The Technologist's Role in Breast Cancer Risk Assessment

Communicating the benefits of comprehensive risk assessment to patients

Cancer genetics 101

2

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Cancer genetics 101: Program overview and disclaimer

Overall course description

In this 1-unit module, attendees will be introduced to the role that genetics play in breast cancer risk, gain an understanding of different hereditary cancer syndromes and genetic mutations that are associated with breast and other cancers, and learn about genetic testing for patients at risk for hereditary cancer.

Disclaimer

This information is provided to help answer questions with respect to hereditary cancer risk assessment and hereditary cancer testing. It is general in nature and is not intended to provide a comprehensive, definitive analysis of specific risks. The information provided herein should be taken into consideration with other medical and research information regarding cancer risks, hereditary cancer risks and pre-dispositional cancer testing and risk factors.

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Cancer genetics 101: Learning objectives

01 Understand basic genetic concepts

02 Discuss hereditary cancer genetics and genetic testing

03 Discuss genetic testing result types and management guidelines

04 Identify key components of informed consent and results disclosure

05 Learn how to appropriately discuss breast cancer genetics with patients in collaboration with your facility and leadership team(s)

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Fast facts:

In the general population, approximately 13% of women will develop breast cancer in their lifetime. In comparison, 45-69% of women carrying a *BRCA2* mutation will develop breast cancer by age 70.

Reference: www.cancer.gov

Basic genetic concepts

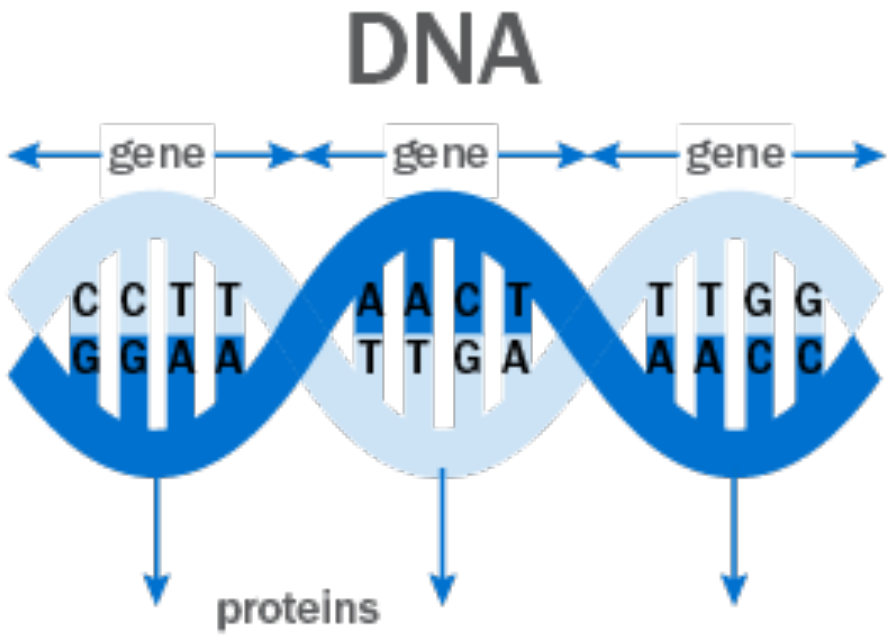
Section 2.1

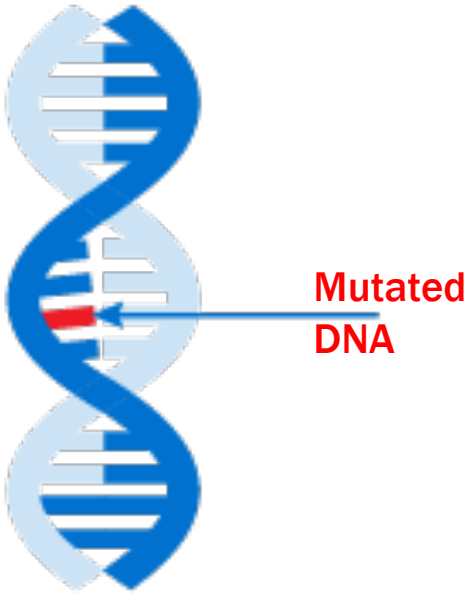
Overview of cancer genetic principles

Key definitions

DNA: The molecule inside cells that contains the genetic information responsible for the development and function of an organism. DNA molecules allow this information to be passed from one generation to the next. DNA is made up of a double-stranded helix held together by nucleotide base pairs: adenine (A) paired with thymine (T), and guanine (G) paired with cytosine (C). Also called deoxyribonucleic acid.

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. (NCI)





