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FDA Centers of Excellence for Regulatory Science

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What is needed in regulatory [genomic] science?

Defined as "to enhance product development" by:

1) Minimizing likelihood for imperfect data (IND)

2) Analyzing and interpreting data in regulatory submissions (NDA, BLA)

- *** Consider all products of the genome**
- *** Consider all genomes**
- *** Integrative biology**
- *** Constructive pharmacology**
- *** Translational analyses**

Pharmacogenetics and Outcome Studies: FDA Division Reviewer Issues

- Retrospective vs. prospective
- Efficacy vs. safety
- Agnostic vs. hypothesis-driven
- Clinical validity + epidemiological strength
  - Stats and magnitude
  - Replication
  - Biological gradient
  - Biologically plausible
  - Supported by analogy and cohesion
- Experimentally supported

FDA Science and Mission at Risk, 2007

- **The FDA Science Board review of Science and Technology at FDA found that the FDA mission was at risk for the following key reasons:**
  - **The FDA scientific base has eroded and its scientific organizational structure is weak at a time when there have been major scientific advances and when new products and technologies under the regulatory authority are more scientifically complex.**
  - **The FDA scientific workforce does not have sufficient capacity and capability.**
  - **The FDA information technology (IT) infrastructure to support the scientific base is inadequate.**

Regulatory authority of new products and technologies are more scientifically complex.

- IT infrastructure can be improved $$$$
- Technologies can be bought if necessary $$
- Scientific expertise needs to be readily available to FDA Review Teams: $$
  - Safety - urgently requires a sane and accurate system
  - Efficacy – no longer “one shoe fits all”
  - Efficacy Pharmacogenetics - In cancer, but beginning in other complex diseases
- Regulatory science depends on genetic diagnostics, with clearly defined clinical parameters, reproducible methodologies, and an over-riding concern for safety and efficacy of products
- It is not exploratory discovery or methods development

FDA Centers of Excellence: "Genomics" or "Genetics"

- **Example: Differences between genomic associations and individual diagnostics**
  - **Much attention and academic publication concerns genome-wide associations. GWAS was developed initially [SNP Consortium 1998] to localize disease gene locations across the genome**
  - **BUT NO ONE INHERITS a DOUBLE STRANDED DNA BLOCK of DNA**
  - **Every individual inherits a single strand from each parent**
  - **Current technology and academic publications emphasize associations – not individuals**
  - **Regulatory science focuses on the individuals genetics for predictive data, not the genome association structures**

Vaccines: A clear clinical victory for products based on "last-generation" sequencing

- **Both annual flu vaccines and HIV mutations affecting drug response are two well-established examples**
- **Mutations in flu virus sequence are found by sequencing laboratories that are testing isolates throughout the world every year: these are used for vaccine production**
- **The analyses are known as phylogenetic mapping with well established technologies for accurate "diagnosis" of new sequence mutations**
- **The application of phylogenetic mapping is not a population screening exercise but is defined by mutation analyses of DNA strands at specific sites.**

