GENETICS IN PRIMARY CARE

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PREVENTIVE ONCOLOGY
UChicago Medicine
Disclosures:
None
Learning Objectives

After today’s lecture, the participant should be able to:

1. Understand role of primary care clinicians in cancer genetics and prevention

2. Understand components of genetic counseling
Models of Genetic Counseling and Testing

Point A: Screening Sites Imaging, OB, GI, GU, PCP

Point B: Genetic Specialists
Main Genetic Counseling Implementation Models

Referral Model
Screening Site screens patients but then refers high risk interested patients to an appointment with a genetic specialist.

Point of Care Scheduling
Screening Site screens patients and all high risk interested patients make an appointment with a genetic specialist before they leave.

Point of Care Counseling
Screening Site screens patients and all high risk interested patients get *counseled immediately*.
New USPSTF Guidelines
Released August 2019
The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations with an appropriate brief familial risk assessment tool.

Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.

(B recommendation)
The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations.

(D recommendation)
Not Just *BRCA 1 / 2* anymore…

- Next-generation sequencing (NGS) technology allows rapid analysis of sets of genes at low/similar costs
  - “When more than one gene can explain an inherited cancer syndrome. Then multi-gene testing can be more efficient and/or cost-effective than single-gene testing.”
    - NCCN 3.2019 Colorectal Guidelines
    - [https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf](https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf)

- Common Cancer Panels
  - High Penetrance Genes
  - Moderate Penetrance Genes
  - ***Increased risks of VUS & not-clearly actionable genes***
and management. The counselor should recommend genetic counseling and testing for at-risk relatives. Since some pathogenic or likely pathogenic variants are associated with rare autosomal recessive conditions (eg, Fanconi anemia is associated with ATM, BRCA2, BRIPl, and PALB2 variants), testing of a partner or a carrier of a pathogenic or likely pathogenic variant may be considered to inform reproductive decision-making.\textsuperscript{61} See Table 3 for a list of pathogenic/likely pathogenic variants associated with autosomal recessive conditions.

**Multi-Gene Testing**

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. Multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multiple studies have shown that this approach may detect pathogenic or likely pathogenic variants not found in single-gene testing.\textsuperscript{62,64} A study of 198 women referred for BRCA1/2 testing who underwent multi-gene testing showed 16 deleterious mutations out of 141 women who tested negative for BRCA1/2 (11.4%; 95% CI, 7.0–17.7).\textsuperscript{65} The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.\textsuperscript{66}

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.\textsuperscript{66} The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a pathogenic or likely pathogenic variant known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of the variant. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. For example, though ovarian cancer is mainly associated with BRCA1/2 pathogenic or likely pathogenic variants, it may also be associated with variants in the following genes: BARD1, BRIP1, MRE11A, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D, and TP53.\textsuperscript{67,70} Genes associated with hereditary breast cancer include the following that could potentially be included in a multi-gene test: BRCA1/2, ATM, BARD1, CHEK2, PALB2, TP53, PTEN, STK11, and CDH1.\textsuperscript{70,65,69–71} In these cases where more than one pathogenic or likely pathogenic variant could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.\textsuperscript{66,70,71} Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is suggestive of an inherited susceptibility.\textsuperscript{66,70}

There are several issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, insurance coverage, and variant reclassification protocol, among others. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully.\textsuperscript{66} Second, in some cases, next-generation sequencing may miss some pathogenic or likely pathogenic variants that would have been detected with traditional single-gene analysis.\textsuperscript{66} Third, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.\textsuperscript{70} A management plan should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

# NCCN Guidelines Version 3.2019

## Genetic/Familial High-Risk Assessment: Colorectal

### Table 1: Multi-Gene Testing Definitions

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-gene panel</td>
<td>Laboratory test that includes testing for pathogenic variants of more than one gene.</td>
</tr>
<tr>
<td>Syndrome-specific panel</td>
<td>Panel that only tests for one syndrome (e.g., LS, adenomatous polyposis).</td>
</tr>
<tr>
<td>Cancer-specific panel</td>
<td>Panel that tests for more than one gene associated with a specific type of cancer.</td>
</tr>
<tr>
<td>“Comprehensive” cancer panel</td>
<td>Panel that tests for more than one gene associated with multiple cancers or multiple cancer syndromes.</td>
</tr>
<tr>
<td>Actionable pathogenic variant</td>
<td>Pathogenic variant that results in a recommendation for a change in clinical management.</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Genetic test result indicating a sequence variant in a gene that is of uncertain significance. Variants are generally not clinically actionable, and most (but not all) are ultimately re-classified as benign.</td>
</tr>
</tbody>
</table>

