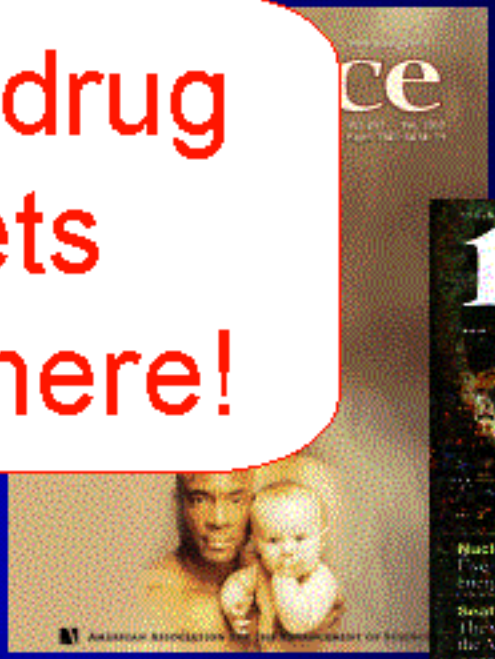
Pharmacogenetics Personalised Safety and Segmented Efficacy

Allen D. Roses, MD

GSK Genetics Research

31 March 2003

All the drug targets are in here!



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GAATTTATTCCCTCGATCGACAAACCTTTCGATCGACTAGCTACGGATCGACTTACGTATCGGT
GAGGTAAATTTAGCCGCTCGCCACGACTTAGCGGCTACGGCATCGGCTT

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Drug Research and Development process

Target identification

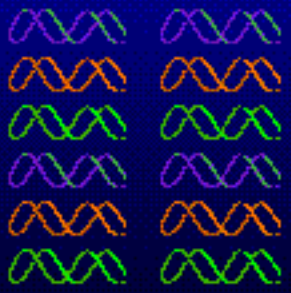
Target validation

Target progression

Molecule progression

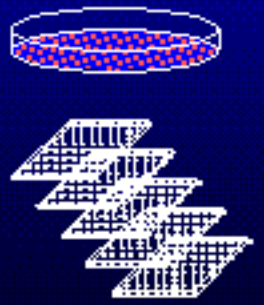
Market access

Product differentiation

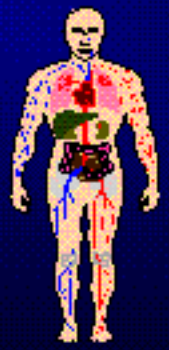


Genetics
Genomics
Bioinformatics

Combo chem
HTS

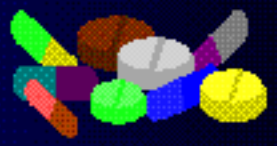


Pharmacology
Toxicology
(efficacy - safety)



Clinical studies
(efficacy - safety)

Pharmacogenetics
Pharmacogenomics



Additional indications

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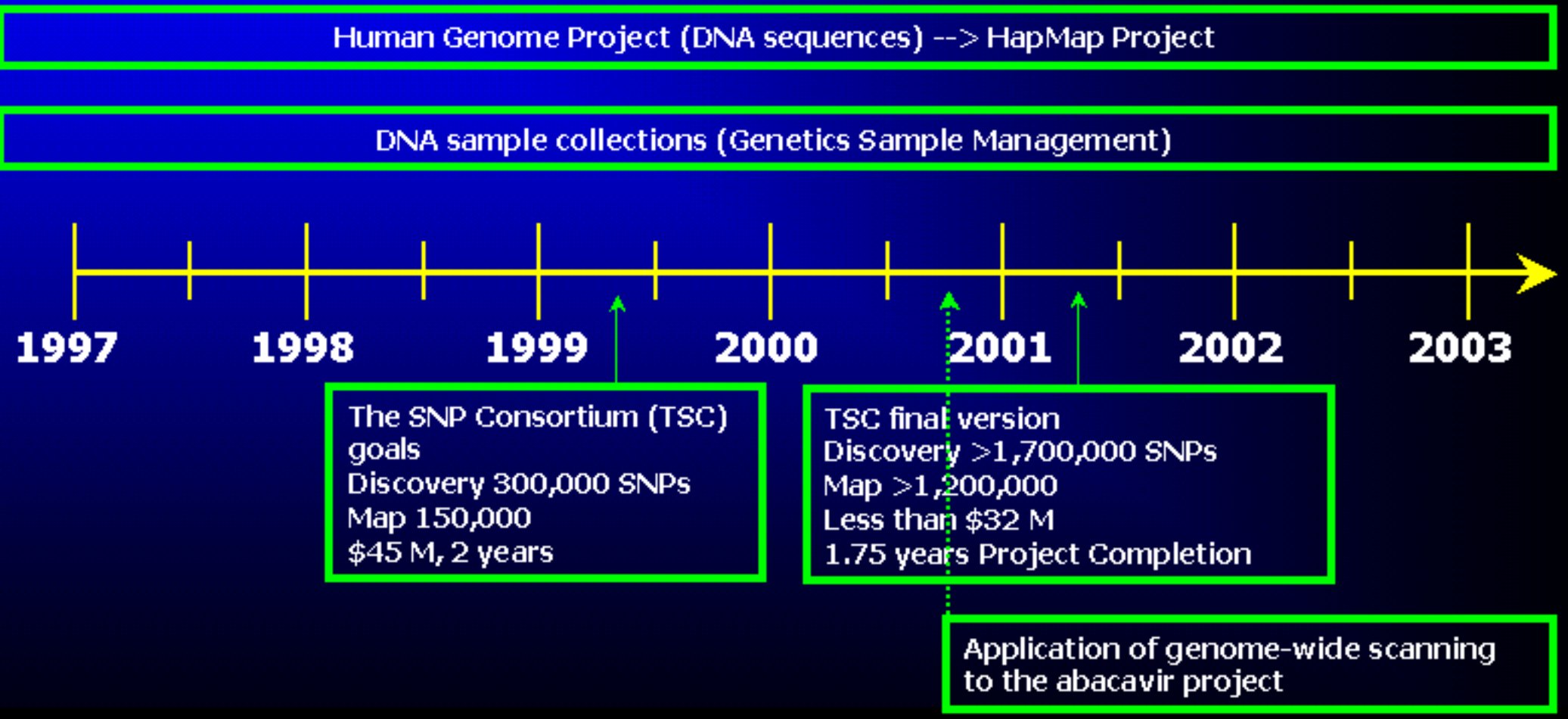
Getting it Right about Delivery Timetables:

Genetics, Genomics and Proteomics → New medicines acting at cause of disease (>7-12 years)

Whole Genome Pharmacogenetics → The right medicine for the right patient (ongoing 2003- 4 years)

Development of resources for genome-wide SNP scanning for pharmacogenetics



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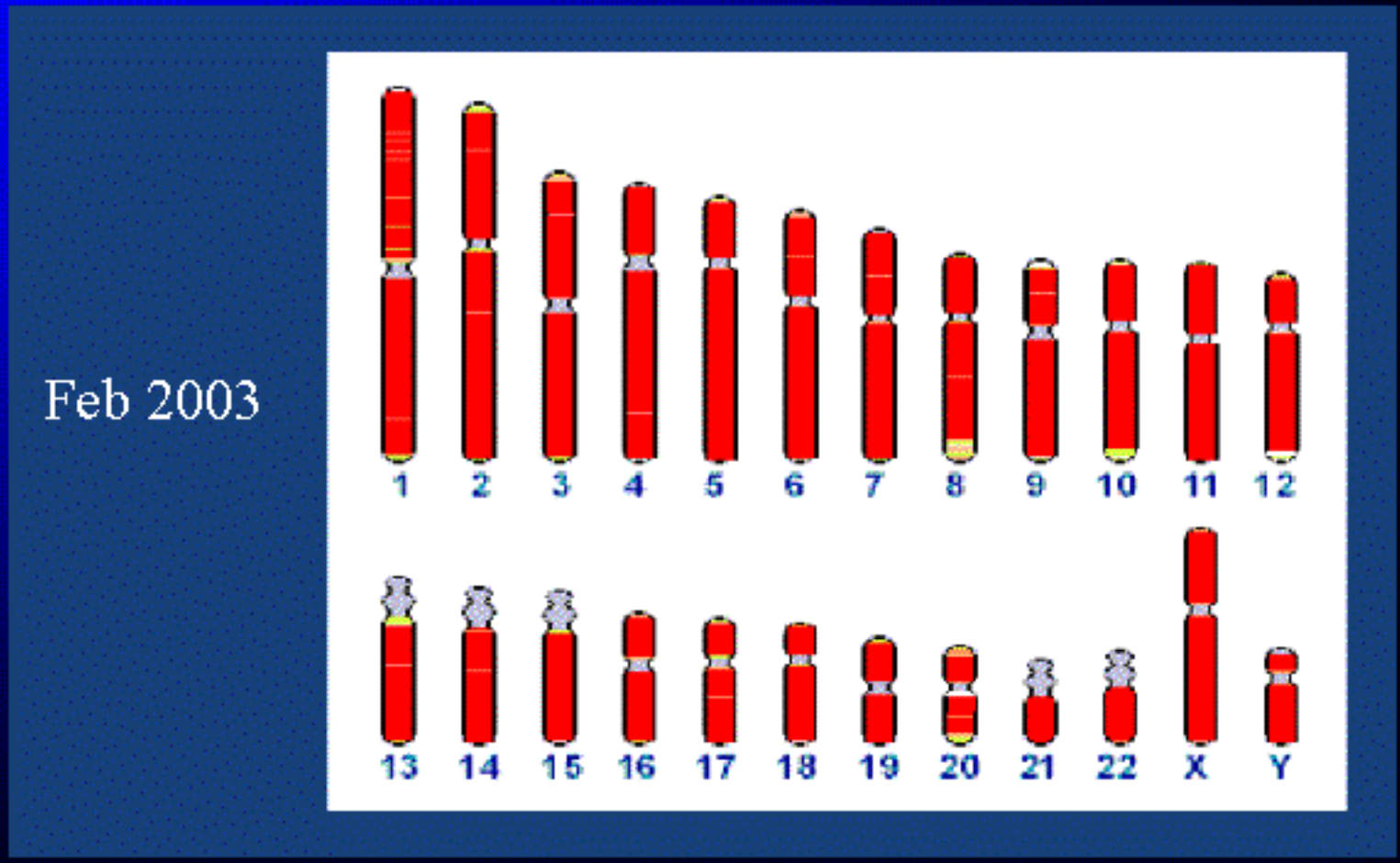
Human Genome Sequencing (>98.8% of the sequences are now publicly available of which 95.8% are available as finished sequences)



