Genetics, Genetic Counseling, and Testing

September 10, 2022

Julie Culver, MS, LCGC, CCRP
Director of Genetic Counseling, **USC** Norris Cancer Hospital
Clinical Instructor of Medicine, Division of Medical Oncology
Keck School of Medicine of **USC**

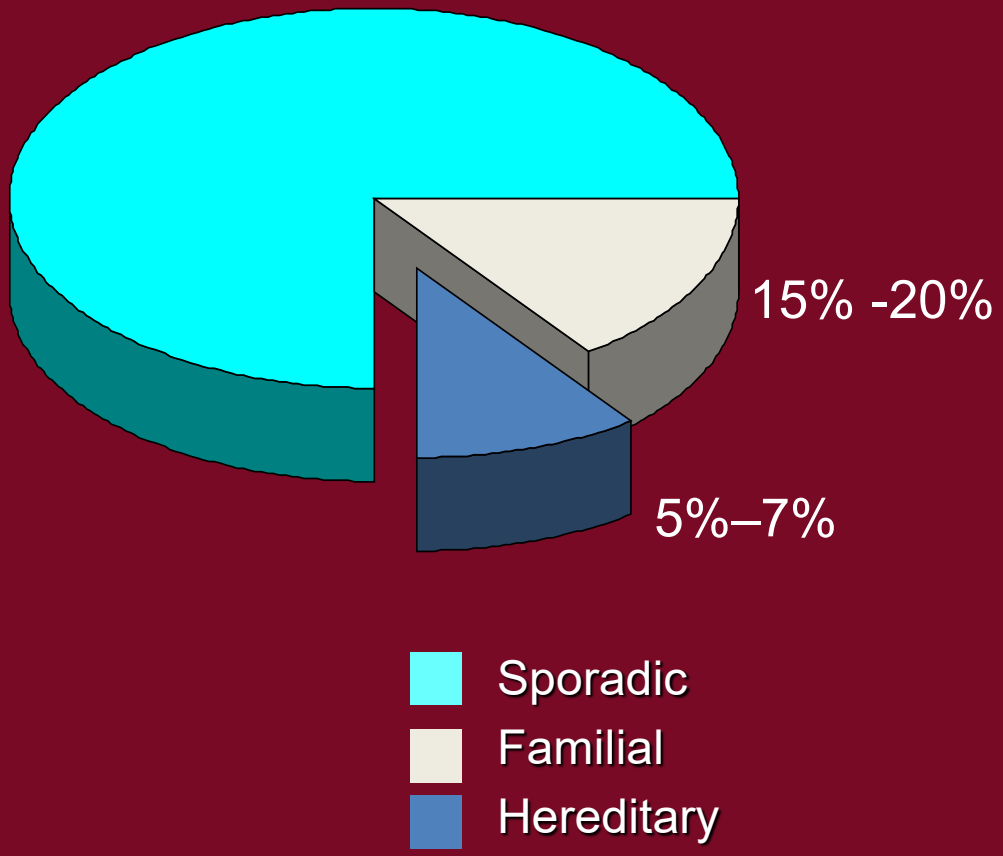
Bandit

No conflicts of interest to disclose

Objectives

1. Identify patients in clinical practice for cancer genetics evaluation
2. Understand the role of cancer genetics in optimizing cancer screening and prevention.
3. Improve familiarity with current genetic tests and how genetic counseling and testing can be incorporated in clinical care.

How Much Cancer Is Hereditary?



Hereditary Cancer Syndromes

In the general *population:*

- Lynch syndrome ~1/300
- *BRCA1* and *BRCA2* ~1/400
- Familial adenomatous polyposis ~1/8,000
- Li-Fraumeni syndrome ~1/25,000

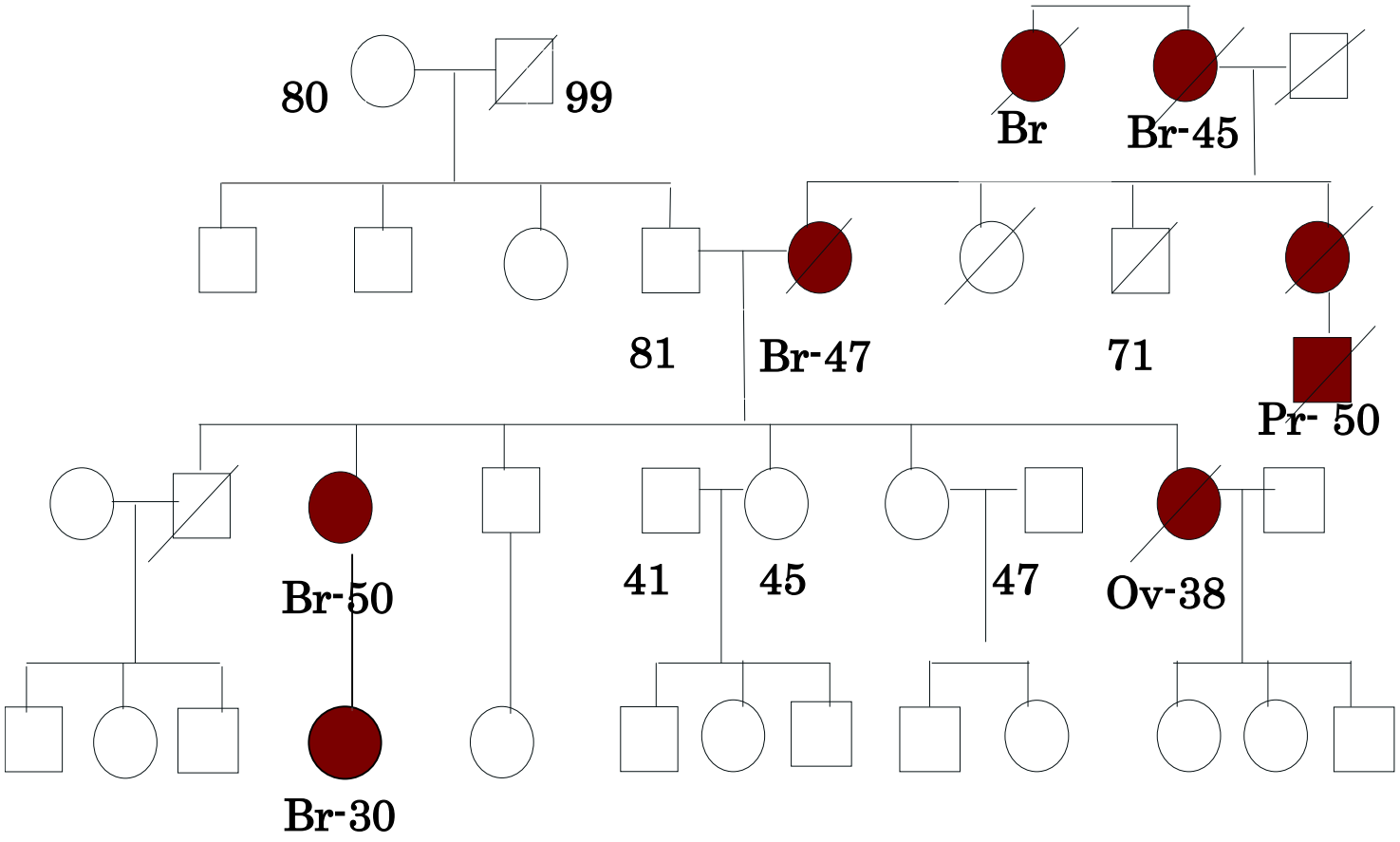
- Hereditary syndromes account for 5-10% of certain solid tumors (breast, colon, endometrial, prostate, gastric, kidney)

- Even higher proportion of others:
  - Ovarian ~20%
  - Pancreatic 15%

Why identify hereditary syndromes?

