New Recommendations for Genetic Testing: How Do I Make Sense Of It All?

Wednesday, December 19, 2018

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WELCOME

June Mandeville-Kamins, LCSW
Senior Support Program Coordinator
Sharsheret

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THANK YOU

This program is made possible
with generous support from

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WHEN DECISIONS MATTER

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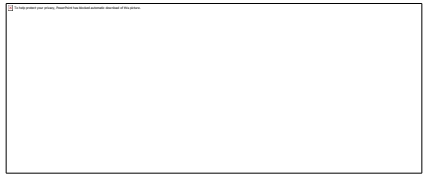
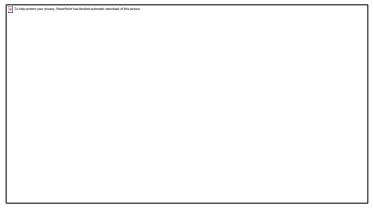
PARTNERS IN COLLABORATION





FORCE
Facing Our Risk of Cancer Empowered

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WHO WE ARE

Sharsheret supports young Jewish women and families facing breast and ovarian cancer at every stage. We help you connect to our community whatever your personal background, stage of life, genetic risk, diagnosis, or treatment.

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HOW DO I MAKE SENSE OF IT ALL?

- Is genetic testing right for me?
- What do the results mean for me and my family?
- What is “Direct to Consumer” testing?
- What are the latest recommendations?

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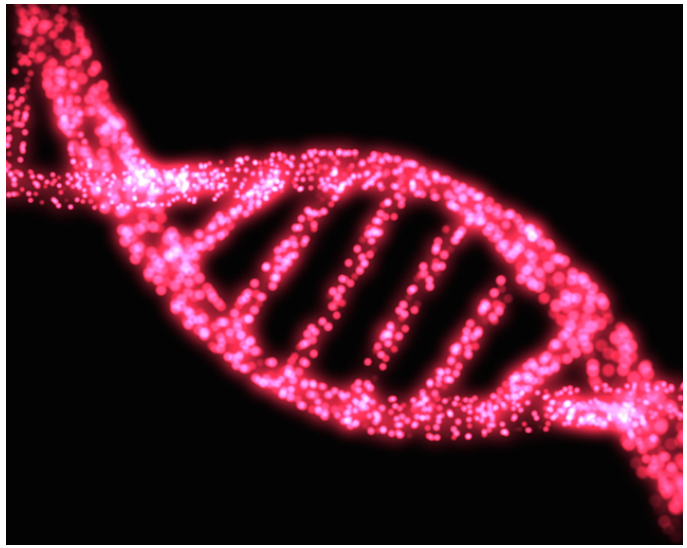
BACKGROUND

- 1 in 40 Ashkenazi Jews carries a BRCA gene mutation
- Up to 88% risk of breast cancer
- Up to 45% risk ovarian cancer



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QUESTIONS

To ask a question, please type your question into the text box to the right of your screen.

Questions will be addressed in the order received during the question and answer session following the presentation.

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NEWEST GUIDELINES AND RESEARCH IN GENETIC TESTING

Beth Karlan, MD

Director

Women's Cancer Program and
Division of Gynecologic Oncology

Professor of Obstetrics and
Gynecology

Cedars-Sinai/David Geffen School of
Medicine

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VERBAL DISCLOSURE

I am on the scientific advisory board of the *Invitae Corporation*

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New Recommendations For Genetic Testing: How Do I Make Sense Of It All?

Agenda:

- Hereditary Cancer Review
- Genetic Testing Update
- PARP inhibitors in Breast and Ovarian Cancer
- Future Directions

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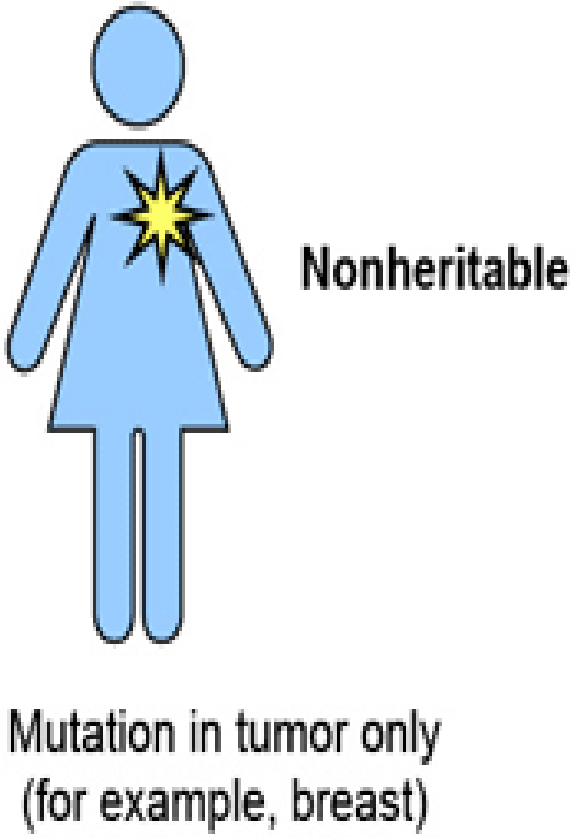
All Cancers are *Genetic Diseases*

