic disorder.

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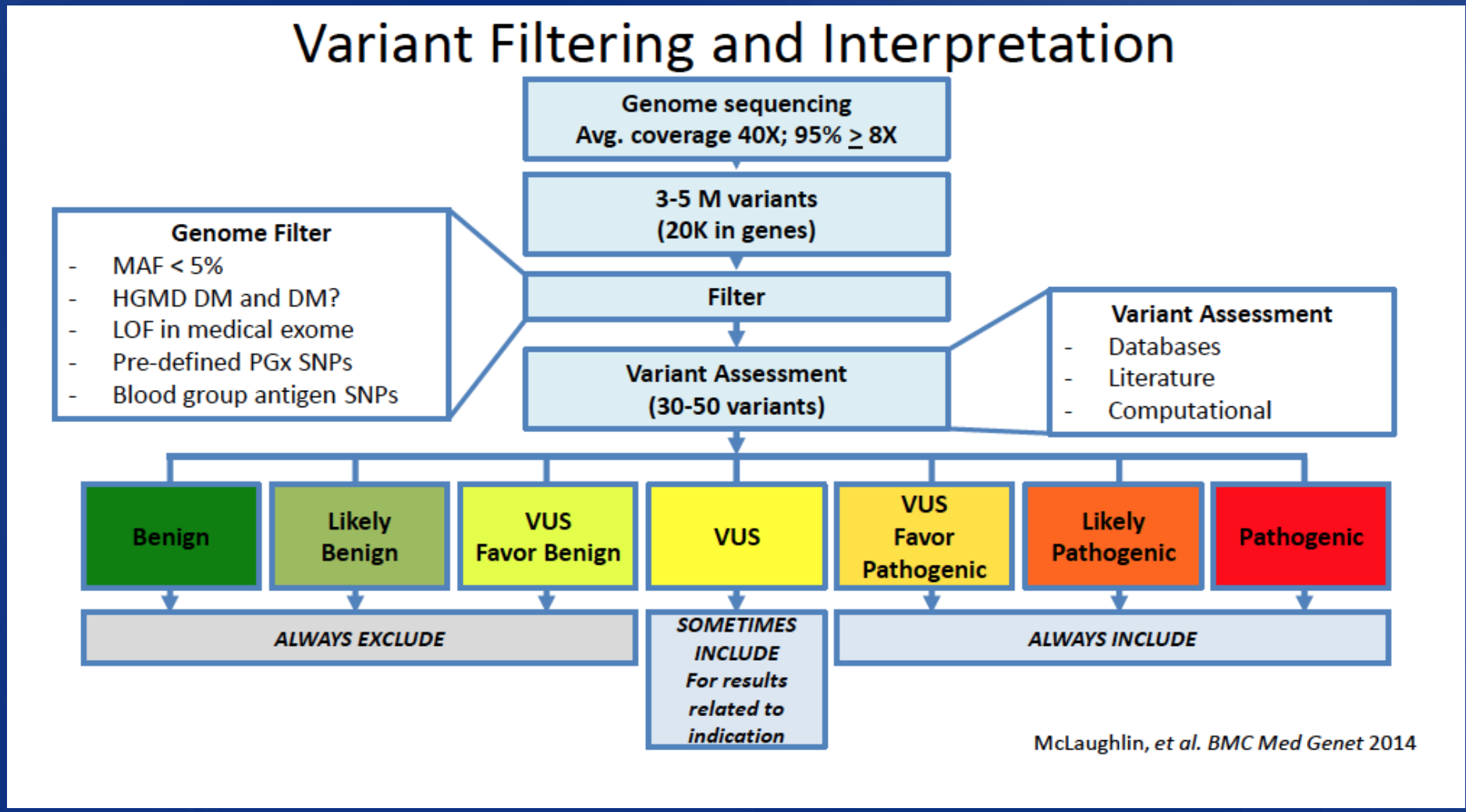
The Genetic Testing Landscape: Possible positive results (variants/mutations).



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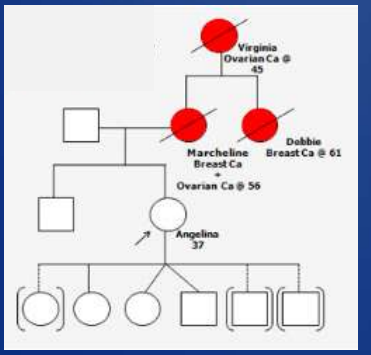
The Genetic Testing Landscape: Possible results.

- Diagnostic or Pathogenic
  - Known gene with known mutation/variant that causes disease
- Variant uncertain significance in a known gene
  - Newly identified mutation/variant with unknown function
- Gene uncertain significance
  - Newly identified gene with uncertain function
- Negative- no sequence alteration
  - **True Negative?**



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What Makes a Good Test?

- **Analytical Validity -** How accurate is the test?
  - What proportion of all mutations in a gene are picked up? Are all the genes associated with disease known?
  - Fragile X vs Diabetes
- **Clinical Validity -** How accurately does the test detect or predict the presence or absence of disease?
  - Huntington Disease vs Cancer
- **Clinical Utility**: what is the clinical utility of the test?
  - Cancer – Diagnosis vs Prediction
- **Ethical, Legal and Social Implications**…

CDC Home

CDC Centers for Disease Control and Prevention

CDC 24/7: Saving Lives. Protecting People.™

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Can One Gene Do it All?

- **Allelic Heterogeneity**
  - Many mutations/variants can cause the same diseases
  - *e.g.* >3000 mutations -> Early onset hereditary breast/ovarian cancer
- **Genetic/Locus Heterogeneity**
  - Different genes result in a similar disease
  - *e.g.* Familial Breast Cancer> BRCA1 or BRCA2 or TP53 or PTEN or…
- **Disease-Gene Heterogeneity**
  - One gene can cause different cancers
  - BRCA1/2> breast and/ or ovarian and/or prostate and/or pancreatic
- **Disease Heterogeneity**
  - Various manifestations of the disease in different individuals in a family. *Penetrance and Variable Expressivity*

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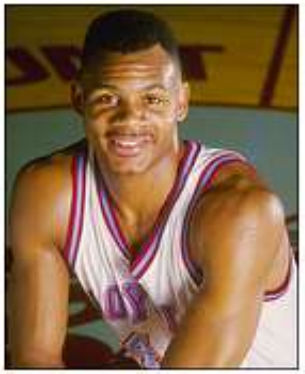
Genes, Environment and Risk

unfavorable

Environment

Probability of Disease



Tim de Frisco/Allsport/Getty Images

Basketball all-star Hank Gathers of Loyola Marymount University in 1989. He died of a heart attack due to an enlarged heart the following year.

