Challenges in Leveraging GWAS Findings during Drug Development: A Case Study

Enabling Precision Medicine:
The Role of Genetics in Clinical Drug Development

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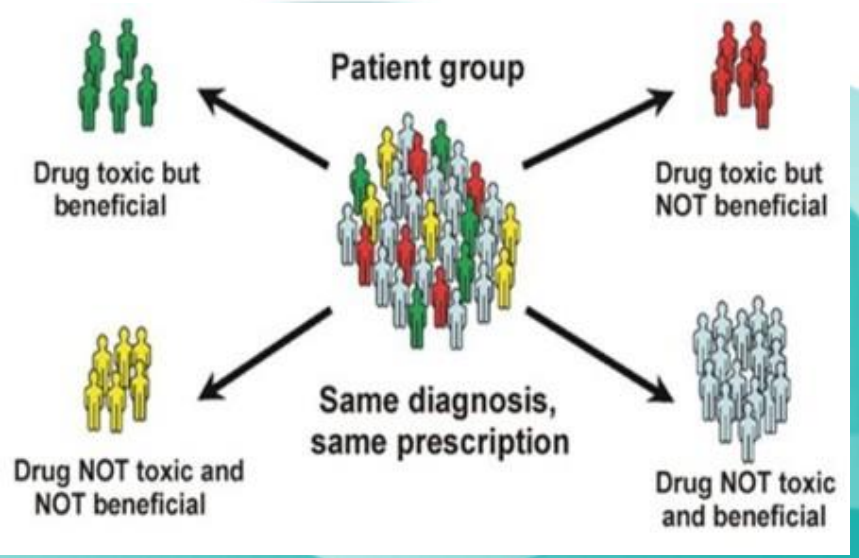
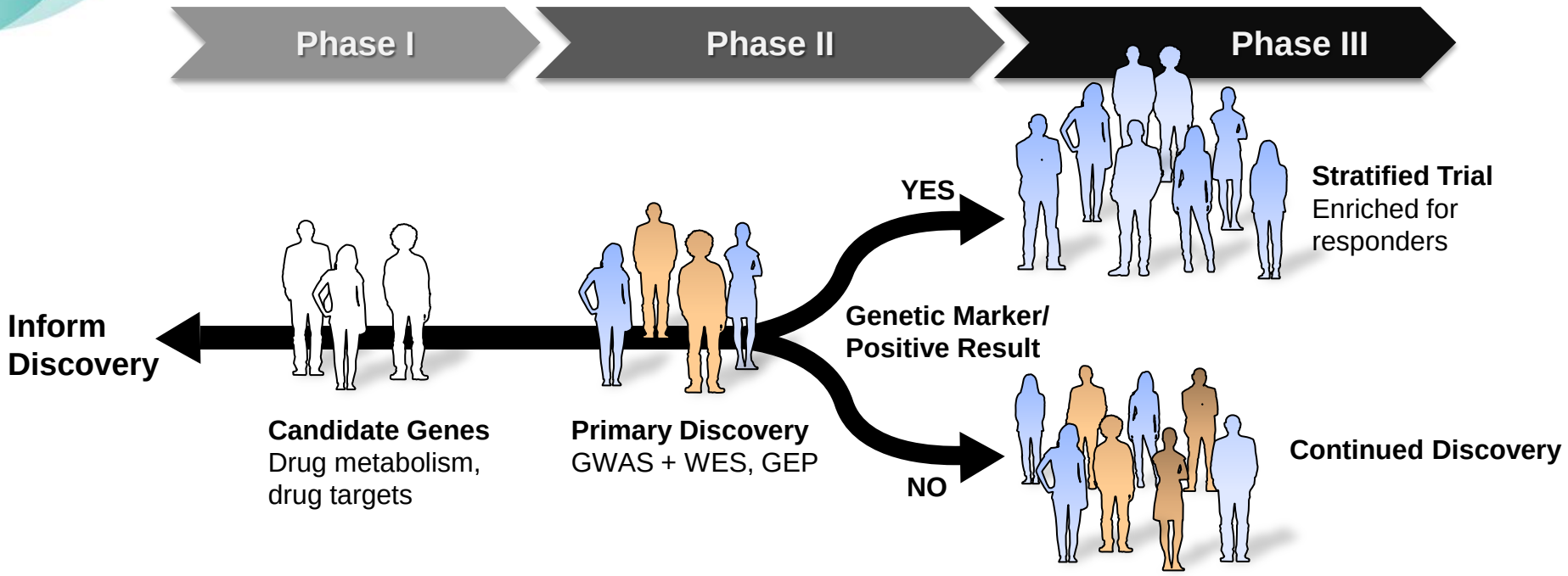


