Medical Genomics
Promise, Peril and Price.

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Washington University School of Medicine

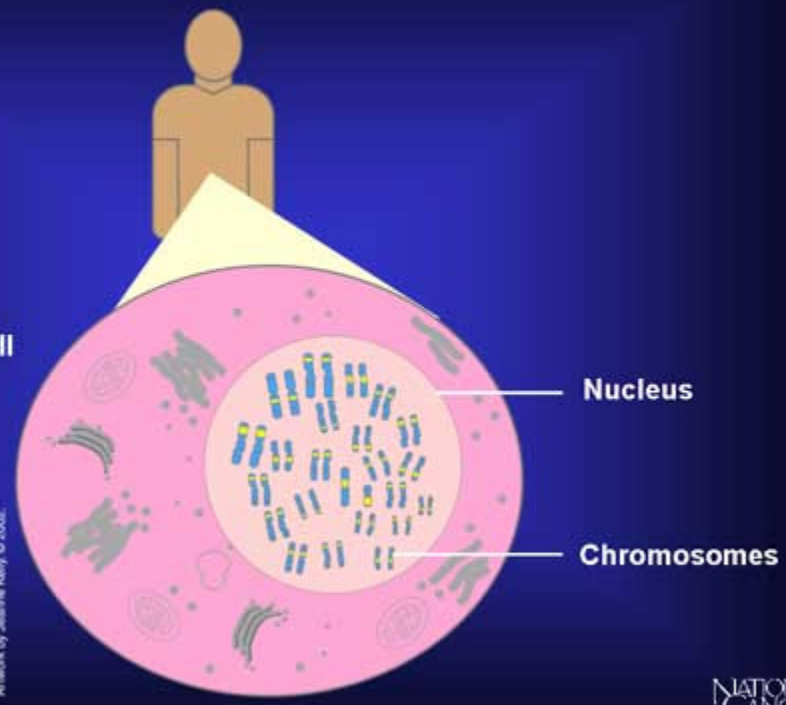
Overview of today's talk

- Genetic testing
- Genomic testing
  - Rare diseases
  - Cancer
- Technical limitations
- Ethical considerations
- The future
  - Pharmacogenomics
  - Common diseases

A few definitions….

- The Genome
- Genes
- Genetic variation
  - Normal
  - Deleterious (mutation or disease associated)
  - Unknown
- Gene testing

What Is the Human Genome?



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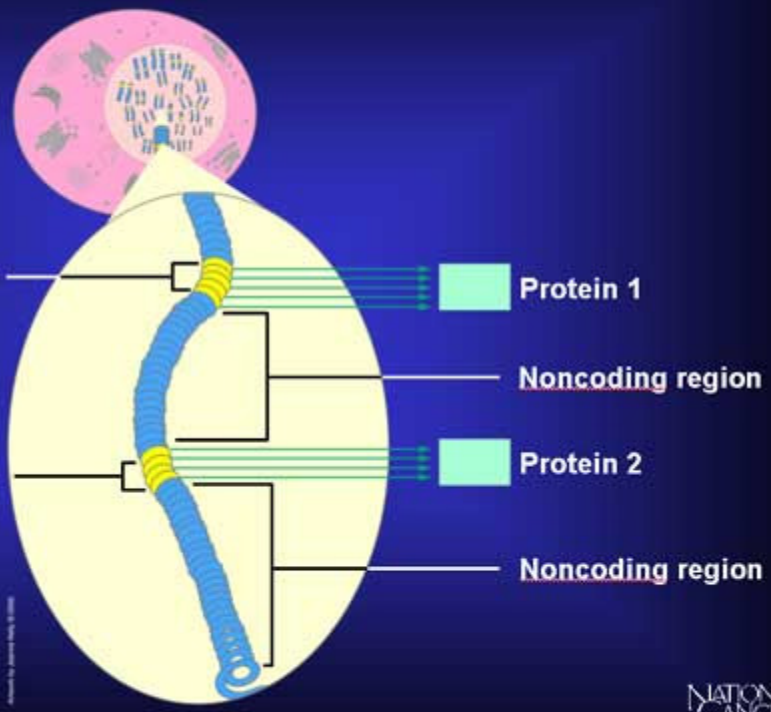
The Genome Contains Genes



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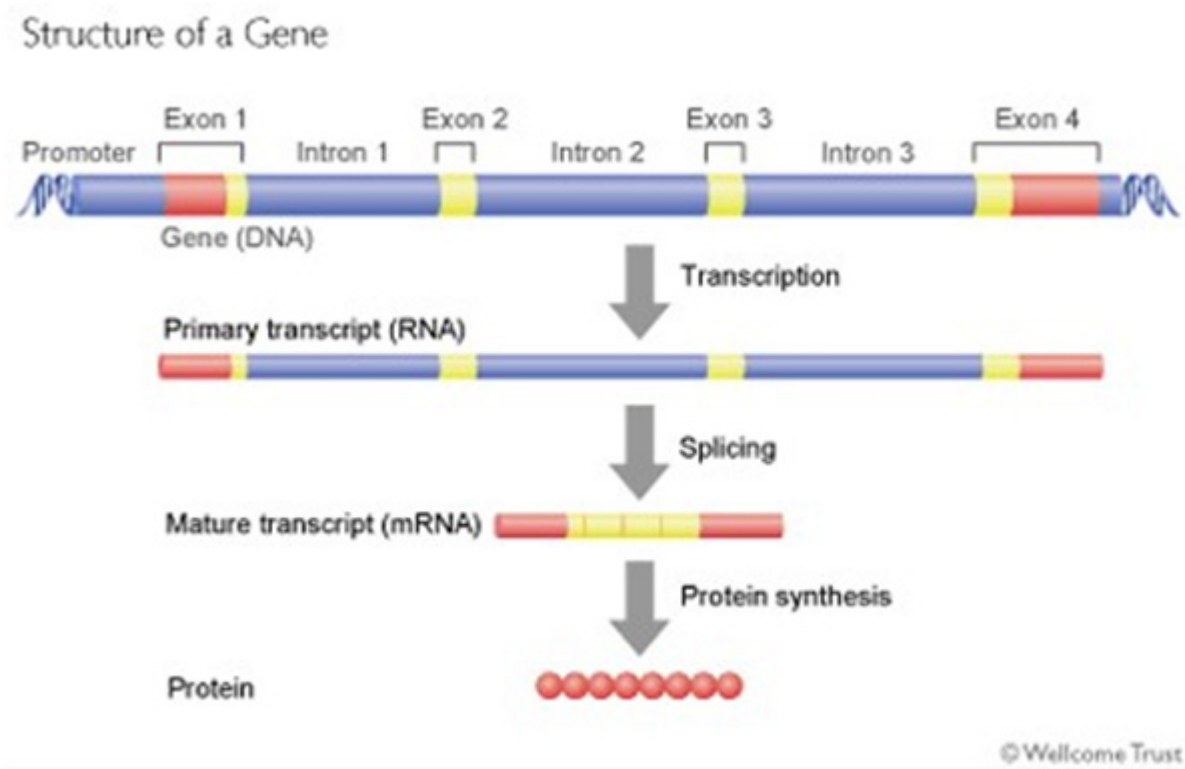
Genes


Structure of a Gene
Exon 1
Exon 2
Exon 3
Exon 4
Promoter
Intron 1
Intron 2
Intron 3
Gene (DNA)
Transcription
Primary transcript (RNA)
Splicing
Mature transcript (mRNA)
Protein synthesis
Protein
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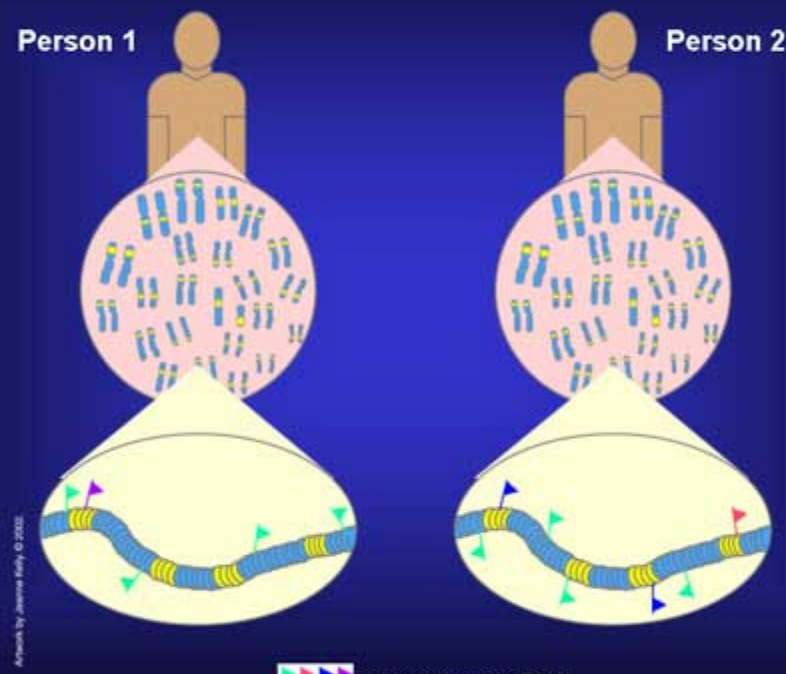
Variation in the Human Genome



