

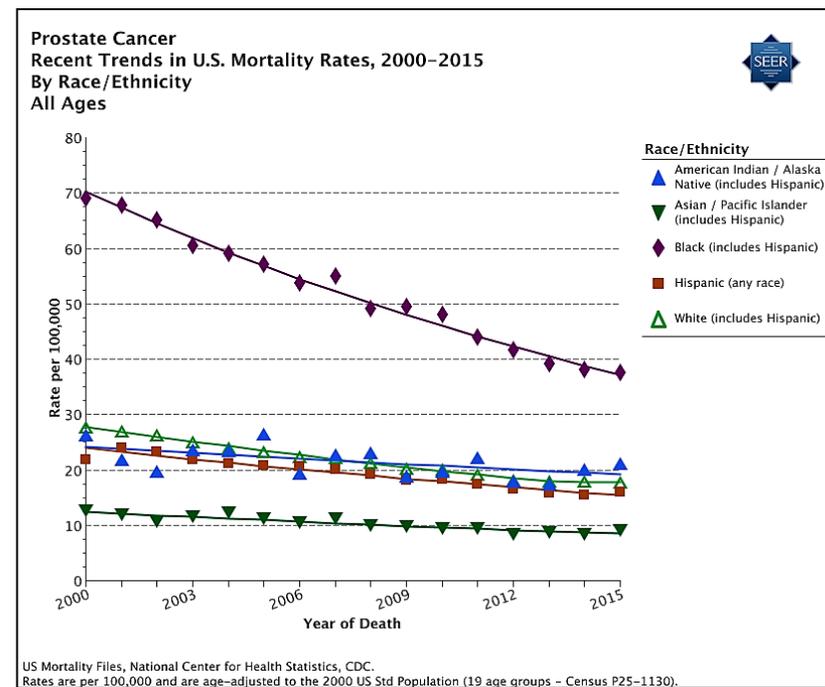
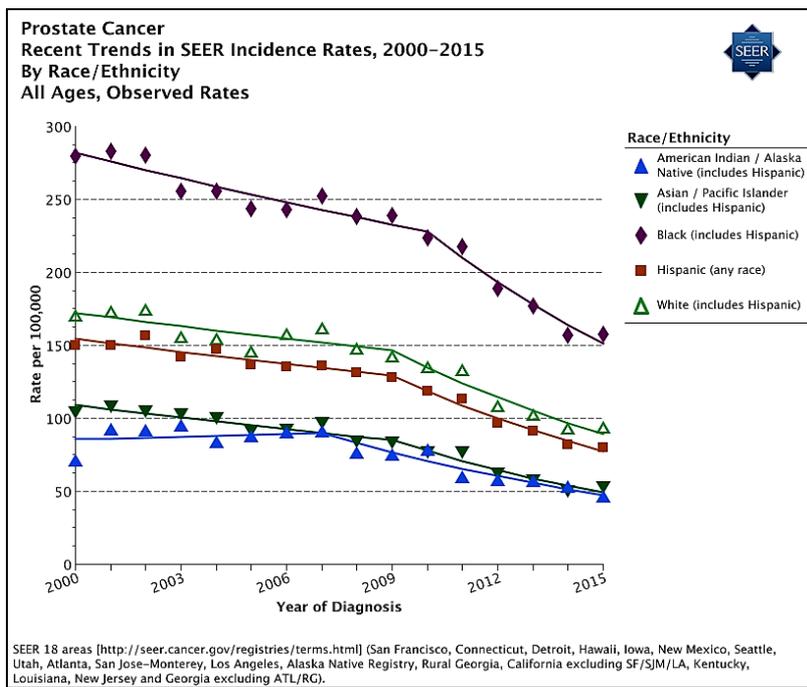
# Genetic Susceptibility to Prostate Cancer in Men of African Ancestry

Chris Haiman, ScD  
December 4, 2018

Center for Genetic Epidemiology  
University of Southern California



# Prostate cancer disparities



## African Americans vs. Whites (and other populations):

- Incidence: 70% greater
  - diagnosed earlier, with more aggressive disease, with greater risk of progression
- Mortality: twice as likely to die from prostate cancer

## Many factors likely contribute to prostate cancer disparities:

- sociodemographics, health behaviors, environmental factors, access to care, variation in screening, detection and treatment
- genetics

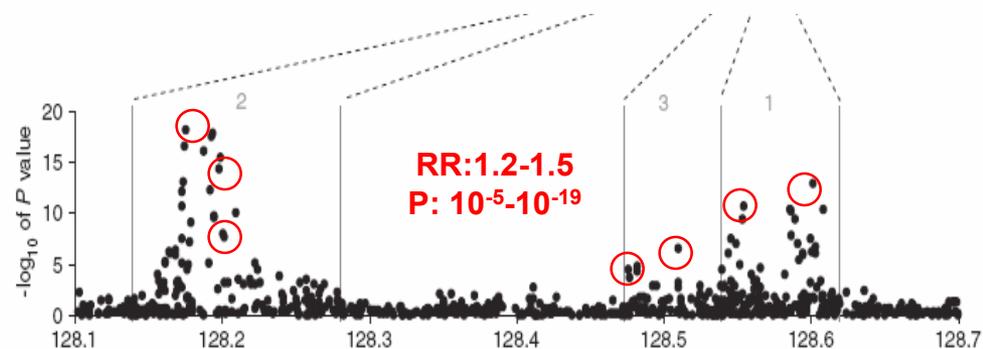
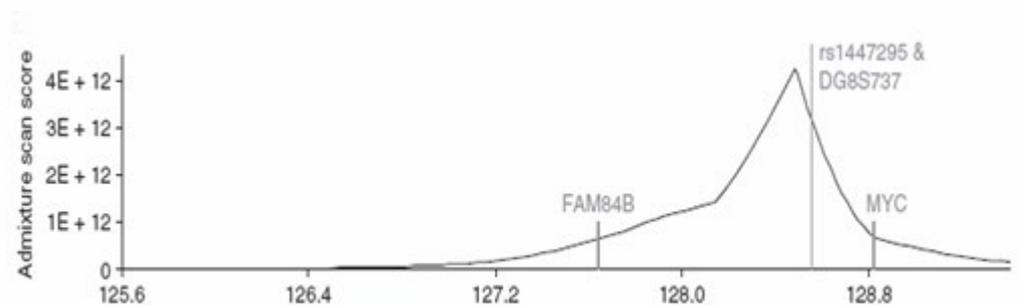
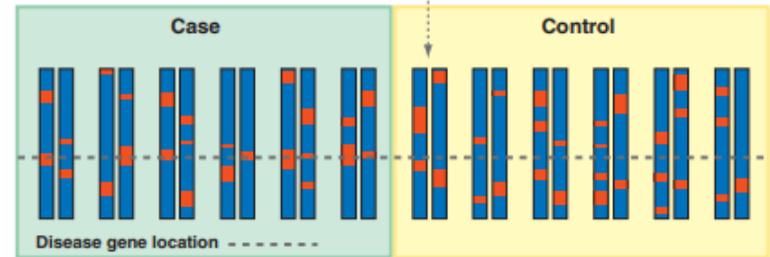
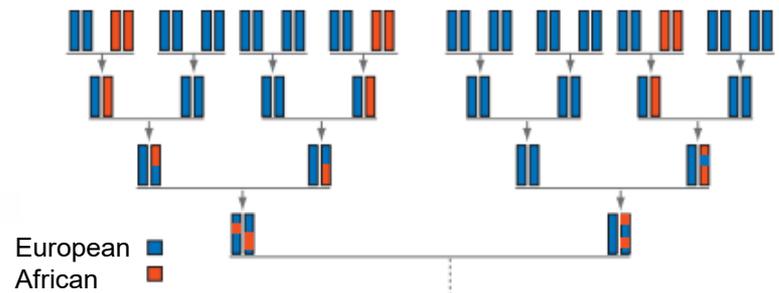
# Genetic ancestry and prostate cancer

Admixture mapping identified risk alleles that track with local genetic ancestry in admixed population

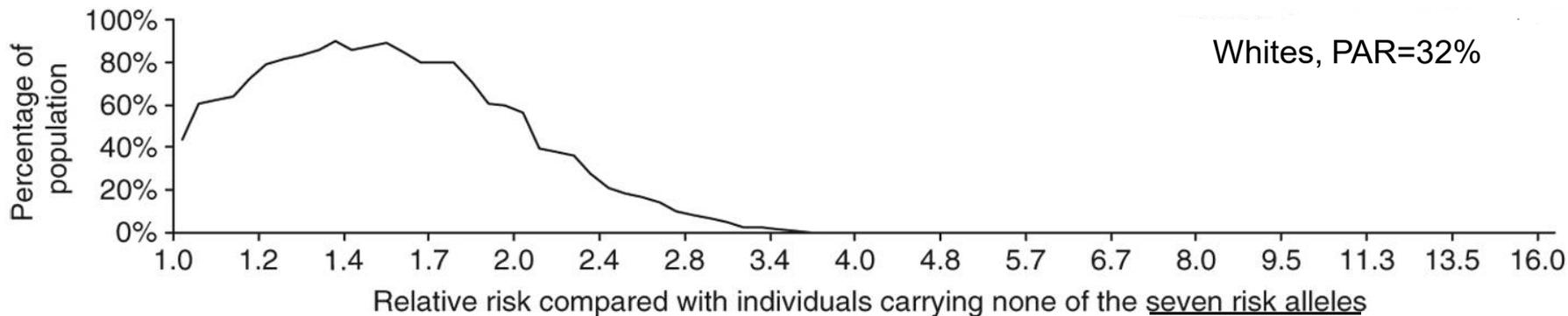
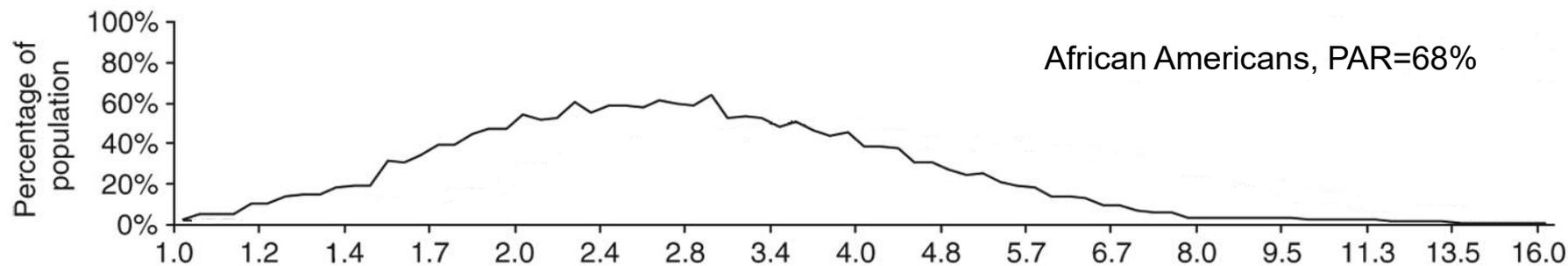
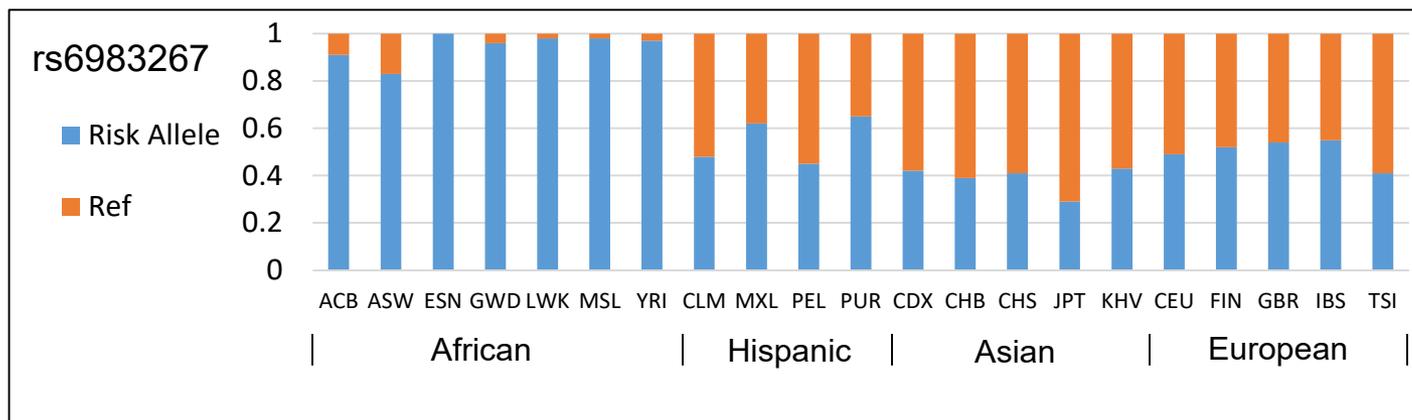
- Admixture scan (n=1,600 AA men): reveals signal at 8q24 (~4 Mb).

