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# Updates in Hereditary Cancer Genetics

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Genetic Support Foundation

August 7, 2019 Pierce County Cancer Survivorship Conference

## Disclosures

I am a fulltime employee of Genetic Support Foundation, a 501c3 nonprofit organization. The mission of GSF is to increase access to independent genetic counseling services and to develop educational resources for patients and providers.

I have no financial conflict of interest to disclose.

# **GOAL:**

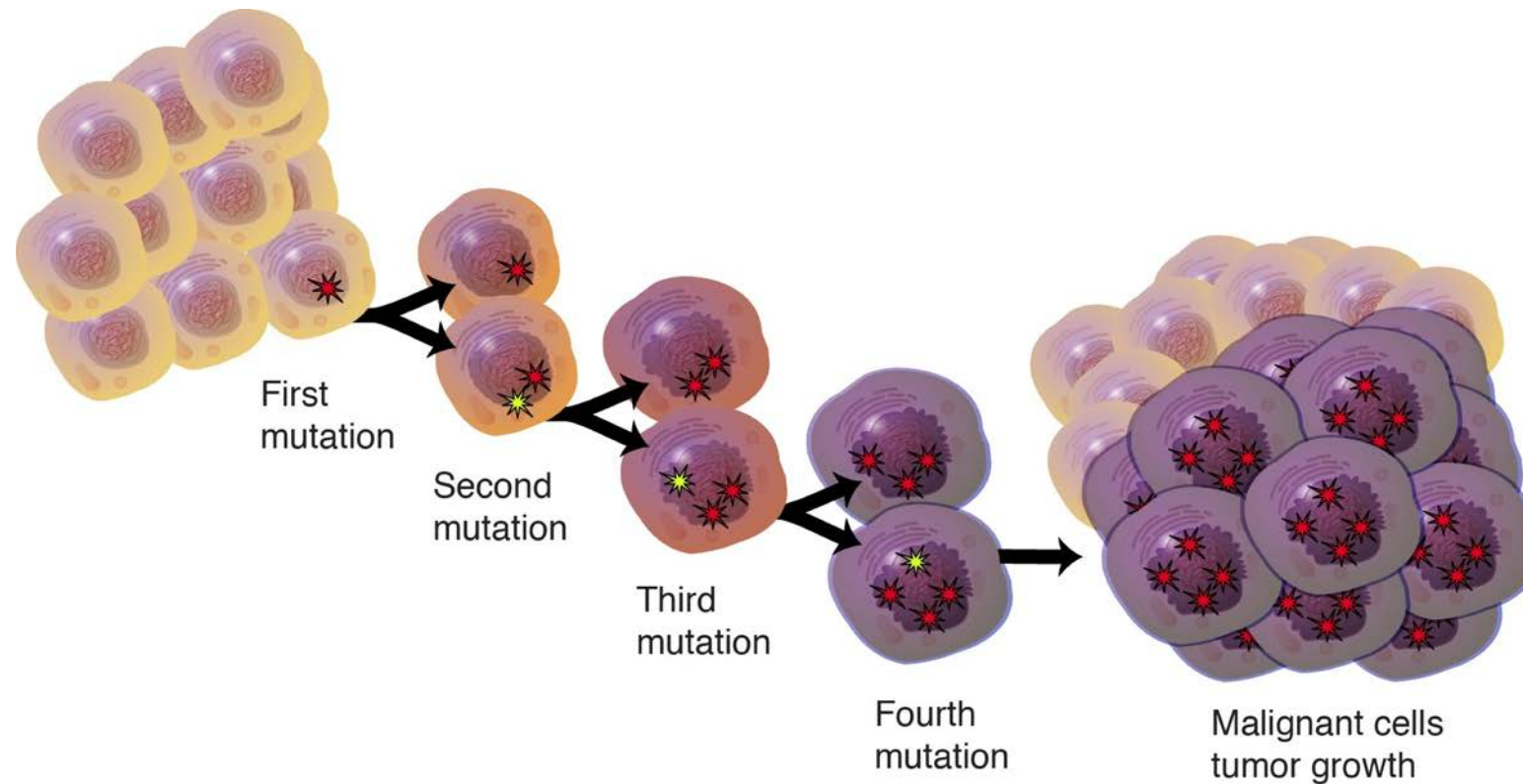
## **BETTER UNDERSTANDING OF GENETIC TESTING AND WHY WE DO IT**

- **Better define lifetime chance of developing cancer**
- **Cancer genetics is complicated- but that's okay. So is cancer.**
- **Genetics is a family ordeal**
- **Genetic testing can bring up more concerns that you haven't considered yet**
- **Not just a simple blood test**
- **There are times when testing is not recommended and reasons why someone may opt out of genetic testing**

