Genetic Panel Testing and Implications for Cancer Care

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Nancy and James Grosfeld Cancer Genetics Center
Professor, OUWB Medical School
MCC Board of Directors Meeting
September 28, 2016
A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015
Outline

• Gene Panel Testing: Overview
• Clinical Applications of Gene Panel Testing
• Hereditary (Germline) Testing
  – Cancer prevention
  – Early detection
  – Therapeutics
• Tumor (Somatic) Testing
  – Prognostic/predictive implications
  – Therapeutic implications
• Future directions
Implications of Genetics on Cancer

Molecular Diagnostics

Tumor Classification
Prognostic/Predictive Information

Targeted Therapies Pharmacogenomics

Molecular Monitoring

Hereditary Cancer Syndromes

Risk Assessment

High Risk Surveillance

Early Detection

Better Outcomes & Improved Survival

Cancer Prevention

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A New Era in Cancer Genetics

• 1990’s: discovery of rare, highly penetrant cancer predisposition genes
  – BRCA1 and 2, p53, APC
• 100+ known cancer susceptibility syndromes
• Significant recent changes
• Next-generation sequencing (NGS) technology
• Multiplex gene-panel testing

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Definition of Terms

• Next-generation sequencing (NGS)
  – Massively parallel sequencing
  – High throughput parallel sequencing of thousands to millions of fragments of DNA

• Multiplex gene-panel testing
  – Targeted analysis of multiple genes of interest simultaneously using NGS

• Variant of unknown significance (VUS)
  – Genetic sequence change whose association with disease is currently unknown
Goal: increasing the signal of each unique molecule by clonal amplification (can be done different ways)

Reads with complementary adapters

Emulsion PCR

Complementary adapters fixed to solid surface

Bridge amplification

Clonal amplification of fixed template into cluster

Sequencing by synthesis

Goal: measure the addition of complimentary bases (different chemistries used)

pH read-out

Light read-out
Gene Panel Testing

- Allows for efficient analysis of multiple genes
- Next generation sequencing (NGS) technology
  - Rapid, simultaneous gene analysis
- Efficiency, decreasing cost
- **Caveat**: Variants of uncertain significance (VUS)
  - Potential for misinterpretation
  - May lead to confusion re: management of risk?
- Clinical utility? – which genes are “actionable”??
- Potential for uncertainty re: optimal management
- Lack of evidence-based guidelines for many genes
- Genetic evaluation/counseling important
Gene Panel Testing

- Multiple labs offering a variety of different combinations of genes including: RAD 51D, RAD 51C, BRIP1, NBN, BARD1, CHEK2, PTEN, CDH1.....
  - Paucity of management guidelines
- Increasingly utilized in clinical setting
  - Germ line (hereditary) testing
  - Somatic (tumor) testing
- 4-16% prevalence of non-BRCA1/2 mutations reported
  - 11% in Beaumont series
- Potential for clinical benefit (?)
- Uncertainty regarding gene panel selection, interpretation of results
  - High VUS rate
  - Discordant interpretation of variants
- Need further research, sharing of data (e.g. “PROMPT”)

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• **Prospective Registry of Multiplex Panel Testing**
• Data collection research project open to any patient undergoing panel testing
• **Goal to collect large numbers of mutation carriers, learn about cancer risks, outcomes, and facilitate classification of uncertain variants**
• Registry of results from large numbers of patients
• Biologic sample collection for translational research
Gene Panel Testing

• **Analytic validity**
  – Accuracy and reproducibility of test

• **Clinical validity**
  – Ability of test to predict disease

• **Clinical utility**
  – Improved health outcomes
    • Early detection, prevention, higher responses
  – Usefulness/added value to patient management
Genetic Testing **Red Flags** (hereditary)

- Early onset breast cancer (or multiple cases)
- Ovarian cancer – **All cases**
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish ancestry
- Male breast cancer
- Pancreatic cancer
- Triple negative breast cancer
Hereditary Breast Cancer Genes
(pre-panel era or “good old days”)

- **Breast Cancer Gene 1** – BRCA1 (1994)
  - Chromosome 17
- **Breast Cancer Gene 2** – BRCA2 (1995)
  - Chromosome 13
- Tumor Suppressor Genes – DNA repair
- Important in repair of double-strand DNA breaks
  - Maintains normal DNA in all individuals
- Alteration (mutation) → high risk of breast cancer
  - Cause inherited breast and ovarian cancer
- Seen more often in Ashkenazi Jews (1 in 40)
# BRCA1/2 Mutations: Lifetime Cancer Risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer to age 80</td>
<td>50-70%</td>
<td>35-60%</td>
</tr>
<tr>
<td>Ovarian cancer to age 80</td>
<td>25-50%</td>
<td>Up to 25%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>1-2%</td>
<td>7-8%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>9%</td>
<td>33%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2-4%</td>
<td>3-6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>No incr.</td>
<td>Slight incr.</td>
</tr>
</tbody>
</table>
Management Of BRCA Carriers

• **High Risk Surveillance**
  – Breast MRI and mammography
  – Other: Ovary, prostate, pancreas ...

• **Chemoprevention**
  – Tamoxifen – 50% reduction of breast cancer risk
  – Novel agents (research)

• **Prophylactic Surgery**
  – Bilateral Mastectomy – 90-95% reduction of risk
  – Risk-reducing salpingo-oophorectomy – 90% reduction
# Surveillance for Breast Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 yrs</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 yrs</td>
<td>6 - 12 months</td>
</tr>
<tr>
<td>Mammography</td>
<td>30 yrs</td>
<td>Yearly</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Screening for Other Cancers

- Prostate (starting at age 40):
  - *BRCA1* Consider prostate screening
  - *BRCA2* Recommend prostate screening

- Male breast:
  - Breast Self Exam training and education at age 35
  - Clinical Breast Exam every 12 mos starting at age 35

- Pancreas – no proven benefit
  - Consider EUS/MRI in high risk families
  - Screening registry enrollment
  - Research trials e.g. CAPS-5
Based on our 20 years’ experience working with families with cancer-predisposing mutations in BRCA1 and BRCA2, it is time to offer genetic screening of these genes to every woman.
Two Decades After \textit{BRCA}: Setting Paradigms in Personalized Cancer Care and Prevention

Fergus J. Couch,\textsuperscript{1*} Katherine L. Nathanson,\textsuperscript{2} Kenneth Offit\textsuperscript{3}

