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GENETICS IN PRIMARY CARE

SARAH BAZZETTA, MMS, MAS, PA-C

PREVENTIVE ONCOLOGY
UChicago Medicine

Genetics in Clinical Cancer Care: From Family Reunions to the Frontline of Developmental Therapeutics
April 17, 2020 to April 19, 2020

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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

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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

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USPSTF

- 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*)

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USPSTF

- 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)

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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

- Common Cancer Panels
  High Penetrance Genes
  Moderate Penetrance Genes
  ****Increased risks of VUS & not-clearly actionable genes*

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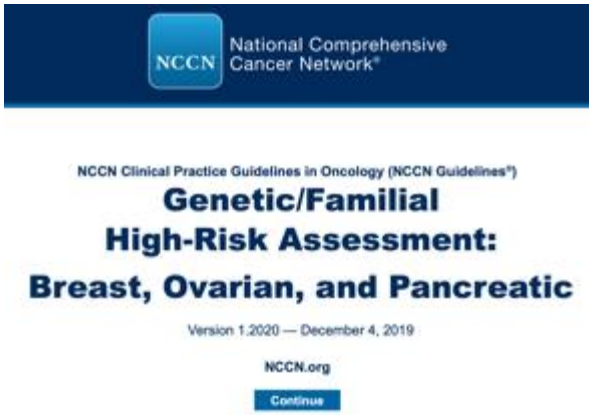

and management. The counselor should recommend genetic counseling and testing for at-risk relatives. Since some pathogenic or likely pathogenic variants are associated with rare autosomal recessive conditions (eg, Fanconi anemia is associated with *ATM, BRCA2, BRIP1,* and *PALB2* variants), testing of a partner of a carrier of a pathogenic or likely pathogenic variant may be considered to inform reproductive decision-making.[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.[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).[63] The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.[65]

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.[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*.[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*.[10,63,69-75] 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.[66,76,77] 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.[66,78]

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.[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.[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.[78] A management plan should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

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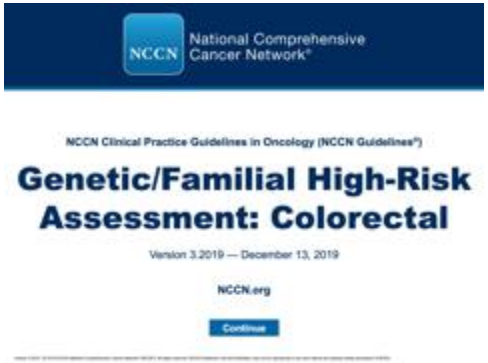
https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf



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NCCN Guidelines Version 3.2019
Genetic/Familial High-Risk Assessment: Colorectal

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MULTI-GENE TESTING

Table 1: Multi-Gene Testing Definitions

TERM	DEFINITION
Multi-gene panel	Laboratory test that includes testing for pathogenic variants of more than one gene.
Syndrome-specific panel	Panel that only tests for one syndrome (eg, LS, adenomatous polyposis).
Cancer-specific panel	Panel that tests for more than one gene associated with a specific type of cancer.
"Comprehensive" cancer panel	Panel that tests for more than one gene associated with multiple cancers or multiple cancer syndromes.
Actionable pathogenic variant	Pathogenic variant that results in a recommendation for a change in clinical management.
Variant of uncertain significance	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.[a,b]

Table 2: Pros and Cons of Multi-Gene Testing for Hereditary Colorectal Syndromes[e]

PROS	CONS
• More efficient testing when more than one gene may explain presentation and family history. • Higher chance of providing proband with possible explanation for cause of cancer. • Competitive cost relative to sequentially testing single genes.	• 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. • Higher chance of identifying variants of uncertain significance that are not actionable; reported rates of finding variants of uncertain significance range from 17%–38%. • 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.

[a] Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 2018;320:1266-1274.
[b] Slavin T, Van Tongeren L, Behrendt C, et al. Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. J Natl Cancer Inst 2018;110(10):1059-1066.
[e] Hall MJ, et al. Gene panel testing for inherited cancer risk. J Natl Compr Canc Netw 2014;12:1339-1346.

Continued

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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https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

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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. *BRCA*PRO (statistical model/associated software)

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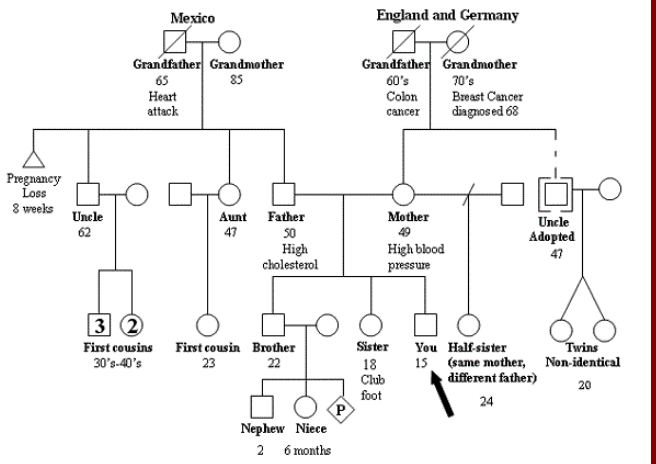
https://jamanetwork.com/journals/jama/fullarticle/2748515

Step 1: ID

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

- YOUNG
- RARE
- MULTIPLE CANCERS



Pass Waiting Room Time…

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Ontario Family History Tool

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

Table 1. Ontario Family History Assessment Tool[a]

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relatives	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset age, y	
20-29	6
30-39	4
40-49	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relatives	
Mother	7
Sibling	4
Second-/third-degree relative	3
Ovarian cancer onset age, y	
<40	6
40-60	4
>60	2
Prostate cancer onset	
Age <50 y	1
Colon cancer onset	
Age <50 y	1
Family total	
Referral[b]	≥10

[a] See Gilpin et al,[15] Oros et al,[16] Panchal et al,[17] Parmigiani et al.[18]

[b] Referral with score of 10 or greater corresponds to doubling of lifetime risk for breast cancer (22%).

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Manchester Scoring System

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

Table 2. Manchester Scoring System[a,b]

Risk Factor (Age at Onset for Relative in Direct Lineage)	*BRCA1* Score	*BRCA2* Score
Female breast cancer, y		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1
Male breast cancer, y		
<60	5[c]	8[d]
≥60	5[c]	5[d]
Ovarian cancer, y		
<60	8	5
≥60	5	5
Pancreatic cancer		
Any age	0	1
Prostate cancer, y		
<60	0	2
≥60	0	1
Total individual genes	10	10
Total for combined = 15		

Abbreviation: *BRCA*, breast cancer susceptibility gene.

