Genomic Screening for Primary Care: Cancer Risk.

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Learning Objectives

1. Understand the different types of cancer genetic and genomic tests.
2. Know the yield of genetic testing for hereditary cancer traits in different populations.
3. Compare the different models for integrating genetic testing into a primary care practice.
4. Know the resources for managing a patient with pathogenic variant in a large effect cancer gene (eg BRCA1/2)

GOAL: Is to make genetic testing more approachable.

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Terms

- **Mutation ⇨ pathogenic variant** "PV". All DNA changes different than the reference sequence are "variants" and are ranked as benign, likely benign, uncertain significance (VOUS), likely pathogenic, pathogenic.
- **Genetics** is the study of single genes and inheritance
- **Genomics** is a more recent term that describes the study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment.

Genetics ⇨ Genomics

- **NCCN** = National Comprehensive Cancer Network
- **SNiP** = Single nucleotide polymorphism (ex change G>T, usual cause a single amino acid change, Alanine to Glycine)

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Genetic and Genomic Cancer Tests

Purpose	Method (Example)
Screen for cancer	Circulating methylated DNA (blood test Galleri by Grail multisite cancer screen)
Treatment of cancer	Circulating tumor DNA - ct DNA ("liquid biopsy" of tumor Guardant 360) Tumor DNA testing (Foundation One)
Prognosis after cancer diagnosis	Gene expression in tumor tissue (Oncotype DX for breast cancer)

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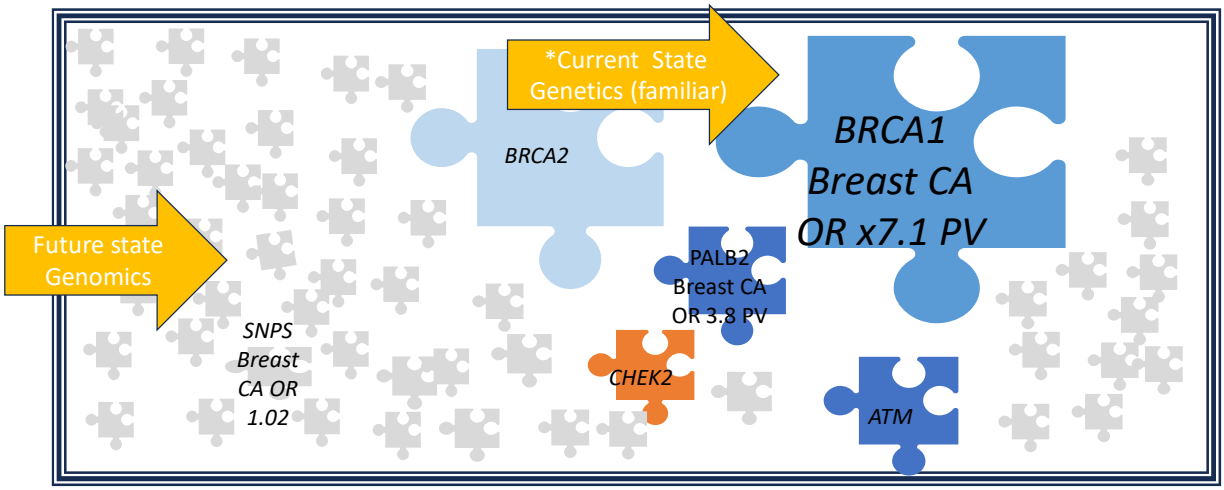
Completing the Puzzle of Genetic Cancer risk
Large, medium and small genetic effects



Much of cancer risk is due to small increases from individual SNPs

N Engl J Med 2021; 384:440-451

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Genetic and Genomic Cancer Tests cont

Current State Genetics **PCP Ordering***

Future state Genomics

Tests to determine cancer risk	Method (Example)
Single genes with **large and medium cancer risk effects**	Multi gene hereditary cancer panel. Offered by many labs, 30 – 80 gene panels. BRCA1/2 and Lynch syndrome + others.
Small cancer risk effect genes	**Polygenic risk scores** Myriad genetic myrisk for breast cancer only test widely used in the US (140 SNPS).
Integrated evaluation History (ex breast density) + large, medium, and small effect risk genes	UK model Canrisk.org

