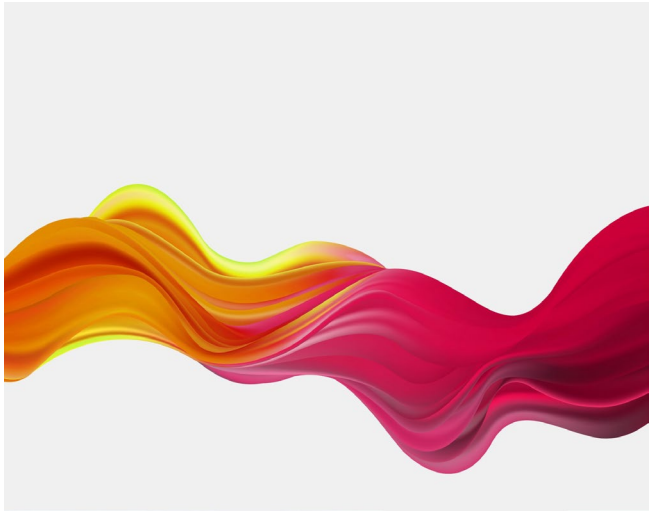
Oncogenetics: What Every Nurse Needs to Know



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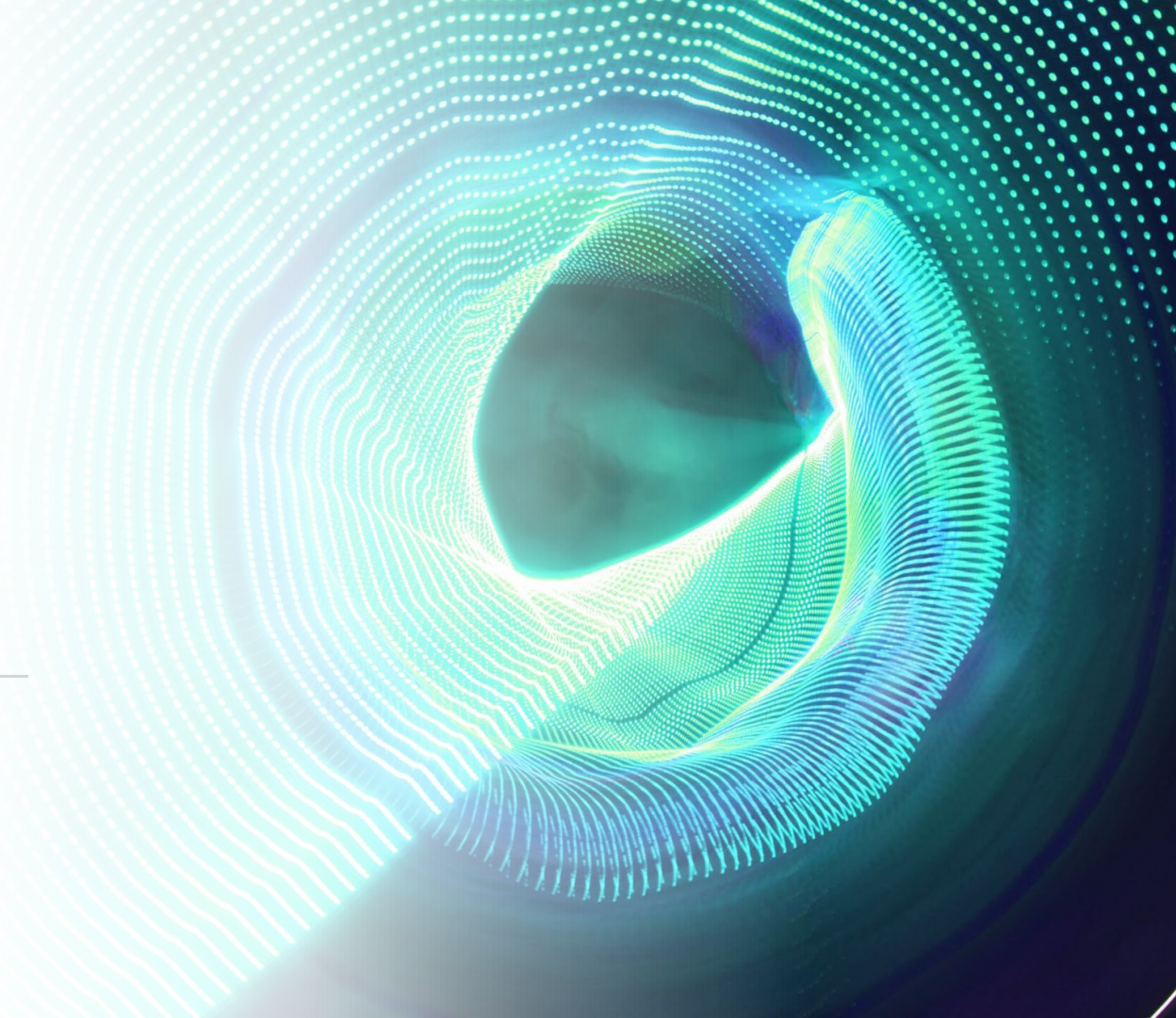
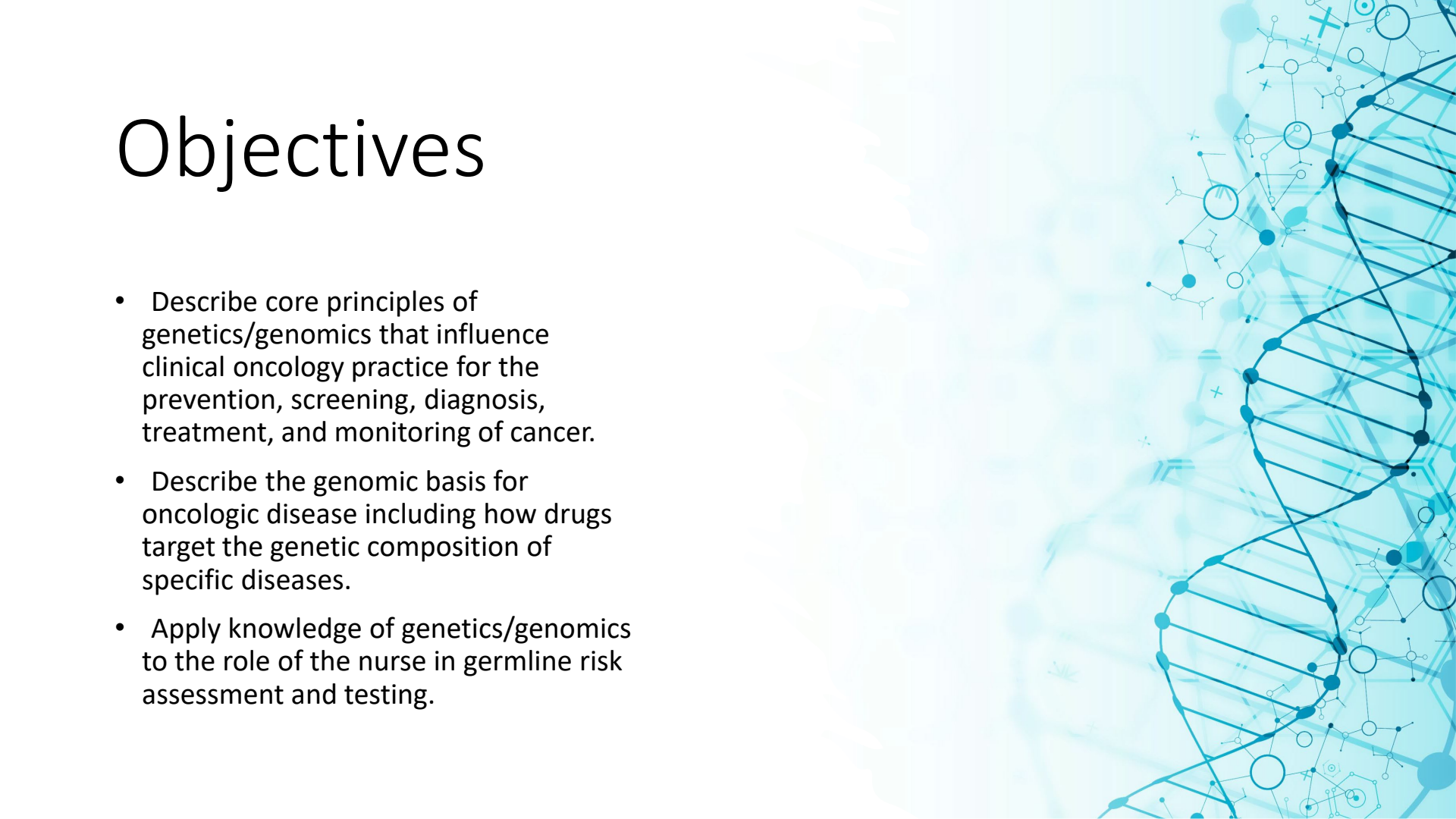
Disclosures

I have no disclosures.



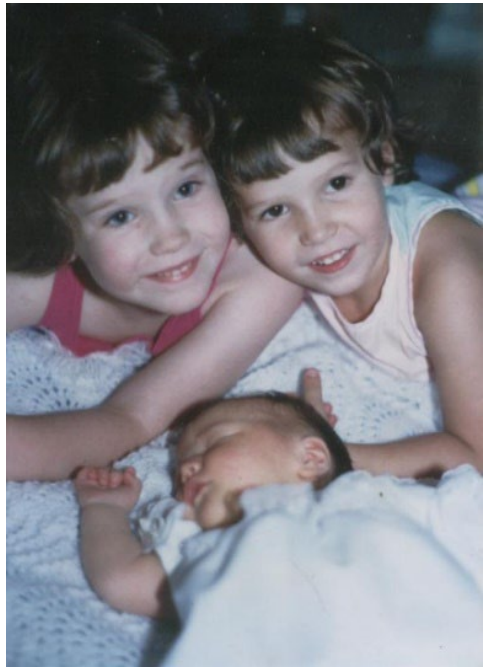
Objectives

- Describe core principles of genetics/genomics that influence clinical oncology practice for the prevention, screening, diagnosis, treatment, and monitoring of cancer.
- Describe the genomic basis for oncologic disease including how drugs target the genetic composition of specific diseases.
- Apply knowledge of genetics/genomics to the role of the nurse in germline risk assessment and testing.