[a] See Oros et al,[16] Parmigiani et al,[18] Antoniou et al,[19] Barcenas et al,[20] Evans et al.[21]

[b] 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.

[c] If testing for *BRCA2*.

[d] If testing for *BRCA1*.

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Referral Screening Tool

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

Table 3. Referral Screening Tool[a,b]

History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist		
Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on same side of family		
Male breast cancer at any age in any relative		
Jewish ancestry		

[a] See Bellcross et al.[22]

[b] Referral if 2 or more checks in table.

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Pedigree Assessment Tool

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

Table 4. Pedigree Assessment Tool[a,b]

Risk Factor	Score for Every Family Member With Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4
Total	

[a] See Hoskins et al,[23] Teller et al.[24]

[b] Score 8 or greater is the optimal referral threshold.

7-Question Family History Tool

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

Table 5. Seven-Question Family History Screening[a,b]

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

[a] See Ashton-Prolla et al,[25] Fischer et al.[26]

[b] One positive response initiates referral.

**Same side of family

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International Breast Cancer Intervention Study Model

JAMA Network

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

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

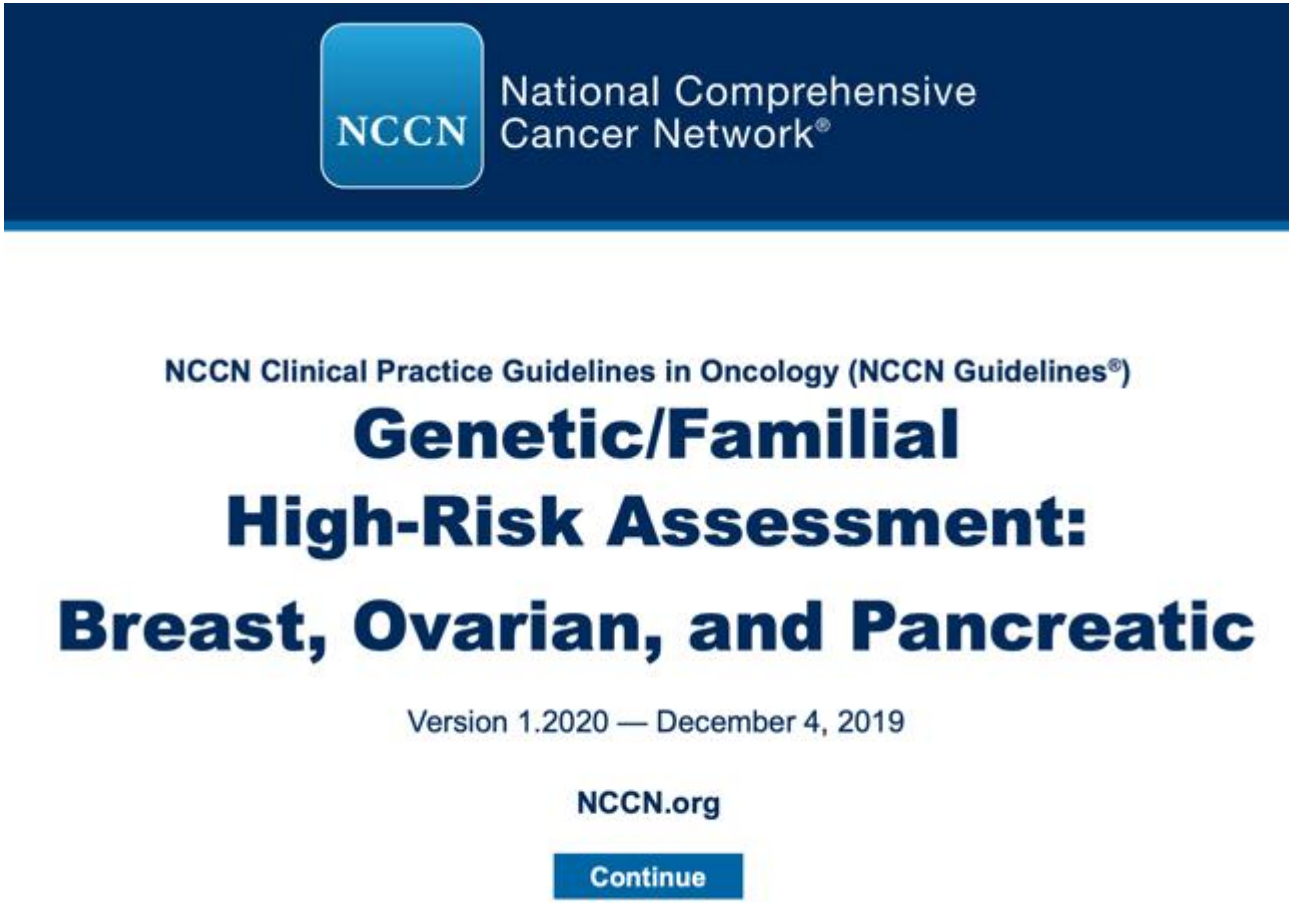
Table 6. International Breast Cancer Intervention Study Model[a,b]

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

[a] See Fischer et al,[26] Cuzick.[27]

