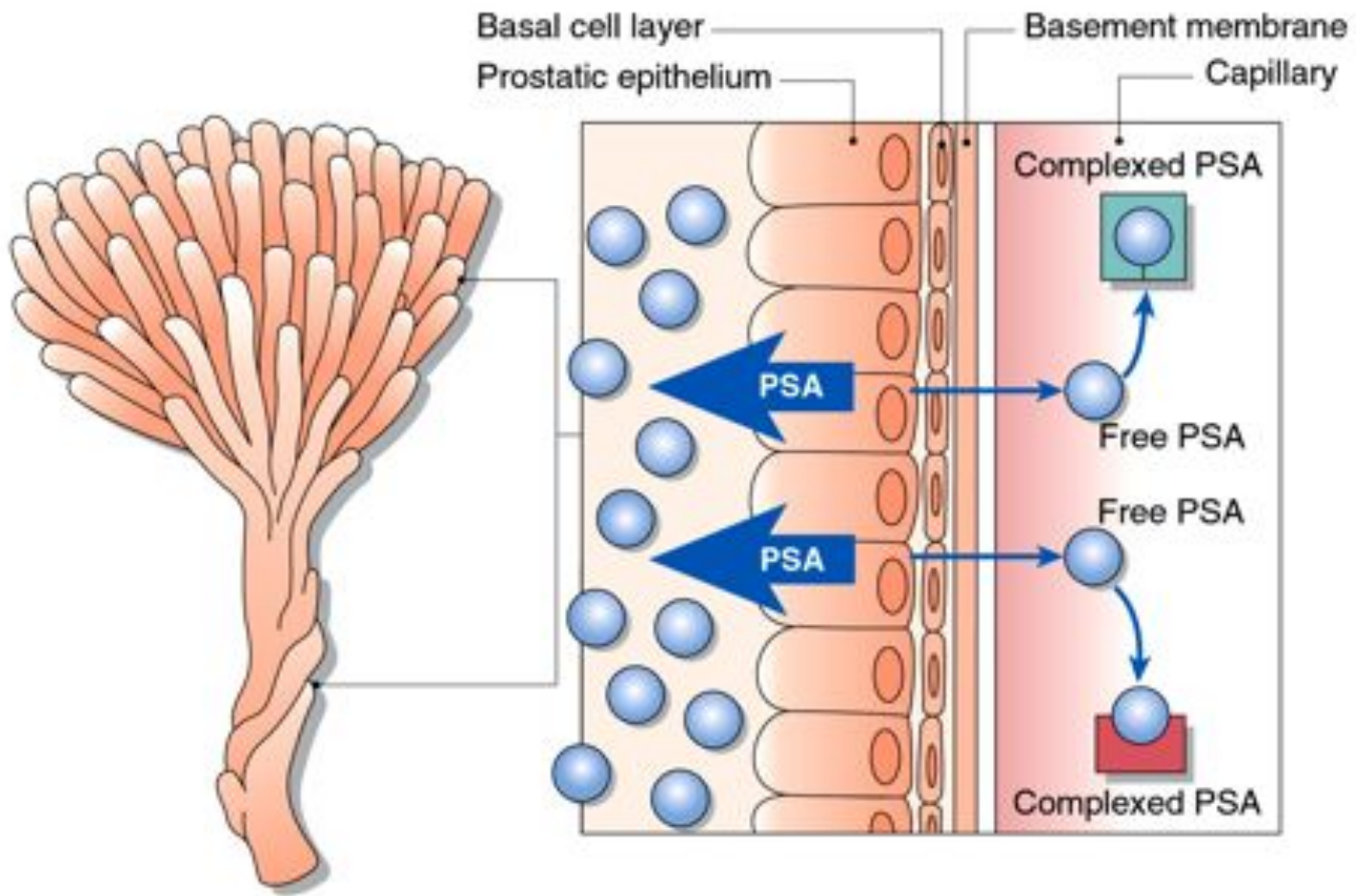


PSA

Provisionally Sent Antigen

Or

Promoter of Stress and
Anxiety?



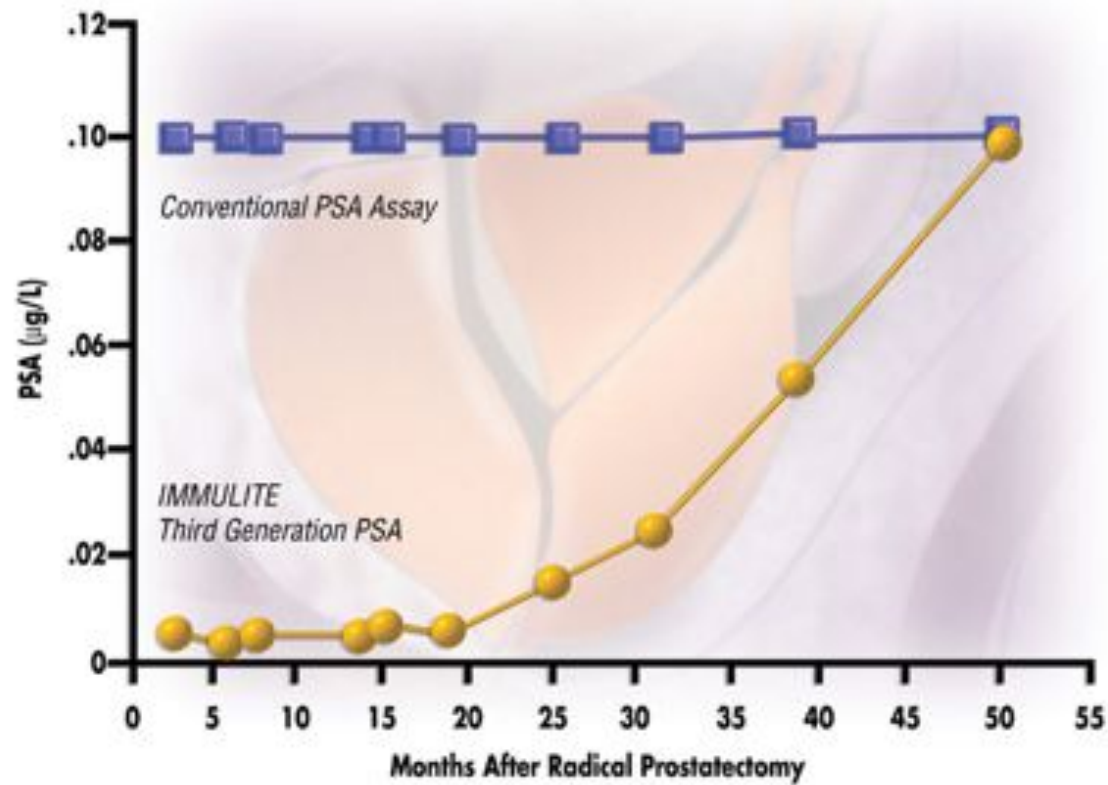
PSA

- Discovered in 1979 by Wang et al
- Biological function is to liquify semen
- Main secretory protein of the prostate
- PSA in blood 1 millionth of that in semen
- Bound in bloodstream to ACT and globulin
- Any “perturbation” may cause rise of PSA
- Consequently CaP, BPH, Prostatitis, UTI and prostate biopsy all cause PSA rise