# Genetics 101

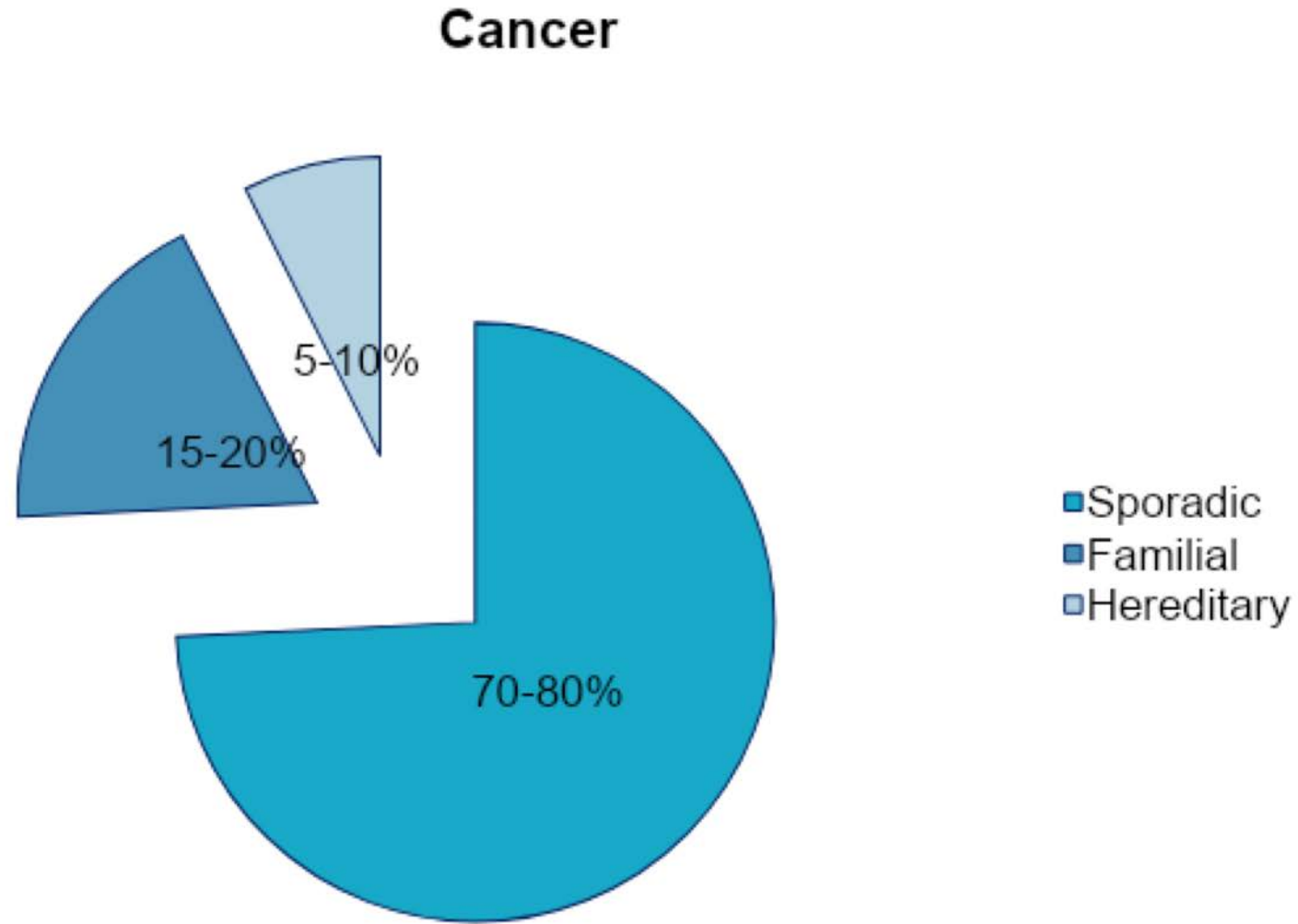


# Cancer= Uncontrolled Cell Growth Caused by DNA Mutations



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Genes, environment, and chance all play a role in cancer risk.



