Predict prostate cancer risk using SNPs:

— *Promising but complex*

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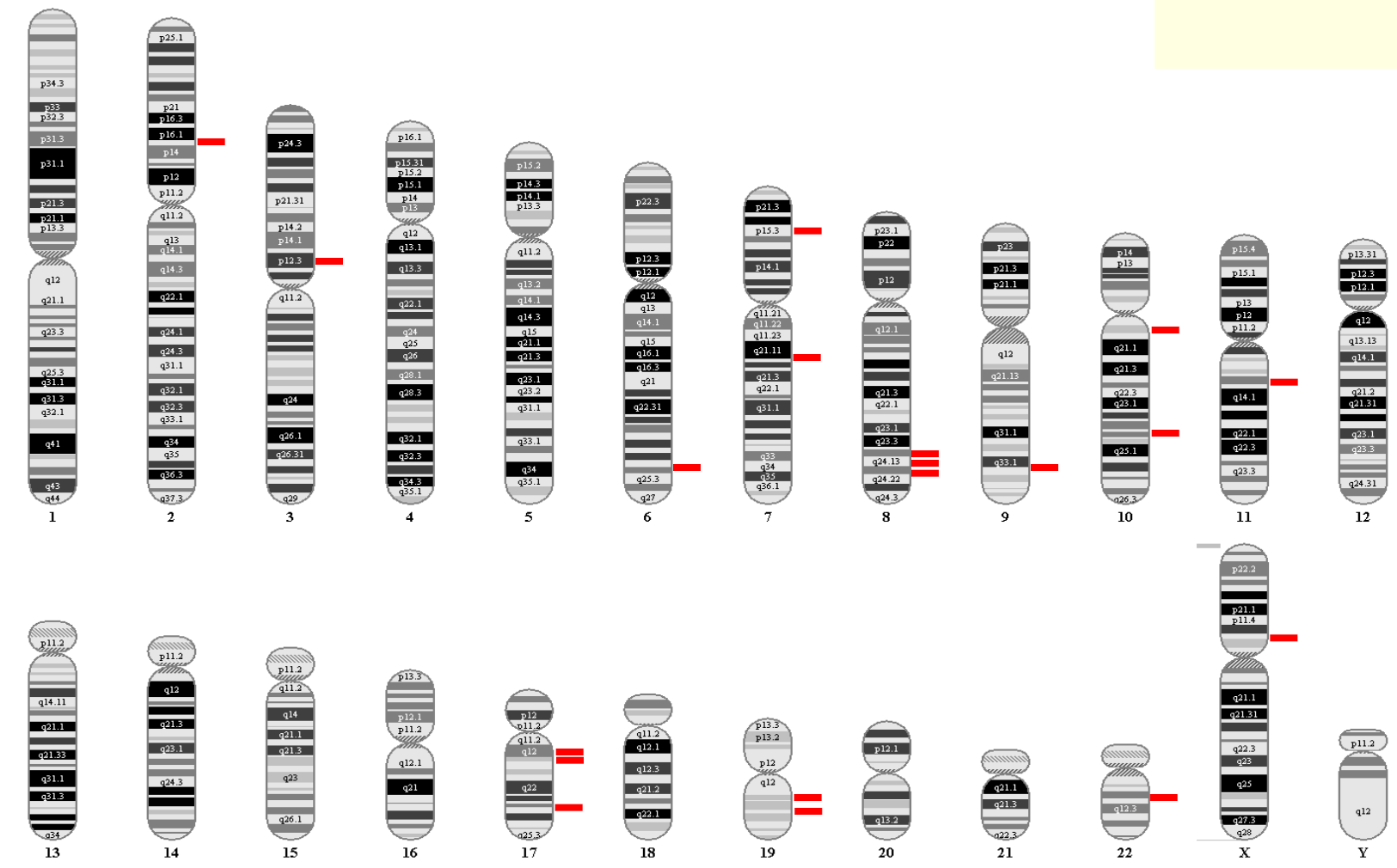
Two important points

- Risk prediction using genetic variants is promising
- It is complex, and much more research is needed