Sporadic cancers

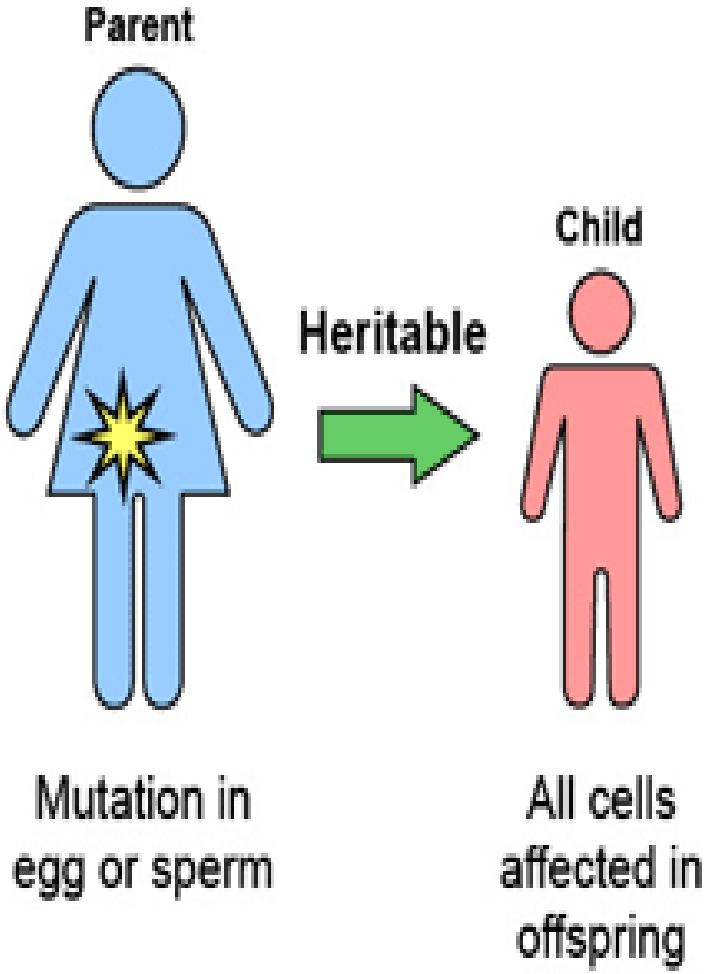


- ✓ Cancer results from accumulated gene alterations that build up in specific tissues and allow them to grow uncontrollably
- ✓ Number of mutations increase with age
- ✓ Environment and lifestyle factors, such as smoking, alcohol, diet, obesity, hormones, play an important role

All Cancers are *Genetic Diseases*

- ✓ Predisposing mutation is passed down at conception
- ✓ Cancers occur at earlier ages since predisposing mutation makes cells susceptible to further genetic injury
- ✓ Environmental factors can add up more quickly
- ✓ Often multiple cancers occur in one person or cluster in one family

Hereditary Cancers



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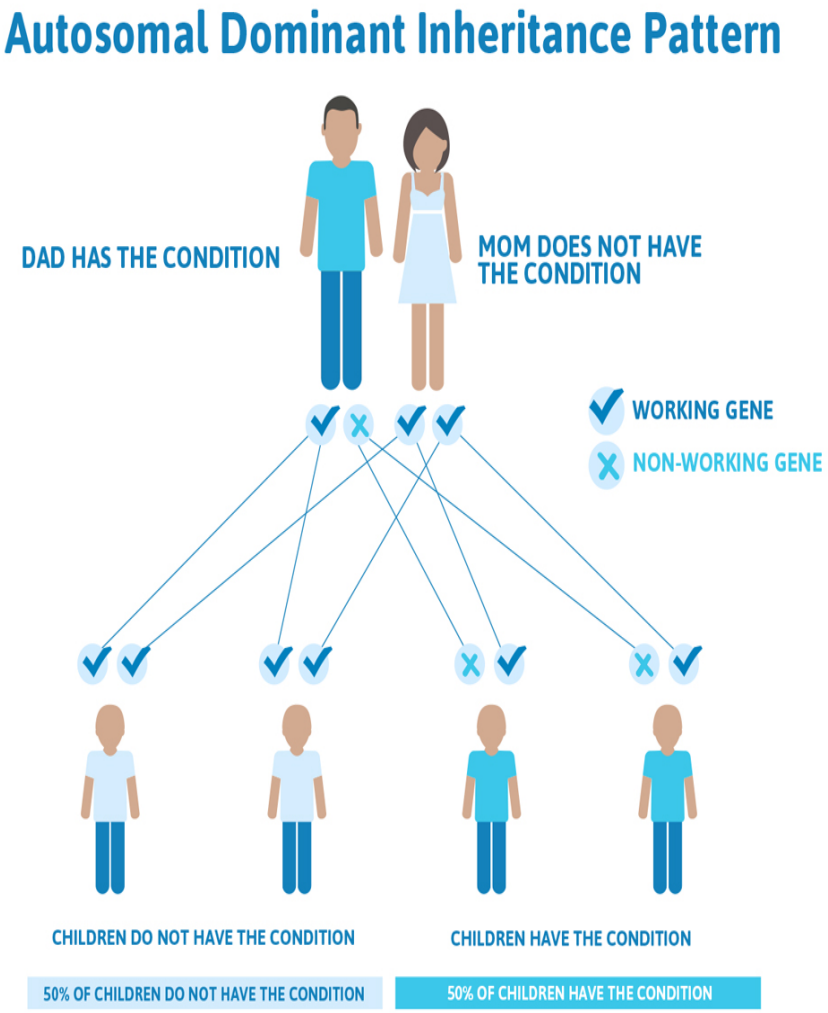
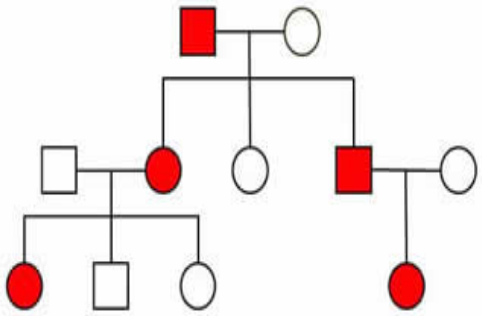
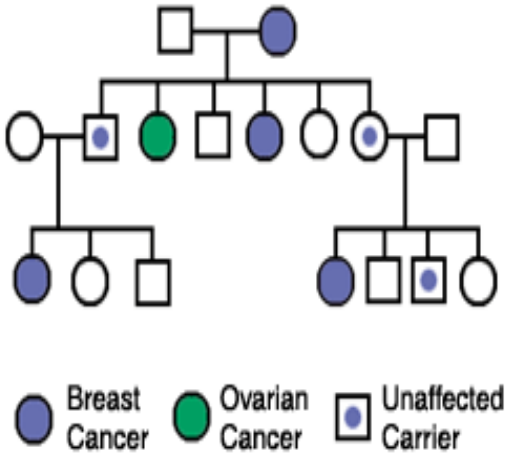
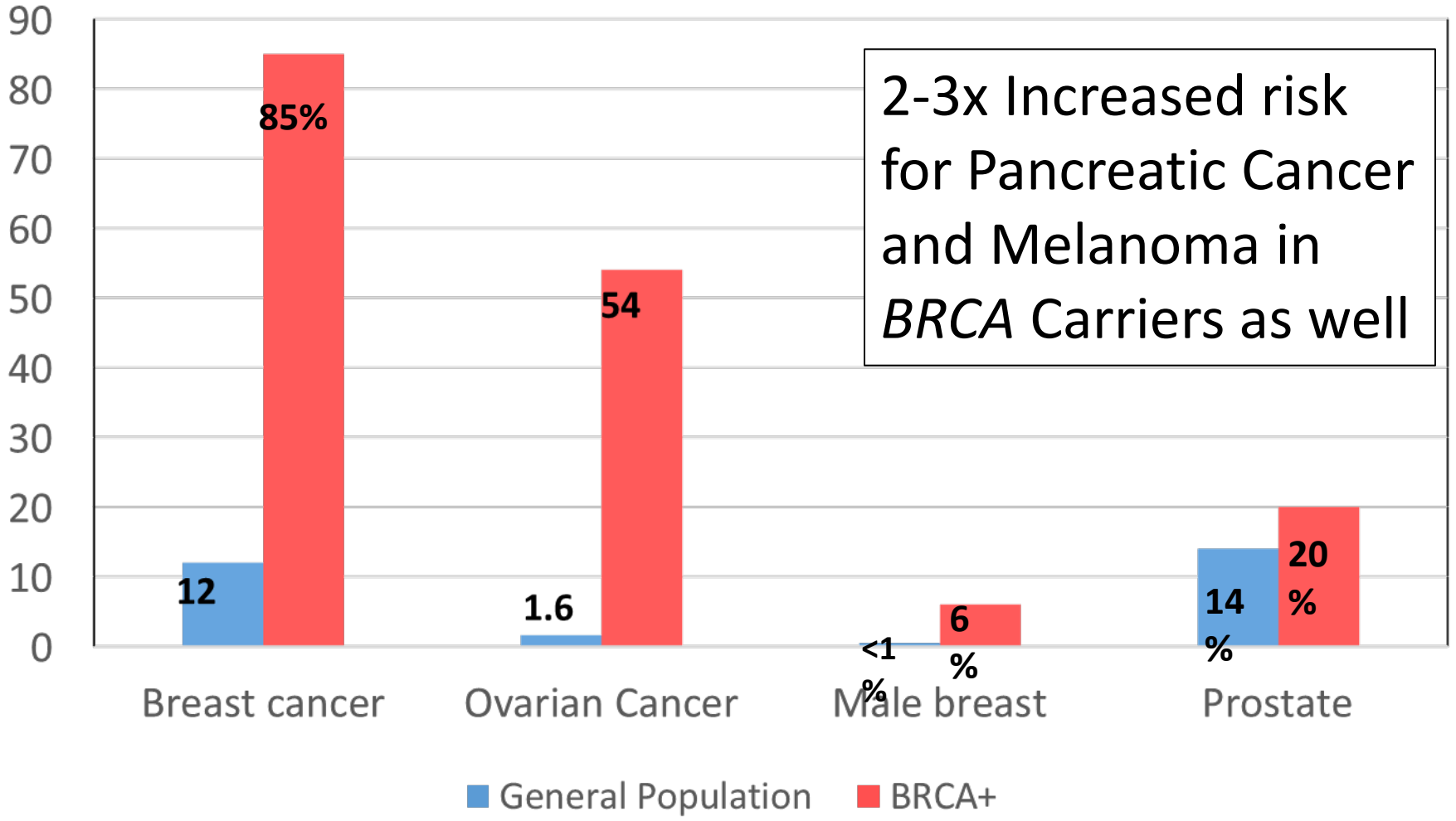
Most hereditary cancer predispositions are inherited in an *autosomal dominant* pattern with *incomplete penetrance*



