Abstract

Commentary on health care delivery prominently expresses two recommendations regarding variation in clinical practice. One calls for systematically different treatment of patients who differ in their observed covariates. The other calls for uniform treatment of patients who are observationally similar. Analysis of patient care as an optimization problem has provided foundation for both recommendations in settings where knowledge of treatment response is strong enough to determine optimal treatments. This paper assesses the recommendations when treatments are chosen under uncertainty. I find that the first is well-motivated, but the second is not. Indeed, variation in treatment of observationally similar patients can be useful. To develop this conclusion, I first consider decision making by a health planner who wants to optimize treatment for a population of patients. When treatment response is uncertain, two motives—diversification and learning—encourage a planner to randomize the treatment of observationally similar patients. I then consider a decentralized health care system in which clinicians make treatment decisions. Variation in clinical practice may not emulate the random variation that a health planner would choose. Nevertheless, it may still provide useful observational evidence about treatment response.
1. Introduction

Commentary on health care delivery prominently expresses two recommendations regarding variation in clinical practice. One calls for systematically different treatment of patients who differ in their observed covariates. The other calls for uniform treatment of patients who are observationally similar.

The recommendation calling for systematic differentiation of observationally different patients stems from longstanding recognition that evidence on patient medical history, symptoms, and test results may help to diagnosis illness and predict treatment response. Moreover, health professionals increasingly emphasize the relevance to treatment choice of genetic variability and patient preferences. Writers focusing on genetic variability often use the term \textit{personalized medicine}, while those focusing on patient preference use the term \textit{patient-centered medicine} [1, 2].

The recommendation calling for uniform treatment of observationally similar patients, commonly expressed in clinical practice guidelines (CPGs), stems from the conviction that variation in treatment of such patients indicates a deficiency in clinical practice. John Wennberg defines \textit{unwarranted variation} in care as variation that [3, p. 687]: "isn't explained by illness or patient preference." The UK National Health Service (NHS) gives its \textit{Atlas of Variation in Healthcare} [4] the subtitle "Reducing unwarranted variation to increase value and improve quality." A report on CPGs by a committee of the Institute of Medicine (IOM) states [5, p. 26]: "Trustworthy CPGs have the potential to reduce inappropriate practice variation." An IOM report on geographic variation in health care spending states [6, p. 2-15]: "geographic variation in spending is considered inappropriate or 'unacceptable' when it is caused by or results in ineffective use of treatments, as by provider failure to adhere to established clinical practice guidelines."

Many discussions of the two recommendations take them to be self-evident. Decision analysts who study patient care as an optimization problem have provided some foundation for them in settings where knowledge of treatment response is strong enough to determine optimal treatments. See, for example, [7, 8, 9, 10]. However, much care is delivered in settings with substantial uncertainty about treatment response,
where optimal treatments are unknown. Considering treatment of cancer, Mullins et al. [11, p. 59] observe that: "there is considerable uncertainty surrounding the clinical benefits and harms associated with oncology treatments." IOM report [5] calls attention to the assertion in 1992 by the Evidence-Based Medicine Working Group that (p. 33): "clinicians must accept uncertainty and the notion that clinical decisions are often made with scant knowledge of their true impact."

Are the two recommendations regarding variation in clinical practice well-motivated when treatment decisions are made under uncertainty? Addressing this question, I find that the first is but the second is not. Indeed, variation in treatment of observationally similar patients can be useful.

I develop this conclusion in two steps. Section 2 considers decision making by a health planner who wants to optimize treatment for a population of patients. I bring to bear my research on planning under ambiguity [12, 13], which shows that two motives—diversification and learning—encourage a planner to randomize the treatment of observationally similar patients.

Financial diversification is a familiar recommendation for portfolio allocation. A portfolio is diversified if an investor allocates positive fractions of wealth to different investments. Diversification enables an investor facing uncertain asset returns to limit the potential negative consequences of placing 'all eggs in one basket.' Analogously, treatment is diversified if a health planner randomly assigns observationally similar patients to different treatments. Treatment diversification enables a planner to avoid gross errors that might occur if all patients were inadvertently given an inferior treatment.

Diversification motivates random variation in clinical practice at a given point in time. Over time, such variation is even more useful because it effectively yields a population-wide randomized clinical trial (RCT) that yields new evidence about treatment response. As time passes and evidence accumulates, a planner can revise the fraction of patients assigned to each treatment in accord with the available knowledge. I have called this idea adaptive diversification.