28 March 2014 VOI 343 SCIENCE www.sciencemag.org
The ‘Other’ Breast Cancer Genes
The “Other” Ovarian Cancer Genes

Germline HR mutations

- BRCA2: 21%
- BRCA1: 54%
- BARD1: 2%
- BRIP1: 5%
- CHEK1: 1%
- CHEK2: 4%
- FAM175A: 2%
- NBN: 1%
- PALB2: 2%
- RAD51C: 3%
- RAD51D: 5%
## Beyond *BRCA*: Other Hereditary Breast Cancer Syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PTEN</em></td>
<td>Cowden Syndrome</td>
</tr>
<tr>
<td><em>P53</em></td>
<td>Li Fraumeni Syndrome (LFS)</td>
</tr>
<tr>
<td><em>PALB2</em></td>
<td>PALB2</td>
</tr>
<tr>
<td><em>CDH1</em></td>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
</tr>
<tr>
<td><em>STK11</em></td>
<td>Peutz Jeghers Syndrome (PJS)</td>
</tr>
</tbody>
</table>
Beyond *BRCA*: Other Hereditary Breast Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden Syndrome (<em>PTEN</em>)</td>
<td>Breast, Uterine, Thyroid Cancers; Large head size; Skin findings</td>
</tr>
<tr>
<td>Li Fraumeni Syndrome (LFS <em>p53</em>)</td>
<td>Breast, Brain, and Lung Cancers, Sarcomas, Adrenocortical Carcinoma; very early age at diagnosis</td>
</tr>
<tr>
<td><em>PALB2</em></td>
<td>Breast and Pancreatic Cancers (? Ovary)</td>
</tr>
<tr>
<td>Hereditary Diffuse Gastric Cancer (HDGC <em>CDH1</em>)</td>
<td>Breast and Stomach Cancers</td>
</tr>
<tr>
<td>Peutz Jeghers Syndrome (PJS) (<em>STK11</em>)</td>
<td>Breast, Colon, Pancreatic and Stomach Cancers; Freckling of lips in childhood</td>
</tr>
</tbody>
</table>

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Breast-Cancer Risk in Families with Mutations in \textit{PALB2}


Study Shows Third Gene as Indicator for Breast Cancer

By NICHOLAS BAKALAR  AUG. 6, 2014
**PALB2 and Cancer Risk**

- **Breast Cancer Risk** (association with triple negative breast cancer)
  - 14% by age 50
  - 35% by age 70
  - Impact of family history
    - 33%-58%
- **Pancreas Cancer Risk**
  - Identified in 3-4% of familial pancreatic cancer cases
- **Ovarian Cancer Risk** – conflicting results
- **Other cancers** (? Male breast, prostate, ovarian?)

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**OvaNext: Analyses of 23 Genes Associated with Hereditary Ovarian Cancer**

**PANEL RESULTS**

- **PALB2**
  - Pathogenic Mutation(s): p.Q66*

**SUMMARY**

**POSITIVE: Pathogenic Mutation Detected**

- This individual is heterozygous for the p.Q66* pathogenic mutation in the PALB2 gene.

- **Cancer Risk estimate:** 33-58% lifetime risk for breast cancer (females only) and increased lifetime pancreatic cancer risk.

- The expression and severity for this individual cannot be predicted.

- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

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No pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected in the other genes analyzed. In total, 23 genes were analyzed as part of this panel: **ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, and TP53**.

Cowden’s Syndrome

- PTEN hamartoma syndrome
- Breast (30-60% lifetime risk), thyroid cancer (3-10%), endometrial cancer (19-28%)
- Skin manifestations:
  - papillomatous papules
  - Trichilemmomas
  - Acral keratoses
- Macrocephaly
- Thyroid nodules, goiter
- Uterine fibroids
- Developmental delay
Two "moles" removed from the back and head grew back.

Dutch

Prostate ca dx 50s
Heart attack

Breast ca 50-60s
Heart attack

50-60s

3

60

Skin BCC
Benign tumor-Brain
Breast fibroadenoma x 2
Kidney-nephrectomy (2000)-benign
Multiple moles
TAH 40s

35
Breast dx 35
Papillary thyroid ca dx 31
HC 58cm

55

60s

German/English

Thyroidectomy
Goiter
Breast mass removed
Moles, benign tumors on back, foot, arm and breast

86

Breast
Melanoma
Benign brain tumor

 Colon
Benign breast masses

Thyroid ca

60s

ADD
Learning disabilities

60s

Pap thyroid ca dx 55
Multiple lipomas
Facial fibromas
Possible renal ca

Melanoma dx 38
Pap thyroid ca dx 40
Melanoma dx 50

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Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk

Douglas F. Easton, Ph.D., Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Marc Tischkowitz, M.D., Ph.D., Sean V. Tavtigian, Ph.D., Katherine L. Nathanson, M.D., Peter Devilee, Ph.D., Alfons Meindl, Ph.D., Fergus J. Couch, Ph.D., Melissa Southey, Ph.D., David E. Goldgar, Ph.D., D. Gareth R. Evans, M.D., Georgia Chenevix-Trench, Ph.D., Nazneen Rahman, M.D., Ph.D., Mark Robson, M.D., Susan M. Domchek, M.D., and William D. Foulkes, M.B., B.S., Ph.D.
Multigene Panel Testing Detects Equal Rates of Pathogenic
BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared
to Limited BRCA1/2 Analysis Alone in Patients at Risk
for Hereditary Breast Cancer

Nimmi S. Kapoor, MD1,2, Lisa D. Curcio, MD, FACS2, Carlee A. Blakemore, BS1, Amy K. Bremner, MD3,
Rachel E. McFarland, BS4, John G. West, MD, FACS1, and Kimberly C. Banks, MS, CGC, MBA4

- 966 patients
  - 629 limited testing (BRCA1/2)
  - 337 panel testing (5-43 genes, 15 avg)
- Deleterious BRCA 1/2 mutations found in 4.0% (limited) and 3.6% (panel)
- Multigene panel testing identified additional 3.9% (up to 11%) non-BRCA mutations
- Most common non-BRCA: PALB2, CHEK2, ATM
FIG. 1 Distribution of pathogenic mutations identified in panel group. 

(a) Separation by BRCA1/2 status. 
(b) Incidence of non-BRCA1/2 gene mutations

- Pathogenic Mutations in Panel Group
  - NON-BRCA1/2: 52%
  - BRCA1/2: 48%

- Non-BRCA1/2 Mutations
  - ATM: 15%
  - CHEK2: 15%
  - PALB2: 23%
  - MUTYH: 15%
  - MRE11A: 8%
  - NBN: 8%
  - TP53: 8%
  - MSH2: 8%
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Positive result. Pathogenic variant identified in MRE11A.

Clinical Summary
- A pathogenic variant, c.1441delA (p.Thr481Hisfs*43), was identified in MRE11A.
  - The MRE11A gene is associated with an increased risk for autosomal dominant breast cancer in individuals who carry a single pathogenic variant (PMID: 14684699, 24894818). To date, the data is limited and cancer risk is not clearly established. MRE11A is also associated with autosomal recessive ataxia-telangiectasia-like disorder (ATLD) (MedGen UID: 348929).
  - Variants in MRE11A have been associated with an increased susceptibility to breast cancer. The data and sample sizes, however, are limited and are based on small studies. Consequently, lifetime risk estimates are not well established (PMID: 14684699, 24894818). Elevated risk for gynecologic cancers has been considered but available evidence is not sufficient to make a determination at this time.
  - Close relatives (children, siblings, and each parent) have up to a 50% chance of being a carrier of this pathogenic variant. More distant relatives may also be carriers. Carriers are at increased risk of developing MRE11A-related cancers and may have reproductive risks related to autosomal recessive MRE11A-related ATLD as well. Testing for this variant is available.
  - These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For a listing of genetic counselors, please visit www.nsgc.org.