= Variations in DNA

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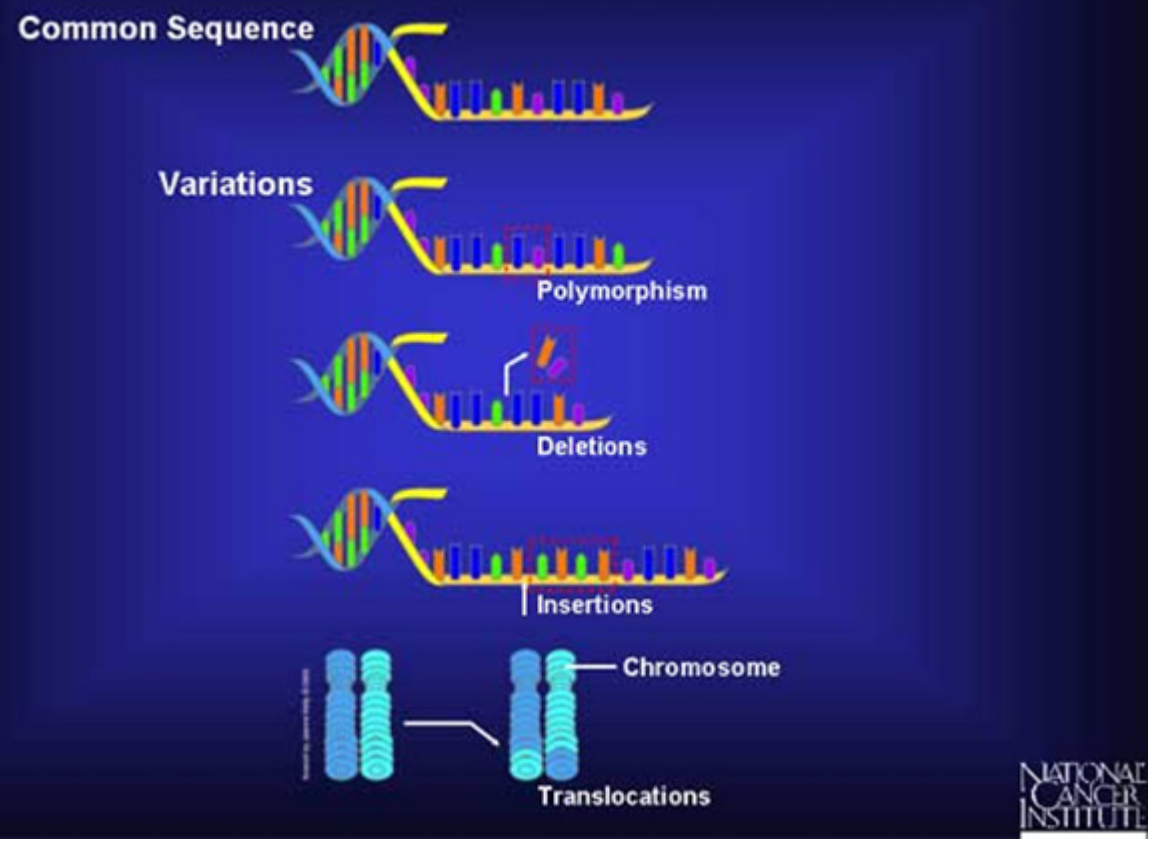
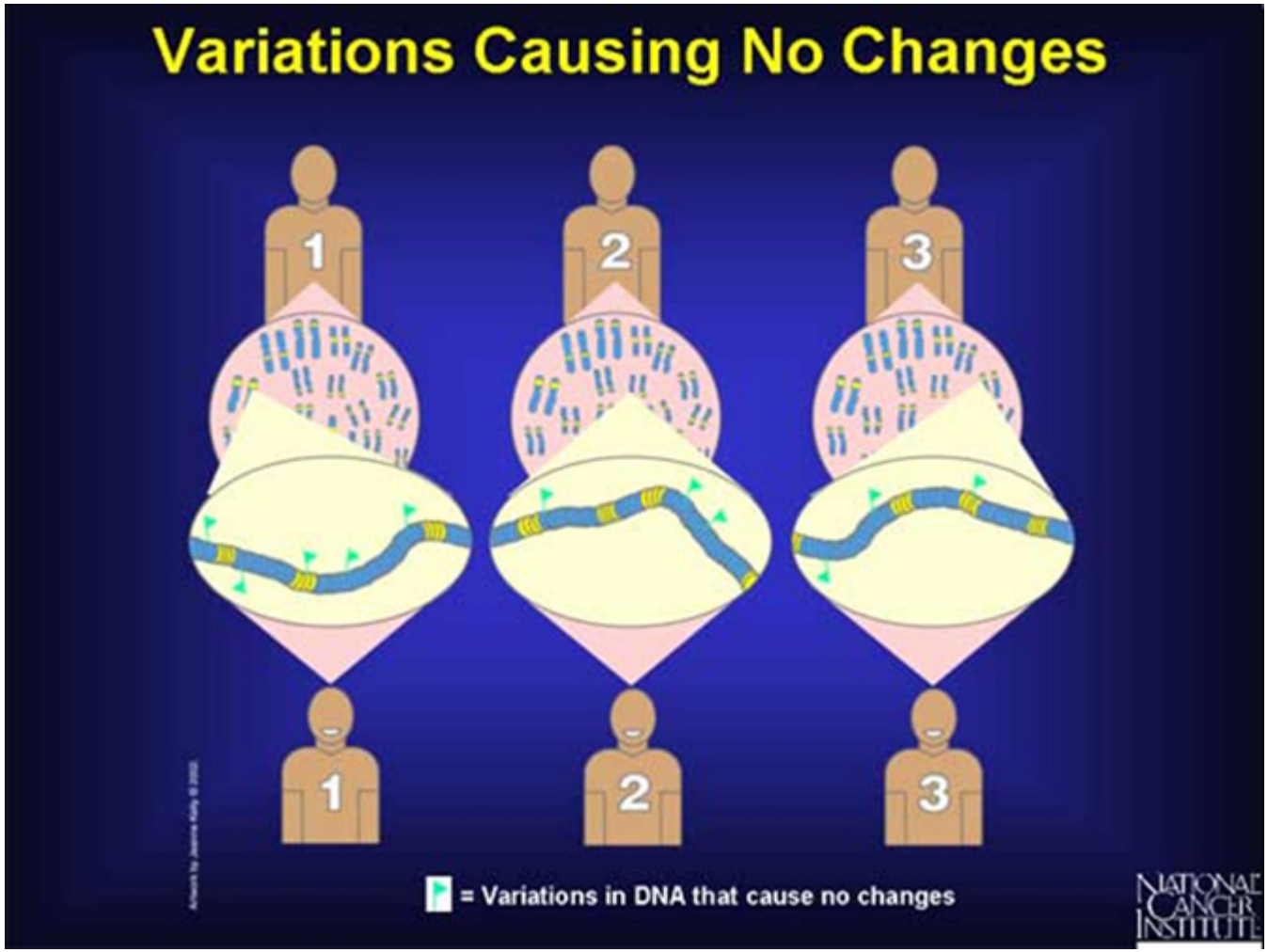
What Is Variation in the Genome?




