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Improving Health Care Outcomes Through Personalized Comparisons of Treatment Effectiveness Based on Electronic Health Records

Sharona Hoffman

Andy Podgurski
Case Western University, andy@eecs.case.edu

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I. Introduction

The unsustainable growth in U.S. health care costs is in large part attributable to the rising costs of pharmaceuticals and medical devices and to unnecessary medical procedures.[1] This fact has led health reform advocates and policymakers to place considerable hope in the idea that increased government support for research on the comparative effectiveness of medical treatments will eventually help to reduce health care expenses by informing patients, health care providers, and payers about which treatments for common conditions are effective and which are not.[2] Comparative effectiveness research (CER) has shown in some cases that expensive but commonly used treatments are significantly less effective than relatively inexpensive alternatives.[3] Critics warn, however, that CER will homogenize patient care, limit patient choices, and lead to improper health care rationing and even to the denial of lifesaving treatments.[4]

In 2009, Congress allocated $1.1 billion in funding for CER, as part of the American Reinvestment and Recovery Act (ARRA).[5] The Patient Protection and Affordable Care Act of 2010 (PPACA) embraced CER as an important health care reform initiative and established the Patient-Centered Outcomes Research Institute to oversee CER in the United States.[6] CER represents a major public health enterprise, since public health, broadly defined, includes all "federal, state, and local governmental efforts to maintain and protect the health of the general population."[7]

This article explores a novel application of CER that could enable physicians to make better treatment decisions for patients by invoking electronic queries of a large electronic health record (EHR) database. The query responses would summarize the outcomes of available treatments administered to patients with similar clinical characteristics.

We propose the development of a broadly accessible framework to enable physicians to rapidly perform, through a computerized service, medically sound personalized comparisons of the effectiveness of possible treatments for patients' conditions. A personalized comparison of treatment effectiveness (PCTE) for a given patient (the subject patient) would be based on data from EHRs of a cohort of patients who are similar to the subject patient (clinically, demographically, genetically), who received the treatments previously and whose outcomes were recorded. The proposed framework would permit the patient's physician to

Sharona Hoffman, J.D., *is a Professor of Law and Bioethics and Co-Director of the Law-Medicine Center at Case Western Reserve University School of Law.* **Andy Podgurski, Ph.D.,** *is a Professor of Electrical Engineering and Computer Science at Case Western Reserve University.*

order a computerized, retrospective study based on EHRs from the patient's cohort within a large and representative database of deidentified EHRs. Experts would establish the parameters, outcome measures, methodology, and technical infrastructure for all PCTEs. The infrastructure would support PCTEs for various conditions.

extent to which physicians' freedom of action should be limited by such evidence.[10] However, in many cases little is known about the comparative effectiveness of different treatments for a given medical condition. In the case of pharmaceuticals and medical devices in the U.S., one reason for this is that the FDA approval processes generally do not require the effectiveness of a new product to be compared to that of existing ones; it is often sufficient for the manufacturer to provide evidence of the product's safety and efficacy as compared to a placebo.[11] According to Alexander and Stafford,

> The FDA's historical focus on common harms and on evaluating efficacy against placebo has led to testing in small, highly selected populations with limited comorbidities. In turn, these studies have failed to provide information most relevant to the clinical contexts in which FDA-approved drugs or devices are ultimately used.[12]

In 2009, the Institute of Medicine (IOM) recognized the need for expanded CER and proposed initial national priorities for it.[13] The IOM report noted that randomized controlled trials (RCTs) are the "gold standard" for determining treatment effectiveness because they minimize bias in determining which patients receive treatment and which serve as controls. However, it recognized that RCTs cannot answer many comparative effectiveness questions and that observational data, such as that in EHRs, can help fill gaps in evidence when RCTs are not possible or are inadequate. Some commentators have posited that retrospective analysis of EHR data should play an important role in bridging the "inferential gap" between "the paucity of what is proved to be effective for selected groups of patients versus the infinitely complex clinical decisions required for individual patients."[14]

PPACA enthusiastically embraced CER as a major health care reform initiative. The Act defines CER as "research evaluating and comparing health outcomes and the clinical effectiveness, risks, and benefits of 2 or more medical treatments, services, and items...."[15]

This article explores a novel application of CER that could enable physicians to make better treatment decisions for patients by invoking electronic queries of a large electronic health record database. The query responses would summarize the outcomes of available treatments administered to patients with similar clinical characteristics.