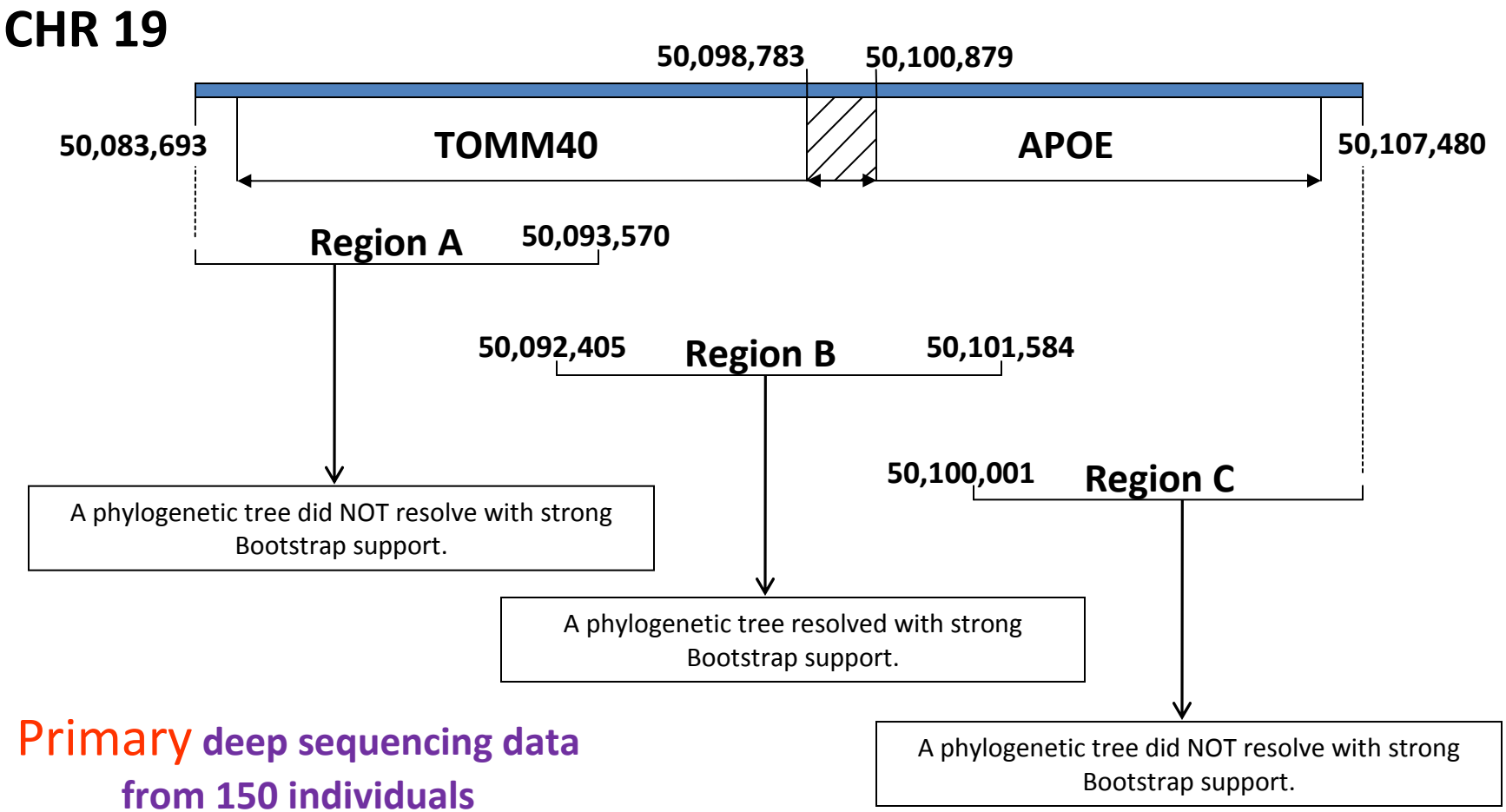
AD - two biologically interactive relevant genes in LD

