Memorial Sloan Kettering Cancer Center

ProstateAndMe: Using genetics to improve prostate cancer care

May 19, 2022

Maria I. Carlo, MD
Genitourinary Oncology Service
Clinical Genetics Service

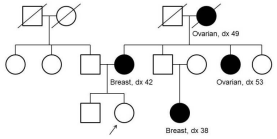
Disclosures

OncLive: Speaker’s fee

Agenda

What is germline genetic testing?

Why is germline genetic testing important in prostate cancer?



Who should get genetic testing?

How should we perform genetic testing?

Future Directions

Memorial Sloan Kettering Cancer Center

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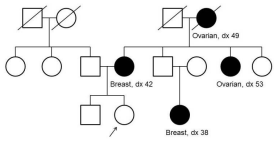

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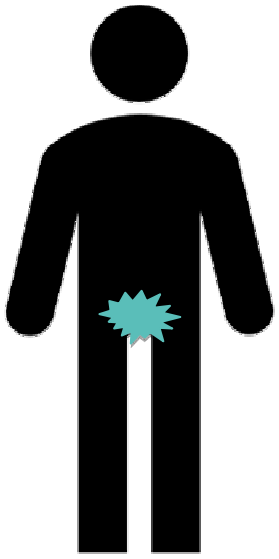
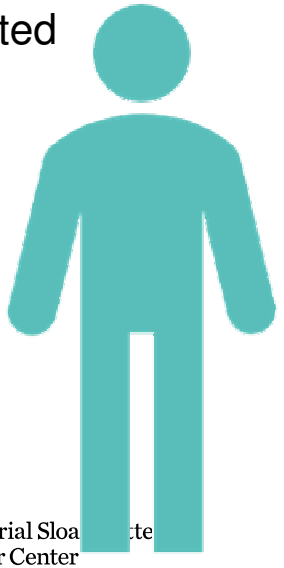
Tumor Genetic Testing

- DNA from **tumor cells** analyzed
- Nearly always there are mutations
- Cannot be inherited



Germline Genetic Testing

- DNA from **blood or saliva cells**
- Sometimes there are mutations
- Almost always inherited



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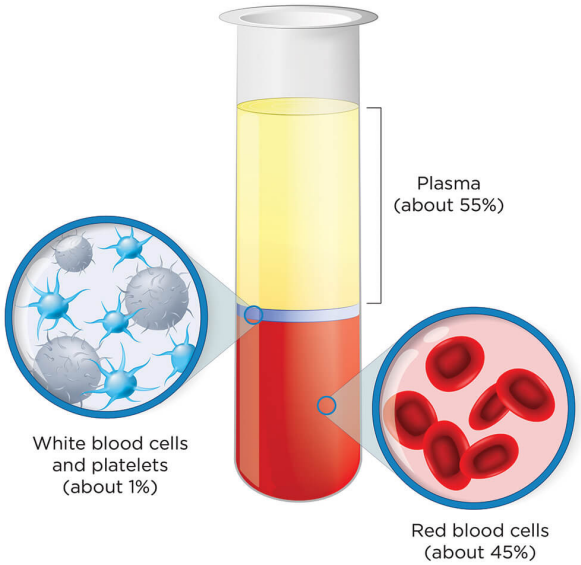
Circulating tumor DNA



Circulating tumor DNA

- DNA free floating in plasma
- May derive from multiple sources:
  - Tumor itself
  - Germline (all cells in body)
  - White blood cells only

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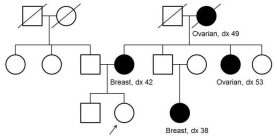

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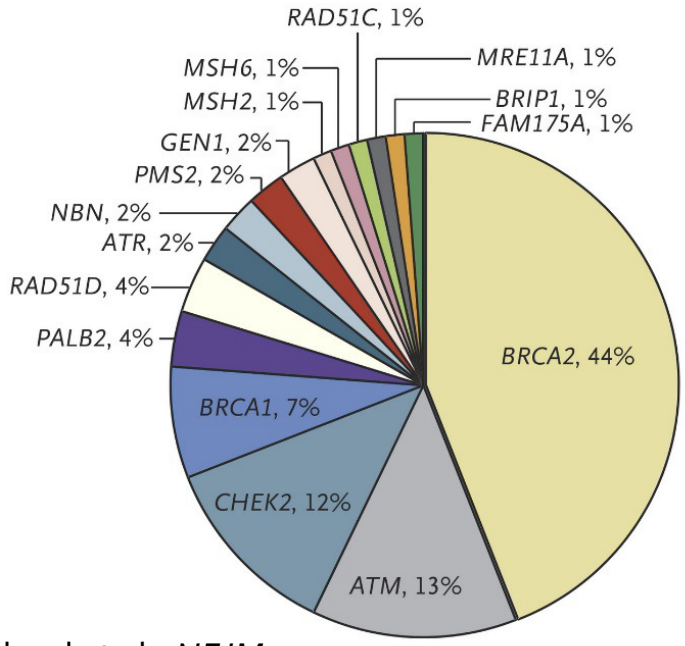
Germline mutations are common in PC patients