Section 3 considers a decentralized health care system in which clinicians make treatment decisions,
perhaps informed or influenced by CPGs. Treatment variation in a decentralized system may not emulate the variation that a health planner would choose. In particular, clinicians may not randomize treatment. Nevertheless, treatment variation may still be useful.

To begin, I point out that when treatment response is uncertain, variation across clinicians in their treatment of similar patients does not per se imply a deficiency in practice. Uncertainty about the optimal treatment implies clinical equipoise, so treatment variation is consistent with medical ethics. Different clinicians may reasonably interpret the available evidence in different ways and may reasonably use different decision criteria to choose treatments. Thus, there is no prima facie reason to view treatment variation as unwarranted, inappropriate, or unacceptable.

Going further, I point out that randomization of treatment is not a prerequisite for learning about treatment response. It is wise to be skeptical of observational studies that draw strong conclusions based on untenable assumptions. Yet cautious observational studies using credible assumptions can yield useful findings. I summarize aspects of my research on partial identification of treatment response [12, 14, 15], which shows that observational studies using weak assumptions yield informative bounds on treatment response. In particular, I show that variation in clinical practice can be informative even if one knows nothing about the way that clinicians make treatment decisions.

Section 4 concludes with discussion of implications for the design of CPGs.

2. Health Planning

2.1. Optimal Treatment Choice

To analyze collective decision problems, economists and other decision analysts often consider how
a planner should behave. One specifies a set of policy alternatives and a social welfare function. One assumes knowledge of the welfare achieved by each policy alternative. With this knowledge, one can derive the optimal policy.

This broad idea has been used to study optimal decision making by a health planner who chooses treatments for a population of patients. In some health care systems, there exists an actual planning entity with considerable power to choose treatments for its patient population. Examples are the Military Health System in the United States, the National Health Service in the United Kingdom, and some private health maintenance organizations.

It has been common to suppose that the planner wants to maximize an additive welfare function, one that sums up the benefits and costs of treatment across the population. It has also been common to assume that treatment is individualistic. This means that the treatment received by one person affects only that individual and not other members of the population. The assumption is realistic when considering non-infectious diseases.

When treatment is individualistic and welfare is additive, the optimization problem has a simple solution. The planner should divide patients into groups having the same observed covariates. He should assign all patients in a group to the treatment that yields the highest within-group mean welfare. Thus, it is optimal to differentially treat patients with different observed covariates if different treatments maximize their within-group mean welfare. Patients with similar covariates should be treated uniformly. These findings motivate the two recommendations regarding variation in clinical practice.

2.2. Derivation of the Optimal Plan

I derive the optimal plan here, paraphrasing the derivation in [12, Section 11.4]. Beyond showing the specific result, the derivation introduces concepts and notation that will be used throughout the paper.
The Choice Set

Let $T$ be a set of feasible treatments. Suppose that a planner must choose a treatment rule assigning a treatment to each member of a population. The planner observes certain covariates $x_j \in X$ for each member $j$ of the population. The covariate space $X$ has finitely many elements and $P(x = \xi) > 0$ for all $\xi \in X$.

Suppose that the treatment chosen for one patient does not constrain the treatments available to other patients. The planner can differentiate persons with different covariate values, but he cannot distinguish among persons with the same observed covariates. Hence, a feasible treatment rule either assigns all persons with the same observed covariates to one treatment or fractionally allocates these persons across treatments in a random manner. Formally, a feasible treatment rule is a function $\delta(\cdot, \cdot)$ that maps $T \times X$ into the unit interval and whose values sum to one across the elements of $T$; that is, $\sum_{t \in T} \delta(t, \xi) = 1$ for all $\xi \in X$. Let $\Delta$ denote the space of all such functions. The planner's choice set is $\Delta$.

A subclass of $\Delta$ are the singleton rules that assign all persons with the same observed covariates to one treatment. Thus, $\delta(\cdot, \cdot)$ is a singleton rule if, for each $\xi \in X$, $\delta(t, \xi) = 1$ for some $t \in T$ and $\delta(s, \xi) = 0$ for all $s \neq t$. Non-singleton fractional rules randomly allocate persons with covariates $\xi$ across multiple treatments, with assignment shares $[\delta(t, \xi), t \in T]$.