favorable

protective

Genes

predisposing

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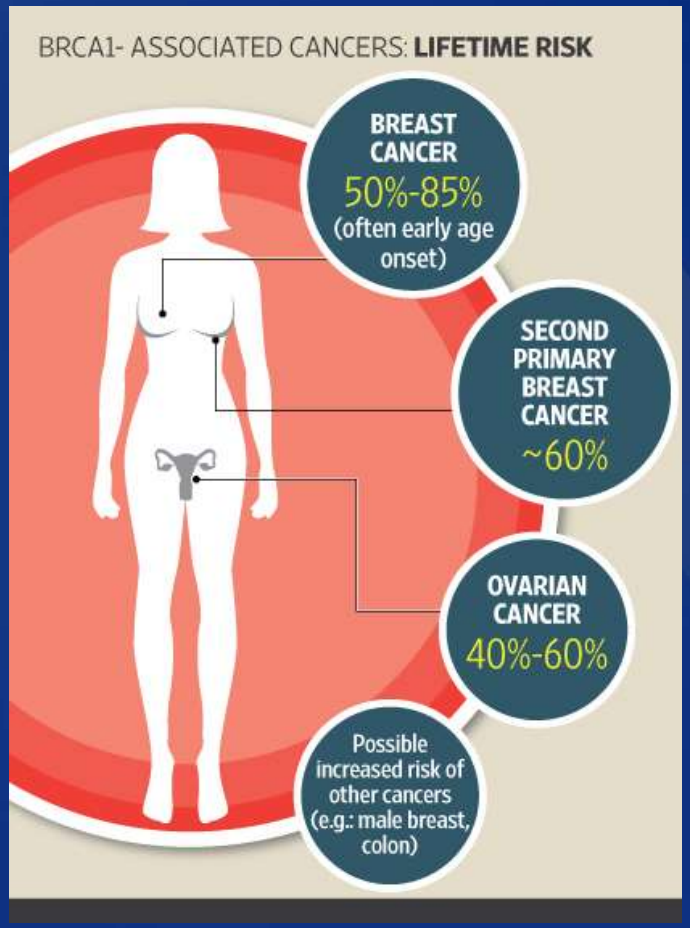
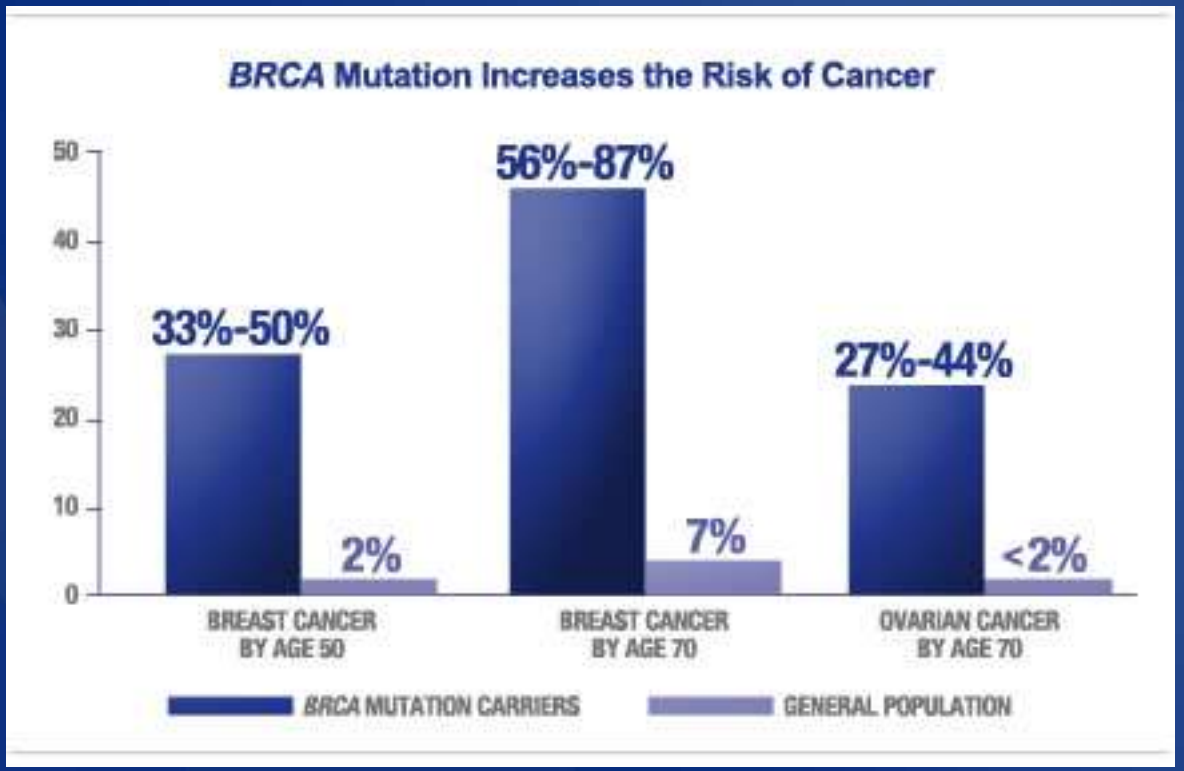
What was she at risk for?





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What was she at risk for?

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	***BRCA2***
Breast	12%	46%-87%%	38%-84%
Second primary breast	2% within 5 years	21.1% within 10 yrs 83% by age 70	10.8% within 10 yrs 62% by age 70
Ovarian	1%-2%	39%-63%	16.5%-27%
Male breast	0.1%	1.2%	Up to 8.9%%
Prostate	6% through age 69	8.6% by age 65	15% by age 65 20% lifetime
Pancreatic	0.50%	1%-3%	2%-7%
Melanoma (cutaneous & ocular)	1.6%		Elevated Risk

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Value of knowing her risk?

- Increase surveillance
  - Begin screening at a younger age or more often for signs of cancer
- Reduce cancer risk via intervention. Consider:
  - prophylactic bilateral mastectomy
  - prophylactic oophorectomy
  - chemoprevention
- Change personal behaviors- quit smoking, get more exercise, and eat a healthier diet
- Impact life decisions? Family Planning
- Share risk information with other relatives

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If It's Genetic-Why Not Test?