[b] 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/



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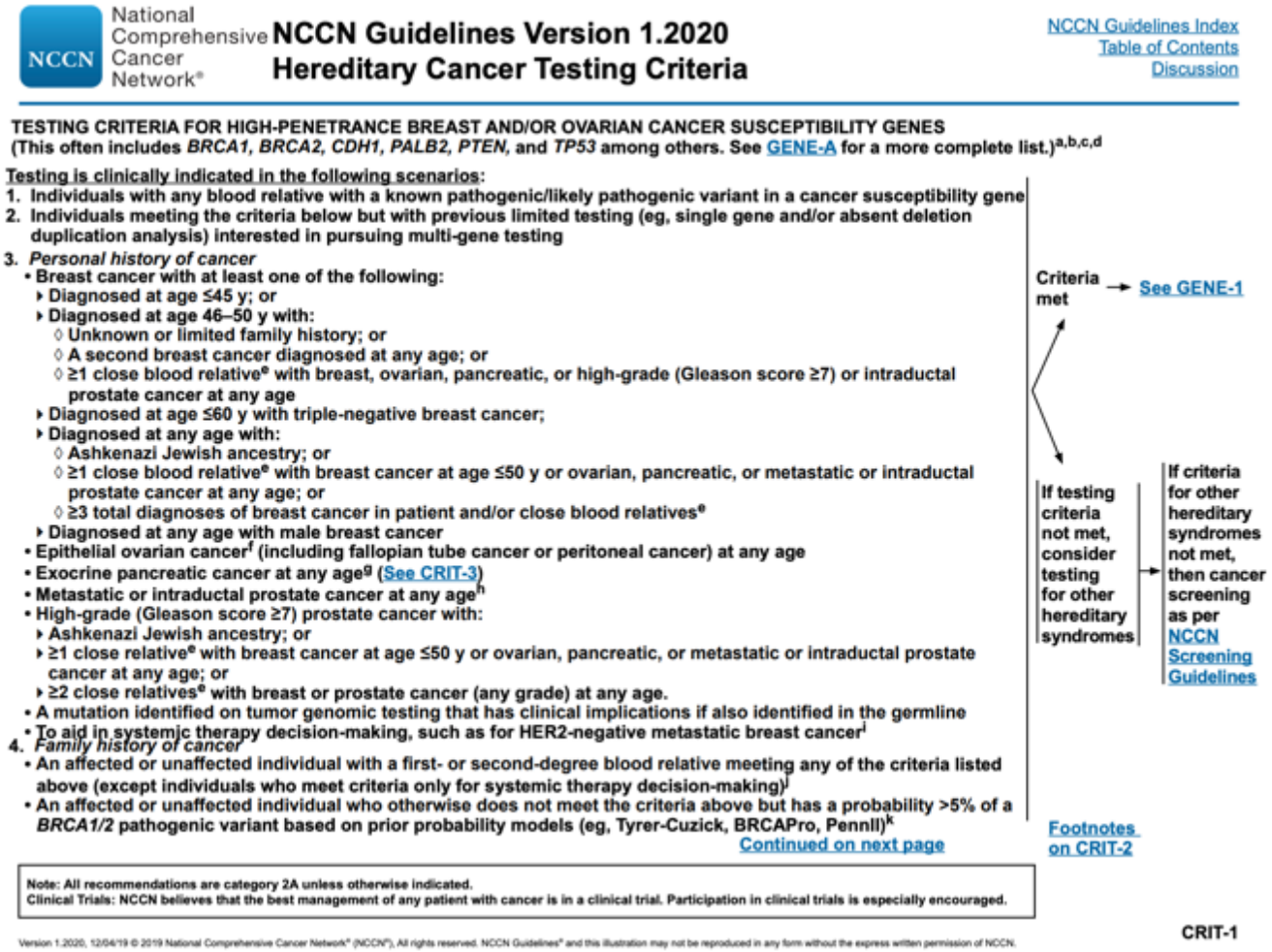

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Hereditary Cancer Testing Criteria

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TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This often includes *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
3. *Personal history of cancer*
   - Breast cancer with at least one of the following:
     - Diagnosed at age ≤45 y; or
     - Diagnosed at age 46–50 y with:
       - Unknown or limited family history; or
       - A second breast cancer diagnosed at any age; or
       - ≥1 close blood relative[e] with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age
     - Diagnosed at age ≤60 y with triple-negative breast cancer;
     - Diagnosed at any age with:
       - Ashkenazi Jewish ancestry; or
       - ≥1 close blood relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
       - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[e]
     - Diagnosed at any age with male breast cancer
   - Epithelial ovarian cancer[f] (including fallopian tube cancer or peritoneal cancer) at any age
   - Exocrine pancreatic cancer at any age[g] (See CRIT-3)
   - Metastatic or intraductal prostate cancer at any age[h]
   - High-grade (Gleason score ≥7) prostate cancer with:
     - Ashkenazi Jewish ancestry; or
     - ≥1 close relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
     - ≥2 close relatives[e] with breast or prostate cancer (any grade) at any age.
   - A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
   - To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer[i]
4. *Family history of cancer*
   - An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making)[j]
   - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, PennII)[k]

Continued on next page

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Footnotes on CRIT-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.

CRIT-1

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TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES (continued)
(This often includes *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

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[l]**
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 (eg, Tyrer-Cuzick, BRCAPro, PennII)[b]**

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

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

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[b] Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (eg, *CDH1* and *TP53* given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (eg, monoallelic *MUTYH*).
[c] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.
[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[e] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. (See EVAL-B)
[f] *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and PJS or Sertoli-Leydig tumors and DICER1-related disorders.
[g] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly aggressive and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (See NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, Yu J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390. Golan T, Hammel P, Reni M, et al. N Engl J Med 2019;381:317-327.)
[h] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes.
[i] Eg, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer. See the relevant NCCN treatment guidelines for further details.
[j] This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable mutations and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility. For probands with pancreatic cancer, only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.
[k] The approximate 5% threshold for probability of carrying *BRCA1/2* pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other than *BRCA1* and *BRCA2* are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with mutations in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. These models are only validated for *BRCA1/2*.
[l] Testing for three founder mutations of *BRCA1/2* may be offered to unaffected men and women as early as age 18–25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial.

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.

CRIT-2

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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

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https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer

"3-2-1 rule"

(3 affected members, 2 generations, 1 under age 50)

Amsterdam II criteria for Lynch syndrome

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)
One should be a first-degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, et al. Gastroenterology 1999; 116:1453.

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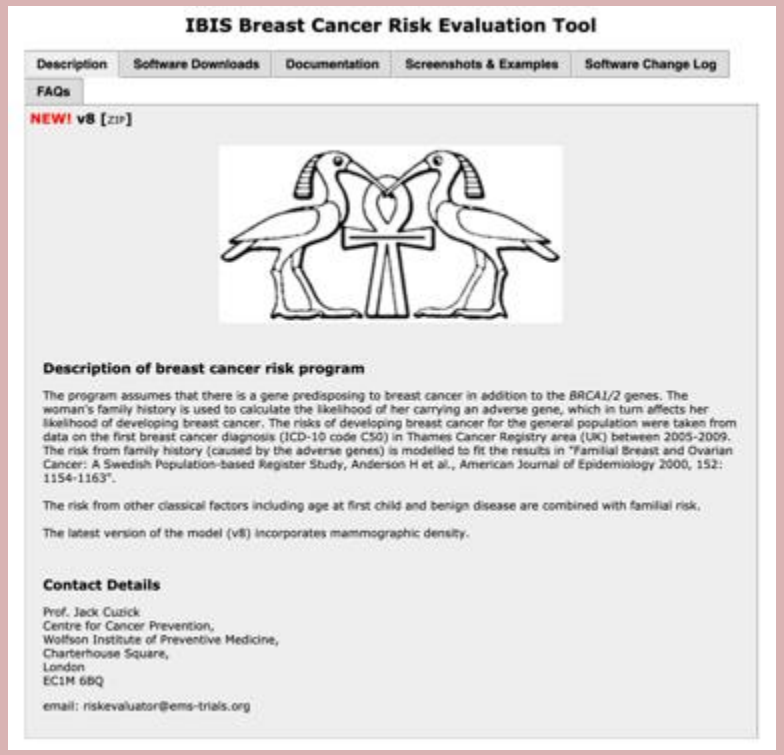
Free Online Calculation Tool

