Unraveling the Strand: Navigating Genomic and Genetic Testing With Your Patients

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LIVING BEYOND BREAST CANCER®

Cooper University Health Care

MD Anderson Cancer Center Cooper
Making Cancer History®

Cooper Medical School of Rowan University

Disclosures

- Dr. Generosa Grana has received grants from Pfizer for breast equity research
- Dr. Evelyn Robles-Rodriguez has received grants from Pfizer and Genentech for breast equity research

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  - AstraZeneca, Genentech, and Exact Sciences for supporting this educational program

Objectives

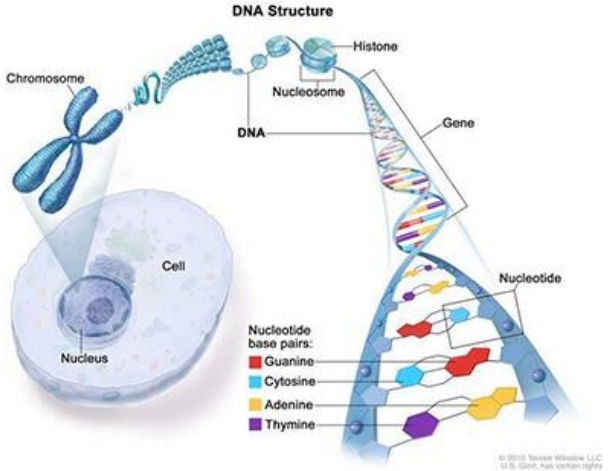
- Review the latest information on genomic testing (tumor biomarker testing) and genetic testing for an inherited mutation, with an emphasis on breast cancer
- Understand barriers in access to testing among ethnically diverse patients
- Discuss patient perceptions of genomic and genetic testing
- Understand the role of shared decision-making between patients and providers
- Describe the psychosocial implications of genomic and genetic testing
- Discuss strategies for increasing patient access to testing
- Describe best practices for communicating with patients about genomic and genetic testing

Cancer is a disease of the genome

All cancer is “genetic” but most cancer is not “hereditary”

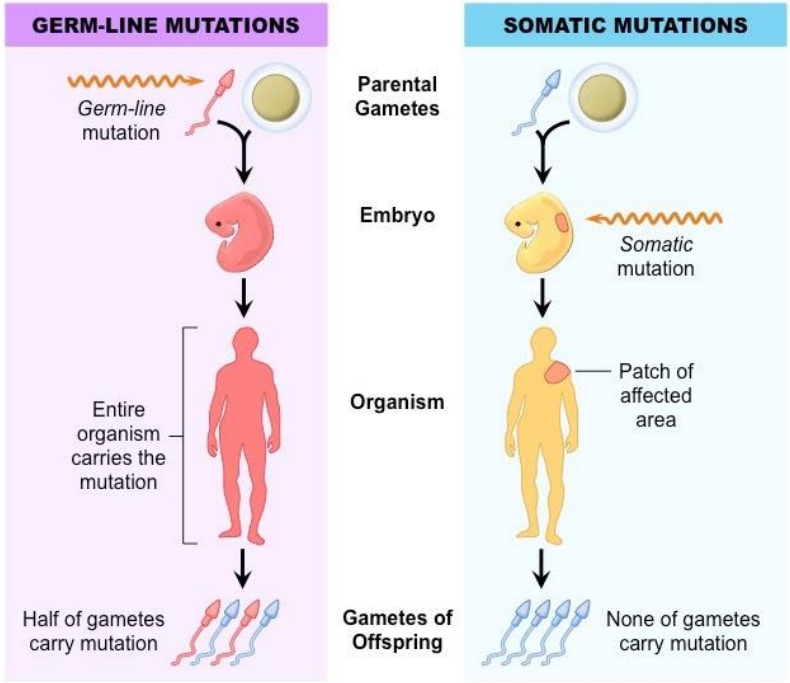
Cancer risk is dependent on:

- Hereditary alterations that an individual is born with (germline)
- Acquired alterations that give a cell capacity for uncontrolled growth (somatic)
- Cancer cell proliferation is driven by genomic changes



Germline vs. Somatic Changes

- Germ-line mutations: every cell in the entire organism will be affected (genetic)
- Somatic mutations: only tissues derived from mutated cell are affected (genomic)



Genetics vs Genomics

Genetics

- Study of single gene inherited at birth (germline)
- Role in how traits are passed on
- Screening, testing and treatment options

Genomics

- All genes (genome)
- Interact with each other and the environment
- Looking at how mutations in these genes impact disease (somatic)

Looking to the Future

GENOMICS

Past/Present vs Future

- We have traditionally looked at cancers by the tissue of origin
- Since 1950, the TNM system has been used to derive a particular stage for any cancer
- Treatment is then based upon the above
  - Stage IIIC Breast Cancer is treated with chemotherapy, radiation, surgery, etc.
- This paradigm is now being challenged in the era of genomics

Impact of Genomics on Treatment Decisions

Maybe tissue of origin and stage do not matter as much as we think?

