Genetic Cancer Risk Assessment

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Disclosure

Presenter has no financial disclosures

Objectives

- Differentiate germline genetic testing from other genetic testing
- Review patient experience during a genetic cancer risk assessment (GCRA)
- Discuss implications of testing including costs and discrimination concerns
- Discuss direct to consumer testing
- Review oncology genetic case studies

Help prepare you to answer questions your patients may have about their personal/family history or oncology genetic testing

Germline

- **Also known as predictive or inherited testing**
- **DNA changes present at birth that increase lifetime risks for cancers. Some mildly above average, others markedly elevated**

Somatic

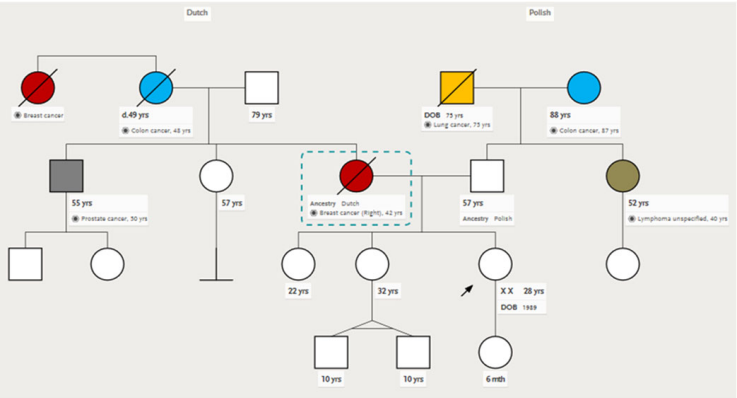
- When cells become cancerous, they develop genetic changes that cause abnormal growth. These genetic changes, that occur after you are born and throughout life are known as somatic mutations
- Also known as acquired mutations or tumor testing
- Becoming one of the fastest growing area of cancer care

Genetic Cancer Risk Assessment

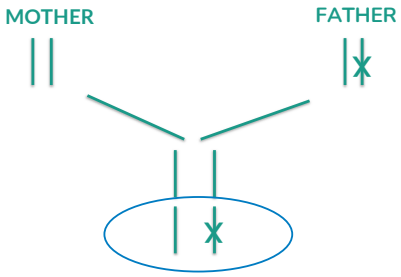
3 generational pedigree

- 1st degree- parents, siblings, children
- 2nd degree- grandparents, aunts/uncles, nieces/nephews, half sibling
- 3rd degree- 1st cousins

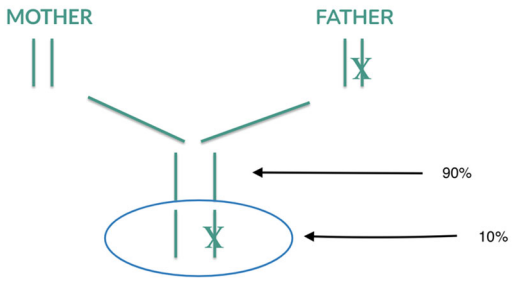
Those with and without cancers, including current ages, ages deceased, and other factors such as hysterectomy status and colon polyp count.

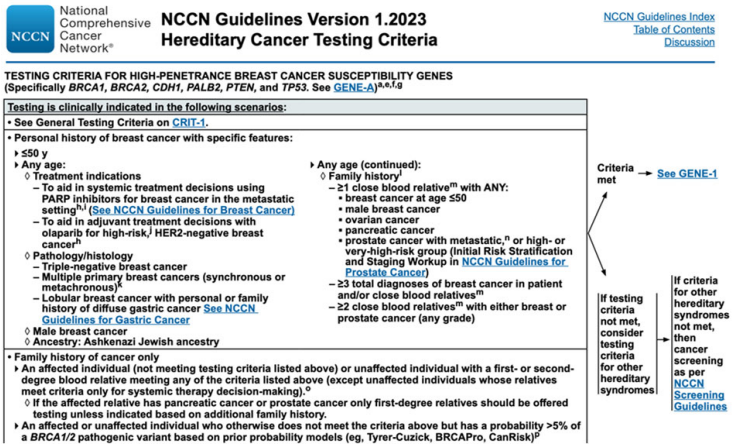


Patient Education



Patient Education





National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Hereditary Cancer Testing Criteria