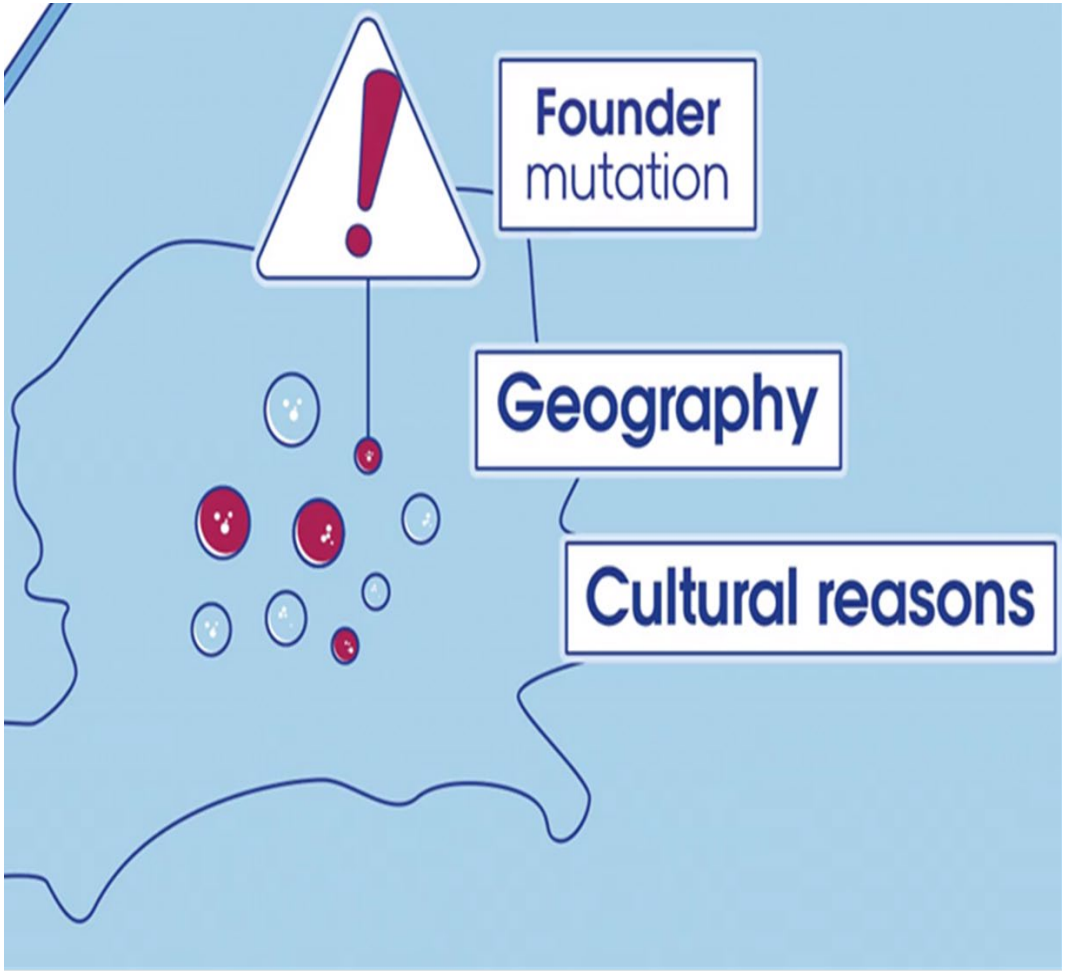




BRCA-Associated Cancer Risks



Many hereditary diseases are due to a ***Founder Mutation*** that is carried with higher frequency in a specific population due to geographic or cultural isolation