First FDA approvals of cancer drugs based not on tumor type but on a genomic results

- May 2017 - Pembrolizumab for MSI high/dMMR
- Nov 2018 – Larotrectinib for NTRK fusion

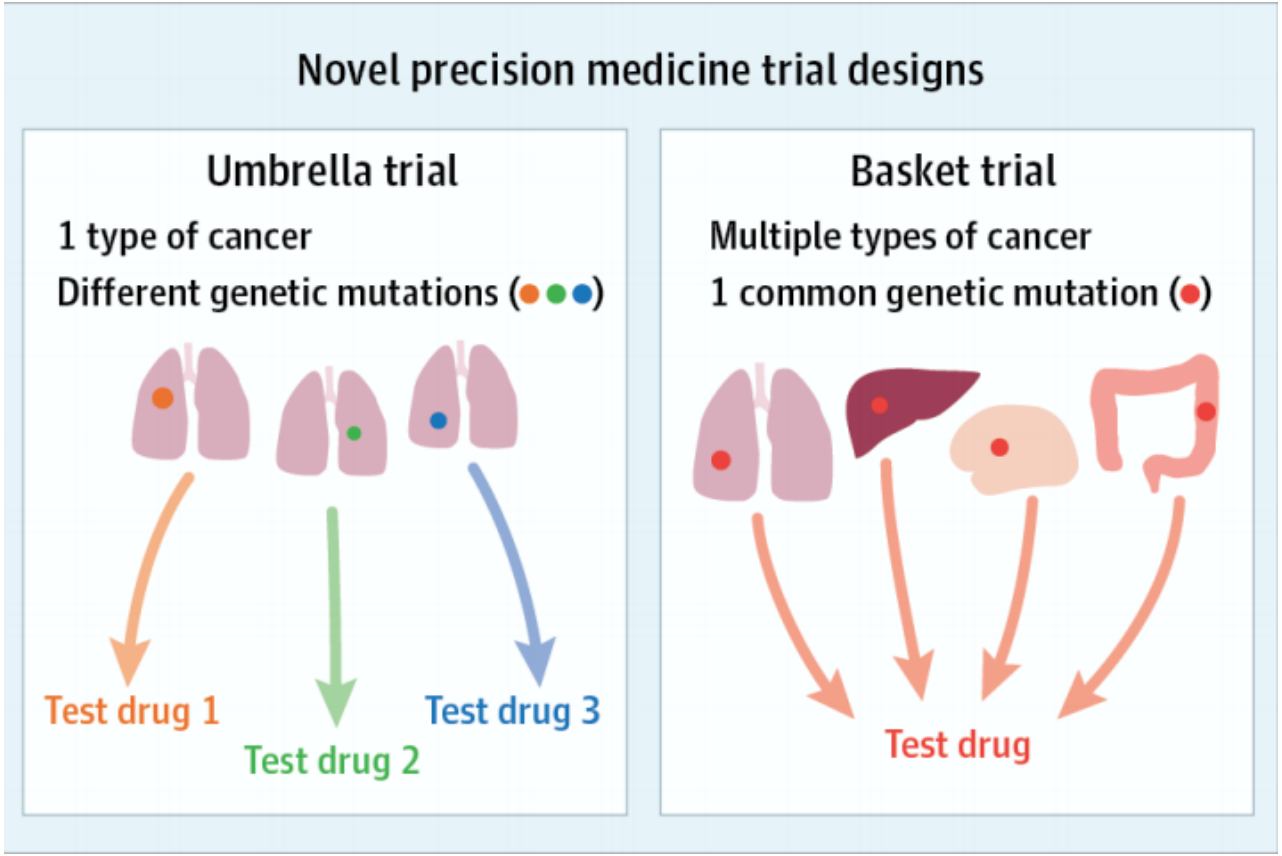
Clinical trials

Genomics has led to a change in how we conduct clinical trials

Most trials to date over the last 50 years have recruited patients with the same type of cancer. This is still a large part of ongoing research.

Basket trials allow people with different types of cancers who all have the same genomic alteration

- As these changes are not common, it's too hard to find enough patients with the same cancer and the mutation



West H, JAMA Oncology. Mar 2017

Comprehensive Genomic Profiling *now commonly utilized in oncology*

- Previously was done with a slow process known as Sanger sequencing that had to look at one gene at a time
- Since 2014, accomplished through a process known as next-generation sequencing (NGS)
- Identifies all classes of alterations across hundreds of genes known to drive cancer

PATIENT RESULTS[‖]

20 genomic findings

2 therapies associated with potential clinical benefit

2 therapies associated with lack of response

18 clinical trials

[‖] Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

TUMOR TYPE: COLON ADENOCARCINOMA (CRC)

Genomic Alterations Identified[†]

KRAS G12D
FBXW7 S668fs*39
STAT3 E616del
APC D156fs*14, R554*
ARID1A W2048*
ASXL1 G645fs*58
FLCN H429fs*39
GATA2 A411fs*72+
GATA4 G16fs*232
MSH2 V437fs*1, Y757fs*30
MSH6 F1088fs*5
NOTCH1 T2132fs*136
PBRM1 L1349fs*4
SMAD4 R97H
SOX9 R264fs*32
TBX3 L473fs*160
TET2 N1118fs*12

Additional Findings[†]

Microsatellite status MSI-High

Additional Disease-relevant Genes with No Reportable Alterations Identified[†]