Genomics Revolution

- 1996 – Beginning of Human Genome Project
- 1998 – Isolation of BRCA1/2
- 2003 – Human Genome Project completed
- 2010 – Implementation of GINA
- 2012 – Medicare coverage
- 2014 – First PARP inhibitor olaparib is approved
- 2016 – Cancer Moonshot initiated
- 2020 - SARS-CoV-2 virus is sequenced
- 2022 – Cancer Moonshot is reignited

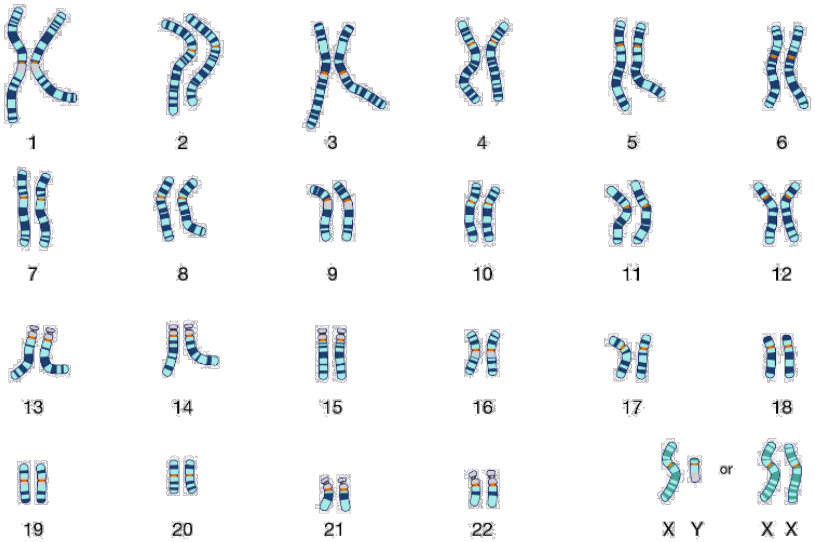


Precision Medicine

- Changing cancer care
- Targeting the genetic change in the tumor

Genetics/Genomics

- The main difference between genetics and genomics is the amount of material involved.
- **Genetics** refers to one gene.
- **Genomics** refers to all genes and their interactions with one another and the environment.



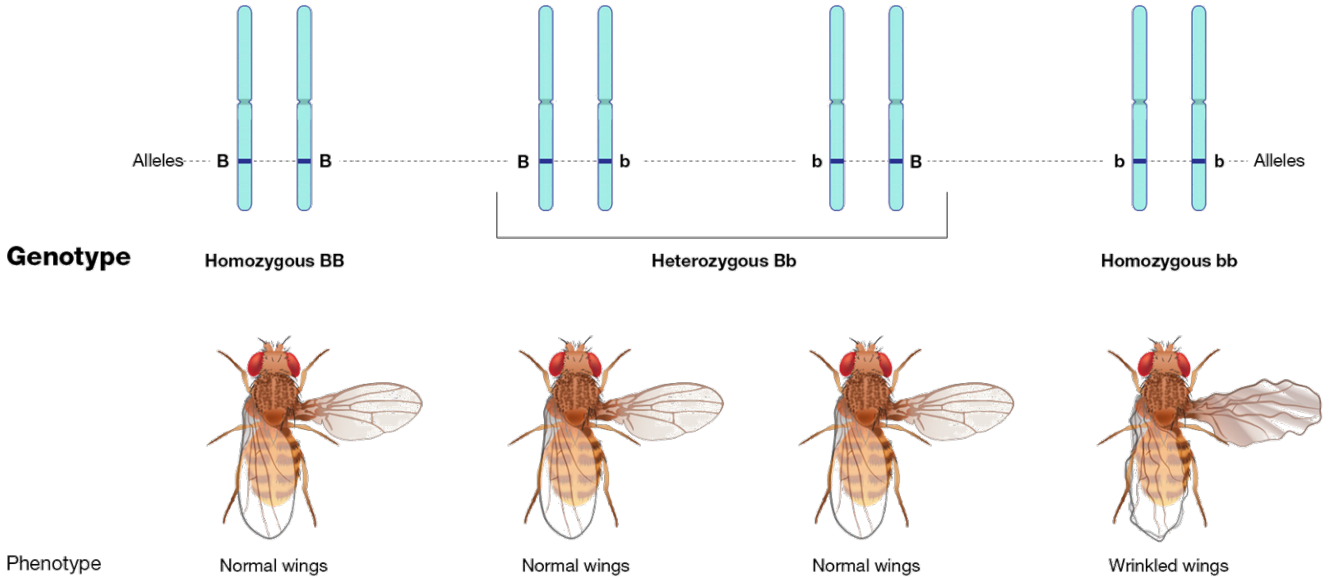
Human cells contain 23 pairs of chromosomes.

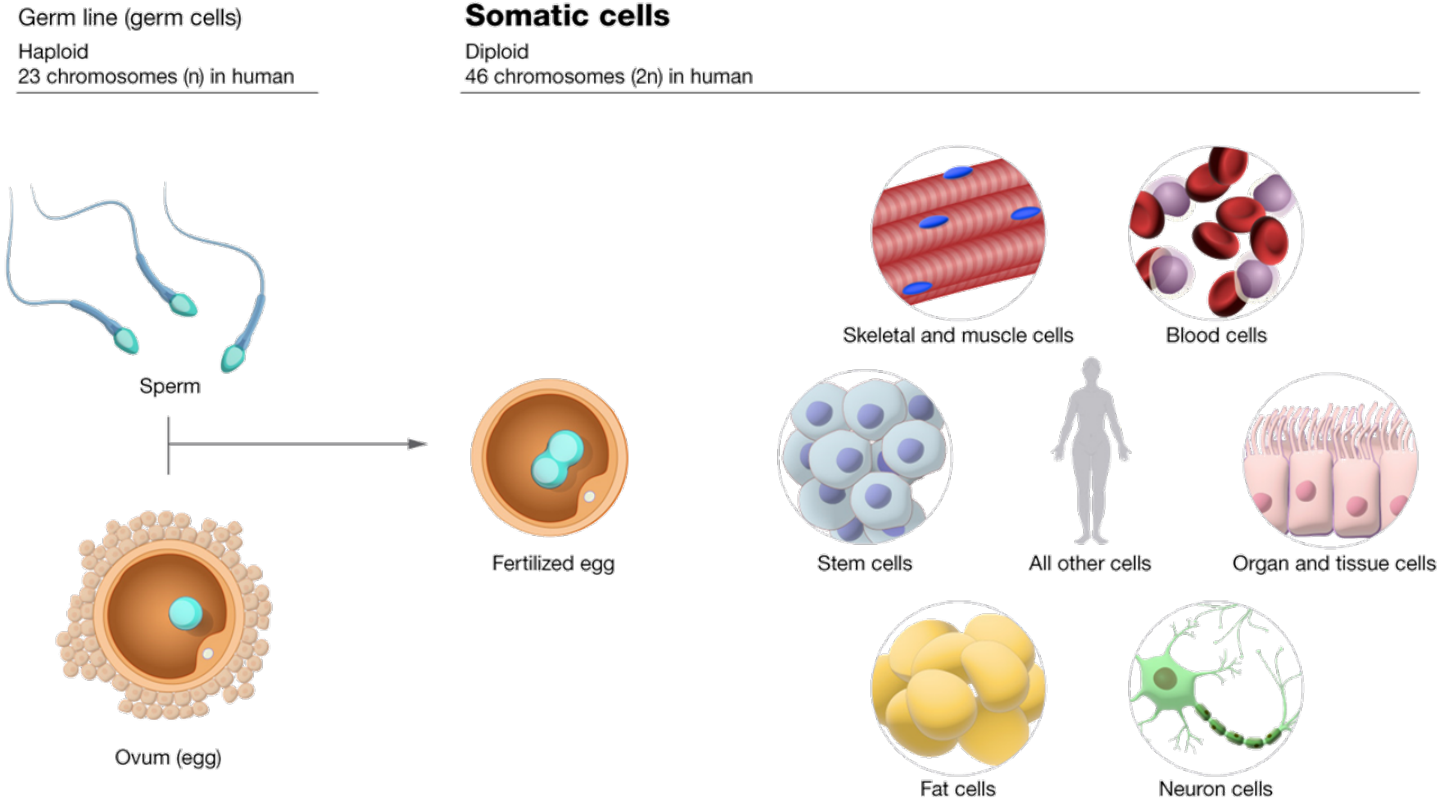
- 22 autosomes
- 1 pair of sex chromosomes

Each chromosome contains many genes (25,000+) made up of 3 billion+ base pairs.

Humans are 99.9% identical and 0.1% different.

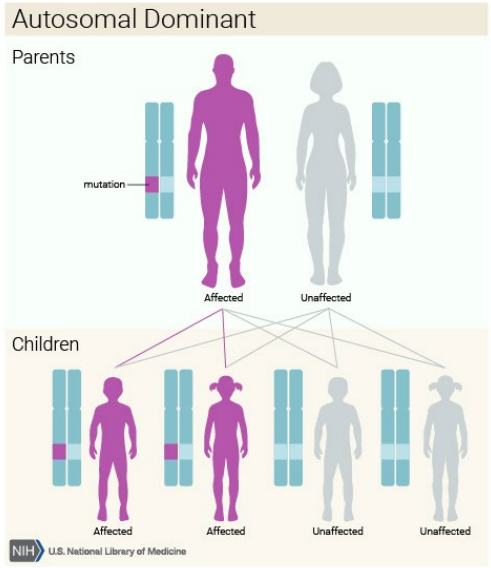
Definitions

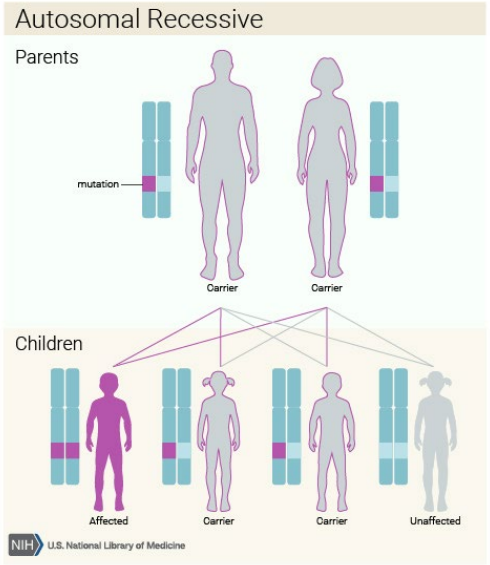

Alleles
B
B
B
b
b
B
b
b
Alleles
Genotype
Homozygous BB
Heterozygous Bb
Homozygous bb
Phenotype
Normal wings
Normal wings
Normal wings
Wrinkled wings

