Fred Hutch Cancer Center

# Identifying and Addressing Disparities in Precision Medicine and Germline Genetic Testing in Prostate Cancer

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**HICOR 8th Value in Cancer Care Summit**
**Bell Harbor Conference Center, Seattle, WA**
**November 2, 2023**

# Disclosures

- **Research Funds to Institution:** Clovis Oncology, Color Health, Janssen, Medivation, Promontory Pharmaceutics, Sanofi
- **Consultant:** AstraZeneca, Janssen, CureBRCA
- **Royalties:** UpToDate



# *Raise your hand if…*

## My Medical Choice

By ANGELINA JOLIE MAY 14, 2013

## Angelina Jolie Pitt: Diary of a Surgery

By ANGELINA JOLIE PITT MARCH 24, 2015

New York Times May 15, 2

Oli Scarff/Getty In

OPINION

## Beyoncé's Dad Has a Mutation More African-Americans Should Be Tested For

An inherited gene that can be discovered early caused Matthew Knowles's breast cancer.

Oct. 16, 2019

Matthew Knowles Johnny Nunez/WireImage

# Outline

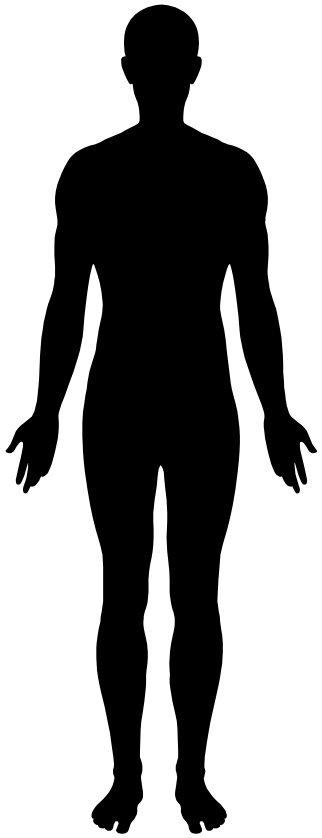
1. **Background** *what is prostate cancer genetics and why does it matter*
2. **Clinical Actionability** *why is it even more important now*
3. **Genetics Care Delivery** *what has been tried (clinical and research)*
4. **Conclusions and Future Directions** *what do we need to do better*

# Prostate Cancer Statistics in 2023

- Most common cancer diagnosis and second-leading cause of cancer death in US men[1]
  - **288,300 new cases** and **34,700 deaths**
- More diagnoses of distant-stage PC[2]
  - Doubled from 4% in 2003 to 8% in 2017
- More life-prolonging therapies[3]
- More men living with metastatic PC[4,5]
  - By 2030, ~192,500 will be living with metastatic PC

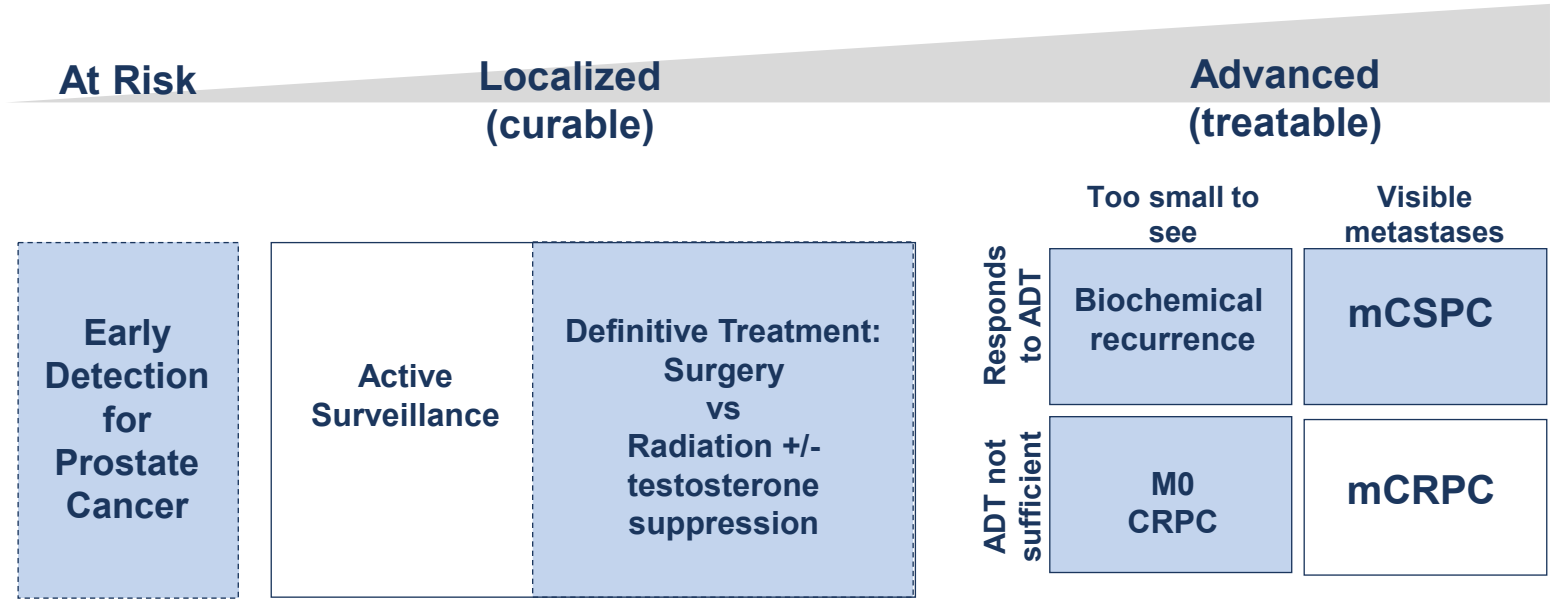
## New Cancer Cases in US Men, 2023[1]

| | | |
|---|---|---|
| **Prostate** | **288,300** | **29%** |
| Lung and bronchus | 117,550 | 12% |
| Colon and rectum | 81,860 | 8% |
| Urinary bladder | 62,420 | 6% |
| Melanoma of the skin | 58,120 | 6% |
| Kidney and renal pelvis | 52,360 | 5% |
| Non-Hodgkin lymphoma | 44,880 | 4% |
| Oral cavity and pharynx | 39,290 | 4% |
| Leukemia | 35,670 | 4% |
| Pancreas | 33,130 | 3% |
| All sites | 1,010,310 | 100% |



1. Siegel. CA Cancer J Clin. 2023;73:17. 2. Siegel. MMWR. 2020;69:1473. 3. NCCN. Prostate cancer. v.1.2023.
4. Kelly. Eur Urol Focus. 2018;4:121. 5. Devasia. Cancer Epidemiol Biomarkers Prev. 2023;[Epub].

# Prostate Cancer Disease States




*Current clinical trials for molecular subtypes*

*FDA-approved targeted therapies options*

ADT = androgen deprivation therapy (testosterone suppression)

**Urology**
**Primary Care**

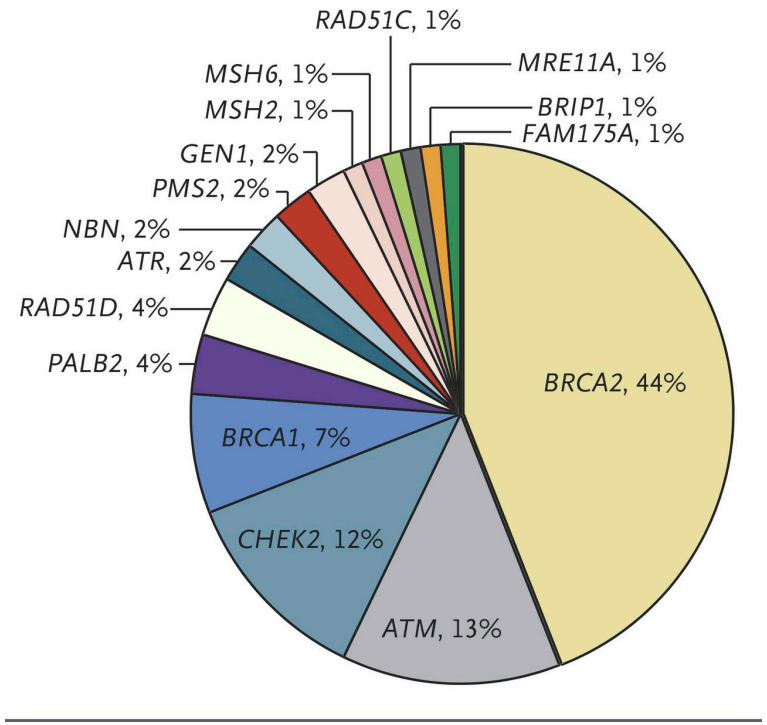
**Urology**

**Urology**
**Radiation Oncology**
Medical Oncology

**Medical Oncology**
**Radiation Oncology**
Urology

# Background

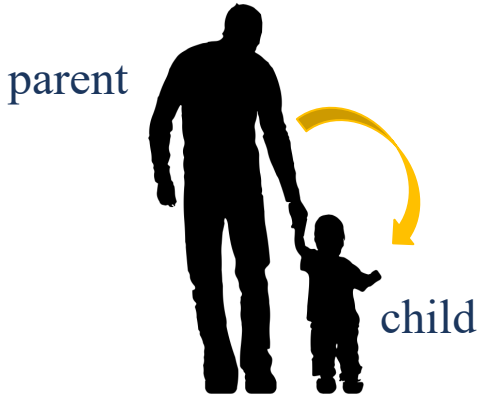
- ~10% of men with metastatic prostate cancer carry inherited mutations in DNA repair genes (inherited cancer risk genes).
- Important because…:
  - Precision therapy (PARP inhibitors, immune checkpoint inhibitors)
  - Prognosis: cancers behave more aggressively
  - Family members may share same cancer risk
  - Cancer screening and prevention implications
- **NCCN guidelines: genetic testing should be considered (2017) then recommended (2019) in patients with metastatic prostate cancer (first consider then recommend)**




Pritchard, et al NEJM 2016

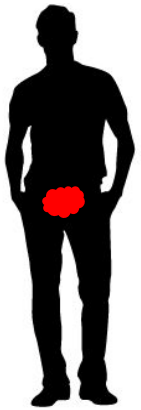
# *Hereditary (Germline) genetics vs Tumor genetics*

## INHERITED DNA
**(Hereditary, Germline DNA)**




- ***"Master Blueprints"*** *Inherit* half of our DNA from each parent
- Changes are in ***ALL*** healthy cells of the body
- Some changes in genes (variants/mutations) are linked with higher risks of cancer
- Typically ***blood or saliva***
- ***Healthy cell DNA doesn't change over time***

