



Targeted Prostate Cancer Screening: Role of Germline Genetic Testing

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UC San Diego
MOORES CANCER CENTER

Disclosures

Patent holder for SNP based prostate cancer risk stratification

Stock Holder and Board Member of SNP Bio

Objectives

- Understand prostate cancer incidence and natural history
- Understand how prostate cancer screening was performed in the past
- Understand controversies surrounding prostate cancer screening
- Understand the potential role for germline genetic tests in future prostate cancer screening algorithms

“1 out of every 6 men will be diagnosed with prostate cancer during their lifetime”

This year

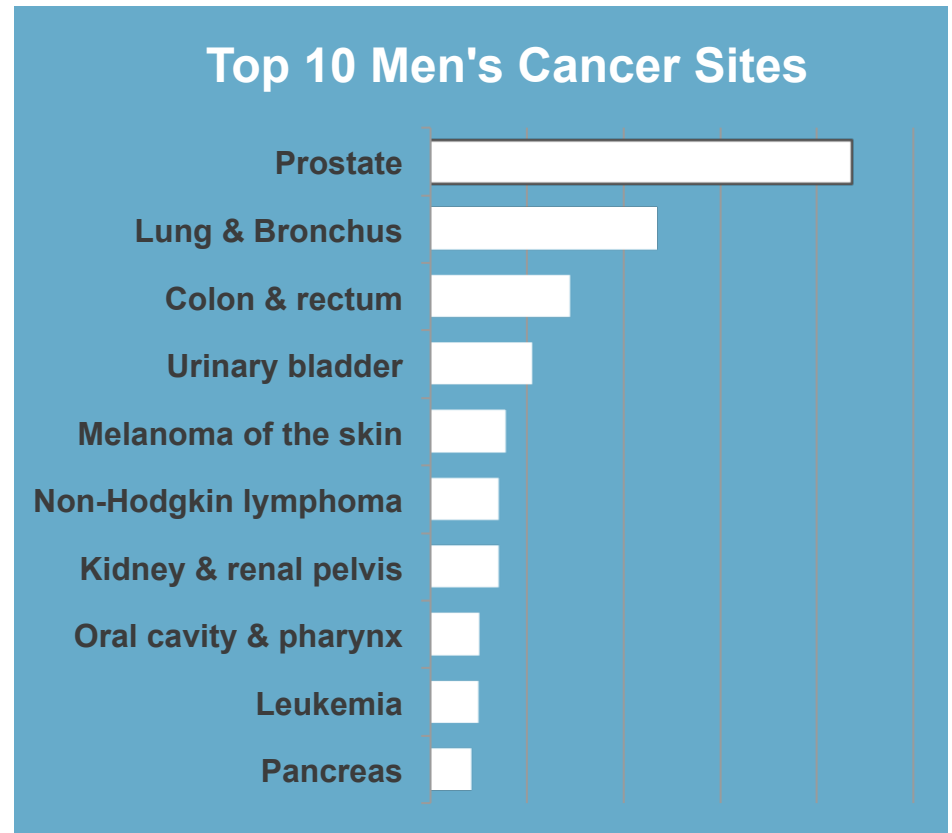
221,000

diagnosed with prostate cancer

27,000

deaths

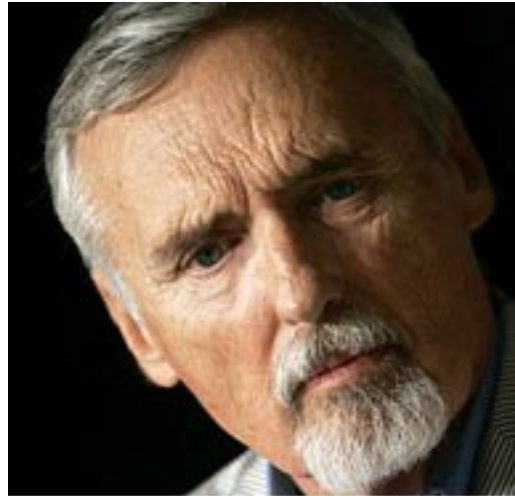
Prostate Cancer is the most common malignancy and 2nd leading cause of cancer death in US men.



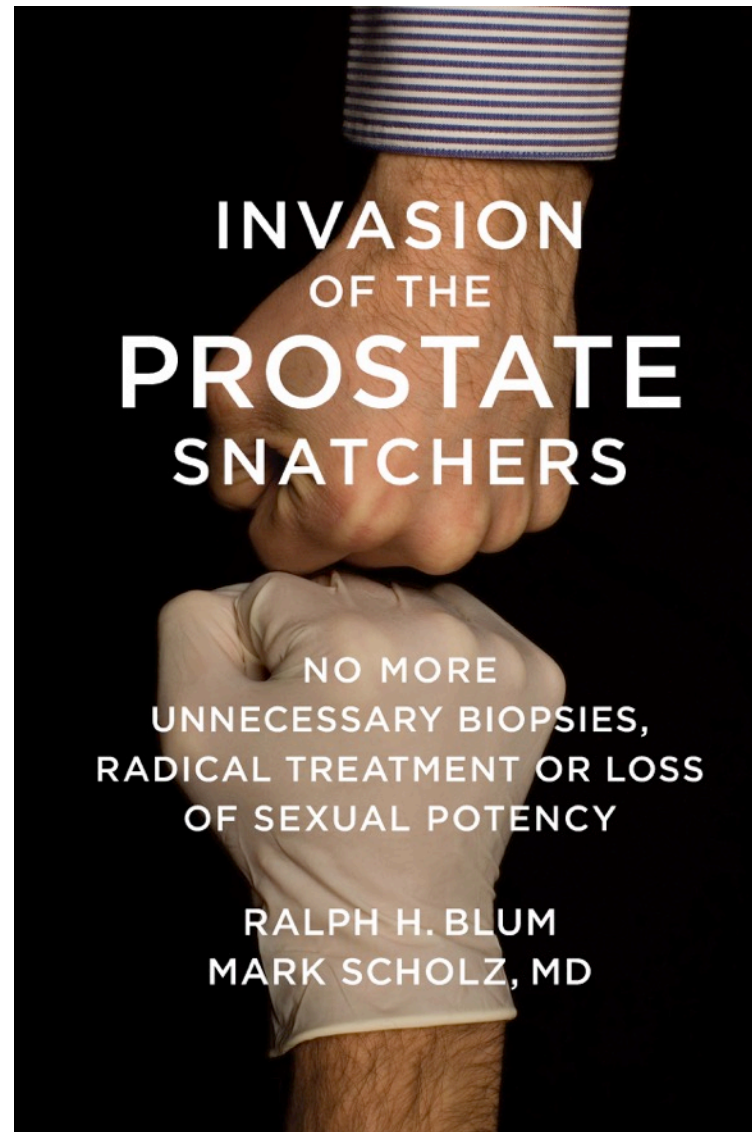
Celebrities with Prostate Cancer-Well after surgery