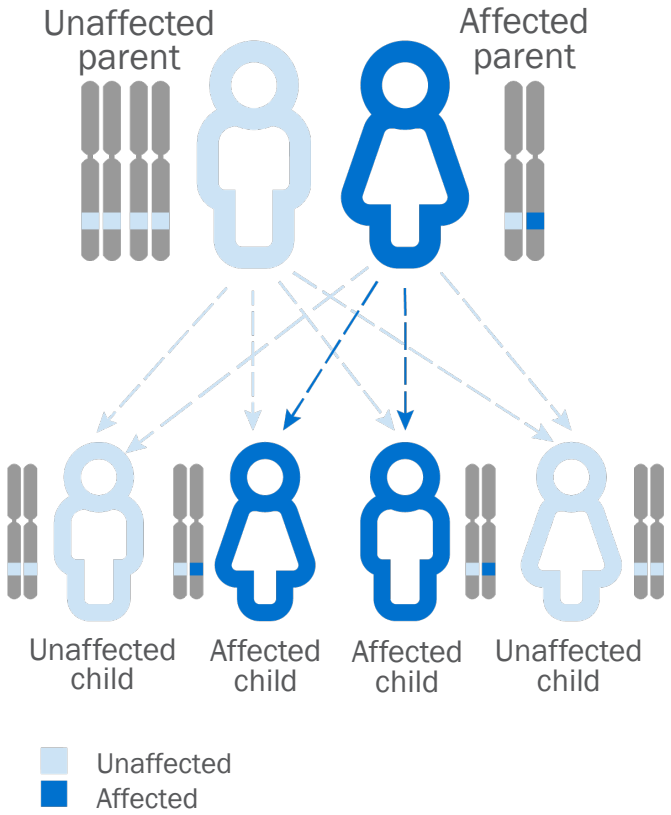
Overview of cancer genetic principles

Key definitions

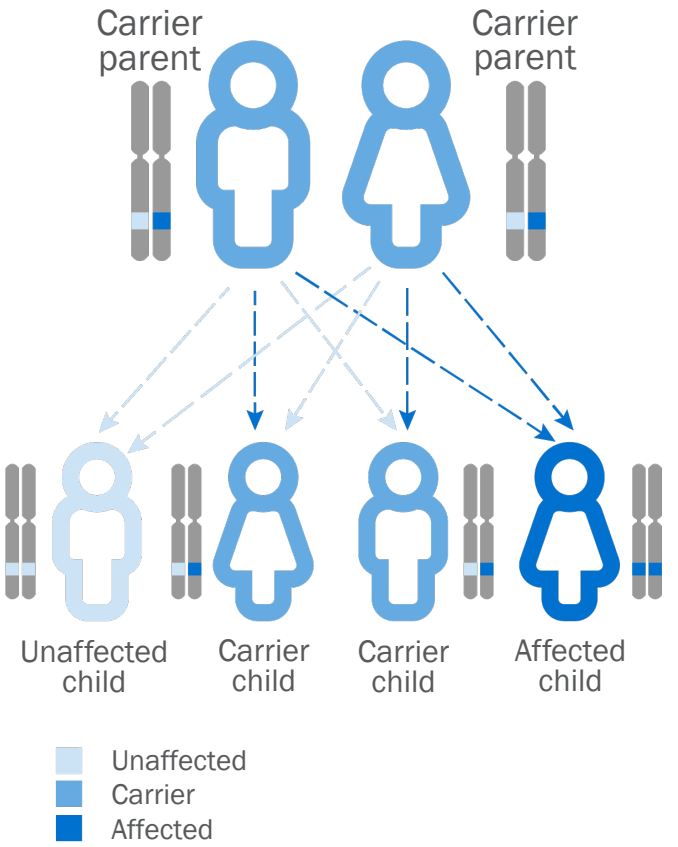
Autosomal Dominant is a way a genetic trait or condition can be passed down from parent to child. One copy of a mutated (changed) gene from one parent can cause the genetic condition. A child who has a parent with the mutated gene has a 50% chance of inheriting that mutated gene (NCI)

Autosomal Recessive, a genetic condition occurs when the child inherits one mutated copy of a gene from each parent. The parents usually do not have the condition. The parents are called carriers because they each carry one copy of the mutated gene and can pass it to their children (NCI)

Autosomal dominant



Autosomal recessive

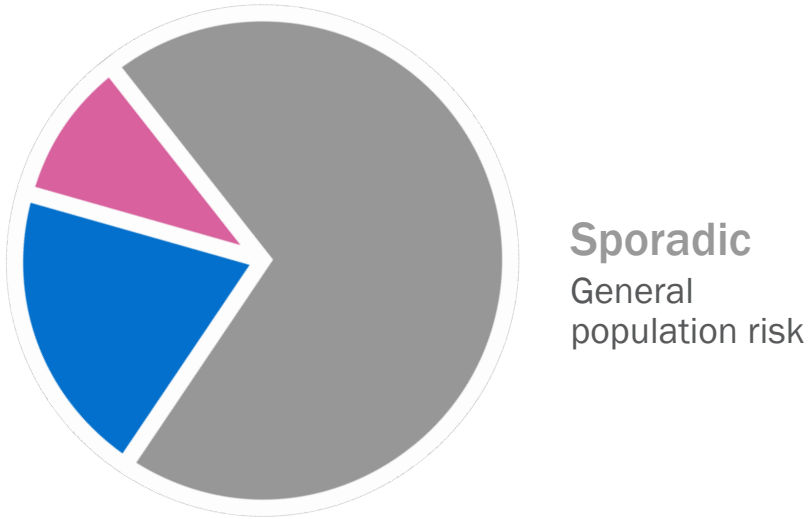


Hereditary cancer genes and genetic testing

Section 2.2

Risk categories

For appropriate patients, genetic testing is the best way to stratify risk between these two groups