BRAF
NRAS

[†] For a complete list of the genes assayed and performance specifications, please refer to the Appendix

Genomic Testing

Pros

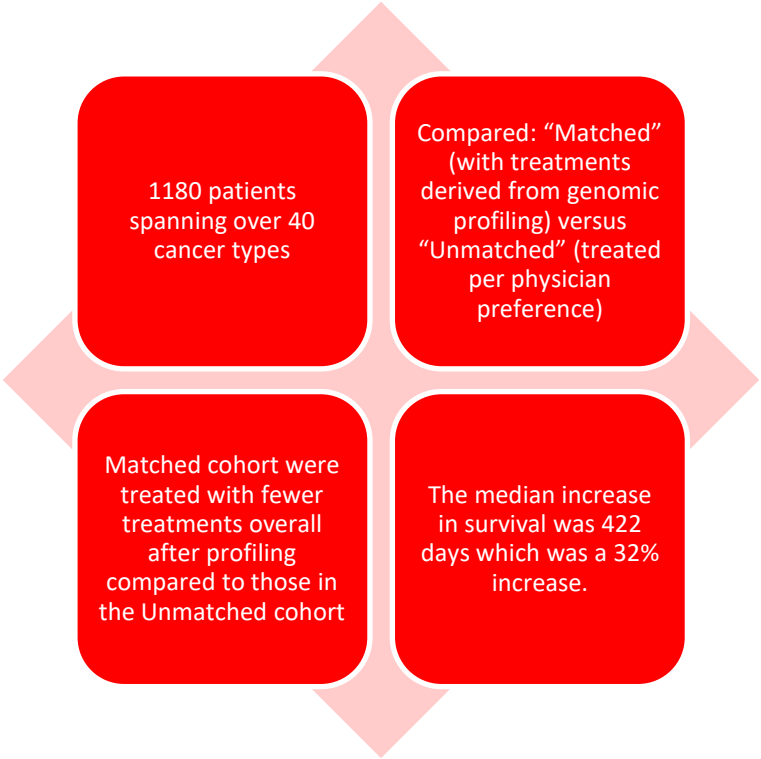
- Identify driver mutations
- Include more effective treatments
- Exclude ineffective treatments
- Improve clinical trial screening efficiency

Cons

- Knowledge of genes in cancer still growing
- Mutations found only in a small % of cancers
- Need for biopsies
- Lots of “passenger mutations”
- ***Information overload for treating oncologists***

Targeted therapy

- Treating (“targeting”) the cancer's specific genes, proteins, or the tissue environment that contribute to cancer growth and survival.



European Journal of Cancer, September 2015, Volume 51, S44.

Present and Future

GENETIC TESTING

Tumor vs. Germline testing

One is not a substitute for the other

Tumor genetic testing (genomic) may detect a mutation that is also in the germline (genetic)

Gene change interpretation differences

- a “mutation” in a tumor might be considered an “uncertain” finding in the germline

May do germline testing to follow up on a mutation found via tumor testing

- dependent on the gene and the personal / family history
- targeted to the mutation or to include full gene analysis +/- other genes

Hereditary cancer syndromes (HCS)

A germline genetic mutation causes increased risk for cancer(s) in a person / family

