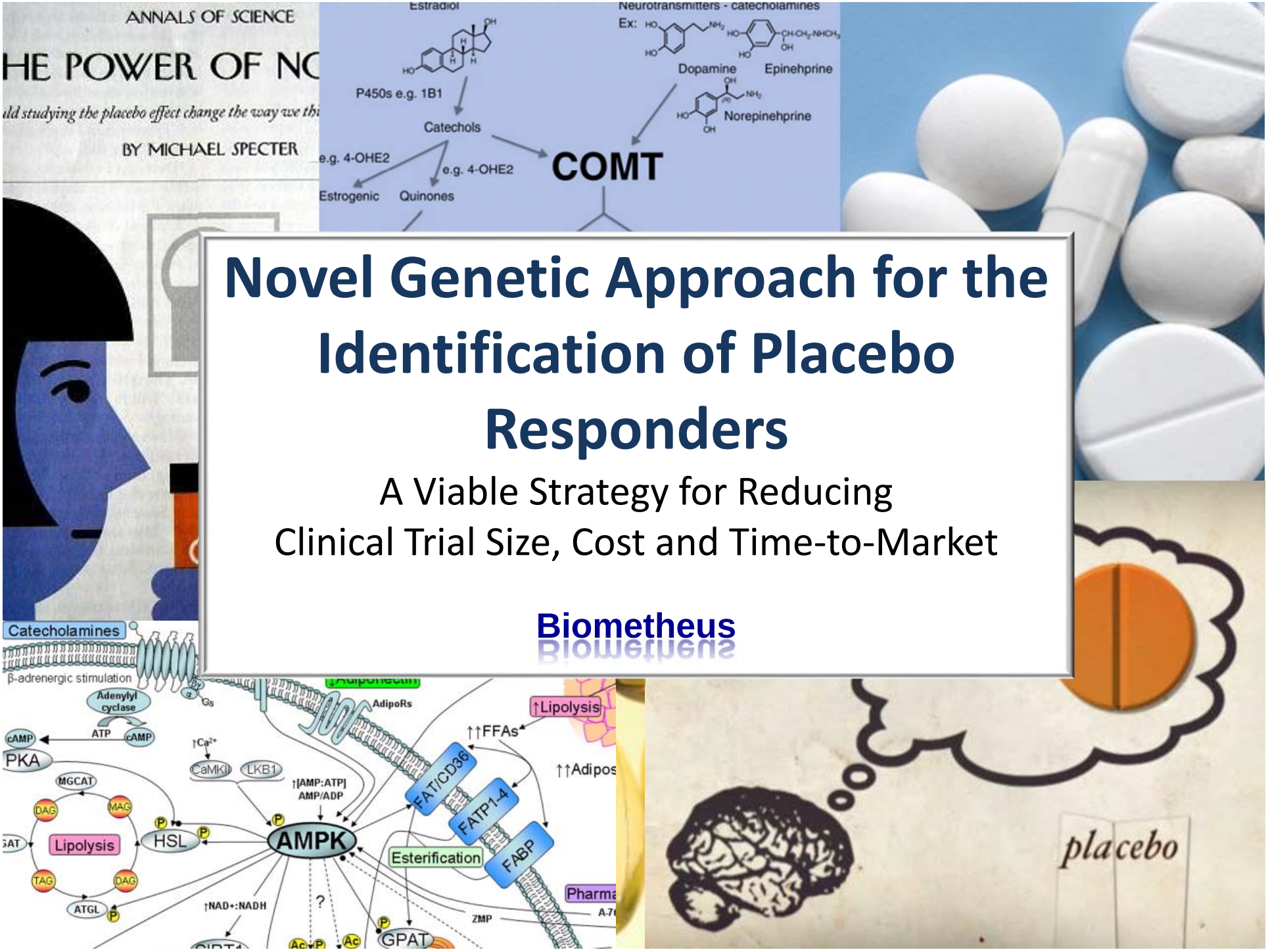

ANNALS OF SCIENCE
HE POWER OF NC
ld studying the placebo effect change the way we thi
BY MICHAEL SPECTER
Estradiol
P450s e.g. 1B1
Catechols
e.g. 4-OHE2
e.g. 4-OHE2
Estrogenic
Quinones
COMT
Neurotransmitters - catecholamines
Ex:
Dopamine
Epinehprine
Norepinehprine
Novel Genetic Approach for the Identification of Placebo Responders
A Viable Strategy for Reducing
Clinical Trial Size, Cost and Time-to-Market
Biometheus
Catecholamines
β-adrenergic stimulation
Adenylyl cyclase
ATP
cAMP
PKA
AdipoRs
↑Lipolysis
↑↑FFAs
↑Ca2+
CaMKII
LKB1
↑[AMP:ATP]
AMP/ADP
FAT/CD36
FATP1-4
FABP
MGCAT
DAG
MAG
Lipolysis
HSL
AMPK
Esterification
TAG
ATGL
↑NAD+:NADH
ZMP
GPAT
placebo

Executive Summary

1. We identified a biomarker for placebo response.

2. Subjects with COMT met/met polymorphism have predisposition for significantly higher placebo response.

3. Approximately 25% of the population is of the met/met type. Subjects can be easily tested for this polymorphism.

4. Pre-identification and exclusion of placebo responders can significantly reduce clinical trial size, cost and time-to-market.