Dense genotyping identified multiple risk alleles at 8q24 that contribute to prostate cancer risk.

- Multiethnic Cohort:  
4,266 cases and 3,252 controls:  
African Americans, Whites,  
Japanese, Latinos, Native Hawaiians
- 7 independent risk alleles in 3 regions



# Polygenic risk model for prostate cancer: 8q24

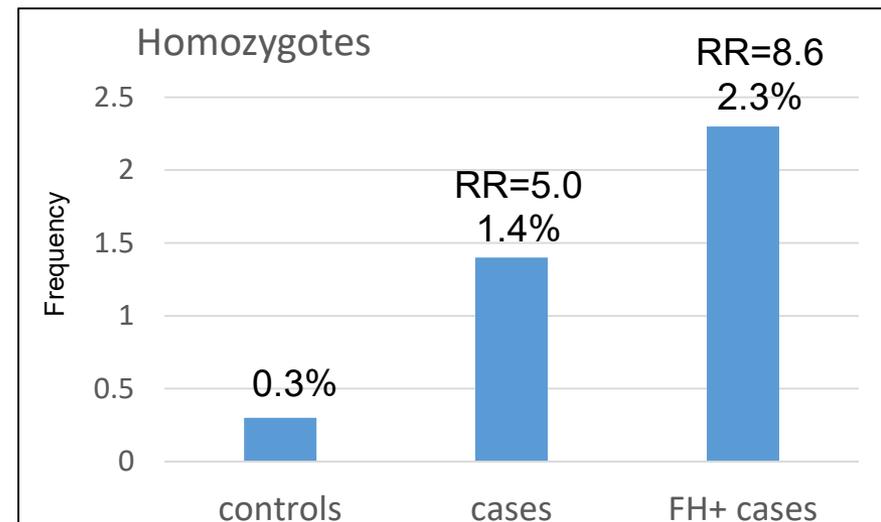
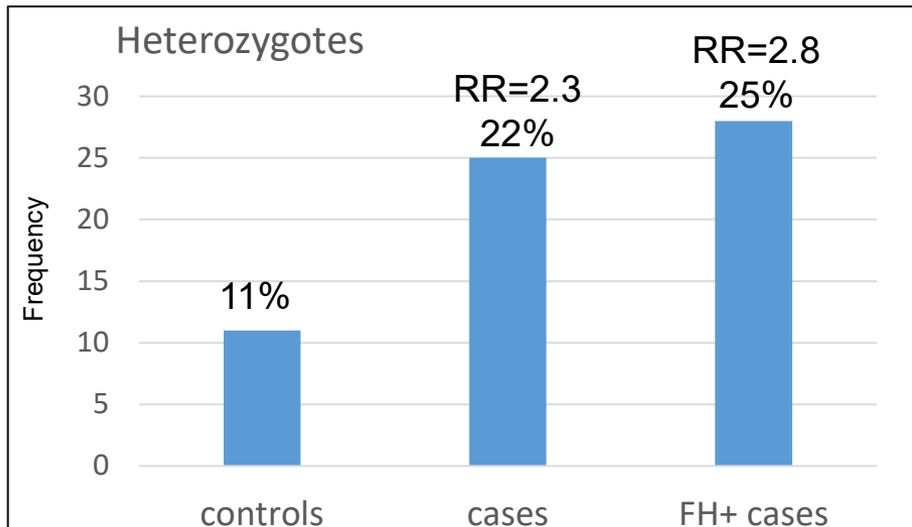
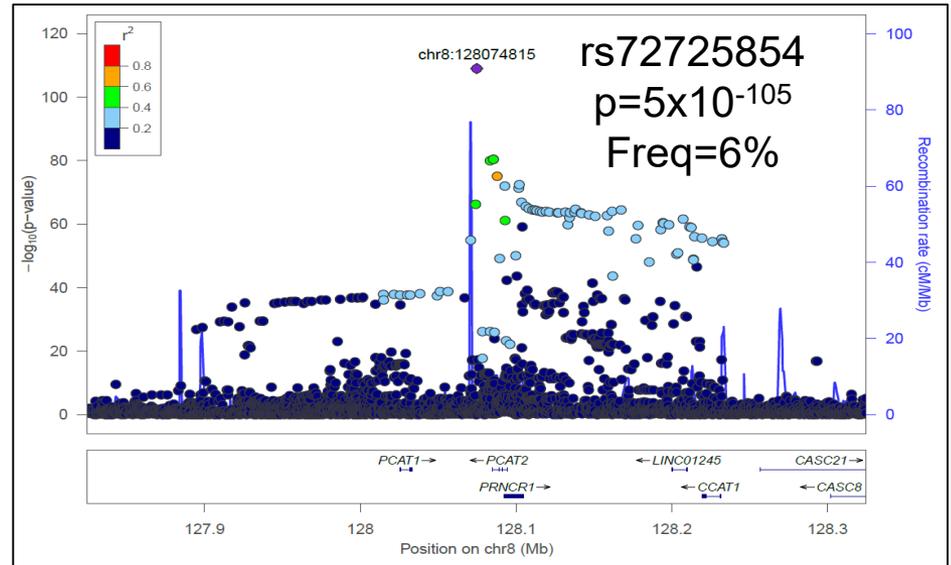
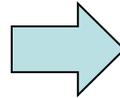
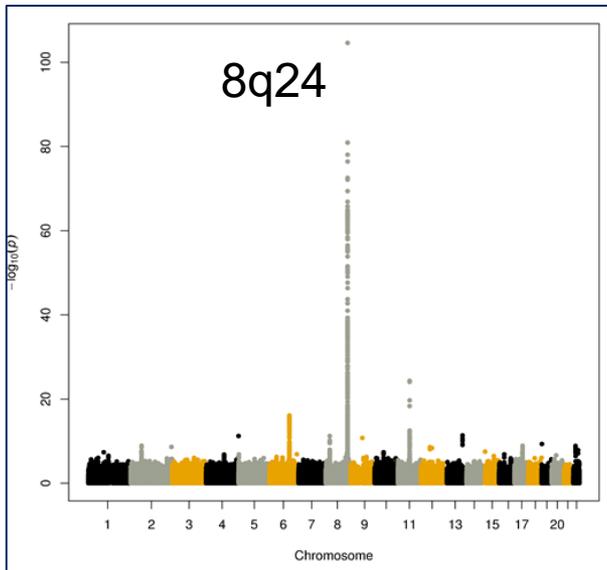


# African Ancestry Prostate Cancer Consortium (AAPC): 2007-2018

Study	Name	Country	Cases	Controls
<b>MEC</b>	Multiethnic Cohort	USA	2429	2429
<b>SCCS</b>	Southern Community Cohort	USA	670	1236
<b>PLCO</b>	Prostate, Lung, Colo and Ov Cancer Screening Trial	USA	286	269
<b>CPS-II</b>	The Cancer Prevention Study II Nutrition Cohort	USA	76	152
<b>MDA</b>	Prostate Cancer Studies at MD Anderson	USA	543	474
<b>IPCG</b>	Identifying Prostate Cancer Genes	USA	368	172
<b>LAAPC</b>	The Los Angeles Study of Aggressive Prostate Cancer	USA	296	303
<b>CaP Genes</b>	Prostate Cancer Genetics Study	USA	75	85
<b>DCPD</b>	Case-Control Study in Washington, DC	USA	292	359
<b>KCPCS</b>	King County Prostate Cancer Study	USA	145	81
<b>GECAP</b>	Gene-Environment Interaction in Prostate Study	USA	234	92
<b>SFPCS</b>	San Francisco Bay Area Prostate Cancer Study	USA	86	37
<b>FMHS</b>	The Flint Men's Health Study	USA	135	353
<b>NCPCS</b>	North Carolina Prostate Cancer Study	USA	214	249
<b>WFPCS</b>	Wake Forest University Prostate Cancer Study	USA	59	66
<b>WUPCS</b>	Washington University Prostate Cancer Study	USA	75	153
<b>SCORE</b>	The Study of Clinical Outcome, Risk and Ethnicity	USA	152	28
<b>SELECT</b>	Selenium and Vitamin E Cancer Prevention Trial	USA	253	734
<b>PCPT</b>	Prostate Cancer Prevention Trial	USA	44	129
<b>NHPC</b>	Nashville Health Prostate Study	USA	179	199
<b>MOFFITT</b>	Moffitt Prostate Cancer Study	USA	81	49
<b>BioVu</b>	Vanderbilt Biobank	USA	214	428
<b>SCPCS</b>	South Carolina Prostate Cancer Study	USA	65	41
<b>PCaP</b>	North Carolina-Louisiana Prostate Cancer Project	USA	1,060	1,000
<b>CDPR</b>	Cntr for Prostate Disease Research	USA	131	69
<b>PROTEuS</b>	The Prostate Cancer and Environment Study	Canada	73	58
<b>UKGPCS</b>	UK Prostate Cancer Study	UK	384	0
<b>ProGene/EPICAP</b>	French Prostate Cancer Case-Control Studies	France	121	94
<b>PCBP</b>	Prostate Cancer in a Black Population	Barbados	246	252
<b>Karuprostate</b>	French West Indies Prostate Study	Guadeloupe	363	386
<b>GHS</b>	The Ghana Men's Health Study	Ghana	498	494
<b>UGPCS</b>	A Case-Control Study in Uganda	Uganda	521	515
<b>TOTAL:</b>			<b>10,368</b>	<b>10,986</b>