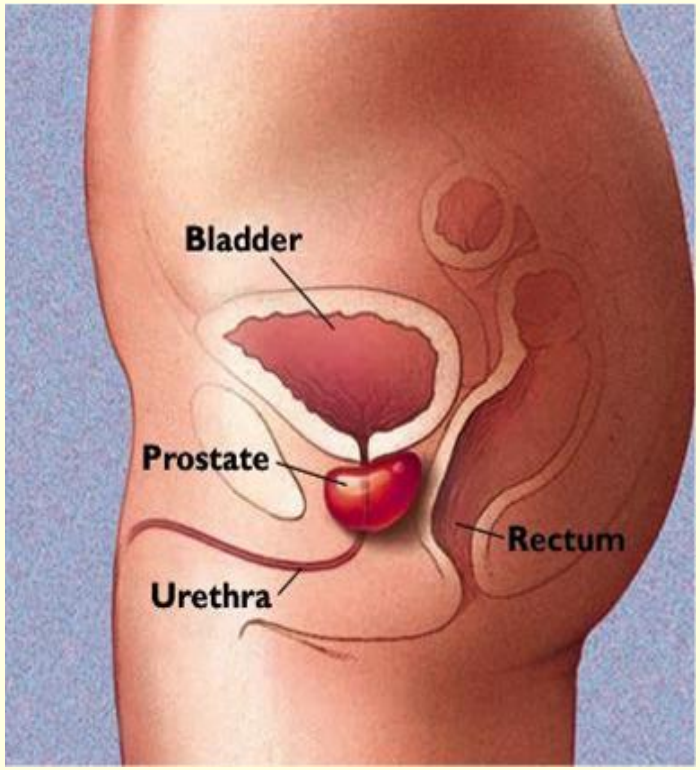
GWAS of prostate cancer



Differences: 2004 - 2008

Risk factors 2004

- Age
- Race
- Family history



Risk factors 2008

- Age
- Race
- Family history
- Locus 1
- Locus 2
- …..
- …..
- Locus 16

Consistently replicated

Prostate cancer risk associated variants identified from GWAS

SNPs	Chr	Position	Allele frequency		OR (95% CI)	*P*
			Cases	Controls		
rs2660753	3p12	87,193,364	0.10	0.08	1.32 (1.13-1.54)	3.4E-04
rs9364554	6q25	160,804,075	0.33	0.31	1.12 (1.02-1.22)	0.02
rs10486567	7p15	27,749,803	0.78	0.76	1.12 (1.01-1.24)	0.03
rs6465657	7q21	97,654,263	0.51	0.47	1.16 (1.06-1.26)	6.7E-04
rs16901979	8q24 (2)	128,194,098	0.06	0.03	1.66 (1.34-2.07)	3.1E-06
rs6983267	8q24 (3)	128,482,487	0.56	0.51	1.22 (1.12-1.33)	3.6E-06
rs1447295	8q24 (1)	128,554,220	0.17	0.14	1.21 (1.08-1.36)	1.6E-03
rs10993994	10q11	51,219,502	0.43	0.39	1.15 (1.05-1.25)	1.6E-03
rs10896449	11q13	68,751,243	0.49	0.46	1.14 (1.05-1.25)	2.1E-03
rs4430796	17q12	33,172,153	0.61	0.56	1.24 (1.14-1.35)	8.5E-07
rs1859962	17q24.3	66,620,348	0.54	0.50	1.17 (1.08-1.28)	2.0E-04
rs5945619	Xp11	51,074,708	0.42	0.38	1.20 (1.06-1.36)	3.5E-03

Frequent in populations

Prostate cancer risk associated variants identified from GWAS

SNPs	Chr	Position	Allele frequency		OR (95% CI)	*P*
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Moderate individual effect