# Causes of Mutations

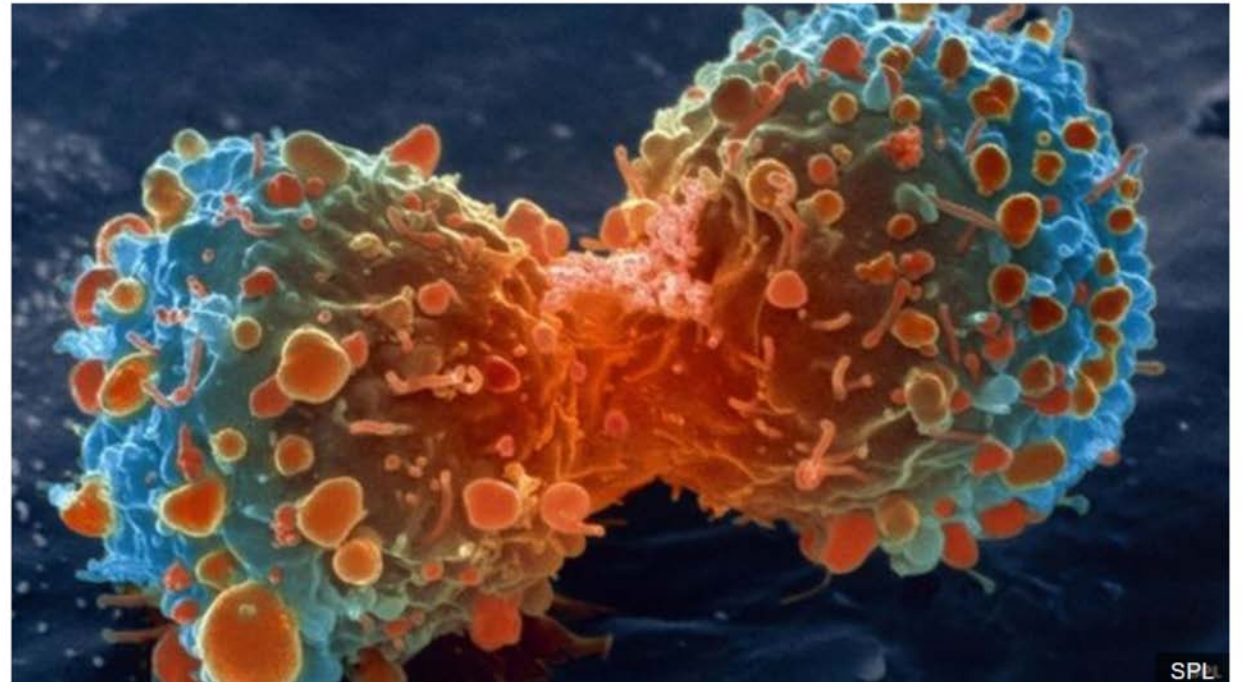
Random chance  
Chemicals and toxins  
Radiation  
Viruses  
Inherited deficiencies