APOE isoforms and tomm40 channels

GWAS: **3 of the top 4 SNPs are *TOMM40***

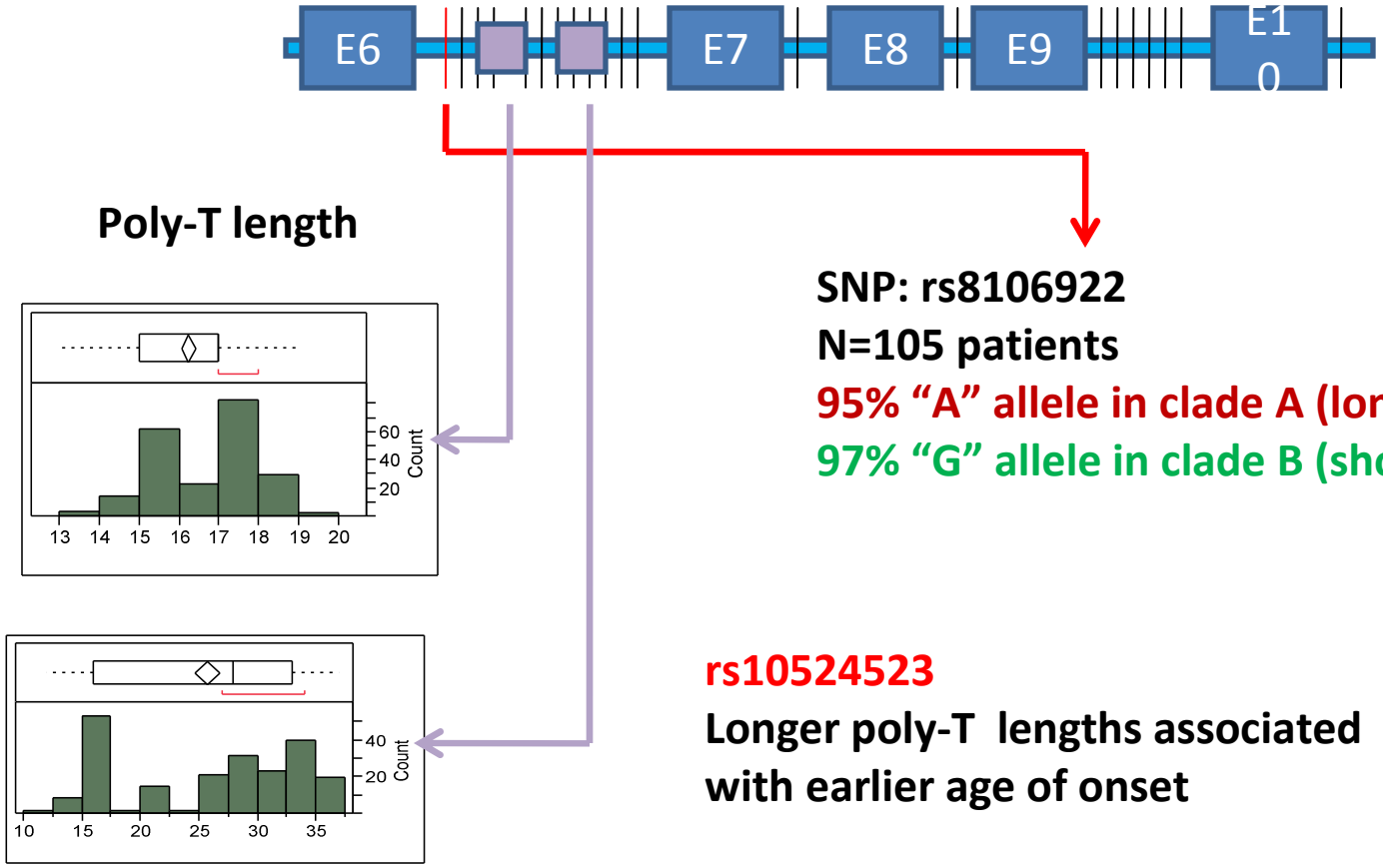
SNP	Gene [closest RefSeq]	Location	P value
rs2075650	**TOMM40**	Intron	1.8E**-157**
rs157580	**TOMM40**	Intron	9.6E**-54**
rs6859	**PVRL2**	3’ UTR	6.9E**-41**
rs106922	**TOMM40**	**Intron**	5.4E**-39**
rs405508	**APOE**	5’ non-coding	4.9E-**37**
rs11136000	**CLU**	Intron	1.2E**-9**
rs3851179	**PICAM**	5’	1.9E**-8**