Complete Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition Group</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE11A</td>
<td>Hereditary Cancers (Breast and Ovarian)</td>
<td>c.1441delA (p.Thr481Hisfs*43)</td>
<td>heterozygous</td>
<td>PATHOGENIC</td>
</tr>
</tbody>
</table>

The following genes were evaluated for sequence changes and exonic deletions/duplications:
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FANCC, MRE11A, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, STK11, TP53

Results are negative unless otherwise indicated

Benign variants, and silent and intronic variants with no evidence towards pathogenicity, are not included in this report but are available upon request.
### Specific Site Analysis of BRIP1

<table>
<thead>
<tr>
<th>RESULTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIP1 SPECIFIC SITE</td>
<td>c.2038_2039dupTT Pathogenic Mutation: Not Detected</td>
</tr>
</tbody>
</table>

### INTERPRETATION

This individual does not carry the c.2038_2039dupTT pathogenic mutation in the BRIP1 gene, which was previously identified in this individual’s relative(s). Therefore, this individual is not expected to be at an increased risk for BRIP1-related cancers due to this familial mutation.
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Summary

Positive result: **Homozygous** Pathogenic variant identified in CDKN2A.

Clinical Summary

- A homozygous, Pathogenic variant, c.148C>T (p.Gln50*) was identified in CDKN2A.
  - The CDKN2A gene is associated with autosomal dominant cutaneous melanoma (MedGen UID: 268851).
  - This result is consistent with a predisposition to, or diagnosis of, CDKN2A-related conditions.
  - Hereditary cutaneous melanoma is characterized by multiple melanocytic nevi and is a hereditary cancer syndrome that increases an individual’s lifetime risk of developing cutaneous melanoma. CDKN2A sequence changes have also been associated with increased risk for pancreatic cancers, and some studies have reported increased incidence of breast cancer (PMID: 10922411, 15879498, 16905682, 17047042, 18981015, 22636603). Individuals who are homozygous for Pathogenic variants in CDKN2A are uncommon, but have been reported in the literature (PMID: 7670475).
  - It is likely that one copy of this Pathogenic variant was inherited from each parent. All children of this individual have a 100% chance to inherit a Pathogenic variant. More distant relatives may also be carriers. Testing for this variant is available.
- In addition, a Variant of Uncertain Significance, c.1008C>A (p.His336Gln), was also identified in PALLD.
  - The PALLD gene has limited evidence supporting a direct causal role in the susceptibility to pancreatic cancer (MedGen UID: 339739, OMIM: 606856). Consequently, the majority of PALLD variants identified to date are classified as Uncertain Significance.
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - Based on our current review of the medical literature there is only limited evidence available to support this gene having a direct causal role for pancreatic cancer. Therefore variants in this gene are not eligible for family tracking as a part of our VUS Resolution Program at this time. Please visit www.invitae.com for more information on our VUS Resolution Program.
  - These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For a listing of genetic counselors, please visit www.nccn.org or tsgc.med.unc.edu/professional-organizations.asp.

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Multiplex Genetic Testing for Cancer Susceptibility: Out on the High Wire Without a Net?

Susan M. Domchek and Angela Bradbury, University of Pennsylvania, Philadelphia, PA
Judy E. Garber, Dana-Farber Cancer Institute, Boston, MA
Kenneth Offit and Mark E. Robson, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY
Management of “New” or Moderate Risk Genes

- Paucity of evidence-based guidelines
- Risk not fully defined - evolving
- Actionability? and lack of consensus
- High rate of variants of unknown significance
  - Improving with added experience
- Implication for family members who test negative? May still be high risk
Original Investigation

Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment

Andrea Desmond, BS; Allison W. Kurian, MD, MSc; Michele Gabree, MS, CGC; Meredith A. Mills, BA; Michael J. Anderson, PhD; Yuya Kobayashi, PhD; Nora Horick, MS; Shan Yang, PhD; Kristen M. Shannon, MS, CGC; Nadine Tung, MD; James M. Ford, MD; Stephen E. Lincoln, BS; Leif W. Ellisén, MD, PhD

**IMPORTANCE** The practice of genetic testing for hereditary breast and/or ovarian cancer (HBOC) is rapidly evolving owing to the recent introduction of multigene panels. While these tests may identify 40% to 50% more individuals with hereditary cancer gene mutations than does testing for *BRCA1/2* alone, whether finding such mutations will alter clinical management is unknown.

**OBJECTIVE** To define the potential clinical effect of multigene panel testing for HBOC in a clinically representative cohort.

**DESIGN, SETTING, AND PARTICIPANTS** Observational study of patients seen between 2001 and

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• 1046 pts seen for genetic testing (BRCA neg)
  – Stanford, MGH, BIDMC 2001-2014
• Multigene panel testing (25-29 genes)
• 40 pts (3.8%) harbored deleterious mutations
• Most commonly: CHEK2, ATM, PALB2
• Additional screening/prevention offered
  – Management change considered in 33 of 40 pts
• Guidelines for management ??
### Table 2. Management Change for Patients and Their Family Members Following Positive Multigene Panel Patient Findings

<table>
<thead>
<tr>
<th>Intervention Criteria</th>
<th>Relevant Genes</th>
<th>Intervention</th>
<th>Patients Recommended for Intervention, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk genes, NCCN management guidelines (n=20)</td>
<td>CDH1, TP53, PTEN, MLH1, MSH2, MSH6, PMS2, APC, MUTYH (biallelic), BMPR1A</td>
<td>Guidelines-based surveillance, prevention</td>
<td>20</td>
</tr>
<tr>
<td>Breast cancer risk ≥40% (&lt;40% pretest risk by IBIS&lt;sup&gt;c,d&lt;/sup&gt;) (n=8)</td>
<td>PALB2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Surgical prevention candidate</td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Breast cancer risk &gt;20%/NCCN l.2015 recommendations&lt;sup&gt;f&lt;/sup&gt; (&lt;20% pre-test risk by IBIS&lt;sup&gt;c,d&lt;/sup&gt;) (n=32)</td>
<td>ATM,&lt;sup&gt;f&lt;/sup&gt; CHEK2,&lt;sup&gt;f&lt;/sup&gt; BRIP1, NBN, RAD51C</td>
<td>Enhanced breast screening candidate</td>
<td>5</td>
</tr>
<tr>
<td>Other cancer risk (pancreas, melanoma) (n=3)</td>
<td>CDKN2A</td>
<td>Pancreas screening candidate</td>
<td>3</td>
</tr>
</tbody>
</table>