Advanced prostate cancer (~12%)



Pritchard et al., *NEJM* 2015

Localized, early stage (~6%)

- In men electing to undergo active surveillance, the prevalence of pathogenic mutations is lower
- 8/437 (2%) men had mutations in *BRCA1/2* or *ATM* (Brady et al *Can Med*, 2022)
- 22/1211 (2%) men had mutations in *BRCA1/2* or *ATM* (Ballentine-Carter EU, 2019)

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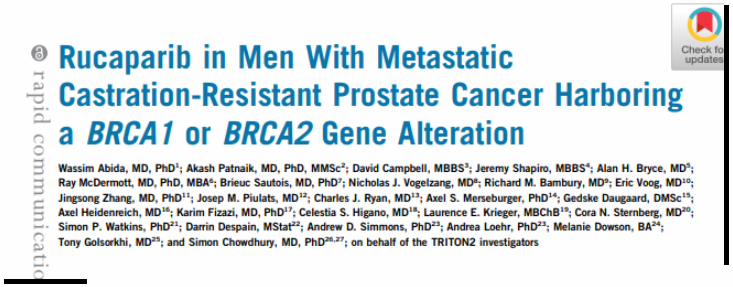
Germline mutations used for therapy selection

- There are FDA-approved therapies for men with advanced disease and certain tumor or germline mutations

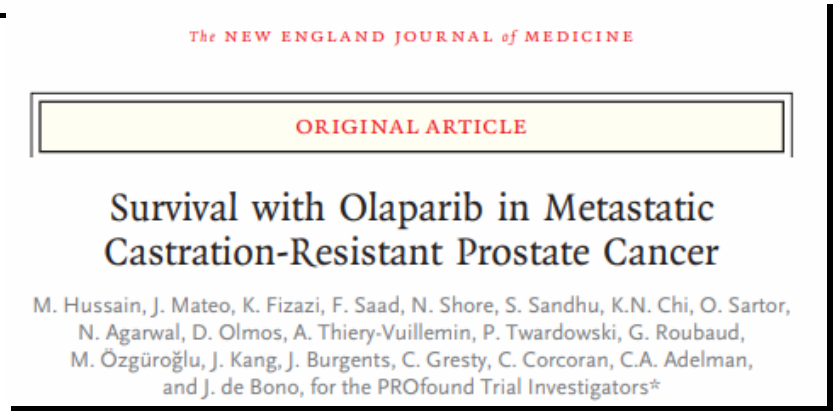
- Potential clinical trial options



rapid communicatio

Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida, MD, PhD[1]; Akash Patnaik, MD, PhD, MMSc[2]; David Campbell, MBBS[3]; Jeremy Shapiro, MBBS[4]; Alan H. Bryce, MD[5]; Ray McDermott, MD, PhD, MBA[6]; Brieuc Sautois, MD, PhD[7]; Nicholas J. Vogelzang, MD[8]; Richard M. Bambury, MD[9]; Eric Voog, MD[10]; Jingsong Zhang, MD, PhD[11]; Josep M. Piulats, MD[12]; Charles J. Ryan, MD[13]; Axel S. Merseburger, PhD[14]; Gedske Daugaard, DMSc[15]; Axel Heidenreich, MD[16]; Karim Fizazi, MD, PhD[17]; Celestia S. Higano, MD[18]; Laurence E. Krieger, MBChB[19]; Cora N. Sternberg, MD[20]; Simon P. Watkins, PhD[21]; Darrin Despain, MStat[22]; Andrew D. Simmons, PhD[23]; Andrea Loehr, PhD[23]; Melanie Dowson, BA[24]; Tony Golsorkhi, MD[25]; and Simon Chowdhury, MD, PhD[26,27]; on behalf of the TRITON2 investigators



