

Individual Treatment Effects: Implications for Research, Clinical Practice, and Policy

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The hypothetical Ms Jones, aged 55 years, has successfully managed her recurrent depression with sertraline. She plans to join her new state health exchange. Based upon the Essential Health Benefits Final Rule, the health exchange need only cover as many medications per class as are included in that state's benchmark plan.¹ Her exchange chose to offer fluoxetine rather than sertraline. Some researchers have posited that selective serotonin reuptake inhibitors (SSRIs) do not substantially differ in terms of maintaining remission; however, these studies have generally examined "average" efficacy.²

Determining which treatment works best for a population, on average, differs from determining what works best for individual patients.³ Ms Jones asks her provider if she is likely to relapse or see less benefit if she switches to the new preferred drug. To aid in decisions that Ms Jones and other patients have to make, there is increasing interest in and funding of comparative effectiveness research (CER) by the Patient-Centered Outcomes Research Institute (PCORI).⁴ While many CER studies will compare the benefits and the harms of alternative treatments in large real-world populations, leading to conclusions based on the "average" treatment effect for a certain population, there is increased discussion and funding to attempt to understand which patients respond differently.⁵⁻⁷

Because patients do not all respond in the same way, treatment decisions, clinical guidelines, and coverage policies applied in a "one-size-fits-all" fashion based upon this average response may prove suboptimal. As an example, although percutaneous coronary interventions achieve similar benefits with less morbidity than bypass surgery for many patients, recent studies indicate that bypass surgery leads to better outcomes in patients with complicated diabetes.⁸

Achieving a proper balance between population-based approaches and individualized decision making is critical. Depending upon how it is applied, CER could yield sub-

ABSTRACT

Funding for comparative effectiveness research (CER) has focused attention on what treatments work best under what specific clinical circumstances, and for whom. Because not all patients respond in the same way, treatment decisions, clinical guidelines, and coverage policies applied in a "one-size-fits-all" fashion based upon the population "average" response may lead to suboptimal outcomes. Existing frameworks focus on why patients respond differently to treatments. We propose a framework that identifies when these differences are likely to be clinically important. Scenarios are presented in which it may be most critical for clinical decisions and policies to distinguish between the average and the individual patient so that treatment recommendations provide the greatest benefits for the largest number of patients. We provide recommendations for researchers to help identify issues to study, for providers to help assist them in recommending optimal treatment for individual patients, and for payers or public health bodies to help balance societal needs with those of the individual.

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stantial benefit for some, little benefit for many, and even harm to others. Various authors and prior frameworks focused on *why* treatment responses differ among individuals; they cited such factors as variability in the underlying clinical condition or patient population, differential risk in therapeutic potential, vulnerability to adverse effects, and patient preferences.⁹ This variability may be attributed to genetic determinants, sociodemographic factors, disease characteristics, or patient comorbidities.¹⁰⁻¹⁴ For further explanation and clinical examples, see the **Table**.

In contrast to prior frameworks that address the cause of variability, we focus on the *implications* of heterogeneity by addressing whether those potential differences are likely to be clinically substantial and should therefore influence the therapeutic choice. Our framework can assist providers as they consider whether to apply a particular CER result to an individual patient, to payers whose policies influence what choices are available, and to policy makers who guide the financing, delivery, access, and quality of healthcare. Both frameworks (*why* treatment response differs and the *implications* of treatment response differences for patient care) can be used by the research community to identify clinical areas in need of further investigation.

For Ms Jones' provider, the ability to predict when treatment response will likely differ for specific patients is important to enable individualized treatment. Ideally, evidence would be available comparing the benefits with the harms of treatment options in patients similar to Ms Jones. However, this level of evidence rarely exists. In an environment of inevitable uncertainty, Ms Jones, her providers, payers, and other policy makers will still have decisions to make. We present a framework that identifies when it may be most critical to distinguish between the average patient and the individual.

Framework to Assess the Impact of Individual Treatment Effects

When treatment response is unpredictable, how risky is it to apply population average results to individual patients? The answer depends upon: (1) the clinical consequences of delaying optimal treatment; (2) the underlying diversity in patient attributes; (3) the likelihood of response to similar treatments in similar ways (treatment independence); and (4) patient preferences (**Figure**). We provide illustrations for each factor below. It should be

Take-Away Points

Because not all patients respond in the same way, treatment decisions, clinical guidelines, and coverage policies applied in a “one-size-fits-all” fashion based upon the population “average” response may lead to suboptimal outcomes. This article includes:

- A framework to identify when it may be most critical for clinical decisions and policies to distinguish between the “average” and the individual patient so that treatment recommendations provide the greatest benefits for the largest number of patients.
- Recommendations to help researchers identify areas to study, help providers make optimal treatment recommendations for individual patients, and help payers or public health bodies to note when it is necessary to balance societal needs with those of the individual.

understood that these factors are not meant to provide a prescriptive or definitive answer, but rather to be considered collectively as a framework for dialogue and presumably improved decision making.