- In Ashkenazi Jews, there are three founder mutations that account for ~90-95% of all *BRCA* mutations
- There are BRCA founder mutations in other groups as well, such as Icelandic or Hispanic populations

There are many Founder Mutations in the AJ community

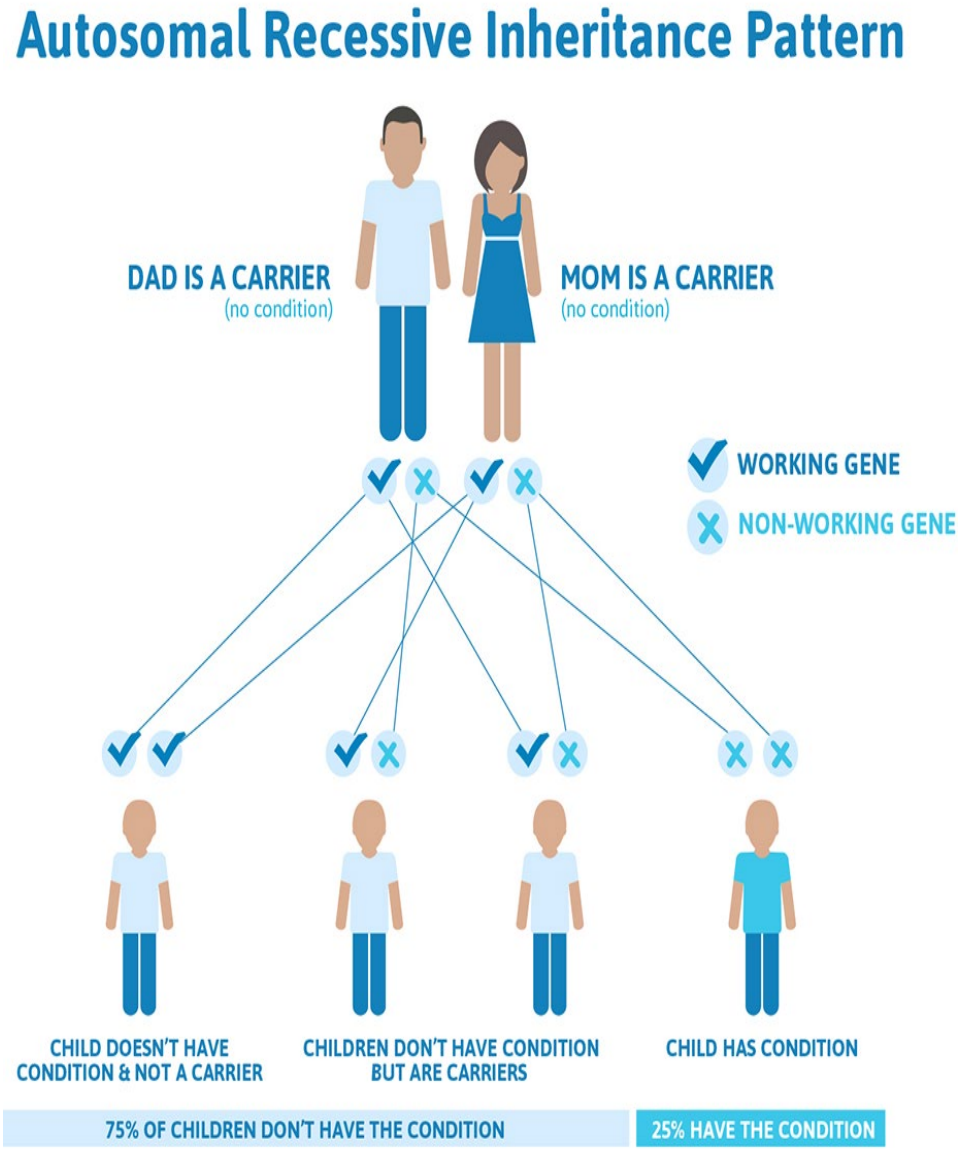
Jewish Disease	Carrier Frequency
Bloom Syndrome	1:134
Canavan Disease	1:55
Cystic Fibrosis	1:24
Dihydrolipoamide Dehydrogenase Deficiency	1:106
Familial Dysautonomia	1:31
Familial Hyperinsulinism	1:68
Fanconi Anemia, Type C	1:100
Gaucher Disease	1:15
Glycogen Storage Disorder, Type 1A	1:64
Joubert Syndrome, Type 2	1:110
Maple Syrup Urine Disease, Type 1B	1:97
Mucolipidosis, Type IV	1:89
Nemaline Myopathy	1:168
Niemann-Pick Disease	1:115
Spinal Muscular Atrophy	1:41
Tay-Sachs Disease	1:27
Usher Syndrome, Type 1F	1:147
Usher Syndrome, Type 3	1:120
Walker Warburg Syndrome	1:120

In fact, 1 in 3 Jews are a carrier for a genetic disease

But there are Founder Mutations in many other populations too:

- Sickle cell anemia in African Americans
- Beta thalassemia in Asians
- Familial Mediterranean Fever in Sephardic Jews