- For patients without cancer:
  - Higher risk for cancer, including early-onset
    - Offer surveillance, risk reducing surgery, medications
    - Begin screening at a younger age
  - Stratification of risk in family members
    - Screen those with predisposition appropriately
    - Avoid over-screening those without predisposition
- For cancer patients:
  - ***Prevention/detection of second primary cancers***
  - ***Targeted therapies***

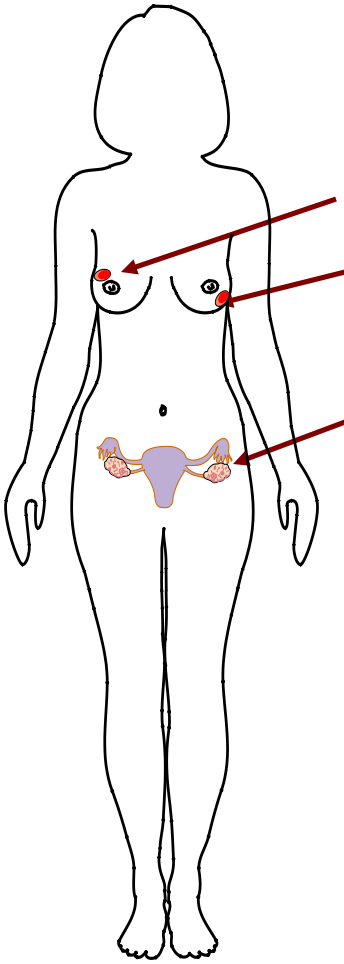
Hereditary pattern of cancer



Hereditary Cancer Principles

- Earlier than average age of cancer diagnosis
- Increase prevalence of bilateral or multiple tumors
- Multiple primary diagnoses
- Rare or characteristic cancers
- Family history of cancers related to a syndrome
  - Breast, ovarian, pancreatic and prostate (*BRCA1* and *BRCA2*)
  - Colon, endometrial, gastric, ovarian (Lynch syndrome)
- Ashkenazi Jewish ancestry & BRCA1/BRCA2 related cancers

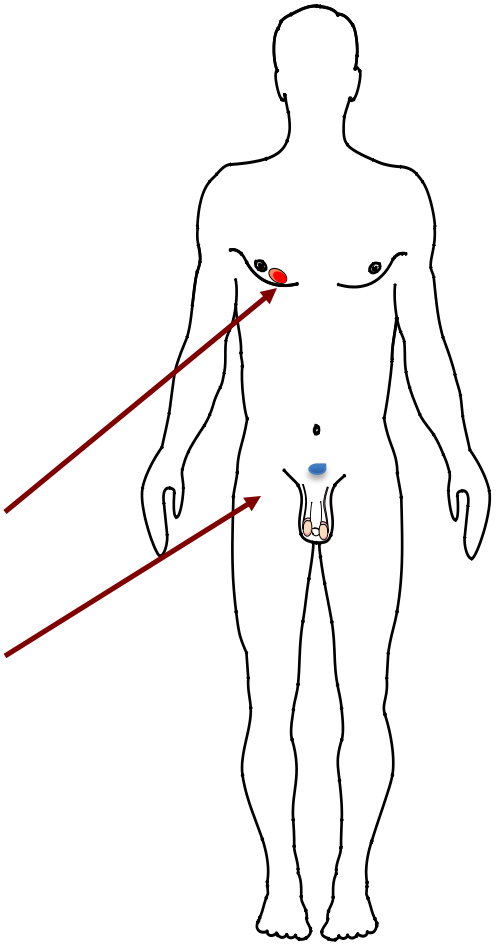
BRCA1 and *BRCA2* Lifetime Cancer Risk



Breast cancer 50%-85%

Second breast cancer 40%-60%

Ovarian cancer 15% (BRCA2)-45% (BRCA1)

