FDA Clinical Pharmacology Advisory Committee
Integrating Pharmacogenomics into Drug Development

Strattera Case Study

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Answers That Matter.

Pharmacogenetics & Pharmacogenomics

EMEA[1] definition: ***Pharmacogenomics*** applies genomic information to drug design, discovery and clinical development, reflecting the state or responses at cellular, tissue, individual or population levels.

PWG definition: ***Pharmacogenetics:*** the study of DNA sequence variation as it relates to differential drug response.

Pharmacogenomics: the study of the genome and its products (including RNA and protein) as it relates to drug discovery and development.

Lilly Definitions:

Discovery Genetics utilizes genetic information to improve target identification/ verification and MOA testing.

Pharmacogenomics utilizes gene based information to predict, assess and evaluate drug response.

1- The European Agency for the Evaluation of Medicinal Products

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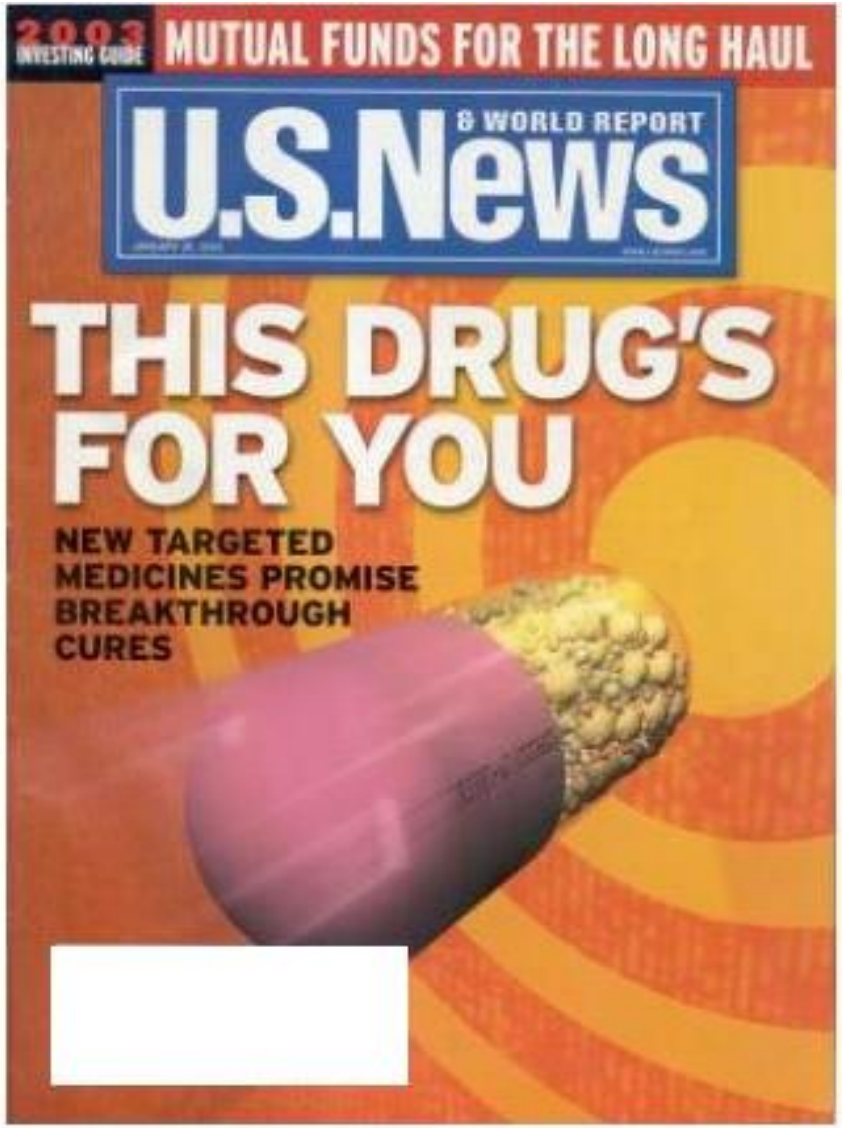
The Promise of Pharmacogenomics



- "Pharmacogenomics will radically change the manner in which we develop drugs."
- "Soon, we will be able to get the right drug into the right patient."
- "Applying pharmacogenomics to drug development will cut cycle times to 1.5 - 2 years."
- "Pharmacogenomics will be able to bring removed drugs back on the market, by predicting who is susceptible to adverse events."