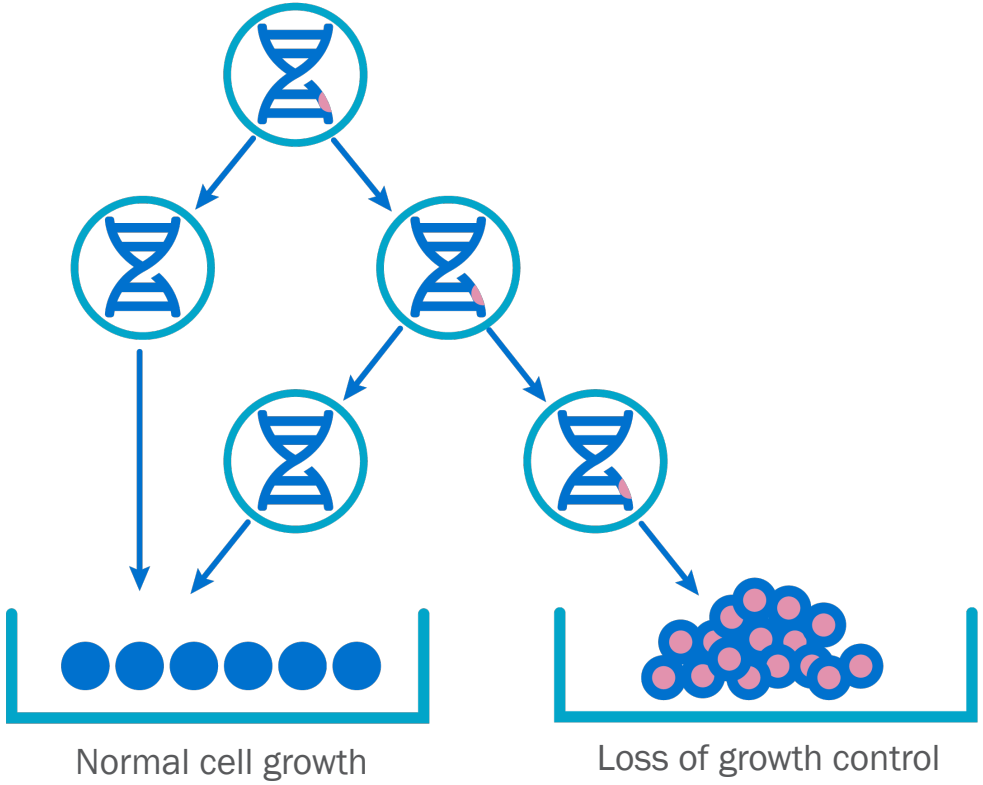


Sporadic cancer risk	Familial cancer risk	Hereditary cancer risk
Occurs by chance	Likely caused by a combination of genetic, lifestyle, and environmental factors	Often occurs when an altered gene is passed down from parent to child
Negative for a known deleterious mutation in the family		More likely to have relatives with the same or related types of cancer

HBOC: *BRCA1 & BRCA2*

Hereditary Breast and Ovarian Cancer syndrome (HBOC)

- Tumor Suppressor Genes
  - Involved in DNA damage recognition and repair
- Autosomal Dominant Inheritance
- Mutation Frequency in General U.S. Population: 1/300 – 1/500
- Mutation Frequency in Ashkenazi Jewish Population: 1 in 40
- Multiple Cancers Implicated:
  breast, ovarian, pancreatic, melanoma, prostate



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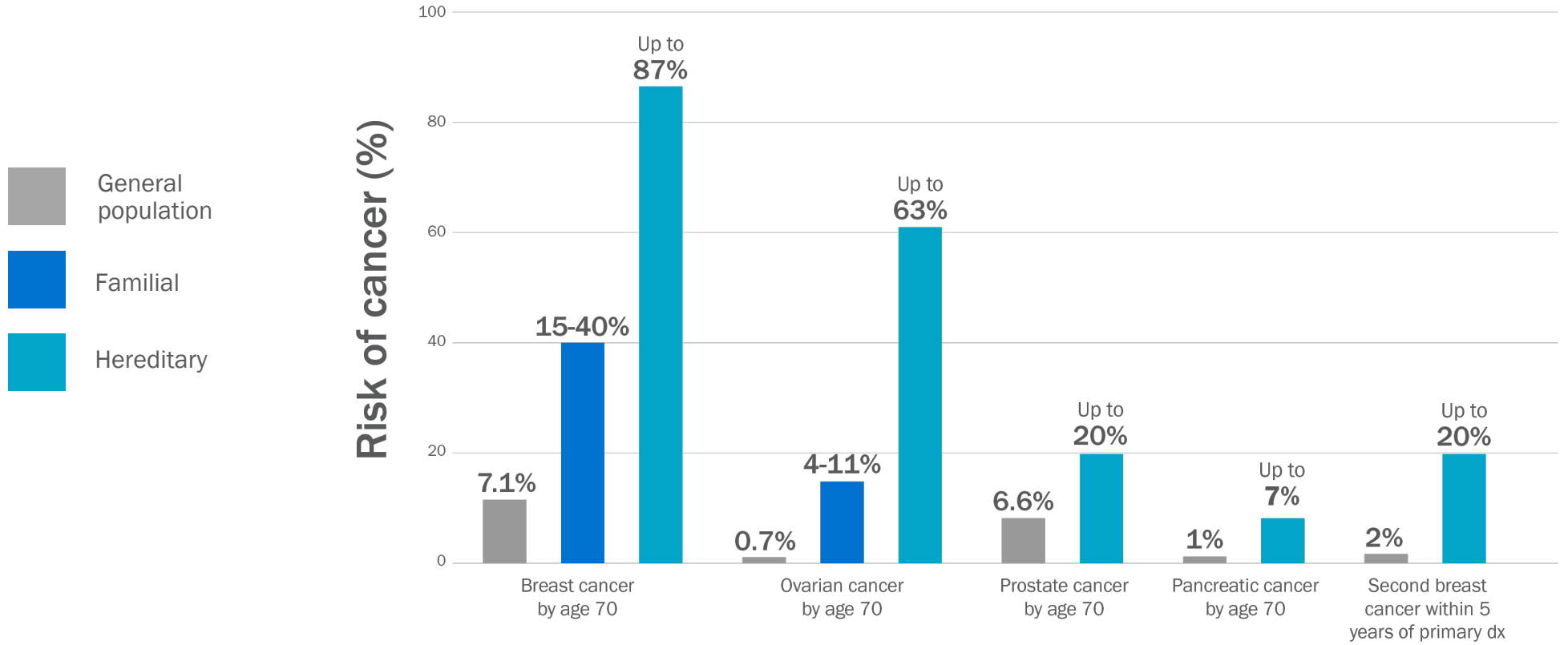
Cancer risks associated with BRCA mutations