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

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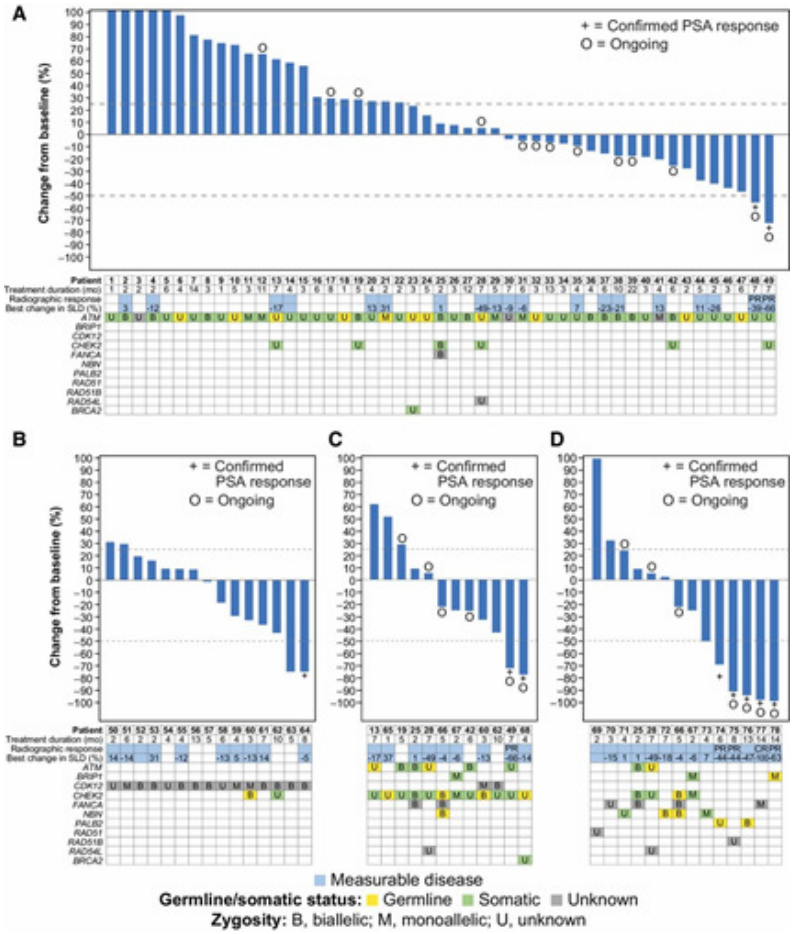
The specific mutated gene may be important

- Responses to PARP-inhibitors may vary by gene
- We need more data to see which genes are most responsive



Abida et al., *Clinical Cancer Research*, 2020

Understand risks of other cancers

- *BRCA1* and *BRCA2* germline mutations increase risk of several cancers in men including:
  - Prostate
  - Male breast cancer
  - Pancreas
  - Melanoma

- Mutations in other genes (like Lynch syndrome) can increase risk of other cancers such as colon, gastric and of the urinary tract

Cancer risks likely vary by gene

BRCA1

BRCA2

Cancer Site	Sex	Age 50 Years	Age 60 Years	Age 70 Years	Age 80 Years
Absolute risk (95% CI) for *BRCA1* carriers					
Breast	Male	0.02 (0.01 to 0.08)	0.07 (0.02 to 0.3)	0.2 (0.05 to 0.7)	0.4 (0.1 to 1.5)
Pancreas	Male	0.1 (0.07 to 0.2)	0.4 (0.3 to 0.7)	1.3 (0.8 to 2.0)	2.9 (1.9 to 4.5)
	Female	0.08 (0.05 to 0.1)	0.3 (0.2 to 0.5)	1.0 (0.6 to 1.5)	2.3 (1.5 to 3.6)
Stomach	Male	0.2 (0.1 to 0.3)	0.6 (0.3 to 1.0)	1.1 (0.6 to 2.2)	1.6 (0.7 to 4.0)
	Female	0.1 (0.06 to 0.2)	0.3 (0.2 to 0.5)	0.5 (0.3 to 0.9)	0.7 (0.3 to 1.7)
Absolute risk (95% CI) for *BRCA2* carriers					
Breast	Male	0.2 (0.1 to 0.5)	0.7 (0.4 to 1.5)	1.8 (0.9 to 3.7)	3.8 (1.9 to 7.7)
Pancreas	Male	0.2 (0.1 to 0.3)	0.9 (0.5 to 1.4)	2.0 (1.2 to 3.3)	3.0 (1.7 to 5.4)
	Female	0.2 (0.09 to 0.2)	0.6 (0.4 to 1.0)	1.5 (0.9 to 2.5)	2.3 (1.3 to 4.2)
Prostate	Male	0.2 (0.2 to 0.3)	2.9 (2.1 to 3.9)	12.6 (9.4 to 16.7)	26.9 (20.5 to 34.7)
Stomach	Male	0.1 (0.08 to 0.2)	0.5 (0.3 to 0.8)	1.4 (0.8 to 2.3)	3.5 (2.1 to 6.1)
	Female	0.2 (0.1 to 0.4)	0.6 (0.3 to 1.0)	1.3 (0.7 to 2.5)	3.5 (1.9 to 6.4)