*Abbreviations: IBIS: Informed Biopsychosocial Intervention System; NCCN: National Comprehensive Cancer Network.*
<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk Category</th>
<th>Management Change Considered</th>
<th>Considered Change</th>
<th>Family Testing Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1 (n=4)</td>
<td>High-risk BR/OV</td>
<td>4 of 4</td>
<td>Prophylactic gastrectomy</td>
<td>4 of 4</td>
</tr>
<tr>
<td>TP53 (n=3)</td>
<td>High-risk BR/OV</td>
<td>3 of 3</td>
<td>Increased cancer surveillance</td>
<td>3 of 3</td>
</tr>
<tr>
<td>PTEN (n=1)</td>
<td>High-risk BR/OV</td>
<td>1 of 1</td>
<td>Increased cancer surveillance</td>
<td>1 of 1</td>
</tr>
<tr>
<td>ATM (n=11)</td>
<td>Mod-/low-risk BR/OV</td>
<td>1 of 11</td>
<td>Increased breast screening</td>
<td>6 of 11</td>
</tr>
<tr>
<td>BRIP1 (n=1)</td>
<td>Mod-/low-risk BR/OV</td>
<td>0 of 1</td>
<td>NA</td>
<td>0 of 1</td>
</tr>
<tr>
<td>CHEK2 (n=15)</td>
<td>Mod-/low-risk BR/OV</td>
<td>2 of 15</td>
<td>Increased breast screening</td>
<td>4 of 13</td>
</tr>
<tr>
<td>NBN (n=2)</td>
<td>Mod-/low-risk BR/OV</td>
<td>0 of 2</td>
<td>NA</td>
<td>0 of 1</td>
</tr>
<tr>
<td>PALB2 (n=8)</td>
<td>Mod-/low-risk BR/OV</td>
<td>5 of 8</td>
<td>Increased screening or mastectomy</td>
<td>7 of 7</td>
</tr>
<tr>
<td>RAD51C (n=3)</td>
<td>Mod-/low-risk BR/OV</td>
<td>2 of 3</td>
<td>Increased breast screening</td>
<td>3 of 3</td>
</tr>
<tr>
<td>MLH1 (n=1)</td>
<td>Lynch syndrome</td>
<td>1 of 1</td>
<td>Increased colorectal/endometrial screening</td>
<td>1 of 1</td>
</tr>
<tr>
<td>MSH2 (n=2)</td>
<td>Lynch syndrome</td>
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<td>Prophylactic colectomy</td>
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## Genetic/Familial High-Risk Assessment: Breast and Ovarian

### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

<table>
<thead>
<tr>
<th>Intervention warranted based on gene and/or risk level</th>
<th>Recommend Breast MRI&lt;sup&gt;d&lt;/sup&gt; (&gt;20% risk of breast cancer&lt;sup&gt;e&lt;/sup&gt;)</th>
<th>Discuss Option of RRM</th>
<th>Recommend/Consider RRSO</th>
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<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53, PALB2</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;sup&gt;f&lt;/sup&gt;, BRIP1, RAD51C, RAD51D</td>
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</tbody>
</table>

- **Intervention warranted based on gene and/or risk level**
- **Recommend Breast MRI (<20% risk of breast cancer)**
- **Discuss Option of RRM**
- **Recommend/Consider RRSO**

**RRM:** risk-reducing mastectomy
**RRSO:** risk-reducing salpingo-oophorectomy

---

<sup>a</sup>Other genes may be included in multi-gene testing.
<sup>b</sup>Intervention may still be warranted based on family history or other clinical factors.
<sup>c</sup>Insufficient evidence for any recommendations for breast MRI, RRSO, or RRM include but are not limited to: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2.
<sup>d</sup>See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
<sup>e</sup>May be modified based on family history or specific gene mutation.
<sup>f</sup>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Distribution of Presumed Pathogenic Germline Mutations.

Usefulness of Multigene Testing
Catching the Train That’s Left the Station

Elizabeth M. Swisher, MD

In the mid-1990s, clinical testing for BRCA1 and BRCA2 mutations rapidly followed gene cloning. Given the lack of clinical experience with BRCA1 and BRCA2 testing, many cancer genetics experts spoke against clinical testing, advocating that testing be done in the research setting only. Increasingly, women and their physicians ignored those recommendations, and testing expanded beyond very high-risk

In line with previous studies, the authors identified 3.8% of BRCA1/2-negative cases to have deleterious mutations in other cancer-risk genes. Reassuringly, more than 90% of these mutations occurred in genes consistent with the personal or family history, demonstrating the clinical relevance of these results and the relative rarity of incidental mutations. Importantly, the majority of mutations resulted in changes in recommendation for cancer screening or prevention. It is important to realize that participants in this study had predominantly
1120 pediatric cancer patients (< 20y)
  - Multigene panel testing
8.5% yield of pathogenic or likely pathogenic mutations germline mutations
Family history not predictive
  - Only 40% had a family history of cancer
May aid in surveillance and prevention of second cancer
A Mutations in 21 Genes Associated with Autosomal Dominant Cancer-Predisposition Syndromes

- Leukemia
- CNS tumor
- Retinoblastoma
- ACT
- Osteosarcoma
- Rhabdomyosarcoma
- Ewing's sarcoma
- Neuroblastoma

No. of Patients
Clinical application of multigene panels: challenges of next-generation counseling and cancer risk management

Edited by: Pamela Pollock, Institute for Health and Biomedical Innovation, Australia

Thomas Paul Slavin*, Mariana Niell-Swiler, Ilana Solomon, Bita Nehoray, Christina Rybak, Kathleen R. Blazer and Jeffrey N. Weitzel*

Division of Clinical Cancer Genetics, Department of Medical Oncology, City of Hope, Duarte, CA, USA

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FIGURE 1 | General characteristics of genetic cancer risk groups. Genetic risk categories are shown with an adjacent matched color descriptor noting the general features specific to each risk tier. Quantification of risk with a categorization of genes in each tier is provided in Table 1. Clinical utility (arrow) increases with higher cancer risk predisposition. The arrow gradient denotes the potential significant overlap between the tiers. Clinical utility and refined risk scores may improve in the future, especially for low and moderate risk genes (19). Penetrance, actionability, and implications for family members have been simplified for conceptual use.

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Case Example

BRCA1+

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Case Example: Impact of Genetics

- Role of genetic testing in personalized care:
  - Surgical management
  - **Novel targeted systemic therapy**
  - Cancer screening
  - Cancer prevention
  - Family members’ decisions
Targeted Treatment - Defined

• Molecular therapies that specifically target pathways

• Require knowledge of underlying cancer-associated abnormality

• Directed specifically against cancer cells
  – Spare healthy cells
  – Fewer adverse side-effects

• “smart drugs”, “personalized medicine”
Targeted Treatment - examples

- Her2 – directed therapy (Herceptin)
- Vascular Endothelial Growth Factor Receptor Inhibitors
- Epidermal Growth Factor Receptor Inhibitor
- PARP Inhibitors
Genetics and Personalized Care

• PARP inhibitors: target the defect in DNA repair in BRCA mutation carriers
  – Poly ADP ribose polymerase (PARP)
    • Important role in DNA repair
  – Olaparib, Veliparib etc – inhibit PARP enzyme
    • Block alternate DNA repair pathway
  – Promising results in BRCA +
  – Expand to other genes (PALB2, CHEK2, ATM)
  – Molecularly targeted treatments for cancer
  – Clinical trials open in breast, ovarian, pancreas, other
  – Personalized Medicine
Homologous recombination defects

Fig. 1 Selective sensitivity of BRCA1/2-associated tumors to genotoxic agents. Normal cells from BRCA1/2 mutation carriers retain full capacity of genome maintenance mechanisms (left). Development of tumors in these patients involves somatic inactivation of the remaining BRCA1/2 allele, therefore malignant cells are unable to cope with double-strand DNA breaks (right).