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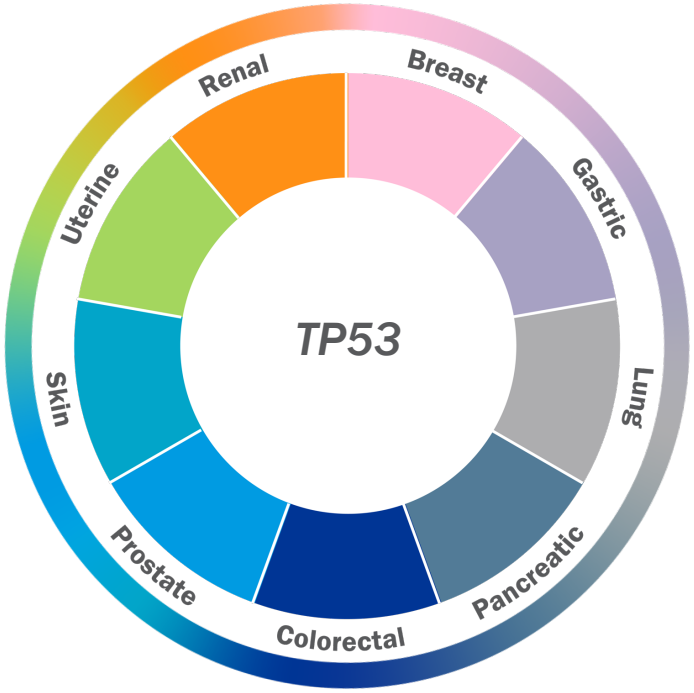
Other breast cancer genes

Gene	Breast cancer risk	Some other cancers associated with gene
BARD1	15-40%	
PALB2	41-60%	Ovarian, pancreatic
ATM	15-40%	Pancreatic, prostate
CHEK2	15-40%	Colorectal
TP53	85%	Sarcoma, brain tumors, leukemia, colorectal, melanoma, pancreatic
STK11	40-60%	Colorectal, endometrial, gastric, lung, ovarian, pancreatic, small bowel, cervical, testicular
CDH1	41-60%	Gastric
PTEN	40- >60%	Colorectal, endometrial, renal, melanoma, thyroid
RAD51C	15-40%	Ovarian
RAD51D	15-40%	Ovarian
NF1	15-40%	Nerve sheath tumors

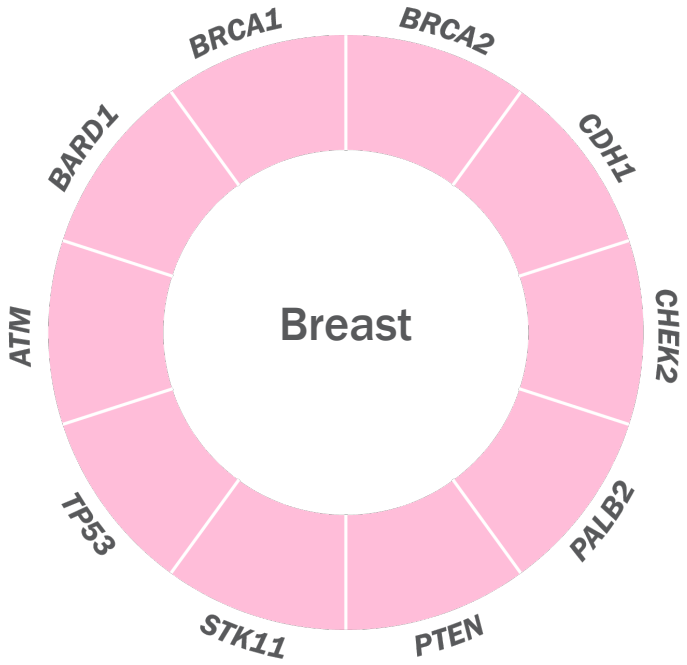
Reference: https://www.nccn.org

Importance of a multi-gene panel approach

Assessment that is too narrow can lead to a false sense of security and patient mismanagement



Multiple cancer risks can be associated with a mutation in a single gene



Multiple genes can be associated with increased risk of a single cancer

Key definitions: Multigene panel testing - Genetic tests that use next-generation sequencing to test multiple genes simultaneously (NCI)

Multi-gene panel testing provides multiple benefits compared to single syndrome testing

- Removes inadequacies of panel selection due to significant overlap in criteria
- Increases mutation detection rate
- Identification of clinically significant mutations unexpected based on family history alone

ASCO 2017, *Yield of Multiplex Panel Testing Exceeds Expert Opinion and Validated Prediction Models.* Idos et al.