Li et al., *JCO*, 2022

Risks of prostate cancer with *BRCA1* likely lower than previously thought- but more data still needed

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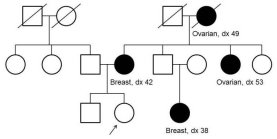

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Criteria to consider germline testing

- “High-risk,” “very high-risk” or metastatic prostate cancer
- Features seen on the pathology (example: intraductal)
- Family history- prostate cancer, breast, ovarian, pancreas
- Ashkenazi Jewish ancestry (1 in 40 probability of having a mutation in *BRCA1* or *BRCA2*)

National Comprehensive Cancer Network (NCCN) Guidelines, 2022

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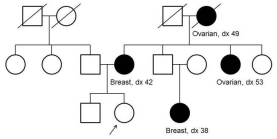

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- DNA of blood or saliva cells
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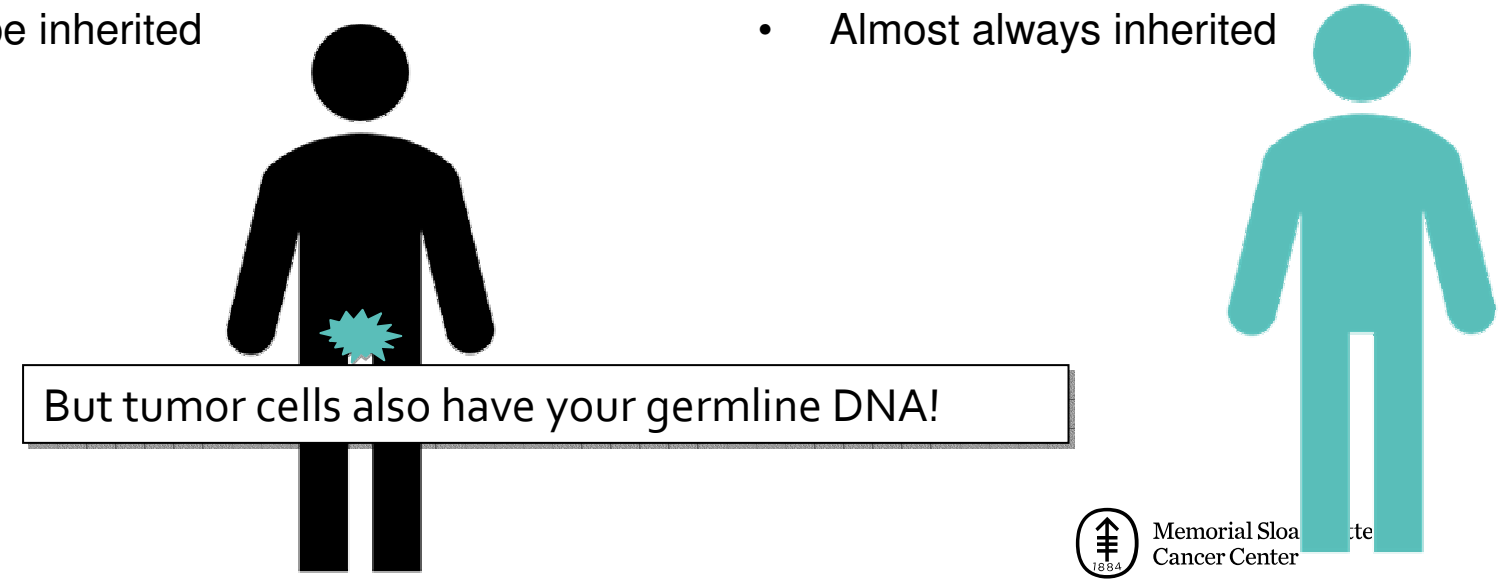

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When should tumor-only sequencing prompt germline testing?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment

NCCN Guidelines Inde
Table of Conten
Discussic

GENERAL TESTING CRITERIA[a]

Testing is clinically indicated in the following scenarios:
• Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
• 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
•