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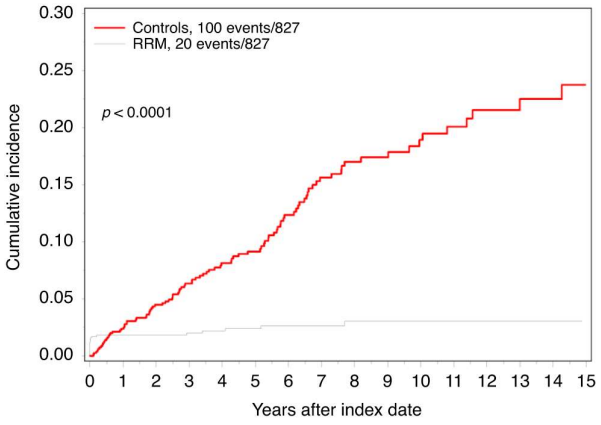
Why identify patients with a hereditary cancer syndromes? (eg BRCA1)

- Primary care prevention
  - Risk reducing mastectomy
- Treatment of active cancer
  - Bilateral mastectomy (vs unilateral)
- Risk for other cancers
  - BRCA1 PV Lifetime risk for OV CA 44%
- Familial counseling
  - Autosomal dominant inheritance.



Risk-reducing mastectomy and breast cancer mortality in women with a BRCA1 or BRCA2 pathogenic variant: an international analysis, British Journal of Cancer **130**, pages 269–274 (2024).

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How common are the large and medium effect pathogenic variants for breast cancer?

- 12 breast cancer predisposition genes were tested in 32K BrCA cases and 32K controls
  - *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD5 1D*, and *TP53*
- All breast cancer patients 5%
- No dx of breast cancer 1.5%
- > 100,000 women in Florida carry a PV in one of these genes, the majority are not diagnosed

N Engl J Med 2021; 384:440-451

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Hereditary Cancer Genetic Testing In Your Practice

- When?
- How?
- What next with a positive result?

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Cancer Genetic Testing In Your Practice

Indications for cancer genetic testing

Selected NCCN Criteria for Testing (Yes to Any ?)
Breast cancer dx Under the age of 50 Breast cancer at any age, with a relative with breast or ovarian cancer
Metastatic prostate cancer, prostate cancer and family member with prostate, breast, or ovarian cancer
Pancreas cancer
Ovarian cancer

"The sensitivity of NCCN criteria was 70% for 9 predisposition genes and 87% for *BRCA1* and *BRCA2*. . ."
Some Cancer Centers now offer testing to all patients with a history of any cancer.

Journal of Clinical Oncology Volume 38, Number 13

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Hereditary Cancer Genetic Testing in Your Practice: How?

Refer out	In Clinic
Patient initiated testing. Pre pay $258 for mail in saliva kit for testing 29 hereditary cancer genes. Normal results are emailed. PV carriers are offered genetic counseling. CLIA / CAP certified.	Contact referral laboratory for clinic visit and staff training. Common model in GYN offices.
Send to a Genomics clinic. Likely will be able to arrange no out of pocket cost with more comprehensive testing. National Society of Genomic Counselors Directory www.nscg.org	

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Do all cancer patients need upfront genetic counseling?

- **Remotely Delivered Cancer Genetic Testing in the Making Genetic Testing Accessible (MAGENTA) Trial: A Randomized Clinical Trial.** JAMA Oncol 2023 Nov 1;9(11):1547-1555.
- **Intervention:** 3839 women randomized to 4 groups, with different combinations of pre and post test counseling.
- **Conclusions and relevance:** Omitting individualized pretest. . counseling for all participants was . . not inferior with regard to posttest distress
- ⇨ PCP can offer genetic testing without upfront counseling.

