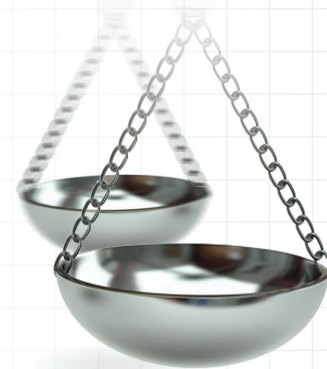




If we recognize heterogeneity of treatment effect can we lessen waste?

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“Here, we describe how inattention to heterogeneity of treatment effect may be an important driver of the overuse of healthcare”

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Much of the waste in healthcare comes from the overuse of resources, which has been defined as the provision of care in circumstances where the potential for harm exceeds the potential for benefit [1]. Overuse of healthcare sometimes causes physical harm to patients [2–4] and regularly contributes to ‘financial injury’ [5,6]. Overuse also harms our healthcare system through diversion of resources from patients who are more likely to benefit [7].

Overuse is pervasive, yet older patients may be particularly vulnerable to overuse and are a valuable population for illustration. Older patients are too frequently screened for illnesses which are unlikely to impact them in their lifetimes [8,9]; they also receive treatments that do not importantly impact their disease course or quality of life during their remaining months or years. Older adults are often subjected to diagnostic or treatment cascades that ensue after an initial test or intervention that, perhaps, should never have happened [10,11]. Similarly, older patients are often subjected to polypharmacy with use of medicines with little added value [12,13]. These are often therapies that are prescribed with good intentions, but are misdirected because clinicians underappreciate heterogeneity of treatment effect. Here, we describe how inattention to heterogeneity of treatment effect may be an important driver of the overuse of healthcare.

Morgan and colleagues developed a framework to conceptualize drivers of overuse that is structured around five domains [14]. One of the five domains is about clinicians’ attitudes and beliefs about healthcare. In this domain, the authors include factors such as poor clinician numeracy and insufficient knowledge of evidence, and past experiences with patients with the same condition (presumably leading to cognitive biases from heuristic strategies). We would propose that this domain might also include clinician’s unrecognition that there will be heterogeneity of treatment effect within their patient population and this should impact their treatment recommendations.

Heterogeneity of treatment effect can be defined as the nonrandom, explainable variability in the direction and magnitude of individual treatment effects, including both beneficial and adverse effects [15]. When clinicians do not recognize that a given patient may have a markedly different response to treatment than the average treatment effect (ATE), there will be overuse of resources if the treatment is recommended or prescribed to patients who are unlikely to benefit. Understanding heterogeneity of treatment effect is critical to decisions that are based on knowing how well a treatment is likely to work for an individual or group of very similar individuals. Underappreciation of this heterogeneity, therefore, contributes to overuse of resources since interventions will be recommended where the magnitude of absolute benefit for an individual is small or the absolute harm exceeds the benefit for that individual. These, then, are wasteful therapies.

Clinicians often do not have the information they need to make treatment recommendations for individual patients. Published clinical trials almost always report only the ATE. The assumption is that this average effect is applicable to all future patients who are ‘similar’ to those who participated in the trial [16]. Ideally, we would like to have estimates of treatment effect at the individual level – ‘individualized’ treatment effect (ITE). However, ITEs

are challenging to obtain and are highly variable. Subgroup analysis is a middle approach between ATE and ITE, where treatment effects are reported in prespecified, clinically important subgroups.

Published trials are often deficient in their reporting of heterogeneity of treatment effect across clinical subgroups, including inadequate reporting of the absolute benefits and absolute harms for important subgroups. A systematic review in 2009 examined published literature in major medical journals for adequacy of addressing heterogeneity of treatment effect, describing whether the studies utilized a formal test for HTE, or reported treatment-by-covariate interaction or reported results in subgroups [17]. Out of the 319 trials included, fewer than a third reported heterogeneity of treatment effect analyses; one-quarter reported subgroup analyses only, without more formally examining heterogeneity of treatment effect. This work was updated in 2016 and showed little improvement [18]. In fact, the percentage of studies demonstrating appropriate methods for heterogeneity of treatment effect evaluation decreased over time. Without this information, clinicians are forced to apply their knowledge of average treatment effects when making decisions with their patients. Older adults are asked to accept treatments where, in truth, their likelihood of benefit is often less than their likelihood of harm. The average treatment effects reported are often not informative to decisions regarding the care of an individual patient. This is a source of overuse of healthcare, although its magnitude has not been quantified.

Similarly, a review of the description of heterogeneity of treatment effect in studies evaluating the cost-effectiveness of therapies, which is downstream to evaluation of efficacy and effectiveness, found similarly little description of heterogeneity of treatment effect within these studies [19]. These authors operationalized sources of patient variability in cost-effectiveness analyses as those due to patient demographic differences, and others including life expectancy, baseline risk of an outcome, treatment effect, patient preferences and cost differences across patients. They found that most studies did not stratify results by observable patient characteristics, suggesting that users of the analyses do not have the information needed to target interventions to certain individuals and groups based on this measure of healthcare value.

In precision (or personalized) medicine initiatives, there too has been inadequate attention to whether the phenotypic (or genotypic) patient subgroups that are emerging from machine learning and from prediction modeling differ in their responses to treatments. If patients with aggressive and less aggressive tumors respond similarly to treatment, there is little value to subsetting by tumor characteristics; patients would be treated similarly regardless of the characteristics of the tumor. As illustrated by Brook and Fang, the probability of an outcome (such as tumor growth and metastasis) and the likelihood of treatment response (shrinkage of tumor with treatment) are different metrics [20]. They remind us that factors that affect the probability of the outcome (prognostic factors) and the factors that affect treatment effectiveness (predictive factors) may be very different. Recognizing that these are unique metrics is essential for reducing overuse of healthcare resources.

We think that the insufficient attention to heterogeneity of treatment in practice effect stems from: uncertainty about subgroup effects and individualized effects, absence of point-of-care information about heterogeneity in effects, and challenges in communicating with patients on this topic to inform decision making. Unquestionably, the tools for subsetting populations based on genetic information, tumor characteristics, biomarkers and phenotypic information are continually being developed and refined. However, equally important is the continued development of study designs, methods and analytic tools that use this information to understand whether responses to treatment vary across subsets, the magnitude of these differences and the importance of these differences when making clinical decisions. This is the information that is needed to choose high-value therapies and reduce waste. The field of individualized health needs more wide-reaching application of analytic tools to evaluate heterogeneity of treatment effect among population subsets, with the goal of getting the right treatment to the right patient. If we do not do this, we will continue to waste resources and harm patients.

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