

Creating a Cancer-free World. One Person, One Discovery at a Time.

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Genetic Counseling and Prostate Cancer

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WEXNER MEDICAL CENTER

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Objectives

- Discuss who is appropriate for genetic counseling
- Explain genetics and prostate cancer
- Describe the genetic counseling and testing process
- Share a patient example from clinic

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What Does a Licensed Cancer Genetic Counselor Do?

- Calculate a cancer risk analysis from acquired personal and family histories (detailed 3-4 generation pedigree)
- Provide in-depth counseling and education about cancer genetics and genetic testing
- Offer a course of action for managing cancer risk that is personally appropriate (genetic testing, screening or long-term follow up)
- Order and interpret genetic tests; facilitate family testing
- Address complex psychosocial issues
- Facilitate entry into research studies

When Should Genetic Counseling and Testing Be Considered?

- Genetic test results will influence medical management
- Patient:
  - Wants to rule out hereditary cause for personal and/or family history
  - Provides an understanding why cancer developed
  - Clarifies the risk of developing a second primary cancer
  - Provide cancer risk for family members
  - Had previous genetic testing and would like to have more information

DNA-Repair Hereditary Gene Mutations

- Germline mutations in men with metastatic prostate cancer was about 12%.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

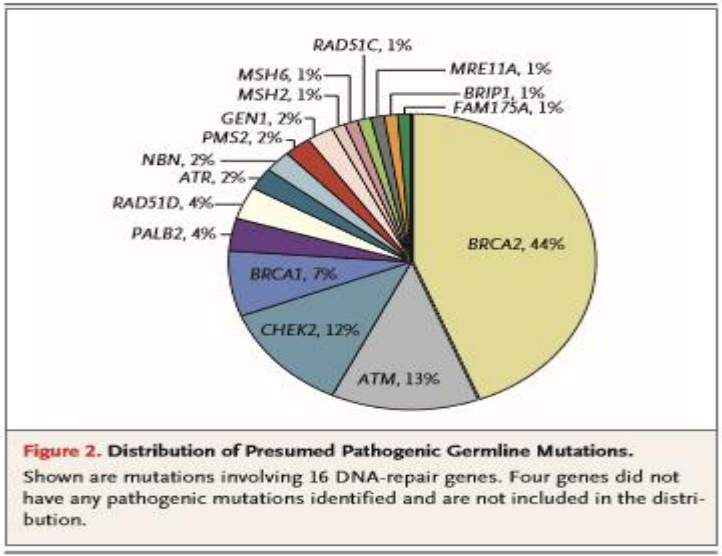

Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

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INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]	Initial Therapy
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Not indicated	See PROS-3
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-4
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-6
High	Has no very-high-risk features and has at least one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[j]	See PROS-7
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

See Footnotes for Initial Risk Stratification And Staging Workup For Clinically Localized Disease (PROS-2A)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This can include *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.

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 tested negative 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;[e] or**
       - **A second breast cancer diagnosed at any age; or**
       - **≥1 close blood relative[f] with breast, ovarian, pancreatic, or 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[f] with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,[g] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer at any age; or**
       - **≥3 total diagnoses of breast cancer in patient and/or close blood relatives[f]**
     - **Diagnosed at any age with male breast cancer**
   - **Epithelial ovarian cancer[h] (including fallopian tube cancer or peritoneal cancer) at any age**
   - **Exocrine pancreatic cancer at any age (See CRIT-3)**
   - **Prostate cancer at any age with:**
     - **Metastatic,[g] intraductal/cribriform histology, or high- or very-high-risk group (see NCCN Guidelines for Prostate Cancer);**
     - **Any NCCN risk group (see NCCN Guidelines for Prostate Cancer) with the following family history:**
       - **Ashkenazi Jewish ancestry; or**
       - **≥1 close relative[f] with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,[g] or intraductal/cribriform prostate cancer at any age; or**
       - **≥2 close relatives[f] with either 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**
   - **Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (see CRIT-4) or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria (see CRIT-5)**
   - **To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer[i]**

Continued on next page

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.

GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER[c]

Risk Group	Clinical/Pathologic Features	Germline Testing[c]	Molecular and Biomarker Analysis of Tumor[c]	Initial Therapy
Regional	Any T, N1, M0	Recommended	Consider tumor testing for homologous recombination gene mutations (HRRm) and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)	See PROS-9
Metastatic[ee]	Any T, Any N, M1	Recommended	Recommend tumor testing for HRRm and consider tumor testing for MSI or dMMR	See PROS-13

Who is Appropriate for Genetic Counseling?

