Improving Translation Research Pipeline pharmacogenetics

Where we are and what works

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GSK Genetics Research

OECD, Rome, 17 October 2005

“Personalised medicines show promise but they have undoubtedly been over-hyped……it will be at least 15-20 years before a patient’s genetic make-up is a major factor in determining which drugs are prescribed”

Sir David Weatherall commenting on the Royal Society Report ‘Personalized medicines: hopes and realities’BBC September 21, 2005


Daily Mail, Monday, December 8, 2003

Most drugs are a waste of time admits scientist

MOST prescription drugs do not actually work on the people that take them, a top drugs company boss has admitted.

By Richard Sparham

'Pioneer of a new culture'

Glaxo Chief: Our Drugs Do Not Work on Most Patients

by Steve Connor (originally appeared 8 Dec 2003 in The Independent)

We all get misquoted out of context.

Overview of presentation

- What GSK does in 2005
- Safety [AE] genetics during the blinded period of Phase III

  – subsequent confirmation when trial blind is broken
- SAE during clinical development in a small number of subjects to determine diagnostic genetic profiles
- Rare SAE during early development – single case diagnostic
- Efficacy hypothesis generation during a Phase IIA study {80 patients}
- Phase IIB efficacy confirmation {~500 patients}
- Comment on dire predictions of the pharmacogenetic future in official reports

Overview of PGx at GSK in 2005

- Default, consented DNA collection and extraction in all Phase I,II and III trials
- Selective collection of other tissues [plasma, serum, urine, etc.] and imaging phenotypes for biomarker studies – a holistic approach
- Identification of PGx opportunities (efficacy and safety) through interactions of Clinical Project Teams with physicians-scientists in Genetics Research

Adverse event profiles in clinical development and surveillance

- AEs are a classic example of environmental interaction with an individual's genetic make-up
- To experience an AE, patient must receive the drug and develop a defined phenotype within a recognized time period
- AEs are personal: "Will I get an adverse event?"

PRESTO Trial-Example of prospective AE PGx during Phase III

- Double-blind placebo trial of 11,500 patients
- 4% of patients in the trial developed hyperbilirubinemia
- During the trial, an association study using candidate genes identified the “7” polymorphism as associated with hyperbilirubinemia. When blinded trial was opened, only 7/7s who received the drug had hyperbilirubinemia.
- Associations can be done during a trial, with segregation of genetic alleles with the AE phenotype available after the code for the double-blind trial is broken.

How few patients does it take to recognize a SNP profile related to an AE during drug development ?

- Mathematical analysis reflects taxonomy principles
- Also highly dependent on the number and the ethnicity of “controls”
- Theoretical analyses suggest that differences in SNP LD patterns can be “diagnosed” *prospectively* with as few as 10-20 patients

Can Safety SNP profiles be identified during trials using as few as 10-20 AE patients? Yes

- 4 SNPs flanking UTP1A1 "6-7 repeat" locus of tranilast hyperbilirubinemia
- Cases from tranilast clinical trial (US Caucasian)
- 3,000 White controls from Aberdeen UK (Caucasian)

Approx # cases	Approx # random controls	SNP poly ID 4082379	3729885	3730948	3737550
10	3000	0.10392	0.01542	0.04623	0.00644
20	3000	0.00143	4.37E-6	0.00014	9.96E-8
30	3000	3.93E-6	2.91E-7	4.14E-5	5.59E-9
50	3000	8.69E-8	7.39E-08	2.47E-5	1.32E-10
100	3000	1.80E-10	3.87E-13	1.24E-8	9.12E-16
120	3000	9.21E-11	1.91E-15	3.26E-10	2.21E-18
146	3000	2.56E-13	2.70E-18	6.10E-13	4.53E-23

What about rare SAEs in early phase studies?

- With a single **severe adverse event** that happened to occur in early development, can genomic methods be used for an accurate "diagnosis?"

- Example: With an early drug asset, a single case of severe hepatotoxicity with elevated bilirubin occurrs, threatening the program - as would occur in major programs

Recognising rare SAEs early in development

- The background science of the drug target and metabolism can suggest several “candidate” hypotheses for hepatitis:
  - Example: a clinical association of hyperbilirubinemic hepatotoxicity with patients who were heterozygous for a rare specific receptor mutation – “beta 13”
  - There were also transgenic animal experiments to confirm an association of this mutation with hepatotoxicity

Recognising rare SAEs early in development

- DNA had already been obtained with informed consent, for pharmacogenetics
- The patient's extracted DNA had been stored [PGX default] and available within days.
- Sequencing of the patient's DNA for this gene, as well as other candidate genes, was performed within a week.
- Diagnostic microarray 384-well plates for hepatocellular toxicity, neuropathy, cardiomyopathy, etc., can be designed and ready – validation by sequencing

Another example:
"Drug C" Side effects – not severe AEs
Early diarrhea and mild rash

- Studied in Phase I subjects and early Phase II patients
- Approximately 15% of 107 treated subjects and patients had side-effects
- Two Phase I volunteers and one Phase IIA patient withdrew from the study due to severe diarrhea

"Drug C" Metabolism

- Preclinical *in vitro* studies show that "drug C" is metabolized predominately by
  - CYP3A4 and CYP3A5
  - and to a lesser extent by CYP2C19
- *In vitro* data suggests that "drug C" interacts with MDR1 (ABCB1) and BCRP (ABCG2)

SNP Coverage per Candidate Gene

Gene	Number of SNPs genotyped within 10 kb of gene	Size of gene (kb)	Avg spacing between SNPs (kb)	Largest gap between SNPs (kb)
ABCG2	45	66.9	1.5	7.5
ABCB1	117	209.6	1.8	13.7
CYP2C19	**57**	**90.2**	**1.6**	**18.3**
CYP3A4	5	27.2	5.4	11.2
CYP3A5	22	31.8	1.4	9.9

Summary of Significant Results

- Association was observed between SNPs in CYP2C19 with rash and diarrhea
- No compelling evidence for association was observed in ABCG2, CYP3A4 or CYP3A5.
- 22 SNPs within the CYP2C19 gene showed association ($p<0.01$) with incidence of rash and 6 of these SNPs showed association ($p<0.01$) with incidence of diarrhea.
- CYP2C19 *2/*2 genotypic p-value was p=0.001 for diarrhea and p=0.0016 for rash.
- 3 of 3 subjects homozygous for CYP2C19*2 had rash and diarrhea (2 healthy volunteers, one patient) and had discontinued the medicine
- Magnitude of association and clinical significance to be determined in follow-up studies.

