# Prostate Cancer Genetic Counselling: Current Status and Evolving Trends

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Male Oncology Research and Education (MORE) Lead
Sunnybrook Odette Cancer Centre

February 8, 2019

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when it matters MOST

# Learning Objectives

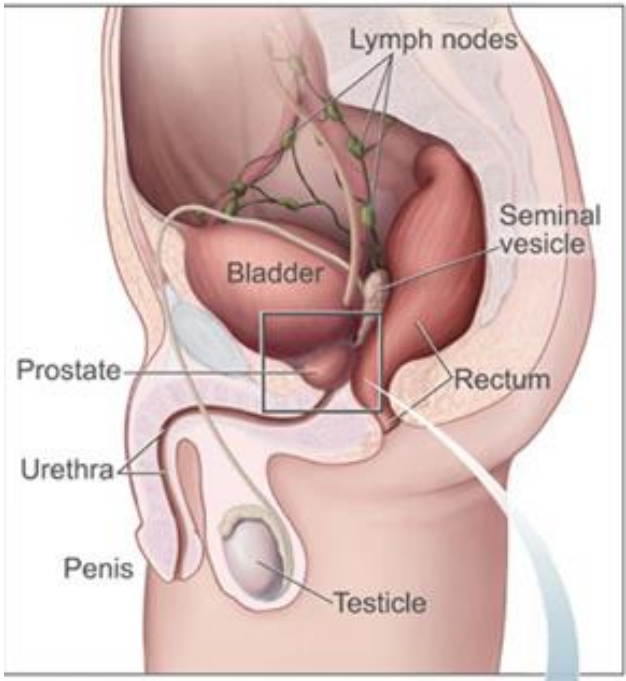
- To apply key components of prostate cancer pathology and treatment to pedigree acquisition and interpretation for hereditary prostate cancer
- To identify families that meet our current (and changing) understanding hereditary prostate cancer
- To evaluate prostate cancer risk in unaffected men with a family history of prostate cancer using evidence-based empirical data

# What to Expect

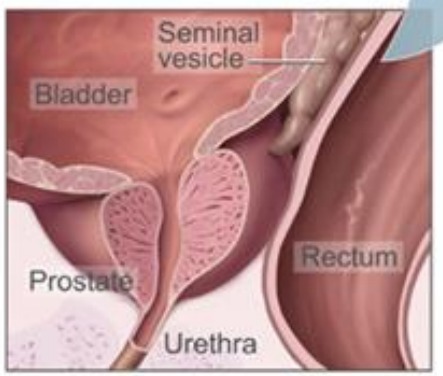
- Prostate Cancer
- Prostate Cancer Screening/Prevention
- High Risk Populations for Prostate Cancer
- Prostate Cancer Genetics
- Genetic Testing Panels for Prostate Cancer
- Genetic Testing Criteria for Prostate Cancer
- Sunnybrook's Familial Prostate Cancer Clinic
- Prostate Cancer Panel Preliminary Data
- Questions

# Prostate

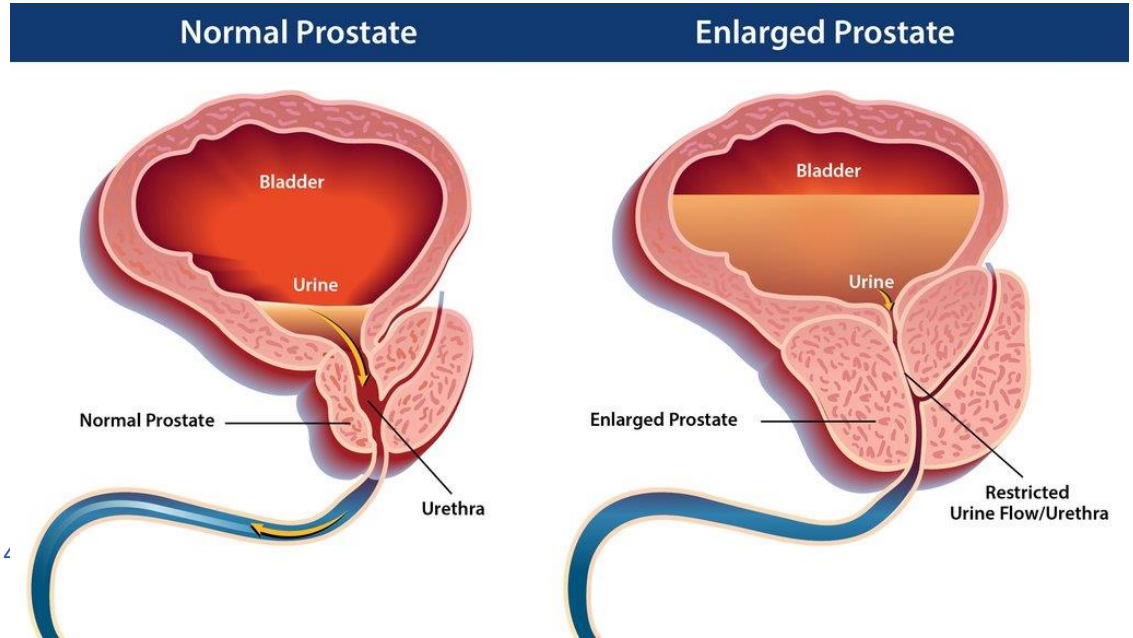
- Prostate is a **gland** that produces PSA
- PSA is a glycoprotein enzyme
  - liquefies semen so sperm can swim free
- In men three organs are always growing



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

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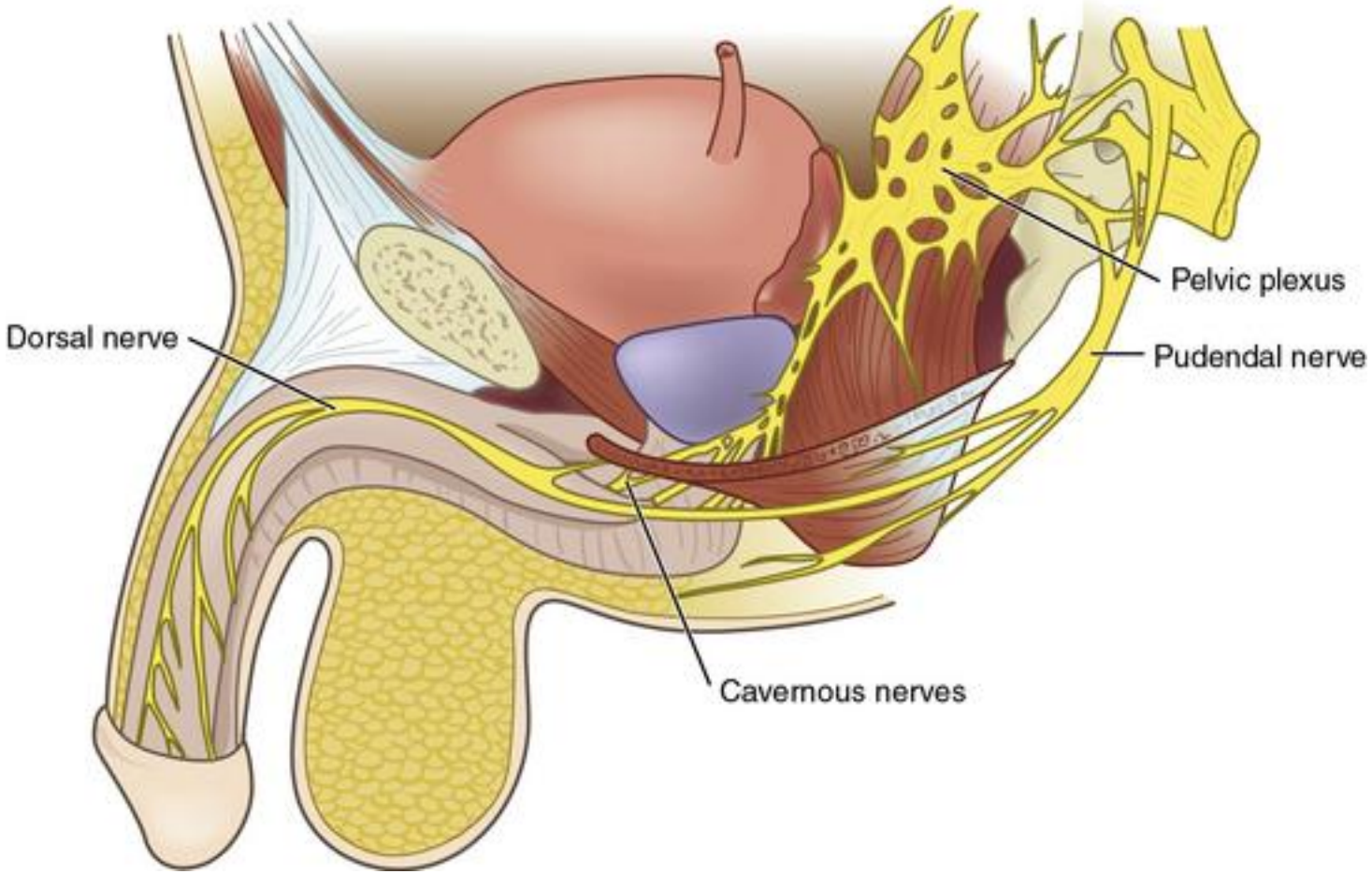
# Prostate



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# Prostate Cancer

| | |
|---|---|
| Estimated New Cases in 2018 | 164,690 |
| % of All New Cancer Cases | 9.5% |

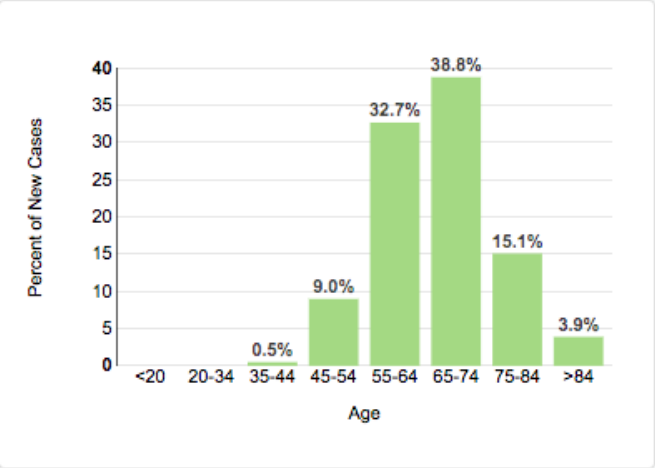
| | |
|---|---|
| **Estimated Deaths in 2018** | 29,430 |
| **% of All Cancer Deaths** | 4.8% |

**Percent Surviving 5 Years**

**98.2%**

2008-2014

**Percent of New Cases by Age Group: Prostate Cancer**




Prostate cancer is most frequently diagnosed among men aged 65-74.