Variations Causing No Changes
1
2
3
1
2
3
= Variations in DNA that cause no changes
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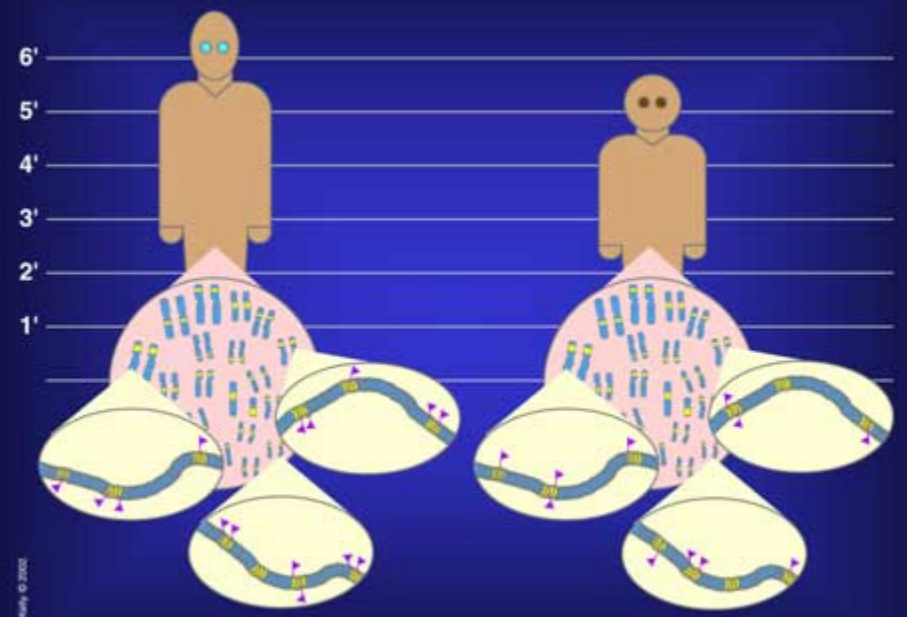
Variations Causing Harmless Changes



= Variations in DNA that cause harmless changes

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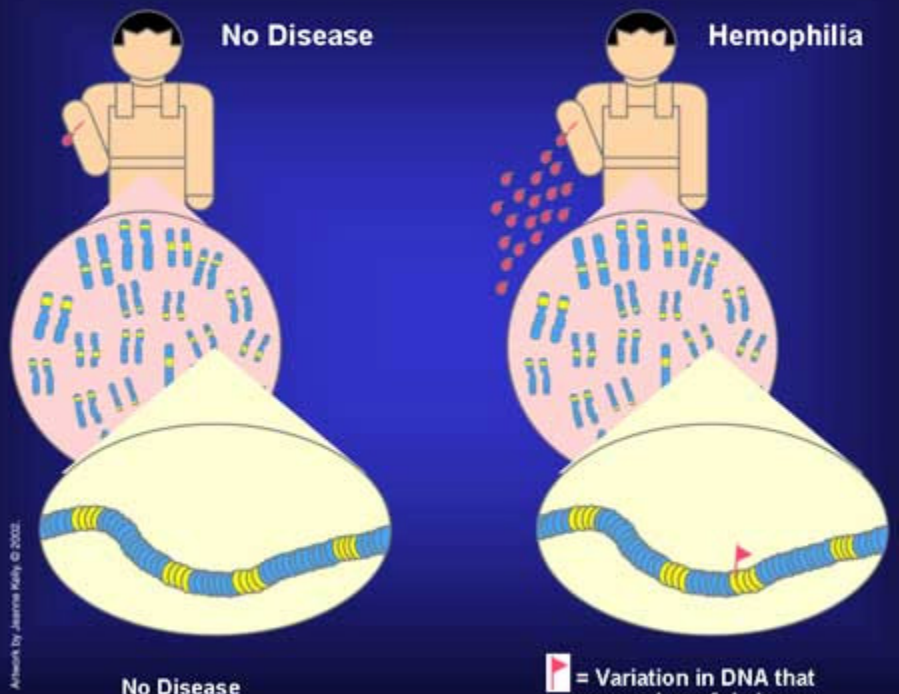
Variations Causing Harmful Changes



Artwork by Jeanne Kelly © 2002.

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Variations we don’t know

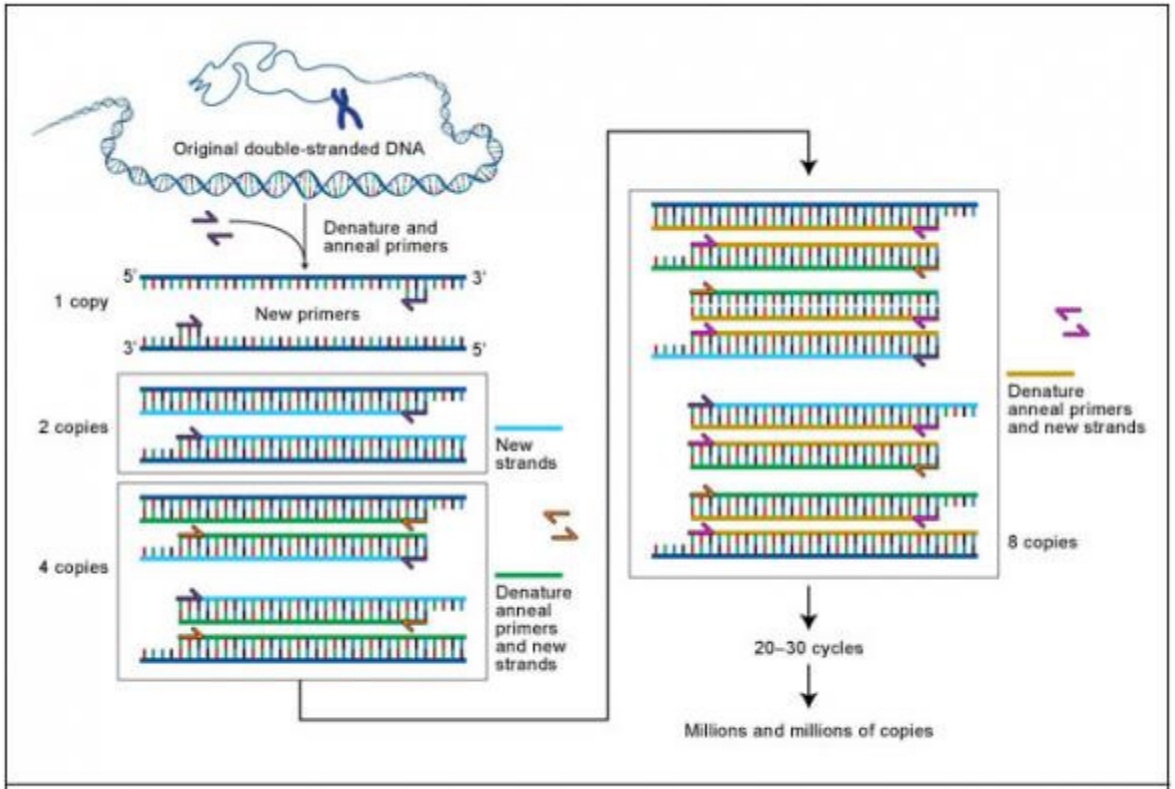
Genetic Testing

- Diagnostic:
  - "Is this Marfan Syndrome?"

- Presymptomatic:
  - "Am I at risk for the disease that runs in my family?" (Breast Cancer)

Genetic Testing

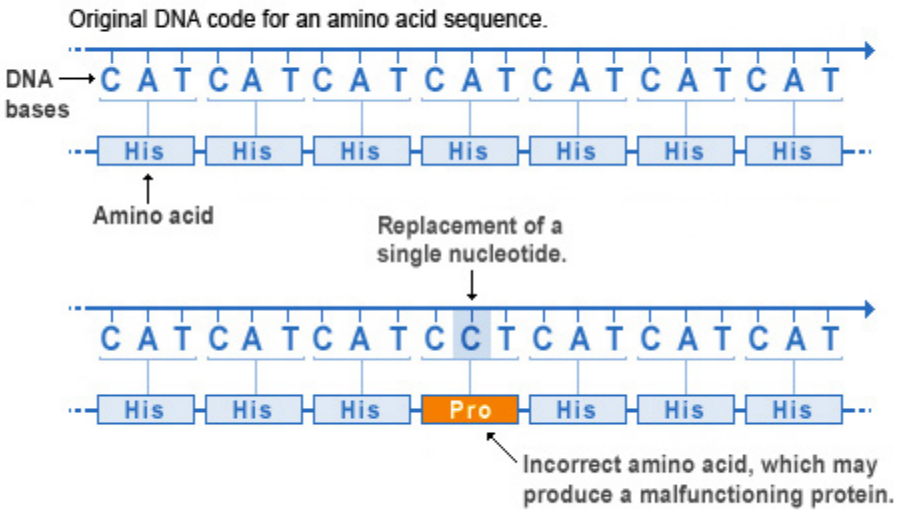
- Start with the family and personal history.
- Identify a clinical syndrome.
- Test a limited number of known genes (1-5).