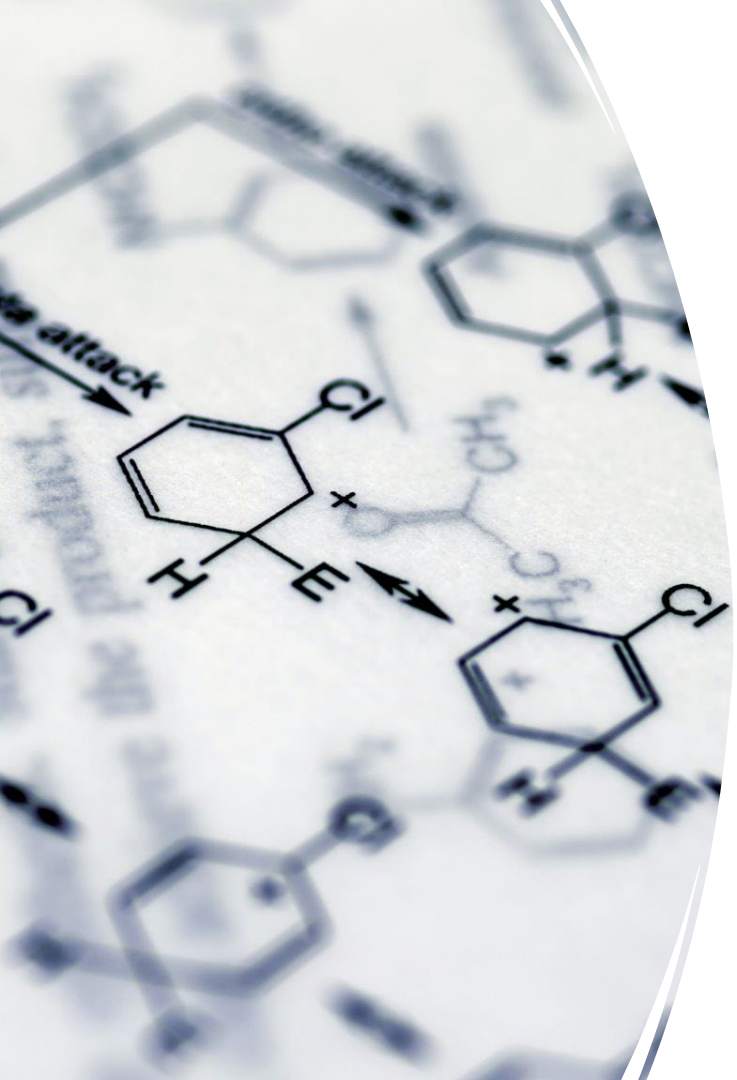

Germ line (germ cells)
Haploid
23 chromosomes (n) in human
Somatic cells
Diploid
46 chromosomes (2n) in human
Sperm
Ovum (egg)
Fertilized egg
Skeletal and muscle cells
Blood cells
Stem cells
All other cells
Organ and tissue cells
Fat cells
Neuron cells

NHGRI

Inheritance Patterns



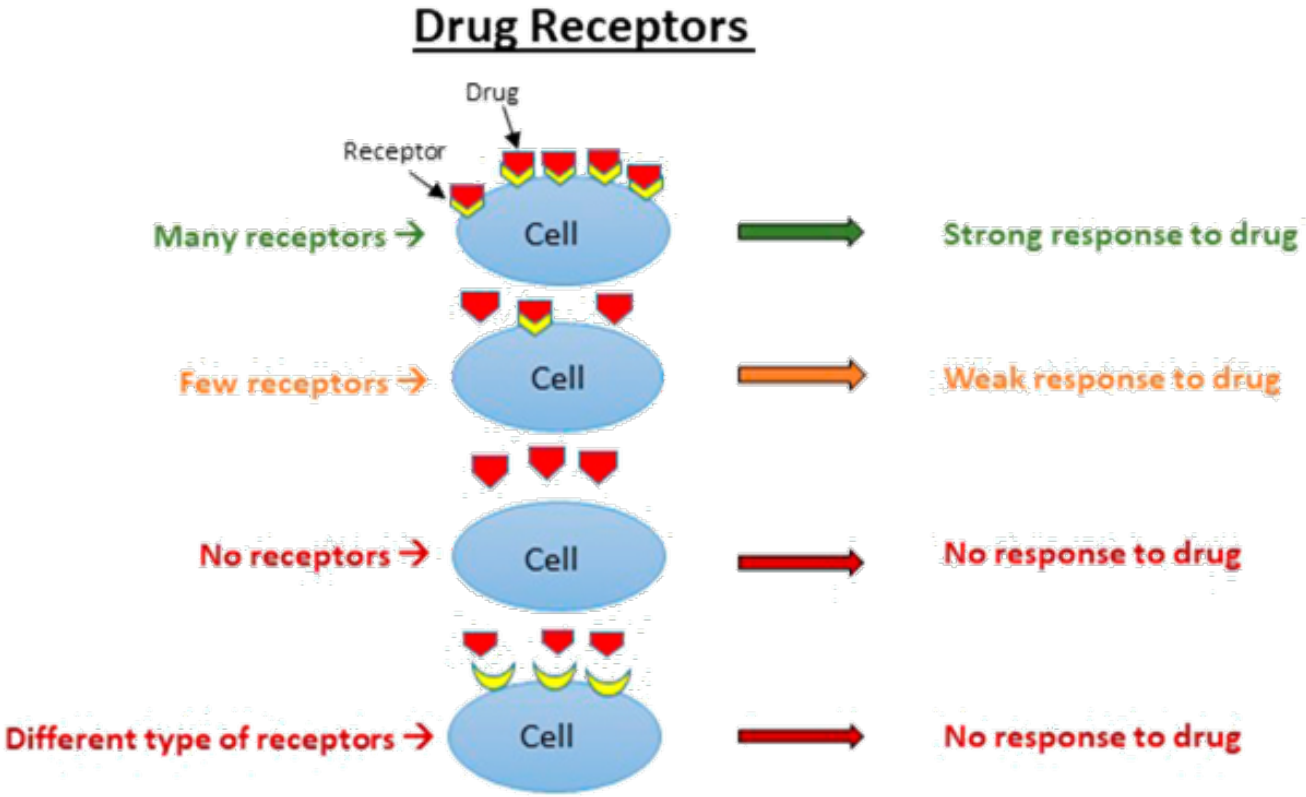




Definitions

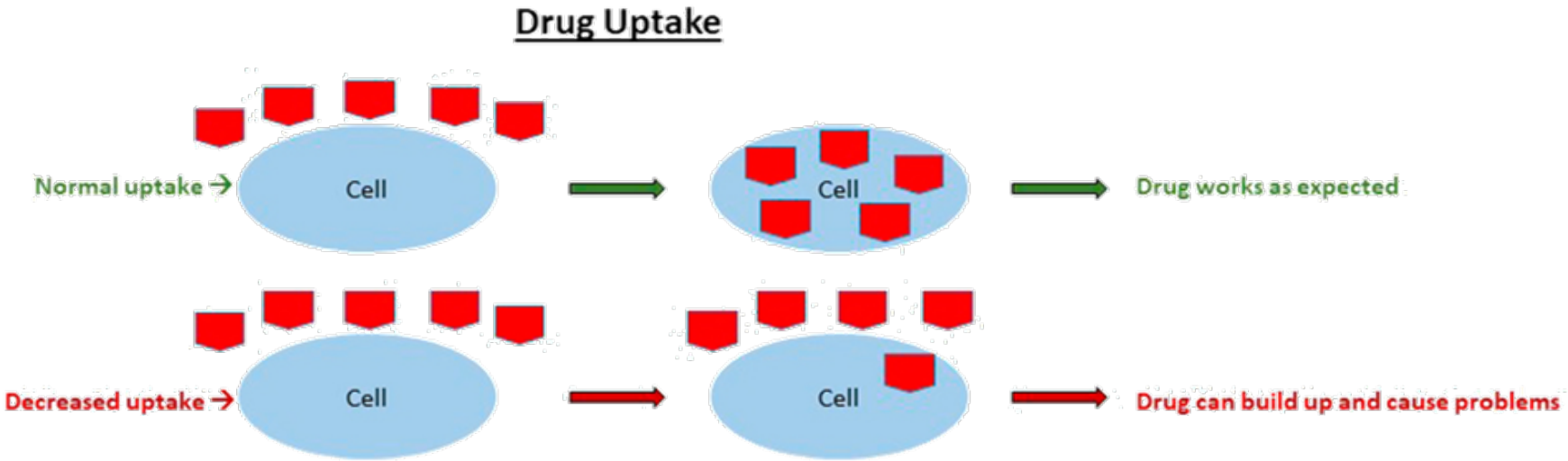
- **Biomarker** is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.
- **Susceptibility**: Potential for developing disease – BRCA1/2
- **Diagnostic**: Detect or confirm presence of disease – HER2 expression
- **Monitoring**: Serially assess status of disease – PSA testing
- **Prognostic**: Likelihood of having a clinical event – Oncotype Dx® testing
- **Predictive**: Likelihood of having a response to a treatment – somatic and germline BRCA pathogenic variant eligible for treatment with PARP inhibitor