Celebrities Diagnosed Too Late

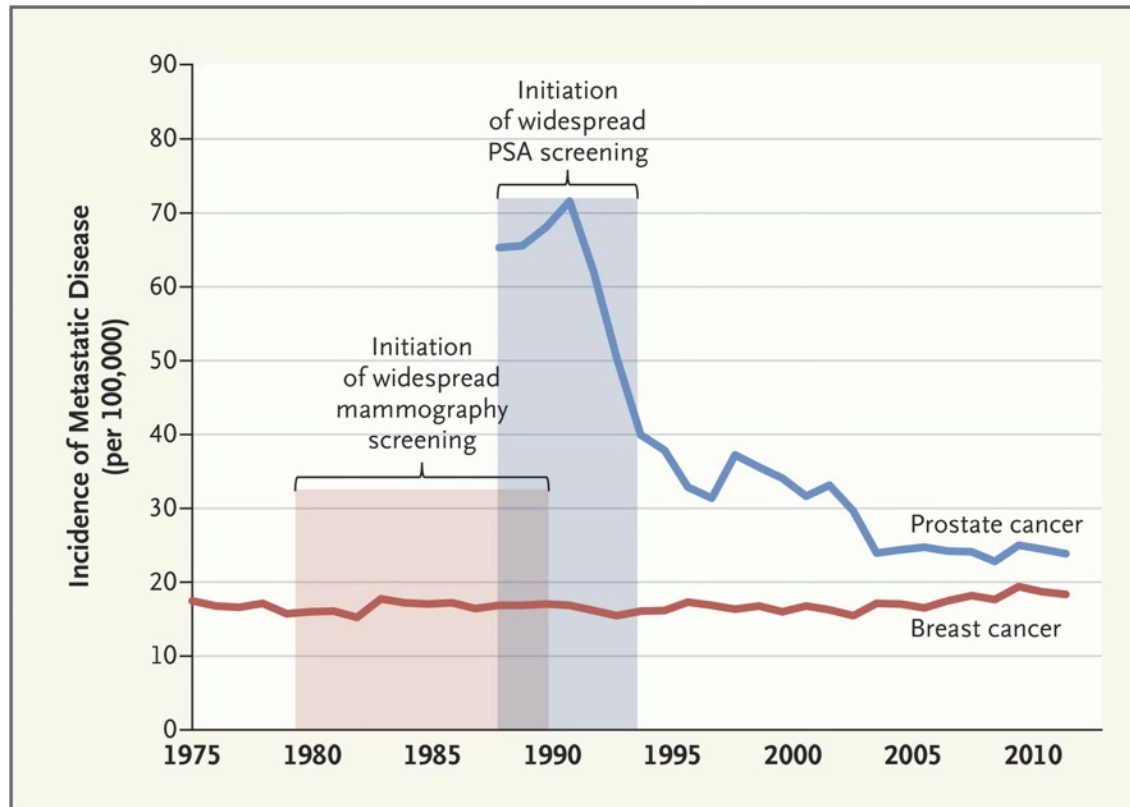


Prostate Cancer Overtreatment



PSA screening worked and is working!

Incidence of Metastatic Prostate Cancer at Initial Diagnosis: 1975–2012



Impact of PSA since the early 90's

- We have witnessed a tremendous stage and grade migration
- Presenting PSAs have dropped well below 10 ng/ml which has affected it's performance
- We are detecting disease so early that it is difficult to distinguish indolent from aggressive disease

Prostate Cancer: The dilemma now

- Not all men need to be diagnosed/screened
- Not all men with prostate cancer need to be treated
- Prostate cancer is the second most common cause of male cancer deaths
- We can cure patients when caught early

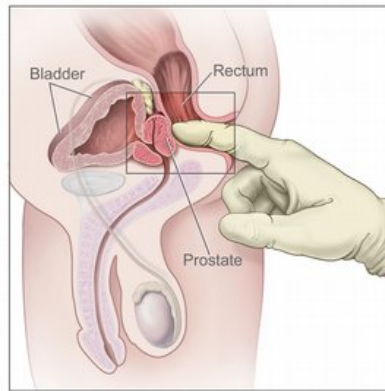
Prostate Cancer Screening

Screening for Prostate Cancer - Rationale

Symptoms are extremely rare until late in the course of the disease for most prostate cancers at which point the window of curability is negligible

Screening for Prostate Cancer – In the past

- Involves yearly
 - digital rectal examinations – finger testing through rectum for any nodules on the prostate



- blood testing – looking for an increased level of an enzyme produced by the prostate called PSA

Screening for Prostate Cancer – The past

- **All** men with a life expectancy greater than 10 years
- Started at age 50
- High risk patients should start screening at age 45
 - High Risk patients include
 - African American
 - Family history

Problems with PSA Based Prostate Cancer Screening

- PSA and DRE are relatively poor markers in early stage patients who are not at high risk
- PSA based prostate cancer screening is costly
- PSA based prostate cancer screening is associated with morbidity
- PSA based prostate cancer screening does not save as many lives as we would hope

PSA and DRE are relatively poor markers in early stage patients who are not at high risk

Use of PSA as a Marker for Prostate Cancer



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volume 324:1156-1161 April 25, 1991 Number 17

Measurement of prostate-specific antigen in serum as a screening test for prostate cancer

WJ Catalona, DS Smith, TL Ratliff, KM Dodds, DE Coplen, JJ Yuan, JA Petros, and GL Andriole

US FDA approved PSA as an aid to early detection of prostate cancer using the 4.0 ng/mL threshold.

Non Malignant Causes of PSA Elevation Affect Specificity

- Infection / inflammation
- Instrumentation
- Urinary retention
- Ejaculation
- Advanced age
- Benign enlargement

There is a Prostate Cancer Risk Regardless of PSA Level

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 27, 2004

VOL. 350 NO. 22

Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter

Ian M. Thompson, M.D., Donna K. Pauler, Ph.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H.,
M. Scott Lucia, M.D., Howard L. Parnes, M.D., Lori M. Minasian, M.D., Leslie G. Ford, M.D.,
Scott M. Lippman, M.D., E. David Crawford, M.D., John J. Crowley, Ph.D., and Charles A. Coltman, Jr., M.D.