## CANCER-SPECIFIC DNA
**(Tumor, Genomic, Somatic DNA)**



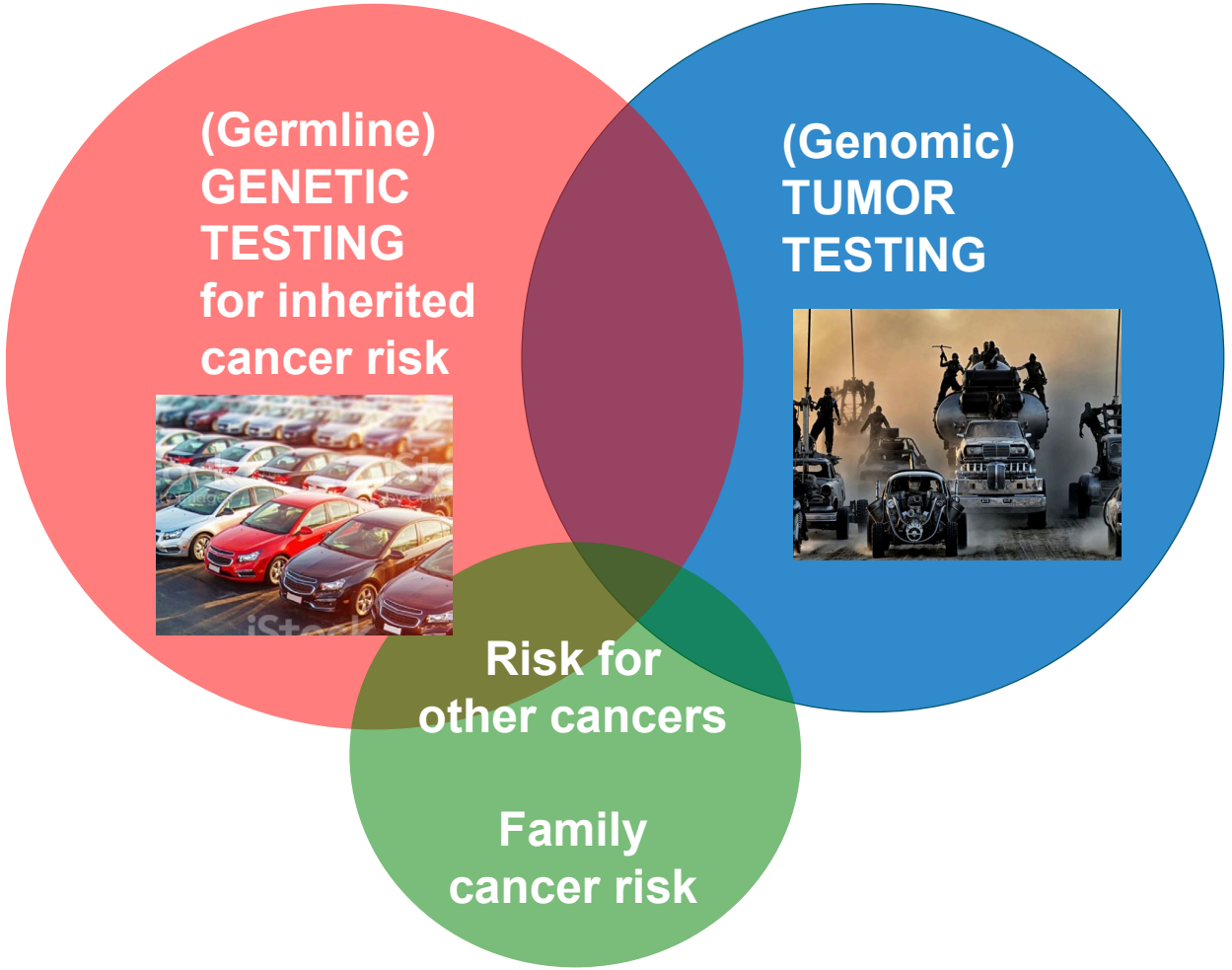
- *"Working Manual" Starts from Master Blueprints, then acquires mistakes over time*
- *Changes are NOT* passed on to children
- Must test *cancer cells/tissue*
- Test methods are evolving
- Cancer may evolve

# *WHY Test for Inherited Cancer Risk:*

1. ***IT MAY HELP YOU*—*understand the risk of prostate and other cancers and find earlier***

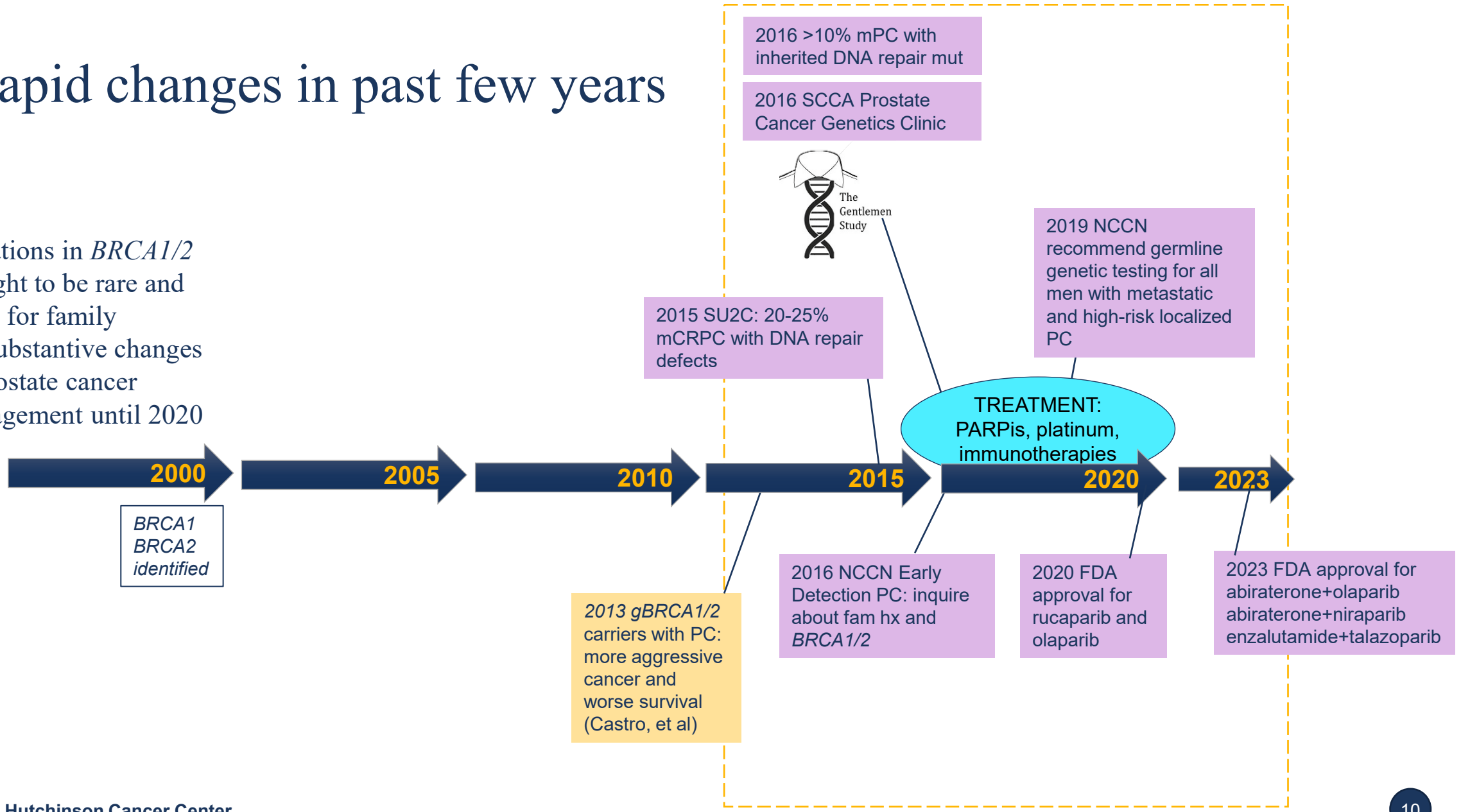
2. ***IT MAY HELP YOUR FAMILY*—*understand their cancer risks, and have potentially life-saving options***

3. ***IT MAY HELP YOU*—*have additional targeted treatment options for your prostate cancer***

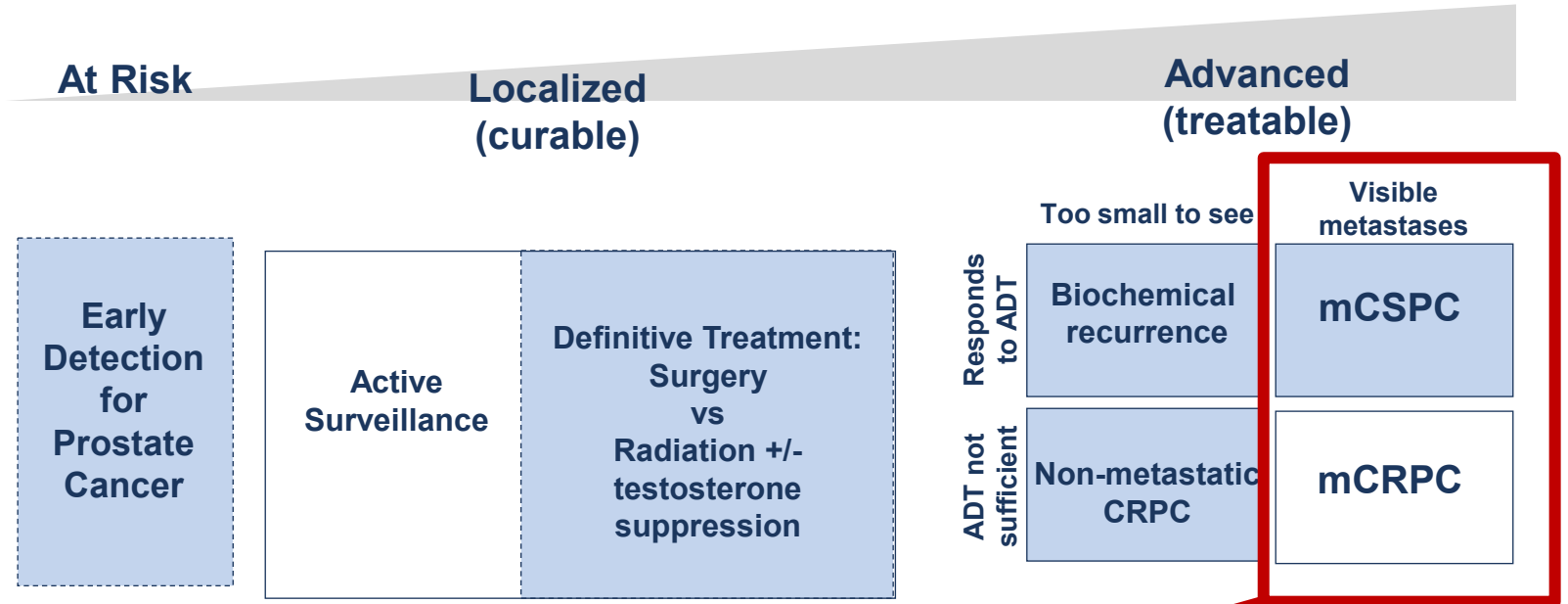


# Rapid changes in past few years

1. Mutations in *BRCA1/2* thought to be rare and more for family
2. No substantive changes to prostate cancer management until 2020