# GWAS in AAPC

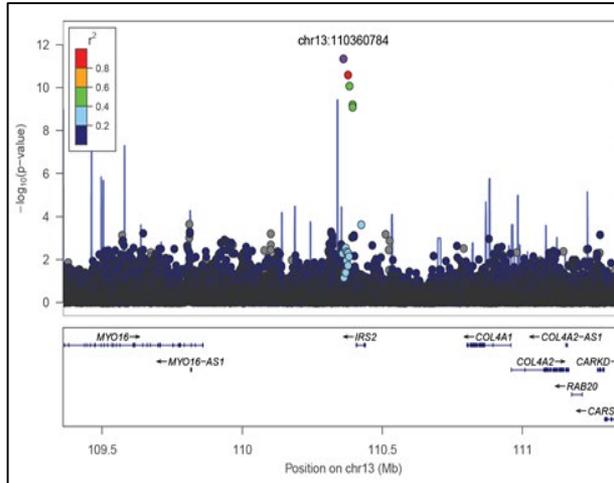
Conti et al, JNCI 2017



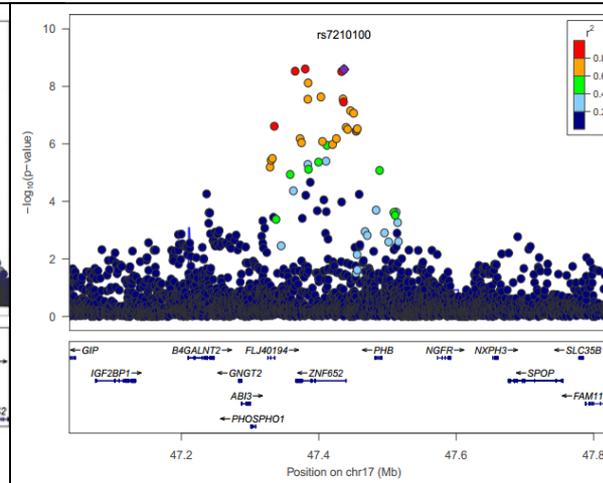
vs. HOXB13: - 0.2% of Whites in U.S. G84E carriers (RR=3); accounts for 5% of hereditary PC

# Population-specific risk alleles

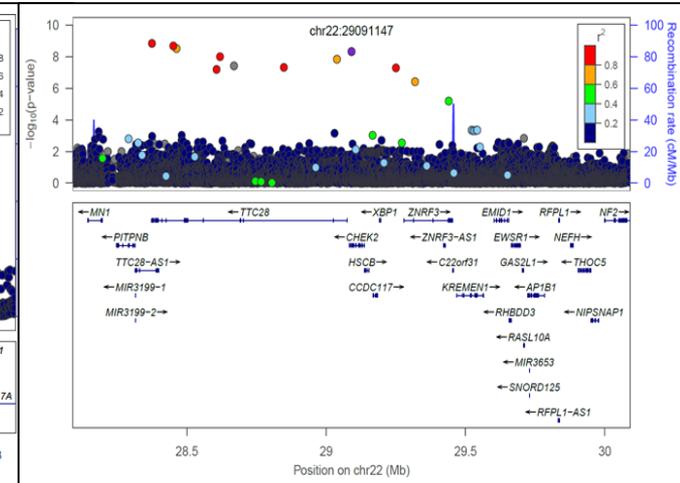
## 13p34 - *IRS2*



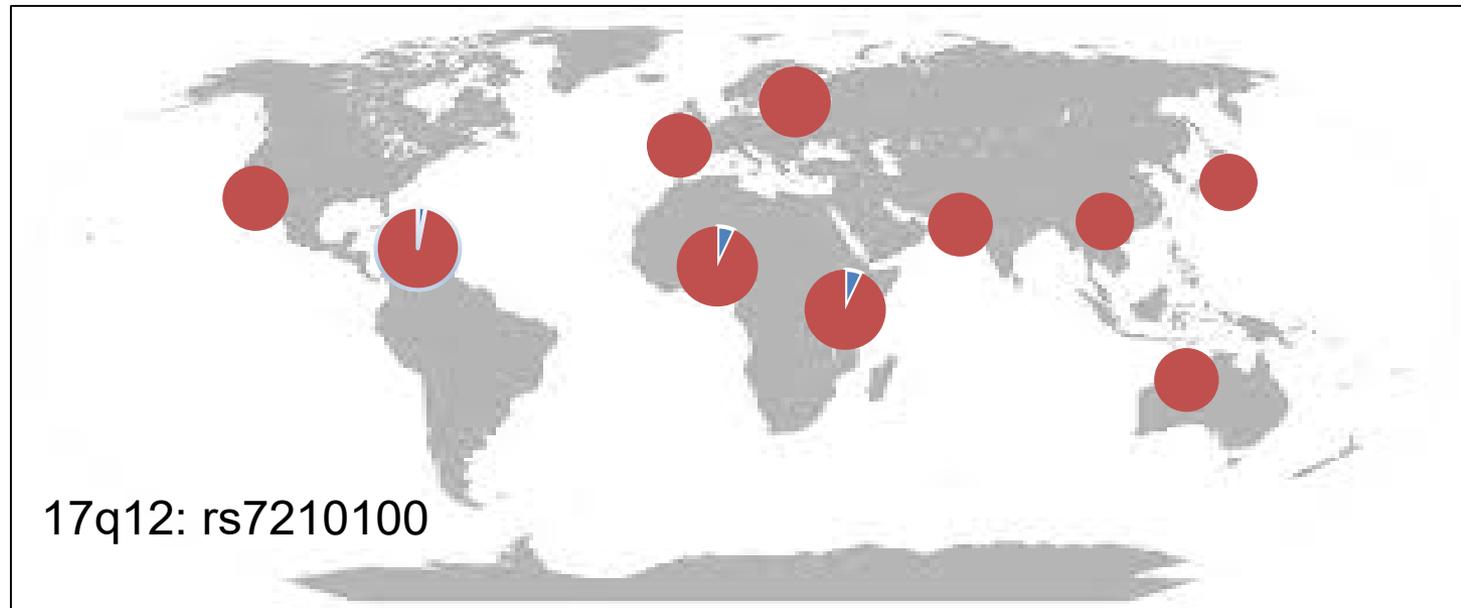
## 17q12 - *ZNF652*



## 22q12 - *CHEK2*



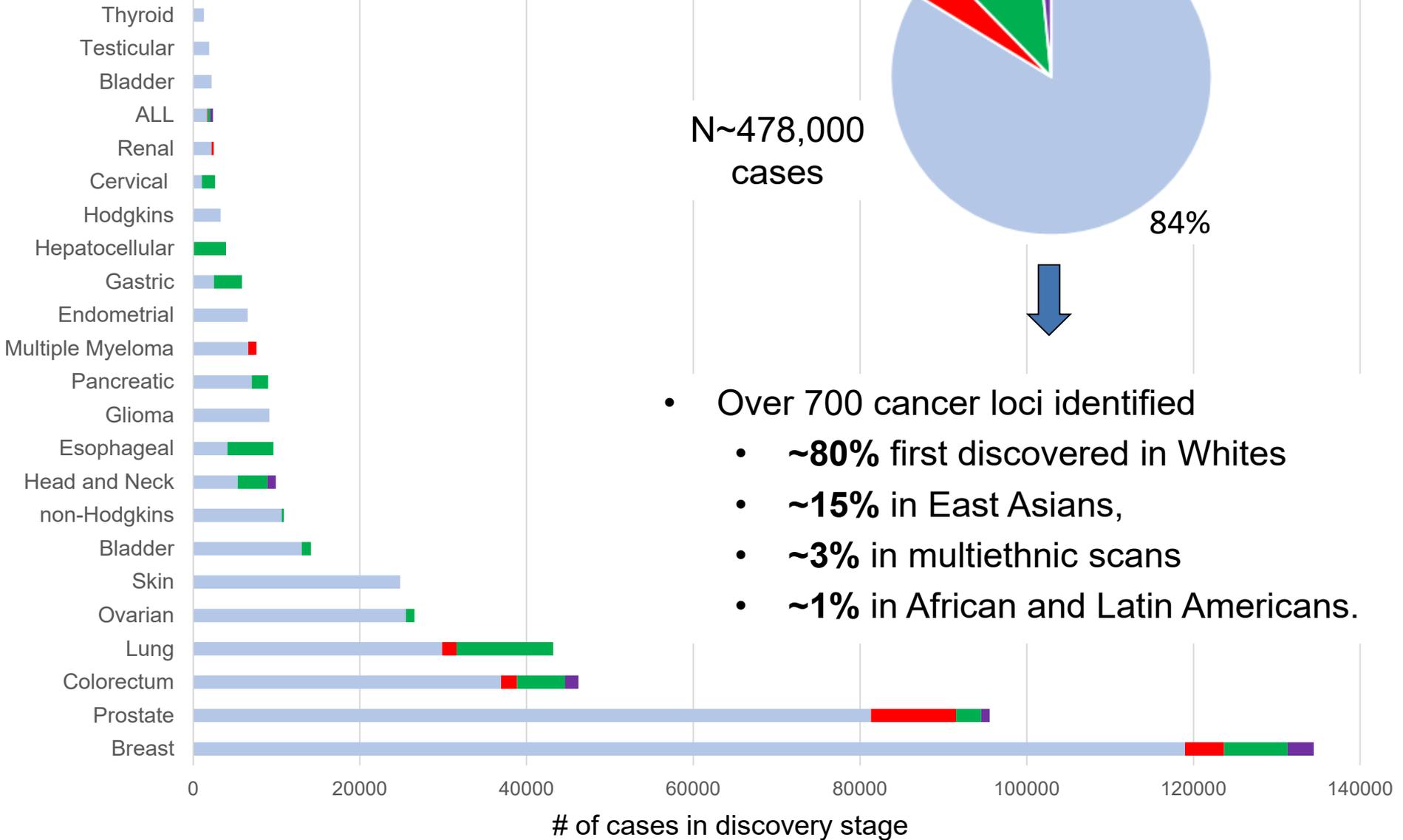
- 2-5% in African ancestry populations
- 0% in other populations
- RR~1.6