Uses of PSA

- To diagnose prostate cancer (case finding)
- To assist in staging the disease
- To monitor response to treatment
- To diagnose recurrence/relapse after Rx
- To assist in medical Rx options for BPH
- To help exclude CaP in prostatitis

PSA Velocity



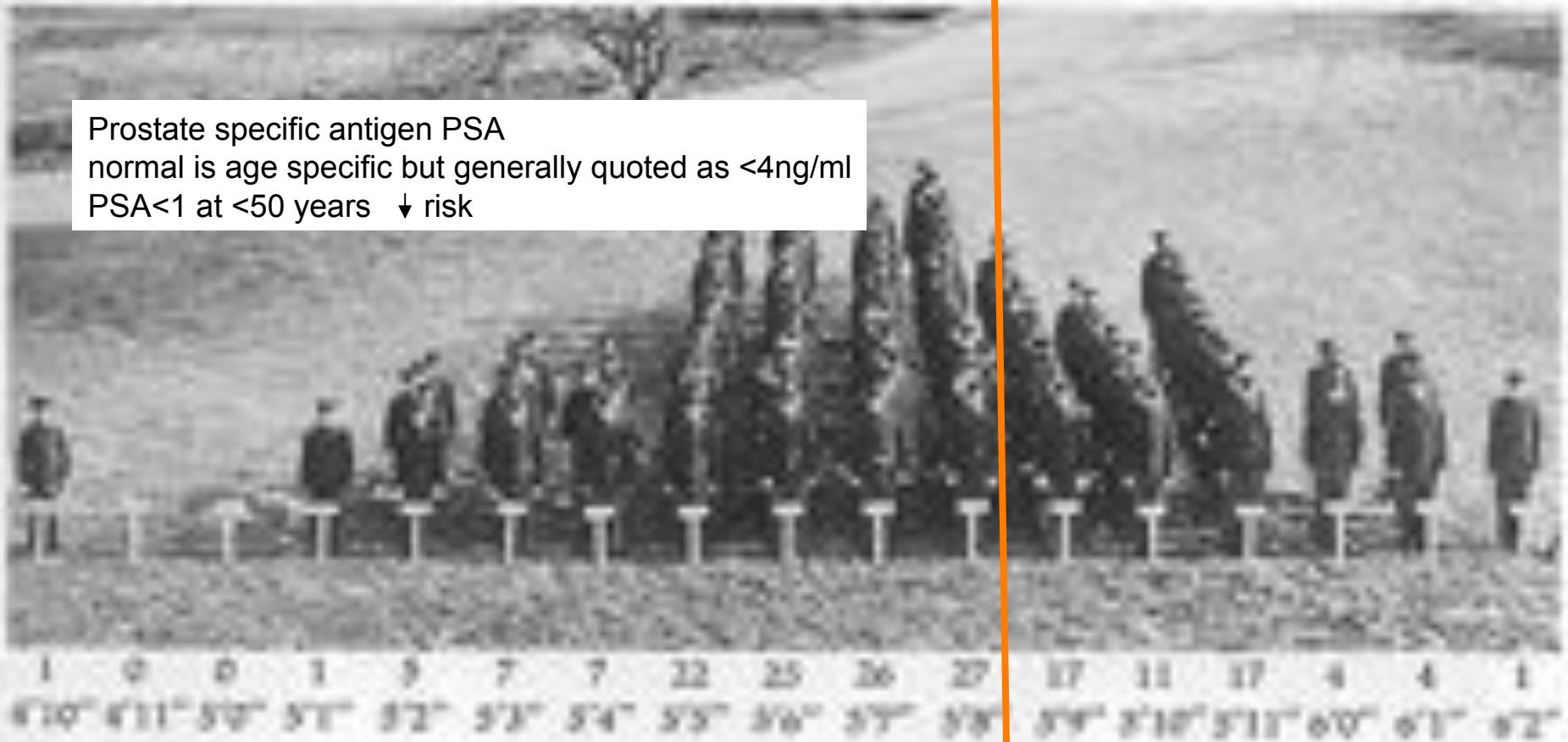
Screening using PSA

- ERSPCS revealed a 20% reduction in mortality (Schroder et al NEJM 2009)
- PLCO study showed no difference between screened individuals and controls (Andriole et al NEJM 2009)
- However 50% PLCO “screened” cohort had been previously tested for PSA
- Therefore “jury still out”

New Screening Strategy

- Identify at risk groups
- Monitor PSA kinetics
- Use genetic profiling and new markers
- Selective biopsy (transperineal)
- Consider intervention in individuals at risk:
- Chemoprevention, active surveillance, RALP, focal therapy or radiotherapy etc

Prostate specific antigen PSA
normal is age specific but generally quoted as <4ng/ml
PSA<1 at <50 years ↓ risk



Differences in height in the same population: heights of conscripts over 60 years ago. (From A. Bakashev, *Journal of Heredity*, vol. 5, 1914.)

Prostate cancer risk distribution has similar pattern

Do we already risk profile- albeit crudely?