www.ems-trials.org/riskevaluator/



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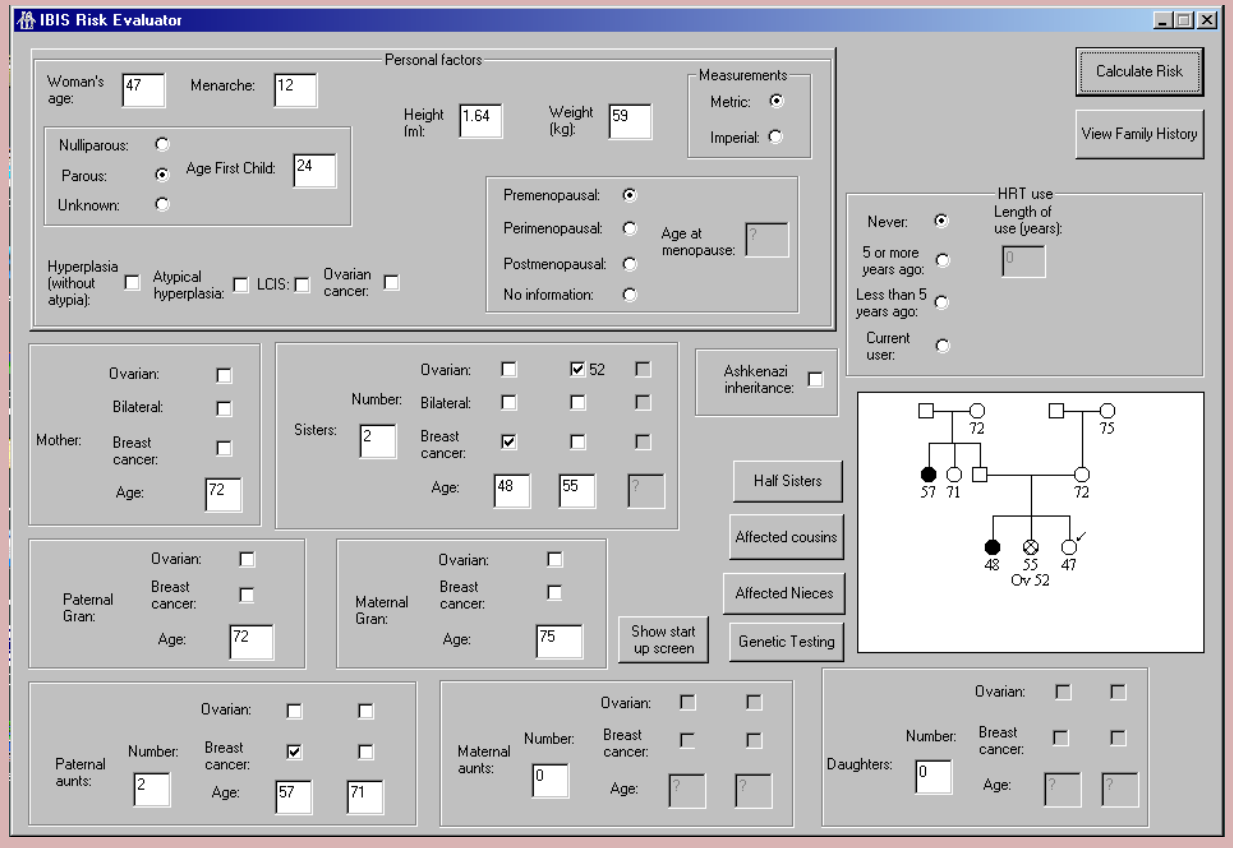

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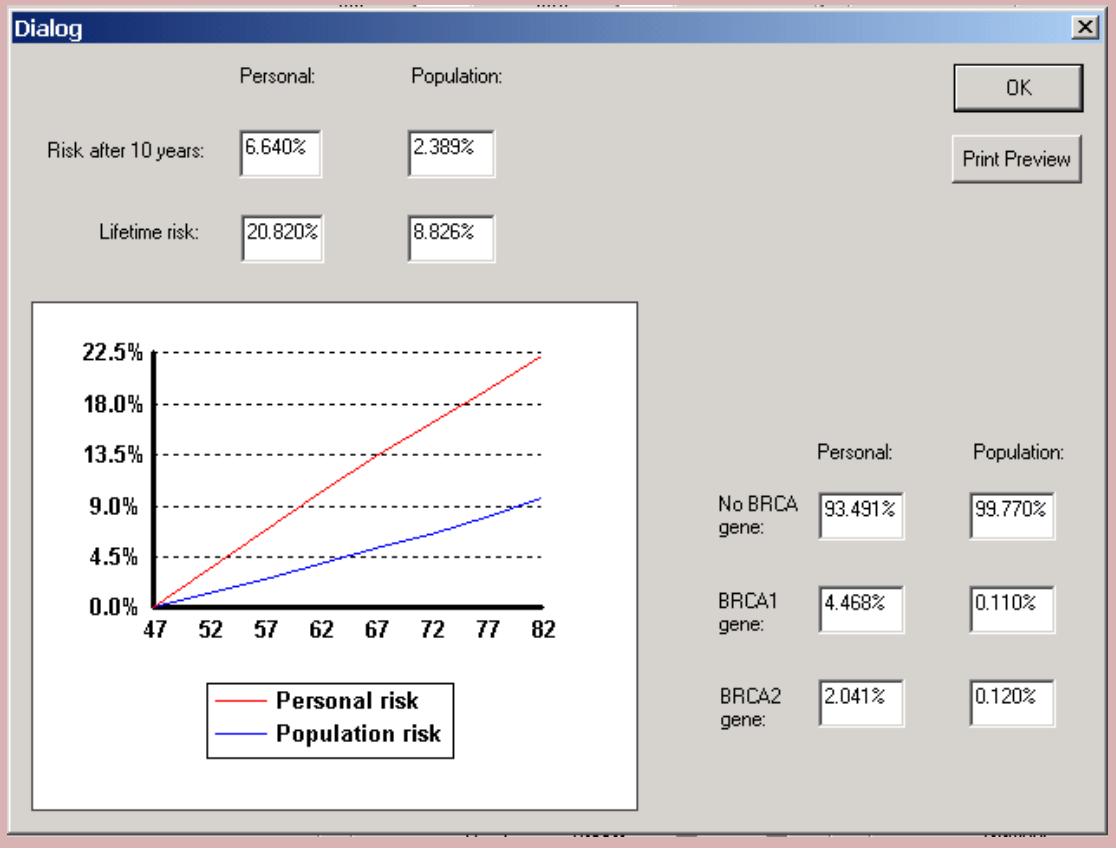

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STEP 2: PATIENT EDUCATION

I, _____, request and permit Invitae to analyze the gene(s) indicated on the test requisition form in: ◯ 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 also 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 implication 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 scientific 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 interpretation and release of 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 only 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/10002328.
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.