Key definitions: Multigene panel testing - Genetic tests that use next-generation sequencing to test multiple genes simultaneously (NCI)

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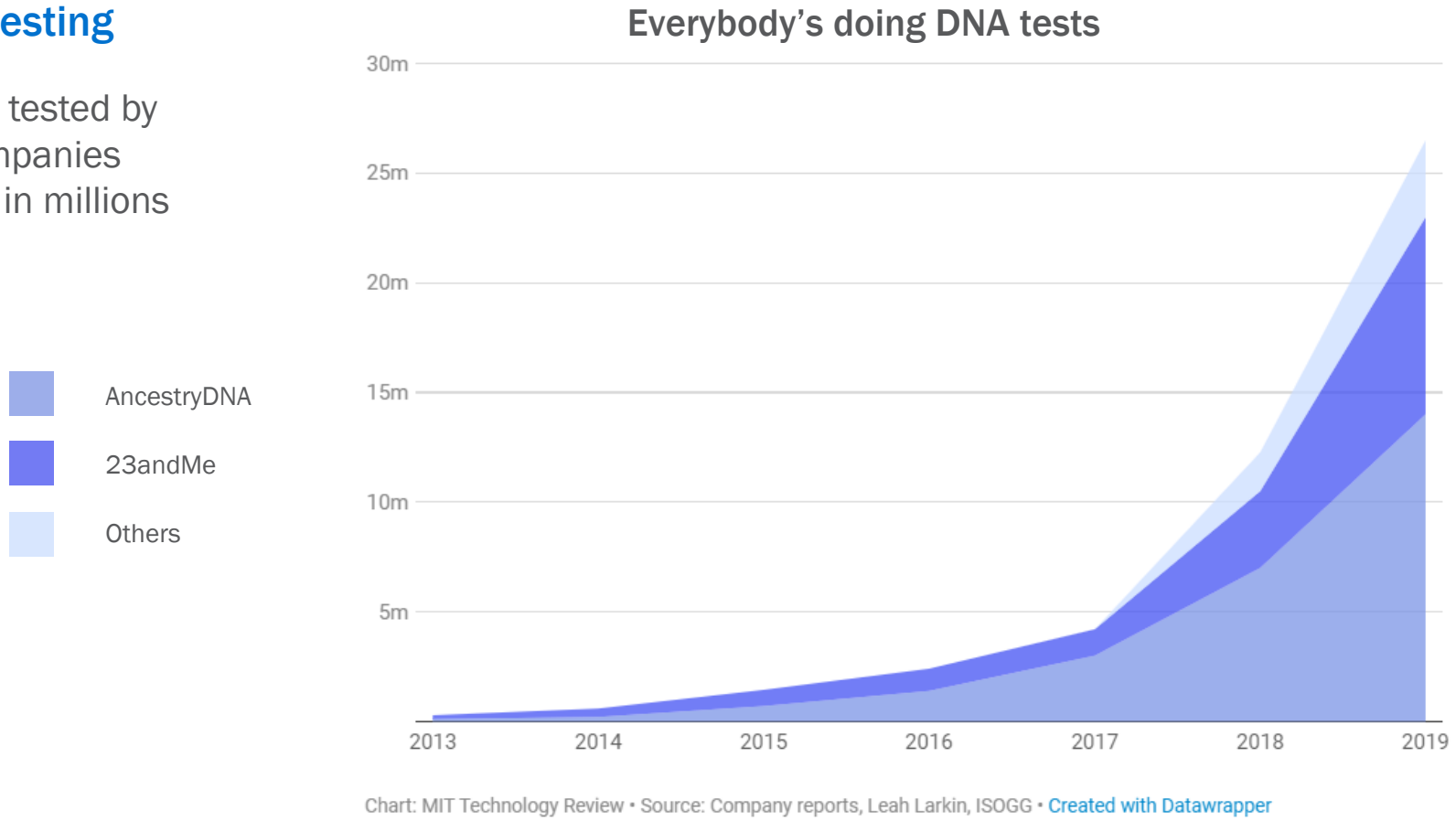
Approaches to testing

Direct to consumer testing

Total number of people tested by consumer genetics companies through January 2019, in millions

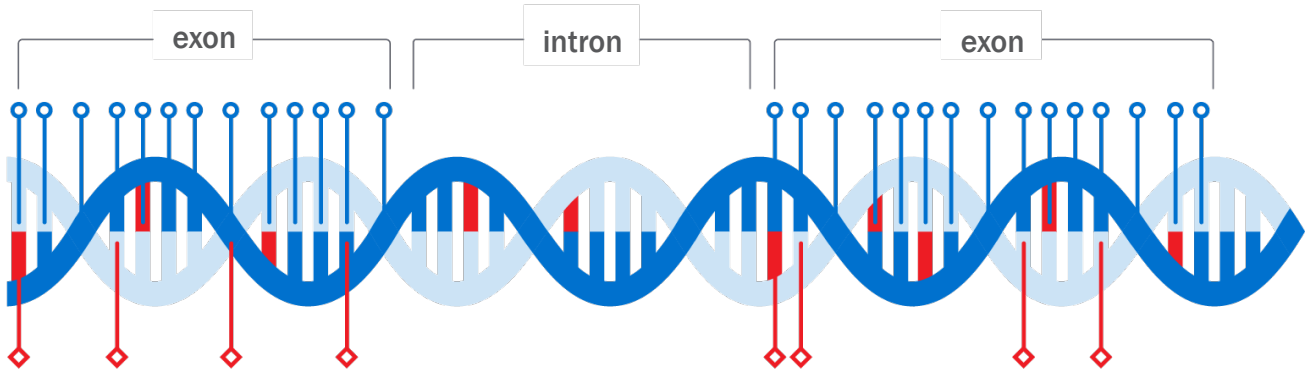


https://www.technologyreview.com/2019/02/11/103446/more-than-26-million-people-have-taken-an-at-home-ancestry-test/