- Higher risk groups
eg blacks have
a 1.6-fold
increased
risk of
prostate cancer
2.5-fold increased risk
of prostate cancer death



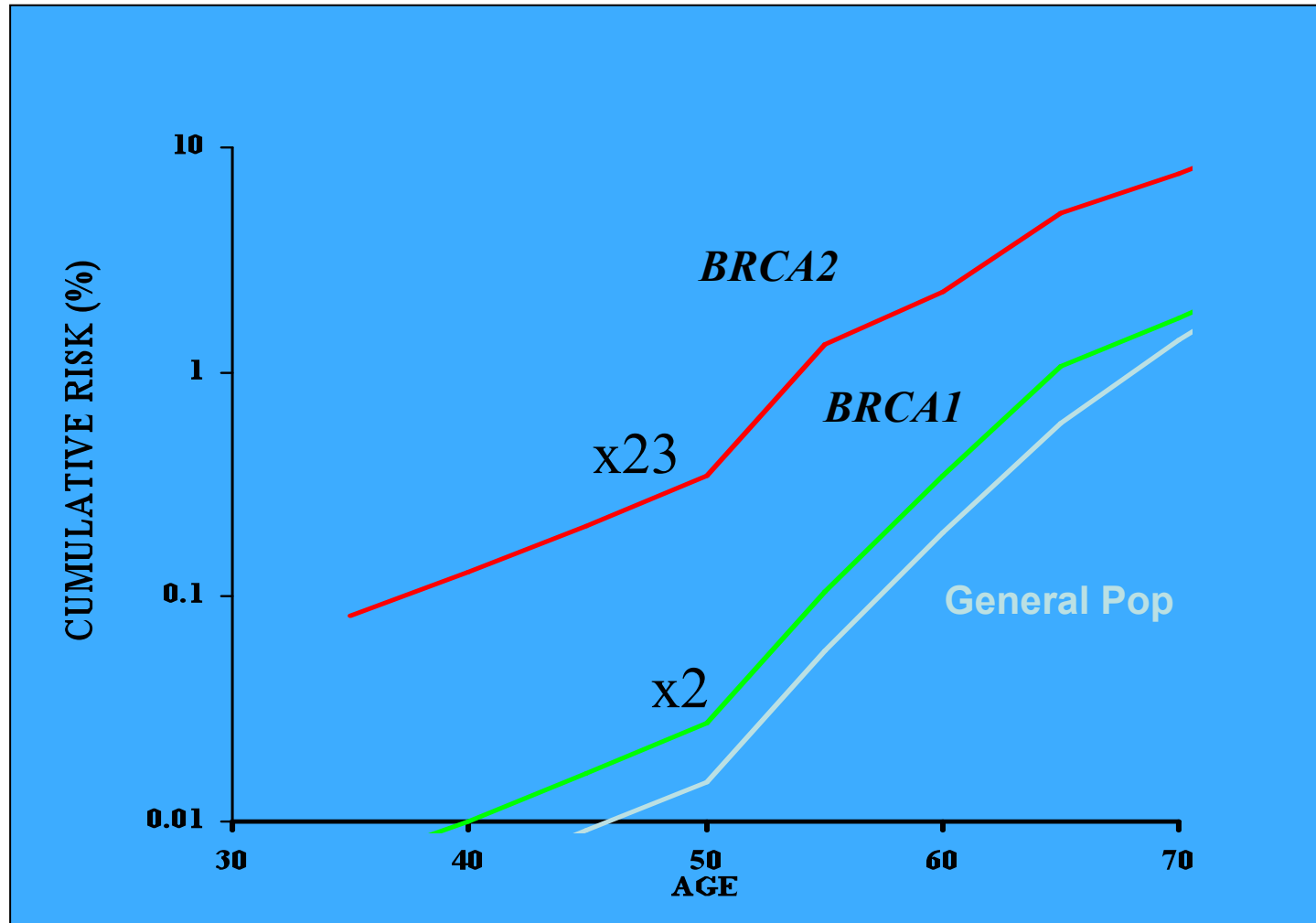


Prostate cancer is 50% more common in identical twins than non-identical ones

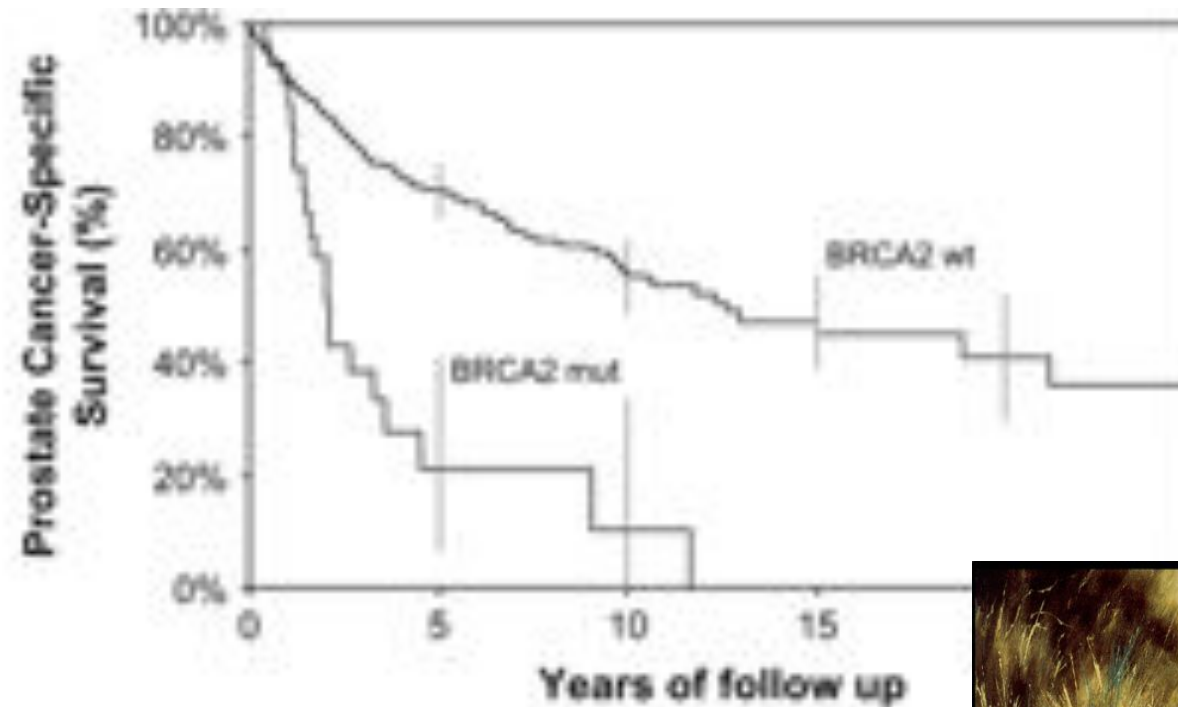
RELATIVE RISK BY NUMBER OF AFFECTEDS AND AGE AT DIAGNOSIS

Age of proband	Hazard Ratio (95% CI) no other affecteds	Hazard Ratio (95% CI) two or more affecteds
50	1.9 (1.2-2.8)	7.1 (3.7-13.6)
60	1.4 (1.1-1.7)	5.2 (3.1-8.7)
70	1.0*	3.8 (2.4-6.0)