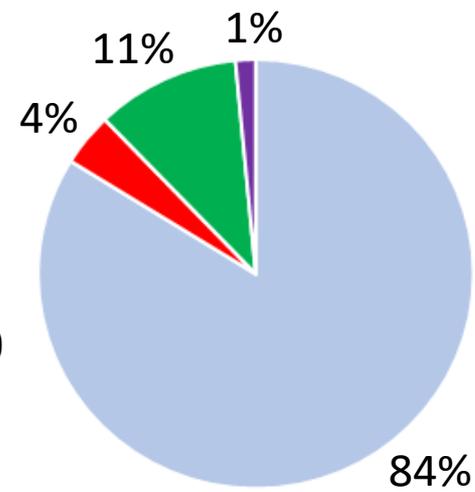
17q12: rs7210100

# GWAS of cancer

(through 2016)



N~478,000 cases



- Over 700 cancer loci identified
  - ~80% first discovered in Whites
  - ~15% in East Asians,
  - ~3% in multiethnic scans
  - ~1% in African and Latin Americans.

■ European ■ African ■ East Asian ■ Latin American

# GWAS of prostate cancer

- PRACTICAL/ELLIPSE NCI GAME-ON Consortium: ~130 studies globally

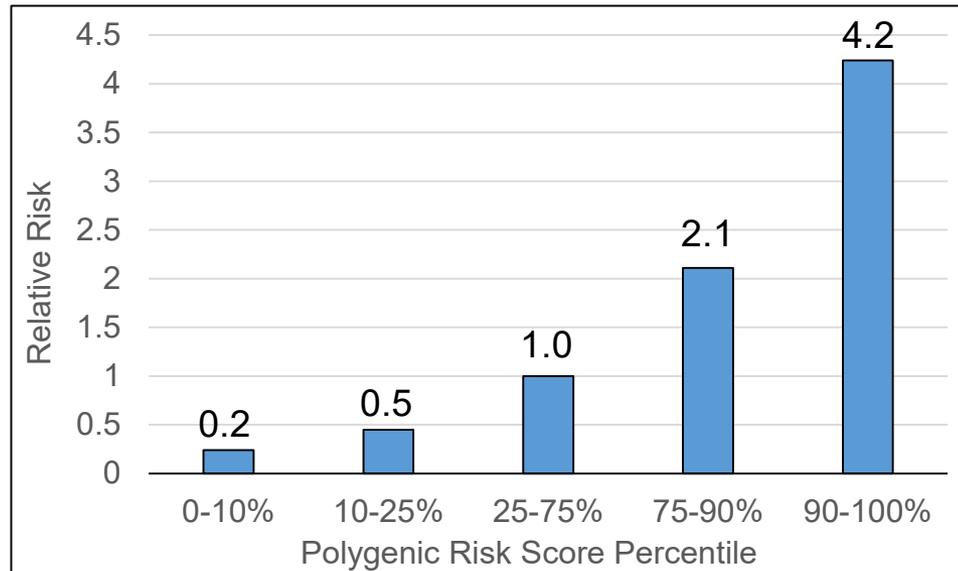
**Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci**

Schumacher et al, Nat Genet 2018

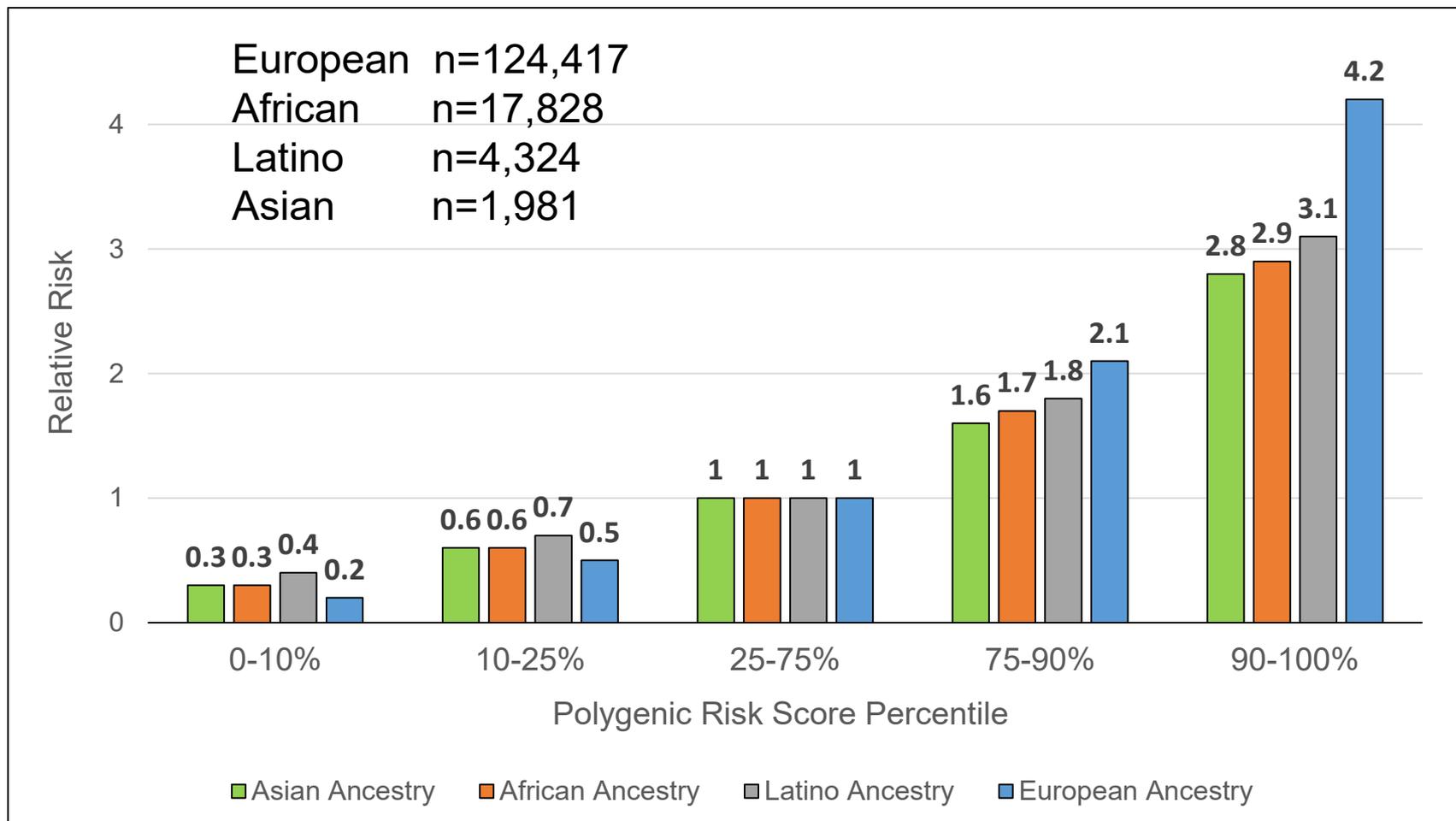
- 181 common risk variants have been identified
  - >80% found in GWAS in whites
  - 37% of familial risk (FR) of prostate cancer in whites
  - modest effects (RR~1.05-1.40)

Polygenic  
Risk  
Score  
(PRS)