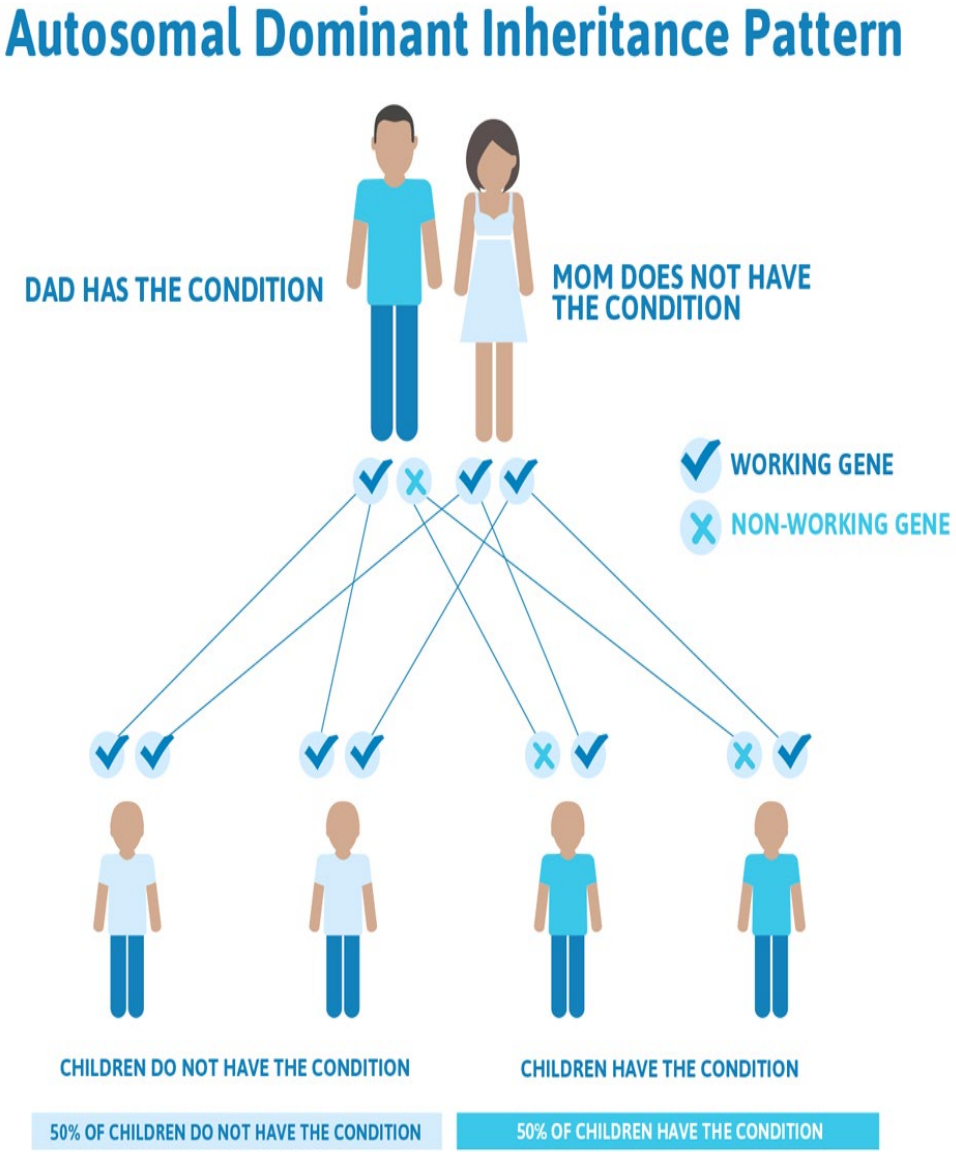
How is *BRCA* testing different than Tay-Sachs Carrier testing?



Tay- Sachs

- **1/30 AJ** individuals is a carrier
- **Carriers have no risk** or symptoms of disease
- Risk for affected child exists when 2 carriers have children together
- **~1/3600** affected individuals

How is *BRCA* testing different than Tay-Sachs Carrier testing?



BRCA

- **1/40 AJ** individuals is a carrier
- All carriers *are* at **increased risk** for cancer, although not all will develop cancer (*incomplete penetrance)*
- Testing for *BRCA* mutations has significant implications for the health of the person being tested
- And all the relatives of a *BRCA* carrier are at a 50% risk for *BRCA+* and getting cancer

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Genetic Testing

- Blood or saliva sample (equal accuracy)
- Analyzes DNA Sequence (genes) to identify *pathogenic variants* or *mutations* that cause the gene not to work properly
- 3 possible test results
  - Positive= pathogenic variant (mutation) identified
  - Negative= no variant identified
  - Variant of Uncertain Significance

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019

NC

BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA1/2 TESTING CRITERIA[a,b]

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood[e] relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

Cascade testing: discuss your results with all your relatives to help save their lives as well

- ~90% of BRCA mutation carriers do not know they are positive!
- Once a carrier is known—50% of their relatives may carry the mutation too

Multigene Panels Are Most Frequently Recommended

Pros

- Cost efficient
- More comprehensive approach
- Help identify hereditary component in atypical families
- Builds data

Cons

- VUS can be confusing
- Limited guidelines and recommendations for certain genes
- Limited data

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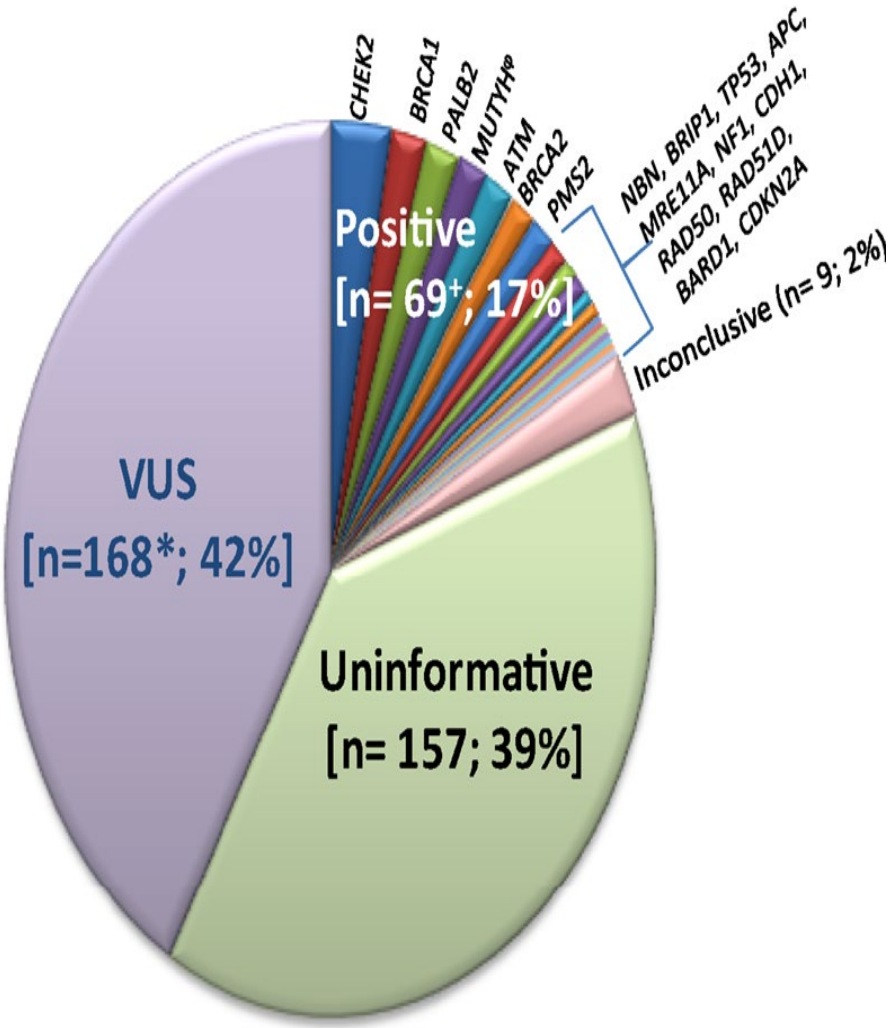
Downside of Panel Testing: Many Variants of Uncertain Significance Results

- A VUS is NOT a mutation
- ~80% of VUS results are eventually reclassified as *benign*
- Screening and management decisions are based on *family history*
- Cascade testing NOT recommended



Weitzel J, et al.: *Frontiers in Oncology*, 2015.