Prostate Cancer Risks



Survival from Prostate Cancer in BRCA2 carriers (Tryggvadóttir et al 2007)



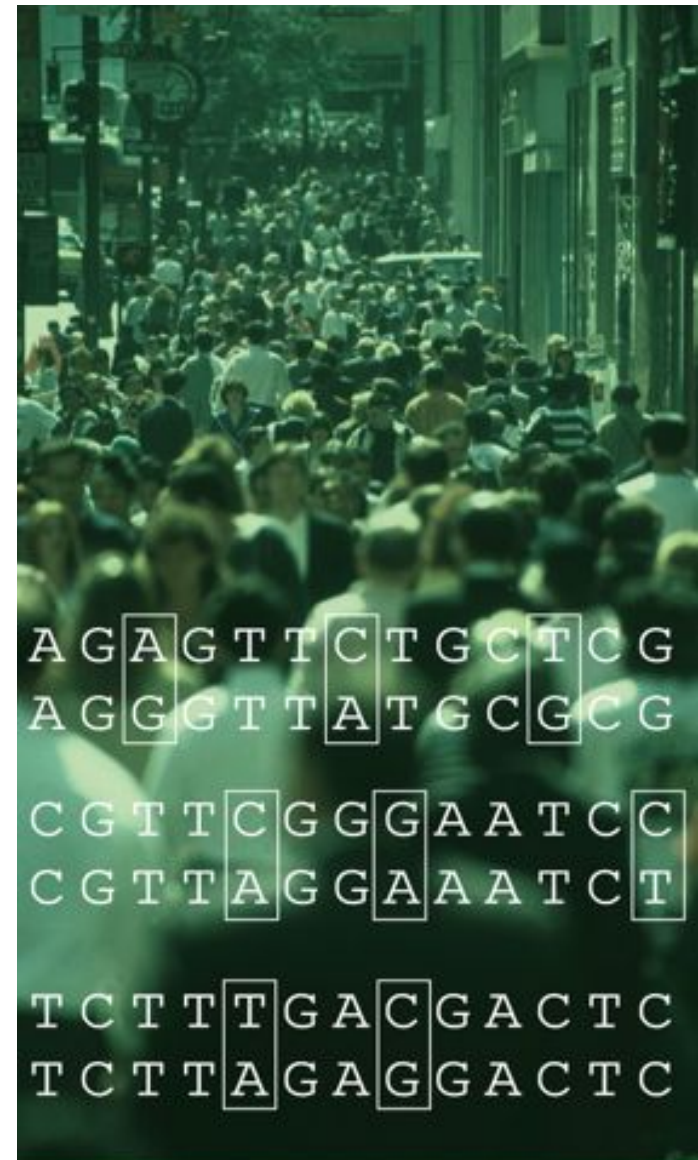
Number at Risk

BRCA2 wt	487	203	65	22
BRCA2 mut	30	3	1	

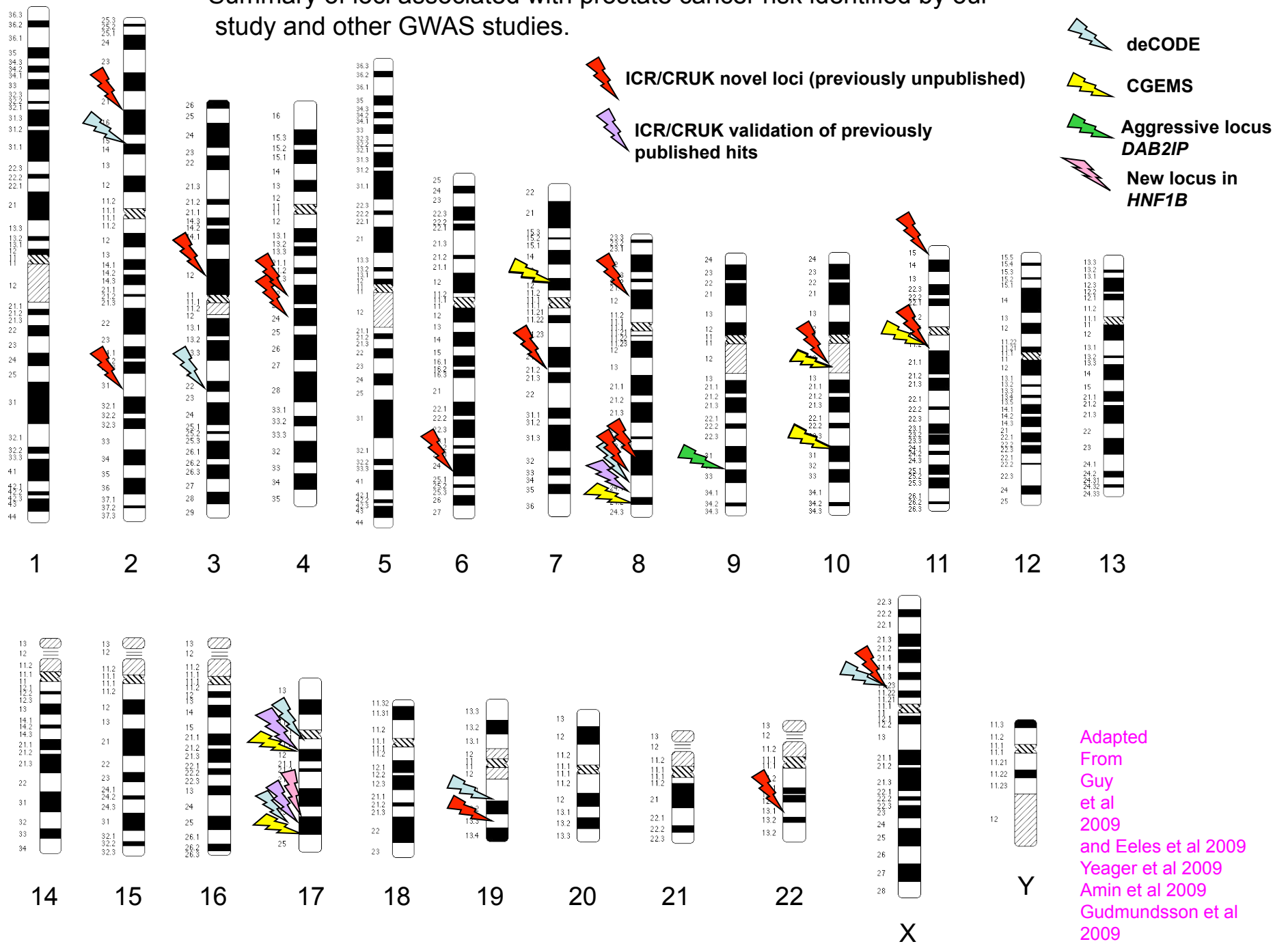


Genome Wide Association Studies (GWAS)