5. The FDA has expressed interest in this technology.

High Cost of New Drug Development is of Concern to the Industry, Researchers and Patients Alike

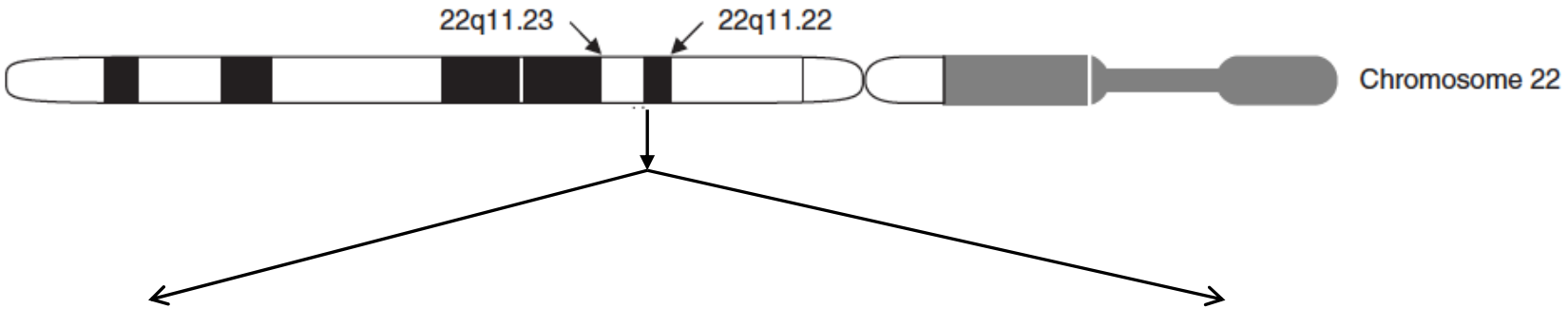
The Challenge with High Placebo Rates in Clinical Studies

- Placebo controlled studies are standard for registration of most new drugs.
- The higher the placebo response rate in an indication the larger the clinical study needs to be to demonstrate efficacy.
- The industry is wasting billions of dollars every year in oversized clinical trials to beat the odds of high placebo rates.
- Enrichment strategies such as “Run In Phases” or “Sequential Parallel Comparison Design” have been applied with poor results.

Discovery of Genetic Predictors of Placebo Response

- The enzyme Catechol-O-Methyl Transferase (COMT) degrades catecholamines including dopamine, epinephrine and norepinephrine.
- This process is critical for the prevention of accumulation of these neurotransmitters.
- Polymorphism of COMT gives rise to an inefficient form of COMT (Met/Met) leading to increased dopamine concentration in the brain.

Catechol-O-methyl transferase polymorphism COMT val158met



Alleles → **val/val** | **val/met** | **met/met**

less dopamine | **intermediate dopamine** | **more dopamine**

"High-activity" thermo stable COMT degrades dopamine more efficiently

rs4680
A or G
Met158 or Val158

"Low-activity" *thermo instable* COMT

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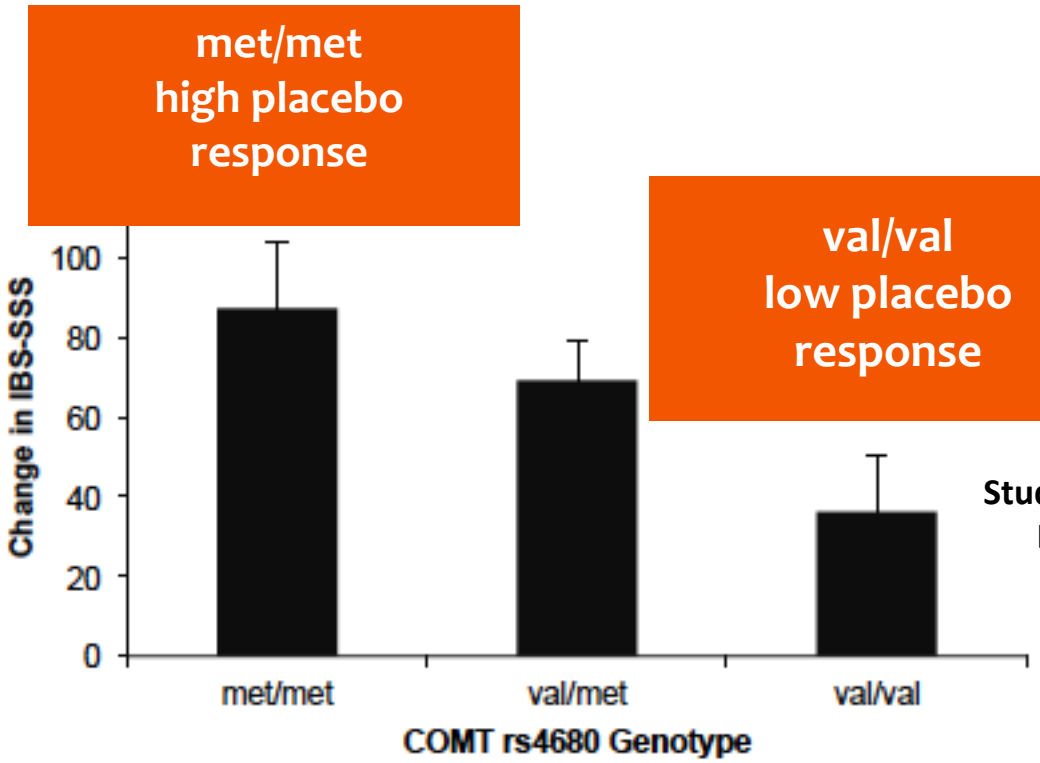
COMT Genotype is Associated With Placebo Response in Clinical Trial - Example IBS

