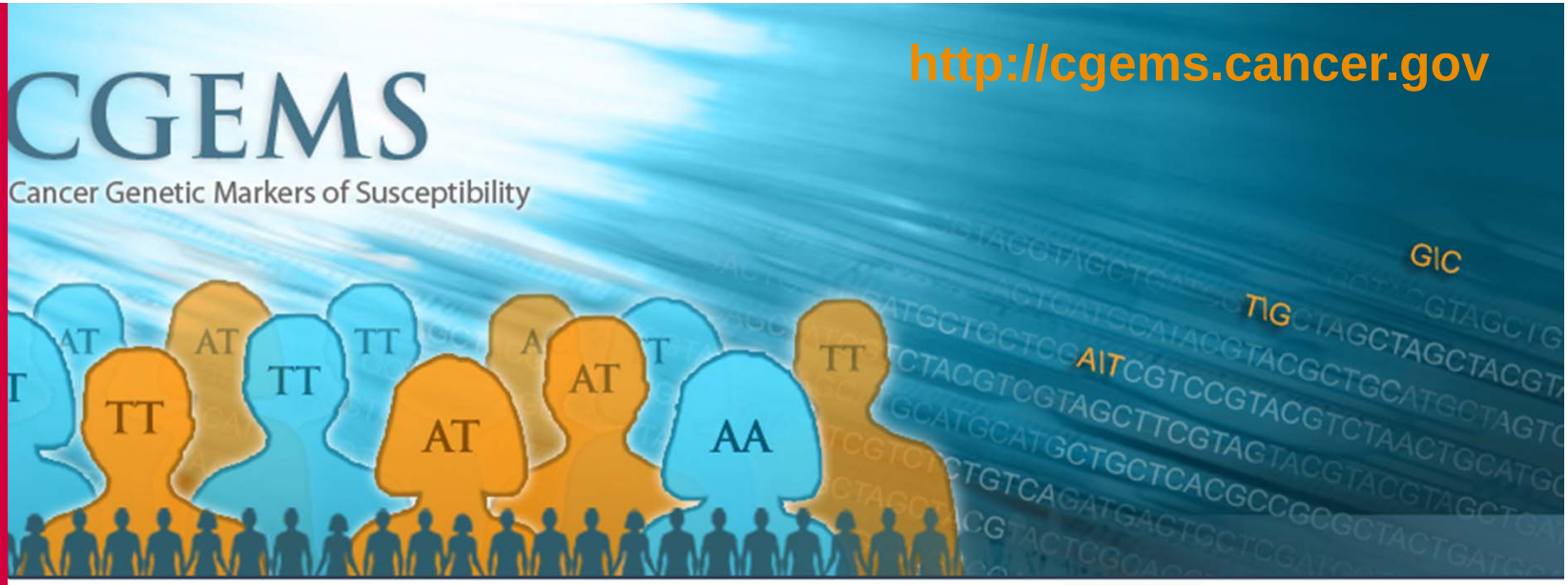
National Cancer Institute



The Promise of Genome-wide Association Studies (GWAS)

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December 1, 2006

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NATIONAL CANCER INSTITUTE

Value of GWAS

- **Identification of promising low-penetrance, high-frequency susceptibility loci**
- **Evaluation of gene-gene interactions and genetic interactions with environmental exposures**
- **Tool for identifying novel mechanisms in cancer**
- **Foundation for strategies for prevention and intervention**

GWAS & NCI Priorities

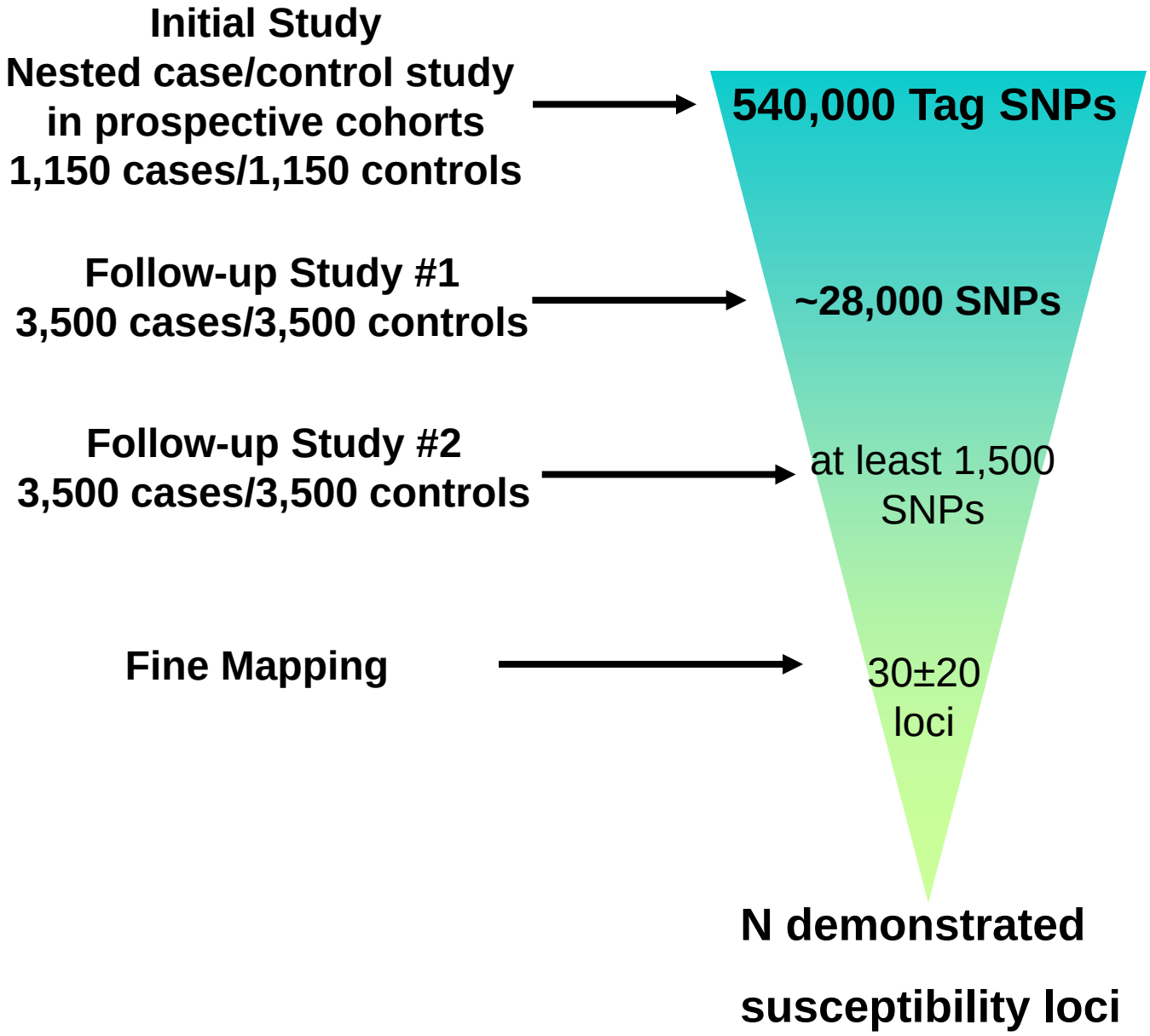
- **Capitalize on revolution in genetics**
  - **Annotation of common genetic variation**
  - **Technology platforms**
- **Intramural capabilities at Core Genotyping Facility**
- **NCI investment in cohorts**
- **Informatics and access: NCICB (caBIG portal)**
- **Coordinate with NIH-wide activities**