Mission: Understand and leverage key genetic determinants of patient response to our drugs

Routine genetic / genomic studies in clinical trials



GENETICS	**Genetic variation explains PK variability**	**Genetic variation explains variable efficacy**	**Validation: Phase II GWAS "hit" predicts for response in Phase 3**
ONCOLOGY	**BMx predictive for response/resistance , new drug combinations, new drug targets**		

Global approach to clinical trial ops

Goal: Incorporate pharmacogenomics routinely into global clinical trials

- Maintaining patient privacy and consenting choice
- Without delaying the trial

Dual consenting approach

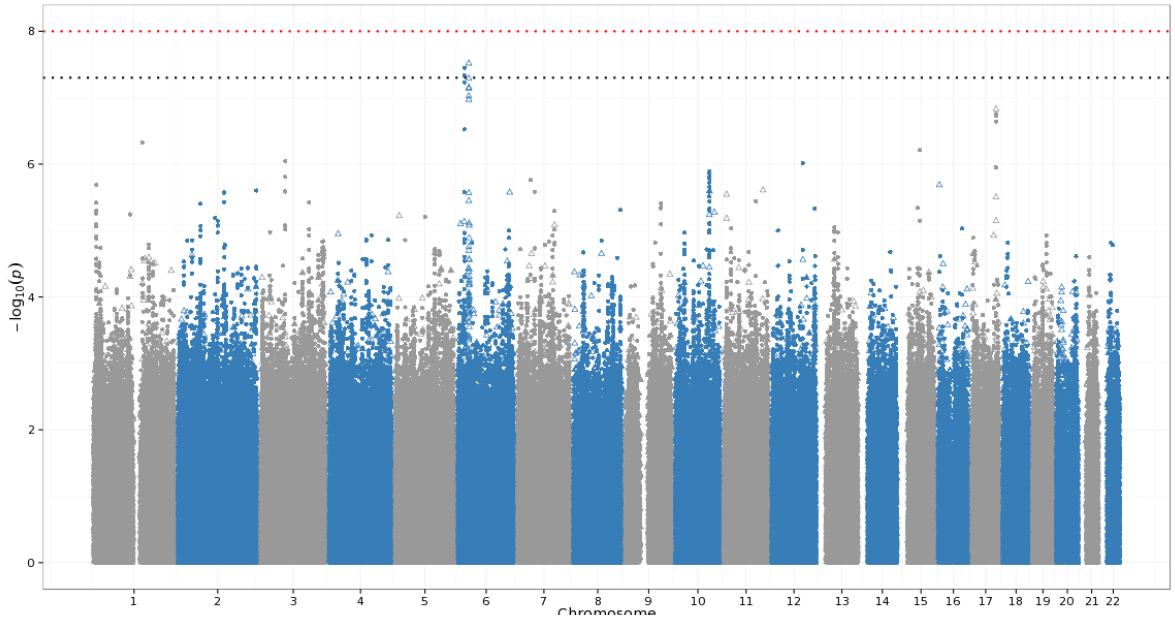
1. **Planned PGx Objective**
2. **Future Biomedical Research (FBR)**