Germline probabilities after PC tumor sequencing

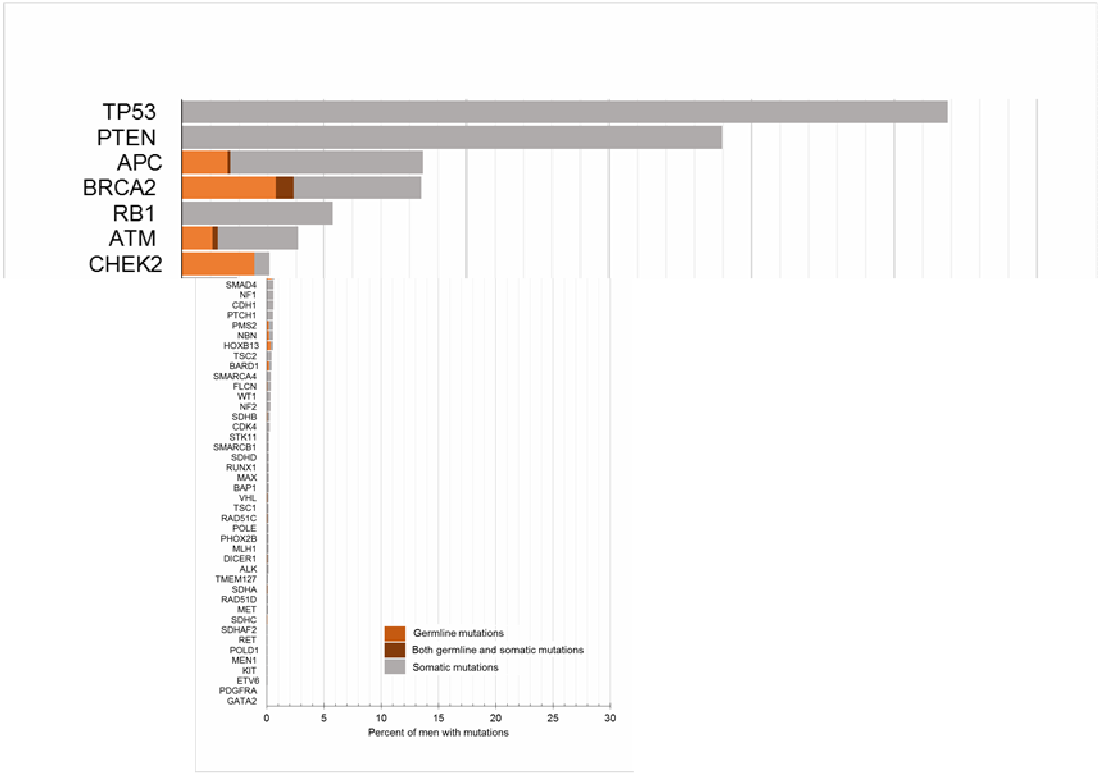
- **Methods**: 1883 men with prostate cancer who underwent both **tumor** and **germline** genetic testing
- **Objective**: Determine the gene-specific **germline probability** of a gene being identified on tumor-only sequencing
- (GERMLINE PROBABILITY= GERMLINE /(GERLIME+SOMATIC)

Germline	+	+	+	+	+	+	-	-	-	-
Tumor	-	-	-	-	+	+	+	+	+	+
	1	1	1	1	2	2	1	1	1	1

12 *BRCA2* mutations
6 *BRCA2* germline
6 *BRCA2* somatic

***BRCA2* germline probability= 6/(6+6)= 50%**

Germline probabilities vary by gene



Truong et al, ASCO 2021

Should we extend germline testing to men with early-stage prostate cancer?

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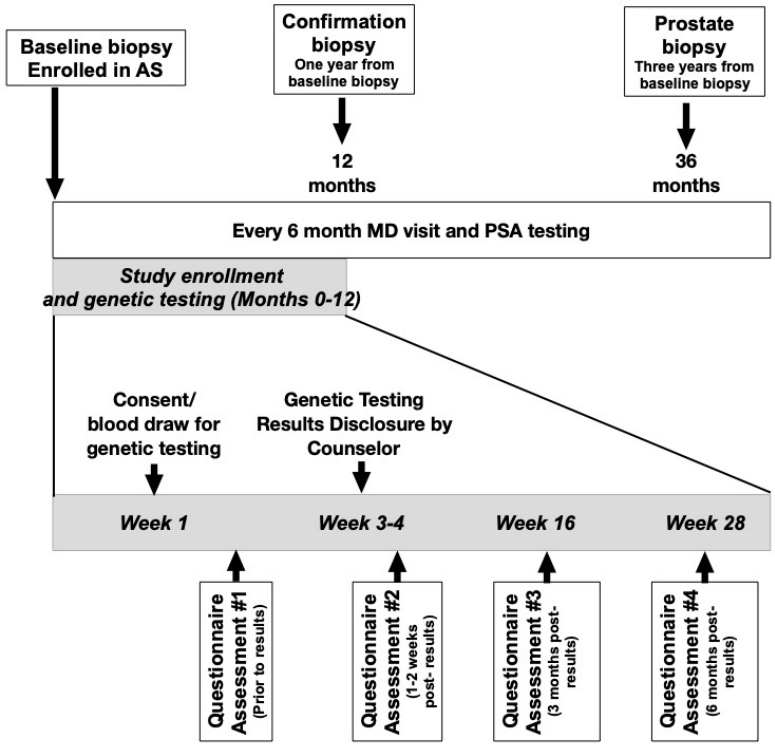
Germline mutations are less frequent in early-stage disease