Mission of Cancer Genetic Markers of Susceptibility

- **Conduct GWAS in 2 cancers**
  - **Prostate (1 in 8 men)**
  - **Breast (1 in 9 women)**
- **Rapid sequential replication studies**
- **Aggressive timeline**
- **Initial scans in nested case-control studies**
  - **Prostate, Lung, Colon, Ovary (PLCO) Project**
  - **Nurses' Health Study**

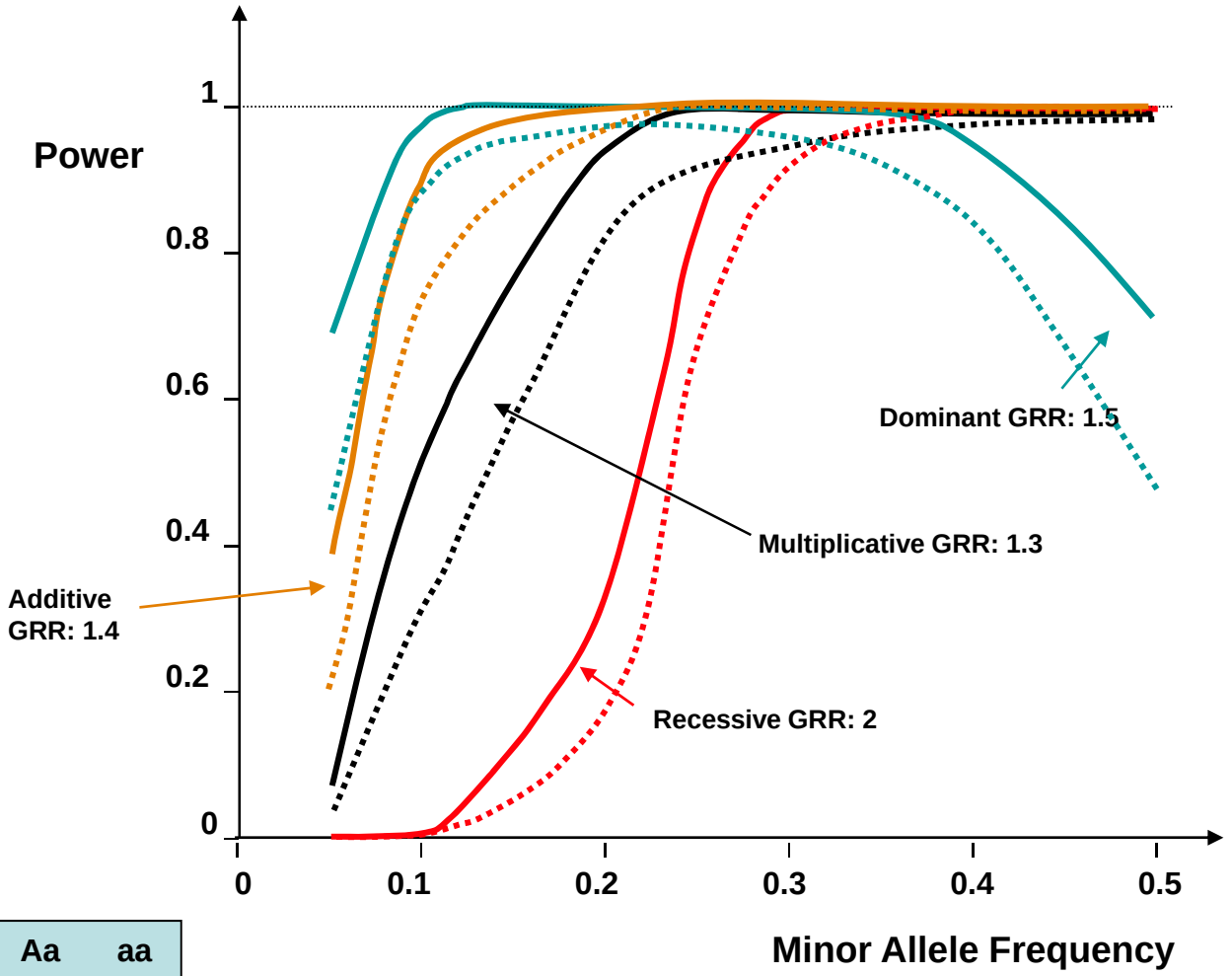
http://cgems.cancer.gov

Strategy for Prostate & Breast Cancer



Power of the First Two Phases of CGEMS

Point-wise significance 10^{-7}; "genome wide" significance 0.05



	GRR	AA	Aa	aa
Recessive	2.0	1.0	1.0	2.0
Dominant	1.5	1.0	1.5	1.5
Additive	1.4	1.0	1.4	1.8
Multiplicative	1.3	1.0	1.3	1.69

Continuous line: power for direct detection ($r^2 = 1$)
Dashed line: power for $r^2 = 0.8$

Skol et al. Nat Genet (2006)

What is available for GWAS in 2006?