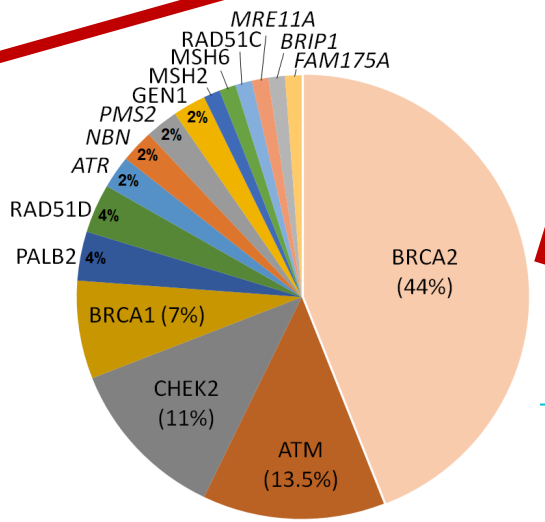


# 10% of men with metastatic prostate cancer carries an inherited mutation in a DNA repair gene

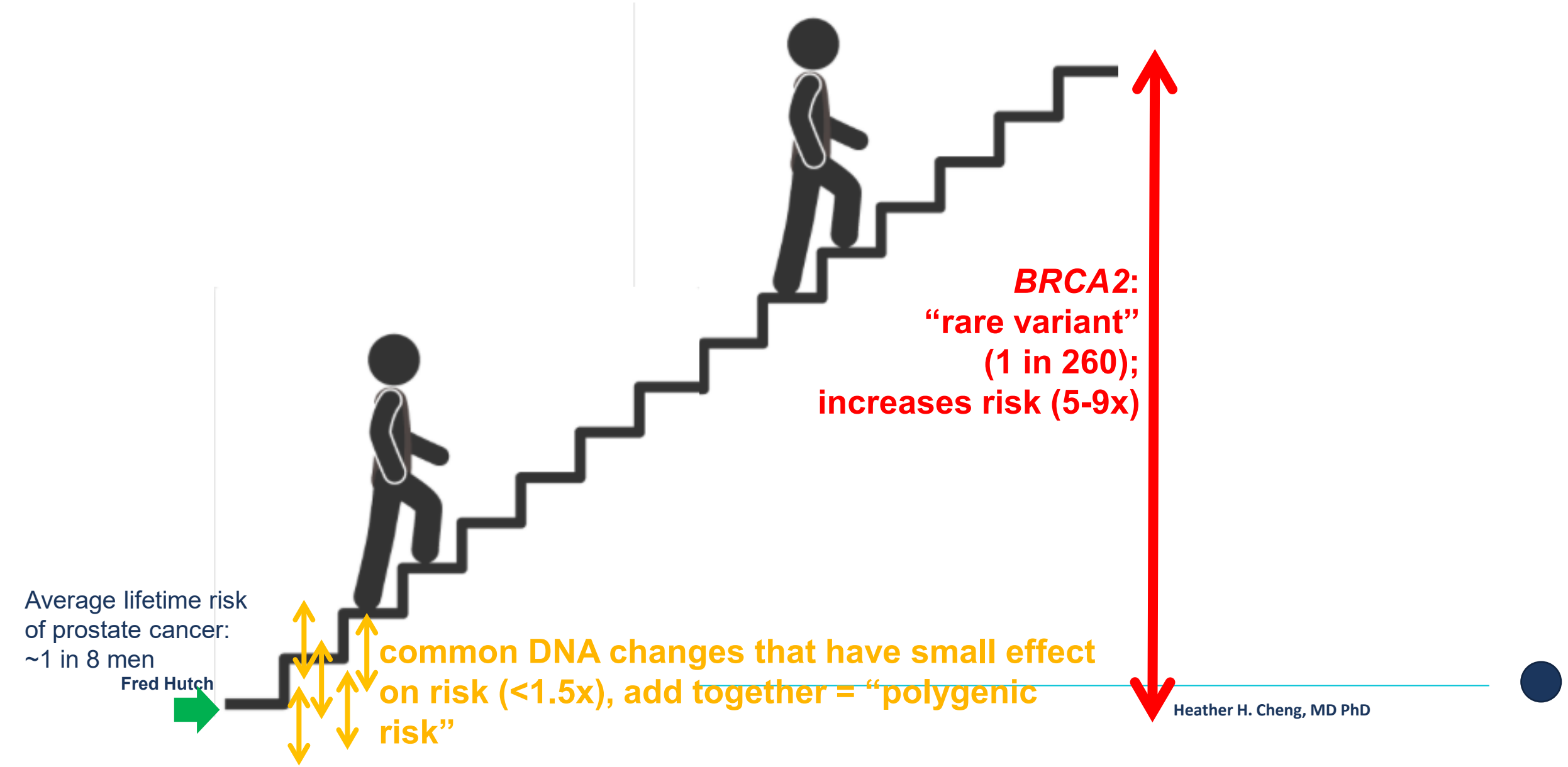



- **11.8%** (82/692) with inherited mutations in DNA repair genes
- Many without family history
- Known/suspected autosomal cancer predisposition

Pritchard, et al. 2016 NEJM



# Genetic effects on cancer risk: small vs large effect gene variants



# Who should be offered genetic testing for inherited cancer risk?

**Recommend in patients with:**

- Metastatic, lymph node positive, Gleason 8-10, PSA>20)
- Family history of known cancer risk gene (*BRCA2, BRCA1,* Lynch Syndrome)
- Family history of cancer, esp. breast, pancreatic, ovarian
- Ashkenazi Jewish ancestry
- A diagnosis of male breast cancer

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2023**
**Prostate Cancer**

NCCN Guidelines Index
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Discussion

**PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS**

**Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:**

- **By prostate cancer stage or risk group (diagnosed at any age)**
  - **Metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer**
- **By family history[a] and/or ancestry**
  - **≥1 first-, second-, or third-degree relative with:**
    - ◊ **breast cancer at age ≤50 y**
    - ◊ **colorectal or endometrial cancer at age ≤50 y**
    - ◊ **male (sex assigned at birth) breast cancer at any age**
    - ◊ **ovarian cancer at any age**
    - ◊ **exocrine pancreatic cancer at any age**
    - ◊ **metastatic, regional, very-high-risk, or high-risk prostate cancer at any age**
  - **≥1 first-degree relative (parent or sibling) with:**
    - ◊ **prostate cancer[b] at age ≤60 y**
  - **≥2 first-, second-, or third-degree relatives with:**
    - ◊ **breast cancer at any age**
    - ◊ **prostate cancer[b] at any age**
  - **≥3 first- or second-degree relatives with:**
    - ◊ **Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer**
  - **A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2,* and *EPCAM***
  - **Ashkenazi Jewish ancestry**
- **Personal history of breast cancer**

**Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:**

- **By prostate cancer tumor characteristics (diagnosed at any age)**
  - ◊ **intermediate-risk prostate cancer with intraductal/cribriform histology[c]**
- **By prostate cancer[b] AND a prior personal history of any of the following cancers:**
  - ◊ **exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal**

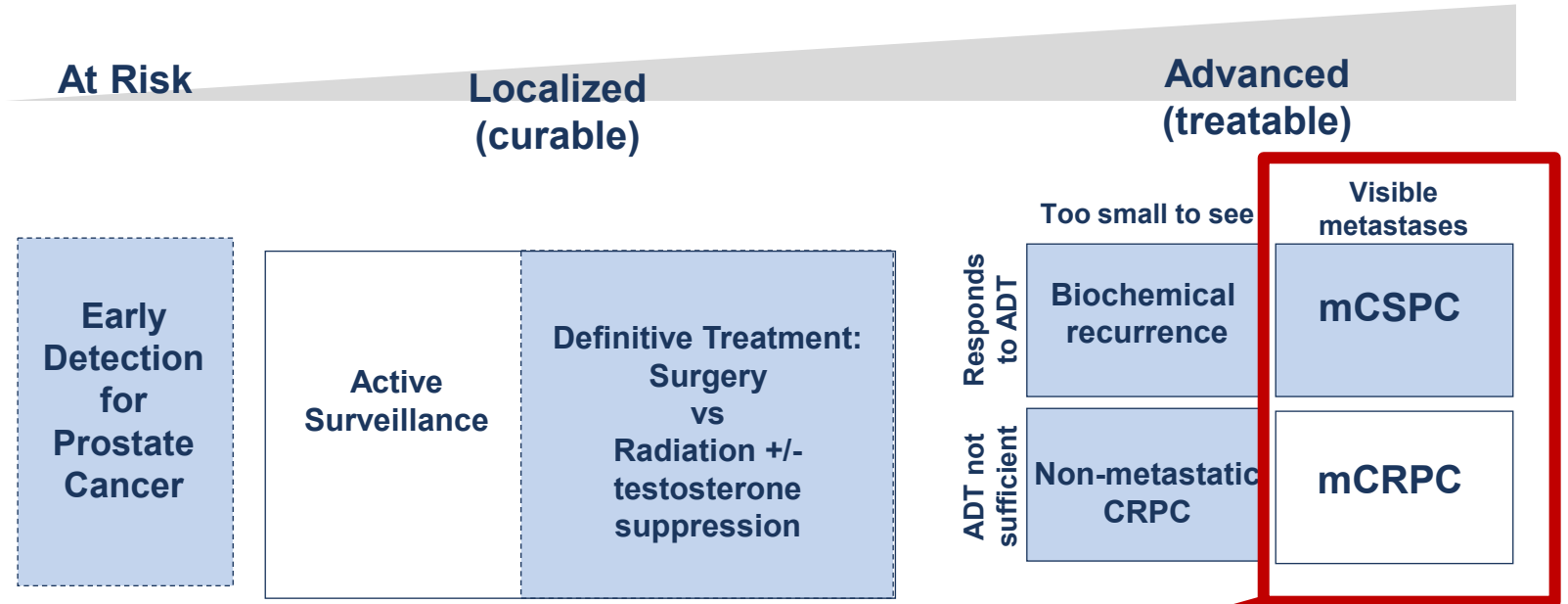
[a] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[b] Family history of prostate cancer should not include relatives with clinically localized Grade Group 1 disease.