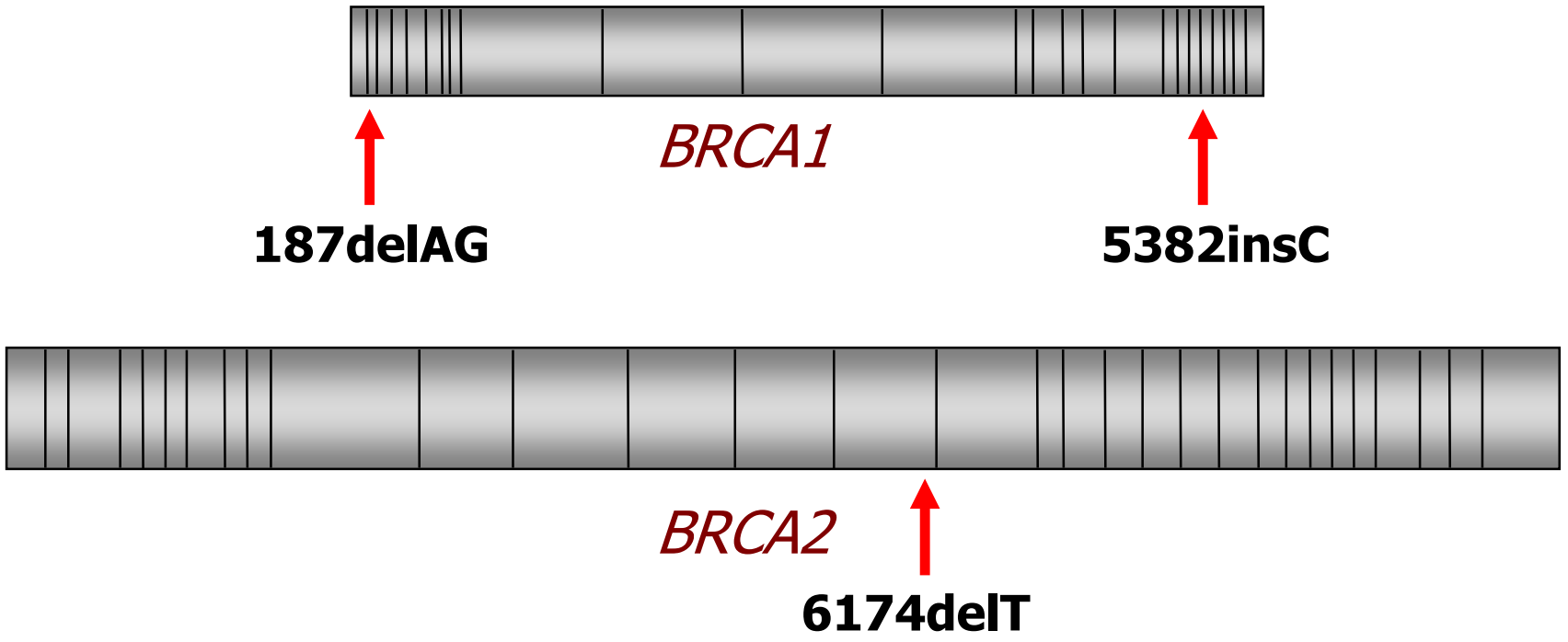


Male breast cancer 6% in BRCA2

Prostate cancer 20%

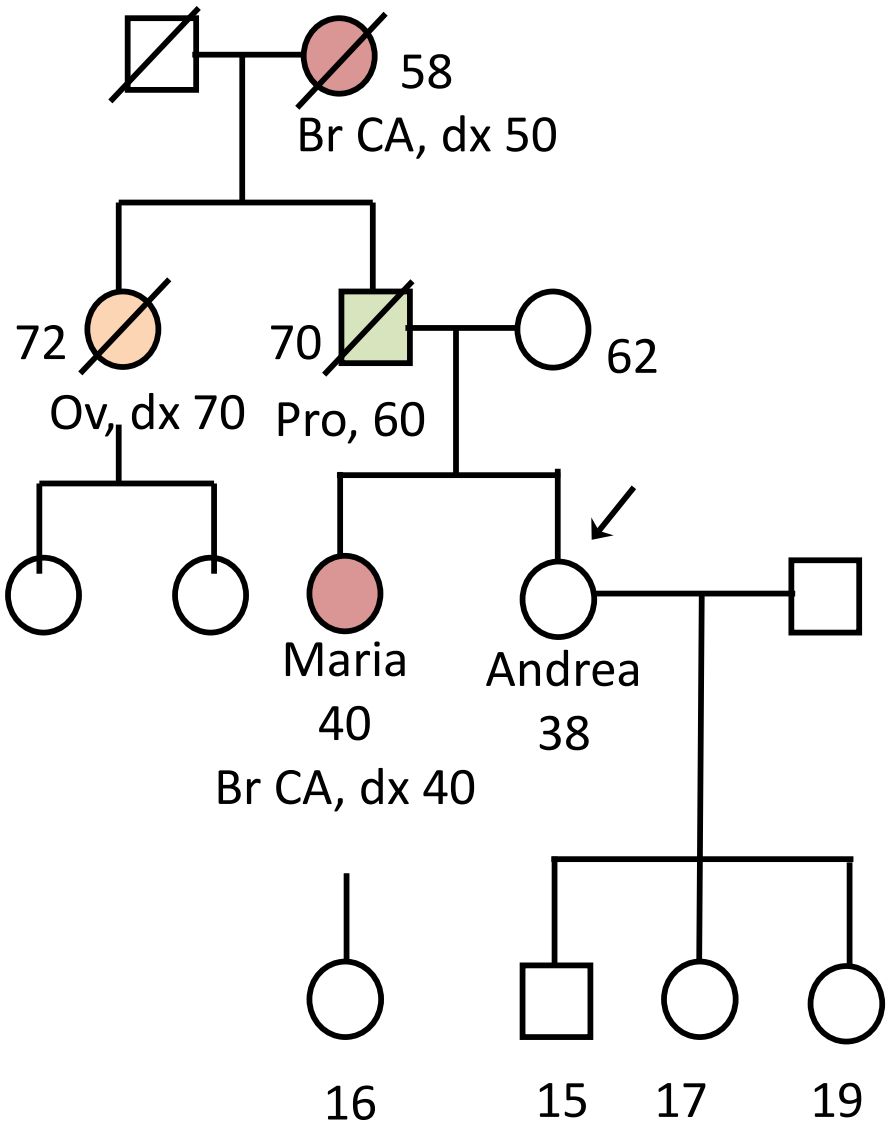
Pancreatic cancer, melanoma risks increased:
risk most notable in *BRCA2*

BRCA1 and *2* Founder Mutations in the Ashkenazi Jewish Population



These mutations are estimated to account for 95% of *BRCA* mutations in this population

The “best” first test



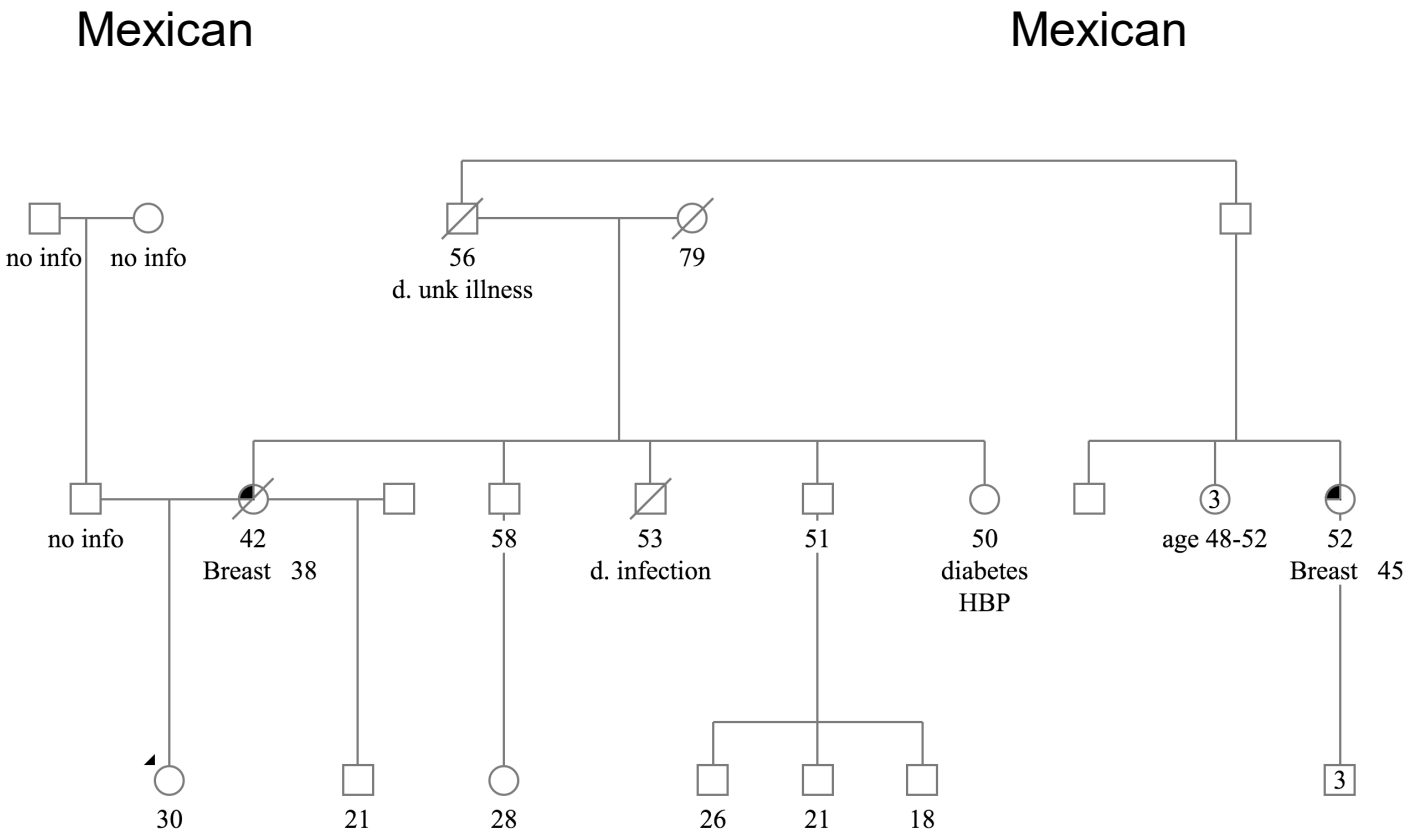
Testing living, affected person <u>first</u> allows for accurate interpretation of test results for family

If PV is found in affected individual, then their relatives can have predictive testing.

Negative result on an unaffected person can never be a <u>true</u> negative

Ideal, but not always possible

30 year old woman presents for GC



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

Ambry Genetics®
A Konica Minolta Company

Ordered By Contact ID:2024397 Org ID:3605

Medical Professional: Spicer, Darcy, MD

Client: USC Norris Comprehensive Cancer Center (05889)

Additional Authorized Recipient:

Culver, Julie MS, CGC

BRCA1/2 Analyses with CustomNext-Cancer® +RNAinsight®

RESULTS

BRCA1 **Pathogenic Mutation: p.R1443***

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.R1443*** pathogenic mutation in the *BRCA1* gene.
- This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
- **Risk estimate**: 57-87% lifetime risk of breast cancer and up to a 40% lifetime risk of ovarian cancer (females only), increased risks of male breast cancer and prostate cancer (males only), and increased lifetime pancreatic cancer risk.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.