### Table 2: Pros and Cons of Multi-Gene Testing for Hereditary Colorectal Syndromes

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More efficient testing when more than one gene may explain presentation and family history.</td>
<td>• Higher chance of identifying pathogenic variants for which clinical management is uncertain. Estimates suggest that 3%-4% (Gastroenterology 2015 Sep;149:604-13.e20; Clin Genet 2014; 86:510-520) of pathogenic variants identified are not clearly clinically actionable, such as finding a pathogenic variant in a moderate-risk gene for which management is unclear.</td>
</tr>
<tr>
<td>• Higher chance of providing proband with possible explanation for cause of cancer.</td>
<td>• Higher chance of identifying variants of uncertain significance that are not actionable; reported rates of finding variants of uncertain significance range from 17%-38%.</td>
</tr>
<tr>
<td>• Competitive cost relative to sequentially testing single genes.</td>
<td>• Higher chance that patient will mistakenly receive overtreatment and overscreening if variants of uncertain significance or pathogenic variants for which clinical management is uncertain are incorrectly interpreted.</td>
</tr>
</tbody>
</table>

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Why is this important for patients?
ACCESS BY THE NUMBERS

375,000+ 1:900

4,000 GCs in entire US
~700 work in Cancer Genetics (1:500,000 Americans)

250,000 practicing PCPs

130,000 PAs
24% in primary care ~31,000 PAs

192,000 NPs
49% in primary care ~94,080 NPs
Steps for Proper Genetic Counseling

1) Identification of candidates for testing
2) Patient education
3) Benefits and harms of genetic testing
4) Interpretation of results after testing
5) Discussion of management options
Step 1: ID

- **Familial risk assessment tools**
  1. Ontario Family History Assessment Tool (Table 1)
  2. Manchester Scoring System (Table 2)
  3. Referral Screening Tool (Table 3)
  4. Pedigree Assessment Tool (Table 4)
  5. 7-Question Family History Screening Tool (Table 5)
  6. International Breast Cancer Intervention Study instrument (Tyrer-Cuzick) (Table 6)
  7. *BRCAPRO* (statistical model/associated software)

https://jamanetwork.com/journals/jama/fullarticle/2748515
Step 1: ID

Each tool weights risks differently, but in general, looks at:

- **YOUNG**
- **RARE**
- **MULTIPLE CANCERS**
Pass Waiting Room Time...
Ontario Family History Tool

From: Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement
## Manchester Scoring System

Table 2. Manchester Scoring System<sup>ab</sup>

<table>
<thead>
<tr>
<th>Risk Factor (Age at Onset for Relative in Direct Lineage)</th>
<th>BRCA1 Score</th>
<th>BRCA2 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male breast cancer, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥60</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ovarian cancer, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>≥60</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any age</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total individual genes</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total for combined = 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BRCA1, breast cancer susceptibility gene.

<sup>a</sup> See Oros et al.,<sup>75</sup> Parmigiani et al.,<sup>76</sup> Antoniou et al.,<sup>79</sup> Barcenas et al.,<sup>20</sup> Evans et al.<sup>20</sup>

<sup>b</sup> A score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a BRCA1 or BRCA2 mutation.

<sup>c</sup> If testing for BRCA2.

<sup>d</sup> If testing for BRCA1.
## Table 3. Referral Screening Tool

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Breast Cancer at Age ≤50 y</th>
<th>Ovarian Cancer at any Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yourself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandmother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandmother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 cases of breast cancer after age 50 y on same side of family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male breast cancer at any age in any relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jewish ancestry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* See Bellcros et al.\(^2\)  
\*\* Referral if 2 or more checks in table.
# Pedigree Assessment Tool

Table 4. Pedigree Assessment Tool\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score for Every Family Member With Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer at age $\geq 50$ y</td>
<td>3</td>
</tr>
<tr>
<td>Breast cancer at age $&lt;50$ y</td>
<td>4</td>
</tr>
<tr>
<td>Ovarian cancer at any age</td>
<td>5</td>
</tr>
<tr>
<td>Male breast cancer at any age</td>
<td>8</td>
</tr>
<tr>
<td>Ashkenazi Jewish heritage</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} See Hoskins et al\textsuperscript{23} Teller et al\textsuperscript{24}