NCCN Guidelines Index | Table of Contents | Discussion

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,e,f,g]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[h,i] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[j] HER2-negative breast cancer[h]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[k]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer See NCCN Guidelines for Gastric Cancer
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - Family history[l]
      - ≥1 close blood relative[m] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[n] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
      - ≥2 close blood relatives[m] with either breast or prostate cancer (any grade)
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[o]
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - 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, CanRisk)[p]

Criteria met → See GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes

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

Family History Red Flags

- Male breast cancers
- Breast cancers <50 yo
- Personal/family hx colon cancer
- Any personal/family member ovarian cancer
- Personal or 1st degree relative with pancreatic cancer
- Metastatic or high grade prostate cancers
- Multiple family members with ovarian, breast, prostate, pancreatic cancers
- Multiple family members with colon, uterine, gastric, pancreatic
- >10 lifetime count colon polyps
- Young cancers
  - Uterine <50

*** Anything that sounds inordinate, makes you suspicious, or the patient is concerned about*

Informed Consent/GINA

- Genetic Information Non Discrimination Act
  - Federal law signed in 2008
  - Protects against discrimination by health insurers and employers
  - Does NOT protect against discrimination by private life , long term care, or disability insurance policies taken out after testing

*** They can never be denied health insurance coverage or employment*

GenomicWorld.org

Costs

- Private Insurance:
  - If guidelines and deductible met often usually no or low cost for testing. Most pay less than $100. If deductible not met costs may be more but self pay option is available.
- Medicare:
  - Will cover if patient is affected. Some labs offer no charge testing to Medicare patients.
- Medicaid:
  - Covers cost if patient meets guidelines
- Self pay:
  - $250

- *Labs offer generous patient assistance programs*
- *Benefits investigations done by most labs to give patients idea of any costs*
- *Most patients pay $100 or less*

Media Coverage

My Medical Choice

By ANGELINA JOLIE MAY 14, 2013

LOS ANGELES

MY MOTHER fought cancer for almost a decade and died at 56. She held out long enough to meet the first of her grandchildren and to hold them in her arms. But my other children will never have the chance to know her and experience how loving and gracious she was.

We often speak of "Mommy's mommy," and I find myself trying to explain the illness that took her away from us. They have asked if the same could happen to me. I have always told them not to worry, but the truth is I carry a "faulty" gene, BRCA1, which sharply increases my risk of developing breast cancer and ovarian cancer.

My doctors estimated that I had an 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer, although the risk is different in the case of each woman.

Direct to Consumer Testing

Hereditary Cancer Test

Learn your risk for common hereditary cancers and how you can use that information.

Buy Color $249

Discounted pricing available for current clients. Learn more

23andMe

ancestry

FDA NEWS RELEASE

FDA authorizes, with special controls, direct-to-consumer test that reports three mutations in the BRCA breast cancer genes

Test only reports 3 out of more than 1,000 known BRCA mutations and negative result doesn't rule out increased cancer risk

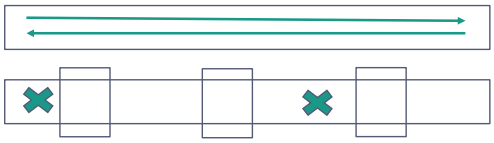
For Immediate Release: March 06, 2018

The U.S. Food and Drug Administration today authorized the Personal Genome Service Genetic Health Risk (GHR) Report for BRCA1/BRCA2 (Selected Variants). It is the first direct-to-consumer (DTC) test to report on three specific BRCA1/BRCA2 breast cancer gene mutations that are most common in people of Ashkenazi (Eastern European) Jewish descent. These three mutations, however, are not the most common BRCA1/BRCA2 mutations in the general population.

The test analyzes DNA collected from a self-collected saliva sample, and the report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The test only detects three out of more than 1,000 known BRCA mutations. This means a negative result does not rule out the possibility that an individual carries other BRCA mutations that increase cancer risk.

23andMe Will Now Test for BRCA Breast-Cancer Genes

It's the first FDA-authorized genetic-cancer-risk test available without a doctor's note.