European Ancestry  
~60,000 cases  
~60,000 controls

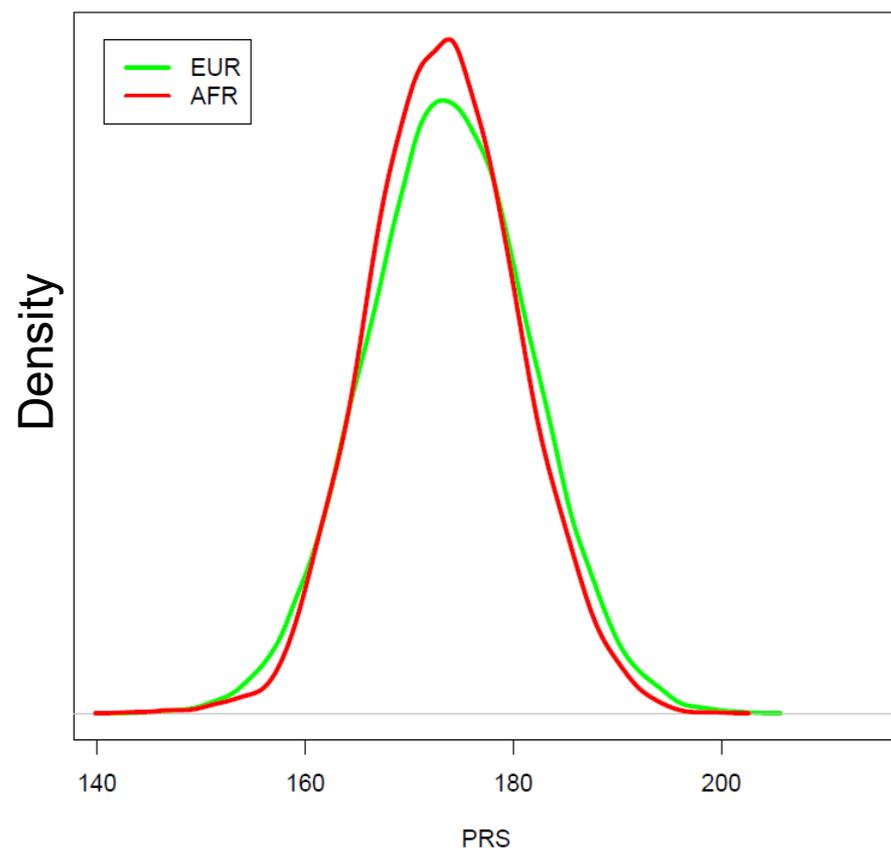
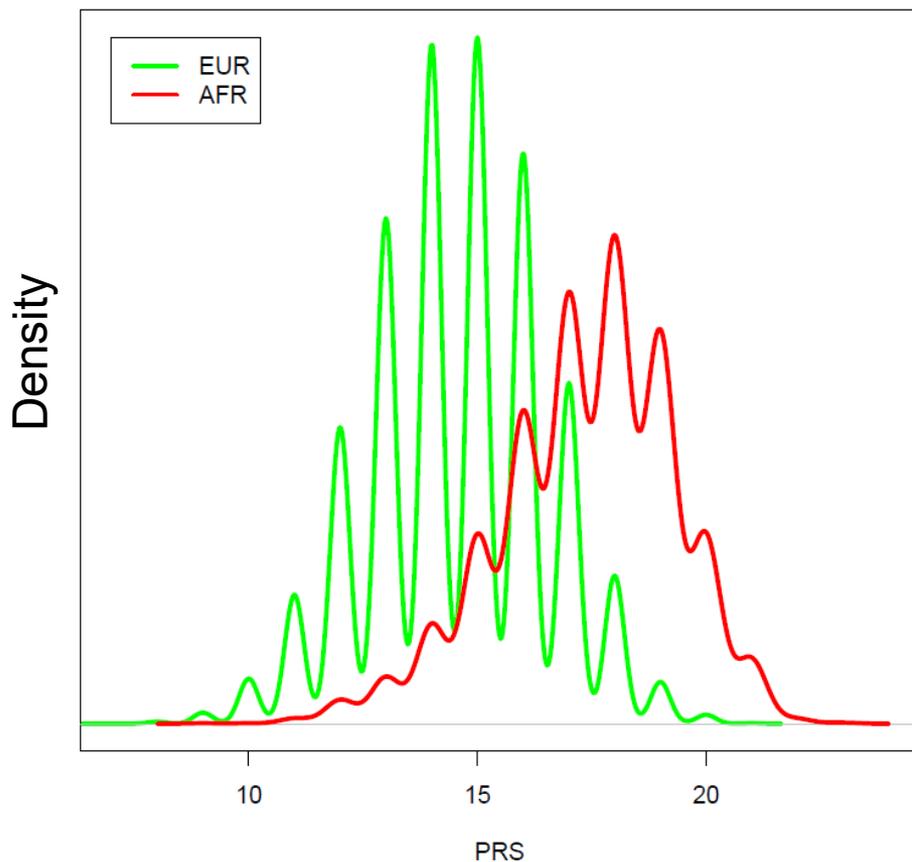


# Prostate cancer PRS by population



- PRS summary (n=181 risk variants):
  - Performance: European > Latino = African = Asian

# Do genetic factors contribute to population differences in prostate cancer risk?



**14 variants at 8q24**



**All 181 variants**

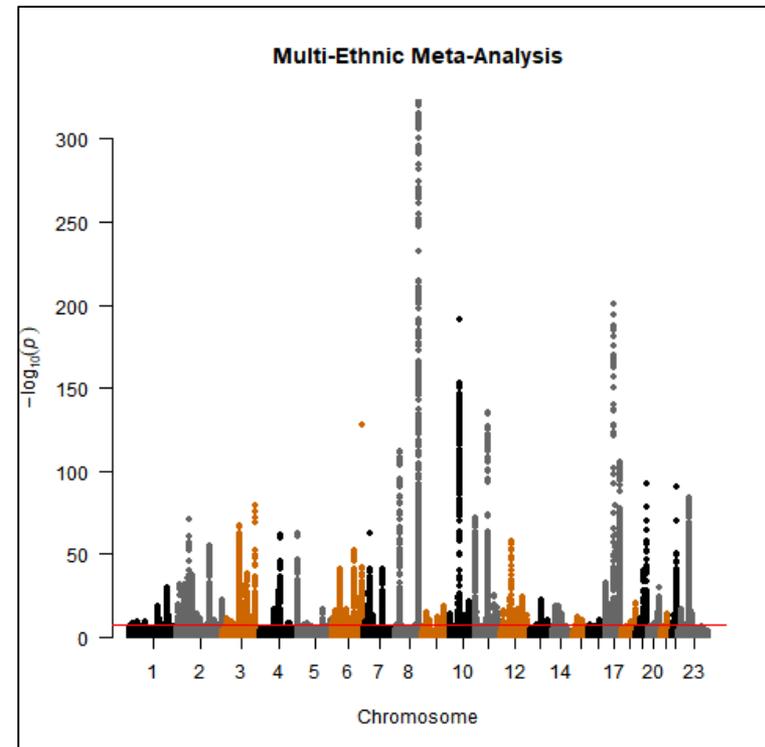
GWAS and fine-mapping in whites

# Multiethnic Studies

- Goal: To combine GWAS data across populations to identify stronger signals in known regions and novel variants with pan-ethnic effects.
- GWAS and fine-mapping meta-analysis:

## PRACTICAL/ELLIPSE+AAPC+ProHealth+RIKEN

Population	Number of Samples		
	Cases	Controls	Total
African	10,368	10,986	21,354
Asian	8610	18,809	27,419
European	88,714	91,940	180,654
Hispanic/Latino	2,714	5,239	7,953
<b>Total</b>	<b>110,406</b>	<b>126,974</b>	<b>237,380</b>

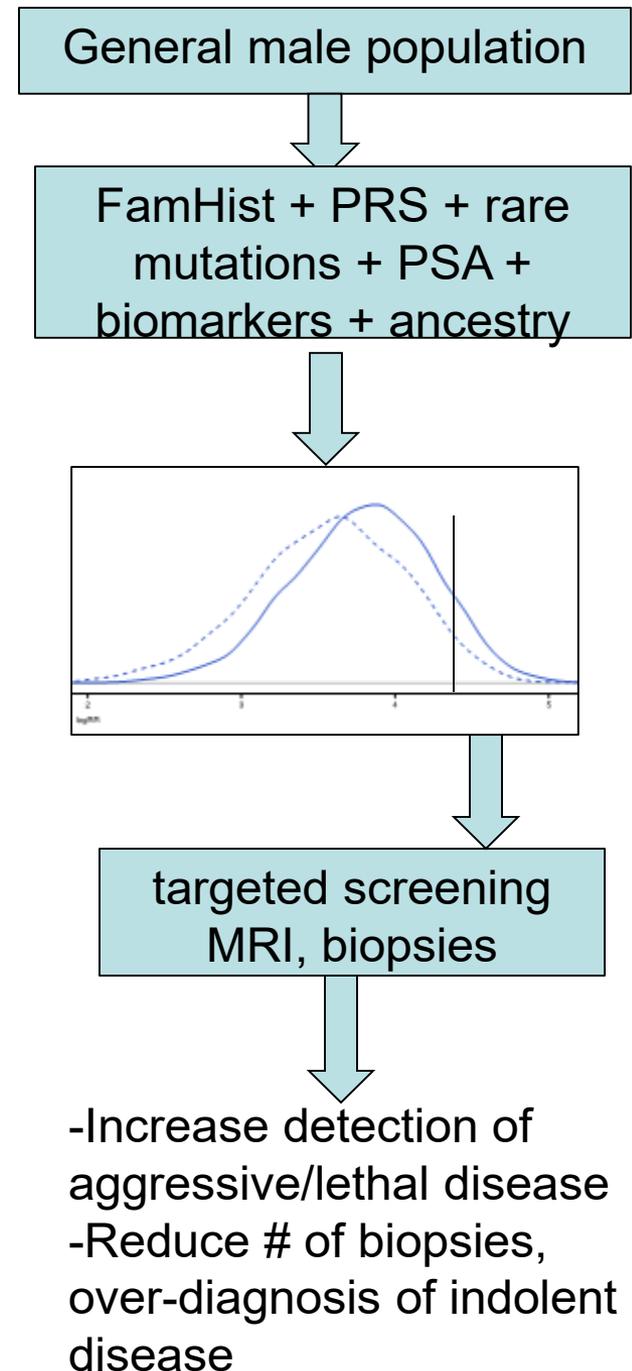


## Results (preliminary):

- ~60 novel risk variants (~240 total)
- ~90 of the 181 known risk ('index') variants have been replaced

# Clinical Utility of GWAS-PRS

- Common risk variants (and the PRS) can't discriminate between a man's risk of aggressive vs. non-aggressive disease
- Ongoing prostate cancer screening studies that incorporate PRS in the UK and Sweden:
  - STHML3
  - BARCODE (includes AA men)
  - PROFILE
- Need genetic markers of aggressive disease