- Rapidly scanning a dense set of markers across genomes of many people to find genetic variations associated with a particular disease
- Time for GWAS now due to
 - the completion of the HapMap project
 - rapidly advancing high through-put technology



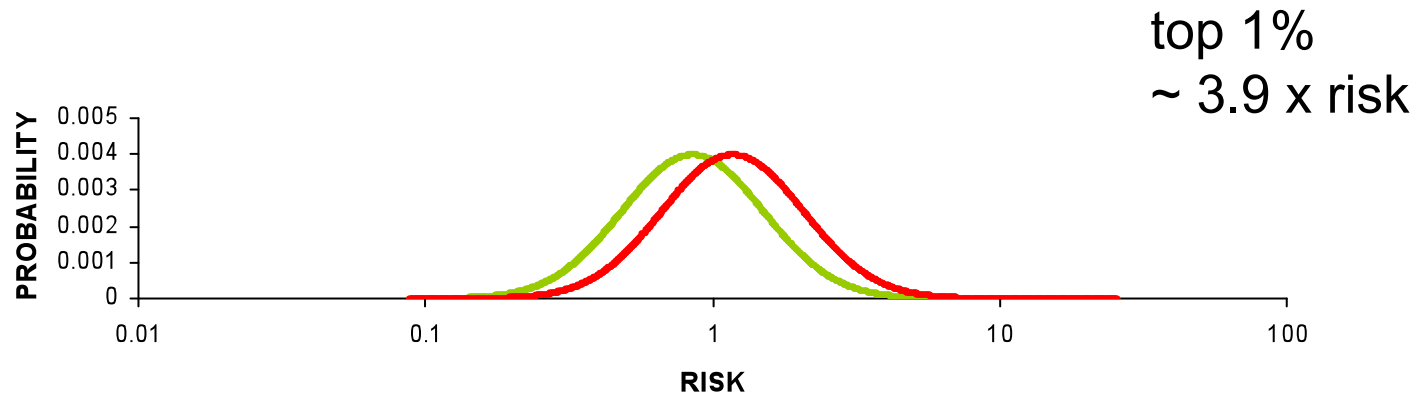
Summary of loci associated with prostate cancer risk identified by our study and other GWAS studies.



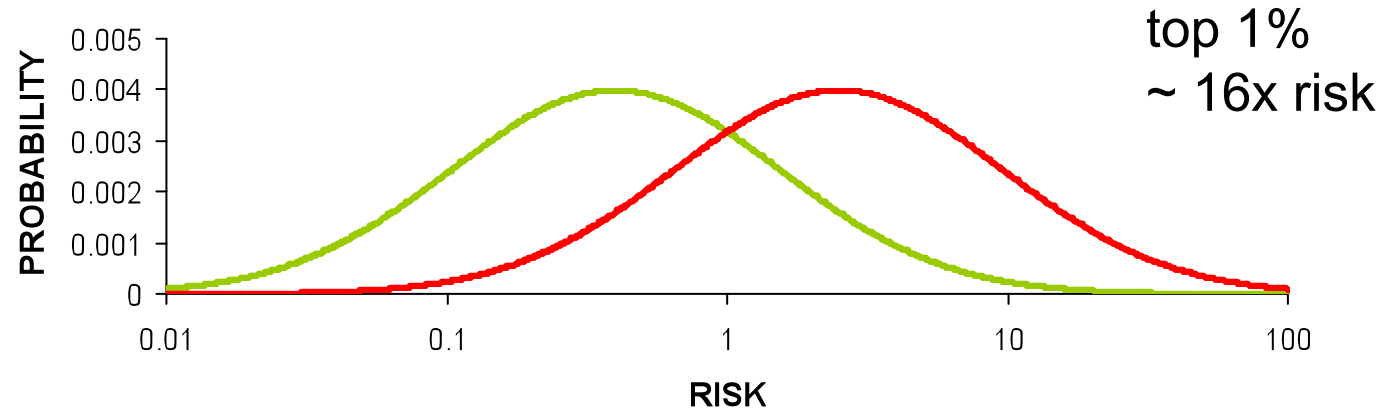
Adapted From
 Guy et al 2009
 and Eeles et al 2009
 Yeager et al 2009
 Amin et al 2009
 Gudmundsson et al 2009