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Targeting DNA Repair

- DNA Strand Break
- Chemotherapy
- Radiotherapy

- DNA Repair

- PARP1
  - Single-strand breaks
  - DNA adducts/base damage
  - Replication lesions

- BRCA1/BRCA2

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Figure 3: Massive Genome Instability Induced by PARPi in BRCA2 Mutant Cells
NSABP B-55 Clinical Trial

• First molecularly targeted trial for BRCA mutation carriers with early stage breast cancer

• Inclusion Criteria:
  – Triple Negative Breast Cancer (> 2cm or lymph node + )
  – ER + , high risk
  – BRCA1/2 mutation carriers

• Chemotherapy given to each patient per std of care
  – Anthracycline, taxane or both

• Olaparib 300mg p.o. twice a day for 12 mos

• Personalized medicine prototype
Lynparza (Olaparib)- FDA approval

- Oral PARP inhibitor
- FDA approved 12/2014 for advanced ov ca in BRCA +
- 4th line treatment
- Single open label trial of 137 patients
  - Overall response rate 34% - 60%
  - Median duration of response 7.9 months
  - Side effects fatigue, nausea, vomiting, headache
- Further studies in progress
- Companion diagnostic test approved
- **Personalized medicine**
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Cytotoxic and targeted therapy for hereditary cancers

Aglaya G. Iyevleva and Evgeny N. Imyanitov
<table>
<thead>
<tr>
<th>Hereditary cancer type</th>
<th>Drug</th>
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<tbody>
<tr>
<td>BRCA1/2-driven cancers (breast, ovarian, prostate, pancreatic, stomach, etc.)</td>
<td>Genotoxic agents: platinum compounds, PARP inhibitors, mitomycin C,</td>
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<tr>
<td></td>
<td>pegylated doxorubicin, etc.; high dose chemotherapy</td>
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<tr>
<td>Hereditary non-polyposis colorectal cancer</td>
<td>Immune checkpoint inhibitors: pembrolizumab</td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>Non-steroidal anti-inflammatory drugs (sulindac) and EGFR inhibitors</td>
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<tr>
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<td>(erlotinib)</td>
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<td>Tumors arising in patients with tuberous sclerosis (giant-cell astrocytomas,</td>
<td>mTOR inhibitors: everolimus</td>
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<td>angiomyolipomas)</td>
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<td>Tumors associated with the basal-cell nevus syndrome (basal-cell carcinomas,</td>
<td>SMO inhibitors (vismodegib), COX2 inhibitors (celecoxib), antifungal</td>
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<td>keratocystic odontogenic tumors)</td>
<td>drugs with Hedgehog pathway inhibitory activity (itraconazole)</td>
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<tr>
<td>Hereditary medullary thyroid cancer</td>
<td>RET inhibitors (vandetanib, cabozantinib)</td>
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Multigene Panel Testing

Germline
Hereditary

Somatic
(Tumor)
Acquired
Tumor (Somatic) Gene Panel Testing

- Progress in understanding genetic basis of cancer
- 1914 - Boveri linked somatic genetic changes to origin of cancer
- 1960 – Discovery of Ph chromosome in CML
- Advent of high-throughput gene sequencing methods
- Discovery of hundreds of recurrent somatic alterations in various malignancies
- Dramatic impact on diagnostic and therapeutic approaches to cancer
- **Personalized (targeted) molecular therapies**
Tumor (Somatic) Testing

- Classification of variants
- Actionability
- Variants of uncertain significance
- Conflicting interpretations
- Decision support (molecular tumor board)
- Incidental findings
- Germline implications/genetic counseling
- Research
- Clinical trial identification
Clinical Tumor Sequencing: Opportunities and Challenges for Precision Cancer Medicine

Senthilkumar Damodaran, MD, PhD, Michael F. Berger, PhD, and Sameek Roychowdhury, MD, PhD

OVERVIEW

Advances in tumor genome sequencing have enabled discovery of actionable alterations leading to novel therapies. Currently, there are approved targeted therapies across various tumors that can be matched to genomic alterations, such as point mutations, gene amplification, and translocations. Tools to detect these genomic alterations have emerged as a result of decreasing costs and improved throughput enabled by next-generation sequencing (NGS) technologies. NGS has been successfully utilized for developing biomarkers to assess susceptibility, diagnosis, prognosis, and treatment of cancers. However, clinical application presents some potential challenges in terms of tumor specimen acquisition, analysis, privacy, interpretation, and drug development in rare cancer subsets. Although whole-genome sequencing offers the most complete strategy for tumor analysis, its present utility in clinical care is limited.
Cancer genomic sequencing assays can aid clinical decision making with potential implications for diagnosis, prognosis, and treatment. Several assays are available to aid in identifying tissue-of-origin in cancer of unknown primary, which may lead to identification of potential favorable subsets and their appropriate treatment options. For patients with metastatic or refractory cancer, multiple testing strategies are available to identify genomic alterations that may provide molecular eligibility for novel targeted therapies in clinical trials.
Next-Generation Sequencing: Role in Gynecologic Cancers

Tarra Evans, MD, and Ursula Marulonis, MD

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<table>
<thead>
<tr>
<th>Genomic Finding</th>
<th>Clinical Observation or Action</th>
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<tbody>
<tr>
<td>Germline BRCA1 or BRCA2 mutation</td>
<td>Risk-reducing surgeries for ovarian and breast cancer[58, 59]</td>
</tr>
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</table>
| Germline mutations in BRIP1, RAD51C, RAD51D, PALB2, BARD1, MSH2, MLH1, PMS2, MSH6 | Entire group of genes: increased risk of ovarian cancer[27-30]  
MSH2, MLH1, PMS2, MSH6: Increased risk of ovarian, endometrial, colorectal cancers[28] |
| Somatic BRCA1 or BRCA2 mutation on NGS of ovarian cancer         | Improved overall survival compared with BRCA wild-type cancers and increased susceptibility to poly(ADP-ribose) polymerase inhibitors and platinum agents[7, 48, 63-65]  
Possible increased sensitivity to immunotherapy agents[64] |
| Cycling E and MDR1 amplification                               | Enhanced resistance to platinum chemotherapy[11]                                             |
| Inactivation of RB1, NF1, RAD51B, PTEN                         |                                                                                               |
| BRCA reversion mutations in HGSOC                              |                                                                                               |
| POLE mutations in endometrial cancer                           | Possible increased sensitivity to checkpoint blockade inhibitors[65]                         |
| Structurally grouped TP53 mutations                            | Missense mutation at the R248 location of TP53 increases taxane and platinum resistance for HGSOC[10] |

Abbreviations: HGSOC, high-grade serous ovarian carcinoma; NGS, next-generation sequencing; POLE, polymerase ε.
Clinical Implications of Genomic Discoveries in Lung Cancer

Charles Swanton, M.D., Ph.D., and Ramaswamy Govindan, M.D.

Lung cancer is one of the leading causes of death globally. Tobacco smoking causes nearly 90% of lung cancers. The major histologic types of lung cancer include adenocarcinoma, squamous-cell carcinoma,
Figure 2. Cells of Origin and Characteristic Alterations According to Histologic Subtype.
The likely cells of origin for the three common histologic subtypes of lung cancer — adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma — are depicted.
The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling?