The Welfare Function and the Optimal Treatment Rule

Let the contribution to welfare from assigning treatment $t$ to person $j$ be $u_j(t) = u[y_j(t), t, x_j]$. Thus, welfare may depend on the treatment a person receives, the outcome of that treatment, and on the person’s covariates. The planner may know the form of the welfare function $u(\cdot, \cdot, \cdot)$ and may observe $x_j$. However, he cannot ex ante observe the potential outcomes $[y_j(t), t \in T]$ of alternative treatments.

An additive welfare function sums up the contributions to welfare of all treatment decisions. Maximizing an additive welfare function is equivalent to maximizing mean welfare in the population. For each feasible treatment rule $\delta(\cdot, \cdot)$, the population mean welfare that would be realized if the planner were
to choose rule $\delta(\cdot, \cdot)$ is

$$
(1) \quad U(\delta, P) = \sum_{\xi \in X} P(x = \xi) \sum_{t \in T} \delta(t, \xi) \cdot E[u(t) \mid x = \xi].
$$

Here $U(\delta, P)$ denotes social welfare when treatment rule $\delta(\cdot, \cdot)$ is applied to a population with distribution $P$ of treatment response. The expression $E[u(t) \mid x = \xi]$ is the mean welfare realized when persons with covariates $\xi$ receive treatment $t$. The fraction of the population with covariates $\xi$ and treatment $t$ is $P(x = \xi)\delta(t, \xi)$. The double summation on the right-hand-side of (1) aggregates welfare across persons with different values of $\xi$ and $t$.

The planner wants to solve the problem

$$
(2) \quad \max_{\delta \in \Delta} U(\delta, P).
$$

Let $S$ denote the unit simplex in $\mathbb{R}^{[T]}$. The maximum is achieved if, for each $\xi \in X$, the planner chooses $\delta(\cdot, \xi)$ to solve the problem

$$
(3) \quad \max_{\delta(\cdot, \xi) \in S} \sum_{t \in T} \delta(t, \xi) \cdot E[u(t) \mid x = \xi].
$$

The maximum in (3) is achieved by a singleton rule that allocates all persons with covariates $\xi$ to a treatment that solves the problem

$$
(4) \quad \max_{t \in T} E[u(t) \mid x = \xi].
$$

Thus, the optimal plan assigns all patients with covariates $\xi$ to the treatment that yields the highest within-
2.3. Static Planning under Uncertainty

*Some Decision Criteria*

To implement the optimal plan, one needs to know enough about treatment response to be able to solve problem (4). Suppose that a planner lacks this knowledge and, hence, cannot determine optimal treatments. Then how should the planner choose treatments?

This normative question has no unambiguously correct answer. There is no best way to make decisions under uncertainty. Decision theory only suggests various reasonable ways; see [12] for a textbook discussion. Among prominent approaches, Bayesian decision theory suggests that a planner place a subjective probability distribution on treatment response and maximize subjective expected welfare. Research on decision making under ambiguity studies ways to make reasonable choices in the absence of a subjective distribution on unknown quantities, developing such ideas as maximin and minimax-regret decision making.

To formalize these decision criteria, let $\Gamma$ index the set of feasible states of nature. Thus, $(P, \gamma \in \Gamma)$ is the set of distributions of treatment response that the planner deems possible. Let $f[U(\delta, P)]$ be a specified strictly increasing function of aggregate welfare. With this notation, we can pose the criteria.

A Bayesian planner places a subjective distribution $\pi$ on $\Gamma$ and solves the optimization problem

\[
\max_{\delta \in \Delta} \int f[U(\delta, P)]d\pi.
\]

The solution depends on $\pi$ and $f()$. A Bayesian planner is called risk-neutral if $f()$ is the identity function and risk-averse if $f()$ is concave.
A planner applying the maximin criterion solves the problem

\[
\max_{\delta \in \Delta} \min_{\gamma \in \Gamma} f[U(\delta, P, \gamma)].
\]

Monotone transformations of welfare do not affect the maximin criterion. The maximin treatment allocation is the same for all choices of \( f(\cdot) \).

A planner applying the minimax-regret criterion solves

\[
\min_{\delta \in \Delta} \max_{\gamma \in \Gamma} f[U^*(P, \gamma)] - f[U(\delta, P, \gamma)].
\]

Here, \( U^*(P, \gamma) \) is the optimal population mean welfare that would be achievable if it were known that \( P = P, \gamma \).