\textsuperscript{b} Score 8 or greater is the optimal referral threshold.
# 7-Question Family History Tool

Table 5. Seven-Question Family History Screening\(^a,b\)

<table>
<thead>
<tr>
<th>No.</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Did any of your first-degree relatives have breast or ovarian cancer?</td>
</tr>
<tr>
<td>2</td>
<td>Did any of your relatives have bilateral breast cancer?</td>
</tr>
<tr>
<td>3</td>
<td>Did any man in your family have breast cancer?</td>
</tr>
<tr>
<td>4</td>
<td>Did any woman in your family have breast and ovarian cancer?</td>
</tr>
<tr>
<td>5</td>
<td>Did any woman in your family have breast cancer before age 50 y?</td>
</tr>
<tr>
<td>6</td>
<td>Do you have 2 or more relatives with breast and/or ovarian cancer?</td>
</tr>
<tr>
<td>7</td>
<td>Do you have 2 or more relatives with breast and/or bowel cancer?</td>
</tr>
</tbody>
</table>

**Same side of family**

\(^a\) See Ashton-Prolla et al.\(^25\), Fischer et al.\(^26\)

\(^b\) One positive response initiates referral.
# International Breast Cancer Intervention Study Model

From: *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement*


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**Table 6. International Breast Cancer Intervention Study Model**[^26] [^27]

<table>
<thead>
<tr>
<th>No.</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Personal history: current age, age at menopause, age at menarche, childbirth history, menopausal status, use of menopausal hormone therapy</td>
</tr>
<tr>
<td>2</td>
<td>Personal breast history, breast density (optional), prior breast biopsy, history of cancer (breast or ovarian), genetic testing</td>
</tr>
<tr>
<td>3</td>
<td>Ashkenazi Jewish inheritance</td>
</tr>
<tr>
<td>4</td>
<td>Family history (genetic risk)—relatives with breast or ovarian cancer, age at diagnosis, genetic testing</td>
</tr>
</tbody>
</table>

[^26]: See Fischer et al. [^27]: Referral for genetic testing if the personal risk level for a mutation in breast cancer susceptibility gene 1 or 2 is 10% or greater.
https://www.nccn.org/

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial
High-Risk Assessment:
Breast, Ovarian, and Pancreatic

Version 1.2020 — December 4, 2019

NCCN.org

Continue
https://www.nccn.org/
Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes (continued)

(Continues from page 25.)

Testing may be considered in the following scenarios [with appropriate pre-test education and access to post-test management]:

1. Bilateral breast cancer, first diagnosed between the ages of 50 and 65 y
2. An unaffected Ashkenazi Jewish individual
3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%–5% probability of BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, PenHilb)

There is a low probability (<2.5%) that testing will have documented clinical utility in the following scenarios:

1. Women diagnosed with breast cancer at age >65 y, with no close relative with breast, ovarian, pancreatic, or prostate cancer
2. Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Simple Pocket Checklists Help…

What is Hereditary Breast and Ovarian Cancer?

A diagnosis of Hereditary Breast and Ovarian Cancer Syndrome (HBOC) is considered when there are multiple cases of **breast cancer** and/or **ovarian cancer** on the same side of the family. The chance that a family has HBOC increases in any of these situations:

- 1 or more women are diagnosed at age **45 or younger**
- 1 or more women are diagnosed with breast cancer before age 50 with an additional family history of cancer, such as **prostate cancer**, **melanoma**, and **pancreatic cancer**
- There are breast and/or ovarian cancers in **multiple generations on the same side** of the family, such as having both a grandmother and an aunt on the father’s side both diagnosed with these cancers
- A woman is diagnosed with a **second breast cancer** in the same or the other breast or has both breast and ovarian cancer
- A **male relative** is diagnosed with breast cancer
- There is a history of breast cancer, ovarian cancer, prostate cancer, and/or pancreatic cancer on the same side of the family
- Having **Ashkenazi Jewish ancestry**

https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer
"3-2-1 rule"
(3 affected members, 2 generations, 1 under age 50)