Prostate cancer risk associated variants identified from GWAS

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Cumulative effect of 5 SNPs

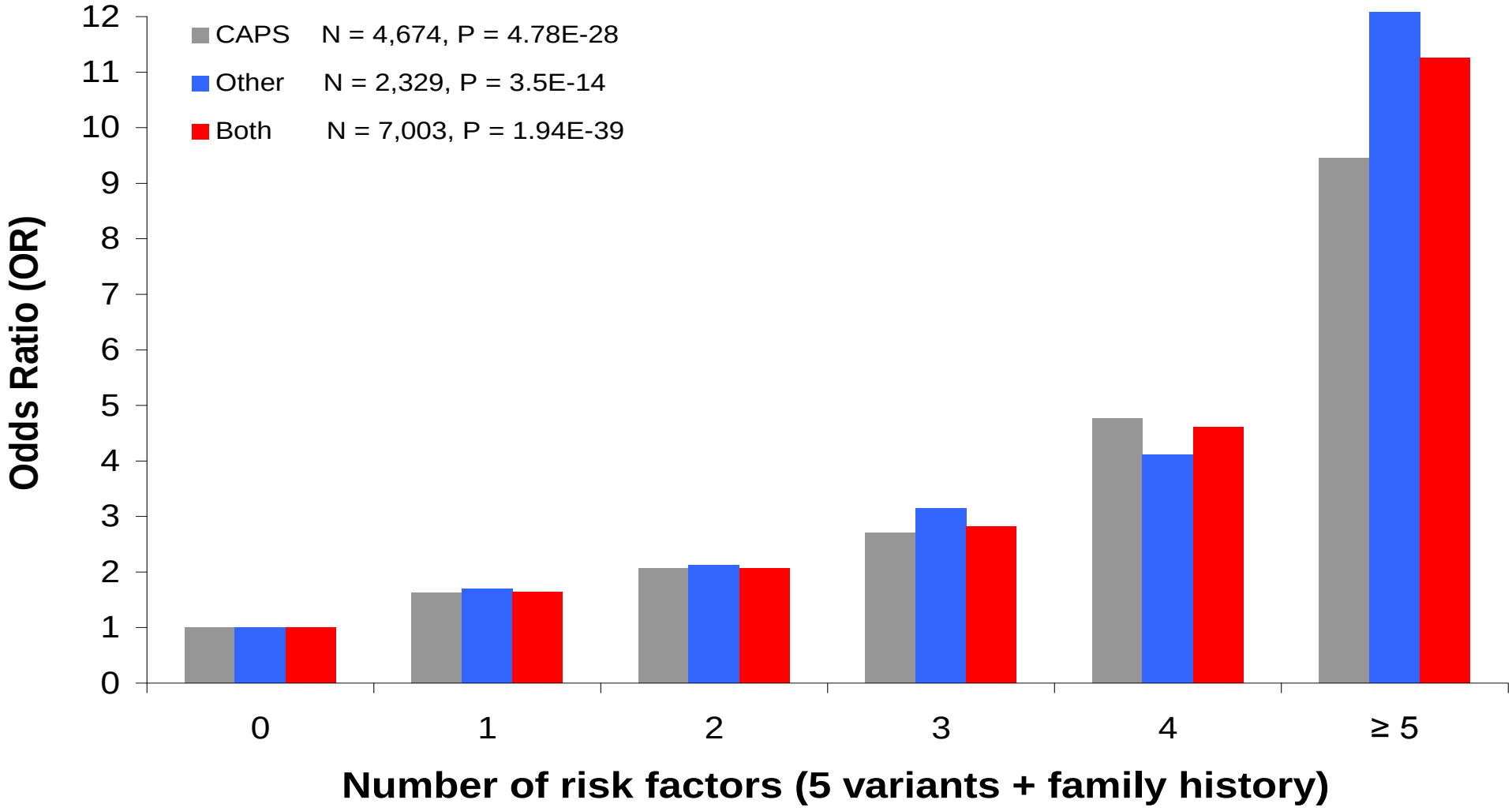
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