The PCTE service could make a novel and valuable contribution to medical practice. PCTEs would focus on identifying, for a given patient, an appropriate reference group (cohort) of similar, previously treated patients whose EHRs would be analyzed to choose the optimal treatment for the patient at issue. This approach contrasts with the use of general clinical prediction models[8] that are intended to capture in a single mathematical construct the relationships among treatment choices, clinical and other predictor variables, and prognoses for a large and diverse population of patients. PCTEs may employ statistical models, but these models would be fitted using data from the cohort of previously treated patients who are (or were) similar to the subject patient in clinically relevant ways. Basing treatment effect estimates on such cohorts will enhance their predictive value. Using a PCTE service, doctors could submit a wide range of narrowly-tailored, treatment-effectiveness queries from their desktop computers.

PCTEs have unique potential to simultaneously improve the quality of health care, reduce its cost, and alleviate public concerns about rationing and "one size fits all" medicine.[9] Therefore, they could serve as an important tool in promoting the goals of the health care reform initiative and make a significant contribution to public health.

II. PCTE Building Blocks: Comparative Effectiveness Research and Electronic Health Record Systems

A. Comparative Effectiveness Research

Many physicians agree that medical decisions should, where possible, be based on a foundation of scientific evidence, although there is disagreement about the

CER is to be conducted through a wide variety of means, including clinical trials, observational studies, and any other appropriate methodologies.[16] The goal of CER is to generate improved patient outcomes while maximizing the value derived from health care expenditures.[17] PPACA emphasizes the importance of developing evidence concerning "variations in patient subpopulations" and of disseminating research findings so that they can be used by those making health care decisions.[18]

Many commentators have expressed concern about the challenges of applying CER findings to achieve health care delivery improvements.[19] CER would be of little worth if its results were not operationalized in the clinical setting. This article's proposed PCTE tool offers a novel, creative mechanism to move CER discoveries from bench to bedside so that it can be utilized effectively by health care providers and patients. PCTEs would fit well within the CER goals articulated in PPACA.

B. Electronic Health Records

An essential resource for CER generally and PCTEs in particular are electronic health records (EHR). The U.S. government has undertaken a major initiative to computerize all Americans' health records by 2014. To that end, President Obama's stimulus legislation, ARRA, dedicated $27 billion to the promotion of health information technology. Under ARRA, clinicians may obtain payments of up to $44,000 from the Medicare incentive program and $63,750 per clinician from the Medicaid program.[20] In the years to come, EHR systems will transform medical practice in the United States. One of their many contributions is likely to be providing health care professionals with unprecedented research capabilities.

Health information technology advocates contemplate the development of a National Health Information Network (NHIN) of interoperable health information systems so that necessary exchanges of health data can occur expeditiously. One of the potential benefits of the NHIN is that it could greatly facilitate CER by providing medical researchers with access to what is in effect a massive database of deidentified EHRs.[21] This database could provide data that is invaluable for assessing the benefits and risks of different medical treatments in actual use.

The importance of large electronic databases for research purposes is well recognized. A 2009 PricewaterhouseCoopers report[22] called for public-private collaboration and a limited government role in enabling the private sector to collect, share, and use health data for secondary purposes, including CER. The Veterans Health Administration already uses its well-established EHR system to conduct extensive assessments of performance and outcomes and to operate an Evidence Synthesis Program.[23] Likewise, the Food and Drug Administration (FDA) is planning to implement a national electronic system called the Sentinel Initiative that will enhance the FDA's ability to monitor the safety of the products it regulates after they reach the marketplace. The FDA hopes to be able to send electronic queries to participating data holders such as health care providers and insurers, and obtain summary responses from them.[24] Broad proposals have also been entertained in the academic and health policy literature. For example, Lynn Etheredge recommended the establishment of both a National Database for Effectiveness Research Studies and a national network of new research registries and linked databases to "capture key data from millions of patient records so that comparative studies can cover all conditions, treatments, and patient groups."[25]

C. Will CER Necessarily Lead to Better Health Care?

There is no guarantee that CER studies will automatically result in improved health outcomes. In the words of one commentator, "having better information is comparable to arriving at the base camp at Mount Everest. Clinicians, patients, managers, and policy makers need to work together to apply the results of comparative research appropriately and consistently if we are to reach the summit of reliable, evidence-based, and patient-centered care."[26] Collecting data through research studies may be far easier than determining how they can be put to good use in the clinical setting.