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Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter

–14.9% of these cancers had Gleason 7 or higher

–Prostate cancer prevalence:

•PSA ≤ 0.5 ng/mL	6.6%
•PSA 0.6 – 1.0 ng/mL	10.1%
•PSA 1.1 – 2.0 ng/mL	17.0%
•PSA 2.1 – 3.0 ng/mL	23.9%
•PSA 3.1 – 4.0 ng/mL	26.9%

–High grade cancer prevalence:





•PSA ≤ 0.5 ng/mL	12.5%
•PSA 3.1 – 4.0 ng/mL	25.0%

DRE is a Relatively Poor Marker of Prostate Cancer Risk

DRE

J. J. KAUFMAN, M. ROSENTHAL AND W. E. GOODWIN

TABLE 1

	 GROUP A 27 CASES	 GROUP B 22 CASES	 GROUP C 35 CASES	 GROUP D 15 CASES
Positive open biopsy	7	9	18	6
Positive TUR	0	1	14	9
Total	7	10	32	15
Positive clinical impression	15	18	34	15
Accuracy	$7/15 = 47\%$	$10/18 = 56\%$	$32/34 = 94\%$	$15/15 = 100\%$

PSA Based Prostate Cancer Screening is Costly

Prostate cancer poses a financial burden on the healthcare system

- \$3.4 Billion - annual cost of screening, diagnosing and staging prostate cancer in the USA¹
- \$9.9 Billion - annual cost of treating prostate cancer²
- By 2019 ~ \$8.7 Billion annually will be spent on pharmaceuticals for advanced prostate cancer treatment³

1) Ekwueme et al; Cost analysis of screening for, diagnosing, and staging prostate cancer based on a systematic review of published studies. *Prev Chronic Dis* 2007;4(4). 2) National Cancer Institute Trends Progress Report-2009/2010 Updated 3) Prostate Cancer Market Snapshot: More Than Provenge, The Pink Sheet, Nov 22, 2010. Elsevier Business Intelligence Publications and Products

PSA Based Prostate Cancer Screening is Associated with Morbidity

PSA Based Prostate Cancer Screening is Associated with Morbidity

- Risks of screening: anxiety
- Risks of biopsy: bleeding, infection, painful, ED
- Risks of treatment: impotence, incontinence, death, proctitis, cystitis, stricture
- Risk of recurrence: as many as 1/3 of men will require a secondary treatment

PSA Based Prostate Cancer
Screening as Currently Practiced Does not
Have a Huge Life Saving Benefit

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

No survival benefit to screening

Gerard A. Anderson, M.D., E. David Crawford, M.D., Robert E. Grubb III, M.D.,
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,
Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D.,
Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D.,
Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S.,
Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D.,
Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D.,
Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D.,
for the PLCO Project Team*

ERSPC - Prostate Cancer Screening Study

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Number needed to screen was 1400
and number needed to treat was 48

Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D.,
Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D.,
Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D.,
Gunnar Aus, M.D., Arnaud Villers, M.D., Xavier Rebillard, M.D.,
Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D.,
Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

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Current Prostate Cancer Screening Recommendations

- US Preventive Services Task Force
 - recommends against prostate-specific antigen (PSA)-based screening for prostate cancer. **This is a grade D recommendation (lowest level)**
- This has been adopted by many primary care associations
- There is talk of financially penalizing physicians who order PSA as a screening test

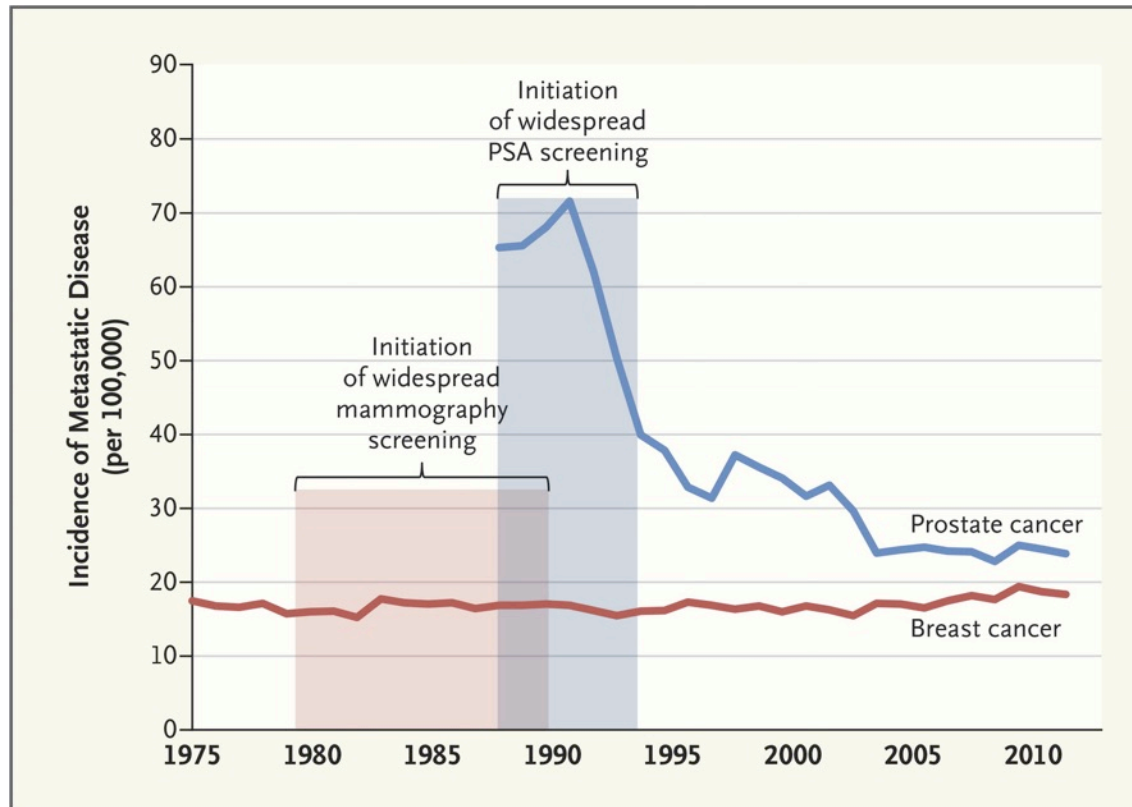
Confusing?

- Men at risk for prostate cancer and their physicians do not know how to proceed



What is the impact of PSA screening?