<table>
<thead>
<tr>
<th>Amsterdam II criteria for Lynch syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>There should be at least three relatives with any Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)</td>
</tr>
<tr>
<td>One should be a first-degree relative of the other two</td>
</tr>
<tr>
<td>At least two successive generations should be affected</td>
</tr>
<tr>
<td>At least one should be diagnosed before age 50</td>
</tr>
<tr>
<td>Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any</td>
</tr>
<tr>
<td>Tumors should be verified by pathological examination</td>
</tr>
</tbody>
</table>

Free Online Calculation Tool

www.ems-trials.org/riskevaluator/
Free Online Calculation Tool

www.ems-trials.org/riskevaluator/
Free Online Calculation Tool

www.ems-trials.org/riskevaluator/

Dialog

Personal: 6.640% 2.383%
Population: 20.920% 8.825%

Risk after 10 years:

Lifetime risk:

22.5% 18.0% 13.5% 9.0% 4.5% 0.0%
47 52 57 62 67 72 77 82

Personal risk
Population risk

No BRCA gene: 93.491% 99.770%
BRCA1 gene: 4.468% 0.110%
BRCA2 gene: 2.041% 0.120%
Steps for Proper Genetic Counseling

1) Identification of candidates for testing
2) Patient education
3) Benefits and harms of genetic testing
4) Interpretation of results after testing
5) Discussion of management options
STEP 2: PATIENT EDUCATION

Why should I consider genetic testing?
1. I __________________________, request and permit Invitae to analyze the gene(s) indicated on the test requisition form: ☐ My sample ☐ My child's sample. No testing apart from that which is ordered will be performed. Additional testing requires my additional, express consent.

I UNDERSTAND THAT:

1. More information about _condition tested_ is available from my healthcare provider and can be found on the Invitae website (www.invitae.com).

2. The results of this DNA test could be:
   a. Positive, and may:
      i. contribute to the diagnosis of a genetic condition.
      ii. reveal carrier status for a genetic condition.
      iii. reveal a predisposition or an increased risk for developing a genetic disease in the future.
      iv. have implications for other family members.
   b. Negative, and may:
      i. reduce but not eliminate the possibility that my condition has a genetic basis.
      ii. reduce but not eliminate my predisposition or risk for developing a genetic disease in the future.
      iii. be uninformative.
      iv. not remove the need for additional testing.
   c. Of uncertain significance and may:
      i. lead to a suggestion that testing additional family members may be helpful.
      ii. remain uncertain for the foreseeable future.
      iii. be resolved over time. My healthcare provider will be notified of any changes to the classification of previously-reported variants that relate to my (my child's) result.

When available, testing an affected family member may be more informative.

3. Molecular genetic tests may not be diagnostic for the selected condition(s) in all individuals. This test may or may not provide actionable information or have an impact on my medical management.

4. Some types of DNA changes that could cause a specific genetic disorder may not be detected by this test. As with most molecular genetic tests, Invitae's test has technical limitations that may prevent detection of specific rare variants due to poor DNA quality, inherent DNA sequence properties, or other types of limitations.

5. There may be possible sources of error including, but not limited to, trace contamination, rare technical errors in the laboratory, rare DNA variants that compromise data analysis, inconsistent classification systems, and inaccurate reporting of family relationships or clinical diagnosis information.

6. Invitae will only interpret the parts of the DNA sequence of gene(s) indicated on the requisition form by my or my child's physician. However, the technology obtains the DNA sequence information related to a broad range of genetic conditions and interprets and releases other parts of the remaining genetic data can be requested through my healthcare provider (additional charges may apply).

7. Invitae's clinical reports are released only to the certified healthcare professional(s) listed on the test requisition form. Clinical reports are confidential and will be released to other medical professionals with my explicit written consent. It has been explained to me that my clinical report is available for me to view or download at the Invitae website (www.invitae.com) after it has been released by my healthcare professional(s). Alternatively, my clinical report can be made immediately available upon completion of the test with the prior approval of my healthcare professional, as indicated on the test requisition form.

8. It is my responsibility to consider the possible impact of my or my child's test results as they relate to insurance rates, obtaining disability or life insurance, and employment. The Genetic Information Nondiscrimination Act (GINA), a federal law, provides some protections against genetic discrimination. For information on GINA visit http://www.genome.gov/10023238.