That is,

\[
U^*(P, \gamma) = \sum_{\xi \in X} P(x = \xi) \left\{ \max_{t \in T} E_t[u(t) \mid x = \xi] \right\}.
\]

The quantity \( f[U^*(P, \gamma)] - f[U(\delta, P, \gamma)] \) is called the regret of rule \( \delta \) in state of nature \( \gamma \). In general, the solution to the minimax-regret problem depends on the specified function \( f(\cdot) \).

The decision criteria described here offer a planner a host of possibilities for treatment choice under uncertainty. Indeed, expected welfare maximization is a class of criteria indexed by \([\pi, f(\cdot)]\) while minimax regret is a class indexed by \( f(\cdot) \). Decision theorists have suggested other criteria as well, such as the Hurwicz criteria that combine aspects of the maximin and maximax criteria. The various criteria coincide in some special cases, but they yield different treatment choices in general.

With this background, consider the two recommendations regarding variation in clinical practice. Manski [13] gives sufficient conditions that justify the recommendation to systematically differentiate
treatment of observationally different patients. Let \( f(\cdot) \) be the identity function and let the state space be rectangular, which means that the planner has no knowledge relating mean treatment response across groups of persons with different covariate values. Then a planner who uses any of the described decision criteria—maximization of subjective expected welfare, maximin, and minimax-regret—divides patients into groups having the same observed covariates and applies the criterion to the patients in the group. Hence, as was the case with known treatment response, treatment decisions vary systematically with patient covariates.

*Treatment Diversification*

The remaining question is whether a planner choosing treatments under uncertainty would adhere to the recommendation calling for uniform treatment of observationally similar patients. A planner cannot systematically differentiate the treatment of observationally similar patients, but he can do so randomly, choosing fractional values of \( \delta(t, \xi), t \in T \). That is, he may diversify treatment. It turns out that whether the planner will, in fact, diversify depends on the decision criterion used.

Economists commonly use the expected utility criterion to motivate financial diversification. Consider an investor who places a subjective probability distribution on investment returns, whose utility function places decreasing marginal value on each additional dollar earned, and who maximizes expected utility. A classical result is that such a risk-averse investor may choose a diversified portfolio. Analogously, a risk-averse health planner may diversify his treatment decisions. Formally, it can be shown that the solution to problem (5) is fractional if \( f(\cdot) \) is concave and the subjective distribution \( \pi \) has sufficient spread.

Manski [13] considers treatment choice under the minimax-regret criterion. Focusing on settings with two feasible treatments, I show that a planner who does not know which treatment is better and who uses this criterion always diversifies, assigning a positive fraction of patients to each treatment. The specific fraction assigned to each treatment depends on the available knowledge of treatment response and on the specified function \( f(\cdot) \). However, the solution always is fractional, even if \( f(\cdot) \) is not concave. Thus, the
minimax-regret criterion yields diversification much more generally than does maximization of expected welfare.

2.4. Dynamic Planning with Learning about Treatment Response

I have thus far considered planning in a static environment. Now consider a multi-period setting where, in each period, a planner chooses treatments for the current cohort of a population. An essential new feature of multi-period problems is that learning about treatment response becomes possible, with observation of the outcomes experienced by earlier cohorts informing treatment choice for later cohorts.

Static decision criteria that yield diversified treatment of observationally similar persons are particularly advantageous for learning treatment response because they generate randomized experiments. As time passes and evidence accumulates, the planner can revise the fraction of patients assigned to each treatment in accord with the available knowledge. This constitutes adaptive diversification [13].

It is natural to ask how adaptive diversification differs from the current practice of randomized clinical trials. One major difference is that adaptive diversification randomizes treatment of the entire patient population. In contrast, current RCTs draw samples of experimental subjects from pools of persons who volunteer to participate. Another difference is that the experiments performed with adaptive diversification are open-ended rather than have fixed durations. Hence, society observes health outcomes of real interest as they unfold over time. In contrast, current RCTs often have short durations, requiring researchers to measure surrogate outcomes rather than outcomes of real interest.

In a setting with two feasible treatments, Manski [13] discusses a particular implementation of adaptive diversification called the adaptive minimax-regret (AMR) criterion. Each period, the AMR criterion diversifies treatment by applying the minimax-regret criterion using the information available at the time. The result is a fractional allocation as long as the planner does not know which treatment is best. The AMR
criterion is adaptive because the allocation of successive cohorts to the two treatments changes as knowledge of treatment response accumulates.

Illustration

To illustrate adaptive diversification, consider a setting with two available treatments for a life-threatening disease, say A and B. Let A be a status quo treatment whose outcome distribution is known from historical experience, while B is an innovation with initially unknown outcome distribution. Each period, a health planner must decide how to treat a new cohort of observationally similar patients.