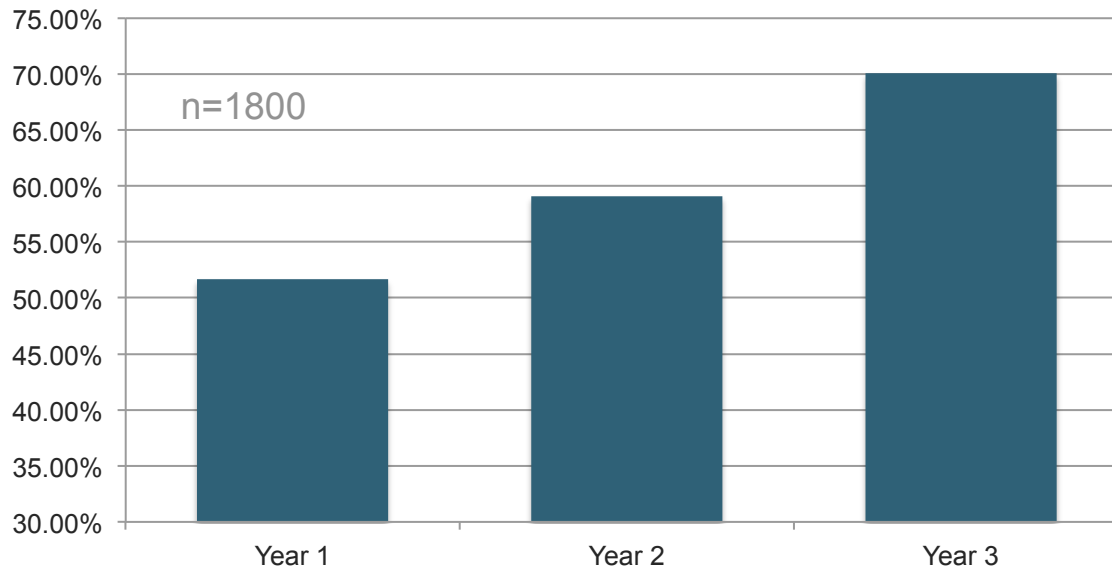
Incidence of Metastatic Prostate Cancer at Initial Diagnosis: 1975–2012



ARS Question 1

- Have you noticed a decrease in referrals for elevated PSA?
 1. 0%
 2. 0-10%
 3. 10-20%
 4. >20%

What will be the result of USPSTF recommendations?



30% increase in the proportion of intermediate and high grade disease in San Diego in the 3 years following the USPSTF recommendations

What is the impact of USPSTF Recommendations?

- number of men referred for elevated PSA in San Diego county decreased by 19.2%
- median pre-biopsy PSA increased from 7.0 ng/ml to 8.1 ng/ml (p=0.0006)
- rise in the proportion of men having PSAs > 10 ng/ml from 28.2% to 38.0%
- men diagnosed with Gleason scores ≥ 8 tumors rose from 21.4% to 30.4% (p=0.0001)

Current Prostate Cancer Screening Recommendations

American Urologic Association

- Each man's doctor should assess his health status to determine if he should have PSA testing at any given age

American Cancer Society

- Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If they are African American or have a father or brother who had prostate cancer before age 65, men should have this talk with a doctor starting at age 45

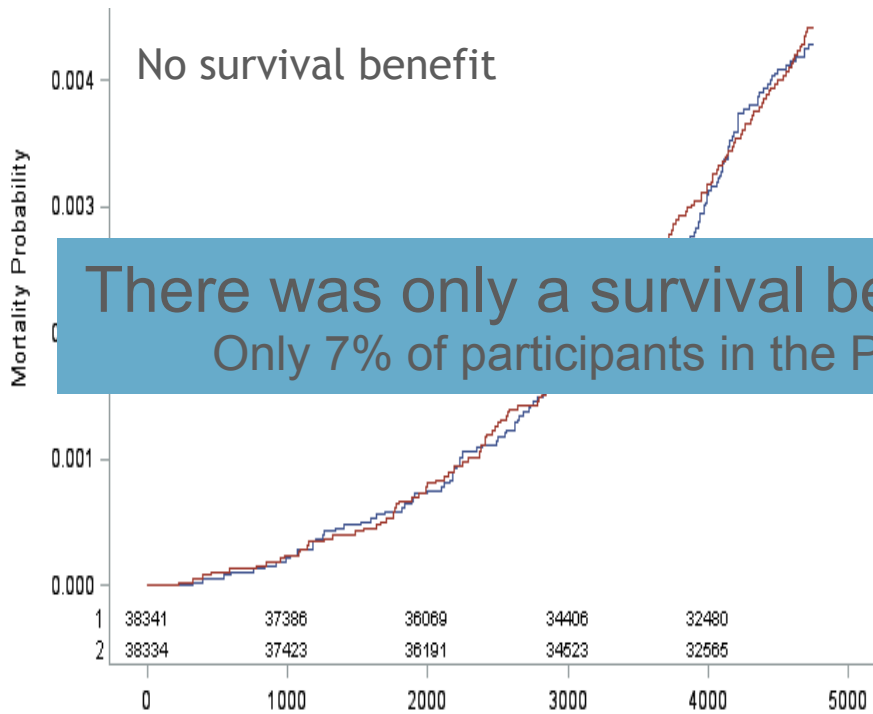
Risk Factors

- Age
- Family history
- Racial origin

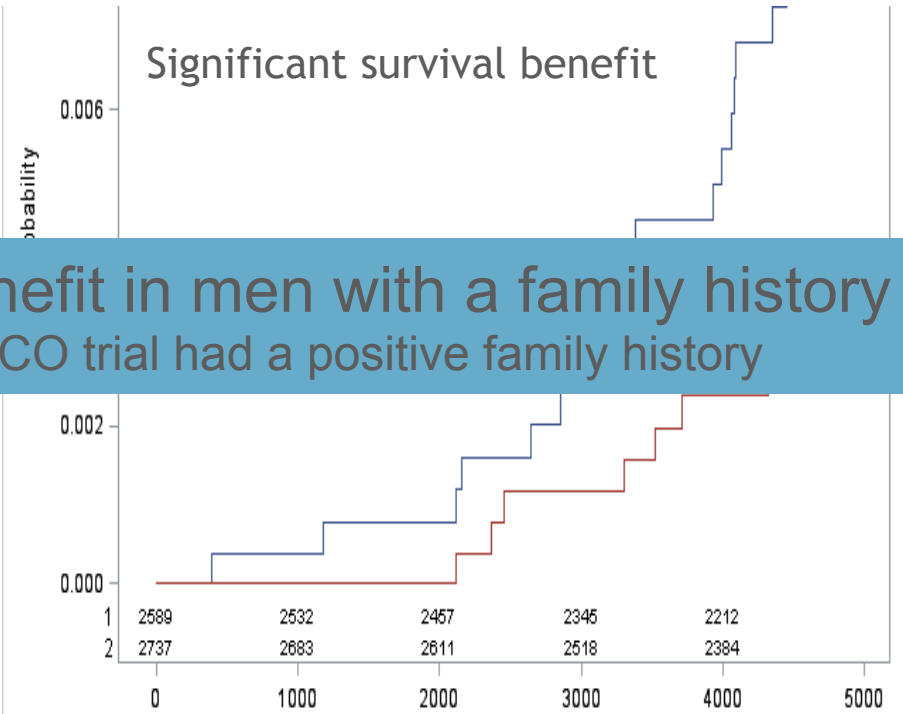
Impact of Limiting Screening to High Risk Groups