Clinical Consequences of Delaying Optimal Treatment.

For certain diseases (eg, hay fever, fibromyalgia), the patient and provider have time to try several treatments without the threat of irreversible consequences. Patients may have uncomfortable symptoms, but their conditions do not irreversibly deteriorate, and trying additional therapies is not likely to jeopardize long-term symptom control. Ms Jones—whose depression has been successfully controlled on sertraline—should feel safe to switch her therapy to fluoxetine, under close observation. Should failure occur, she would have the opportunity to begin the next therapeutic option. In other circumstances (ie, a patient with a more acute depressive presentation, or in whose case the switch in therapy results in discontinuation) the risks may well be far greater, and the consequences much less reversible (eg, suicide attempt). Other scenarios include patients who may have only 1 chance for treatment success prior to disease progression (eg, chemotherapy in oncology) or organ damage (eg, sepsis resulting in kidney failure). In circumstances when the consequences of being “wrong” are low—or when they are high but information exists and is accessible regarding who responds best—policies that narrow treatment choices may be appropriate. In other circumstances, when there is a high degree of treatment diversity, little evidence to determine which patients are likely to respond well, and the consequences of suboptimal treatment are high, policies should permit greater flexibility and access to treatment choices for the patient and provider.

Diversity in Patient Attributes. Some clinical conditions are well characterized by a set of defining attributes (eg, ST-vs non-ST-elevated myocardial infarction), whereas others are far more heterogeneous (eg, systemic lupus erythematosus presenting with dermatologic, arthritic, or vascular complications).¹⁰ Applying population results

■ **Table.** Rationale for Individual Treatment Effects and Examples Across a Variety of Clinical Conditions