Mutation passed parent → child

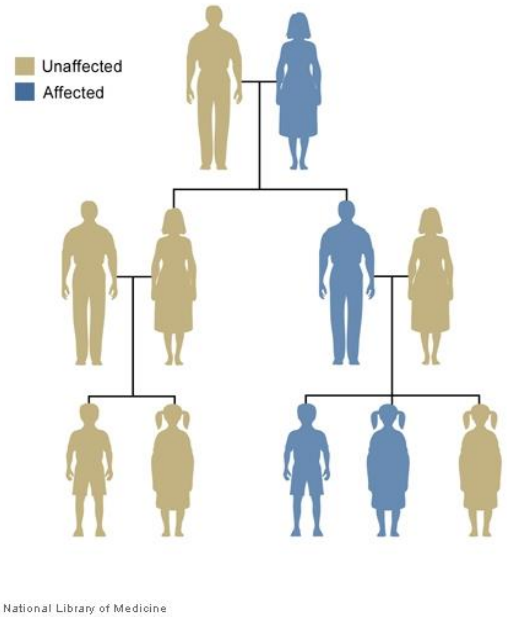
- 50% chance regardless of gender

Variable lifetime risks for cancers

- High / moderate / "increased"
- May be gender-dependent

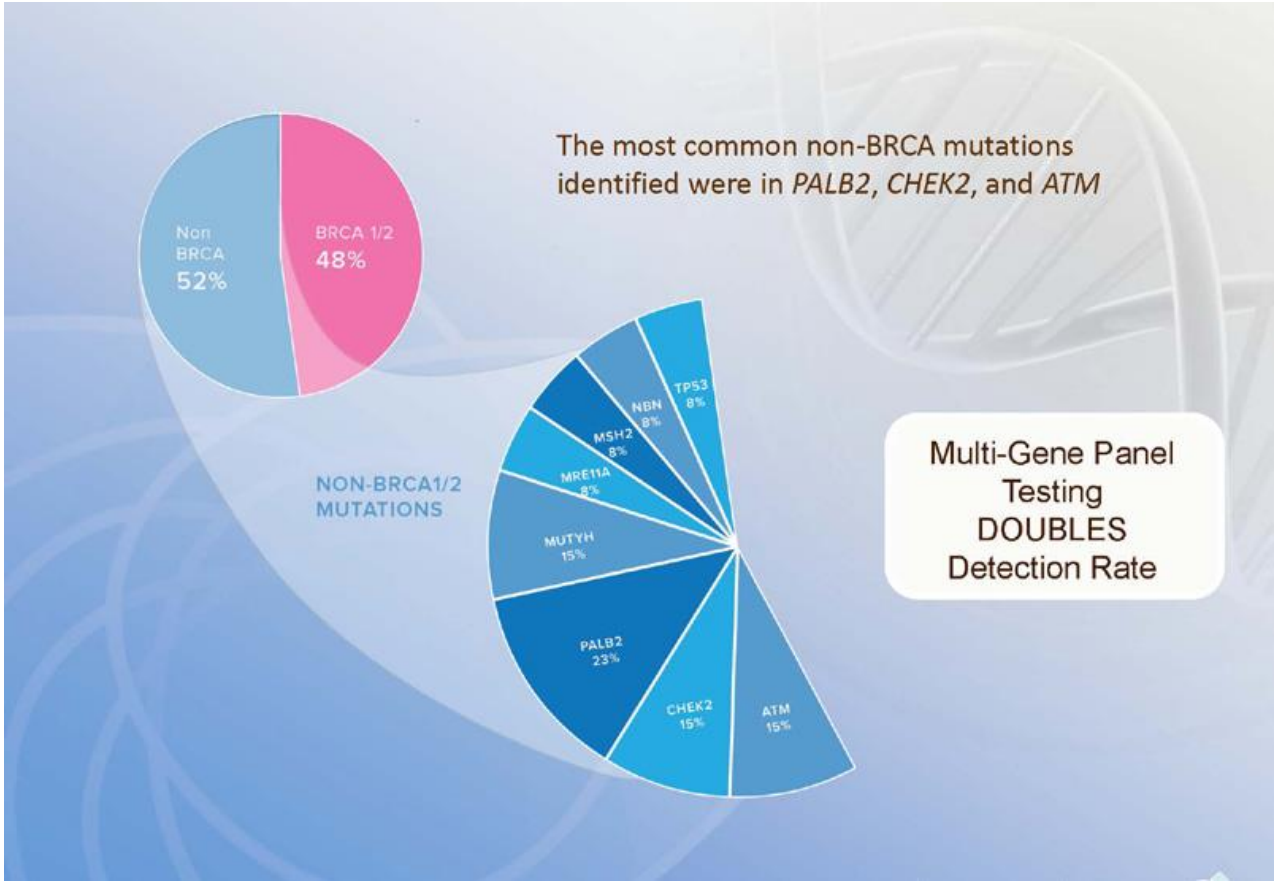
Variability within & between families

- Germline genetic testing may help confirm (cannot exclude) a diagnosis of a HCS for a family



http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

Image from Genetics Home Reference: https://ghr.nlm.nih.gov/handbook/inheritance?show=all



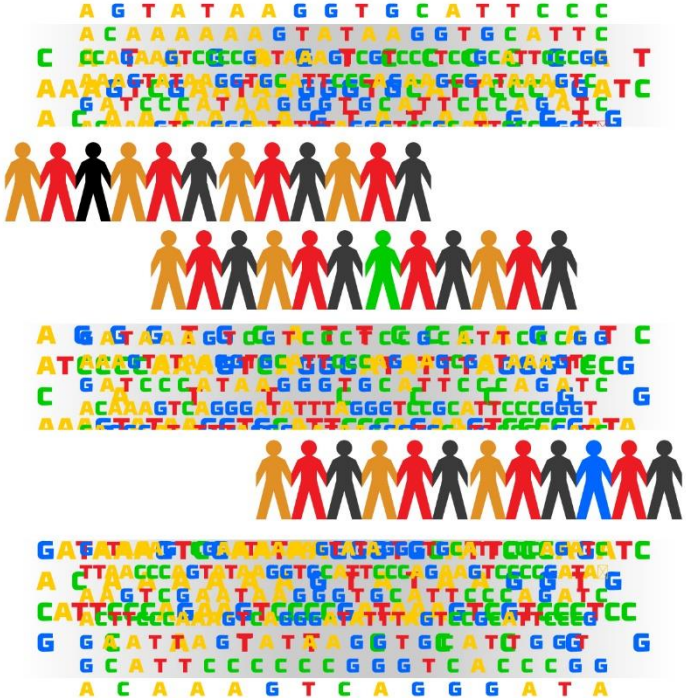
http://www.breastlink.com/wp-content/uploads/2015/04/Nimmi-S-Kapoor-MD-Genetic-Testing-American-Society-Breast-Surgeons.pdf

The Evolving Face of Gene Testing

Hereditary breast cancer genes		
High risk (~40%-60%+ absolute risk)	**Moderate risk (20%-40% absolute risk)**	**Potential increased risk / insufficient data**
BRCA1	***ATM***	***BRIP1***
BRCA2	***BARD1***	***MLH1***
CDH1	***CHEK2***	***MSH2/EPCAM***
PALB2	***NF1***	***MSH6***
PTEN	***RAD51C***	***PMS2***
STK11	***RAD51D***	
TP53		

Based on NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2023 (Gene Summary: Risks and Management GENE-A 1-10) https://www.nccn.org/

Emerging technologies for diagnosis of hereditary cancer syndromes / risk factors



- **Whole exome sequencing**
  - Analyze every region of the human genome that codes for a protein
  - Issues:
    - High likelihood for variants of uncertain significance
    - Unexpected / unrelated findings

What is a Variant of Uncertain Significance?