How Close Are We?

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Integrating Emerging Technology

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Pharmacogenomics: applications and key activities

- **Three broad applications**
  - Discovery
    - Target Identification
    - Mechanism of Action
    - Target Differentiation
    - Biomarker Identification
  - Pre-clinical Toxicology
    - Toxicogenomics
    - In vivo Mechanism of Action
    - Biomarker Identification
  - Clinical
    - In vivo Mechanism of Action
    - Biomarker Development & Validation

- **Two key activities**
  - **Identify & Understand Targets**
  - **Develop Human Biomarkers**

Genetics in Drug Development

Genetic Changes as Biomarkers

- Disease Susceptibility Biomarkers
  - Single Disease Genes (Mendelian Inheritance)
  - Genetic Associations in Complex Diseases
  - Genetic Changes Associated with Tumorogenesis
    - Inherited Mutations
    - Spontaneous Mutations in the Tumor
    - Multiple Transcript Changes Leading to Reclassification
- Drug Activity Biomarkers
  - Genetic Polymorphisms Predicting Drug Metabolism
  - DNA Variations Predicting Drug Response
  - DNA Variations Predicting Adverse Events

Genetic in drug development

Conditions when Lilly would choose to include genetics in drug development

- Early phase development (Candidate selection through phase II)
  - Animal toxicity profile to predict human toxicity
  - Mechanism of action
  - Early target/receptor interaction and PK/PD effects
- Phase III/Phase IV development
  - When medically necessary
    - Safety issue
- When test can differentiate drug
  - Better response profile
  - Adverse event management

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Strattera and CYP2D6 Metabolism

- Primarily metabolized by CYP2D6
  - Plasma clearance
    - EM 0.35 L/hr/kg PM 0.03 L/hr/kg
  - AUC PM:EM 10 fold difference
  - T1/2
    - EM 5.2 hours PM 21.6 hours
- Safety vs Tolerability vs Efficacy Issues
  - Interplay has impact on label