Prostate cancer risk prediction

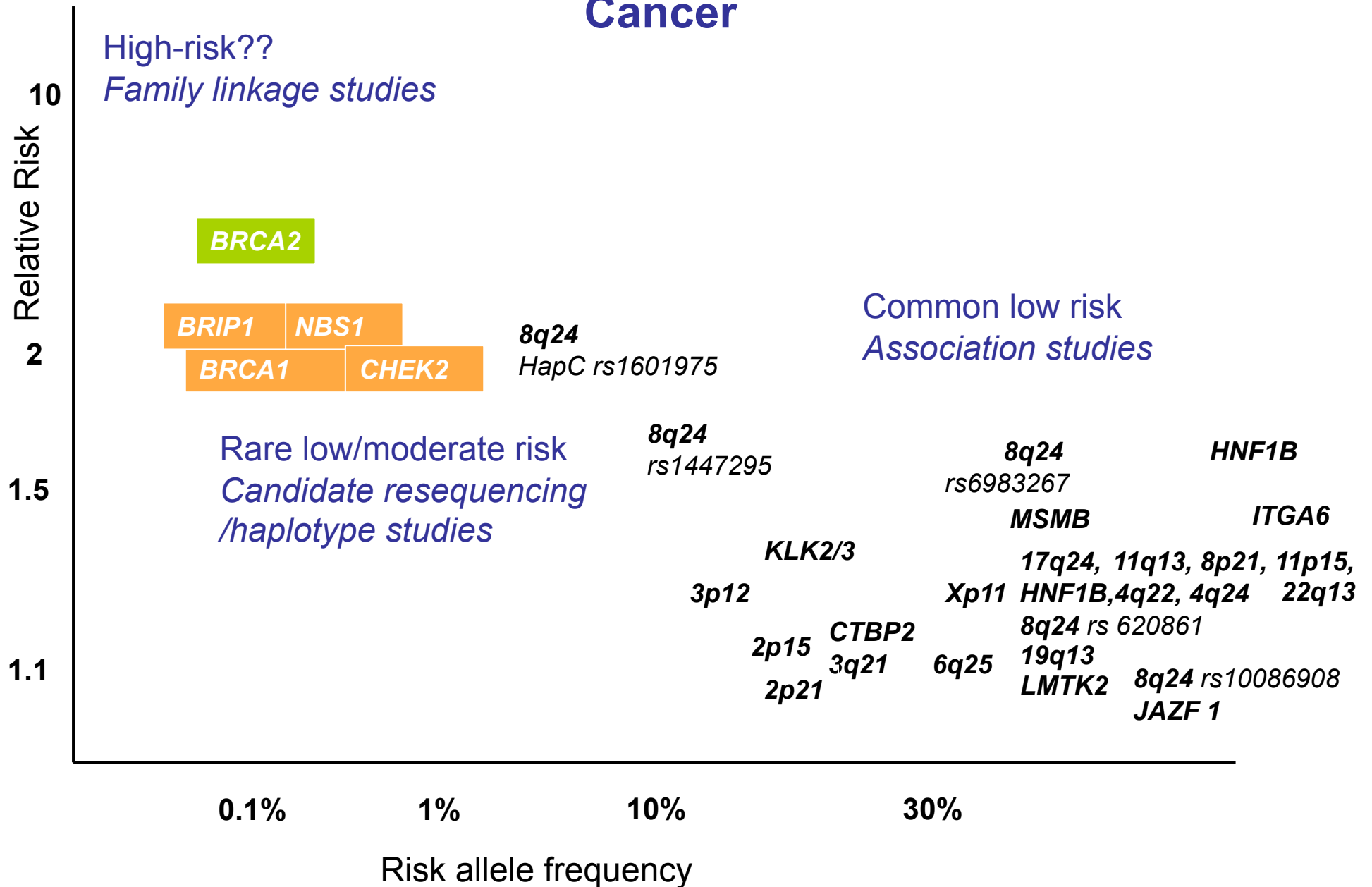
Current 27 loci

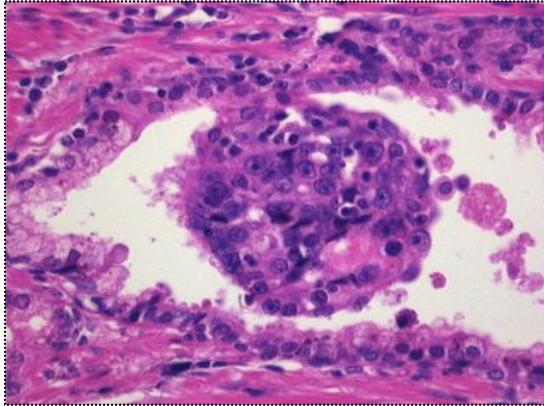


Theoretical maximum

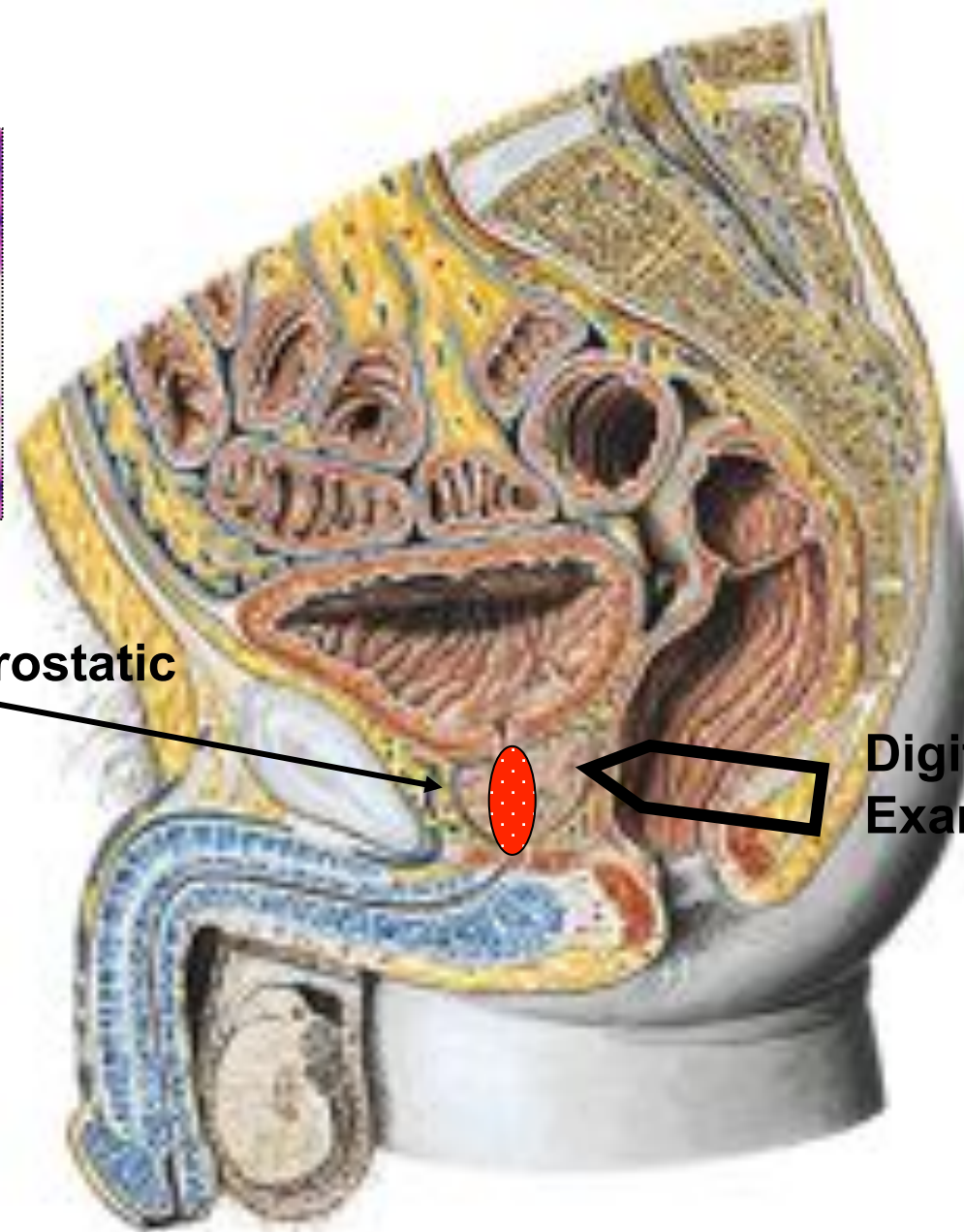


The Pattern of Genetic Predisposition to Prostate Cancer



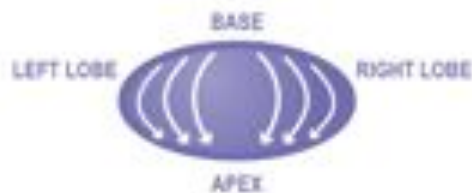


Cells in prostatic urethra



Digital Rectal Exam (DRE)