Polymerase Chain Reaction

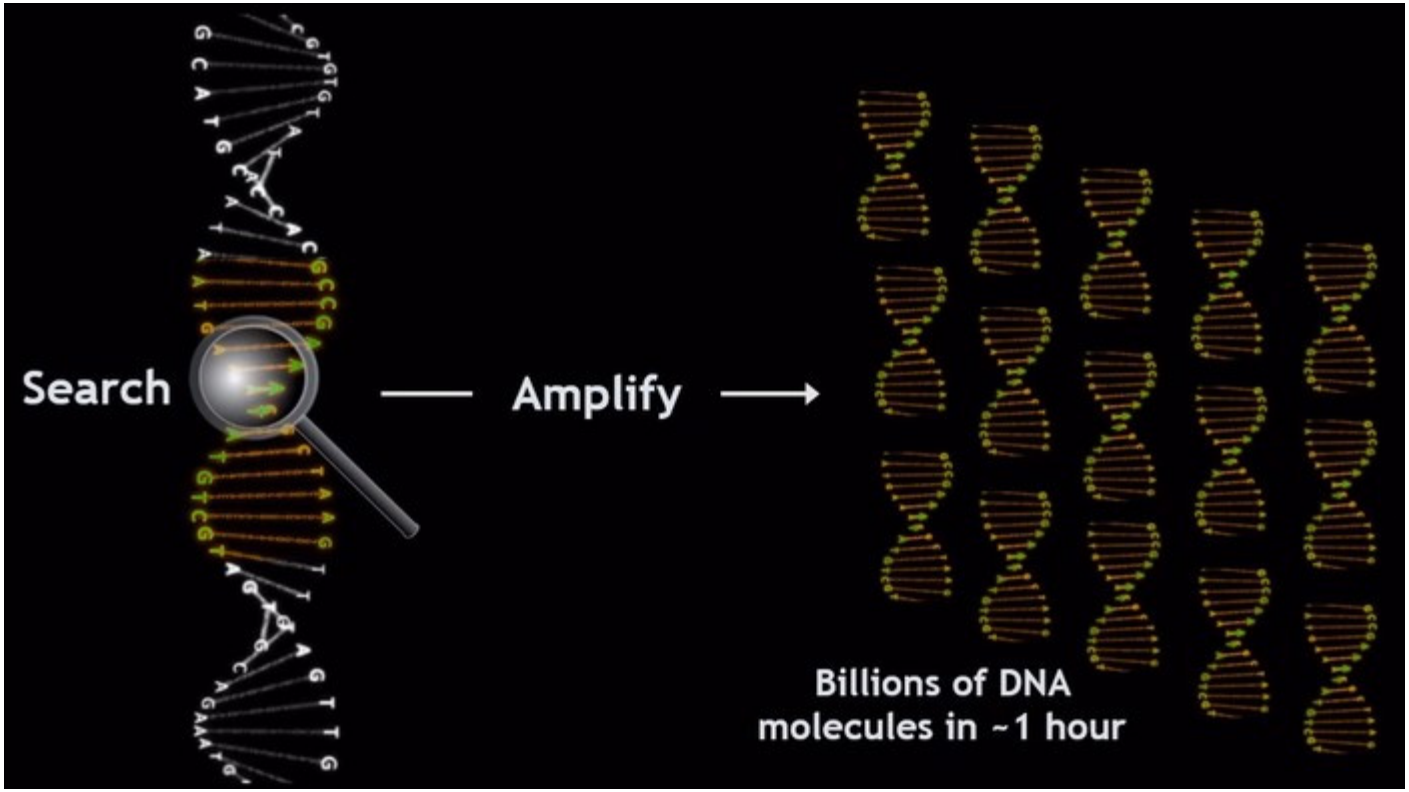
Source: National Human Genome Research Institute; *Artist:* Darryl Leja

Missense mutation



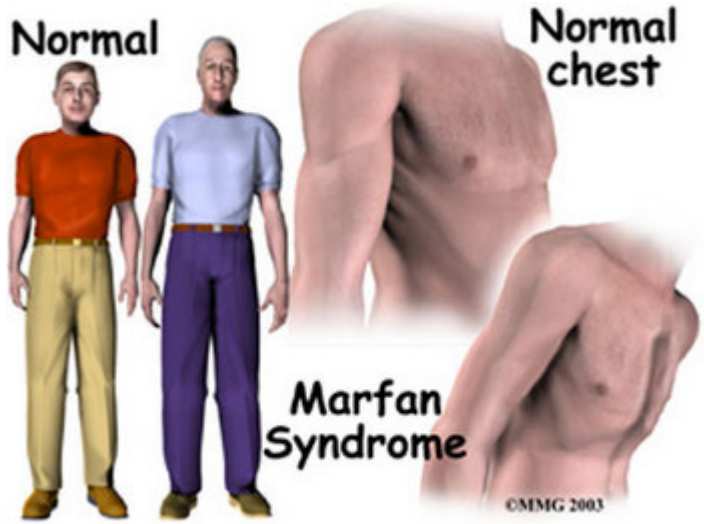
U.S. National Library of Medicine

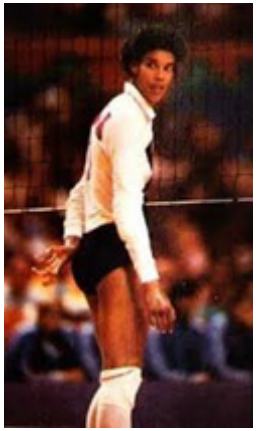
Only looking at a small part of the genome

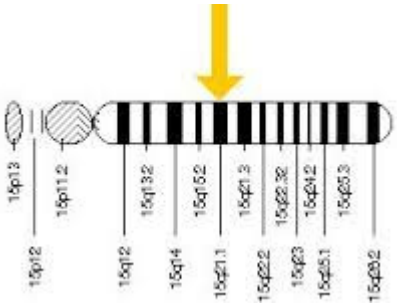


Example: Marfan Syndrome

- SS

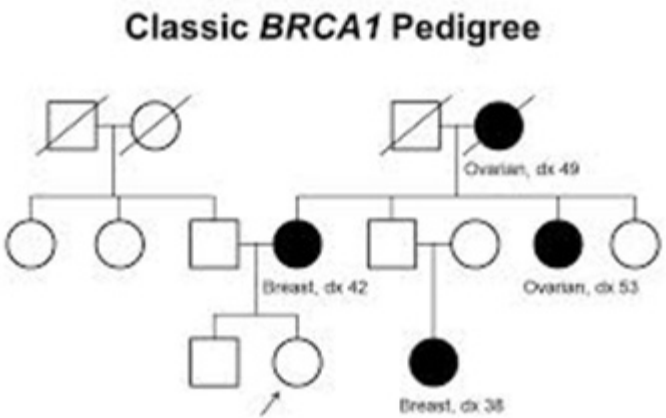


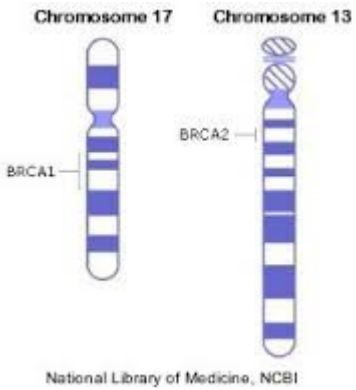




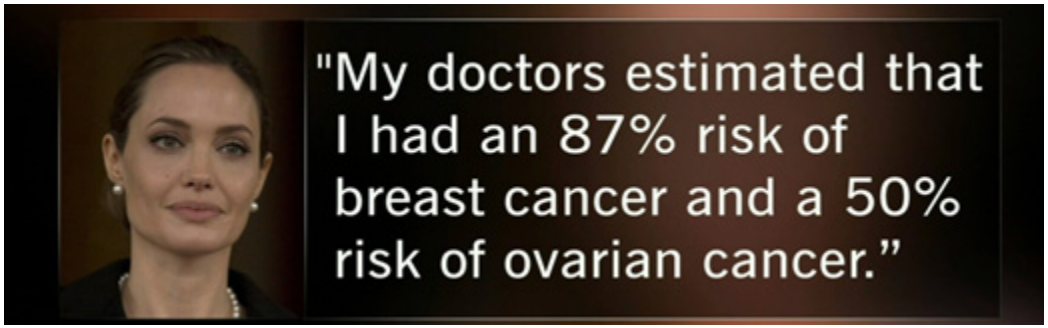
Fibrillin1 Gene identifies Mutations in the vast Majority of “Classic Marfan Syndrome”