Regions Studied for Phylogenetic Analysis



Primary **deep sequencing data from 150 individuals (cases and controls)**

SNP and structural variants are prevalent in regions of the *TOMM40* gene



SNP: rs8106922

N=105 patients

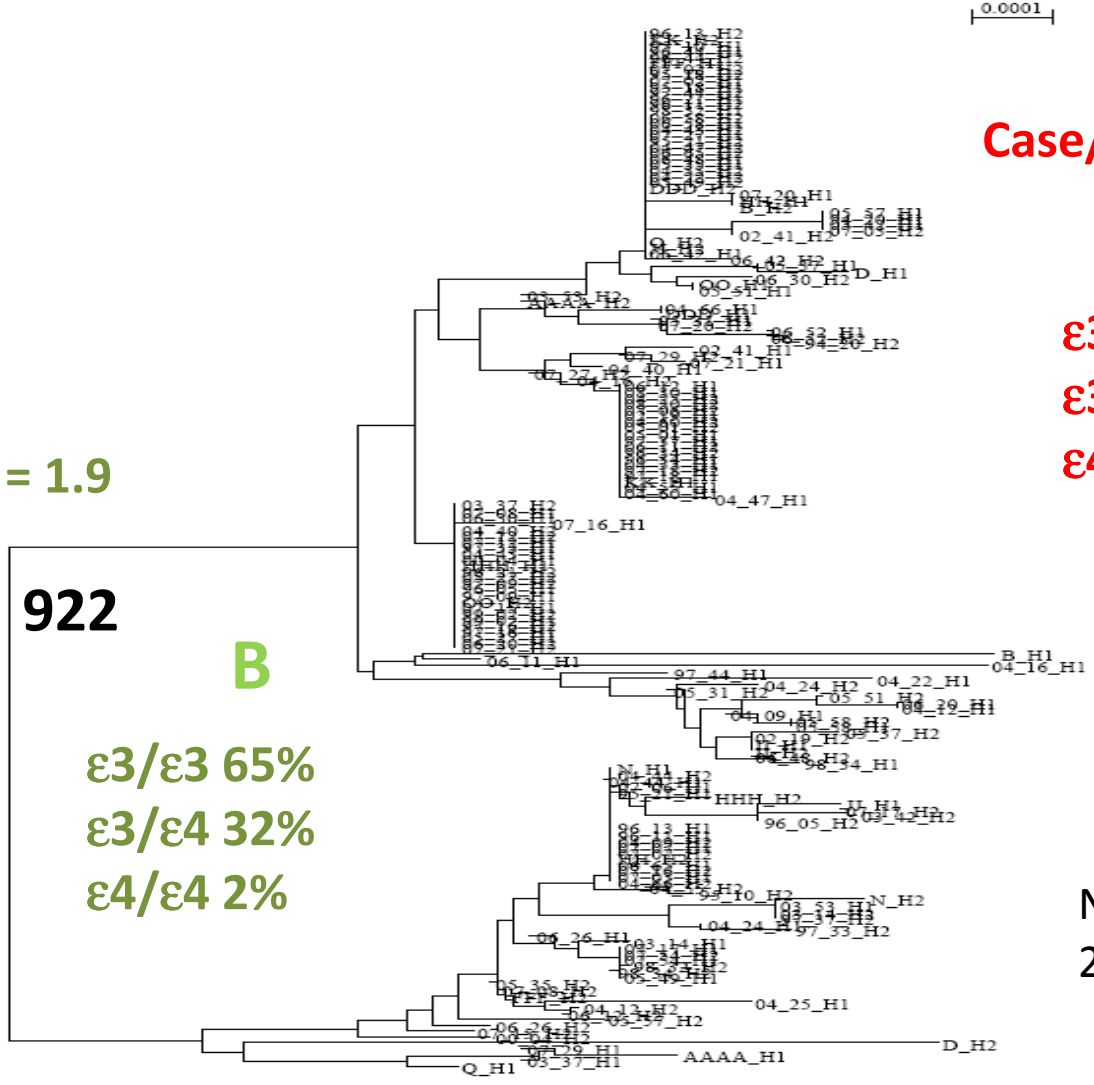
95% "A" allele in clade A (long)

97% "G" allele in clade B (short)

rs10524523

Longer poly-T lengths associated with earlier age of onset

Phylogenetic Analysis of 10Kb Region of *TOMM40* – *uses all the individual strand sequence variants*