	NEJM Study	Johns Hopkins/NorthShore	Multi-institutional Study
Number of Patients in Study	692	1211	437
Clinical Characteristics	Metastatic	On Active Surveillance	On Active Surveillance
Any germline mutations	78 (11.3%)	106 (6.9%)	29 (6.6%)
BRCA1, BRCA2 or ATM Germline mutations	37 (5.3%)	27 (2.2%)	8 (1.8%)

Pritchard et al, *NEJM*, 2015; Brady et al *Can Med*, 2022; Ballentine-Carter *European Urology*, 2019

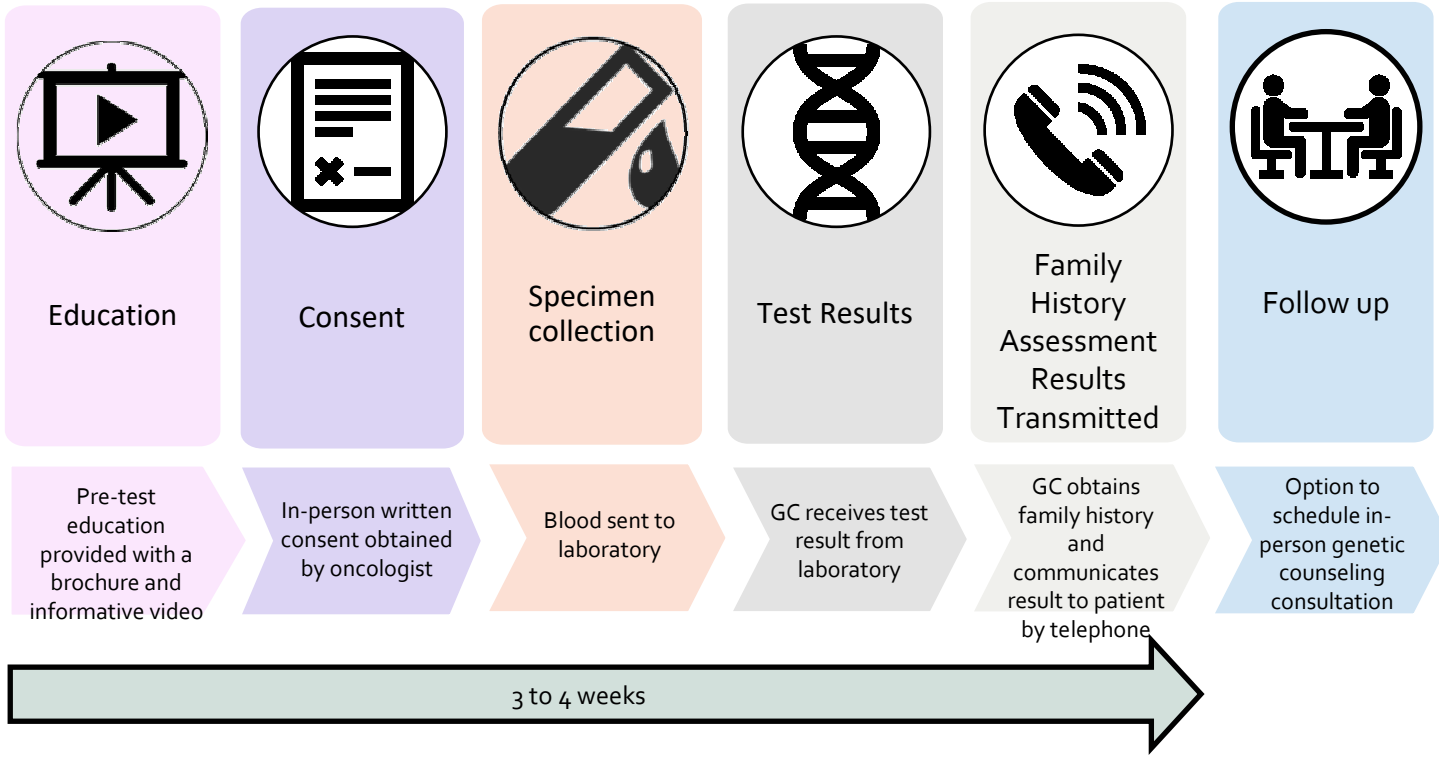
Germline testing for men with PC on active surveillance



Goals of Study:

- Prevalence of mutations in this population
- Association with cancer progression
- Effect on decision making for patients and urologists

Model for germline genetic testing



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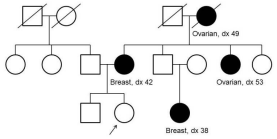