Rishi Jain, MD, MS¹; Michelle J. Savage, CGC²; Andrea D. Forman, CGC²; Reetu Mukherji, BS³; and Michael J. Hall, MD, MS⁴

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Karki et al. BMC Medical Genomics (2015) 8:37

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<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
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<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
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<td>Familial adenomatous polyposis</td>
<td>APC</td>
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<td>MYH-associated polyposis; adenomas; multiple colorectal cancers; familial amyloid polyneuropathy type 2; colorectal adenomatous polyposis, autosomal recessive, with pilimetricomas</td>
<td>MUTYH</td>
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<td>Von Hippel-Lindau syndrome</td>
<td>VHL</td>
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<td>Multiple endocrine neoplasia type 1</td>
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<td>PTEN hamartoma tumor syndrome</td>
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<td>Hereditary paraganglioma-pheochromocytoma syndrome</td>
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<td>TSC1, TSC2</td>
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<td>WT1-related Wilms syndrome</td>
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<td>Neurofibromatosis type 2</td>
<td>NF2</td>
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<td>Ehlers-Danlos syndrome (vascular type)</td>
<td>COL3A1</td>
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<td>Marfan syndrome, Loey-Dietz syndrome, familial thoracic aortic aneurysms and dissections</td>
<td>FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11</td>
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<td>Hypertrophic cardiomyopathy, dilated cardiomyopathy</td>
<td>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</td>
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<td>Catecholaminergic polymorphic ventricular tachycardia</td>
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<td>Arrhythmogenic right-ventricular cardiomyopathy</td>
<td>PKP2, DSP, DSC2, TMEM43, DSG2</td>
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<td>Romano-Ward Long QT syndrome types 1, 2, and 3; Brugada syndrome</td>
<td>KCNQ1, KCNH2, SCN5A</td>
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<td>Familial hypercholesterolemia</td>
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<td>Malignant hyperthermia susceptibility</td>
<td>RYR1, CACNA1S</td>
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On Cancer

Tumor Sequencing Test Brings Personalized Treatment Options to More Patients

Tumor-Only Genetic Sequencing May Misguide Cancer Treatment in Nearly Half of All Patients, Study Shows

Johns Hopkins scientists say the genetic code of tumors must be compared to patients’ noncancer genome to get a true picture.
### PATIENT RESULTS

1. Genomic Alterations Identified
   - **BRCA2**: K1881fs*27
   - **IDH1**: R132H
   - **GLI1**: P535S

2. Therapies associated with potential clinical benefit
3. Therapies associated with lack of response
4. Clinical trials

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**TUMOR TYPE: LUNG ADENOCARCINOMA**

**Patient Name**

**Report Date**
04 September 2015

**Tumor Type**
Lung adenocarcinoma

**Specimen Received**
25 August 2015

**Specimen Site**
Pleural Fluid

**Date of Collection**
18 February 2015

**Specimen Type**
Block

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**ABOUT THE TEST:**
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.
# Gene Sequence & Deletion/Duplication Analyses of BRCA1 & BRCA2

<table>
<thead>
<tr>
<th>RESULTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1 FULL GENE</strong></td>
<td>Pathogenic Mutation(s): None Detected</td>
</tr>
<tr>
<td>Variant(s) of Unknown Significance:</td>
<td>None Detected</td>
</tr>
<tr>
<td><strong>BRCA1 DEL/DUP</strong></td>
<td>Gross Deletion(s)/Duplication(s): None Detected</td>
</tr>
<tr>
<td><strong>BRCA2 FULL GENE</strong></td>
<td><strong>Pathogenic Mutation(s):</strong> c.5641_5644delAAAT</td>
</tr>
<tr>
<td>Variant(s) of Unknown Significance:</td>
<td>None Detected</td>
</tr>
<tr>
<td><strong>BRCA2 DEL/DUP</strong></td>
<td>Gross Deletion(s)/Duplication(s): None Detected</td>
</tr>
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<thead>
<tr>
<th>SUMMARY</th>
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**POSITIVE: Pathogenic Mutation Detected**

**INTERPRETATION**

This individual is heterozygous for the **c.5641_5644delAAAT** pathogenic mutation in the **BRCA2** gene, which is associated with hereditary breast and ovarian cancer (HBOC) syndrome. However, the expression level of this mutation cannot be predicted.

Since this individual was found to carry a pathogenic mutation in the **BRCA2** gene, the OvaNext hereditary cancer panel was not performed.

Genetic counseling is a recommended option for all patients undergoing genetic testing.

**ALTERATION INFORMATION**

The **c.5641_5644delAAAT** pathogenic mutation, located in coding exon 10 of the **BRCA2** gene, results from a deletion of 4 nucleotides from nucleotide positions 5641 to 5644, causing a translational frameshift with a predicted alternate stop codon. This pathogenic mutation, also referred to as 5869delAAAT, has been reported in several individuals diagnosed with breast and/or ovarian cancer (Liede A et al. *Am. J. Hum. Genet.* 2002 Sep;71(3):595-606; Machackova E et al. *BMC Cancer* 2008;8:140; Couch FJ et al. *J. Clin. Oncol.* 2015 Feb; 33(4):304-11). In addition to the clinical data presented in the literature, since frameshifts are typically deleterious in nature, this alteration is interpreted as a disease-causing mutation (ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations. Revision 2007. *Genet Med.* 2008;10:294).

\[= p.\text{Lys1881GlnfsTer27 a.k.a. K1881fs*27} \]
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<table>
<thead>
<tr>
<th>GENE</th>
<th>INTERPRETATION</th>
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</table>
| **PIK3CA** | **E542K**  
Gene and Alteration: PIK3CA encodes the protein p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of cellular functions, including cell growth, proliferation, differentiation, motility, and survival. PIK3CA activating mutations in the amino acids E542, E545, E546, Q546, M547, and H1047 of p110-alpha have been characterized as activating and are predicted to be oncogenic.  
Frequency and Prognosis: PIK3CA mutation was observed in 35% of invasive breast cancer cases. In lobular breast carcinoma, PIK3CA mutation has been observed in 36–49% of cases. PIK3CA kinase domain mutations (such as H1047R) located in exon 22 have been associated with a better prognosis.

Potential Treatment Strategies: PIK3CA activating mutations or amplification may predict sensitivity to inhibitors of the mTOR pathway[4]. The mTOR inhibitor everolimus has been approved for use in combination with exemestane, an aromatase inhibitor, in postmenopausal women with hormone receptor-positive, Her2-negative advanced breast cancer[5]. Temsirolimus is another mTOR inhibitor that has been approved for use in advanced renal cell carcinoma[6]. These therapies and other mTOR inhibitors are in clinical trials in breast cancer and other solid tumor types. Inhibitors of PI3K and 4B1, alone or in combination with other therapies, are also currently in clinical trials for solid tumors. A preclinical study indicates that PIK3CA mutations predict sensitivity to the PIKCA-specific inhibitor 2’V, 2’J, which may have a bigger therapeutic window than pan-PI3K inhibitors[7]. Furthermore, CDK4/6 inhibitors were shown to sensitize PIK3CA mutant breast cancer to PIK3 inhibitors[8]. PIK3CA mutations may play a role in resistance to hormonal therapy in ER+ breast cancers[9]. Activating mutations in PIK3CA may also confer resistance to anti-Her2 therapies; combined inhibition of 4B1 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation[8,10,11,12]. |
| **BRCA2** | **Q737**  
Gene and Alteration: The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[13]. Mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell-cycle checkpoints, which can lead to tumorigenesis[14]. BRCA2 truncation mutations that disrupt the BRC repeats (e.g. 702-2895), DNA binding domain (e.g. 279-3192) and/or C-terminal Rad51 binding domain (334-679), such as the mutation seen here, are expected to be biologically inactive. Germinal mutations in BRCA1 or BRCA2 are associated with breast-ovarian cancer (BRCA-1 and BRCA-2) associated cancers also known as breast-ovarian cancer (BRCAX). The lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[15,16], and increased risk of other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, at a frequency range of 20–60%[17]. The estimated prevalence of deleterious germline BRCA-1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[18,19,20,21,22,23,24]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

