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Introduction

The commonplace use of evidence-based medicine, clinical treatment guidelines, formulary entries, and quality-of-care measures applies average effects based on results in heterogeneous clinical trial populations to the treatment of individual patients. Yet individual patients and key subgroups receiving the same treatment often experience responses that can vary greatly, ranging from optimal resolution of the condition to detrimental or even lethal adverse events. These different responses to treatment are known as heterogeneity of treatment effects (HTE). Concerns about HTE are becoming a more prominent focus of consideration in the current healthcare environment.

Although HTE has always existed, this phenomenon has not yet been well characterized or investigated. The spectrum of effects reflects the numerous variables present within and acting upon every patient population. Key variables leading to HTE include factors such as illness severity and risk of poor outcome, age, sex, hepatic and renal function, use of concomitant medications, care setting, comorbidities, genetic variations, and diet; the list grows as our understanding of this phenomenon increases. HTE remains, even in well-designed clinical trials of investigational therapies in which attempts are made to control these confounding factors and variables.

A conference held in Washington, DC, on March 9, 2006, examined in depth the phenomenon of HTE and its implications for guidelines, payment, and quality-of-care assessment. The program began with several scientific and clinical presentations, followed by a policymaker roundtable discussion. The articles in this supplement to *The American Journal of Medicine* summarize the important information delivered in these presentations.

In the first article, my coauthors and I describe the sources of HTE within trials that can compromise the interpretation of results, the sources of HTE in the target population that limit the generalizability of trials, and strategies for understanding and managing HTE. We focus on 2 evolving phenomena that impair the ability to develop guidelines, payment rules, and quality-of-care measures based on randomized controlled trials. First, there is now a broader spectrum of illness severity inclusion, permitting patients with less severe disease, who are less likely to benefit from a drug or treatment, to be included in randomized controlled trials. These people are less likely to respond to an agent than are sicker patients, thereby reducing the power for the trial and yielding negative or null results for the trial. Second, although the general population is living longer with more chronic diseases, randomized controlled trials often exclude such longer-lived patients, only to have findings subsequently generalized from younger trial-eligible patients to these older, complex patients whose mortality from comorbid diseases reduces treatment effectiveness. Together, these phenomena impose challenges on the usefulness of the results of randomized controlled trials for clinical and policy applications.

In the second article, Dr. Barry J. Materson examines the presence of HTE in the treatment of hypertension. There are several layers of variables recognized in the measurement and treatment of hypertension. Use of blood pressure measurement guidelines and consistent techniques help to reduce the potential variability associated with clinician measurements. Intrinsic patient characteristics, such as age and race/ethnicity, can affect blood pressure and the efficacy and adverse events observed with antihypertensive medications. Dr. Materson also discusses clinical examples of mutations that affect antihypertensive response, including multiple polymorphisms within components of the renin-angiotensin-aldosterone system.

The third article, by Dr. David B. Goldstein, reviews the pharmacogenetic influences on HTE. Drug response may be dictated by variation in genes involved in both pharmacokinetic (PK) and pharmacodynamic (PD) pathways. Functional polymorphisms of PK genes can result in patients being poor, intermediate, efficient, or ultrarapid metabolizers of specific agents, thereby influencing efficacy and/or susceptibility to adverse drug reactions and necessitating individualized dosing. Variants of genes regulating PD pathways may alter drug target pathways, potentially affecting patient outcomes in a more pronounced manner. These PK and PD polymorphisms may act independently or in combination to affect drug response. Better understanding of these pharmacogenetic factors may help to clarify

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sources of HTE that were once considered intangible, thereby affecting patient treatment decisions.

The treatment of mental illness presents another opportunity to examine HTE. In general, outcome measures for psychiatric conditions are subjective, with symptomatology and treatment results varying greatly among patients. In the fourth article, Dr. T. Scott Stroup discusses HTE in the context of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) research program sponsored by the National Institute of Mental Health (NIMH). The CATIE trial studied schizophrenia, a disease state inherently prone to HTE, and was designed with broad inclusion and minimal exclusion criteria to create a realistic and varied sample population. Dr. Stroup identifies some of the sources of treatment response variability within this diverse trial population. Collectively, the CATIE results highlight the extent of variable drug efficacy and tolerability response in the treatment of psychoses, demonstrating the need for individualized therapy for schizophrenia.

During the afternoon roundtable, healthcare policymakers discussed the clinical presentations on HTE and examined how such information could be incorporated into their decision-making process. In the final article, written on behalf of the HTE Policy Roundtable Panel, Dr. Michael J. McLaughlin presents their findings. The panel members agreed that HTE should be considered when determining healthcare policy. Their discussion highlights the implications of this phenomenon beyond patient–physician interactions, extending throughout seemingly disparate sectors of the healthcare system, e.g., government agencies, third-party payers, and employers. Some of the panel members have even taken steps within their own organizations to deliver individualized, quality healthcare in light of the existence of HTE. The consensus of the roundtable was that more data from clinical trials, patient databases, and similar sources should be made available to physicians and policymakers so that well-informed decisions can be implemented.

The implications of HTE for today's medicine are extensive. By recognizing the factors associated with HTE, researchers can design clinical trials that better characterize those individuals and groups of individuals who will benefit from various therapeutic options. Clinicians and healthcare administrators can then make pragmatic use of the results by implementing policy changes to renovate healthcare in light of this significant phenomenon. More HTE-related clinical data, along with access to multiple pharmacotherapeutic options, appear to be the most promising ways to address the response variability relative to the delivery of quality healthcare.

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