Pro?

- Less invasive
- Establish a diagnosis
- Can determine the risk of developing a disease (high risk, carriers)
- Allow early detection & prevention/mgmt
- Help with family planning
- Help with life planning
- Provide reassurance (non-carriers)

Con?

- Technical Limitations
  - Genetic heterogeneity
    - Can't id disease mutations
- Can't predict efficacy of some interventions
- Can't predict the course of the disease
- Cost
- Continued risk sporadic cancer
- Emotional impact?

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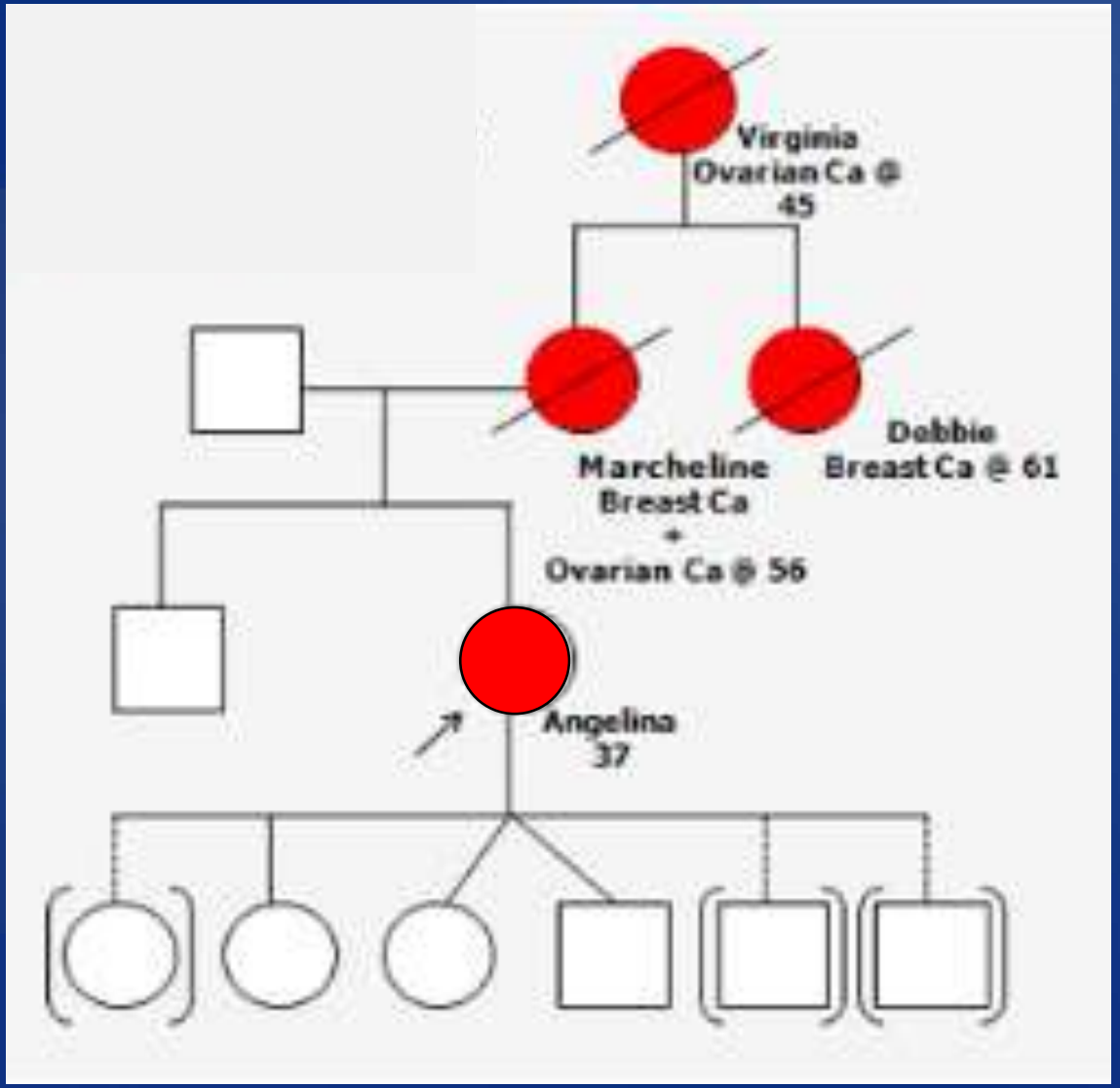
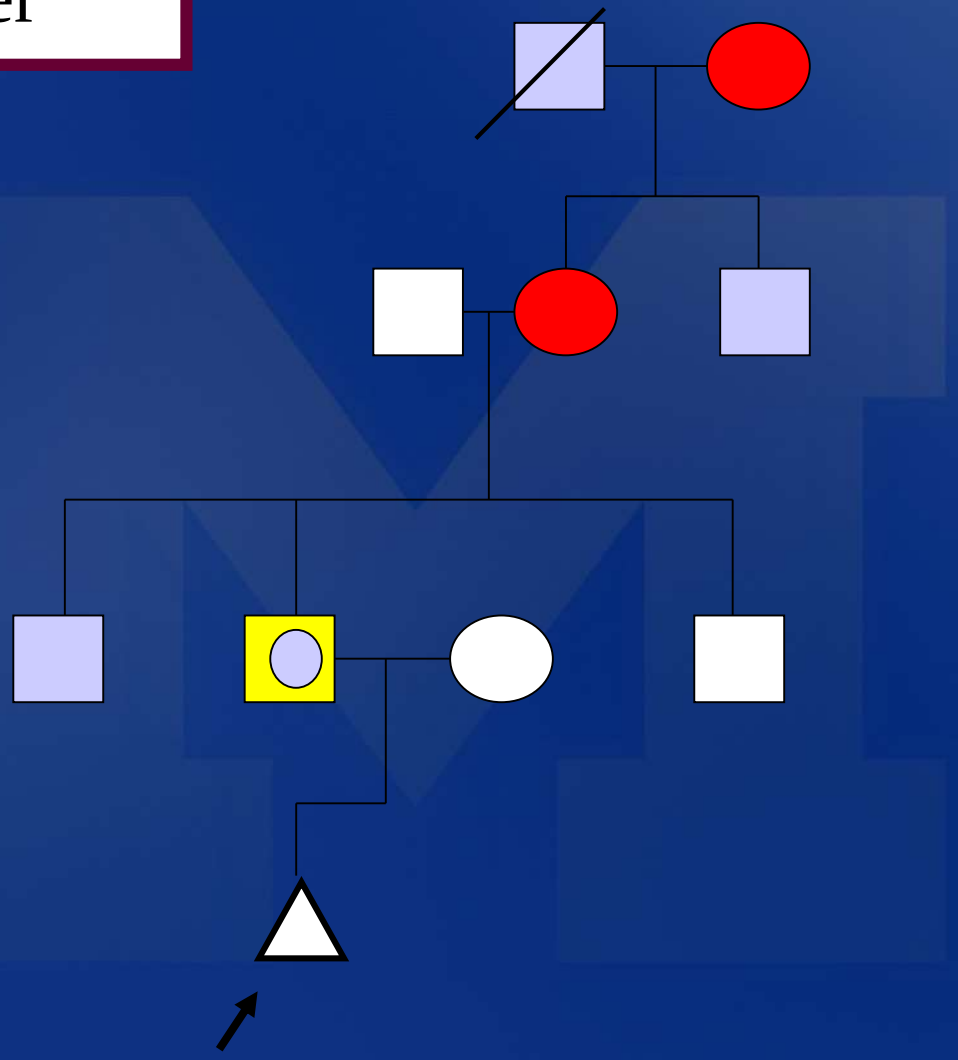
Who else is at risk?