Another concern is that CER will yield results that are not sufficiently individualized and that do not take into account all of the factors that make particular patients different from others. Thus, if doctors wrongly assume that certain CER findings are generalizable to all patients and base treatment decisions on these research results, they may make erroneous decisions in specific cases. Over-reliance on CER could lead doctors to ignore lifestyle, genetic, medical history, or patient preference factors that make a particular recommended therapy inappropriate for the individual in question.[27]

It is not surprising that treatment guidelines derived from estimates of average treatment effects for a diverse population can lead to suboptimal or even harmful results if they are applied naively to atypical subpopulations or individuals. This fact is illustrated by a 2009 retrospective study of the initiation of anticoagulation therapy with the drug warfarin in 5,052 patients.[28] The investigators found that a pharmacogenetic algorithm for estimating the appropriate ini-

tial dose of warfarin, which considered both clinical and genetic factors, outperformed a standard dose of 35 mg per week (and also outperformed an algorithm that considered only clinical factors), principally because the pharmacogenetic algorithm's estimated doses were more efficacious (and presumably safer) for "outliers" — patients who required 21 mg of warfarin or less per week or who required 49 mg or more per week. In an accompanying editorial, Woodcock and Lesko concluded that a "better understanding of individual differences in the response, either positive or negative, to medicines should be an overarching goal for pharmacotherapy over the next decade. Pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'"[29]

CER is most controversial when it is discussed in the context of cost effectiveness analysis (CEA) of different treatments.[30] Proponents of CEA, such as the American College of Physicians, see it as one valuable tool (among others) for informing those responsible for making decisions about medical expenditures.[31] Critics, however, warn that CEA will lead to homogenized medicine, in which the treatment that is most cost effective *on average* for a particular condition will be given to all patients with the condition, even if it is inappropriate for them.

Some warn that a primary focus of CER will in fact be cost control. This could lead to care rationing and denial if specific treatments are perceived as insufficiently cost effective or individuals are deemed unlikely to experience sufficient enhancements of life-quality or longevity. PPACA aims to provide the public with reassurance in this regard, stating explicitly that "[t]he Secretary shall not use evidence or findings from comparative clinical effectiveness research…in determining coverage, reimbursement, or incentive programs…in a manner that treats extending the life of an elderly, disabled, or terminally ill individual as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill."[32]

The best way to realize the potential benefits of CER in the face of legitimate public concerns is to foster a rational and appropriate demand for its results, based on individual physicians' and patients' perceptions of their own best interests. PCTEs constitute a CER approach that could well serve this goal.

III. Personalized Comparisons of Treatment Effectiveness

A. Overview

PCTEs would enable a patient's physician to rapidly perform, through a computerized service, a medically sound personalized comparison of the effectiveness of possible treatments for the patient's condition(s), the results of which would be provided, in readily comprehensible forms, to both the physician and the patient (or guardian). This personalized comparison would be based on the EHRs of a cohort of other patients with the same condition who are similar to the given patient in other ways that are relevant clinically, demographically, and perhaps genetically.

In technical terms, the proposed framework would permit the patient's physician to order a computerized, retrospective study based on EHRs from the patient's cohort within a very large and representative database of deidentified EHRs. The results from this study would be adjusted statistically to take into account potential biases, confounding variables, and the results of well-regarded prior studies of the treatments in question, especially randomized controlled trials. Admittedly, for some patients, no valid comparison would be possible, e.g., because no suitable cohort could be identified in the EHR database. Before PCTEs could be conducted on behalf of patients with a particular condition, experts would establish the parameters, outcome measures, methodology, and technical infrastructure for them, as described in Part D.

Thus, for example, a doctor who wishes to use a PCTE to help determine what treatment is best for a particular patient with hyperthyroidism would access an Internet service supporting PCTEs for hyperthyroidism patients. The physician would upload from his or her patient's EHR the values of relevant clinical and demographic variables required for the PCTE. The PCTE service would then mine the database to identify EHRs of patients with similar values for those variables who were treated previously for hyperthyroidism. The records of patients who received particular treatment options would be sorted into corresponding treatment groups from which well-matched comparison groups would be selected, if possible. The treatment outcomes that were experienced by patients in the comparison groups (as characterized by an approved set of outcome measures) would then be compared statistically. Finally, the PCTE service would present to the physician and patient, in understandable ways, results that accurately characterize the relative effectiveness of the treatments for the patient's cohort. The entire process would be automated.

PCTE service providers would typically be commercial enterprises that would profit from use of PCTEs. Health care providers could pay per query or be charged monthly rates for unlimited use of the service. PCTE service providers should be motivated by the prospect of economic gain to provide high quality products and maximize user satisfaction.