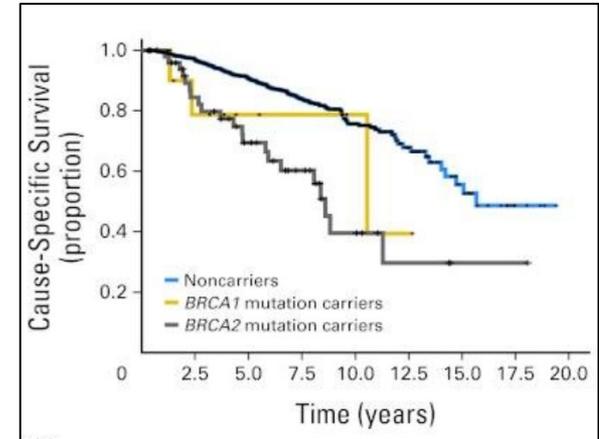


# Rare pathogenic mutations in DNA repair genes

## BRCA1/2

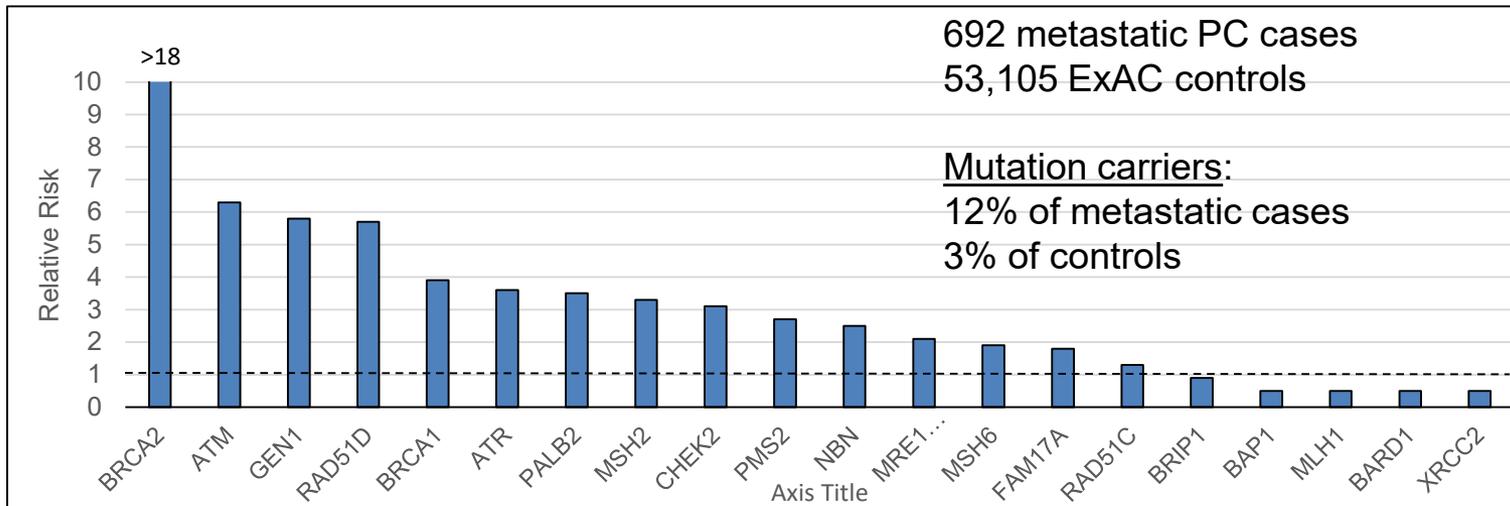
- 1% of prostate cancer cases carry a mutation
- BRCA1: RR>2
- BRCA2: RR>5
- Carriers develop more aggressive disease and have poor survival

Kote-Jarai et al, Br J Cancer 2011



Castro et al, JCO 2013

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

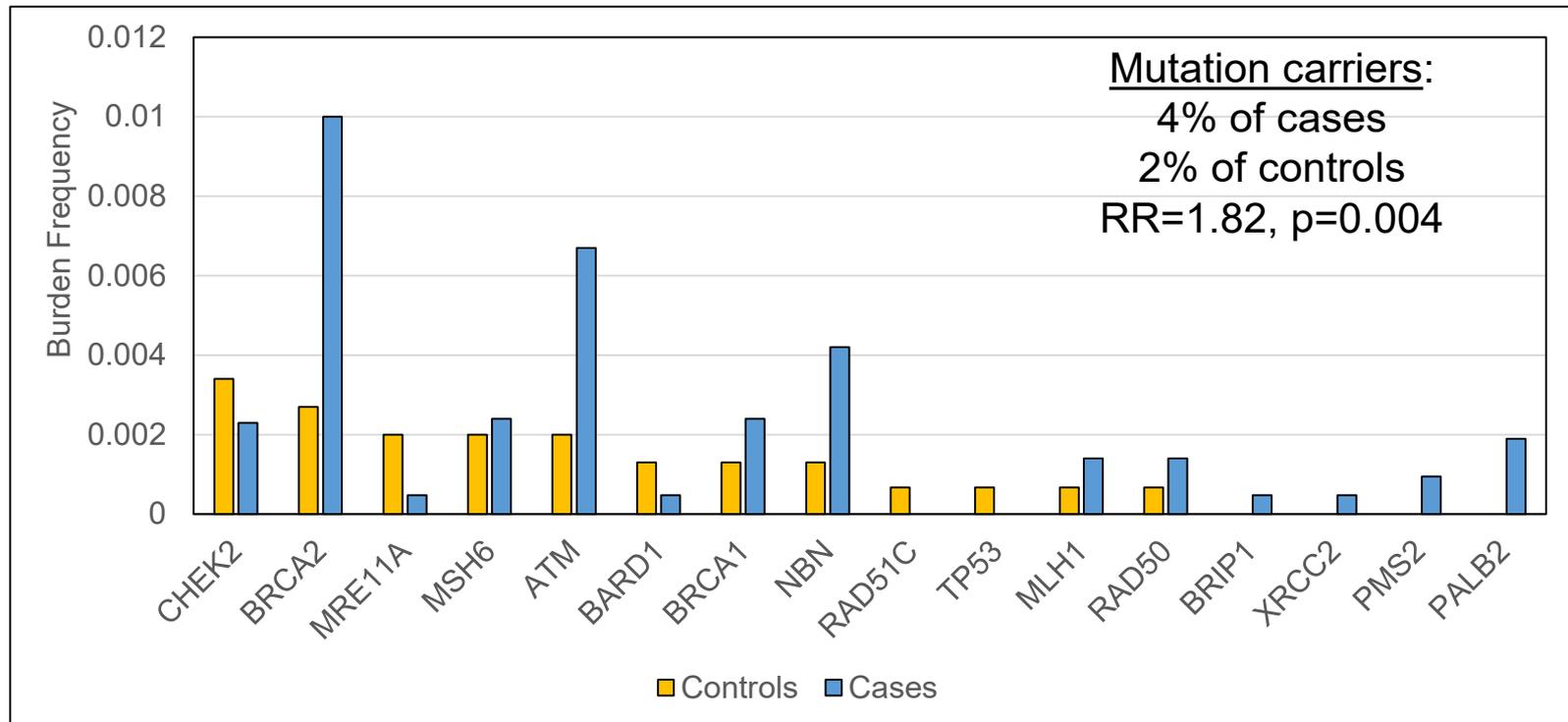


Pritchard, NEJM 2016

# Rare coding variants and prostate cancer risk in men of African ancestry

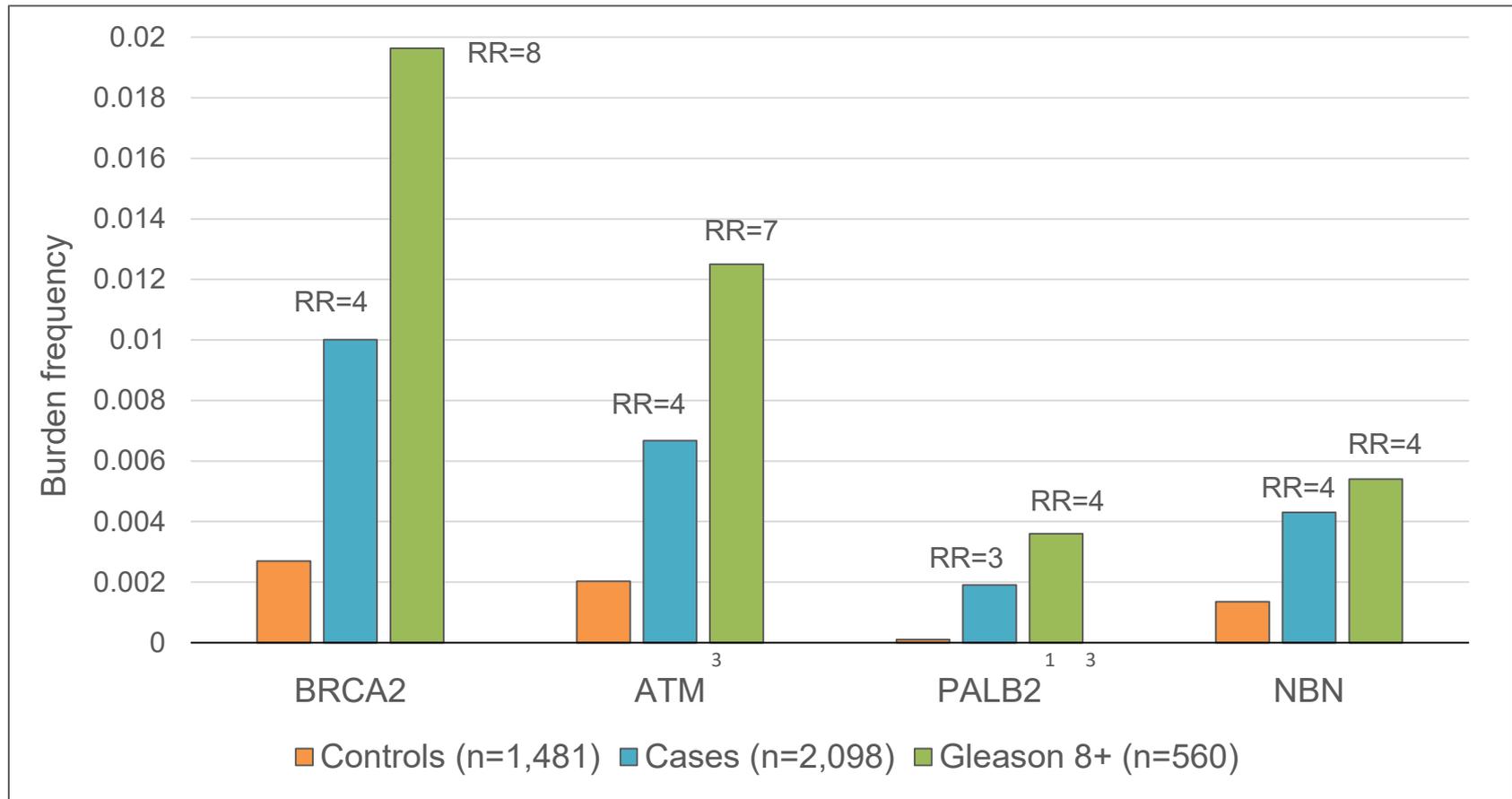
	Controls	Cases
African American	995	1447
Ugandan	486	651
<b>Total</b>	<b>2098</b>	<b>1481</b>

- DNA repair and cancer susceptibility gene panel (16 genes)
- Rare pathogenic mutations (protein truncating, ClinVar-missense)



# Rare coding variants and prostate cancer risk in men of African ancestry

- RR ~3-4 for overall prostate cancer (*BRCA2*, *ATM*, *PALB2*, *NBN*)
- Larger effects for aggressive phenotypes