Breast Cancer Risk Management (NCCN, 2022)

- Increased surveillance
  - BSE training and education, begin at age 18
  - CBE, every 6-12 months, begin at age 25*
  - Annual MRI, age 25-75*
  - Annual mammogram, age 30-75*
  - After age 75, individualize screening

Options

- Risk-reducing mastectomy

  >90% risk reduction

- Chemoprevention (tamoxifen or Evista)

  50-60% risk reduction

*Individualized based on earliest age at diagnosis in the family

Ovarian Cancer Risk Management (NCCN, 2022)

- Risk-reducing bilateral salpingo-oophorectomy at age 35-40 and upon completion of child-bearing. * Okay to delay until 45 in BRCA2 carriers.
  - ~96 % ovarian cancer risk reduction
  - >50 % breast cancer risk reduction
- Limited evidence for CA-125 screening and transvaginal ultrasound. NCCN guidelines indicate screening can be considered at age 30-35, with major caveats about sensitivity and specificity
- Oral contraceptives

*Individualized based on earliest age at diagnosis in the family

30 year old woman

- Mammogram was BIRADS 4A on the right
- Biopsy revealed fibroadenoma with a focus of atypical ductal hyperplasia
- Subsequently decided to have bilateral mastectomy

A RIGHT AXILLARY SENTINEL NODE #1, HOT AND BLUE:
- Four lymph nodes are negative for malignancy (0/4).

B LEFT NIPPLE SPARING MASTECTOMY:
- Focal atypical ductal hyperplasia (ADH).
- Fibrocystic changes, usual ductal hyperplasia (UDH) and fibroadenoma.
- Columnar cell change.
- Microcalcifications associated with fibrocystic changes and benign breast ducts.
- Previous biopsy site changes.
- Benign skin.
- No carcinoma identified.

C RIGHT NIPPLE SPARING MASTECTOMY:
- Atypical ductal hyperplasia (ADH) with microcalcifications.
- Flat epithelial atypia (FEA).
- Fibrocystic changes, usual ductal hyperplasia (UDH) and fibroadenoma.
- Pseudoangiomatous stromal hyperplasia (PASH).
- Microcalcifications associated with fibrocystic changes and benign breast ducts.
- Previous biopsy site changes.
- Benign skin.
- No carcinoma identified.

Other BRCA Cancer Risk Management

Options

- Pancreatic cancer screening, if family history is present
- Melanoma screening

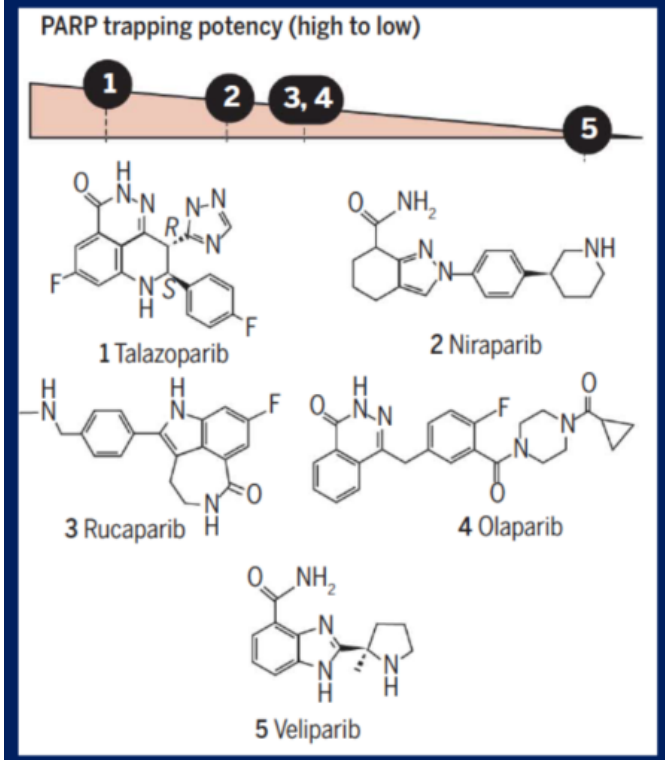
30 year old woman

- Followed by gynecologic oncology at Keck
- Using oral contraceptives to reduce ovarian cancer risk
- Plans pregnancy in the near future
- Later will have BSO after completion of childbearing, consideration of hysterectomy
- HRT will be recommended

Men with *BRCA* mutations

- BSE starting at 35
- CBE, every 12 months, begin at 35
- Prostate cancer screening, begin age 40
- Consider mammogram if gynecomastia
- Depending on family history: skin screening, pancreatic cancer screening

PARP Inhibitors and FDA Approval Status



Lord Science 2017

Drug	Approval Status (Relevant Trials)	Disease Setting of Trials
Olaparib	Approved in 2014 (NCT01078662), 2018 (OLYMPIAD) 2019 (POLO), **2021 (OlympiA)**	• **Ovarian**: germline (g) *BRCA1/2*, relapsed, ≥3 therapies; expanded to encompass any *BRCA1/2* status • **Breast**: g*BRCA1/2*, metastatic, **adjuvant** • **Pancreatic:** g*BRCA1/2*, metastatic
Rucaparib	Approved in 2016 (ARIEL2)	• **Ovarian**: somatic or *gBRCA1/2*, relapsed, ≥2 therapies; expanded to encompass any *BRCA1/2* status
Niraparib	Approved in 2017 (NOVA)	• **Ovarian**: recurrent, maintenance in platinum response, irrespective of *BRCA1/2* status
Talazoparib	Approved in 2018 (EMBRACA)	• **Breast**: g*BRCA1/2*, metastatic
Veliparib	No approval yet (BROCADE trials)	• **Breast**: gBRCA1/2, metastatic, with carboplatin/taxol • Not effective as monotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Poly(adenosine diphosphate–ribose) polymerase inhibitors target cancers with defects in homologous recombination repair by synthetic lethality. New therapies are needed to reduce recurrence in patients with *BRCA1* or *BRCA2* germline mutation–associated early breast cancer.

METHODS

We conducted a phase 3, double-blind, randomized trial involving patients with human epidermal growth factor receptor 2 (HER2)–negative early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomly assigned (in a 1:1 ratio) to 1 year of oral olaparib or placebo. The primary end point was invasive disease–free survival.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Tutt at the Breast Cancer Now Toby Robins Research Centre, the Institute of Cancer Research, 237 Fulham Rd., London SW3 6JB, United Kingdom, or at andrew.tutt@icr.ac.uk.

*The members of the OlympiA Steering Committee and the trial investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 3, 2021, at NEJM.org.

N Engl J Med 2021;384:239
DOI: 10.1056/NEJMoa2105

- Among patients with *BRCA1/2* mutations at high risk for disease progression, those assigned to a year of olaparib adjuvant therapy had 3-year invasive disease–free survival of 86%, versus 77% among those who were assigned to placebo

- *First evidence that germline-targeted therapy may improve the cure rate for a common cancer: a game-changer for the relevance of genetic testing*

Integration of Universal Germline Genetic Testing for All Newly Diagnosed Breast Cancer Patients

Genetic testing is recommended for all women with breast cancer by the American Society of Breast Surgeons

138 Newly Diagnosed Breast Cancer Patients Attended Multidisciplinary Breast Cancer Clinic

95% Accepted Genetic Counseling

93% Accepted Genetic Testing

15 (12%) of those tested carried a pathogenic mutation, including 8 (7%) with mutations in breast cancer genes

Median time to STAT genetic test results was 8 days.

For STAT patients undergoing surgery, results were available prior to surgery for 98%

Culver et al. *Ann Surg Oncol.*, (accepted)
Visual Abstract by @Culver_Julie for @AnnSurgOncol

ANNALS OF SURGICAL ONCOLOGY

Keck School of Medicine of USC

Henry Mayo Newhall Hospital

Hereditary Breast Cancer

- Known high-risk syndromes
  - Hereditary breast and ovarian cancer, *BRCA1* and *BRCA2*
    - Breast, ovarian, pancreatic, & prostate cancer
  - Li-Fraumeni syndrome, *TP53*
    - Breast, brain, sarcomas, adrenocortical cancer, & others
  - Cowden syndrome, *PTEN*
    - Breast cancer, hamartomas of the oral mucosa, skin, & intestine; cancer of the thyroid & uterus
  - Hereditary Diffuse Gastric Cancer, *CDH1*
    - Diffuse gastric cancer & lobular breast
  - Peutz-Jegher syndrome, *STK11*
    - Gastrointestinal polyps & mucocutaneous , pigmentation ; cancer of the GI tract, etc.