- Prostate diagnosed at age 55 and younger
- Metastatic prostate cancer
- Prostate cancer Gleason 8 or higher
- Prostate cancer Gleason 7 with:
  - Ashkenazi Jewish ancestry.
  - Family history of the following cancers: breast, ovarian, prostate, pancreatic, male breast, colorectal, and/or endometrial
- Known mutation in a cancer susceptibility gene found on tumor genomic testing (e.g: *BRCA1/2*) by Foundation Medicine or similar report

Cancer Genetics and Prostate Cancer

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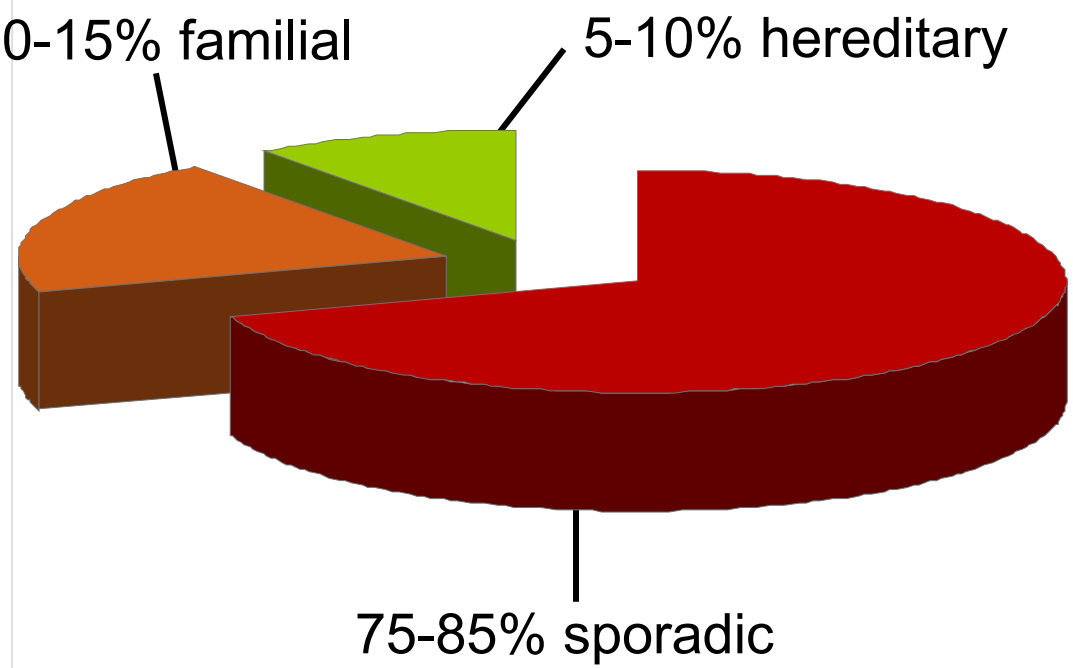
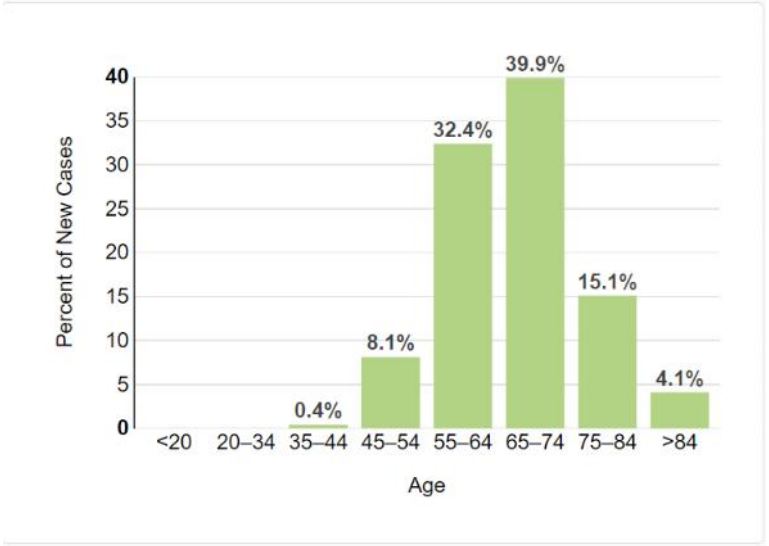
Most Cancers are not Inherited



Prostate Cancer

- 1 in 8 men will be diagnosed with prostate cancer, with average age of 66.