Hereditary Breast/Ovarian Cancer

Who else is at risk?



DNA test-Positive family mutation

Affected

Unaffected

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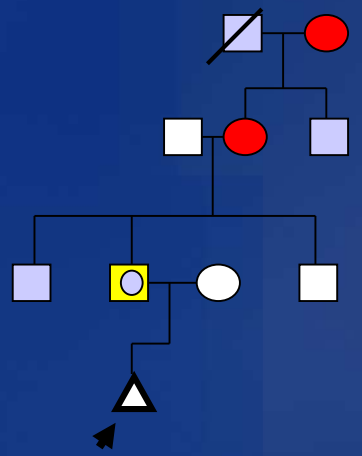
Should Genetic Testing Be Performed on Children?

Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents
Am. J. Hum. Genet. 57:1233-1241, 1995 & GIM 2013:15(3):234–245



The Impact of Potential Benefits and Harms on Decisions about Testing

- Timely medical benefit to the child
- Substantial psychosocial benefits
- If the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred.
- Testing should be discouraged when the provider determines that potential harms of genetic testing in children and adolescents outweigh the potential benefits

The Family's Involvement in Decision Making

- Education and counseling for parents and the child, commensurate on maturity, should precede genetic testing.

Medical issues

- Treatment - prevention - surveillance.

Psychosocial issues

- Reduction of uncertainty.
- Alteration of self-image.
- Impact on family relationships and life planning

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What about the rest of us?

What should we think about?

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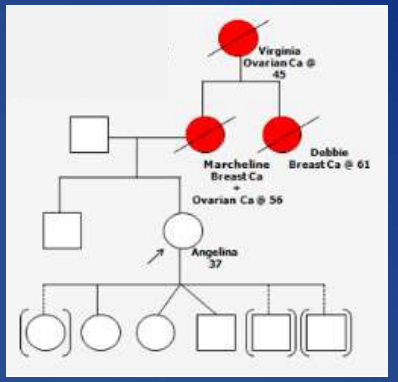
Who should have BRCA1/2 testing?



- Family member with a BRCA1/2 gene mutation
  - (or other inherited gene mutation linked to breast cancer)
- A personal history of breast cancer AND:
  - at age 45 or younger OR
  - at any age and a family member dx with breast cancer at age 50 or younger OR
  - at any age and two or more family members diagnosed with breast, pancreatic and/or aggressive prostate cancer at any age OR
  - Ashkenazi Jewish heritage and a personal history of breast or pancreatic cancer
- A personal history of triple negative breast cancer (breast cancer that is estrogen receptor-negative, progesterone receptor-negative and HER2-negative) diagnosed at age 60 or younger
- A personal or family history of ovarian cancer
- A personal or family history of male breast cancer
- A family member (parent, sibling, child, grandparent, grandchild, uncle, aunt, nephew or niece) diagnosed with breast cancer at age 45 or younger

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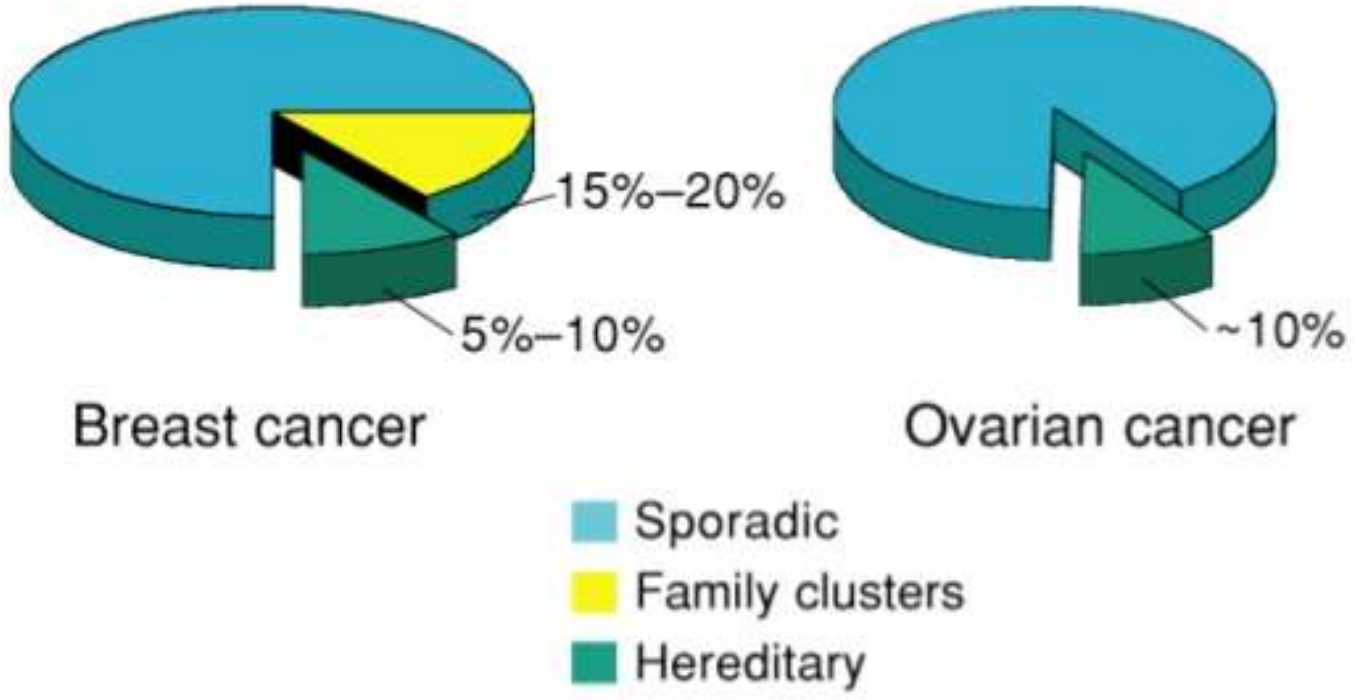
How much breast and ovarian cancer is hereditary?