http://www.ncbi.nlm.nih.gov/genome/seq/

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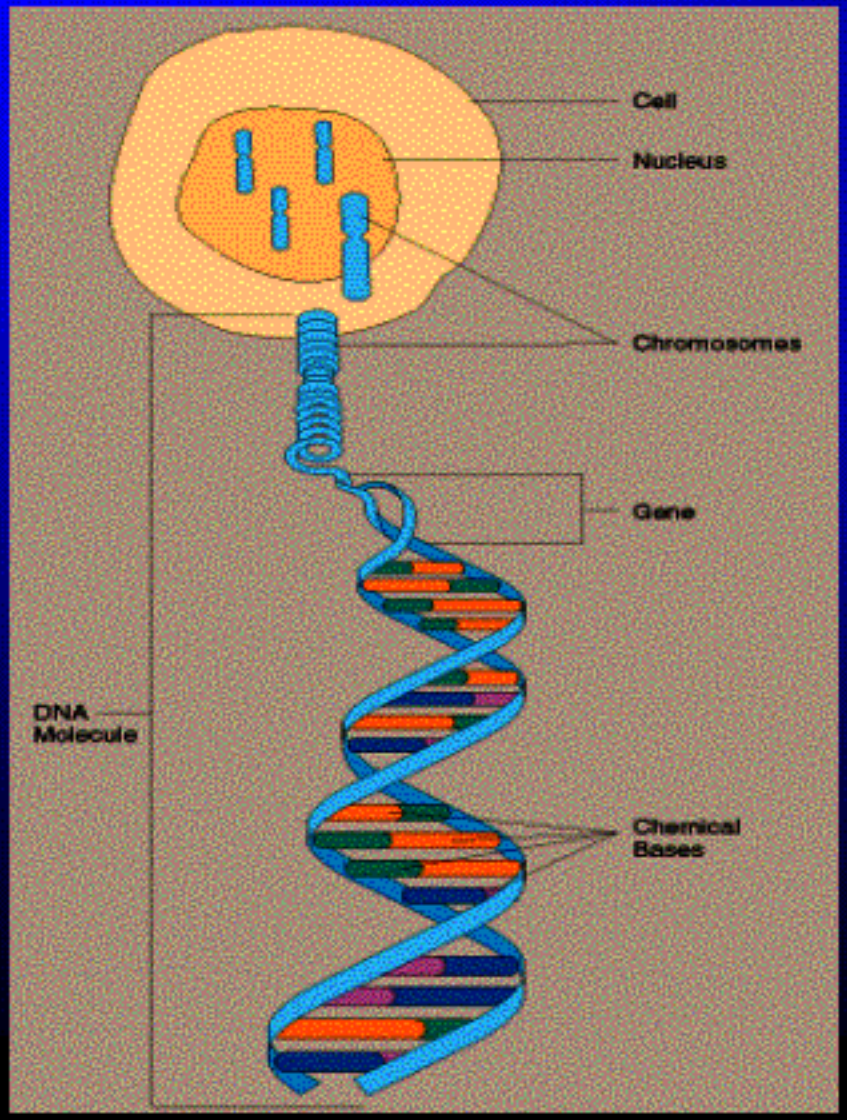
What is a SNP?



Example order of bases in a section of DNA on a chromosome:

…G G **T** A A C T G…

…G G **C** A A C T G…

Some people have a different base at a given location

This is a Single Nucleotide Polymorphism, or SNP

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The SNP Consortium (TSC) Membership

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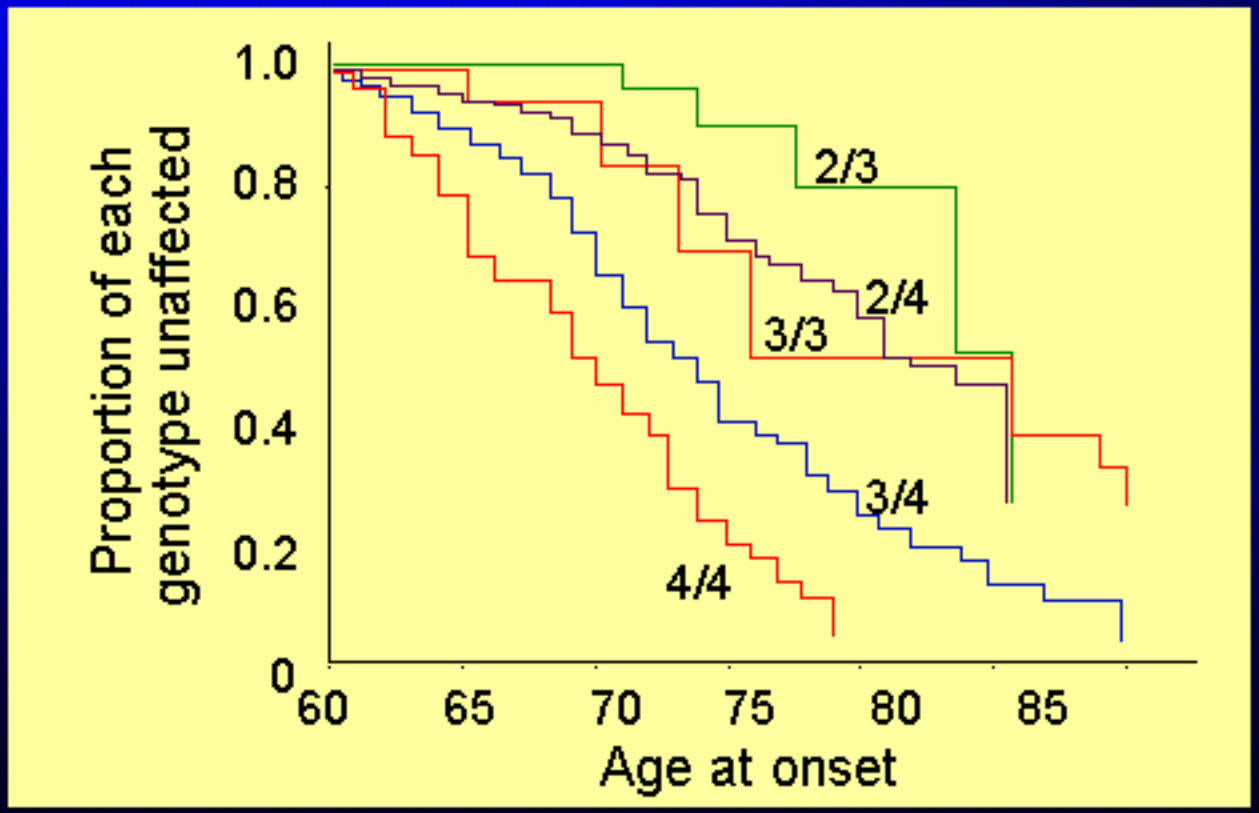
Two Approaches of Pharmacogenetics to Medicine Response Profiles

Pre-2003 ***Generate specific hypotheses about genes causing differential drug responses, and test in responders and non-responders (Candidate gene approach)***

2003 and the future ***Seek SNP profiles [SNP Prints℠] from whole genome SNP scans that correspond to efficacy or adverse events in appropriate populations ("Forensic" precision approach)***

APOE4 - a susceptibility gene variant for common forms of Alzheimer disease



Mean age of onset of Alzheimer disease as a function of the inheritance of the five common APOE genotypes