Approaches to testing

Direct to consumer testing

**23andMe health predisposition reports include both reports that meet FDA requirements for genetic health risks and reports which are based on 23andMe research and have not been reviewed by the FDA. The test uses qualitative genotyping to detect select clinically relevant variants in the genomic DNA of adults from saliva for the purpose of reporting and interpreting genetic health risks. It is not intended to diagnose any disease. Your ethnicity may affect the relevance of each report and how your genetic health risk results are interpreted. Each genetic health risk report describes if a person has variants associated with a higher risk of developing a disease, but does not describe a person's overall risk of developing the disease. The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment. Our carrier status reports can be used to determine carrier status, but cannot determine if you have two copies of any genetic variant. These carrier reports are not intended to tell you anything about your risk for developing a disease in the future, the health of your fetus, or your newborn child's risk of developing a particular disease later in life. For certain conditions, we provide a single report that includes information on both carrier status and genetic health risk. [Back to content]*



Full-exon sequencing
maximizes detection rates by looking at the entire exon to a select depth, identifying disease causing mutations, as well as deletions

Targeted sequencing
Focuses only on specific areas of the exon where mutations are associated with a disorder

Approaches to testing

When to consider update testing

- Only tested for *BRCA1* & *BRCA2* with a family history consistent of HBOC/only tested for Lynch related genes with a family history consistent with lynch syndrome
- Single syndrome panel performed (likely if tested prior to 2013)
- New genes added related to cancers in family history
- When family history of cancer changes (new diagnosis in family)
- Diagnosis of cancer

Key definitions: *BRCA1* and *BRCA2* - genes on chromosome 17 and 13, respectively, that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a the *BRCA1* or *BRCA2* genes have a higher risk of getting breast, ovarian, prostate, and other types of cancer (NCI)

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Result types and medical management changes

Section 2.3

Results

Pathogenic/Likely pathogenic

Uncertain significance (VUS)

Likely benign/benign

Positive:
Clinically significant mutation identified in tested genes

Negative:
No clinically significant mutation identified in tested genes. Genetic result does not change management.

Key definitions: **Pathogenic** - A genetic alteration that increases an individual's susceptibility or predisposition to a certain disorder or disease, such as cancer. VUS - A variation in a genetic sequence for which the association with disease risk is unclear (NCI)

Results

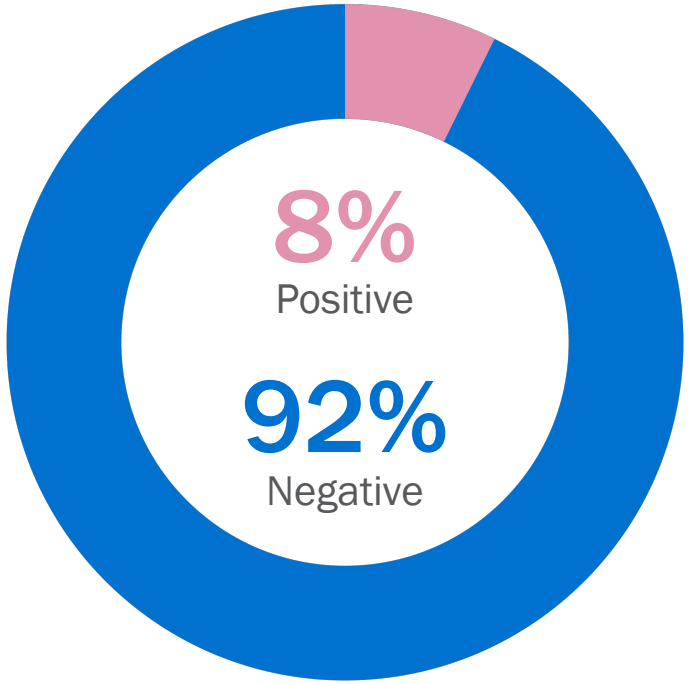
Uncertain Significance (VUS)

- Variant of Uncertain Significance (VUS): Evidence Insufficient to alter medical management.
- Per NCCN, VUSs alone should not change management. Manage based on risk conferred by cancers in family history
- Literature has shown that ~90% of VUSs are reclassified as benign/likely benign

Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing. JAMA. 2018;320(12):1266–1274. doi:10.1001/jama.2018.13152

Key definitions: VUS - A variation in a genetic sequence for which the association with disease risk is unclear (NCI)

Results



Changes include:

- Increased screening/surveillance
- Chemoprevention
- Family planning changes
- Surgery
- Referral to specialists

Screening recommendations for BRCA mutation carriers

	Procedure	Age to begin	Frequency
Breast cancer surveillance	Breast awareness	18 years	—
	Clinical breast exam	25 years	Every 6-12 months
	MRI with contrast** and/or mammography	• Age 25–29 years, annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present. • Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast.	Annually
Ovarian cancer surveillance	**Studies do not support routine ovarian cancer screening***		
	Consider trans-vaginal ultrasound and CA-125 measurement	30-35 years	Individualized

*Limited efficacy, limited data. **MRI should be performed between days 7-15 of cycle for premenopausal women.