Patients respond to placebo according to their genotype



Study at Beth Israel Deaconess Harvard Medical School
N=104
(p =0.02)

Hall KT, Lembo AJ, Kirsch I, Ziogas DC, et al. (2012) Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome. PLoS ONE 7(10): e48135. doi:10.1371/journal.pone.0048135

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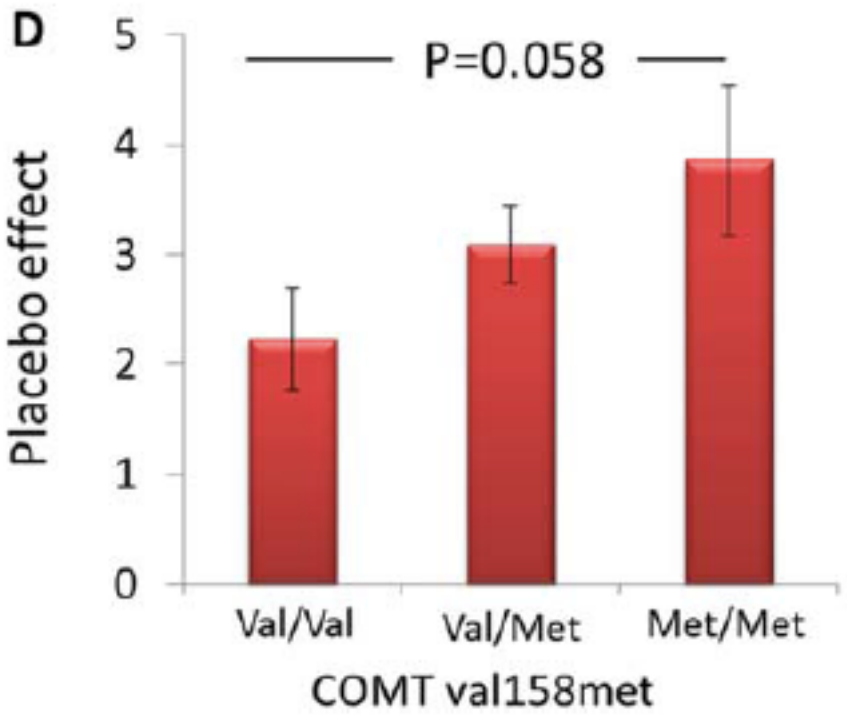
COMT Genotype is Associated With Placebo Response in Clinical Trial - Example Pain

Patients respond to placebo according to their genotype

val/val
low placebo
response



met/met
high placebo
response

Study at Mass General Hospital
Harvard Medical School
N=48
(p =0.058)

Rongjun Yu, Randy L. Gollub, Mark Vangel, Ted Kaptchuk, Jordan W. Smoller and Jian Kong (2014), Placebo Analgesia and Reward Processing: Integrating Genetics, Personality, and Intrinsic Brain Activity, Human Brain Mapping

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The FDA Expressed Support for Technology That Reduces Placebo Response Rates

FDA has expressed interest in technology that allows prescreening and exclusion of patients with predisposition for a high placebo response

- Technologies aiding the reduction in clinical trial size, cost and speed fit with FDA's Critical Path initiative
- Exclusion of placebo responders from proof-of-concept studies is an immediate, viable and acceptable strategy
- In discussions with the FDA our Harvard consultants learned that this technology fits with FDA priorities and they were asked to consider convening a working group of industry representatives and FDA policy makers to discuss the implementation in confirmatory registration studies

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Placebo Responder Identification Summary

1. COMT is associated with placebo responders.

2. Subjects with COMT met/met polymorphism have predisposition for significantly higher placebo response.

3. Pre-screening of subjects for COMT polymorphism holds promise for enrichment of low placebo responders in clinical studies.

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