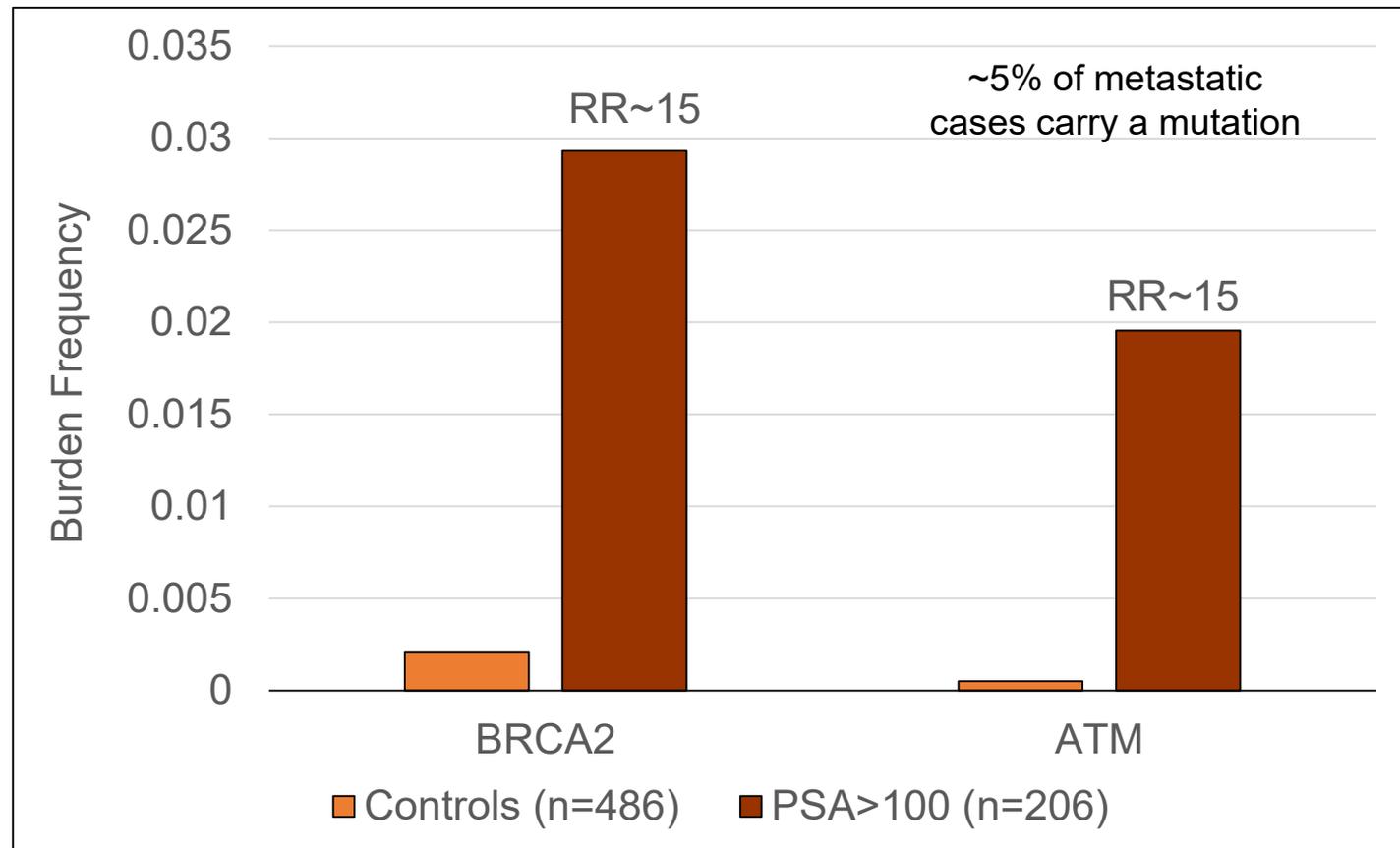


$P < 0.001$  for most RR's

# Rare coding variants and prostate cancer risk in men of African ancestry

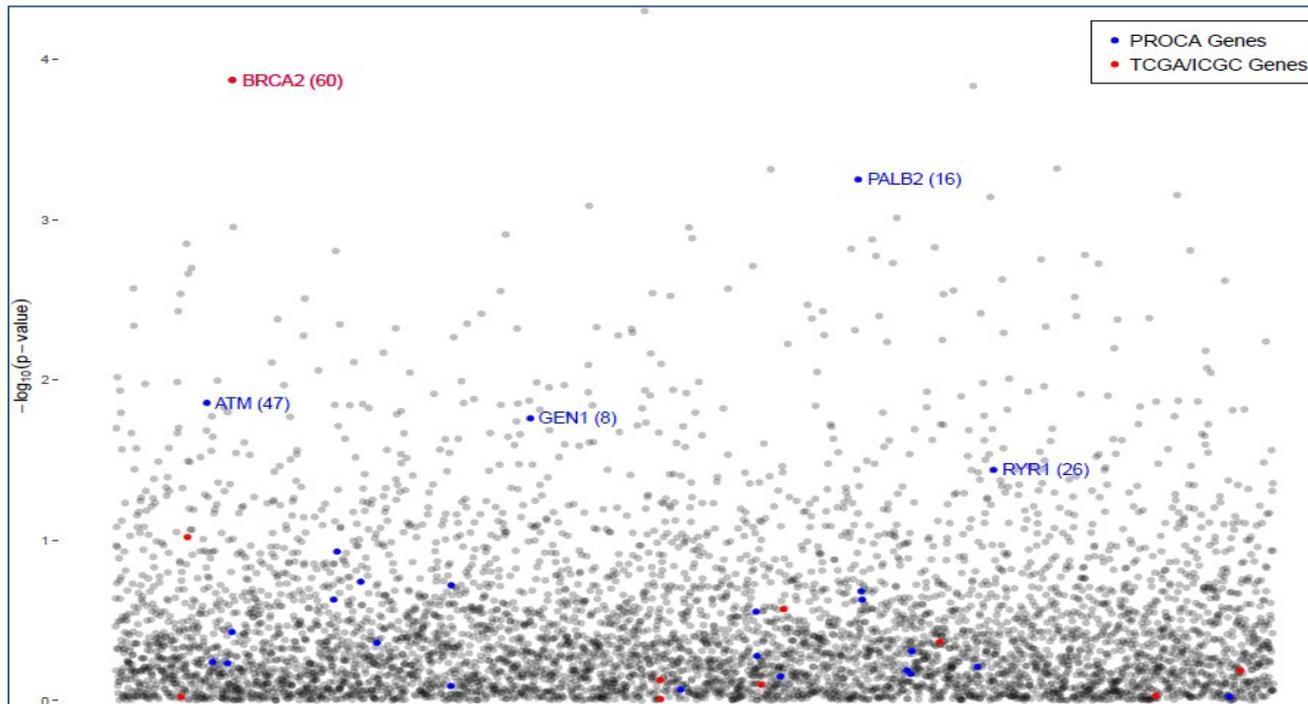
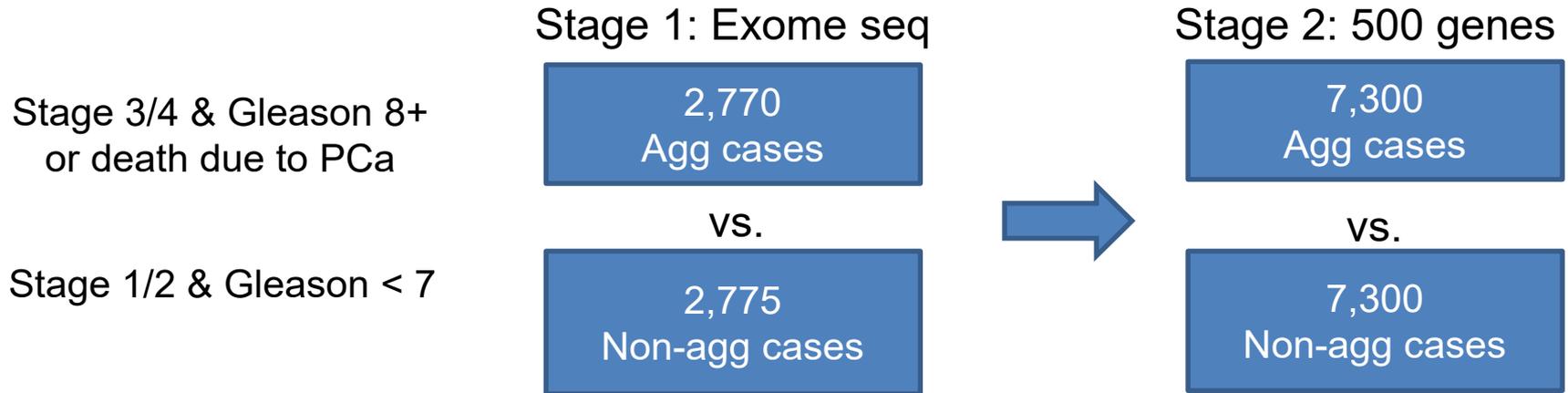
## Metastatic disease:

- African Americans: <70 metastatic cases
- Ugandans: no information on stage; *32% of cases with PSA>100 ng/ml at dx*



P's<0.001

# Rare variant discovery for aggressive prostate cancer: 20,000 cases of European ancestry



selected for  
validation  
(Spring 2019)



# RESPOND

## Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers and Social Stress

- U19 in collaboration with NCI-DCEG Intramural investigators
- Objective: to define sociological and biological factors and their inter-relationships that contribute to aggressive PCa in African American men
- Recruit 10,000 African American men with prostate cancer
  - baseline survey, saliva and tumor samples
- Scientific questions to be addressed:
  - genetic susceptibility (GWAS and exome seq)
  - social factors that contribute to lifetime stress
  - lifestyle factors and health behaviors
  - medical care-related factors (e.g. access to care and screening)
  - tumor-related features: somatic mutations and local inflammation
- Cores: admin, pathology, recruitment, data analysis
- Funding: NCI, NIMHD and PCF

[www.RESPONDstudy.org](http://www.RESPONDstudy.org)

CLICK HERE TO PARTICIPATE OR LEARN MORE!

**RESPOND**  
A National Study of Prostate Cancer  
in African American Men

HOME WHAT IS RESPOND? WHO ARE WE? FAQs HOW TO PARTICIPATE

African American men are more likely to develop prostate cancer than men of any other race and the disease is often more aggressive when diagnosed.

If you are African American, and have been diagnosed with prostate cancer, join the nation-wide RESPOND study!

Working together, we can understand how to prevent this disease and improve survival for African American men.