Immediate future

- In house 500k SNP chip scans for whole blood DNA
- In house tissue expression profiles of microRNA
- In house tissue messenger RNA [mRNA] transcriptomics
- Next steps will prepare GSK for “instant analyses for any AEs or efficacy profiles for current and future “drug C” trials

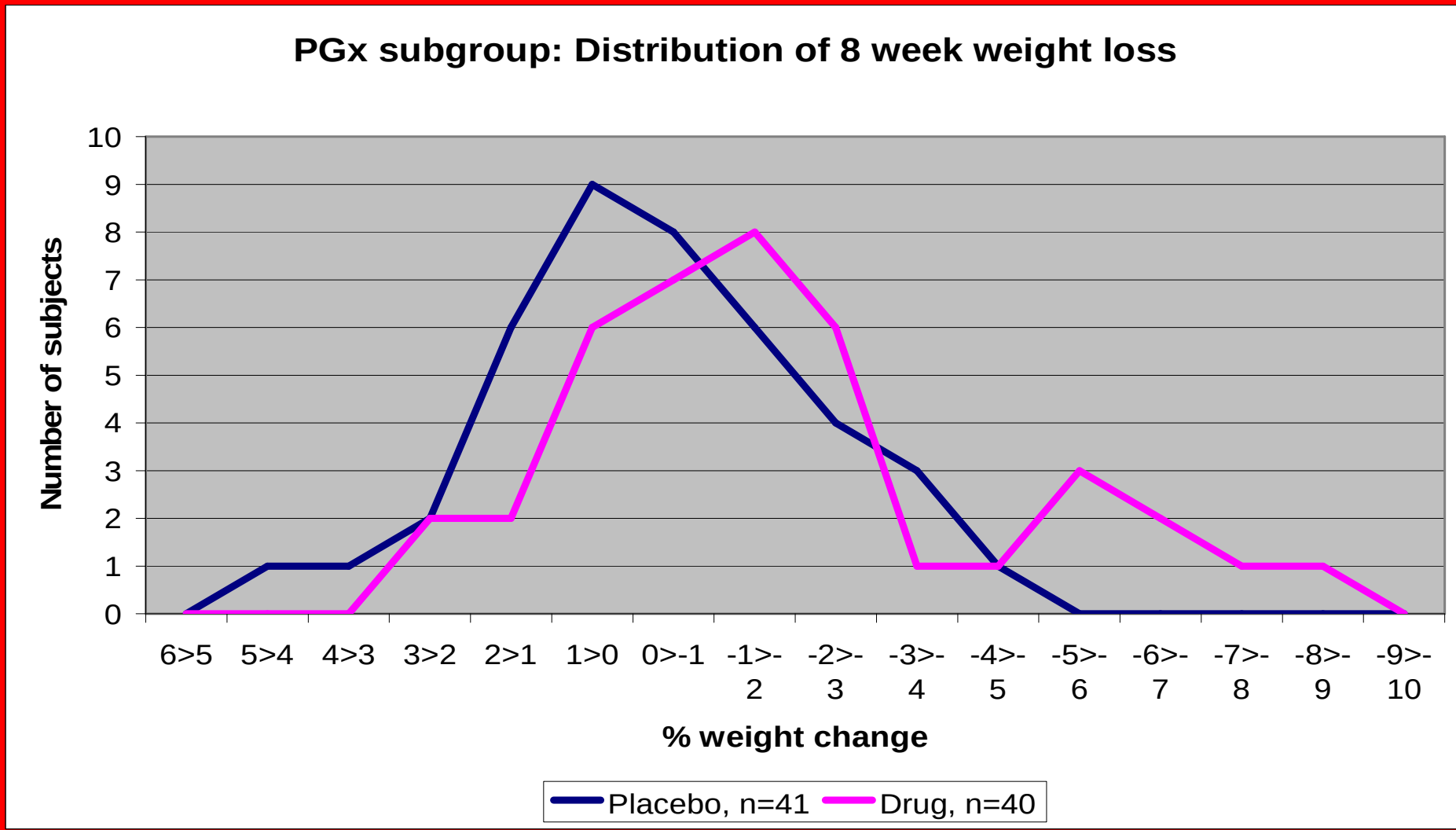
Phase IIA efficacy profiles

- Development example:

  Weight loss for obesity

  Measure weight gained or lost during clinical trial

1,1 1,2 2,2



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Effect of genotype on absolute mean weight loss (Kg) for combined (capsule and tablet) high dose groups

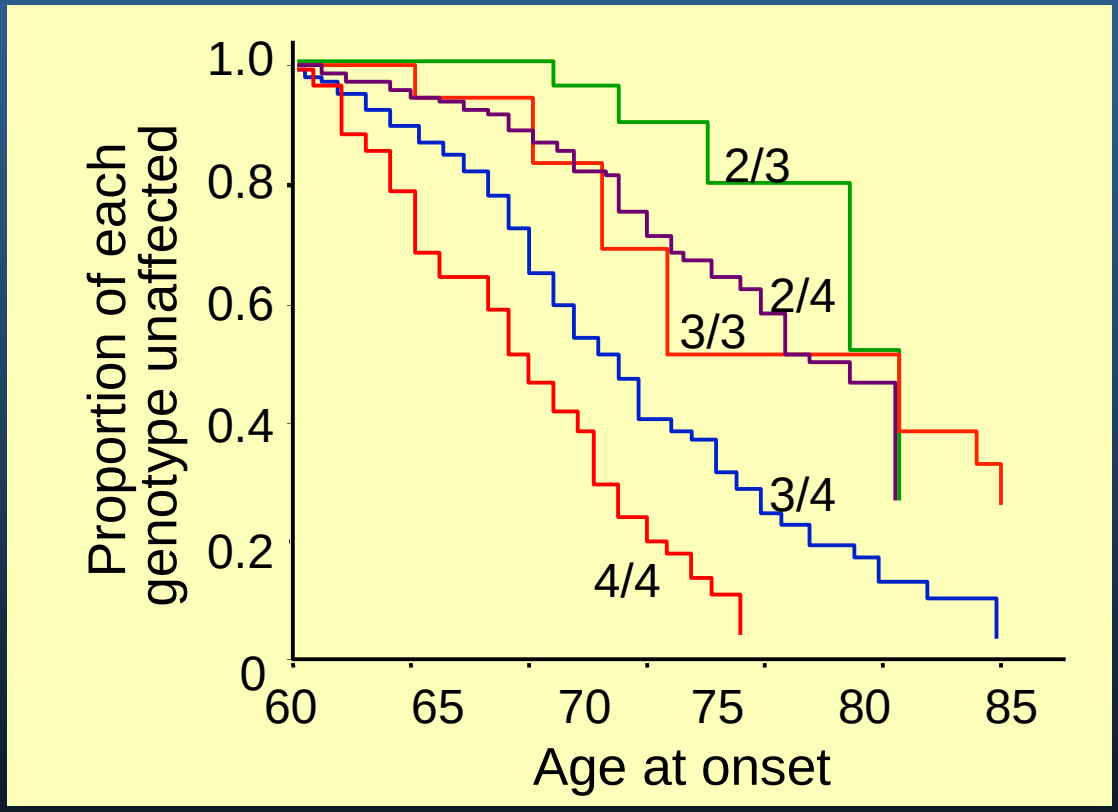
SNP	P value*	1,1	1,2	2,2
Gene 1	0.018	+ 1.03	- 1.55	- 3.36
Gene 2	0.025	+ 1.44	- 2.32	- 3.54
Gene 3	0.092	+ 1.16	- 1.52	- 3.57

*

Prospective Efficacy PGx during Phase IIB Proof of Efficacy

- Create efficacy hypotheses as early as Phase IIA for reiterative analyses during subsequent development
- Genetic-based profiles can be applied to define clinically responsive populations for more patient-focused trials
- For the first time in pharmaceutical history, non-responders can be identified for follow-up with follow-on candidate molecules