Let the outcome of interest be the number of years that a patient survives within a five-year time horizon following treatment. Thus, \( y_j(t) \) is the number of years that patient \( j \) would live during the five years following receipt of treatment \( t \). Let welfare equal years of survival; thus, \( u_j(t) = y_j(t) \). Let \( \alpha = E[u(A)] \) and \( \beta = E[U(B)] \) denote the social welfare that would obtain if all patients were to receive treatment A or B respectively. The health planner knows \( \alpha \) from observation of past patient outcomes under the status quo treatment. When the innovation B is introduced, suppose that he knows nothing about \( \beta \) except that it necessarily lies in the interval \([0, 5]\).

If the planner randomly assigns a positive fraction of new patients to B, then evidence on treatment response accumulates over time and the planner eventually learns \( \beta \). To see this, suppose that patient \( j \) receives treatment B. At the time of treatment, his outcome \( y_j(b) \) can take any of the values \([0, 1, 2, 3, 4, 5]\). A year later, one can observe whether \( j \) is still alive and hence can determine whether \( y_j(b) = 0 \) or \( y_j(b) \geq 1 \). If he lives, then another year later, one can observe whether \( j \) is still alive and hence can determine whether \( y_j(b) = 1 \) or \( y_j(b) \geq 2 \). And so on until year five, when the outcome is fully observable.

Table 1 presents hypothetical data on annual death rates following treatment by the status quo and the innovation. The entries show that 20 (10) percent of the patients who receive the status quo (innovation) die within the first year after treatment. In each of the later years, the death rates are 5 and 2 percent
respectively. Overall, the mean years lived after treatment are $\alpha = 3.5$ and $\beta = 4.3$. The former value is known at the outset from historical experience. The latter gradually becomes observable. The table shows the bound $[\beta_{Ln}, \beta_{Un}]$ that the planner can place on $\beta$ in each year $n$, using the evidence available at the time.

Table 1: Treating a Life-Threatening Disease

<table>
<thead>
<tr>
<th>cohort or year (n or k)</th>
<th>death rate in $k^{th}$ year after treatment</th>
<th>bound on $\beta$ for cohort n</th>
<th>AMR allocation for cohort n</th>
<th>mean life span for cohort n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Status Quo (A)</td>
<td>Innovation (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>[0, 5]</td>
<td>0.30</td>
<td>3.74</td>
</tr>
<tr>
<td>1</td>
<td>0.20</td>
<td>0.10</td>
<td>[0.90, 4.50]</td>
<td>0.28</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.02</td>
<td>[1.78, 4.42]</td>
<td>0.35</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>0.02</td>
<td>[2.64, 4.36]</td>
<td>0.50</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.02</td>
<td>[3.48, 4.32]</td>
<td>0.98</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>0.02</td>
<td>[4.30, 4.30]</td>
<td>1</td>
</tr>
</tbody>
</table>

Now consider decision making. The adaptive minimax-regret rule applies the minimax-regret criterion to each successive cohort, using the knowledge of $\beta$ available at the time. In the present setting, the analysis of [13] shows that the fraction of patients who receive treatment B at year $n$ is

\[
\delta_{\text{AMR}(n)} = 0 \quad \text{if } \beta_{Un} < \alpha, \\
= (\beta_{Un} - \alpha)(\beta_{Un} - \beta_{Ln}) \quad \text{if } \beta_{Ln} \leq \alpha \leq \beta_{Un}, \\
= 1 \quad \text{if } \beta_{Ln} > \alpha.
\]

The initial bound on $\beta$ is $[\beta_{Ln0}, \beta_{Un0}] = [0, 5]$. Hence, the initial AMR treatment allocation is $\delta_0 = 0.30$. In year 1 the planner observes that, of the patients in cohort 0 assigned to the innovation, 10 percent died in
the first year following treatment. This enables him to deduce that $P[y(b) \geq 1] = 0.90$. The planner uses this information to tighten the bound on $\beta$ to $[\beta_{L1}, \beta_{U1}] = [0.90, 4.50]$. It follows that $\delta_1 = 0.28$. In each subsequent year the planner observes another annual death rate, tightens the bound on $\beta$, and computes the treatment allocation accordingly. The result is that $\delta_2 = 0.35$, $\delta_3 = 0.50$, and $\delta_4 = 0.98$. In year 5 he knows that the innovation is better than the status quo, and so sets $\delta_5 = 1$.