Median Age At Diagnosis

**66**

SEER 18 2011-2015, All Races, Males



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# A PSA on Prostate Cancer Screening






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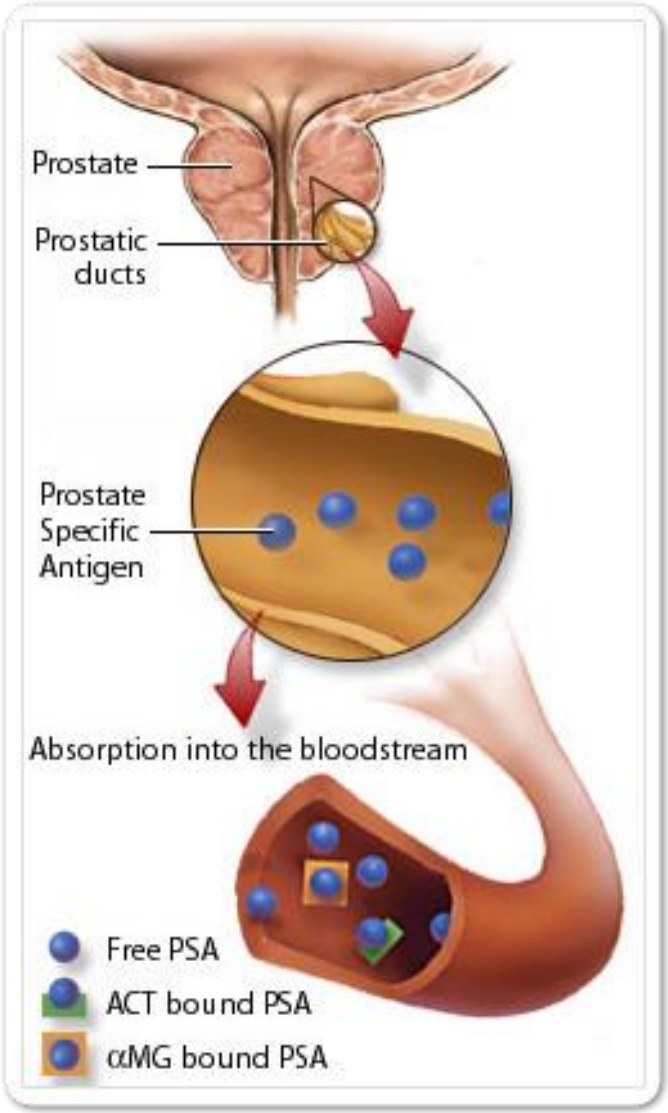
# A PSA on Prostate Cancer Screening



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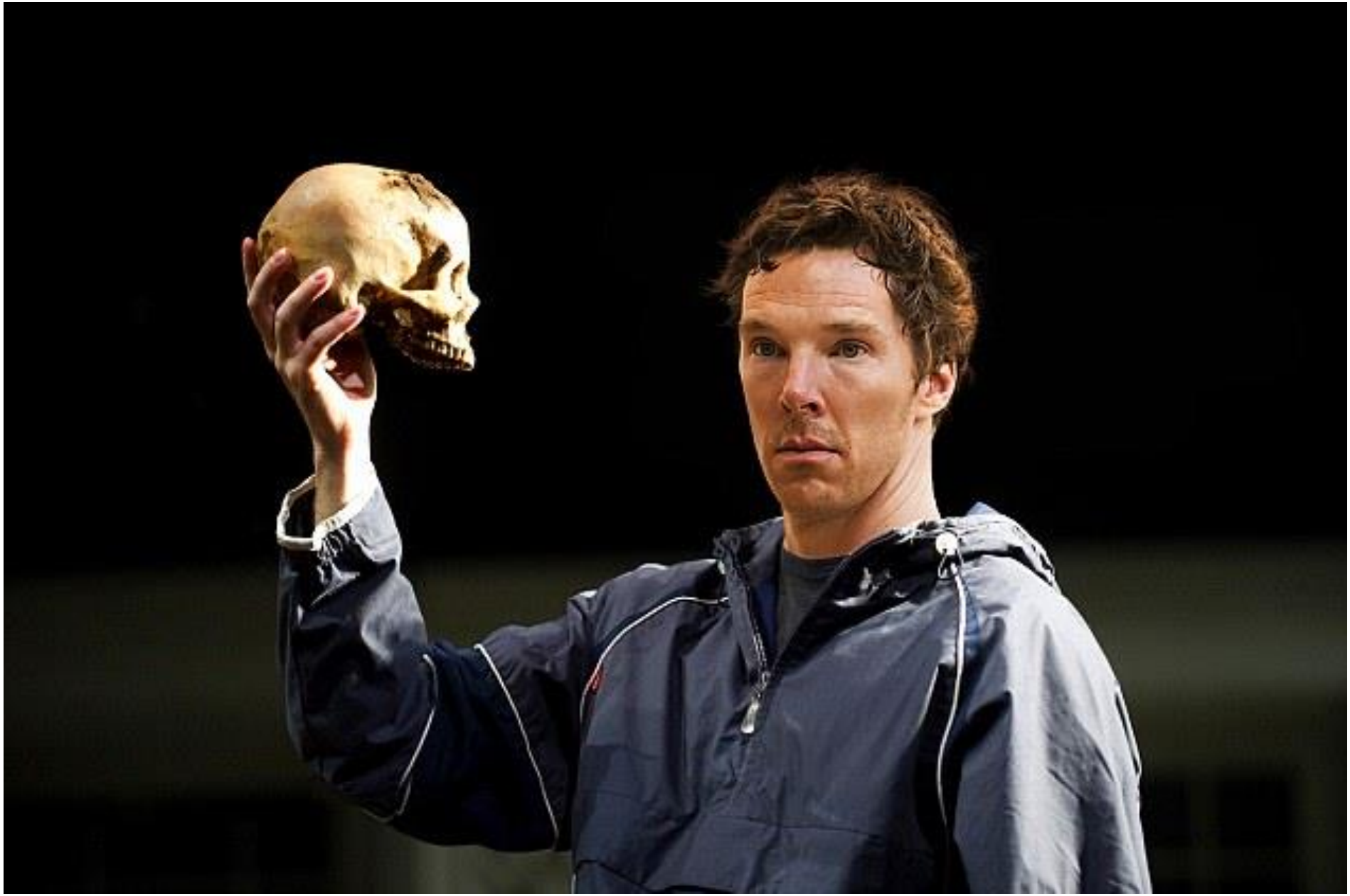
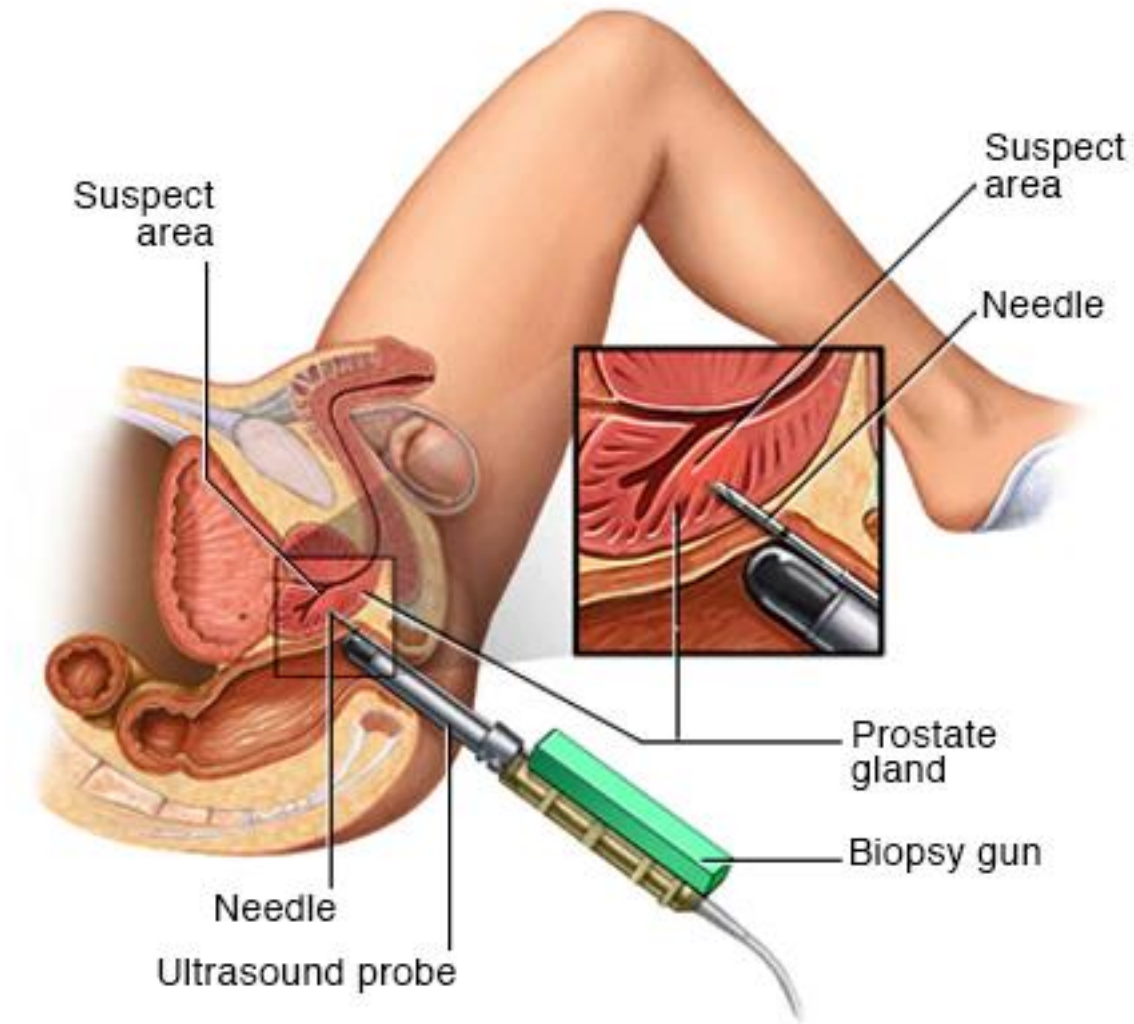