10. I will be offered genetic counseling with a geneticist, genetic counselor or other qualified healthcare provider who can answer questions, provide information and advise about alternatives before and after having this test. Further testing or additional physician consults may be warranted.
11. My (my child's) data and personal information will be stored and protected in strict confidence complying with regulatory requirements (e.g. HIPAA and equivalent protections), and acknowledge that I have read and understand Invitae's Privacy Policy and Notice of Privacy Practices. My (my child's) individually identifiable health information (i.e., "Protected Health Information" under HIPAA) will NOT be used in FOR PROFIT research without my additional, explicit consent.
12. Because the understanding of genetic information will improve over time, Invitae may notify me of clinical updates related to my (my child's) genetic profile (in consultation with my primary clinician as indicated). I may request additional notifications and resources relevant to my genetic profile by creating an account at www.invitae.com/patients.
13. I have the right to receive a copy of this consent form.
14. New York residents only: My (or my child's) sample shall be destroyed no more than 60 days after the sample was taken or at the end of the testing process, whichever occurs later, unless I agree otherwise by logging in to the Invitae patient portal (www.invitae.com/patients/signin) and navigating to Account Settings > Preferences. Samples will not be used for research or quality control purposes without my expressed written consent which can be provided by logging in to the Invitae patient portal (www.invitae.com/patients/signin) and navigating to Account Settings > Preferences.

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.

Patient signature	Date
Patient name (please print)	Email address
Signature of parent/guardian, if patient is a minor	Date
Parent's/guardian's name (please print)	Email address

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.

Healthcare provider signature	Date

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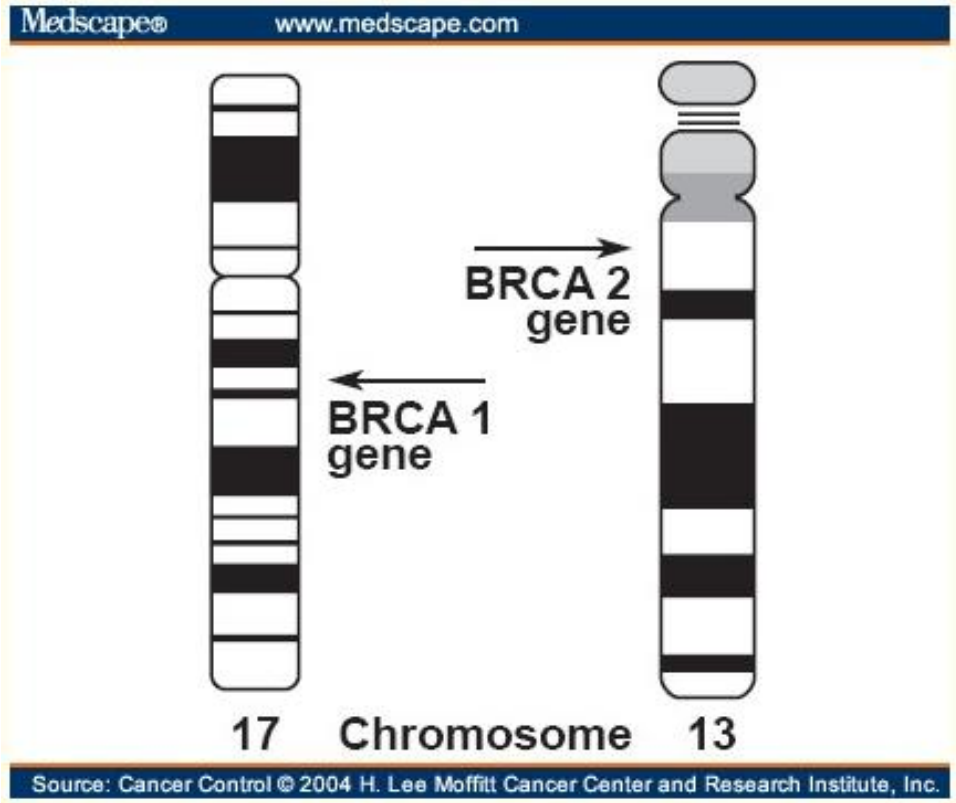
Important to be able to explain mechanisms: Tumor Suppressor Genes



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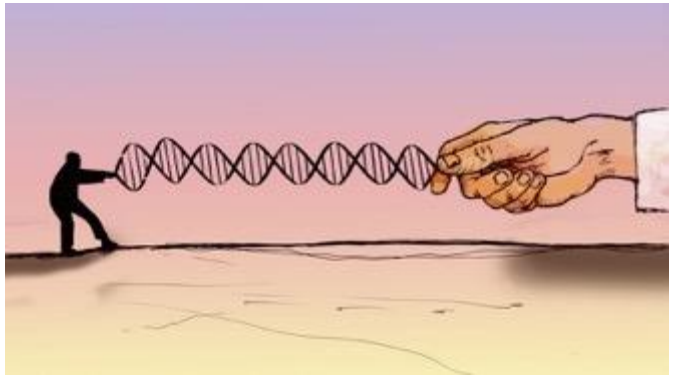
Step 3: Risks & Benefits

- **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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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.