The use of a computerized tool to facilitate individual treatment decisions has precedents. For example, *Adjuvant! Online* allows a doctor and cancer patient to input information about the patient and receive assistance in deciding upon the best course of treatment after surgery.[33] *Adjuvant! Online* uses comparative effectiveness research that has already been conducted to provide a treatment recommendation. Under our proposal, the PCTE service would conduct a comparative effectiveness analysis even if no formal CER study had been completed.

Each PCTE would be based on a cohort of clinically similar patients rather than on a general model or a set of clinical practice guidelines. Thus, PCTEs would be uniquely well-suited to simultaneously improve the quality of health care, reduce its cost, and alleviate public concerns about rationing and "one size fits all" medicine.

There are numerous hurdles to successfully implementing and operating the proposed framework for PCTEs, including technical, social, educational, economic, ethical, legal, and political ones. Our proposal requires integrating cutting-edge developments in medicine, health information technology, computer science, and statistics. However, success is quite feasible, and the potential long-term benefits, in terms of improved health, alleviated suffering, reduced health care costs, and reduced health disparities easily justify the investment required.

B. PCTEs and Personalized Medicine

Personalized comparisons of treatment effectiveness, as proposed here, constitute a form of personalized medicine. Personalized medicine can be defined as "the delivery of health care in a manner that is informed by each person's unique clinical information; genetic, genomic, and other molecular/biological characteristics; and environmental influences."[34]

PCTEs would be consistent with this approach because they would be based on relevant patient variables whose values are recorded in EHRs, such as variables representing demographic information, clinical measures, aspects of medical or family history, and known risk factors, possibly including genetic or genomic factors.[35] We use the term "covariates" to refer to the set of variables used in a PCTE that do not represent medical treatments or outcomes and whose values were acquired before any outcome measures were obtained. Ideally, the covariates, treatment variables, and outcome variables would capture, in suitable form, all of the information about individual patients that is necessary to accurately estimate effect differences for treatments of a given condition. There may be several, or even dozens, of covariates that are relevant to a particular PCTE. We will also use the term "profile" to mean a complete, ordered set of covariates characterizing a patient. Different covariates will of course be appropriate for different conditions.

In a PCTE, a very large EHR database is searched to find a cohort for a patient needing treatment. Intuitively, this is the set of patients represented in the database who were treated for the same condition, who had similar profiles at the time they were treated, and whose treatment outcomes were recorded. Given an appropriate metric for measuring profile similarity or dissimilarity,[36] the cohort of a patient Jane Doe may be defined as all patients whose profiles are within a numeric similarity threshold T of Jane's profile. The threshold T should be chosen based upon a statistical analysis of the distribution of profiles and treatments for patients treated for Jane's illness. The cohort should be reasonably large and relatively homogeneous in terms of covariate values. It should also be possible to select suitable treatment comparison groups from the cohort, each consisting of patients who received a given treatment. These groups should be approximately balanced with respect to both size and covariate distribution. A number of techniques have been developed for constructing such matched groups.[37] A personalized assessment of the relative effectiveness of two treatments can be obtained, for example, by estimating the average difference in treatment effects between matched individuals in the corresponding comparison groups.[38]

Note that PCTEs will be precluded for some patients because suitable comparison groups cannot be found (e.g., because the patients have unusual characteristics). Several techniques exist to detect lack of balance among comparison groups.[39] If multiple outcome measures exist for a condition, a PCTE may indicate that one treatment is best with respect to one measure and that another treatment is best by another measure. In this case the patient's physician would help him or her interpret the results and decide on a course of action. PCTEs should be used to compare only established treatments or treatments that have been found to be safe and efficacious based on RCTs.

C. PCTEs and Observational Studies

Personalized comparisons of treatment effectiveness would rapidly provide doctors with actionable results, based on computerized observational studies. Observational evidence has been recognized by commentators as an important component of CER.[40] Observational studies allow investigators to examine very large bodies of data based on treatments that were given to diverse populations of patients in real world clinical settings.