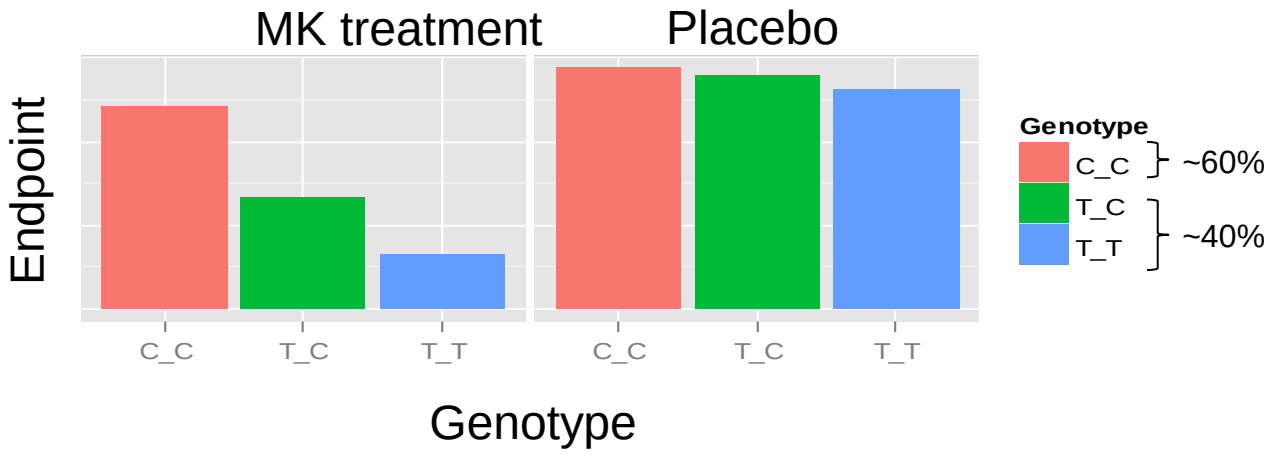
Planned PGx	Future Biomedical Research

• PGx objective in protocol
• Consented via the main clinical trial consent
• Required element for protocol enrollment
	• Separate voluntary FBR consent
	• Allows patient choice
	  • participate in broad research
	  • long term sample retention

Consent form clearly informs that we do not return research data, including genetics data, to study participants

Case Study GWAS:
SNP association with primary clinical endpoint



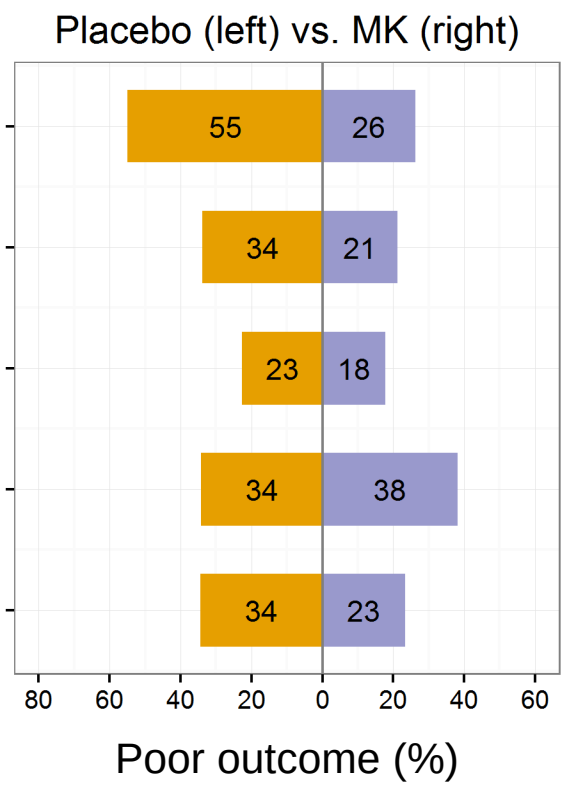


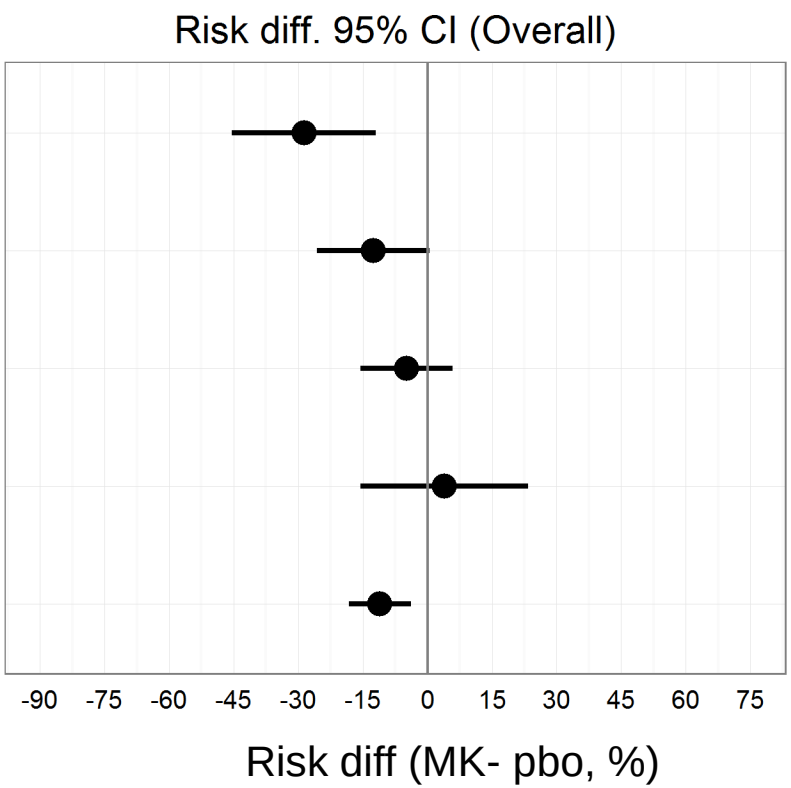
- 2 randomized,, controlled Phase III studies
- demonstrated efficacy in overall population
- GWAS on ~ 1000 pts
- T allele associated with better response
- Drug approved for “high risk” patients