Prostate Cancer Specific Mortality and Family History from PLCO

Men Without a Family History



Men With a Family History



There was only a survival benefit in men with a family history
 Only 7% of participants in the PLCO trial had a positive family history

Red – Screened Blue – Not screened

Potential Role of Genetic Markers on Prostate Cancer Screening

Genetic Polymorphisms

- Polymorphisms are natural genetic variations within the human genome
- They are the genetic factors which distinguish individuals and are one of the major research byproducts of the genome project
- Most common type is a single nucleotide polymorphism (SNP)

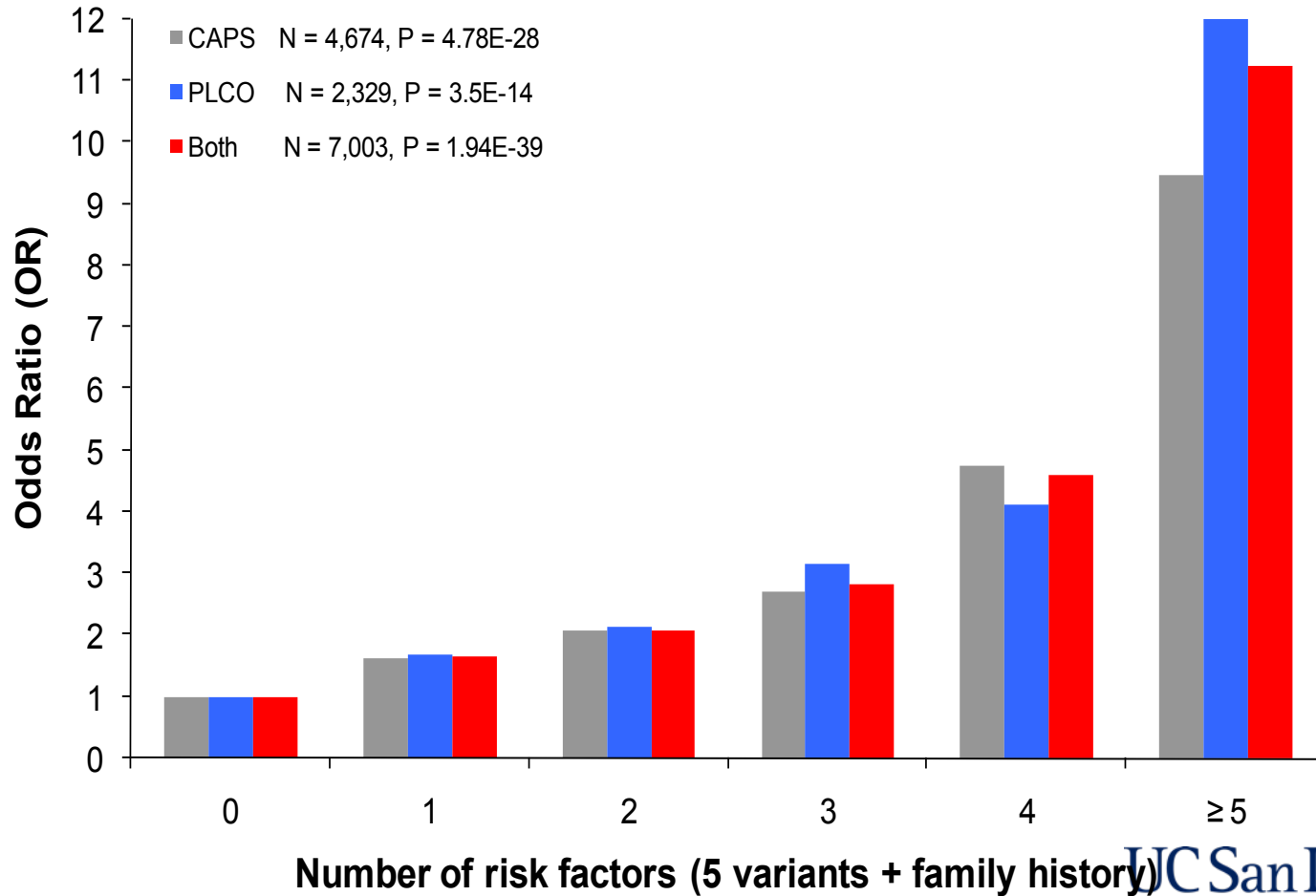
Genomewide Association Studies - GWAS

In approximately 2007 a breakthrough technologies emerged which allowed for the unbiased assessment of SNP associations with complex traits throughout the genome