ASCO

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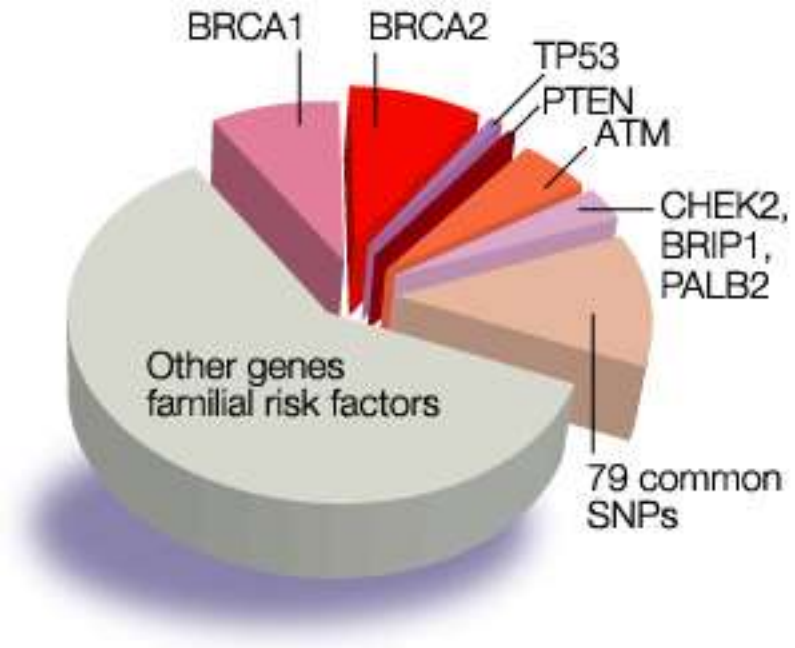
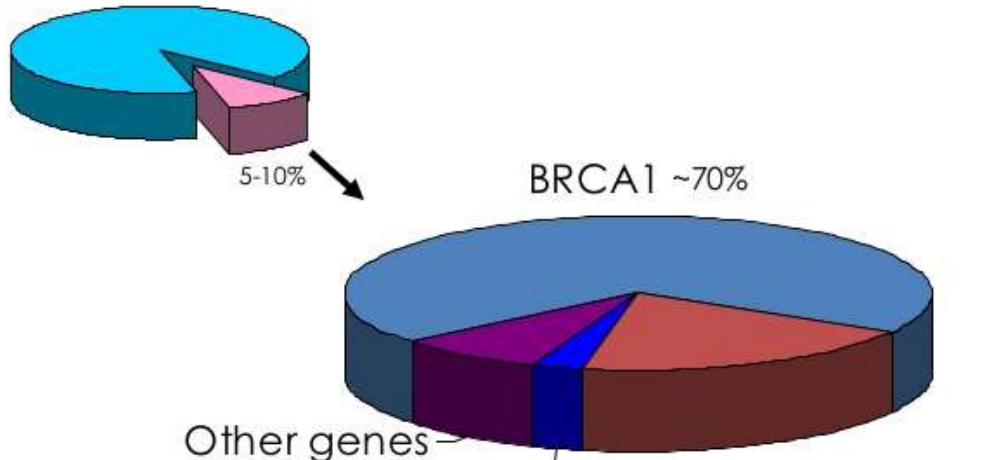
Contribution of known genes to familial aggregation of breast cancer



Hereditary Ovarian Cancer



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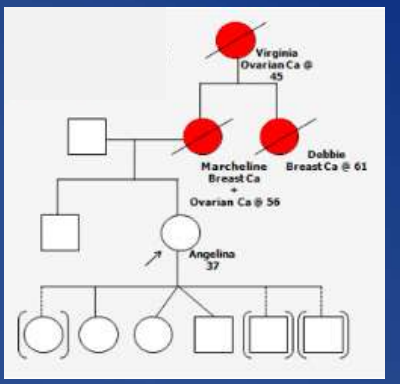
How could you know? Red Flags……



- Young age(s) cancer diagnoses
- Several different types of cancer that have occurred independently in the same person
- Cancer that has developed in both organs in a set of paired organs
  - both kidneys or both breasts
- Several close blood relatives that have the same type of cancer (for example, a mother, daughter, and sisters with breast cancer)
- Unusual cases of a specific cancer type (for example, breast cancer in a man)
- The presence of birth defects, such as certain noncancerous (benign) skin growths or skeletal abnormalities, that are known to be associated with inherited cancer syndromes
- Being a member of a racial/ethnic group that is known to have an increased chance of having a certain hereditary cancer syndrome and having one or more of the above features as well

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Genetic Counselors: Integral Members of the Healthcare Team