Coverage analysis based on HapMap II Data

Build 20 MAF $\geq$ 5%, $r^2 \geq 0.8$ (pair-wise)

		CEU	YRI	JPT/CHB
Illumina	**HumanHap300**	**80%**	**35%**	**40%**
Illumina	**HumanHap500**	**91%**	**58%**	**88%**
Affymetrix*	**500k Mapping**	**63*%**	**41%**	**63%**

*77% **(with 50k MegA)**

http://tagzilla.nc.nih.gov

CGEMS Scans

Prostate Cancer

Two Scans

Illumina

317k
(available)

240k
(February 2007)

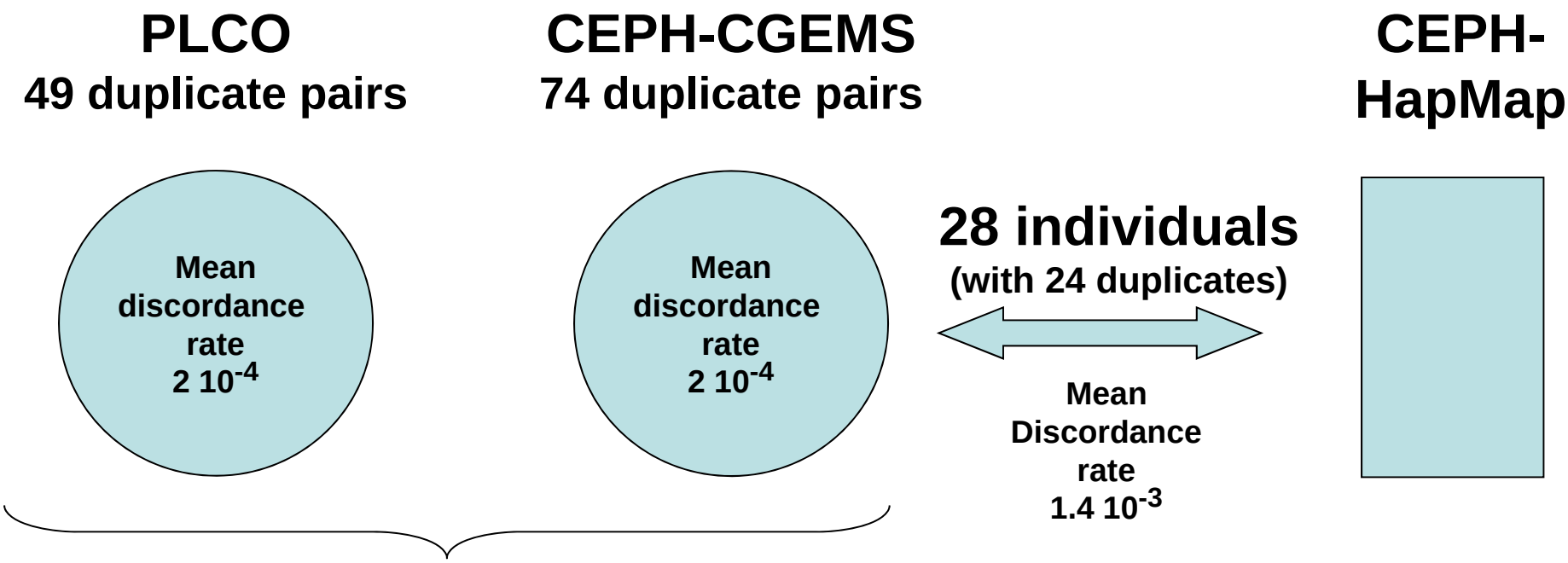
Breast Cancer

One Scan

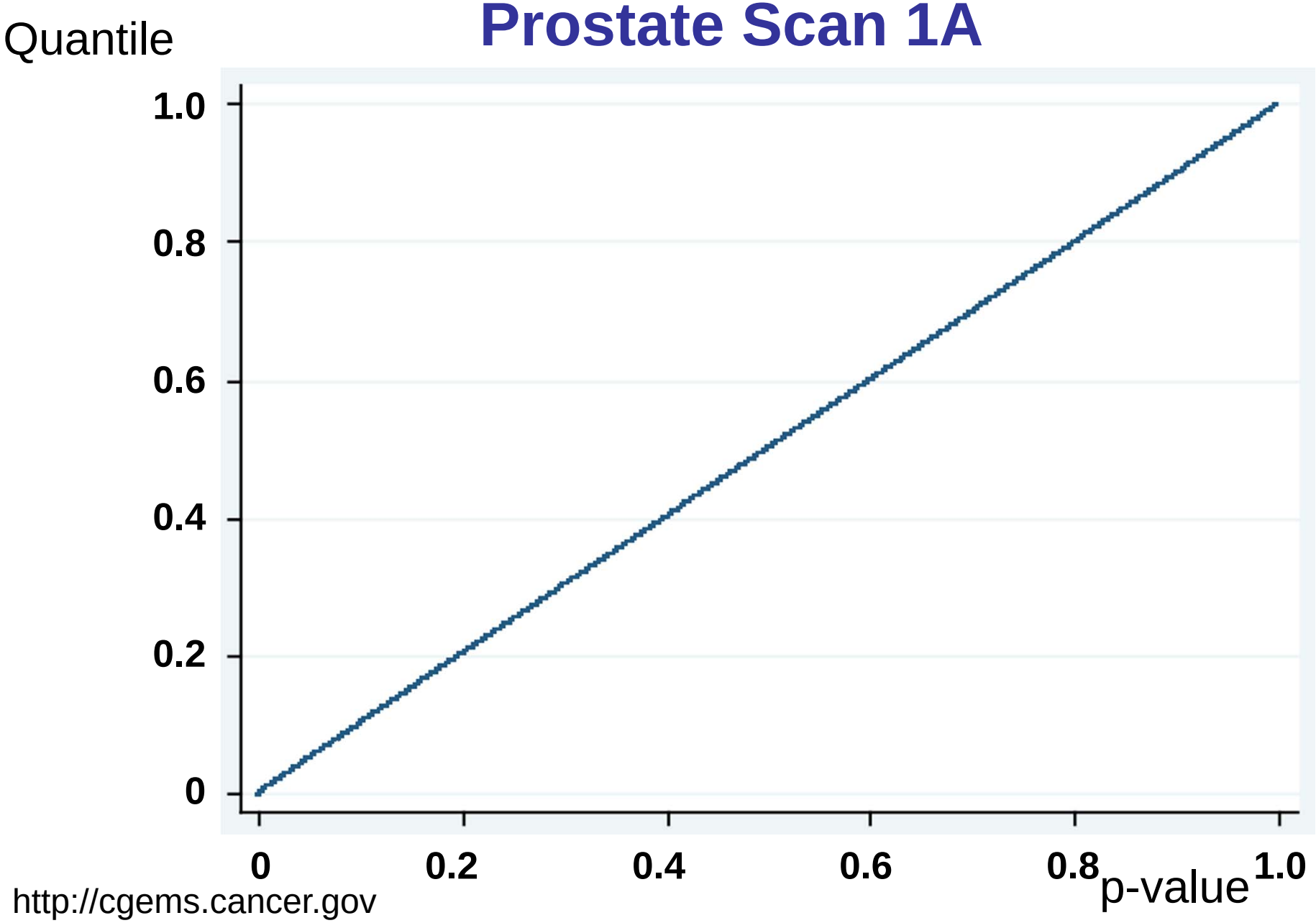
Illumina

550k
(March 2007)

Discordance Rates in Genotype Analysis



QQ Plot for p-values of ~300k SNPs in Prostate Scan 1A



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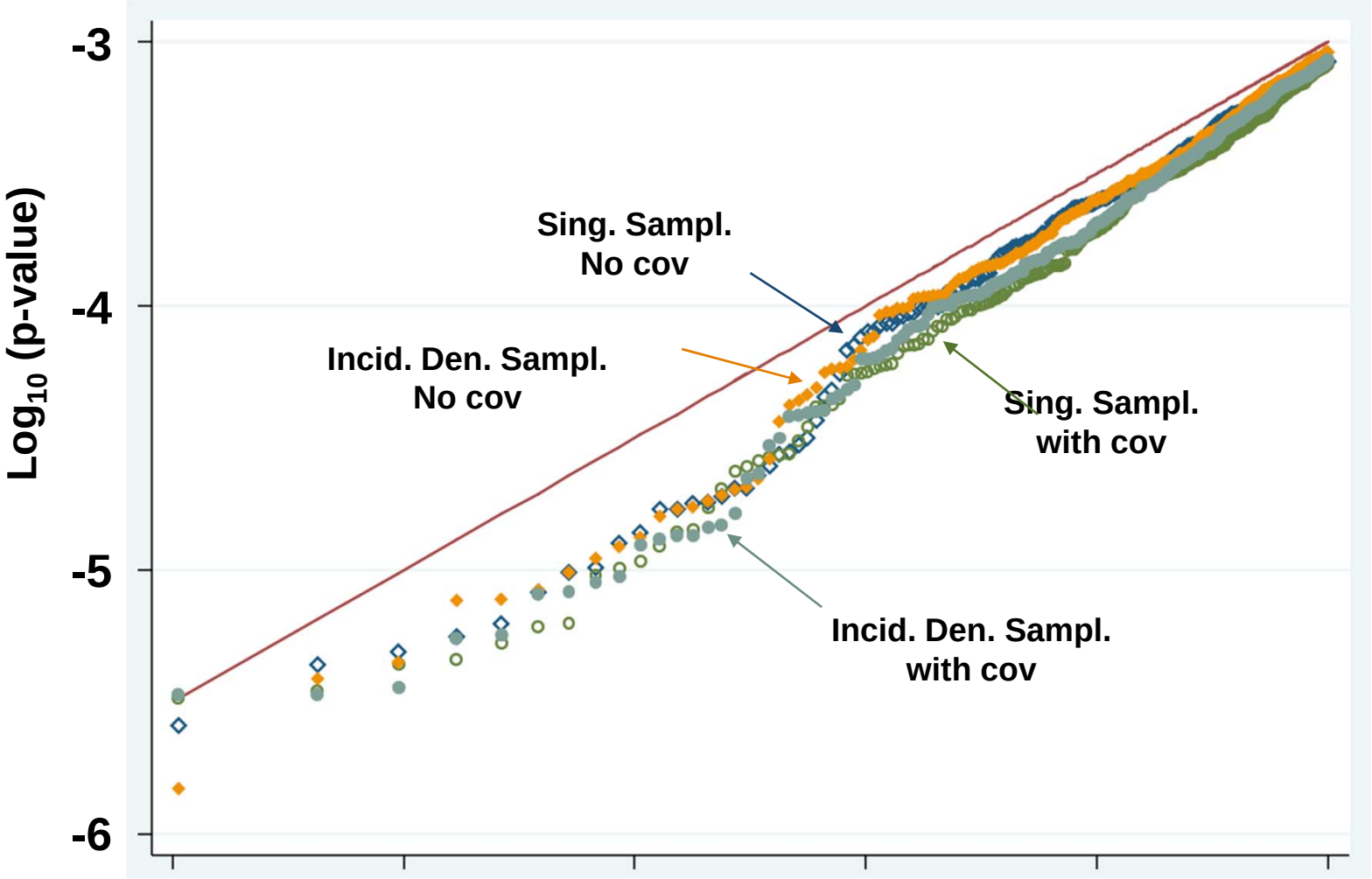
Log-Log Quantile Plot for p-values for the Four Statistical Tests Used