Reference: Version 2.2022, 03/09/22 © 2022 National Comprehensive Cancer Network®

Ovarian cancer risk-reducing agents

If childbearing not completed

Oral contraceptive pills

- Combined Estrogen and Progestin

50%

Risk reduction for 5+ years

1. Narod SA, et al. Oral contraceptives and the risk of hereditary ovarian cancer. NEJM. 1998;339:424-428. **2.** Narod SA, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. JNCI. 2002;94:1773-9. **3.** Modan B, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. NEJM. 2001;345:235-40. **4.** McLaughlin JR, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol. 2007 Jan;8(1):26-34. **5.** Haile RW, et al. BRCA1 and BRCA2 Mutation Carriers, Oral Contraceptive Use, and Breast Cancer Before Age 50. Cancer Epidemiol Biomarkers Prev. 2006 Oct;15(10):1863-70. **6.** McGuire V, et al. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. Am J Epidemiol. 2004 Oct 1;160(7):613-8. **7.** Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Petro R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008 Jan 26;371(9609):303-14. **8.** Figueiredo JC, et al. Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and non-carriers: the WECARE Study. Breast Cancer Res Treat. 2010 Feb;120(1):175-83. **9.** Iodice S et al. Oral contraceptives and breast or ovaian cancer risk in BRCA1/2 carriers: a meta-analysis. European Journal of Cancer. 2010; 46:2275-84. **10.** NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V1 2020. Available at http://www.nccn.org.

Surgical options to prevent cancer

Bilateral Salpingo-Oophorectomy and risk-reducing mastectomy

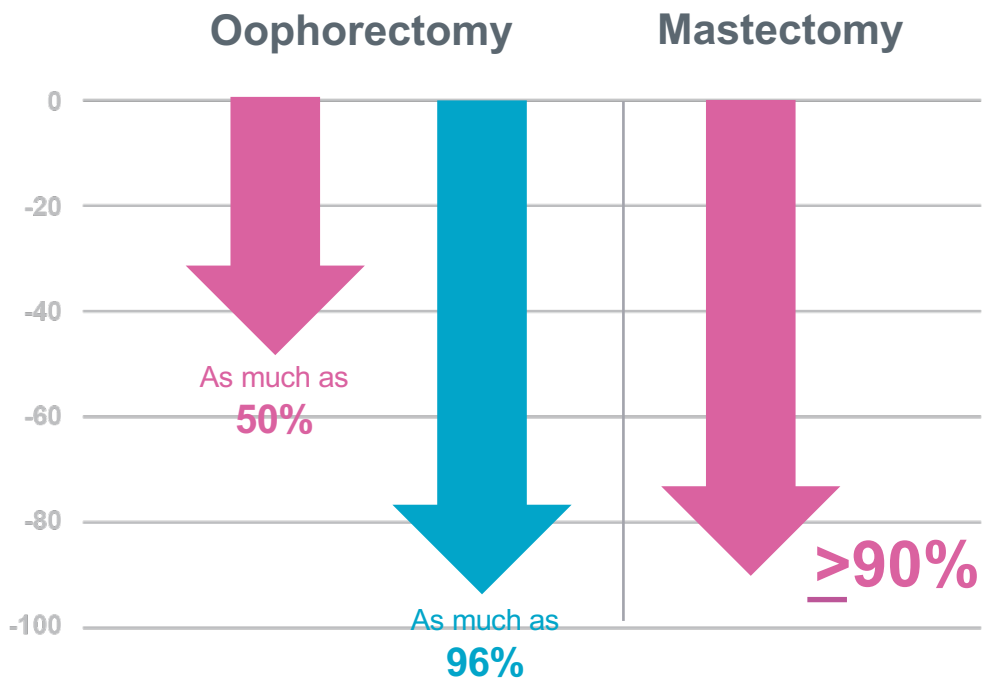
Occult ovarian cancer risk:
Up to 26%

- Breast cancer risk reduction
- Ovarian cancer risk reduction

Occult breast cancer risk:
~3%

- Breast cancer risk reduction

Consider skin-sparing, nipple-sparing bilateral risk-reducing mastectomy



1. JAMA 2010;304(9):967-75 **2.** NEJM 2002;346:1609-1615 **3.** JNCI 2001;93:1633-7 **4.** JCO 2004;22:1055-62 **5.** JAMA 2006;296:185-92 **6.** Clin Oncol 2005 Mar 10;23(8):1656-63 **7.** NEJM 2002;346:1616-1622 **8.** J Natl Cancer Inst. 2009 Jan 21;101(2):80-7 **9.** NCCN Clinical Practice Guidelines in Oncology v3 2019 Genetic/Familial High-Risk Assessment: Breast and Ovarian. Accessed at www.nccn.org **10.** J Clin Oncol 2005;23(1):127-32. **11.** Gynecol Oncol 2002;87(1):52-6. **12.** Br J Cancer 2004;90:1492-7 **13.** ACOG CO 634: Hereditary Cancer Syndromes and Risk Assessment, June 2015.