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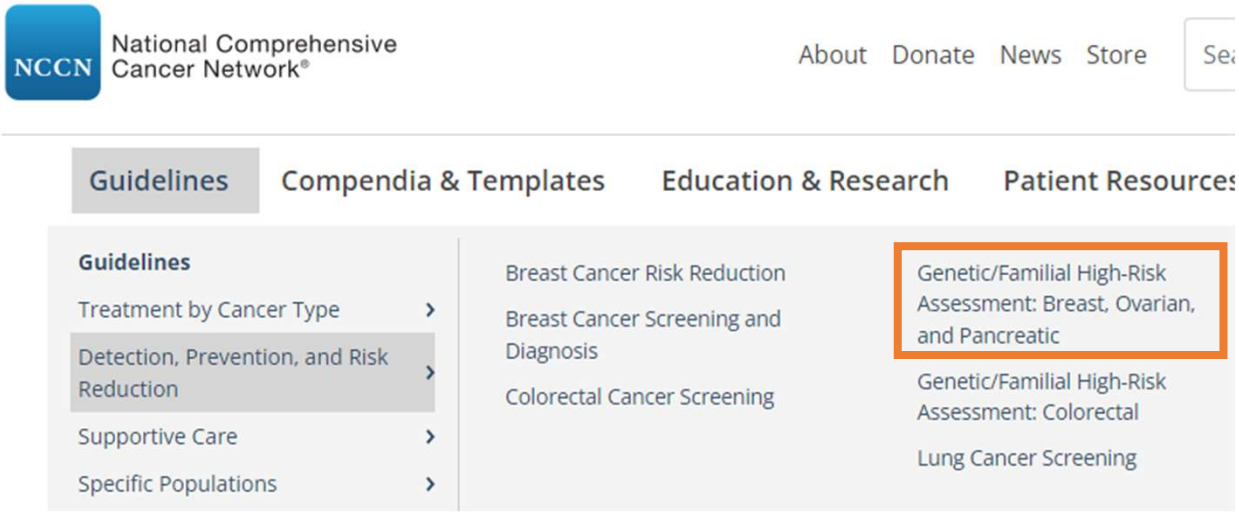
What next after a positive result? NCCN Management guidelines are the most used in the US and should be attached to laboratory report.



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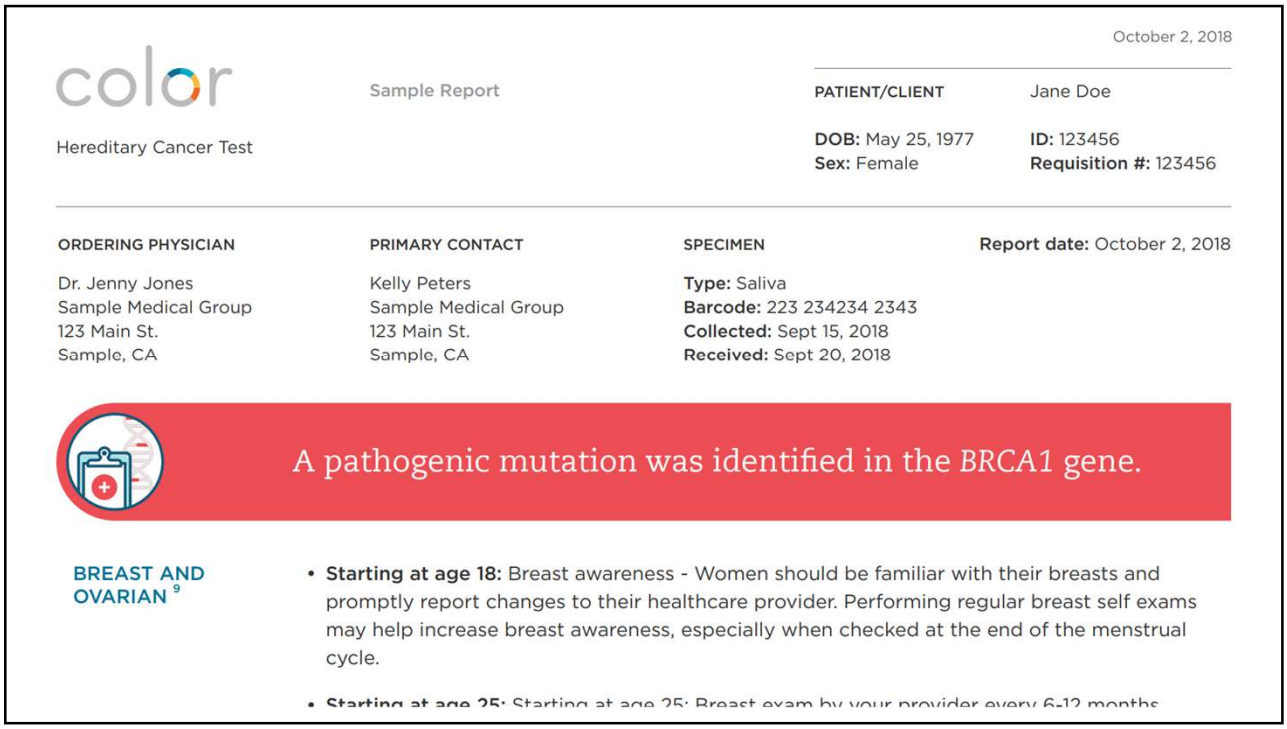