307,256 SNPs



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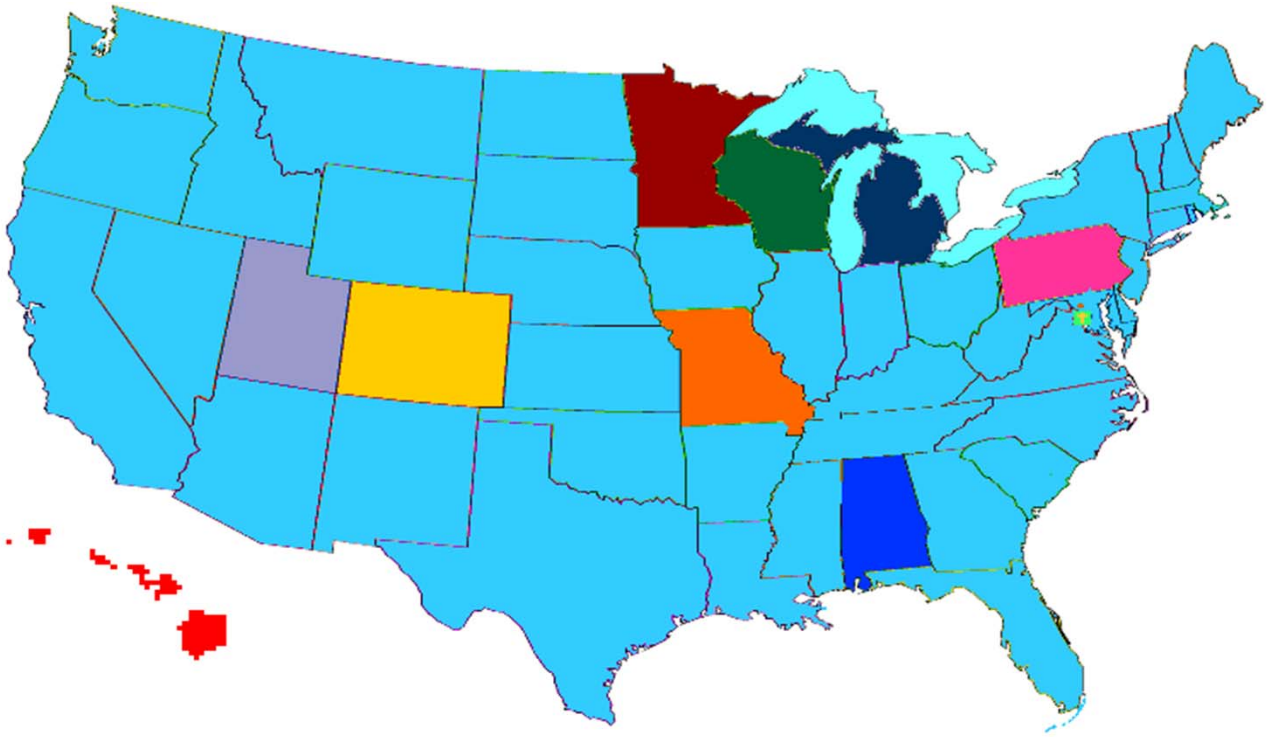
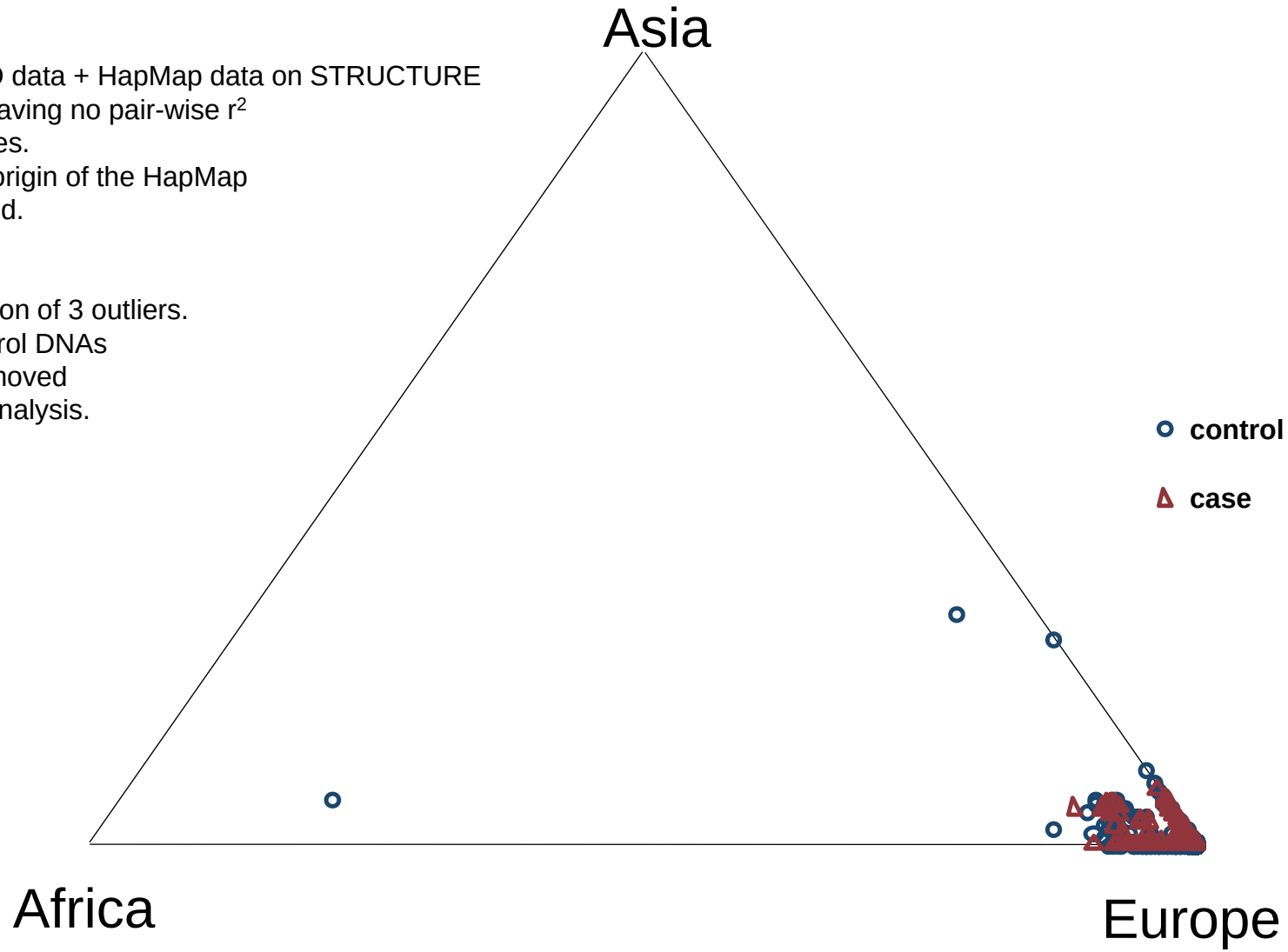
PLCO Recruitment Sites Opportunity to Look at Geographic Differences