- Alteration in a gene with limited and/or conflicting evidence regarding pathogenicity
- Classification may vary between labs due to multiple sources of data
- Discourage family member clinical testing specific for the variant
- Variant re-classification may take years
- Re-classification may contribute to cancer risk data

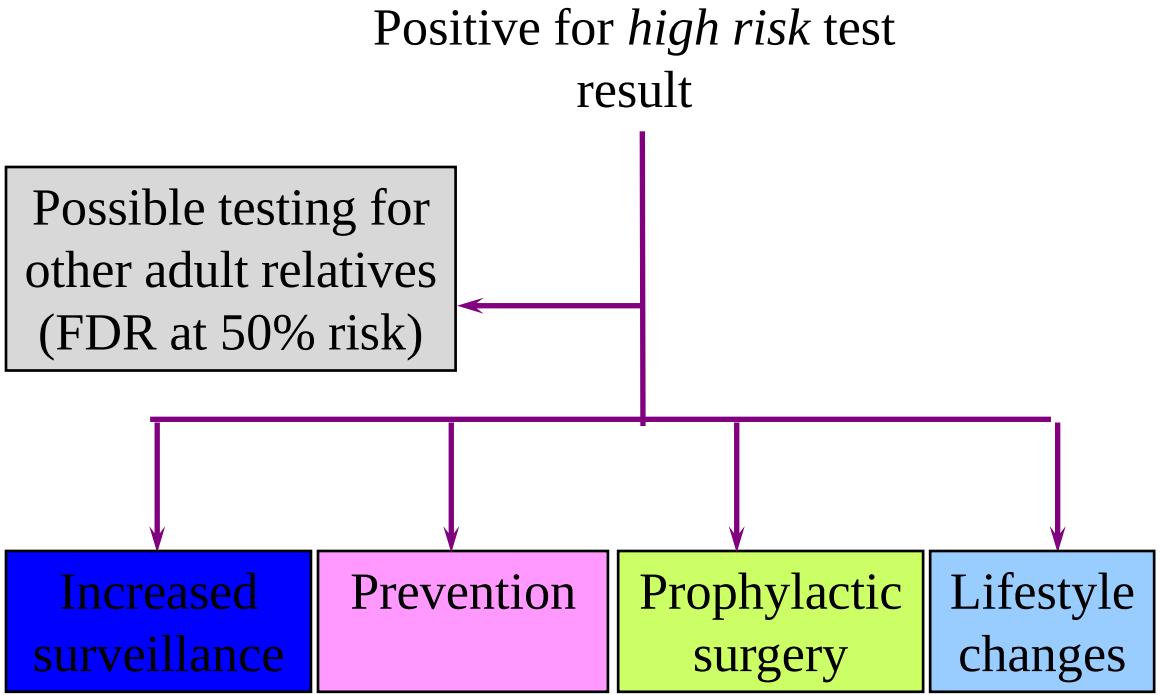
Negative/Uncertain test result

Cancer risk(s) may still be increased based on personal risk factors &/or family history

Cancer treatment decisions (if applicable)	• Not impacted by result
Cancer screening and risk reduction options	• Based on personal medical and family history
Information for the family	• A negative/variant result does not eliminate the possibility of hereditary cancer in the family • Other family members may still wish to consider genetic testing

Positive Test Result

- ***Cancer risk increased due to a hereditary gene mutation***
- **Cancer treatment decisions (if applicable)**
  - Surgical decisions, chemotherapy options, clinical trial eligibility
- **Cancer screening and risk reduction options**
  - Increased surveillance, prophylactic surgery, chemoprevention, lifestyle changes
- **Information for the family**
  - A “diagnosis” for the family
  - Testing of relatives with / without cancer for the known mutation
- **May not influence clinical care and management**


Positive for *high risk* test result
Possible testing for other adult relatives (FDR at 50% risk)
Increased surveillance
Prevention
Prophylactic surgery
Lifestyle changes

Barriers to Care

DISPARITIES IN TESTING

Black populations are underserved in hereditary cancer genetic testing

- Genetic testing is underutilized by the Black population
- Multiple barriers of receiving genetic counseling and testing have been identified in the literature
- The lack of sufficient diversity in genetic testing participation further perpetuates difficulties for Black people who do undergo hereditary cancer genetic testing

Lumpkins, CY, Philp, A, Nelson, KL, Miller, LM, Greiner, KA. A road map for the future: An exploration of attitudes, perceptions, and beliefs among African Americans to tailor health promotion of cancer-related genetic counseling and testing. *J Genet Couns*. 2020; 29: 518–529. https://doi.org/10.1002/jgc4.1277