	Common Types of Cancer	Estimated New Cases 2020	Estimated Deaths 2020
1.	Breast Cancer (Female)	276,480	42,170
2.	Lung and Bronchus Cancer	228,820	135,720
3.	**Prostate Cancer**	**191,930**	**33,330**
4.	Colorectal Cancer	147,950	53,200
5.	Melanoma of the Skin	100,350	6,850
6.	Bladder Cancer	81,400	17,980
7.	Non-Hodgkin Lymphoma	77,240	19,940
8.	Kidney and Renal Pelvis Cancer	73,750	14,830
9.	Uterine Cancer	65,620	12,590
10.	Leukemia	60,530	23,100



NCI SEER Data

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Table 1. Relative Risk (RR) Related to Family History of Prostate Cancer[a]

Risk Group	RR for Prostate Cancer (95% CI)
Brother(s) with prostate cancer diagnosed at any age	3.14 (2.37–4.15)
Father with prostate cancer diagnosed at any age	2.35 (2.02–2.72)
One affected FDR diagnosed at any age	2.48 (2.25–2.74)
Affected FDRs diagnosed <65 y	2.87 (2.21–3.74)
Affected FDRs diagnosed ≥65 y	1.92 (1.49–2.47)
Second-degree relatives diagnosed at any age	2.52 (0.99–6.46)
Two or more affected FDRs diagnosed at any age	4.39 (2.61–7.39)

CI = confidence interval; FDR = first-degree relative.

[a]Adapted from Kiciński et al.[25]

The American Cancer Society recommends men start screening:

- At age 50 who are at average risk
- At age 45 who are at increased risk:
  - If they are African American
  - If they have a first degree relative (father, brother or son) who was diagnosed with prostate cancer younger than 65
- At age 40 who are at high risk:
  - If they have more than 1 first relative diagnosed under 65

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NCI PDQ Prostate Cancer Genetics
Kicinski et al. PLoS One 2011

Somatic mutations

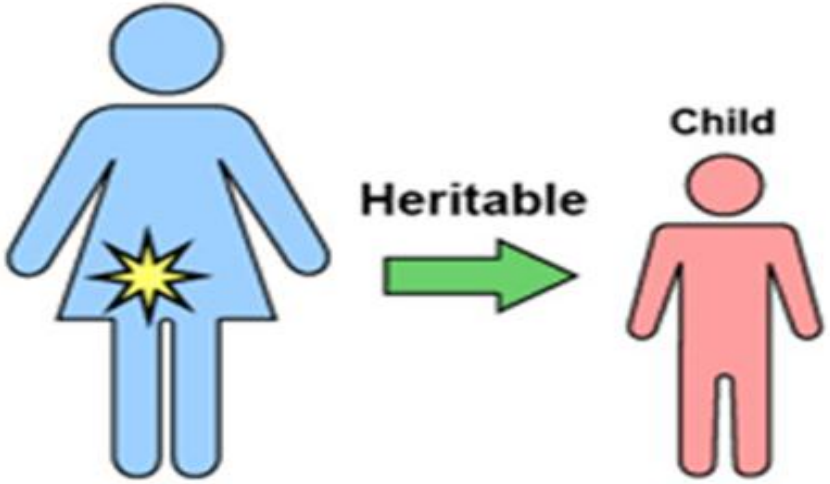
- Occur in ***nongermline*** tissues
- Cannot be inherited

Nonheritable

Mutation in tumor only
(for example, breast)