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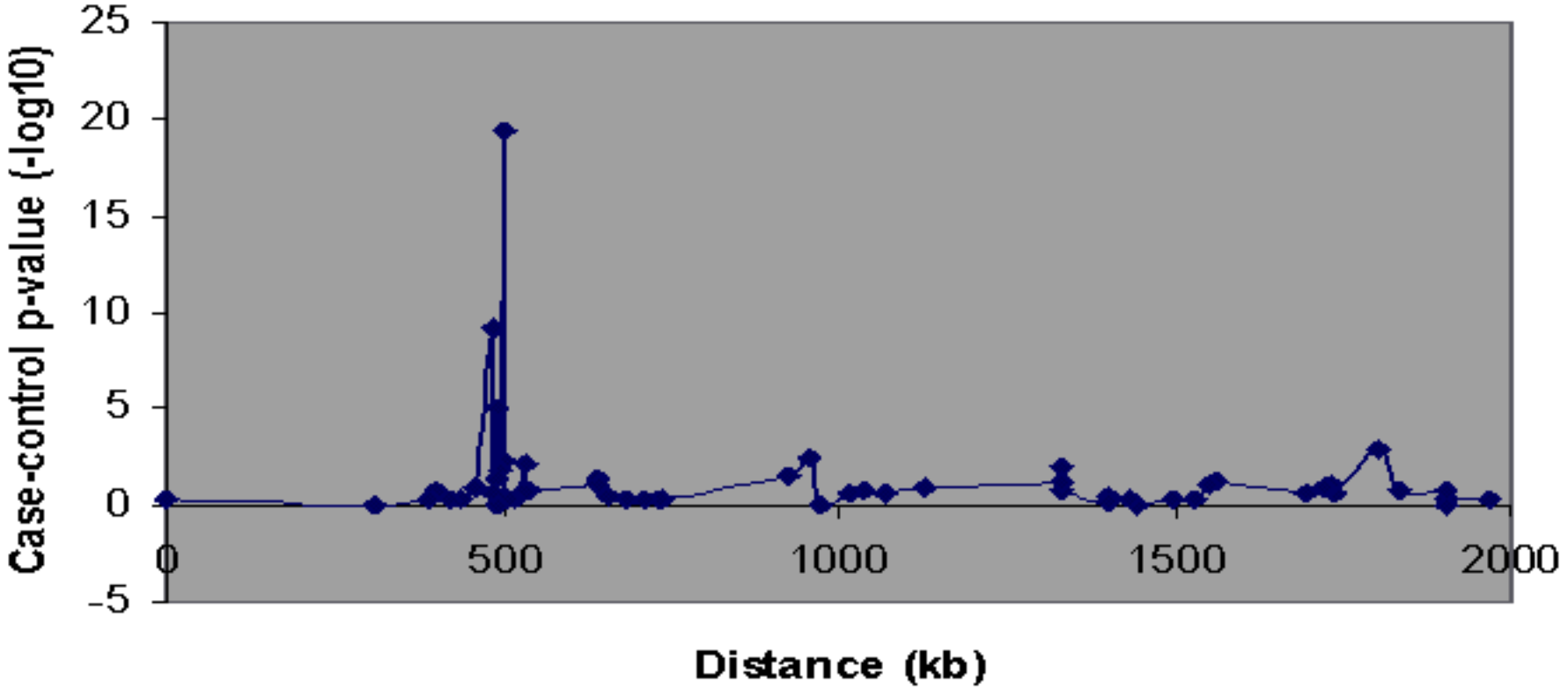
SNP Mapping of the APOE Region



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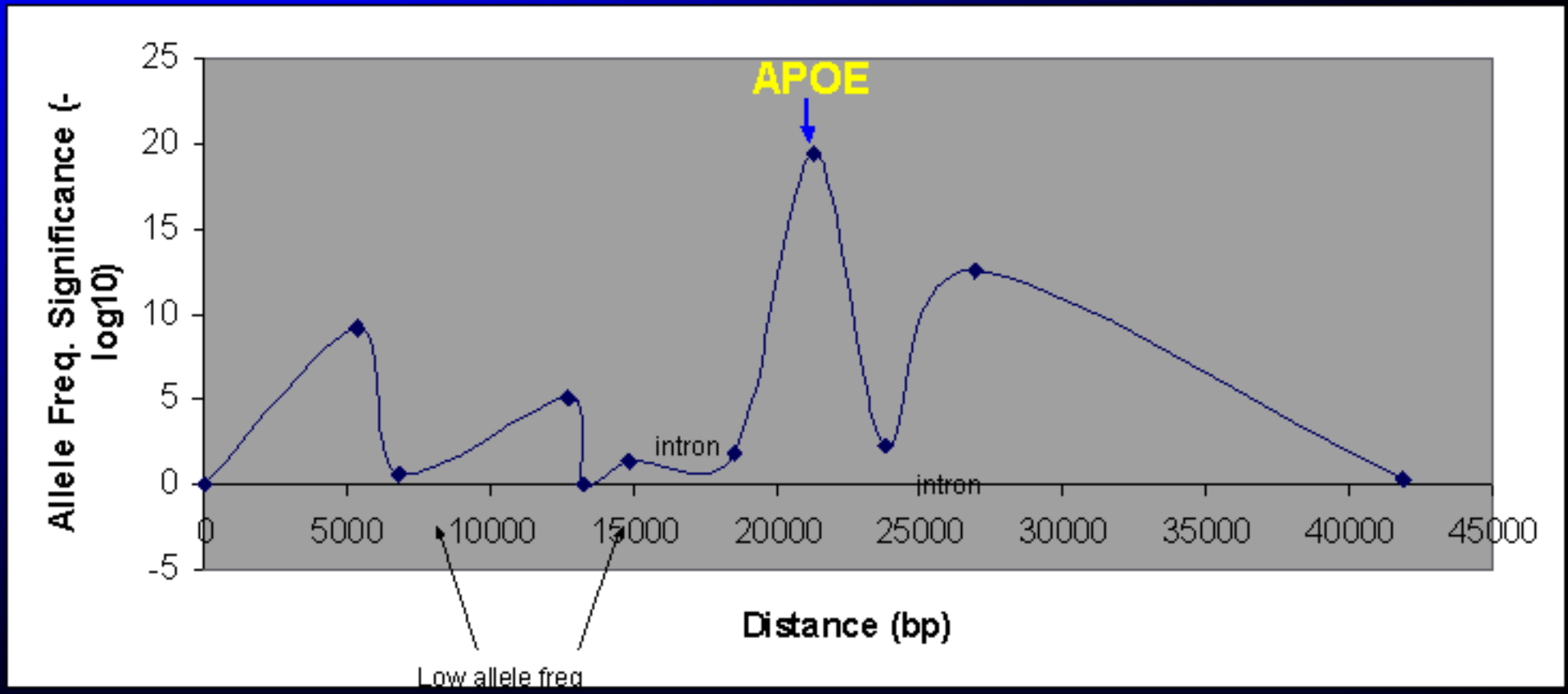
High Density SNP Map around APOE



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In 2002, dense-ordered SNP maps have identified disease-associated gene variants

- **Three published examples from GSK:**
  - **APOE in Alzheimer disease [Genomics 1998]**
  - **SLC12A8** (Solute carrier family 12, member 8) **in psoriasis [Genomics 2002]**
  - **Insulin receptor in aura positive migraine [Genomics 2002]**
- **Other examples entering literature:**
  - **Chronic enteric colitis [Nature Genetics 2002]**
- **Density of SNPs that have worked ~ 15 - 40 Kb**
- **Can subsequently fine map or sequence the identified gene for all common variants**

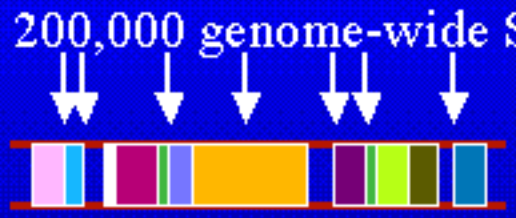
Two Approaches of Pharmacogenetics to Medicine Response Profiles

Pre-2003 ***(Candidate gene approach)***

2003 and the future ***Seek SNP profiles [SNP Prints^{sm}] from whole genome SNP scans that correspond to efficacy or adverse events in appropriate populations ("Forensic" precision approach)***

Applications of the whole genome SNP maps

200,000 genome-wide SNP map



Data Analysis:
Single point association
Multiple point likelihood
Haplotype analysis

•Clinical Genetics Networks
•Clincal trial samples
Database of well characterized patients & their DNA
200 - 1,000 per experiment

40 - 200 millions genotypes per experiment

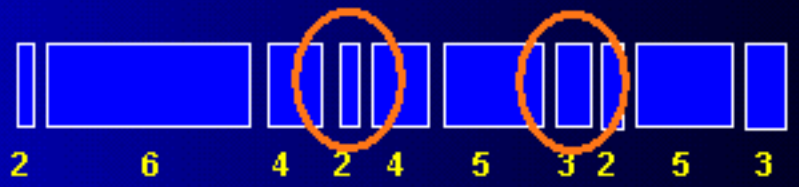
Applications:
•Disease genes as drug targets
•Pharmacogenetics
Drug response
Adverse drug reaction

SNP PRINT^{sm} or SNP LD Profiles

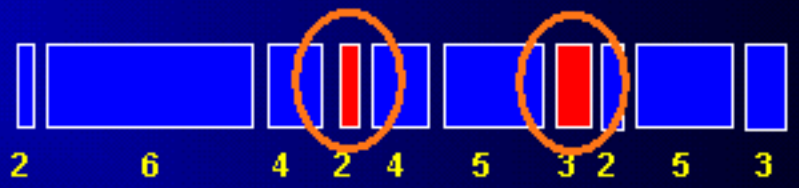
Response to Medicine or surveillance

Section of SNP profile (number of SNPs below)

Patients without a side effect during surveillance



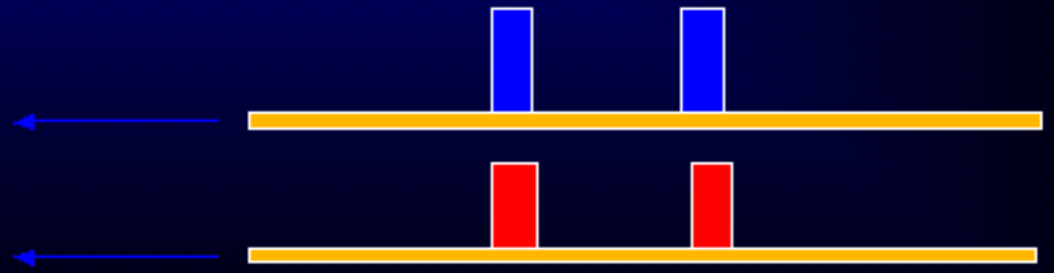
Patients with a side effect during surveillance



The genome scan indicates the SNPs that correlate with the patients' response to the medicine. This profile (an abbreviated SNP LD profile) will be used to identify those patients likely to experience an AE.