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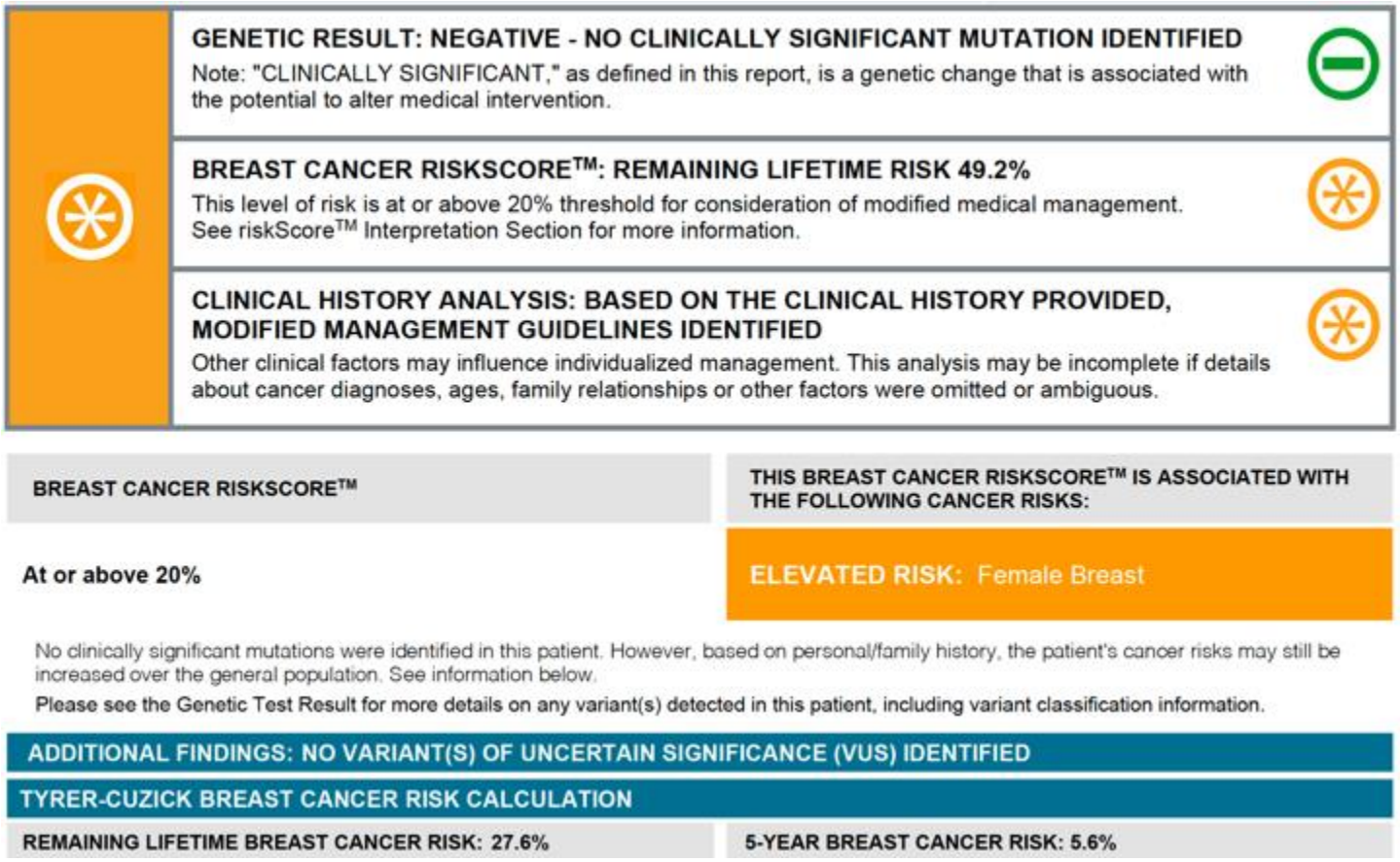
Result Sample #1:



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

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Result Sample #2:

RESULT: NO PATHOGENIC VARIANTS IDENTIFIED

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ALK	c.4264C>G (p.Pro1422Ala)	heterozygous	Uncertain Significance

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.

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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.

DETAILS

GENE	MUTATION	CLASSIFICATION
BRCA1	c.5266dupC (p.Gln1756Profs*74) *Alternate name(s): g.41209082dupG, BIC: 5382insC, 5385insC* *Transcript: ENST00000357654* *Zygosity: Heterozygous*	Pathogenic

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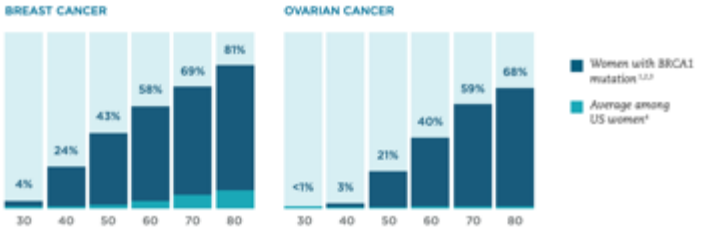
Result Sample #3:

Risk and Family Information

RISK BY AGE WITH A *BRCA1* MUTATION

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.



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.

CANCER TYPE	RISK WITH *BRCA1* MUTATION	AVG. US WOMAN
Pancreatic	Elevated (3-5%)	< 1%

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

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.

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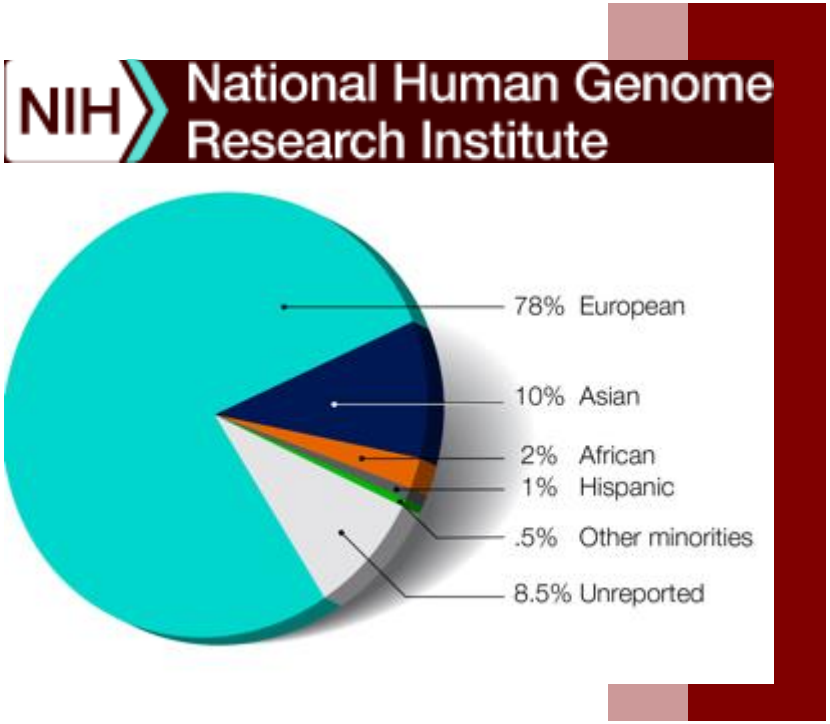
Genetics is Rapidly Evolving: Polygenic Risk Scores