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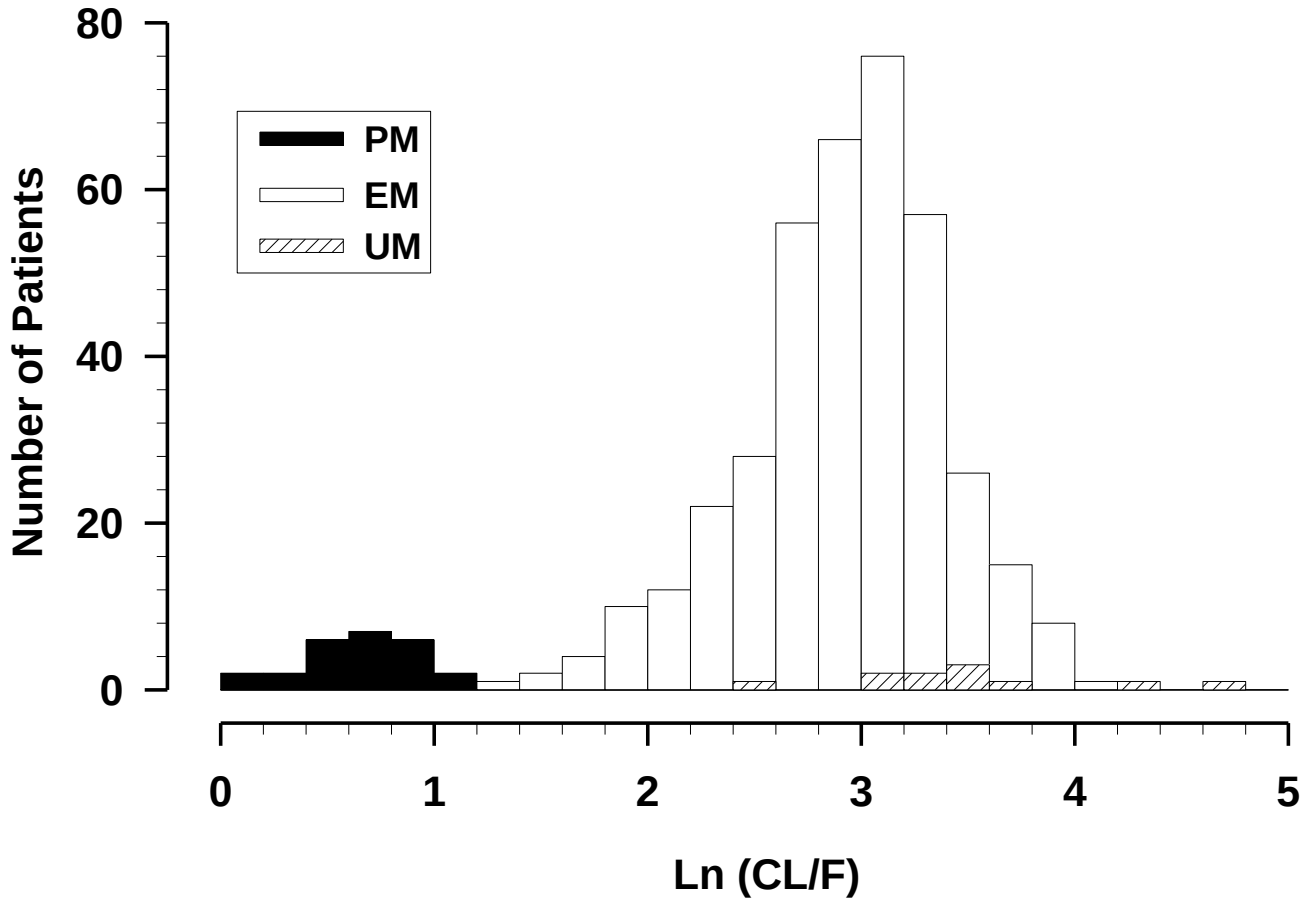
Empirical Bayesian Estimates of Clearance for each Patient in Population PK Analysis



Witcher et al. 2001. Population Pharmacokinetic Analysis of Atomoxetine in Pediatric Patients. Population Pharmacokinetics Report. Lilly Research Laboratories.