Why is genetic testing important?

PREVENTION!

- Identifying a mutation in an individual provides valuable information for the family as well
  - First degree relatives have a 50% chance of carrying the same mutation
- Personalized healthcare recommendations
- Consider risk reducing surgeries
- Early detection strategies
- Family planning and preimplantation testing

Actions if you test positive

- Breast cancer prevention:
  - Mammography and breast MR screening starting at age 25
  - Consider prophylactic mastectomies
  - Consider medications to reduce risk by 50%
- Ovarian Cancer Prevention:
  - Risk reducing salpingo-oophorectomy when childbearing complete
  - Consider earlier salpingectomy
  - Screening with CA125 and TVS – although imperfect
  - Birth control pills to reduce risk
- Prostate Cancer:
  - Consider early PSA screening
- Pancreas Cancer:
  - Consider endoscopy and imaging screening protocols
- Melanoma:
  - Regular complete skin and eye exams

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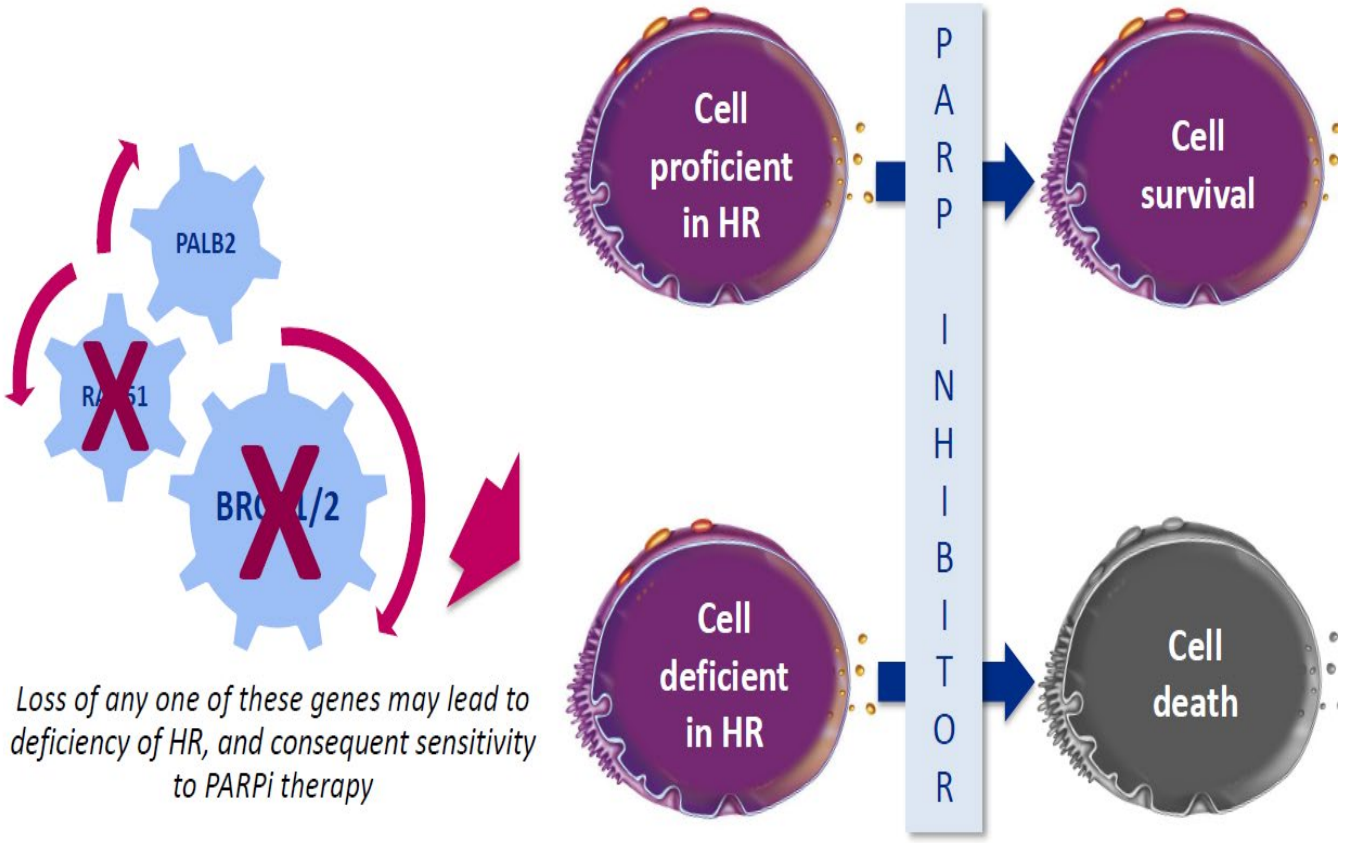
PARP Inhibitors target and intrinsic defect in BRCA-cancer cells

"Synthetic Lethality" by PARP Inhibition cases Fatal Flaw in DNA Repair



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PARP Inhibitors…in clinical practice

- Niraparib (Zejula), Olaparib (Lynparza), and Rucaparib (Rubraca) FDA-approved for use as *maintenance therapy* for ovarian cancer: for patients who are in remission after platinum-based chemotherapy. Clinical benefit demonstrated whether or not there is a BRCA mutation.
- Olaparib and Rucaparib also approved for use as *treatment* for recurrent ovarian cancer.
- Olaparib and talazoparib (Talzenna) approved for *treating* BRCA1/2 patients who have metastatic HER2-negative breast cancer.
- All approvals based on demonstrating significant improvement in progression free survival

PARP Inhibitors…in clinical practice

- Even though PARP inhibitors are "just a pill," there are still adverse events and toxicities
- Most toxicities are manageable, but symptoms not the same for all PARPs and for all patients
- Monitoring should be *at least* once a month during the first few cycles of therapy
- Choice of which PARP inhibitor is right for you needs to be individualized based on clinical indication, prior therapies and toxicities

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Genetic testing for cancer risk: Unmet needs and opportunities

- Fewer than 20% of women with ovarian or breast cancer meeting NCCN guidelines have undergone genetic testing
- Need to identify barriers to genetic testing for affected individuals and expand cascade testing of family members of known carriers
- >90% unaffected carriers have yet to be identified, representing 10,000s of cancers that could be prevented!
- Scientific advances in have identified new options for screening, prevention, and treatment for carriers

Childers, CP, JCO 2017
Hughes, K, JCO 2017

Journal of Clinical Oncology®

Beitsch, PD, et al; December 2018

Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?

