Simultaneous Confidence Intervals for Assessing the Effects of a SNP on Treatment Efficacy in Personalized Medicine Development

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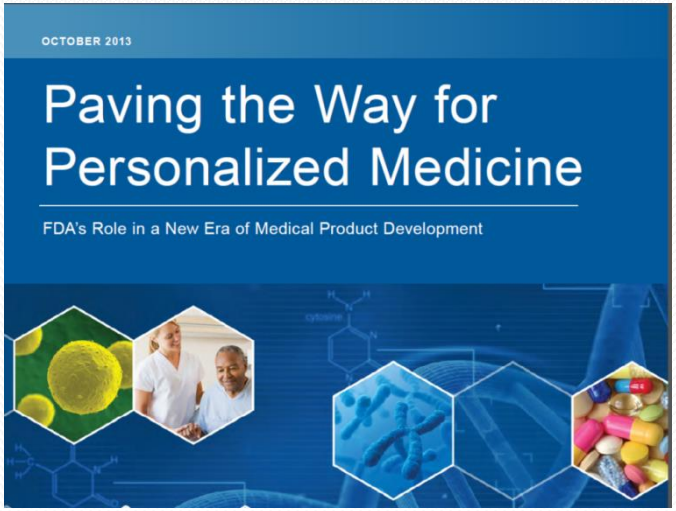

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Guideline on the investigation of subgroups in confirmatory clinical trials

The NEW ENGLAND JOURNAL *of* MEDICINE

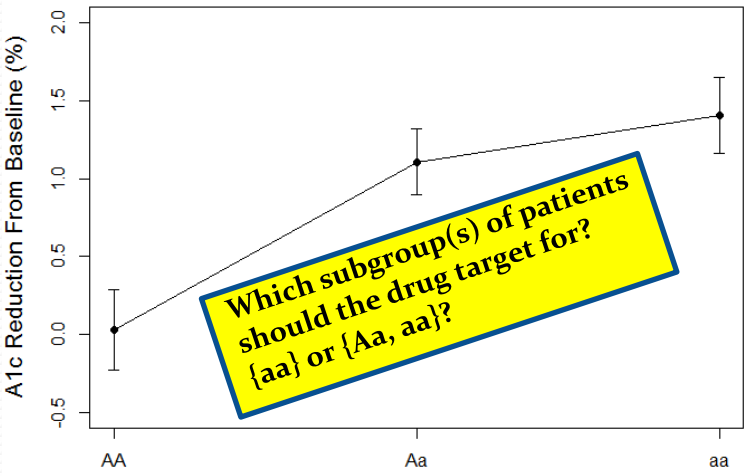
ORIGINAL ARTICLE

Effects of CYP2C19 Genotype on Outcomes of Clopidogrel Treatment

patients with atrial fibrillation. Patients were genotyped for three single-nucleotide polymorphisms (*2, *3, *17) that define the major *CYP2C19* alleles.

Treatment efficacy v.s. association detection

- Testing for SNPs predictive of treatment efficacy is fundamentally different from association detection for a quantitative trait.
  - clinical effect size vs merely statistical significance
  - Identify genetic subgroups for the drug to target vs detect genetic characteristics associated with the disease



Correct and useful statistical inference

- Strong control of FWER => correct inference
- Directly align statistical inference with decision-making process => useful inference
- Correct patient population to target
  - ✓ Infer '*A*' is dominant when the truth is '*A*' is dominant
  - ✗ Reject due to a significant finding of '*a*' recessive when the truth is '*A*' dominant
  - ✗ Reject due to an existence of a non-zero contrast which is not biologically meaningful (e.g., $(\frac{1}{2}\mu_{Aa}+\frac{1}{3}\mu_{AA})-\frac{5}{6}\mu_{aa}>0$)