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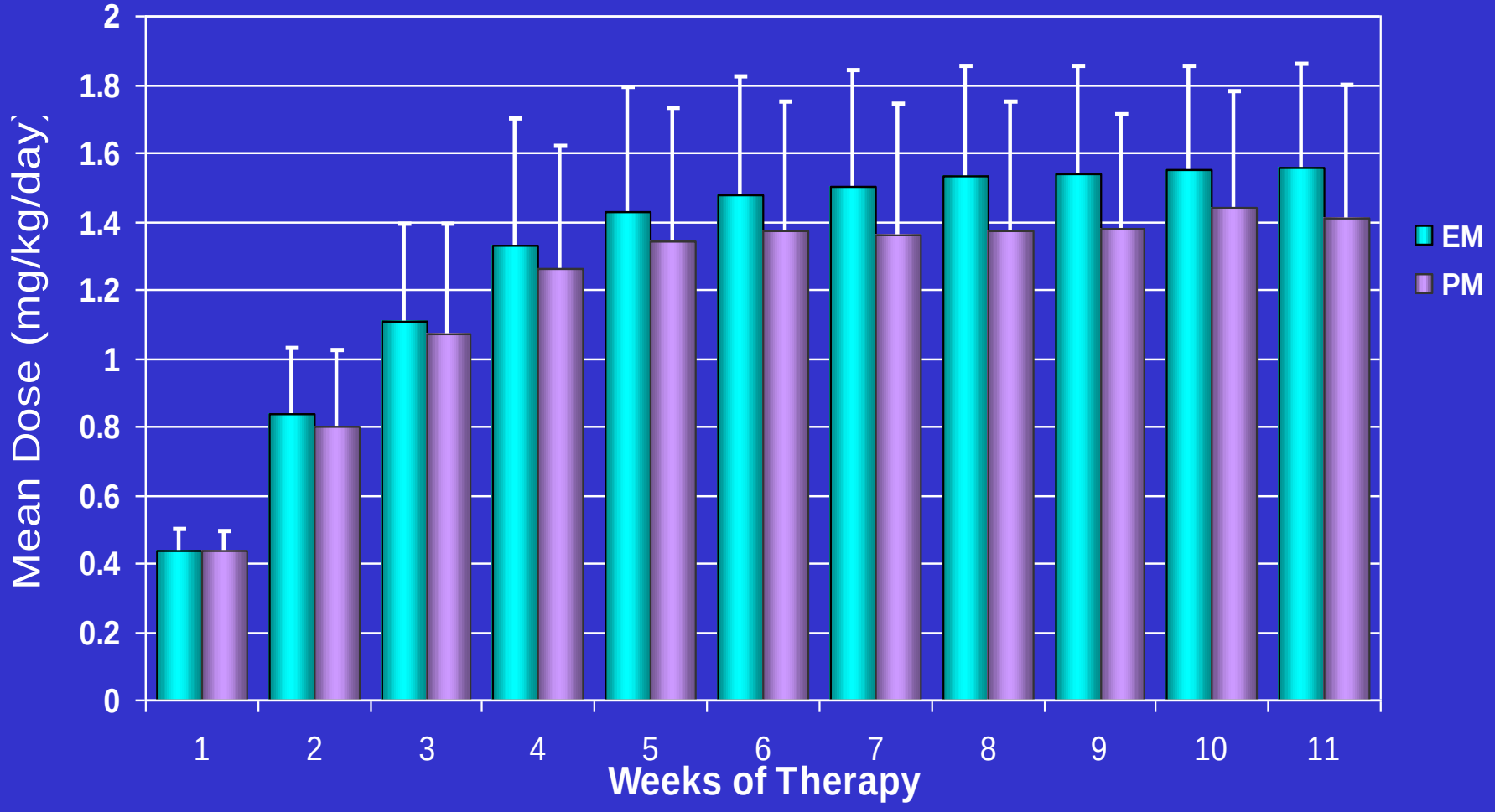
CYP2D6 Polymorphisms: Assessing Safety

- Initial clinical pharmacology studies above proposed maximum dose
- CYP2D6 genotype obtained under double-blind conditions in clinical trials
- Clinicians adjust dose and assess safety/tolerability/efficacy without knowledge of metabolic status

Mean Dose by Visit and Metabolic Rates



N	789/50	770/50	758/50	743/47	721/46	695/44	676/43	644/41	614/37	590/37	535/36

EM vs PM Summary

- Safety & Tolerability
  - Adverse event discontinuations - all studies
    - EM 6% PM 9%
    - Close label comparison Strattera 3.5% Placebo 1.5%
      - Insomnia, Irritability
- Efficacy
  - PMs have a statistically significant decrease in ADHDRS compared to EMs

Strattera Label

- CYP2D6 status mentioned 7 times in label
  - Pharmacokinetics section
  - Adverse events
  - Drug:drug interaction
  - Laboratory Testing

- Poor metabolizers (PMs) of CYP2D6 have a 10 fold higher AUC and a 5 fold higher peak concentration to a given dose of Strattera compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of Strattera (see adverse reactions).