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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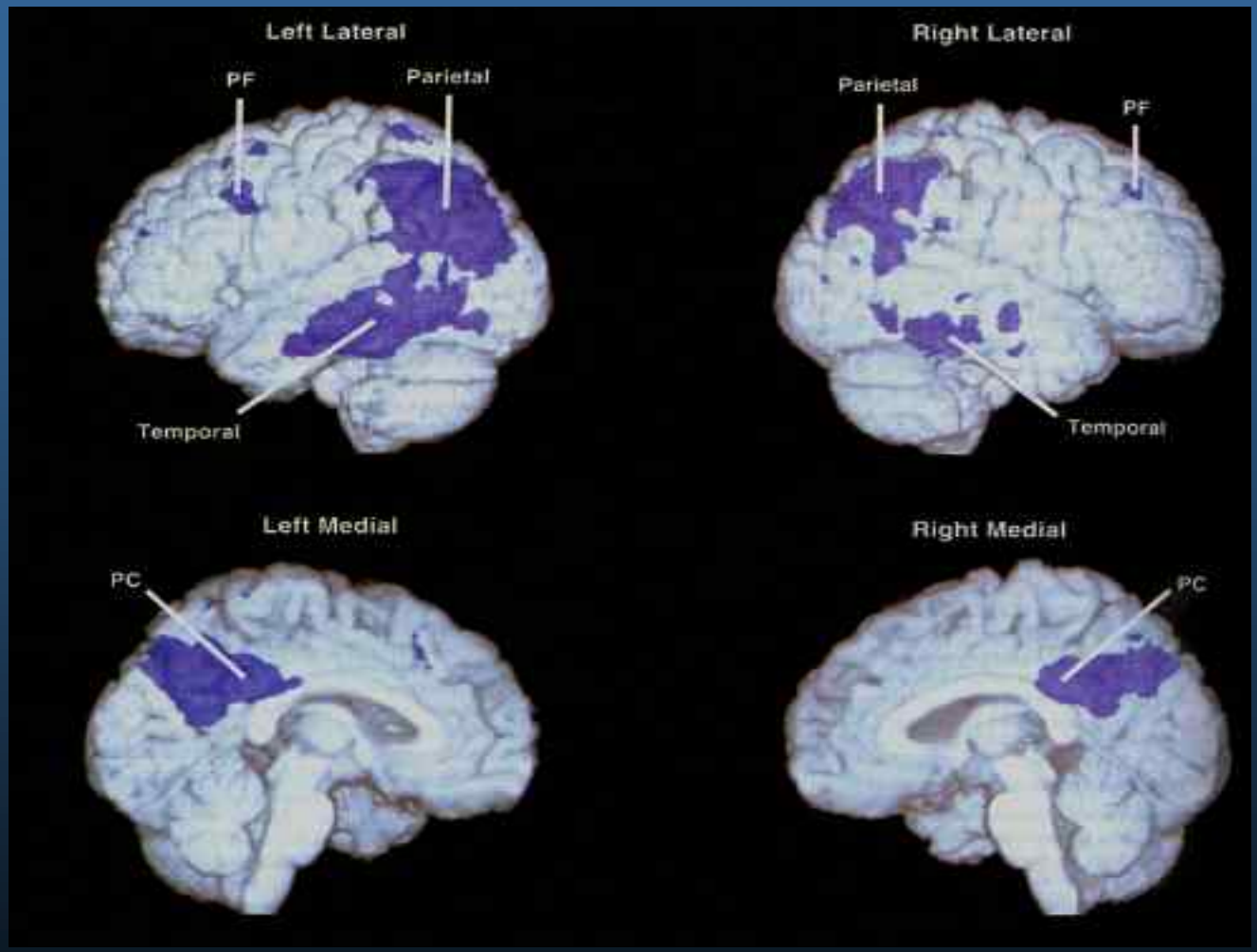
Symptomatic Alzheimer Disease



Source: Reiman et al NEJM 334 p752

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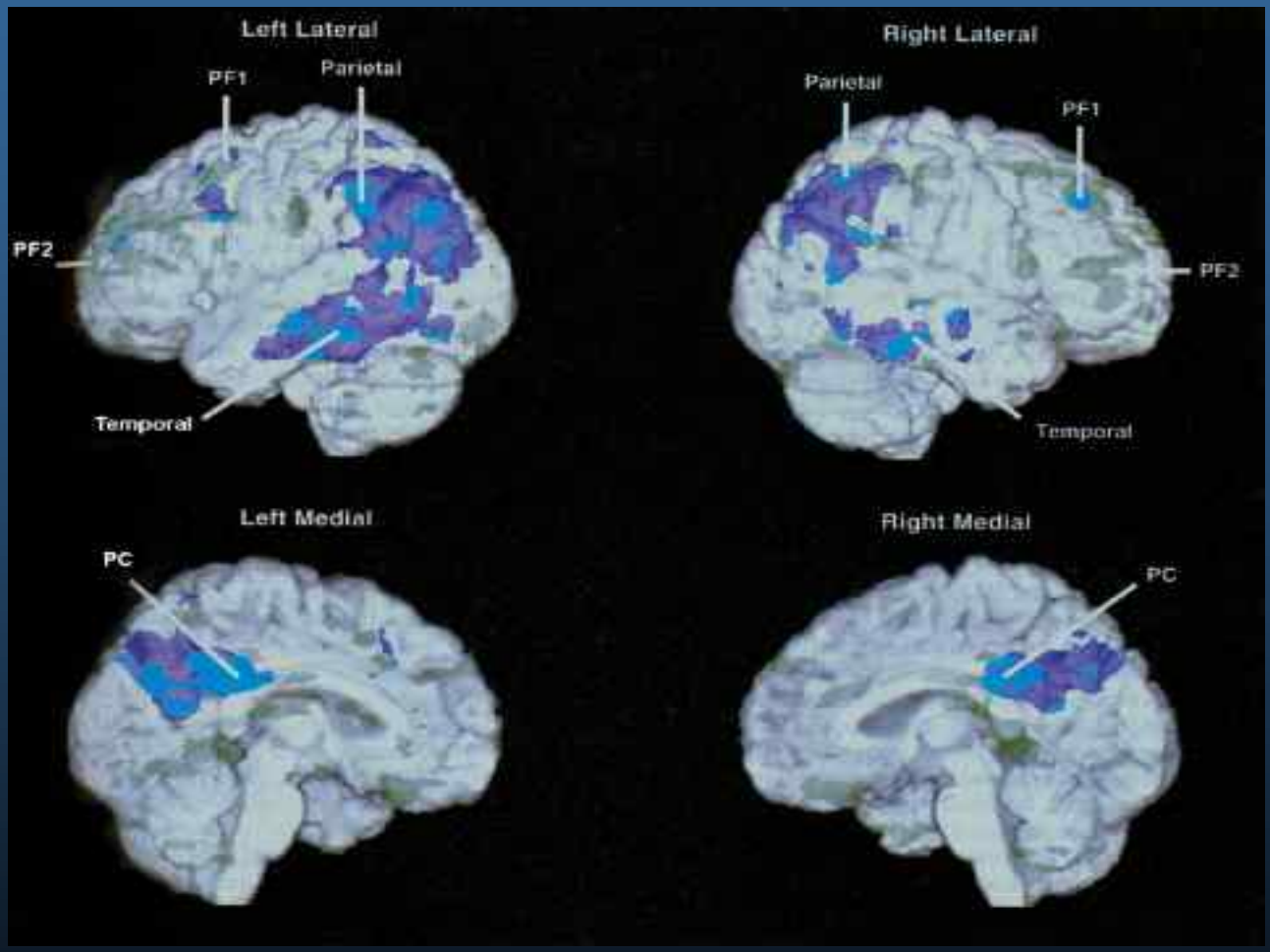
APOE4 non-demented homozygotes mean age = 50 years