- *PALB2*
  - Breast and pancreatic cancer risk managed like *BRCA1* and *BRCA2*
  - Data maturing regarding ovarian and prostate cancer risk

- Moderate breast cancer risk (2-4 fold increased risk of breast cancer)
  - *ATM*
  - *CHEK2*
  - *BARD1*
  - *NF1**

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

ABSTRACT

BACKGROUND

Genetic testing for breast cancer susceptibility is widely used, but for many genes, evidence of an association with breast cancer is weak, underlying risk estimates are imprecise, and reliable subtype-specific risk estimates are lacking.

METHODS

We used a panel of 34 putative susceptibility genes to perform sequencing on samples from 60,466 women with breast cancer and 53,461 controls. In separate analyses for protein-truncating variants and rare missense variants in these genes, we estimated odds ratios for breast cancer overall and tumor subtypes. We evaluated missense-variant associations according to domain and classification of pathogenicity.

RESULTS

Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a risk of breast cancer overall with a P value of less than 0.0001. Protein-truncating variants in 4 other genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*) were associated with a risk of breast cancer overall with a P value of less than 0.05 and a Bayesian false-discovery probability of less than 0.05. For protein-truncating variants in 19 of the remaining 25 genes, the upper limit of the 95% confidence interval of the odds ratio for breast cancer overall was less than 2.0. For protein-truncating variants in *ATM* and *CHEK2*, odds ratios were higher for estrogen receptor (ER)–positive disease than for ER-negative disease; for protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative disease than for ER-positive disease. Rare missense variants (in aggregate) in *ATM*, *CHEK2*, and *TP53* were associated with a risk of breast cancer overall with a P value of less than 0.001. For *BRCA1*, *BRCA2*, and *TP53*, missense variants (in aggregate) that would be classified as pathogenic according to standard criteria were associated with a risk of breast cancer overall, with the risk being similar to that of protein-truncating variants.

CONCLUSIONS

The results of this study define the genes that are most clinically useful for inclusion on panels for the prediction of breast cancer risk, as well as provide estimates of the risks associated with protein-truncating variants, to guide genetic counseling. (Funded by European Union Horizon 2020 programs and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Easton at the University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, United Kingdom, or at dfe20@medschl.cam.ac.uk.

*A complete list of collaborators and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Dr. Dorling, Dr. Carvalho, and Mr. Allen and Drs. Teo, Devilee, and Easton contributed equally to this article.

This article was published on January 20, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa1913948

ORIGINAL ARTICLE

A Population-Based Study of Genes Previously Implicated in Breast Cancer

C. Hu, S.N. Hart, R. Gnanaolivu, H. Huang, K.Y. Lee, J. Na, C. Gao, J. Lilyquist, S. Yadav, N.J. Boddicker, R. Samara, J. Klebba, C.B. Ambrosone, H. Anton-Culver, P. Auer, E.V. Bandera, L. Bernstein, K.A. Bertrand, E.S. Burnside, B.D. Carter, H. Eliassen, S.M. Gapstur, M. Gaudet, C. Haiman, J.M. Hodge, D.J. Hunter, E.J. Jacobs, E.M. John, C. Kooperberg, A.W. Kurian, L. Le Marchand, S. Lindstroem, T. Lindstrom, H. Ma, S. Neuhausen, P.A. Newcomb, K.M. O'Brien, J.E. Olson, I.M. Ong, T. Pal, J.R. Palmer, A.V. Patel, S. Reid, L. Rosenberg, D.P. Sandler, C. Scott, R. Tamimi, J.A. Taylor, A. Trentham-Dietz, C.M. Vachon, C. Weinberg, S. Yao, A. Ziogas, J.N. Weitzel, D.E. Goldgar, S.M. Domchek, K.L. Nathanson, P. Kraft, E.C. Polley, and F.J. Couch

ABSTRACT

BACKGROUND

Population-based estimates of the risk of breast cancer associated with germline pathogenic variants in cancer-predisposition genes are critically needed for risk assessment and management in women with inherited pathogenic variants.

METHODS

In a population-based case–control study, we performed sequencing using a custom multigene amplicon-based panel to identify germline pathogenic variants in 28 cancer-predisposition genes among 32,247 women with breast cancer (case patients) and 32,544 unaffected women (controls) from population-based studies in the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium. Associations between pathogenic variants in each gene and the risk of breast cancer were assessed.

RESULTS

Pathogenic variants in 12 established breast cancer–predisposition genes were detected in 5.03% of case patients and in 1.65% of controls. Pathogenic variants in *BRCA1* and *BRCA2* were associated with a high risk of breast cancer, with odds ratios of 7.62 (95% confidence interval [CI], 5.33 to 11.27) and 5.23 (95% CI, 4.09 to 6.77), respectively. Pathogenic variants in *PALB2* were associated with a moderate risk (odds ratio, 3.83; 95% CI, 2.68 to 5.63). Pathogenic variants in *BARD1*, *RAD51C*, and *RAD51D* were associated with increased risks of estrogen receptor–negative breast cancer and triple-negative breast cancer, whereas pathogenic variants in *ATM*, *CDH1*, and *CHEK2* were associated with an increased risk of estrogen receptor–positive breast cancer. Pathogenic variants in 16 candidate breast cancer–predisposition genes, including the c.657_661del5 founder pathogenic variant in *NBN*, were not associated with an increased risk of breast cancer.

CONCLUSIONS

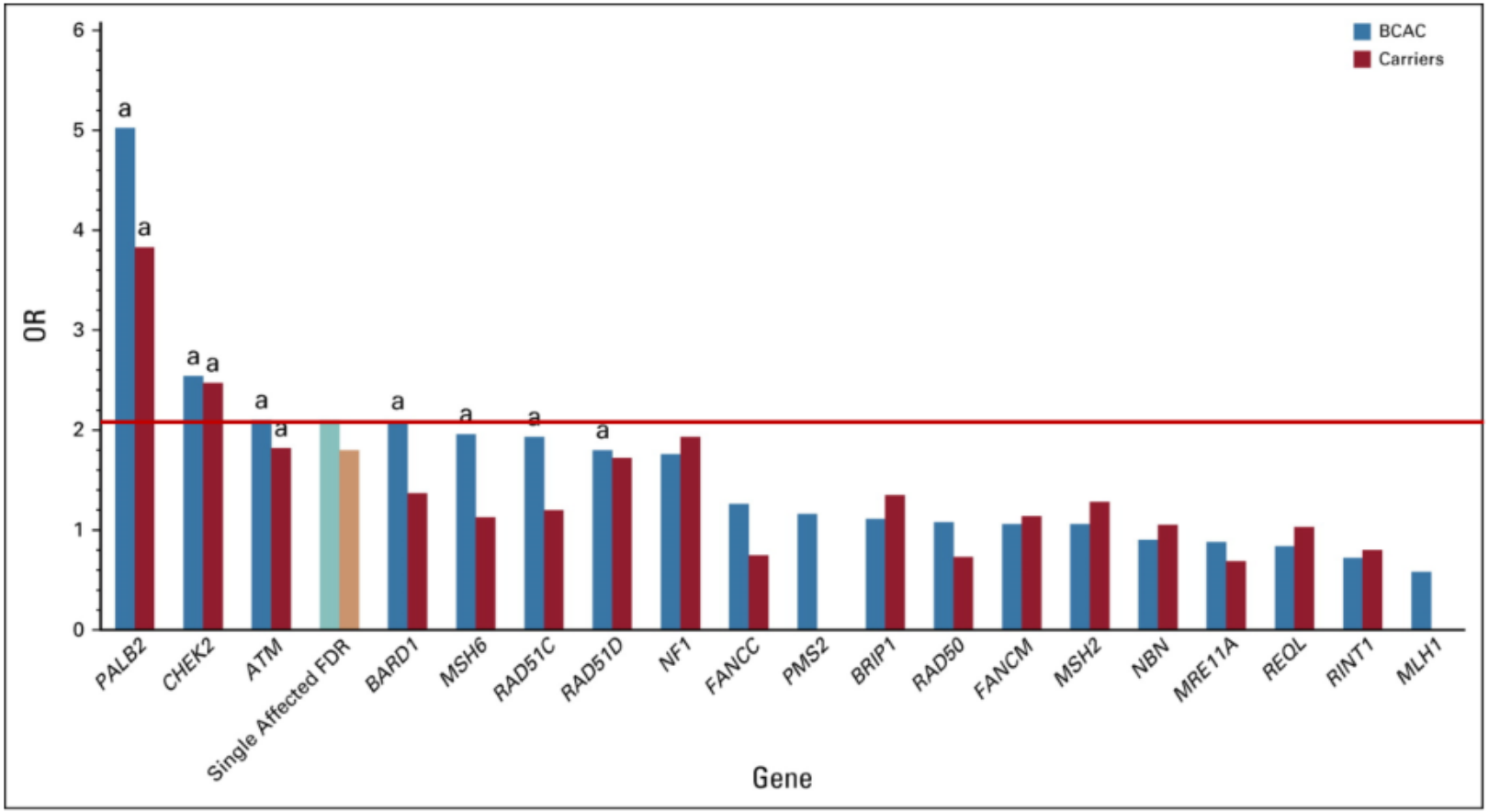
This study provides estimates of the prevalence and risk of breast cancer associated with pathogenic variants in known breast cancer–predisposition genes in the U.S. population. These estimates can inform cancer testing and screening and improve clinical management strategies for women in the general population with inherited pathogenic variants in these genes. (Funded by the National Institutes of Health and the Breast Cancer Research Foundation.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Couch at the Department of Laboratory Medicine and Pathology, Mayo Clinic, Stabile 2-42, 200 First St. SW, Rochester, MN 55905, or at couch.fergus@mayo.edu.