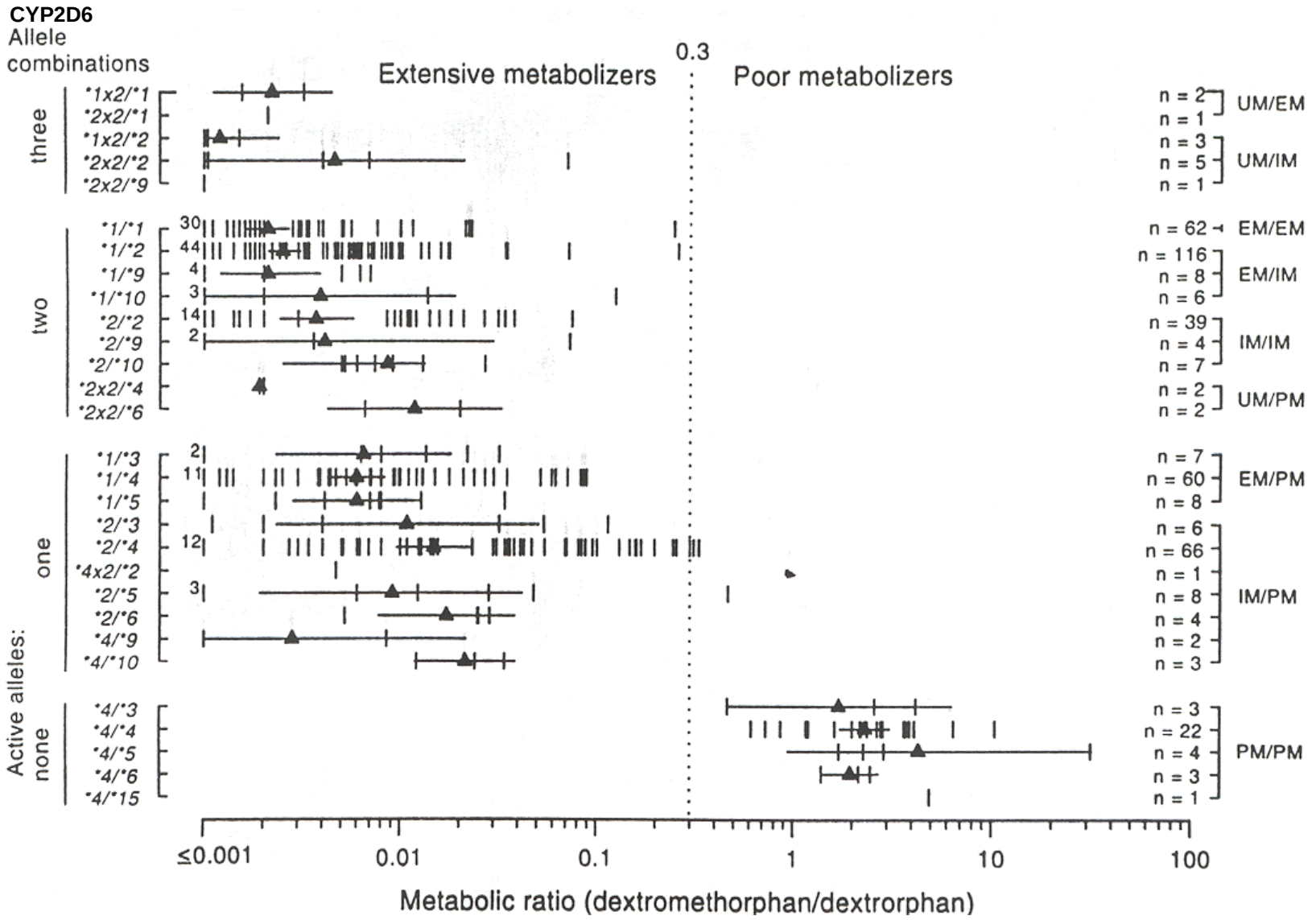
Genetics in Drug Labelling

- How to define PM status?
  - Easy in some CYP P450s
    - 2C9 - 3 alleles, *2 and *3 are both classified as PMs
    - 2C19 - similar
  - CYP2D6 is more problematic
    - >40 alleles defined
    - ~10 are currently classified as greatly decreased, or null
    - At least two are classified as decreased, or intermediate
    - Duplication exists, leading to classification as ultrametabolizers
    - Significant variations of frequency in ethnic backgrounds

CYP2D6 Genotypes by Ethnicity

- Caucasians
  - UM = 1 - 2%
  - EM = 92 - 95%
  - PM = 5 - 7%
- African American
  - UM = 3 - 5%
  - EM = 92 - 95%
  - PM = 2 - 3%
- Asians
  - UM = ??%
  - EM = 70 - 80%
  - IM = 20 - 30%
  - PM = ≤1%
- Hispanics
  - UM = ???
  - EM = ???
  - PM = ???

CYP2D6 Genotype vs Phenotype



Sachse et al. Am J Hum Genet 60:284 1997

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CYP2D6 Phenotyping vs. Genotyping

- Phenotyping Advantages
  - Phenotype is the desired designation.
  - Ethical considerations are small.
  - High sensitivity.
  - Very Low False Negatives.
- Genotyping Advantages
  - Requires no extra sampling.
  - Requires no follow-up visit.
  - High sensitivity and specificity.
  - Analysis not altered by patient taking other drugs.