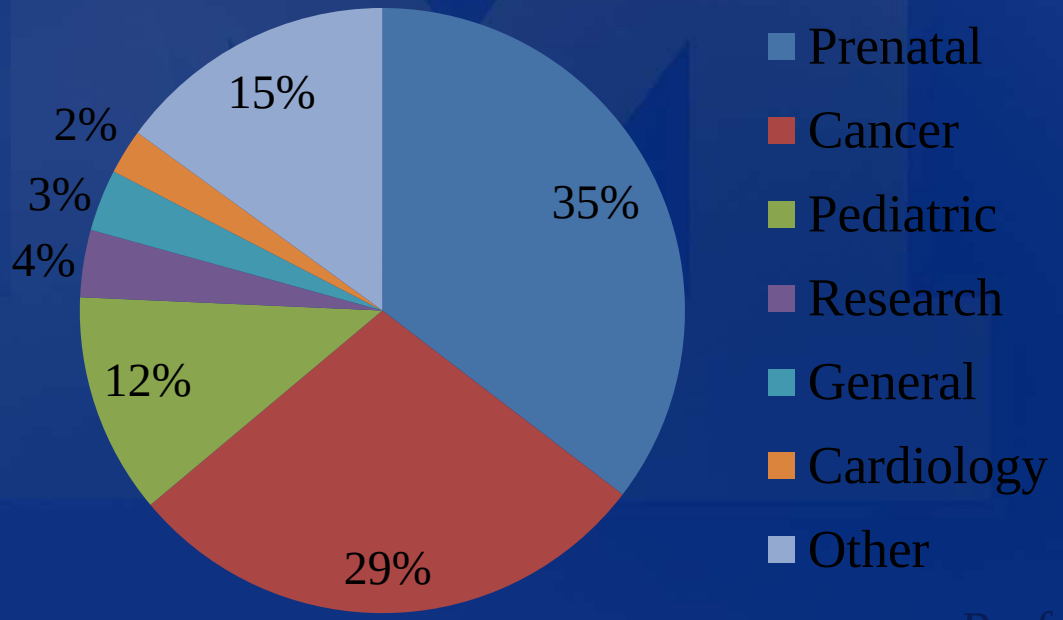
- Interpret and provide comprehensive information about the risk of medical conditions that may have a genetic contribution
- Ascertain utility of genetic technologies
- Support and address individual needs of patients
- Unique patient advocates
- Educators and resources for other healthcare providers and the public

http://www.nsgc.org

Most genetic counselors work in a clinic or hospital, and often work with obstetricians, oncologists and other doctors. Like doctors, genetic counselors can work in a variety of settings and provide different services. They may provide general care, or specialize in one or more areas, including:

- Prenatal and Preconception – for women who are pregnant or thinking about becoming pregnant
- Pediatric – for children and their family members
- Cancer – for patients with cancer and their family members
- Cardiovascular – for patients with diseases of the heart or circulatory system and their family members
- Neurology – for patients with diseases of the brain and nervous system and their family members.
- And more

Additionally, some genetic counselors focus on research, including collecting information such as detailed family histories and pregnancy information, that helps researchers and advances care for people with genetic conditions.



2014 NSGC Professional Status Survey

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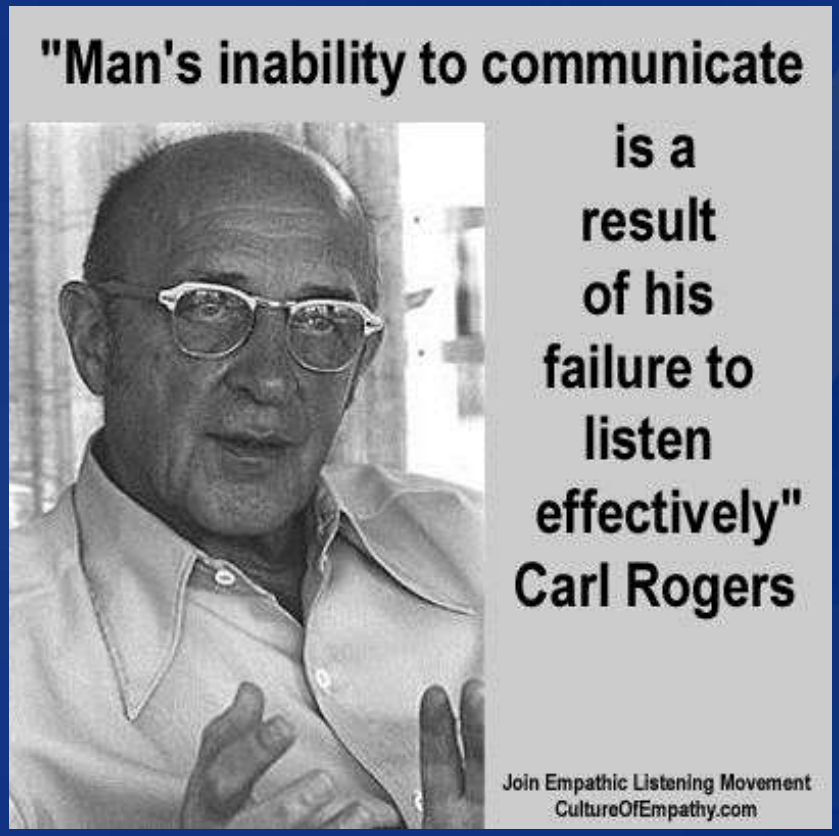
Ethos of Genetic Counseling



- Informed decision making based on client's/patient's beliefs
- A shared process

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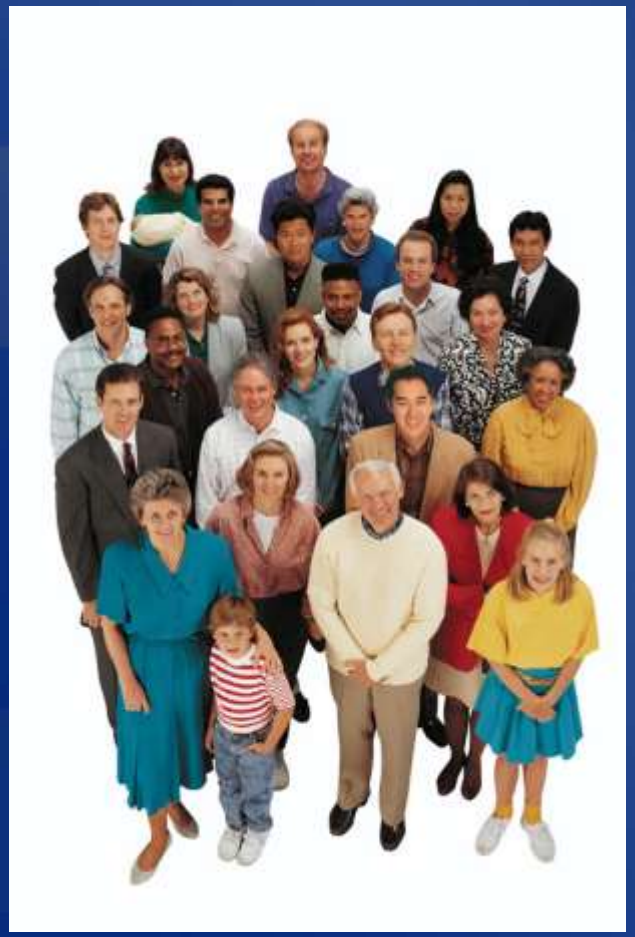
The Genetic Testing Landscape

Genetic Diagnosis & Screening

- **Confirm or make clinical dx**
- **Detect carriers**
- **Predict responsiveness to therapy**
- Preconception counseling
- Prenatal screening
- Newborn screening
- Asymptomatic individual
  - Suggestive family history
  - Ethnicity driven
  - Worried well



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Heard at the Genetics Clinic:

"Can you take out the bad gene?"