3. Decentralized Health Care

3.1. Clinical Decisions under Uncertainty

Section 2 showed that when a health planner chooses treatments under uncertainty, it is useful to randomly vary the treatment of observationally similar patients. In a static planning environment, treatment diversification enables avoidance of avoid gross errors that might occur if all patients were inadvertently given an inferior treatment. In a dynamic environment, randomization yields new evidence that enables society to learn treatment response and improve treatment choice.

Now consider a decentralized health care system in which clinicians make treatment decisions. As discussed in Section 1, commentators regularly exhort clinicians to adhere to clinical practice guidelines that recommend uniform treatment of similar patients. For example, two recent IOM reports [5, 6] used the negative term 'inappropriate' to describe deviations from CPGs. Yet Section 2 showed that there is no best way for a planner to make decisions under uncertainty. It is therefore questionable whether CPGs should recommend uniform treatment when treatment response is uncertain.

It is instructive to consider clinicians as planners treating their own population of patients. As planners, clinicians may reasonably use different decision criteria to cope with uncertainty. Some may
maximize subjective expected welfare, others may use the maximin criterion, and yet others may minimize maximum regret. Those who maximize expected welfare may use different subjective distributions $\pi$, welfare functions $U(\cdot)$, and monotone transformations $f(\cdot)$. Clinicians may practice adaptive diversification. Thus, thinking of clinicians as planners yields a benign interpretation of variation in patient care. This interpretation rejects the prevailing view that non-uniform treatment of similar patients implies a deficiency in clinical practice.

Whether clinicians actually behave as planners is an empirical question, regarding which I have no evidence to present. One may not think it credible to assume that clinicians behave as planners. In the absence of knowledge of clinician decision processes, might it be prudent to recommend uniform treatment of similar patients? I cannot answer this question in generality, but I can point out that uniform treatment is counterproductive from the perspective of learning about treatment response.

For simplicity, consider a setting with two available treatments, say A and B. Suppose that a CPG recommends treatment A for certain patients and that all clinicians adhere to the recommendation. Then observation of patient outcomes reveals response to treatment A but is uninformative about response to B. This is fine if A is the better treatment for these patients, but not if B is actually the better treatment. Then adherence to the CPG generates a large error in patient care in the short run and prevents the health care system from learning the superiority of B in the long run.

A more complex version of this setting occurs when a clinician may order a diagnostic test prior to prescribing treatment. Clinical practice guidelines often call for aggressive treatment of an illness if a test result is positive and active surveillance (aka watchful waiting) if it is negative or if the patient is not tested. Manski [10] characterizes the conclusions about test results and treatment response that can be drawn when clinicians adhere to this CPG. Optimization of testing and treatment requires knowledge of eight distinct quantities. The available evidence reveals nothing about three of them and partially identifies the other five.

These scenarios demonstrate that adherence to a CPG may have unfortunate consequences, but they
do not imply that observational studies of clinical practice helps one to learn about treatment response. It is wise to be skeptical of observational studies that use untenable assumptions to draw strong conclusions. However, studies using credible assumptions can yield useful findings. Even without knowledge of clinical decision processes, observational studies yield informative bounds on treatment response. Variation in practice can strengthen the conclusions that may be drawn. I explain below, applying results originally proved in [14].

3.2. Learning About Treatment Response from Observation of Clinical Practice

Inference When Clinicians Are Undifferentiated

To begin, suppose that one observes data on treatment decisions and patient outcomes aggregated across the clinicians who treated a past cohort of patients. For example, a national cancer registry may report the treatments and outcomes of patients diagnosed with a specific cancer in a given year. I will later suppose that one can stratify clinicians into groups, perhaps geographically. For example, a cancer registry may report treatments and outcomes grouped by state, city, or hospital. Such stratification strengthens the conclusions about treatment response that may be drawn from the evidence.

Let $t \in T$ be a specified treatment and let $z_j$ denote the treatment actually received by patient $j$. If $z_j = t$, outcome $y_j(t)$ is observable but outcomes $y_j(s), s \neq t$ are counterfactual. Hence, welfare outcome $u_j(t)$ is observable but $u_j(s), s \neq t$ are counterfactual. Suppose that welfare outcomes have finite range $[u_{0}, u_{1}]$. Then counterfactual welfare outcomes can be no smaller than $u_{0}$ and no larger than $u_{1}$.