Source: Reiman et al NEJM 334 p752

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Phase IIB efficacy profiles

Measuring clinical improvement in Alzheimer disease

Phase IIB dose-ranging trial of a drug based on a hypothesis involving APOE isoform-specific mitochondrial toxicity with >500 mild to moderate AD patients

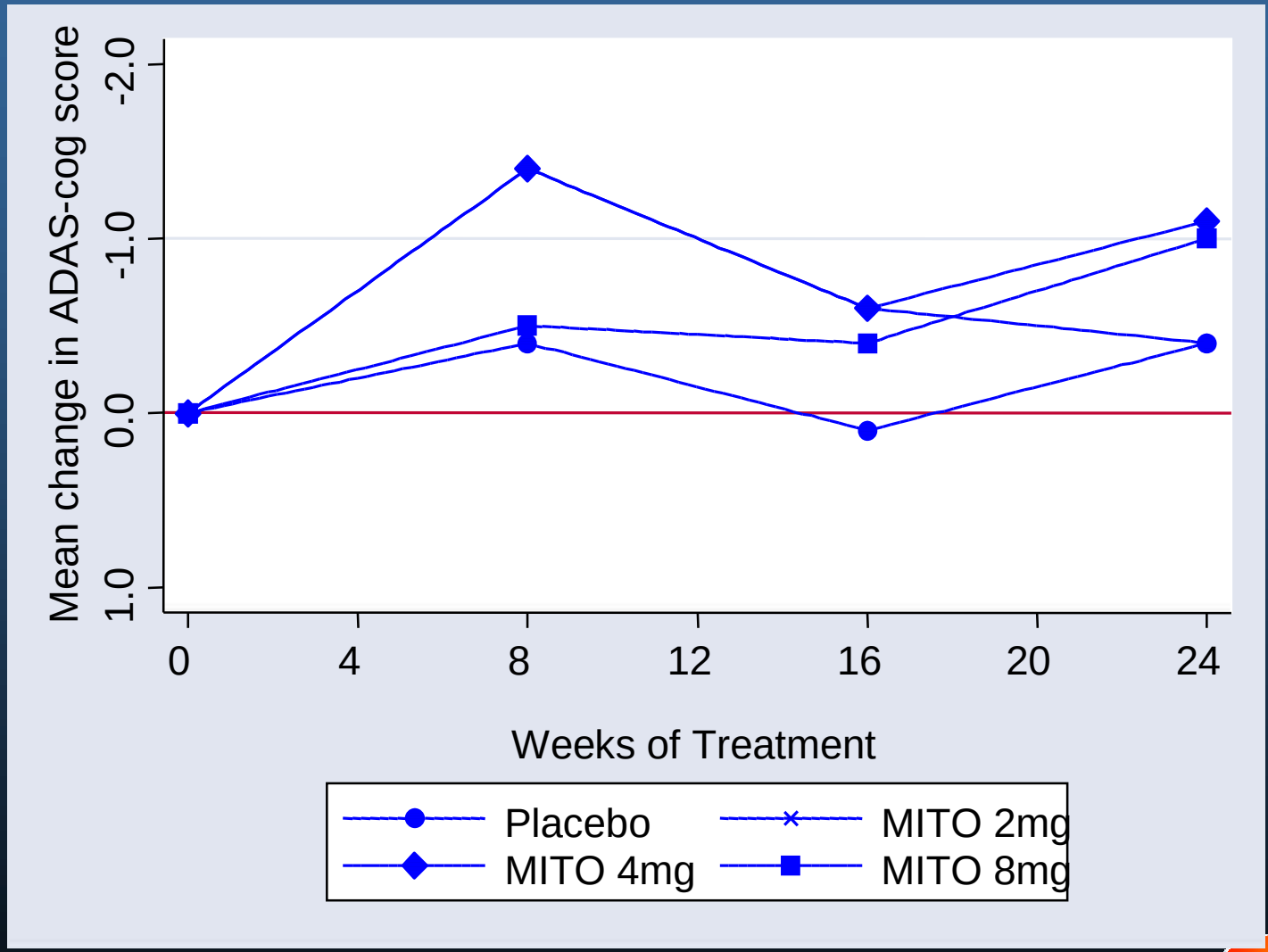
Prospective hypothesis from small Phase IIA study:

"Patients inheriting one or two APOE4 alleles will respond differently than patients who carry no APOE4 alleles"

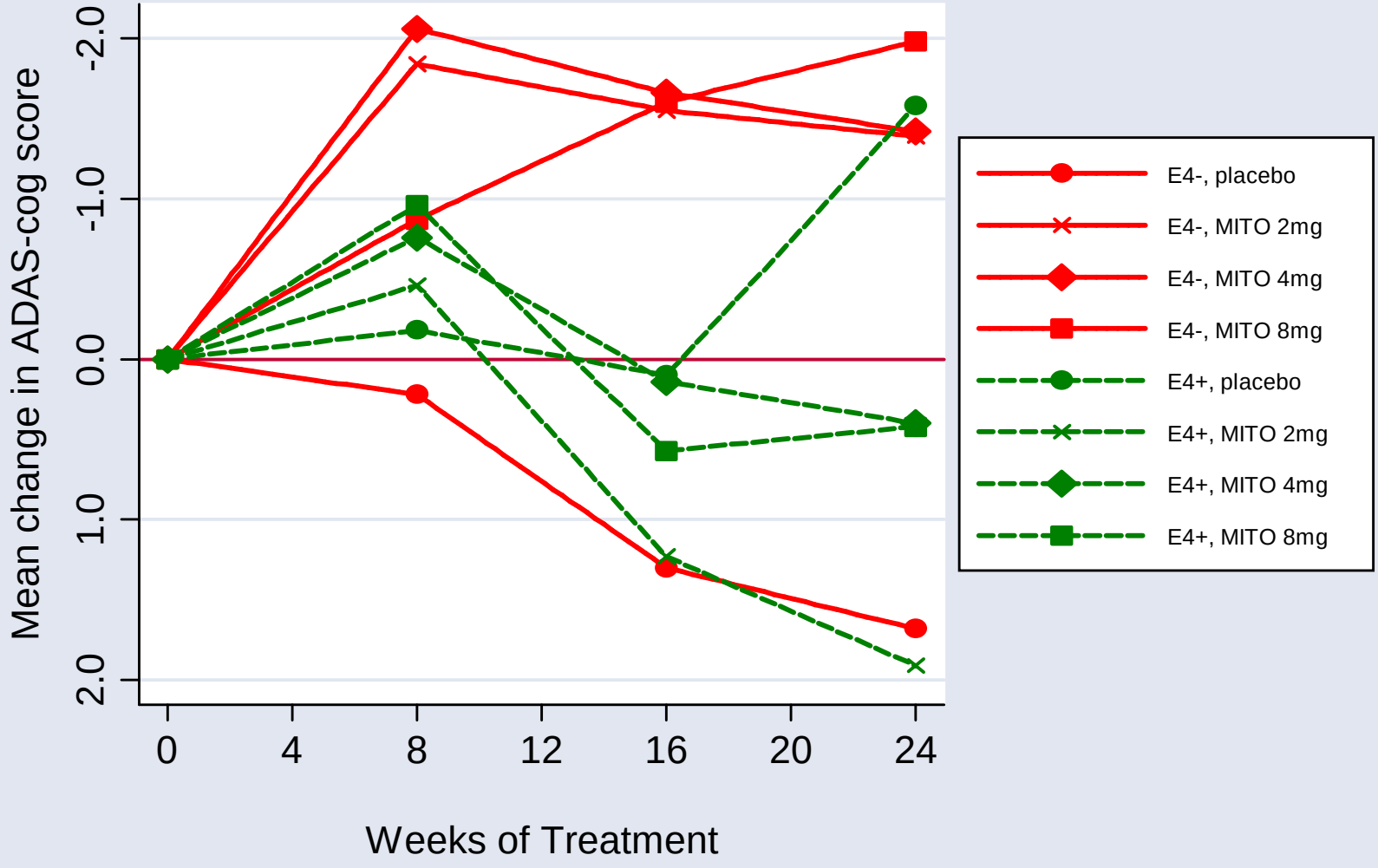
PGX efficacy for AD with a new drug directed against a mitochondrial energy pathogenesis Drug "MITO"

