



CIBC 2019

Breast Cancer Genetic Screening

Peter J. Hulick, MD, MMSc, FACMG
Medical Director, Mark R. Neaman Center for Personalized Medicine
NorthShore University HealthSystem



Chicago International Breast Course
The Westin Chicago River North
November 1-3, 2019

Disclosure

- No real or apparent relationships to report.



Personalized Medicine ... the why

- Better risk assessment
- Better screening strategies
- Better and more targeted treatment
- Better care and outcomes for patients

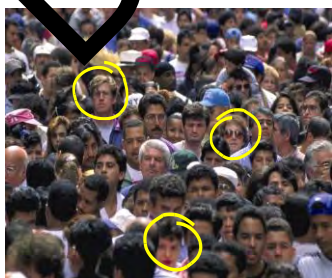


Health and disease risk

- Environmental
- Lifestyle choices
- Genetic factors
- Other "omics"



Who Is a High Risk?



"Traditional" Personalized Medicine: Hereditary Cancer

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Pattern of cancers suggestive of a specific cancer syndrome
- Evidence of autosomal dominant transmission



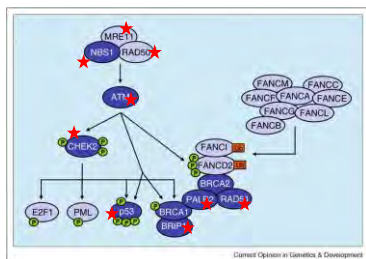
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DNA Repair Pathway



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Shift in Cancer Genetic Testing

- From single gene testing ...
 - e.g. BRCA1/2 then consider other individual genes based on pattern of cancers
- To panel approach
 - Assess many genes linked to specific cancer risk, including BRCA1/2, at same time
- Bridge to whole exome and genome analysis
 - Polygenic Risk Scores

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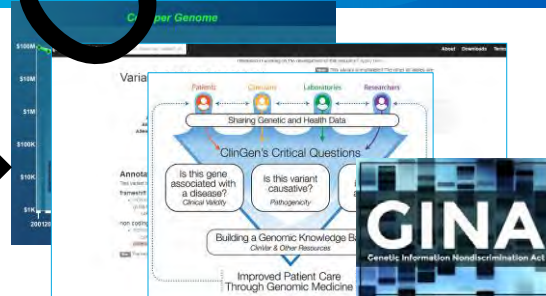
Background ... the why

- 2001 "Completion"
- Lots of promise, hype
- Reality
 - Starting blueprint
 - Costs high
 - GINA not enacted
 - *What is normal?*



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The time is right ... the why



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GINA

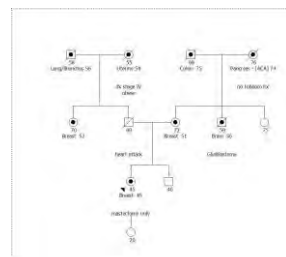
- The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects individuals from genetic discrimination in health insurance and employment
 - Separate from Affordable Care Act
 - <http://ginahelp.org/>

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Single Gene Approach

Historically

- BRCA testing - \$4000
- Costs coming down with competition
- Risk on both sides of the family
- If results are normal ...



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Single Gene Approach

Affordable pricing

We're dedicated to driving down the cost of testing so you can benefit from your genetic information. We offer two easy ways to pay:

INSURANCE

Genetic testing with results in the US have this option to pay!

SELF-PAY

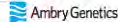
Don't have insurance? No problem. Use your HSA/FSA.

[LEARN MORE](#)

- Li-Fraumeni syndrome (\$1000-\$2000)
- PALB2 gene (\$1000-\$2000)
- CHEK2 gene (\$1000)

Accessible. Affordable. Actionable.

You can't pay more than you should. Without unnecessary testing. (MSKCC 2017)



A Kinexa Health Company

color

Hereditary Cancer Test: \$249 self-pay or insurance accepted

Color's Provider Platform makes ordering testing easy and fast. Save time and place your order online or request your patient to purchase while at home. Alternatively, collect the patient's sample in the office using a Color kit. You can choose if results are released at the same to your patient, or after a delay. Your patient will provide their personal and family history on our HIPAA-compliant website.