[c] Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate, or ductal adenocarcinoma component have increased genomic instability, and germline testing may be considered.

# Clinical Actionability:
## Precision Treatment

# 10% of men with metastatic prostate cancer carries an inherited mutation in a DNA repair gene

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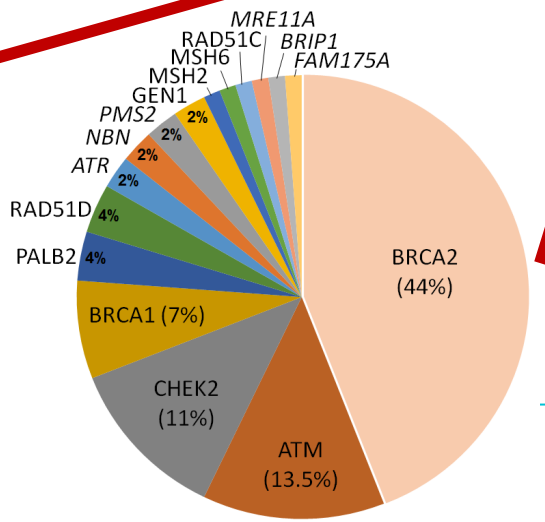
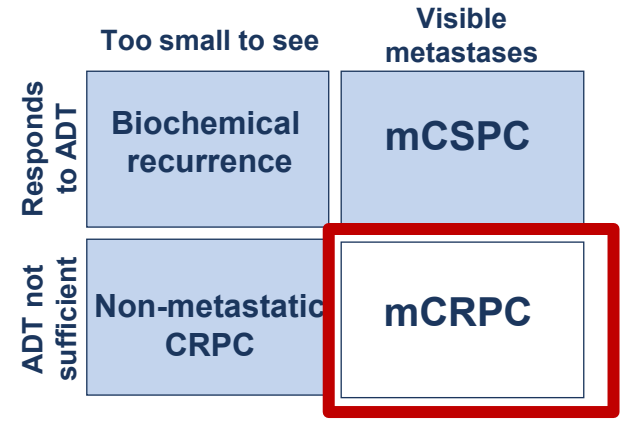
Pritchard, et al. 2016 NEJM

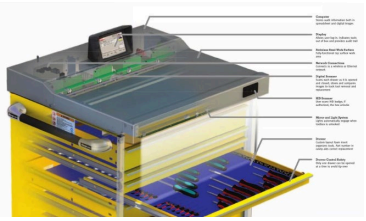


# Treatment Toolbox for Advanced Prostate Cancer

**At Risk** → **Advanced (treatable)**

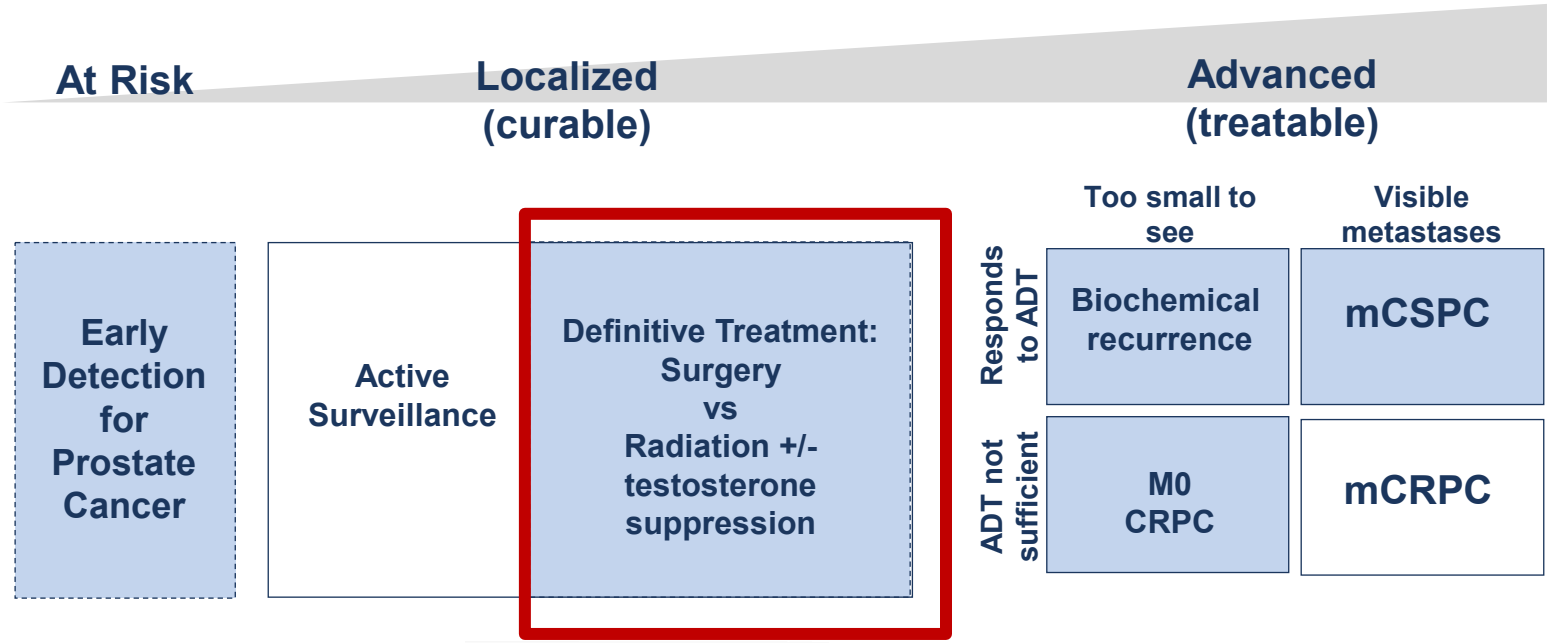
1. Androgen deprivation therapy (ADT)
2. Abiraterone (Zytiga)
3. Docetaxel (Taxotere)
4. Apalutamide (Erleada)
5. Darolutamide (Nubeqa)
6. Sipuleucel-T (Provenge)
7. Enzalutamide (Xtandi)
8. Cabazitaxel (Jevtana)
9. Radium-223 (Xofigo)
10. Vipivotide tetraxetan (Pluvicto)

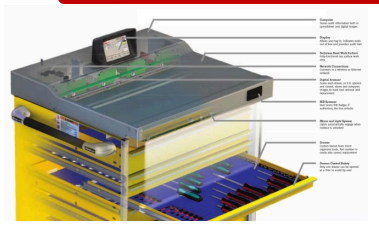


a. Pembrolizumab
b. Rucaparib
c. Olaparib
d. Abiraterone/olaparib
e. Abiraterone/niraparib
f. Enzalutamide/talazoparib
g. Carboplatin

# Prostate Cancer Disease States



**Could we use targeted treatments prior to surgery to improve chance of cure?**

# SWOG S2210: A PHASE II STUDY OF CARBOPLATIN BEFORE SURGERY FOR HIGH RISK LOCALIZED PROSTATE CANCER IN PEOPLE WITH INHERITED *BRCA1/2* MUTATIONS

***Activated August 14, 2023!***

**Potentially curable prostate cancer, but high risk for not being cured (Gleason 8-10, GG4-5, PSA>20)**

and **inherited *BRCA1/2* mutations**

→ **4 doses of carboplatin (known to be very effective in *BRCA1/2* cancers**

→ **surgery to remove prostate**

→ **<u>Primary Endpoint:</u>**
**Pathologic complete response rate (at time of surgery, no residual cancer is found)**
-Overall survival


Megan Keim


Sam Callis


Cathy Tangen


Tanya Dorff


Evan Yu


Dan Lin


Nick Vogelzang
*(in memoriam)*

# Care Delivery & Implementation

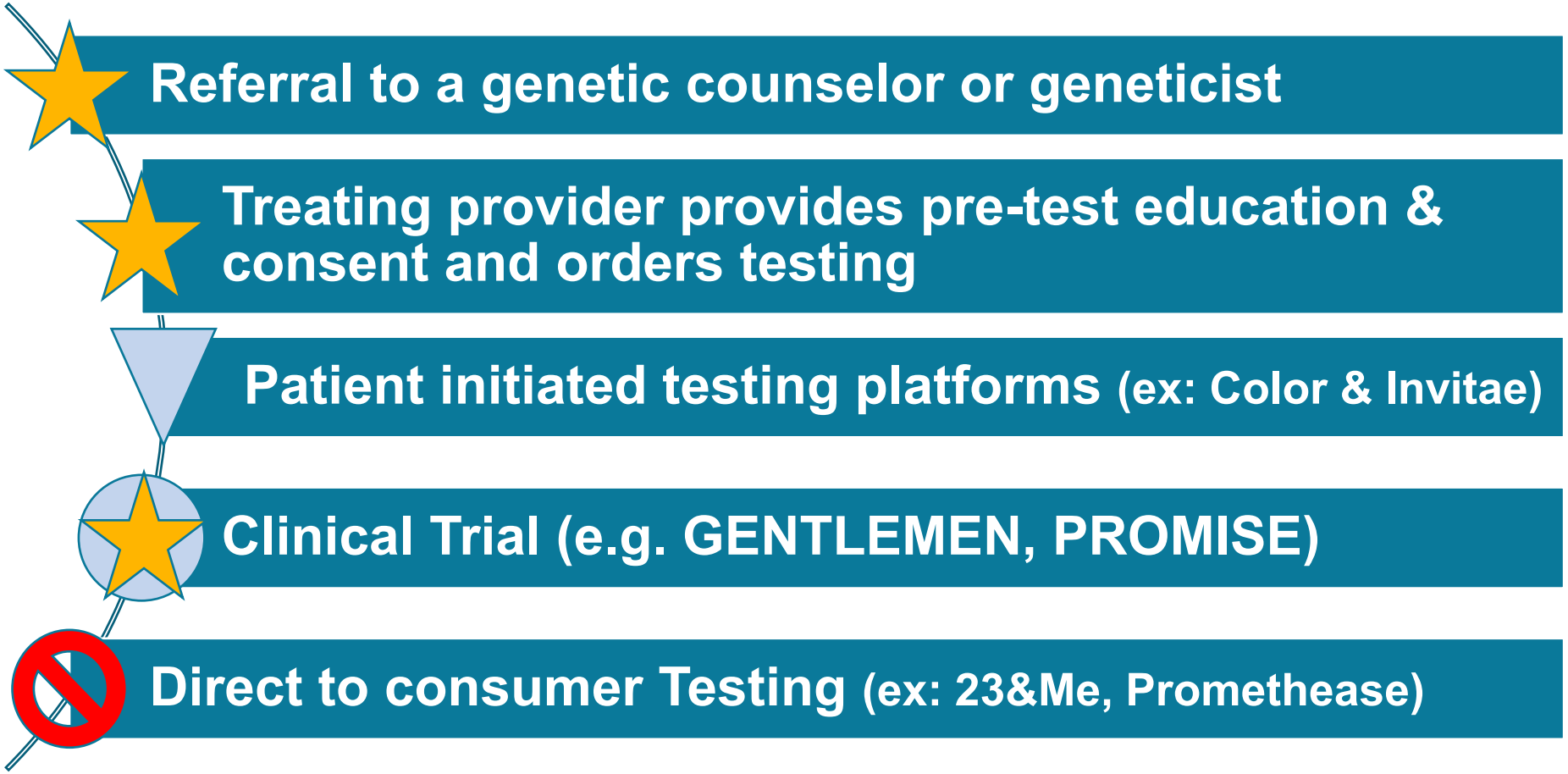
JAMA

Medical News & Perspectives

It Takes an Average of 17 Years for Evidence to Change Practice—the Burgeoning Field of Implementation Science Seeks to Speed Things Up