Case/Control = 1.9

Case/Control = 2.7

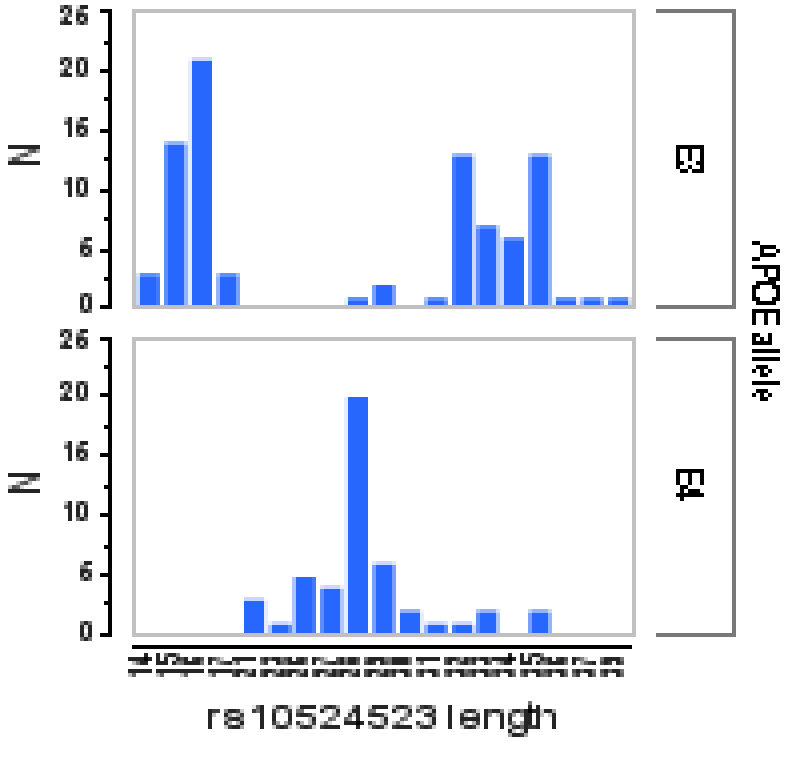
A

ε3/ε3 38%
ε3/ε4 38%
ε4/ε4 24%

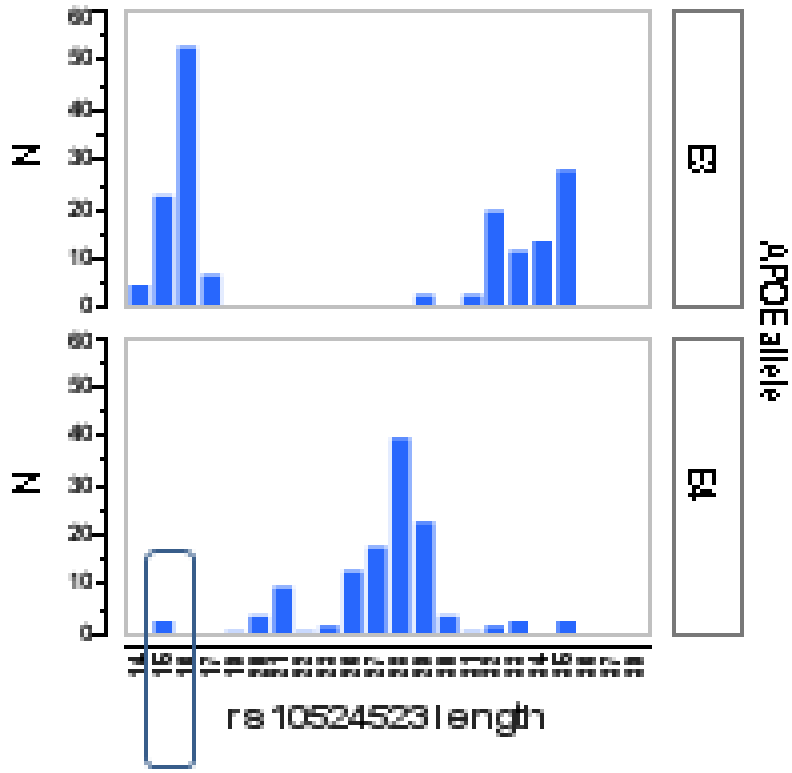
N = 105 patients,
210 haplotypes

Comparison of Arizona and Canada series

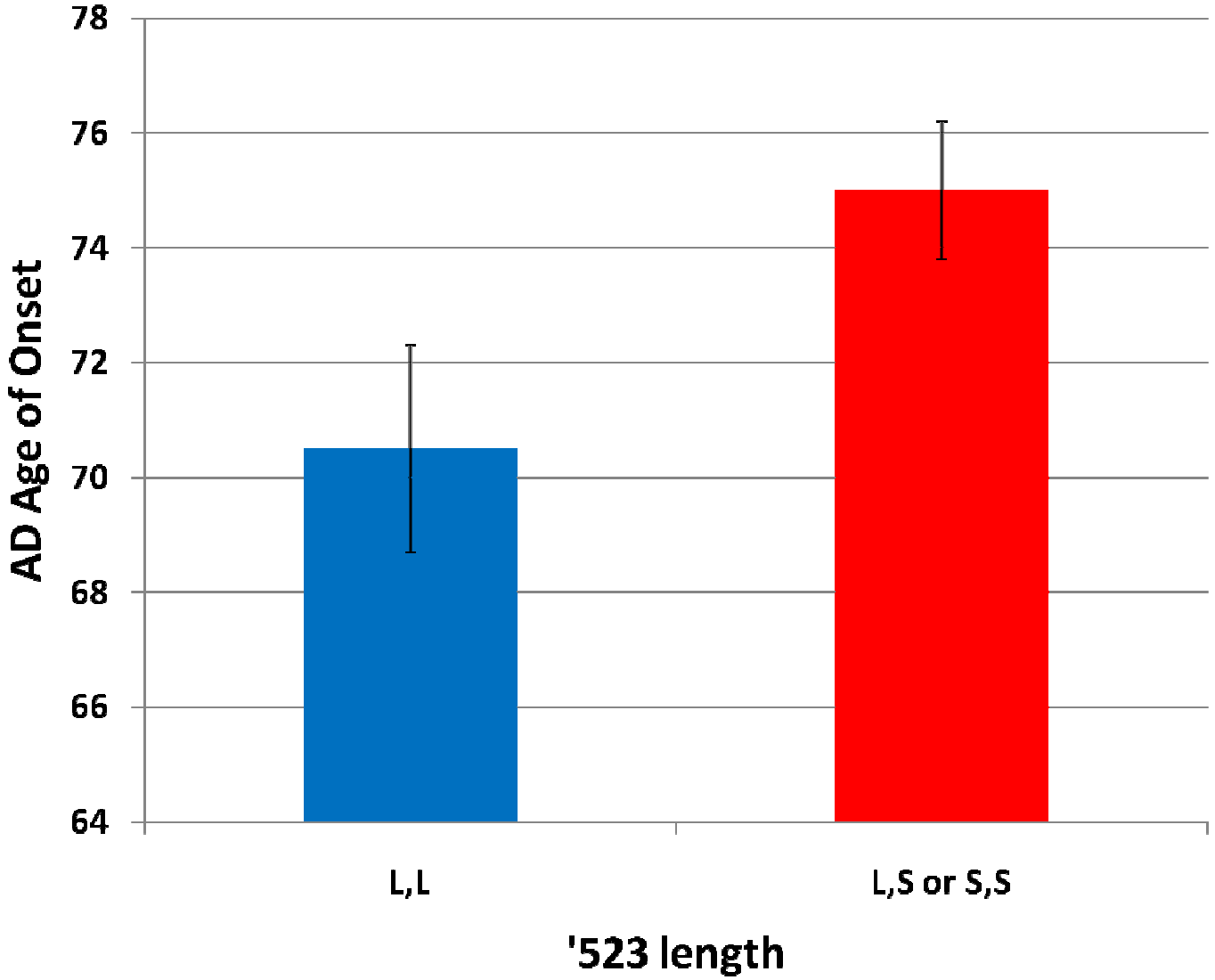
Frequency of TOMM40 poly-T repeats in APOE E3 and APOE E4 in patients and controls on the same DNA strand [Arizona series]



Frequency of TOMM40 poly-T repeats in APOE E3 and APOE E4 in patients and controls on the same DNA strand [Canadian series]