9. Results from the Invitae test are analyzed with the assumption that correct information on family relationships has been provided. Due to the type of test performed there is the possibility that inconsistencies in information on family relationships could be identified if multiple family members are tested. For example, this test may detect misattributed paternity, where the stated father of an individual is found to not be the true biological father. It may be necessary to report these findings to an individual who requested testing.

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**BY SIGNING BELOW, I ATTEST TO THE FOLLOWING:**

1. I have been informed of the likelihood of finding a change in the gene(s) for which I, or my child, am being tested and have received test-specific clinical information.

2. I have read and understand the information provided on this form and have had an opportunity to have any questions answered by my healthcare provider.

---

**HEALTHCARE PROVIDER STATEMENT**

By signing below, I attest that I am the referring physician or authorized healthcare professional. I have explained the purpose of test described above. The patient has had the opportunity to ask questions regarding this test and/or seek genetic counseling. The patient has voluntarily decided to have this test performed by Invitae.

---

**HEADQUARTERS | 1401 16th Street, San Francisco, CA 94103 | ONLINE | www.invitae.com | CONTACT | customer-service@invitae.com | 800-433-3007 | 415-273-4164 | © 2013 Invitae Corporation. All Rights Reserved.**
Important to be able to explain mechanisms:
Tumor Suppressor Genes
Steps for Proper Genetic Counseling

1) Identification of candidates for testing
2) Patient education
3) Benefits and harms of genetic testing
4) Interpretation of results after testing
5) Discussion of management options
Step 3: Risks & Benefits

- **PERSONALIZED MEDICINE**
  - Increased surveillance can identify cancer at its earliest, most treatable stage.
  - Risk-reducing surgery and/or chemoprevention can significantly decrease the chance of future cancers.

- **FAMILY BENEFITS**
  - Relatives at high risk can undergo enhanced surveillance, while those without the family variant may be able to avoid unnecessary procedures (and unnecessary worry).

- **TREATMENT OPTIONS**
  - Rapid genetic test results can inform quick surgical decisions without disrupting treatment timelines.
  - Genetic information may qualify patients for participation in clinical trials or research studies.

- **INCONCLUSIVE RESULTS**

- **HIPAA**
  - Privacy protections

- **GINA**
  - 2008 Genetic Information Nondiscrimination Act (GINA) protects against discrimination by health insurance plans based on an individual’s genetic information.

- **ACA**
  - Prohibits health plans from turning people down or charging them more because they have a pre-existing condition.

**Family Planning & Family Stress**

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**UChicago Medicine**

Comprehensive Cancer Center

**NCI**

Comprehensive Cancer Center

A Cancer Center Designated by the National Cancer Institute
Steps for Proper Genetic Counseling

1) Identification of candidates for testing
2) Patient education
3) Benefits and harms of genetic testing
4) Interpretation of results after testing
5) Discussion of management options
Step 4: Interpretation of Results

1) **Negative** genetic test for a disease may not completely rule out that disease.
   - If known mutation in family, this can be more informative.
   - If affected relatives were not tested, there is still familial risk.

2) **Positive** result may mean that patient is predisposed to developing a disease, though the actual degree of which may vary and is often less than 100% (penetrance).

3) **Variant of uncertain significance (VUS)** is currently uncertain for impact on health, more research is needed and it should be resolved over time.
GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED
Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

BREAST CANCER RISKSORE™: REMAINING LIFETIME RISK 49.2%
This level of risk is at or above 20% threshold for consideration of modified medical management. See riskScore™ Interpretation Section for more information.

CLINICAL HISTORY ANALYSIS: BASED ON THE CLINICAL HISTORY PROVIDED, MODIFIED MANAGEMENT GUIDELINES IDENTIFIED
Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

BREAST CANCER RISKSORE™
At or above 20%
THIS BREAST CANCER RISKSORE™ IS ASSOCIATED WITH THE FOLLOWING CANCER RISKS:

ELEVATED RISK: Female Breast

No clinically significant mutations were identified in this patient. However, based on personal/family history, the patient's cancer risks may still be increased over the general population. See information below.
Please see the Genetic Test Result for more details on any variant(s) detected in this patient, including variant classification information.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

TYRER-CUZICK BREAST CANCER RISK CALCULATION
REMAINING LIFETIME BREAST CANCER RISK: 27.6%  5-YEAR BREAST CANCER RISK: 5.6%
RESULT: NO PATHOGENIC VARIANTS IDENTIFIED

Variant(s) of Uncertain Significance identified.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>ZYGOSITY</th>
<th>VARIANT CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>c.4264C&gt;G (p.Pro1422Ala)</td>
<td>heterozygous</td>
<td>Uncertain Significance</td>
</tr>
</tbody>
</table>

About this test
This diagnostic test evaluates 84 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.
Result Sample #3:

A pathogenic mutation was identified in the BRCA1 gene.