Underlying Mechanism and Rationale	Clinical Examples
Variability in the Underlying Clinical Condition or Patient Population	
<ul style="list-style-type: none"> Diversity in the type and severity of clinical symptoms Demographics (age, gender, ethnicity) Prognostic risk (disease severity, number and type of synergistic comorbidities) Genetic risk Socioeconomic factors (health literacy and education) 	<p>Diversity in the type and severity of clinical symptoms: Depression severity is often rated by the Hamilton Depression Rating Scale (HAM-D). The scale comprises 17 questions, each with 3 to 5 possible responses based upon the severity of symptoms such as low mood, insomnia, agitation, anxiety, and weight loss. The scores are summed; higher scores indicate greater depression severity. Different patients can have different symptom complexes but be rated with the same overall score. These different symptoms may reflect the patient-specific neurohormonal imbalance and suggest optimal therapy.³⁶</p> <p>Prognostic risk: Primary prevention of stroke with anticoagulants is recommended for patients with nonvalvular atrial fibrillation. However, for an individual patient without additional risk factors the benefits associated with warfarin anticoagulation may not outweigh the risks.³⁷</p> <p>Genetic risk: Among women with hormone-receptor-positive, HER2: negative breast cancer, treatment may involve adjuvant endocrine therapy plus or minus adjuvant chemotherapy. For an individual patient with a high or intermediate risk of breast cancer recurrence based upon the 21-gene reverse transcription polymerase chain reaction assay, use of adjuvant chemotherapy may be the optimal treatment.³⁸</p>
Different Potential for Treatment Response	
<p>Therapeutic Potential</p> <ul style="list-style-type: none"> Pharmacologic differences in absorption, distribution, metabolism, or elimination <ul style="list-style-type: none"> Target effects based upon receptor availability or blood-brain barrier penetration Metabolic differences secondary to ethnicity/race, or cytochrome p450 expression Excretion differences secondary to impaired renal function Changes in receptor site availability or affinity for binding Therapeutic modifiers or interactions Narrow therapeutic window Smoking Genetic risk Socioeconomic factors (eg, healthcare access, income) 	<p>Pharmacologic differences: The proportion of patients in a population who are expected to be “poor” metabolizers varies with the enzyme system active in the metabolism of a given compound and the racial composition of the target population. For example, the proportion of patients who are poor metabolizers for the CYP2D6 enzyme system varies from 5 to 10% in white, to 3.8% in African Americans, to 0.9% in Asians. This can result in clinically important differences in safe and effective dosing regimens for drugs that are primarily metabolized by this enzyme system.³⁹</p> <p>Target effect due to receptor site availability: The ability of SSRIs to have a therapeutic effect has consistently been shown to be associated with at least 80% or higher receptor occupancy in most regions of the brain. One critical step toward receptor occupancy is receptor affinity. Thereby, patients with a greater number of receptors, or lower receptor affinity based upon genetics, are less likely to receive treatment benefit at similar dosages, thus requiring higher doses or treatments with an alternative mechanism of action.⁴⁰</p> <p>Therapeutic modifiers: Among patients with atrial fibrillation and a medium risk of stroke, warfarin may be preferred to aspirin for many patients. If a patient is unable to comply with warfarin monitoring, then aspirin may be preferred.</p> <p>Genetic risk: According to hypertension guidelines, thiazide-type diuretics may be a first line of treatment, and other agents such as calcium channel blockers are reserved for use in combination as second- or third-line agents. However, recent data suggest many African American patients with hypertension have CACNA1H genetic variations.⁴¹ Calcium channel blockers, which target these genes, may have better treatment effects among patients with this variation.</p> <p>Setting characteristics: Many guidelines recommend triaging patients with an ST-elevated myocardial infarction to hospitals offering percutaneous coronary intervention (PCI). However, for patients who live more than 60 minutes from a hospital with PCI capability, fibrinolytic therapy may be the optimal therapy.⁴²</p>
Vulnerability to Adverse Effects	
<ul style="list-style-type: none"> Disease worsening (or worsening of other comorbid conditions) Narrow therapeutic windows Drug-drug interactions Tolerability of side effects 	<p>Tolerability of side effects: Among patients with systemic lupus erythematosus, high-dose daily glucocorticoid therapy has been shown to improve survival. However, for many patients their sensitivity to steroids may result in metabolic complications, hypertension, osteoporosis, or more frequent infections. For patients needing but unable to tolerate high-dose glucocorticoids, other steroid-sparing agents or alternative dosing may be the optimal therapy.⁴³</p>
Patient Preferences	
<ul style="list-style-type: none"> Family history/relevance of condition to the patient Behavioral factors 	<p>Relevance of condition to the patient: Males aged ≥65 years diagnosed with low-risk localized prostate cancer may prefer active surveillance vs treatment with brachytherapy or radical prostatectomy, based upon weighing the risk of prostate cancer death against the reductions in quality of life, or other side effects, that treatment could cause.⁴⁴</p> <p>Behavioral factors: Most diabetes guidelines recommend intensive glucose control to avoid diabetes complications. However, among older patients with type 2 diabetes mellitus and less social support, patients are willing to risk future complications associated with high blood sugar and were more worried about dizziness, falls and other low blood sugar complications. Although intensive therapy may be best from a quality-of-care perspective, it may not be optimal for all patients aged ≥65 years.⁴⁵</p>

to individual patients is likely to be more appropriate in the former and more worrisome in the latter. Perhaps Ms Jones' depressive disorder manifests as anxiety and agitation rather than the classic symptoms of sadness, anorexia, or insomnia. For her, the optimal treatment would address the former symptoms, whereas other patients with the latter manifestations may need alternative treatments.

Population average results might blur these important distinctions and using these blended results could lead to suboptimal patient outcomes. Diversity in clinical attributes, outcomes, and response to treatment may also reflect comorbidities. One patient may have potential adverse consequences due to concomitant medications for a secondary disease while another may have a higher side effect risk due to renal dysfunction. A third patient may not suffer from any of the above. Unless a CER study analysis differentiates those patient subtypes or can predict which outcomes are likely, guidelines based upon the CER study might be appropriate for some patients but clinically inappropriate for others.

In general, the patient's clinical presentation is known to the provider, who can target the treatment regimen accordingly. In some environments, electronic data systems have the breadth and depth of data and the clinical logic applied to it (eg, prior depressive hospitalization within the last month vs no hospitalization; presence vs absence of comorbidities; or potential drug interactions) so that clinical decision support tools and payer policies that access that electronic information could similarly tailor appropriate access to needed medications. At other times, the clinical diversity may depend upon patient symptomatic complaints, patient adherence, laboratory test results, or imaging findings—elements not “visible” to most payers or automated systems that influence care. In these circumstances, policies should offer patients and providers more flexibility to select the appropriate treatment. When the condition is well defined, or if the implications of diversity are readily accessible, application of population-level treatment protocols or protocols that can account for this diversity may be appropriate.