- Genetic testing offered to any woman with a previous or current diagnosis of breast cancer who has not had previous genetic testing (80 gene panel, regardless of family history)
- Rate of pathogenic variants was similar among patients who *did* and *did not* meet 2017 NCCN guidelines for genetic testing. (9.39% vs 7.9%, *P*=.42)
- Conclusions:
  - Current guidelines do not adequately account for variation in family histories, especially in genes other than BRCA1/2.
  - Identifying pathogenic variants is important for treatment, risk management, and cascade testing.
  - Substantial modification of scope and intent of existing genetic testing guidelines is critically overdue.
- **Guidelines may need to be updated and expanded to include genetic testing of all patients with breast cancer**

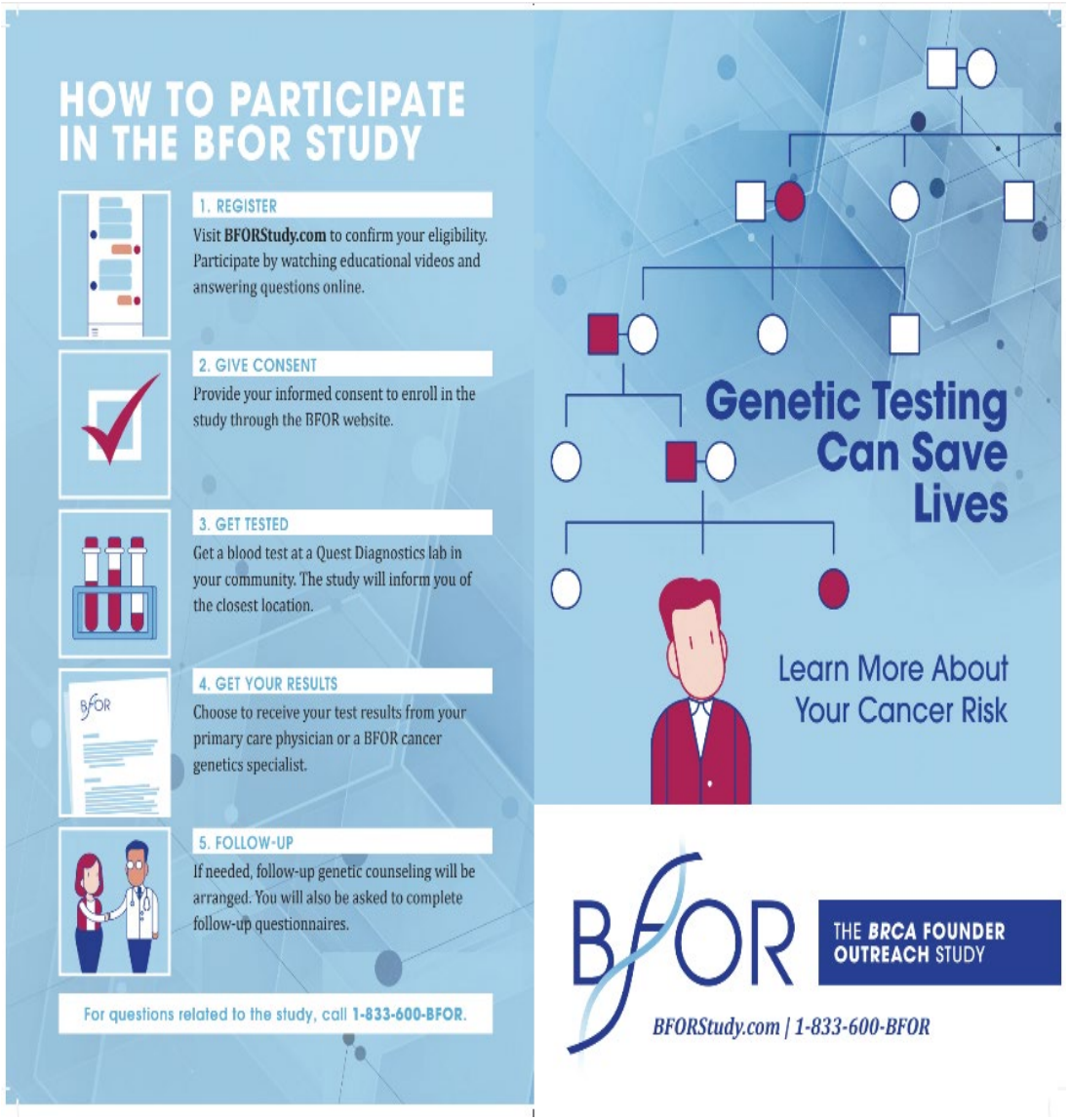
Next steps:

- We need new models to better reach men and women at risk.
- Better education of the public and their care providers.
- Wider insurance coverage for preventative genetic testing.
- Accelerated research discoveries for new approaches for treatment and prevention.

BRCA Founder OutReach Study

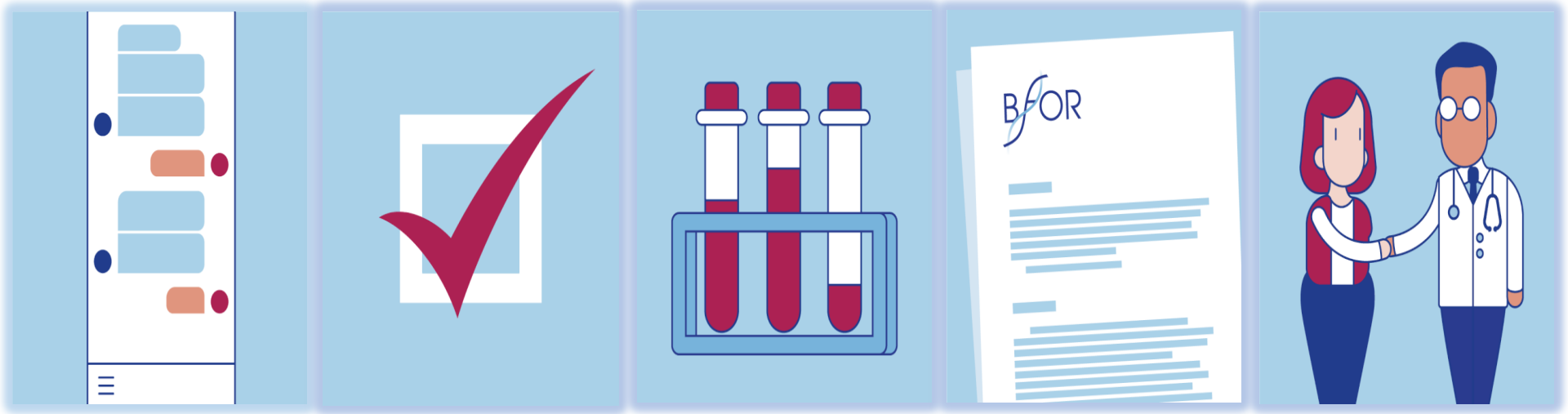
Purpose:

- To develop a new/improved model for access to genetic testing
- Reduce cancer risks and improve outcomes for BRCA carriers
- Identify best practices for incorporating PCPs in genetic testing and follow up



How to Participate in the BFOR Study:

Go to **bforstudy.com**



Register **Give consent** **Get tested** **Get your results** **Follow-up**

BFOR
BRCA Founder Outreach Study

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DIRECT TO CONSUMER TESTING: HOW DOES IT IMPACT ME?