## Most cancer types 'just bad luck'

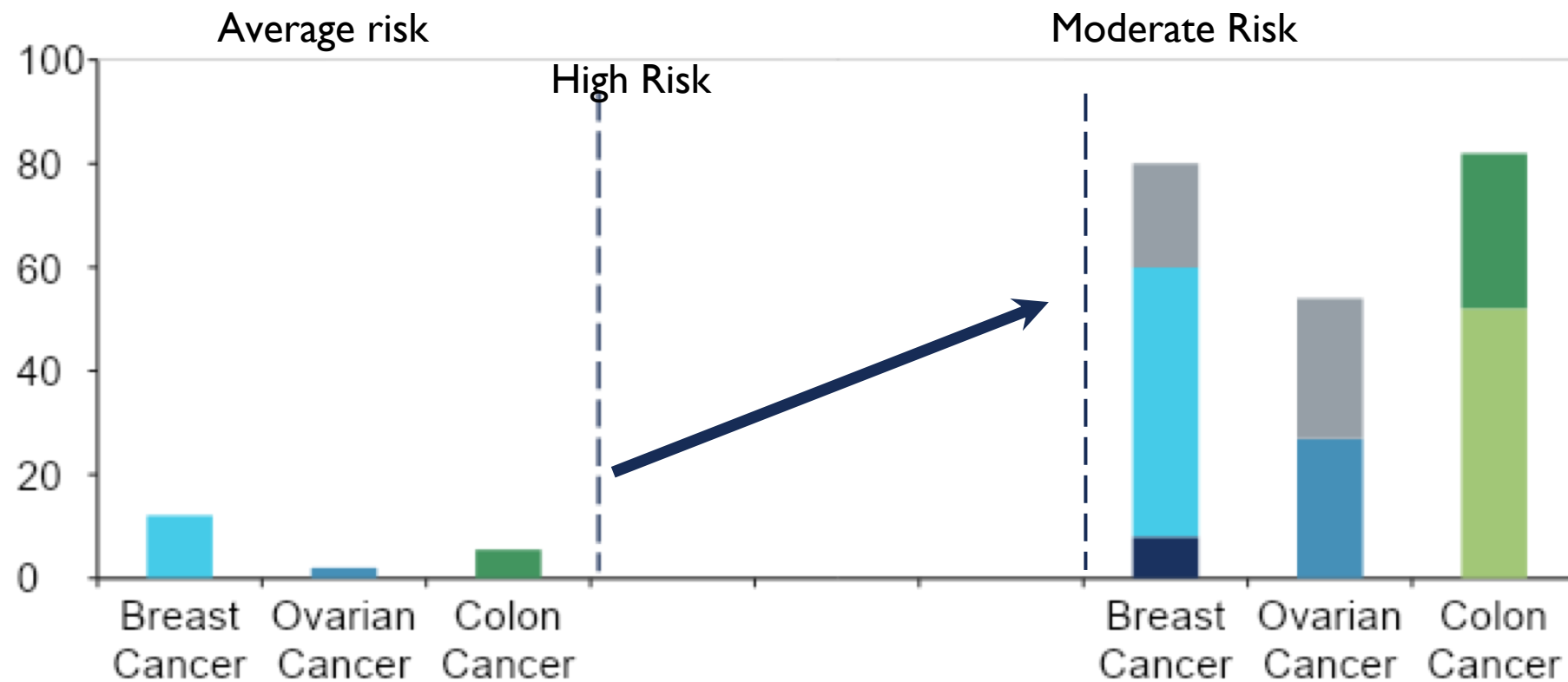
By James Gallagher  
Health editor, BBC News website

🕒 2 January 2015 | Health | 💬

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# Changes to lifetime chance of developing cancer with genetic testing



## Single Gene testing

Targeted testing for a specific condition or already identified gene in your family

Tactical approach with a high yield

Pros: Cheaper, quicker results, more targeted for decision making

Cons: could miss something in the family, insurance allowances for once per lifetime

“This was difficult for me and my children...but I now I’m glad that we know”

69yo man with prostate cancer referred for genetic counseling

His sister was diagnosed with breast cancer and tested positive for a mutation in the *BRCA2* gene

He was tested and found to also carry the *BRCA2* mutation

Working through this information with family members can be difficult



## “Genetic testing was helpful.... and frustrating”

54yo woman with breast cancer previously diagnosed at 38 referred for genetic counseling

Her sister also was diagnosed with breast cancer at 35 and previously tested negative for the *BRCA1/2* genes

She was tested with updated testing (more genes) and found to have a *CHEK2* mutation

*CHEK2* is a moderate risk gene, meaning it causes an increase in the chance for breast cancer, but may not be the whole picture for this family.



## Multi-Gene Panel testing

Analyzes many genes simultaneously

Multiple rare genes that collectively account for a significant amount of hereditary cancer susceptibility

Pros: Helpful when family history shares features of several different hereditary cancer syndromes, picks up conditions you wouldn't otherwise have symptoms

Cons: Can overwhelm with information, more unknown or uncertain results

# Multi-Gene Panel testing

- Considerations: Not all panels are created equal
  - Some are small are targeted, for example for a rare type of tumor
  - Some are targeted for genes we know a lot about or have guidelines
  - Some are trying to capture any or all genes that may cause a higher chance to get cancer

ALK, AKT1, APC, ATM, ATR, AXIN2, BAPI, BARD1, BMPRIA, BRCA1, BRCA2, BRIPI, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, CTNNA1, EPCAM, FANCM, FAM175A, FANCM, FH, FLCN, GALNT12, GEN1, GREM1, HOXB13, KIF1B, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, NFI, NTHL1, PALB2, PALLD, PDGFRA, PHOX2B, PIK3CA, PMS2, POLD1, POLE, POT1, PRKARIA, PRSSI, PTCH1, PTEN, RAD51B, RAD51C, RAD51D, RBBP1, RECQL, RET, RINT1, RPS20, SDHB, SDHC, SDHD, SLX4, SMAD4, SMARCA4, TP53, VHL, and XRCC2.