Reported barriers to genetic counseling and testing access for minority populations

Lack of referrals

- It has been reported that Black women are less likely to be referred for genetic counseling and testing than white women

Cost

- The cost of genetic testing has significantly decreased in recent years however lack of insurance or the financial burden of a cancer diagnosis may also limit additional spending if clinical utility is not explained

Self-motivation

- If the utility of testing is not understood, people may be less likely to present for counseling or testing
- Some people are unaware that genetic testing is available for more than determining ancestry

Roberts, ME, Susswein, LR, Janice Cheng, W, et al. Ancestry-specific hereditary cancer panel yields: Moving toward more personalized risk assessment. *J Genet Couns*. 2020; 29: 598– 606. https://doi.org/10.1002/jgc4.1257
Saulsberry, K., & Terry, S. F. (2013). The need to build trust: a perspective on disparities in genetic testing. *Genetic testing and molecular biomarkers*, *17*(9), 647–648. https://doi.org/10.1089/gtmb.2013.1548

Reported barriers to genetic counseling and testing access for minority populations

Emotional impact of results

- Genetic testing results can prompt strong feelings such as fear, guilt, shame, anger
- Genetic testing results can impact the entire family and can cause conflicts between family members

Confidentiality/Discrimination concerns

- Worry for these results to impact their care
- Uninformed about Federal and State laws used to protect employment and health insurance coverage (GINA)

Mistrust of physicians and the medical system

- Patients may have experienced poor experiences with previous providers that have made them cautious in trusting their health care team
- Major events have occurred in the US's history of medical research that have had lasting effects on current peoples' views of the American health system

Roberts, ME, Susswein, LR, Janice Cheng, W, et al. Ancestry-specific hereditary cancer panel yields: Moving toward more personalized risk assessment. *J Genet Couns*. 2020; 29: 598– 606. https://doi.org/10.1002/jgc4.1257
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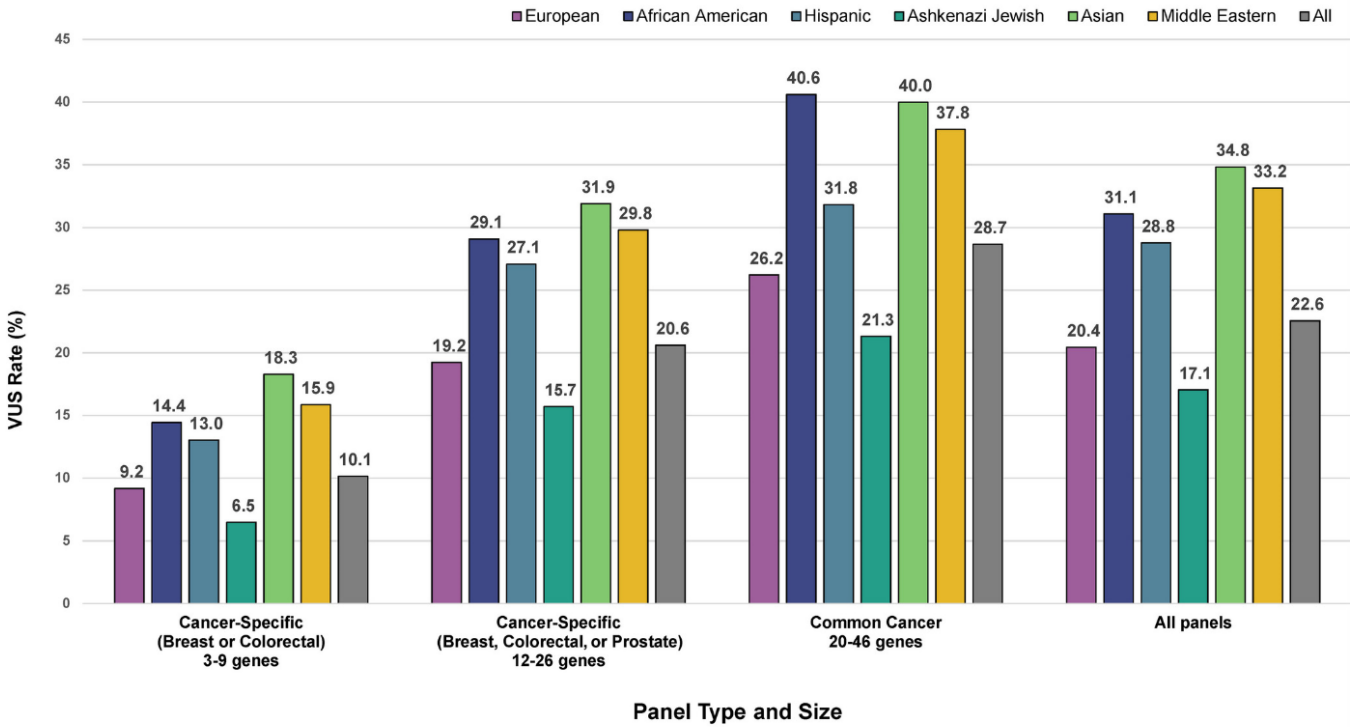
VUS rates among hereditary cancer multi-gene panels