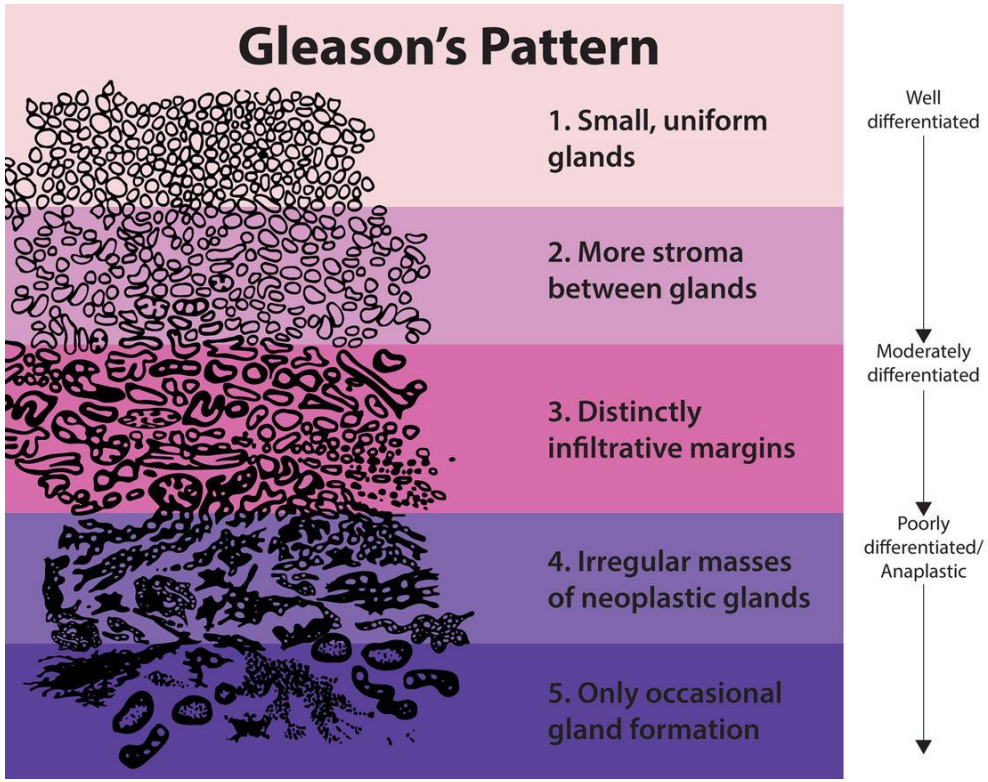
# Prostate Cancer Diagnosis



# Prostate Cancer Classification

- Adenocarcinoma (almost always)
- Gleason scores classification

- Grade Group 1 = Gleason 6
- Grade Group 2 = Gleason 3+4=7
- Grade Group 3 = Gleason 4+3=7
- Grade Group 4 = Gleason 8
- Grade Group 5 = Gleason 9-10



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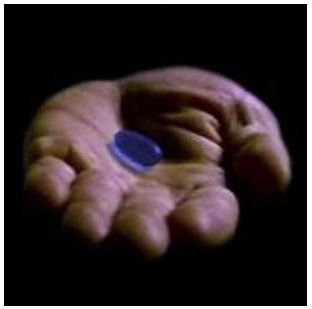
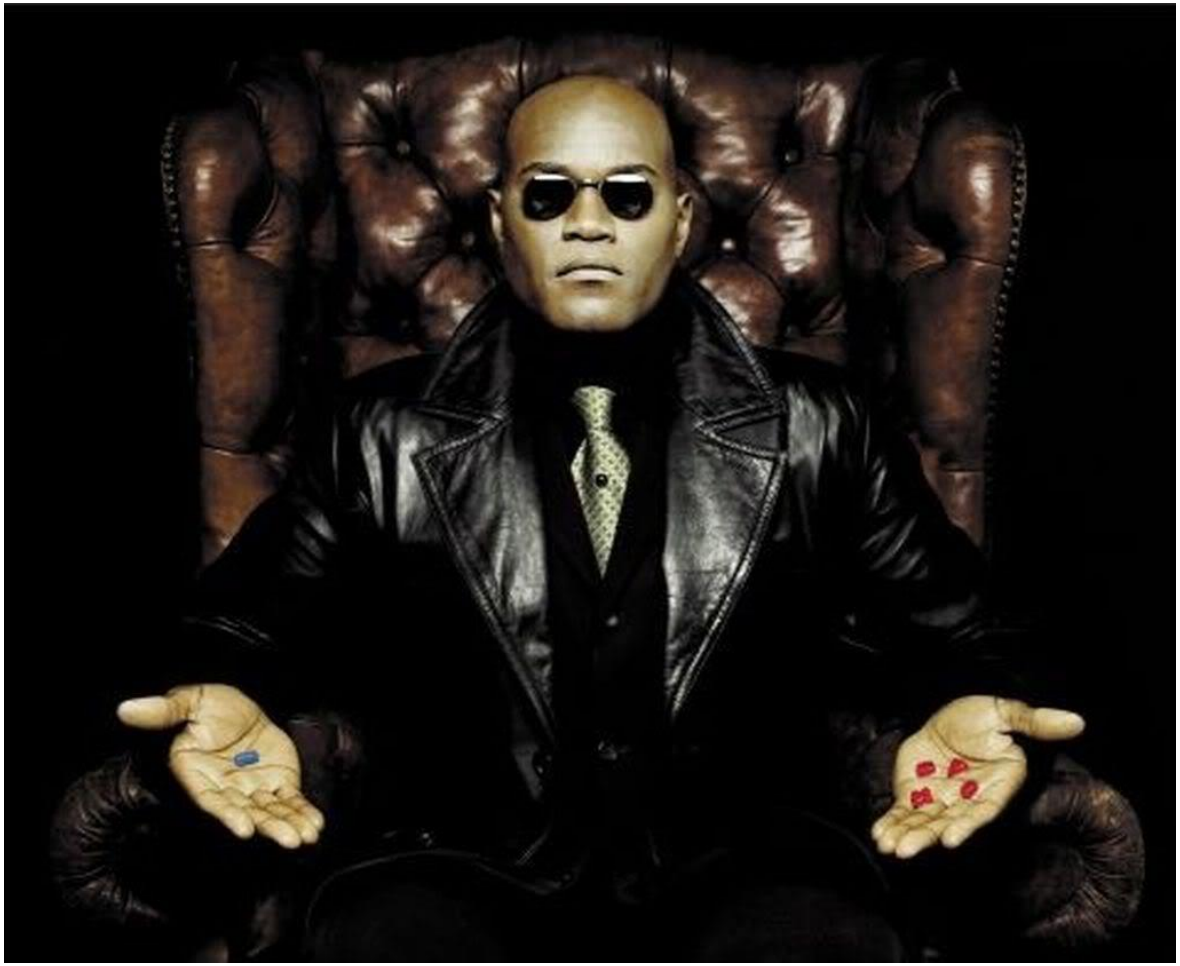
# Prostate Cancer Treatment

- Prostatectomy
  - Robotic
  - Hand



- Radiation
  - External beam
  - Brachytherapy



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# Prostate Cancer Treatment

## APPROACH PROSTATE CANCER *with* ACTIVE SURVEILLANCE

**Active surveillance** is a strategy that involves monitoring your prostate cancer closely and choosing to undergo treatment if it advances. It's an option for men who have "low-risk" prostate cancer.

**Criteria:**

- PSA level is under 10ng/ml
- Gleason score of 6 or less
- Cancer stage T2a or lower
- Your age and overall health

**How to monitor your prostate cancer**

**Regular DREs**

Regular digital rectum exams help monitor any tumor growth.

**Periodic PSA Testing**

To check for increases in blood levels that may indicate progression of the cancer.

**MRI Scans**

If needed, an MRI helps your doctor visualize portions of the prostate gland they can't feel during DREs.

**Biopsy**

Generally done once a year or so.