Case #1

41 year old female presents to genetics after recently being diagnosed with right triple negative breast cancer found via first screening mammogram.

No prior history of cancer, breast disease, or concerns.

Denied palpating or skin changes.

Mother and father both alive, in 60s with no cancers.

Numerable aunts and uncles on both sides, also without cancers.

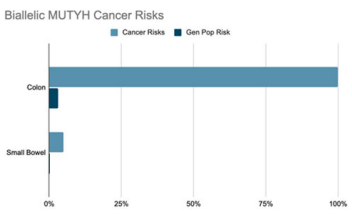
Patient has 3 children, ages 10, 6, & 2.

Summary

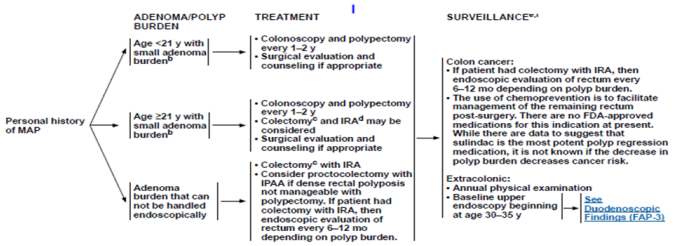
Positive result. One Pathogenic variant and one Likely Pathogenic variant identified in MUTYH.

Clinical Summary

- A Pathogenic variant, c.536A>G (p.Tyr179Cys), and a Likely Pathogenic variant, c.691-1G>A (Splice acceptor), were identified in MUTYH. These variants are on opposite chromosomes.
  - The MUTYH gene is associated with autosomal recessive MUTYH-associated polyposis (MAP) (MedGen UID: 332993). Additionally, the MUTYH gene has preliminary evidence supporting a correlation with breast cancer (PMID: 19732775, 21952991) and several other cancer types (PMID: 19732775, 21171015, 21952991).
  - This result is consistent with a predisposition to, or diagnosis of, MUTYH-associated polyposis (MAP).
  - MAP is characterized by adult-onset multiple colorectal adenomas and increased colorectal cancer (CRC) risk. Lifetime risk for CRC is estimated at 43% to almost 100% in the absence of timely surveillance (PMID: 23035301, 19620482). CRC has been reported in some individuals with homozygous MUTYH variants in the absence of polyposis. Duodenal adenomas are found in 17-25% of individuals with MAP (PMID: 23035301). An increased risk of extraintestinal malignancies such as ovarian, bladder, breast, endometrial, skin and thyroid cancers has also been reported (PMID: 23035301, 19732775, 17956577, 21952991). Clinical management guidelines for MAP can be found at www.nccn.org.
  - It is likely that one variant was inherited from each parent. When two parents each carry a Pathogenic variant, their chance of having an affected child is 25%. Other relatives may also be carriers. Testing for these variants is available.



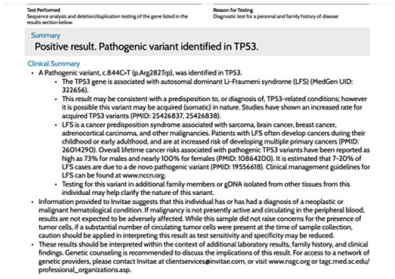
Invitae Lab



Case Study #2

27 year old male. Hx leukemia at age 6. Treated with chemotherapy with good response. Reports overall good health until recently. Began feeling "pressure" in his stomach. Imaging showed mass which was biopsied and found to be a abdominal sarcoma.

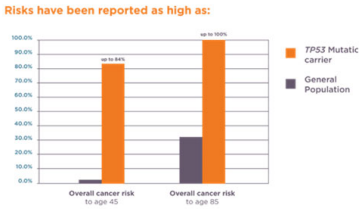
No significant family hx of cancer. Both parents alive and well. 2 daughters ages 6 & 4.



Positive result. Pathogenic variant identified in TP53.