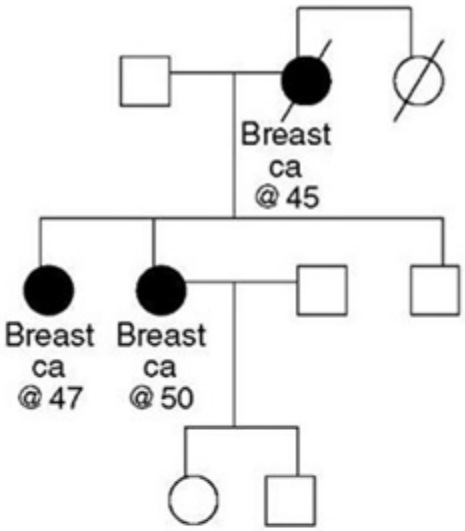
Example: Hereditary Breast Cancer BRCA1 and 2



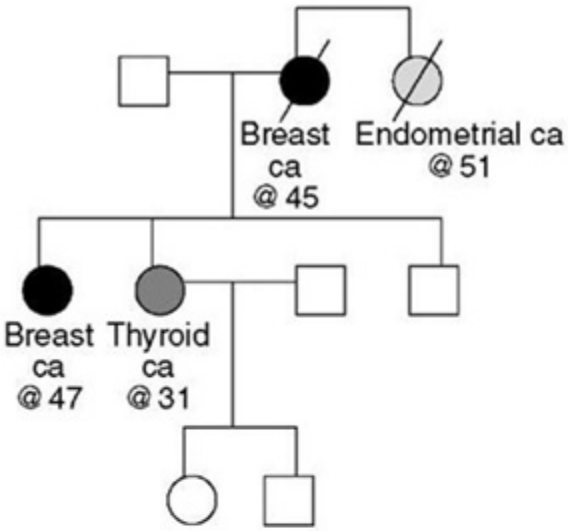


BRCA testing identifies a mutation in 85% of high risk families. What about the others?

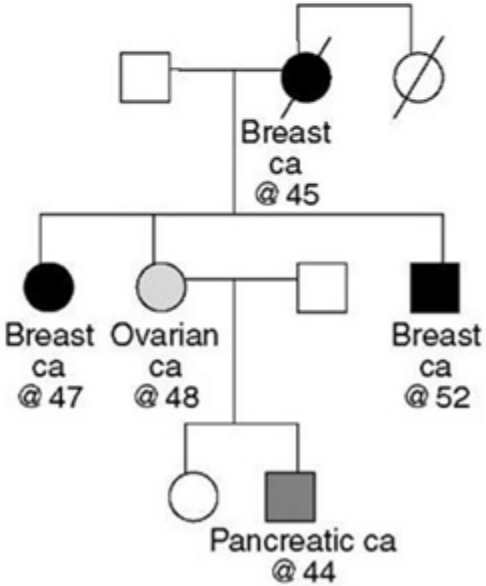




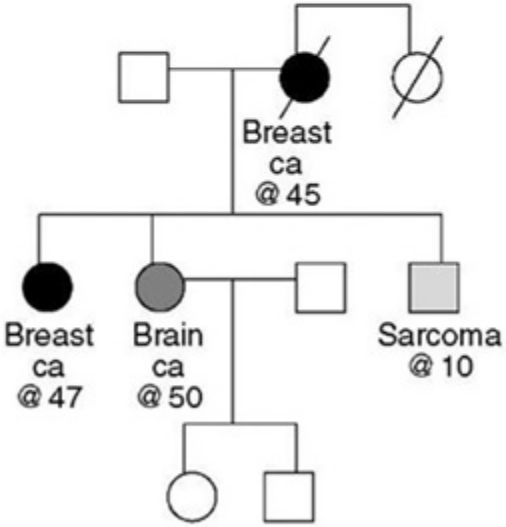
(a) Hereditary site-specific breast cancer



(b) Cowden syndrome



(c) Hereditary breast–ovarian cancer



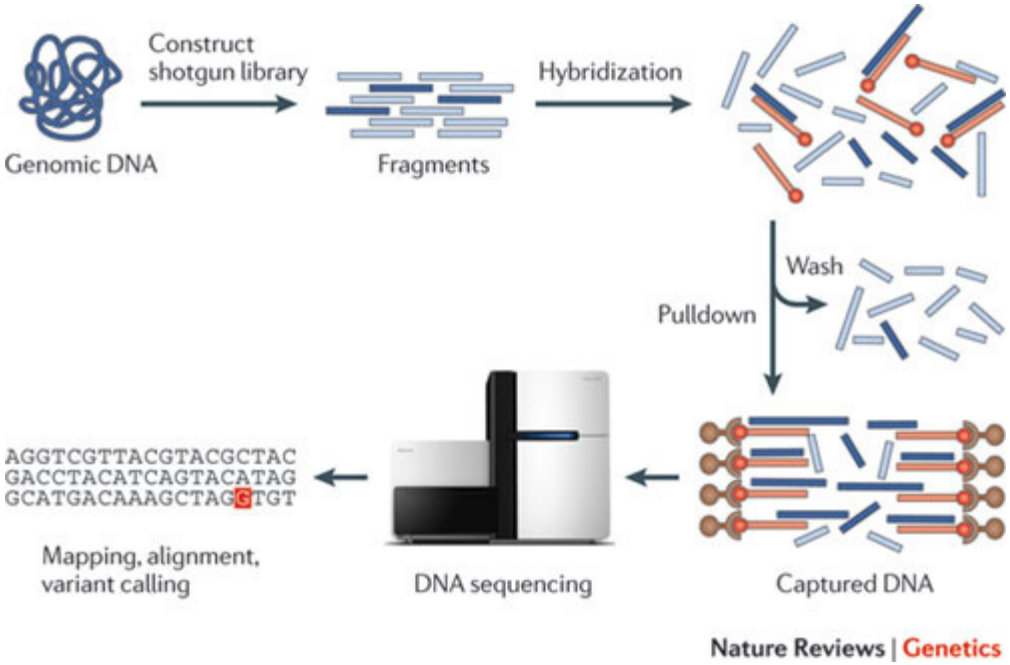
(d) Li–Fraumeni syndrome

Genetic Testing

- Pros:
  - Targeted, “affordable” testing.
  - Typically good data on risks and inheritance.
- Cons:
  - Limited number of syndromes had/have known genes.
  - Not all high-risk pedigrees “fit” a known syndrome…. we have more cancer genes to find.
  - Expensive.