- Patients selected for inclusion in clinical trial with mild to moderate AD, not based on any genotyping
- Clinical status measured over a six month period using ASAS-cog, as well as other clinical scores
- Patients were genotyped during the trial and, after analysis without these data
- Patients were segmented into e4 allele carriers, and patients who did not carry an e4 allele

Model-adjusted Mean Change from Baseline in ADAS-cog: Intent To Treat population, Observed Cases



ADAS-cog by APOE4 carrier status, all subjects
Model-adjusted Mean Change from Baseline



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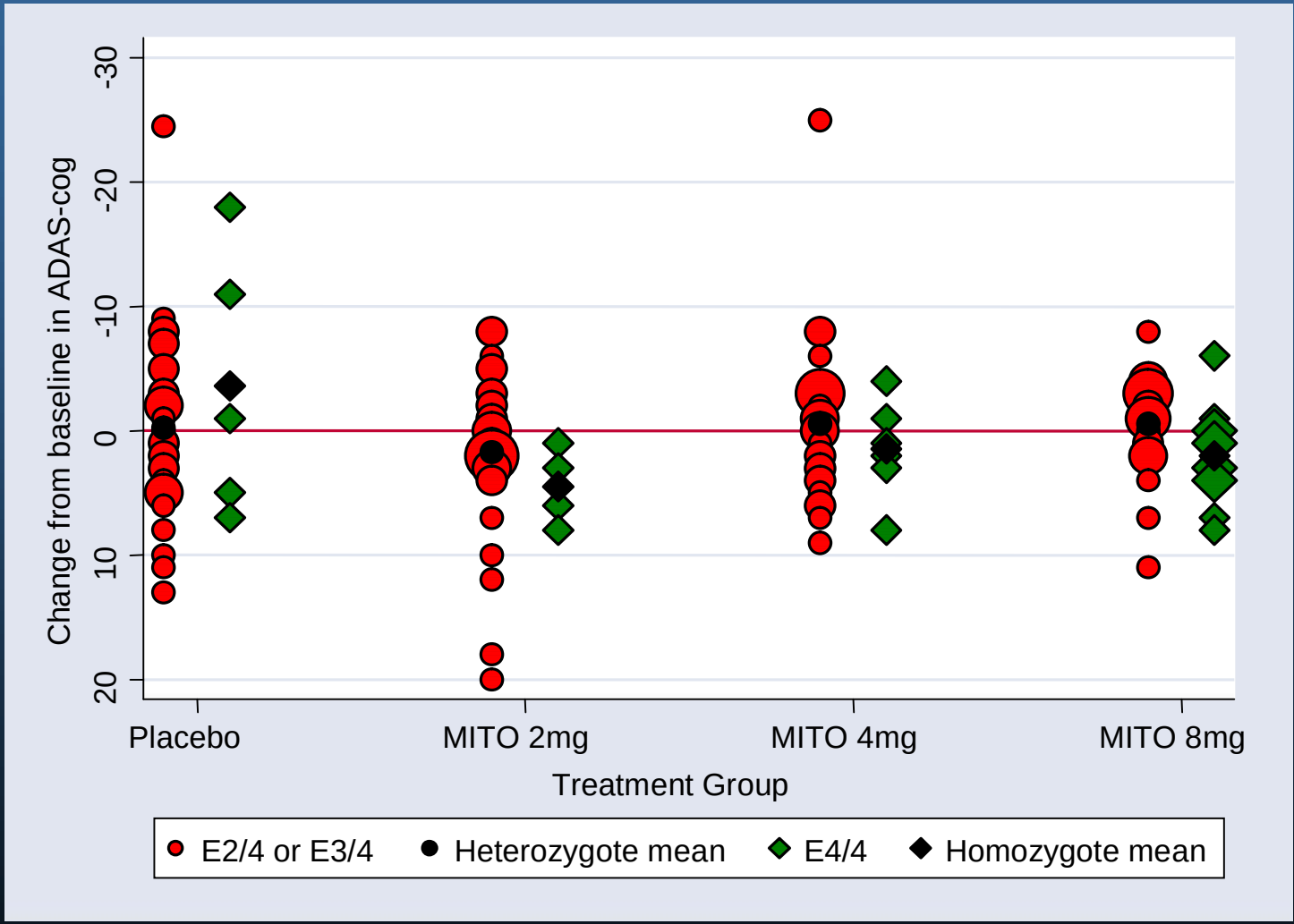
APOE4 carrier subjects only

Distribution of Change from Baseline in ADAS-cog at Week 24 LOCF



Individual points proportional to number of subjects with same change in score

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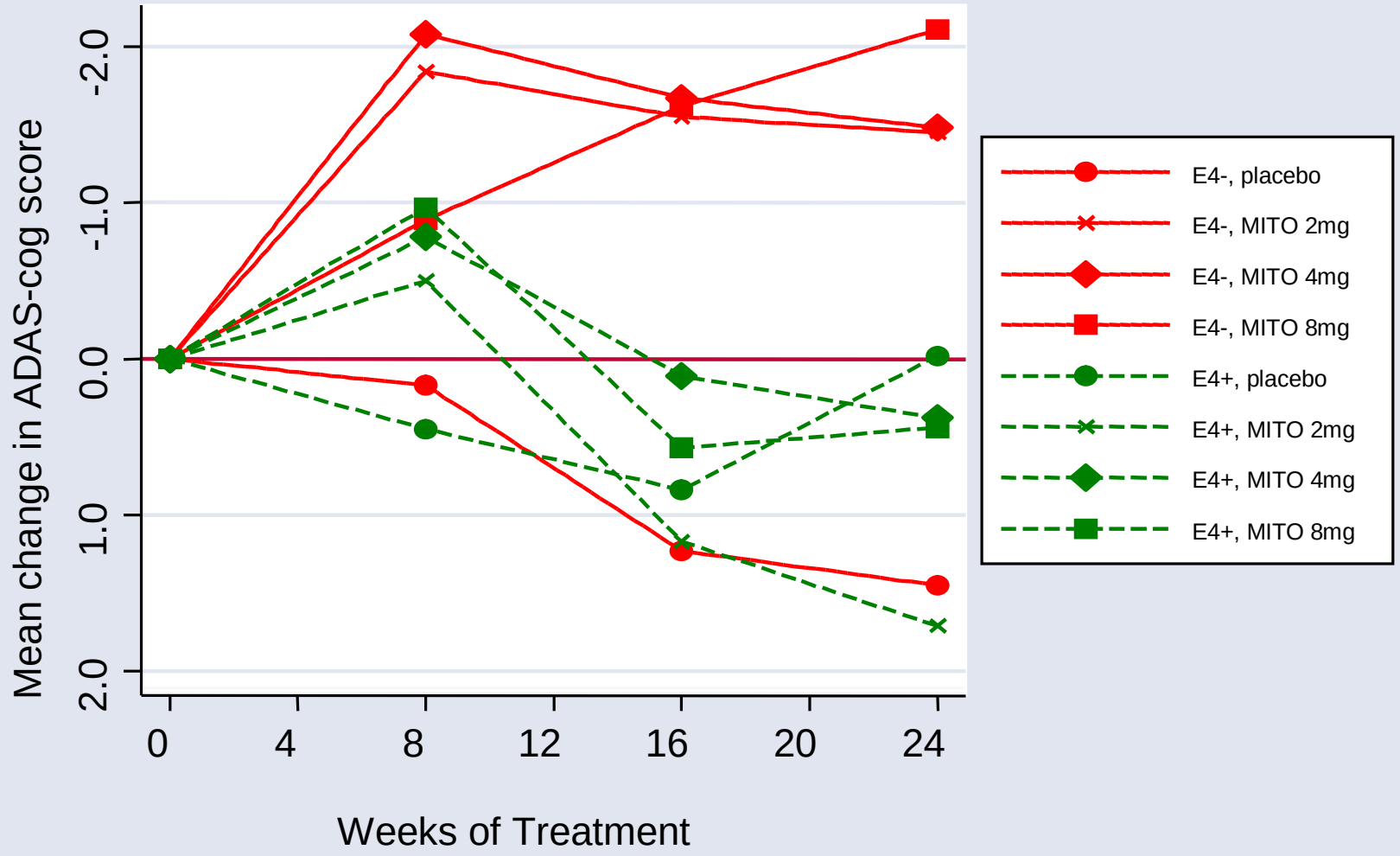
ADAS-cog by APOE4 carrier status*