Testing positive for a pathogenic variant (also called a mutation) in the BRCA1 gene means your risks of developing breast and ovarian cancers are greater than that of the average US woman. Your risk of pancreatic cancer is also increased by this mutation.

There have been many studies that show that mutations in the BRCA1 gene are linked to increased cancer risk. Research on this gene is ongoing. As additional information is gathered, risk estimates and associated cancers may change. If this happens, we will try to contact you.

<table>
<thead>
<tr>
<th>DETAILS</th>
<th>GENE</th>
<th>MUTATION</th>
<th>CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td>c.5266dupC (p.Gln1756Profs*74)</td>
<td>Pathogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternate name(s): g.41209082dupG, BIC: 5382insC, 5385insC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transcript: ENST00000357654</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zygosity: Heterozygous</td>
<td></td>
</tr>
</tbody>
</table>
Result Sample #3:

**Risk and Family Information**

Risk among US women with a BRCA1 mutation to develop specific cancers by different ages in their lives. The risk listed represents the maximum risk at that age.

- **Breast Cancer**
  - Age 30: 4%
  - Age 40: 24%
  - Age 50: 43%
  - Age 60: 56%
  - Age 70: 69%
  - Age 80: 81%

- **Ovarian Cancer**
  - Age 30: <1%
  - Age 40: 3%
  - Age 50: 21%
  - Age 60: 40%
  - Age 70: 59%
  - Age 80: 68%

**Increased Risk for Other Cancers**

In addition to increasing a woman’s risk for breast and ovarian cancers, mutations in the BRCA1 gene are known to increase the risk of developing pancreatic cancer.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk with BRCA1 Mutation*</th>
<th>Avg. US Woman†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>Elevated (3-5%)</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

*The risk of developing cancer by age 80.
†The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

**About the BRCA1 Gene**

The BRCA1 gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don’t work properly, cells can grow out of control, which can lead to cancer. The primary role of BRCA1 is repairing damaged DNA before a cell divides to make more copies of itself. BRCA1 works together with other genes such as BARD1, PALB2, and BRCA2 to direct the repair of the DNA damage.

**Impact of BRCA1 Mutations**

Like most genes, each person has two copies of the BRCA1 gene: one inherited from each parent. A mutation in a single copy of the BRCA1 gene inherited from either parent is known to increase risk of specific cancers (breast, ovarian, prostate, and pancreatic) over a lifetime.
Researchers identify genomic variants associated with complex diseases by comparing the genomes of individuals with and without those diseases.

The enormous amount of genomic data now available enables researchers to calculate which variants tend to be found more frequently in groups of people with a given disease. There can be hundreds or even thousands of variants per disease.

A polygenic risk score can only explain the relative risk for a disease.

The data used for generating a polygenic risk score comes from large scale genomic studies. These studies find genomic variants by comparing groups with a certain disease to a group without the disease.

https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores#three
Steps for Proper Genetic Counseling

1) Identification of candidates for testing
2) Patient education
3) Benefits and harms of genetic testing
4) Interpretation of results after testing
5) Discussion of management options
Interdisciplinary Teams for Positive Pts & High Risk Calculations
**NCCN Guidelines Version 1.2020**

**Genetic Testing Process**

### CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| ATM  | Increased risk of female breast cancer<sup>f</sup>  
- Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y<sup>g,h</sup>  
- RRM: Evidence insufficient, manage based on family history | Potential increase in ovarian cancer risk  
- RRSO: Evidence insufficient; manage based on family history |  
- Pancreatic  
- See PANC-A  
- Unknown or insufficient evidence for prostate cancer |

**Comments:** Counsel for risk of autosomal recessive condition in offspring. ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.