Germline mutations

- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

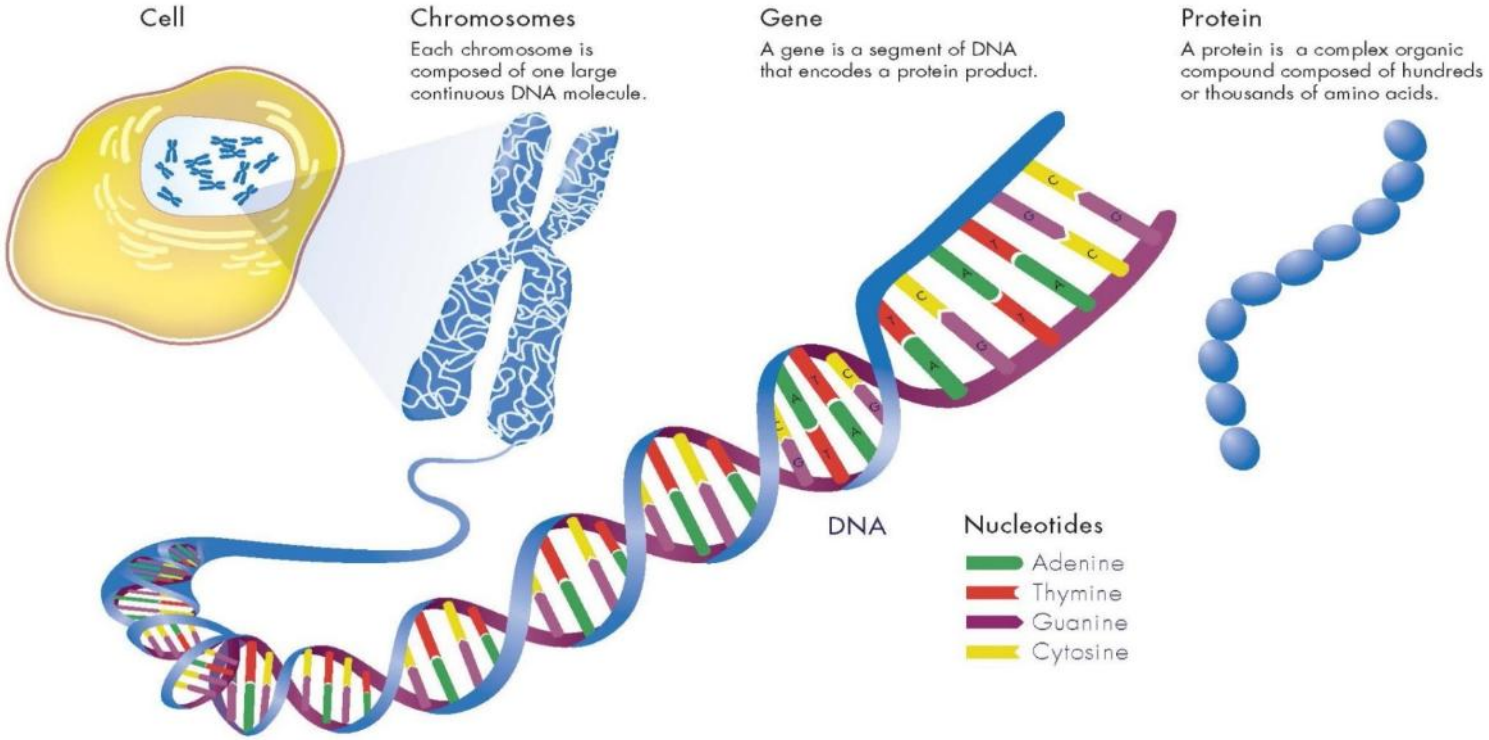


Mutation in
egg or sperm

All cells
affected in
offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology

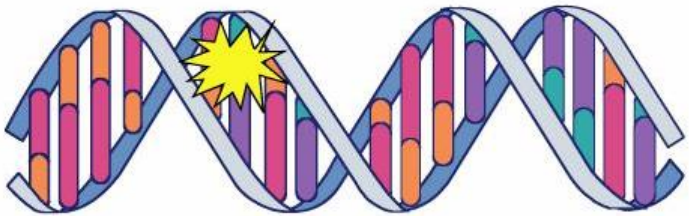
Basic Genetics



Slide Courtesy Greenwood Genetics

DNA and Mutations

A mutation is a change in the normal base pair sequence



A→T

G→C

- Example
  - Normal DNA THE DOG RAN OUT
  - DNA mutation THE TTD OGR ANO UT
  - DNA mutation TAE DOG RAN OUT
  - DNA mutation THE OGR ANO UT_

Genetic Counseling Process

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Genetic Counseling Appointment