Pharmacogenomics



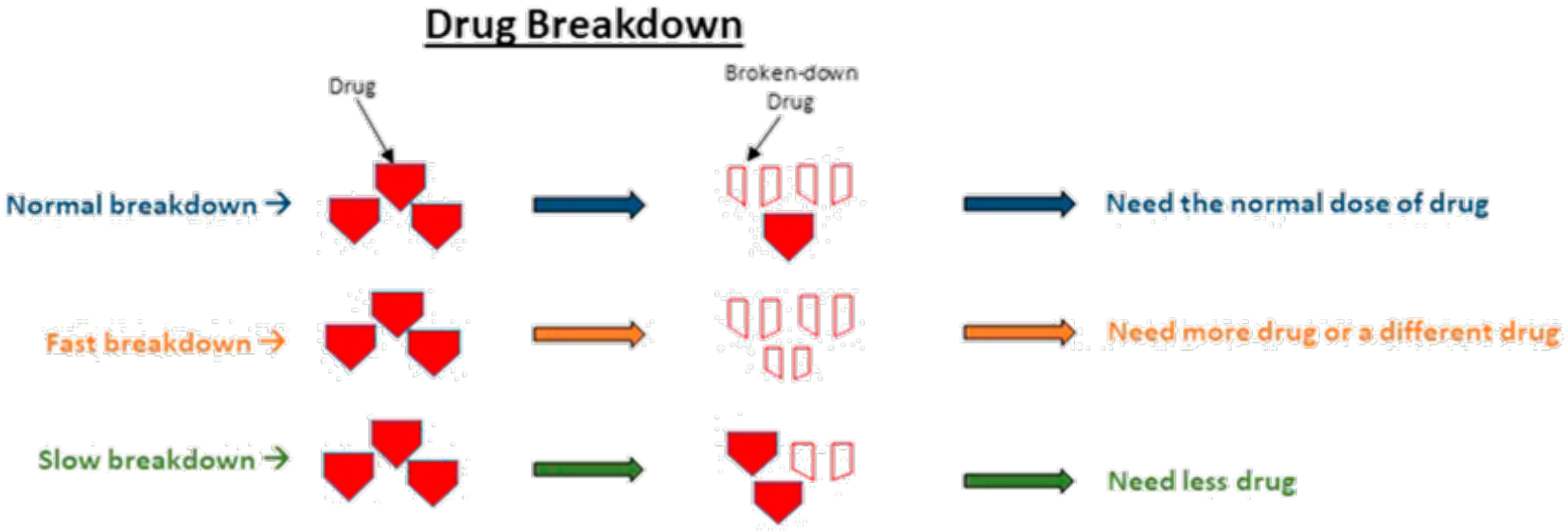
CDC

Pharmacogenomics

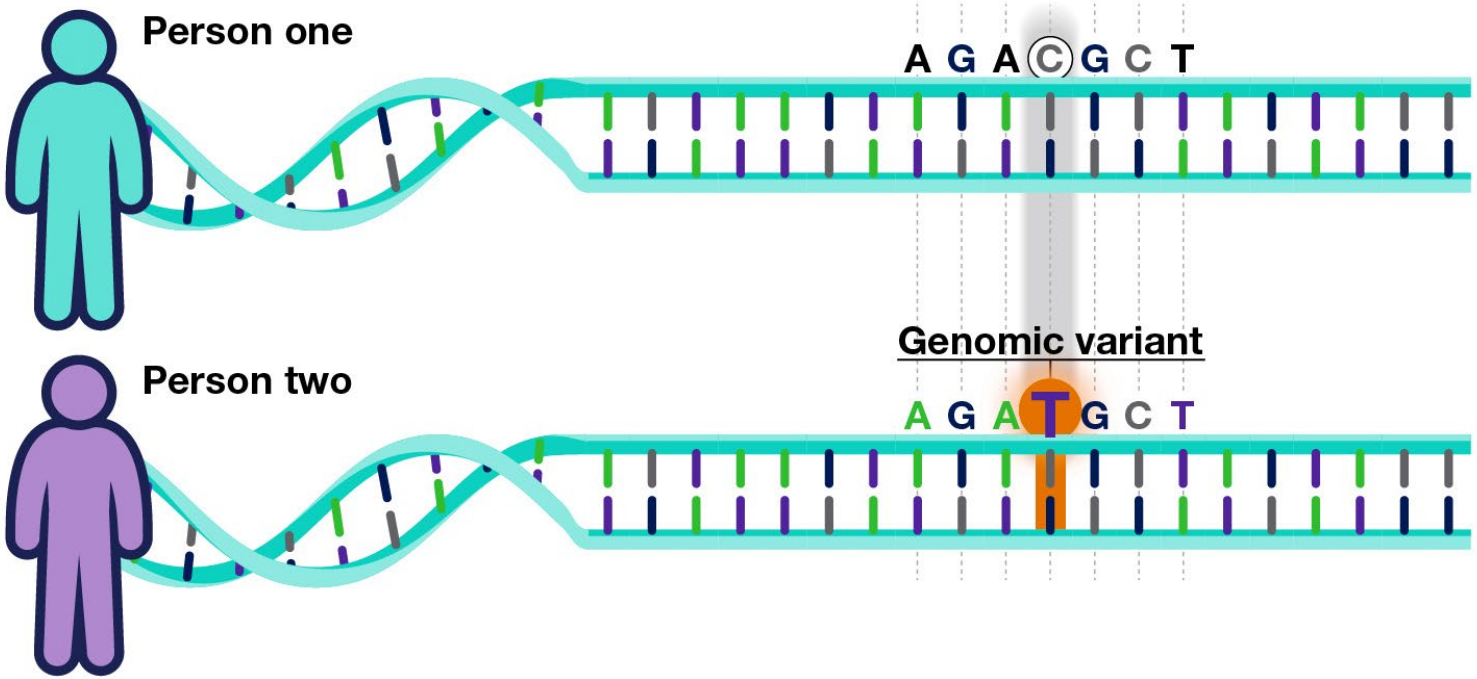


CDC 2022

Pharmacogenomics



CDC



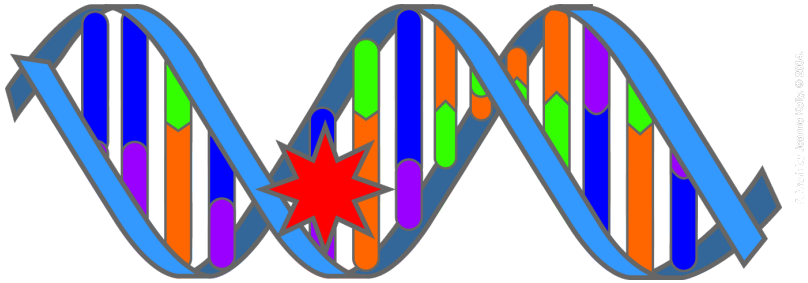
NHGRI

Types of Testing

- Single nucleotide variant
- Sequence a gene
- Next-generation sequencing
- Whole exome testing
- Whole genome
- Carrier

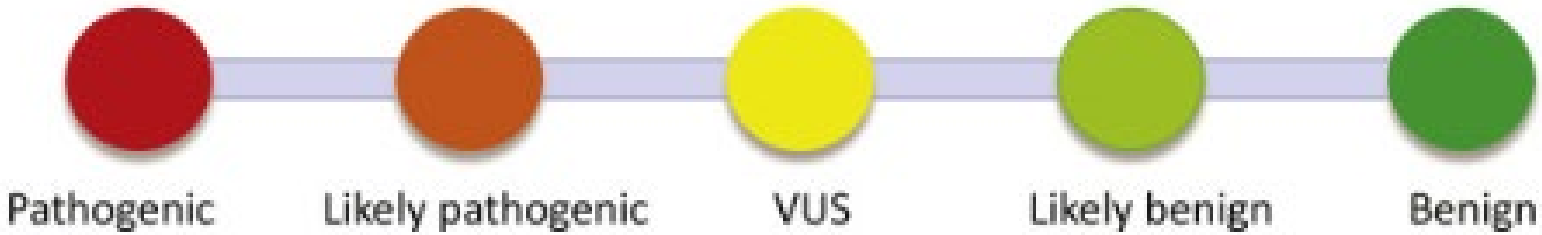
~~Mutations~~

Pathogenic Variant



Commonly used to define DNA sequence changes that alter protein function

Classification of Germline Variants



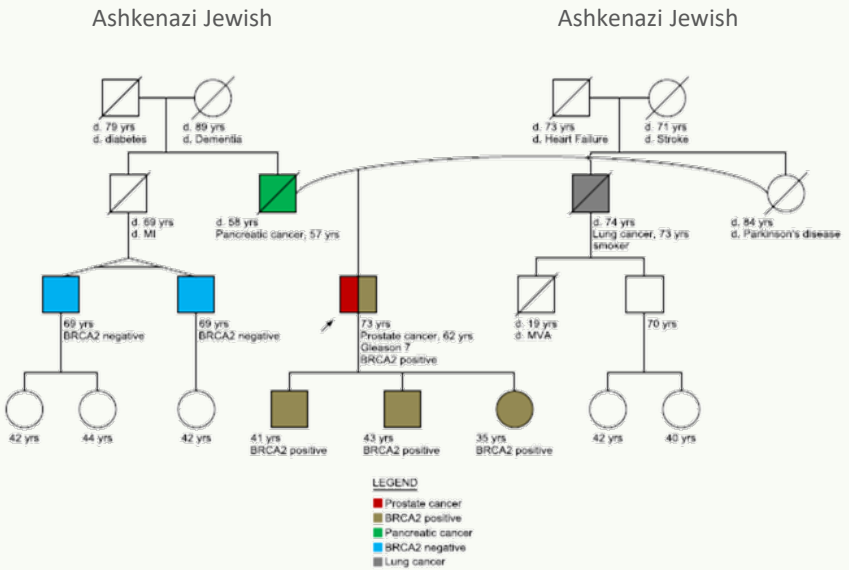
Family History

The most powerful genetic tool available

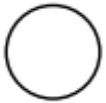
Includes a minimum of 3 generations

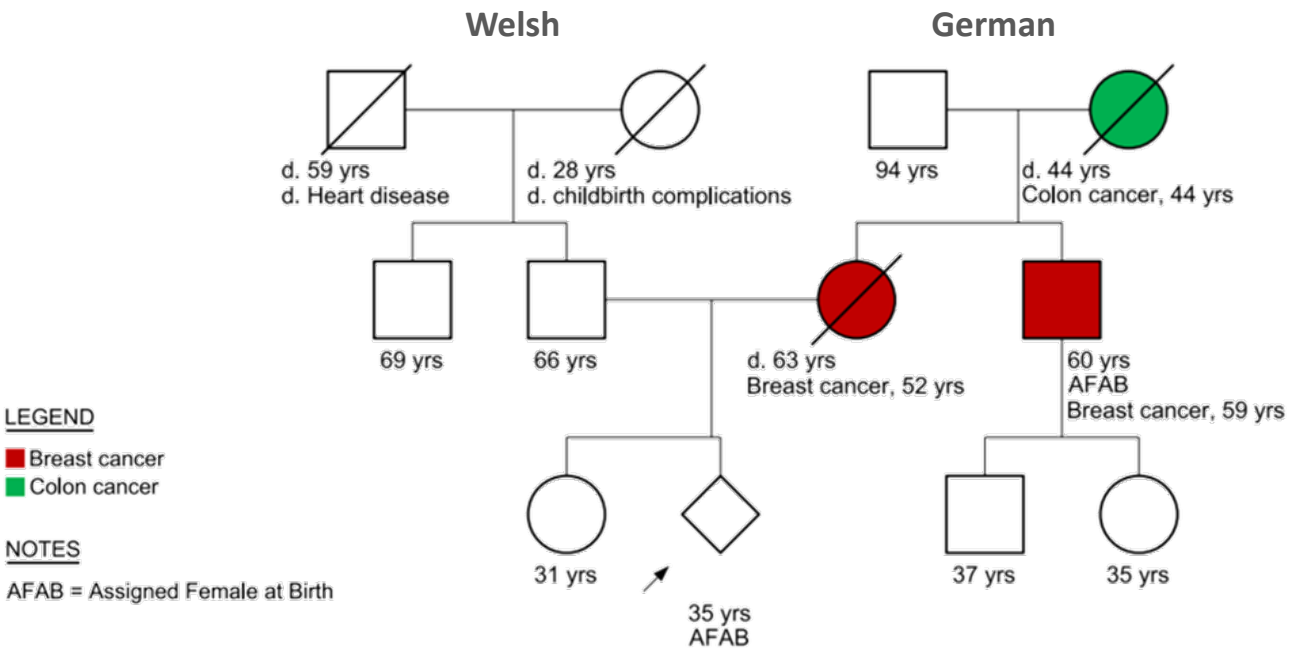
Constructed as a pedigree that includes:

- Ethnicity, culture, religious background
- Living or deceased, age at death, cause of death
- Physical, mental, or developmental conditions