Likelihood of not responding to similar treatments in similar ways (treatment independence). Based upon the success or failure of prior therapy, variation in response may be predictable. For example, if a patient fails 1 angiotensin-converting-enzyme (ACE) inhibitor for management of hypertension either for reasons of efficacy or safety, she is unlikely to respond well to another ACE inhibitor. Similarly, if amoxicillin is not successful for a urinary tract infection, another penicillin-like agent is less likely to resolve the problem compared with an agent in another

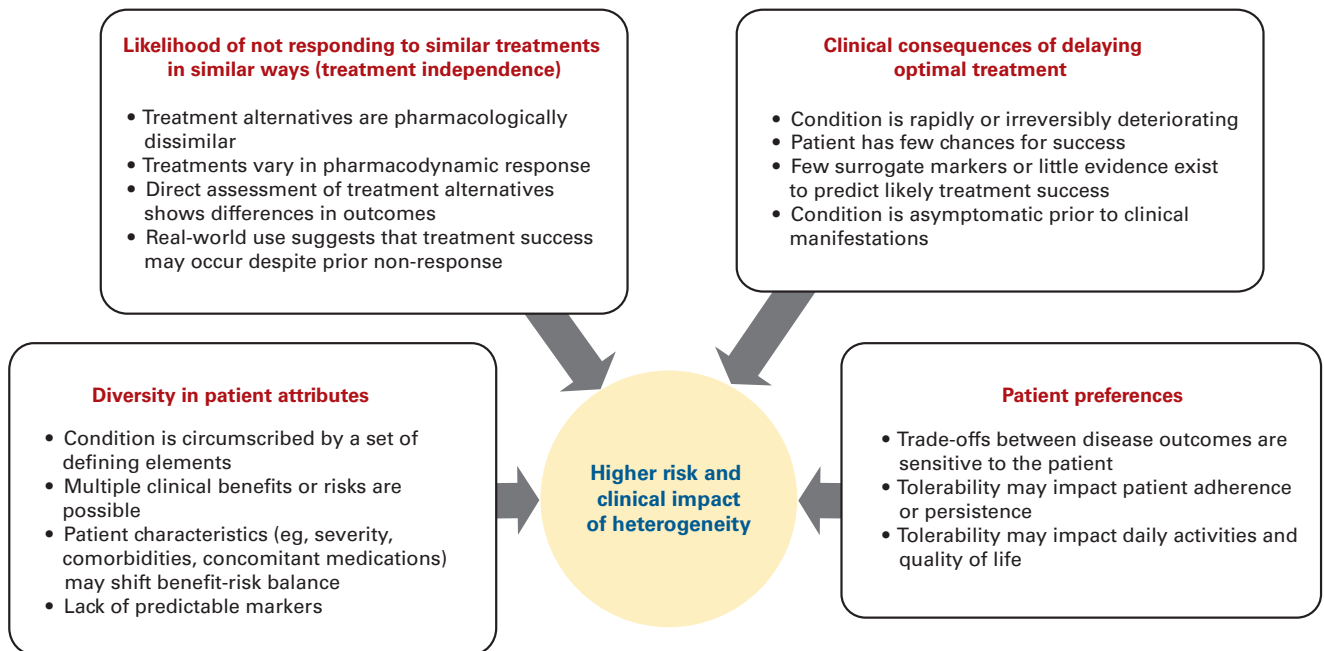
therapeutic class (eg, ciprofloxacin, sulfamethoxazole/trimethoprim). In these scenarios, the responses to available treatments within the same drug class are highly correlated, and treatment options are “dependent” on prior treatment success or failure. In contrast, for patients with depression like Ms Jones who are faced with a change in regimen, success with sertraline may not be matched by similar success with fluoxetine (eg, another SSRI).¹⁵ Here, treatment response is more “independent” of prior treatment success or failure.

Independence may vary from illness to illness, across treatment alternatives, or within a class of treatments.¹⁶ From a decision-making standpoint, when treatment independence is low (or dependence is high), patients may need to try only 1 therapy in a particular class since related treatments are not likely to be substantially more or less beneficial. In these circumstances, policies that narrow choices within a drug class may be appropriate. However, when treatment independence is high, response to treatment “A” does not eliminate the need for trials of treatments “B” or “C” even when the drugs are within the same therapeutic class. For these patients, access to multiple medications and flexibility to choose among them is needed. For Ms Jones, especially if her disease becomes unstable, the restricted antidepressant formulary of her state exchange that requires her to switch from sertraline to fluoxetine may prove problematic.