This article was published on January 20, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2005936

What makes something actionable?

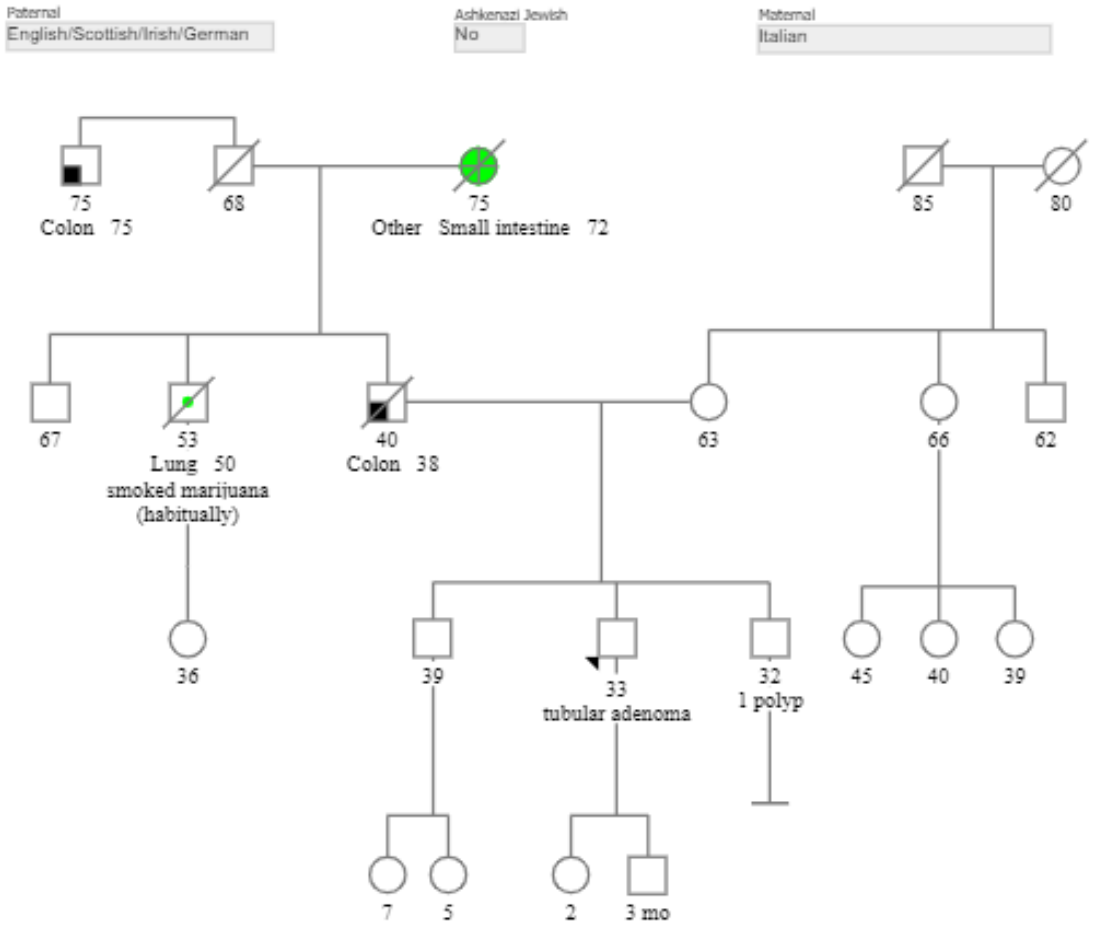


Robson, JCO 2021

Features of Lynch syndrome (LS)

- Most common inherited colorectal cancer syndrome
- Early onset of disease
- Overrepresentation of right-sided disease
- ~90% of tumors will be MMR deficient by MSI or IHC
- Lifetime risks differ by gene, but highest risks are for colorectal and endometrial cancers
  - Other cancers
    - Gastric and ovarian
    - Prostate, urothelial, and bladder
    - Pancreatic
    - Sebaceous skin neoplasms
    - Small bowel, CNS

33 year old with family history



52160820

COLARIS^{PLUS} with Myriad myRisk™ Hereditary Cancer

myRisk Genetic Result

MYRIAD myRisk™ Hereditary Cancer | Powered by Vision™

RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT

RESULT: POSITIVE - 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.

GENE	MUTATION	INTERPRETATION
MSH2	c.942+3A>T Heterozygous	**High Cancer Risk** This patient has Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC).

DETAILS ABOUT: **MSH2 c.942+3A>T: NM_000251.2; (aka: IVS5+3A>T)**

Functional Significance: Deleterious - Abnormal Protein Production and/or Function

The heterozygous germline *MSH2* mutation c.942+3A>T is located 3 nucleotide(s) downstream of exon 5. This mutation occurs within a consensus splice junction, and it is predicted to result in abnormal mRNA splicing. This mutation, which results in the in-frame deletion of amino acids 265-314, has been previously characterized as deleterious in HNPCC kindreds (Liu B et al. Cancer Research 54:4590-4, 1994).

Clinical Significance: High Cancer Risk

This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

GENE	VARIANT(S) OF UNCERTAIN SIGNIFICANCE	INTERPRETATION
BARD1	c.575C>A (p.Ser192Tyr)	**UNCERTAIN CLINICAL SIGNIFICANCE** There are currently insufficient data to determine if these variants cause increased cancer risk.
BRIP1	c.2220G>T (p.Gln740His)	