To determine optimal treatments, a planner or clinician with additive welfare function wants to learn the values of $E[u(t)|x = \xi]$ for $t \in T$ and $\xi \in X$. By the Law of Iterated Expectations,

$$E[u(t)|x = \xi] = E[u(t)|x = \xi, z = t] \cdot P(z = t|x = \xi) + E[u(t)|x = \xi, z \neq t] \cdot P(z \neq t|x = \xi).$$
Observation of clinical practice reveals $P(z = t|x = \xi)$ and $P(z \neq t|x = \xi)$, the fraction of patients who actually received treatment $t$ and the fraction who received another treatment. It also reveals $E[u(t)|x = \xi, z = t]$, the mean welfare realized by patients who actually received treatment $t$.

The evidence does not reveal $E[u(t)|x = \xi, z \neq t]$, the mean welfare that patients who received another treatment would have achieved if they had received treatment $t$ instead. This counterfactual mean can take any value in the interval $[u_0, u_1]$. Hence, the evidence reveals that $E[u(t)|x = \xi]$ lies in the interval obtained by letting $E[u(t)|x = \xi, z \neq t]$ range over its possible values. That is,

$$
E[u(t)|x = \xi, z = t] \cdot P(z = t|x = \xi) + u_0 \cdot P(z \neq t|x = \xi) \leq E[u(t)|x = \xi] \leq E[u(t)|x = \xi, z = t] \cdot P(z = t|x = \xi) + u_1 \cdot P(z \neq t|x = \xi).
$$

The derivation shows that, even with nothing known about how clinicians make treatment decisions, observation of clinical practice yields a bound on $E[u(t)|x = \xi]$. The width of the bound is $(u_1 - u_0)P(z \neq t|x = \xi)$, the range of possible outcome values times the fraction of patients for whom $t$ is a counterfactual treatment. Hence, the bound is informative if a positive fraction of patients actually received treatment $t$. When the bound is informative, $E[u(t)|x = \xi]$ is said to be partially identified.

**Inference with Stratification of Clinicians**

Now suppose that in addition to observing patient covariates, one also observes some covariates of the clinicians who treat them. For example, one may observe clinician location. The *Dartmouth Atlas of Health Care* [16] documents treatment variation across hospital and regions in the United States, while the *Atlas of Variation in Healthcare* [4] does the same for the United Kingdom. Both atlases report the treatments and outcomes of clinicians who practice in a given hospital or region.

Let $V$ denote the set of all possible values of the observed clinician covariates. For example, $V$ may
index the hospitals in a region or the regions in a nation. For each $\eta \in V$, application of bound (11) to the group of clinicians with covariates $\eta$ yields this bound on $E[u(t)|v = \eta, x = \xi]$:

\[
E[u(t)|v = \eta, x = \xi, z = t] \cdot P(z = t|v = \eta, x = \xi) + u_0 \cdot P(z \neq t|v = \eta, x = \xi) \leq E[u(t)|v = \eta, x = \xi]
\]

This bound expresses the conclusions about $E[u(t)|v = \eta, x = \xi]$ that can be drawn from the data alone, with no prior knowledge of clinical decision making or treatment response.

One can learn more if one finds it credible to assume that the patients treated by different groups of clinicians have the same mean treatment response. Formally, assume that

\[
E[u(t)|v = \eta, x = \xi] = E[u(t)| x = \xi] \quad \text{for all } \eta \in V.
\]

In econometric jargon, assumption (13) makes $v$ an instrumental variable.

Assumption (13) is often made in studies of geographic variation in clinical practice. For example, when examining variation in hospital re-admissions rates between hospitals in Boston and New Haven, Fisher et al. [17] discussed the reasons why they believed the patient populations in the two cities to be similar to one another. The assumption is also maintained in analyses of RCTs that combine data on patient outcomes across multiple treatment centers, which commonly suppose that patients in different centers respond similarly to treatment.

Assumption (13) has identifying power. If $E[u(t)|v = \eta, x = \xi]$ equals $E[u(t)| x = \xi]$ for all $\eta \in V$, it follows that $E[u(t)| x = \xi]$ lies in the intersection of all the $\eta$-specific bounds stated in (12). Hence, $E[u(t)| x = \xi]$ must be at least as large as the maximum of the $\eta$-specific lower bounds and no larger than the minimum of the $\eta$-specific upper bounds. That is,
The width of this intersection bound necessarily is no larger than the width of each of the $\eta$-specific bounds and typically is narrower. This formalizes the idea that observation of variation in clinical practice can be useful for learning about treatment response.