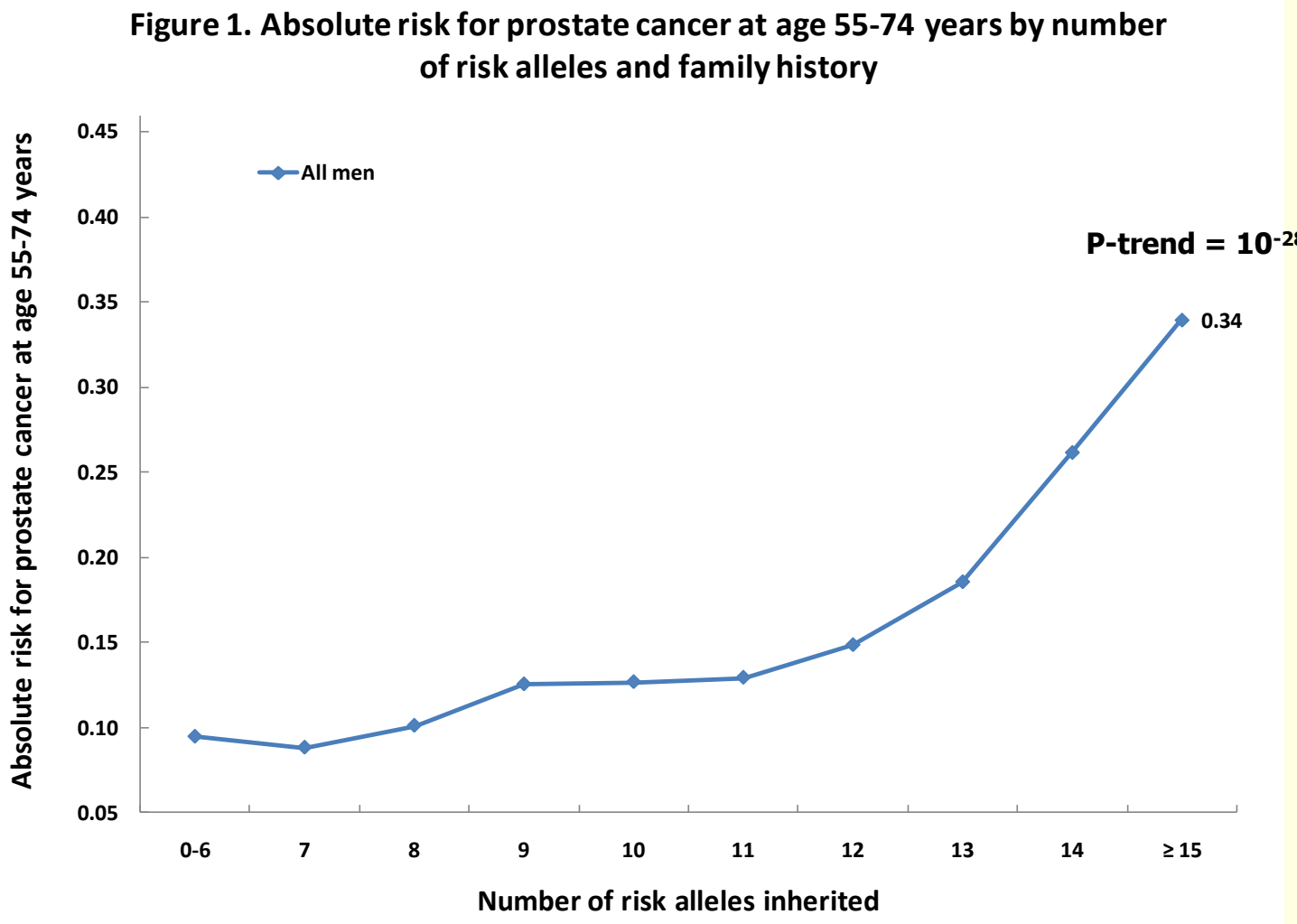
Cumulative Association of Five Genetic Variants with Prostate Cancer

S. Lilly Zheng, M.D., Jielin Sun, Ph.D., Fredrik Wiklund, Ph.D., Shelly Smith, M.S., Pär Stattin, M.D., Ph.D., Ge Li, M.D., Hans-Olov Adami, M.D., Ph.D., Fang-Chi Hsu, Ph.D., Yi Zhu, B.S., Katarina Bälter, Ph.D., A. Karim Kader, M.D., Ph.D., Aubrey R. Turner, M.S., Wennuan Liu, Ph.D., Eugene R. Bleecker, M.D., Deborah A. Meyers, Ph.D., David Duggan, Ph.D., John D. Carpten, Ph.D., Bao-Li Chang, Ph.D., William B. Isaacs, Ph.D., Jianfeng Xu, M.D., D.P.H., and Henrik Grönberg, M.D., Ph.D.