Rita Rubin, MA

# How Can Patients Get Hereditary (Germline) Genetic Testing?






Szymaniak and Facchini, et al. J Onc Practice, *2019*

# Prostate Cancer Genetics Clinic (c.2016)

1. **Medical Oncology/Urology**
   - Review of genetics (inherited and tumor)
   - Treatment, clinical trial and research
   - Cascade genetic testing

2. **Genetic Counselor**
   - Pre/post- test genetic counseling
   - Navigating insurance coverage
   - Guidance on cascade testing for family

3. **Comprehensive Cancer Genetics Care**
   - For carriers: tailored cancer screening—
   - Prostate, breast, ovary, pancreas, etc.

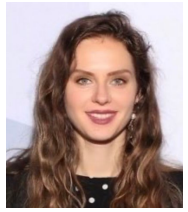
The Gentlemen Study

# GENetic Testing for MEN with metastatic prostate cancer

www.gentlemenstudy.org

*Started 2016*

Deb Bowen
*(in memoriam)*



Alexandra Sokolova

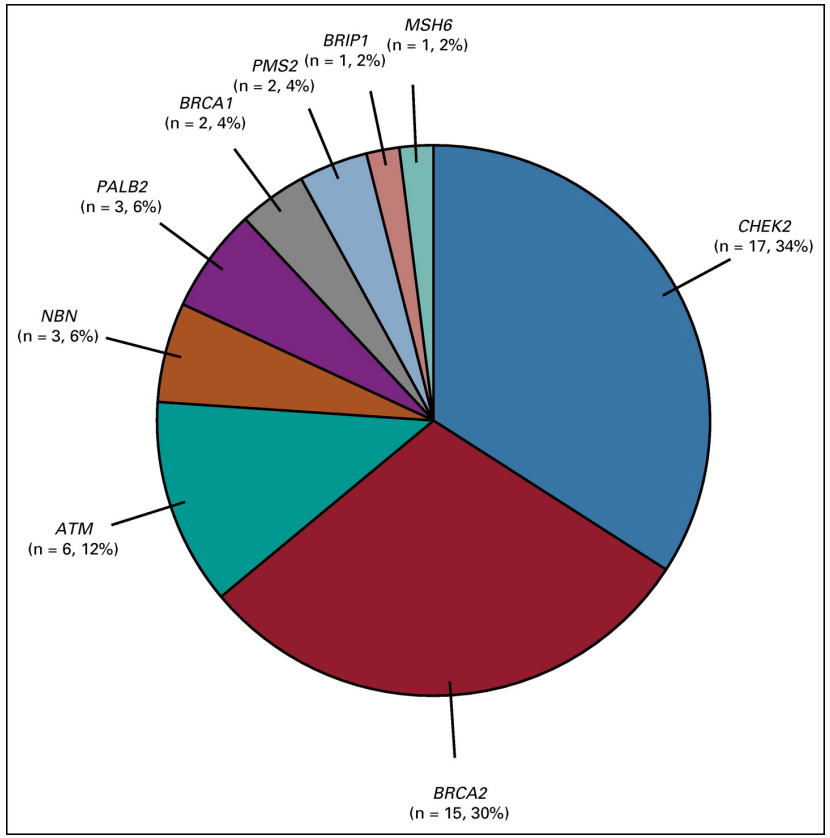
**Roman Gulati**
**Hannah Loesch**
**Brianna Woo**
**Colin Sievers**
**Katerina Alexander**
**Nola Klemfuss**

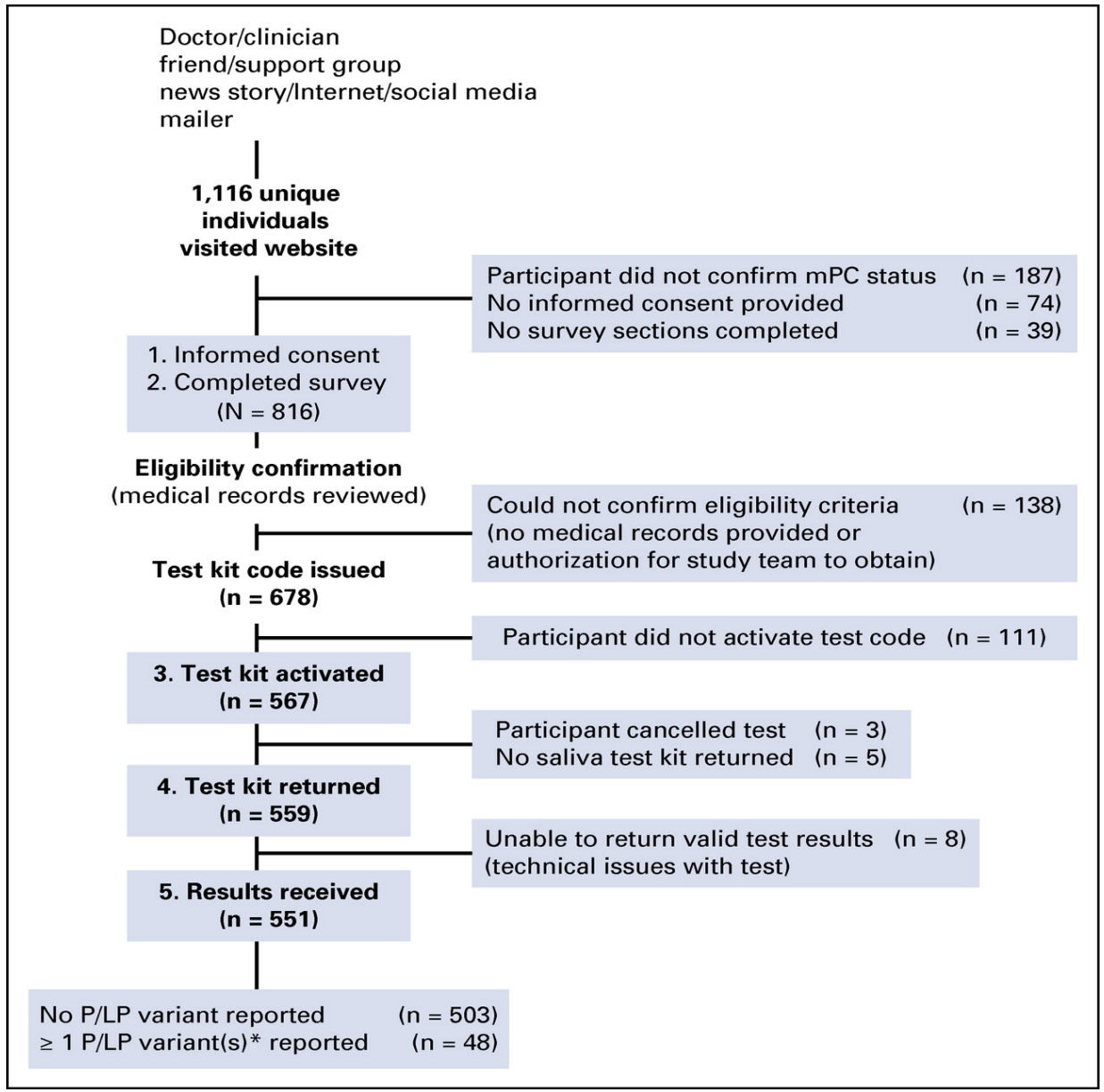
**Evan Yu**
**Pete Nelson**
**Bruce Montgomery**

OBJECTIVE: **Remove barriers** to genetic testing that may provide critical information for men with metastatic prostate cancer living in Washington State (later U.S.) and their families

1. ***Recruitment from clinic, support groups, newsletters, social media outreach***
2. ***Self-enrolled, Web-based informed consent***
3. Web-based patient survey: family history, knowledge, behavior, distress
4. Upload supporting data to verify metastatic PCa: PSA, pathology, scans
5. Patients are mailed **Color Genomics** saliva kit (costs covered by study)
6. Color Genomics pre-test video and post-test phone access to counselors
7. Patients receive result; invited to follow-up additional genetic counseling, cascade testing, opportunities for research/registry participation, etc.