Model-adjusted Mean Change from Baseline



*Excluding patients 364, 737 and 1027

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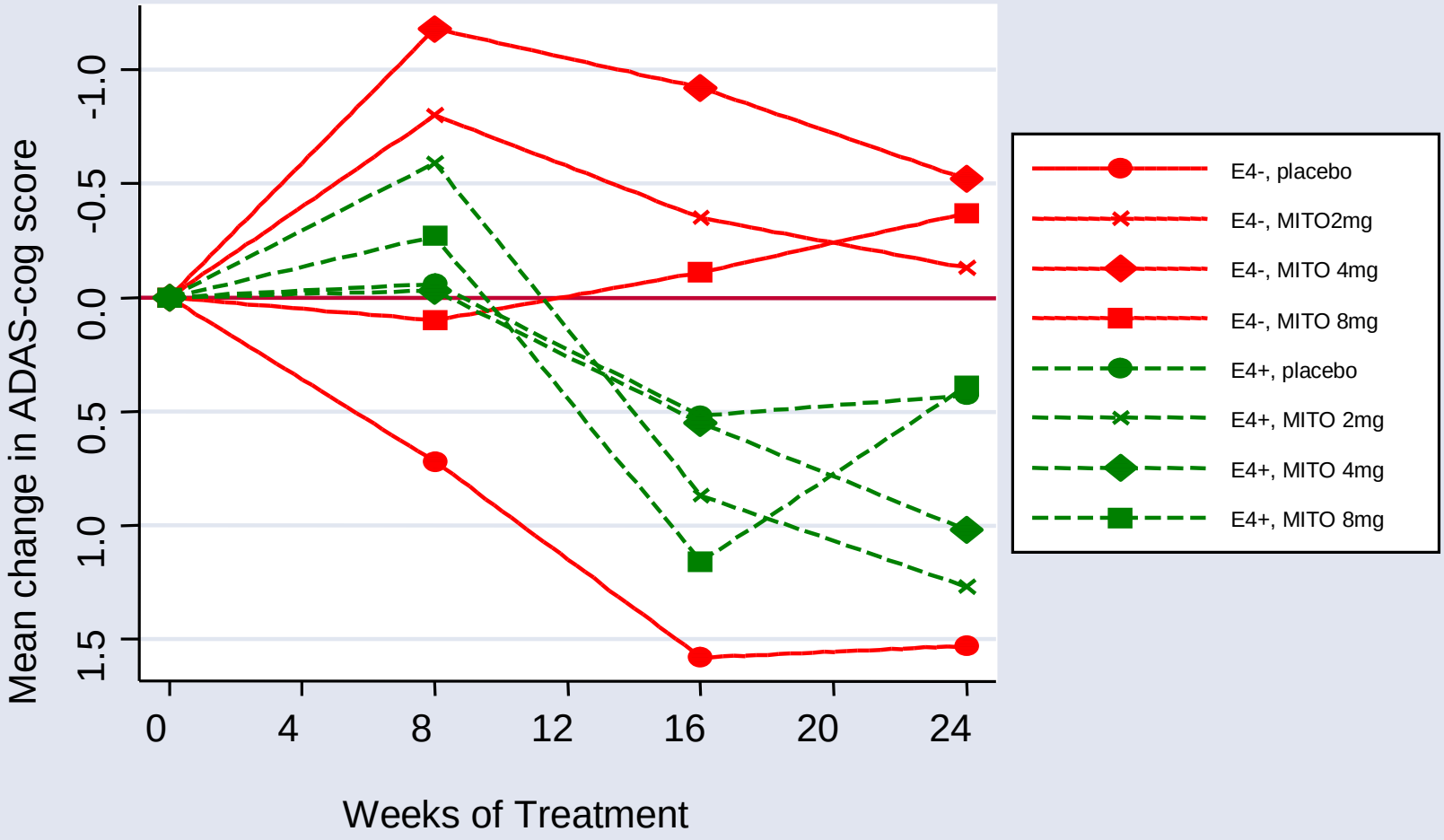
Memory Items* of ADAS-cog by APOE4 carrier status

Model-adjusted Mean Change from Baseline



*Sum of items 1, 7 and 8

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New Phase III hypothesis

Phase IIB hypothesis generated results:

> **"AD patients without an APOE4 allele responded better than patients who carry either 1 or 2 APOE4 alleles"**

Prospective Phase III APOE hypothesis to be tested:

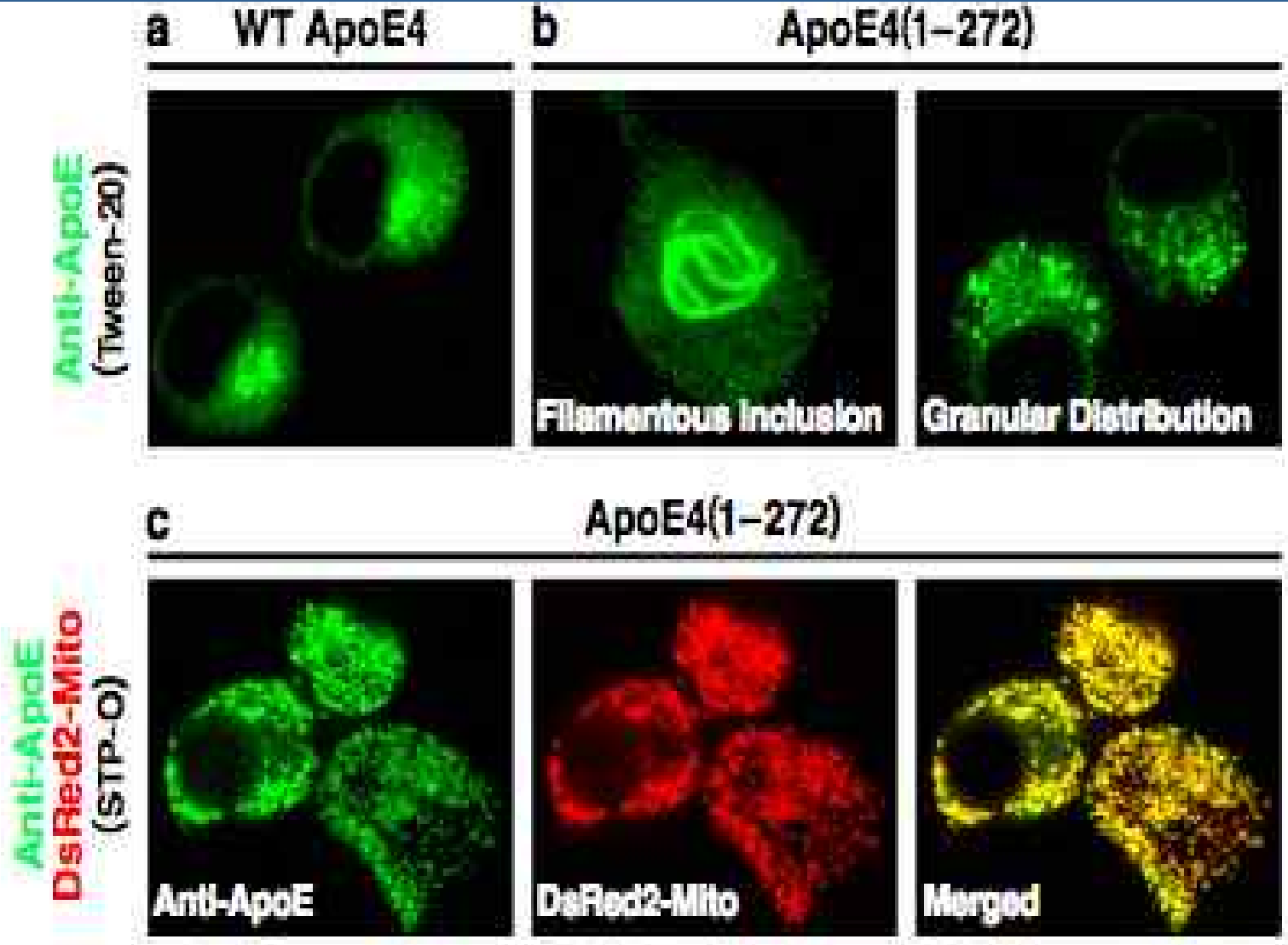
> **"Patients without an APOE4 allele will improve better than patients who carry an APOE4 allele"**

PGX efficacy with Drug “MITO”

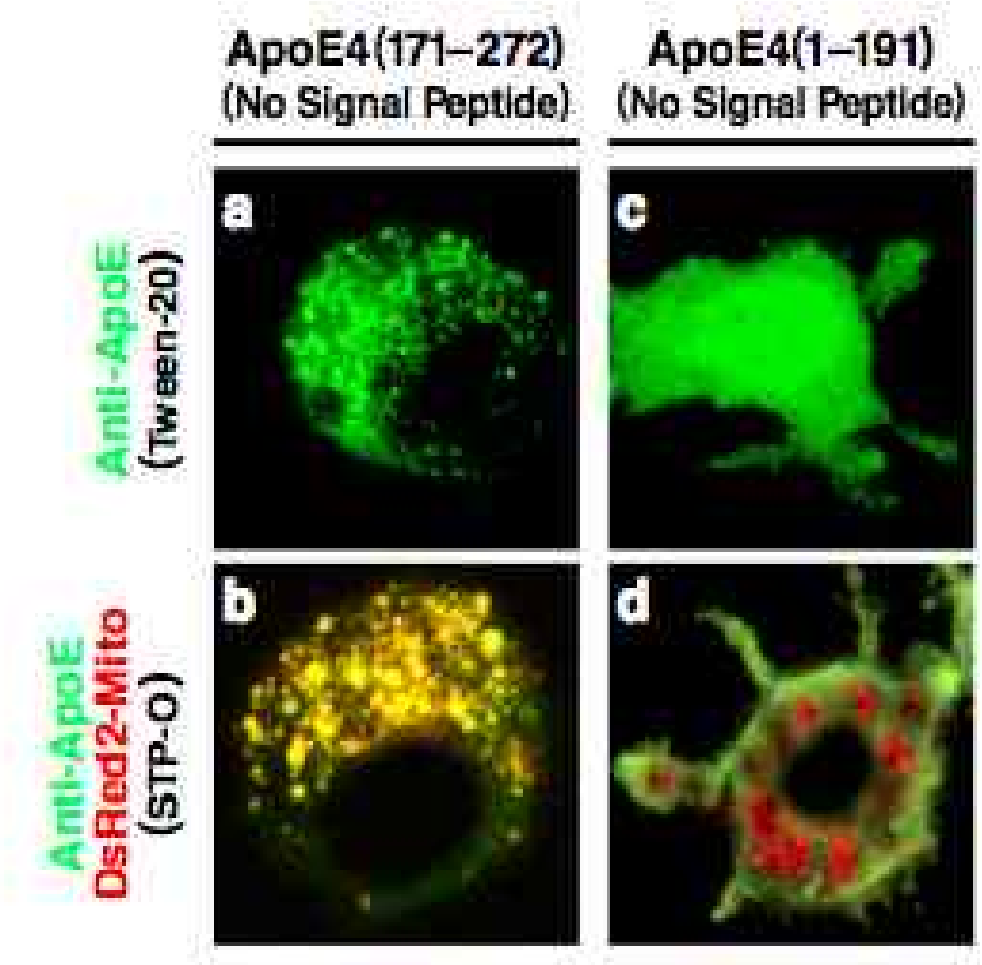
- There was no positive clinical effect of treatment in ITT population
- In PGX analyses, patients without an e4 allele improved, while e4+ carriers did not improve compared to baseline on ADAS-cog and other clinical scales.
- Design of Phase III studies will be powered using APOE genotype status