Critics may object, however, to making treatment decisions based on nonrandomized studies. The main limitation of observational studies, and the main reason that randomized trials are preferred for estimating treatment effects, is that since treatment selection (selection of patients to receive a particular treatment, or to serve as controls) is not explicitly randomized in an observational study, it may be influenced by confounding variables in ways that can seriously bias estimated treatment effects. For example, suppose that doctors choosing between available treatments A and B for a particular serious condition tend to order treatment A for younger, healthier patients and treatment B for older, sicker patients, because of concern about side effects of A in the latter individuals. If the estimated benefit of treatment A over the entire patient population is greater than that of treatment B, then this may be due to the prior conditions of the patients who received the treatments and not to the superiority of treatment A. Doctors may not even be aware of their own subtle treatment biases, e.g., ones resulting from having treated a particular mix of patients in the past. Random treatment assignment, as in clinical trials, helps to avoid such biases by tending to yield comparison groups that are approximately balanced in terms of possible confounding factors. Even in clinical trials, however, the groups might not be representative of the overall population of patients with the condition because of bias in the recruitment of subjects, loss of subjects, and other factors.

Many physicians may be unaware that there has been substantial progress in redressing the limitations of observational studies for clinical research and for causal inference generally. This progress has been spurred by a confluence of ideas and results from such diverse fields as epidemiology, economics, social science, statistics, and computer science.[41] The computer scientist Judea Pearl has presented a conceptual framework and a methodology for causal inference[42] which unifies the major lines of causal inference research and which provides a foundation for conducting PCTEs. A key part of Pearl's methodology is formulating causal assumptions using ordinary scientific language and representing their structural aspects in graphical form. The result is called a causal model.

Even with state-of-the-art causal inference techniques, there is reason to doubt whether treatment selection bias due to doctors' and patients' highly subjective judgments about prognoses, frailty, pain, and other factors, made on the basis of information that is not completely captured in patients' EHRs, can be adequately controlled for based on standard EHR data.[43] In order to address this issue, EHRs intended for use in PCTEs could include physicians' and patients' own ratings of hard-to-measure factors like level of frailty or pain, e.g., on a numerical scale of one to ten.[44] These ratings would require normalization through appropriate statistical adjustments to account for rater tendencies, such as a consistent propensity to provide high scores. In any case, the computerized service that conducts a PCTE should subject the results to a procedure called quantitative bias analysis before reporting it to the physician and patient.[45] This analysis would aim to detect any evidence that the results were seriously confounded by unknown variables, in which case the problem would be reported to the patient's physician.

D. PCTE Oversight Committees

To be widely accepted, PCTEs must be subject to rigorous processes for their design, approval, and long-term monitoring. In light of space constraints, not every aspect of these processes can be detailed in this article, but a general operational framework is outlined below.

We envision that a commercial venture seeking to provide PCTE services for a particular disease would approach a leading professional organization for specialists in that area and request the formation of one or more PCTE Oversight Committees (POC) to oversee the design and implementation of its PCTE services. Thus, a company wishing to focus on a type of cancer could turn to the American Society of Clinical Oncologists; one interested in cardiology PCTEs could approach the American College of Cardiology; and a PCTE service provider for diabetes could work with the American Association of Clinical Endocrinologists.

Pursuant to a negotiated contract, the PCTE service provider would pay the professional association a sum of money that would be used to support each POC. The association would then recruit POC members and pay them an annual honorarium for their work. POCs should consist of knowledgeable researchers, clinicians, statisticians, and patient advocates. In order to limit the amount of work each POC must do, a professional organization might create several POCs, each of which is tasked with addressing a subset of disease problems.

For each kind of PCTE, the POC and PCTE service provider, working together, should specify a causal model that represents the known or suspected causal relationships among treatments, covariates, outcome measures, and other factors that could influence treatment results.[46] Patient input should be obtained concerning what outcome measures are most important to them. For example, these may involve not only disease cures, but also pain, recovery time, impact on personal

appearance, complication rates, and side effects. The POC and the PCTE service provider should also specify the techniques to be employed to measure similarity between patients and to identify cohorts. They should ensure that the EHR database to be used is adequately representative, and agree on a sound plan for validating the PCTE model and its implementation. The POC should oversee the implementation and evaluation of the PCTE service, approving or rejecting the results.

Large health care providers such as the Cleveland Clinic or Kaiser Permanente might wish to implement an internal PCTE service using their own patients' EHRs. Such providers would not need to partner with a professional organization, but rather, could use their own experts. Nevertheless, they too would be required to utilize a POC that meets regulatory requirements, as described below.