# GENTleMEN results





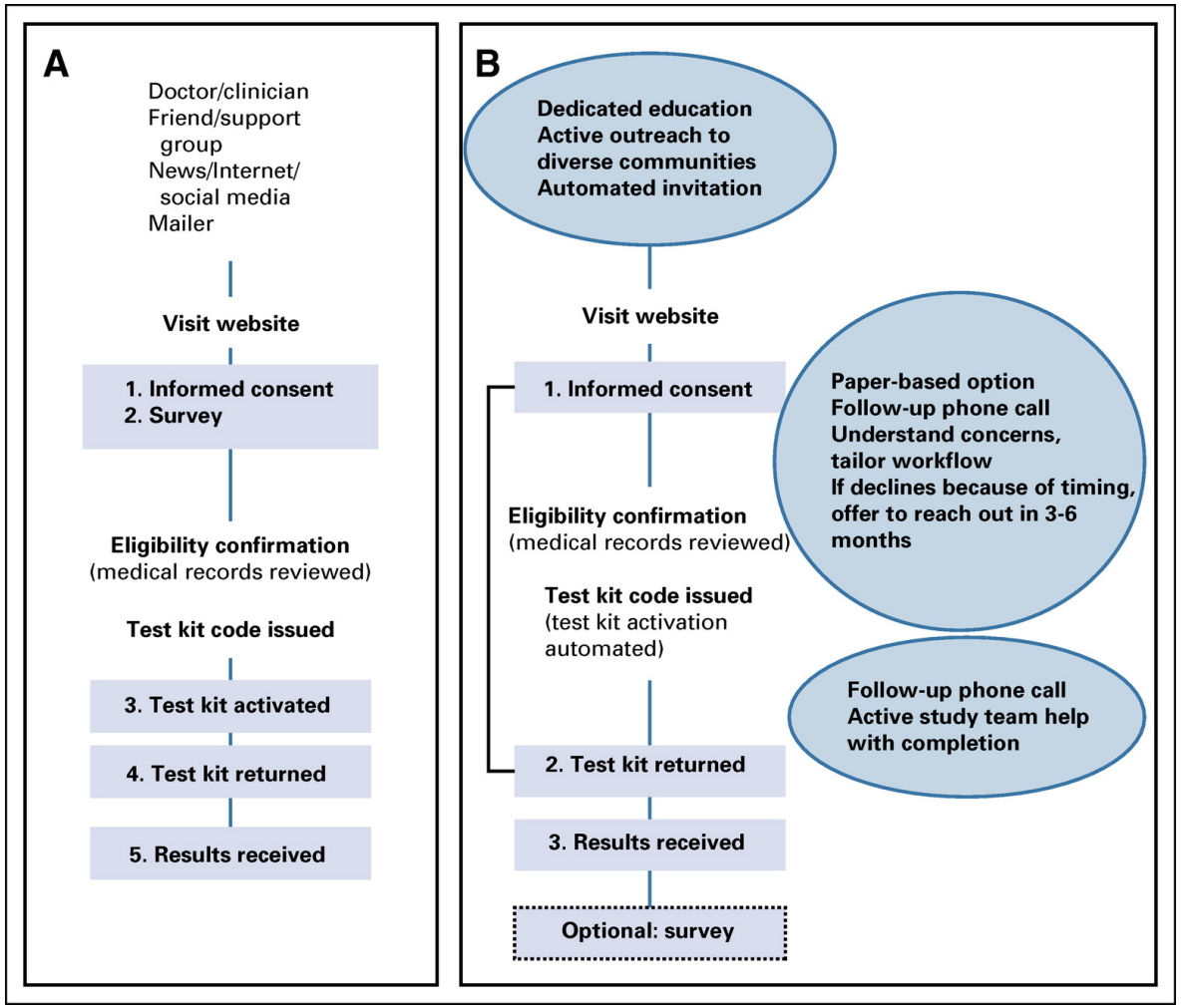

Cheng, et al. 2023 JCO PO

# GENTleMEN…yes, we can…

1. We can deliver genetic testing remotely
2. We can engage patients in research remotely
3. More on demographics in a moment
4. Drop off can be improved, e.g….

*WHAT CAN WE DO BETTER?*

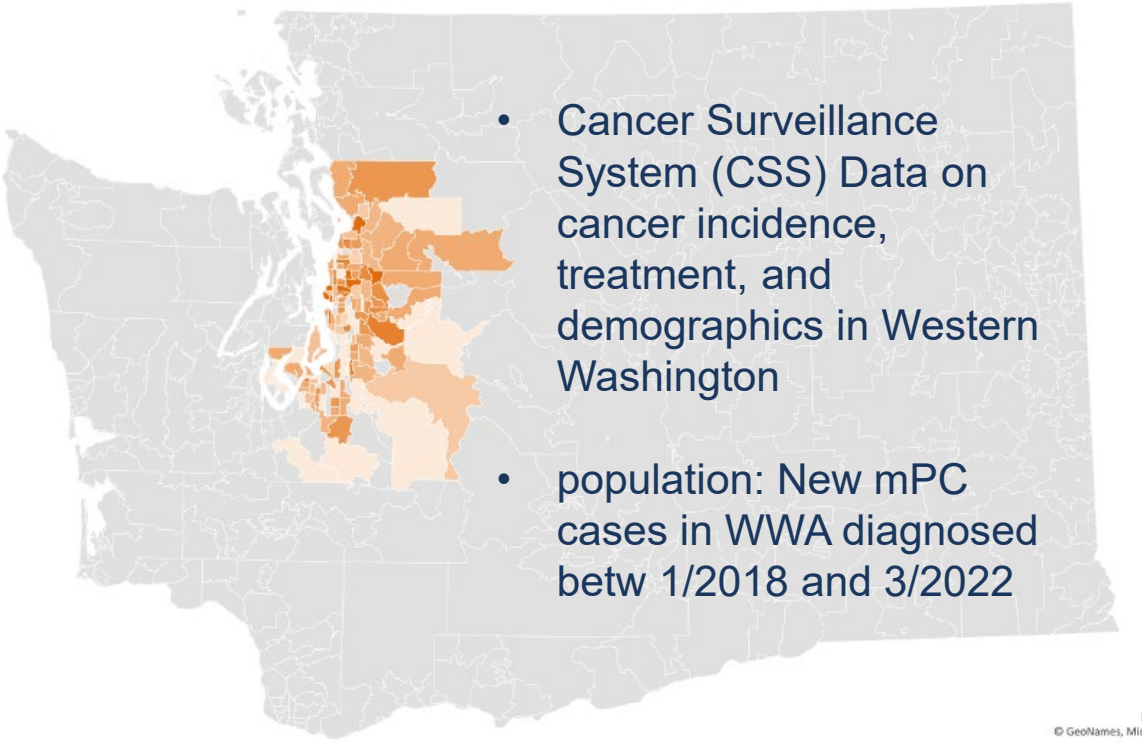
*WHO ARE WE MISSING?*






Cheng, et al. 2023 JCO PO

# Using Cancer Registry to Learn Which Patients May be Missed: GIFTS



- Cancer Surveillance System (CSS) Data on cancer incidence, treatment, and demographics in Western Washington
- population: New mPC cases in WWA diagnosed betw 1/2018 and 3/2022


Janet Stanford


Risa Wong


Hiba Khan

OBJECTIVES

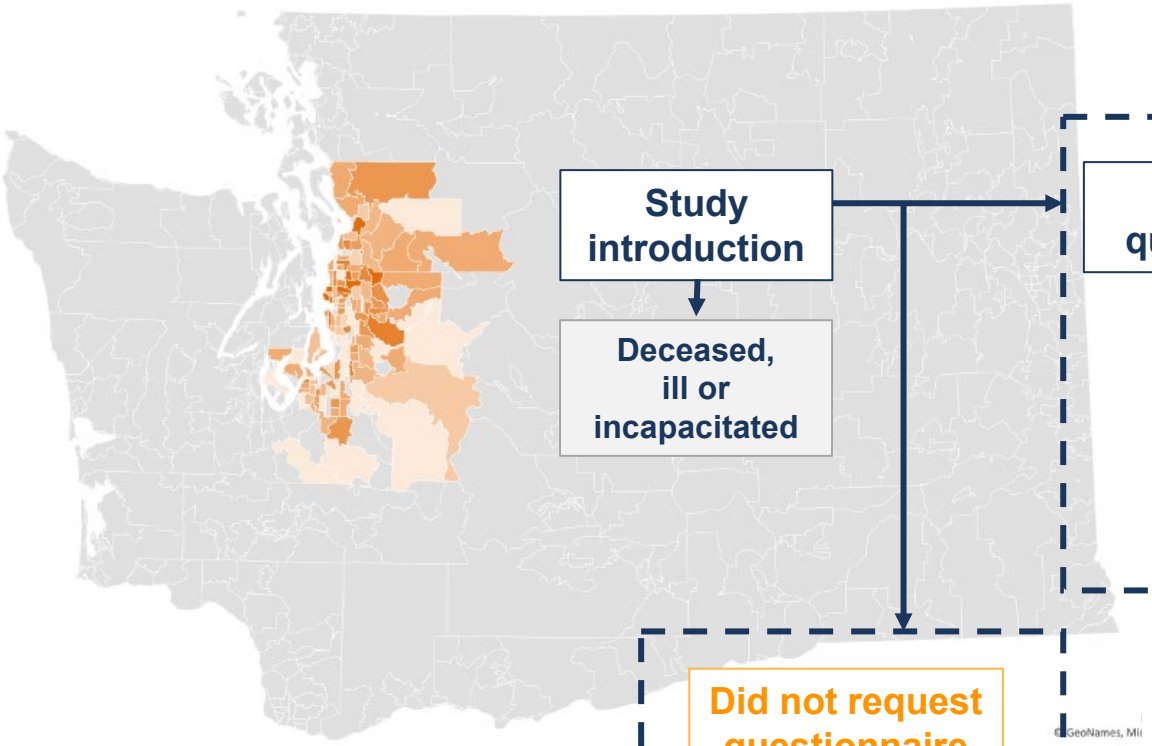
1. Describe the patterns and gaps in testing amongst patients with mPC in the Western Washington community
2. Offer free testing for mPC patients in our community who have not yet undergone germline genetic testing (a la GENTLEMEN)
3. Understand uptake of testing when offered ***with phone assistance*** and with no cost