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

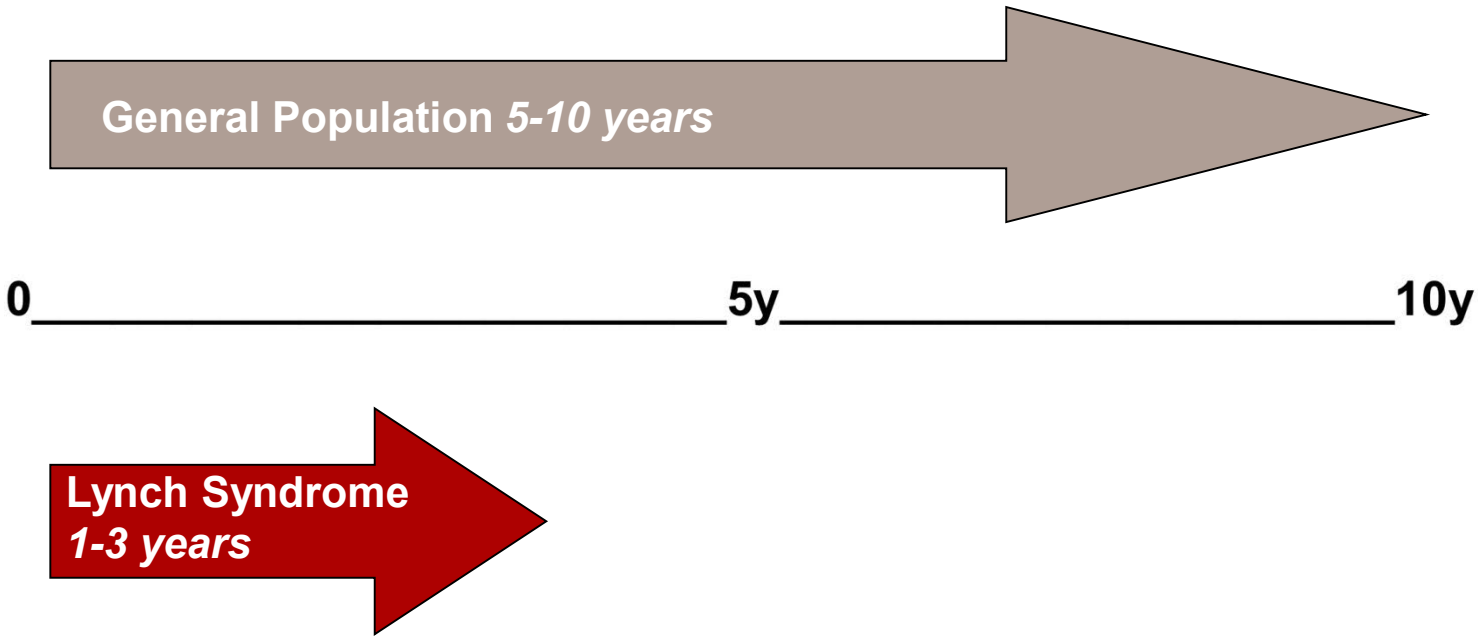
Screening and Surveillance Recommendations for Lynch Syndrome

- Colonoscopy every 1-2 years, starting 20-25 years or 2-5 years prior to the earliest colon cancer if diagnosed before 25 years
- Risk-reducing hysterectomy and bilateral salpingo-oophorectomy (BSO) for women who have completed childbearing should be considered
- Oral contraceptives for risk reduction of uterine and ovarian cancer

-NCCN 2022 guidelines

RATIONALE FOR FREQUENT COLONOSCOPY

- Accelerated progression from adenoma to cancer



Am J Med 1999;107:68-77.
Gut 2002 Feb;50(2):228-34.
Clin Gastroenterol Hepatol 2011;9(4):340-43.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

ABSTRACT

BACKGROUND

Somatic mutations have the potential to encode "non-self" immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

METHODS

We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti–programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days in patients with mismatch repair–deficient colorectal cancers, patients with mismatch repair–proficient colorectal cancers, and patients with mismatch repair–deficient cancers that were not colorectal. The coprimary end points were the immune-related objective response rate and the 20-week immune-related progression-free survival rate.

RESULTS

The immune-related objective response rate and immune-related progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair–deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair–proficient colorectal cancers. The median progression-free survival and overall survival were not reached in the cohort with mismatch repair–deficient colorectal cancer but were 2.2 and 5.0 months, respectively, in the cohort with mismatch repair–proficient colorectal cancer (hazard ratio for disease progression or death, 0.10 [P<0.001], and hazard ratio for death, 0.22 [P=0.05]). Patients with mismatch repair–deficient noncolorectal cancer had responses similar to those of patients with mismatch repair–deficient colorectal cancer (immune-related

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Diaz at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, 1650 Orleans St., Rm. 590, Baltimore, MD 21287, or at ldiaz1@jhmi.edu.

This article was published on May 30, 2015, at NEJM.org.

N Engl J Med 2015;372:2509-20.
DOI: 10.1056/NEJMoa1500596

Pembolizumab for metastatic Lynch-related cancer

New Frontier of genetic testing

- Single Gene testing vs. panel testing
- Single gene
  - Step wise testing going from highest down in differential dx list
  - Example BRCA with reflex to PTEN
- Panel testing
  - Allows for testing of multiple genes at one time (includes lower penetrant genes)

Multigene Panel Testing

- Prior to 2013, most testing was single syndrome testing
- Single gene/syndrome approach
  - Step-wise testing from highest probability condition down to lowest that is clinical indicated, based on the differential
    - Example *BRCA* with reflex to *PTEN* with reflex to *TP53*
- Multigene panel testing
  - Allows for testing of multiple genes at one time (includes lower penetrant genes)

MYRIAD myRisk™ Hereditary Cancer

BR = Breast
OV = Ovarian
CO = Colorectal
EN = Endometrial
ME = Melanoma
PA = Pancreatic
GA = Gastric
PR = Prostate
OC = Other Cancers / Clinical Features

Gene	Syndrome	Associated Cancers								
		BR	OV	CO	EN	ME	PA	GA	PR	OC
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	◉	◉				○		○	
BRCA2		◉	◉			○	◉		○	
MLH1	Lynch Syndrome / Hereditary Non-Polyposis Colorectal Cancer (HNPCC)		◉	◉	◉		○	◉		◉
MSH2			◉	◉	◉		○	◉		◉
MSH6			○	◉	◉		○	○		○
PMS2			○	◉	◉		○	○		○
EPCAM			◉	◉	◉		○	◉		◉
APC	Familial Adenomatous Polyposis (FAP)/ Attenuated FAP (AFAP)			◉			○	○		◉
MUTYH	MUTYH-Associated Polyposis (MAP) Cancer Risk			◉						◉
CDKN2A (p16INK4A)	Melanoma-Pancreatic Cancer Syndrome (M-PCS)					◉	◉			
CDKN2A (p14ARF)	Melanoma Cancer Syndrome (MCS)					◉	○			
CDK4						◉	○			
TP53	Li-Fraumeni Syndrome (LFS)	◉	○	○	○	○	○	○	○	◉
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)	◉		○	◉					◉
STK11	Peutz-Jeghers Syndrome (PJS)	◉	◉	◉	◉		◉	◉		◉
CDH1	Hereditary Diffuse Gastric Cancer (HDGC)	◉		○				◉		
BMPR1A	Juvenile Polyposis Syndrome (JPS)			◉			○	◉		○
SMAD4	Juvenile Polyposis Syndrome (JPS) & Hereditary Hemorrhagic Telangiectasia (HHT)			◉			○	◉		◉
PALB2	PALB2-Associated Cancer Risk	◉					○			
CHEK2	CHEK2-Associated Cancer Risk	◉		○					○	
ATM	ATM-Associated Cancer Risk	◉					○			
NBN	NBN-Associated Cancer Risk	○							○	
BARD1	BARD1-Associated Cancer Risk	○								
BRIP1	BRIP1-Associated Cancer Risk	○	◉							
RAD51C	RAD51C-Associated Cancer Risk	○	○							
RAD51D	RAD51D-Associated Cancer Risk		○							

◉ High Risk (see pg 8) ○ Elevated Risk (see pg 8)