VS

BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53

“I already had testing that was negative but worry it missed something”

52 yo woman with history of triple negative breast cancer at 45, negative BRCA1/2 genetic testing

Her brother was diagnosed with colon cancer at 40

She qualified for updated testing, including a large panel. Discovered a Lynch syndrome mutation, not explaining the breast cancer but increasing her chance for colon and other cancer

Young adult son is also positive, can start colon screening early with goal of colon cancer prevention

Sisters test negative for Lynch, still qualify for increased breast screening given her history



## Genetic testing at home

Can order from the comfort of your couch

Tests for ancestry, fun genetic traits, can now include some cancer related genes

Pros: Cheaper, no doctor visit required, can pick up families who wouldn't qualify for testing based on guidelines

Cons: Requires saliva, incomplete testing, falsely reassuring, unintended information

# “I tried to get this done years ago but insurance denied”

60 yo woman with history of breast cancer 20 years ago

Two grown daughters with children of their own  
Initially tried to get genetic testing but insurance did not cover it, leaving a large bill

Insurance guidelines have been updated, now qualify

Found a BRCA2 gene change, able to make decisions for her own screening

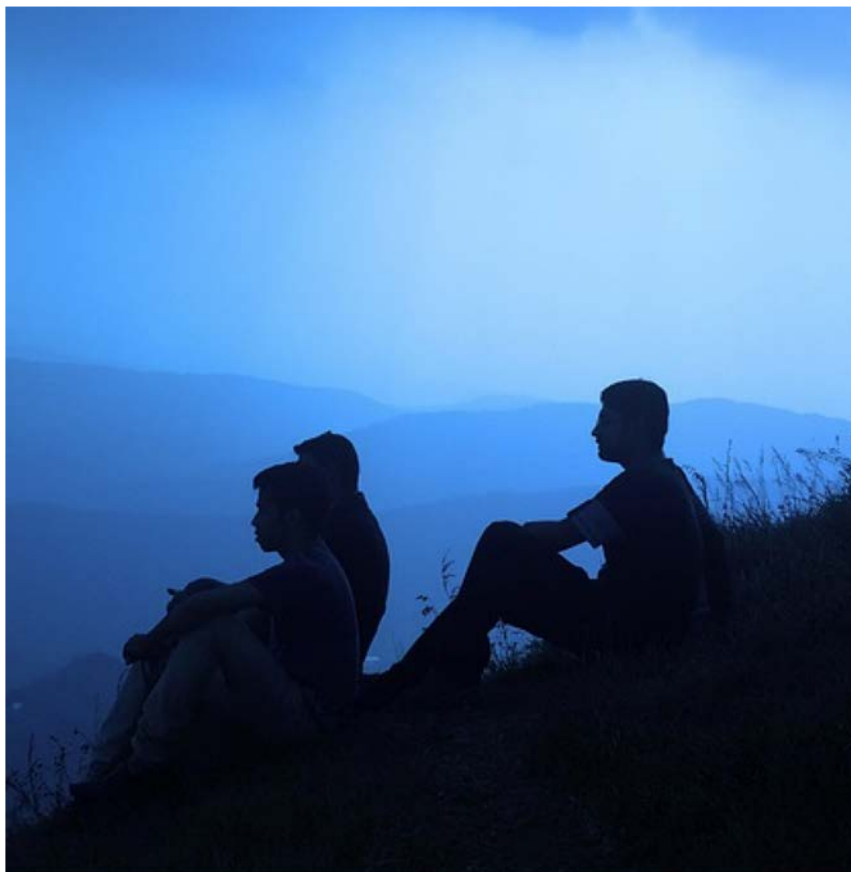
Offers a specific test for her daughters



## Examples of who should consider genetic testing

- Any breast, colon, or uterine cancer at 50 or younger
- Triple negative breast cancer at 60 or younger
- Metastatic breast or prostate cancer
- Ovarian, male breast, pancreatic cancer at any age
- More than 10 colon polyps
- Ashkenazi Jewish ancestry – with history of breast, prostate, pancreatic cancer
- Relatives of a mutation carrier
- Multiple relatives with these cancers
- More than one of these cancers in the same person
- Unusual or rare types of cancer

“I want to know more about what this means for my kids”



32yo man with colon cancer

Two school age children

A brother and a sister

Family history was significant for:

Maternal grandfather with prostate cancer at age 72

Paternal grandmother with colon cancer at age 67

Seeking information for his children and family

Genetic test results demonstrated biallelic mutations in the *MUTYH* gene

## Benefits of genetic risk assessment

Helpful in guiding care for patient and relatives

Goal is early detection and cancer prevention!