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Hereditary Cancer Test

Sample Report

October 2, 2018

PATIENT/CLIENT Jane Doe

DOB: May 25, 1977
Sex: Female

ID: 123456
Requisition #: 123456

ORDERING PHYSICIAN

Dr. Jenny Jones
Sample Medical Group
123 Main St.
Sample, CA

PRIMARY CONTACT

Kelly Peters
Sample Medical Group
123 Main St.
Sample, CA

SPECIMEN

Type: Saliva
Barcode: 223 234234 2343
Collected: Sept 15, 2018
Received: Sept 20, 2018

Report date: October 2, 2018

A pathogenic mutation was identified in the *BRCA1* gene.

BREAST AND OVARIAN [9]

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25:** Starting at age 25: Breast exam by your provider every 6-12 months

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Management

Most hereditary cancer traits have patient groups that provide the NCCN recommendations in a more approachable format

FORCE
Facing Hereditary Cancer EMPOWERED
25 years

Cancer risk, screening, prevention and treatment for people with inherited mutations

Mutations in these genes have been linked to increased risk for different types of cancer. Learn more about the risks, expert guidelines, resources and research for each gene. If you have an inherited mutation in a gene not listed here, please contact us for information and resources.

Last updated June 11, 2023

APC | ATM | BARD1 | BRCA1 | BRCA2 | BRIP1 | CDH1 | CDKN2A | CDK4

CHEK2 | EPCAM (Lynch syndrome) | HOXB13 | MLH1 (Lynch syndrome) | MSH2 (Lynch syndrome)

MSH6 (Lynch syndrome) | MUTYH | NBN | PALB2 | PMS2 (Lynch syndrome)

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Breast cancer risk management in women

Beginning age	Recommendation	Additional information
18	Learn to be aware of changes in your breasts.	
25	Breast exam by doctor every 6-12 months.	
25	Yearly breast MRI with and without contrast beginning at age 25 and continuing until age 75.	If MRI is not available, mammogram screening should begin at age 25.
30	Yearly mammogram.	
No set age	Discuss the benefits, risks and costs of double mastectomy with your doctor.	Risk-reducing mastectomy lowers breast cancer risk by 90%, but has not been shown to improve survival. Even after double mastectomy, some breast tissue, and therefore cancer risk remains.
No set age	Discuss the benefits, risks and costs of medications to lower the risk for breast cancer with your doctor.	Tamoxifen or other estrogen-blocking drugs may lower breast cancer risk. Medications or vaccines are being studied in clinical trials.
75	Consider whether to continue, stop or change breast screening.	

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Summary: Key Learning Points

- Patients can have several different types of genetic testing. Some for risk stratification (PVs in high and medium risk genes), some for diagnosis, some for CA treatment.
- About 1 % of the population has a PV in a hereditary cancer syndrome gene. The more selective testing criteria, the decrease in sensitivity. I offer genetics testing to all patients with a cancer diagnosis.
- PCPs can order or refer patients for CA genetic testing without genetic counseling pretest.
- There are many resources for management after a positive test (ex report).

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Citations and References (evidence-based, peer-reviewed)

1. A population-based study of genes previously indicated in breast cancer. N Engl J Med 2021; 384:440-451

2. MAGENTA trial. JAMA Oncol 2023 Nov 1;9(11):1547-1555.

3.National Comprehensive Cancer Network. NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 3.2023. Accessed 3/7/2024. genetics_bop.pdf (nccn.org)

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END

Questions?

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