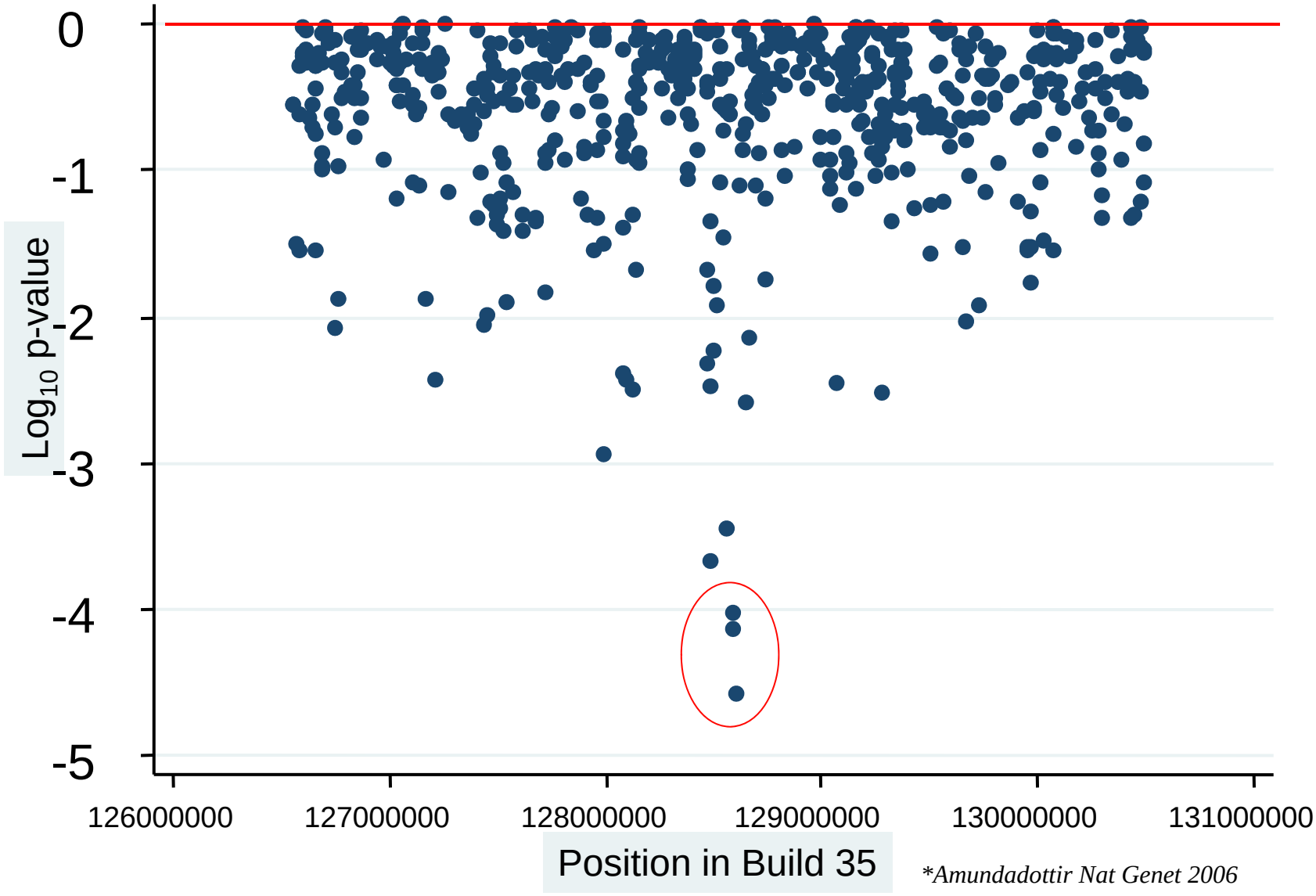
Admixture Coefficient in PLCO Prostate Study Samples

Method:
Run merged PLCO data + HapMap data on STRUCTURE with 6,000 SNPs having no pair-wise r^2 and high FST values.
The population of origin of the HapMap samples is specified.

Result:
Reliable identification of 3 outliers.
They are all 3 control DNAs
and have to be removed
from subsequent analysis.