Key definitions: Salpingo-oophorectomy - Surgical removal of the fallopian tubes and ovaries (NCI)

Other breast cancer genes management

Gene	Breast awareness	Clinical breast exams	Mammogram, with consideration of tomosynthesis and consideration of breast MRI with contrast	Consider risk reducing mastectomy/strategies
BARD1	Individualized	When genetic risk is identified but not before 21. Every 6-12 months.	40 or modified to a younger age based on family history. Annually	Individualized
PALB2	Individualized	When genetic risk is identified but not before 21. Every 6-12 months.	Age 30 or modified to a younger age based on family history. Annually	Individualized
ATM	Individualized	When genetic risk is identified but not before age 21. Every 6-12 months	Age 40 or modified to a younger age based on family history. Annually.	Individualized
CHEK2	Individualized	When genetic risk is identified but not before 21. Every 6-12 months.	Age 40 or modified to a younger age based on family history. Annually.	Individualized
TP53	18 years old	Age 20 or at the age of earliest diagnosis in the family if under 20. Every 6-12 months	Age 20 for MRI. Age 30 for both MRI and mammogram. Annually.	Individualized
STK11	18 years old	30 years old. Every 6 months	30 years for both mammogram and breast MRI with contrast. Annually	Individualized
CDH1	18 years old	25 years old. Annually.	30-40 for mammogram with consideration of tomosynthesis. 30 for breast MRI with contrast. Annually.	Between 30-60
PTEN	18 years old	25 or 5-10 years younger than earliest diagnosis in family. Every 6-12 months.	30-35 or 5-10 years younger than the earliest diagnosis in the family. Annually	Individualized
RAD51C	Individualized	Individualized	Individualized	Individualized
RAD51C	Individualized	Individualized	Individualized	Individualized
NF1			30 years for mammogram with consideration of tomosynthesis. 30-50 for MRI consideration.	Individualized

Reference: https://www.nccn.org

Patient conversations

Section 2.4

Pre-test conversation

Informed consent

- Cancer types (sporadic, familial, hereditary) and what in family history is suggestive of hereditary cancer
- People with gene mutations have higher risk for getting certain cancers, however, there are management changes that can be done (screening, risk reducing surgeries, preventative medications, etc.)
- Testing options
- Possible result types: positive, negative, uncertain (VUS)
- Test coverage and privacy (HIPAA and GINA)
- Benefits and limitations
- Next Steps including family impact and management plan

Key definitions: **GINA** - The Genetic Information Nondiscrimination Act became federal law in 2008 and GINA prohibits discrimination based on genetic information in determining health insurance eligibility or rates and suitability for employment (NCI)

Post-test conversation

- Results disclosure should include:
- Genetic test result (positive or negative)
- How the genetic result affects management
  - Negative: no change in management based solely on this result
  - Positive: Guideline driven medical management implementation
  - VUS if applicable
- Family implications:
  - If positive: others at risk to have this mutation
  - If negative: informative genetic testing if applicable

Negative result: Example discussion

> Your genetic testing result was negative, meaning no mutations were found in the genes tested to suggest managing your cancer risk differently.

> This does not rule out a mutation in your family, so other relatives may still consider genetic testing. We are going to manage your care based on your personal and family history.

Key definitions: **Mutation** - A genetic alteration that increases an individual's susceptibility or predisposition to a certain disorder or disease, such as cancer (NCI)

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Positive result: Example discussion

> Your genetic testing results show that you have a mutation in the _____ gene. This might explain some or all of the cancer diagnoses in your family. This means you have an increased risk for _____ cancers.

> It's really helpful to have this information. Now that we know you're at an increased risk for cancer, we can make a specific plan to help manage your risks.

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Variant of uncertain significance: **Example discussion**

> There was a change identified in one or more of the genes on the panel called a Variant of Uncertain Significance (VUS).This is a common finding, and at this time there is not enough evidence to say it impacts your cancer risk. Most VUSs turn out to be harmless and do not increase your risk for cancer. For now, we will continue to manage you based on your personal and family history.

Testing other family members

Positive results

- First degree relatives, including **children**, are at 50% risk to carry the mutation; more distant relatives are also at risk
  - In general, genetic testing for adult-onset cancer syndromes can be considered starting at age 18*
- **All close family members** should be offered testing to guide management

Negative & elevated risk results

- In general, children do not need to be tested, unless the other biological parent has a significant family history
- **Other relatives** (especially those affected with cancer) should still consider testing
- There may be a mutation in the family that your patient did not inherit

*There are some genes for which testing in minors are appropriate.

Key takeaway points

Section 2.5

Key takeaway points

- Highest risk for cancer is those who have a hereditary predisposition to cancer
- Many genes can cause an increase for breast cancer, although BRCA1 and BRCA2 are the most common
- Medical management changes for those with a hereditary predisposition to cancer include increased/earlier screening, surgery, and other risk reducing agents.
- Results for genetic testing include positive, negative, and VUS (variant of uncertain significance)
- Those positive for a genetic mutation causing a hereditary predisposition to cancer their first degree relatives (parents, siblings, children) have a 50% to have that mutation too.

Apply what you've learned, put into practice, and tips for implementation

Within the guidelines of your clinical practice in collaboration with your multi-disciplinary team

1. Develop script to introduce the idea of genetic testing to your patient
2. Provide an example of appropriate patient information as "take-aways" for patients

Example verbiage:

"In addition to your mammogram today we looked at the family history you have provided. Which indicates you could be at additional risk.

We have a program here to help you better understand that risk. I am going to take you to a spot where we have you watch a short video and then speak to a patient educator with expertise in genetic risk assessment.

It will take a few additional minutes, but we highly recommend this based on your family history."

Resources

Patient resources

- FORCE: https://www.facingourrisk.org/
- Sharsheret: https://sharsheret.org/
- Prevent Cancer Foundation: https://www.preventcancer.org/

Society resources

- National Comprehensive Cancer Network (NCCN) Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic: https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1503

Thank you for joining!

The Technologist's Role in Breast Cancer Risk Assessment

Communicating the benefits of comprehensive risk assessment to patients

Program 2: Cancer genetics 101

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