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23andMe ... Did You Know?

- BRCA1/BRCA2 (Selected Variants)
 - BRCA1 185delAG and 5382insC variants
 - BRCA2 6174delT variant
 - Ashkenazi Jewish Founder Mutations



BRCA1/BRCA2 (Selected Variants)

Specific genetic variants in the BRCA1 and BRCA2 genes are associated with an increased risk of developing certain cancers, including breast cancer (in women and men) and ovarian cancer. These variants may also be associated with an increased risk for prostate cancer and certain other cancers. This test includes three genetic variants in the BRCA1 and BRCA2 genes that are most common in people of Ashkenazi Jewish descent.

you have a greatly increased risk of developing breast and ovarian cancer.

You have one of the three genetic variants we tested. Women with this variant have a much higher than average risk of developing breast and ovarian cancer. Risk for certain other cancers may also be increased.

1 variant detected in the BRCA2 gene

Please share your result with a healthcare professional. **It is important to confirm this result in a clinical setting before taking any medical action.**

How to Use This Test

This test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.

Please talk to a healthcare professional about additional testing to confirm this result and to better understand your potential cancer risk.

Demystifying the Genetics Reports: Core Elements

What should I focus on?

1. Outcome - Result
 - Clinical
 - Patient and Family
 - Scientific

There's an over abundance of information!



Demystifying the Genetics Reports

Outcome - Result

- Pathogenic or likely pathogenic variant (mutation) → "Positive"
- Benign or Likely Benign variant → "Negative"
 - Many labs do not report out LB/B variants
 - Family history may still be significant
- Variant of Uncertain Significance
 - "Don't Panic" → Majority end up being reclassified as benign
 - Center for Medical Genetics available
- Get the correct mindset for the information ...



High Level of What Tested

Outcome/Result

High Level Clinical Summary

More Detailed Risks - Guidelines and Resources

Implications for family members

Pathogenic result: Pathogenic variant identified in BRCA2 Variant of Uncertain Significance Identified in BRCA1.

Clinical Summary

A pathogenic variant, C1202C, of BRCA2 was identified in BRCA2. The BRCA2 gene is associated with an increased risk for developing breast and possibly ovarian cancer. This variant is associated with an increased risk for developing breast and possibly ovarian cancer. This variant is associated with an increased risk for developing breast and possibly ovarian cancer. This variant is associated with an increased risk for developing breast and possibly ovarian cancer.





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Sequencing → Contrast to 23andMe

"Can you tell me what I was tested for?"

"Are there 'false positives'?"
Scientific Interpretation

Scientific Interpretation – VUS
Genetics referral appropriate

Important Information for Geneticist ... Zzzzzzz

Scientific Interpretation – VUS
Genetics referral appropriate

Important Information for Geneticist ... Zzzzzzz

ClinVar

Assertion and evidence details

Genomic region	Review status (Assessment method)	Collection method	Significance (Mode of inheritance)	Origin	CHROM	Submitter (Last submitted)	Submission access
17q21.31	Classified to single submitter (clinical testing)	Retrospective only	Pathogenic	germline	5	QIMM (Jan 15, 2014)	SCV00025179
17q21.31	Classified to single submitter (clinical testing)	Clinical testing	Pathogenic	germline	5	QIMM (Jan 15, 2014)	SCV00025179
17q21.31	Classified to single submitter (clinical testing)	Clinical testing	Pathogenic	germline	5	QIMM (Jan 25, 2014)	SCV00025179

genomex Nov 3, 2014

Who Doesn't Meet Criteria?

NCCN Guidelines Version 3.2019
BRCA-Related Hereditary Breast and/or Ovarian Cancer Syndrome

BRCA TESTING CRITERIA**

THE AMERICAN SOCIETY OF
Breast Surgeons
Official Statement

Consensus Guideline on
Genetic Testing for Hereditary Breast Cancer

Case for Universal Screening ... Have we arrived?