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- Germline mutations in the *BRCA1* and *BRCA2* genes are estimated to be found in about 1/400-800 within the general population
  - The likelihood of a familial pathogenic mutation significantly increases when there is a history of multiple women with breast cancer and even more so when there is a family history of breast and ovarian cancers
  - Estimated risks to carry a pathogenic mutation after a breast cancer diagnosis can vary by ethnicity

	BRCA1	BRCA2
Ashkenazi Jewish	8.3-10.2%	2.1%
Non-AJ White	2.2%-2.9%	
Asian American	0.5%	
African American	1.3%-1.4%	2.6%
Hispanic	3.5%	

PDQ® Cancer Genetics Editorial Board. PDQ Genetics of Breast and Gynecologic Cancers. Bethesda, MD: National Cancer Institute. Updated <MM/DD/YYYY>. Available at: https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq. Accessed <MM/DD/YYYY>. [PMID: 26389210]

Triple Negative Breast Cancer (TNBC)

- Triple Negative Breast Cancer(TNBC)
  - ER: Negative, PR: Negative, Her2: Negative
- TNBC is more common in Black women than in White women
- TNBC diagnosed ≤60yo with or without a family history meets NCCN criteria for genetic testing
- There is a West African founder mutation in *BRCA1* (c.943ins10)
- A study by Rummel *et. al* (2013) a higher percent of *BRCA1* mutations was found in TNBC of Black women than White women

Richardson LC, Henley J, Miller J, Massetti G, Thomas CC. Patterns and trends in black-white differences in breast cancer incidence and mortality—United States, 1999–2013. *MMWR* 2016;65(40):1093–1098.

Rummel, S., Varner, E., Shriver, C.D. *et al.* Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer. *Breast Cancer Res Treat* **137,** 119–125 (2013). https://doi.org/10.1007/s10549-012-2348-2

Ricks-Santi, L., McDonald, J. T., Gold, B., Dean, M., Thompson, N., Abbas, M., Wilson, B., Kanaan, Y., Naab, T. J., & Dunston, G. (2017). Next Generation Sequencing Reveals High Prevalence of BRCA1 and BRCA2 Variants of Unknown Significance in Early-Onset Breast Cancer in African American Women. *Ethnicity & disease*, *27*(2), 169–178. https://doi.org/10.18865/ed.27.2.169

Lack of diversity among genetic counselors

- The population of individuals providing genetic counseling services does not mirror the diversity of individuals they serve
- In the 2020 Professional Status Survey from the National Society of Genetic Counselors, approximately 90% of genetic counselor self-identify as White or Caucasian; only approximately 2% reported being Black or African American.
  - In the 2008 edition of this survey 92% were reported to be White or Caucasian and 1% were reported to be Black or African American

National Society of Genetic Counselors. (2008). *Professional Status Survey Reports* (Rep.). Retrieved 2020, from https://www.nsgc.org/p/cm/ld/fid=68
National Society of Genetic Counselors. (2020). *Professional Status Survey Reports* (Rep.). Retrieved 2020, from https://www.nsgc.org/p/cm/ld/fid=68

Women of Color Understanding of Genetics and Genomics

EQUITY GRANT

We want to hear from YOU!

Breast cancer treatment has many layers. We want to talk with Black and/or Latina women about your understanding of cancer testing and how you make decisions about your cancer care.

Please join us for a 90-minute small group discussion in English or Spanish if you:

- Are a Black and/or Latina woman age 18 or older with an early breast cancer (stage I, II, or III) who has completed treatment within the past year, or you are living with metastatic (stage IV) breast cancer

We will use the information you share to help people better understand cancer-related tests and access the care they need. **Your voice can make a difference!**

Study Participants

- Virtual focus groups
- Women were treated at MD Anderson Cancer Center at Cooper
- 29 women participated in 8 focus groups (29 of 60 women scheduled)
- 8 women were Latina and 21 Black
- Ages ranged from 39 to 79 yo

Key Questions

What do Black and/or Latina women who have completed treatment in the last year for breast cancer (stage I, II, or III) and/or live with metastatic cancer (stage IV) know about genetic and genomic tests?

How do Black and/or Latina women who have completed cancer treatment in the past year for breast cancer (stage I, II, or III) and/or live with metastatic cancer (stage IV) describe their barriers to access of care?

How do Black and/or Latina women who have completed cancer treatment in the last year for breast cancer (stage I, II, or III) and/or live with metastatic cancer (stage IV) describe their role and that of their healthcare providers in making decisions for their care and treatment?

How do Black and/or Latina women who have completed cancer treatment in the last year for breast cancer (stage I, II, or III) and/or live with metastatic cancer (stage IV) describe their preferred ways to learn about complex health information?