"Can you fix that gene?"

"Can you remove the extra chromosome?"

"By the time my daughter gets the disease, will there be gene therapy to treat it, or at least to her babies"

"Are doctors working on gene therapy for this?"

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Variables in Clinical and Molecular Genetics/Genomics

- Pattern of inheritance
- Molecular basis
- Penetrance
- Age of onset
- Clinical question

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Technology: So many options…

- Individual gene(s)
- Gene panels
- Chromosomal microarrays
- Whole exome sequencing
- Whole genome sequencing
- Right test- right person-right time

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Universal Screening?

> *"There is no reason now that any woman with BRCA1 or BRCA2 should ever die of breast or ovarian cancer."*
> – Dr. Mary-Claire King

- Offer every woman sequencing of BRCA1 and BRCA1 at age ~30 as part of medical care
- Refer every woman with a damaging BRCA mutation to a high risk clinic
- Report only damaging BRCA mutations
- Add more genes as evidence of pathogenicity increases


Mary-Claire King, PhD

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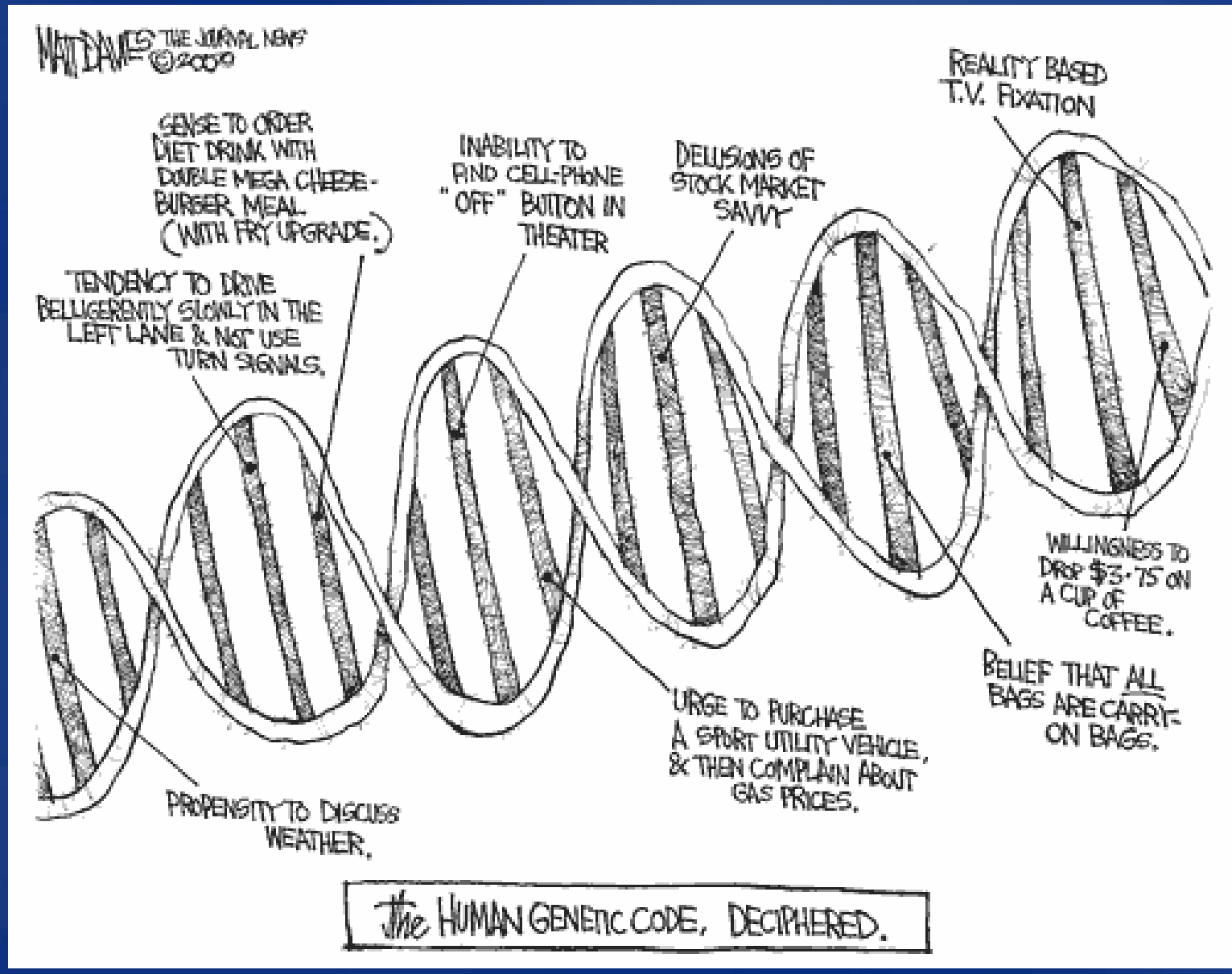

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How Do We Enhance Clinical Utility?

