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

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• Dr. Evelyn Robles-Rodriguez has received grants from Pfizer and Genentech for breast equity research
• Thank you to:
  o Genentech for a grant to LBBC and MD Anderson Cancer Center at Cooper whose research on genetics and genomics we will review today
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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
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
• 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

• 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
  o Stage IIIC Breast Cancer is treated with chemotherapy, radiation, surgery, etc.
• This paradigm is now being challenged in the era of genomics
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
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.
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
# TUMOR TYPE: COLON ADENOCARCINOMA (CRC)

## Genomic Alterations Identified†

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

## Additional Findings†

- **Microsatellite status**: MSI-High

## Additional Disease-relevant Genes with No Reportable Alterations Identified†

- **BRAF**
- **NRAS**

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*Reduced sensitivity due to sample quality – See Appendix. Performance Specifications for details.
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identify driver mutations</td>
<td>• Knowledge of genes in cancer still growing</td>
</tr>
<tr>
<td>• Include more effective treatments</td>
<td>• Mutations found only in a small % of cancers</td>
</tr>
<tr>
<td>• Exclude ineffective treatments</td>
<td>• Need for biopsies</td>
</tr>
<tr>
<td>• Improve clinical trial screening efficiency</td>
<td>• Lots of “passenger mutations”</td>
</tr>
<tr>
<td></td>
<td>• <em>Information overload for treating oncologists</em></td>
</tr>
</tbody>
</table>
Targeted therapy

- Treating ("targeting") the cancer's specific genes, proteins, or the tissue environment that contribute to cancer growth and survival.
1180 patients spanning over 40 cancer types

Compared: “Matched” (with treatments derived from genomic profiling) versus “Unmatched” (treated per physician preference)

Matched cohort were treated with fewer treatments overall after profiling compared to those in the Unmatched cohort

The median increase in survival was 422 days which was a 32% increase.

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


The most common non-BRCA mutations identified were in \textit{PALB2}, \textit{CHEK2}, and \textit{ATM}.

Multi-Gene Panel Testing DOUBLES Detection Rate

# The Evolving Face of Gene Testing

## Hereditary breast cancer genes

<table>
<thead>
<tr>
<th>High risk (~40%-60%+ absolute risk)</th>
<th>Moderate risk (20%-40% absolute risk)</th>
<th>Potential increased risk / insufficient data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td><strong>ATM</strong></td>
<td><strong>BRIP1</strong></td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td><strong>BARD1</strong></td>
<td><strong>MLH1</strong></td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td><strong>CHEK2</strong></td>
<td><strong>MSH2/EPCAM</strong></td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td><strong>NF1</strong></td>
<td><strong>MSH6</strong></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td><strong>RAD51C</strong></td>
<td><strong>PMS2</strong></td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td><strong>RAD51D</strong></td>
<td></td>
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<tr>
<td><strong>TP53</strong></td>
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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/](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
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
• **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
Clinical Management of Mutation-Positive Patient

Positive for *high risk* test result

Possible testing for other adult relatives (FDR at 50% risk)

- Increased surveillance
- Prevention
- Prophylactic surgery
- Lifestyle changes
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

### Reported barriers to genetic counseling and testing access for minority populations

<table>
<thead>
<tr>
<th>Lack of referrals</th>
<th>Cost</th>
<th>Self-motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It has been reported that Black women are less likely to be referred for genetic counseling and testing than white women</td>
<td>• 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</td>
<td>• 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</td>
</tr>
</tbody>
</table>

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


• Germline mutations in the **BRCA1** and **BRCA2** genes are estimated to be found in about 1/400-800 within the general population
  o 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
  o Estimated risks to carry a pathogenic mutation after a breast cancer diagnosis can vary by ethnicity

<table>
<thead>
<tr>
<th></th>
<th><strong>BRCA1</strong></th>
<th><strong>BRCA2</strong></th>
</tr>
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<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>8.3-10.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Non-AJ White</td>
<td>2.2%-2.9%</td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.3%-1.4%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.5%</td>
<td></td>
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</table>

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

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.
  
  o 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


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!
• 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
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)
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
Barriers to Care

- 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
- Psychologists and social workers were highly valued
- Often a gap in service

Peer support
- Relished support from those with past experience
- Family and friends who had been treated previously

Faith
- Great source of support for most patients
  - Religious institution
  - Personal faith or spirituality

Children/Partners
- 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

- Be open to questions throughout the treatment process
- Encourage support person to attend appointments
- Consider your role as a director of care, expert advisor, emotional support and source of information for decision making
- Discuss with your patient how they best like to communicate and come to a decision
- You may need to play more than one role
- Your role may differ at different times of the cancer journey
• 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?