Patient Preferences. For Ms Jones, tolerability regarding such potential side effects as weight gain or sexual dysfunction may influence her treatment adherence and subsequently her ability to make the optimal therapeutic choice. These types of preferences vary from person to person and reflect attitudes associated with preferred outcomes (eg, increased survival vs greater quality of life); tolerability regarding side effects (eg, willingness to accept being drowsy); differences in socio-cultural preferences (eg, low-sodium diets in the American South); route of administration (eg, oral vs injectable medications), or willingness to make behavioral changes (eg, active vs sedentary lifestyle). Preferences also may change over time as symptoms worsen, conditions progress, or patients adapt to their health status.

There is increasing evidence that patient preferences influence health outcomes and costs.¹⁷ In treating hepatitis C, preferences for efficacy and treatment side effects are associated with adherence to antiviral therapy, a key component of achieving sustained viral response.¹⁸ For several common conditions (eg, cardiac angina, benign uterine fibroids, benign prostatic hyperplasia, hip pain, knee pain, and back pain), overall medical care costs were

■ **Figure.** Considerations for Assessing the Clinical Impact of Heterogeneity



shown to be reduced when patient preferences were considered in the decision-making process.¹⁹ For example, when joint replacement candidates were informed of the treatment benefits and risks, fewer patients chose to undergo costly surgeries.²⁰ Unfortunately, population-level comparative studies rarely assess patient preferences and we don't know whether individual preferences might lead to therapeutic choices which differ from the published "average" results.

For a provider, determining optimal treatment for an individual patient requires factoring in the available population-level evidence on benefits, risks, and costs to inform an individual patient's preferences. In some conditions (eg, hospital patients with pneumonia or acute myocardial infarction), patient preferences may not greatly differ and a standardized treatment protocol could be more appropriate. However, in patients with preference-sensitive conditions or conditions in which the potential risks and benefits of treatments differ greatly (eg, prostate cancer, bleeding due to uterine fibroids), it would be important to elicit those preferences and enable patients to choose among the alternative approaches: to not, in other words, strictly apply population-level findings. In scenarios where patient preference plays a critical role in determining the optimal choice among alternatives with different costs (eg, when adherence or patient expectations are important), a tension will exist between efficient resource allocation and patient choice. In some cases,

there may be limited evidence to justify a costly treatment for a terminal condition. In other cases, patient preference may come at a cost to other health plan members. In these cases, health plans and policy makers will need to consider the plan's purpose and deliberate on how benefit designs or policy statements could account for these tradeoffs to minimize costs and optimize health outcomes.

Implications for Research

Although genomic information will continue to offer the potential to predict individual response, it will not resolve all sources of variability. Research directly comparing treatment alternatives in the same patient is needed. However, direct assessment of treatment alternatives in the form of crossover studies or n-of-1 designs infrequently occurs. It is beyond the scope of this paper to address, but others researchers have discussed the benefits and limitations of using alternative research methods and analyses (eg, risk prediction models, latent growth mixture models, classification and regression analyses, and non-parametric models) to elucidate who will likely respond or will not to particular treatment approaches.²¹

For experimental and non-experimental studies, pre-specification of subgroups and collection of multiple baseline patient characteristics (eg, clinical, demographic, patient preferences) can help identify which patients differ in their treatment response and point to potential causal effects. Methods research on how to best elicit patient pref-

erences in clinical practice, and how to utilize information generated by patient-powered information sources and networks, could improve our ability to identify patient preferences; demonstration projects could incorporate these approaches into shared decision making. For payers and policy makers, studies on the clinical and economic impact of preferences on patients' ability to manage their health are needed.²² The information on the clinical and economic impact of patient preferences when treating depression would likely assist Ms Jones' healthcare provider in answering her question about the advisability of switching to the health exchange's preferred medication, and it would enable her payer to support rational decision making and balance the tension between costs and preferences.