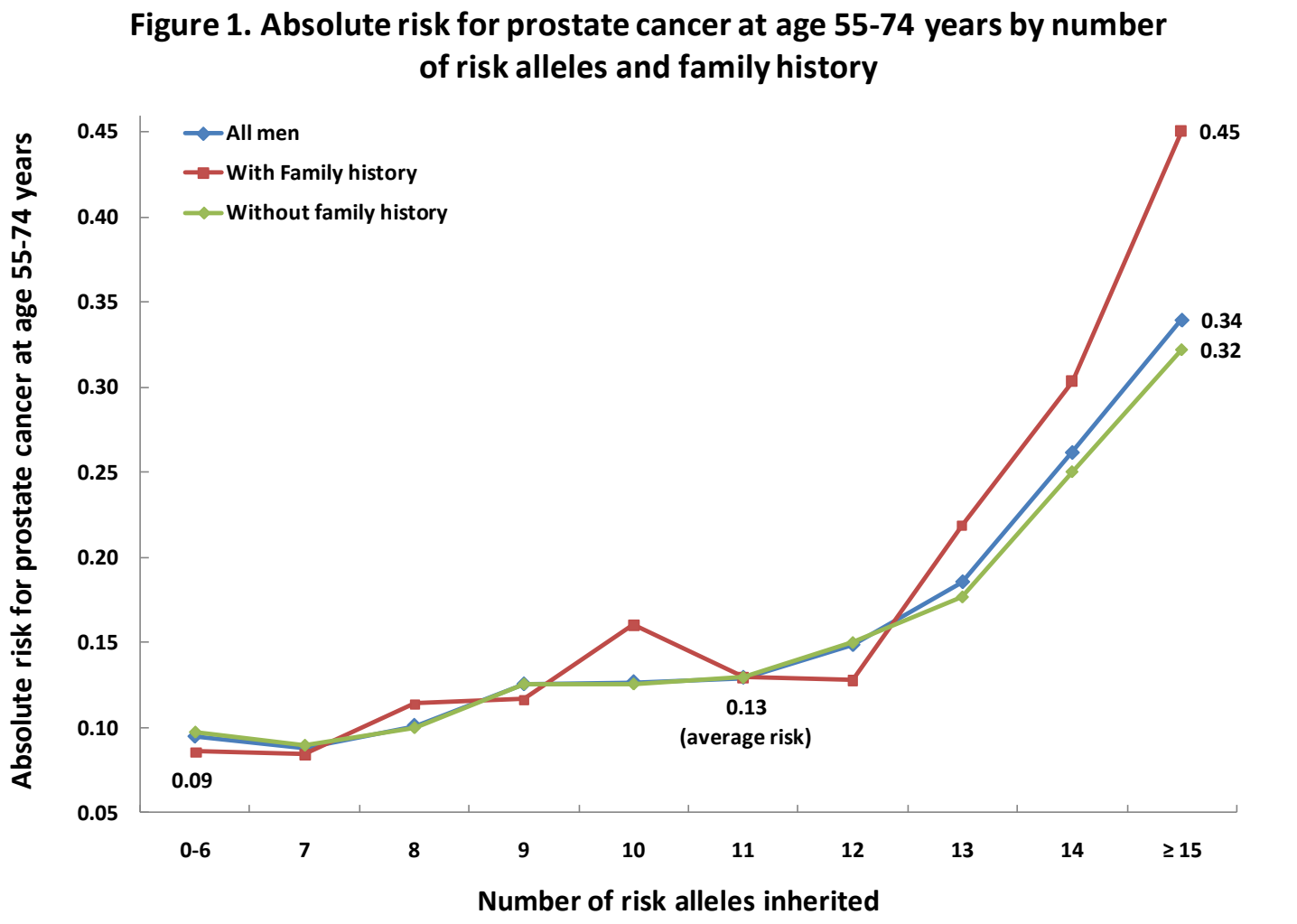
Cumulative effect of five risk variants and family history on prostate cancer risk



Stronger cumulative effect



Even stronger with positive family history



Can we use it to predict prostate cancer risk ?

- Not that fast !