# RESPOND Investigators

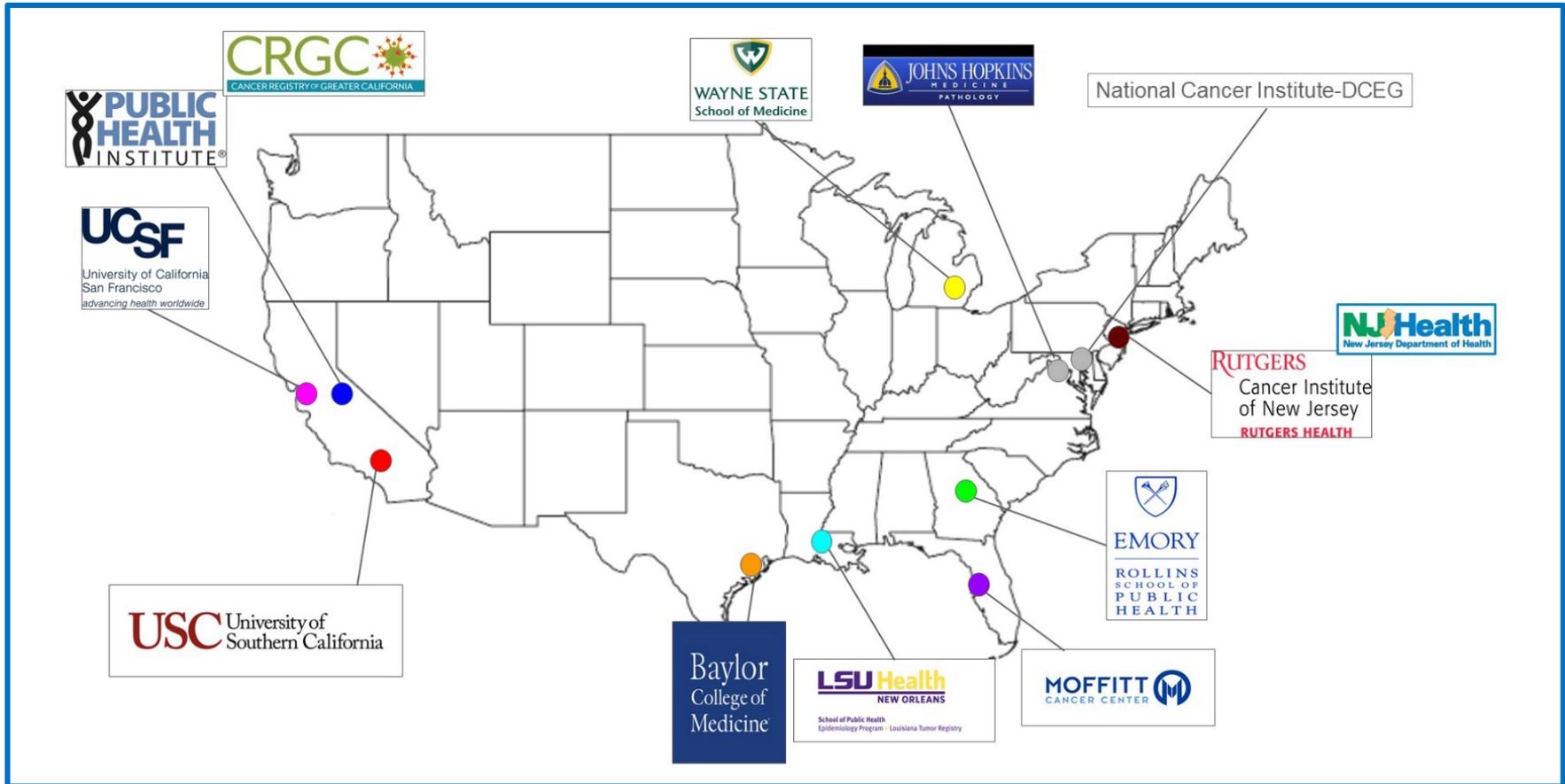
<u>NAME</u>	<u>INSTITUTION</u>	<u>NAME</u>	<u>INSTITUTION</u>
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Ann Hamilton, PhD	USC	Rosemary Cress, PhD	Public Health Inst.
David Conti, PhD	USC	Kevin Ward, PhD, MPH	Emory University
John Carpten, PhD	USC	Karen Pawlish, ScD, MPH	N. J. Dept. of Health
David Craig, PhD	USC	Antoinette Stroup, PhD	Rutgers University
William Gauderman, PhD	USC	Jong Park, PhD, MPH	Moffitt Cancer Center
Scarlett Gomez, PhD, MPH	UCSF	Thomas Sellers, PhD, MPH	Moffitt Cancer Center
Iona Cheng, PhD, MPH	UCSF	Jennifer Beebe-Dimmer, PhD, MPH	Karmanos Cancer Inst.
Mindy DeRouen, PhD, MPH	UCSF	Melissa Bondy, PhD	Baylor University
Salma Shariff-Marco, PhD, MPH	UCSF	Stephen Chanock, MD	NCI
Franklin Huang, MD, PhD	UCSF	Sonja Berndt, PhD	NCI
Angelo De Marzo, MD, PhD	Johns Hopkins	Michael Cook, PhD	NCI
Tamara Lotan, MD	Johns Hopkins	Meredith Yeager, PhD	NCI
Karen Sfanos, PhD	Johns Hopkins		

Multi-disciplinary team: epidemiologists, oncologists, urologists, pathologists, genomicists, bioinformaticians and biostatisticians with track records in population-based and clinical prostate cancer and health disparities research

EAC: Lee Green (Moffitt), Scott Tomlins (Michigan), Daniel Schaid (Mayo), Isaac Powell (Wayne St.), Amani Allen (Berkeley), Westley Sholes (Advocate)



# Recruitment and Research Sites



- Goal: Recruitment of 10,000 African American prostate cancer cases
- Contact and recruitment through SEER and NPCR cancer registries covering 7 states representing ~40% of African American men in the U.S.

# Challenges in Recruitment

## Attitudes Toward Genomic Testing and Prostate Cancer Research Among Black Men

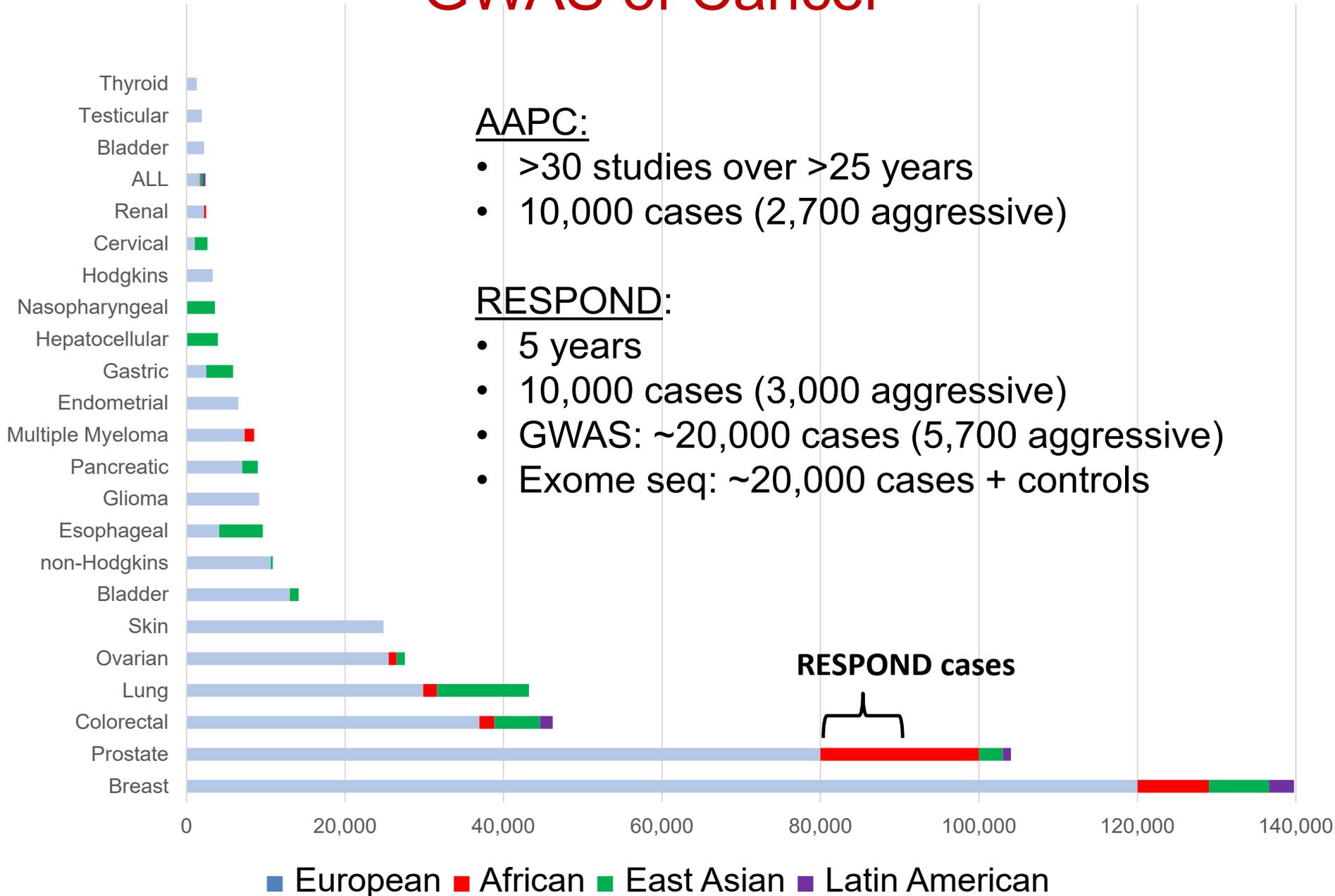
Rodgers et al, Am J Prev Med, 2018



Distrust Of Health Care System May Keep Black Men Away From Prostate Cancer Research October 17, 2018 · 11:30 AM ET

- Focus groups of African American prostate cancer patients at each recruitment site (n=7-10) reviewed study materials and were asked about how we can build trust:
  - What is the benefit for me or my family?
  - Clearly define the disparity.
  - Research vs. testing
  - Transparency
  - Confidentiality of data/results
  - Buy-in from Black community leaders, institutions, organizations & churches, etc.
  - Include African American researchers/colleges
  - A celebrity face for the study would build credibility
  - Include Black study staff members and face to face interaction
  - Publicize to build credibility
  - Health education & literacy
  - Keep us informed

# GWAS of Cancer



# Acknowledgements



## Multiethnic Cohort

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Lynne Wilkens

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Doug Easton  
Ali Amin Al Olama  
Hidewaki Nakagawa  
Fredrik Wiklund  
Graham Giles

## Uganda

Stephen Watya  
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CA164973, RC2 CA148085, U01 CA1326792, U01  
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## AAPC Consortium

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Iona Cheng  
Xiao-Cheng Wu  
Rosemary Cress

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Dimmer  
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Salma Shariff-Marco  
Meredith Yeager  
Sonia Berndt  
Michael Cook  
Stephen Chanock  
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Franklin Huang