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

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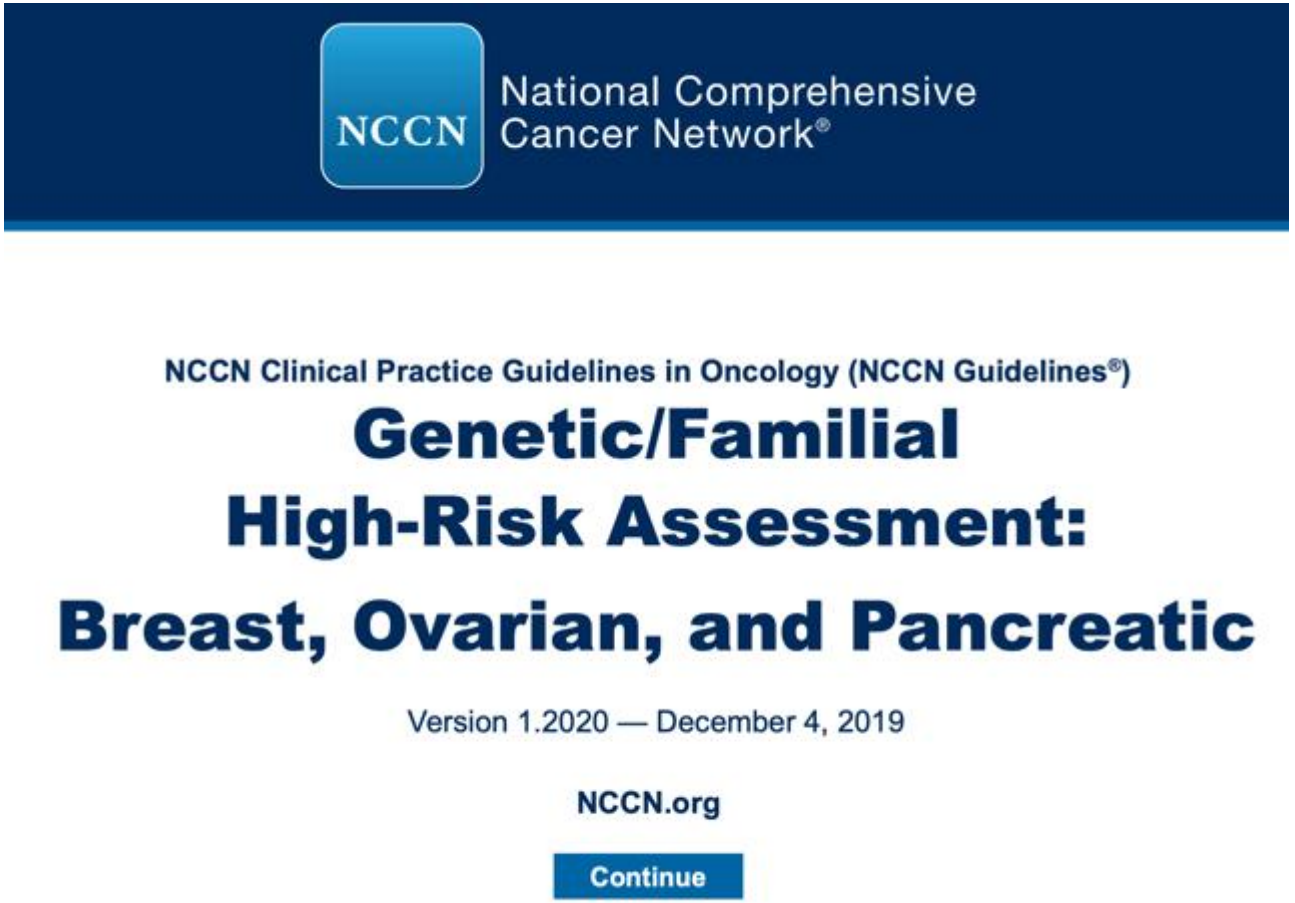
Interdisciplinary Teams for Positive Pts & High Risk Calculations

https://www.nccn.org/



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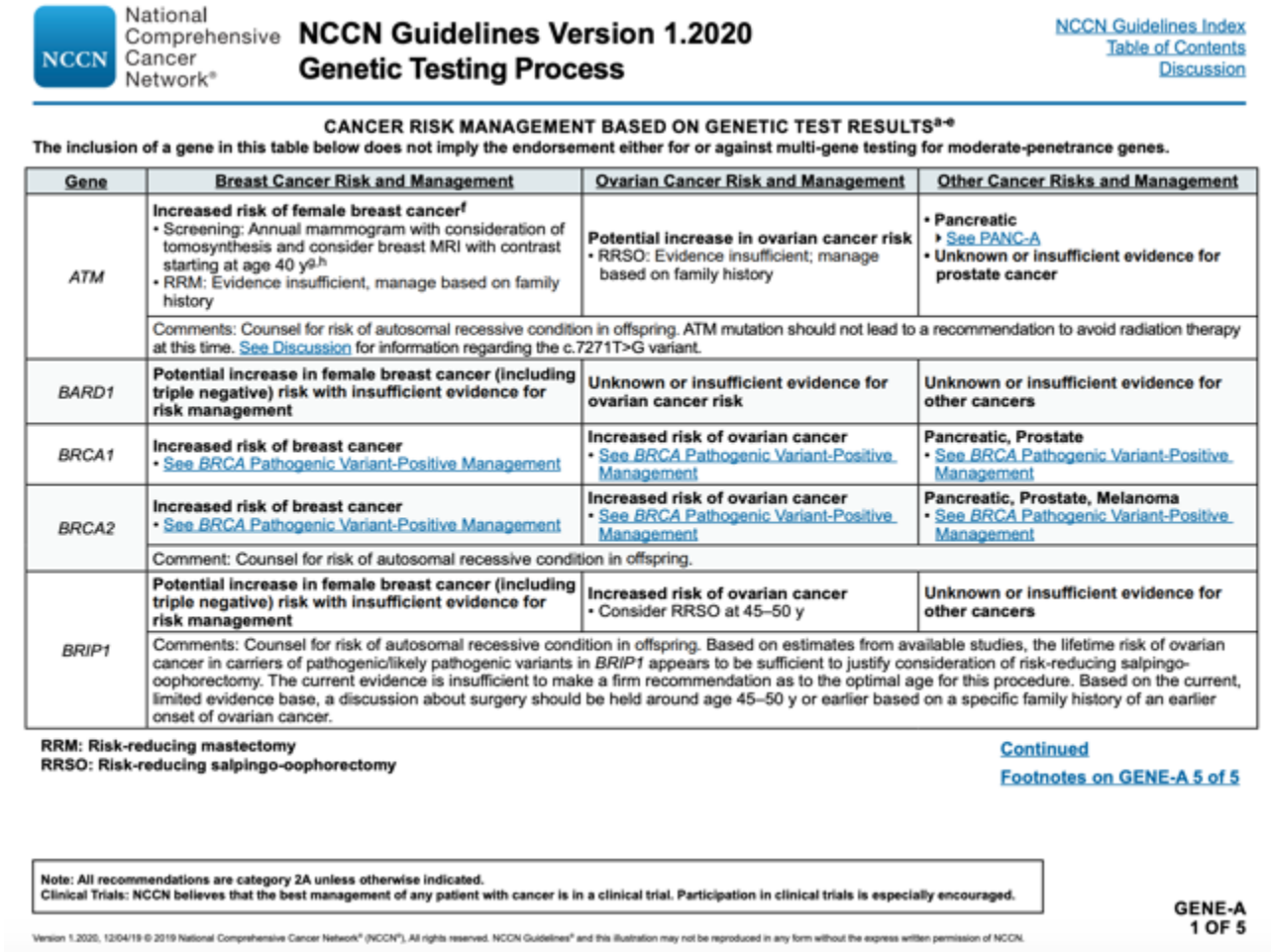