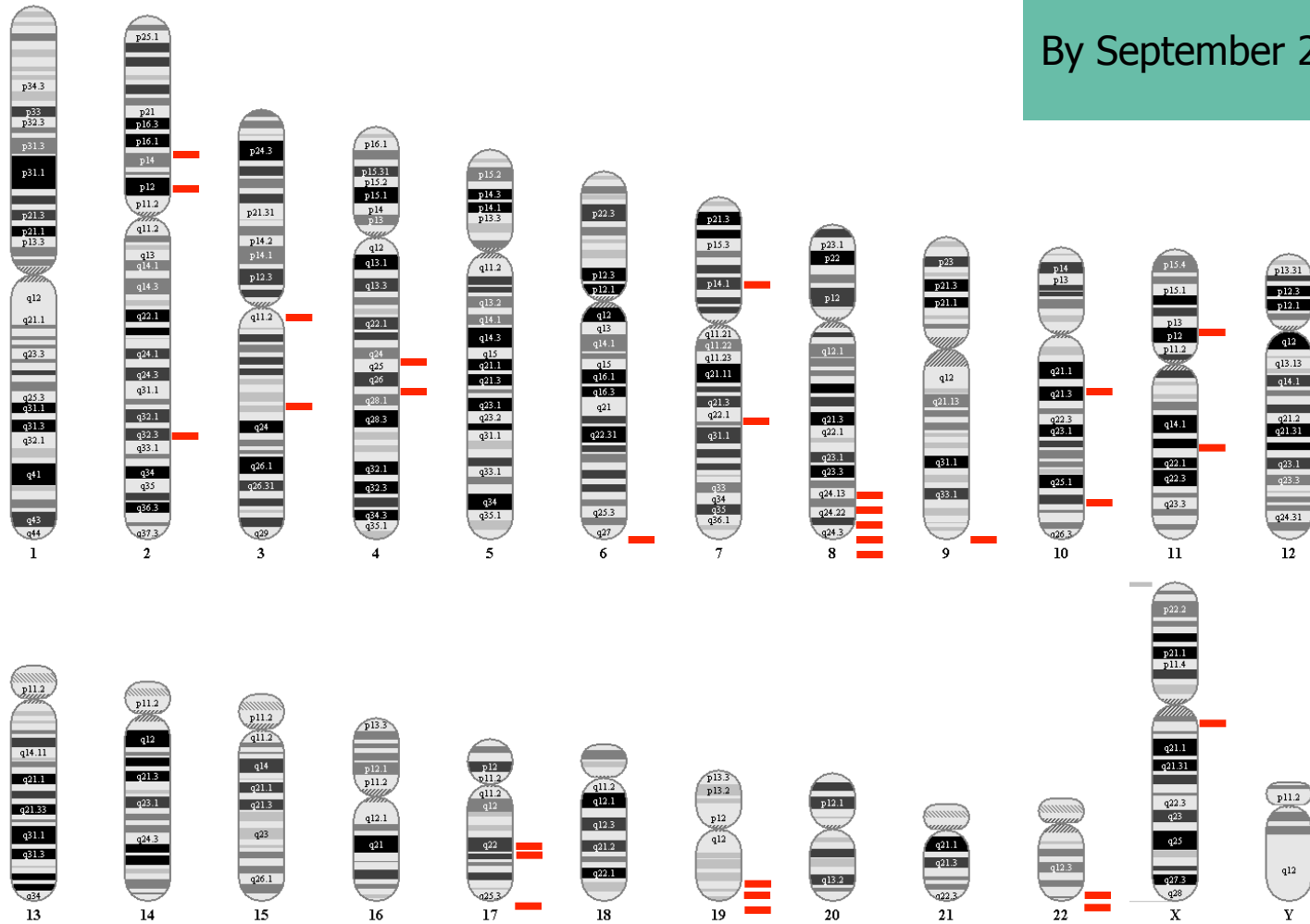
GWAS and PCa

- Initially 5 SNPs
- Consistently seen in multiple studies
- Studies to date restricted to Caucasians
- Each SNP has only modest effect on risk ORs of 1.5
- Most not in known genes

Cumulative Association of Five Genetic Variants with Prostate Cancer



Prostate Cancer Risk SNPs identified from GWAS



By September 2009

Prostate Genetic Score (PGS)

- Combination of 33 PCa associated SNPs
- Validated in multiple populations and within the context of large clinical trials (REDUCE, PLCO and PCPT)
- Highly associated with a positive prostate biopsy ($p = 3.41 \times 10^{-8}$)
- Outperformed all existing biomarkers for overall PCa risk in the REDUCE study

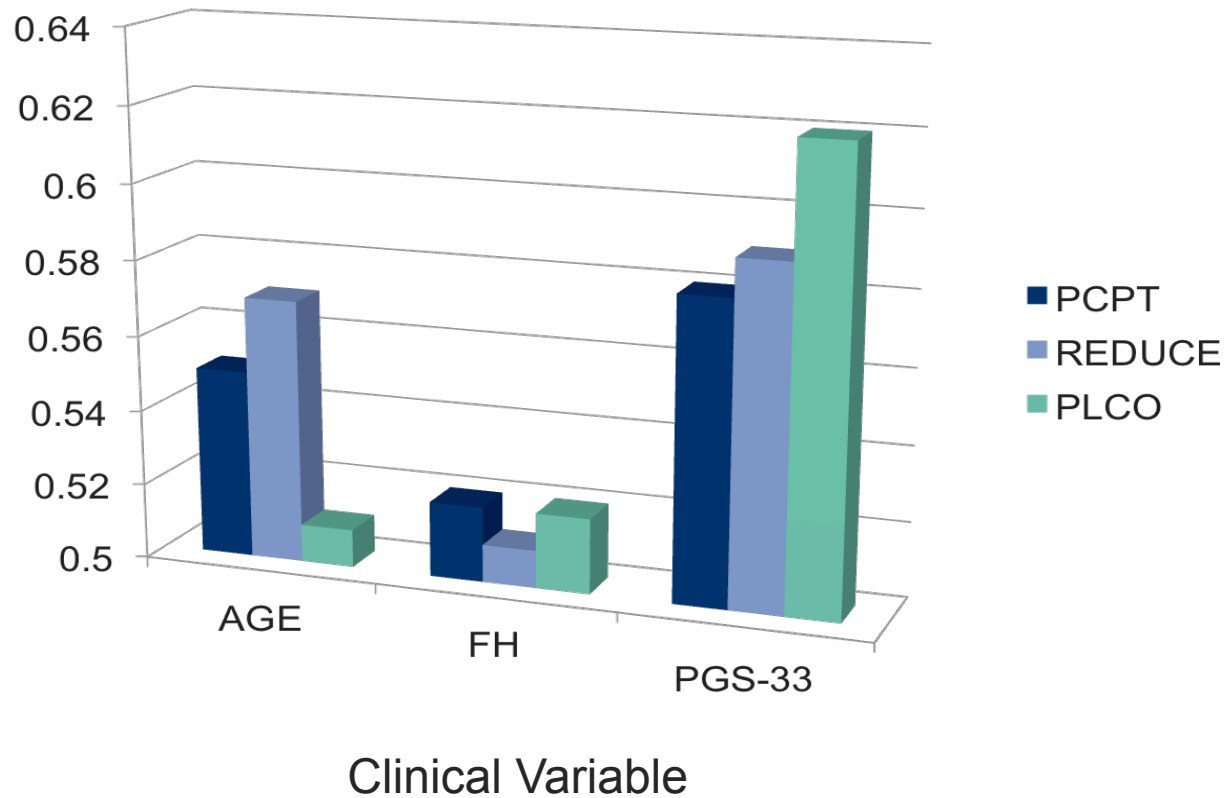
Prostate Genetic Score (PGS)