Predictive of no side effect

Predictive of a side effect



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Pharmacogenetics across the pipeline
Development of Medicine Response Tests

Phase II clinical trials

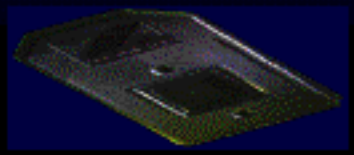
SNP profile for efficacy (and common AEs)

Smaller, more efficient and less expensive Phase III trials

Approval with efficacy medicine response profile [MRP]

SNP profile for less common serious AEs

Enhancement with comprehensive post-marketing surveillance AE MRPs for product management



Comprehensive medicine response profile for efficacy and AEs

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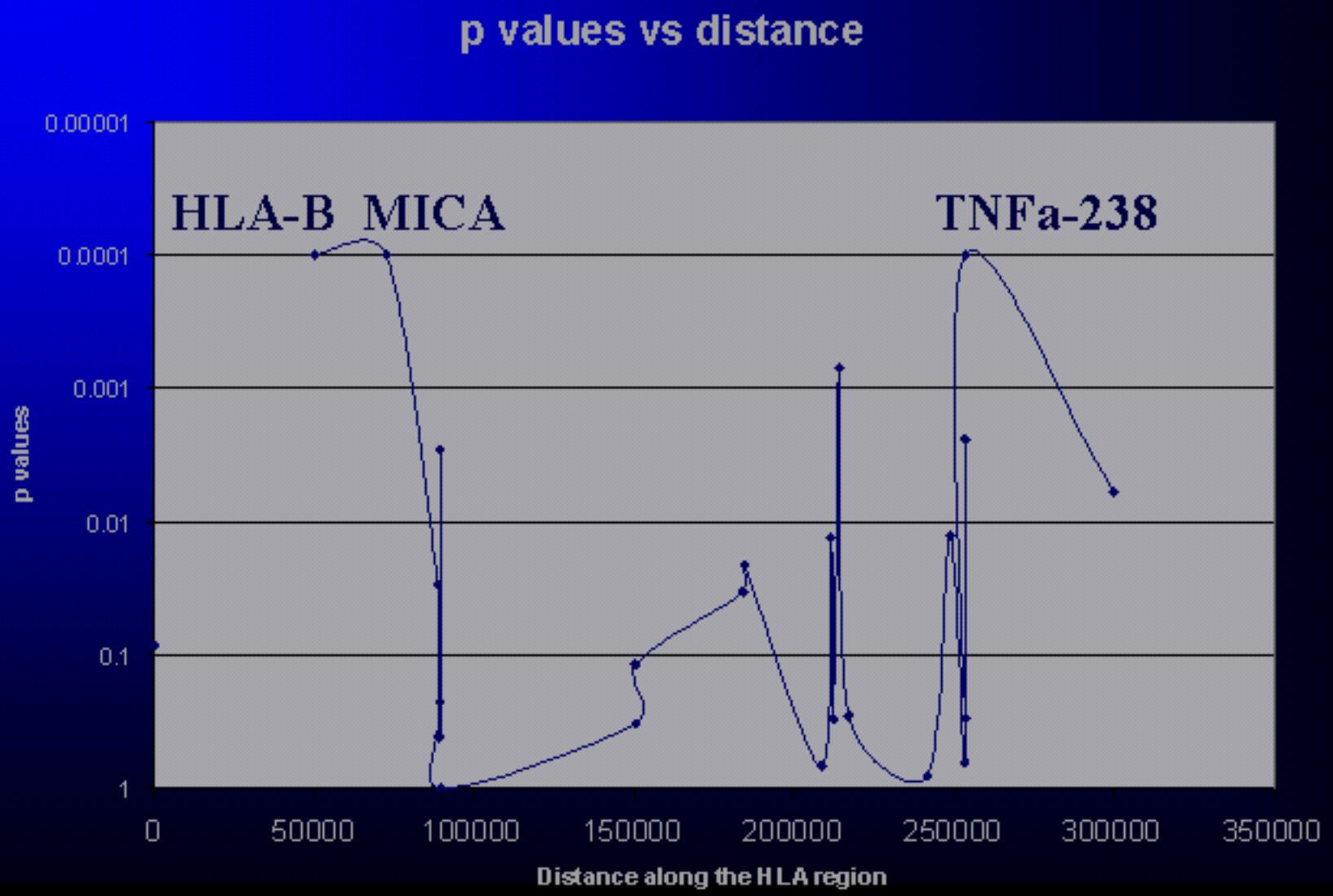
Abacavir Proof of Principle Timelines

Data Collection and Analysis	Collection of DNA samples	completed
	Candidate gene analysis	Lancet, March 2002
	Use of >200K SNP maps to analyse samples SNP Print^{sm}	March 2003 results
Development and Application	Development of a MRT Test	2003
	Registration and Clinical Use	2005

Two Candidate Genes ~ 150 Kb apart in ~/> LD bin



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Association of HLA-B57 and HSR

	Cases (n=84)	*Controls (n=113)*	
HLA-B57 Present	39 (46%)	4 (4%)	P<0.0001

The presence of HLA-B57 is more common in cases (46%) than controls (4%)
95% CI around the point estimate of .46 is (.31,.61)

TNFα G(-238)A Results

Genotype	*Case N=58*	*Controls N=93*	*p*
G,G	33 (57%)	92 (93%)	<0.0001
G,A	23 (40%)	6 (6%)	<0.0001
A,A	2 (3%)	1 (1%)	=0.1573

The presence of the A allele is more common in cases (43%) than controls (7%)

Hypersensitivity to abacavir data - independently confirmed

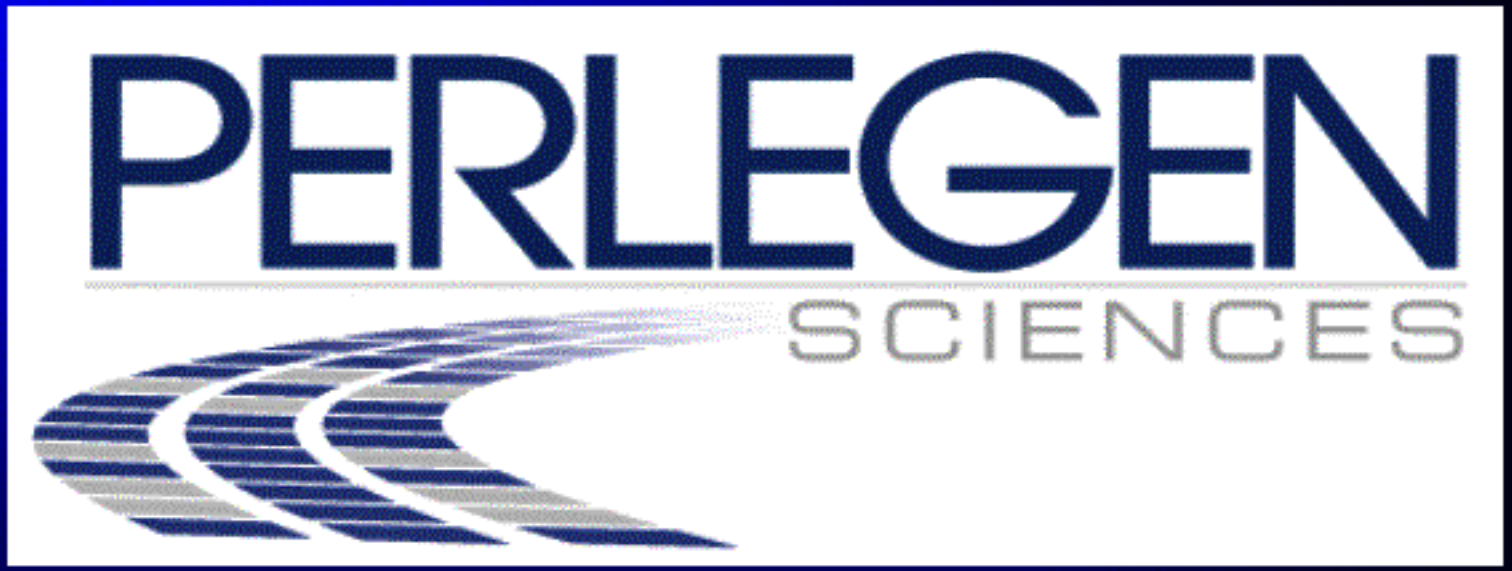
- UWA: Mallal et al., Lancet, [March 2002]
  - 57.1 haplotype, defined by the presence of HLA-B*5701 - DRB1*0701 - DQ3
    sensitivity to abacavir = **72%** [13/18 cases]

- GSK: Hetherington et al, Lancet, [March 2002]
  - Case control: HLA-B*5701was **55%** (36/65) - add DRB1*0701 - reduces sensitivity from **55% to 33%**