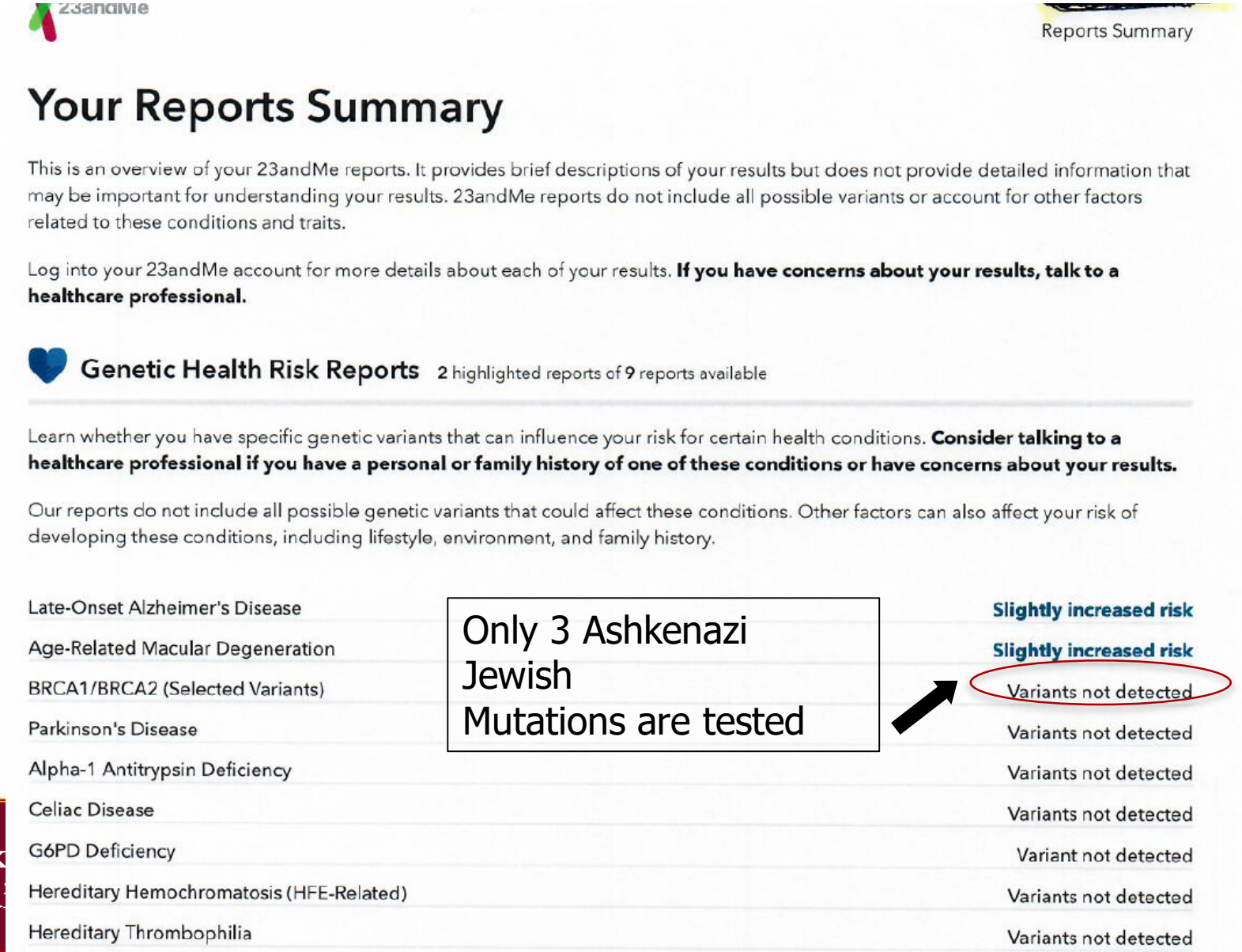
Next Generation Sequencing: Cancer Gene Panels

- Approach
  - Multiple genes associated with one identified syndrome (i.e MMR genes)
  - Multiple genes associated with the same disease (i.e breast cancer)
  - Genes conferring high risk only, or both high and moderate risk
  - Large cancer panels with 28-122 genes
- Increased likelihood of findings uncertain variants
- Unanticipated findings
- Moderate genes with lower cancer risks
  - Unclear clinic impact
  - Associated cancer risks
- Lower cost = Greater access (perhaps?)

Interpreting Genetic Test Results

- Pathogenic Variant (PV) = “Mutation” Detected = “Positive”
  - There is a disease-associated mutation that increases cancer risk; specific screening/preventive measures can be taken
  - “Likely Pathogenic” is managed clinically the same way as “Pathogenic”
- No PV detected = “Negative”
  - There is no PV in the gene(s) analyzed, but a relative could have a PV
  - Could be a PV in a gene not tested or discovered
- Variant of Uncertain Significance = “Uncertain”
  - Variant for which clinical significance has not yet been determined
  - Majority (>85-90%) will eventually be downgraded to favor polymorphism
  - More common in patients of diverse racial/ethnic backgrounds
  - These variants should not be used to influence clinical decisions

Negative on a 23&Me Test (incomplete/irrelevant for most patients)



23andMe

Reports Summary

Your Reports Summary

This is an overview of your 23andMe reports. It provides brief descriptions of your results but does not provide detailed information that may be important for understanding your results. 23andMe reports do not include all possible variants or account for other factors related to these conditions and traits.

Log into your 23andMe account for more details about each of your results. **If you have concerns about your results, talk to a healthcare professional.**

Genetic Health Risk Reports

2 highlighted reports of 9 reports available

Learn whether you have specific genetic variants that can influence your risk for certain health conditions. **Consider talking to a healthcare professional if you have a personal or family history of one of these conditions or have concerns about your results.**

Our reports do not include all possible genetic variants that could affect these conditions. Other factors can also affect your risk of developing these conditions, including lifestyle, environment, and family history.

Late-Onset Alzheimer's Disease	**Slightly increased risk**
Age-Related Macular Degeneration	**Slightly increased risk**
BRCA1/BRCA2 (Selected Variants)	Variants not detected
Parkinson's Disease	Variants not detected
Alpha-1 Antitrypsin Deficiency	Variants not detected
Celiac Disease	Variants not detected
G6PD Deficiency	Variant not detected
Hereditary Hemochromatosis (HFE-Related)	Variants not detected
Hereditary Thrombophilia	Variants not detected

Only 3 Ashkenazi Jewish Mutations are tested

Pre-testing Genetic Counseling

What can the patient expect?

- Questions about personal and family cancer history and any genetic testing in the family
- Initial visit is usually 45 minutes, includes education, discussion of test to be performed, clinical impact for the patient, information about insurance verification process
- If testing is indicated and patient consents
  - If in-person patient, sample collection done day of the initial visit
  - If virtual patient, remote phlebotomy can be arranged or saliva kit is sent to home
- Offer for research participation
- 3 week wait for genetic test results after sample is received by the lab; STAT testing can also be arranged for urgent breast cancer cases with 7-10 day turn-around.

Genetics Evaluation – Post-testing

Results disclosure

- Interpretation of results and implications for patient care, including cancer treatment and preventive screening
- Results discussed within the context of family history
- Explanation of report and genes tested
- Discussion of both pathogenic and uncertain variants
- Genetic testing recommendations for family, including writing family letters for relatives at risk for pathogenic variant
- Routine cancer screening also reviewed
- Often, coordination of care for patients testing positive

Risk assessment (especially breast cancer)

- Risk calculation
- Screening recommendations

Resources

- NCCN Guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
  - NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreas
  - NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - NCCN Guidelines for Breast Cancer Screening and Diagnosis
- NCI PDQ guidelines http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1
  - Genetics of Breast and Ovarian Cancer

Conclusions

- Identification of mutation carriers can lead to screening and preventive practices above and beyond what is indicated by family history
- Panel testing can identify mutation carriers in moderate risk genes which are associated with varying risk of cancer and for which the evidence continues to evolve
- Genetic testing has implications for cancer treatment
- Genetic counseling can assist in results interpretation and patient understanding

USC Norris Cancer Hospital
Genetic Counseling

Genetic Counselors
Julie Culver, MS, LCGC, CCRP
Jacob Comeaux, MS, LCGC
Emmeline Chang, MS, LCGC
Rebecca Waggoner, MS, LCGC

Phone: 323-865-0911
Fax: 323-865-0933

Referrals:
DL-USC-Genetics@med.usc.edu

Email: jculver@med.usc.edu