The benefit of tighter inference is achieved at the cost of maintaining assumption (13). The credibility of this assumption must be assessed on a case-by-case basis. One may think it credible when considering treatment of some diseases, for some clinician stratifications, and conditioning on some patient covariates. In other settings, one may question the assumption. In any case, one should keep in mind that the assumption imposes no restrictions on clinical decision making. It only asserts that the patients treated by different groups of clinicians respond similarly to treatment on average.

Someone who thinks it credible to maintain assumption (13) may think it credible to impose a stronger assumption asserting that the patients treated by different groups of clinicians not only have the same mean treatment response but the same distribution of treatment response. Manski [15, Sec. 7.4] shows that this assumption yields a bound that is tighter than (14). The derivation is considerably more complex than the one presented above, so I omit it here.

Illustration

To illustrate bound (14), let there be two observable groups of clinicians, with $\eta = 1$ and $\eta = 2$ perhaps indexing two cities or hospitals. Let the treatment outcome of interest be a binary indicator of survival, with $y(t) = 1$ if a patient survives for a specified length of time and $y(t) = 0$ otherwise. Moreover, let $u(t) = y(t)$. Then $u_0 = 0$, $u_1 = 1$, and the mean of $u(t)$ equals the probability that $u(t) = 1$.

To simplify the notation, suppress the conditioning of probabilities on the patient covariates $x$. 
Define $p(\eta) = P[u(t) = 1|v = \eta, z = t]$ and $f(\eta) = P(z = t|v = \eta)$. Then (14) reduces to

\begin{equation}
(15) \quad \max \{p(1) \cdot f(1), p(2) \cdot f(2)\} \leq P[u(t) = 1] \leq \min \{p(1) \cdot f(1) + 1 - f(1), p(2) \cdot f(2) + 1 - f(2)\}.
\end{equation}

Suppose, for example, that $p(1) = 0.8$, $f(1) = 0.6$, $p(2) = 0.5$, and $f(2) = 0.5$. Then the $\eta$-specific bounds (12) are $0.48 \leq P[u(t) = 1|v = 1] \leq 0.88$ and $0.25 \leq P[u(t) = 1|v = 2] \leq 0.75$. The intersection bound (14) is $0.48 \leq P[u(t) = 1] \leq 0.75$. Whereas the $\eta$-specific bounds have widths 0.4 and 0.5, the intersection bound has width 0.27.

One would, ideally, like to draw a precise conclusion about the survival rate that patients would realize under treatment $t$. Obtaining a bound of width 0.27 may seem inadequate relative to this ideal. However, the ideal may be unattainable in practice. A bound of width 0.27 may be useful when one keeps in mind that it is achieved without performance of an RCT and, indeed, without imposing any assumption on clinical decision making.

4. Implications for the Design of CPGs

Medical professional societies publish numerous CPGs that aim to inform and influence clinical practice. CPGs inform practice by synthesizing the state of medical knowledge regarding alternative treatments. They influence practice by making recommendations for patient care.

The objective of informing practice is uncontroversial. Careful summaries of the state of knowledge have substantial potential to improve care. To be helpful, they should draw on all available evidence, experimental and observational. They should maintain assumptions that are sufficiently credible to be taken seriously. They should combine the evidence and assumptions to draw logically valid conclusions.
CPGs commonly recommend uniform treatment of observationally similar patients. This is sensible in settings where treatment response is known and there is societal consensus on optimal treatments. However, when treatment response is uncertain, I am aware of no compelling medical argument for CPGs to recommend uniform treatment. The adjective 'medical' is necessary because one might cite administrative or legal arguments for uniform treatment. A health insurance plan may require adherence to a CPG as a condition for reimbursement of the cost of treatment. Concerned with the possibility of malpractice suits, a clinician may adhere to a CPG to exhibit due diligence. These considerations may affect clinical practice, but they are not directly medical in nature.

The analysis of this paper suggests that when treatment response is uncertain, CPGs should not recommend one treatment as "best practice." Instead, CPGs should help clinicians recognize that treatment choice may reasonably depend on how one interprets the available evidence and on the decision criterion that one uses. Going further, one might use the analysis of this paper to argue that CPGs should actively encourage random variation in clinical practice in order to promote diversification and learning. I am not certain whether CPGs should go this far, but I think that the idea warrants consideration.
References