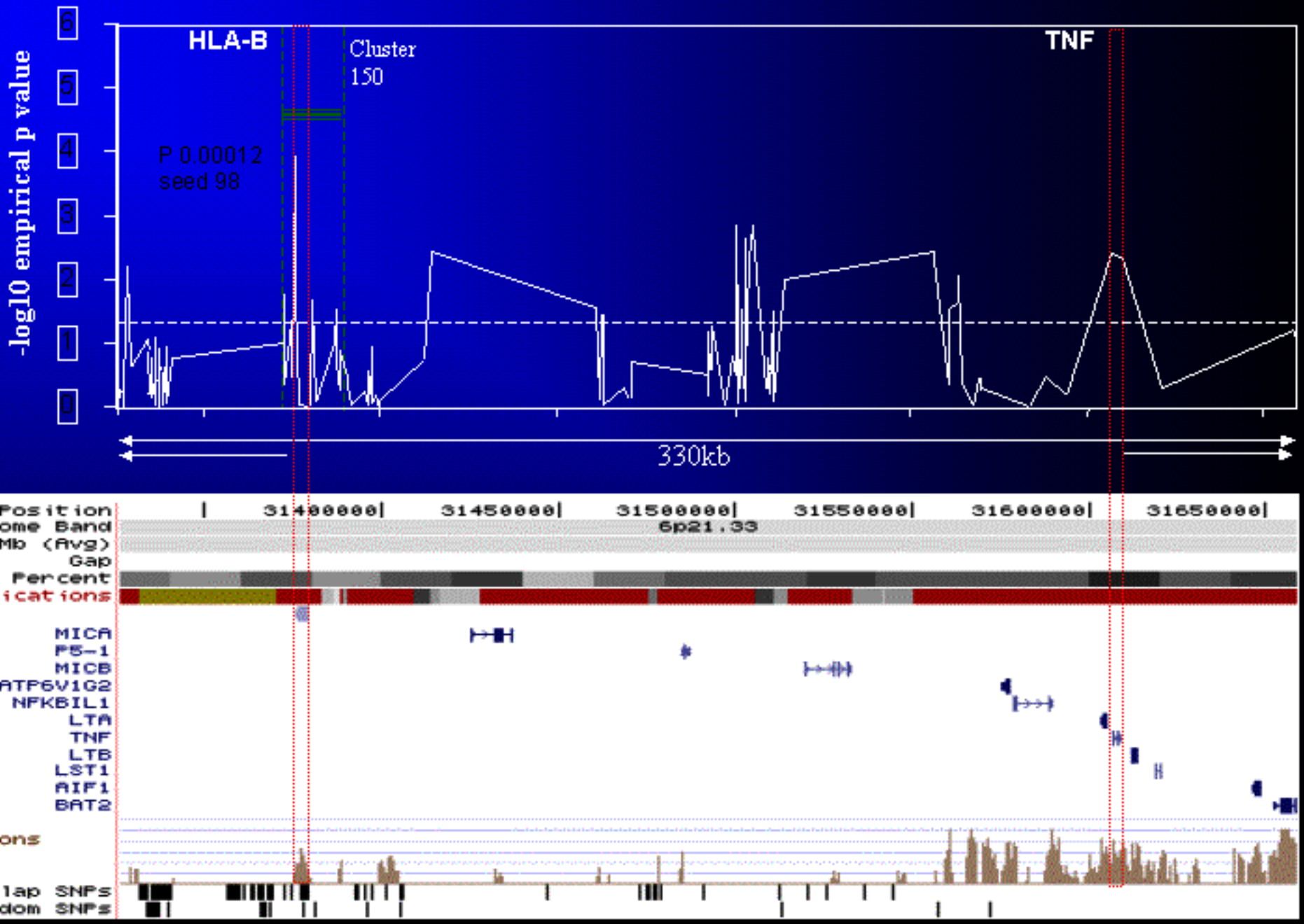
Is the association of HLA B-57 found in minority samples?

(CNA30032 Subjects: Summary of Allelic Test Results)

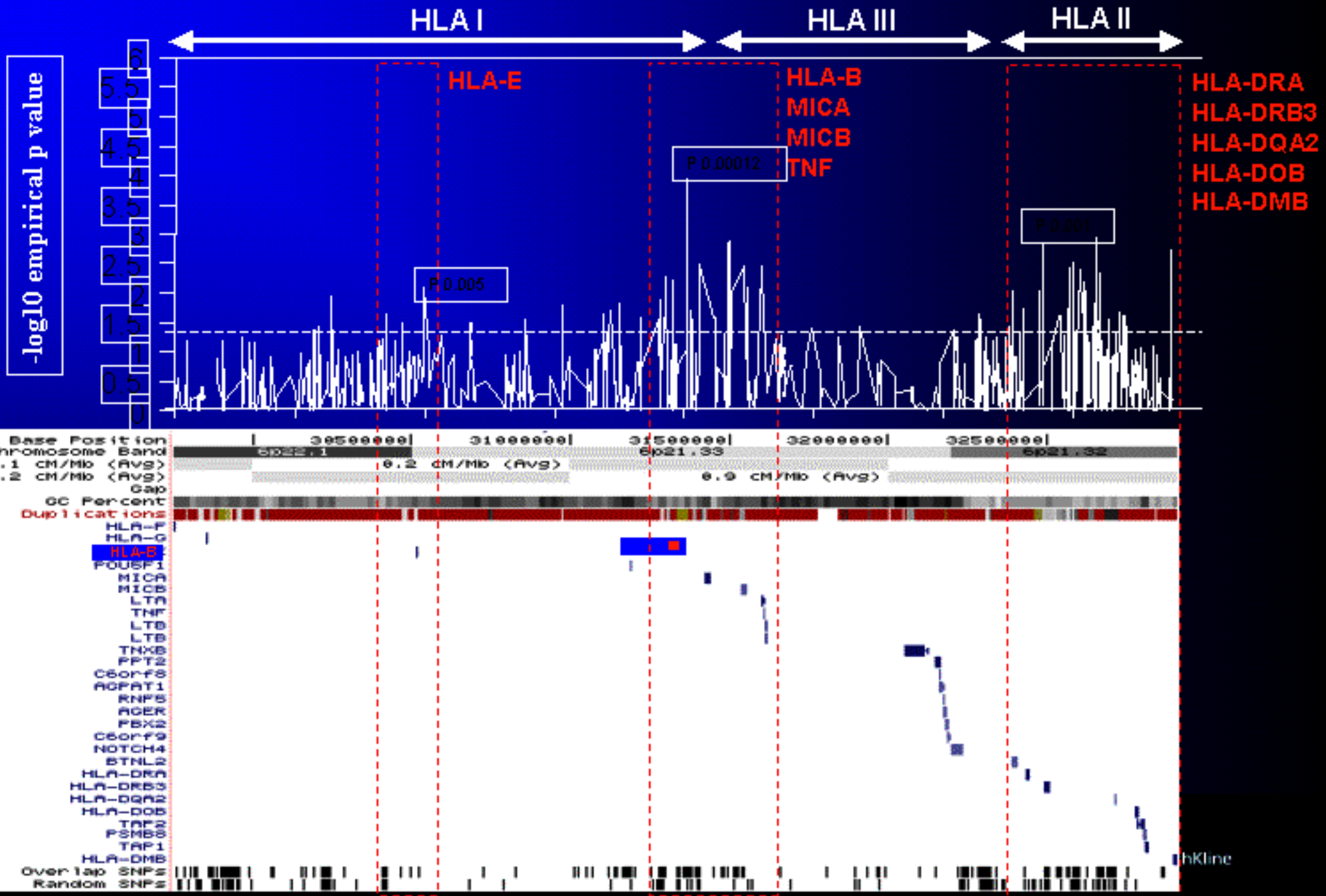
Ethnicity / Gender	Cases / Controls	Allele 57 Freq. Cases / Controls	Allelic Association p
All Ethnicities	165 / 139	17% / 2%	2.51×10^{-11}
Whites	82 / 74	23% / 1%	7.27×10^{-10}
White Males	56 / 52	23% / 1%	1.34×10^{-7}
White Females	26 / 22	23% / 2%	2.69×10^{-3}
Blacks	36 / 29	8% / 5%	0.07
Black Males	21 / 19	10% / 8%	1.00
Black Females	15 / 10	7% / 0%	0.51
Hispanics	43 / 27	11% / 0%	1.27×10^{-2}
Hispanic Males	32 / 21	9% / 0%	0.08
Hispanic Females	11 / 6	14% / 0%	0.54


PERLEGEN
SCIENCES

Perlegen empirical p values (-log10) across HLA-B and TNF region



Perlegen empirical p values (-log10) across the entire HLA region (HLA I, II & III)



Summary of Results for Drug B

	[*Abacavir HLA-B57*]	Chr 4 Drug B	Chr 3 Drug B	Chr 5 Drug B	Chr 18 Drug B
Allelic p-value	6.2×10^{-8}	7.2×10^{-8}	4.8×10^{-4}	4.5×10^{-4}	1.8×10^{-5}
Genotypic p-value	-	1.7×10^{-6}	9.8×10^{-4}	8.9×10^{-5}	4.9×10^{-5}
Sensitivity (%)	52	98	41	88	46
Specificity (%)	97	44	94	44	97
PPV (%)	46	9	26	8	42
NPV (%)	97	99.8	97	99	97

