Heterogeneity of Treatment Effects
A Reassessment in the Era of Comparative Effectiveness Research

Panel Leaders
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Panel Objectives
- Provide broad overview of the concept of heterogeneity of treatment effects (HTE)
- Present traditional approach to handling HTE in randomized clinical trials (RCTs)
- Present alternative viewpoints on HTE and implications for clinical trial design
- Engage in discussion on the importance & impact of HTE in era of comparative effectiveness research and personalized medicine

Heterogeneity of Treatment Effects: Not a new concept ...
"It's far more important to know what person the disease has than what disease the person has" - Hippocrates
"Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease" - Sir William Osler

Heterogeneity of Treatment Effects: And recently from modelers ...
Heterogeneity of Treatment Effects: What is it?

- HTE refers to the fact that different patients respond differently to the same treatment.
- Statistically, HTE is evidenced by interaction between the treatment effect and individual patient effect(s):
  - Variability of individual treatment effects about the mean.
  - Statistically significant coefficients for control variables in multivariate analyses of trial results.
  - Different mean treatment effects across subgroups in stratified analyses.
- HTE means that the 'average treatment effect' commonly reported in RCTs will vary in its applicability to individual patients.

Heterogeneity of Treatment Effects: What does it look like statistically?

- Sample 1 is centered but fails to reflect the diversity of the population in terms of net treatment benefit. Sample 2 is centered of individuals who happen to derive much more net benefit from the treatment than does the average member of the population. Only sample 3 is broadly representative of the population in terms of risk, responsiveness, and vulnerability.

From: Kravitz, Duan & Braslow (2004)

Heterogeneity of Treatment Effects: Where does it come from?

- Kravitz, Duan & Braslow (2004) identify four sources (or "dimensions") of HTE:
  1. Risk without Treatment: likelihood that an untreated patient will experience a disease-related event (aka "baseline risk" or "susceptibility/prognosis").
  2. Responsiveness to Treatment: likelihood that a treated patient will experience clinically significant benefit (and magnitude of benefit).
  3. Vulnerability to Side Effects: likelihood that a treated patient will experience clinically significant adverse effects (and severity).
  4. Utilities: patients' preferences (usually implicit) for different outcomes.

Heterogeneity of Treatment Effects: Patient-Related Factors Affecting Responsiveness

- Sociodemographic differences:
  - Age, sex, race/ethnicity
- Clinical differences:
  - Severity of illness, comorbidities
- Genetic/biologic differences:
  - Presence/absence of a gene, rates of drug absorption/metabolism, concentration of drug receptors
- Behavioral differences:
  - Treatment compliance, alcohol consumption, tobacco use

Heterogeneity of Treatment Effects: Why does it matter to patients?

- As a result of HTE, patients may...
  - be receiving treatments that confer no benefits or, worse, cause harm
  - not be receiving treatments that could benefit them
- Failure to recognize HTE therefore can lead to suboptimal treatment outcomes.

Heterogeneity of Treatment Effects: Why does it matter to payers?

- As a result of HTE, payers may be...
  - reimbursing for ineffective—and potentially—harmful treatment
  - failing to realize cost offsets associated with effective treatment (when it is not administered to a patient who could benefit)
  - reimbursing for downstream consequences of ineffective first-line therapy
- Failure to recognize HTE can lead to higher costs, poorer outcomes, and inefficient resource allocation.
Heterogeneity of Treatment Effects: The problem of averages from clinical trials ...

- ‘Personalized medicine’ is all about moving away from naïve expectation that data on average treatment effect are sufficient to inform decision making for individual patients.

These data on average treatment effect are helpful, but when I look at my patients I see individuals—not averages.

Heterogeneity of Treatment Effects: Implications for Randomized Controlled Trials

- HTE sets up a tug-o-war between internal validity vs external validity in clinical trial design & data analysis.

Internal validity is maximized by rooting out extraneous sources of variation, so as to isolate the 'pure' treatment effect. Statistical analyses can control for any such variation that remains.

External validity (generalizability) is maximized by designing trial to be more reflective of everyday clinical practice. Stratified analyses can provide treatment effects for relevant patient subgroups.

Heterogeneity of Treatment Effects: Turning art into science ...

“If it were not for the great variability among individuals, medicine might as well be a science and not an art.”
- Sir William Osler

- Pharmacogenomics and other advances offer the potential to bring scientific thought and better data into new realms.
- Can better approaches to HTE replace the art of medicine with science?
- In the era of comparative effectiveness research, is that what is expected from us?

Heterogeneity of Treatment Effects: Discussion Questions

- HTE seems to cause tension between internal & external validity in trial design—does it have to be this way? Is there a “sweet spot” where we can adequately satisfy both?
- Historically, subgroups have been formed on the basis of overt phenotypic variation (eg, age, sex) among patients—is that enough to address HTE or do we need to assess genotypic variation as well?
- Statistically, forming subgroups based on numerous co-variates quickly becomes problematic for power—how promising are composite scoring techniques?
- What are the implications of HTE for related fields, such as meta-analysis and economic modeling?