Intracellular distribution of various forms of apoE4 as determined by IHC and CM

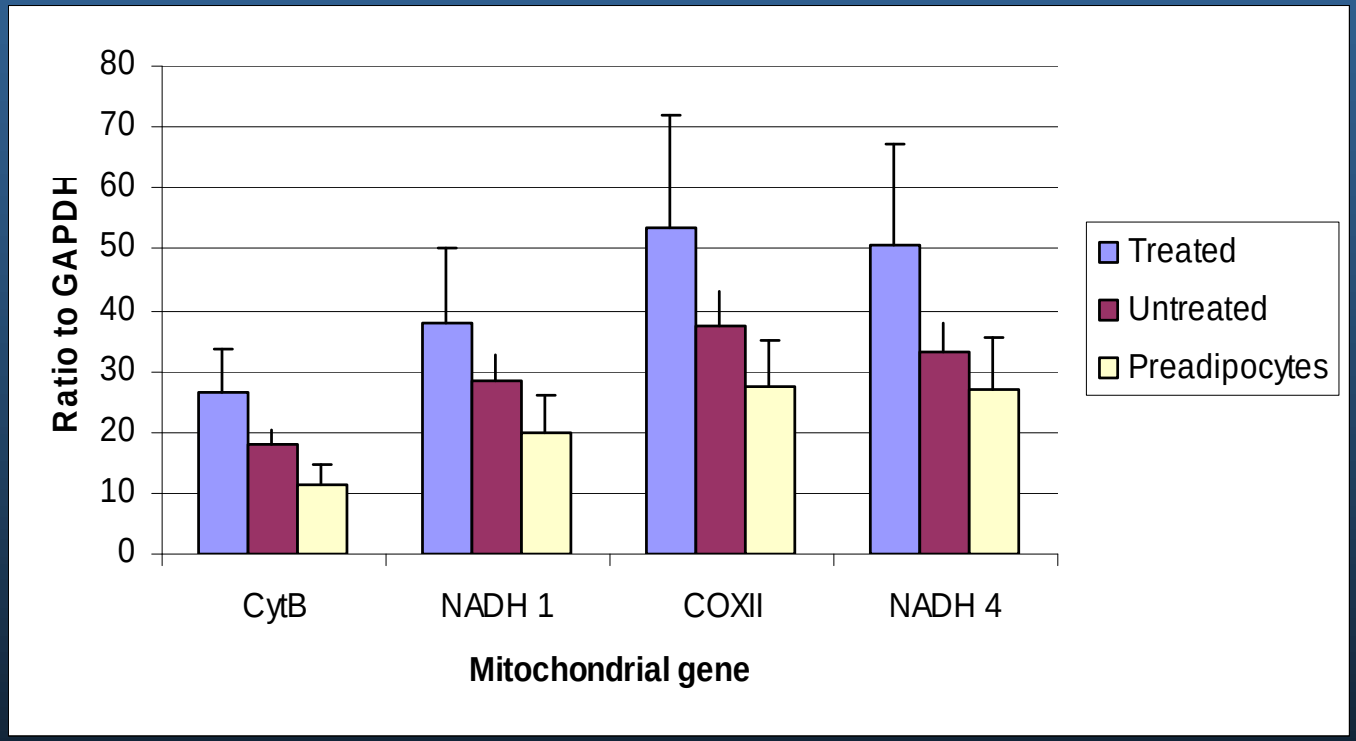
Chang et al.2005



The apoE4 receptor binding region is required to escape the secretory pathway and the lipid binding region mediates mitochondrial interaction



MITO treatment increases mitogenesis and increase in mitochondrial DNA



Approximate 2 fold increase in mitochondria with differentiation and MITO treatment

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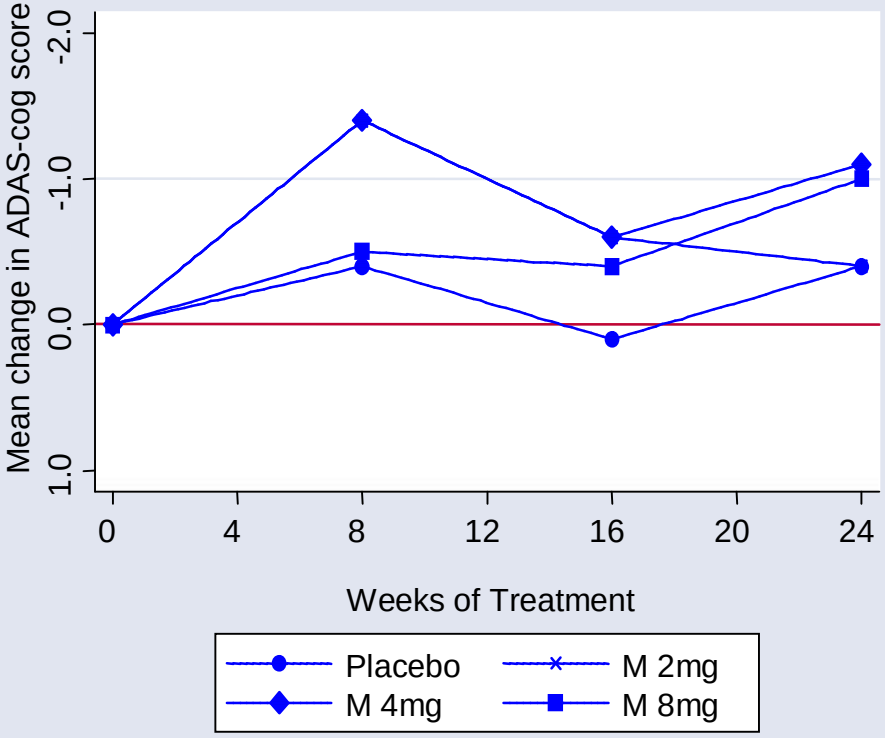
Benefits and risks of Pipeline PGx

- The most important benefit is the ability to discover and develop new drugs for bad diseases with a higher probability of efficacy and a lower risk of a safety concern
- Differentiation of the marketplace will benefit patients, health care providers and payers

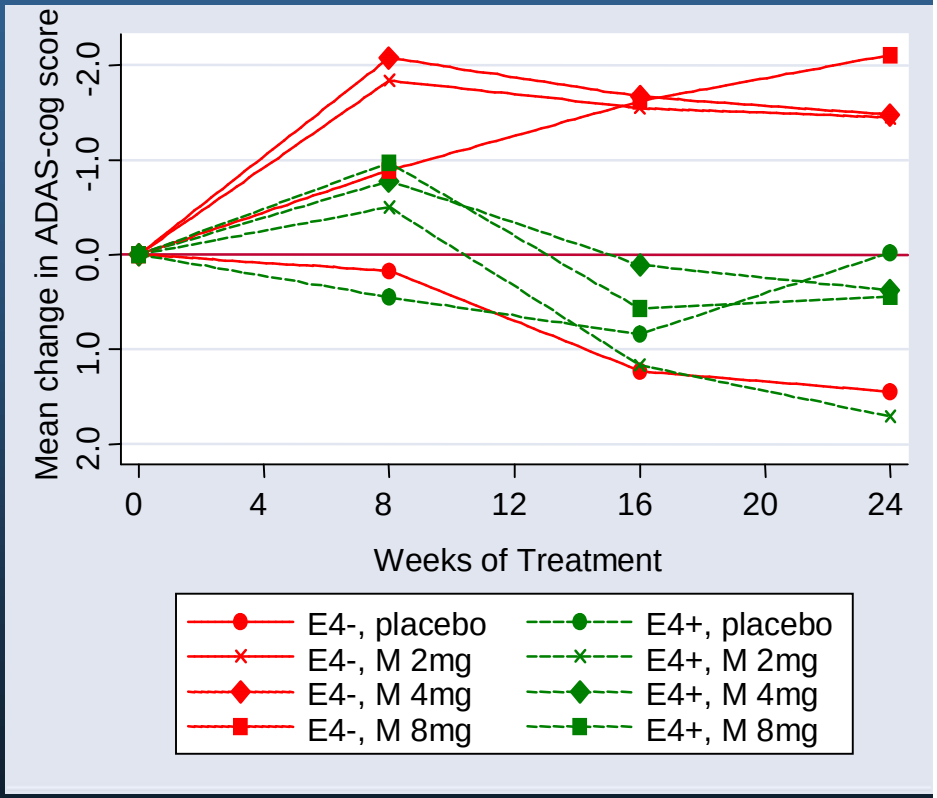
- Application of new science to a highly regulated field requires education and understanding
- The biggest risk is the status quo [and believing pessimistic predictions]

Model-adjusted Mean Change from Baseline in ADAS-cog by treatment week

ITT population



PGx ITT population by APOE4 status*



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