Table. Cost effectiveness* of Breast Imaging and Testing Strategies in the United States

Source	Testing Strategy	Age Range of Female Population, y, and Risk Factor	Cost-effectiveness Ratio (QALYs, \$)
Plevritis et al., ² 2006	Annual mammography	25-69, BRCA1	19 000
	Annual mammography + MRI	25-69, BRCA2	29 400
Grain et al., ³ 2011	Annual mammography	35-54, BRCA1	55 400
	Annual mammography + MRI	35-54, BRCA2	130 700
Schouber et al., ⁴ 2011	Annual mammography	35-64, BRCA1	116 400
	Annual mammography + MRI	35-64, BRCA2	481 800
Moore et al., ⁵ 2009	Annual MRI	30-65, BRCA2	88 100
	Annual MRI	30-65, BRCA2	247 400
Current study	Annual mammography	40-49, BI-RADS 1-2	140 000-362 700
	Annual mammography	40-49, BI-RADS 3-4	74 500-87 800
	Annual mammography	50-79, BI-RADS 1-2	63 700-208 700
	Annual mammography	50-79, BI-RADS 3-4	21 400-51 000

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System category; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

* Incremental cost-effectiveness ratios are relative to the comparator strategy; cost-saving implies that the strategy increases QALYs while saving money.

Invitae: "Traditional Lab"

genomeweb

Invitae Begins Offering Consumer-Initiated Testing Via Early Access Program

Save for later

NEW YORK (Genomeweb) – Invitae announced at the annual iMP (Integrating Molecular Pathology) Conference being held this week in San Francisco that all of its tests that have traditionally been physician ordered, will also be available for consumer-initiated ordering.

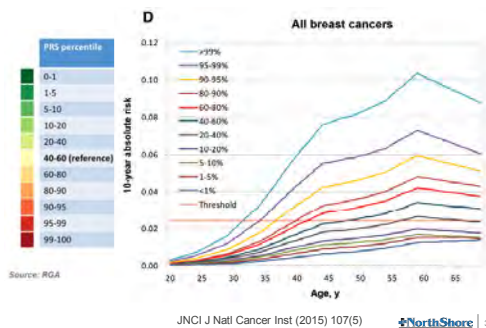
The strategy is aimed at filling a niche that patients may face in accessing genetic testing due to cost, outdated guidelines, or restrictive insurance coverage policies. The company is testing information offered by the company is important to people at all stages in their lives, said Invitae CEO Sean George, but he noted that the pace of scientific advancements in the genomics space has outpaced the ability of the healthcare system to use this information.



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Polygenic Risk Scores ... What's Next?



Family History Remains Important

Table 1. Various risk assessment models and the factors considered in assessing the risk of breast cancer.

Gail model	Claus model	BRCAPRO model	Tyrer-Cuzick model	BOADICEA model
<ul style="list-style-type: none"> Age of the person Age at menarche Age at first live birth Breast biopsies (ABI) Family history First-degree relatives 	<ul style="list-style-type: none"> Age of the person Age at menarche Age at first live birth Family history First-degree relatives Second-degree relatives 	<ul style="list-style-type: none"> Age of the person Family history First-degree relatives Second-degree relatives Age at onset of breast cancer Bilateral breast cancer Ovarian cancer Male breast cancer 	<ul style="list-style-type: none"> Age of the person Body mass index Age at menarche Age at first live birth Age at menopause Hormone replacement therapy use Breast biopsies (ABI) Family history First-degree relatives Second-degree relatives Age at onset of breast cancer Diabetes Ovarian cancer Male breast cancer 	<ul style="list-style-type: none"> Age of the person Family history First-degree relatives Second-degree relatives Third-degree relatives Age at onset of breast cancer Bilateral breast cancer Ovarian cancer Male breast cancer

Abb: atypical hyperplasia; LCIS, lobular carcinoma in situ; BOADICEA, breast and ovarian cancer incidence and carrier estimation algorithm

DOI: 10.3332/ecancer.2013.363

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Take home points

- Cost of testing continues to decrease
- Criteria for genetic testing continues to expand
- Emergence of polygenic risk scores potential to change landscape of risk assessment
- Family history remains important tool

Thank you ...

phulick@northshore.org
@ph4235

www.northshore.org/personalized-medicine

847-570-GENE (4363)

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