PCORI's focus on patient variation and patient subgroups will improve our knowledge of heterogeneity.⁷ However, simply funding research on the topic will not be sufficient. Among top-tier journals, only 1 in 3 trials reported heterogeneity in treatment response.²³ To expand the availability of this evidence, journal editors could adopt usage of a CONSORT-like statement, in which authors would indicate the likelihood of heterogeneity (eg, high, medium, or low); report whether measures of heterogeneity were assessed; and list the factors that explain any heterogeneity.²⁴⁻²⁷ Transparent pre-specification of subgroups (eg, via time-stamped analysis plans on clinicaltrials.gov) and standardized subgroup reporting (eg, via online appendices, in databases managed by clinical condition consortia, or as specified by data standards groups) would enable meta-analysts to use this information and better explore patient differences. In turn, these meta-analyses would be able to identify areas in which individual treatment response varies or to suggest future research priorities.

Implications for Providers

As detailed CER results become available, providers will need to focus beyond the study-level conclusions and understand the patient associated with treatment response characteristics. With the large number of CER studies anticipated,²⁸ it is likely that providers will increasingly depend upon professional societies and clinical practice guidelines to assist them in sorting through this voluminous and often conflicting information. Providers would be greatly assisted if guideline developers would synthesize the information on treatment variability, treatment independence, and patient preferences, and then formulate practice recommendations with this level of detail. These same concepts should be considered by those

responsible for developing quality metrics, so that their clinical and policy decisions will not be affected in appropriate conclusions based on misleading population-level data.²⁹⁻³¹

In the future as mobile health (mHealth) communications between patients and providers become more widely adopted, providers will be able to quickly view a patient's symptoms, preferences, and clinical markers and determine if subsequent trials of alternative treatments are needed. As bedside information technology becomes more prevalent and sophisticated, providers will gain greater ability to offer evidence-based and individualized treatment recommendations. By mining large electronic databases, Ms Jones' provider could identify patients "similar" to her and determine how they responded to a switch from sertraline to fluoxetine.^{32,33}

Evidence regarding treatment independence could also guide providers on the likely "success rate" with second-line treatment. When treatment independence is high, rather than immediately switching to a medication in a different class, it may be appropriate to switch to other agents in the same class. In cases where treatment dependence is high (eg, treatment response is correlated with prior treatment success or failure due to similar pharmacologic or pharmacodynamic characteristics), altering the treatment strategy by using a drug in a different therapeutic class may be the preferred course. Finally, tools and training are needed to facilitate the provider-patient discussion of treatment options that incorporate individual preferences for possible risks and benefits.

Implications for Payers

Payers typically make population-based rather than highly individualized coverage and reimbursement decisions. This choice reflects limitations in the available information as well as the need to avoid creating an overly complex benefit design. When treatment independence is low, there is either minimal variation in treatment response or more variability that is predictable based on information accessible to the payer. In such scenarios, there is little risk of clinical deterioration; therefore, insurance designs that direct therapy toward preferred options through utilization management (eg, narrow or closed formularies, therapeutic substitution, step-therapy, or prior authorization) or by instituting financial incentives (eg, lower copayments for preferred tiers) may be acceptable.

Conversely, logistical burdens and financial incentives to access what the payer has deemed optimal treatment may be less acceptable when 1 or more of the following is present: 1) marked variation in treatment effects; 2) mini-

mal ability to predict individual response by the payer or clinical system; 3) treatment response with 1 treatment is not correlated to response with alternative treatments; 4) the consequences of suboptimal initial therapy are high. In these cases, more flexible utilization management designs or provider-directed decision making (within a range of evidence-based therapies) may be preferable.

Treatment heterogeneity also raises ethical dilemmas in reimbursement. Patients with a given biologic predisposition may find that treatments that are optimal for them are not the preferred agents based upon population “average” results. Currently, these patients would be required to pay higher amounts to access the non-preferred medications. To account for ethical standards of fairness,³⁴ patient co-payments for these patients should be similar to those of the preferred treatment options for the population “average.” With the increased sophistication of benefit design and electronic records, it may be feasible to account for biology or genetics and tailor co-payments accordingly.³⁵

CONCLUSIONS

CER will increasingly provide evidence about what treatments work best. For CER to achieve the greatest benefit, we need that evidence for groups of patients as well as for those individuals who may respond differently. We also need to understand the implications of applying population results to particular patients. In some circumstances, population results can and should be applied broadly. In other circumstances, caution is warranted. It is our hope that the framework discussed here begins to address this choice. We hope to encourage discussion about the importance of recognizing when additional research is needed, and about why providers, payers, and policy makers should acknowledge the implications of variation in treatment effect. Doing so should ultimately lead to improvements in health not only for the population as a whole, but also for individual patients like Ms Jones.

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