More researched is needed

- Larger sample size and prospective studies
- Issues of PSA detection bias
- Aggressive vs. non-aggressive disease
- Race-specific effects
- Supplement PSA in predicting positive biopsy
- Targeted chemoprevention (e.g. finasteride)

Larger cohort studies are needed

- To obtain more stable and unbiased estimates of RR

Table 2. Associations prostate cancer risk with number of risk alleles of 14 SNPs in CAPS

# of risk alleles	No. of subjects (%)		All prostate cancer		Family history (yes)		Family history (no)	
	Controls	Cases	OR	95% CI	OR	95% CI	OR	95% CI
0-6	89 (5.17)	92 (3.17)	0.73	(0.52-1.01)	0.66	(0.23-1.87)	0.75	(0.53-1.07)
7	99 (5.75)	102 (3.52)	0.68	(0.50-0.94)	0.65	(0.26-1.60)	0.69	(0.49-0.97)
8	183 (10.63)	211 (7.28)	0.78	(0.61-1.01)	0.88	(0.42-1.86)	0.77	(0.59-1.01)
9	214 (12.43)	307 (10.59)	0.97	(0.76-1.22)	0.90	(0.46-1.75)	0.97	(0.75-1.24)
10	270 (15.69)	399 (13.77)	0.98	(0.79-1.22)	1.24	(0.63-2.47)	0.97	(0.77-1.22)
11	285 (16.56)	417 (14.39)	1.00	--	1.00	--	1.00	--
12	254 (14.76)	441 (15.22)	1.15	(0.93-1.43)	0.99	(0.54-1.84)	1.16	(0.92-1.47)
13	163 (9.47)	363 (12.53)	1.44	(1.13-1.83)	1.70	(0.84-3.46)	1.37	(1.06-1.78)
14	93 (5.40)	281 (9.70)	2.04	(1.54-2.70)	2.37	(1.02-5.47)	1.95	(1.45-2.64)
≥15	71 (4.13)	285 (9.83)	2.66	(1.96-3.60)	3.55	(1.36-9.26)	2.52	(1.82-3.47)

Based on number of risk alleles from the 14 prostate cancer risk associated SNPs (0-21 observed in CAPS from 27 possible alleles

Zheng et al, 2009, CCR

PSA detection bias

- Association of SNPs with PSA levels in controls

TABLE II. Multivariate Analysis of PSA Levels Among Meno Without a Diagnosis of Prostate Cancer

	Region	Position[a]	Regression coefficient	*P*-value[b]
Age (year)			0.04	4.0E-21
Geographic region (2 vs. 1)			0.11	0.1
rs10486567	7p15	27,749,803	0.14	3.0E−04
rs10993994	10q11	51,219,502	0.12	4.0E−04
rs4962416	10q26	126,686,862	0.10	9.0E−03
rs4430796	17q12	33,172,153	0.13	8.0E−05
rs2735839	19q13	56,056,435	0.11	0.03
rs5945619	Xp11	51,074,708	0.11	0.02

[a]Build35.
[b]Test were based on log-transformed PSA levels and assuming an additive model for each SNP.