- Right Person
- Right Test
- Right Time

- Right Interpretation

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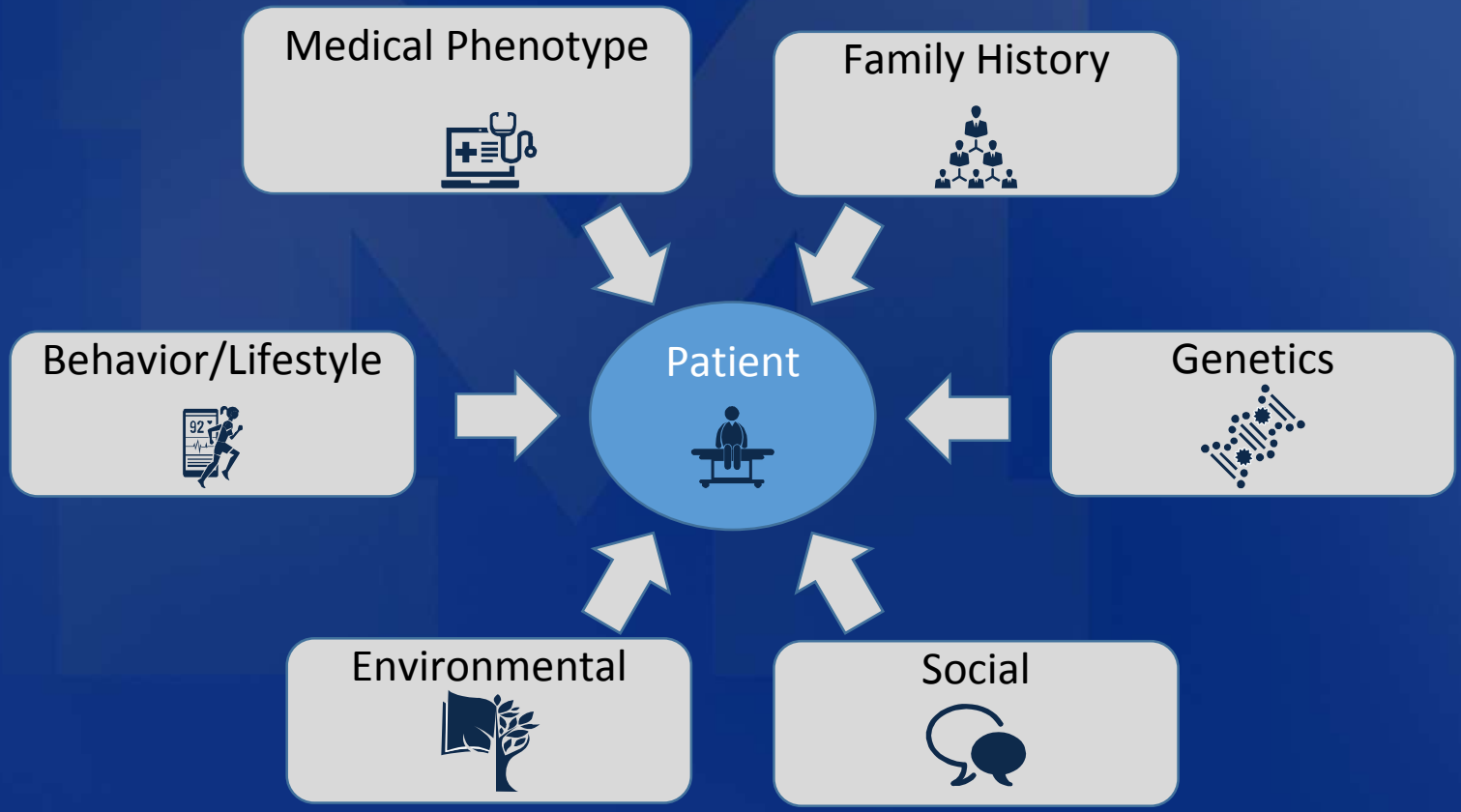
Precision Health considers individual variability in genes, lifestyle, environment

Traditionally healthcare only included medical phenotype and family history; Precision Health integrates interdisciplinary approach to support patient health



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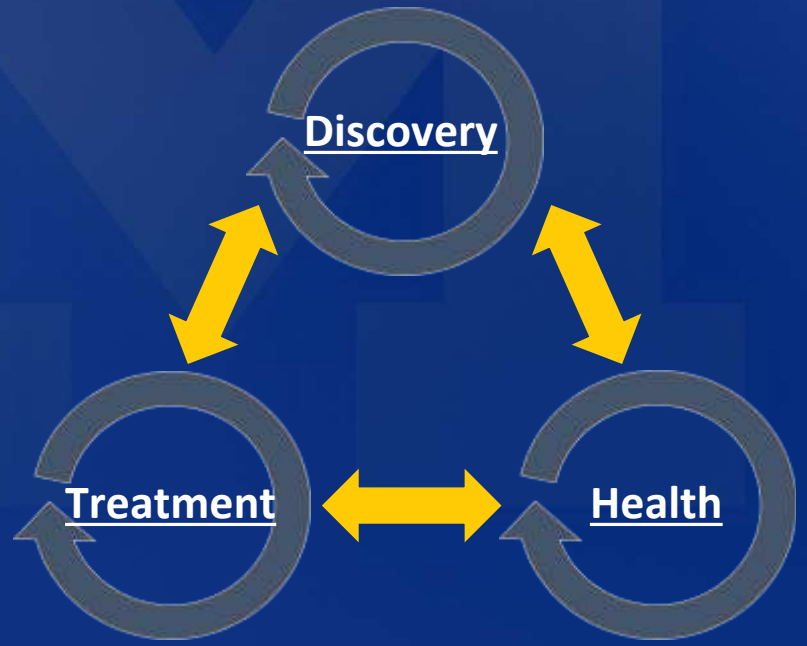
Precision Health: from research through treatment to health

Precision Health is a population-based strategy, targeted to discover and validate markers that influence disease prevention and health outcomes, which can subsequently be used to make actionable decisions to personalize an individual's pursuit of wellness.

- Identifying new biomarkers or mechanisms of diseases
- Novel sensors and computational methods
- Developing therapies to utilize novel markers and profiles



- Validating precision discoveries through new methods for clinical trials
- Improved care outcomes through precision treatment

- Faster dissemination of validated treatments and corresponding protocols
- More effective approaches to population health management
- Value evaluation & Policy reform

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Precision Pain Management and Prevention of Opioid Abuse

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Goal: Reduce Downstream Chronic Opioid Use, Diversion, Abuse, and Overdose through a Precision Prevention Strategy

Deep Phenotyping and Population-Based Analytics Drive Novel Personalized Prescribing

Opioid Naïve Patient → Chronic Opioid Use → Opioid Abuse → Opioid Overdose




Proposed Precision Preventative Strategy

Focus of Existing Public Health Measures

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Precision Pain Management

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Predictors

- ✓ Source of pain
- ✓ Genetics
- ✓ Phenotyping
- ✓ Pain
- ✓ Medication use history
- ✓ Social support
- ✓ Mood

- ✓ # of pills
- ✓ Risk of abuse
- ✓ Risk of diversion

Preoperative Consultation

Outcomes

Patient Benefit

- Eliminate new chronic opioid use
- Decreased potential for opioid abuse

Community Benefit

- Reduction in excess pills available for diversion
- Decreased opioid-related morbidity and mortality