Khan, oral presentation at ASCO 2022
Khan et al., *in preparation*

# GIFTS Design

Hiba Khan



Study introduction

Deceased, ill or incapacitated

Requested questionnaire

Completed questionnaire

Offered free genetic testing through GIFTS

41%

Reported prior genetic testing

11%

Did not request questionnaire

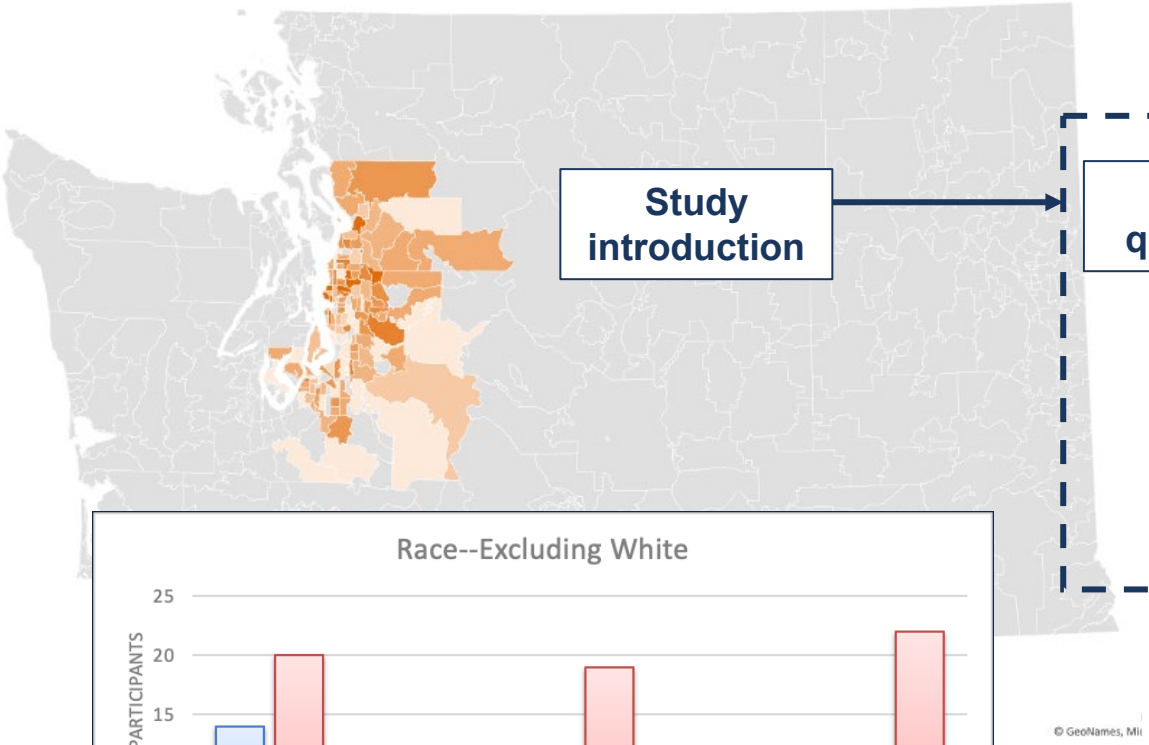
48%



Khan, oral presentation at ASCO 2022
Khan et al., *in preparation*

# GIFTS Results

Hiba Khan



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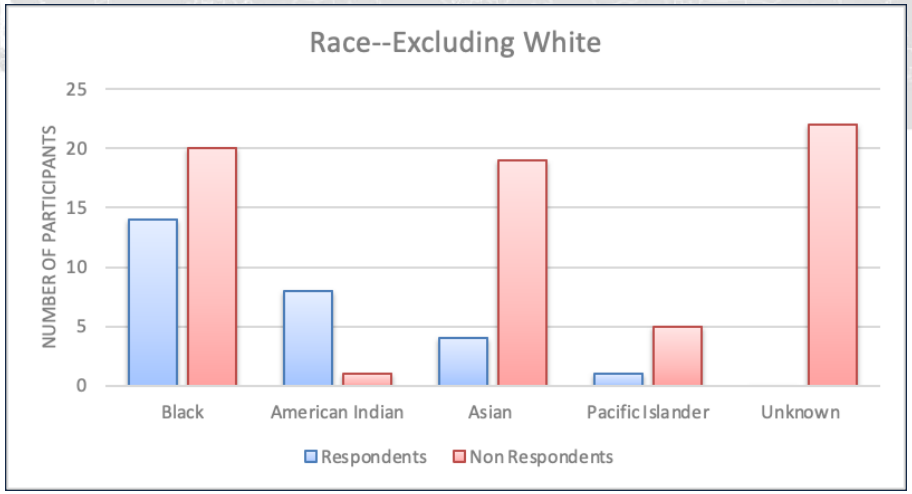



**Demographics of Respondents compared to Non-Respondents:**

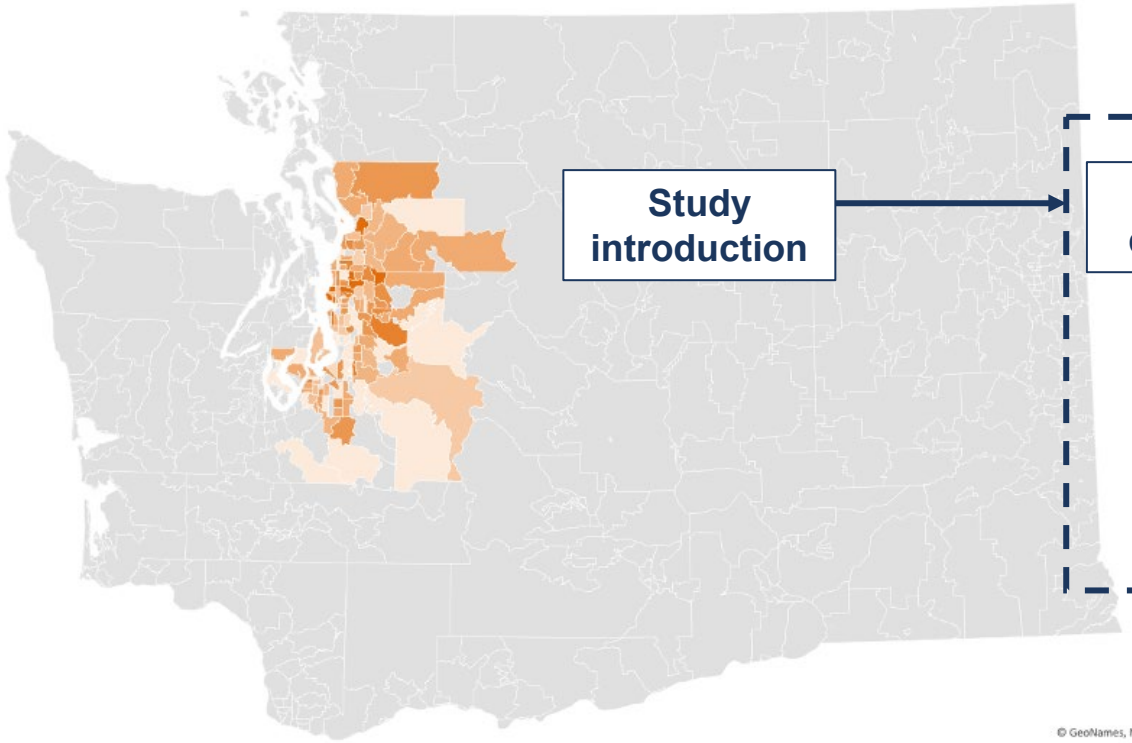
- **Majority of respondents were White**
- **Proportion esp. low among Black, Asian, Pacific Islanders**
- **Particularly high among American Indian men**



Khan, oral presentation at ASCO 2022
Khan et al., *in preparation*

# GIFTS Results

Hiba Khan



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**88%** (168/192) of those who indicated interest in genetic testing received testing

Of all respondents who had any genetic testing, 7% (9/128) of them had pathogenic variant identified, including in *ATM (1)*, *BRCA2 (3)*, *BRIP1* (1), *CHEK2 (1)*, *PALB2 (1)*, and *PMS2 (2)*



Khan, oral presentation at ASCO 2022
Khan et al., *in preparation*

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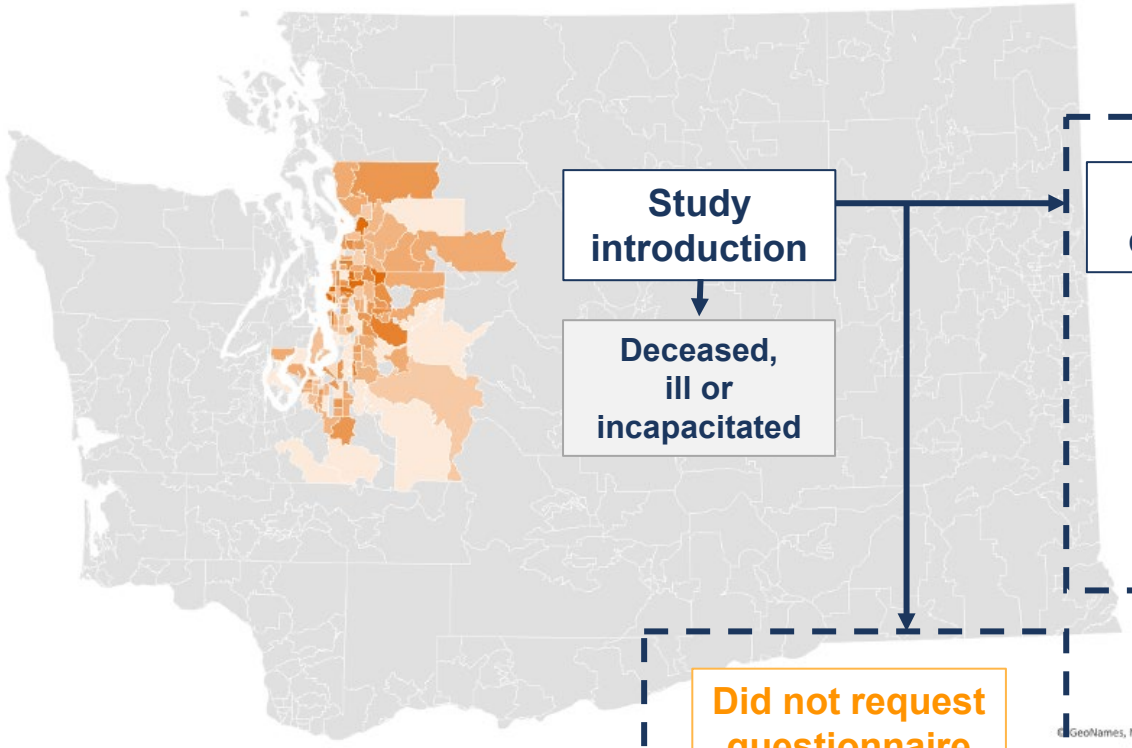
Hiba Khan



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***About half did not indicate interest in testing after outreach…WHY?***



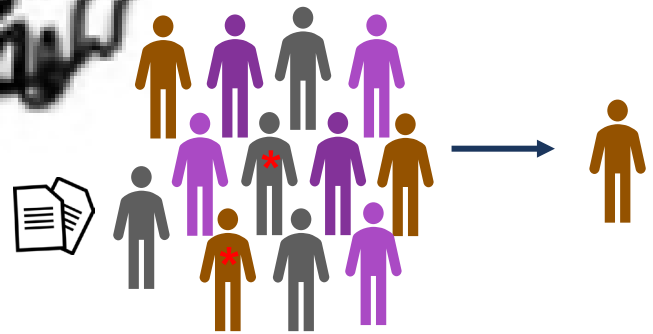
Khan, oral presentation at ASCO 2022
Khan et al., *in preparation*

IFTS

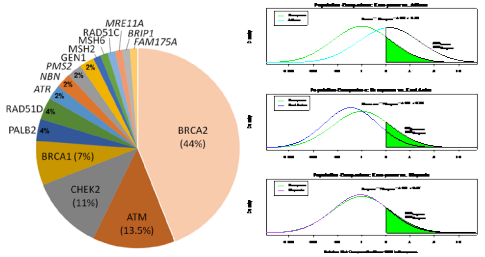
Genetic Information to Inform Treatment and Screening for Prostate Cancer

## SPORE Project 1
## Aim 1: Define the interaction of *BRCA1/2* and multi-ancestry PRS across diverse populations.

**Newly diagnosed prostate cancer cases identified in CSS and now WA State Cancer Registry**



Incident PCa in multi-ancestry (not exclusively white) patients




*gDRG



PRSm

Burcu Darst

Colin Pritchard

Dan Lin

Yaw Nyame

Fred Hu

# Promise.

## Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness

**Participant Outreach**
PROMISE Registry advertised in pamphlets, online advertisements, support groups, or by word of mouth