Results may provide new strategies for cancer prevention, early detection and treatment

May provide explanation for family members



“I don’t want to know, but my kids are strongly encouraging me”

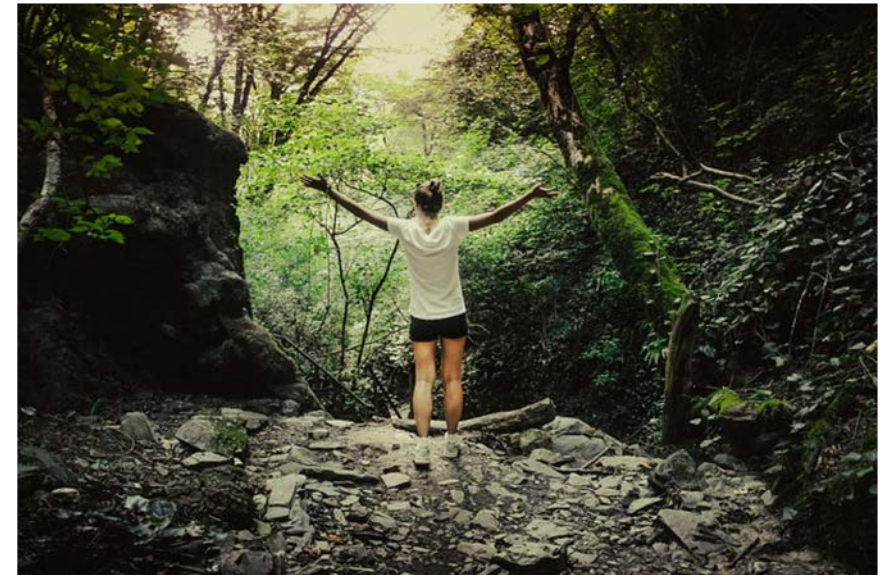
55 yo woman with breast cancer referred for genetic counseling

Her sister was also diagnosed with breast cancer and tested positive for a mutation in the *BRCA1* gene

She did not want to know this information, would feel guilty if passed it on to her kids and anxious about her own future

Discussed that we all carry these gene changes just happen

With the information, your kids can use it to make decisions about their health, screening and lifestyle based on their risk



# Risks and Limitations of Genetic Testing

Family Structure differences

Limited information in some cases

Lack of guidelines

Concerns for insurance discrimination

Unexpected results

Cost



- Family history may influence the chance of developing cancer.
- Management recommendations may change based on family history, even if genetic testing is negative.

## All genetic tests are not equal

**The New York Times**



### *The Online Gene Test Finds a Dangerous Mutation. It May Well Be Wrong.*

Growing number of reports of false positive results – especially for hereditary cancer and genetic cardiac conditions

Could be from test report provided by the laboratory, or from third party interpretation services

<https://www.nytimes.com/2018/07/02/health/gene-testing-disease-nyt.html>

## Sequencing

Analyzing entire genes

Whole exome

Whole genome

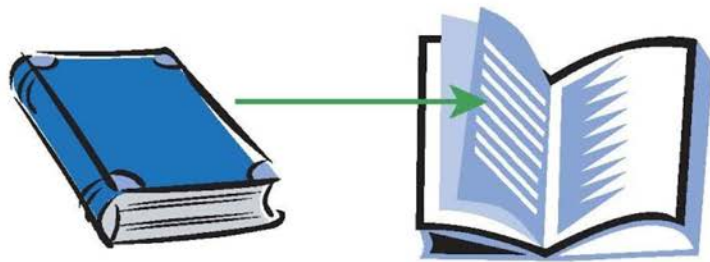
Example: Myriad, Invitae, GeneDx

## Genotyping

Looks at select variants

Example: 23andMe

## Types of Gene Mutations



**Chromosomes** are like chapters in a book; one set is from the mother, one set is from the father.

**Genes** are like sentences in a chapter.

**Mutations** are like misspelled words or the disruption of a sentence.

**Missense Mutations** change one word or letter

THE CAR WAS RED. → THE CAR WAS HAT.  
→ THE CAR WAS RDD.