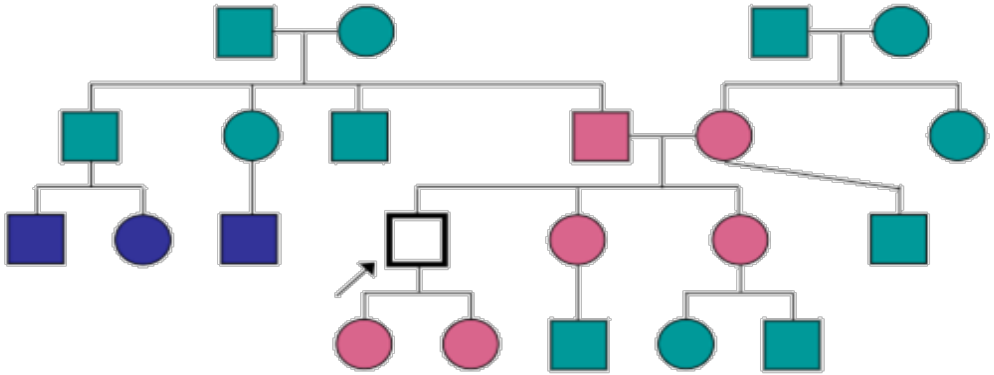


Standard Pedigree Symbols

Gender Identity	Sex Assigned Birth *Male*	*Female*	*Unassigned at Birth*
Man		 AFAB	 UAAB
Woman	 AMAB		 UAAB
Nonbinary	 AMAB	 AFAB	 UAAB


Welsh
German
d. 59 yrs
d. Heart disease
d. 28 yrs
d. childbirth complications
94 yrs
d. 44 yrs
Colon cancer, 44 yrs
69 yrs
66 yrs
d. 63 yrs
Breast cancer, 52 yrs
60 yrs
AFAB
Breast cancer, 59 yrs
31 yrs
35 yrs
AFAB
37 yrs
35 yrs
LEGEND
Breast cancer
Colon cancer
NOTES
AFAB = Assigned Female at Birth

Degrees of Relationship



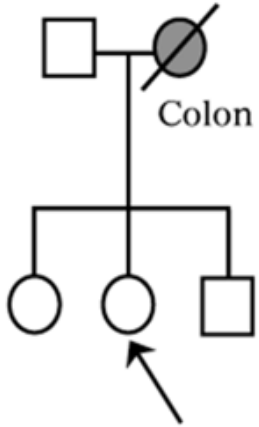
First-degree relatives : parents, siblings, children

Second-degree relatives : half-siblings, aunts, uncles, grandparents, nieces & nephews

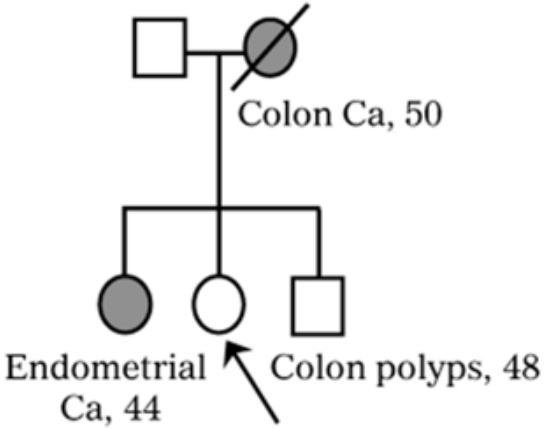
Third-degree relatives : first cousins

Family Histories are Dynamic

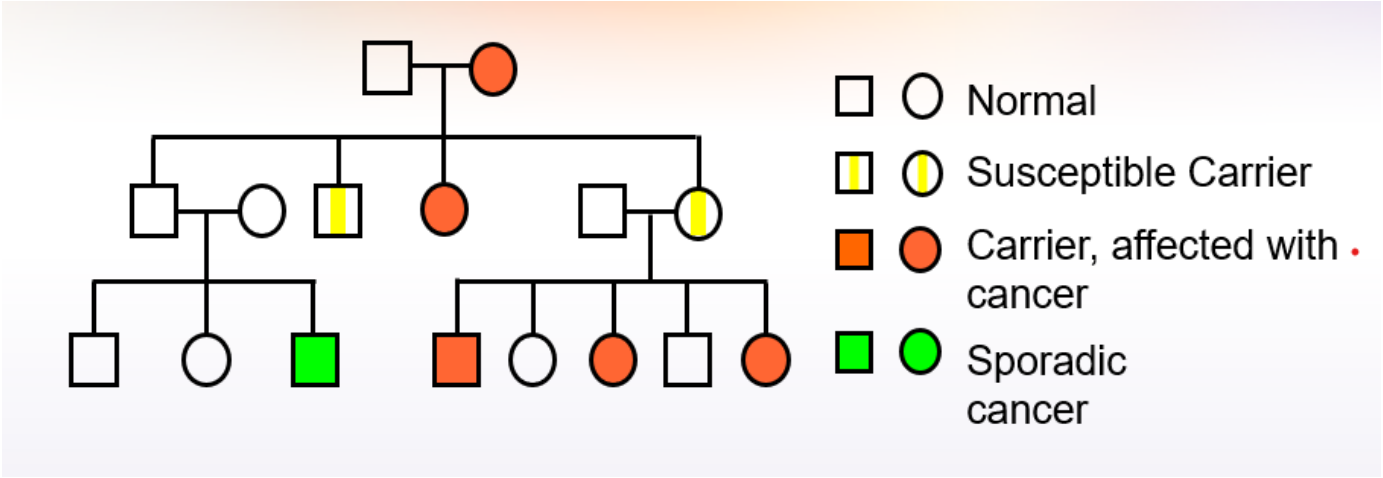
Initial History



2 years later



Most Cancer Susceptibility Genes are Dominant With Incomplete Penetrance



Patient Factors Affecting Pedigree Construction

- Inaccurate family history
- Lack of desire to explore family history
- Limited family history
- Patient is adopted
- Small family history
- Unknown paternity

Provider Factors Affecting Pedigree Construction

Failure to recognize hereditary cancer syndromes

Time to construct a three-generation pedigree

System Factors Affecting Pedigree Construction

No inclusion of decision support and red flags for referral to a genetics provider in the electronic medical record

No reimbursement of time for accurate pedigree construction

No visual representation of the pedigree in the electronic medical record

Considerations for Germline Testing

- Reasonable chance of detecting a pathogenic germline variant
- Genetics professional available to provide pre- and post-test counseling, interpretation of results, and coordination of care for the family
- Will change management for the patient and/or the family

3 Major Considerations Suggestive of Germline Risk

- Patient characteristics
- Tumor characteristics
- Family characteristics

Patient Characteristics

- Cancer occurring at a younger age than expected
- More than one primary cancer in one person or bilateral cancer in a paired organ
- Presence of premalignant conditions
- A diagnosis of a rare cancer or cancer associated with hereditary risk

Tumor Characteristics

- Microsatellite instability in colon or endometrial cancer
- Triple negative breast cancer (especially in a woman under 60 years of age)
- Gleason score greater than 7 in prostate cancer
- Higher allele count on tumor (somatic) testing in a germline gene

Family History Characteristics

- Evidence of autosomal-dominant inheritance
- Any pattern of cancer(s) associated with a known cancer syndrome
- A family history of rare cancers
- A known pathogenic variant in the family
- Member of an ethnic group associated with increased risk of hereditary cancer

A Multi-Step Process: Pre-test Counseling

Assess

- Personal and family medical history
- Risk perception and motivation for testing

Educate

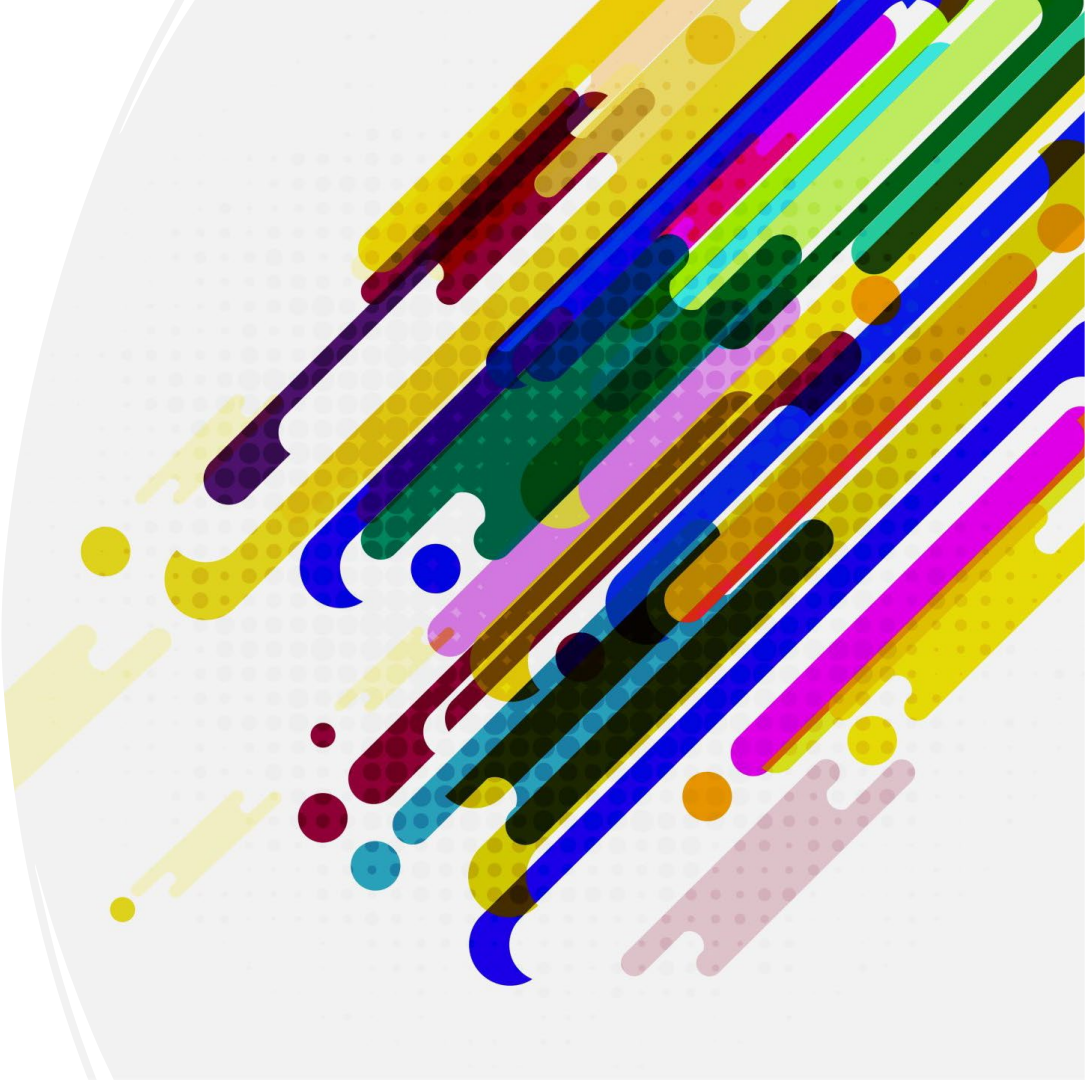
- Basic genetics and inheritance
- Cancer or other disease genetics and risk