- **Privacy and the Ethical, Legal and Social Implications**
- Utility of the information/biomarker
- Translation into clinical practice
- Resistance to pharmacogenomic stratification
- Regulatory approval
- Realistic timelines and expectations

Ethical, Legal and Social Implications

- Consistent guidelines for the review and approval of informed consent procedures and of pharmacogenomic protocols by ethics committees
- Sampling procedures selected have important consequences for patient privacy, sample access and control, and ultimately gene discovery, and drug development
  - PWG and CPMP definitions
- Access to the genetic information, and the medical and medical use consequences of third parties.

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Methodological and Other Considerations

- Privacy and the Ethical, Legal and Social Implications
- **Utility of the information/biomarker**
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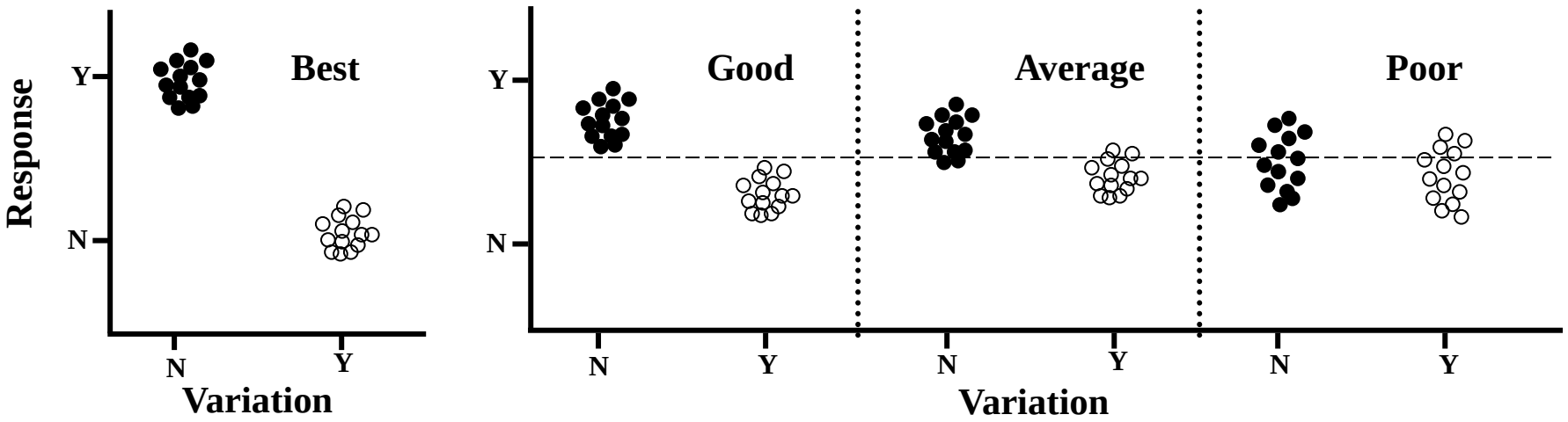
Utility of the information/biomarker



- Examples
  - ErbB-2 over-expression and response to Herceptin
  - ALOX5 promoter in asthma
  - Cholesteryl ester transfer protein and response to statins
  - B2 adrenergic gene in asthma
  - RNA levels and response to 5FU in colon cancer

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CYP2D6 Recommendations

- PM genotype predicts PM phenotype in ≥99% of cases in two large studies (*3,4,5,6,&9, no interfering drugs).
- To avoid confusion, FDA should specify that both phenotyping and genotyping are acceptable methods of determining PM status. This should include a recommendation for what is minimal genotyping.
- The genotypic designations of UM, IM and EM have distinguishable phenotypes, but only in population studies. Classification of individual patients as UM, IM, and EM is NOT indicated by current data.
- Genotyping for CYP2D6 mutants is warranted only when a compound's margin of safety is exceeded in PMs.

The Biotech/Genomics Revolution:

Right Target

Right Drug

Right Patients

Right Timeline

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