These are single marker analyses

Pharmacogenetics - efficacy profiles are distinct from safety profiles

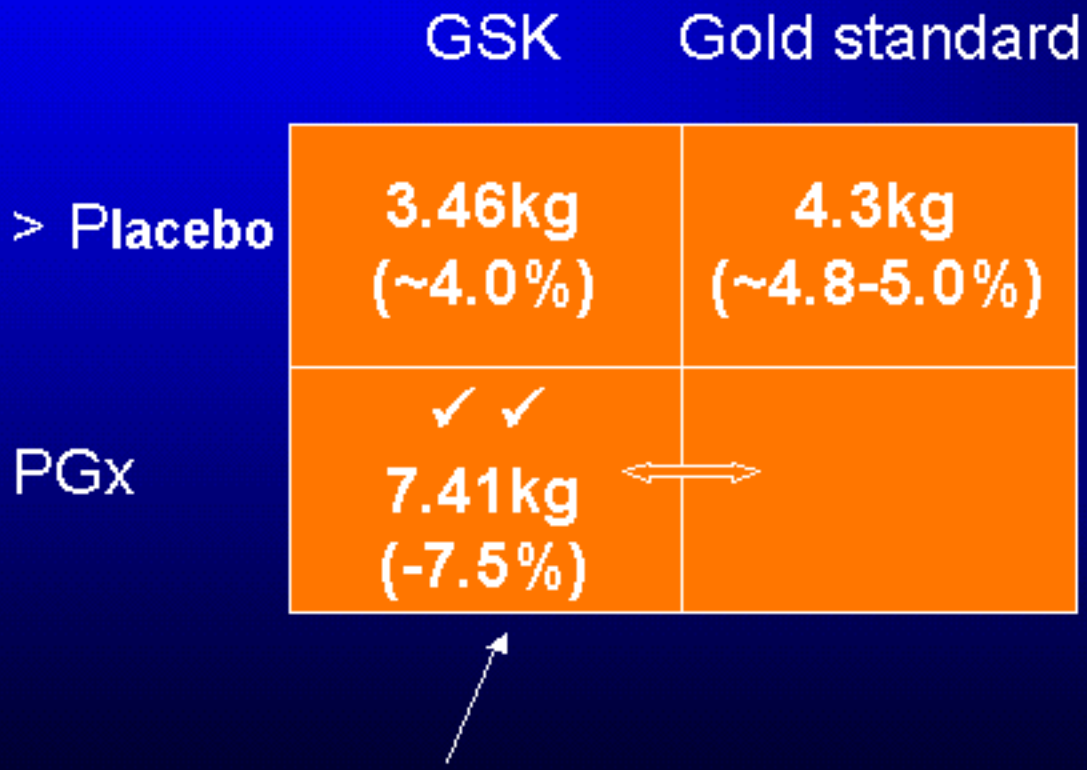
- Safety patients are highly selected from the population

  For adverse events, patients must receive the drug and developed a defined phenotype within a recognised time period. Phenocopies are rare, and NPVs must be high - "personalised"

- Efficacy patients are chosen from a general population by their disease indications

  Genetic profiles are less exact due to a gradient of therapeutic efficacy and placebo effects [phenocopies]. The population is segmented not individualised

GSK Molecule can have a Superior Product Profile



- Better than placebo
- Better than gold standard

PGx = 2X efficacy in 35% subjects, with CV effects better than gold standard

Pharmacogenetics - efficacy profiles are distinct from safety profiles

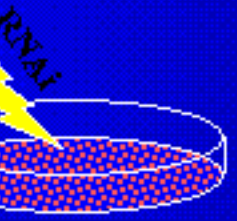
- The SNP profiles for drug efficacy will be quite distinct from the SNP profile for particular adverse events
- Defining efficacy predictors can be done in Phase II and tested in Phase III
- AEs are a numbers game, and standardised post-marketing surveillance would be much more effective than current reliance on clinical development programs [250,000 patients versus 10,000 patients]

Why Expression Proteomics?

Same Genome,

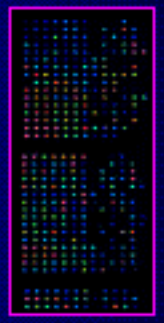
Different Proteome

Genomic and Proteomic Sciences



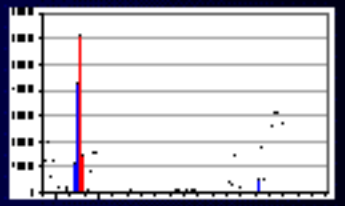
Gene Interference

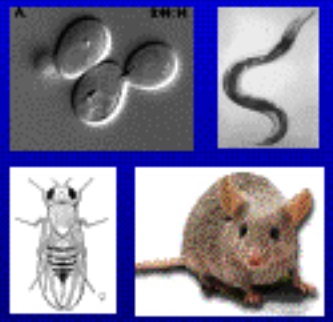
Gene Cloning



Transcriptome Analysis

Quantitative Expression



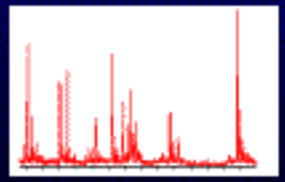


Comparative Genomics

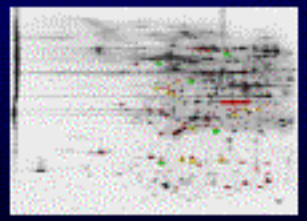
Genome
Proteome

Genomic Histology

Pathway Discovery



Proteomic Technologies



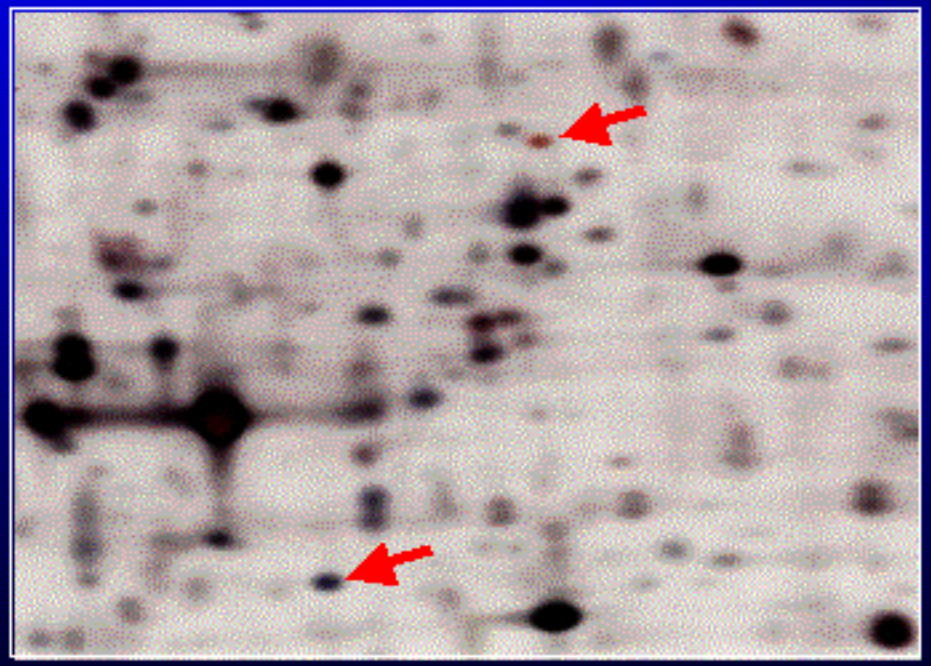
Expression Proteomics

Highly specialized platform technologies (genome-wide scale)