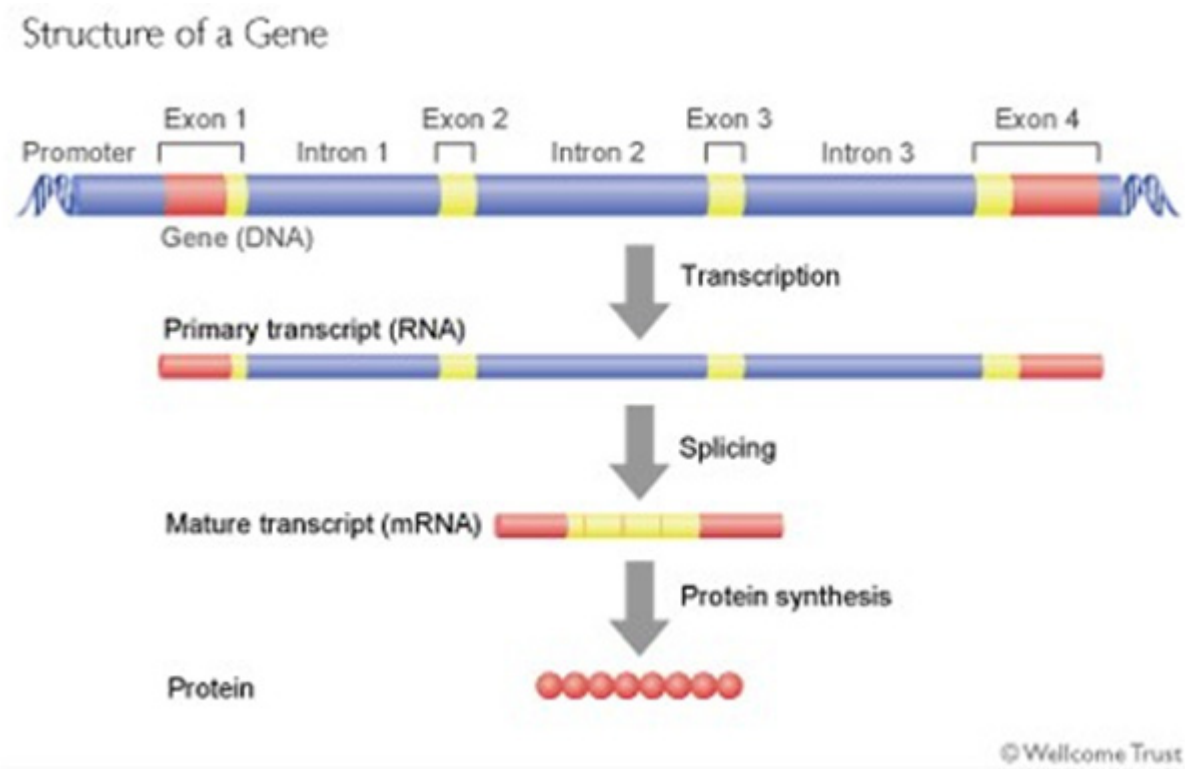
Next GEN sequencing
A few more definitions….

- Whole Genome Sequencing
- Exomes
- Whole Exome Sequencing (WES)



Nature Reviews | Genetics

Genes


Structure of a Gene
Exon 1
Exon 2
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Exon 4
Promoter
Intron 1
Intron 2
Intron 3
Gene (DNA)
Transcription
Primary transcript (RNA)
Splicing
Mature transcript (mRNA)
Protein synthesis
Protein
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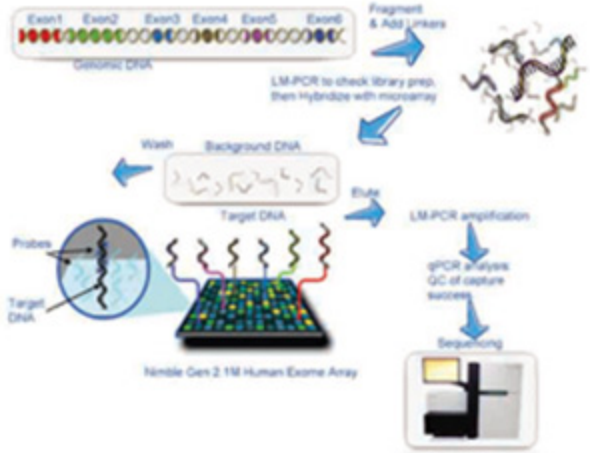
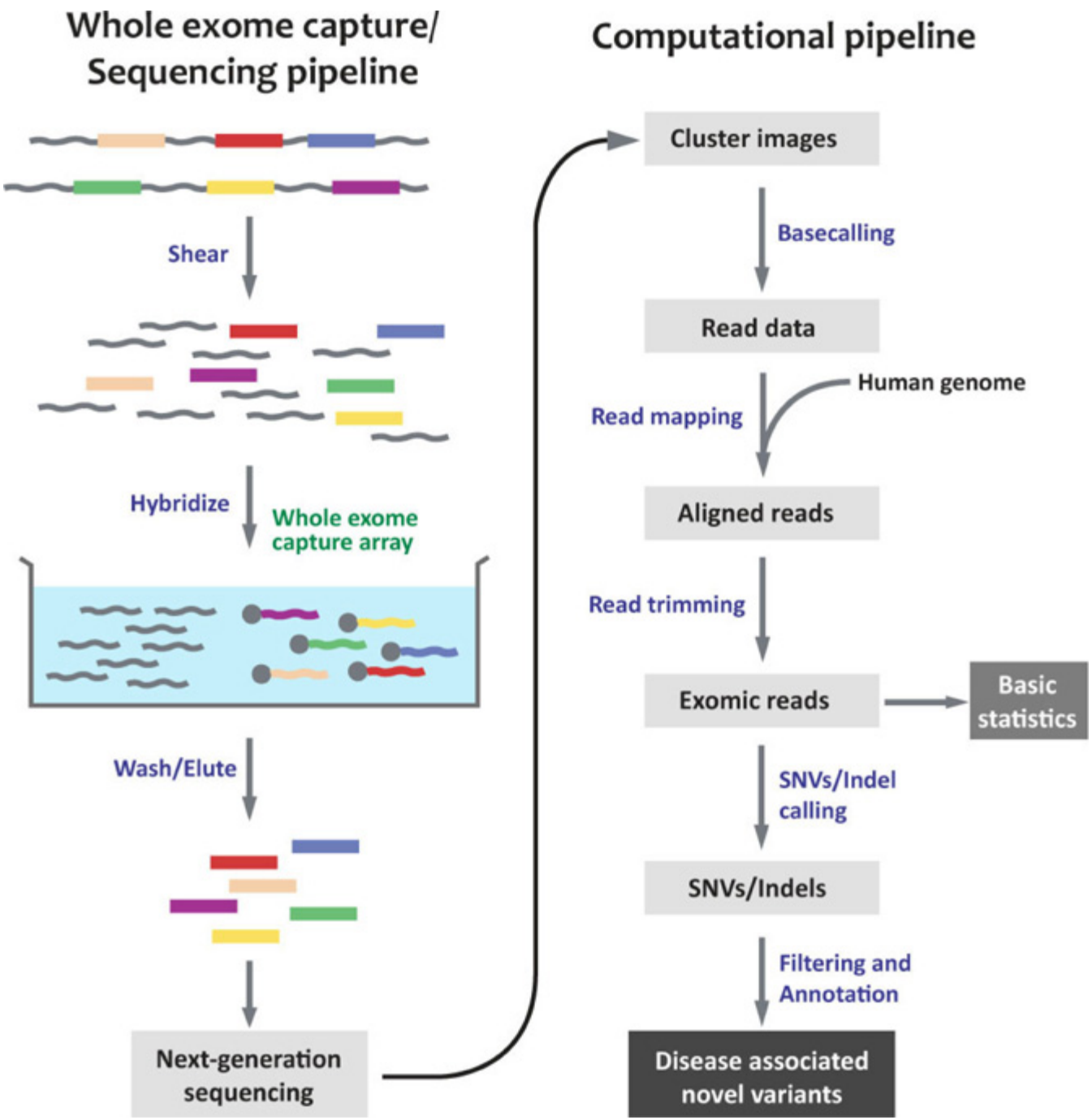
Exome & Targeted Resequencing




Whole exome capture/
Sequencing pipeline
Shear
Hybridize
Whole exome
capture array
Wash/Elute
Next-generation
sequencing
Computational pipeline
Cluster images
Basecalling
Read data
Human genome
Read mapping
Aligned reads
Read trimming
Exomic reads
Basic
statistics
SNVs/Indel
calling
SNVs/Indels
Filtering and
Annotation
Disease associated
novel variants

Clinical Exome Sequencing

- Rare genetic diseases
- Cancer Genomics

Autism Case

- A 3 year-old boy had slow development, autistic behaviors, and mild physical findings (short stature, misshaped ears, small mouth).
- Family history was unrevealing.
- Chromosome testing.
- Fragile X testing normal.

Autism case, continued

- At age 5 he was re-examined.
- No changes in history or exam. Development progressing but still delayed. Autistic behaviors continue. The parents were interested in having more children and were seeking recurrence risk information.

- Gene Panel for Autism (61 Genes).
  - Normal

Autism case, continued

- At age 6 (this year) he was again re-evaluated. He has started school. He now has a 9-month old sister who is doing well. His parents are still seeking answers.

- Whole Exome Sequencing is ordered.
  - What needs to be considered?