Simple, non-invasive urine specimen collected post-DRE



1.
DRE
(3 STROKES PER LOBE)



2.
FIRST CATCH URINE SPECIMEN
(20-30 mL)



3.
TRANSFER URINE TO TRANSPORT TUBE
FOLLOW INSTRUCTIONS FOR STORING
AND SHIPPING CONDITIONS

PCA3 and PSA mRNA concentrations are used to calculate the PCA3 Score

Using transcription-mediated amplification technology, PCA3 mRNA molecules are amplified



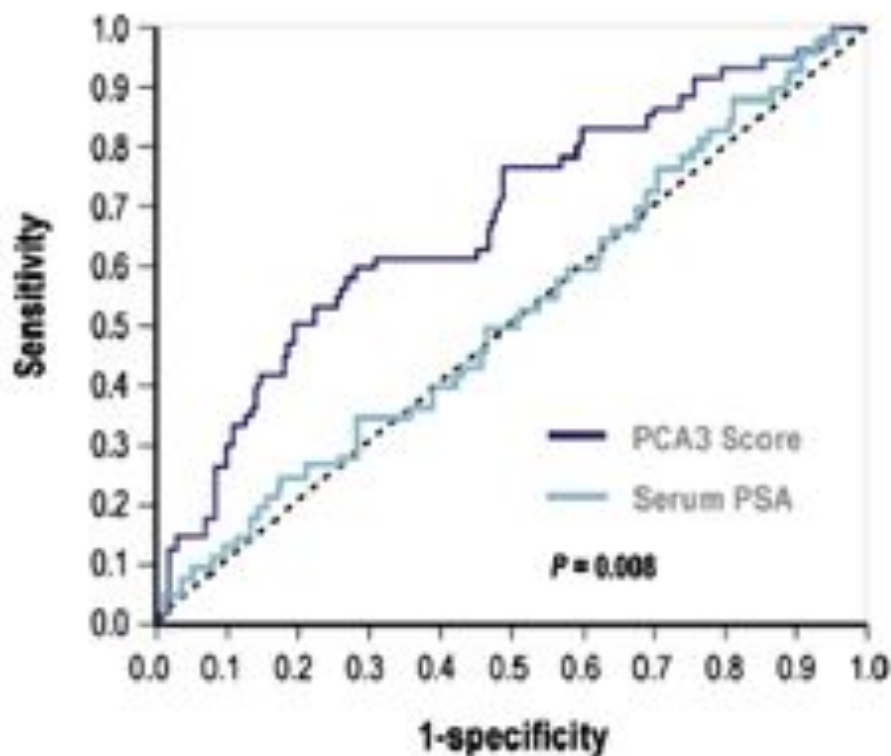
PCA3 Assay



PCA3 Score



The PCA3 Score has a greater diagnostic accuracy than serum PSA for repeat biopsy



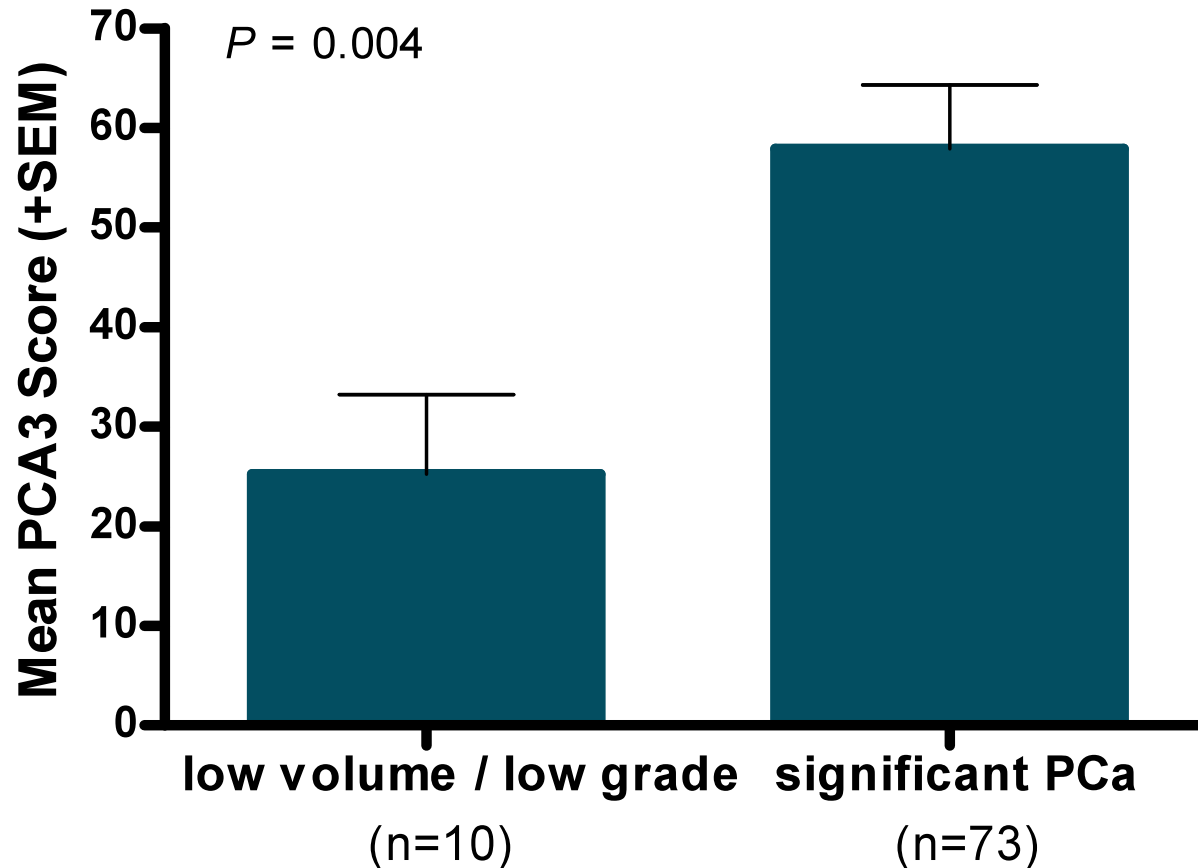
AUC ROC
Serum PSA: 0.524
PCA3 Score: 0.678