In other instances, business enterprises might wish to compete with existing PCTE service providers and to offer a different PCTE service, just as Google competes with other search engine providers. Professional associations should be free to contract with and provide POC services to multiple commercial ventures. Associations should not have to establish entirely new POCs for different commercial ventures. POCs should be able to share the same causal model for a given condition and the same criteria for identifying cohorts with any commercial PCTE service providers, and the POC should inform all providers of refinements to the model or criteria. A POC would not, however, share a PCTE service provider's proprietary design details with other service providers, and legal safeguards would have to be implemented to protect intellectual property rights and trade secrets. Sharing the same well-researched causal model and cohort identification criteria with all PCTE service providers that are focusing on a particular condition would safeguard the consistency and quality of PCTE results. Patient outcomes should not depend upon the PCTE service used by their physician and should not suffer because some commercial ventures are forced to obtain data from second-rate sources. Moreover, because of the limited number of leading medical professional organizations, exclusive contracts could preclude competitors from entering the market and thus violate antitrust law.[47]

Use of professional associations should optimize the value of PCTEs and minimize the likelihood of conflicts of interest. If commercial PCTE service providers were to hire experts directly to formulate PCTEs, they might pressure such independent contractors to produce a large volume of work quickly, to the detriment of quality, in order to launch the service as soon as possible. Unlike commercial enterprises, professional associations would not be motivated by the prospect of large profits, because they would be limited to the specified contractual payment. In addition, professional organizations should have the interest of their members as their top priority, and therefore, they will wish to ensure that PCTEs are as helpful as possible to physicians and minimize medical malpractice exposure. To that end, the organizations should ensure that all POC members have appropriate and current expertise and are free of conflict of interest.

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Professional associations already have experience in formulating guidelines for clinicians. The National Guideline Clearinghouse lists over 2,500 clinical practice guidelines, many of which are published by associations.[48]

Because POCs would consist of individuals who chose to serve on the committees, their members can be expected to be dedicated to the work. The fact that POC members will be paid by the association should increase their accountability and sense of responsibility. For the sake of clarity, contracts between professional associations and PCTE service providers should specify conditions under which a contract will be deemed to have been breached (e.g., if a POC is not

formed by the association within a specified period of time or a particular phase of the project is not completed by a deadline).

Much as research institutions maintain ongoing Institutional Review Boards (IRBs), professional associations would need to maintain POCs on a long-term basis. Long-term monitoring of PCTE services would be necessary to ensure that results remain trustworthy in light of emerging research and input from physicians and patients who use the service. POCs should conduct continuing reviews, periodically surveying member physicians concerning their PCTE experiences as well as periodically auditing a sample of recent PCTEs and investigating the health status of the patients for whom they were conducted.[49] In addition, physicians and patients who use the service should be able to report concerns about it to the relevant POC, with the assurance that concerns will be considered carefully.

Government oversight over both POCs and PCTE service providers would be essential to ensure the safety and efficacy of PCTE services. Just as federal regulations govern the composition of IRBs,[50] the Department of Health and Human Services (HHS) should formulate regulations concerning POC membership, requiring that they include qualified researchers, clinicians, and community members who are patient advocates. The responsibilities of POCs should also be specified in regulations.

PCTE service providers must be required by regulation to utilize an appropriate POC to determine PCTE covariates and a causal model and to avoid conflicts of interest because of which commercial profit might be prioritized over patient care. In addition, HHS should be authorized to mandate periodic reports from PCTE service providers and to investigate suspected problems.

E. Technical Infrastructure

Conducting PCTEs on a large scale requires designing and implementing a technically complex PCTE query service. Such a service would require a distributed software system that would, when invoked by a physician in order to conduct a PCTE for a patient, retrieve (or prompt for) the data about the patient that is required by the PCTE's causal model, mine the EHR database to identify a suitable cohort, execute causal inference procedures needed to characterize the relative effectiveness of the treatments under consideration, and characterize statistical uncertainty about the results. The service's user interface would be critically important. It must guide the physician so he or she does not make mistakes that would invalidate the PCTE. It must also help the physician to properly interpret the results and warn of any limitations of the analysis. In essence, the user interface must serve the role of the physician's own clinical research consultant. The entire PCTE service should be developed with adherence to the best practices for software engineering, health informatics, and information security, and it should be required to undergo rigorous pre- and post-deployment evaluation.[51]

The most realistic approach to developing a comprehensive PCTE service is to do so incrementally,[52] beginning with medical conditions that are both common and especially well suited to PCTEs. If the initial offerings were successful, the number of PCTE types available to physicians would be likely to grow over the years, as new PCTE service providers enter the market and as more POCs are formed to oversee the establishment of PCTEs for additional conditions.