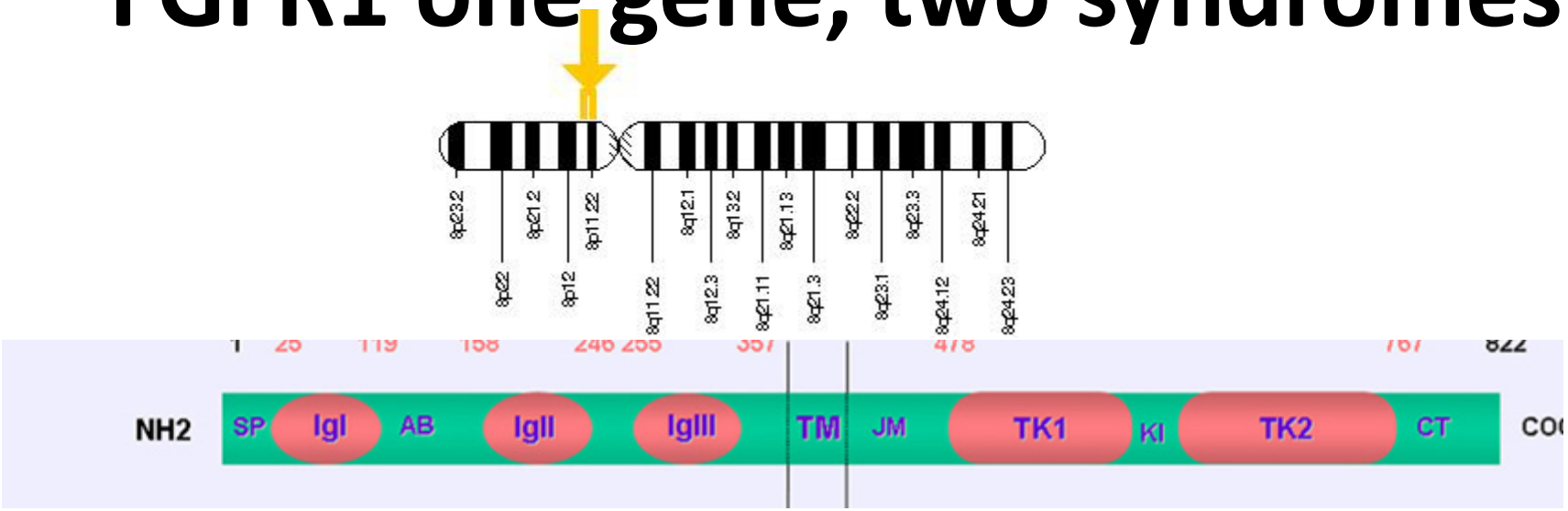
Whole Exome Sequencing (WES): Technical Challenges and Limitations

- No longer targeted testing--looking at all of the genes.
  - LOTS of data.
    - Need highly qualified bioinformatics technicians.
  - What is real vs. technical error?
    - Need intense quality controls.
- Not looking at the entire genome.
  - Will miss certain types of mutations.

Whole Exome Sequencing: Clinical Challenges

- Interpreting variations is challenging.
  - Is it a variation that causes no change?
  - Is it a harmless variation?
  - Is it a harmful variation (a mutation)?
  - Or is it one we cannot tell for sure (variant of unknown significance)?
- We are still learning what genes DO!
  - Some genes cause two very different syndromes.
  - Some genes we have no idea what they do!

FGFR1 one gene, two syndromes



Kallman Syndrome

- Delayed or absent Puberty
- Inability to smell

Pfeiffer Syndrome

- Early fusion of skull bones
- Other bony abnormalities

Whole Exome Sequencing: Ethical Challenges

- What to report
  - How certain do you have to be that the variation is disease causing?
  - Incidental findings.
- Informed consent
  - Massive information.
  - Testing in children.
- Constantly evolving/expanding knowledge
- Who gets tested?

WES Ethical Challenges: What to Report. Incidental Findings.

- In your search for an autism gene, what if you find a cancer predisposition gene, or Cystic fibrosis, or Alzheimer's gene…..?
- American College of Medical Genetics recommends:
  - Actively assessing 56 disease-related genes that are “actionable.”
  - Allowing patients to opt out of receiving the information.

WES Ethical Challenges: Knowledge is Constantly Evolving/Expanding

~~If~~ When the ACMG expands the list of "actionable genes."

When there is new information that reclassifies a "variant of unknown significance" as "a mutation."

Who follows up?

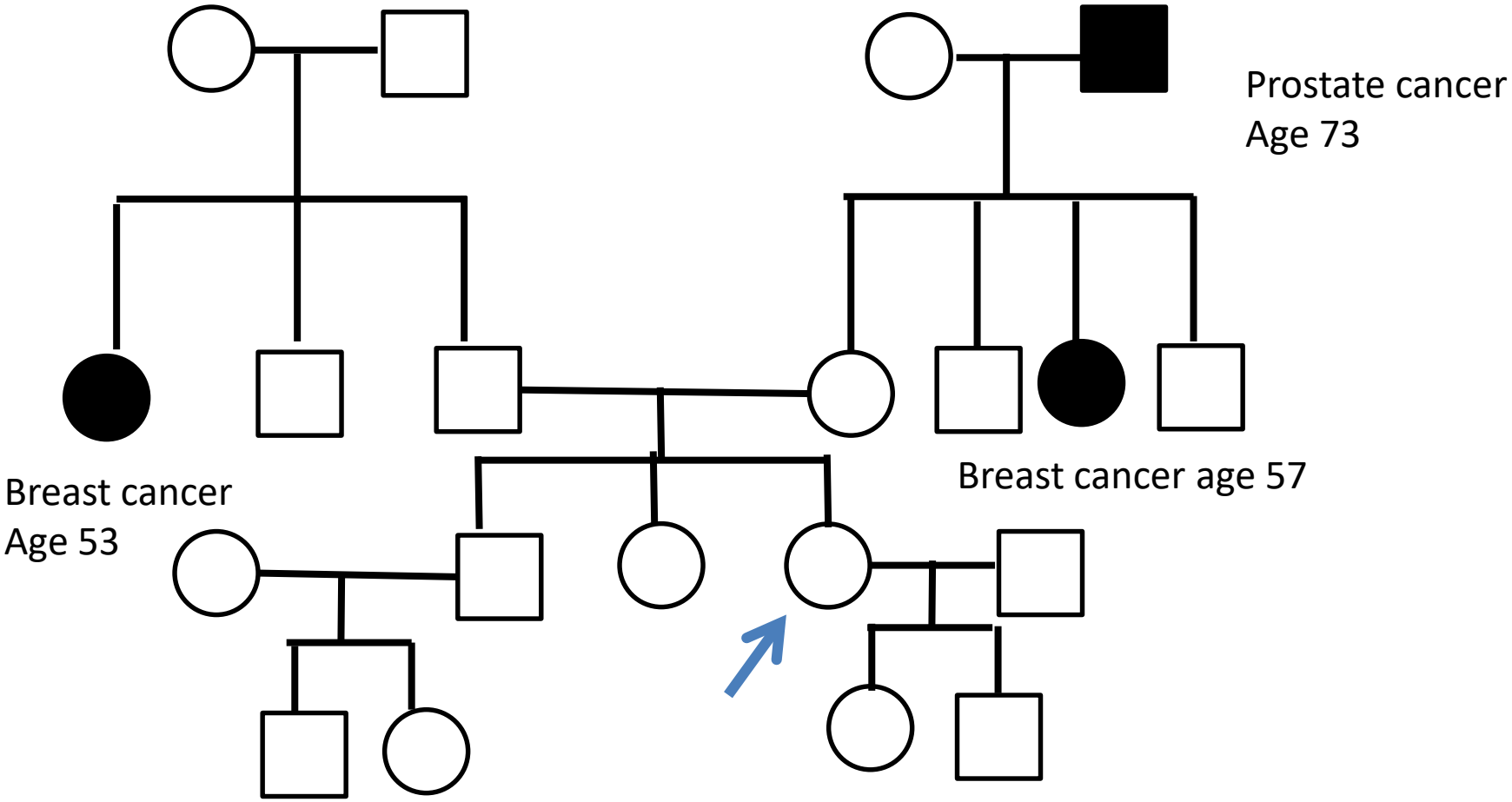
WES Ethical Challenges: Informed Consent