MERCK
Be well

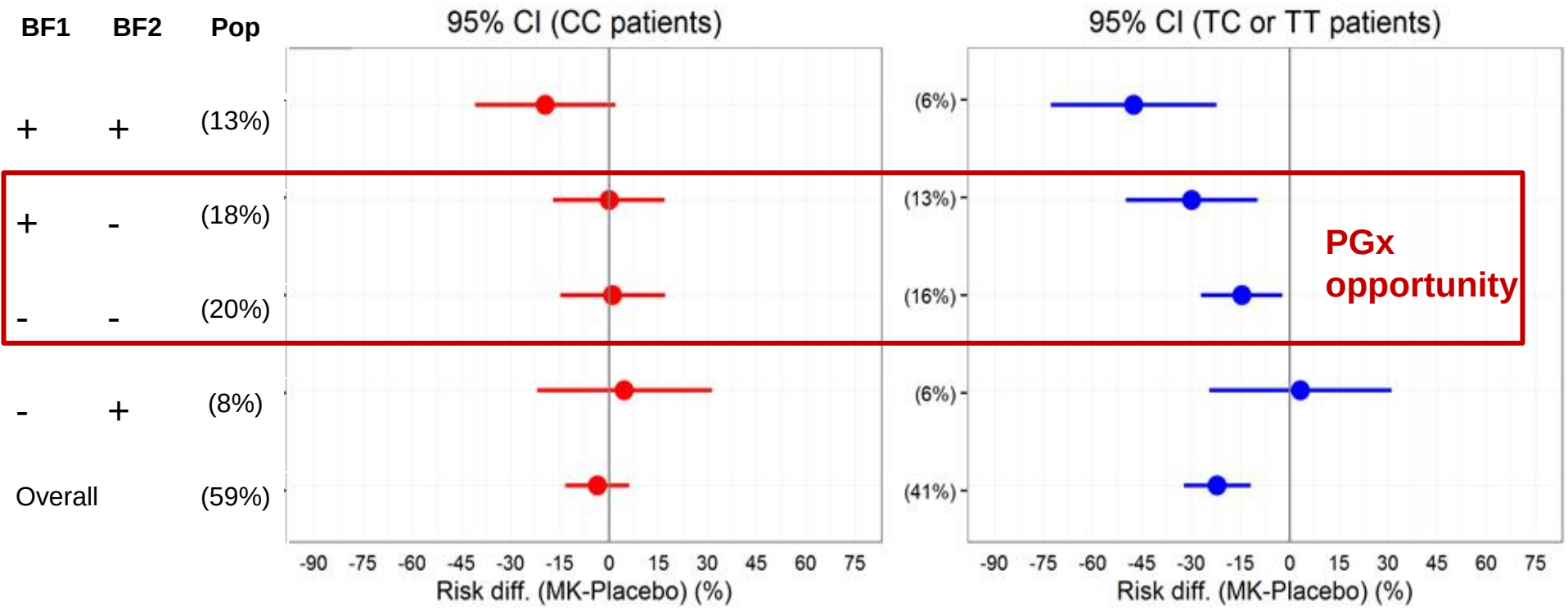
Therapy is most beneficial in patients with specific baseline risk factors

BF1	BF2	Pop
+	+	(19%)
+	-	(31%)
-	-	(36%)
-	+	(15%)
Overall		(100%)





PGx impact by genotype in sub-groups with baseline risk factors (BF)



PGx might identify responders *and* have positive impact on market uptake

PGx opportunity assessment

- Market research conducted in 3 large global markets
  - N = 50 physicians per market
- Physicians introduced to product profile and genetic results
- Asked about how they would use a diagnostic test in 2 different scenarios
  - Test optional for prescribing (complementary diagnostic)
  - Test required for prescribing (companion diagnostic)
- Results indicated that
  - Physicians would test > 50 % of pts in mandatory scenario and > 40% of patients in optional setting
  - For both scenarios, the test was most likely to be used in the “high risk” population (where the test is not required)
  - Drug likely to be used less frequently even among those patients who did not require a test and had high medical need

Challenges for PGx impact

- Difficult to obtain IRB and Health Authority approval to conduct genomic research in world wide settings
- Return of genetic data/incidental findings is a “hot topic”
- Late stage trials are where there is most power to detect an association
  - Difficult to adjust development strategy in late stage
- Significant education is required
  - IRBs
  - Health Authorities
  - Physicians
  - Payors