<table>
<thead>
<tr>
<th>BARD1</th>
<th>Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management</th>
<th>Unknown or insufficient evidence for ovarian cancer risk</th>
<th>Unknown or insufficient evidence for other cancers</th>
</tr>
</thead>
</table>
| BRCA1 | Increased risk of breast cancer  
- See BRCA Pathogenic Variant-Positive Management | Increased risk of ovarian cancer  
- See BRCA Pathogenic Variant-Positive Management | Pancreatic, Prostate  
- See BRCA Pathogenic Variant-Positive Management |
| BRCA2 | Increased risk of breast cancer  
- See BRCA Pathogenic Variant-Positive Management | Increased risk of ovarian cancer  
- See BRCA Pathogenic Variant-Positive Management | Pancreatic, Prostate, Melanoma  
- See BRCA Pathogenic Variant-Positive Management |

**Comment:** Counsel for risk of autosomal recessive condition in offspring.

| BRIP1 | Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management | Increased risk of ovarian cancer  
- Consider RRSO at 45–50 y | Unknown or insufficient evidence for other cancers |
|-------|-------------------------------------------------------------|------------------------------------------------|--------------------------------------------------|

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

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**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness\(^a\) starting at age 18 y.
- Clinical breast exam, every 6–12 mo,\(^a\) starting at age 25 y.
- Breast screening\(^b\)
  - Age 25–29 y, annual breast MRI\(^c\) screening with contrast\(^d\) (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI\(^c\) screening with contrast.
  - Age >75 y, management should be considered on an individual basis.
- For women with a BRCA pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described above.

- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.

- Recommend risk-reducing salpingo-oophorectomy (RRSO),\(^e\) typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with BRCA2 pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with BRCA1 pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with BRCA2 pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.

- Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, hormone replacement therapy, and related medical issues.

- Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be genespecific.

- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a BRCA1 pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the BRCA population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a BRCA1 pathogenic/likely pathogenic variant prior to surgery. Women who undergo hysterectomy at the time of RRSO are candidates for estrogen alone hormone replacement therapy, which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which is required when the uterus is left in situ (Chlebowski R, Rohan T, Manson J, et al. JAMA Oncol 2015;1:296-305).

- Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.

- For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician’s discretion starting at age 30–35 y.

- Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).

- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

Footnotes on BRCA-A

continued

BRCA-A

1 OF 2

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

https://www.nccn.org/
ACMG

- The American College of Medical Genetics and the American Society of Clinical Oncology recommend testing for BRCA1/2 mutations only when an individual has personal or family cancer history suggestive of inherited cancer susceptibility, the test can be adequately interpreted, and the results will aid in management.

ASBrS

- The American Society of Breast Surgeons recommends that genetic testing be made available to all patients with a personal history of breast cancer.

ACOG

- The American College of Obstetricians and Gynecologists recommends performing a hereditary cancer risk assessment and subsequent referral to a specialist in cancer genetics if necessary.

SGO

- The Society for Gynecologic Oncology recommends that individuals with a likelihood of inherited predisposition to cancer based on personal or family history should be offered genetic counseling.
Summary
Clinical Summary: Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer

| Population | Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations | Women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations |
| Recommendation | Assess with an appropriate brief familial risk assessment tool. | Do not perform routine risk assessment, genetic counseling, or genetic testing. |
| Grade: B | Grade: D |

Risk Assessment
Patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful BRCA1/2 mutations should be assessed using a familial risk assessment tool. The USPSTF found adequate evidence that these tools are accurate in identifying women with increased likelihood of BRCA1/2 mutations. Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of BRCAPRO. These tools should be used to guide referrals to genetic counseling.

Genetic Counseling
Genetic counseling about BRCA1/2 mutation testing should be done by trained health professionals, including suitably trained primary care providers. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful BRCA1/2 mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options.

Genetic Testing
Tests for BRCA1/2 mutations are highly sensitive and specific for known mutations. Testing for BRCA1/2 mutations should be done when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision making.

Treatment and Interventions
In general, women with harmful BRCA1/2 mutations are managed with a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.

Relevant USPSTF Recommendations
The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low risk for adverse medication effects. It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer. The USPSTF recommends against screening for ovarian cancer in women. This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (eg, BRCA1/2 mutations). The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.
Thank You

Genetics in Clinical Cancer Care: From Family Reunions to the Frontline of Developmental Therapeutics

April 17, 2020 to April 19, 2020