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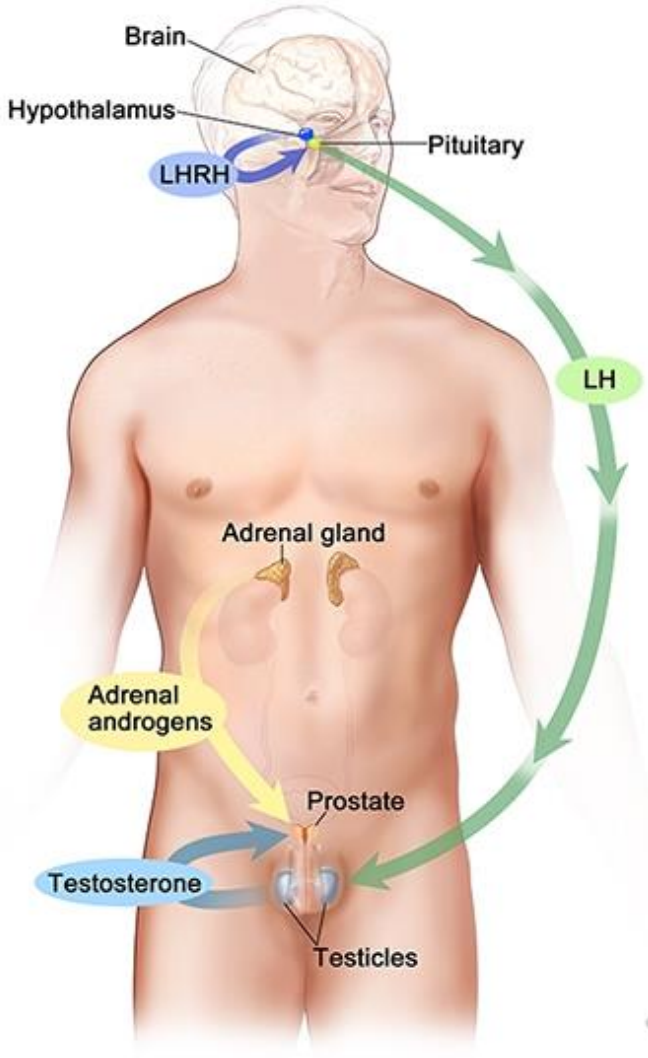
# Prostate Cancer Treatment



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# Prostate Cancer Treatment



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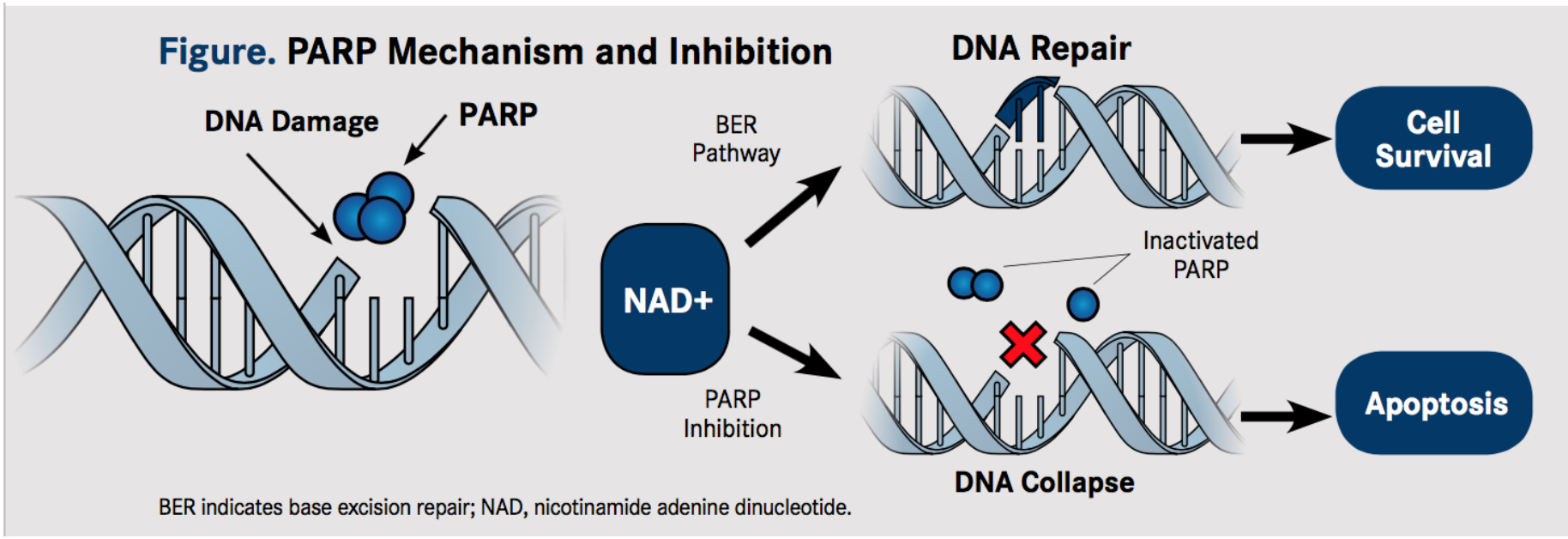
# Prostate Cancer Treatment



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# Prostate Cancer Prevention



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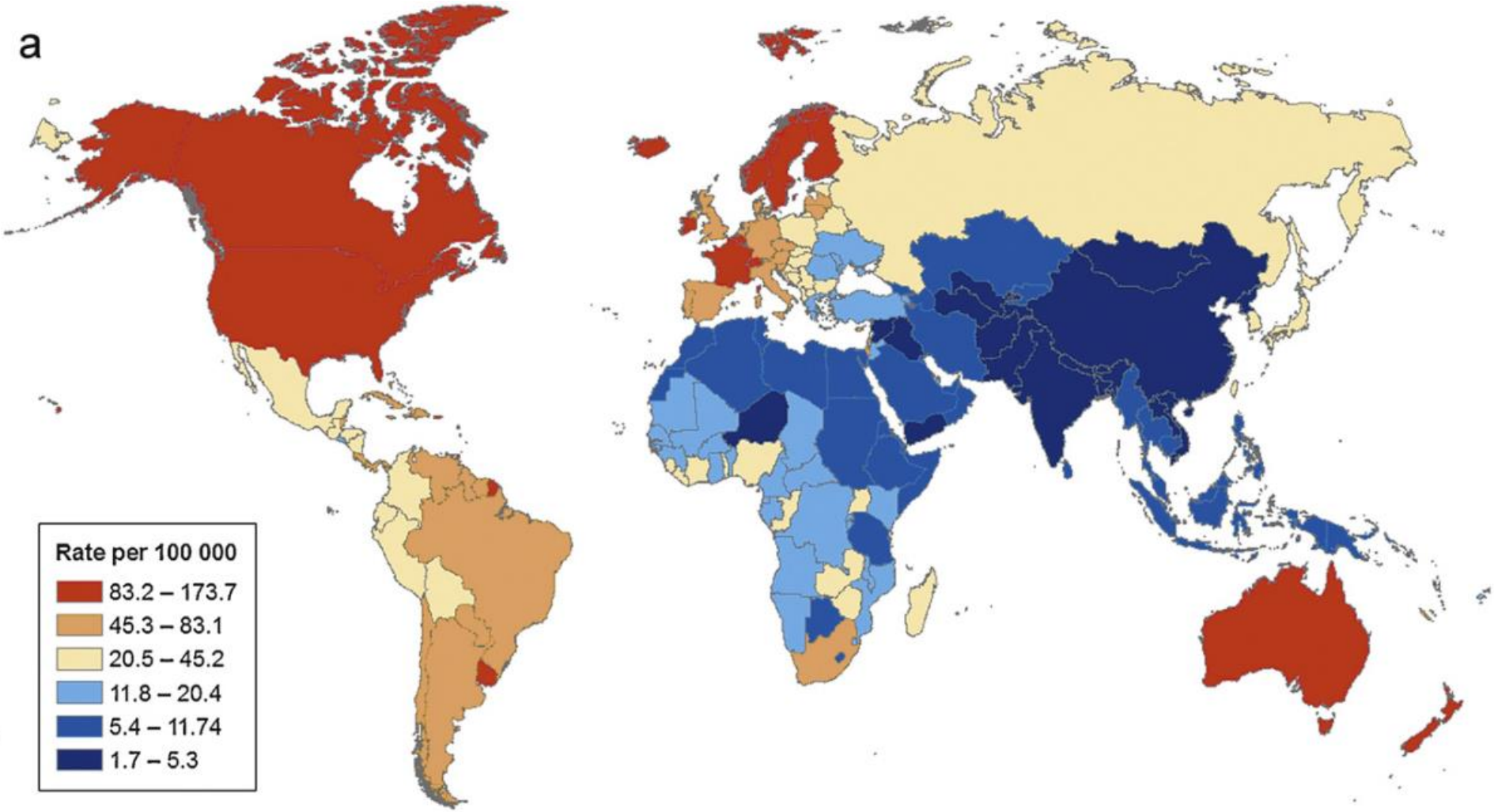
# West African/Caribbean Ancestry

- **West Africa**
  - Sierra Leone
  - Liberia
  - Ivory Coast
  - Ghana

- **Caribbean**
  - Trinidad & Tobago
  - Jamaica
  - Turks and Caicos
  - The Bahamas
  - Saint Vincent
  - Honduras
  - Haiti
  - Grenada
  - Barbados