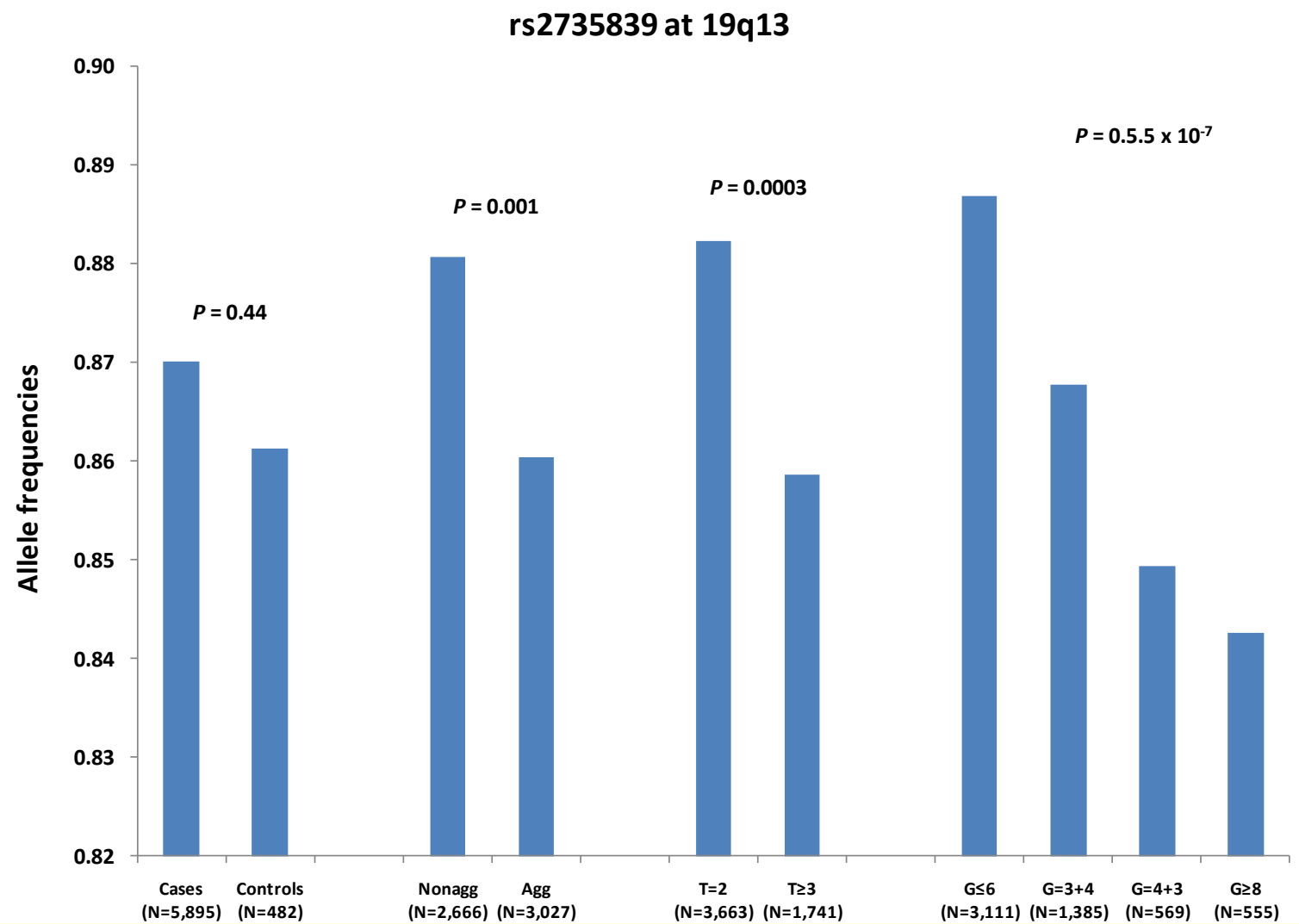
Wiklund et al, 2009, Prostate

No differences between aggressive and non-aggressive disease

GWAS risk SNPs in JHH cases

CHR	SNP	Note	Freuency (%) Cont N=482	Agg N=3,027	Nonagg N=2,666	*P*
2	rs721048	2p15	0.20	0.21	0.22	0.23
3	rs2660753	3p12	0.12	0.13	0.14	0.18
6	rs9364554	6q25	0.27	0.30	0.28	0.076
7	rs10486567	7p15	0.80	0.78	0.80	0.26
7	rs6465657	7q21	0.54	0.52	0.52	0.97
8	rs16901979	8q24 (2)	0.04	0.05	0.05	0.85
8	rs6983267	8q24 (3)	0.50	0.56	0.56	0.43
8	rs1447295	8q24 (1)	0.08	0.13	0.13	0.74
9	rs1571801	GASP1	0.23	0.25	0.25	0.63
10	rs10993994	10q11	0.43	0.47	0.49	0.14
10	rs4962416	10q26	0.28	0.31	0.32	0.61
11	rs10896449	11q13 (1)	0.52	0.58	0.57	0.47
17	rs11649743	17q12 (2)	0.82	0.83	0.84	0.055
17	rs4430796	17q12 (1)	0.51	0.57	0.57	0.70
17	rs1859962	17q24.3	0.52	0.49	0.47	0.36
19	rs2735839	19q13 (KLK3)	0.86	0.86	0.88	**0.001**
23	rs5945619	Xp11	0.33	0.40	0.39	0.45