- Information overload
- Testing in children

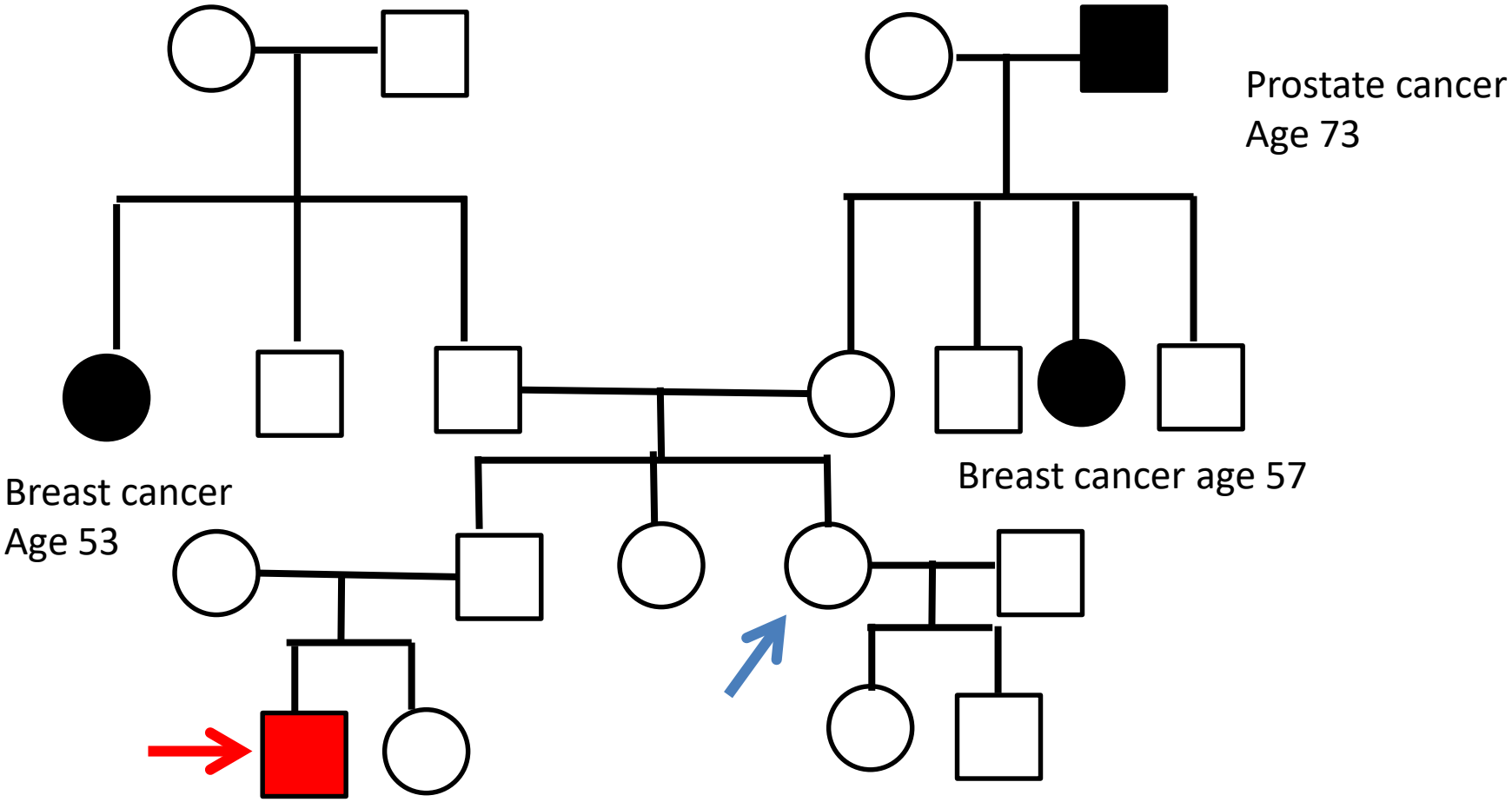
WES Ethical Challenges: Who Gets Tested?

- Access
  - Does your physician stay up to date on changes in genetics?
  - Is direct to consumer advertising opening access or causing harm?
  - Insurance coverage is variable.

A 47 year-old woman was seen in the Hereditary Cancer Clinic seeking BRCA1 testing

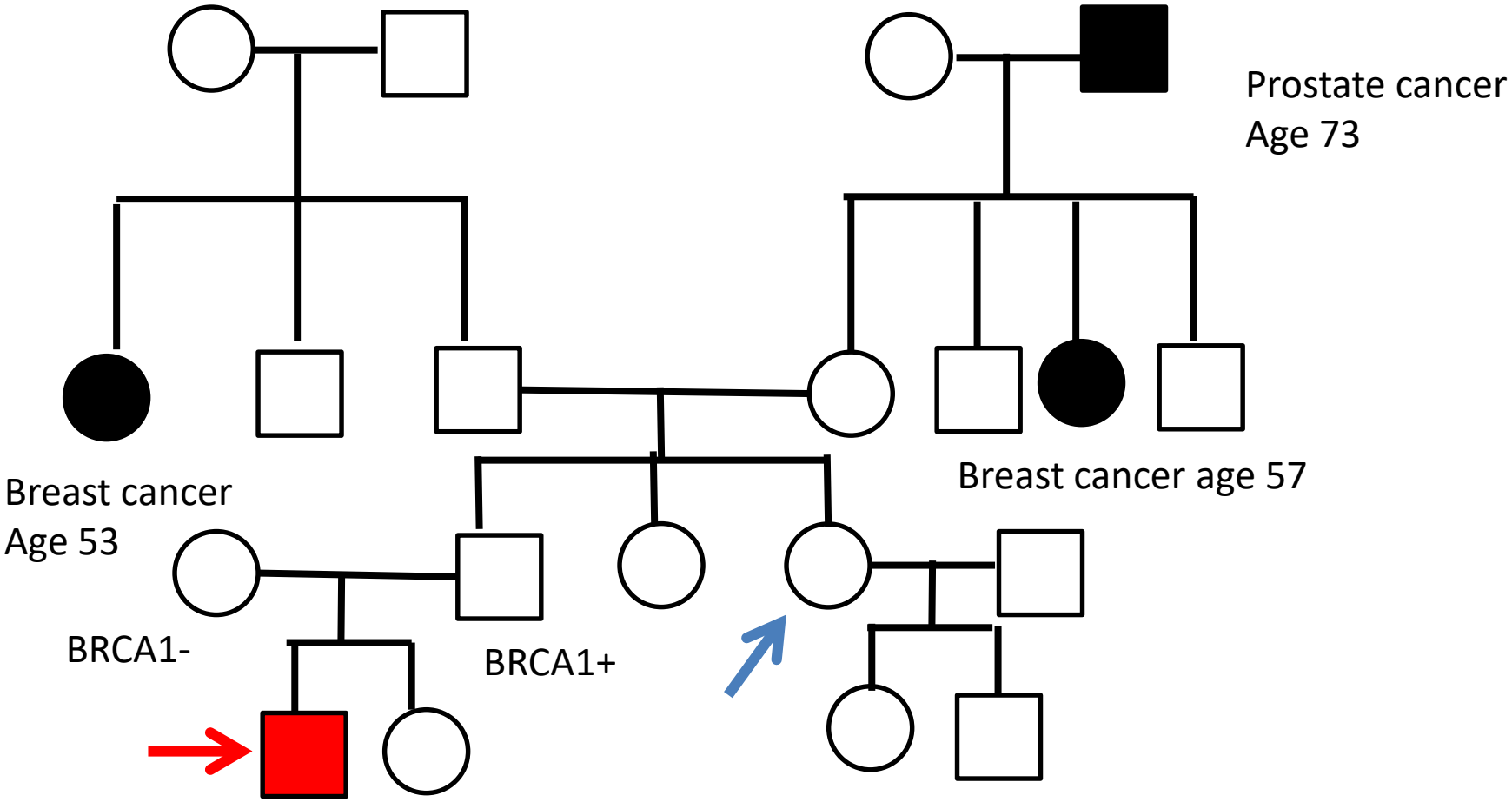


Her 6 year-old nephew is the boy with autism who had WES



A possible autism gene mutation identified. A definite BRCA1 mutation was identified

Her 6 year-old nephew is the boy with autism who had WES



A possible autism gene mutation identified. A definite BRCA1 mutation was identified

Final Thoughts

New services launching special
Human Exome 150X
/ Transcriptome 10Gb
for $1,999*!
until end of
October