Study Results

PATIENT PERCEPTIONS

Genetic testing more recognized due to lived experience

Varied perceptions around the value of genetic testing due to “inconclusive results”

Most frequent reason for testing – family (past, present and future)

Genomics

- The word genomics not well recognized
- However, when described, several patients recognized hearing about this and spoke about targeted therapies for specific types of cancer

- Cost of care despite insurance (gaps in coverage)
- Information shared too late or not at all (tx options, severity of SE)
- Pressure to act quickly (internal or external led to inability to weigh options)
- Lack of follow-up by health care provider (after acute period is over)
- COVID-19 related isolation (attending appts alone, unable to access resources)

Shared Decision Making – Role of Provider

Director of care

- positive and negative

Expert advisor

- help choose best course of action

Source of emotional support

- hugs, phone number to reach them, photos, bond

Source of information on options

- provide clear, comprehensive information to allow pt to choose

- more often associated with surgical vs medical options

Preferred Way to Learn

Just in time content

Provide info at multiple times, in multiple ways so that info can be accessed when pt ready

Effective resources should be provided pre-, during and post- active treatment

Visual format

Videos for education, reading materials

Opportunity to see the impact of treatments on others to prepare for what to expect

Online resources

Positive and negative resource

Led to better understanding and questions to discuss with providers or was a stressor

Notebooks

Personalized treatment book with general and pt specific information

Space to write notes

Psychosocial Implications

Mental health resources	Peer support	Faith	Children/Partners

• Psychologists and social workers were highly valued
• Often a gap in service
	• Relished support from those with past experience
	• Family and friends who had been treated previously
		• Great source of support for most patients
		  • Religious institution
		  • Personal faith or spirituality
			• Complex
			• Either source of support or
			• Stressed about how to protect them from the diagnosis and treatment

Enhancing Equity

IMPROVING ACCESS AND SUPPORT

Strategies to Increase Access to Genetic and Genomic Testing

Educate patients of importance of testing

Promote awareness of the value to the patient

Utilize terms that are easy to understand

Use a combination of educational tools (visual, peers, reading materials, reliable internet sites)

Provide education at multiple times throughout their treatment journey

Utilize laboratory resources

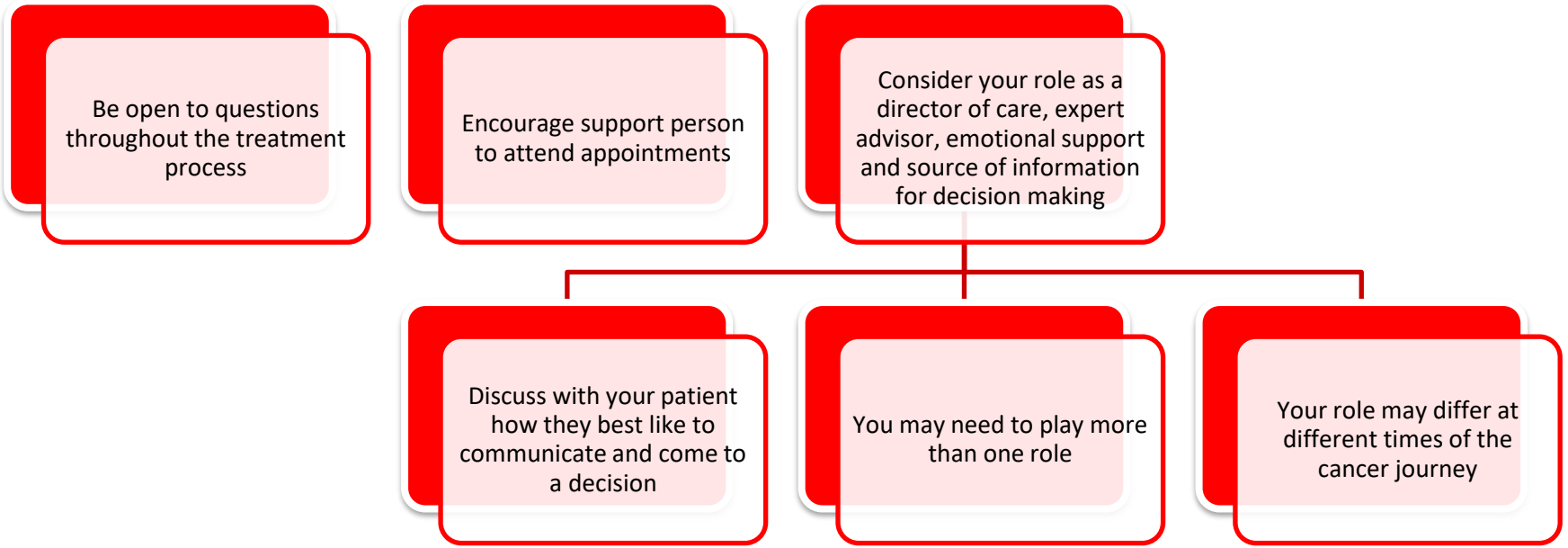
Patient in need support

Provide culturally and linguistically competent care and educational tools

Understand common barriers to testing and develop education and seek resources to address these barriers

Use the language most comfortable for the patient

Best Practices for Shared Decision Making



Final Words

- Genetics and genomics are complex but exciting opportunities to enhance the lives and care of our patients
- The growth in these fields has been tremendous and keeping up with innovations can be challenging
- Women of color have different challenges that affect their decision making and how they like to communicate
- Educational tools should be varied and provided throughout the cancer journey
- Seeking resources and support to educate and encourage genetic and genomic testing can help improve equity in this field for women of color

Any Questions or Comments?