Fortunately, it is not necessary to establish a nationwide network of interoperable EHR systems, such as the proposed NHIN, or a comprehensive solution to the problem of representing medical concepts unambiguously in concrete data structures[53] before implementing PCTEs. The most important requirements for the EHR database to be queried are that its records be representative of the actual patient population and that it be large enough to enable suitable cohorts to be identified for most patients. If a patient's relevant characteristics are unusual, only a very large EHR database is likely to contain a sufficient number of records of patients with similar characteristics to enable valid statistical inferences to be made about treatment effects.

The required EHR database could be created from the EHRs of one large health care system or those of multiple health care providers who agree to share their EHR data and to adopt common data standards. A major health system such as the Cleveland Clinic or Mayo Clinic is likely to have a sufficiently large and diverse patient population to permit using its own EHR system as a database for conducting PCTEs, and health care networks will be motivated to implement such a service if it is shown to improve outcomes and to add to their profits. On the other hand, relatively small and resource-poor institutions that wish to conduct PCTEs will not be able to rely on their own EHRs alone. Instead, they will have to either participate in a federated system[54] that searches the EHRs of multiple organizations or employ a PCTE service provided by a larger organization.

Carol Diamond and her coauthors note that, in the context of public health, a federated system obviates the need for different organizations to share their data about individuals and thereby eliminates a number of attendant problems, including privacy risks.[55] Organi-

zations participating in a federated system can share group-level summary data, such as means and proportions, which are computed locally.

A federated system would not be unprecedented. DARTNet is an existing federated network that consists of electronic health data from eight organizations representing more than 500 clinicians and over 400,000 patients, which was created to facilitate observational CER about prescription medications and medical devices.[56] DARTNet does not allow a full set of patient data to leave individual clinical sites; however, it permits queries that return deidentified data about individuals.

To reduce privacy risks, a federated system for conducting PCTEs could, at each participating organization, identify a local "sub-cohort" (subset of a cohort) for a subject patient, based on the latter's deidentified profile, but return to the PCTE service only summary statistics about the sub-cohort and possibly a fitted statistical model (e.g., a regression model) characterizing the relationships between treatments, covariates, and outcome(s) for the sub-cohort. The PCTE service would combine the data characterizing each sub-cohort (e.g., using multilevel modeling techniques)[57] to produce final predictions of treatment effects for the subject patient. The participating organizations would each need to support a common communication protocol and common set of statistical operations, but they would not have to provide one another with data about individual patients even in deidentified form.

F. Data Quality

Two of the greatest challenges to realizing the potential benefits of PCTEs are the quality and completeness of the data contained in EHRs.[58] Amanda Terry et al. list five characteristics of EHR data that affect their use in research:

> (i) providers decide where to put information (uniqueness of use); (ii) information may be entered in free-text form instead of being entered in defined fields or picked from a structured list of medical terms; (iii) providers use different terms for the same information (lack of standardization); (iv) information may not be stored in a way that is readily searchable and (v) data that are not important to clinical care [but are important for research] may be missing.[59]

The authors identify two issues as central to data quality: (1) the need to code all presenting comorbidities and (2) developing criteria for identifying patients who have the specific condition to be studied.

A particularly noteworthy difficulty is that in some cases, treatment outcomes are not reported. A patient who receives medication and whose condition improves may not require follow-up and is unlikely to contact the doctor to report her satisfaction with the course of therapy. A lack of further patient visits may suggest treatment success, but it may also indicate that the patient is economically disadvantaged and does not have regular access to health care providers. An absence of definitive data in this regard could be problematic for PCTE purposes.[60]

Increasing use of electronic means for collecting patient data, such as remote patient monitoring,[61] has the potential to mitigate problems with the completeness and accuracy of EHR data. Furthermore, health care organizations that wish to offer PCTEs may be willing to create strong incentives for internal compliance with standards for patient follow-up and data entry, because they view data quality as essential to their goals.

Ultimately, the federal regulations suggested above may need to address data integrity. It would be advisable for regulators to establish and enforce national standards for interoperability and data quality.[62]

G. Evaluation of PCTE Services

It will also be important to conduct clinical trials to evaluate the safety and efficacy of particular PCTE services. To illustrate, a clinical trial could include breast cancer patients who are randomly assigned to two arms: one in which physicians use PCTEs and one in which they do not. Investigators must recognize that the results of such studies will be somewhat obfuscated by the fact that physicians will be at liberty to disregard PCTEs in light of their own judgment or patients' rejection of the recommended treatment. Therefore, researchers would need to evaluate not only the ultimate outcomes of patients in both study arms, but also the actual recommendations that the PCTEs made and physicians' reasons for ignoring any of them.