# West African/Caribbean Ancestry




EUROPEAN UROLOGY 61 (2012) 1079–1092



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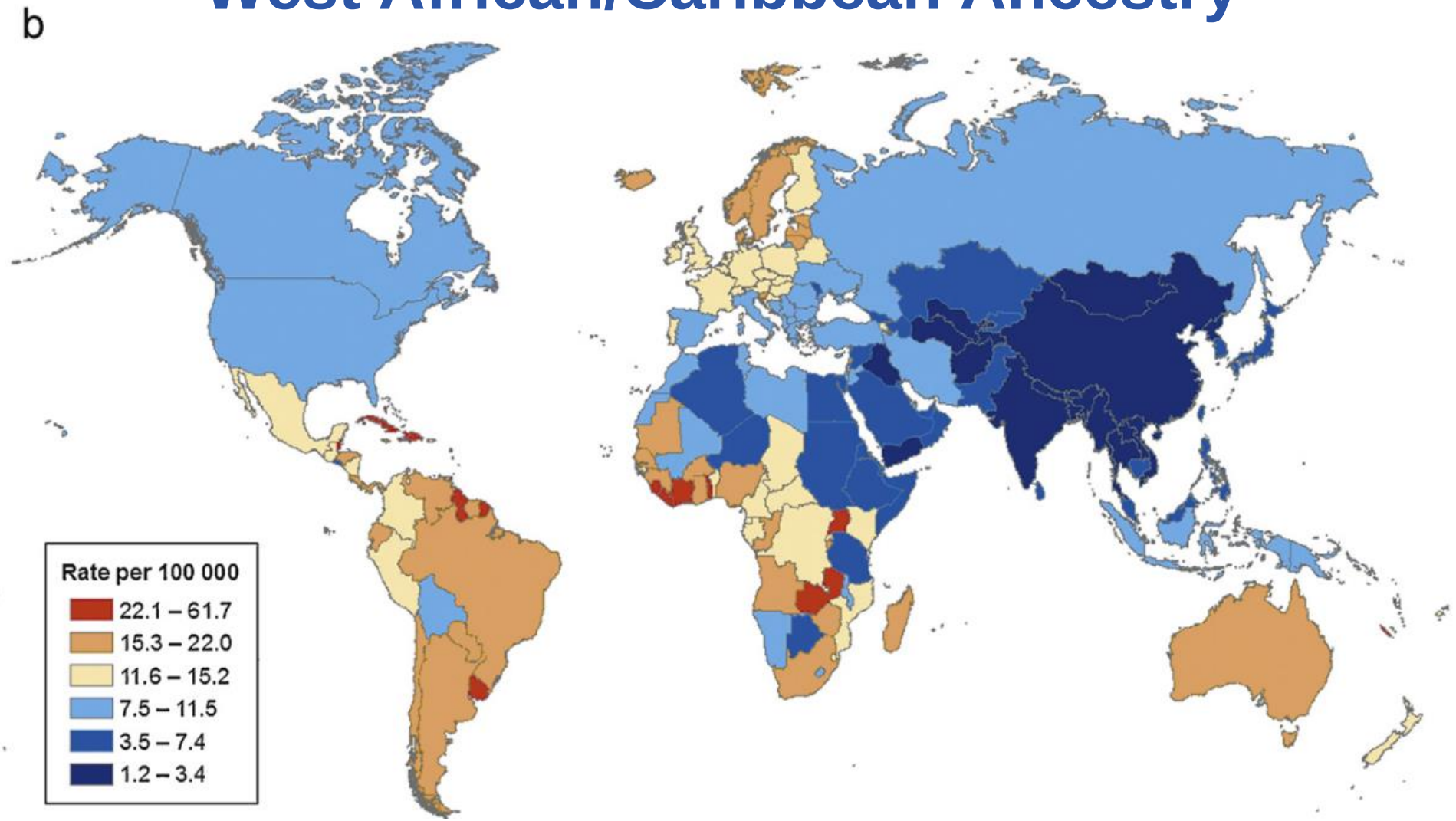
# West African/Caribbean Ancestry




EUROPEAN UROLOGY 61 (2012) 1079–1092



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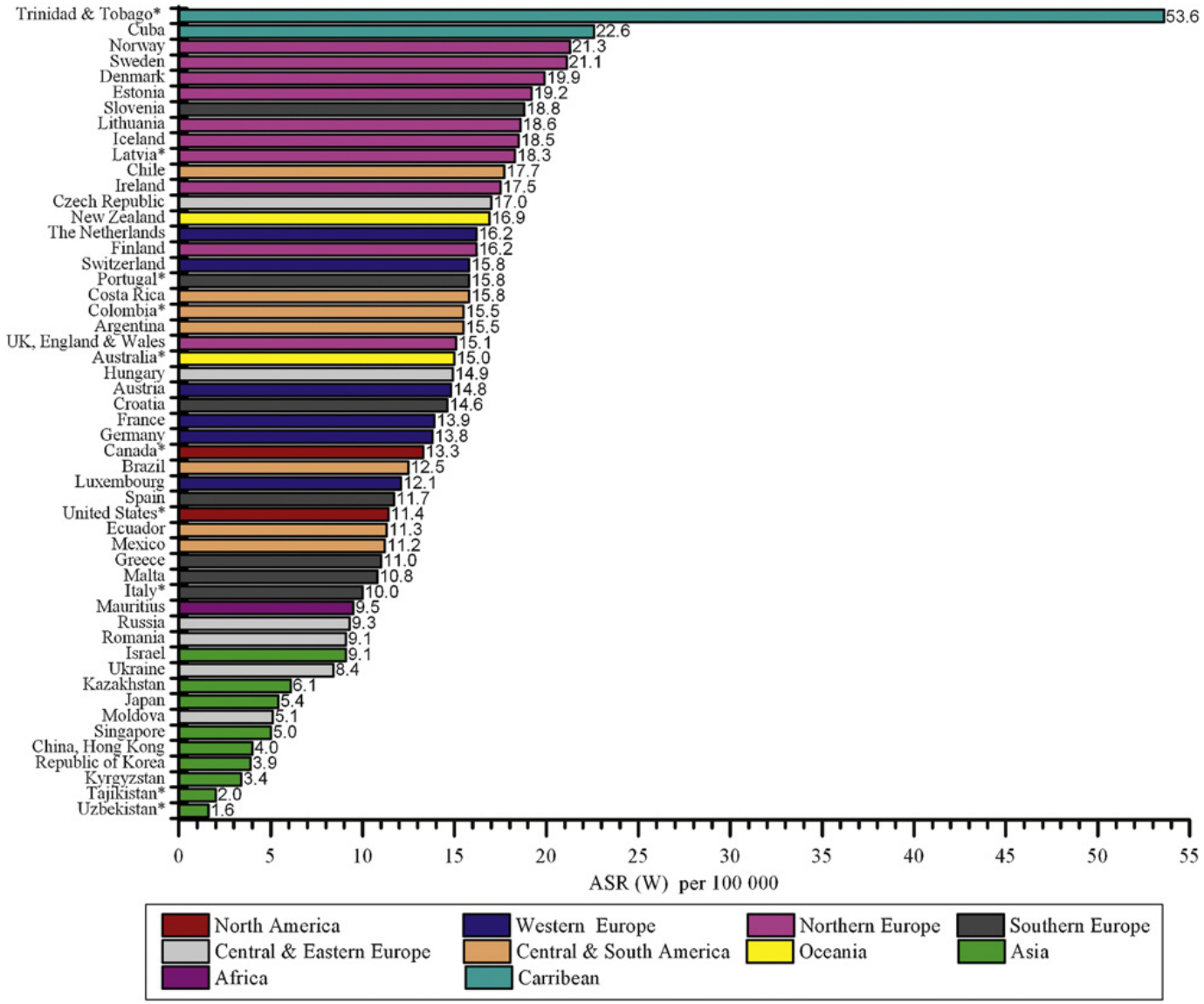
# West African/Caribbean Ancestry




Source: WHO Mortality Database *Average of rates for six or fewer years in the time period 2000-2006

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# Family History

| Risk Group | RR |
|---|---|
| Brother with prostate cancer diagnosed at any age | **3.4** |
| Father with prostate cancer diagnosed at any age | 2.2 |
| One affected FDR diagnosed at any age | 2.6 |
| One affected SDR diagnosed at any age | 1.7 |
| Affected FDRs diagnosed age <65 y | **3.3** |
| Affected FDRs diagnosed age >65 y | 2.4 |
| Two or more affected FDRs diagnosed at any age | **5.1** |

# How Genetic Is Prostate Cancer?

## Concise Handbook of Familial Cancer Susceptibility Syndromes – Second Edition FREE

Noralane M. Lindor, Mary L. McMaster, Carl J. Lindor, Mark H. Greene

| | Utah (16) | | Sweden (17,19) | | |
|---|---|---|---|---|---|
| **Site** | FRR (total) | FRR (early onset) | FRR (child) | FRR (sibling) | PAF (%) |
| **Prostate** | 2.2 | 4.1 | 2.8 | **9.4** | **20.5** |
| **Breast** | 1.8 | 3.7 | 1.9 | 2.0 | 10.6 |
| **Colorectal** | 2.5 | 4.5 | 1.9 | 4.4 | 6.9 |
| **Ovary** | 2.0 | – | 2.9 | 2.5 | 4.9 |
| **Pancreas** | 1.2 | – | – | – | 1.0 |

FRR = familial relative risk

PAF = population attributable risk - indicates % of cases that would *not occur* in a population if a factor (in this case heredity) were eliminated