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Targeted *BRCA1/2* Population Screening Among Ashkenazi Jewish Individuals Utilizing a Web-enabled Medical Model: An Observational Cohort Study

Genet Med. 2021 Dec 3; Online ahead of print

BFOR
BRCA Founder Outreach Study

Courtesy of Dr Ken Offit

INTRODUCTION

- Less than 10% of individuals predicted to have mutations *BRCA1* or *BRCA2* gene have been identified to date
- There is an unmet need to facilitate broader testing for the BRCA1/2 genes
- Traditional model models are time consuming and limited by availability of trained providers

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INTRODUCTION

The *BRCA* Founder OutReach (BFOR) study piloted a novel service delivery model that sought to combine the patient-centeredness and convenience of direct-to-consumer testing through use of a digital portal with risk-adapted medical follow-up and engagement of primary care providers in results sharing and management

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METHODS: ENROLLMENT

- Participants Enrolled from December 2017-March 2020; Target accrual 4,000 participants
- Enrollment regions (participating institutions):
  - New York (Memorial Sloan Kettering Cancer Center)
  - Philadelphia (Basser Center for BRCA at the University of Pennsylvania)
  - Boston (Dana Farber Cancer Institute, Beth Israel Deaconess Medical Center)
  - Los Angeles (David Geffen School of Medicine at the University of California Los Angeles)
- Participant eligibility criteria:
  - Age ≥25
  - ≥1 grandparent of AJ ancestry
  - No previous medical *BRCA* testing
  - Healthcare insurance
  - Residence within an eligible zip code
  - English literacy
- Participants were recruited via community-based outreach and enrolled via a chatbot based digital health tool

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METHODS: RECRUITMENT

- Articles in Jewish media
- Partnerships with Jewish leaders
- Community Advisory Board
- Community events
- Distribution of BFOR materials
- Informational talks & webinars
- Social Media
- Email blasts
- Cable TV

JEWISH JOURNAL

JEWISH EXPONENT
— WHAT IT MEANS TO BE JEWISH IN PHILADELPHIA —

New Move To Crowdsource BRCA Screening

THE NEW YORK JEWISH WEEK

HEALTH

BRCA Testing Saved My Life

genomeweb

New study on cancer risk in Ashkenazi Jews aims to be model for genetic testing

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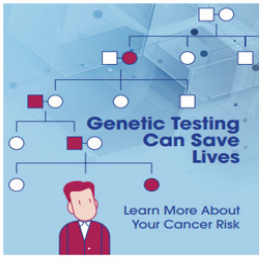
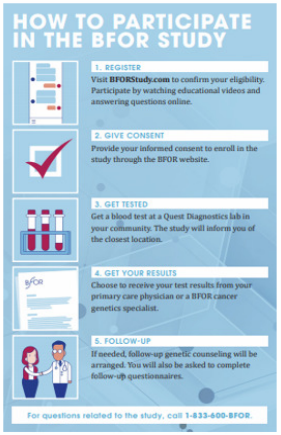
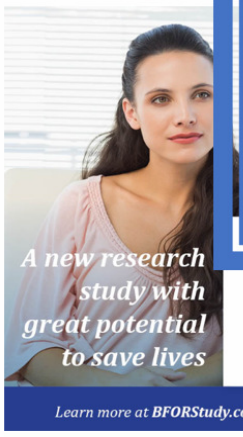
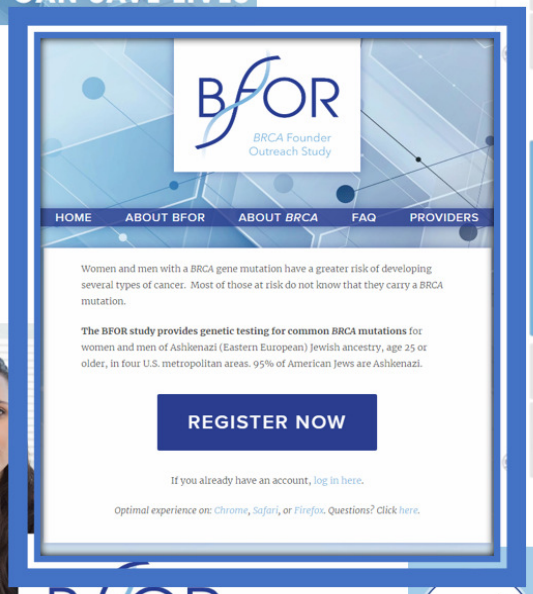
COMMUNITY OUTREACH | BFOR STUDY LANDING PAGE | REGISTRATION & ENROLLMENT