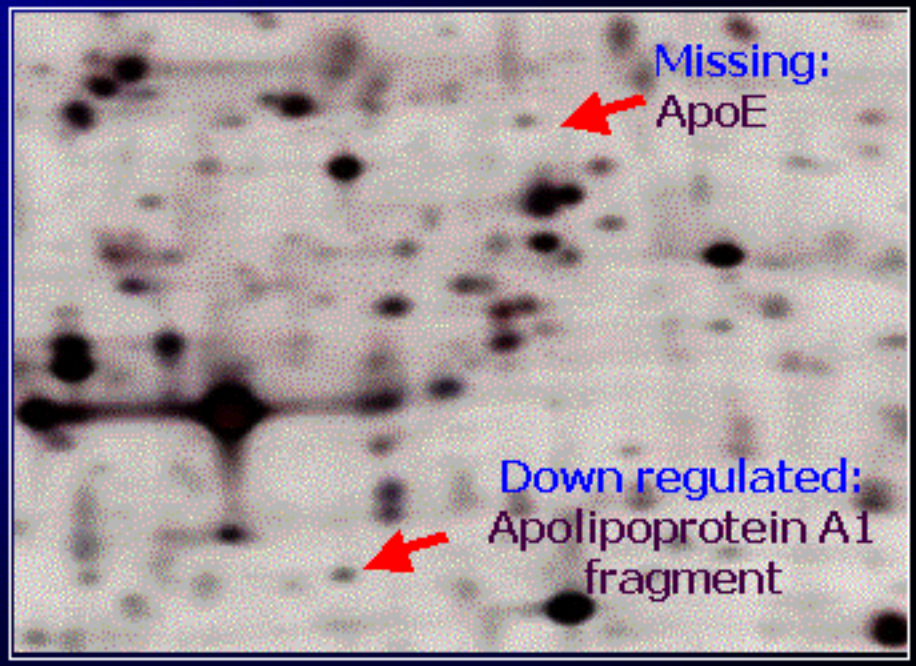
Expression Profiling

Expression Proteomics

Differential expression of proteins in ApoE KO and wild type mice



Wild type



ApoE knockout

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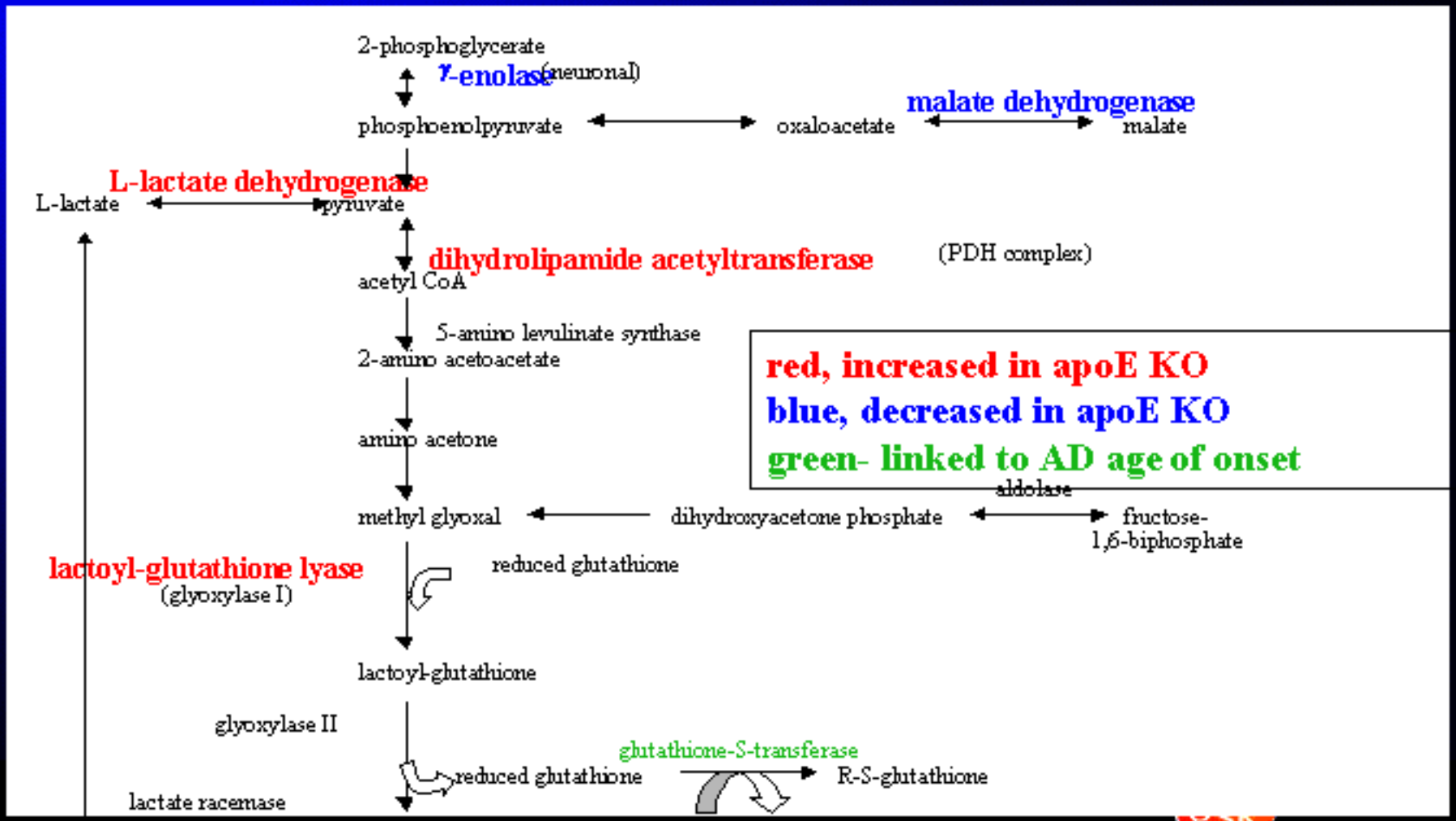
ApoE Expression Proteomics

Absence of apoE affects abundance of enzymes involved in glucose metabolism and bioenergetics



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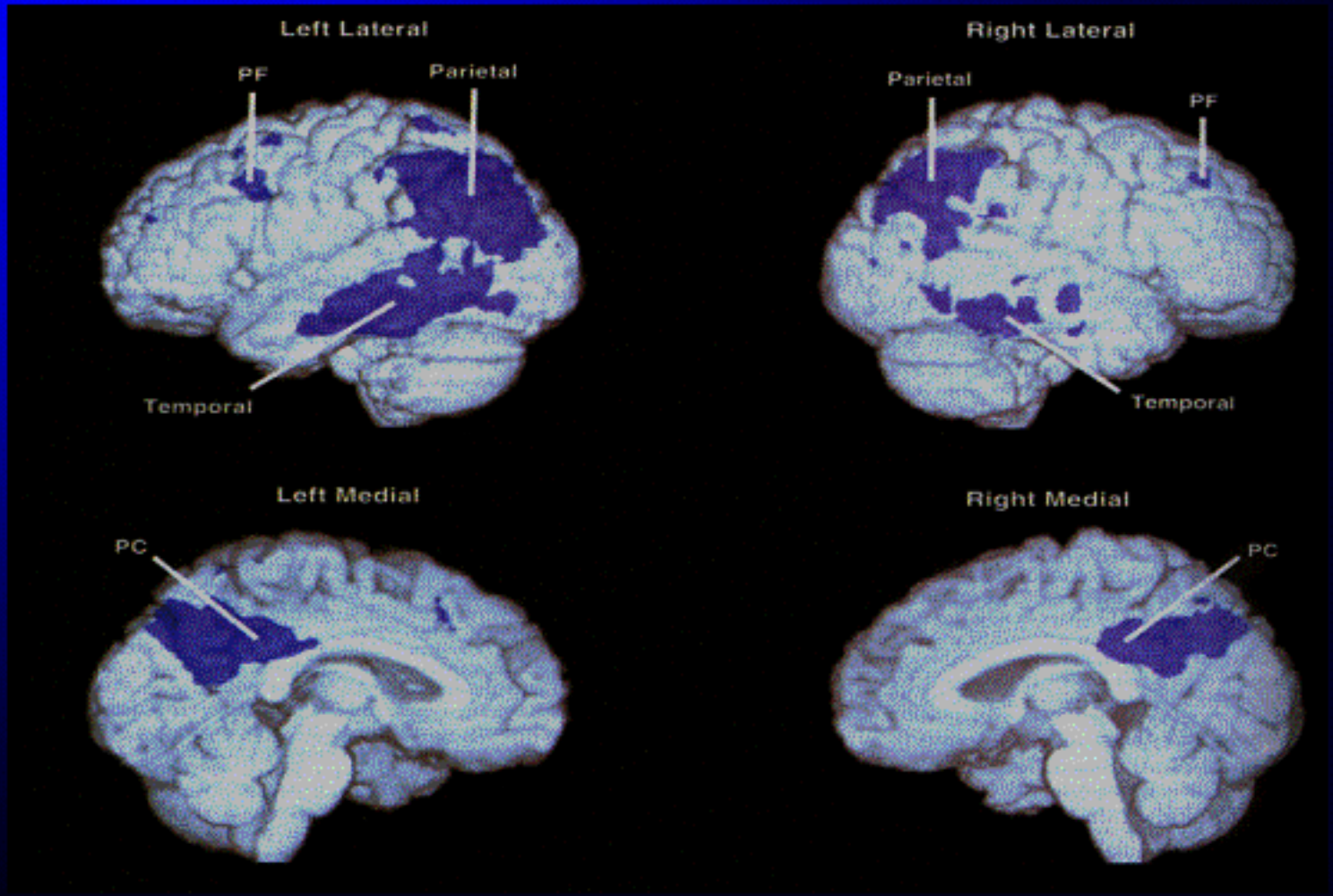
Symptomatic Alzheimer Disease



Source: Reiman et al NEJM 334 p752

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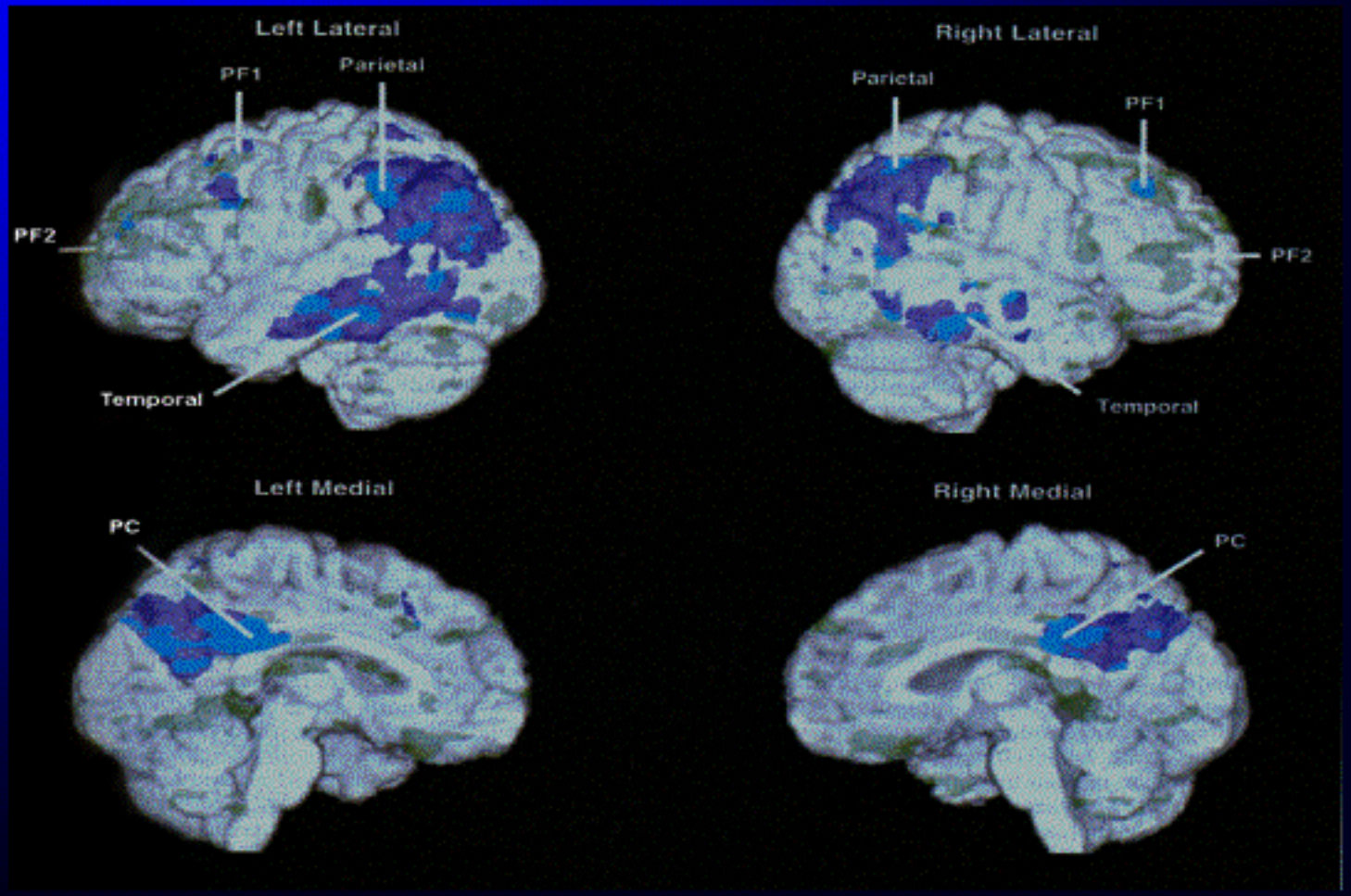
APOE4 Homozygotes