Clinical Summary

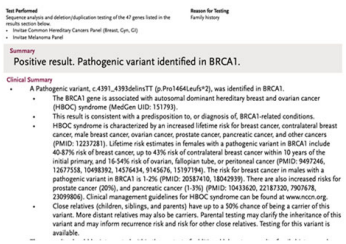
- A Pathogenic variant, c.844C>T (p.Arg282Trp), was identified in TP53.
  - The TP53 gene is associated with autosomal dominant Li-Fraumeni syndrome (LFS) (MedGen UID: 3226561).
  - This result may be consistent with a predisposition to, or diagnosis of, TP53-related conditions; however it is possible this variant may be acquired (somatic) in nature. Studies have shown an increased rate for acquired TP53 variants (PMID: 25426837, 25426838).
  - LFS is a cancer predisposition syndrome associated with sarcoma, brain cancer, breast cancer, adrenocortical carcinoma, and other malignancies. Patients with LFS often develop cancers during their childhood or early adulthood, and are at increased risk of developing multiple primary cancers (PMID: 26014290). Overall lifetime cancer risks associated with pathogenic TP53 variants have been reported as high as 73% for males and nearly 100% for females (PMID: 10864202)). It is estimated that 7-20% of LFS cases are due to a de novo pathogenic variant (PMID: 19556618). Clinical management guidelines for LFS can be found at www.nccn.org.
  - Testing for this variant in additional family members or gDNA isolated from other tissues from this individual may help clarify the nature of this variant.
- Information provided to Invitae suggests that this individual has or has had a diagnosis of a neoplastic or malignant hematological condition. If malignancy is not presently active and circulating in the peripheral blood, results are not expected to be adversely affected. While this sample did not raise concerns for the presence of tumor cells, if a substantial number of circulating tumor cells were present at the time of sample collection, caution should be applied in interpreting this result as test sensitivity and specificity may be reduced.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.med.sc.edu/professional_organizations.asp.



Case #3

50 year old female presents at the request of her primary care provider to assess genetic risks based on significant family hx of cancer. Has no personal cancer history. Reports overall good health. Denies any breast concerns. Recent mammogram revealed no abnormalities. Denies any gynecological concerns. No recent gynecological evaluation or imaging. Has had a recent colonoscopy w/ no polyps.

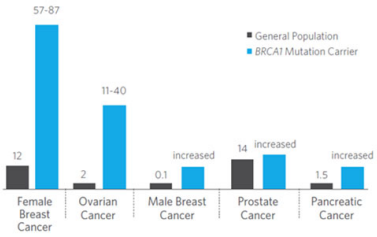
Family hx includes multiple females with breast and ovarian cancers on her paternal side. 3 paternal aunts with breast cancer, including 2 before age 45 and an aunt and a cousin with ovarian cancer. No family members have had genetic testing to her knowledge.



Positive result. Pathogenic variant identified in BRCA1.

Clinical Summary

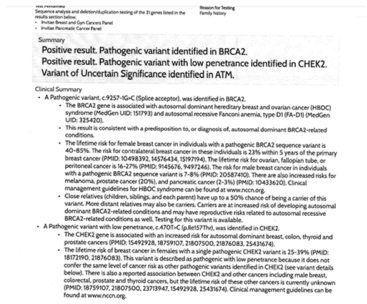
- A Pathogenic variant, c.4391_4393delinsTT (p.Pro1464Leufs*2), was identified in BRCA1.
  - The BRCA1 gene is associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome (MedGen UID: 151793).
  - This result is consistent with a predisposition to, or diagnosis of, BRCA1-related conditions.
  - HBOC syndrome is characterized by an increased lifetime risk for breast cancer, contralateral breast cancer, male breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and other cancers (PMID: 12237281). Lifetime risk estimates in females with a pathogenic variant in BRCA1 include 40-87% risk of breast cancer, up to 43% risk of contralateral breast cancer within 10 years of the initial primary, and 16-54% risk of ovarian, fallopian tube, or peritoneal cancer (PMID: 9497246, 12677558, 10498392, 14576434, 9145676, 15197194). The risk for breast cancer in males with a pathogenic variant in BRCA1 is 1-2% (PMID: 20587410, 18042939). There are also increased risks for prostate cancer (20%), and pancreatic cancer (1-3%) (PMID: 10433620, 22187320, 7907678, 23099806). Clinical management guidelines for HBOC syndrome can be found at www.nccn.org.
  - Close relatives (children, siblings, and parents) have up to a 50% chance of being a carrier of this variant. More distant relatives may also be carriers. Parental testing may clarify the inheritance of this variant and may inform recurrence risk and risk for other close relatives. Testing for this variant is available.