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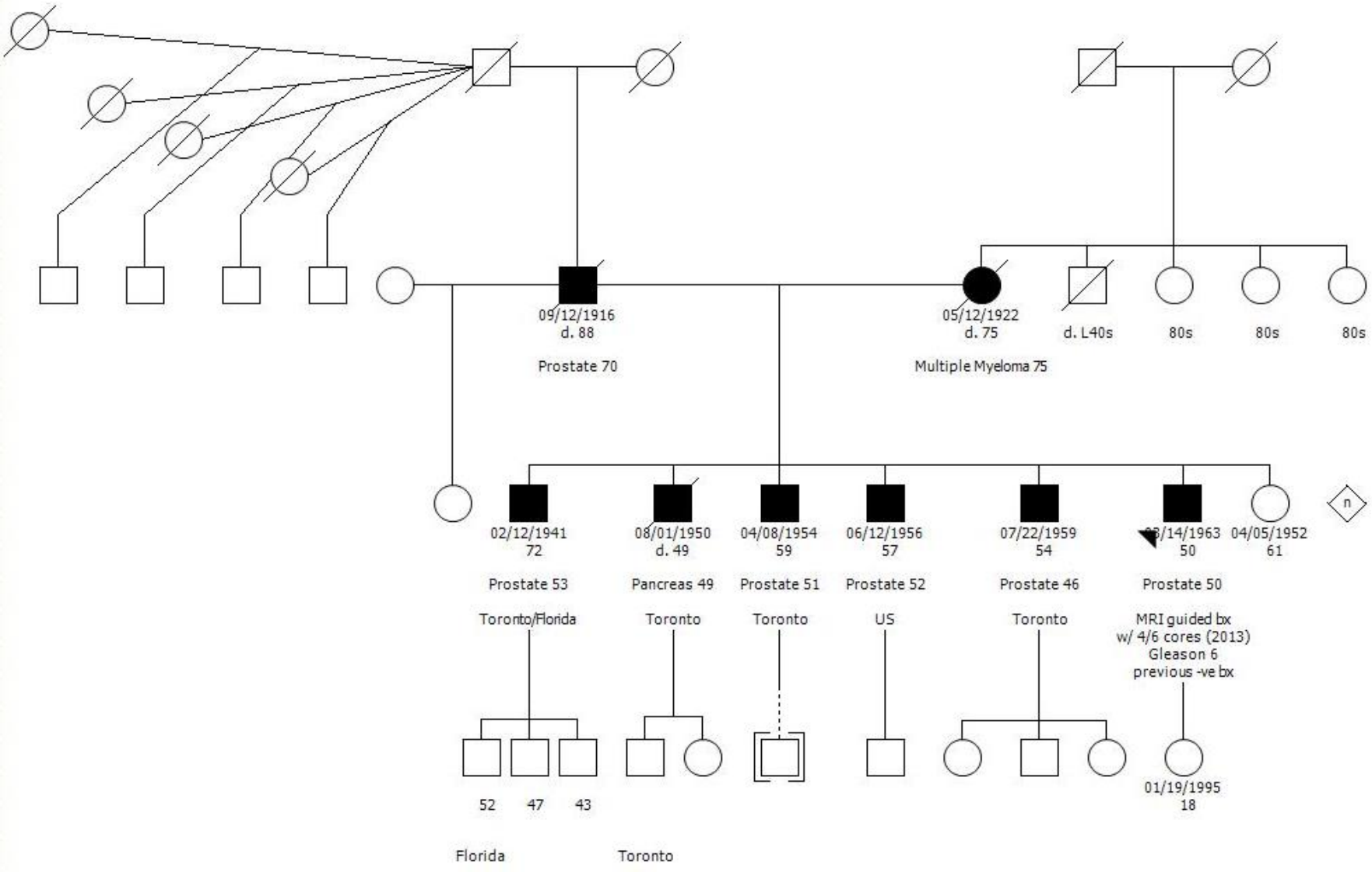
# Family History



# Germline Pathogenic Mutations

- Median survival
  - BRCA1: 8 years
  - BRCA2: 4 years

British Journal of Cancer (2008) 99, 371 – 374

www.bjcancer.com

Rapid progression of prostate cancer in men with a *BRCA2* mutation

SA Narod*,[1], S Neuhausen[2], G Vichodez[1], S Armel[3], HT Lynch[4], P Ghadirian[5], S Cummings[6], O Olopade[6], D Stoppa-Lyonnet[7], F Couch[8], T Wagner[9], E Warner[10], WD Foulkes[11], H Saal[12], J Weitzel[13], A Tulman[1], A Poll[1], R Nam[10] and P Sun[1], the Hereditary Breast Cancer Study Group[14]

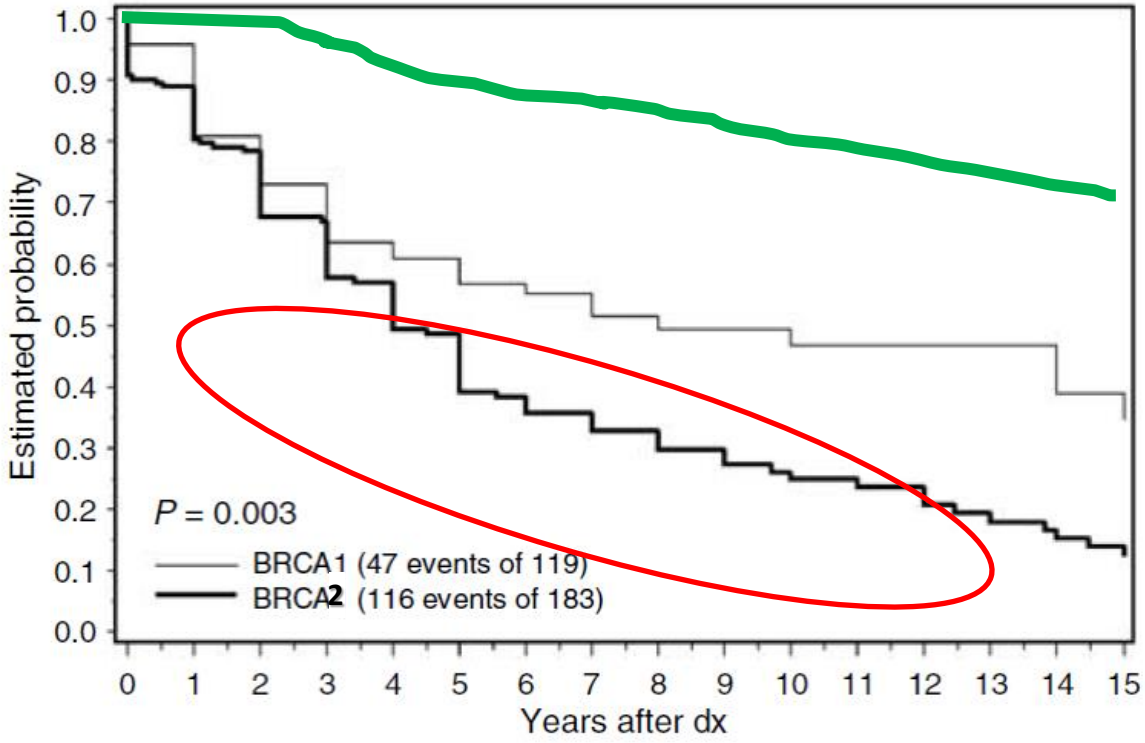



**Figure 1** Probability of survival after prostate cancer in men from families with *BRCA1* and *BRCA2* mutations (all causes of death).

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# Germline Pathogenic Mutations



ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

## Prostate cancer incidence in males with Lynch syndrome

Sigurdis Haraldsdottir, MD, MS[1], Heather Hampel, MS[2], Lai Wei, PhD[3], Christina Wu, MD[1], Wendy Frankel, MD[4], Tanios Bekaii-Saab, MD[1], Albert de la Chapelle, MD, PhD[5] and Richard M. Goldberg, MD[1]

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# Germline Pathogenic Mutations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Germline Mutations in *HOXB13* and Prostate-Cancer Risk

Charles M. Ewing, M.S., Anna M. Ray, M.S., Ethan M. Lange, Ph.D., Kimberly A. Zuhlke, B.A., Christiane M. Robbins, M.S., Waibhav D. Tembe, Ph.D., Kathleen E. Wiley, M.S., Sarah D. Isaacs, M.S., Dorhyun Johng, B.A., Yunfei Wang, M.S., Chris Bizon, Ph.D., Guifang Yan, B.S., Marta Gielzak, B.A., Alan W. Partin, M.D., Ph.D., Vijayalakshmi Shanmugam, Ph.D., Tyler Izatt, M.S., Shripad Sinari, M.S., David W. Craig, Ph.D., S. Lilly Zheng, M.D., Patrick C. Walsh, M.D., James E. Montie, M.D., Jianfeng Xu, M.D., Dr.P.H. John D. Carpten, Ph.D., William B. Isaacs, Ph.D., and Kathleen A. Cooney, M.D.



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# Germline Pathogenic Mutations

VOLUME 26 · NUMBER 18 · JUNE 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Risk of Cancer by *ATM* Missense Mutations in the General Population

*Sarah Louise Dombernowsky, Maren Weischer, Kristine Højgaard Allin, Stig Egil Bojesen, Anne Tybjærg-Hansen, and Børge Grønne Nordestgaard*



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# Germline Pathogenic Mutations

Hindawi Publishing Corporation
Prostate Cancer
Volume 2014, Article ID 294575, 9 pages
http://dx.doi.org/10.1155/2014/294575

*Review Article*

## *CHEK2** 1100delC Mutation and Risk of Prostate Cancer

**Victoria Hale,[1] Maren Weischer,[2] and Jong Y. Park[1]**

[1] *Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA*
[2] *Department of Clinical Biochemistry, Herlev Hospital, 2730 Herlev, Denmark*