- Risk assessment
  - 3 generation pedigree
- Discuss genetics and genetic testing
  - Risks – potential emotional distress, impact on family relationships, false reassurance, etc.
  - Benefits – changes in medical management or expectations from testing
  - Limitations – not testing for every gene associated with all genetic conditions, false negative results

Misconceptions About Genetic Counseling and Testing

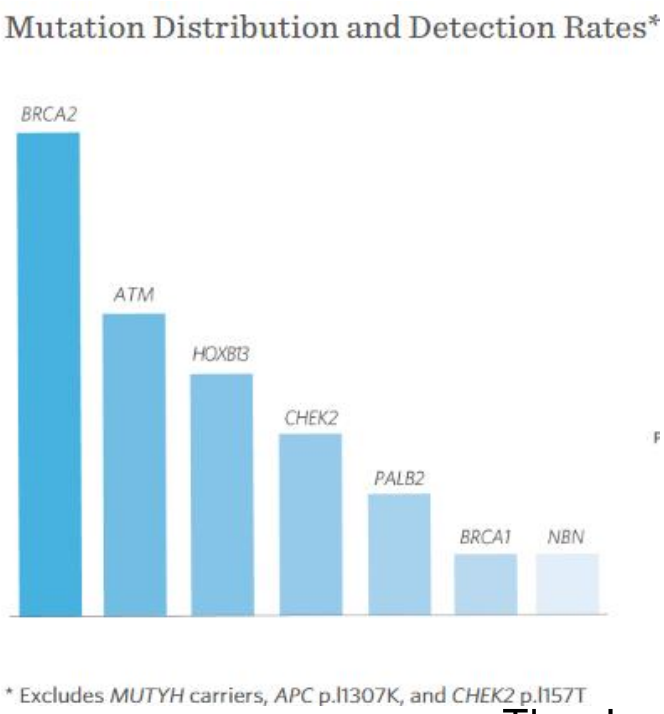
- Insurance does not cover genetic counseling
  - Most insurance companies will cover the majority of the cost associated with genetic counseling.
- Insurance doesn't cover genetic testing
  - Most insurance companies cover some if not 100% of the cost of testing
- If someone gets testing they will be discriminated against
  - There are laws in place to protect against genetic discrimination (health insurance, employment, etc) GINA (Genetic Information Nondiscrimination Act)
- Its just a blood test
  - Blood draw is only part of the genetic assessment
- Genetic counseling = genetic testing

Genetic Testing

- Sample is usually blood or buccal (spit)
- Turn around time for results is generally 2-3 weeks
- Most insurances recognize prostate cancer as criteria. If not self pay is $250
- Most patients pay less than $100 for genetic testing when appropriate and have insurance coverage.

Genes and Associated Cancer Risks

GENE	PROSTATE CANCER RISK
ATM	elevated
BRCA1	~20%
BRCA2	~20%
CHEK2	elevated
EPCAM	up to 30%
HOXB13	up to 60%
MLH1	up to 30%
MSH2	up to 30%
MSH6	up to 30%
NBN	elevated
PMS2	up to 30%
TP53	unknown



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Invitae and Ambry Genetics

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Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- ***BRCA1* and *BRCA2***

- ~1 in 400 people in the general population

- ~1 in 40 people of Ashkenazi Jewish ancestry (3 founder mutations)
- Recommend men who test positive to have breast exam and self exams at age 35 and prostate cancer screening starting at age 40.

Risk of Malignancy in Individuals with a Germline *BRCA1* or *BRCA2*-Pathogenic Variant.

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	*BRCA2*
Breast	12%	46%-87%	38%-84%
Second primary breast	2% within 5 years	21.1% within 10 yrs 83% by age 70	10.8% within 10 yrs 62% by age 70
Ovarian	1%-2%	39%-63%	16.5%-27%
Male breast	0.1%	1.2%	Up to 8.9%
Prostate	6% through age 69	8.6% by age 65	15% by age 65 20% lifetime
Pancreatic	0.50%	1%-3%	2%-7%
Melanoma (cutaneous & ocular)	1.6%		Elevated Risk

1. Ford et al [1994], Easton et al [1995], Ford et al [1998], Robson et al [1998], Breast Cancer Linkage Consortium [1999], Verhoog et al [2000], Satagopan et al [2002], Thompson & Easton [2002], Hearle et al [2003], Kirova et al [2005], Robson et al [2005], van Asperen et al [2005], Chen et al [2006], Risch et al [2006], Tai et al [2007], Graeser et al [2009], Evans et al [2010], van der Kolk et al [2010], Kote-Jarai et al [2011], Iqbal et al [2012], Leongamornlert et al [2012], Moran et al [2012], Mavaddat et al [2013], van den Broek et al [2015]