Case #4

61 year old patient presents to clinic today at urging of PCP to evaluate significant family hx of cancer. Reports overall good health. Due to strong family hx of cancer and cardiac events follows vegetable rich diet, stress management, and stays active 6-7 days a week. Mammo earlier this year negative per report. Retains ovaries and uterus with no complaints. Colonoscopy at 50 and 60 with no polyps.

Family history includes a sister deceased from breast cancer at age 48, mother deceased from from ovarian cancer at 55, multiple aunts and cousins with "cancers" on maternal side, believes some uncles with prostate cancers as well. Limited knowledge due to geography and/or estrangement.



Positive result. Pathogenic variant identified in BRCA2.
Positive result. Pathogenic variant with low penetrance identified in CHEK2.
Variant of Uncertain Significance identified in ATM.

Clinical Summary

- A Pathogenic variant, c.9257-1G>C (Splice acceptor), was identified in BRCA2.
  - The BRCA2 gene is associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome (MedGen UID: 155793) and autosomal recessive Fanconi anemia, type D1 (FA-D1) (MedGen UID: 325420).
  - This result is consistent with a predisposition to, or diagnosis of, autosomal dominant BRCA2-related conditions.
  - The lifetime risk for female breast cancer in individuals with a pathogenic BRCA2 sequence variant is 40-85%. The risk for contralateral breast cancer in these individuals is 23% within 5 years of the primary breast cancer (PMID: 10498392, 14576434, 15197194). The lifetime risk for ovarian, fallopian tube, or peritoneal cancer is 16-27% (PMID: 9145676, 9497246). The risk for male breast cancer in individuals with a pathogenic BRCA2 sequence variant is 7-8% (PMID: 20587410). There are also increased risks for melanoma, prostate cancer (20%), and pancreatic cancer (2-3%) (PMID: 10433620). Clinical management guidelines for HBOC syndrome can be found at www.nccn.org.
  - Close relatives (children, siblings, and each parent) have up to a 50% chance of being a carrier of this variant. More distant relatives may also be carriers. Carriers are at increased risk of developing autosomal dominant BRCA2-related conditions and may have reproductive risks related to autosomal recessive BRCA2-related conditions as well. Testing for this variant is available.
- A Pathogenic variant with low penetrance, c.470T>C (p.Ile157Thr), was identified in CHEK2.
  - The CHEK2 gene is associated with an increased risk for autosomal dominant breast, colon, thyroid and prostate cancers (PMID: 15492928, 18759107, 21807500, 21876083, 25431674).
  - The lifetime risk of breast cancer in females with a single pathogenic CHEK2 variant is 25-39% (PMID: 18172990, 21876083). This variant is described as pathogenic with low penetrance because it does not confer the same level of cancer risk as other pathogenic variants identified in CHEK2 (see variant details below). There is also a reported association between CHEK2 and other cancers including male breast, colorectal, prostate and thyroid cancers, but the lifetime risk of these other cancers is currently unknown (PMID: 18759107, 21807500, 23713947, 15492928, 25431674). Clinical management guidelines can be found at www.nccn.org.

BRCA2

CANCER	GENETIC CANCER RISK
Breast	High Risk
Male Breast	High Risk
Ovarian	High Risk
Pancreatic	High Risk
Prostate	High Risk
Skin	Elevated Risk

CHEK2

CANCER	GENETIC CANCER RISK
Breast	High Risk
Colorectal	Elevated Risk
Male Breast	Elevated Risk

The Future of Oncology Genetics….

- Somatic testing/ targeted therapy- expanded
- Tumor signatures
- Pharmacogenetics
- Genetic disease monitoring
- *Individualized* care based on germline and somatic genetics

Questions?

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Resources

NCCN https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pd

City of Hope https://www.cityofhope.org/education/health-professional-education/cancer-genetics-education-program

ASK2ME https://www.ask2me.org/

Ambry Genetics http://www.ambrygen.com/