Individual variables at baseline

Age at baseline (Age)	0.56
Digital rectal examination at baseline (DRE)	0.51
Total PSA levels at baseline	0.54
Free/total PSA ratio at baseline (f/t PSA)	0.54
Prostate volume at baseline (PV)	0.56
Number of cores sampled at base biopsy (No. of cores)	0.55
Family history at baseline (FH)	0.53
Genetic score based on 33 PCa risk SNPs (Genetic score)	0.59

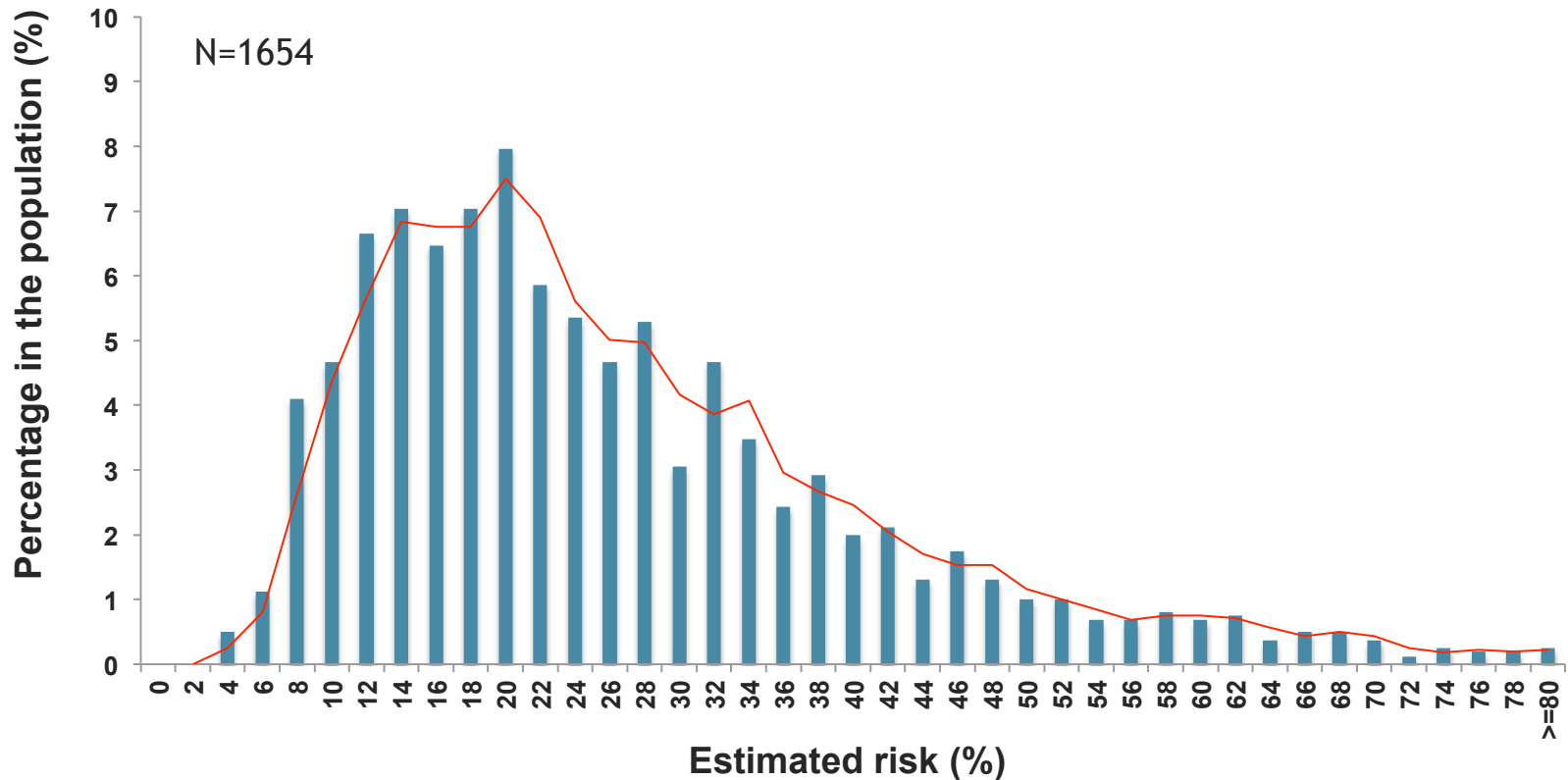
PGS-33 - Outperforms Age and Family History