Discuss

- Risks, benefits, and limitations of testing
- Test procedure – blood or saliva
- Alternatives to testing
- Management options – depending on test results

Informed Consent: Potential Benefits of Germline Genetic Testing

- Improved risk management
- Relief from uncertainty and anxiety about risk
- Information for individual and family members
- Lifestyle decision making



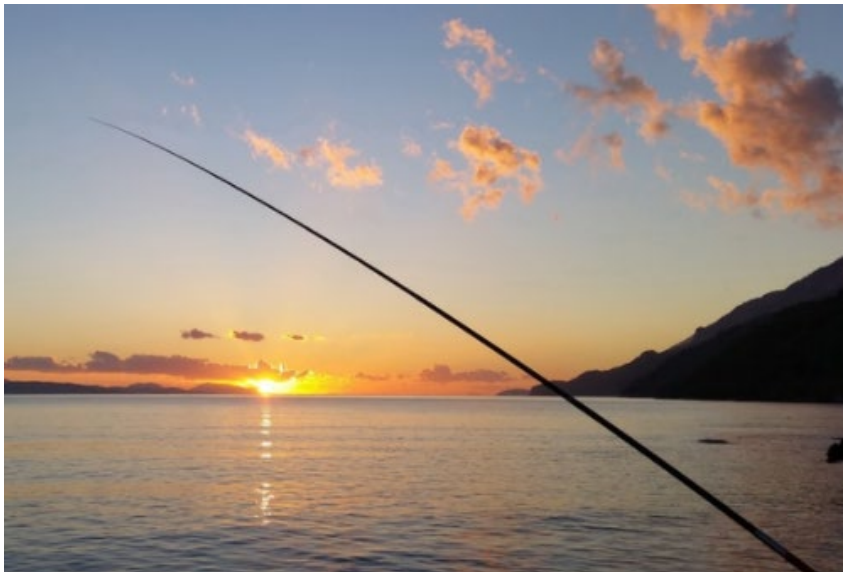
Informed Consent:
Potential Risks of Germline Genetic Testing

- Psychological distress
- Loss of privacy
- Problems obtaining life or disability insurance
- Change in family dynamics
- False sense of security

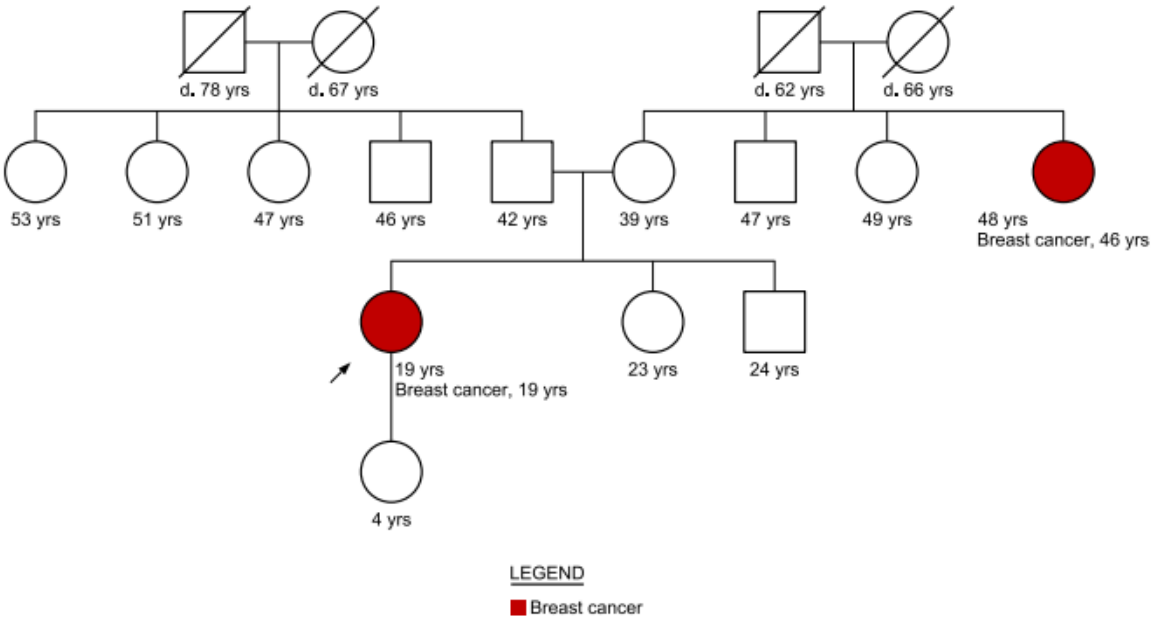
Informed Consent: Limitations of Germline Testing

- Not all pathogenic variants are detectable
- Uncertain significance of some pathogenic variants
- Negative result is fully informative only if a pathogenic variant has been identified in family
- Results indicate probability, not certainty, of developing disease
- Unproven efficacy of some interventions

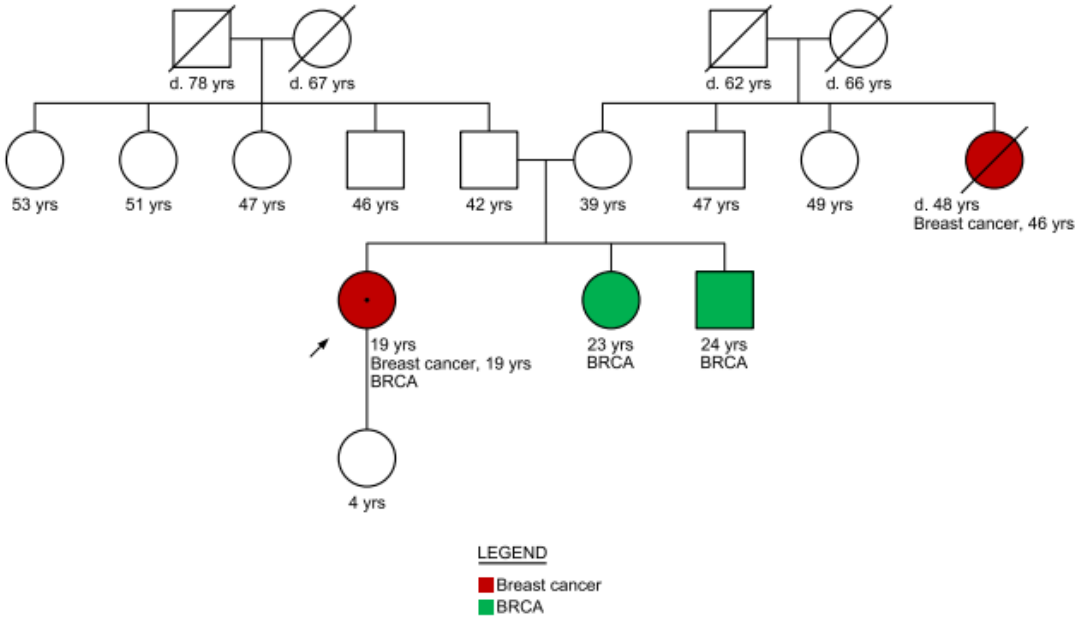
15% to 25% chance of a VUS
85% will be reclassified as benign



Case Study


d. 78 yrs
d. 67 yrs
d. 62 yrs
d. 66 yrs
53 yrs
51 yrs
47 yrs
46 yrs
42 yrs
39 yrs
47 yrs
49 yrs
48 yrs
Breast cancer, 46 yrs
19 yrs
Breast cancer, 19 yrs
23 yrs
24 yrs
4 yrs
LEGEND
Breast cancer

Case Study


d. 78 yrs
d. 67 yrs
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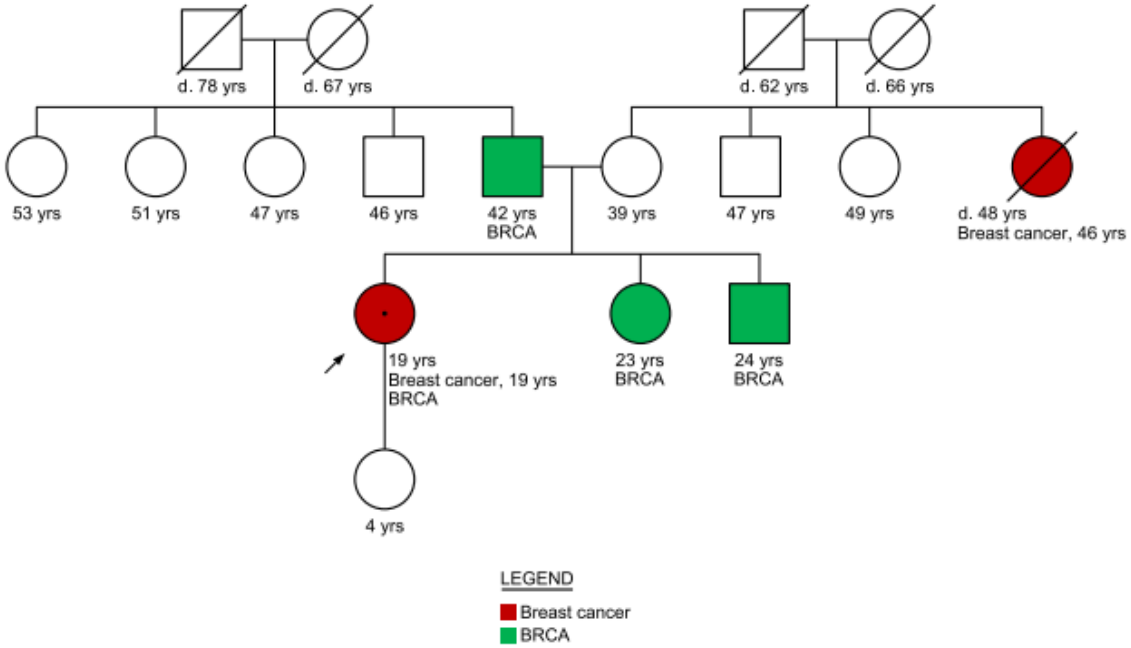
42 yrs
39 yrs
47 yrs
49 yrs
d. 48 yrs
Breast cancer, 46 yrs
19 yrs
Breast cancer, 19 yrs
BRCA
23 yrs
BRCA
24 yrs
BRCA
4 yrs
LEGEND
Breast cancer
BRCA