BFOR THE BRCA FOUNDER OUTREACH STUDY
BFORStudy.com | 1-833-600-BFOR

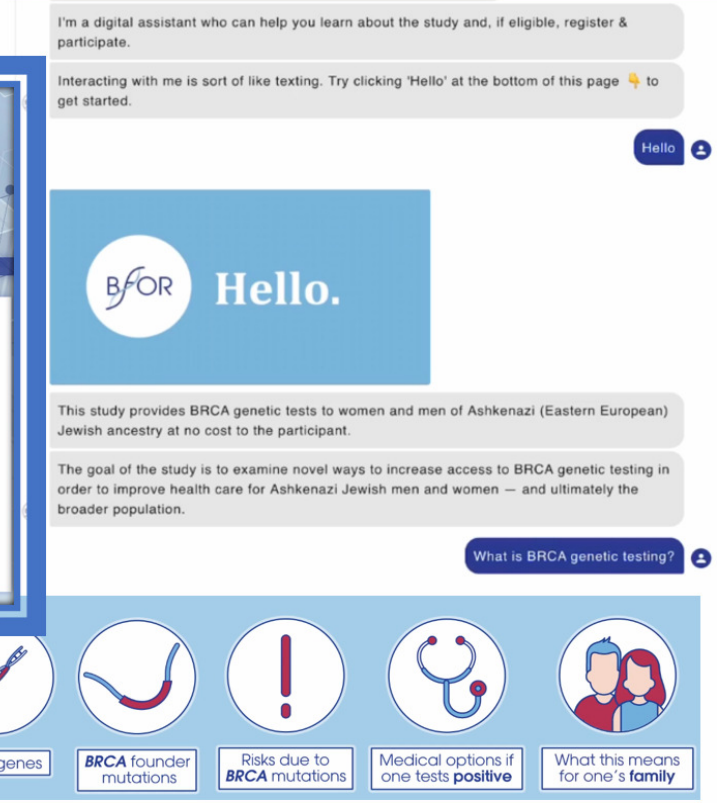






BFOR BRCA Founder Outreach Study

Learn more at BFORStudy.com | 1-833-600-BFOR



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RESULTS: PARTICIPANT DEMOGRAPHICS

5,193 participants enrolled in the study and 4,109 participants completed genetic testing. Demographics are summarized below:

Completed genetic testing	4,109 (79.1%)	
Male/Female	940 (22.9%) / 3,169 (77.1%)	
Median Age, Range	54, 25-93 25-44: 33.4% 45-64: 40.2% **65-84: 25.8%** Over 85: 0.5%	
Personal history of cancer	511 (12.4%)	
Low Prior Probability of a PV	2,304 (56.1%)	490 (21.3%) Male
		1,814 (78.7%) Female
Increased Prior Probability of a PV	1,490 (36.3%)	301 (20.2%) Male
		1,189 (79.8%) Female
Familial PV	315 (7.7%)	149 (47.3%) Male
		166 (52.7%) Female

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RESULTS: GENETIC TEST RESULTS AND BRCA PRIOR PROBABILITY

Result	BRCA Prior Probability	Sex
138 (3.4%) Positive Genetic Testing	21 (15.2%) Low Prior Probability of a PV	8 (38.1%) Male
		13 (61.9%) Female
	31 (22.5%) Increased Prior Probability of a PV	11 (35.5%) Male
		20 (64.5%) Female
	86 (62.3%) Familial PV	57 (66.3%) Male
		29 (33.7%) Female
3,971 (96.6%) Negative Genetic Testing	**2,283 (57.5%) Low Prior Probability of a PV**	482 (21.1%) Male
		1,801 (78.9%) Female
	1,459 (36.7%) Increased Prior Probability of a PV	290 (19.9%) Male
		1,169 (80.1%) Female
	229 (5.8%) Familial PV	92 (40.2%) Male

RESULTS: EARLY MEDICAL FOLLOW-UP

- 45% of participants reported referring at least one family member to participate in the BFOR study

- 86% of participants who tested positive reported planning to increase their cancer screening frequency based on their results

DISCUSSION

- **Over a 27-month period, the BFOR study achieved its target accrual of 4,000 participants**

- Rates of genetic testing completion and participant knowledge following pre-test education were comparable to studies including traditional pre-test counseling

- Over a quarter of enrollees were >65 years old, demonstrating that older age was not an inherent barrier to a web-based initiative

- Participants with a known familial mutation represented 7.7% of all participants tested, supporting the utility of this web-based model for cascade testing

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Conclusions

- Germline mutations are common (~12%) in men with advanced prostate cancer
- Knowledge of germline mutation can help guide treatment, help for screening for other cancers and useful for family members
- The specific gene matters for cancer risks and for response to therapy
- Important to follow-up tumor only sequencing to understand risks of germline mutations
- Novel methods of genetic testing are being studied and seem promising

Thank you

Questions?

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