Peggy Cottrell, MS, CGC
Sharsheret Genetics
Program Coordinator

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BRIEF HISTORY OF DTC

- Human genome project completion leading to genome wide association studies
- First DTC companies offered a mix of information
- Growth as cost of genetic testing plummeted
- FDA got involved, eventually shutting down health information portion of testing
- FDA is gradually giving back approval for certain tests to DTC companies

Direct-to-Consumer Testing 2.0: Emerging Models of Direct-to-Consumer Genetic Testing. Megan A. Allyse, PhD et al. Mayo Clinic Proceedings

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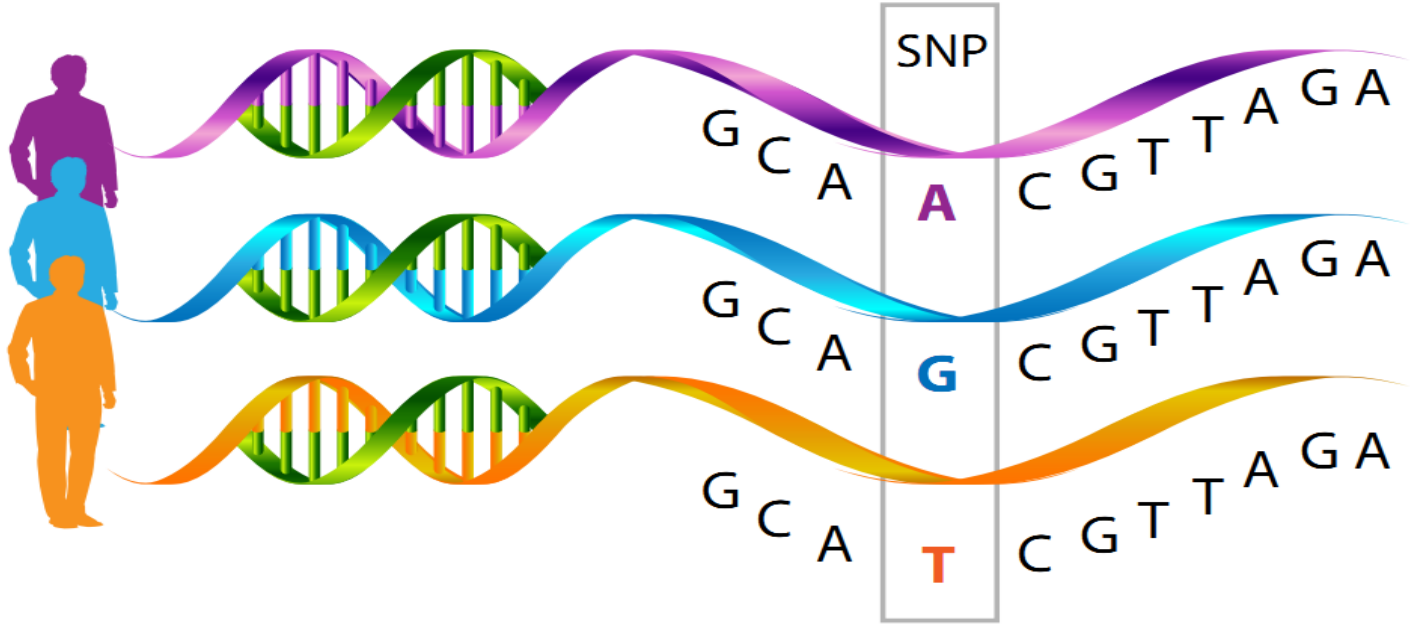
TESTING METHODOLOGY VARIES



- Most DTC companies use SNP testing
  - DNA microarray chip that can access hundreds of thousands of SNPs
- Sequencing is not done

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MEDICAL GRADE CANCER GENETIC TESTING

- Generally done with Next Generation Sequencing
  - Cost saving technology
  - Full DNA sequence
- Test is targeted to the medical issues indicated by the family history
- These labs are under special regulation by federal agencies
  - CLIA - Clinical Laboratory Improvement Amendments

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WHO SHOULD CONSIDER DTC TESTING

- "Entertainment Genetics"
  - Curiosity about ancestry, paternity, finding relatives
  - Curiosity about non-medical traits
- If you are concerned about the cancer in your family, you will benefit most from a medical grade test

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DTC TESTING IS ABLE TO IDENTIFY THE *BRCA1* AND *BRCA2* FOUNDER MUTATIONS

- These mutations originated before there was a separation between Ashkenazi, Sephardic and Mizrachi populations
- Population factors concentrated these among Ashkenazim during the Middle Ages
- One in 40 Ashkenazi Jews will carry one of these three mutations.
- Testing for these mutations can be done on a DNA microarray chip because they are technically “SNPs”

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HOW SHOULD YOU INTERPRET DTC TESTING RESULTS

- If the results are positive, they need to be confirmed with a medical grade test
- Insurance is very likely to cover this cost
- Avoid making any medical management decisions until result is confirmed

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NEGATIVE RESULTS FOR CANCER PREDISPOSITION ON DTC TESTING LEADS TO UNCERTAINTY

- You may still have a mutation in *BRCA1* or *BRCA2* that is not one of the founder mutations
- You may carry a mutation in a different cancer predisposition gene
- Many genes that predispose to cancer are not yet identified

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WHAT SHOULD I DO IF I WANT TO FIND OUT MORE ABOUT MY HEREDITARY RISK FOR CANCER?

FIND A GENETIC COUNSELOR

A searchable directory of genetic counselors

- Genetic counselors are uniquely trained to help guide the choice and interpretation of genetic testing: www.nsgc.org
- Sharsheret offers the opportunity to speak to a genetic counselor about your genetic concerns

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PERSONAL STORY

Laura shares her personal story about navigating direct to consumer genetic testing.

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QUESTION & ANSWER SESSION

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866.474.2774

info@sharsheret.org

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