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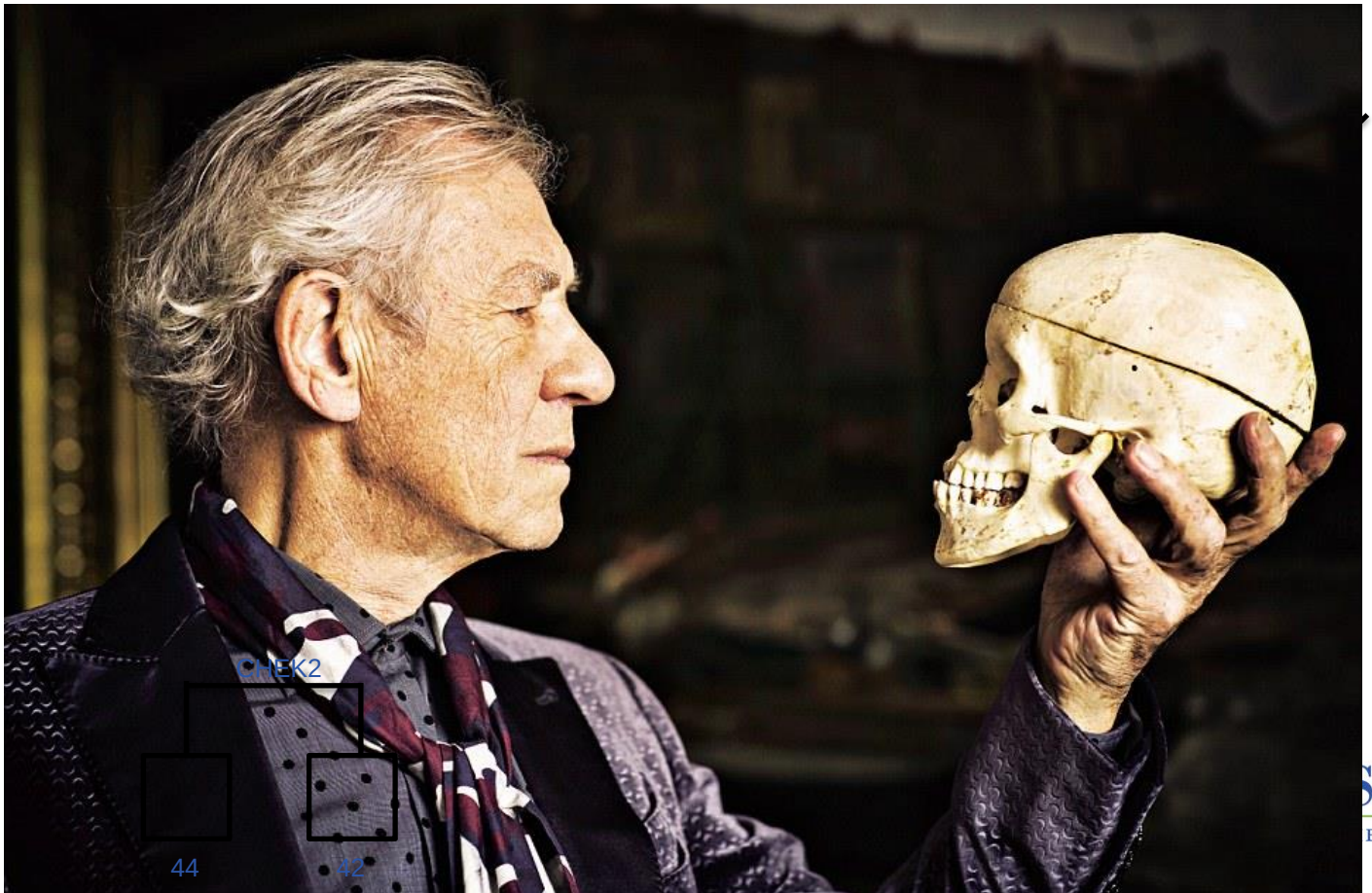
# Prostate Cancer Genetics

- The prostate cancer genetic testing conundrum:
  - Are we certain known genes account for the FHx of prostate cancer?
  - Does prostate cancer screening differ for carriers vs men with FHx?
  - Does a predictive negative give me assurance?



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# Prostate Cancer Panels

| | Invitae | Ambry | GeneDx | Fulgent | Philadelphia Consensus | Genetic Condition | Prostate Cancer Risk |
|---|---|---|---|---|---|---|---|
| HOXB13 | X | X | X | X | X | FPC | 60% |
| BRCA1 | X | X | X | X | X | HBOC | 30% |
| BRCA2 | X | X | X | X | X | HBOC | 30% |
| EPCAM | X | X | X | X | X | Lynch Syndrome | ? |
| MLH1 | X | X | X | X | X | Lynch Syndrome | 30% |
| MSH2 | X | X | X | X | X | Lynch Syndrome | 30% |
| MSH6 | X | X | X | X | X | Lynch Syndrome | 30% |
| PMS2 | X | X | X | X | X | Lynch Syndrome | ? |
| ATM | X | X | X | X | **X** | | 30% |
| CHEK2 | X | X | X | X | | | 30% |
| NBN | X | X | X | X | | | increased risk |
| TP53 | X | X | X | X | | Li Fraumeni Syndrome | increased risk |
| PALB2 | **X** | X | X | X | | HBOC | ? |
| RAD51C | **X** | X | X | | | H(B?)OC | ? |
| RAD51D | **X** | X | X | | | H(B?)OC | ? |
| BRIP1 | **X** | X | | | | | ? |
| FANCA | **X** | | | | | | ? |

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# Prostate Cancer Panel Study

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,

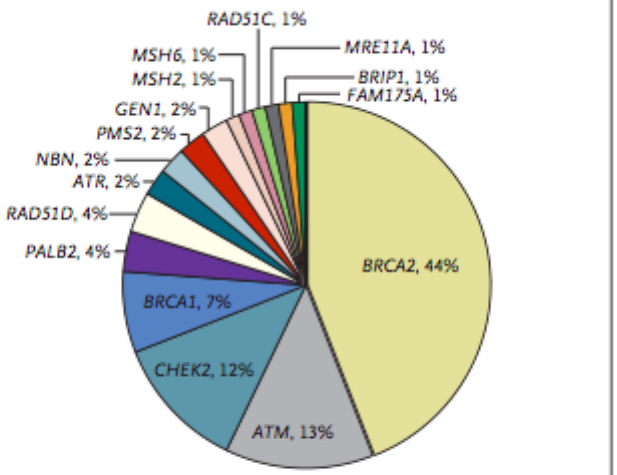


**Figure 2. Distribution of Presumed Pathogenic Germline Mutations.**
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

- 692 metastatic prostate cancer unselected for FHx of cancer and age at diagnosis
- 20-gene cancer panel
- 84 deleterious mutations in 82 men (11.8%)
- 72 have FHx info
  - **51 have a FDR with cancer other than prostate**
    - 24 breast
    - 18 GI
    - 10 ovarian
    - 6 pancreatic

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# Prostate Cancer Panel Study

Research

JAMA Oncology | Original Investigation

## Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines

Piper Nicolosi, PhD; Elisa Ledet, PhD; Shan Yang, PhD; Scott Michalski, MS, LCGC; Brandy Freschi, MS, CGC; Erin O'Leary, MS, CGC; Edward D. Esplin, MD, PhD; Robert L. Nussbaum, MD; Oliver Sartor, MD

| Gene | Exome Aggregation Consortium | Pritchard, et al. | Nicolosi, et al. |
|---|---|---|---|
| BRCA1 | 0.22% | 0.87% | 1.25% |
| BRCA2 | 0.29% | 5.35% | 4.74% |
| ATM | 0.25% | 1.59% | 2.03% |
| CHEK2 | 0.61% | 1.87% | 2.37% |
| PALB2 | 0.12% | 0.43% | 1.12% |

- 3607 men with prostate cancer
  - 2250 (62%) had a 14-gene prostate panel
  - **1357 had 2 to 80-gene panel!**

- 620 (17.2%) had PVs
  - 234 (22.7%) Jewish
  - 85 (12.7%) were in APC/MUTYH
  - 229 (37%)would not have been IDed using only NCCN familial breast/ovarian guidelines

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# Prostate Cancer Genetic Testing Criteria

- Criteria Does Exist - Do “U” Have a Criteria?
  - NCCN
  - John Hopkin’s
  - ACMG/NSGC
  - Philadelphia Consensus

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# Prostate Cancer Genetic Testing Criteria

| # | Criteria | Philadelphia | NCCN | ACMG NSGC | John Hopkin's |
|---|---|---|---|---|---|
| 1 | PHx of metastatic (castrate-resistant) prostate cancer | X | X | | |
| 2 | 2 relatives with prostate cancer diagnosed ≤55 years | | | X | X |
| 3 | 3 successive generations of prostate cancer | | | | X |
| 4 | ≥3 FDR with prostate cancer | | | X | X |
| 5 | PHx of prostate cancer and a family that meet LS and HBOC and HPC criteria | X | | | |
| | PHx of prostate cancer and 2 relatives with any HBOC, Lynch, FPC-related cancers (age cut-off?) | X | | | |
| 6 | Gleason score ≥7 and ≥2 individuals with breast, ovarian, pancreatic cancer | | | X | |
| | PHx of prostate cancer (GS ≥7) and 2 family members with breast, pancreatic, or prostate cancer with GS ≥7 at any age | | X | | |
| 7 | PHx GS ≥7 and ≥1 close family member with breast cancer diagnosed ≤50 years and/or invasive ovarian cancer | | X | | |
| 8 | Prostate tumour showing somatic mutation to be offered germline genetic testing | X | | | |

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# Prostate Cancer Testing Criteria

- Take criteria creation into your own hands
- Discuss with your team what makes sense for your clinic
  - Gleason score ≥7 prostate cancer equivalent to breast cancer ≥50, pancreatic cancer, colon cancer ≥50
  - I give you permission to make an index case of a man with Gleason score ≥7 prostate cancer
  - If genetic testing changes treatment there is evidence to support you testing a man with prostate cancer

# Familial Prostate Cancer Clinic

- We see men at high-risk for prostate cancer
  - Men with a germline pathogenic mutation in a prostate cancer-associated gene
  - Men with a family history of prostate cancer
  - Men with of West African/Caribbean Ancestry

- What do we do?
  - Annual DRE
  - Annual PSA starting at 40
  - Mammogram starting between 50-60
  - Refer to dermatology
  - Refer to gastroenterology
  - Refer to geneticist


Sorry I'm late for your digital-rectal exam...
I slammed my finger in my car door.

# Male Oncology Research and Education (MORE) Program

## Unlocking prostate cancer's genetic secrets

*Researchers are on the trail of risks lurking within DNA*

I'm told that I have the prostate of a 20-year old," says 58-year old Martin S., "which is a great pickup line, except that I'm happily married."

Martin's prostate is the subject of more than a quirky pickup line.

Because he has a gene mutation associated with prostate cancer, Martin was invited to take part in the Male Oncology Research Program at Sunnybrook's Odette Cancer Centre. He has BRCA2, which, along with BRCA1, is a gene mutation that can increase risk for prostate, breast and ovarian cancers. (For privacy, Martin asked that his full name not be used.)

The research program's confidential registry, database and biobank for men with genetic dispositions for prostate cancer are a collaborative undertaking by several institutions that is led by Sunnybrook.