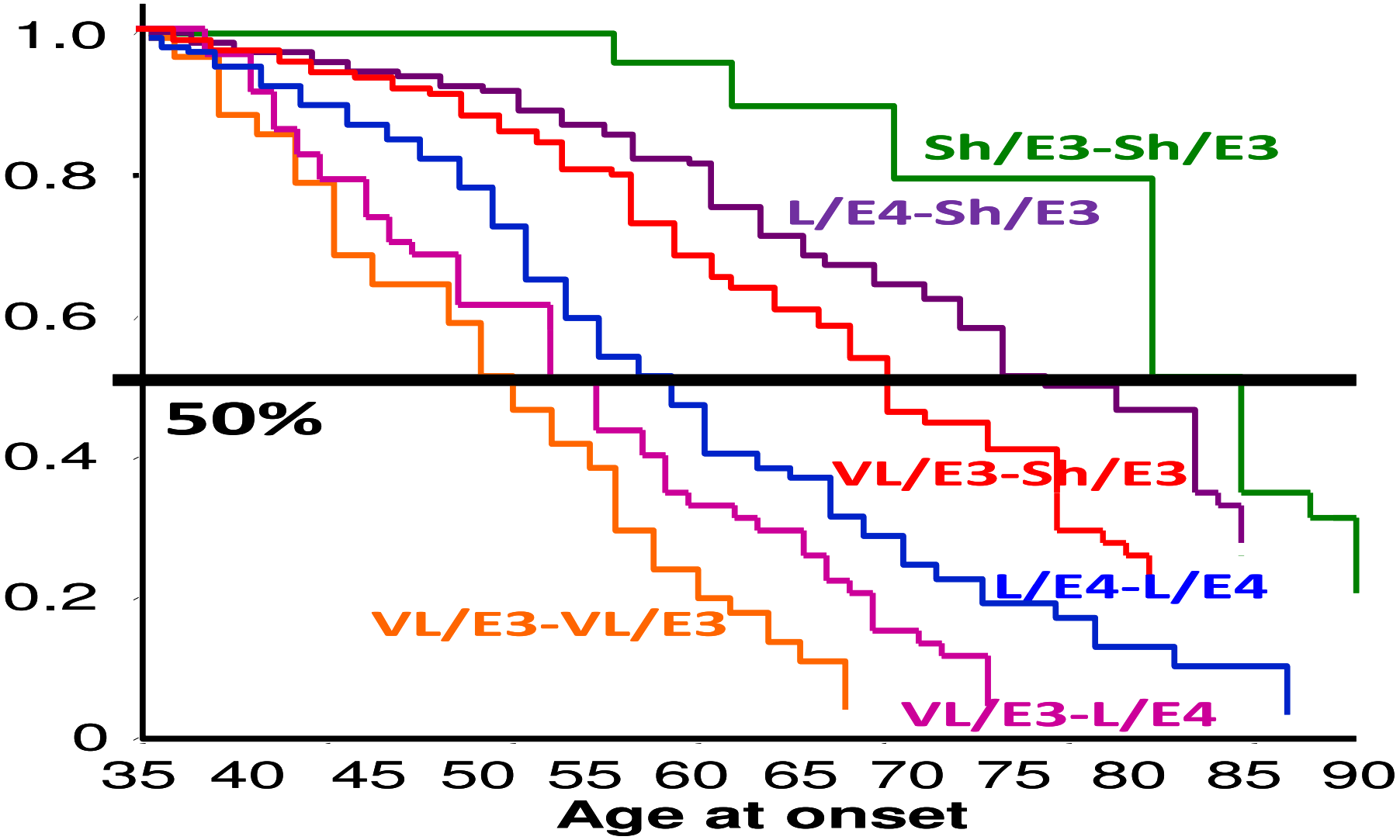


All AD patients, all APOE3 and APOE4 alleles, Arizona cohort
N = 65 p < 0.03

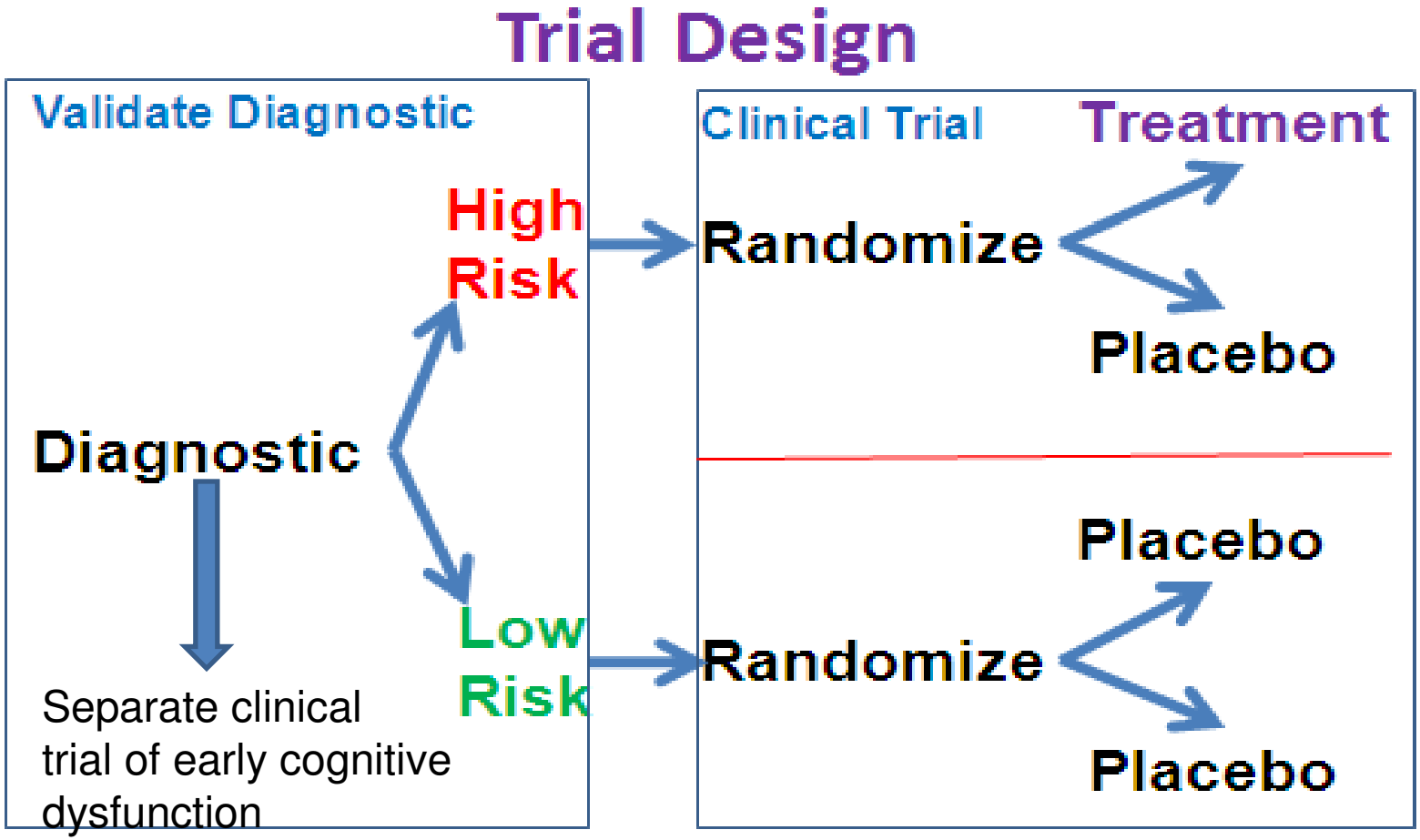


Hypothetical “523” age of onset distribution

Accuracy for 523 with APOE3 equivalent to that accepted for APOE4/4



FDA Voluntary Exploratory Data Submission - concluded on 7 October 2009



Conclusions

- **FDA VxDS works – here were data addressed for regulatory purposes for a year before publication, and ?? years before academic acceptance**
- **The FDA needs to be able to contract for timely regulatory sciences, and thus have the expertise for due diligence and an efficient support mechanism.**
- **The structure of academic FDA-supported Centers should not duplicate NIH Translational Centers, but be directly and efficiently responsive to the needs of the FDA reviewers, regulatory emergencies, and the mission of safety and efficacy.**
- **The FDA's mission is not that of the NIH – by statute.**