Source: Reiman et al NEJM 334 p752

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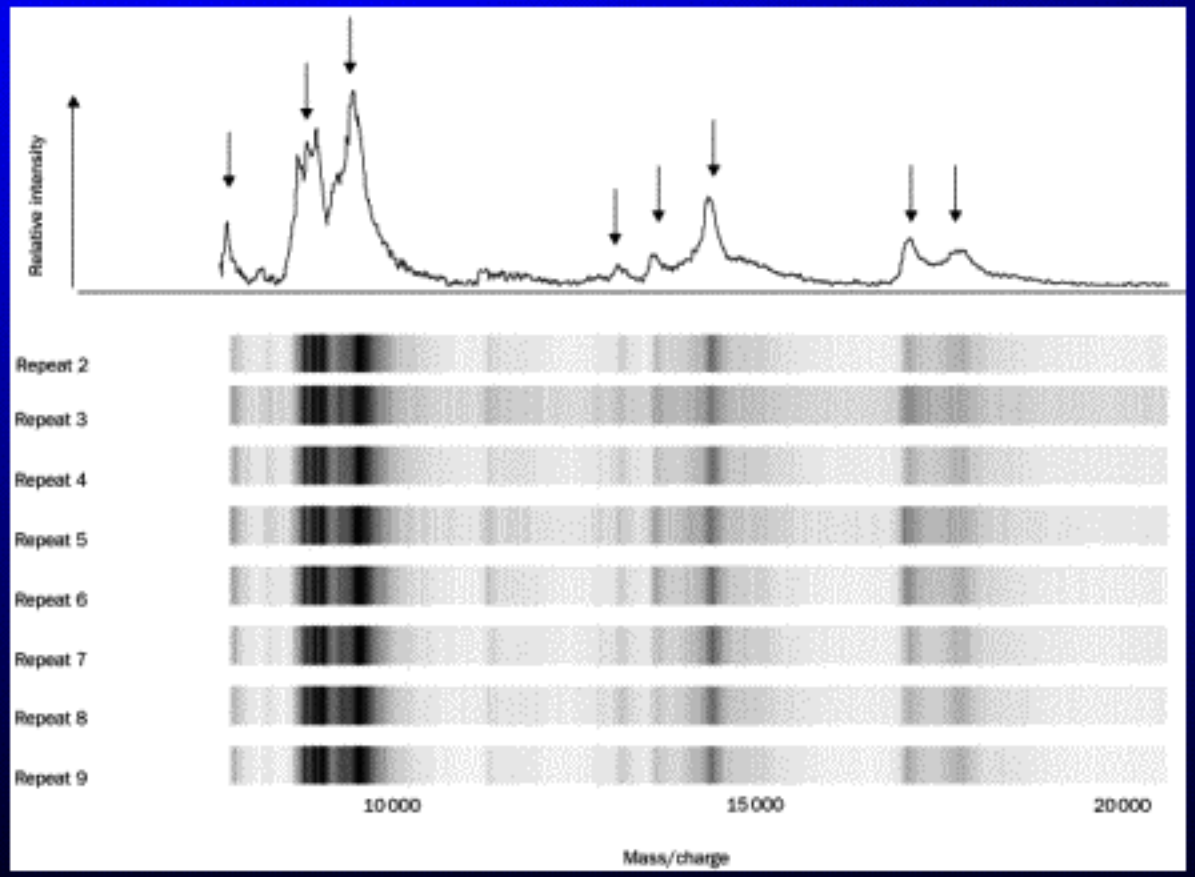
Proteomics pattern of serum for ovarian Ca



- Petricoin et al., Lancet 359, 572, Feb 16,2002
- Between-chip reproducibility of mass spectra, can normalize peak amplitudes
- For genome SNP profiles [SNP Prints^{sm}], can plot phenotype-control associations along the genome using similar cluster analyses

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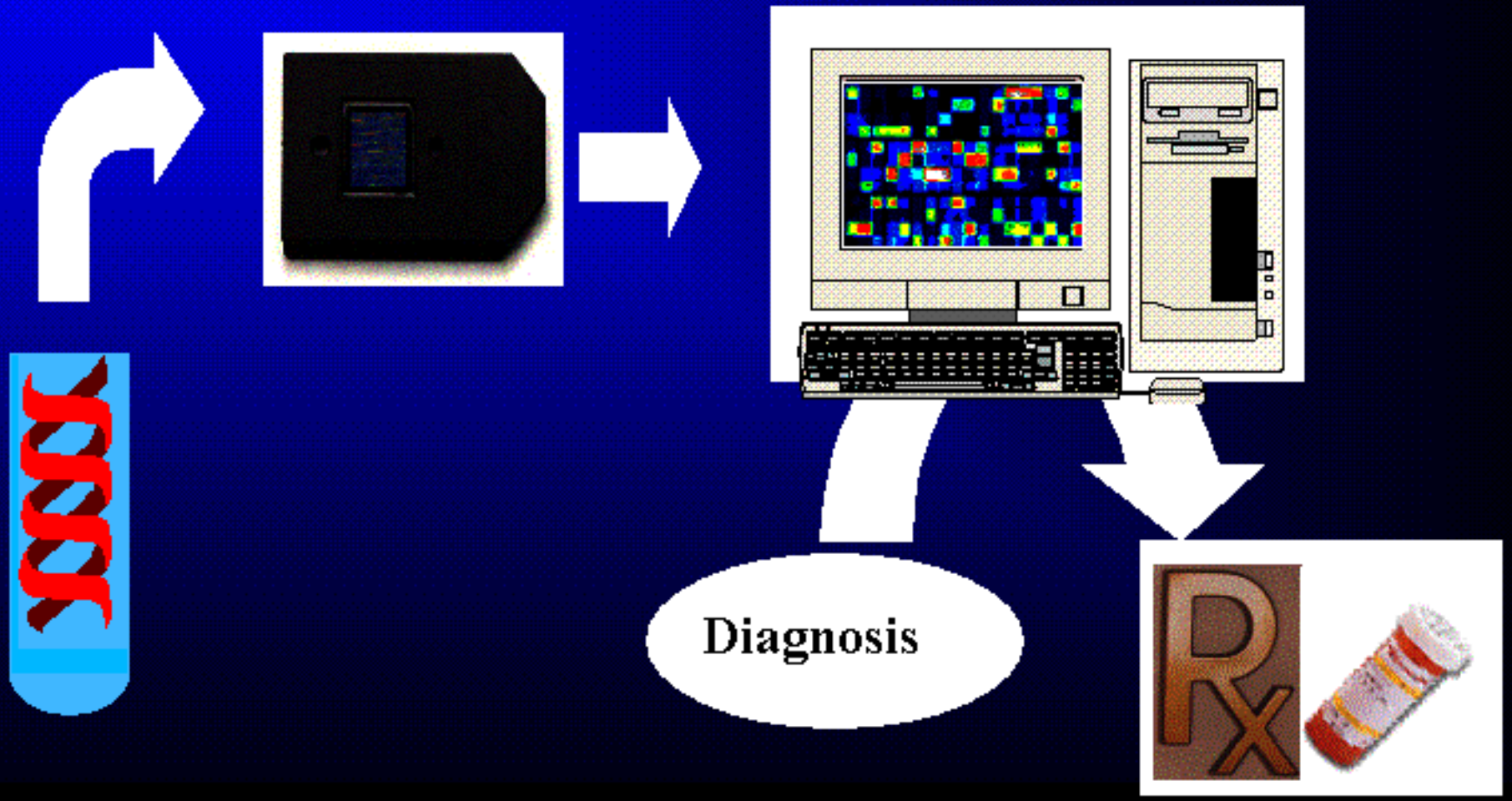
Use of SNP Medicine Response Profiles to Deliver Right Medicine to Right Patient



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Acknowledgements

GSK R & D Executive Board

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All the Drug Discovery and Clinical Development (including Regulatory) Teams