Log_{10} p-value of the 4 d.f. $\chi 2$ test Plotted Against the Position of the 8q24 SNP (rs#1447295)* in Build 35



Amundadottir Nat Genet 2006

Freedman PNAS 2006

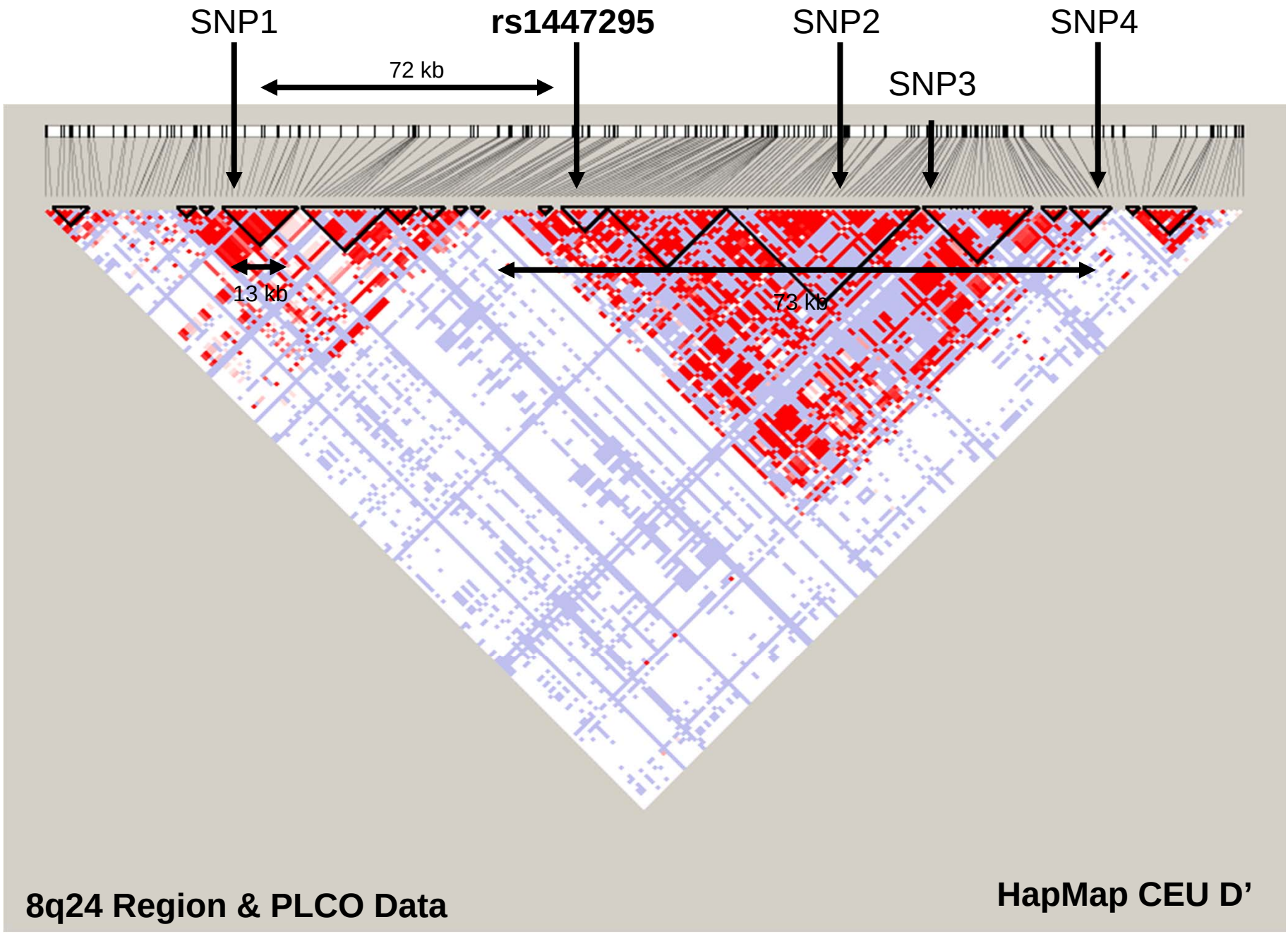
Prostate Scan
8q24 Region

CGEMS
Cancer Genetic Markers of Susceptibility

			Genotype RR for Indolent		Genotype RR for aggressive	
rs number	susceptibility allele	allele frequency	Heterozyg.	Homozig.	Heterozyg.	Homozig.
rs1447295	A	0.1	1.08	1.45	1.24	1.46
rs4242382	A	0.1	1.13	1.39	1.27	1.39
rs7017300	C	0.13	1.14	1.63	1.17	1.37
rs7837688	T	0.1	1.14	1.36	1.26	1.54

Key Findings:

1. Comparable risk as original reports in Nat Genet and PNAS
2. Comparable risk for BPC3 (~6,500 cases/controls)
3. Discovery of 1 and perhaps 2 additional loci


SNP1
rs1447295
SNP2
SNP4
72 kb
SNP3
13 kb
73 kb
8q24 Region & PLCO Data
HapMap CEU D'

Value-added Analysis in CGEMS

Opportunity to Investigate

- **Determinants of risk factors**
  - **BMI, smoking, hormone levels**
- **Multi-SNP analysis**
- **Gene: Gene interactions**
  - **Explore pathways**