"Ancestry, family history and known genetic predispositions such as BRCA mutations are important factors in a risk assessment for prostate cancer," says Justin Lorentz, a genetic counsellor at the Odette Cancer Centre. "We know that men of Ashkenazi Jewish ancestry are 10 times more likely to have a BRCA1 or BRCA2 gene mutation compared to men who are not of Ashkenazi Jewish ancestry."

"Men of West African/Caribbean ancestry are also known to have higher risks for prostate cancer and more aggressive disease, and men with a family history of prostate cancer are known to be at increased risk," adds Lorentz.

"We are actively working to engage men of West African ancestry or men with strong family histories, to better understand how prostate cancer is inherited and how best to support these patients," adds Dr. Danny Vesprini, a radiation oncologist and researcher at Sunnybrook with a specific interest in the genetic predisposition to develop prostate cancer.

"One of our challenges is to get guys into the clinic to participate in this kind of research," says Lorentz.

Martin, however, was glad to get involved. So far, he's in good health with the prostate of, well, a 20-year-old. And he knows that not all men with BRCA mutations will develop cancer. Nevertheless, he explains, "my maternal grandmother died from breast cancer, my mother and an aunt died from breast cancer in their 40s. Until I had genetic counselling at Sunnybrook, I hadn't realized the mutation could be passed on to sons and then passed on by them."

*Justin Lorentz (left) is looking at how genetic mutations such as BRCA tend to affect certain ethnic groups, among other factors.*

More recently, research such as that ongoing at Sunnybrook has found that men with BRCA mutations carry up to double the risk for prostate cancer and are more likely to be diagnosed at an earlier age; in addition, the cancer is likely to be more aggressive compared to men in the general population who develop the disease.

"Prostate cancer is often slow-growing, though it can also be aggressive in men in the general population. In the case of men with BRCA mutations or other known genetic predispositions, and those with strong family histories (given their higher risk), we really want to monitor these guys closely for early diagnosis and timely intervention," says Dr. Vesprini.

He strongly believes other mutations and markers will be found, most likely sooner rather than later. "We'll likely find something heritable in families with strong family histories," he says.

Sunnybrook is one of only a handful of hospitals researching men with known genetic predispositions like BRCA1 and BRCA2, and men with a strong family history of cancer or who are of West African/Caribbean ancestry.



**Prostate Cancer Canada Network – NEWMARKET**
**Volume 23, Issue 3** **November 15, 2017**
A support group that provides understanding, hope and information to prostate cancer patients and their families.

*Topics for the upcoming November Meeting…*

### Research and the Genetics of Prostate Cancer

The Cancer Genetics and High Risk Program at Sunnybrook offers cancer risk assessment, genetic counselling and/or genetic testing to eligible individuals and families who may be at risk for hereditary cancer.

**Danny Vesprini, MD, MSc, FRCPC** is a Radiation Oncologist who treats both prostate and breast cancer at the Sunnybrook Odette Cancer Centre in Toronto, Affiliate Scientist in the Biological Sciences at the Sunnybrook Research Institute and an Assistant Prof. in the Dept. of Radiation Oncology at the Univ. of Toronto. Dr Vesprini's research includes a focus on the genetic predisposition to aggressive prostate cancer. He is one of the Principal Investigators of the Sunnybrook Active Surveillance Program as well as the Director of the Male Oncology Research and Education (MORE) program which focusses on men at increased risk of developing prostate cancer, including men of with a strong family history of the disease, men with a BRCA mutation and men of Caribbean/Western African heritage.

**Justin Lorentz**, MSc, CGC, has worked at the Sunnybrook Odette Cancer Centre since 2012 as a cancer genetic counsellor and Male Oncology Research and Education (MORE) Program Lead. His research interests include evaluating alternative prostate cancer screening options for men at high risk for prostate cancer and identifying inherited genetic factors that predispose men to prostate cancer.

**Meeting Date:** **Thursday, November 16, 2017**
**Place:** **Newmarket Seniors Meeting Place**
**474 Davis Drive, Newmarket**
**Time:** **6:30 pm to 9:00 pm**

**Prostate Cancer Canada Network – Newmarket**
**Newmarket, ON**

http://www.newmarketprostatecancer.com
info@newmarketprostatecancer.com

A member of the Prostate Cancer Canada Network

Assisted by
**Canadian Cancer Society, Holland River Unit**
(905) 830-0447
Cancer Information Service: 1-888-939-3333

**Your Executives**

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*The Newmarket Prostate Cancer Support Group does not recommend products, treatment modalities, medications, or physicians. All information is, however, freely shared.*

# MORE Program

- Men with a germline (likely) pathogenic mutation in a prostate cancer-related gene
- Men with a personal and/or family history of prostate cancer
- Men with of West African/Caribbean Ancestry

- What do we do?
  - Enroll in registry
  - Collect serum and DNA for our biobank
  - Contact patients for research studies
    - Mannogram
    - MRI/biopsy
    - Prostate Cancer Panel
    - Active Surveillance Panel
    - Retrospective Analysis

# MORE Program Prostate Cancer Panel Study

- **Prostate Cancer Panel Study**
  - 100 men need to be tested
  - Personal and family history of prostate cancer in absence of LS or HBOC-related cancers (colon and breast cancer >60 are fair game)
  - Offer 17-gene Invitae Prostate Cancer Panel

- So far…
  - 34 tested
    - 1 CHEK2 likely pathogenic
    - 1 TP53 pathogenic (likely clonal hematopoiesis of IP)
    - 1 TP53 likely pathogenic
    - 10% pick-up rate?

# Acknowledgments


- **Sunnybrook Familial Prostate Cancer Clinic/MORE Program**
  - **Dr. Danny Vesprini, Radiation Oncology**
  - Dr. Laurent Milot, Interventional Radiology
  - Dr. Stanley Liu, Radiation Oncology
  - Dr. Linda Sugar, Pathology
  - Angela Commisso, Clinical Trials

- **Prostate Cancer Canada BRCA Consortium**
  - Dr. Robert Bristow, Manchester Cancer Research Centre
  - Dr. Steven Narod, Women's College Hospital




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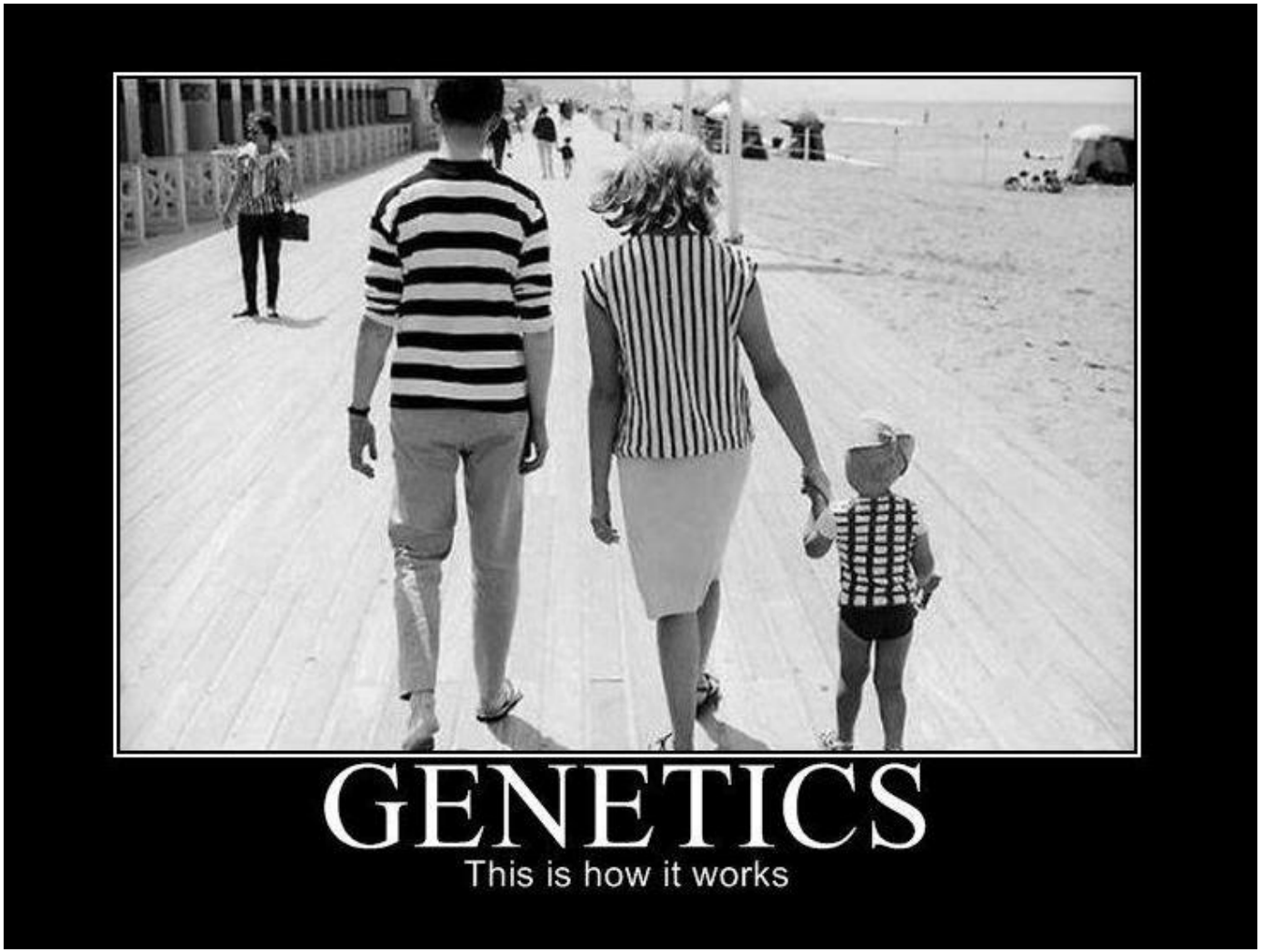
# Questions?



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