Case Study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BRCA
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47 yrs
49 yrs
d. 48 yrs
Breast cancer, 46 yrs
19 yrs
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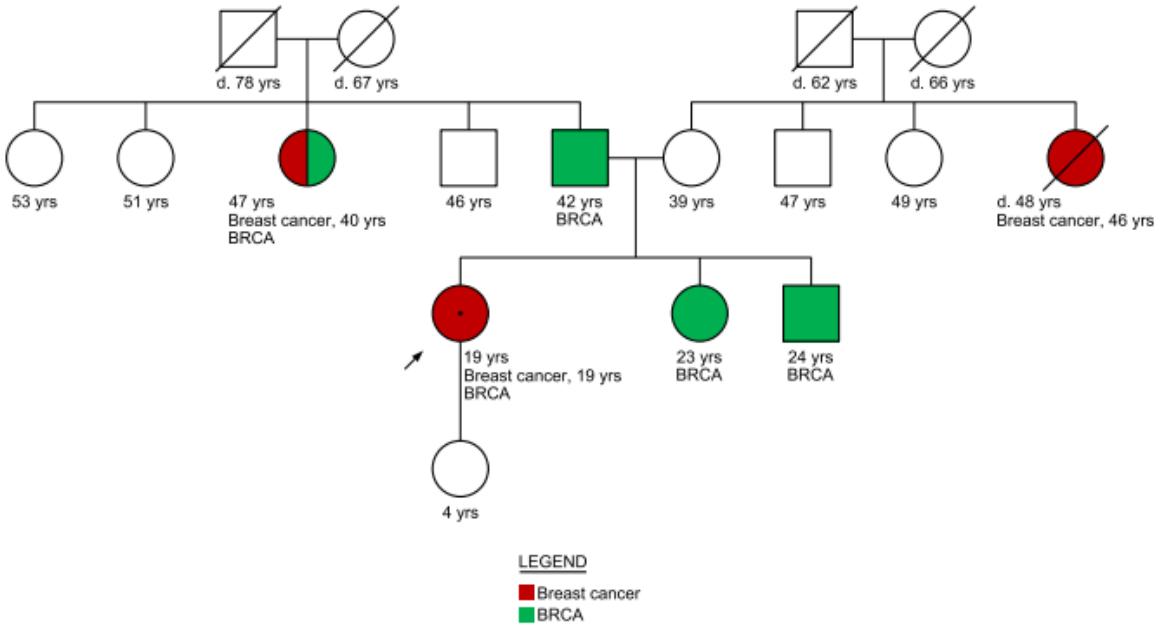
BRCA
23 yrs
BRCA
24 yrs
BRCA
4 yrs
LEGEND
Breast cancer
BRCA

Case Study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Breast cancer, 40 yrs
BRCA
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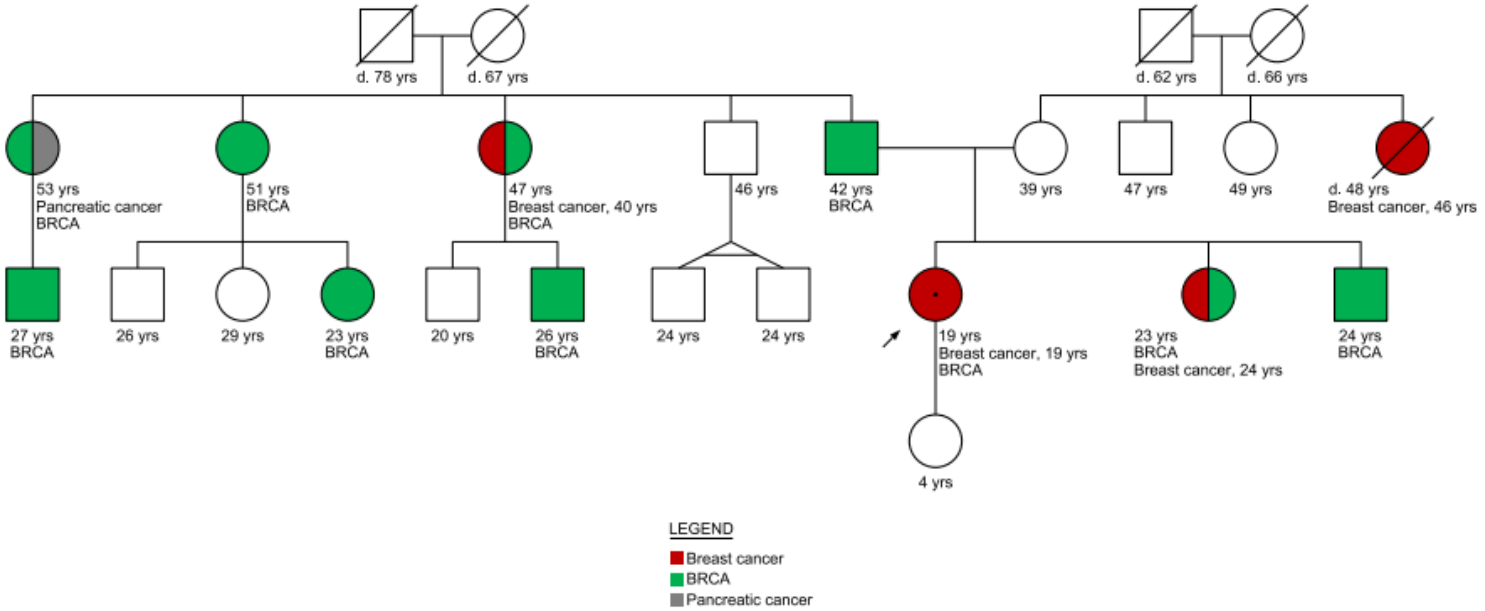
42 yrs
BRCA
39 yrs
47 yrs
49 yrs
d. 48 yrs
Breast cancer, 46 yrs
19 yrs
Breast cancer, 19 yrs
BRCA
23 yrs
BRCA
24 yrs
BRCA
4 yrs
LEGEND
Breast cancer
BRCA

Case Study


d. 78 yrs
d. 67 yrs
d. 62 yrs
d. 66 yrs
53 yrs
Pancreatic cancer
BRCA
51 yrs
BRCA
47 yrs
Breast cancer, 40 yrs
BRCA
46 yrs
42 yrs
BRCA
39 yrs
47 yrs
49 yrs
d. 48 yrs
Breast cancer, 46 yrs
27 yrs
BRCA
26 yrs
29 yrs
23 yrs
BRCA
20 yrs
26 yrs
BRCA
24 yrs
24 yrs
19 yrs
Breast cancer, 19 yrs
BRCA
23 yrs
BRCA
Breast cancer, 24 yrs
24 yrs
BRCA
4 yrs
LEGEND
Breast cancer
BRCA
Pancreatic cancer

Check Back Every 12 Months

- Family history
- Variant classification
- Recommendations

Susceptibility Testing

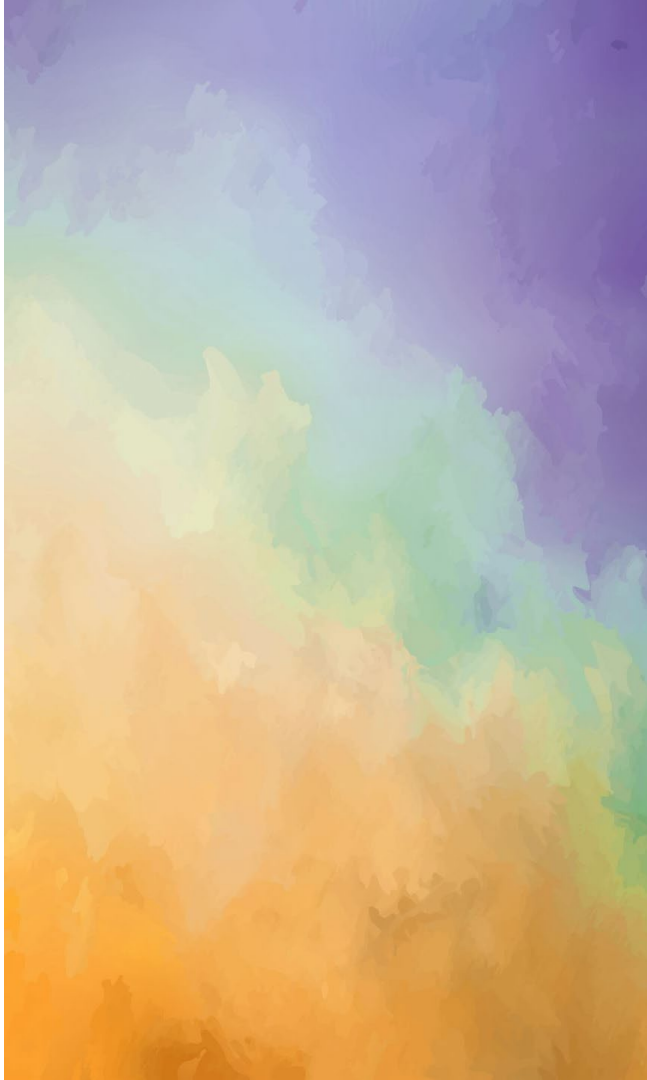
- A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or malignancy
- Germline testing
- BRCA1/2; Lynch syndrome
- Consider penetrance and expressive variability

Diagnostic Biomarker

- A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease
- Estrogen/progesterone receptor testing
- HER2 testing in breast cancer to guide treatment

Prognostic Biomarker

- A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease
- Oncotype DX®



Predictive Biomarker

- A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from a treatment
- PARP inhibitors with a pathogenic BRCA1 variant
- Erlotinib for NSCLC with a pathogenic EGFR variant

Monitoring Biomarker

- A biomarker measured serially for assessing status of a disease
- CEA in colon cancer
- PSA in prostate cancer

Somatic Variant Classification

- **Tier I:** Variants of strong clinical significance
  FDA-approved therapy; included in professional guidelines
- **Tier II:** Variants of potential clinical significance
  FDA-approved therapies for different tumor types or investigational therapies
- **Tier III:** Variants of unknown significance
  No convincing published evidence of cancer association
- **Tier IV:** Variants of known insignificance (i.e., likely benign or benign)

Intersection of Germline and Somatic Testing

- Are there any patient, tumor, or family history red flags of germline risk?
- Is there a pathogenic variant in a gene associated with germline risk for developing malignancy?
- Consider type of testing (paired, somatic, or germline) and number of genes tested
- Variant allele frequency (VAF)