Area Under the ROC Curve

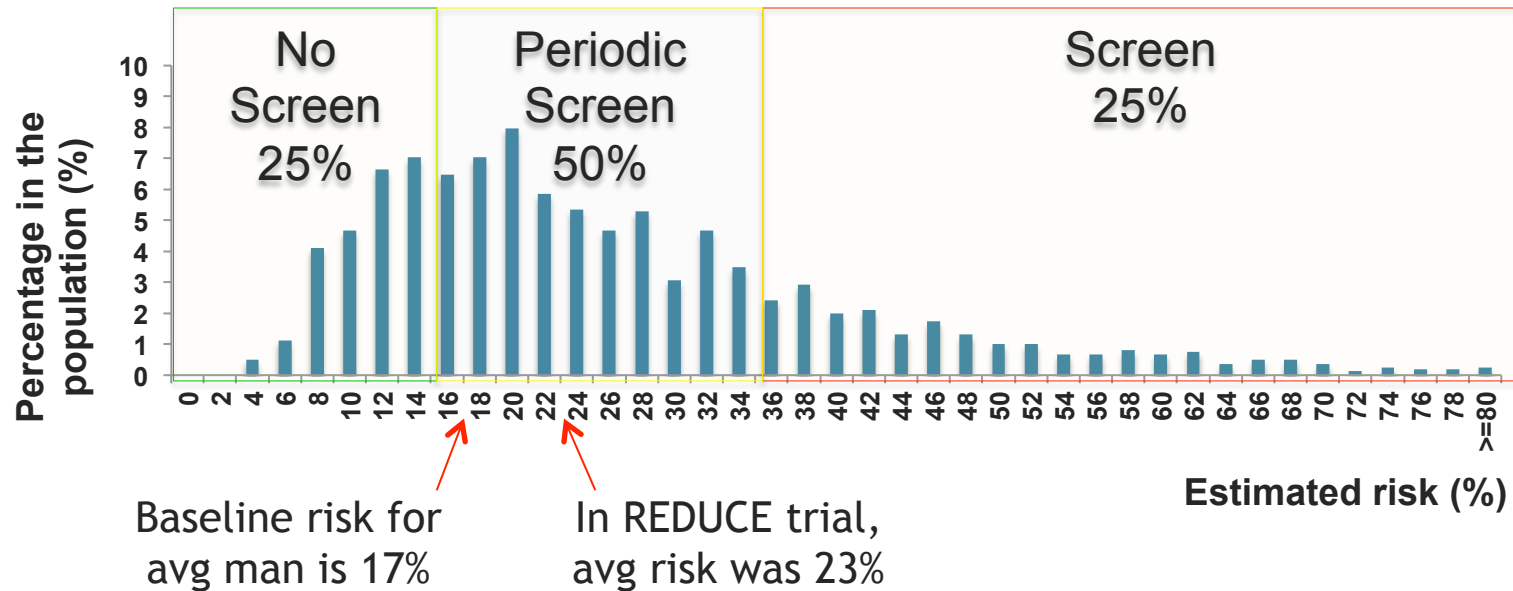


Provides Continuous Variable of Individual Risk of Developing Prostate Cancer

PGS-33

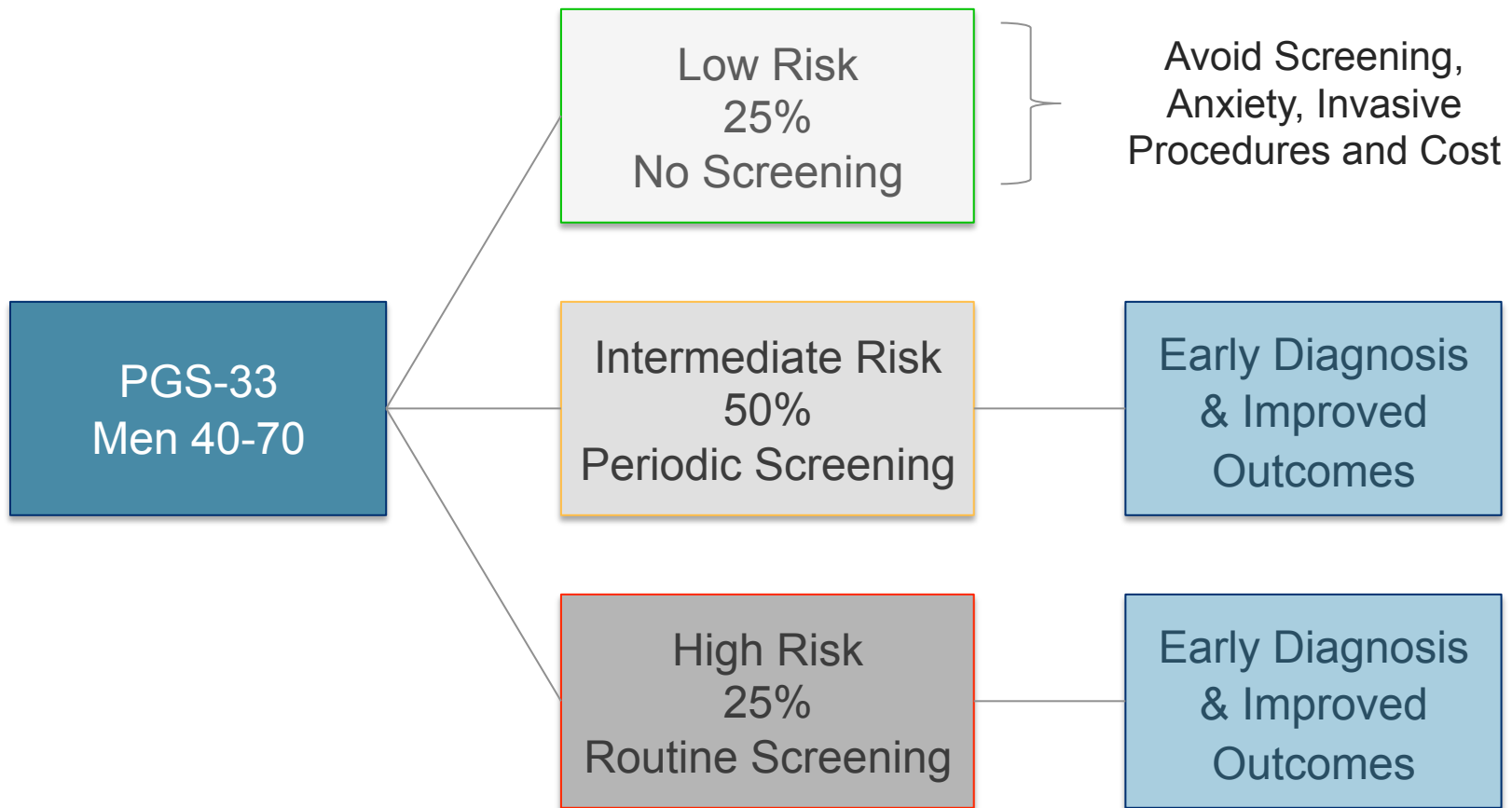


Many men could safely limit or forego screening with a low risk PGS-33 result



- If PSA Screening were applied to those 25% of men at highest risk, 55% of intermediate and high risk prostate cancer would be identified
- If you were to forego screening the 25% of men with the lowest risk scores you would miss 8% of the intermediate and high risk prostate cancers

Possible Risk Adapted Screening Algorithm



PGS-33 in men with metastatic PCa

- tested 100 men at UCSD with metastatic PCa
- 4 patients had a PGS <0.6 and negative FH
- no association between the PGS and FH of PCa
- 21 patients had a known FH
- using a PGS threshold of 1.3, an additional 34 patients would have been classified as “high genetic risk” over FH alone.

Prostate Genetic Score

- Stable marker available at birth
- Compares favorably to PSA
- Should be a thought of as a better, more informative family history
- Can be used to risk stratify men for later, tailored screening

ARS Question 2

- Do you think that risk adapted screening will play a role in the future?
 1. Yes
 2. No

Prostate Cancer Screening In the Future

Prostate Cancer Screening in the Future

- Will likely be limited to high risk groups (positive family history, AA race, high genetic score) thus improving efficiency
- Newer tests will likely be coupled to PSA prior to biopsy to reduce the negative biopsy rate
- Prostate biopsy tissue will be evaluated with new biomarkers of indolent vs aggressive disease


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- Jae Lin Sun



Thank-You
See you in May