CGEMS: caBIG Posting
Pre-computed Analysis

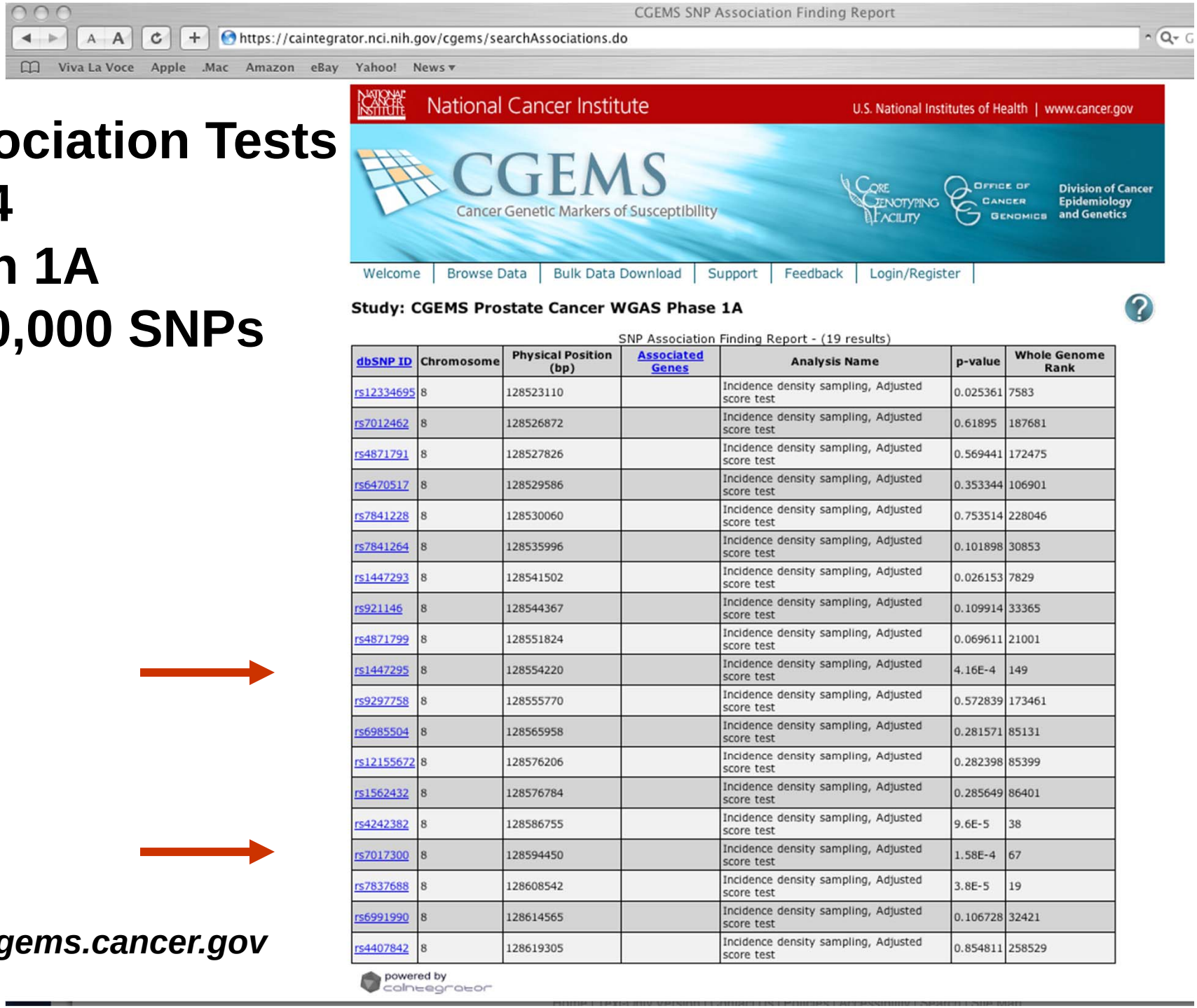
Pre-computed Analysis
No Restrictions

Raw Genotype
- **Case/control**
- **Age (in 5 yrs)**
- **Family Hx (+/-)**

Registration

http://cgems.cancer.gov

Association Tests
8q24
Scan 1A
~300,000 SNPs



dbSNP ID	Chromosome	Physical Position (bp)	Associated Genes	Analysis Name	p-value	Whole Genome Rank
rs12334695	8	128523110		Incidence density sampling, Adjusted score test	0.025361	7583
rs7012462	8	128526872		Incidence density sampling, Adjusted score test	0.61895	187681
rs4871791	8	128527826		Incidence density sampling, Adjusted score test	0.569441	172475
rs6470517	8	128529586		Incidence density sampling, Adjusted score test	0.353344	106901
rs7841228	8	128530060		Incidence density sampling, Adjusted score test	0.753514	228046
rs7841264	8	128535996		Incidence density sampling, Adjusted score test	0.101898	30853
rs1447293	8	128541502		Incidence density sampling, Adjusted score test	0.026153	7829
rs921146	8	128544367		Incidence density sampling, Adjusted score test	0.109914	33365
rs4871799	8	128551824		Incidence density sampling, Adjusted score test	0.069611	21001
rs1447295	8	128554220		Incidence density sampling, Adjusted score test	4.16E-4	149
rs9297758	8	128555770		Incidence density sampling, Adjusted score test	0.572839	173461
rs6985504	8	128565958		Incidence density sampling, Adjusted score test	0.281571	85131
rs12155672	8	128576206		Incidence density sampling, Adjusted score test	0.282398	85399
rs1562432	8	128576784		Incidence density sampling, Adjusted score test	0.285649	86401
rs4242382	8	128586755		Incidence density sampling, Adjusted score test	9.6E-5	38
rs7017300	8	128594450		Incidence density sampling, Adjusted score test	1.58E-4	67
rs7837688	8	128608542		Incidence density sampling, Adjusted score test	3.8E-5	19
rs6991990	8	128614565		Incidence density sampling, Adjusted score test	0.106728	32421
rs4407842	8	128619305		Incidence density sampling, Adjusted score test	0.854811	258529

http://cgems.cancer.gov

GWAS in Pancreatic Cancer: PanScan Objectives

- **Identify loci associated with pancreatic cancer**
  - **1,200 cases and 1,200 controls drawn from 12 cohort studies**
- **Define susceptibility loci for common genetic variants (MAF > 5%)**
- **Follow-up studies in cohort and case control studies**
- **Public access for data**
  - **Pre-computed association testing – Open**
  - **Raw genotype data with limited phenotype data- registered access**

What is down the road?

2-4 Year Forecast

- **Cheaper and denser SNP technologies**
  - **Better coverage of genome**

4-8 Year Forecast

- **Whole Genome Sequencing**
  - **Replace SNPs**
  - **Magnification of Challenge of Confidentiality**
  - **Challenge to Epidemiologic Rigor**

Follow-up of GWAS: Steps to Clinical Implementation

- **Fine mapping of notable regions**
- **Functional determination of causal variants**
- **Design issue for analysis in clinical studies**
  - **Population-based studies**
  - **Sequence of clinical studies**
- **Validation criteria**