Frequency and Prognosis: The incidence of BRCA2 mutation is low in sporadic breast cancer[25,26]. BRCA2 mutations and deletions have been found in 5% and 7% of breast carcinomas, respectively (COSMIC, Jun 2019).
Potential Treatment Strategies: BRCA2 alterations may predict sensitivity to DNA-targeting therapies, such as cisplatin and carboplatin, and to PARP inhibitors. The PARP inhibitor olaparib is FDA-approved to treat ovarian cancer patients with BRCA1/2 alterations, and has also demonstrated clinical activity for patients with breast cancer and BRCA1/2 mutations, with one study reporting a response rate of 41% for patients with BRCA1/2 mutant breast cancer.

Gene and Alteration: CDH1 encodes the transmembrane protein E-cadherin, which plays an important role in epithelial cell-cell adhesion; loss of E-cadherin expression leads to decreased cell adhesion and results in cell migration and cancer metastasis.

CDH1 truncation mutations that result in loss of the cadherin-binding domain, such as the mutation observed here, are predicted to be inactivating due to disruption of the functional E-cadherin-catenin adhesion complex. Germ-line CDH1 mutations have also been associated with invasive lobular breast carcinoma.

Frequency and Prognostic: CDH1 mutations have been reported at high frequencies in invasive lobular breast carcinoma (62–100% of cases), and in a study of recurrent CDH1-mutant invasive lobular breast cancers, 27% (5/19) of cases were found to have concurrent alterations in PTEN.

Loss of the E-cadherin protein has been associated with poor prognosis and lymph node metastasis in breast carcinoma in general.

Potential Treatment Strategies: There are no available therapies to compensate directly for CDH1 mutations or loss of E-cadherin function.
Original Investigation

Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA

Kasmintan A. Schrader, MBBS, PhD, FRCPC, DABMG; Donavan T. Cheng, PhD; Vijai Joseph, PhD; Meera Prasad, MS; Michael Walsh, MD; Ahmet Zehir, PhD; Ai Ni, PhD; Tinu Thomas, MS; Ryma Benayed, PhD; Asad Ashraf, MS; Annie Lincoln, MS; Maria Arcila, MD; Zsofia Stadler, MD; David Solit, MD; David M. Hyman, MD; Liying Zhang, MD, PhD; David Klimstra, MD; Marc Ladanyi, MD; Kenneth Offit, MD; Michael Berger, PhD; Mark Robson, MD

Importance Tumor genetic sequencing identifies potentially targetable genetic alterations with therapeutic implications. Analysis has concentrated on detecting tumor-specific variants, but recognition of germline variants may prove valuable as well.

Published online November 10, 2015. Corrected on February 11, 2016.
Figure 2. Total Presumed Pathogenic Germline Variants (PPGVs) Identified in 61 Genes

- Variants in ACMG cancer-related genes with modes of inheritance consistent with potential for phenotypic expression in the participant (79 individuals, 5%)
- Additional cancer-related genes with modes of inheritance consistent with potential for phenotypic expression in the participant (penetrance: moderate or not established) (59 individuals, 4%)
- High-penetrant cancer-related genes beyond the ACMG list, with modes of inheritance consistent with potential for phenotypic expression in the participant (33 individuals, 2%)
- Noncancer OMIM genes with modes of inheritance consistent with potential for phenotypic expression in the participant (12 individuals, 1%)
- Genes with likely blood-related somatic mosaic variants unrelated to the presenting cancer (27 individuals, 2%)
- Cancer-related genes in the ACMG list with modes of inheritance NOT consistent with phenotypic expression in the participant (23 individuals, 1%)
- Cancer-related genes beyond the ACMG list with modes of inheritance NOT consistent with phenotypic expression in the participant (18 individuals, 1%)
- Noncancer OMIM genes with modes of inheritance NOT consistent with phenotypic expression in the participant (17 individuals, 1%)

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How Far Do We Go With Genetic Evaluation? Gene, Panel, and Tumor Testing

Filipa Lynce, MD, and Claudine Isaacs, MD, FRCPC

OVERVIEW

The traditional model by which an individual was identified as harboring a hereditary susceptibility to cancer was to test for a mutation in a single gene or a finite number of genes associated with a particular syndrome (e.g., BRCA1 and BRCA2 for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome). The decision regarding which gene or genes to test for was based on a review of the patient’s personal medical history and their family history. With advances in next-generation DNA sequencing technology, offering simultaneous testing for multiple genes associated with a hereditary susceptibility to cancer is now possible.
<table>
<thead>
<tr>
<th>Table 1. Examples of Genes Included on Some Next-Generation Sequencing Cancer Panels*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Comprehensive Panels</strong></td>
</tr>
<tr>
<td>Ambry Genetics</td>
</tr>
<tr>
<td>GeneDx</td>
</tr>
<tr>
<td>Myriad Genetics</td>
</tr>
<tr>
<td>Invitae</td>
</tr>
<tr>
<td><strong>Breast/Ovarian Panels</strong></td>
</tr>
<tr>
<td>Ambry Genetics</td>
</tr>
<tr>
<td>BreastNexT&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>OvaNexT&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Invitae</td>
</tr>
<tr>
<td>Breast Cancer Guidelines Based Panel&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Color Genomics&lt;sup&gt;19&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>Invitae</td>
</tr>
<tr>
<td><strong>Gastrointestinal Panels</strong></td>
</tr>
<tr>
<td>Ambry Genetics</td>
</tr>
<tr>
<td>Invitae</td>
</tr>
<tr>
<td>Myriad Genetics</td>
</tr>
<tr>
<td>COLARIS&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>GeneDx</td>
</tr>
<tr>
<td>Lynch/Colorectal High Risk Panel&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviation: VUS, variants of uncertain significance.
*Current as of February 2, 2016.
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Multigen Gene Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype-directed testing</td>
<td>More cost effective (less expensive per gene cost)</td>
</tr>
<tr>
<td>Cancer risks and management options often more established</td>
<td>More time efficient</td>
</tr>
<tr>
<td>Lower likelihood of detecting VUS</td>
<td>Decrease in testing fatigue for patients and providers</td>
</tr>
<tr>
<td>More rapid turnaround time</td>
<td>Efficient use of single specimen</td>
</tr>
<tr>
<td></td>
<td>Higher mutation detection rate, genes individually rare but collectively significant</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Increased prevalence of VUS</td>
</tr>
<tr>
<td>Higher risk of loss to follow-up during sequential testing multiple single genes (test fatigue)</td>
<td>Cancer risks and management options often not well-defined, particularly for some moderate- and low-penetrance genes</td>
</tr>
<tr>
<td>Less comprehensive</td>
<td>Unexpected findings such as “off-phenotypic-target” gene mutation</td>
</tr>
<tr>
<td></td>
<td>Longer turnaround time</td>
</tr>
<tr>
<td></td>
<td>Panels may include genes that patients don’t wish to test for</td>
</tr>
</tbody>
</table>

Abbreviation: VUS, variants of uncertain significance.
The Role of Genetic Testing in the Selection of Therapy for Breast Cancer
A Review

Polly Niravath, MD; Burcu Cakar, MD; Matthew Ellis, MB, BCHir, PhD, FRCP

IMPORTANCE The application of next-generation sequencing (NGS) genomic testing for somatic mutations in breast oncology has been slower than anticipated due to issues with clinical applicability and natural heterogeneity of breast cancer. This review summarizes the state of the field and considers approaches for more effective implementation.