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NCCN Guidelines Version 1.2020
Genetic Testing Process

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

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.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • 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.		
BARD1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Unknown or insufficient evidence for ovarian cancer risk**	**Unknown or insufficient evidence for other cancers**
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**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

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

Continued
Footnotes on GENE-A 5 of 5

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.

GENE-A
1 OF 5

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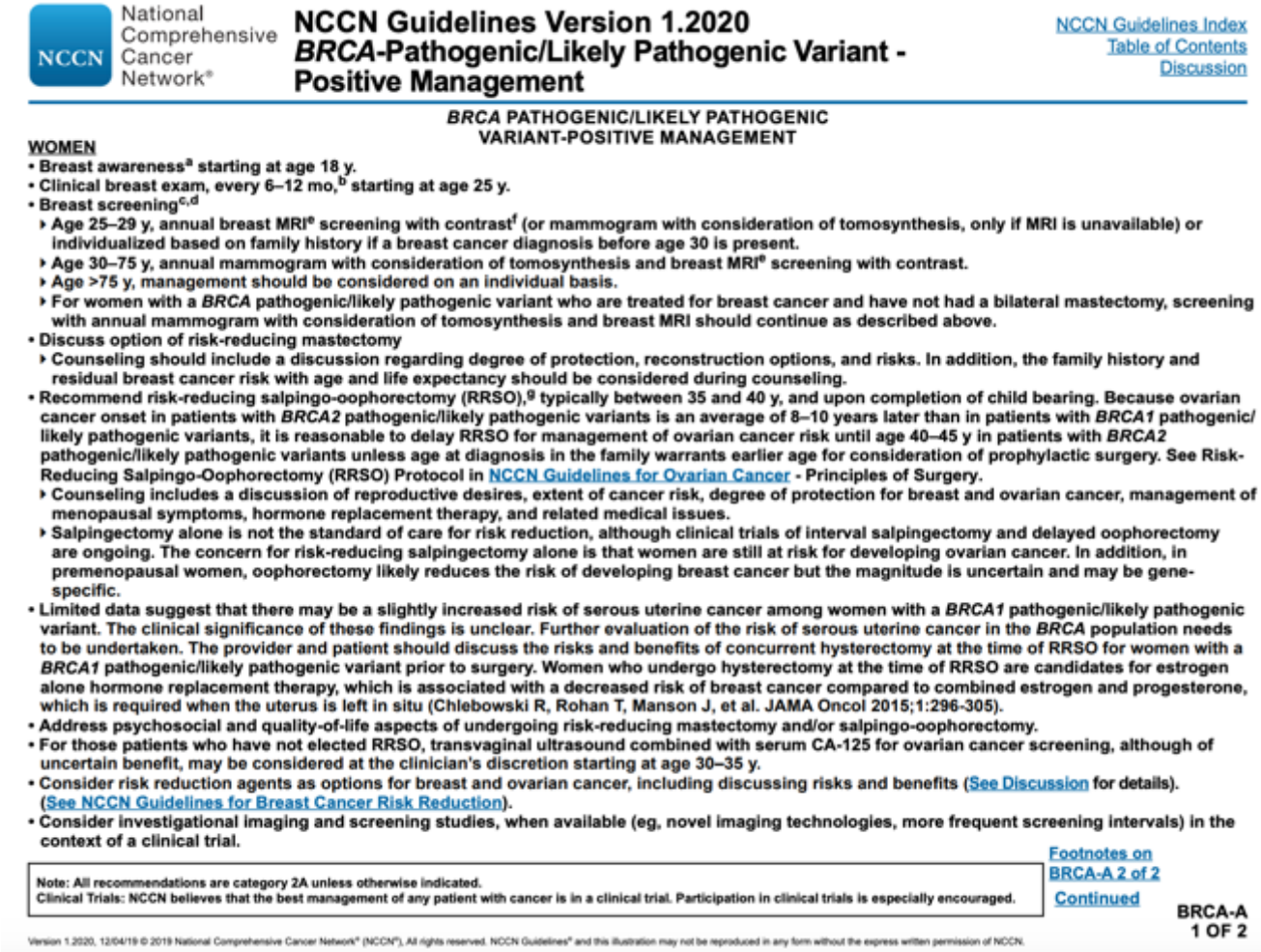

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NCCN Guidelines Version 1.2020
BRCA-Pathogenic/Likely Pathogenic Variant - Positive Management

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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,[b] starting at age 25 y.
- Breast screening[c,d]
  - Age 25–29 y, annual breast MRI[e] screening with contrast[f] (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[e] 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),[g] 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 gene-specific.
- 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.

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.

Footnotes on BRCA-A 2 of 2
Continued

BRCA-A 1 OF 2

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- ACMG
  - The American College of Medical Genetics and the American Society of Clinical Oncology recommend testing for *BRCA*1/2 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.

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Summary

https://uspreventiveservicestaskforce.org/home/getfilebytoken/y3mQMyN2Y8mxKvPPXjM6kV

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.** **Grade: B**	**Do not perform routine risk assessment, genetic counseling, or genetic testing.** **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.

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