**Participant Self-Consent**
Participant visits the PROMISE Portal through Color's website, fills out consent and provides cancer care provider's contact information


**Saliva Collection Kit**
Color sends physician-ordered kit to participant, who completes at home and sends back to Color for germline genetic testing

**POSITIVE for Pathogenic or Likely Pathogenic Variant (n=400)**
Participant and provider informed of PROMISE Registry eligibility

**PRESENCE of Variant of Uncertain Significance (n=100)**
Clinical and research results evaluated by PROMISE Investigators to determine participant's eligibility

**NEGATIVE for PV, LPV or VUS**
Participant informed he is not eligible for long-term follow-up


**Return of Results**
Clinical report returned to participant, provider, and PROMISE through PROMISE Portal

**Required Genetic Counseling**
Participant schedules counseling appointment through PROMISE Portal to discuss results and their implications for self and family

**Clinical Data Collection**
PROMISE Data Team obtains medical records from participant's physician

**Ongoing Clinical Data Collection**
PROMISE Data Team requests updated medical records every 6 months

**Patient-Reported Outcomes**
Participant completes PRO surveys in PROMISE Portal every 6 months

**Educational Newsletters**
Newsletters sent on regular basis with updated information about **pathogenic and likely pathogenic variants**, **variants of uncertain significance**, and the available treatments/clinical trials


**Return of Results**
Clinical report returned to participant, provider, and PROMISE through PROMISE Portal

**Optional Genetic Counseling**
Participant schedules counseling appointment through PROMISE Portal to discuss results and their implications for self and family

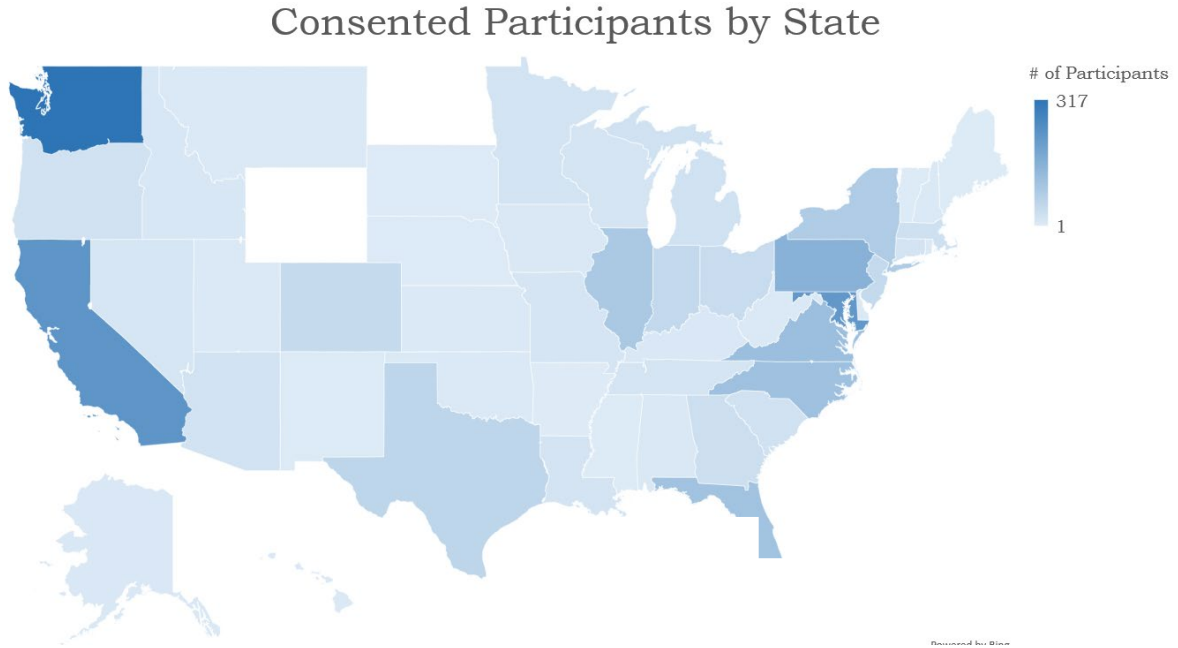
# Promise.

## Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness

**2,689 consented participants**
(goal: 5,000)

**1,932 genetic testing results returned**

**240 participants eligible for long-term follow-up**
(goal: 500)

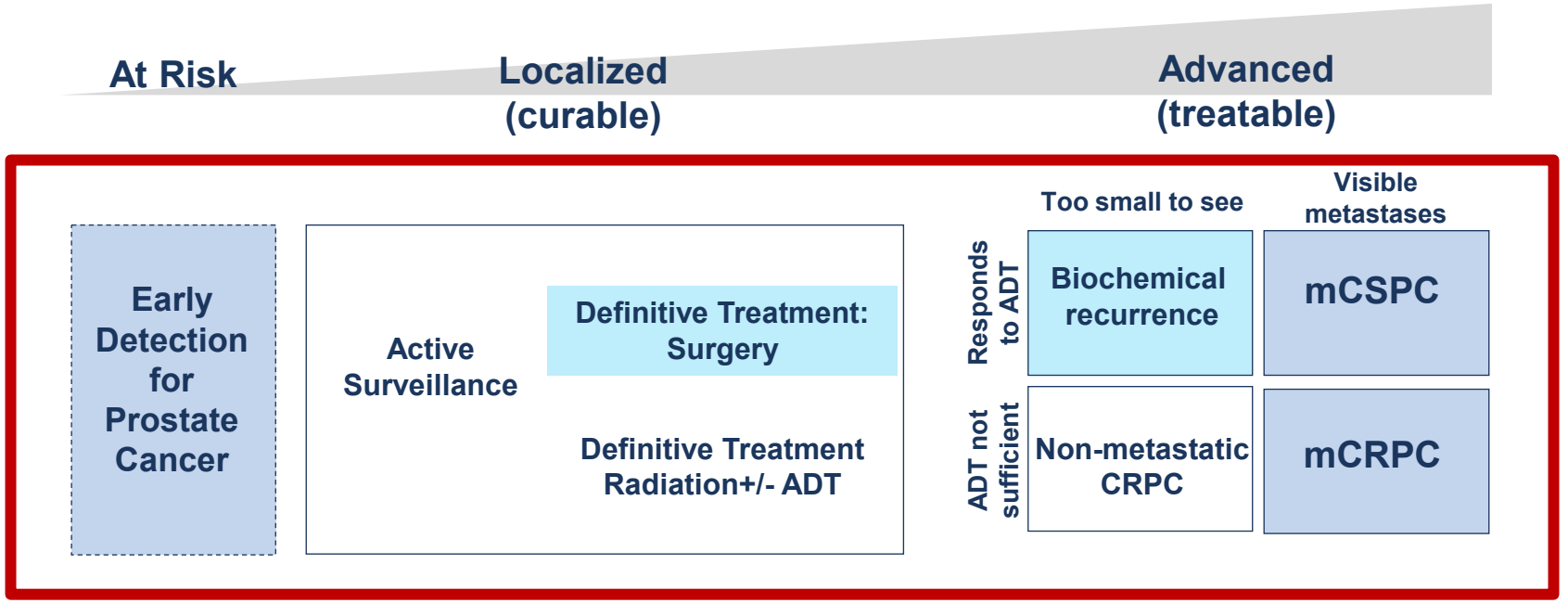



**ProstateCancerPromise.org**

**Clinicaltrials.gov ID**: NCT04995198

Fred Hutchinson Cancer Center
Heather H. Cheng, MD PhD

# Moving towards tailored options at every step….



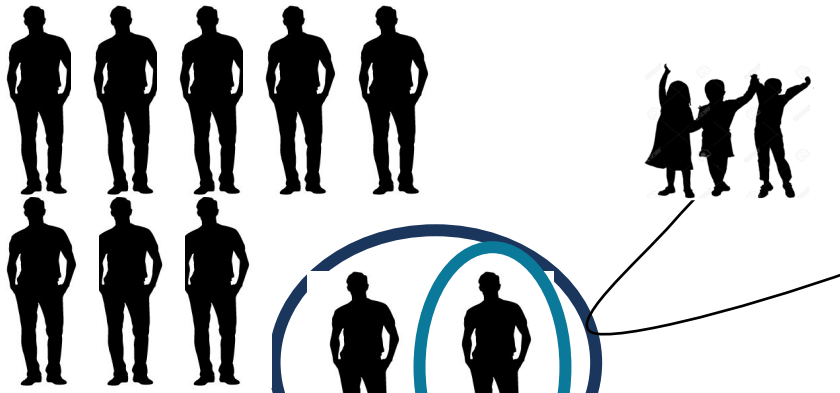

**Urology**
**Primary Care**

**Urology**

**Urology**
**Radiation Oncology**
Medical Oncology

**Medical Oncology**
**Radiation Oncology**
Urology

# VISION



~2 in 10 men with metastatic prostate cancer have a DNA repair gene mutation[1]

Targeted therapies: platinum, PARPi

**GIFTS**
GENTleMEN
**Prostate Cancer Genetics Clinic**

**FIRST DEGREE RELATIVES:**
**50% likelihood of sharing risk variant**
**Cascade testing**

**SISTERS**
↑risk of breast, ovarian cancer
**Breast and Ovarian Cancer Prev**

**BROTHERS**
↑risk of prostate cancer
**PATROL: Prostate cancer early detection study**

**DAUGHTERS**
↑risk of breast, ovarian cancer
**Breast and Ovarian Cancer Prev**

**SONS**
↑risk of prostate cancer
**PATROL: Prostate cancer early detection study**

# Conclusions

1. Inherited (germline) genetic testing for cancer risk is recommended for high-risk localized, node positive and metastatic prostate cancer patients, regardless of family history of cancer.

2. This genetic testing is increasingly important for cancer treatment options, clinical trials and potentially life-saving for family members

3. Cancer Care Delivery:
   - We can deliver germline genetic testing via internet-based methods
   - We can use cancer registries (and health systems) to do better, but key disparities persist

# Future Directions *(Welcome your ideas and partnership)*

1. Need better understanding of barriers and improve tailored education and workflow, esp. in diverse populations, health systems and communities

2. Engage health systems to provide systematic/automated invitations and multi-tiered support for prostate cancer screening and earlier intervention

3. Standardize coverage of genetic testing, and encourage cascade testing (How can we help relatives across healthcare plans?)

4. How can we better engage males and people at risk for prostate cancer to be proactive in health (genetics and PSA screening)

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Fred Hutch Cancer Center

pcctc The Prostate Cancer Clinical Trials Consortium

IPCR Institute for Prostate Cancer Research

Prostate Cancer Foundation Curing Together.

Advancing Cancer Treatment

University of Washington 1861

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# Thank You!

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