PSA gene SNP with pathologic variables



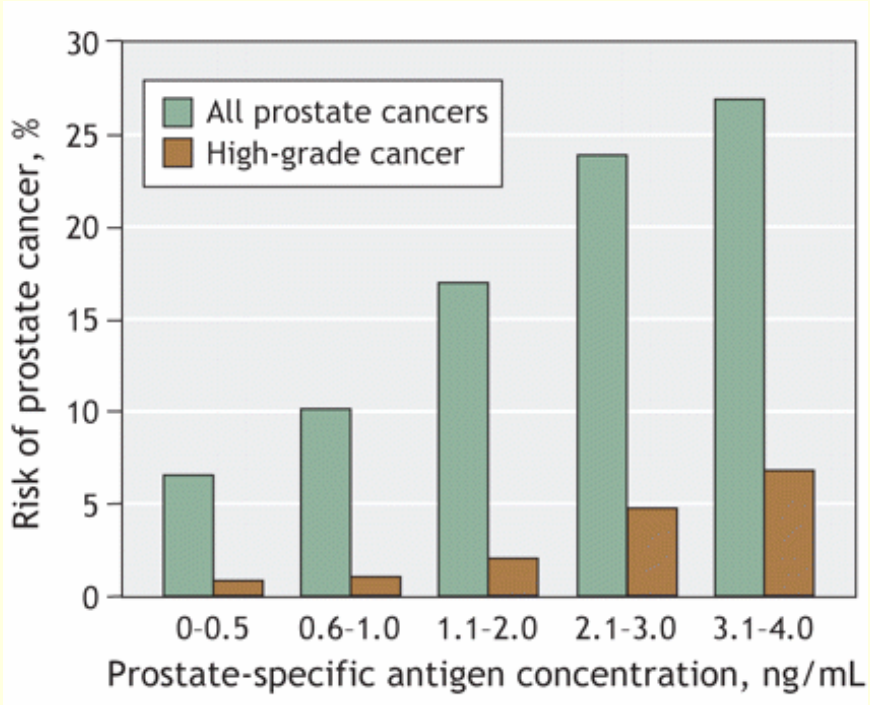
"European" GWAS SNPs in African Americans

Table 1. Summary results of prostate cancer association in African Americans

		Allele frequency		Allelic test		
CHR	**SNP**	**Case**	**Cont**	**OR**	**95% CI**	***P*-ajusted**
2p15	rs721048	0.06	0.05	1.24	0.91-1.71	0.1758
3p12	rs2660753	0.49	0.47	1.15	1.00-1.32	0.05477
6q25	rs9364554	0.07	0.07	0.88	0.66-1.17	0.3838
7p15 (JAZF1)	rs10486567	0.74	0.72	0.91	0.78-1.07	0.2551
7q21 (LMTK2)	rs6465657	0.85	0.86	0.96	0.78-1.18	0.6773
8q24 (2)	rs16901979	0.48	0.42	1.38	1.18-1.60	**3.10E-05**
8q24 (3)	rs6983267	0.90	0.89	0.82	0.65-1.04	0.1043
8q24 (1)	rs1447295	0.32	0.32	1.04	0.89-1.21	0.6277
10q11 (MSMB)	rs10993994	0.61	0.60	0.92	0.80-1.06	0.2371
10q26 (CTBP2)	rs4962416	0.18	0.18	1.06	0.88-1.27	0.5192
11q13 (2)	rs12418451	0.13	0.13	0.90	0.73-1.11	0.3148
11q13 (1)	rs10896449	0.69	0.68	0.96	0.82-1.11	0.5612
17q12 (2) (HNF1B)	rs11649743	0.94	0.93	0.86	0.65-1.15	0.3113
17q12 (1) (HNF1B)	rs4430796	0.36	0.33	1.13	0.97-1.31	0.109
19q13 (KLK3)	rs2735839	0.68	0.70	1.11	0.95-1.29	0.1771
Xp11	rs5945619*	0.40	0.37	1.10	0.90-1.35	0.3531

Can genetic variants complement PSA ?

- Improve predictive value of positive biopsy
- Reduce need for multiple biopsies
- Clinical trials needed



Which subset of men are the best candidates for targeted chemoprevention ?

- Finasteride reduces PCa diagnosis by 25% (PCPT)
- Finasteride also reduces aggressive PCa diagnosis by 27%
- Men at increased risk to PCa may benefit more from chemoprevention, under a multi-factorial model

Summary

- Promising but complex
- Genetic testing is more important for prostate cancer because few risk factors are known
- Complexity is the norm rather than the exception
  - Therefore, responsible implementation will require the input of many viewpoints, including geneticists, clinicians, epidemiologists, and genetic counselors
  - A single test of the whole genome for all diseases is difficult
- No need to be afraid, but clearly more research is needed

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