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Genetic Testing Results

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Genetic Testing: Results

- Deleterious mutation (Positive)
- No mutation detected (Negative)
  - Informative if familial mutation is known, otherwise uninformative (still need to consider risk based on family history)
- Variant of uncertain significance

Genetic Testing: Results

- Variant of Uncertain Significance (VUS)
  - Change in gene identified
    - Could be a normal variation
    - Could be deleterious
  - **VUSes are typically treated as a negative result**
  - **MAKE RECOMMENDATIONS BASED ON FAMILY CANCER HISTORY AND LEVEL OF HEREDITARY SUSPICION**

Post-test Counseling

- Discussion of genetic test result ***in context of personal and family history***
- Medical management recommendations based on test result and/or family history
  - For patient and family members
- Determine if other testing is appropriate or if patient qualifies for any research studies
- Address psychosocial issues (guilt, denial, survivor guilt, anger, depression, etc.)

Patient Example

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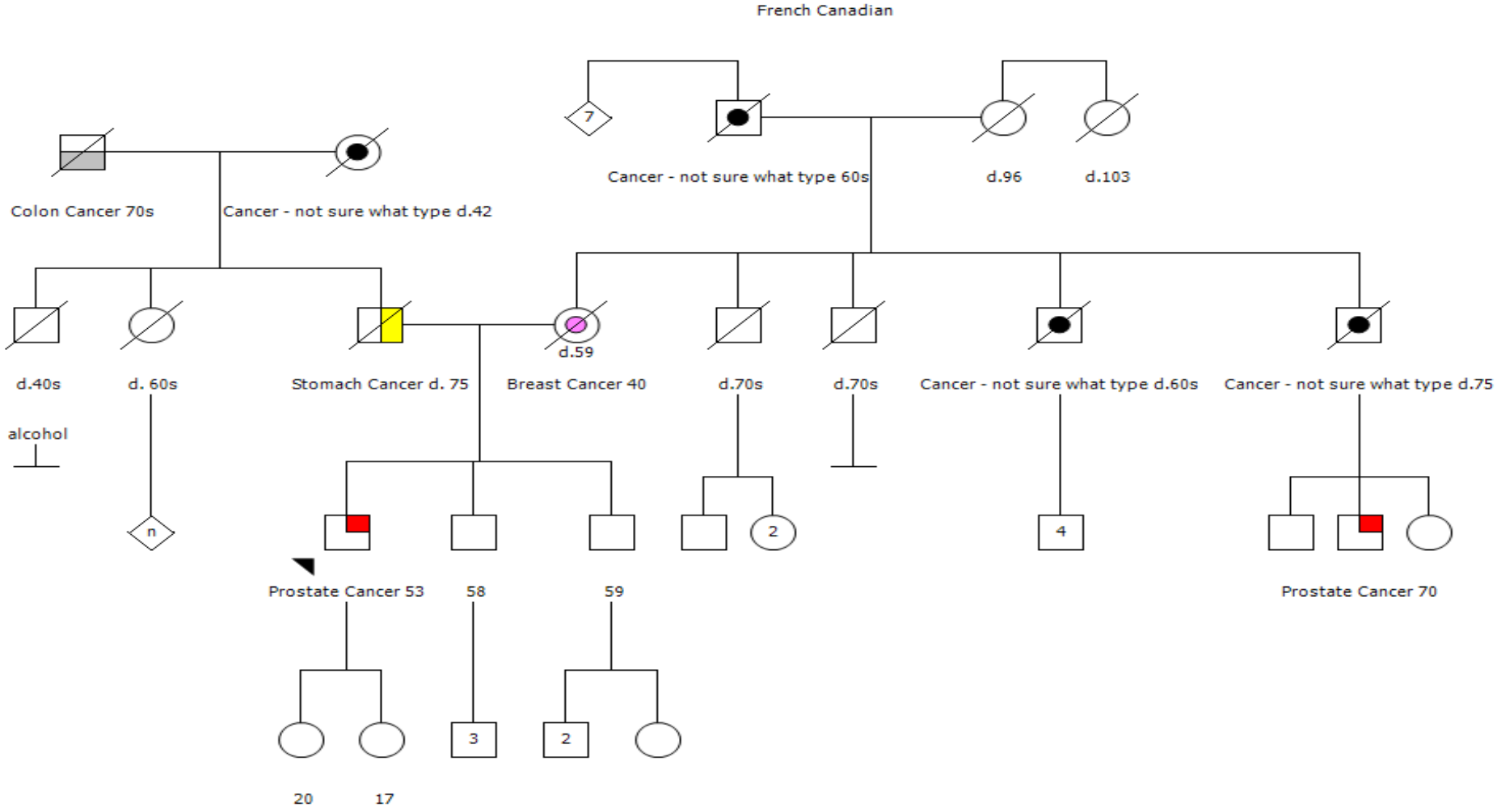
French Canadian
7
Cancer - not sure what type 60s
d.96
d.103
Colon Cancer 70s
Cancer - not sure what type d.42
d.40s
alcohol
d. 60s
n
Stomach Cancer d. 75
d.59
Breast Cancer 40
d.70s
d.70s
Cancer - not sure what type d.60s
4
Cancer - not sure what type d.75
Prostate Cancer 70
2
Prostate Cancer 53
58
59
3
2
20
17