PCTE services should facilitate reporting by physicians and HIT personnel of adverse events related to their use, such as serious usability problems or failures that lead to improper recommendations. This could be accomplished by incorporating a well-designed problem-reporting mechanism into the service, which could be invoked simply by clicking an icon. The occurrence of adverse events should promptly be shared with the POC and appropriate federal authorities for assessment.

H. The Risks and Benefits of PCTEs

PCTEs are likely to raise concerns about privacy. Despite deidentification of records, many patients

may worry about confidentiality and the ability of third parties to trace sensitive information to them.[63] Consequently, careful attention should be paid to ensuring the integrity of the deidentification process and the security of EHR databases.[64] In addition, questions may be raised concerning whether patients have a property right in their health information[65] and to what extent they should be asked to consent to their records' use in PCTEs. For example, should patients have an opportunity to opt out of inclusion in the PCTE enterprise altogether? Should they be allowed to limit use of their deidentified records, such as by refusing to have them included in PCTEs relating to reproductive services? Would complying with such patient preferences be administratively feasible? These matters warrant further consideration.

PCTE service providers would also have to be trusted to maintain patient confidentiality. When processing PCTE queries, they would receive sensitive information concerning patients and their medical conditions. Although patients would not be identified by name to the service provider, patients might become identifiable through various demographic details and the name of their treating physicians.[66] Patients may worry that PCTE service providers will furnish search information to health insurers, who in turn might refuse to pay for treatments in instances in which a physician deviated from PCTE recommendations. Potential disclosures to other third parties, such as employers, financial institutions, and marketers would also be of concern.[67]

PCTE service providers who have contracts with hospitals or health networks are likely to be considered business associates by the HIPAA Privacy Rule and to be bound by its confidentiality mandates.[68] However, PCTE service providers with a pay per query arrangement rather than contracts may not be covered entities. Consequently, the HIPAA Privacy Rule would need to be amended to state explicitly that PCTE service providers fall within its scope.

Another obstacle to adoption of PCTEs may be physicians' attitude toward them. Some physicians may object to giving a computerized service significant influence in treatment decisions, and some may even feel threatened by PCTEs. Physicians may also feel that they cannot afford the time required to initiate PCTEs and interpret the results. These concerns can be alleviated by a combination of skillful design of the service, strong evidence for the benefits of PCTEs, and appropriate incentives for using them implemented by physicians' employers, hospitals, and others.

It is also possible that PCTEs will exacerbate health disparities because not all patients will be able to pay for their use. If patients must pay out of pocket for PCTE queries, then only those with sufficient financial resources will be able to pay for the service. However, if PCTE use is shown to be cost effective because it improves outcomes and, when appropriate, leads clinicians to opt for less expensive treatments than they may have otherwise selected, then private and public insurers may well choose to cover the cost of the service.

There is good reason to hope that PCTEs will help lower health care costs by addressing the imbalance of information that often exists between buyers and sellers of health services.[69] Ideally, the results of PCTEs would lead physicians and patients to choose treatments that better control symptoms and cure diseases, thus reducing the need for further medical care.

Patients who must absorb a significant portion of the cost of care because of high deductibles or copayments may also appreciate accurate information that allows them to make cost-effective decisions. For example, they may choose to forego a very expensive treatment and opt for a relatively inexpensive one that is only marginally less effective overall.

Physicians would utilize PCTE services only when they believe doing so would be beneficial, and we would not support institutional policies that require doctors and patients to follow PCTE recommendations. Doctors should maintain their professional discretion and patients their autonomy. PCTE services are meant to be only one tool in the medical toolbox, but they have the potential to be a very valuable asset for health care providers and to facilitate optimal treatment decisions.

IV. Conclusion

This article proposes the development of a national framework to allow physicians to conduct electronic comparisons of treatment effectiveness (PCTEs) that are personalized with respect to individual patients' clinically relevant characteristics. Each comparison would be based on the electronic health records of a cohort of clinically similar patients. Substantial groundwork must be laid before PCTEs can be made widely available. Given that EHR systems are not yet in general use,[70] adequate EHR data about individuals' long-term treatment effects is likely to be unavailable for some time. However, with proper design and oversight, PCTEs hold great promise to empower patients and physicians, reduce medical costs, and significantly improve public health.

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