JAMA Oncol. doi:10.1001/jamaoncol.2016.2719
Published online August 25, 2016.
Table 1. The 10 Most Frequently Mutated Genes In Breast Cancer, Listed In Descending Order of Frequency, With Potentially Associated Therapeutic Implications

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gain or Loss of Function</th>
<th>Potential Therapeutic Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Loss</td>
<td>Lack of p53 mutation predicts resistance to MDM2 inhibitors</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Gain</td>
<td>Susceptibility to PI3K, AKT, or mTOR inhibitors</td>
</tr>
<tr>
<td>MYC</td>
<td>Gain</td>
<td>None</td>
</tr>
<tr>
<td>CCND1</td>
<td>Gain</td>
<td>Sensitivity to CDK4/6 inhibition</td>
</tr>
<tr>
<td>PTEN</td>
<td>Loss</td>
<td>Susceptibility to PI3K, AKT, or mTOR inhibitors</td>
</tr>
<tr>
<td>ERBB2/HER2</td>
<td>Gain</td>
<td>Sensitivity to anti-HER2 agents&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ZNF703/FGFR1</td>
<td>Gain</td>
<td>Sensitivity to FGFR inhibitor</td>
</tr>
<tr>
<td>GATA3</td>
<td>Loss</td>
<td>None</td>
</tr>
<tr>
<td>RB1</td>
<td>Loss</td>
<td>Resistance to CDK4/6 inhibition</td>
</tr>
<tr>
<td>MAP3K1</td>
<td>Loss</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; MDM2, murine double minute 2 homolog; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3 kinase.

<sup>a</sup> This is the only therapeutic implication that has been proven with level 1 evidence; the remainder of the associations are largely speculative.
Through collaboration of many stakeholders, we propose creation of a clinically relevant, financially feasible model to collect millions of ctDNA liquid biopsy specimens, which would eventually inform a publicly available, international database that could help clinicians act on somatic tumor mutations in a rational, evidence-based manner.
NCI MATCH TRIAL

Precision Medicine Trial

Molecular Analysis for Therapy Choice

Opened Aug 2015
Reached 500 pts 10/15
Pause for analysis 11/15
Reopened 5/16
900 Sites

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• Molecular analysis of tumors to identify a genetic alteration which may serve as a target
• Tumor biopsy specimens sent for sequencing
• Targeted drugs selected to “match” the genetic defect (initial match: 9%; goal: over 20%)
• Plan to analyze over 24 agents
• Molecular targets include ALK, BRAF, EGFR, cKIT, ROS1
## NCI-MATCH 24 Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Target</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>EGFR mut</td>
<td>Afatinib</td>
</tr>
<tr>
<td>B</td>
<td>HER2 mut</td>
<td>Afatinib</td>
</tr>
<tr>
<td>C1</td>
<td>MET amp</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>C2</td>
<td>MET ex 14 sk</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>E</td>
<td>EGFR T790M</td>
<td>AZD9291</td>
</tr>
<tr>
<td>F</td>
<td>ALK transloc</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>G</td>
<td>ROS1 transloc</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>H</td>
<td>BRAF V600</td>
<td>Dabrafenib+trametinib</td>
</tr>
<tr>
<td>I</td>
<td>PIK3CA mut</td>
<td>Taselisib</td>
</tr>
<tr>
<td>N</td>
<td>PTEN mut</td>
<td>GSK2636771</td>
</tr>
</tbody>
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• First-ever ASCO clinical trial
• Patients with advanced cancer
• Genomic profile/tumor sequencing
• Molecular Tumor Board support
• Actionable genomic variant(s)
• Molecularly targeted anticancer agents
  – Provided free of charge
• Safety and efficacy end points
• Non randomized trial
• 37 sites
• 49 participants
  – 18 on treatment, 31 in screening
• Evaluating use of targeted agents in different tumor types
• Off label use of FDA approved agents
EDITORIAL

Getting Ready for Gene-Based Medicine

Harold Varmus, M.D.

• Human genome sequenced 2001
• Knowledge of genetics increasingly important
• Need to educate physicians
• Shortage of genetic counselors
• “How can increasingly complex genetic knowledge be made readily accessible to all?" 
• “Need to anticipate and plan for consequences of profound change in medicine”
Perspective
SEPTEMBER 22, 2016

Toward a Shared Vision for Cancer Genomic Data

Robert L. Grossman, Ph.D., Allison P. Heath, Ph.D., Vincent Ferretti, Ph.D., Harold E. Varmus, M.D.,
Douglas R. Lowy, M.D., Warren A. Kibbe, Ph.D., and Louis M. Staudt, M.D., Ph.D.
The recent explosion of cancer genome analysis has left in its wake a trail of data ambiguity that must be addressed and rectified.
Figure 1. Functionality and Utility of the National Cancer Institute Genomic Data Commons (GDC).

The GDC will accept cancer genomic and clinical data from a number of different sources, harmonize the data using consistent bioinformatic pipelines, and allow users to make discoveries regarding the genetic basis of cancer and its impact in the clinic and potentially to identify patients whose tumor profiles make them eligible for particular clinical trials.
American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Mark E. Robson, Angela R. Bradbury, Banu Arun, Susan M. Domchek, James M. Ford, Heather L. Hampel, Stephen M. Lipkin, Sapna Syngal, Dana S. Wollins, and Noralane M. Lindor
Multigene (panel) testing is rapidly expanding

Clinical utility of testing for moderate risk genes is not fully established

Genetic counseling is important

ASCO encourages research to delineate optimal use of panel testing and development of evidence-based practice guidelines, and education of providers
ASCO Recommendations 2015

- Germ-line implications of somatic profiling
- Multigene panel testing for hereditary cancer
- Collaboration and sharing of databases
- Quality assurance in genetic testing
- Education of Oncology professionals
- Access to cancer genetic services
ASCO Leadership Statement

• “Robust discussions among a diverse set of stakeholders will be needed to ensure that all perspectives are listened to and that genetic cancer susceptibility services are comprehensive and patient-centric.”

• Julie M. Vose, MD, MBA
• Peter Yu, MD
• Daniel F. Hayes, MD
A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015
Summary

- NGS technology allows for efficient and thorough analysis of molecular basis of cancer
- Understanding of the genetic basis and molecular biology of cancer has dramatically improved
- Gene panel testing is an integral part of both hereditary risk assessment and novel cancer treatment approaches
Conclusions

• An individualized approach to cancer is at the core of current innovation in Oncology
• Understanding of oncogenic mechanisms will guide risk assessment, screening, prevention, and therapy of cancer
• Further research is needed to identify the “best” targets for novel personalized therapies
• Partnership among clinicians, researchers, laboratories is needed to assure success
Thank you