PCA3 Score 10
Specificity: 28%
Sensitivity: 87%
Odds ratio: 2.5

PCA3 Score 35:
Specificity: 72%
Sensitivity: 58%
Odds ratio: 3.6

PCA3 Score 50:
Specificity: 81%
Sensitivity: 47%
Odds ratio: 3.7

The PCA3 Score in low volume /low grade PCa is significantly lower than in significant PCa

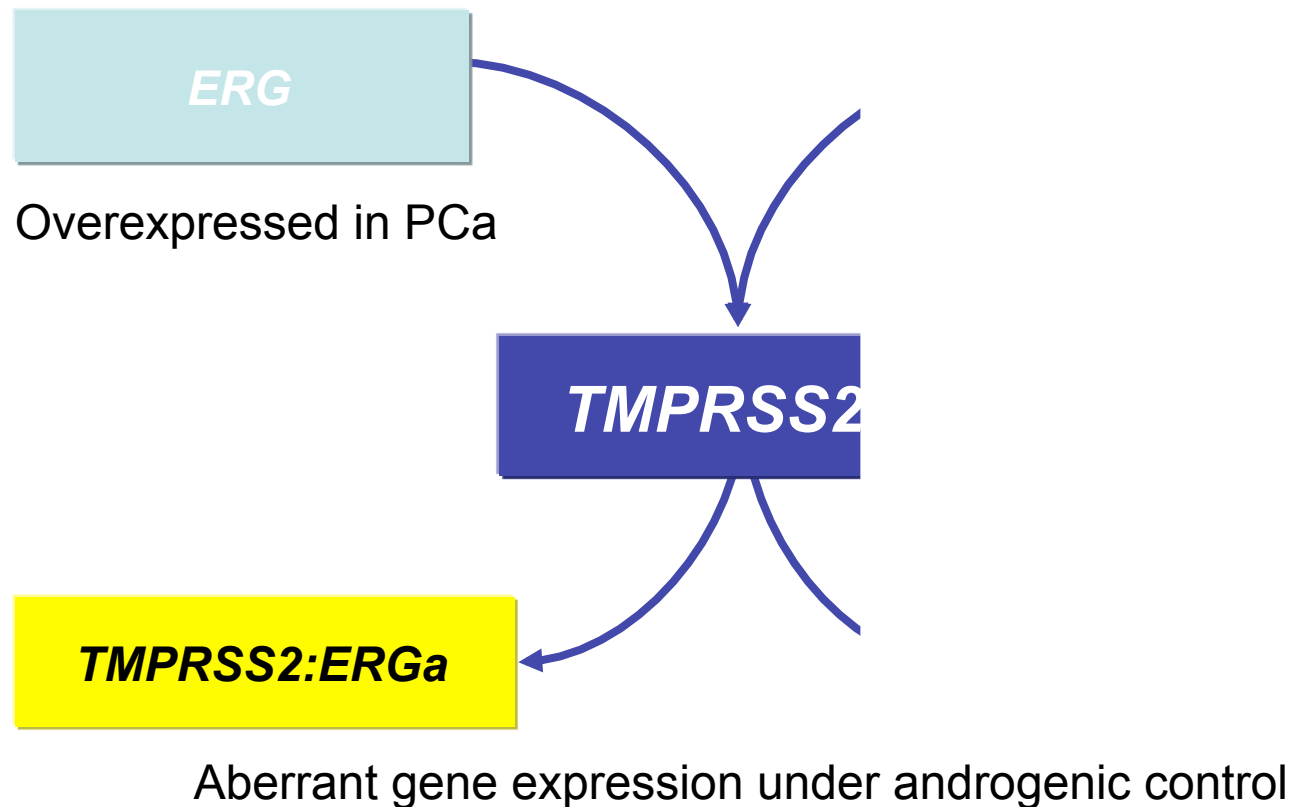


Low volume: tumour volume < 0.5 mL; Low grade: Gleason Score \leq 6

Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer

Scott A. Tomlins,¹ Daniel R. Rhodes,^{1,2} Sven Perner,^{7,9}
Saravana M. Dhanasekaran,¹ Rohit Mehra,¹ Xiao-Wei Sun,⁷
Sooryanarayana Varambally,^{1,6} Xuhong Cao,¹ Joelle Tchinda,⁷
Rainer Kuefer,¹⁰ Charles Lee,⁷ James E. Montie,^{3,5,6}
Rajal B. Shah,^{1,3,5,6} Kenneth J. Pienta,^{3,4,5,6} Mark A. Rubin,^{7,8}
Arul M. Chinnaiyan^{1,2,3,5,6*}

Recurrent chromosomal rearrangements in PCa



'TMPRSS2-erg' in urine

	PCa	No malignancy	
ERG +	14	2	16
ERG -	23	29	52
	37	31	

Sensitivity: 0.38 (max. ~60%)

Specificity: **0.94**

NPV: 0.56

PPV: **0.88**

T2:ERG Urine Test: *Clinical Performance from SDVA/Laval study*

	T2:ERG assay
Sensitivity (95% C.I.)	41% (34-45)
Specificity (95% C.I.)	95% (90-98)
Accuracy (95% C.I.)	71% (65-75)

- High specificity vs. biopsy outcome agrees with previous publication.*
- Sensitivity consistent with T2:ERG prevalence in prostate tumors

*Hessels, et al (2007) *Clin Cancer Research*. 13(17); pp5103-5108.

Synergy between PCA3 and T2:ERG

SDVA/Laval Study

	Sensitivity	Specificity
PCA3 Score (cutoff = 35)	52%	86%
T2:ERG (urine sediment)	41%	95%
PCA3 + T2:ERG	75%	83%

PCA3 + T2:ERG

- 23% increase in sensitivity w/ only 3% loss in specificity.
- Similar results obtained by Hessels, et al.

Conclusions

- Every man over 50 should know his PSA
- However PSA is not a perfect test
- Higher sensitivity and specificity is required
- Genetic screening may identify high risk individuals
- Newer panel of markers eg PCA3 and T2-ERG have sens: 73-75 % spec: 69-83 %