**Nonsense Mutations** end the instructions too soon

THE CAR WAS RED. → THE CAR. \_\_\_\_\_

**Insertion Mutations** add one word or letter

THE CAR WAS RED. → THE CAR WAS RED RED.  
→ THE CAR WAS RED.

**Deletion Mutations** change the meaning by subtracting words or letters

THE CAR WAS RED. → THE \_\_\_\_ WAS RED.  
→ THE \_AR WAS RED.

## GENOTYPING

THE CAR WAS RED.  
THE CAR WAS RAD.

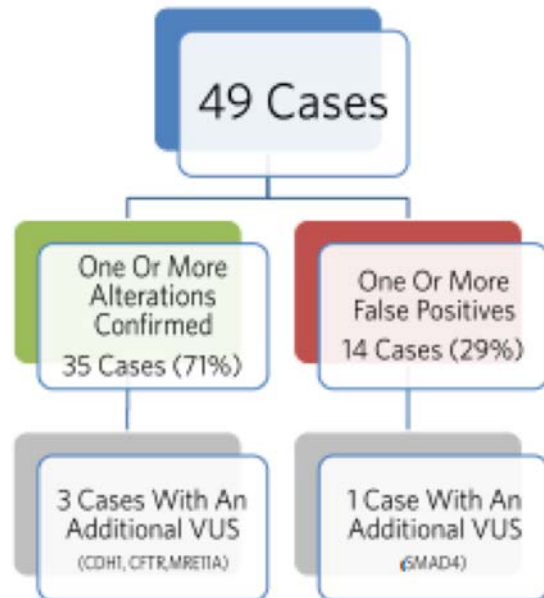
## SEQUENCING

THE CAR WAS RED.  
THE CAR WAS RAD.

# Positive DTC results are often not confirmed

## CASE BREAKDOWN

- 20/49 - we received a copy of the DTC report/raw data
- 29/49 - the alteration was listed on the TRF or in a clinic note



Ambry genetics reported that in 40% of cases that were sent for follow-up to abnormal DTC results – the mutation was not confirmed

*BRCA1*

*BRCA2*

*TP53*

*CHEK2*

*ATM*

*MLH1*

*COL3A1*

## At home complete gene analysis

Currently 2 laboratories are offering complete genetic testing that you can order at home

- Work with your doctor or the laboratory associated doctor

- Saliva kit can be sent to your home for ease

- Typically offer discounted prices to family members

- Can work with many insurances or, as of today, out of pocket \$250

# Genomic Profiling

## Personalized medicine

More information about your specific tumor and its drivers

Later today, opportunity to hear more in depth information about tumor profiling and cell therapy research

## Targeted chemotherapies

For example, people with BRCA1/2 gene mutation with metastatic cancer get a PARP inhibitor

# Genomic Profiling- Few Examples of FDA approved targeted therapies

**Adenocarcinoma of the stomach or gastroesophageal junction:** Trastuzumab (Herceptin®), ramucirumab (Cyramza®)

**Bladder cancer:** , nivolumab (Opdivo®), durvalumab (Imfinzi™)(Imfinzi™), avelumab (Bavencio®), pembrolizumab (Keytruda®), erdafitinib (Balversa™)

**Brain cancer:** Bevacizumab (Avastin®), everolimus (Afinitor®)

**Breast cancer:** Everolimus (Afinitor®), tamoxifen (Nolvadex), toremifene (Fareston®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla®), palbociclib (Ibrance®), ribociclib (Kisqali®), neratinib maleate (Nerlynx™), abemaciclib (Verzenio™), olaparib (Lynparza™), atezolizumab (Tecentriq®), alpelisib (Piqray®)

**Cervical cancer:** Bevacizumab (Avastin®), pembrolizumab (Keytruda®)

**Colorectal cancer:** Cetuximab (Erbix®), panitumumab (Vectibix®), bevacizumab (Avastin®), ziv-aflibercept (Zaltrap®), regorafenib (Stivarga®), ramucirumab (Cyramza®), nivolumab (Opdivo®), ipilimumab (Yervoy®)

**Dermatofibrosarcoma protuberans:** Imatinib mesylate (Gleevec®)



# Questions?

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