



**Heterogeneity in Treatment Response:
What is it, why is it important, and how to find it**


Károly Kulich, PhD
PRO Expert
Novartis Pharmaceuticals



One Size Does NOT Fit All!




Confidential Information



Background

- RCTs are the cornerstone of evidence-based medicine
- Randomization provides the best estimate of average treatment effect
- However, some patients within the study and outside the study will receive either more or less benefit than the reported average
- This variation is called "heterogeneity of treatment effects"
- Personalized medicine and comparative effectiveness is based on the above assumption

Confidential Information




Reasons for Heterogeneity

- The drug
 - Absorption, distribution, metabolism, rate of elimination, etc.
- Physiology
 - Drug concentration at target site
 - Number and functionality of target receptors

Some patients metabolize Isoniazid rapidly, thereby diminishing its effectiveness against tuberculosis.
Sykes 2000

Confidential Information



Reasons for Heterogeneity

- Underlying risk
 - Widely differing prognosis depending on the severity of the primary illness
 - Number of comorbidities
 - Type of comorbidities

Patients with atrial fibrillation and rheumatic heart disease are 18 times more likely to experience a stroke compared with those free of valvular heart disease (Lip and Lowe 1996)

Confidential Information



Reasons for Heterogeneity

- Responsiveness to treatment
 - Physiological
 - Functional
 - Personality: anxious patients tend to be less responsive to drugs, high placebo responders
 - Genetic
 - 7% of whites cannot metabolize codeine, so they do not get any pain relief from codeine

The variation in response to penicillin in the US can be attributed to the prevalence of penicillin-resistance bacteria (McCormick et al. 2003)

Confidential Information



Reasons for Heterogeneity

- Vulnerability to adverse effects
 - Genetics
 - Schizophrenics with alterations in the serotonin 2A receptor gene are more vulnerable to tardive dyskinesia when treated with conventional antipsychotics
 - Institutional or geographic differences

SEPTEMBER 20, 2005, 7:50 PM EDT
U.S. ranks high on cancer care, lowest on diabetes treatment
True or false: U.S. health care is the best in the world. Both true and false, according to Mark Pearson, who painted a

Confidential Information



Reasons for Heterogeneity

- Patient-reported outcomes
 - Patient expectations
 - Patient preferences
 - Cultural differences not related to translation quality

Confidential Information