Tumor vs. Germline Testing

32-year-old female with metastatic rectal cancer

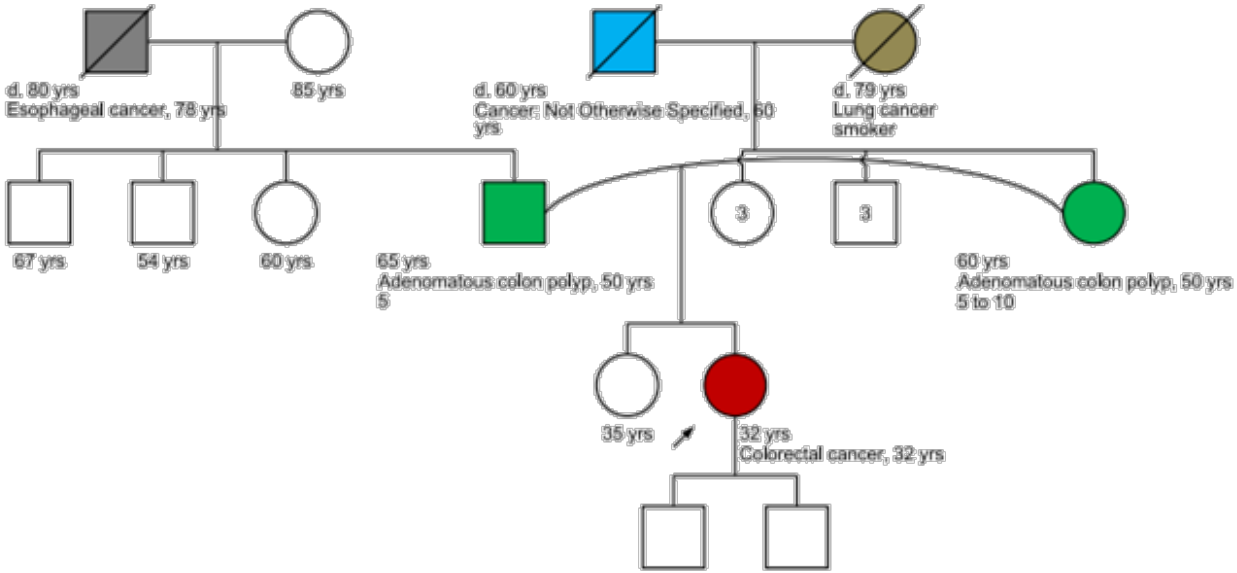
Tumor testing to select therapy

Tumor showed pathogenic variants in TP53, BRCA2, PTEN, and APC as well as 21 VUS

Germline testing was offered based on early-onset colorectal cancer

Western European

Western European



Comprehensive Cancer Panel

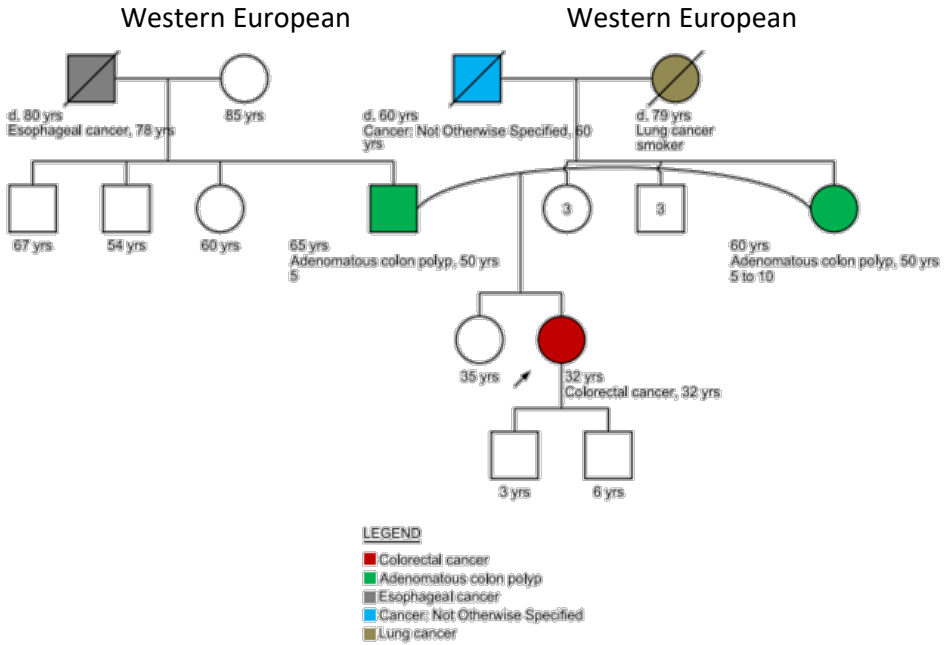
Genes Evaluated: APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SCG5/GREM1, SMAD4, STK11, TP53, VHL, XRCC2 (32 genes)

Test Indication

Personal history of rectal cancer. Family history of esophageal and other cancers, as well as adenomatous colon polyps. Rectal tumor was shown to be microsatellite stable with presence of MLH1, MSH2, MSH6 and PMS2 proteins on immunohistochemistry (IHC). Genetic testing of this patient's rectal tumor identified multiple variants at an outside laboratory, including BRCA2 L2357fs. MSH2 Exons 1-7 Inversion Analysis was negative at this laboratory.

Results Summary: POSITIVE

Gene	Variant	Classification	Zygosity
BRCA2	**c.7069_7070delCT (p.Leu2357ValfsX2)**	**PATHOGENIC**	**HETEROZYGOUS**


Western European
Western European
d. 80 yrs
Esophageal cancer, 78 yrs
85 yrs
d. 60 yrs
Cancer: Not Otherwise Specified, 60 yrs
d. 79 yrs
Lung cancer
smoker
67 yrs
54 yrs
60 yrs
65 yrs
Adenomatous colon polyp, 50 yrs
5
3
3
60 yrs
Adenomatous colon polyp, 50 yrs
5 to 10
35 yrs
32 yrs
Colorectal cancer, 32 yrs
3 yrs
6 yrs
LEGEND
Colorectal cancer
Adenomatous colon polyp
Esophageal cancer
Cancer: Not Otherwise Specified
Lung cancer

Reading a Somatic Report

- Variants detected
- Variant tier
- FDA-approved therapies
- Therapies not likely to be effective
- Clinical trials
- FDA-approved therapies in other tumor types
- Genes tested
- Immunotherapy/Microsatellite instability
- Prognostic and diagnostic variants
- VAF

Patient	Physician	Specimen
Name: Disease: Date of Birth: Sex: Health Record #:	Ordering Physician: Facility: Medical Faculty ID: Pathologist: Additional Recipients:	Specimen Type: FFPE Specimen Site: Left lung Tumor Type: Lung adenocarcinoma Collection Date: 3/30/2022 Date of Analysis: 4/10/2022

CLINICALLY SIGNIFICANT VARIANTS

A Actionable Variant	B Classification	C FDA-Approved Therapies With Clinical Benefit	D Therapies Not Likely to Be Effective	E FDA-Approved Therapies in Different Cancer Type	F Potential Clinical Trials
EGFR amplification; T790M	Tier I	Osimertinib (Tagrisso®)	Gefitinib (Iressa®), erlotinib (Tarceva®), afatinib (Gilotrif®), dacomitinib (Vizimpro®)	None	60 current trials

G

Immunotherapy Biomarkers	Actionability
Microsatellite status: MS-Stable	No therapies or clinical trials
Tumor Mutational Burden: 8 Muts/Mb	No therapies or clinical trials

H

Prognostic or Diagnostic Variants

Biomarker	Classification	Associated Cancer Types	Associated Clinical Outcomes
TP53	Prognostic	Ovarian, esophageal, colorectal, head and neck, lung, leukemia, sarcoma, testicular, melanoma, cervical	More aggressive disease, increased rates of resistance to chemotherapy, shorter survival

Biomarker Interpretation

This patient has one variant of potential clinical significance (Tier 1) in the gene *EGFR*. Alterations of *EGFR* occur in approximately 10% of Caucasian patients and up to 50% of Asian patients with non-small cell lung cancer. Clinical correlation is required.

I

Gene	Variant	VAF/Copy	Depth	Functional Impact	Class	Type
EGFR	amplification; T790M	49.1%	1650X	Gain of function	Tier I	Therapeutic

J

Variants to Consider for Follow-up Germline Testing

Consider follow-up germline testing and genetic counseling based on the cancer susceptibility biomarker, EGFR p.T790M variant.

K

Variants of Uncertain Significance

Gene	Variant
AKT3	p.P449S c.1345C>T
RB1	p.S302Y c.905C>A

The clinical significance of these variants is unknown. Clinical decisions cannot be based on these findings.

L

Genes Tested

NCCN currently recommends broad panel biomarker testing for non-small cell lung cancer including at a minimum:

EGFR, *BRAF*, METex14 skipping variants, *RET* rearrangements, *ALK* fusions, *ROS1* fusions, *NTRK* gene fusions, high-level *MET* amplification, *ERBB2* variants and TMB

F

Available Clinical Trials

EGFR amplification; T790M

1. ClinicalTrials.gov ID: NCT05256290:
A Phase 1 Study to Assess BDTX-1535, an Oral EGFR Inhibitor, in Participants with Glioblastoma or Non-Small Cell Lung Cancer
Drug(s): BDTX-1535 Monotherapy; BDTX-1535 Monotherapy Dose Escalation

EGFR amplification; T790M

2. ClinicalTrials.gov ID: NCT04862780:
A Phase 1/2 Study Targeting Acquired Resistance Mechanisms in Patients with EGFR Mutant Non-Small Cell Lung Cancer
Drug(s): BLU-945; osimertinib

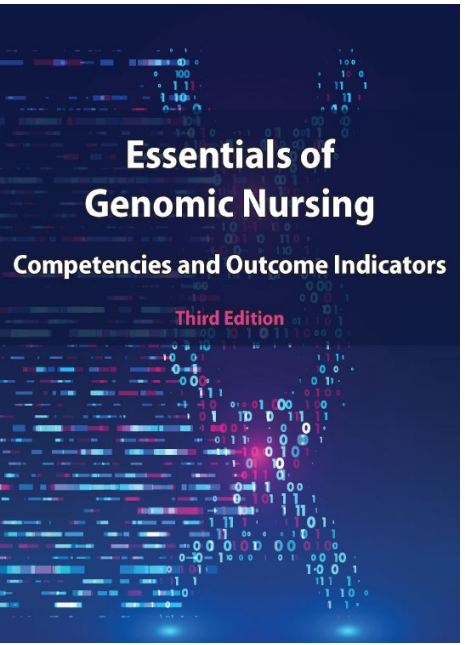
EGFR amplification; T790M

3. ClinicalTrials.gov ID: NCT04862780: (SYMPHONY)
Phase 1/2 Study Targeting EGFR Resistance Mechanisms in NSCLC
Drug(s): BLU-945; osimertinib

Why is this so important?

- Oncology nurses provide education about germline and somatic variants to patients and families.
- Biomarker testing that drives genomic cancer care provide information about susceptibility, prognosis, diagnosis, monitoring, and treatment choices.

Oncology Nursing Society Genomics and Precision Oncology Learning Library



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