Patient Somatic Tumor Genetic Test Results

ABOUT THE TEST:

FoundationOne® Liquid is a next-generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating tumor DNA and matches them to targeted therapies and clinical trials.

PATIENT RESULTS

- 1 genomic alteration
- 4 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 10 clinical trials

TUMOR TYPE: PROSTATE ACINAR ADENOCARCINOMA

Genomic Alteration Identified†

BRCA2 F1182fs*1

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
BRCA2 F1182fs*1	48.4%	None	Niraparib Olaparib Rucaparib Talazoparib	Yes, see clinical trials section

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Patient's Germline Genetic Testing Results

BRCA1/2 Analyses with CustomNext-Cancer

RESULTS		
BRCA2	**Pathogenic Mutation:**	**c.3545_3546delTT**
CHEK2	**Pathogenic Mutation:**	**c.1100delC**
NBN	Variant, Unknown Significance:	p.T76N

SUMMARY

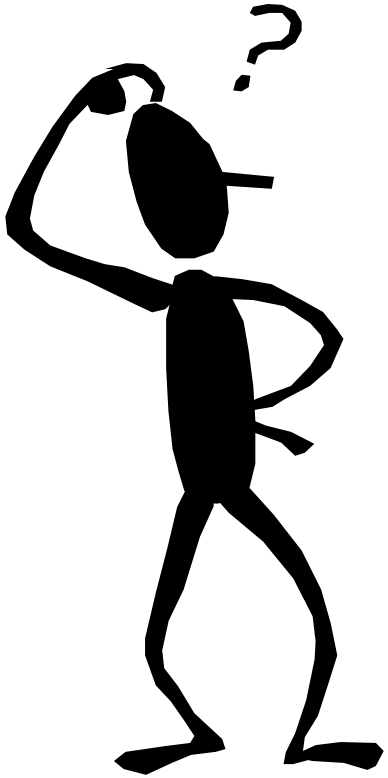
POSITIVE: Pathogenic Mutations Detected

INTERPRETATION

- This individual is heterozygous for the **c.3545_3546delTT** pathogenic mutation in the *BRCA2* gene.
  - This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
  - **Risk estimate**: 45-84% lifetime risk of breast cancer and 11-18% lifetime risk of ovarian cancer (females only), at least a 6% lifetime risk of male breast cancer and 15% risk of prostate cancer by age 65 (males only), and increased lifetime pancreatic cancer risk.
- This individual is heterozygous for the **c.1100delC** pathogenic mutation in the *CHEK2* gene.
  - **Risk estimate**: up to a 2 fold increased risk of breast cancer and colon cancer.
- The expression and severity of disease for this individual cannot be predicted.
- The interactive effect and relative contribution of these alterations on clinical phenotype is unknown at this time.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

Family Genetic Testing

- Free single mutation testing for 90 days
- Discuss timing of genetic testing (age, life insurance)
- If not local, find a Genetic Counselor to coordinate testing
  - National Society of Genetic Counselors https://www.nsgc.org/



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Thank you!

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